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Expeditious and practical synthesis of tertiary alcohols from esters enabled by highly polarized organometallic compounds under aerobic conditions in Deep Eutectic Solvents or bulk water

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ABSTRACT

An efficient protocol was developed for the synthesis of tertiary alcohols via nucleophilic addition of organometallic compounds of s-block elements (Grignard and organolithium reagents) to esters performed in the biodegradable choline chloride/urea eutectic mixture or in water. This approach displays a broad substrate scope, with the addition reaction proceeding quickly (20 s reaction time) and cleanly, at ambient temperature and under air, straightforwardly furnishing the expected tertiary alcohols in yields of up to 98%. The practicability of the method is exemplified by the sustainable synthesis of some representative *S*-trityl-L-cysteine derivatives, which are a potent class of Eg5 inhibitors, also via telescoped one-pot processes.

1. Introduction

Tertiary alcohols are important structural subunits in chemical building blocks and common amongst biologically active compounds [1]. The additions of organometallic compounds of s-block elements (typically organolithium and Grignard reagents) to ketones or esters are among the most efficient and direct routes to accessing tertiary alcohols. At about this point, teaching textbooks are clear: highly polarized organometallic reagents need to be reacted at low temperature (often −78 °C), in aprotic solvents such as Et_2O or THF, under a dry, inert atmosphere of argon or nitrogen, with the corresponding reactions usually coming to an end within a few hours [2]. As for the addition to esters, these reactions, once run under the aforementioned conditions, are sometimes plagued by the production of reduced secondary alcohols, and mixtures of ketones and carbinols can also be obtained, depending on the conditions employed (Scheme 1a) [3]. The increasing awareness towards environmental pollution and climate changes has impelled research in organic synthesis to search for more environmentally responsible and less impactful solvents in place of toxic and often hazardous volatile organic compounds (VOCs), which are known to account for about 80–90% of the total mass used in any organic reaction [4], thereby reshaping long-established paradigms [5]. In this vein, the past decade witnessed an explosive growth of applications of bio-based solvents [e.g., glycerol, ethyl lactate, 2-methyltetrahydrofuran, γ-valerolactone] [6] and aqueous media [7] in several fields of chemistry. Deep Eutectic Solvents (DESs) are among an emerging class of neoteric, nature-inspired designer solvents comprising at least one hydrogen bond donor and one hydrogen bond acceptor that, when mixed in a proper molar ratio, strongly associate with each other via hydrogen bond interactions, thereby forming an eutectic mixture with a melting point much lower than those of the individual components, and that of an ideal liquid mixture [8]. In addition, they are non-flammable, highly thermally stable, and characterized by low volatility. Recent

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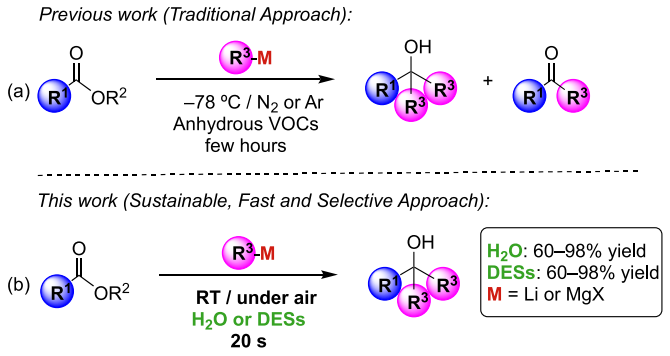


Scheme 1. Synthesis of tertiary alcohols employing esters and highly polarized organometallic compounds (Grignard and organolithium reagents) using: (a) a traditional approach with VOCs (Volatile Organic Compounds), and (b) non-conventional, environmentally friendly solvents like DESs (Deep Eutectic Solvents) or H_2O (RT = room temperature).

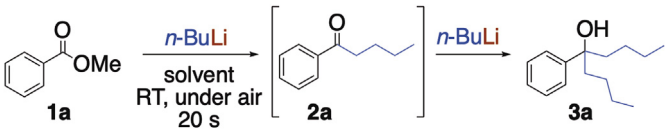
independent ground-breaking studies by the groups of Hevia, García-Álvarez and Capriati have shown that s-block organometallic compounds are truly compatible with bio-inspired protic solvents like DESs, glycerol and even water [9]. Indeed, they have been successfully used to promote either the nucleophilic addition to carbonyl compounds [10], imines [11], styrene derivatives [12], amides [13], and nitriles [11b,14] or cross-coupling reactions with aryl halides under "on water" conditions [15]. On the basis of these precedents, our main aim was to investigate the addition of highly polarized organometallic compounds to esters in protic environmentally friendly reaction media to prepare valuable tertiary alcohols. Herein, we report that this nucleophilic addition takes place smoothly and cleanly working at room temperature (RT, 25 °C) and under air, thereby granting access to tertiary alcohols in up to 98% yield, with a broad substrate scope, and within 20 s reaction time (Scheme 1b).

Comparison between water and DESs as reaction media as well as between organolithium and Grignard reagents in terms of reactivity have been provided and discussed. Additionally, this work also represented an opportunity for targeting a sustainable synthesis of *S*-trityl-L-cysteine (STLC) and three of its derivatives, which are potent and selective inhibitors of the human kinesin Eg5, that has proven antitumor activity by preventing mitotic progression [16].

2. Results and discussion

We initiated our investigation using methyl benzoate (**1a**, 0.5 mmol) as the model substrate: 1 equivalent of *n*-BuLi (2.0 M in cyclohexane) was quickly spread throughout a suspension of **1a** in water (1 mL) at RT under air, with vigorous stirring to generate an emulsion (vortex). After 20 s reaction time, the mixture was diluted with the environmentally friendly cyclopentyl methyl ether (CPME) [17] (1 mL). An analysis of the crude mixture by GC-MS and ^{1}H NMR revealed the formation of the desired tertiary alcohol **3a** in 30% yield only. The precursor ketone **2a** was still detected, but formed in less than 5% yield (Table 1, entry 1). Pleasingly, alcohol **3a** could be isolated in 98% yield as the sole product just by increasing the amount of *n*-BuLi up to 2.5 equivalents (Table 1, entries 2,3). Of note, upon replacing water with some prototypical choline chloride (ChCl)-based eutectic mixtures, namely ChCl/glycerol (Gly) (1:2 M ratio) and ChCl/urea (1:2), the effectiveness of this transformation was still maintained as **3a** was isolated in 96–98% yield (Table 1, entries 4,5). A reaction yield of 95% was instead achieved in Gly when using it as the reaction medium (Table 1, entry 6).

Table 1
Addition reaction of *n*-BuLi to methyl benzoate (**1a**) under air, at room temperature and in various green protic solvents to obtain tertiary alcohol **3a** via ketone **2a**.



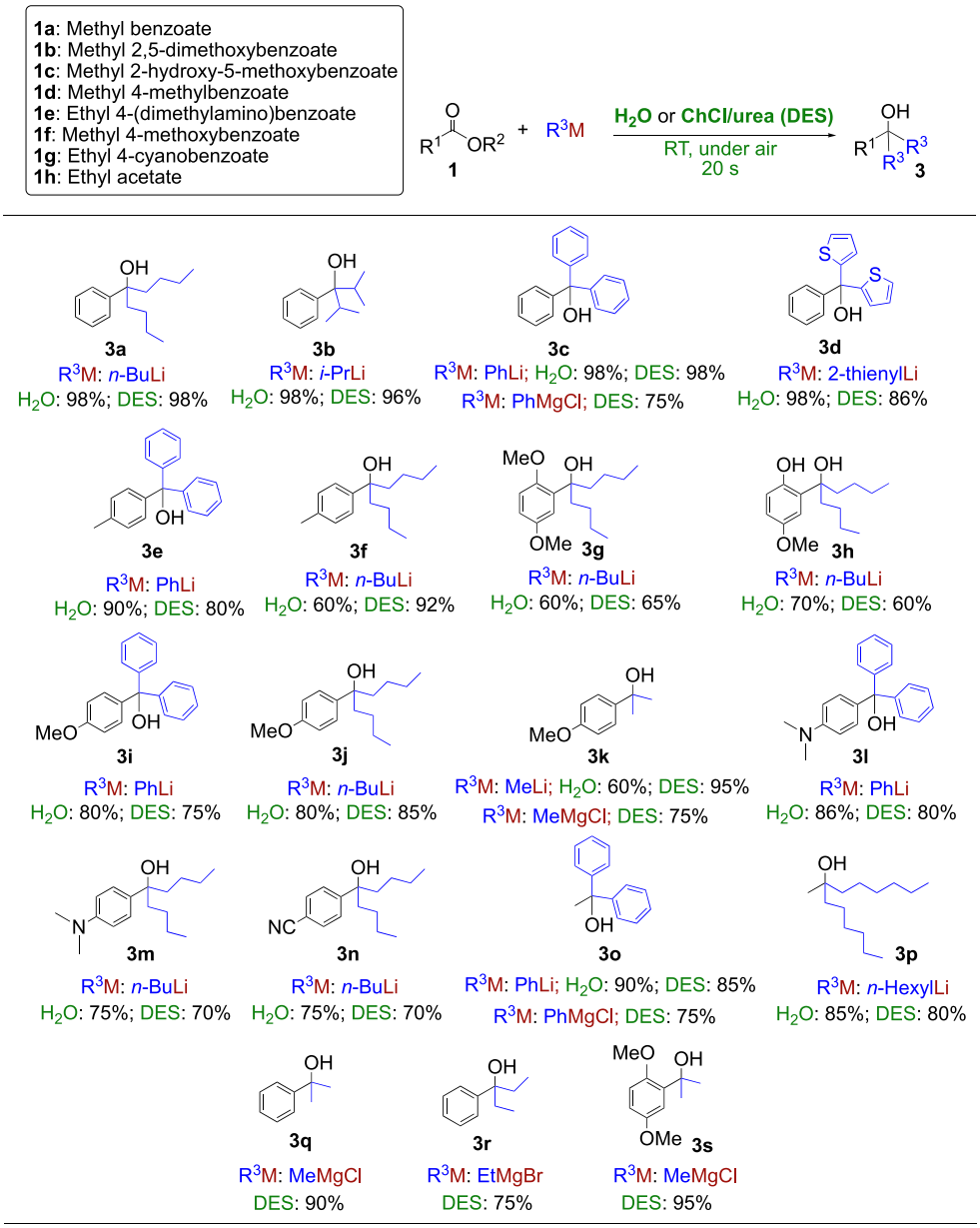
Entry	Solvent	*n*-BuLi (equiv)	**3a** yield (%)
1	H_2O[a]	1	30[b]
2	H_2O[a]	2	90[c]
3	H_2O[a]	2.5	98[c]
4	ChCl/Gly[d]	2.5	96[c]
5	ChCl/urea[e]	2.5	98[c]
6	Gly	2.5	95[c]

[a] H_2O: 1 mL per 0.5 mmol of **1a**.
[b] Calculated by ^{1}H NMR analysis of the crude reaction mixture by using an internal standard technique (NMR internal standard: CH_2Br_2).
[c] The yields reported are for products isolated and purified by column chromatography.
[d] ChCl (choline chloride)/Gly (glycerol) (1:2 molar ratio): 1 g per 0.5 mmol of **1a**.
[e] ChCl (choline chloride)/urea (1:2 molar ratio): 1 g per 0.5 mmol of **1a**.

The chemistry of highly polar organometallic compounds in protic media has been recently discussed in a *Concept* article [9a]. Various studies have assessed the unusual kinetic stability exhibited by these reagents in the unique tridimensional hydrogen-bonding structure, which is common to both DESs and water. It is thought that this network can contribute in shielding the organometallic reagent from competitive protonolysis processes.

The substrate scope of the reaction was evaluated next, by treating several functionalized esters with some typical, commercially available organolithium compounds either in water or in ChCl/urea as the representative eutectic mixture at RT and under air (Scheme 2). With regard to unsubstituted benzoate **1a**, excellent yields (86–98%) of the desired alcohols (**3a**–**3d**) were obtained both in water and in ChCl/urea when it was reacted with either aliphatic or aromatic organolithium reagents (*i*-PrLi, *n*-BuLi, PhLi and 2-thienylLi). At this point, it is important to note that in all cases the formation of **3a**-**3d** occurs chemoselectively with no side products observed in the crude reaction mixture. Substituted benzoates bearing electron-donating (Me, MeO, OH, Me_2N) or electron-withdrawing (CN) groups at the *ortho*-, *meta*-, and *para*-positions (**1b**–**1g**) effectively participated as electrophilic partners as well, thereby providing in the reaction with both aliphatic (MeLi, EtLi, *n*-BuLi) and aromatic (PhLi) organolithium reagents the expected adducts **3e**–**3n** in comparable range yields [water: 60–90%; ChCl/urea: 60–95%]. Again, it is important to highlight the high chemoselectivity of the studied process as we do not observe: *i*) metalation of activated benzylic position in benzoate **1d** or *ortho*-lithiation processes in vicinal position to the methoxy group in benzoates **1b**, **1c** and **1f**; or *ii*) competitive addition to nitrile group in benzoate **1g**. An aliphatic ester like ethyl acetate (**1h**) also served as competent reaction partner, delivering alcohols **3o** and **3p** in 80–90% yield in the reaction with PhLi and *n*-hexylLi, respectively, in water or in DES.

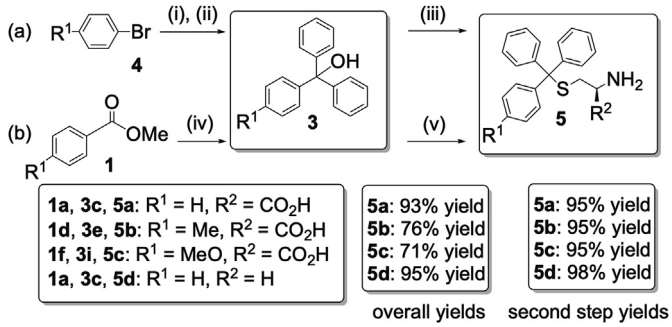
Encouraged by these initial findings, which glimpse the potential that water or ChCl/urea eutectic mixture have as green solvents for the chemoselective addition of organolithium reagents to esters under standard bench experimental techniques, we then assessed the scope of this methodology by extending our studies to a range of Grignard reagents. Under the best experimental conditions, upon switching organolithiums for organomagnesium reagents (e.g., MeMgCl, PhMgCl) as the nucleophilic partners, lower yields (75%)



Scheme 2. Synthesis of alcohols **3** by addition of organolithium or Grignard reagents to esters **1** in H_2O or in ChCl/urea, at ambient temperature (RT) under air (reaction conditions: ester: 0.5 mmol; organometallic reagent: 1.25 mmol; H_2O: 1 mL; ChCl/urea: 1 g). The yields reported are for products isolated and purified by column chromatography.

were observed in ChCl/urea in the synthesis of some representative alcohols like **3c**, **3k** and **3o**. The latter, indeed, had been previously prepared in 85–98% yields when using the corresponding organolithium reagents (MeLi, PhLi) in DES. Benzoates **1a** and **1b** also underwent nucleophilic addition of MeMgCl and EtMgBr in ChCl/urea to afford tertiary alcohols **3q**–**3s** in 75–95% yield. On the other hand, the reaction of Grignard reagents with esters in water proved to be ineffective. We propose that the large decrease in the polarity of the metal-carbon bonds in these commodity reagents (RMgX), when compared with organolithium compounds, may be the key to explain the experimentally observed decrease of activity when Grignard reagents are alternatively employed in water or in protic eutectic mixtures.

The application of this method was then highlighted by the sustainable synthesis of *S*-trityl-L-cysteine (STLC) (**5a**) and related analogues **5b**–**5d**, which have been proven potent and selective inhibitor of human mitotic kinesin Eg5, that represents a novel mitotic spindle target for cancer chemotherapy (Scheme 3) [16a]. The above STLC derivatives are currently prepared in two steps including the synthesis of the intermediate trityl alcohols **3**, and the reaction with L-cysteine (**5a**–**5c**) or cysteamine hydrochloride (**5d**), the latter performed in trifluoroacetic acid (TFA) as the sole solvent. Tertiary aromatic alcohols **3**, in turn, were furnished by exploiting a preliminary regioselective bromine-lithium exchange reaction with *n*-BuLi at −78 °C in THF for 1 h on the selected aryl bromide **4**, followed by a nucleophilic addition to benzophenone. The reaction was then stirred for 4–6 h at −78 °C, then RT overnight (Scheme 3a). According to our protocol, by reacting benzoates **1a**, **1d** and **1f** (0.5 mmol each) with PhLi (1.25 mmol) in ChCl/urea, at RT under air, the corresponding alcohols **3c**, **3e** and **3i** were isolated in 75–98% yield, the reaction time being 20 s only. The isolated alcohols were finally suspended in ChCl/urea (1 g) in the presence of



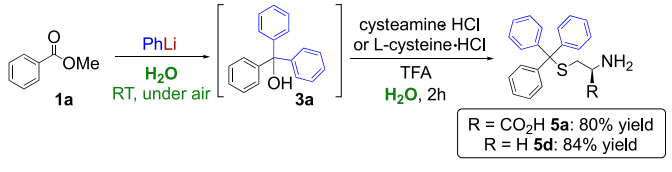
Scheme 3. (a) General route for the synthesis of thiothers; reagents and conditions: (i) *n*-BuLi, −78 °C, 1 h; (ii) Ph_2CO, THF, −78 °C, 4–6 h, then RT overnight; (iii) cysteamine hydrochloride or L-cysteine, TFA, RT, 3 h. (b) This work: reagents and conditions: (iv) **1** (0.5 mmol), PhLi (1.25 mmol), ChCl/urea (1 g), RT, under air, 20 s; (v) **3** (0.5 mmol), ChCl/urea (1 g), TFA (0.2 mL), cysteamine hydrochloride (0.5 mmol) or L-cysteine hydrochloride (0.5 mmol), 2 h.

0.2 mL TFA, and reacted with L-cysteine or cysteamine hydrochloride. After 2 h reaction time, the desired targets **5a**–**5d** were isolated in 95–98% yield (overall yields for the two steps: 71–95%) (Scheme 3b).

Finally, we decided to investigate a telescoped, one-pot tandem process for the preparation of STLC derivatives using water as the sole reaction medium, under aerobic conditions. These one-pot tandem protocols are attractive processes in the toolbox of synthetic chemistry for improving the economic efficiency of chemical reactions as they allow: *i*) the drastic reduction of isolation and purification steps of intermediates of reaction (thus minimizing both the generation of chemical waste and the required time and energy); and *ii*) the possibility to work with unstable reaction intermediates as no isolation of highly reactive and transitory species is needed [18]. To this end, benzoate **1a** (0.5 mmol) was suspended in water (1.0 mL) and treated, at RT under air, with PhLi (2.5 equiv) under vigorous stirring. After 1 min, cysteamine hydrochloride (0.5 mmol) or L-cysteine hydrochloride (0.5 mmol) and TFA (0.2 mL) were sequentially added. After 2 h stirring at RT, the dropwise addition of an aqueous solution of NaOH (4 N) favored the precipitation of **5a** (pH = 5–6) or **5d** (pH = 9). The latter were isolated by filtration in both good yield (80–84%) and purity, with no need of column chromatography (Scheme 4) (see experimental part for details).

3. Conclusion

In summary, we have shown that the nucleophilic addition of organolithium reagents to esters can be conveniently carried out using bulk water or ChCl/urea, working under air and at RT. These reactions proceeded smoothly in such strongly hydrogen-bonded associated media, under heterogeneous conditions, and also very quickly (20 s reaction time), straightforwardly delivering tertiary alcohols in very good yields (60–98%). Similarly to other cases, they are thought to occur at the oil/water (or DES) phase boundary



Scheme 4. Telescoped, one pot nucleophilic addition/thioetherification reactions from benzoate **1a** in a water mixture, leading to STLC derivatives **5a** and **5d**, via tertiary alcohol **3a**.

[9a,10d,11b]. Grignard reagents proved to be effective nucleophilic partners as well in ChCl/urea, though providing the desired alcohols in lower yields in comparison with organolithiums. The practicability of this methodology was demonstrated by the sustainable preparation of some *S*-trityl-L-cysteine derivatives, which are pharmaceutically relevant molecules. The latter could also be straightforwardly obtained via telescoped, one pot nucleophilic addition/thioetherification processes run in water starting from esters, through the tertiary alcohol intermediates, which allowed the isolation of the target molecule by filtration only. These results, which are in the footsteps of others [9–15], attest to the synthetic power, versatility and excellent performance of main group organometallic compounds when used in protic bio-based solvents under aerobic conditions. The adoption of these conditions is thus expected to have practical implications for synthetic organic chemistry, when reshaping other classical main-group-mediated transformations, which are traditionally carried out in VOC media.

4. Experimental section

^{1}H NMR,^{13}C NMR were recorded on a Varian-Mercury 300 MHz or a Bruker 400 MHz spectrometers and chemical shifts are reported in parts per million (δ). FT-IR spectra were recorded on a PerkinElmer 681 spectrometer. GC analyses were performed on a HP 6890 model, Series II by using a HP1 column (methyl siloxane; 30 m × 0.32 mm × 0.25 μm film thickness). Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F_{254}; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5% (w/v) ammonium molybdate and 0.2% (w/v) cerium (III) sulfate in 100 mL 17.6% (w/v) aq. sulphuric acid and heating to 473 K until blue spots appeared. Chromatography was run by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC-MS analyses were performed on HP 5995C model. Cyclopentyl methyl ether (CPME) or ethyl acetate (EtOAc) were used as the solvents in the work-up procedures. High-resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. Methyl 2,5-dimethoxybenzoate (**1b**) and methyl 2-hydroxy-5-methoxybenzoate (**1c**) were prepared according to the reported procedure [19].

Reactions were carried out in deionized water (pH = 6.1, determined by pH meter 507 Crison). The following solutions of organolithium reagents were furnished by Albemarle (Germany) and were used with the following concentrations: *n*-BuLi, 2.0 M in cyclohexane; EtLi, 0.5 M in hexane; *i*-PrLi, 0.7 M in pentane; 2-thienylLi, 1.0 M in THF/hexane; MeLi, 1.6 M in Et_2O; PhLi, 1.9 M in Bu_2O. The following solutions of Grignard or organolithium reagents were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and were used with the following concentrations: MeMgCl, 3.0 M in THF; EtMgBr, 3.0 M in Et_2O; PhMgCl, 2.0 M in THF; *n*-hexylLi, 2.3 M in hexane.

Full characterization data, including copies of ^{1}H and ^{13}C NMR spectra (see Supplementary Material), have been reported for both the newly synthesized (**3d**, **3f**, **3g**, **3h**, **3j**, **3m**, **3n**) and the known (**3a**, **3b**, **3c**, **3e**, **3i**, **3k**, **3l**, **3o**, **3p**, **3q**, **3r**, **3s**, **5a**, **5b**, **5c**, **5d**) compounds. The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, br s = broad singlet. Deep Eutectic Solvents [urea/choline chloride (ChCl) (2:1 mol/mol); glycerol (Gly)/ChCl (2:1 mol/mol)] were prepared by heating under stirring at 60–80 °C for 10–30 min the corresponding individual components until a clear solution was

obtained.

SAFETY NOTE: Organolithiums were handled under an inert atmosphere until they were mixed with a suspension of the substrate in water (or DES), under an air atmosphere and with vigorous magnetic stirring, whereupon they react quickly. No particular problems were experienced during the addition. Organolithiums, however, are notoriously prone to ignition in air, and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

4.1. Synthesis of aryl esters **1b**, **1c**. Typical procedure

According to the procedure reported by Paquette [20], HCl 37% (1 mL) was carefully added to a solution of the corresponding benzoic acid derivative (15.6 mmol) in MeOH (20 mL). The reaction mixture was refluxed for 2 h. MeOH was removed under reduced pressure, and the reaction mixture was extracted with CPME (3.0 mL × 3). The volatiles were removed under reduced pressure to give the methyl ester **1b** or **1c** without further purification.

4.2. Synthesis of alcohols **3** by addition of organolithium or Grignard reagents to esters **1** in water or DES. General procedure

In a 10 mL Schlenk-like flask, aryl or alkyl ester **1** (0.5 mmol) was added to 1.0 mL of water or 1.0 g of DES, at room temperature in air, and the resulting mixture was vigorously stirred. A solution of the corresponding organolithium or Grignard reagent (2.5 equiv), handled under argon using conventional Schlenk techniques, was rapidly spread over the mixture under air and with vigorous stirring at room temperature to generate an emulsion. After 20 s, the reaction mixture was diluted with 2 mL of water, and then extracted with CPME (3.0 mL × 3). The volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 8/2) to provide the desired product **3**.

4.2.1. 5-Phenylnonan-5-ol (**3a**) [19]

n-BuLi, water: 98%, DES: 98%; colorless oil; R_f 0.43; υ_{max} (liquid film) 3609, 3419, 3399, 2957, 2934, 2861, 1654, 1648, 1508, 1494, 1458, 1379, 1113, 1078, 764, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.30 (4H, m), 7.25–7.19 (1H, m), 1.89–1.68 (4H, m), 1.68 (1H, br s), 1.32–1.17 (6H, m), 1.08–0.99 (2H, m), 0.83 (6H, t, *J* 7.0 Hz); δ_C (75 MHz, $CDCl_3$) 146.5, 128.1, 126.2, 125.2, 77.2, 42.7, 25.6, 23.1, 14.0; *m/z* (70 eV) 220 (11, M^+), 202 (35), 163 (100), 145 (10), 138 (10), 117 (3), 105 (5), 91 (7), 77 (9), 51 (8); HRMS (ESI): $[M - H]^-$, found 219.1750. $C_{15}H_{23}O$ requires 219.1754.

4.2.2. 2,4-Dimethyl-3-phenylpentan-3-ol (**3b**) [21]

i-PrLi, water: 98%, DES: 96%; viscous oil; R_f 0.40; υ_{max} (liquid film) 3605, 3088, 2966, 2876, 1634, 1468, 1384, 1318, 1156, 980, 759, 705 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.23 (5H, m), 2.38–2.29 (2H, m), 1.58 (1H, s), 0.88 (6H, d, *J* 6.6 Hz), 0.79 (6H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 142.9, 127.3, 126.7, 126.2, 81.0, 33.8, 17.5, 16.5; *m/z* (70 eV) 192 (23, M^+), 149 (100), 131 (10), 105 (52), 91 (14), 77 (23), 71 (20), 51 (7), 43 (11). HRMS (ESI): $[M+H]^+$, found 193.1582. $C_{13}H_{21}O$ requires 193.1587.

4.2.3. Triphenylmethanol (3c) [22]

PhLi, water: 98%, DES: 98%; PhMgCl, DES: 75%; white solid, m.p. 161–163 °C; R_f 0.30; υ_{max} (KBr) 3584, 3467, 3063, 2924, 1597, 1489, 1444, 1329, 1156, 1030, 1010, 888, 756, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.27 (15H, m), 2.82 (1H, br s); δ_C (75 MHz, $CDCl_3$) 146.8, 127.9, 127.3, 82.0; *m/z* (70 eV) 260 (37, M^+), 239 (6), 183 (100), 165 (14), 154 (30), 165 (16), 154 (30), 105 (76), 77 (56), 51 (94). HRMS (ESI): $[M - H]^-$, found 259.1126. $C_{19}H_{15}O$ requires 259.1128.

4.2.4. Phenylbis(thiophen-2-yl)methanol (**3d**)

2-ThienylLi, water: 98%, DES: 86%; white solid, m.p. 165–167 °C; R_f 0.3; υ_{max} (KBr) 3650, 3066, 2930, 1490, 1445, 1228, 1157, 1067, 1012, 945, 824, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.56–7.51 (2H, m) 7.42–7.29 (5H, m), 7.01–6.98 (2H, m), 6.92–6.91 (2H, m), 3.29 (1H, br s); δ_C (75 MHz, $CDCl_3$) 151.9, 146.0, 128.0$_4$, 128.0$_2$, 127.9, 126.7, 126.5, 125.9, 125.8, 65.9; *m/z* (70 eV) 272 (44, M^+), 255 (35), 239 (80), 221 (14), 195 (78), 171 (20), 161 (43), 134 (8), 111 (100), 77 (30), 51 (7); HRMS (ESI): $[M+Na]^+$, found 295.0193. $C_{15}H_{12}S_2ONa$ requires 295.0222.

4.2.5. Diphenyl(p-tolyl)methanol (**3e**) [23]

PhLi, water: 90%, DES: 80%; colourless solid, m.p. 65–66 °C [24]; R_f 0.45; υ_{max} (KBr) 3466, 3058, 3028, 2920, 1957, 1914, 1599, 1510, 1488, 1446, 1407, 1329, 1276, 1207, 1184, 1155, 1117, 1080, 1009, 922, 894, 842, 814, 755, 722, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33–7.10 (14H, m), 2.34 (1H, s); δ_C (75 MHz, $CDCl_3$) 147.0, 144.0, 139.9, 128.6, 127.9$_2$, 127.9$_5$, 127.1, 81.9, 21.0; *m/z* (70 eV) 274 (28, M^+), 257 (39), 197 (100), 183 (19), 168 (22), 165 (12), 119 (34), 105 (70), 91 (17), 77 (35), 65 (3); HRMS (ESI): $[M - H]^-$, found 273.1284. $C_{20}H_{17}O$ requires 273.1285.

4.2.6. 5-(p-Tolyl)nonan-5-ol (**3f**)

n-BuLi, water: 60%, DES: 92%; colourless oil. R_f 0.35; υ_{max} (liquid film) 3469, 3052, 2956, 1677, 1611, 1512, 1466, 1405, 1378, 1231, 1181, 1112, 975, 819, 726 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.5 Hz), 7.13 (2H, d, *J* 8.5 Hz), 2.33 (3H, s), 1.81–1.70 (4H, m), 1.66 (1H, br s), 1.29–1.10 (6H, m), 1.09–0.86 (2H, m), 0.83 (6H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 143.5, 135.6, 128.6, 125.1, 76.6, 42.7, 25.6, 23.0, 20.9, 14.0; *m/z* (70 eV) 234 (10, M^+), 177 (100), 159 (5), 132 (9), 105 (7), 91 (8), 77 (6), 57 (11). HRMS (ESI): $[M - H]^-$, found 233.1910. $C_{16}H_{25}O$ requires 233.1911.

4.2.7. 5-(2,5-Dimethoxyphenyl)nonan-5-ol (**3g**)

n-BuLi, water: 60%, DES: 65%; colourless oil. R_f 0.43; υ_{max} (liquid film) 3503, 2955, 1737, 1586, 1492, 1465, 1378, 1277, 1260, 1219, 1178, 1094, 876, 803 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.87 (1H, d, *J* 3.0 Hz), 6.82 (1H, d, *J* 6.0 Hz), 6.72 (1H, dd, *J* 3.0 Hz, *J* 6.0 Hz), 3.81 (3H, s), 3.77 (3H, s), 2.00–1.92 (2H, m), 1.79–1.72 (2H, m), 1.29–1.09 (9H, m), 0.85 (6H, t, *J* 6 Hz); δ_C (75 MHz, $CDCl_3$) 153.4, 151.2, 135.0, 117.0, 114.6, 112.3, 77.5, 56.0, 55.5, 40.4, 26.0, 23.1, 14.0; *m/z* (70 eV) 280 (5, M^+), 223 (100), 205 (25), 190 (8), 174 (3), 151 (18), 121 (5), 91 (3), 57 (5); HRMS (ESI): $[M - H]^-$, found 279.1967. $C_{17}H_{28}O_3$ requires 279.1966.

4.2.8. 5-(2-Hydroxy-5-methoxyphenyl)nonan-5-ol (**3h**)

n-BuLi, water: 70%, DES: 60%; colourless oil; R_f 0.35; υ_{max} (liquid film) 3502, 2957, 1747, 1588, 1468, 1428, 1376, 1220, 1179, 1029, 876, 803,750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.77 (1H, d, *J* 6.0 Hz), 6.70 (1H, dd, *J* 6.0, 3.0 Hz), 6.48 (1H, d, *J* 3.0 Hz), 3.75 (3H, s), 1.94–1.88 (2H, m), 1.82–1.76 (2H, m), 1.34–1.26 (8H, m), 1.25 (1H, br s), 0.87 (6H, t, *J* 6.0, 3 Hz); δ_C (75 MHz, $CDCl_3$) 153.4, 149.6, 130, 118.3, 114.6, 112.0, 77.5, 55.6, 40.4, 25.9, 23.1, 14.0; *m/z* (70 eV) 266 (M^+, 7), 248 (80), 206 (11), 191 (100), 177 (13), 163 (28), 151 (18), 137 (50), 121 (23), 91 (11) 77 (11), 57 (13); HRMS (ESI): $[M+H]^+$, found 267.1956. $C_{16}H_{27}O_3$ requires 267.1955.

4.2.9. 1-(4-Methoxyphenyl)diphenylmethanol (**3i**) [24]

PhLi, water: 80%, DES: 75%; colourless oil; R_f 0.40; υ_{max} (liquid film) 3565, 3055, 2932, 1606, 1488, 1296, 1116, 1081, 1005, 896, 795, 754, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.25 (10H, m), 7.17 (2H, d, *J* 8.7 Hz),6.84 (2H, d, *J* 8.7 Hz), 3.80 (3H, s), 2.80 (1H, s); δ_C (75 MHz, $CDCl_3$) 159.1, 147.5, 139.6, 129.6, 128.3, 128.2, 127.6, 113.6, 82.1, 55.7; *m/z* (70 eV) 290 (37, M^+), 273 (8), 213 (100), 185 (11), 165 (8), 135 (30), 105 (39), 77 (24), 51 (3); HRMS (ESI): $[M - H]^-$, found 289.1231.

$C_{20}H_{17}O_2$ requires 289.1234.

*4.2.10. 5-(4-Methoxyphenyl)nonan-5-ol (**3j**)*

n-BuLi, water: 80%, DES: 85%; colourless oil. R_f 0.48; υ_{max} (liquid film) 3478, 3037, 2932, 1613, 1583, 1513, 1463, 1412, 1378, 1337, 1247, 1178, 975, 898, 831, 801, 752, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.7 Hz), 6.86 (2H, d, *J* 8.7 Hz), 3.80 (3H, s), 1.80–1.73 (4H, m), 1.68 (1H br s), 1.31–1.17 (6H, m), 1.10–0.99 (2H, m), 0.83 (6H, t, *J* 6.1 Hz); δ_C (75 MHz, $CDCl_3$) 157.9, 138.7, 126.3, 113.3, 76.6, 55.1, 42.7, 25.6, 23.1, 14.0; *m/z* (70 eV) 250 (M^+, 10), 232 (6), 193 (100), 175 (88), 148 (20), 135 (8), 121 (8), 103 (6), 91 (8), 77 (9), 57 (10). HRMS (ESI): [M − H], found 249.1861. $C_{16}H_{25}O_2$ requires 249.1860.

*4.2.11. 2-(4-Methoxyphenyl)propan-2-ol (**3k**) [25]*

MeLi, water: 60%, DES: 95%; MeMgCl, DES: 75%; colourless oil. R_f 0.33; υ_{max} (liquid film) 3774, 3418, 3039, 2973, 2933, 2837, 1701, 1668, 1614, 1583, 1514, 1415, 1361, 1300, 1247, 1179, 1097, 1034, 954, 864, 832, 797 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, *J* 6.0 Hz), 6.87 (2H, d, *J* 6.0 Hz), 3.80 (3H, s), 1.56 (6H, s); δ_C (75 MHz, $CDCl_3$) 154.3, 137.4, 121.7, 109.5, 68.2, 51.3, 27.9, 27.8; *m/z* (70 eV) 166 (M^+, 20), 151 (100), 148 (33), 133 (23), 109 (9), 77 (20), 65 (6), 43 (10). HRMS (ESI): $[M+H]^+$, found 165.0922. $C_{10}H_{15}O_2$ requires 165.0921.

*4.2.12. [4-(Dimethylamino)phenyl]diphenylmethanol (**3l**) [26]*

PhLi, water: 86%, DES: 80%; colourless oil; R_f 0.45; υ_{max} (liquid film) 3586, 3467, 3063, 2924, 1598, 1489, 1444, 1329, 1124, 1156, 1030, 1016, 888, 756, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.27 (10H, m), 7.12 (2H, d, *J* 8.6 Hz), 6.69 (2H, d, *J* 8.6 Hz), 2.97 (6H, s), 2.77 (1H, br s); δ_C (75 MHz, $CDCl_3$) 149.6, 147.3, 128.9, 127.9, 127.8, 126.9, 111.8, 81.8, 40.5; *m/z* (70 eV) 303 (37, M^+), 226 (14), 183 (100), 154 (36), 120 (8), 105 (11), 91 (16), 77 (55), 51 (94). HRMS (ESI): $[M+H]^+$, found 304.1695. $C_{21}H_{22}ON$ requires 304.1696.

*4.2.13. 5-[4-(Dimethylamino)phenyl]nonan-5-ol (**3m**)*

n-BuLi, water: 75%, DES: 70%; m.p. 170–172 °C; R_f 0.40; υ_{max} (KBr) 3584, 3411, 2956, 1611, 1519, 1463, 1348, 1224, 1196, 1124, 1016, 947, 815 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5 Hz), 6.73 (2H, d, *J* 8.5 Hz), 2.95 (6H, s), 1.81–1.74 (4H, m), 1.64 (1H, br s), 1.31–1.02 (8H, m), 0.83 (6H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 148.9, 139.6, 126.8, 126.0, 112.5, 112.2, 76.0, 42.5, 40.8, 40.7, 31.1, 30.6, 23.2_4, 23.2_1, 14.1, 14.0; *m/z* (70 eV) 263 (15, M^+), 230 (6), 190 (10), 176 (100), 146 (15), 134 (42), 120 (46), 105 (20), 91 (16), 77 (21), 51 (15); HRMS (ESI): $[M - H]^-$, found 262.2175. $C_{17}H_{28}NO$ requires 262.2176.

*4.2.14. 4-(5-Hydroxynonan-5-yl)benzonitrile (**3n**)*

n-BuLi, water: 75%, DES: 70%; m.p. 160–162 °C; R_f 0.30; υ_{max} (KBr) 3610, 3399, 2958, 2934, 2861, 2315, 1654, 1649, 1508, 1494, 1458, 1379, 1113, 1078, 754, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (2H, d, *J* 8.5 Hz), 6.46 (2H, d, *J* 8.5 Hz), 1.89–1.68 (4H, m), 1.60 (1H, br s), 1.49–1.39 (6H, m), 1.26–1.19 (2H, m), 0.83 (6H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 151.8, 127.9, 125.5, 118.3, 109.3, 79.4, 42.8, 25.5, 23.0, 14.0; *m/z* (70 eV) 245 (34, M^+), 228 (10), 189 (100), 173 (6), 145 (15), 105 (20), 91 (16), 77 (21), 51 (15); HRMS (ESI): $[M+H]^+$, found 246.1851. $C_{16}H_{24}NO$ requires 246.1852.

*4.2.15. 1,1-Diphenylethanol (**3o**) [27]*

PhLi, water: 90%, DES: 85%; PhMgCl, DES: 75%; colourless oil. R_f 0.40; υ_{max} (liquid film) 3418, 3059, 3020, 2977, 1682, 1594, 1547, 1493, 1446, 1372, 1220, 1192, 1176, 926, 903, 830, 749, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.44–7.40 (4H, m), 7.35–7.21 (6H, m), 1.96 (3H, s); δ_C (75 MHz, $CDCl_3$) 148.0, 128.1, 126.9, 125.8, 76.0, 30.8; *m/z* (70 eV) 198 (M^+, 10), 183 (100), 178 (5), 165 (8), 155 (6), 121 (10), 105 (50), 77 (26), 51 (7), 43 (20); HRMS (ESI): $[M - H]^-$, found 179.0972. $C_{14}H_{13}O$ requires 179.0972.

*4.2.16. 7-Methyltridecan-7-ol (**3p**) [28]*

HexylLi, water: 85%, DES: 80%; colorless oil. R_f 0.40; υ_{max} (liquid film) 3309, 2957, 2931, 1464, 1376, 1143, 925, 880 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.43–1.41 (4H, m), 1.31–1.25 (16H, m), 1.14 (3H, s), 0.89–0.87 (6H, m); δ_C (125 MHz, $CDCl_3$) 72.7, 41.8, 31.8, 29.9, 26.9, 23.8, 22.6, 14.0; *m/z* (70 eV) 213 (2), 129 (100), 111 (8), 69 (25), 43 (14); HRMS (ESI): $[M - H]^-$, found 213.2215. $C_{14}H_{29}O$ requires 213.2224.

*4.2.17. 2-Phenylpropan-2-ol (**3q**) [29]*

MeMgCl, DES: 90%; colourless oil; R_f 0.30; υ_{max} (liquid film) 3393, 3087, 3026, 2976, 2871, 1950, 1808, 1602, 1494, 1446, 1364, 1290, 1173, 1101, 1073, 1029, 954, 764, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54–7.51 (2H, m), 7.39–7.26 (3H, m), 1.97 (1H, br s), 1.62 (6H, s); δ_C (75 MHz, $CDCl_3$) 149.1, 128.2, 126.7, 124.4, 72.5, 31.7; *m/z* (70 eV) 136 (34, M^+), 121 (100), 105 (6), 91 (9), 77 (20), 51 (9); HRMS (ESI): $[M+Na]^+$, found 159.0789. $C_9H_{12}ONa$ requires 159.0786.

*4.2.18. 3-phenylpentan-3-ol (**3r**) [30]*

EtMgBr, DES: 75%; colourless oil; R_f 0.45; υ_{max} (liquid film) 3472, 3435, 2968, 2936, 1645, 1493, 1460, 1377, 1162, 1031, 961, 894, 757, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.22 (5H, m), 1.96–1.77 (4H, m), 1.68 (1H, br s), 0.78 (6H, t, *J* 7.4 Hz); δ_C (75 MHz, $CDCl_3$) 145.7, 128.0, 126.3, 125.5, 65.9, 35.0, 7.8; *m/z* (70 eV) 164 (34, M^+), 135 (100), 117 (6), 105 (8), 91 (8), 77 (13), 57 (41), 51 (10); HRMS (ESI): $[M+Na]^+$, found 187.1085. $C_{11}H_{16}ONa$ requires 187.1093.

*4.2.19. 2-(2,5-Dimethoxyphenyl)propan-2-ol (**3s**) [31]*

MeMgCl, DES: 95%; colourless oil; R_f 0.35; υ_{max} (liquid film) 3300, 2954, 2923, 2853, 1514, 1463, 1456, 1377, 1302, 1248, 1169, 954, 829 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.87 (1H, d, *J* 3.0 Hz), 6.83 (1H, d, *J* 8.8 Hz), 6.72 (1H, dd, *J* 3.0 Hz, *J* 8.8 Hz), 3.87 (3H, s), 3.77 (3H, s), 1.25 (1H, br s); δ_C (75 MHz, $CDCl_3$) 153.3, 150.9, 143.8, 115.7, 115.1, 112.3, 77.1, 55.9, 55.5, 30.0; *m/z* (70 eV) 196 (M^+, 91), 181 (100), 163 (19), 151 (20), 135 (12), 124 (13), 105 (11), 91 (10), 77 (14), 43 (5); HRMS (ESI): $[M - H]^-$, found 195.1027. $C_{11}H_{15}O_3$ requires 195.1026.

*4.3. Synthesis of S-trityl-L-cysteine thioethers **5a–c**. General procedure in DES*

L-Cysteine hydrochloride (0.5 mmol), alcohol **3c** or **3e** or **3i** (0.5 mmol) and 0.2 mL of trifluoroacetic acid (TFA) were sequentially added to the eutectic mixture ChCl/urea (1.0 g) at room temperature under air. After stirring for 2 h at room temperature, 2 mL of water were added. An aqueous NaOH solution (4 N) was then added dropwise in water up to a pH of about 5–6. The reaction mixture was extracted three times with EtOAc (5 mL × 3). The resulting organic phase was dried (Na_2SO_4), filtered, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 9:1) to provide the desired product **5a–c**.

*4.3.1. S-Trityl-L-cysteine (**5a**) [32]*

White solid, 95% yield. R_f 0.33; m.p. 190–192 °C; υ_{max} (KBr) 3028, 2974, 1732, 1651, 1598, 1556, 1490, 1442, 1395 cm^{-1}; δ_H (300 MHz, CD_3OD) 7.47–7.44 (6H, m), 7.35–7.22 (9H, m), 3.09 (1H, dd, *J* 4.1, 9.1 Hz), 2.80 (1H, dd, *J* 13.3, 4.1 Hz), 2.70 (1H, dd, *J* 13.3, 9.1 Hz); δ_C (75 MHz, CD_3OD) 176.6, 145.7, 130.5, 129.1, 128.1, 68.2, 54.6, 34.6; HRMS (ESI): $[M+Na]^+$, found 386.1186. $C_{22}H_{21}NO_2SNa$ requires 386.1185.

*4.3.2. S-4-Methyltrityl-L-cysteine (**5b**)*

White solid, 95% yield. R_f 0.43; m.p. 198–200 °C; υ_{max} (KBr) 3032, 2970, 1724, 1650, 1600, 1554, 1495, 1440, 1385 cm^{-1}; δ_H (300 MHz, CD_3OD) 7.42 (4H, d, *J* 6.5 Hz), 7.30–7.18 (8H, m), 7.11 (2H,

d, *J* 8.2 Hz), 3.20–3.16 (1H, m), 2.70 (2H, d, *J* 6.0 Hz) 2.28 (3H, s); δ_C (75 MHz, CD_3OD) 173.0, 144.1$_4$, 144.0$_9$, 141.0, 136.7, 129.2, 129.1, 128.4, 127.7, 126.7; HRMS (ESI): $[M+Na]^+$, found 400.1343. $C_{23}H_{23}NO_2SNa$ requires 400.1342.

4.3.3. *S*-4-Methoxytrityl-L-cysteine (**5c**)

White solid, 95% yield. R_f 0.40; m.p. 178–180 °C; υ_{max} (KBr) 3029, 2978, 1730, 1658, 1597, 1550, 1495, 1442, 1395 cm^{-1}; δ_H (300 MHz, CD_3OD) 7.43 (2H, d, *J* 8.2 Hz), 7.33–7.18 (10H, m), 6.83 (2H, d, *J* 8.2 Hz), 3.74 (3H, s), 3.14–3.08 (1H, m), 2.83–2.67 (2H, m); δ_C (75 MHz, CD_3OD) 171.1, 158.4, 144.5, 136.0, 130.5, 129.1, 127.7, 126.5, 112.9, 66.2, 54.3, 53.5, 32.7; HRMS (ESI): $[M+Na]^+$, found 416.1290. $C_{23}H_{23}NO_3SNa$ requires 416.1291.

4.4. Synthesis of 2-(tritylthio)ethan-1-amine **5d**. Typical procedure in DES

Cysteamine hydrochloride (0.5 mmol), alcohol **3c** (0.5 mmol) and 0.2 mL of TFA were sequentially added to the eutectic mixture ChCl/urea (1.0 g) at RT under air. After stirring for 2 h at RT, 2 mL of water were added. An aqueous NaOH solution was added dropwise in water up to a pH of about 9. The reaction mixture was then extracted three times with EtOAc (5 mL × 3), dried (Na_2SO_4) and filtered, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (AcOEt/hexane 1:1) to provide the desired product **5d**.

4.4.1. 2-(Tritylthio)ethan-1-amine (**5d**) [16a]

White solid, 98% yield. R_f 0.33; m.p. 146–148 °C; υ_{max} (KBr) 3379, 3057, 2932, 1680, 1484, 1439, 1206, 1130, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39 (6H, d, *J* 6 Hz), 7.27 (6H, t, *J* 6 Hz), 7.20 (3H, t, *J* 6 Hz), 2.57 (2H, m), 2.33 (2H, m); δ_C (75 MHz, $CDCl_3$) 146.7, 130.1, 129.1, 127.7, 67.6, 41.6, 36.2; HRMS (ESI): $[M+H]^+$, found 320.1466. $C_{21}H_{22}NS$ requires 320.1467.

4.5. One-pot synthesis of **5a** or **5d**. Typical procedure in water

In a 10 mL Schlenk-like flask, methyl benzoate **1a** (68 mg, 0.5 mmol) was added under stirring to 1.0 mL of water at room temperature in air. A solution of PhLi in Bu_2O (2.5 equiv, 0.63 mL of a 2 M solution), handled under argon using conventional Schlenk techniques, was rapidly spread over the mixture under air and with vigorous stirring at room temperature to generate an emulsion. After 1 min, cysteamine hydrochloride (56.5 mg, 0.5 mmol) or L-cysteine hydrochloride (78.81 mg, 0.5 mmol) and 0.2 mL of TFA were sequentially added to the reaction mixture, at room temperature under air. After additional stirring for 2 h at room temperature, an aqueous NaOH solution (4 N) was added dropwise in water up to pH of about 9 (for the synthesis of **5d**) or pH of about 5–6 (for the synthesis of **5a**). The resulting white precipitate was collected by filtration. The crude product was further washed with water (1.0 mL) and hexane (2.0 mL), and then dried to obtain **5a** (from L-cysteine hydrochloride) as a white solid in 80% yield or **5d** (from cysteamine hydrochloride) as a white solid in 84% yield [33].

*Alternative work-up procedure for **5d**:* After stirring the whole mixture for 2 h at room temperature, an aqueous NaOH solution (4 N) was added dropwise in water up to a pH of about 9. The reaction mixture was then extracted three times with EtOAc (5 mL × 3). The resulting organic phase was dried (Na_2SO_4), filtered, and the volatiles were removed under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2/CH_3OH 9:1; R_f 0.43) to provide the desired product **5d** in 86% yield.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131898.

Supplementary Material

Supplementary Material to this article, which contains ^1H and ^{13}C NMR spectra of all synthesized compounds, can be found in a separate electronic file.

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