

PAPER

An enhanced stereoselective synthesis of α,β -unsaturated esters through the Horner–Wadsworth–Emmons reaction in deep eutectic solvents†

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A new scalable synthesis of (*E*)- α,β -unsaturated esters has been developed using protic, non-toxic, and biodegradable deep eutectic solvents through the Horner–Wadsworth–Emmons reaction between triethyl phosphonates and (hetero)aromatic carbonyl compounds, encompassing electron-withdrawing and electron-donating groups. Stereoselective preparation of disubstituted or trisubstituted ethyl cinnamate derivatives is achieved in the presence of LiOH, K_2CO_3 , or DBU as bases, at room temperature and under air. Demonstrated with the synthesis of (*E*)-ethyl 3-(4-bromophenyl)acrylate, the same eutectic mixture (choline chloride/urea) proved to be reusable for three consecutive runs. Gram-scale reactions (10 mmol) can be carried out without the formation of side products, thereby ensuring high atom economy and an EcoScale score of 71.

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Introduction

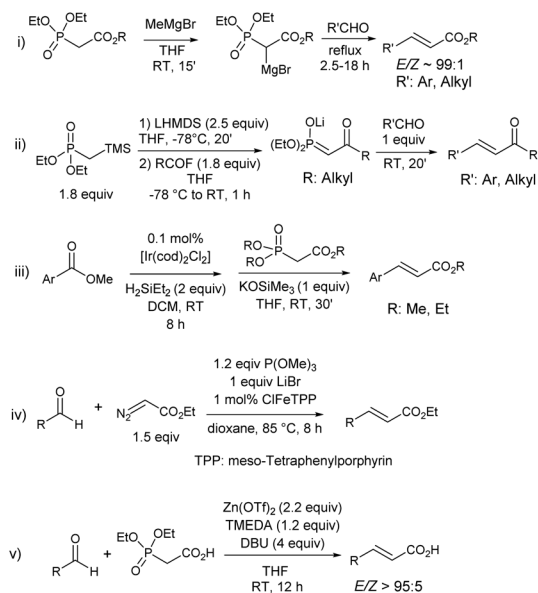
α,β -Unsaturated esters constitute a class of organic compounds commonly found in nature, renowned for their pleasant odors that contribute to the aromatic profiles of numerous fruits and flowers.¹ They frequently serve as key constituents in essential oils utilized by perfume manufacturers. Furthermore, they are crucial substrates for synthesizing pharmacologically active compounds.²

Cinnamic acid derivatives, in particular, are highly versatile synthons utilized in the formulation of hypolipidemics,³ anti-diabetic agents, antioxidants,⁴ antifungal medications,⁵ and anti-inflammatory compounds.⁶

Among various synthetic methodologies, the Horner–Wadsworth–Emmons (HWE) reaction is frequently employed for the synthesis of (*E*)- α,β -unsaturated esters.⁷ This method allows for high-yielding production of olefins with notable selectivity, utilizing stabilized phosphonate anions as nucleophilic partners of carbonyl compounds.

In several instances reported in the literature, organolithiums, Grignard reagents, NaH, and alkoxides stand out as the frequently employed bases for generating phosphonate-

stabilized carbanions in an inert atmosphere.⁸ Within numerous documented examples, the achievement of highly (*E*)-selective HWE reactions include approaches using (i) MeMgBr in tetrahydrofuran (THF) at room temperature (RT) (Scheme 1);⁹ (ii) LHMDS as a base, starting from trimethylsilyl-



Scheme 1 Stereoselective syntheses of α,β -unsaturated esters by HWE reactions.

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methylphosphonate;¹⁰ (iii) iridium-catalyzed reductive HWE olefination, with silyl acetals as reaction intermediates;¹¹ (iv) phosphoranes bearing semi-stabilizing groups and porphyrin catalysts;¹² and (v) zinc-promoted reactions of aldehydes with phosphates for the synthesis of cinnamic acid derivatives (Scheme 1).¹³

Limited synthetic approaches utilizing ketones for the synthesis of trisubstituted alkenes have been reported.¹⁴ However, these methods typically rely on conventional, toxic, and flammable volatile organic compounds (VOCs), resulting in observed low to moderate *E*-selectivity and yields (a–c, Scheme 2).

Within these strategies, Hou and colleagues have notably demonstrated the effective utilization of a suspension of NaH in THF for the synthesis of β -phenylbutenoates. This process involves the reaction between triethyl phosphonoacetate and acetophenone (Scheme 2a).¹⁵ α -Methyl- α,β -unsaturated esters were alternatively synthesized from aliphatic and aromatic aldehydes by Ando's research group. They employed various bases including alkali hydroxides, 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), carbonates, in a HWE reaction run at RT and solvent-free conditions (Scheme 2b). This method achieved higher yields (83–98%) and selectivities (*E*:*Z* = 98:2) compared to reactions carried out in other solvents, all without the need for expensive catalysts (Scheme 2c).¹⁶

The advancement of sustainable and environmentally friendly processes with reduced energy impact has gathered increased attention in recent years. This interest stems from the imperative to address, mitigate, and prevent greenhouse gas emissions, as well as the effects of climate change.

Within this framework, various “solvent-free” processes have emerged as alternatives to conventional VOCs. Nevertheless, their practical applicability is constrained by the need for exclusive use of liquid reagents, and often involves concentrations that are incompatible with large-scale industrial processes. In recent decades, safer approaches for both human health and the environment have been introduced. These methods involve the use of safer solvents, chosen for their properties such as biodegradability, non-volatility, and non-flammability.¹⁷ Among these solvents are the so-called deep eutectic solvents (DESs),¹⁸ usually obtained by combining two or three safe and cost-effective components comprising Lewis or Brønsted acids and bases, which are strongly associ-

ated with each other, usually *via* hydrogen bond interactions, to form a eutectic mixture with a melting point far below that of an ideal liquid mixture. Most DESs are readily sourced from renewable feedstock and exhibit high biodegradability and non-toxicity. Typically, they are created through the careful mixture and mild heating of a quaternary ammonium salt (*e.g.*, choline chloride, ChCl) and a neutral hydrogen-bond donor (HBD) [*e.g.*, glycerol (Gly), urea, carbohydrates, carboxylic acids] in a specific molar ratio. DESs have found successful applications in extraction and separation processes, material sciences, the synthesis of heterocycles, bio- and organo-catalysis, as well as in metal-catalyzed and metal-mediated organic reactions, and energy technology.¹⁹ Therefore, in our ongoing research aimed at developing new eco-friendly synthetic methodologies, we focused towards a sustainable synthesis of α,β -unsaturated esters, utilizing a ChCl/urea eutectic mixture as an environmentally responsible solvent.

This innovative synthetic strategy encompasses (a) a wide substrate scope and high stereoselectivity for the synthesized alkenes, achieved in good to excellent yields (up to 99%) under mild reaction conditions, and (b) a remarkably low environmental impact, as determined by EcoScale analyses, in the synthesis of valuable drug precursors.^{20,21}

Results and discussion

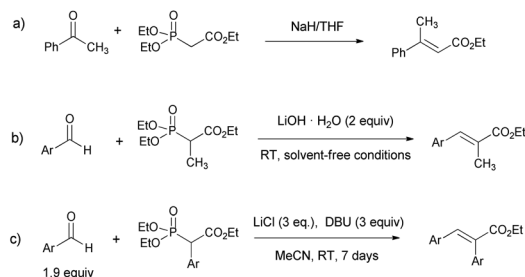
We initiated our investigation at RT, using an eutectic mixture of ChCl/urea (1:2 mol/mol), employing the reaction conditions well-established in our laboratory for the preparation of ketone enolates.²² Table 1 presents the optimized results of HWE reaction between triethyl phosphonoacetate (**1a**) and benzaldehyde (**2a**) as a model reaction.

Various bases were tested at different time intervals to identify milder and more versatile reaction conditions compared to previously reported solvent-free reactions.

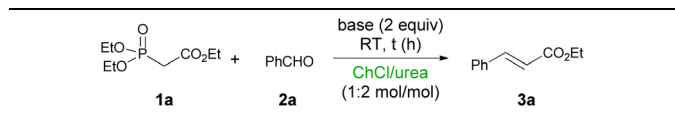
When reacting a stoichiometric amount of **2a** with phosphonate **1a** in the presence of 2 equiv. of LiOH (entry 1, Table 1), a partial conversion (46%) was achieved after 4 h. However, a higher yield (91%) was observed after 8 h (entry 2, Table 1), reaching almost completeness (98%) after 12 h (entry 3, Table 1). Surprisingly, the reaction consistently proceeded with high stereoselectivity, yielding (*E*)-ethyl cinnamate (**3a**) as the sole stereoisomer in every case. These findings suggest that the stereochemistry of the reaction is under steric control, in accordance with the most plausible mechanism of HWE (Scheme 3), where the (*E*)-geometry of the final product arises from the more stable oxaphosphetane intermediate.²³

A lower yield of (*E*)-**3a** was obtained from reactions with NaOH and NaH (entries 4–8, Table 1), likely due to the competitive hydrolysis of phosphonate **1a**, which is no longer detectable within the reaction mixture after 4 h.

Other bases were screened, both inorganic (K_2CO_3 , Na_2CO_3 , CS_2CO_3) and organic (*t*-BuOK, DBU). Low yields of (*E*)-**3a** were obtained with Na_2CO_3 and CS_2CO_3 (up to 17%; entries 9 and

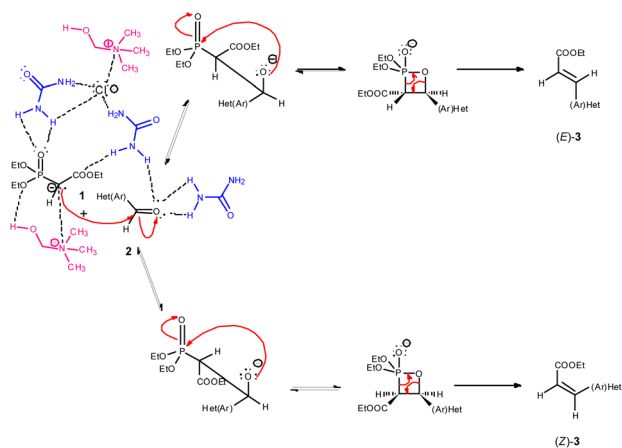


Scheme 2 Syntheses of trisubstituted α,β -unsaturated esters by HWE.

Table 1 Synthesis of (*E*)-ethyl cinnamate (**3a**) by HWE reaction between triethyl phosphonoacetate (**1a**) and benzaldehyde (**2a**)

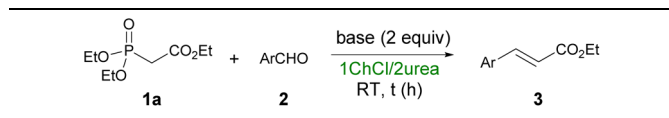
Entry	Base (equiv.)	Time (h)	Conversion ^a (%)	Yield ^b (%)
1	LiOH (2)	4	85	46 ^c
2	LiOH (2)	8	>98	91
3	LiOH (2)	12	>98	98
4	NaOH (2)	12	>98	50
5	NaOH (2)	7	>98	28
6	NaOH (2)	4	>98	52
7	NaOH (2)	2	60	25 ^c
8	NaH (2)	4	50	4
9	Na ₂ CO ₃ (2)	4	5	Trace
10	Cs ₂ CO ₃ (2)	4	27	17
11	K ₂ CO ₃ (2)	4	78	67
12	K ₂ CO ₃ (2)	4	30 ^c	29
13	K ₂ CO ₃ (2) ^d	4	46	20
14	K ₂ CO ₃ (2)	15	>98	80
15	<i>t</i> -BuOK (2)	4	>98	20
16	DBU (2)	4	>98	80
17	DBU (2) + LiCl (20%)	4	>98	75
18	DBU (1.2)	4	80	75

^a Determined by GC-FID. ^b Yields calculated by ¹H NMR using CH₂Br₂ as an internal standard. ^c Warmed at 40 °C. ^d 2.5 equiv. of PhCHO were used.

**Scheme 3** Plausible mechanism for HWE reaction between aldehydes and phosphonate-stabilized carbanions in DES.

10, Table 1), while a good yield (80%) was observed with K₂CO₃ after 15 h only (entries 11–14, Table 1) at RT. Unsatisfactory results were observed with *t*-BuOK (entry 15, Table 1), while very good yields of (*E*)-**3a** were achieved using DBU after 4 h at RT (75–80%; entries 16 and 17, Table 1), and also with only 1.2 equiv. of the latter base (75%; entry 18, Table 1).

Following the initial optimization study, we decided to further investigate the behaviour of different aromatic alde-

Table 2 Stereoselective syntheses of α,β-unsaturated esters by Horner–Wadsworth–Emmons reaction in DESs

Entry	Ar	Base	Time (h)	Yield (%)	<i>E/Z</i> ^a
1	4-Cl-C ₆ H ₄ (2b)	LiOH	12	89	99:1
2	4-Cl-C ₆ H ₄ (2b)	DBU	2	80 ^b	99:1
3	4-Br-C ₆ H ₄ (2c)	DBU	4	88 ^b	96:4
4	4-Br-C ₆ H ₄ (2c)	DBU ^c	4	87 ^b	96:4
5	4-Br-C ₆ H ₄ (2c)	— ^d	4	NR ^e	—
6	2-I-C ₆ H ₄ (2j)	DBU	4	78	98:2
7	4-NO ₂ -C ₆ H ₄ (2d)	LiOH	12	89	99:1
8	4-NO ₂ -C ₆ H ₄ (2d)	DBU	4	90 ^b	99:1
9	4-CF ₃ -C ₆ H ₄ (2i)	LiOH	12	60	98:2
10	4-CF ₃ -C ₆ H ₄ (2i)	DBU	4	77	98:2
11	4-OMe-C ₆ H ₄ (2e)	LiOH	12	20	99:1
12	4-OMe-C ₆ H ₄ (2e)	K ₂ CO ₃	14	32 ^b	99:1
13	4-OMe-C ₆ H ₄ (2e)	DBU	4	75 ^b	98:2
14	3,4,5-(OMe) ₃ -C ₆ H ₂ (2f)	DBU	4	90 ^b	99:1
15	4-OH-C ₆ H ₄ (2g)	LiOH	12	NR ^e	—
16	4-OH-C ₆ H ₄ (2g)	DBU	4	NR ^e	—
17	5-Br-2-OH-C ₆ H ₃ (2h)	DBU	4	15 ^b	99:1
18	4-COOH-C ₆ H ₄ (2k)	DBU	4	68	99:1
19	4-COOMe-C ₆ H ₄ (2l)	DBU	4	40 ^f	99:1
20	4-CONEt ₂ -C ₆ H ₄ (2m)	DBU	4	43	99:1
21	4-(NMe ₂)-C ₆ H ₄ (2n)	DBU	4	65	99:1

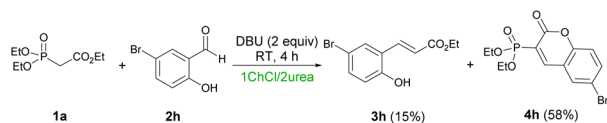
^a Determined by GC-MS. ^b Yields calculated by ¹H NMR using CH₂Br₂ as an internal standard. ^c Reaction carried out in a 1ChCl/2H₂O mixture. ^d Reaction carried out in a 1ChOAc/2urea mixture. ^e NR = no reaction. ^f Other by-products of hydrolysis and transesterification were also detected in the reaction crude.

hydes to find the general conditions for the stereoselective synthesis of 3-aryl-α,β-unsaturated esters **3b–n** (Table 2).

Excellent yields (up to 90%) and high stereoselectivities (*E/Z* up to 99:1) were observed with both electron-withdrawing (halogens, nitro, CF₃; entries 1–10, Table 2) and electron-donating groups (*e.g.*, OMe; entries 11–14, Table 2) on the aromatic ring, in 1ChCl/2urea or 1ChCl/2H₂O. DBU was found to be excellent as a base, although LiOH or K₂CO₃ can alternatively be used in the HWE reaction, proceeding faster in DES and competitively with the phosphonate hydrolysis. As far as we are aware, there is only one documented instance of an HWE reaction in DES media for the synthesis of stilbenes from benzylphosphonates and aromatic aldehydes.²⁴

The reaction was unsuccessful when initiated with *p*-OH-benzaldehyde (**2g**) (entries 15 and 16, Table 2). In contrast, only a minimal amount of product was observed with 5-bromosalicylaldehyde (**2h**) (entry 17, Table 2). This was attributed to the formation of a coumarin derivative **4h** (58%) as the primary product, resulting from the competitive nucleophilic substitution of the phenolic OH group on phosphonate **1a**. This phenomenon has already been documented in the literature (Scheme 4).²⁵

Remarkably, our reaction conditions facilitated the preparation of a variety of cinnamate derivatives featuring various reactive groups under mild conditions and in a “one-pot”



Scheme 4 Diethyl(6-bromocoumarin-3-yl)phosphonate (**4h**) formation from 5-bromosalicylaldehyde (**2h**) and phosphonate (**1a**).

fashion. This stands in contrast to other multi-step synthetic methodologies relying on cross-coupling reactions.²⁶

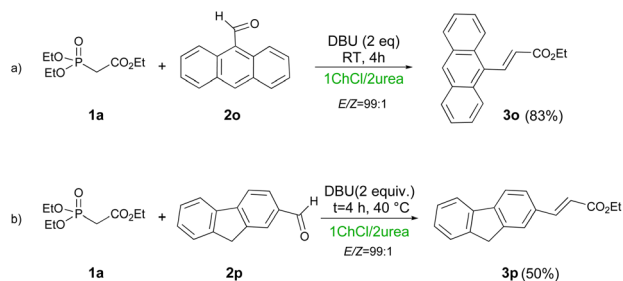
Aldehydes with carbonyl-containing electron-withdrawing groups (COOH, CONET₂, COOMe; entries 18–20, Table 2) and an electron-donating group (–NMe₂) on the aromatic ring (entry 21, Table 2) afforded cinnamates **2k–n** in fair to good yields (40–68%), but with high stereoselectivities (*E/Z* up to 99 : 1) in all cases.

Excellent stereoselectivities (*E/Z* = 99 : 1) were observed also with both polycyclic aldehydes **2o,p** (Scheme 5). Ethyl (*E*)-3-(anthracen-9-yl)acrylate (**3o**) was obtained with 83% yield, whereas in the reaction involving fluorene-2-carbaldehyde (**2p**), several unidentified side products were also formed alongside the desired product **3p**.²⁷ The latter was successfully isolated in a good yield (50%) after the reaction with DBU at higher temperature (40 °C), as depicted in Scheme 5.

The HWE reaction scope was further investigated by reacting heteroaromatic aldehydes **2q–u** with the anion of **1a**, generated in the presence of different bases (Table 3). The stereoselective formation of α,β -unsaturated esters **3q–u** proceeded smoothly, with good yields (73–98%) and selectivities (up to 99 : 1) when DBU was used as a base, at RT and under air, eliminating the need for VOCs: only 50% of **3s** was isolated from 1*H*-pyrrole-2-carbaldehyde (**2s**).

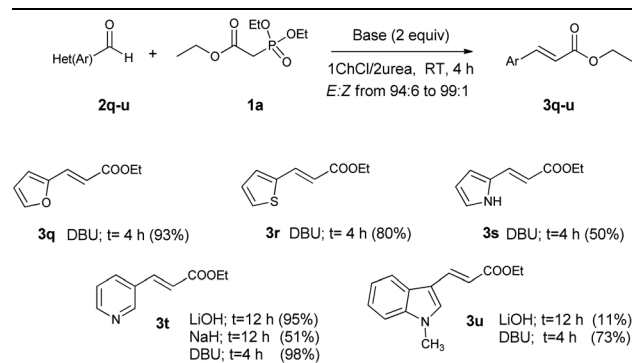
(*E*)-Ethyl 3-(pyridin-3-yl)acrylate (**3t**) was obtained in high yield and *E*-selectivity from **1a** in the presence of LiOH or DBU, while a lower yield (51%) was observed with NaH. Solid 1-methyl-1*H*-indole-3-carbaldehyde (**2u**) was also easily converted into the corresponding HWE product **3u** with a 73% yield with DBU, while only a 11% yield was obtained after 12 h at RT using LiOH (2 equiv.) and under air.

The synthesis of trisubstituted alkenes in DESs was also investigated, starting from the reaction between **1a** and acetophenone (**2v**) as a model reaction (Table S1, ESI[†]). Various



Scheme 5 HWE reaction between phosphonate (**1a**) and polycyclic aldehydes **2o,p**.

Table 3 Synthesis of α,β -unsaturated esters **3q–u** by HWE reaction between phosphonate (**1a**) with heteroaromatic aldehydes **2q–u**

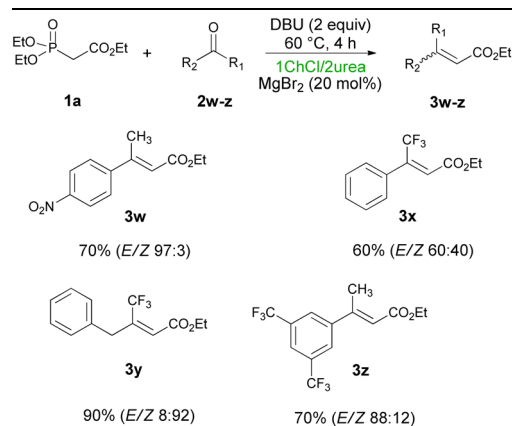


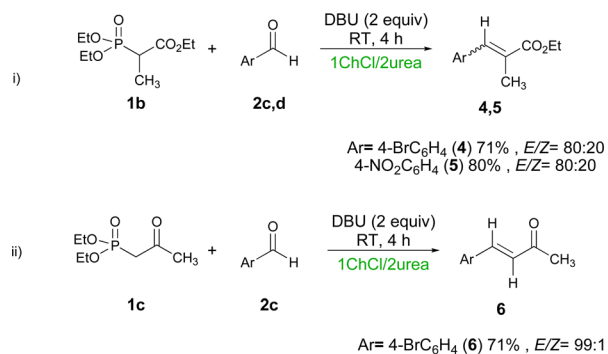
reaction conditions were explored, by varying the reaction time, temperature, the eutectic mixture, or additives (MgBr₂, LiCl, Al₂O₃, ZnCl₂) (Tables S1 and 2, ESI[†]). However, satisfactory yields were observed only when activated ketones were employed in the presence of DBU (2 equiv.) and MgBr₂ (20 mol%) as a Lewis acid in 1ChCl/2urea, upon warming the reaction mixture up to 60 °C (Table 4). The best conversions were achieved by reacting **1a** with *p*-nitroacetophenone (**2w**), 1,1,1-trifluoroacetophenone (**2x**), 1,1,1-trifluoro-3-phenylpropan-2-one (**2y**), or 1-[3,5-bis(trifluoromethyl)]acetophenone (**2z**). Conversely, very low conversions were observed when aliphatic ketones were alternatively employed (e.g., 4-phenylbutan-2-one, 1-phenylpropan-2-one, 4-chloro-1-phenylbutan-1-one, cyclohexanone; Tables S1 and 2, ESI[†]).

The same reaction conditions were applied to various phosphono derivatives. Consistently, high yields of trisubstituted alkenes (**4, 5**) with a diastereomeric ratio *E/Z* = 80 : 20 were achieved by reacting aromatic aldehydes **2c,d** with triethyl 2-phosphonopropanoate (**1b**).

Additionally, 4-aryl-3-buten-2-ones can be successfully prepared starting from 2-oxopropylphosphonate (**1c**), as illustrated

Table 4 Synthesis of trisubstituted α,β -unsaturated esters (**3w–z**) by HWE reaction between phosphonate (**1a**) with activated ketones **2w–z**





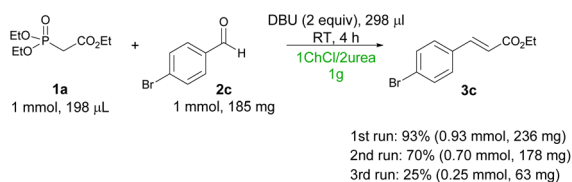
Scheme 6 Synthesis of (i) ethyl (*E*)-3-(4-bromophenyl)-2-methylacrylate (**4**) and (*E*)-2-methyl-3-(4-nitrophenyl)acrylate (**5**) from phosphono propanoate (**1b**) and aldehydes **2c,d**; (ii) (*E*)-4-(4-bromophenyl)-3-buten-2-one (**6**) from 2-oxopropylphosphonate (**1c**) and **2c**, by HWE reaction.

in Scheme 6 for the stereoselective synthesis of (*E*)-4-(4-bromophenyl)-3-buten-2-one (**6**).

Finally, solvent reuse was tested in the HWE reaction involving 4-bromobenzaldehyde (**2c**) and triethyl phosphonoacetate (**1a**) as the model reaction. After the initial cycle (4 h), upon removal of the product and residual starting materials using AcOEt, and the introduction of fresh reagents (**1a**, **2c**, and DBU), the solvent (1ChCl/2urea) could be successfully reused for two additional reaction runs, with yields of 93% and 70%, respectively (Scheme 7 and Fig. S3, ESI†).

Lower yields were instead obtained by attempting to reuse the solvent together with the DBU for two consecutive cycles (yields of 81% and 32%, respectively), carrying out the reaction on gram-scale, and isolating the final liquid product by decantation without a solvent extraction (see ESI†).

Subsequently, we run a gram-scale reaction between **2c** (10 mmol, 1.85 g) and **1a** (10 mmol, 2.23 g) in 1ChCl/2urea (10 g). The reaction proceeded smoothly at RT in the presence of air, yielding **3c** in an impressive 90% yield (2.28 g): the EcoScale calculation analysis tool was then employed to assess the sustainability of the organic preparation, based on six parameters (Table 5):^{20,21} (1) yield, (2) cost of reaction components to obtain 10 mmol of the end product, (3) safety of the reactants using hazard warning symbols, (4) technical setup of the processes, (5) temperature and time, and (6) ease of workup/purification processes. Given that an ideal reaction achieves an EcoScale value of 100, the calculated value for the synthesis of product **3c** (71) underscores the sustainability of



Scheme 7 Reuse of 1ChCl/2urea in the HWE reaction of 4-bromobenzaldehyde (**2c**) to afford α,β -unsaturated ester **3c**.

Table 5 Ecoscale score calculation for the gram-scale synthesis of product **3c** by HWE reaction between phosphonate (**1a**) with aldehyde **2c**

EcoScale parameters	Penalty points
Yield (100 – %yield)/2	
90%	5
Price of reaction components to obtain 10 mmol of end-product:^a	
4-Br-benzaldehyde (0.011 mol, 2.053 g)	0
Triethylphosphonoacetate (0.011 mol, 2.475 g)	0
DBU (0.02 mol, 3.33 g)	0
DES component: ChCl (5.91 g)	0
DES component: urea (5.02 g)	0
Safety of the reactants	
Triethylphosphonoacetate (N)	5
DBU (T)	5
Technical setup	
Common setup	0
Temperature/time:	
Room temperature, 4 h	1
Workup/purification processes	
Dilution with H ₂ O and HCl 10% v/v	0
Extraction with AcOEt and washing with brine	3
Drying over anhydrous Na ₂ SO ₄	0
Filtration over Celite pad	0
Evaporation of AcOEt	0
Flash column chromatography	10
Penalty points total	29

^a Prices listed on the Sigma Aldrich catalogue. N = dangerous for environment, T = toxic.

the process. This value was determined by deducting penalty points, where applicable, from the maximum score of 100, as outlined in the following equation (ESI†).

$$\text{EcoScale} = 100 - \sum \text{penalty points} = 100 - 29 = 71$$

Conclusions

In conclusion, we have developed a straightforward, scalable and environmentally friendly protocol for synthesizing (*E*)- α,β -unsaturated esters through the HWE reaction. This innovative approach employs protic, nontoxic, biodegradable, and cost-effective eutectic solvents, thereby eliminating the need for VOCs. Highly efficient HWE reactions were successfully run using DBU, LiOH or K₂CO₃ as bases in a ChCl/urea (1:2) eutectic mixture as a green solvent, with all steps performed at RT and under ambient air conditions. The current protocol displays remarkable stereoselectivity in the synthesis of (*E*)- α,β -unsaturated esters from **1a** and (hetero)aromatic aldehydes containing halogens (Cl, Br, I), electron-withdrawing (*e.g.*, NO₂, CF₃), and electron-donating groups (*e.g.*, OR).

This versatile synthetic strategy was extended to produce tri-substituted alkenes in DES when activated ketones were employed. Good yields were achieved with DBU (2 equiv.) as a base in a ChCl/urea (1:2) and MgBr₂ (20 mol%) mixture heated to 60 °C. The described methodology also proved successful with substituted triethyl 2-phosphonopropanoate (**1b**), yielding trisubstituted α,β -unsaturated esters in good yields (71–80%) and with satisfactory *E*-stereoselectivity. The green

solvent (1ChCl/2urea) was successfully re-used for three consecutive reaction runs. Furthermore, a gram-scale reaction (10 mmol) run at RT and under ambient air conditions resulted in a high 90% yield (2.28 g) of product **3c**. This synthesis showcased a commendable EcoScale score, absence of side products, and adherence to the principles of Green Chemistry.

Author contributions

Conceptualization (ANP, MS, PV). Data curation (ANP, MS, MP). Formal analysis (ANP, MS, MP, FMP). Funding acquisition (VC, FMP, PV). Investigation (ANP, MS, MP). Methodology (ANP, PV, FMP). Project administration (ANP, PV, FMP). Resources (VC, FMP). Supervision (FMP, PV). Validation (ANP, MP). Visualization (ANP, VC, FMP, PV). Writing – original draft (ANP, VC, FMP, PV). Writing – review & editing (ANP, MP, FMP, PV).

Conflicts of interest

There are no conflicts to declare.

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- The sole instance of a Wittig–Horner reaction in DES was documented by Y. H. Ge, D. H. Pan, J. Y. Kang in the patent CN104591959A (2015) (Preparation method of toluylene compounds). This patent, which expired in 2022, outlines a method for synthesizing stilbene derivatives. This involves utilizing substituted benzylphosphonates and aromatic aldehydes in a 1ChCl/2urea mixture as the reaction

1 medium, with NaOH present in a molar ratio of 1 : 1.5. The
reaction was run for 1–4 h, at temperatures ranging from
30 to 60 °C, yielding 61–86%, with the added benefit of
5 being able to reuse the eutectic solvent for up to three consecutive runs. In contrast to this process, our approach achieves the stereoselective preparation of disubstituted or trisubstituted (*E*)-ethyl cinnamate derivatives using DBU as the base. This is carried out at room temperature and under ambient air, yielding up to 98%. Furthermore, the solvent can be reused for two consecutive runs, distinguishing it from the previous method.

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