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A practical and sustainable protocol for direct amidation of unactivated esters under transition-metal-free and solvent-free conditions†

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In this paper, a NaO*t*Bu-mediated synthesis approach was developed for direct amidation of unactivated esters with amines under transition-metal-free and solvent-free conditions, affording a series of amides in good to excellent yields at room temperature. In particular, an environmentally friendly and practical workup procedure, which circumvents the use of organic solvents and chromatography in most cases, was disclosed. Moreover, the gram-scale production of representative products **3a**, **3w** and **3au** was efficiently realized by applying operationally simple, sustainable and practical procedures. Furthermore, this approach was also applicable to the synthesis of valuable molecules such as moclobemide (a powerful antidepressant), benodanil and fenfuram (two commercial agricultural fungicides). These results demonstrate that this protocol has the potential to streamline amide synthesis in industry. Meanwhile, quantitative green metrics of all the target products were evaluated, implying that the present protocol is advantageous over the reported ones in terms of environmental friendliness and sustainability. Finally, additional experiments and computational calculations were carried out to elucidate the mechanistic insight of this transformation, and one plausible mechanism was provided on the basis of these results and the related literature reports.

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Introduction

The amide bond, one of the most fundamental functional groups in chemistry and living cells, has been widely represented in natural products,[1] pharmaceuticals,[2] agrochemicals[3] and functional materials.[4] Due to its great importance, amide bond formation has been recognized as one of the most frequently utilized transformations in academic research for the synthesis of active pharmaceutical ingredients,[5] and it has also been labeled as a high-priority research field in the pharmaceutical industry.[6] As a consequence, expedient synthesis approaches using diverse substrates have been developed,[7] and the majority of them proceeded by the reaction of amines with activated carboxylic acids or their derivatives.[8] However, these methods highlighted several drawbacks including poor atom economy and generation of harmful or toxic wastes. In contrast, direct amide synthesis from amines and unactivated esters (especially alkyl esters) was seldomly executed for a long time since alkyl esters possess much higher $n_O \rightarrow \pi^*_{C=O}$ isomerization than the aryl counterparts.[9] Indeed, these unactivated esters possess intrinsic advantages as acylating reagents due to their good stability and ready availability. Accordingly, amide synthesis directly from alkyl esters (especially methyl esters) is an appealing alternative to traditional methods, with improved atom/step economy in many cases and alcohol (only methanol for a methyl ester) as the sole byproduct, which is in accordance with the principles of green chemistry and sustainability.[10]

Recently, utilization of alkyl esters for the construction of the amide bond under various conditions has been developed using versatile reagents or catalysts, including transition-metal-based homogeneous catalysts,[11] organocatalysts,[12] N-heterocyclic carbenes (NHCs),[13] ionic liquids,[14] heterogeneous catalysts,[15] enzymes[16] and metal salts or bases.[17] However, most of them suffer from at least one of the follow-

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†Electronic supplementary information (ESI) available: Comparison of this work with the literature reports, detailed calculated green metrics, supplementary results, characterization data and original spectra of all the target compounds. See DOI: 10.1039/d1gc00720c

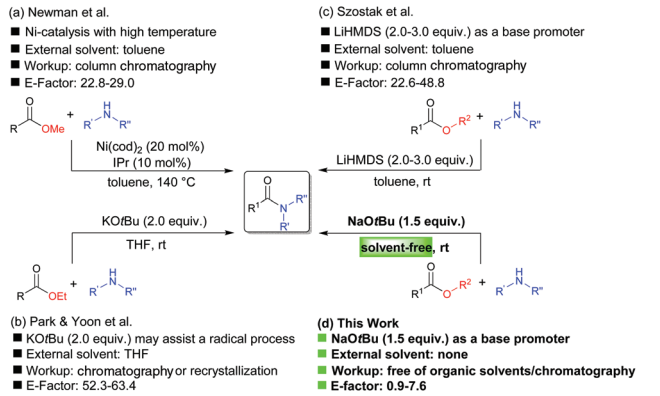


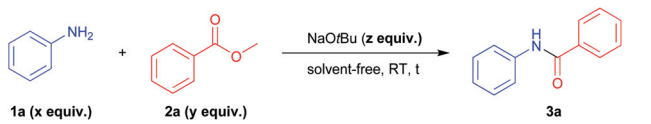
Fig. 1 Selected approaches for direct amidation of unactivated esters. (a) Newman's work, (b) Szostak's work, (c) Park & Yoon's work, (d) this work.

ing drawbacks: limited substrate scope,[12h] time-consumption,[11e] unfavorable reaction conditions (high temperature[11o,12a] or use of toxic catalysts[17d]), and utilization of transition-metal catalysts[11b,c,i,j,l–p] or rare-metal catalysts,[11e] thus limiting their potential application in industry and/or introducing hazardous substances into the environment. On the other hand, most of the reported approaches involve organic solvents during reaction set-up and product purification (Fig. 1a–c as representative examples), which does not meet the criteria of green and sustainable chemistry.[10] Since non-benign organic solvents are major wastes generated in organic synthesis, it is highly desirable to develop environmentally benign synthesis methods. Inspired by the ability of NaO*t*Bu in promoting the solventless transamidation of tertiary amides with amines in our previous work,[18] we were intrigued to incorporate this base-promoted solventless strategy into the direct amidation of alkyl esters with amines. To our delight, a practical and sustainable strategy was developed for this transformation at room temperature, in the absence of transition metals and solvents (Fig. 1d). This protocol features a broad substrate scope, solventless reaction conditions, easy operation (a benchtop setup instead of a glovebox setup) and practical work-up procedures (without utilizing organic solvents and chromatography techniques for most products). More significantly, this methodology is scalable and can be applied to the synthesis of commercial drugs/pesticides. Furthermore, green metrics of this work and representative references were calculated and compared, which demonstrates the advantages of our synthesis method in terms of greenness and sustainability. A comparison of the present protocol with the reported ones is given in Table S1.† Finally, a plausible reaction mechanism was proposed based on a few additional experiments, computational calculations and several related publications.

Results and discussion

With the above consideration in mind, the reaction of aniline (**1a**) and methyl benzoate (**2a**) was selected as a model reaction

Table 1 Optimizations of reaction conditions[a]



Entry	*x*	*y*	Base (*z* equiv.)	*t* (h)	Yield[b] (%) 3a	Yield[b] (%) Unreacted 1a
1	1.0	3.0	NaO*t*Bu (1.5)	0.5	88	10
2	1.0	2.0	NaO*t*Bu (1.5)	0.5	90	5
3	1.0	1.5	NaO*t*Bu (1.5)	0.5	85	12
4	1.0	1.2	NaO*t*Bu (1.5)	0.5	73	25
5	1.0	1.0	NaO*t*Bu (1.5)	0.5	66	30
6	**1.0**	**1.5**	**NaO*t*Bu (1.5)**	**1.0**	**96**	—
7	1.0	1.5	NaO*t*Bu (0.5)	1.0	51	46
8	1.0	1.5	NaO*t*Bu (1.0)	1.0	65	32
9	1.0	1.5	NaO*t*Bu (2.0)	1.0	96	—
10	1.0	1.5	LiO*t*Bu (1.5)	1.0	20	73
11	1.0	1.5	KO*t*Bu (1.5)	1.0	60	36
12	1.0	1.5	NaOH (1.5)	1.0	—[c]	99
13	1.0	1.5	KOH (1.5)	1.0	—[c]	97
14	1.0	1.5	Na_2CO_3 (1.5)	1.0	—[c]	95
15	1.0	1.5	K_2CO_3 (1.5)	1.0	—[c]	96
16	1.0	1.5	Cs_2CO_3 (1.5)	1.0	—[c]	98
17	1.0	1.5	KOAc (1.5)	1.0	—[c]	96
18	1.0	1.5	DIPEA (1.5)	1.0	—[c]	97
19	1.0	1.5	DBU (1.5)	1.0	—[c]	96

[a] Conditions: a mixture of **1a** (*x* equiv.), **2a** (*y* equiv.) and base (*z* equiv.) was stirred at room temperature under argon for an assigned period. [b] Isolated yields on a 2.15 mmol scale. [c] **3a** was not detected.

to optimize the reaction conditions (as listed in Table 1). An initial hit stemmed from the optimized reaction conditions in our previous work.[18] With NaO*t*Bu (1.5 equiv.) as a base, the reaction of **1a** (1.0 equiv.) and **2a** (3.0 equiv.) was carried out at room temperature under a solventless condition for 0.5 h, leading to 88% of *N*-phenylbenzamide (**3a**) and 10% of unreacted **1a** (entry 1). This result inspired us to continue the optimization. From a perspective of green and sustainable chemistry, the ratio of each reagent should be as close to equal molar as possible. Therefore, the ratio of **2a**/**1a** was systematically assessed (entries 1–5). Decreasing the ratio from 3.0/1.0 to 2.0/1.0 or 1.5/1.0 gave rise to the comparable yield of **3a** (entries 2 and 3 *vs.* entry 1), while an even smaller ratio (1.2/1.0 or 1.0/1.0) led to poor results from the viewpoint of reaction efficiency (entries 4 and 5 *vs.* entry 3). To further increase the yield of **3a**, the reaction times for the reactions listed in entries 3–5 were extended (as detailed in Fig. S1†). Under all circumstances, the yield of **3a** was gradually increased until a plateau was reached, and the best result was obtained at a ratio of 1.5/1.0 after 1.0 h, which resulted in a 96% yield of **3a** and 0% of unreacted **1a** (entry 6). Subsequently, the amounts of NaO*t*Bu were screened (entries 6–9). If the equivalents (equiv.) of NaO*t*Bu were reduced from 1.5 to 0.5–1.0, only a moderate yield of **3a** was observed, with substantial amounts of **1a** remaining (entries 7 and 8). On the other hand, an increased amount of NaO*t*Bu (2.0 equiv.) resulted in a constant yield of **3a** (entry 9 *vs.* entry 6). Therefore, 1.5 equiv. of NaO*t*Bu

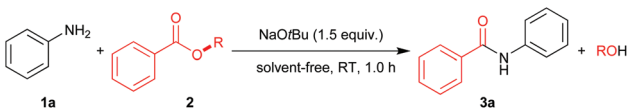
was identified as the most suitable amount. Afterwards, different bases were screened to evaluate their effects on this transformation. Among various metal salts, LiO*t*Bu (entry 10) and KO*t*Bu (entry 11) delivered **3a** in low to moderate yields (20–60%). Besides, other bases including hydroxides (entries 12 and 13), carbonates (entries 14–16), potassium acetate (KOAc, entry 17) and organic bases (entries 18 and 19) were also attempted. Unfortunately, the above bases were entirely ineffective (entries 12–19). These results illustrate that efficient formation of **3a** with an excellent yield is accomplished under transition-metal-free and solvent-free conditions, with the optimized reaction conditions discovered as follows: **1a** (1.0 equiv.), **2a** (1.5 equiv.), NaO*t*Bu (1.5 equiv.), and room temperature for 1 h (entry 6).

Apart from methyl benzoate (**2a**), a few derivatives of **2a** bearing varied R groups [ethyl benzoate (**2a-Et**), isopropyl benzoate (**2a-*i*Pr**), *tert*-butyl benzoate (**2a-*t*Bu**), benzyl benzoate (**2a-Bn**), phenyl benzoate (**2a-Ph**) and benzoic acid (**2a-H**)] were attempted to react with aniline (**1a**) under the optimized conditions (as listed in Table 2). It was found that the steric hindrance of R had a significant influence on this reaction, and the yield of **3a** gradually decreased as the steric bulk increased (entries 1–4). It has been well documented that a benzyl ester (R = Bn) is prone to the C(sp^3)–O cleavage,[17u] so this reactive ester delivered **3a** in a 95% yield (entry 5). Generally, the relative reactivity of these esters followed the order of **2a** ≈ **2a-Bn** > **2a-Et** > **2a-*i*Pr** > **2a-*t*Bu** (entries 1–5). As for **2a-Ph**, **3a** was isolated in a 51% yield and 40% of **1a** remained, which is probably attributed to the high viscosity of the reaction mixture causing the interference in the interaction of the two reactants (entry 6). As expected, benzoic acid (**2a-H**) cannot go through direct amidation with aniline (**1a**) under the standard conditions (entry 7), probably due to the high activation energy between a carboxylic acid and an amine, consistent with the result in the literature.[19] From the aspects of both reactivity and atom economy, methyl esters were selected for further investigations.

After achieving the optimal reaction conditions and selecting methyl esters as the preferred substrates, we then explored the substrate scope and limitations of this method. Firstly, the compatibility of the current protocol in the reactions of methyl benzoate (**2a**) with various amines was studied (as shown in Scheme 1). Various amides (**3a–3ah**) were efficiently obtained from primary amines (aromatic and aliphatic, **1a–1ac**) or secondary amines (**1ad–1ah**) in good to excellent yields. In detail, anilines with either electron-donating (**1b–1d**) or electron-withdrawing (**1e–1j**) groups reacted well with **2a** to furnish the corresponding amides (**3b–3j**) in 81–99% yields, which indicates that the electronic properties of aniline substituents have no obvious impact on this process. It appears that the substituent positions marginally affect the yield of the desired products, with amides **3b**, **3k** and **3l** being prepared in similar yields, ranging from 88% to 97%. Apart from *mono*-substituted anilines, *di*-substituted substrates **1m** and **1n** were also tested, delivering amides **3m** and **3n** in 99% and 96% yields, respectively. Moreover, amines comprising unique bioactive substructures,[20] such as [1,1′-biphenyl]-2-amine (**1o**), 4-phenoxyaniline (**1p**), and N^1-phenylbenzene-1,4-diamine (**1q**), were screened to further expand the scope of this methodology. To our delight, these three substrates could be efficiently transformed into the corresponding amides (**3o–3q**) in 81–98% yields. Particularly, only *mono*-benzoylated product **3q** was isolated in 90% yield, which implies that secondary aromatic amines are probably incompatible for this transformation. Meanwhile, amidation of **2a** with heteroaromatic amines **1r–1u** proceeded smoothly to yield the corresponding amides (**3r–3u**) in 75–85% yields. Furthermore, the primary aliphatic amines such as benzylamine (**1v**), 2-phenylethan-1-amine (**1w**), furan-2-ylmethanamine (**1x**) and hexane-1-amine (**1y**) exhibited remarkable reactivity, generating the desired products **3v–3y** in good to excellent yields (80–98%). Interestingly, *t*-butyloxy carbonyl (Boc)-protected amines **1z** and **1aa** were also tolerated, albeit only 70–76% of amides **3z** and **3aa** were obtained. It is worthwhile to mention that these two amides could permit further functionalization to synthesize potentially useful chemicals.[21] Furthermore, anilines bearing base-sensitive groups such as methyl 4-aminobenzoate (**1ab**) and 4′-aminoacetophenone (**1ac**) were also tolerated, affording the desired amide products (**3ab** and **3ac**) in 44–73% yields. In addition to primary aliphatic amines, secondary counterparts were also suitable substrates. Cyclic secondary amines (**1ad** and **1ae**) and *N*-benzylmethylamine (**1af**) gave rise to amides **3ad–3af** in 82–94% yields, while *N*-methylaniline (**1ag**) and *N*,4-dimethylaniline (**1ah**) provided amides **3ag–3ah** in 25–55% yields. Unfortunately, diphenylamine (**1ai**) was not a suitable substrate for our protocol, and amide **3ai** could not be obtained.

To further enhance the utility of this protocol, the reactions of aniline (**1a**) with different methyl esters were examined (as shown in Scheme 2). Initially, an array of aromatic methyl esters was tested. It appears that this protocol is not very sensitive to the electronic and steric environment around the aryl substitutions of esters. Substrates containing either electron-rich (**2aj** and **2ak**) or electron-deficient (**2al** and **2am**) groups performed well to yield the corresponding amides in satisfactory yield. In addition, compared with methyl 4-methyl-

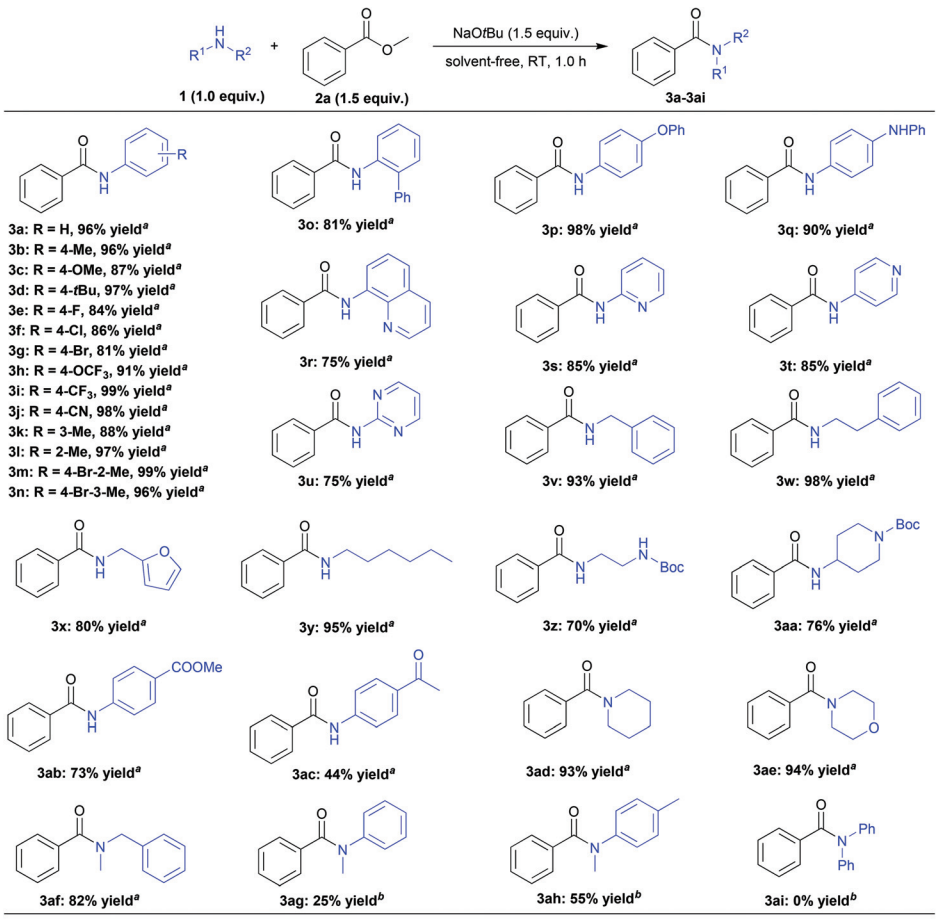
Table 2 Reactivity of **2a** and its derivatives[a]



1a 2 3a

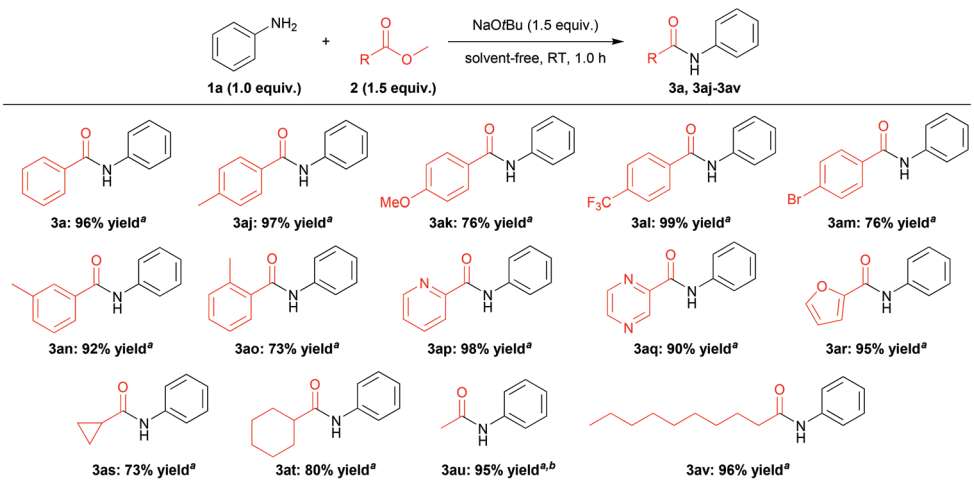
Entry	R	Yield of **3a**[b] (%)
1	Me	96
2	Et	72
3	*i*Pr	55
4	*t*Bu	30
5	Bn	95
6	Ph	51
7	H	0

[a] Conditions: aniline (**1a**, 1.0 equiv.), an ester (1.5 equiv.), NaO*t*Bu (1.5 equiv.), room temperature for 1.0 h. [b] Isolated yields on a 2.15 mmol scale.



Condition: An amine (1.0 equiv.), an ester (1.5 equiv.), NaO*t*Bu (1.5 equiv.), room temperature for 1.0 h. [a] Isolated yields (average of two runs) on a 2.15 mmol scale. [b] Isolated yields on 2.15 mmol scale at 50°C.

Scheme 1 NaO*t*Bu-promoted direct amidation of methyl esters with amines: scope of amines.



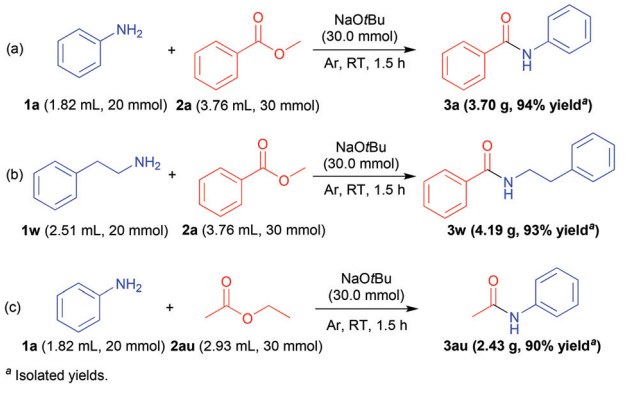
Condition: 1a (1.0 equiv.), an ester (1.5 equiv.), NaO*t*Bu (1.5 equiv.), room temperature for 1.0 h. [a] Isolated yields (average of two runs) on a 2.15 mmol scale; [b] EtOAc was used instead of MeOAc.

Scheme 2 NaO*t*Bu-promoted direct amidation of methyl esters with amines: scope of methyl esters.

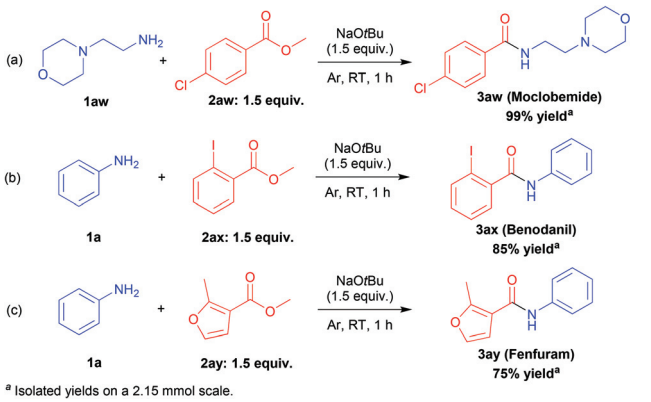
benzoate (**2aj**), methyl 3-methylbenzoate (**2an**) selectively generated the respective product (**3an**) in comparable yield, while methyl 2-methylbenzoate (**2ao**) exclusively provided product **3ao** in a slightly lower yield. Importantly, heterocycle-containing esters **2ap–2ar** also coupled with **1a** to efficiently give amides bearing pyridine (**3ap**), pyrazine (**3aq**) and furan (**3ar**)

moieties in excellent yields (90–98%). Notably, a few aliphatic methyl esters including cyclic (**2as** and **2at**) and acyclic (**2au** and **2av**) ones were also attempted, and the corresponding amides (**3au–3av**) were obtained in good to excellent yields (73–96%).

From the perspective of potential application in industry, an environmentally friendly and practical workup procedure is of great significance. In practice, the workup procedure is equally important for the reaction setup. Therefore, we endeavored to optimize the workup procedure in an eco-friendly and practical fashion. As for a standard reaction, slightly excess amounts of NaO*t*Bu and a methyl ester were used, and ice water was added dropwise to quench the reaction. In the presence of water, NaO*t*Bu would be converted into water-soluble substances (NaOH and *t*BuOH). Besides, the excess methyl ester could easily undergo hydrolysis under basic aqueous solutions, affording the corresponding carboxylates. Therefore, all the above-mentioned by-products could be dissolved in water, which inspired us to develop a workup process mediated only with water. Moreover, most of the amides are solid products, which could be collected by vacuum filtration and washed several times with pure water. In this way, products with enough purity were obtained in most cases. It is crucial to note that this protocol features not only the solvent- and transition-metal-free conditions for reaction setup, but also an eco-friendly and practical process for product separation and purification. On the other hand, the scalability of a protocol is also a pivotal factor for industrial application. Therefore, production of representative products **3a**, **3w** and **3au** were conducted on a larger scale (20 mmol, as shown in Scheme 3). *N*-Phenylbenzamide (**3a**, 3.70 g, 18.8 mmol) was efficiently prepared in a 94% yield at room temperature for 1.5 h *via* the reaction of aniline (**1a**, 1.82 mL, 20 mmol), methyl benzoate (**2a**, 3.76 mL, 30 mmol) and NaO*t*Bu (2.88 g, 30 mmol) (Scheme 3a). Similarly, *N*-phenethylbenzamide (**3w**, 4.19 g, 18.6 mmol) and *N*-phenylacetamide (**3au**, 2.43 g, 18.0 mmol) were prepared in 93% and 90% yields, respectively (Scheme 3b and c). Notably, the above water-mediated workup procedure is also applicable to these larger-scale reactions. Furthermore, the diversity of this methodology is illustrated by the synthesis of amide-containing pharmaceuticals and fungicides (as depicted in Scheme 4). Moclobemide (**3aw**, Scheme 4a), benodanil (**3ax**, Scheme 4b), and fenfuram (**3ay**, Scheme 4c) were successfully prepared from the corresponding methyl esters and amines in good to excellent yield. On the whole, all the above results demonstrate the great potential of this protocol in industrial applications.



Scheme 3 Preparation of representative amide products (**3a**, **3w** and **3au**) on a 20 mmol scale.



Scheme 4 Application of this protocol in medicinal and pesticide chemistry: synthesis of (a) moclobemide (**3aw**, an antidepressant drug), (b) benodanil (**3ax**, an agricultural fungicide) and (c) fenfuram (**3ay**, an agricultural fungicide).

To verify the greenness and sustainability of the present protocol, quantitative green metrics, including atom economy (AE), E-factor, carbon efficiency (CE), reaction mass efficiency (RME), mass intensity (MI) and mass productivity (MP), were evaluated.[10a,d] The above-mentioned green metrics of this work (Fig. 2b, d and f) and representative references (Fig. 2a, c and e)[11o,17q,u] were calculated and compared based on the reported methods (as detailed in Table S2†).[10a,d] AE is a theoretical value that only takes the starting materials and products into account. Since all the methods are applied to the same type of reactions, the AE values for the same products are identical (except the reference in Fig. 2a, which used ethyl esters instead of methyl esters). Meanwhile, the E-factor, a parameter that considers the generated wastes from all the consumed reagents, was examined. To our delight, the E-factor values obtained in this work (0.9–7.6) are much lower than those of the representative references (22.6–63.4), indicating that the current process is more beneficial to the environment. This result is evidently attributed to the solvent- and transition-metal-free conditions of this protocol. Subsequently, the calculation of CE and RME values illustrates good efficiency of our protocol, even though these values are comparable or marginally lower than those in the literature approaches. For the mass-related green metrics including MI and MP, the present work also exhibits considerably better results in comparison with the selected references. Based on these findings, we envisage that this NaO*t*Bu-promoted amidation process is relatively greener and more sustainable than the reported ones.

Subsequently, additional experiments were carried out to give further insight into the reaction mechanism (as listed in Table 3). Interestingly, the reaction could proceed smoothly under dry air, with a comparable yield than that under argon

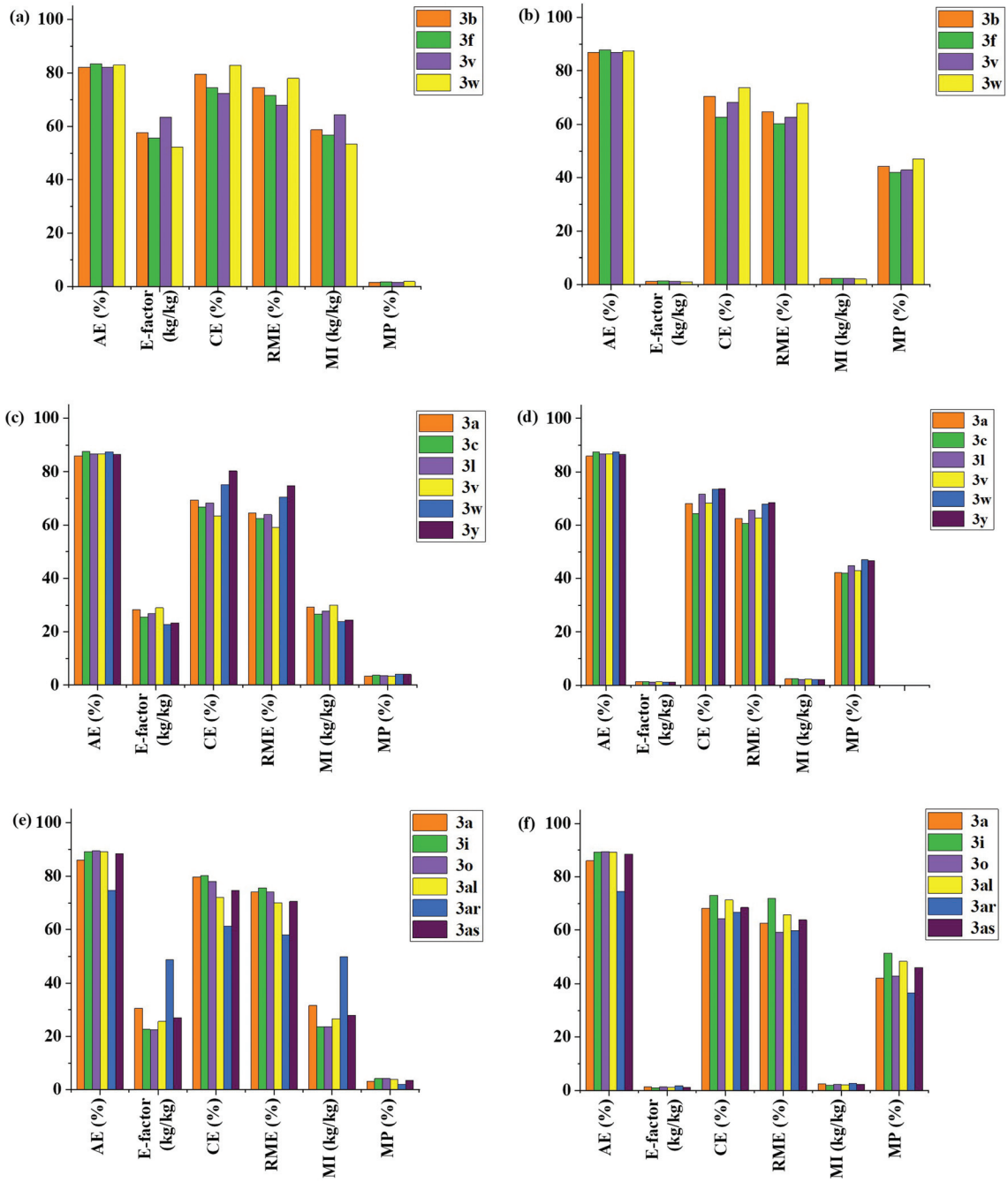
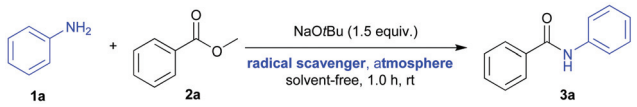


Fig. 2 Comparison of green metrics between representative references and this work: (a) KO*t*Bu-promoted amidation of ethyl esters.[17q] (c) Ni-catalyzed amidation of methyl esters.[11o] (e) LiHMDS-promoted amidation of methyl esters.[17u] (b), (d) and (f) This work.

(92% *vs.* 96%, entry 2 *vs.* entry 1). In order to further confirm whether a radical process was involved in this transformation, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, entry 3) and 1,1-diphenylethylene (entry 4) were added into the reaction mixture. It is worth noting that the addition of these radical scavengers has no significant effect on the yield of **3a** (90% and 91% *vs.* 96%, entries 3 and 4 *vs.* entry 1). Therefore, the radical-mediated process is excluded for this transformation, unlike the KO*t*Bu-promoted amidation of esters with amines which possibly involves a radical process reported by Yoon and co-workers.[17q] This KO*t*Bu-promoted amidation could only proceed smoothly in air with a water-containing solvent, but neither in argon nor in an anhydrous solvent. As reported, KO*t*Bu is a good electron transfer reagent and has been widely studied in transition-metal-free cross-coupling reactions[22] and transamidation of amides[23] *via* a radical process. In contrast, NaO*t*Bu has been rarely involved in a radical process. Accordingly, we believe that our NaO*t*Bu-mediated process

Table 3 Additional experiments[a]

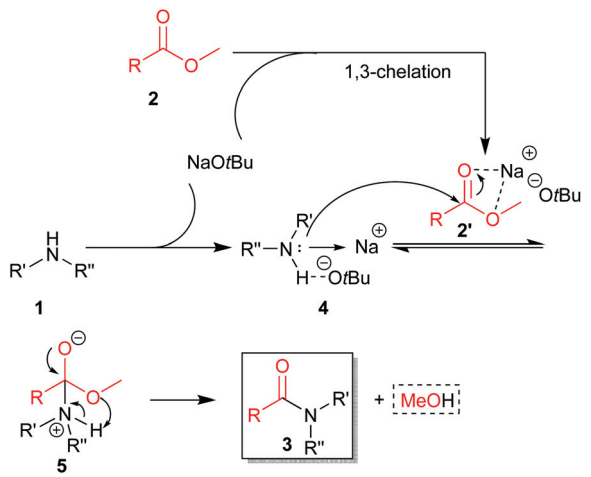


Entry	Radical scavenger	Atmosphere	Yield of 3a[b] (%)
1	None	Argon	96
2[c]	None	Dry air	92
3	Tempo (1.0 equiv.)	Argon	90
4	1,1-Diphenylethylene (1.0 equiv.)	Argon	91

[a] Conditions: a mixture of **1a** (200 mg, 2.15 mmol), **2a** (439 mg, 1.5 equiv.), NaO*t*Bu (309.9 mg, 1.5 equiv.) and radical scavenger (0 or 1.0 equiv.) was stirred at room temperature for 1.0 h. [b] Isolated yields. [c] Equipped with a $CaCl_2$-containing drying tube.

undergoes a different reaction pathway from the reported KO*t*Bu-promoted amidation.[17q]

On the basis of the above results and previously related publications, we proposed a plausible mechanism comprising 1,3-chelation of an ester with NaO*t*Bu[24] and subsequent nucleophilic addition by the activated amine[18] (as shown in Scheme 5). As reported, Na^+ can form strong interactions with the oxygen atoms of the methyl ester, and such interaction can lead to the activation of a carbonyl group.[24] In our previous report, NaO*t*Bu could activate amine **1** *via* coordination to generate intermediate **4**.[18] Meanwhile, ester **2** was transformed into intermediate **2′** *via* a 1,3-chelation step,[24] followed by nucleophilic addition of **4** into **2′** to deliver an unstable tetrahedral intermediate (**5**).[14a,17n] Ultimately, elimination of MeOH from **5** results in the formation of the desired amide **3**.[14a,25] Furthermore, the stability of key intermediates **2′** and **4** was evaluated *via* the computational calculation. The vibrational frequencies and changes in Gibbs free energy (ΔG) at 298 K were both calculated. No imaginary frequency appears



Scheme 5 A plausible mechanism.

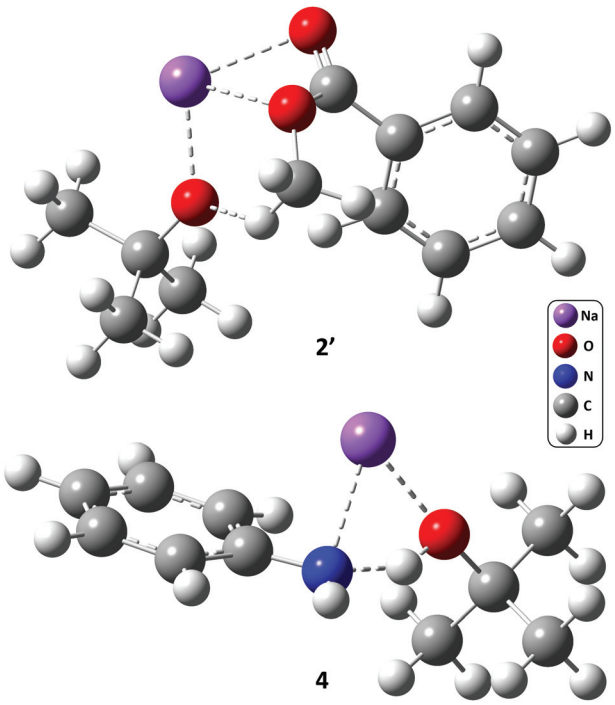


Fig. 3 Optimized structures of key intermediates **2′** and **4** *via* computational calculations.

(data of the vibrational frequency are shown in the ESI†), which indicates that **2′** and **4** are stable intermediates instead of transition states. The optimized structures of **2′** and **4** are shown in Fig. 3. Meanwhile, changes in ΔG for the transformations of **1** to **4** and **2** to **2′** were calculated as −0.096 eV and 0.193 eV, respectively (as listed in Table S3†), which implies that the formation of both intermediates is favored at 298 K. Therefore, we can conclude that intermediates **2′** and **4** are stable on the basis of the computational calculation.

Experimental

General considerations

All the reactions were carried out using standard Schlenk techniques unless otherwise mentioned. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 500 spectrometer in $CDCl_3$ or DMSO-d_6, with tetramethylsilane (TMS) as an internal reference. Multiplicities were shown using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, and dq = doublet of quartets. Melting points of products in solid states were taken on a Buchi M-560 melting point apparatus without calibration. High resolution mass spectrometry (HRMS) analyses were carried out with a Thermo Fisher Q Exactive™ UHMR Orbitrap™ instrument. NaO*t*Bu was obtained from Adamas Beta® (99% purity), and used directly without any pre-treatment. Besides, all the common reagents, including amines (**1a–1ai**, **1aw**), methyl benzoate (**2a**) and its derivatives (**2a-Et**,

2a-*i*Pr, **2a-*t*Bu**, **2a-Bn**, **2a-Ph**, **2a-H**), and other methyl esters (**2aj–2ay**), were purchased from commerical suppliers and used directly without further purification.

General procedure for direct amidation of alkyl esters with amines

To an oven-dried 25 mL Schlenk flask was added an amine (**1**, 2.15 mmol), an alkyl ester (**2**, 3.22 mmol) and NaO*t*Bu (309.9 mg, 3.22 mmol). The flask was subjected to three cycles of evacuation-backfilling with argon, and then stirred at room temperature for 1.0 h under argon. Subsequently, water (20 mL) was added dropwise to quench the reaction, and the resulting mixture was stirred for another 1.0 h. The solid was then collected by vacuum filtration, washed with water (3 × 5 mL), dried in an oven to afford the desired products (**3**). Note: compounds **3s**, **3t**, **3u** and **3ac–3ah** were purified by column chromatography on silica gel using hexane/EtOAc (6/1–3/1) as eluents.

For the gram-scale synthesis of **3a**, methyl benzoate (**2a**, 3.76 mL, 30 mmol) was added dropwise into a mixture of NaO*t*Bu (2.88 g, 30.0 mmol) and aniline (**1a**, 1.82 mL, 20.0 mmol). The resulting mixture was then stirred at room temperature under argon for 1.5 h. A similar workup procedure with the standard one was used to afford compound **3a** (3.70 g, 94% yield) as a white solid. For the gram-scale synthesis of *N*-phenethylbenzamide (**3w**) and *N*-phenylacetamide (**3au**), similar procedures as used for **3a** were exploited.

Calculation of green metrics

The green metrics of the selected references and this work was calculated based on the literature methods.[10a,d]

Computational methods

All calculations were done using Gaussian 16.[26] The geometry optimization calculation for **1**, **2**, **2′**, **4** and NaO*t*Bu was performed by using the B3LYP DFT method.[27] The basis set used for C, H, O and N atoms was 6-31G(d), and the LANL2DZ pseudopotential basis set was employed for the Na atom. The vibrational frequency was computed at the same level of theory to check whether each optimized structure was an energy minimum or a transition state, and to evaluate its zero-point energy (ZPE) and the thermal corrections at 298 K (all ΔG values were based on these calculations).

Conclusions

In summary, a NaO*t*Bu-promoted, green, practical and user-friendly protocol was developed for the facile construction of the amide bond, which efficiently converted various alkyl esters (mainly abundant methyl esters) and amines into the desired amides in good to excellent yields at ambient temperatures. Gratifyingly, the protocol was realized under solvent- and transition-metal-free conditions. It is also worth emphasizing that an eco-friendly and practical workup procedure was obtained without the use of organic solvents and chromatography techniques in most cases. Moreover, the gram-scale synthesis of representative target compounds (**3a**, **3w** and **3au**), as well as preparation of an antidepressant drug (moclobemide) and agricultural fungicides (benodanil and fenfuram) were accomplished, which provides evidence for the practical importance of the present protocol in industrial applications. In view of the quantitative green metrics, this NaO*t*Bu-promoted amidation displays relatively better performance than the reported processes in terms of greenness and sustainability. On the basis of additional experiments, computational calculations and related papers, one plausible reaction mechanism involving 1,3-chelation of an ester and subsequent nucleophilic addition was proposed.

Author contributions

Rui Zhang: conceptualization, funding acquisition, investigation, project administration, resources, methodology, supervision, writing – original draft, writing–review & editing; Wei-Zhong Yao: investigation, methodology, data curation, software, visualization; Liang Qian: investigation, methodology; Wei Sang: data curation, formal analysis, software; Ye Yuan: formal analysis, software; Min-Chen Du: formal analysis, software; Hua Cheng: formal analysis, data curation, resources, software, funding acquisition, writing – review & editing. Cheng Chen: conceptualization, funding acquisition, formal analysis, project administration, resources, supervision, writing – original draft, writing – review & editing; Xin Qin: funding acquisition, formal analysis, resources, writing – review & editing. All authors approve the current version of the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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