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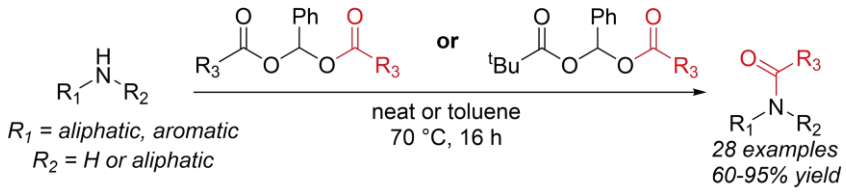

1,1-Diacyloxy-1-Phenylmethanes as Versatile *N*-Acylating Agents for Amines

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ABSTRACT: 1,1-Diacyloxy-1-phenylmethanes and 1-pivaloxy-1-acyloxy-1-phenylmethanes have been used as bench stable *N*-acylating reagents for primary and secondary amines and anilines under solvent-free conditions to afford their corresponding amides in good yield.

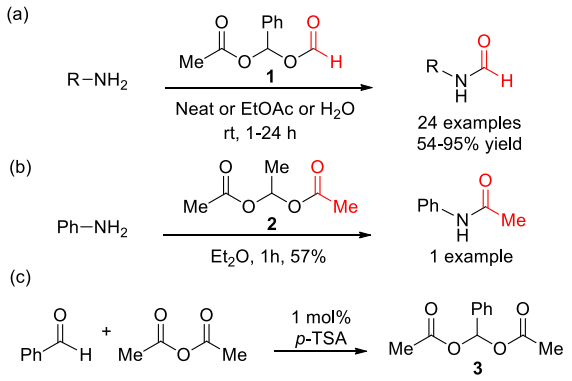
N-Acylation reactions of primary and secondary amines are important transformations in organic chemistry, because they provide direct access to the highly versatile amide group.[1] The amide bond occurs widely throughout nature and is present in many drug molecules, which means that *N*-acylation reactions are some of the most widely carried out transformations.[2] Consequently a range of synthetic protocols have been developed that employ different reagents for *N*-acylation, many of which are used in the presence of catalysts to increase their rate of reaction.[2,3] For example, acyl chlorides are commonly employed as acylating agents for amines, often in conjunction with acyl transfer catalysts (e.g. DMAP), or Lewis acid catalysts.[2] However, there are problems associated with using acid chlorides, because they are volatile, moisture-sensitive and easily hydrolyzed, whilst their reactions with amines are often exothermic and produce HCl as a by-product that can cause problems in the presence of acid sensitive functional groups.[4] Therefore, a range of alternative *N*-acylating reagents and conditions have been developed to address these problems,[5] most notably the use of stoichiometric coupling agents (e.g. DCC) for peptide synthesis.[6] A range of *N*-acylating reagents for direct reaction with amines have also been developed for amide bond formation, including *N*-acyl benzotriazoles,[4] *N*-acyl DBN·BPh_4 salts,[7] and 2-acyl-pyridazin-3-ones.[8] Given this precedent, we now report herein that 1,1-acylals may be used as moisture tolerant *N*-acylating agents for amines and also demonstrate how mixed 1-pivaloxy-1-acyloxy-1-phenylmethanes **10a-h** can be used as selective *N*-acyl transfer agents.

We have recently reported that formyloxyacetoxyphenylmethane **1** can be used as a versatile *N*-formylating reagent for amines under solvent free conditions, with exclusive transfer of its *O*-formyl group occurring over its *O*-acetyl group (Scheme 1a).[9] We reasoned that 1,1-acylals[10] containing identical *O*-acyl groups might also function as useful reagents for the *N*-acylation of amines. A review of the literature revealed a single report where ethylidenene diacetate **2** had been used to *N*-acylate aniline under non-optimal conditions, to afford *N*-acetyl-acetanilide in 57% yield (Scheme 1b).[11] In this non-optimal protocol, aniline was reacted with ethylidene acetate in ether at rt for 1 h, with acetaldehyde and solvent then being removed by passing air through the reaction mixture for 1 h to afford a mixture that was fractionally distilled to afford acetic acid and acetanilide.[11]

Given this precedent, we decided to carry out a full investigation into the potential of using benzylidene diacetate (BDA) **3** as an acylating agent for amines.[12] BDA **3** was chosen as an *N*-acylating agent to avoid potential side reactions that can arise from competing elimination reactions of acetate groups from 1,1-diacylals such as ethylidene

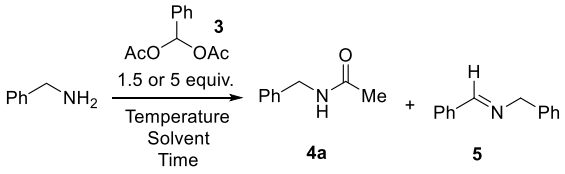
diacetate **2** that would afford unwanted vinyl acetates.

Scheme 1: (a) Formyloxyacetoxyphenylmethane **1** as an *N*-formylating agent for amines. (b) Ethylidene diacetate **2** as an *N*-acetylating reagent for aniline.[11] (c) Synthesis of benzylidene diacetate (BDA) **3**



BDA **3** was prepared in 95% yield *via* treatment of benzaldehyde and acetic anhydride with a catalytic amount of *para*-toluene sulfonic acid (*p*-TSA) (Scheme 1c).[13] Initial treatment of 1 equiv. of benzylamine with 1.5 equiv. of BDA **3** in EtOAc, at rt for 2h resulted in formation of a 50:50 mixture of the desired *N*-benzyl acetamide **4a** and *N*-benzylidenebenzylamine **5** (Table 1, Entry 1). A solvent screen was then carried out to identify conditions that would suppress competing formation of imine **5**. Repeating the acetylation reaction in toluene or CH_2Cl_2, gave similar results, affording essentially 50:50 mixtures of acetamide **4a** and imine **5** (Table 1, Entries 2-3). Reaction of benzylamine with 1.5 or 5 equiv. of BDA **3** under solvent free conditions for 2 or 16 h also gave equimolar mixtures of acetamide **4a** and imine **5** (Table 1, Entries 4-6). However, using 1.5 equiv. of BDA **3** under solvent free conditions at 50 °C gave a 65:35 ratio of acetamide **4a**:imine **5** after 16 h (Table 1, Entry 7). Finally, carrying out the acetylation reaction of benzylamine at 70 °C for 16 h gave a 95:5 ratio in favor of the desired acetamide **4a** (Table 1, Entry 8). A solvent screen revealed that EtOAc, toluene and $CHCl_3$ could also be used as cosolvents where necessary, affording >90:10 ratio of acetamide **4a** to imine **5** in each case.

Table 1. Optimization of the *N*-acetylation reactions of benzylamine using BDA **3** as an acyl donor.



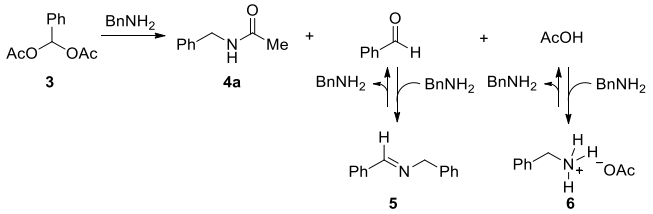
Entry	Solvent	Time (h)	Temp (°C)	4a:5
1	EtOAc	2	rt	50:50
2	toluene	2	rt	48:52
3	CH_2Cl_2	2	rt	51:49
4	-	2	rt	53:47
5	-	16	rt	51:49
6[a]	-	16	rt	52:48
7	-	16	50	65:35
8	**-**	***16***	***70***	***95:5***
9	EtOAc	16	70	90:10
10	toluene	16	70	94:6
11	$CHCl_3$	16	70	92:8

Product ratios determined from integrals of diagnostic resonances for **4a** and **5** in ^{1}H NMR spectra of crude reaction products. [a]5 equiv. of BDA **3** used.

Sampling the solvent free acetylation reactions of benzylamine using 1.5 equiv. of BDA **3** at 70 °C over time, revealed that the pH of the reaction mixture remained neutral around pH 7.0 until the majority of benzylamine had been consumed. After this time, the reaction mixture became more acidic (pH 3.0). This study also revealed that all the benzylamine was consumed after 1 h affording a 60:40 ratio of acetamide **4a** to imine **5** which gradually increased to a ratio of 95:5 in favor of amide **4a** over the next 15 h. A plausible mechanism (Figure 1) to explain these observations, involves irreversible reaction of benzylamine with one of the acetyl groups of BDA **3** to afford acetamide **4a**, with benzaldehyde and acetic acid being formed as by-products. The benzaldehyde produced may then react with benzylamine in a reversible manner to competitively afford imine **5**. The acetic acid by-product may also react with

benzylamine to afford benzylammonium acetate **6**, which can act as a buffer to maintain neutrality in the initial stages of the acetylation reaction. Since formation of benzylammonium acetate **6** is reversible, equilibration may occur to regenerate benzylamine and acetic acid, which results in all the benzylamine eventually being consumed to afford a 60:40 mixture of acetamide **4a** and imine **5** after 1 h. This equilibration process results in a gradual decrease in the amount of benzylammonium acetate **6** present over time, that coincides with a proportional increase in the amount of acetic acid present. Overall, this results in a decrease in buffering capacity (decrease in benzylammonium acetate **6**) and a decrease in pH (increase in acetic acid) of the reaction mixture as it proceeds beyond 1 h. The reversible nature of the acid-catalysed imine bond forming reaction, results in gradual regeneration of benzylamine, that can then react irreversibly with BDA **3** to drive the equilibria towards acetamide **4a** formation. This results in gradual conversion of imine **5** into acetamide **4a** over time, as witnessed by the change in ratio of acetamide **4a** to imine **5** from 60:40 (1 h) to 95:5 (16 h).

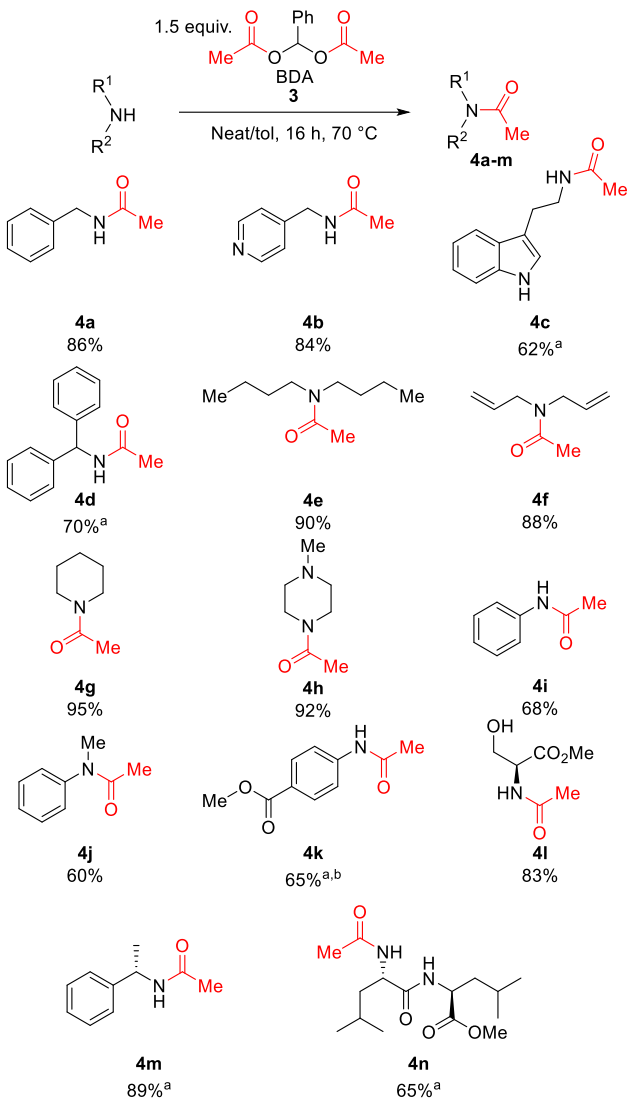
Figure 1. Plausible mechanism for *N*-acetylation of benzylamine using BDA **3** as an acetyl donor.



With optimized conditions in hand, a range of primary and secondary amines were reacted with 1.5 equiv. of BDA **3** under solvent free conditions at 70 ^{o}C for 16 h which afforded fourteen acetamides **4a-n** in 60-95% isolated yields (Scheme 2). Most of these *N*- formylation reactions were carried out under solvent-free conditions, however, toluene was employed as a solvent where the parent amine was insoluble in neat BDA **3**. Crude amide products could be purified directly *via* chromatography, without the need for any aqueous work up. The primary amines benzylamine and 4-aminomethyl-pyridine were *N*-acetylated to afford acetamides **4a-b** in 84% and 86% yields respectively, whilst tryptamine was *N*-acetylated to afford acetamide **4c** in 62% yield, with no acetylation of its indole nitrogen occurring. Sterically hindered benzhydrylamine gave its corresponding acetamide **4d** in 70% yield, whilst acyclic and cyclic secondary amines were acetylated to give 88-95% yields of the acetamides **4e-h**, respectively. Pleasingly, electron-deficient aniline and its secondary *N*-methyl analogue gave their corresponding acetamides **4i-j** in 60-68% yields, with acetylation of electron deficient methyl para-aminobenzoate affording acetamide **4k** in 65% yield after 24 h. The selectivity of BDA **3** for *N*-acetylation over *O*-acetylation was confirmed via treatment of L-serine methyl ester with 1.5 equiv. of BDA **3** at 70 °C for 16 h to afford *N*-acetyl-L-serine methyl ester **4l** in 83% yield, with no evidence of any competing *O*-acetylation, or racemization having occurred. For example, *N*-acetylation of (*S*)-α-methylbenzylamine gave (*S*)-*N*-(1-phenylethyl)acetamide **4m** in 89% yield which gave an $[\alpha]_D^{25}$ of -143 (*c* 1.0, EtOH), which compared favorably with the value previously reported for (*S*)-**4m** (>99% ee) of -145 (*c* 1.0, EtOH).[14] Furthermore, *N*-acetylation of the methyl ester of dipeptide L-Leu-L-Leu proceeded in 65% yield, with only a single diastereomer (*S,S*)-**4n** being present in the ^{1}H NMR spectra of the crude reaction product. This means that this *N*-acylation reaction proceeds without epimerization and that reversible formation of the benzylimine of L-Leu-L-Leu proceeds in a racemization free manner.

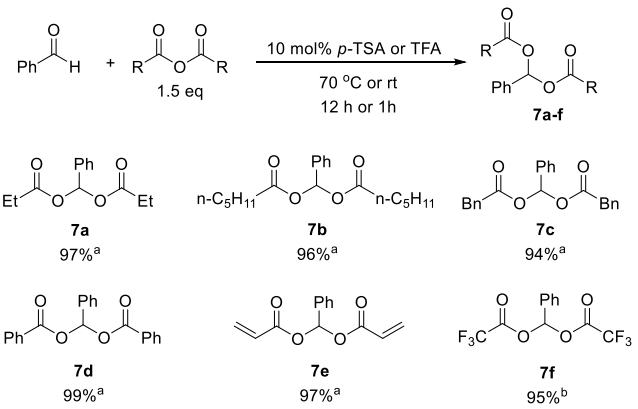
Our attention then turned to investigating the potential of using other 1,1-acylals as reagents for the *N*-acylation of benzylamine with different acyl donors. Treatment of benzaldehyde with a range of acid anhydrides in the presence of a catalytic amount of PTSA for 12 h gave their corresponding 1,1-acylals **7a-f** in excellent 90-97% yield after chromatographic purification (Scheme 3). Synthesis of highly reactive trifluoroacetyl 1,1-diacylal **7f** required use of 10 mol% of trifluoroacetic acid as catalyst for 12 h, which was used immediately without purification, due to its sensitivity to hydrolysis that led to rapid decomposition on standing.

Scheme 2: BDA **3** as an *N*-acetylating agent for primary and secondary amines.



Reaction conditions: 1 mmol of amine, 1.5 equiv. BDA **3**, 16 h, 70 °C. [a]Toluene employed as solvent. [b]24 h reaction time.

Scheme 3. Synthesis of a range of 1,1-acylals **7a-f**

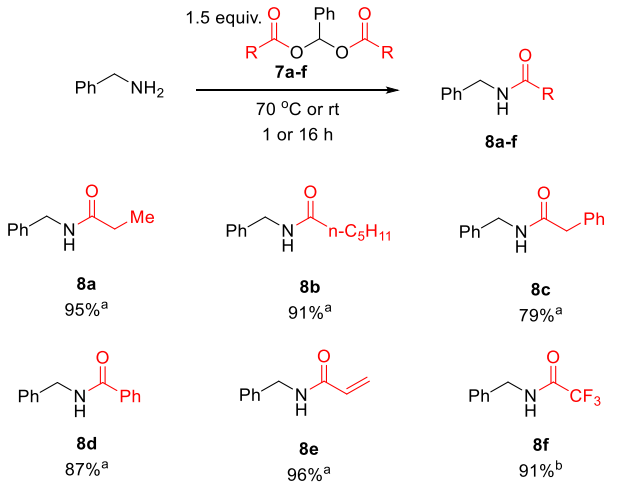


Reaction conditions; [a]1 equiv. benzaldehyde**,** 1.5 equiv. acid anhydride, 10mol%, 70 °C, 16 h. pTSA. [b]1 equiv. benzaldehyde, 1.5 equiv. acid anhydride, 10mol% TFA, rt, 1 h.

These 1,1-diacylal reagents **7a-e** were then used to *N*-acylate benzylamine at 70 °C for 16 h with a range of acyl, benzoyl, and acryloyl groups being transferred under solvent free conditions to give five *N*-acyl benzylamides **8a-e** in 79-96% yield respectively (Scheme 4). The 1,1-trifluoroacylal reagent **7f** proved to be much more reactive, with trifluoroacetylation of benzylamine proceeding to completion at rt after only 1 h to afford *N*-trifluoroacetyl-benzylamide **8f** in 91% yield (Scheme 4).

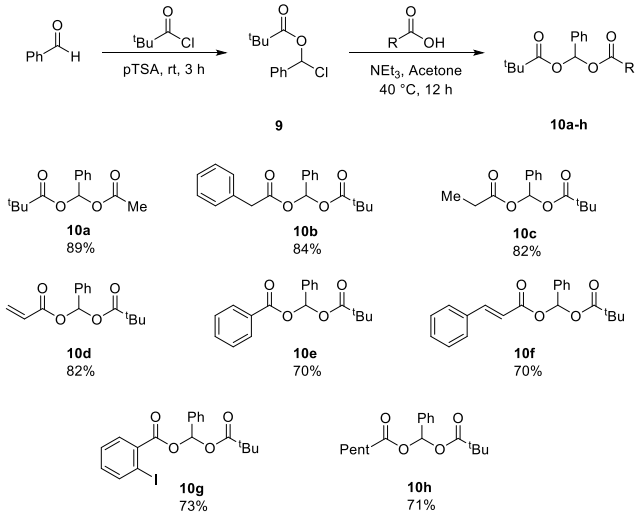
We next decided to investigate whether mixed 1-pivaloxy-1-acyloxy-1-phenylmethanes **10** could be used as selective *N*-acyl donors for amines**.** It was reasoned that the steric demand of the pivalic acid group of a mixed 1-pivaloxy-1-acyloxy-1-phenylmethane **10** would prevent nucleophilic attack at its proximal carbonyl, thus ensuring that selective transfer of its donor acyl group would occur. This would avoid the wastage of one equivalent of the acylating group that occurs when symmetric 1,1-acylals **3**, **7** are used as *N*-acylating reagents. In order to prepare these reagents, benzaldehyde was first treated with 1.5 equiv. of pivaloyl chloride, in the presence of a catalytic amount of *p*-TSA to afford chloro(phenyl)methyl pivalate **9**,[15] that was then reacted immediately with a series of carboxylic acids and Et_3N in acetone at 40 °C to afford eight mixed 1-pivaloxy-1-acyloxy-1-phenylmethanes **10a-h** in 70-89% yield (Scheme 5).[16]

Scheme 4. *N*-acylation reactions of benzylamine with 1,1-acylals **7a-f** to afford *N*-acyl benzylamides **8a-f**



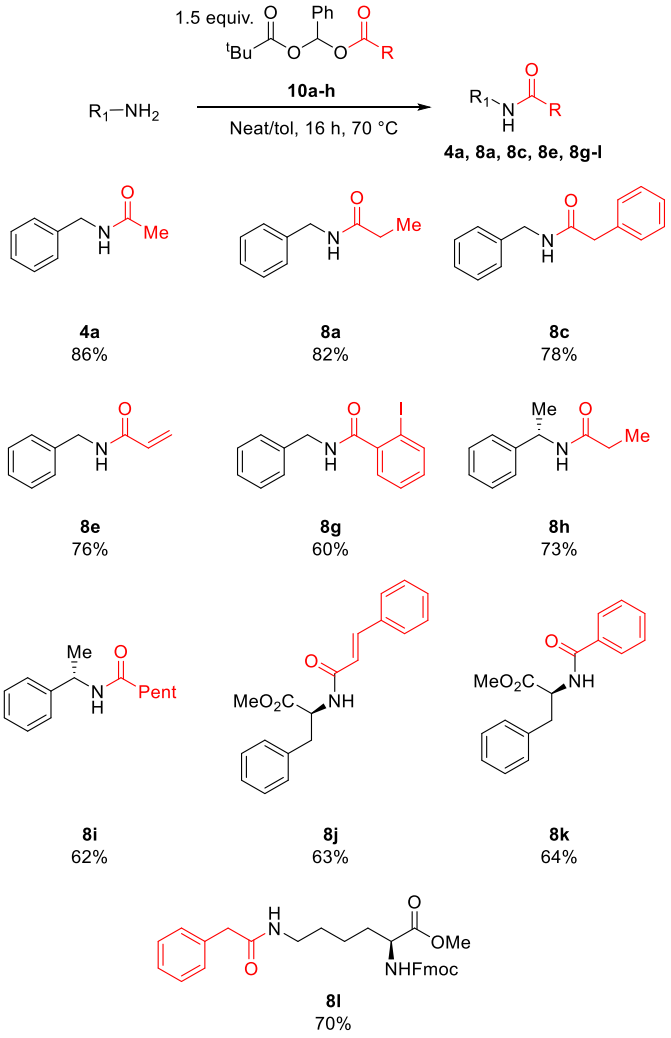
Reaction conditions: [a]1 mmol of amine, 1.5 equiv. 1,1-acylal **7a-e**, 16 h, 70 °C. [b]1 mmol of amine, 1.5 equiv. acylal **7f**, rt, 1 h.

Scheme 5. Synthesis of mixed 1-pivaloxy-1-acyloxy-1-phenylmethanes **10a-h**



These mixed 1-pivaloxy-1-acyloxy-1-phenylmethanes **10a-h** were then used to *N*-acylate a range of primary amines to give ten amides **4a, 8a, 8c, 8e, 8g-l** in 60-86% yield (Scheme 6). Pleasingly, no evidence of any products arising from pivaloyl transfer were detected in the ^{1}H NMR spectra of the crude products of any of these reactions. Mixed pivaloyl acylals could be used for the *N*-acylation of (*S*)-α-methylbenzylamine and (*S*)-phenylalanine methyl ester to afford amides **8j-l** with retention of configuration. The ω-amino group of α-*N*-Fmoc-L-lysine could also be acylated using **10b** to afford amide (*S*)-**8l** in 70% yield, thus highlighting the potential of this type of 1,1-acylal for carrying out *N*-acylation reactions on sensitive substrates under racemization free conditions.

Scheme 6. *N*-acylation reactions of 1-pivaloxy-1-acyloxy-1-phenylmethanes **10a-h** to afford *N*-acyl amides **4a, 8a, 8c, 8e, 8g-l**



In conclusion, we have shown that bench stable 1,1-diacylals can be used as moisture-tolerant *N*-acylating reagents for primary and secondary amines and anilines under solvent-free conditions, affording their corresponding acetamides in good yields. This *N*-acylation methodology has been further extended to enable mixed pivaloyl 1,1-acylals to be used as more efficient *N*-acylating agents for the selective transfer of donor acyl groups to a wide range of amines.

EXPERIMENTAL SECTION

General conditions

Unless preparative details are given, reagents and solvents were obtained from commercial suppliers. All reactions were performed without air exclusion, at room temperature and with magnetic stirring unless otherwise stated. Anhydrous $MgSO_4$ or Na_2SO_4 were used as drying agents for organic solutions. Petrol refers to petroleum ether with a boiling range of 40-60 °C. Thin layer chromatography (TLC) was carried out on Macherey-Nagel aluminium-backed plates that were precoated with silica. Compounds were visualised by quenching of UV fluorescence at 254 nm or by staining with potassium permanganate, phosphomolybdic acid (PMA) or vanillin dip followed by gentle heating. Purification by flash column chromatography was performed using high-purity grade 60 Å silica gel (60 Å pore size, 40-75 μm particle size). Capillary melting points were determined using a Stuart digital SMP10 melting point apparatus and are reported to the nearest °C. An Optical Activity Ltd AA-10 Series Automatic Polarimeter with a path length of 1 dm was used to measure optical rotations, with concentration (*c*) quoted in g/100 mL. Nuclear Magnetic Resonance (NMR) spectroscopy experiments were performed in deuterated solvent at 298 K on either a Brüker Avance 250, 300, 400 or 500 MHz spectrometer or an Agilent ProPulse 500 MHz spectrometer, with proton decoupling used for all ^{13}C NMR spectra. ^{1}H and ^{13}C NMR chemical shifts, δ, are quoted in parts per million (ppm) and where possible are referenced against the residual, non-deuterated solvent peak. A PerkinElmer Spectrum 100 FTIR spectrometer with Universal ATR FTIR accessory was used to record infrared (IR) spectra; with samples run neat and the most relevant, characteristic absorbances quoted as ν in cm^{-1}. High resolution mass spectrometry (HRMS) results were acquired on an externally calibrated Bruker Daltonics micrOTOF™ time-of-flight mass spectrometer coupled to an electrospray source (ESI-TOF). Molecular ions were detected in positive mode as either the protonated or sodiated form, with Bruker Daltonics software, DataAnalysis™ used to process the data.

General Procedures General Procedure A: *N*-acetylation of amines

Amine (1.0 mmol) was added to phenylmethylene diacetate **3** (0.291 g, 1.5 mmol) and the reaction stirred at 70 °C for 16 h. The crude reaction product was then purified by silica gel chromatography to give the desired acetamide. In those cases, where the reaction mixture was not homogeneous, then 2 mL of EtOAc or toluene were added as cosolvent at the start of the reaction. These reactions were worked-up by removing the cosolvent in vacuo, followed by purification of the crude reaction product by chromatography.

General Procedure B: Synthesis of acylals

para-Toluenesulfonic acid (mono hydrate) (0.18 g, 0.94 mmol) was added to a mixture of benzaldehyde (1.0 g, 9.4 mmol) and anhydride (18.8 mmol) at rt. The reaction was stirred for 12 h and then diluted with Et_2O (50 mL) and washed with saturated Na_2CO_3 (3 x 20 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound which was used without further purification unless stated otherwise.

General Procedure C: *N*-acylation of amines

Amine (1.0 mmol) was added to the acylating reagent (1.5 mmol) and the reaction stirred at 70 °C for 16 h. The crude reaction product was then purified by silica gel chromatography to give the desired amide.

General Procedure D: Synthesis of mixed acylals

Trimethylacetyl chloride (0.813 mL, 6.60 mmol) was added dropwise to a mixture of benzaldehyde (0.489 g, 4.40 mmol) and *para*-toluenesulfonic acid (0.083 g, 0.44 mmol) at rt and the reaction mixture stirred for 3 h. The reaction was then quenched via addition of saturated $NaHCO_{3(aq)}$ (10 mL) and diluted with Et_2O (50 mL). The reaction was then extracted with saturated $NaHCO_{3(aq)}$ (3 x 20 mL), the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to afford chloro(phenyl)methyl pivalate (1.0 g, 4.40 mmol) as a yellow oil that was used without further purification. Triethylamine (0.60 mL, 4.40 mmol) was added dropwise to a solution of chloro(phenyl)methyl pivalate (4.40 mmol) and carboxylic acid (4.40 mmol) in

acetone (10 mL). The reaction was stirred at 40 °C for 12 h during which time a white ppt formed. The reaction product was then filtered through celite® and concentrated *in vacuo* to afford a crude reaction product that was purified by silica gel chromatography (5% EtOAc in pet ether) to give the title compound.

Phenylmethylene diacetate **3**[15]

General procedure B was followed to afford the title compound as a clear oil in 98% yield (1.92 g, 9.21 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H, C*H*$(OAc)_2$), 7.55 – 7.48 (m, 2H, Ar*H*), 7.46 – 7.37 (m, 3H. Ar*H*), 2.13 (s, 6H, 2 x C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 135.6, 129.9, 128.8, 126.8, 89.8, 21.0. I.R (thinfilm) ν_{max} (cm^{-1}): 2981 (ArC-H), 1746 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{12}O_4$: requires: 231.0633 for $[M+Na]^+$; found: 231.0683.

N-Benzylacetamide **4a**[17]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a cream solid in 86% yield (0.128 g, 0.86 mmol). m.p. 61-62 °C (lit.[18] 61-62 °C). ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.39 – 7.21 (m, 5H, Ar*H*), 5.89 (s, 1H, N*H*), 4.42 (d, *J* = 5.7 Hz, 2H, C*H*$_2$), 2.01 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 138.3, 128.8, 128.0, 127.7, 43.9, 23.4.

N-(Pyridin-4-ylmethyl)acetamide **4b**[19]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc:Et_3N (70:29:1)] to afford the title compound as an orange oil in 84% yield (0.126 g, 0.84 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 – 8.48 (m, 2H, Ar*H*), 7.22 – 7.14 (m, 2H, Ar*H*), 6.07 (s, 1H, N*H*), 4.44 (d, *J* = 6.1 Hz, 2H, C*H*$_2$), 2.07 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 150.1, 147.5, 122.4, 42.6, 23.3.

N-(2-(1H-Indol-3-yl)ethyl)acetamide **4c**[20]

General procedure A was followed to afford a crude product that was purified by chromatography [EtOAc] to give the title compound as a pale brown solid in 62% yield (0.125 g, 0.62 mmol). m.p. 76-78 °C (lit.[21] 77-78°C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H, N*H*), 7.61 (ddt, *J* = 7.8, 1.5, 0.8 Hz, 1H, Ar*H*), 7.39 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar*H*), 7.22 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, Ar*H*), 7.13 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, Ar*H*), 7.06 – 7.03 (m, 1H, Ar*H*), 5.54 (s, 1H, N*H*), 3.60 (q, *J* = 6.5 Hz, 2H, CH_2CH_2NH), 2.98 (td, *J* = 6.7, 0.9 Hz, 2H, CH_2CH_2NH), 1.92 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.5, 127.5, 122.4, 122.2, 119.7, 118.8, 113.1, 111.4, 77.4, 39.9, 25.4, 23.6.

N-Benzhydrylacetamide **4d**[22]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (80:20] to afford the title compound as a crystalline white solid in 70% yield (0.158 g, 0.70 mmol). m.p. 148-150 °C (lit.[23] 151 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (qt, *J* = 6.2, 1.8 Hz, 5H, Ar*H*), 7.30 – 7.18 (m, 5H, Ar*H*), 6.26 (d, *J* = 8.0 Hz, 1H, C*H*), 6.04 (s, 1H, N*H*), 2.08 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 141.6, 128.8, 127.6, 127.5, 57.1, 23.6.

N,N-Dibutylacetamide **4e**[24]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a clear oil in 90% yield (0.154 g, 0.90 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 – 3.24 (m, 2H, NC*H*$_2$), 3.23 – 3.15 (m, 2H, NC*H*$_2$), 2.06 (s, 3H, C*H*$_3$), 1.49 (dddd, *J* = 15.2, 9.2, 7.8, 5.4 Hz, 4H, $CH_2CH_2CH_2$), 1.30 (hept, *J* = 7.4 Hz, 4H, $CH_2CH_2CH_3$), 0.92 (dt, *J* = 10.0, 7.3 Hz, 6H, 2x CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 48.7, 45.6, 31.1, 30.0, 21.7, 20.4, 20.2, 14.0, 14.0.

N,N-Diallylacetamide **4f**[24]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a yellow oil in 88% yield (0.122 g, 0.88 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 – 5.64 (m, 2H, C*H*=CH_2), 5.25 – 5.04 (m, 4H, CH=C*H*$_2$), 3.98 (dt, *J* = 6.1, 1.4 Hz, 2H, NCH_aH_b), 3.86 (dt, *J* = 4.9, 1.8 Hz, 2H, NCH_aH_b), 2.09 (s, 3H, C*H*$_3$).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 133.4, 132.7, 117.4, 116.7, 50.1, 47.9, 21.5.

1-(Piperidin-1-yl)ethanone **4g**[17]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (80:20)] to afford the title compound as a yellow oil in 95% yield (0.121 g, 0.95 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 – 3.49 (m, 2H, NCH_{AX}), 3.38 (dd, J = 6.2, 4.6 Hz, 2H, NCH_{EQ}), 2.07 (s, 3H, CH_3), 1.71 – 1.43 (m, 6H, CH_2CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 47.6, 42.6, 26.6, 25.6, 24.6, 21.7.

1-(4-Methylpiperazin-1-yl)ethanone **4h**[25]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a yellow oil in 92% yield (0.131 g, 0.92 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 – 3.58 (m, 2H, AcNCH_{AX}), 3.51 – 3.42 (m, 2H, AcNCH_{EQ}), 2.38 (dt, J = 10.0, 5.2 Hz, 4H, CH_2NCH_3), 2.30 (s, 3H, CH_2NCH_3), 2.08 (s, 3H, (C=O)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 55.2, 54.7, 46.3, 46.1, 41.4, 21.5.

N-Phenylacetamide **4i**[17]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (80:20)] to afford the title compound as a pale yellow solid in 68% yield (0.92 g, 0.68 mmol). m.p. 114-115 °C (lit.[26] 114-115 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H, ArH), 7.32 (t, J = 7.9 Hz, 2H, ArH), 7.15 – 7.06 (m, 1H, ArH), 2.18 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 138.0, 129.2, 124.5, 119.9, 24.8.

N-Methyl-N-phenylacetamide **4j**[27]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a pale green solid in 60% yield (0.089 g, 0.60 mmol). m.p. 100-102 °C (lit.[28] 101-102 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 8.3, 6.5 Hz, 2H, ArH), 7.37 – 7.30 (m, 1H, ArH), 7.23 – 7.15 (m, 2H, ArH), 3.27 (s, 3H, NCH_3), 1.87 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 144.7, 129.9, 127.8, 127.2, 37.3, 22.6.

Methyl 4-acetamidobenzoate **4k**[29]

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to afford the title compound as a pale yellow solid in 65% yield (0.126 g, 0.65 mmol). m.p. 126-128 °C (lit.[30] 128 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.92 (m, 2H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.42 (s, 1H, NH), 3.90 (s, 3H, CO_2CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 166.7, 142.2, 131.0, 125.7, 118.8, 52.2, 25.0.

(S)-Methyl 2-acetamido-3-hydroxypropanoate **4l**

Et_3N (0.42 mL, 3.21 mmol) was added in a dropwise manner to a stirred suspension of serine methyl ester hydrochloride salt (0.5 g, 3.21 mmol) in acetone (3 mL). The reaction mixture was stirred for 10 min, filtered through a Celite® pad, and the filtrate concentrated *in vacuo* to give serine methyl ester which was used as a substrate for N-acylation without further purification.

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:MeOH (95:5)] Eluent 5% to afford the title compound as a brown oil in 83% yield (0.428 g, 2.56 mmol), $[\alpha]_D^{20}$ = -9.5 MeOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H, NH), 4.67 (dt, J = 7.3, 3.6 Hz, 1H, CHNH), 3.95 (qd, J = 11.2, 3.6 Hz, 2H, CH_2OH), 3.79 (s, 3H, OCH_3), 2.80 (s, 1H, OH), 2.07 (s, 3H, (C=O)CH_3), ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 170.8, 63.6, 54.9, 52.9, 23.3. $[\alpha]_D^{20}$ = -9.5 in MeOH. I.R (thin-film) ν_{max} (cm^{-1}): 3291 ((C=O)NH and OH), 1738, 1648 (C=O); HRMS (ESI): m/z calculated for $C_6H_{11}NO_4$: requires: 162.0766 for $[M+H]^+$; found: 162.0788.

(S)-N-(1-phenylethyl)acetamide **4m**

General procedure A was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (60:40)] to afford the title compound as a white solid in 89% yield (0.145 g, 0.89 mmol). $[\alpha]_D^{20}$ = -143 (c 1.0, EtOH) (lit.[14a] $[\alpha]_D^{20}$ = -145 (c 1.0, EtOH), >99% *ee*). m.p. 97-99 °C (lit.[14b] 99-100 °C). ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.39 – 7.26 (m, 5H, ArH), 5.67 (s, 1H, NH), 5.23 – 5.03 (m, 1H, CHN), 1.99 (s, 3H. CH_3), 1.49 (d, J = 6.9 Hz, 3H, PhCHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 143.2, 128.8, 127.6, 126.4, 48.94, 23.7, 21.8.

N-acetyl-L,L-leucyl-leucine methyl ester **4n**

General procedure C was followed to afford a crude product was purified by chromatography [petroleum ether:EtOAc (90:10)] to give the title compound as a white solid (0.189g, 0.63 mmol) in 63% yield. m.p. 99 - 101 °C, $[\alpha]_D^{20}$ = -52 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.39 (d, 1H, *J* = 8.0 Hz, 1H, N*H*), 5.96 (d, 1H, *J* = 8.0 Hz, N*H*), 4.59 – 4.55 (m, 1H, NC*H*), 4.50-4.55 (m, 1H, NC*H*), 3.73 (s, 3H, OCH_3), 2.00 (s, 3H, C(=O)CH_3), 1.63 – 1.49 (m, 6H, 2CH_2 and 2CH_2C*H*(CH_3)$_2$), 0.95 – 0.91 (m, 12H, 2CH(CH_3)$_2$) . ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.2, 172.0, 170.2, 52.5, 51.7, 50.9, 41.5, 41.3, 25.0, 24.9, 23.3, 23.0, 22.9, 22.4, 22.0. I.R (thin-film) ν_{max} (cm^{-1}): 3275, 3072, 2957, 1749 (C=O ester), 1643 (C=O amide), 1547 (C=O amide). HRMS (ESI): m/z calculated for $C_{15}H_{28}N_2O_4$: requires: 323.1941 for $[M+Na]^+$; found: 323.1941.

Phenylmethylene dipropionate **7a**[31]

General procedure B was followed to afford the title compound as a clear oil in 97% yield (2.15 g, 9.12 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H, C*H*($OCOEt)_2$), 7.51 (qd, *J* = 3.8, 1.5 Hz, 2H, Ar*H*), 7.41 (ddt, *J* = 4.3, 3.1, 1.6 Hz, 3H, Ar*H*), 2.40 (tt, *J* = 7.4, 3.6 Hz, 4H, 2 x CH_2CH_3), 1.16 (t, *J* = 7.5 Hz, 6H, 2 x CH_2CH_3). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.47, 135.81, 129.80, 128.72, 126.78, 89.72, 27.55, 8.89. I.R (thinfilm) ν_{max} (cm^{-1}): 2983 (ArC-H), 1756 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{12}O_4$: requires: 259.0946 for $[M+Na]^+$; found: 259.0995.

Phenylmethylene dihexanoate **7b**[32]

General procedure B was followed to afford the title compound as a clear oil in 96% yield (2.89 g, 9.02 mmol). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 (s, 1H, C*H*Ph), 7.51 (qd, *J* = 3.7, 1.5 Hz, 2H, Ar*H*), 7.40 (ddt, *J* = 4.2, 3.1, 1.6 Hz, 3H, Ar*H*), 2.37 (td, *J* = 7.4, 2.3 Hz, 4H, 2 x (C=O)CH_2CH_2), 1.70 – 1.58 (m, 4H, 2 x (C=O)CH_2CH_2), 1.30 (dq, *J* = 7.2, 3.7, 3.3 Hz, 8H, 2 x (C=O)CH_2CH_2), 0.94 – 0.82 (m, 6H, 2 x CH_2CH_2CH_3). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 171.8, 135.9, 129.8, 128.7, 126.8, 89.6, 34.2, 31.3, 24.5, 22.4, 14.0. I.R (thinfilm) ν_{max} (cm^{-1}): 2956 (ArC-H), 1752 (C=O); HRMS (ESI): m/z calculated for $C_{19}H_{28}O_4$: requires: 343.1885 for $[M+Na]^+$; found: 343.1898.

Phenylmethylene bis(2-phenylacetate) **7c**

General procedure B was followed to afford the title compound as a clear oil in a 94% yield (3.18 g, 8.84 mmol). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (s, 1H, C*H*Ph), 7.43 – 7.16 (m, 15H, Ar*H*), 3.64 (s, 4H, 2 x CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 135.3, 133.2, 129.9, 129.5, 129.4, 128.7, 127.4, 126.7, 90.3, 41.1. I.R (thinfilm) ν_{max} (cm^{-1}): 3032, 2981 (ArC-H), 1759 (C=O); HRMS (ESI): m/z calculated for $C_{23}H_{20}O_4$: requires: 383.1259 for $[M+Na]^+$; found: 383.1259.

Phenylmethylene dibenzoate **7d**[31]

General procedure B was followed to afford the title compound as a clear oil in 99% yield (3.09 g, 9.30 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.06 (m, 5H, C*H* and Ar*H*), 7.75 – 7.64 (m, 3H, Ar*H*), 7.62 – 7.50 (m, 4H, Ar*H*), 7.49 – 7.40 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 162.5, 134.7, 133.7, 130.7, 130.2, 129.9, 129.2, 129.0, 128.9, 128.6, 126.9, 90.8. I.R (thinfilm) ν_{max} (cm^{-1}): 3064 (ArC-H), 1722 (C=O); HRMS (ESI): m/z calculated for $C_{21}H_{16}O_4$: requires: 355.0946 for $[M+Na]^+$; found: 355.0929.

Phenylmethylene diacrylate **7e**

General procedure B was followed to afford the title compound as a clear oil in 97% yield (2.12 g, 9.12 mmol). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 (s, 1H, C*H*Ph), 7.65 – 7.48 (m, 2H, Ar*H*), 7.51 – 7.36 (m, 3H, Ar*H*), 6.52 (dd, *J* = 17.3, 1.4 Hz, 2H, CH_aH_b=CH), 6.27 – 6.03 (m, 2H, CH_aH_b=C*H*), 5.93 (dd, *J* = 10.5, 1.3 Hz, 2H, CH_aH_b=CH). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.0, 134.8, 132.8, 129.9, 128.8, 127.6, 126.8, 90.1. I.R (thinfilm) ν_{max} (cm^{-1}): 3040 (ArC-H), 1732 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{12}O_4$: requires: 255.0633 for $[M+Na]^+$; found: 255.0667.

Phenylmethylene bis(2,2,2-trifluoroacetate) **7f**

Trifluoroacetic acid (0.035 mL, 0.47 mmol) was added in a dropwise manner to a solution of benzaldehyde (0.50 g, 4.7 mmol) and trifluoroacetic anhydride (0.98 mL, 7.08 mmol) at rt. After 2 h, the reaction was concentrated *in vacuo* to give the

title compound as a yellow oil in 95% yield (1.4 g, 4.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H, Ar*H*), 7.62 – 7.45 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (q, ^2JC-F = 44.7 Hz), 134.4, 131.8, 129.4, 127.0, 114.1 (q, ^1JC-F = 285.5 Hz), 93.8. I.R (thinfilm) ν_{max} (cm^{-1}): 1809 (C=O)

N-Benzylpropionamide **8a**[33]

General procedure C was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a fluffy white solid in 95% yield (0.155 g, 0.95 mmol). m.p. 49-50 °C (lit.[34] 49-50 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H, Ar*H*), 5.80 (s, 1H, N*H*), 4.43 (d, *J* = 5.7 Hz, 2H, CH_2Ph), 2.24 (q, *J* = 7.6 Hz, 2H, CH_2CH$_3$), 1.18 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.5, 128.8, 128.0, 127.6, 43.7, 29.8, 10.0.

N-Benzylhexanamide **8b**[35]

General procedure C was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a white solid in 91% yield (0.186 g, 0.91 mmol). m.p. 53-55 °C (lit.[36] 54-55 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, Ar*H*), 5.68 (s, 1H, N*H*), 4.45 (d, *J* = 5.7 Hz, 2H, CH_2Ph), 2.21 (dd, *J* = 8.6, 6.7 Hz, 2H, (C=O)CH_2CH$_2$CH$_2$), 1.73 – 1.60 (m, 2H, (C=O)CH$_2$CH_2CH$_2$), 1.32 (dq, *J* = 7.2, 3.8, 3.2 Hz, 4H, (C=O)CH$_2$CH$_2$CH_2CH_2), 0.95 – 0.83 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.5, 128.9, 128.0, 127.7, 43.7, 37.0, 31.6, 25.6, 22.6, 14.1.

N-Benzyl-2-phenylacetamide **8c**[35]

General procedure C was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a pale brown solid in a 79% yield (0.178 g, 0.79 mmol). m.p. 120-122 °C (lit.[37] 121-123 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 8H, Ar*H*), 7.22 – 7.13 (m, 2H, Ar*H*), 5.69 (s, 1H, N*H*), 4.42 (d, *J* = 5.8 Hz, 2H, PhCH_2NH), 3.64 (s, 2H, PhCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.2, 134.9, 129.6, 129.2, 128.8, 127.6, 127.6, 44.0, 43.7.

N-Benzylbenzamide **8d**[33]

General procedure C was followed to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a cream solid in 87% yield (0.184 g, 0.87 mmol). m.p. 105-106 °C (lit.[38] 105.8-106.2 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.68 (m, 2H, Ar*H*), 7.56 – 7.28 (m, 8H, Ar*H*), 6.40 (s, 1H, N*H*), 4.66 (d, *J* = 5.6 Hz, 2H. CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.7, 129.0, 128.8, 128.1, 127.8, 127.1, 44.3.

N-Benzylacrylamide **8e**[39]

General procedure C was followed. to afford a crude product that was purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a cream solid in 96% yield (0.154 g, 0.96 mmol). m.p. 58-59 °C (lit.[40] 58-59 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H, Ar*H*), 6.33 (dd, *J* = 16.9, 1.5 Hz, 1H, C*H*=CH$_a$H$_b$), 6.11 (dd, *J* = 17.0, 10.2 Hz, 1H, CH=CH_aH$_b$), 5.88 (s, 1H, N*H*), 5.67 (dd, *J* = 10.2, 1.5 Hz, 1H, CH=CH$_a$$H_b$), 4.52 (d, *J* = 5.8 Hz, 2H, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 138.1, 130.7, 128.9, 128.7, 128.7, 128.1, 128.0, 127.8, 127.0, 126.8, 43.8.

N-Benzyl-2,2,2-trifluoroacetamide **8f**[41]

Benzylamine (0.107 g, 1.0 mmol) was added to phenylmethylene- bis(2,2,2-trifluoroacetate) (0.474 g, 1.5 mmol) and the reaction mixture stirred at rt for 1 h. The crude reaction product was then purified by chromatography [CH_2Cl_2:EtOAc (70:30)] to give the title compound as a white solid in 91% yield (0.184 g, 0.91 mmol). m.p. 74-76 °C (lit.[42] 75-76 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 3H, Ar*H*), 7.32 – 7.27 (m, 2H, Ar*H*), 6.63 (s, 1H, N*H*), 4.53 (d, *J* = 5.8 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (q, ^2JC-F = 37.2 Hz), 135.9, 129.1, 128.4, 128.1, 116.0 (q, ^1JC-F = 287.8 Hz), 44.0.

Acetoxy(phenyl)methyl pivalate **10a**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a clear oil in 89% yield (0.97 g, 3.92 mmol). ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.7 (s, 1H, OC*H*O), 7.6 – 7.4 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 3H, Ar*H*), 2.1 (s, 3H, C(O)CH_3), 1.2 (s, 9H,

C(O)C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 176.4, 169.1, 135.8, 129.7, 128.7, 126.7, 89.9, 39.0, 27.0, 21.1. I.R (thin film) ν_{max} (cm^{-1}): 1745 (C=O). HRMS (ESI): m/z calculated for $C_{14}H_{18}O_4$: requires: 273.11027 for $[M+Na]^+$; found: 273.1103.

Phenyl(2-phenylacetoxy)methyl pivalate **10b**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a clear oil in 84% yield (1.20 g, 3.69 mmol). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.7 (s, 1H, OC*H*O), 7.5 – 7.4 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 3H, Ar*H*), 7.4 – 7.2 (m, 5H, Ar*H*), 3.7 (s, 2H, CH_2Ph), 1.2 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 176.3, 169.6, 135.7, 133.4, 129.7, 129.4, 128.7, 128.7, 127.4, 126.6, 90.0, 41.3, 38.9, 27.0. I.R (thinfilm) ν_{max} (cm^{-1}): 2995, 2983 (ArC-H), 1769, 1756 (C=O); HRMS (ESI): m/z calculated for $C_{20}H_{22}O_4$: requires: 349.1410 for $[M+Na]^+$; found: 349.1473.

Phenyl(propionyloxy)methyl pivalate **10c**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a clear oil a 82% yield (0.95 g, 3.62 mmol).^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.7 (s, 1H, OC*H*O), 7.5 – 7.4 (m, 2H, Ar*H*), 7.4 – 7.4 (m, 3H, Ar*H*), 2.4 (qd, *J* = 7.5, 3.0 Hz, 2H, CH_2CH$_3$), 1.2 (s, 9H, C(CH_3)$_3$), 1.2 (t, *J* = 7.5 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 176.4, 172.5, 135.9, 129.7, 128.7, 126.7, 89.8, 39.0, 27.6, 27.0, 9.0. I.R (thinfilm) ν_{max} (cm^{-1}): 2978 (ArC-H), 1754, 1750 (C=O); HRMS (ESI): m/z calculated for $C_{15}H_{20}O_4$: requires: 287.1254 for $[M+Na]^+$; found: 287.1268.

Phenyl(pivaloyloxy)methyl acrylate **10d**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a clear oil in 82% yield (0.94 g, 3.61 mmol). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.8 (s, 1H, OC*H*O), 7.6 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.4 (m, 3H, Ar*H*), 6.5 (dd, *J* = 17.3, 1.4 Hz, 1H, C*H*=CH$_a$H$_b$), 6.2 (dd, *J* = 17.3, 10.4 Hz, 1H, CH=C*H*$_a$H$_b$), 5.9 (dd, *J* = 10.4, 1.4 Hz, 1H, CH=CH$_a$*H*$_b$), 1.2 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 176.4, 164.1, 135.8, 132.6, 129.8, 128.7, 127.7, 126.7, 90.0, 39.0, 27.0. I.R (thinfilm) ν_{max} (cm^{-1}): 2975, 2875 (ArC-H), 1744 (C=O); HRMS (ESI): m/z calculated for $C_{15}H_{18}O_4$: requires: 285.1097 for $[M+Na]^+$; found: 285.1149.

Phenyl(pivaloyloxy)methyl benzoate **10e**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a colourless oil (0.874 g, 2.80 mmol) in 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.94 (s, 1H, C*H*Ph), 7.61 – 7.42 (m, 8H, Ar*H*), 1.25 (s, 9H, 3xCH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.4, 164.6, 136.0, 133.6, 130.1, 129.7, 129.4, 128.8, 128.6, 126.7, 90.4, 77.4, 77.2, 76.9, 39.1, 27.0. I.R (thin film) ν_{max} (cm^{-1}): 1732 (C=O). HRMS (ESI): m/z calculated for $C_{19}H_{20}O_4$: requires: 335.1254 for $[M+Na]^+$; found: 335.1270.

Phenyl(pivaloyloxy)methyl cinnamate **10f**

General procedure D was followed and the crude product was purified by column chromatography (petroleum ether : ethyl acetate (95:5), R_f = 0.45) to give the title compound as a white solid (0.950 g, 2.81 mmol) in 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (s, 1H, C*H*Ph), 7.77 (d, *J* = 16.0 Hz, 1H, CH=C*H*Ph), 7.58 – 7.52 (m, 4H, Ar*H*), 7.45 – 7.38 (m, 6H, Ar*H*), 6.47 (d, *J* = 16.0 Hz, 1H, C*H*=CHPh), 1.26 (s, 9H, 3xCH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.4, 164.9, 146.6, 136.1, 134.3, 130.8, 129.7, 129.1, 128.7, 128.4, 126.7, 117.2, 90.0, 39.0, 27.1. I.R (thin film) ν_{max} (cm^{-1}): 1743 (C=O), 1712 (C=O). HRMS (ESI): m/z calculated for $C_{21}H_{22}O_4$: requires: 361.1410 for $[M+Na]^+$; found: 361.1436.

Phenyl(pivaloyloxy)methyl 2-iodobenzoate **10g**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a colourless oil (1.276 g, 2.91 mmol) in 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.90 (s, 1H, C*H*Ph), 7.82 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.62 – 7.60 (m, 2H, Ar*H*), 7.45 – 7.15 (m, 4H, Ar*H*), 7.16 (t, *J*

= 7.4 Hz, 1H, Ar*H*), 1.27 (s, 9H, 3xCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.3, 164.4, 141.7, 135.6, 134.1, 133.2, 131.5, 129.9, 128.8, 128.1, 126.9, 94.5, 90.9, 39.1, 27.1. I.R (thin film) ν_{max} (cm^{-1}): 1747 (C=O). HRMS (ESI): m/z calculated for $C_{19}H_{19}O_4I$: requires: 461.0220 for $[M+Na]^+$; found: 461.0250.

Phenyl(pivaloyloxy)methyl hexanoate **10h**

General procedure D was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (95:5)] to give the title compound as a colourless oil (0.875 g, 2.86 mmol) in 71% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (s, 1H, C*H*Ph), 7.51 – 7.39 (m, 5H, Ar*H*), 2.42 – 2.31 (m, 2H, C(=O)CH_2), 1.64 (app quin., *J* = 7.1, 2H, C(=O)CH_2CH_2), 1.32 – 1.29 (m, 4H, C(=O)$CH_2CH_2CH_2CH_2$), 1.23 (s, 9H, 3xCH_3), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3) . ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.4, 171.9, 136.0, 129.7, 128.7, 126.7, 89.7, 39.0, 34.3, 31.3, 27.0, 24.6, 22.4, 14.0. I.R (thin film) ν_{max} (cm^{-1}): 1752 (C=O). HRMS (ESI): m/z calculated for $C_{18}H_{26}O_4$: requires: 329.1723 for $[M+Na]^+$; found: 329.1746.

N-Benzyl-2-iodobenzamide **8g**[43]

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (70:30)] to give the title compound as a white solid (0.202g, 0.60 mmol) in 60% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.41 – 7.30 (m, 7H, Ar*H*), 7.09 (td, *J* = 7.5, 1.8 Hz, 1H, Ar*H*), 6.07 (s, 1H, N*H*), 4.63 (d, *J* = 5.8 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.3, 142.2, 140.0, 137.7, 131.3, 128.9, 128.4, 128.3, 127.9, 92.6, 44.4.

(S)-N-(1-Phenylethyl)propionamide **8h**[44]

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (60:40)] to give the title compound as a white solid (0.128 g, 0.73 mmol) in 73% yield. $[\alpha]_D^{20}$ = -136 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 – 7.25 (m, 5H, Ar*H*), 5.65 (s, 1H, N*H*), 5.16 (app. quin., *J* = 7.0 Hz, 1H, C*H*N), 2.24 – 2.17 (m, 2H, CH_2), 1.49 (d, *J* = 6.9 Hz, 3H, PhCHCH_3), 1.15 (t, *J* = 7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.9, 143.4, 128.8, 127.5, 126.3, 48.7, 30.0, 21.9, 9.9.

(S)-N-(1-Phenylethyl)hexanamide **8i**

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (60:40)] to give the title compound as a pale yellow oil (0.136 g, 0.62 mmol) in 62% yield. $[\alpha]_D^{20}$ = -61 (c 1.0, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 – 7.17 (m, 5H, Ar*H*), 5.63 (s, 1H, N*H*), 5.07 (app. quin., *J* = 7.2 Hz, 1H, C*H*Ph), 2.09 (t, *J* = 7.4 Hz, 2H, C(=O)CH_2), 1.56 (app quin., *J* = 7.4, 2H, C(=O)CH_2CH_2), 1.41 (d, *J* = 7.0 Hz, 3H, CHCH_3), 1.26 – 1.20 (m, 4H, C(=O)$CH_2CH_2CH_2CH_2$), 0.81 (t, *J* = 7.0 Hz, 3H, CH_2CH_3) . ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.3, 143.4, 128.8, 127.5, 126.3, 48.7, 37.0, 31.6, 25.6, 22.5, 21.8, 14.1. I.R (thin film) ν_{max} (cm^{-1}): 1634 (C=O amide). HRMS (ESI): m/z calculated for $C_{14}H_{21}NO$: requires: 242.1515 for $[M+Na]^+$; found: 242.1523

Methyl cinnamoyl-L-phenylalaninate **8j**

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (70:30)] to give the title compound as a brown oil (0.194 g, 0.63 mmol) in 63% yield. $[\alpha]_D^{20}$ = +60 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 15.6 Hz, 1H, CH=C*H*Ph), 7.51 – 7.49 (m, 2H, Ar*H*), 7.38 – 7.35 (m, 3H, Ar*H*), 7.31 – 7.25 (m, 3H, Ar*H*), 7.13 – 7.11 (m, 2H, Ar*H*), 6.39 (d, *J* = 15.6 Hz, 1H, C*H*=CHPh), 6.07 (d, *J* = 7.5 Hz, 1H, N*H*), 5.04 (m, 1H, C*H*N), 3.76 (s, 3H, CH_3), 3.22 (m, 2H, CH_2Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.2, 165.4, 142.0, 136.0, 134.8, 130.0, 129.5, 129.0, 128.8, 128.0, 127.3, 120.1, 53.4, 52.5, 38.1. I.R (thin film) ν_{max} (cm^{-1}): 1739 (C=O ester), 1655 (C=O amide). HRMS (ESI): m/z calculated for $C_{19}H_{19}NO_3$: requires: 310.1438 for $[M+H]^+$; found: 310.1437.

Methyl benzoyl-L-phenylalaninate **8k**[45]

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (70:30)] to give the title compound as a yellow oil (0.181 g, 0.64 mmol) in 64% yield. $[\alpha]_D^{20}$ = +65 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.74 – 7.71 (m,

2H, Ar*H*), 7.51 – 7.41 (m, 3H, Ar*H*), 7.31 – 7.25 (m, 3H, Ar*H*), 7.15 – 7.12 (m, 2H, Ar*H*), 6.57 (d, *J* = 6.5 Hz, 1H, N*H*), 5.10 (m, 1H, C*H*N), 3.77 (s, 3H, CH_3), 3.26 (m, 2H, CH_2Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.2, 167.0, 136.0, 134.0, 131.9, 129.5, 128.8, 127.3, 127.1, 53.7, 52.6, 38.1.

(S)-Methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-6-(2-phenylacetamido)hexanoate **8l**

General procedure C was followed to afford a crude product that was purified by chromatography [Petroleum ether:EtOAc (50:50)] to give the title compound as a white solid in 70% yield (0.511 g, 1.02 mmol), m.p. 114-115 °C, $[\alpha]_D^{20}$ = +3.50 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.71 (m, 2H, Ar*H*), 7.60 (dd, *J* = 7.7, 4.2 Hz, 2H, Ar*H*), 7.40 (tdd, *J* = 7.5, 2.1, 1.2 Hz, 2H, Ar*H*), 7.36 – 7.22 (m, 7H, Ar*H*), 5.43 (s, 1H, N*H*), 5.37 (d, *J* = 8.3 Hz, 1H, N*H*), 4.47 – 4.29 (m, 3H, CH_2CO(O) and C*H*CO_2Me), 4.22 (t, *J* = 7.1 Hz, 1H, C*H*CH_2CO(O)), 3.74 (s, 3H, CO_2CH_3), 3.55 (s, 2H, CH_2Ph), 3.20 (q, *J* = 6.7 Hz, 2H, NC$H_2CH_2CH_2CH_2CHCO_2$Me), 1.88 – 1.76 (m, 1H, $NCH_2CH_2CH_2CH_aH_bCHCO_2$Me), 1.72 – 1.60 (m, 1H, $NCH_2CH_2CH_2CH_aH_bCHCO_2$Me), 1.46 (dq, *J* = 13.9, 6.7, 6.3 Hz, 2H, $NCH_2CH_2CH_2CH_2CHCO_2$Me), 1.36 – 1.22 (m, 2H, $NCH_2CH_2CH_2CH_2CHCO_2$Me). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.0, 171.2, 156.1, 144.0, 143.9, 141.5, 141.5, 135.1, 129.6, 129.2, 127.9, 127.5, 127.2, 125.22, 125.21, 120.14, 120.13, 67.2, 53.8, 52.6, 47.3, 44.0, 39.3, 32.2, 29.1, 22.5. I.R (thin film) ν_{max} (cm^{-1}): 1738, 1690, 1638 (C=O). HRMS (ESI): m/z calculated for $C_{30}H_{32}N_2O_5$: requires: 501.2384 for $[M+H]^+$; found: 501.2442.

ASSOCIATED CONTENT

Complete experimental procedure and relevant spectra (^{13}C and ^{1}H NMR spectra) for all compounds.

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Notes

The authors declare no competing financial interest.

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