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A photochemical approach to phenylalanines and related compounds by alkylation of glycine

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Abstract—Phenylalanines can be prepared on UV photolysis of protected glycines in the presence of di-*tert*-butyl peroxide, substituted toluenes and the photosensitiser benzophenone. These reactions, which lead to highly selective mono-alkylation at the α-position of glycines, involve coupling of captodative α-glycine radicals with benzyl radicals. This method can be used to selectively alkylate a variety of glycine derivatives using a range of substituted toluenes under neutral reaction conditions. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

α-Amino acids are an important class of organic compounds, which have been shown to exhibit an extraordinary range of biological and physiological properties as individual molecules or as constituent members of proteins or peptides.[1] One particularly interesting group of α-amino acids are phenylalanines.[2] A variety of phenylalanine derivatives are of medicinal importance including dopa, melphalan and levothyroxin, which are used in the treatment of Parkinson's disease, cancer and myxoedema, respectively. The nonpolar nature and steric bulkiness of the aromatic side chain also results in phenylalanine derivatives being one of the key pharmacophores in peptidomimetics. For example, most peptidomimetics designed to inhibit aspartyl proteases (such as HIV protease, renin, and cathepsins D and E) contain phenylalanine mimics or other bulky hydrophobic groups.[2c]

As these types of compounds have found widespread use in pharmaceuticals, the synthesis of phenylalanines and other α-amino acids has attracted the attention of organic chemists for many years.[3] This has led to the development of several 'classical' syntheses including the Strecker, Hell–Volhardt–Zelinsky and Gabriel reactions. These ionic transformations have long been used to prepare racemic amino acids and asymmetric variations of these and many related ionic processes are currently being developed.[4] In comparison, the preparation of α-amino acids using radical carbon–carbon bond forming reactions has received considerably much less attention.[5,6] This is surprising because radical reactions not only proceed under mild (neutral) conditions but radicals are compatible with a wide range of common functional groups including amides and esters. Thus, radical carbon–carbon bond forming reactions offer a potential solution to the problems of racemisation and polyalkylation, which can plague ionic amino acid alkylations.

The alkylation of glycine using an intermolecular radical coupling reaction was first reported by Elad and co-workers (Scheme 1).[7] This work showed that UV irradiation of ethyl *N*-acetylglycinate **1** in the presence of acetone and excess toluene produces phenylalanine **4**, although the yield of **4** was extremely low (3–5%). The proposed mechanism for this reaction involved coupling of captodative[8] radical **2** with a benzyl radical **3**, these radicals being derived from abstraction of a hydrogen atom from glycine **1** and toluene, respectively, by an excited acetone molecule. This method was extended to selectively alkylate glycine residues within peptides and proteins,[9] and this could be accomplished using visible light, when an α-diketone and di-*tert*-butyl peroxide were used in place of acetone.[10] For example, irradiation of a mixture of biacetyl, di-*tert*-butyl peroxide, toluene and the dipeptide Tfa-Gly-Val-OMe with visible light, resulted in the selective formation of Tfa-Phe-Val-OMe. The fact that glycine residues can be selectively alkylated has been explained on the basis of radical stability: the intermediate captodative radical derived from glycine is more stable than related α-amino acid radicals because this can adopt a favourable planar geometry, which leads to maximum orbital overlap and radical stabilisation.[11]

More recently, these radical coupling reactions have been carried out in the absence of an alkylating agent, to form amino acid dimers.[12] For example, Obata and Niimura[12a]

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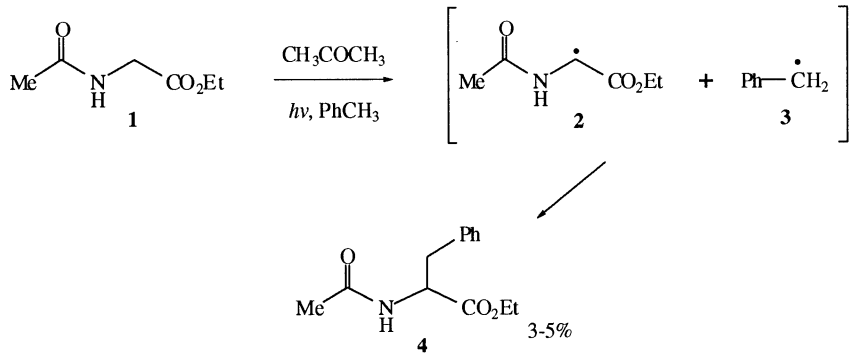
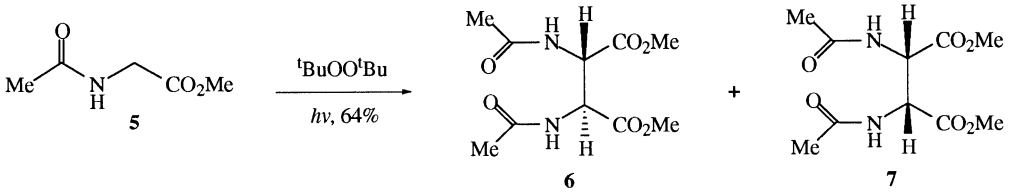


Scheme 1.



Scheme 2.

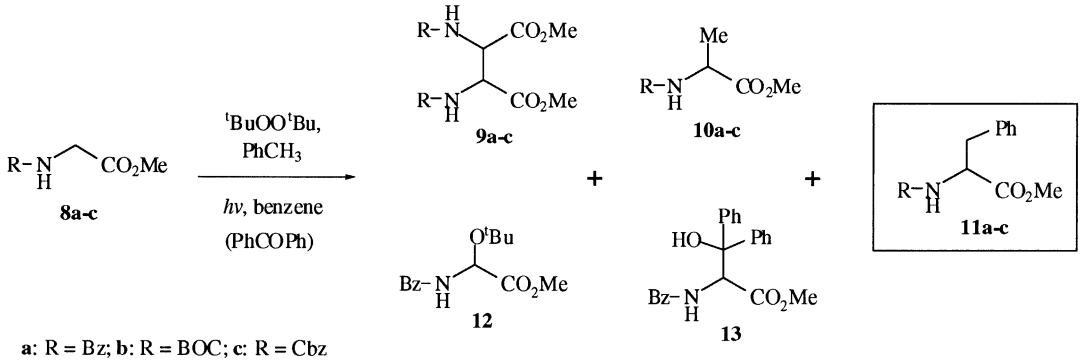
have isolated dehydrodimerisation products on UV irradiation of methyl pyroglutamate or methyl *N*-acetylglycinate **5** in the presence of di-*tert*-butyl peroxide (Scheme 2). In these reactions the *tert*-butoxyl radical (^{t}BuO$^{\cdot}$) can abstract an α-hydrogen atom from the amino acids and, for example, for glycinate **5** this produces similar amounts of the diastereoisomeric dimers (±)-**6** and *meso*-**7**. Although the use of di-*tert*-butyl peroxide, in place of acetone, leads to more efficient α-hydrogen-atom abstraction, related work by Easton and co-workers[13] have reported a competitive reaction (to dimerisation) leading to the formation of an alanine. This was attributed to coupling of the intermediate captodative radical with a methyl radical, which can be derived from β-scission of the *tert*-butoxyl radical. With a view to developing an efficient photochemical approach to phenylalanines, this paper describes the novel alkylation of various glycine derivatives using di-*tert*-butyl peroxide in the presence of substituted toluenes and related compounds.[14]

2. Results and discussion

Initial investigations involved UV irradiation of methyl *N*-benzoylglycinate **8a** in the presence of toluene and di-*tert*-butyl peroxide (Table 1). The mixture was irradiated using a 125 W lamp in degassed benzene and a variety of reactions were carried out using different concentrations of the reagents (entries 1–4). In all cases, 1,2-diphenylethane (derived from dimerisation of benzyl radical **3**) and small amounts of butanedioate **9a** (as an approximately 1:1 mixture of racemic and *meso* isomers) and alanine **10a** were isolated, but the major product was the desired phenylalanine **11a**. When a 1:2:5 ratio of glycine **8a**–peroxide–toluene was used, phenylalanine **11a** was formed in 27 or 59% yield based on recovered glycine **8a** (entry 1). Increasing the number of equivalents of peroxide and/or toluene did not improve the yield and/or selectivity for **11a** (entries 2–4). This reagent ratio was therefore employed in subsequent reactions using alternative glycine derivatives. Hence, although reaction using the corresponding *N*-benzenesulfonyl protected glycine did not produce any alkylated products,[15] reaction of *N*-Boc and *N*-Cbz glycines, **8b** and **8c**, formed phenylalanines **11b** and **11c**, respectively, in similar yields to **11a** (entries 5 and 6). The selective alkylation of **8c** is of particular note because competitive hydrogen-atom abstraction at the benzylic position of the Cbz protecting group is also possible although no products derived from this reaction were isolated. Surprisingly, there was also no evidence of benzylic radical formation from photolysis of related, but simpler amines, including PhNHCbz and ^{t}BuNHCbz (under similar conditions).[16]

With a view to decreasing the reaction time, the alkylation of glycine **8a** was also carried out using a more powerful 400 W UV lamp (entry 7) and this dramatically increased the rate of the reaction. After 6 h, 91% of the starting material was consumed as compared to 70% after 64.5 h when using the 125 W lamp. The use of the more powerful lamp also gave rise to an additional product, namely α-*tert*-butoxy-glycine **12**, which was isolated in 13% yield. The formation of **12** presumably reflects a higher concentration of the ^{t}BuO$^{\cdot}$, which could couple with the captodative radical, when using the more powerful lamp. It should also be noted that α-*tert*-butoxy-glycine **12** could be formed from reaction of the captodative radical with di-*tert*-butyl peroxide in an S_H2 reaction.

Table 1. Photoalkylation of glycines **8a–c** leading to phenylalanines **11a–c**



a: R = Bz; **b**: R = BOC; **c**: R = Cbz

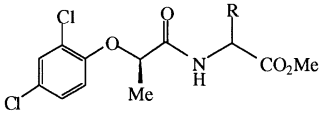
Entry	8	Reaction conditions (W, h)	Conc. of 8 (mol dm^{-3})	Equiv. of peroxide	Equiv. of toluene	9a–c (%)[a]	10a–c (%)[a]	11a–c (%)[a]	12 (%)[a]	13 (%)[a]	Total[b] yield (%)
1	**a**	125, 64.5	0.03	2	5	1(3)	4(8)	27(59)	–	–	70
2	**a**	125, 48.0	0.03	4	5	3(6)	6(15)	25(59)	–	–	80
3	**a**	125, 72.0	0.03	4	10	3(6)	7(12)	26(49)	–	–	67
4	**a**	125, 50.5	0.03	2	10	3(8)	2(6)	18(55)	–	–	69
5	**b**	125, 70	0.03	2	5	9(18)	–	27(51)	–	–	69
6	**c**	125, 64.5	0.03	2	5	–	4(12)	21(64)	–	–	76
7	**a**	400, 6	0.03	2	5	1(2)	14(27)	19(38)	13(24)	–	91
8	**a**	400, 12	0.13	2	5	11(21)	6(11)	29(54)	1(3)	–	89
9	**a**	400, 12	0.13	5	5	4(6)	3(5)	31(52)	9(14)	–	77
10	**a**	400, 12	0.26	5	5	7(13)	3(5)	19(34)	4(7)	–	77
11	**a**	400, 12[c]	0.13	5	5	18(20)	21(22)	30(33)	3(3)	3(4)	82
12	**a**	400, 12[c]	0.13	5	7.5	4(5)	13(17)	26(34)	–	4(5)	61
13	**a**	400, 12[c]	0.13	5	10	2(4)	11(17)	37(57)	–	4(6)	84

[a] Yields in brackets are based on recovered glycine **8a–c**.
[b] Total yield based on recovered glycine **8a–c**.
[c] In the presence of 5 equiv. of benzophenone.

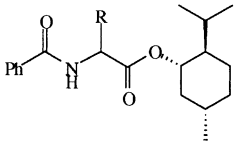
In an attempt to minimise the formation of **12**, the concentration of glycine **8a** was increased from 0.03 to 0.13 mol dm^{-3}. This had the desired effect and α-*tert*-butoxy-glycine **12** was isolated in only 1% yield while the yield of phenylalanine **11a** increased from 19 to 29% (entry 8). However, increasing the concentration of **8a** also resulted in more captodative radical dimerisation leading to a greater yield of butanedioate **9a**.[17] When the number of equivalents of peroxide was increased from 2 to 5 this was found to lower the yield of **9a** (to 3%) and phenylalanine **11a** was isolated in an excellent 31% yield (entry 9). Attempts to increase the yield of **11a** even further by increasing the concentration of **8a** (to 0.26 mol dm^{-3}) were however, unsuccessful (entry 10).

Further experiments investigated the addition of photosensitisers and when benzophenone was used in combination with 10 equiv. of toluene an optimum yield of 37% (or 57% based on recovered **8a**) was isolated for **11a** (entries 11–13). In this case, the triplet state of benzophenone, rather than ^{t}BuO$^{\cdot}$, could abstract an α-hydrogen atom from **8a**, although it was found that addition of both benzophenone and di-*tert*-butyl peroxide are required for good yields of **11a**.[18] The use of benzophenone also produced minor amounts of the serine derivative **13**, derived from coupling of the captodative radical with $Ph_2(HO)C^{\cdot}$. Indeed, when the same photolysis was carried out in the absence of toluene, tertiary alcohol **13** was isolated in 23% yield (or 50% based on recovered **8a**). This compares favourably with photolysis of methyl *N*-acetylglycinate **5** and benzophenone or 4,4′-dimethoxybenzophenone, which has been reported to give the corresponding tertiary alcohols in only 7.7 and 6.4% yield, respectively.[19] It should also be noted that related intramolecular (photochemical) reactions of quinones with glycine residues have been reported.[20]

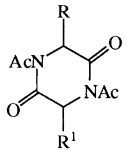
Having optimised the formation of phenylalanine **11a**, our attention turned to the photolysis of toluene with alternative glycine derivatives, namely chiral glycinates **14** and **16**, under similar reaction conditions. Reaction of **14** resulted in the selective formation of phenylalaninate **15** in 28% yield (or 62% yield based on recovered **14**) as a 1:1.1 mixture of inseparable diastereoisomers. Although a small amount of the dimer was isolated (3%) no product derived from alkylation at the amide side chain was isolated. The menthyl ester **16** underwent a similar reaction to give phenylalaninate **17** in 34% yield (or 42% yield based on recovered **16**) as a 1:1.2 mixture of inseparable diastereoisomers. This demonstrates that α-alkylation can proceed selectively for glycines with alternative secondary and even tertiary C–H bonds. The piperazine-2,5-dione **18** could also be selectively alkylated in the presence of 10 equiv. of toluene, to give the mono-benzylated compound **19** in 29% yield. Only a small amount of dialkylation (4%) to give **20** (as a 1:1 mixture of diastereoisomers) was observed together with the α-*tert*-butoxy derivative **21** in 4% yield. Increasing the number of equivalents of toluene to 20 also resulted in the predominant formation of **19** (in 20% yield); the yield of **20** only increased to 13%.



14: R = H; **15**: R = Bn



16: R = H; **17**: R = Bn



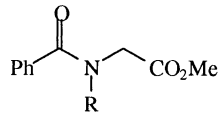
18: R = R^1 = H

19: R = Bn; R^1 = H

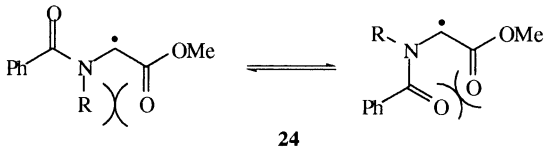
20: R = R^1 = Bn

21: R = O^{t}Bu; R^1 = H

The effect of introducing *N*-alkyl groups on the glycine derivatives was also probed by reaction of the tertiary amides **22** and **23**. Photolysis of these derivatives under the optimised conditions for the preparation of phenylalanine **11a** produced at best, trace amounts of the phenylalanine products. This surprising result may be explained by the stability of the intermediate radicals of type **24**; the introduction of *N*-alkyl groups may lead to 'non-bonding' interactions, which could prevent efficient orbital overlap.[21]



22: R = Me; **23**: R = Bn



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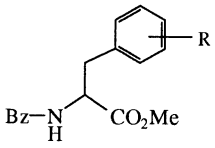
Following the successful alkylation of numerous glycine derivatives using toluene, our attention turned to the reaction of substituted toluenes. Hence, a variety of toluenes were reacted with **8a** under the optimal conditions used for the formation of phenylalanine **11a**. This allowed the formation of phenylalanines **25**–**31** in 12–36% isolated yield or 35–87% yield based on recovered **8a**. A variety of functional groups can therefore be incorporated onto the benzene ring without significantly affecting the photoalkylation process. Thus, for example, although the introduction of 4-bromo or 4-iodo groups on the toluene resulted in preferential carbon–halogen bond cleavage, both chloro and fluoro substituents can be successfully introduced. The formation of fluoro-substituted phenylalanines is of particular interest because these derivatives have been used as probes to elucidate biological pathways.[22] All of these reactions were carried out using a 400 W lamp except for the formation of **31**, which employed a 1000 W lamp.

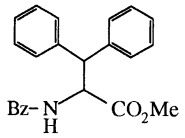
Although a number of substituents could be introduced on the benzene ring, the reaction proved to be very sensitive to variation of the (toluene) methyl group. When substituents were introduced at this site the yields of alkylation decreased and, for example, reaction of glycinate **8a** with diphenylmethane or fluorene, produced **32** or **33** in only 10 and 8% yield, respectively. This could be a consequence of the ^{t}BuO$^{\cdot}$ radical preferentially reacting with the weaker benzylic C–H bonds in diphenylmethane and fluorene (compared to toluene)[23] resulting in a lower concentration of the captodative radical derived from glycinate **8a**.



25: R = 2-F; 33% (45%)
26: R = 4-F; 36% (64%)
27: R = 2-Cl; 35% (49%)
28: R = 3-Cl; 26% (61%)
29: R = 4-Cl; 19% (35%)
30: R = 4-Me; 12% (48%)
31: R = 4-Ph; 22% (87%)

25-31

(Yields in brackets are based on recovered **8a**)



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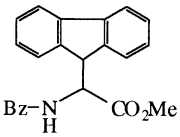

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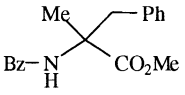
It is interesting to note that in all reactions, no products derived from dialkylation of glycinate **8a** (or related compounds) were observed. Indeed, attempts to deliberately alkylate alanine **10a** or phenylalanine **11a**, by photolysis with toluene/peroxide resulted in typically ≤1% yield of dialkylated product **34**. Similarly, the presence of a second ester served to hinder the alkylation of malonate **35** and photolysis in the presence of di-*tert*-butyl peroxide (2 equiv.) and toluene (5 equiv.) produced **36** in 13% yield (or 58% yield based on recovered **29**). This reaction also produced a small amount (3%) of phenylalanine **11a**, presumably derived from photo-decarboxylation of **36**. The fact that highly selective monoalkylation occurs in these reactions is presumably due to the exceptional stability of the intermediate captodative radical derived from glycinate **8a**.[11]



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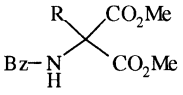

35: R = H; **36**: R = Bn

This work has shown that a variety of glycine derivatives can be alkylated to form phenylalanines on UV photolysis in the presence of substituted toluenes, di-*tert*-butyl peroxide and benzophenone (as a photo-sensitiser). Whereas related anionic alkylations are often complicated by poly-alkylation, this mild free-radical method allows the selective formation of mono-alkylated products in reasonable to good yields. The efficiency of these alkylation reactions has been shown to be affected by the nature of the glycine protecting group and particularly, by substitution of the toluene alkylating agent.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Joel EX 270

Spectrometer; the carbon spectra were recorded at 67.5 MHz and were assigned with the aid of DEPT experiments. Coupling constants (*J*) were recorded to the nearest 0.5 Hz. IR spectra were recorded on an ATI Mattson Genesis Series FT IR spectrometer. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Spectrometer system for both low and high-resolution EI and CI spectra. Thin layer chromatography was performed on Merck 5554 aluminium-backed silica gel plates and compounds were visualised by a UV lamp or by staining with alkaline potassium permanganate solution or iodine. Column chromatography was carried out under gravity using silica gel (Matrex Silica 60 70–200 microns Fisons or ICN Biomedicals GmbH flash silica 32–63 Å) and the specified eluent. Melting points were recorded on Kofler hot-stage melting point apparatus. Petroleum ether refers to the fraction of boiling range 40–60°C. Photolyses were carried out using the following lamps: a 125 W medium pressure mercury arc UV lamp; a 400 W medium pressure mercury arc UV lamp; an ILC 3102 300 W Xenon UV–Visible lamp; or a 1000 W ESR spectrometer high pressure mercury arc UV lamp. Quartz immersion-well reaction vessels were used in all photolyses except those initiated by the 1000 W lamp.

3.1. General procedure for photolysis of glycinate 8a using a 125 W lamp

Methyl *N*-benzoylglycinate **8a**[24] (0.83–1.00 g, 4.27–5.18 mmol) was dissolved in benzene (106–135 ml) and di-*tert*-butyl peroxide (2.0–4.0 equiv.) and toluene (5.0–10.0 equiv.) were added. The total volume of the solution was such that the concentration was always 0.03 mol dm^{-3} and photolysis using the 125 W lamp was continued for 48–72 h. The solutions were degassed (by bubbling nitrogen gas through the solutions) prior to photolysis and agitated by the same means through the reaction. The water flow was regulated to maintain the temperature of the reaction mixture between 25–40°C. At the end of the irradiation, the lamp was cooled and evaporation of the mixture gave an orange oil (1.32–2.00 g), which was purified by column chromatography (silica; petroleum ether–ethyl acetate, 1:1). The products were eluted in the following order: 1,2-diphenylethane,[25] methyl *N*-benzoylphenylalaninate **11a**,[26] methyl *N*-benzoylalaninate **10a**,[27] recovered starting material **8a** and a 1:1 mixture of (±)- and *meso*-dimethyl 2,3-dibenzamidobutanedioate **9a**.[13]

3.2. Representative example: 125 W photolysis using a 1:4:5 ratio of glycinate 8a–peroxide–toluene

Photolysis (48 h) of glycinate **8a** (1.00 g, 5.18 mmol), di-*tert*-butyl peroxide (4.0 equiv., 3.03 g, 3.8 ml, 20.7 mmol) and toluene (5.0 equiv., 2.38 g, 2.8 ml, 25.9 mmol) as a solution in benzene (133 ml) afforded an orange oil (1.81 g) after evaporation in vacuo. Column chromatography (silica; petroleum ether–ethyl acetate, 1:1) afforded 1,2-diphenylethane (0.44 g), methyl *N*-benzoylphenylalaninate **11a** [0.36 g, 25% (59% based on recovered **8a**)], alaninate **10a** [0.068 g, 6% (15%)], recovered glycinate **8a** (0.58 g, 58%) and a 1:1 mixture of (±): *meso*-butanedioate **9a** [0.053 g, 3% (6%)].

3.3. 125 W Photolysis of methyl *N*-*tert*-butyloxycarbonylglycinate 8b

Methyl *N*-*tert*-butyloxycarbonylglycinate **8b** (1.00 g, 5.29 mmol) was dissolved in benzene (135 ml) and di-*tert*-butyl peroxide (1.55 g, 1.9 ml, 10.6 mmol) together with toluene (2.43 g, 2.8 ml, 26.5 mmol) were added and the mixture photolysed for 70 h. The crude orange oil (1.78 g) was purified by column chromatography (silica; petroleum ether–ethyl acetate, 2:1) to afford methyl *N*-*tert*-butyloxycarbonylphenylalaninate **8b** [0.40 g, 27% (51% based on recovered **8b**)],[28] 1,2-diphenylethane (>0.27 g), recovered starting material **8b** (0.47 g, 47%) and *meso*- and (±)-dimethyl 2,3-bis-*tert*-butyloxycarbonylaminosuccinate **9b** [0.19 g, 9%, (18% based)][29] as a 1:1 mixture of diastereoisomers.

3.4. 125 W Photolysis of methyl *N*-benzyloxycarbonylglycinate 8c

A mixture of Cbz-protected glycine **8c** (1.00 g, 4.48 mmol), di-*tert*-butyl peroxide (1.31 g, 1.64 ml, 8.96 mmol) and toluene (2.06 g, 2.4 ml, 22.4 mmol) in benzene (156 ml) was irradiated for 64.5 h. This gave an orange oil (1.46 g) which was purified by column chromatography (silica; petroleum ether–diethyl ether, 1:3) to produce methyl *N*-benzyloxycarbonylphenylalaninate **11c**[30] [0.30 g, 21% (64% based on recovered **8c**)] and methyl *N*-benzyloxycarbonylalaninate **10c**[31] [0.042 g, 4% (12%)]. Recovered starting material **8c** (0.67 g, 67%) and 1,2-diphenylethane (≤0.82 g) were also eluted.

3.5. Representative example for photolysis of glycinate 8a using a 400 W lamp in the absence of benzophenone

Methyl *N*-benzoylglycinate **8a** (5.00 g, 25.9 mmol), di-*tert*-butyl peroxide (5.0 equiv., 18.91 g, 23.8 ml, 0.13 mol) and toluene (11.91 g, 13.8 ml, 0.13 mol) in benzene (162 ml) were photolysed (12 h) using a 400 W UV lamp. After photolysis, the solvent was removed and a small sample (1.23 g, 12.5% of the crude mass) was purified to identify and quantify the products formed. Column chromatography (silica, petroleum ether–ethyl acetate, 1:1) afforded phenylalaninate **11a** [0.286 g, 2.28 g scaled, 31%, (52% based)], the *tert*-butoxy adduct **12** [0.074 g, 0.59 g, scaled, 9%, (14%)], alaninate **10a** [0.019 g, 0.152 g scaled, 3%, (5%)], recovered glycine **8a** (0.248 g, 1.98 g scaled, 40%) and dimers **9a** [0.023 g, 0.184 g scaled, 4%, (6%)] as a 1:1 mixture of diastereoisomers.

3.5.1. Methyl *N*-benzoyl-2-*tert*-butoxyglycinate 12. R_F 0.6 (petroleum ether–ethyl acetate, 3:2); ν_{max} (CH_2Cl_2) 3544 (s), 3439 (s), 3330 (s), 1656 (s), 1526 (w), 1481 (w), 1192 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.87–7.80 and 7.60–7.41 (5H, m, aromatics), 7.14 (1H, d, *J*=9.5 Hz, N*H*), 6.03 (1H, d, *J*=9.5 Hz, NHC*H*CO), 3.78 (3H, s, CO_2CH_3), 1.31 (9H, s, $C(CH_3)_3$); *m*/*z* (CI, NH_3) 283 ($M+NH_4^+$, 80%), 266 ($M+H^+$, 100), 227 (20), 210 (50), 194 (10), 139 (30), 122 (60), 105 (30). Found: $M+H^+$, 266.1390. $C_{14}H_{19}NO_4$ requires for $M+H^+$, 266.1392.

3.6. Representative example for photolysis of glycinate 8a using a 400 W lamp in the presence of benzophenone

The mixture of glycinate **8a** (5.00 g, 26.0 mmol), di-*tert*-butyl peroxide (5.0 equiv., 18.98 g, 23.8 ml, 0.13 mol), benzophenone (5.0 equiv., 23.57 g, 0.13 mol) and toluene (10.0 equiv., 23.83 g, 27.7 ml, 0.26 mol) in benzene (149 ml) was photolysed for 12 h using a 400 W UV lamp. After evaporation an orange oil (40.30 g) was isolated and a fraction of this [1.70 g (4.2% of crude mass)] was purified by column chromatography (silica; petroleum ether–ethyl acetate, 1:1). This afforded the β,β-diphenylserinate **13** [0.015 g, scaled to 0.36 g, 4%, (6%)], the phenylalaninate **11a** [0.115 g, scaled to 2.74 g, 37%, (57%)], alaninate **10a** [0.025 g, scaled to 0.60 g, 11%, (17%)], recovered **8a** (0.074 g, scaled to 1.76 g, 35%) and a 1:1 ratio of *meso*-:(±)-**9a** [0.005 g, scaled to 0.119 g, 2%, (4%)].

3.6.1. Methyl *N*-benzoyl-β,β-diphenylserinate 13. R_F 0.5 (petroleum ether–ethyl acetate, 1:1); White solid; mp 151–154°C; (found: C, 73.49; H, 5.60; N, 3.38. $C_{23}H_{21}NO_4$ requires C, 73.58; H, 5.64; N, 3.73%); ν_{max} (CH_2Cl_2) 3443 (s), 3358 (s), 3321 (m), 1738 (m), 1650 (s), 1525 (w), 1487 (w), 1445 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.83–7.14 (15H, m, aromatics), 7.04 (1H, br d, J=8.0 Hz, N*H*), 5.85 (1H, d, J=8.0 Hz, NHC*H*CO), 3.53 (3H, s, CO_2CH_3), 1.64 (1H, br s, O*H*); δ_C (67.5 MHz, $CDCl_3$) 172.9 (CO_2CH_3), 167.2 (N*C*O), 143.5, 142.0, 133.4 (*C*=CH), 131.8, 130.0, 128.6, 128.4, 128.2, 127.6, 127.4, 127.0, 125.3, 125.1 (C=*C*H), 79.3 (Ph_2COH), 57.4 (NH*C*HCO), 52.5 (CO_2CH_3); *m/z* (CI, NH_3) 376 ($M+H^+$, 80%), 358 (MH^+-H_2O, 100), 298 (10), 183 (20), 105 (20). Found: $M+H^+$, 376.1544. $C_{23}H_{21}NO_4$ requires for $M+H^+$, 376.1549.

3.6.2. Synthesis of methyl 2*R*-[*N*-(2,4-dichlorophenoxy)-propanoyl]glycinate 14. A solution of *R*-2-(2,4-dichlorophenoxy)propionic acid (10.00 g, 42.0 mmol), thionyl chloride (1.5 equiv., 7.50 g, 4.6 ml, 63.0 mmol) together with 2–3 drops of *N*,*N*′-dimethylformamide (*Care*: noxious fumes!) was heated for 2 h. The excess thionyl chloride was removed by rotary evaporation to afford the crude acid chloride as an orange oil. This was added dropwise to a solution of glycine methyl ester hydrochloride (1.05 equiv., 5.53 g, 44.0 mmol) and triethylamine (1.05 equiv., 4.44 g, 6.12 ml, 44.0 mmol) in dichloromethane (100 ml) at 0°C. The mixture was allowed to stir for 2 h during which time the solution was allowed to warm to room temperature. The solution was washed with water (100 ml), separated, dried ($MgSO_4$) and evaporated to afford crude product (13.06 g). Purification by column chromatography (silica; petroleum ether–ethyl acetate, 1:1) gave methyl 2*R*-[*N*-(2,4-dichlorophenoxy)propanoyl]glycinate **15** (7.49 g, 58%) as an off-white solid; mp 97–100°C. (found: C, 47.14; H, 4.18; N, 4.34. $C_{12}H_{13}Cl_2NO_4$ requires C, 47.08; H, 4.28; N, 4.58%); R_F 0.3 (petroleum ether–ethyl acetate, 1:1); ν_{max} ($CHCl_3$) 3430 (m), 3010 (m), 1752 (s), 1680 (s), 1526 (s), 1477 (s), 1439 (m), 1284 (m), 1243 (s), 1105 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.42–7.41 (1H, m, aromatic), 7.22–7.18 (1H, m, aromatic), 6.90–6.86 (2H, m, aromatic and N*H*), 4.74 (1H, q, J=7.0 Hz, OC*H*CH_3), 4.10 (2H, d, J=5.5 Hz, NHCH_2CO), 3.77 (3H, s, CO_2CH_3), 1.64 (3H, d,J=7.0 Hz, CH_3CH); δ_C (67.5 MHz, $CDCl_3$) 171.5 (CO_2CH_3), 169.7 (*C*ON), 151.2, 127.5, 124.7 (*C*= CH), 130.3, 127.9, 116.1 (C= *C*H), 76.5 (O*C*HCH$_3$), 52.5 (CO_2CH_3), 40.9 (NH*C*H$_2$CO), 18.4 (*C*H$_3$CH); *m/z* (CI, NH_3) 323 ($^{35,35}M+NH_4^+$, 100%), 308 ($^{35,37}M+H^+$, 60), 306 ($^{35,35}M+H^+$, 90) 270 (30), 161 (20), 144 (20), 116 (10). Found: $^{35,35}M+H^+$, 306.0297. $C_{12}H_{13}{}^{35,35}Cl_2NO_4$ requires for $M+H^+$, 306.0300.

3.7. Photolysis of methyl 2*R*-[*N*-(2,4-dichlorophenoxy)-propanoyl]glycinate 14

Methyl 2*R*-[*N*-(2,4-dichlorophenoxy)propanoyl]glycinate **14** (7.96 g, 25.9 mmol), di-*tert*-butyl peroxide (5.0 equiv., 18.98 g, 0.13 mol), benzophenone (5.0 equiv., 23.57 g, 0.13 mol) and toluene (10 equiv., 23.92 g, 0.26 mol) in benzene (149 ml) were photolysed for 12 h. After evaporation in vacuo, the crude mixture of products was isolated as a yellow oil (40.07 g). A small sample (1.38 g, 3.4% of crude mass) was purified by column chromatography (silica; petroleum ether–ethyl acetate, 2:1) to afford methyl 2*R*-[*N*-(2,4-dichlorophenoxy)propanoyl]-(*R*,*S*)-phenylalaninate **15** [0.14 g, scaled to 2.91 g, 28%, (62% based)] as an inseparable 1:1.1 mixture of diastereoisomers (from the ^{1}H NMR spectrum) and dimethyl 2,3-bis-[2*R*-(2,4-dichlorophenoxy)propanoylamino]succinate [0.008 g, scaled to 0.233 g, 3%, (6%)] as a mixture with recovered glycinate **14** (0.149 g, scaled to 4.33 g, 54%).

3.7.1. Methyl 2*R*-[*N*-(2,4-dichlorophenoxy)propanoyl]-*R*,*S*-phenylalaninate 15. R_F 0.3 (petroleum ether–ethyl acetate, 2:1); ν_{max} (thin film) 3412 (s), 2959 (m), 1746 (s), 1675 (s), 1521 (s), 1477 (s), 1445 (m), 1283 (s), 1259 (s), 1104 (s) cm^{-1}. *Diastereoisomer 1*: This was indicated by: δ_H (270 MHz, $CDCl_3$) 7.38–7.08 (8H, m, aromatics), 6.94 (1H, d, J=5.5 Hz, N*H*), 4.88 (1H, m, NHC*H*CO), 4.62 (1H, apparent quintet, J=7.0 Hz, OC*H*(CH_3)CO), 3.75 (3H, s, CO_2CH_3), 3.22 (1H, dd,J=14.0 and 5.5 Hz, CH_AH_BPh), 1.60 (3H, d, J=6.5 Hz, CH_3CH). *Diastereoisomer 2*: This was indicated by: δ_H (270 MHz, $CDCl_3$)) 7.38–7.08 (8H, m, aromatics), 6.68 (1H, d, J=9.0 Hz, N*H*), 4.88 (1H, m, NHC*H*CO), 4.62 (1H, apparent quintet, J=7.0 Hz, OC*H*(CH_3)CO), 3.70 (3H, s, CO_2CH_3), 3.02 (1H, dd,J=14.0 and 7.5 Hz, CH_AH_BPh), 1.50 (3H, d, J=6.5 Hz, CH_3CH); δ_C (67.5 MHz, $CDCl_3$) 171.4, 171.3, 170.9, 170.6 (CO_2CH_3 and *C*ON of each diastereomer), 76.3, 76.2 (O*C*H(CH_3)CO), 52.7, 52.6, 52.4, 52.3 (NH*C*HCO and CO_2CH_3), 37.9, 37.7 (CH_2Ph), 18.4, 18.2 (*C*H$_3$*C*H); *m/z* (CI, NH_3) 398 ($^{37,35}M+H^+$,60%), 396 ($^{35}M+H^+$, 100), 362 (MH^+-Cl, 20), 234 (70), 206 (10), 120 (10). Found: $^{35}M+H^+$, 396.0767. $C_{19}H_{20}{}^{35}Cl_2NO_4$ requires for $M+H^+$, 396.0769.

3.7.2. Dimethyl 2,3-bis-[2*R*-(2,4-dichlorophenoxy)propanoylamino]succinate. The presence of this was indicated by: δ_H (270 MHz, $CDCl_3$) 5.52–5.16 (1H, m, NHCH_ACO), 5.13–5.09 (1H, m, NHCH_BCO); *m/z* (CI, NH_3) 628 ($^{35}M+NH_4^+$, 10%), 611 ($^{35}M+H^+$, 100), 575 (10), 447 (40), 378 (20), 285 (20), 214 (30). Found: $^{35}M+H^+$, 609.0363. $C_{24}H_{24}{}^{35}Cl_4N_2O_8$ requires for $M+H^+$, 609.0365.

3.8. Photolysis of (1*S*,2*R*,5*S*)-menthyl *N*-benzoylglycinate 16

(1*S*,2*R*,5*S*)-Menthyl *N*-benzoylglycinate **16**[32] (8.24 g, 25.9 mmol), di-*tert*-butyl peroxide (5.0 equiv., 18.98 g, 23.8 ml, 0.13 mol), benzophenone (5.0 equiv., 23.57 g, 0.13 mol) and toluene (10.0 equiv., 23.92 g, 27.7 ml, 0.26 mol) in benzene (149 ml) were photolysed using a 400 W lamp. After 12 h irradiation, the solution was evaporated in vacuo to afford crude product as an orange oil (34.87 g). A small sample (0.94 g, 2.7% of crude mass) was purified by column chromatography (silica; petroleum ether–ethyl acetate, 15:1) to afford (1*S*,2*R*,5*S*)-menthyl *N*-benzoylphenylalaninate **17**[33] (0.097 g, scaled to 0.36 g, 34%, [42% based on recovered **16**]) as an inseparable 1:1.2 mixture of diastereoisomers (from the ^{1}H NMR spectrum) and recovered glycinate **16** (0.044 g, scaled to 1.62 g, 26%).

3.9. Photolysis of 1,4-diacetylpiperazine-2,5-dione 18

1,4-Diacetylpiperazine-2,5-dione **18**[34] (5.15 g, 25.9 mmol), di-*tert*-butyl peroxide (5.0 equiv., 18.98 g, 23.8 ml, 0.13 mol), benzophenone (5.0 equiv., 23.57 g, 0.13 mol) and toluene (10.0 equiv., 23.92 g, 27.7 ml, 0.26 mol) in benzene (149 ml) were photolysed for 12 h. Evaporation of the volatile components afforded an orange oil (39.80 g). A sample (1.51 g, 3.8% by mass) was purified by column chromatography (silica; petroleum ether–diethyl ether, 1:1) to elute 1,4-diacetyl-3-benzylpiperazine-2,5-dione **19**[35] (0.083 g, scaled to 2.19 g, 29%) as a mixture with (±)-*cis*-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione **20**[35,36] (0.016 g, scaled to 0.42 g, 4%) and a mixture of *trans*-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione **20**[35,36] (0.014 g, scaled to 0.37 g, 4%) with 1,4-diacetyl-3-*tert*-butoxypiperazine-2,5-dione **21** (0.016 g, scaled to 0.42 g, 6%).

3.9.1. 3-*tert*-Butoxy-1,4-diacetylpiperazine-2,5-dione 21. The presence of this was confirmed by the following: R_F 0.4 (petroleum ether–diethyl ether, 1:1); δ_H (270 MHz, $CDCl_3$) 6.28 (1H, s, NHC*H*OC$(CH_3)_3$), 5.09 (1H, d, *J*=17.5 Hz, NCH_AH_BCO), 4.31 (1H, d, *J*=17.5 Hz, NCH$_A$$H_B$CO), 2.54 (3H, s, C$H_3$CO), 2.52 (3H, s, C$H_3$CO), 1.28 (9H, s, C$(CH_3)_3$); *m/z* (CI, NH_3) 288 ($M+NH_4^+$, 100%), 271 ($M+H^+$, 30). Found: $M+H^+$, 271.1292. $C_{12}H_{18}N_2O_5$ requires for $M+H^+$, 271.1294.

3.10. General procedure for photolysis of 8a in the presence of substituted toluenes and related compounds

To the pyrex reaction vessel of the 400 W lamp was added methyl *N*-benzoylglycinate **8a** (5.00 g, 25.9 mmol) and benzene (133–176 ml). The solution was degassed and agitated to aid the dissolving process by use of a steady stream of dry nitrogen passing through the gas inlet (0.5 h). After this period, di-*tert*-butyl peroxide (5.0 equiv., 18.98 g, 23.8 ml, 0.13 mol), benzophenone (5.0 equiv., 23.57 g, 0.13 mol) and the toluene, diphenylmethane or fluorene (10.0 equiv., 0.26 mol) were added to give in all cases, homogenous solutions. The quartz immersion well was inserted along with the lamp and photolysis proceeded for 12 h. The water flow was regulated to maintain the temperature of the reaction mixture between 25–40°C. Upon completion the lamp was extinguished and allowed to cool for 0.5 h. The lamp was then removed and the resultant orange solution transferred to a round-bottomed flask and the solvent removed in vacuo to leave an orange sticky liquid (20.39–71.69 g) from which a small sample was purified by column chromatography on silica.

3.10.1. Methyl *N*-benzoyl-2-fluorophenylalaninate 25. White solid; mp 119–120°C (lit.,[22b] 111–112°C); R_F 0.5 (petroleum ether–ethyl acetate, 1:1); ν_{max} ($CHCl_3$) 3327 (w), 1744 (s), 1648 (s), 1581 (w), 1531 (s), 1490 (s), 1445 (m), 1281 (s), 1235 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73–7.70 (2H, m, *ortho*-H aromatics), 7.56–6.99 (7H, m, aromatics), 6.78 (1H, br d, *J*=7.5 Hz, N*H*), 5.06 (1H, dt, *J*=7.5 and 6.0 Hz, NHC*H*CO), 3.75 (3H, s, CO_2CH_3), 3.33 (1H, dd, *J*=15.0 and 6.0 Hz, NHCH_AH_BAr), 3.26 (1H, dd,*J*=15.0 and 6.0 Hz, NHCH$_A$$H_B$Ar); δ_F (254 MHz, $CDCl_3$) −117.6 (1F, s, CH=C*F*); δ_C (67.5 MHz, $CDCl_3$) 171.9 (CO_2CH_3), 166.9 (*C*ON), 161.2 (d, ^1J=243.0 Hz, *C*F), 133.7 (*C*–C=O), 131.7 (d, ^3J=4.0 Hz, *C*–CH=CH–CF), 131.7 (*C*=CH–CH=C–CO), 129.0 (d, ^3J=8.0 Hz, *C*H–CH=CF), 128.5, (*C*H=C–CO), 127.1 (*C*H–CH=C–CO), 124.1 (d, ^4J=4.0 Hz, FC–CH=CH–CH), 122.9 (d, ^2J=16.0 Hz, FC=*C*), 115.3 (d, ^2J=22.0 Hz, FC=*C*H), 52.8 (NH*C*HCO), 52.4 (CO_2CH_3), 31.3 (CH*C*H$_2$Ar); *m/z* (CI, NH_3) 302 ($M+H^+$, 100%), 180 (20), 122 (10), 105 (50), 77 (10). Found: $M+H^+$, 302.1187. $C_{17}H_{16}FNO_3$ requires for $M+H^+$, 302.1192.

3.10.2. Methyl *N*-benzoyl-4-fluorophenylalaninate 26. White solid; mp 79–80°C (lit.,[22b] 96–97°C); R_F 0.15 (petroleum ether–diethyl ether, 1:1); ν_{max} ($CHCl_3$) 3433 (w), 3022 (w), 3009 (w), 1740 (m), 1662 (s), 1511 (s), 1486 (w), 1219 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.74–7.71 (2H, apparent d, *J*=7.0 Hz, *ortho*-H aromatics), 7.56–7.40 (3H, m, aromatics), 7.12–6.93 (4H, m, aromatics), 6.64 (1H, br d, *J*=7.0 Hz, N*H*), 5.07 (1H, dt, *J*=7.0 and 5.5 Hz, NHC*H*CO), 3.77 (3H, s, CO_2CH_3), 3.29 (1H, dd, *J*=14.0 and 5.5 Hz, NHCH_AH_BAr), 3.19 (1H, dd,*J*=14.0 and 5.5 Hz, NHCH$_A$$H_B$Ar); δ_F (254 MHz, $CDCl_3$) −115.4 (1F, s, CH=C*F*); δ_C (67.5 MHz, $CDCl_3$) 171.9 (CO_2CH_3), 166.7 (*C*ON), 162.0 (d, ^1J=245.0 Hz, *C*F), 133.7 (*C*–C=O), 131.8 (*C*=CH), 131.6 (d, ^4J=11.0 Hz, *C*–CH=CH–CF), 130.8 (d, ^3J=8.0 Hz, *C*H–CH=CF), 128.6, 126.9 (*C*H=C), 115.6 (d, ^2J=22.0 Hz, FC=*C*), 53.5 (NH*C*HCO), 52.5 (CO_2CH_3), 37.1 (CH*C*H$_2$Ar); *m/z* (CI, NH_3) 302 ($M+H^+$, 100%), 180 (20), 122 (10), 105 (30). Found: $M+H^+$, 302.1187. $C_{17}H_{16}FNO_3$ requires for $M+H^+$, 302.1192.

3.10.3. Methyl *N*-benzoyl-2-chlorophenylalaninate 27. Colourless oil; R_F 0.2 (petroleum ether–ethyl acetate, 3:1); ν_{max} ($CHCl_3$) 3466 (br, m), 3066 (w), 2976 (w), 2955 (w), 1749 (s), 1664 (s), 1524 (s), 1484 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73 (2H, d, *J*=7.0 Hz, aromatics), 7.71–7.17 (7H, m, aromatics), 6.78 (1H, d, *J*=7.5 Hz, N*H*), 5.10 (1H, dt,*J*=7.5 and 6.0 Hz, NHC*H*CO), 3.75 (3H, s, CO_2CH_3), 3.43 (1H, dd, *J*=14.0 and 6.0 Hz, CH_AH_BAr), 3.33 (1H, dd, *J*=14.0 and 6.0 Hz, CH$_A$$H_B$Ar); δ_C (67.5 MHz, $CDCl_3$) 172.0 (CO_2CH_3), 166.9 (*C*ON), 134.3, 134.1, 133.6 (*C*=CH), 132.0, 131.7, 131.3, 129.4, 128.6, 128.4, 127.6 (C=*C*H), 52.9 (NH*C*HCO), 52.6 (CO_2CH_3), 35.3 (*C*H$_2$Ar); *m/z* (CI, NH_3) 320 ($^{37}M+H^+$,

30%), 318 ($^{35}M+H^+$, 100), 282 (10), 194 (10), 161 (10), 122 (10), 105 (20). Found: $^{35}M+H^+$, 318.0893. $C_{17}H_{16}{}^{35}ClNO_3$ requires for $M+H^+$, 318.0897.

3.10.4. Methyl *N*-benzoyl-3-chlorophenylalaninate 28. White solid; mp 91–94°C; R_F 0.7 (petroleum ether–ethyl acetate, 1:1); ν_{max} (thin film) 3419 (w), 3324 (m), 3061 (w), 2953 (m), 2929 (w), 1745 (vs), 1660 (vs), 1646 (vs), 1602 (m), 1578 (m), 1525 (s), 1484 (s), 1440 (m), 1360 (w), 1266 (m), 1216 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.93–7.72 (2H, m, aromatics), 7.60–7.00 (6H, m, aromatics), 6.69 (1H, br d, J=7.5 Hz, NH), 5.08 (1H, dt, J=7.5 and 5.5 Hz, NHCHCO), 3.77 (3H, s, CO_2CH_3), 3.28 (1H, dd, J=14.0 and 6.0 Hz, CH_AH_BAr), 3.19 (1H, dd, J=14.0 and 6.0 Hz, CH_AH_BAr); δ_C (67.5 MHz, $CDCl_3$) 171.8 (CO_2CH_3), 167.0 (Ph*C*ON), 138.0, 134.4, 133.6 (*C*=CH), 131.9, 129.8, 129.5, 128.7, 127.5, 127.4, 127.2, 127.0 (C=*C*H), 53.4 (NH*C*HCO), 52.6 (CO_2CH_3), 37.6 (CH_2Ar); *m/z* (CI, NH_3) 320 ($^{37}M+H^+$, 30%), 318 ($^{35}M+H^+$, 100), 284 (20), 122 (10), 105 (10). Found: $^{35}M+H^+$, 318.0897. $C_{17}H_{16}{}^{35}ClNO_3$ requires for $^{35}M+H^+$, 318.0897.

3.10.5. Methyl *N*-benzoyl-4-chlorophenylalaninate 29. White solid; mp 100–102°C (lit.,[2e] 98–99°C); R_F 0.62 (petroleum ether–ethyl acetate, 1:1); ν_{max} ($CHCl_3$) 3424 (m), 3361 (m), 3303 (m), 2951 (w), 1741 (s), 1653 (s), 1529 (m), 1444 (m), 1356 (w), 1298 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.74–7.71 (2H, m, aromatics), 7.58–7.19 (5H, m, aromatics), 7.05 (2H, d, J=8.5 Hz, ClCC*H*=CH or ClCCH=CH–C*H*), 6.66 (1H, d, J=7.5 Hz, N*H*), 5.07 (1H, dt, J=7.5 and 5.5 Hz, NHC*H*CO), 3.76 (3H, s, CO_2CH_3), 3.29 (1H, dd, J=14.0 and 6.0 Hz, CH_AH_BAr), 3.18 (1H, dd, J=14.0 and 6.0 Hz, CH_AH_BAr); δ_C (67.5 MHz, $CDCl_3$) 171.8 (CO_2CH_3), 166.8 (Ph*C*ON), 133.6, 132.0, 131.8 (*C*=CH), 130.6, 128.6, 128.6, 127.1, 126.9 (C=*C*H), 53.4 (NH*C*HCO), 52.4 (CO_2CH_3), 37.1 (CH_2Ar); *m/z*(CI, NH_3) 320 ($^{37}M+H^+$, 30%), 318 ($^{35}M+H^+$, 100), 196 (20), 122 (10), 105 (10), 49 (10). Found: $^{35}M+H^+$, 318.0896. $C_{17}H_{16}{}^{35}ClNO_3$ requires for $^{35}M+H^+$, 318.0897.

3.10.6. Methyl *N*-benzoyl-4-methylphenylalaninate 30. R_F 0.2 (petroleum ether–ethyl acetate, 3:1+1% toluene); ν_{max} (thin film) 3422 (br, w), 3337 (br, w), 2952 (w), 1744 (s), 1646 (s), 1579 (w), 1533 (s), 1520 (s), 1488 (m), 1442 (m), 1216 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75–7.72 (2H, m, aromatics), 7.60–7.26 (3H, m, aromatics), 7.10 (2H, d, J=8.0 Hz, 2×CH_3C–C*H*=CH), 7.02 (2H, d,J=8.0 Hz, 2×CH_3–CH=C*H*), 5.07 (1H, dt,J=7.5 and 5.5 Hz, NHC*H*CO), 3.77 (3H, s, CO_2CH_3), 3.26 (1H, dd, J=14.0 and 5.5 Hz, CH_AH_BAr), 3.19 (1H, dd, J=14.0 and 5.5 Hz, CH_AH_BAr), 2.32 (3H, s, CH_3C=CH); δ_C (67.5 MHz, $CDCl_3$) 172.3 (CO_2CH_3), 167.0 (*C*ON), 137.0, 134.1, 132.8 (*C*=CH), 132.0, 129.2, 128.9, 128.5, 127.2 (C=*C*H), 53.6 (NH*C*HCO), 52.7 (CO_2CH_3), 37.6 (CH_2Ar); *m/z* (CI, NH_3) 298 ($M+H^+$, 100%), 194 (10), 176 (20), 105 (20). Found: $M+H^+$, 298.1439. $C_{18}H_{19}NO_3$ requires for $M+H^+$, 298.1443.

3.10.7. Methyl *N*-benzoyl-4-phenylphenylalaninate 31. White solid; mp 130–132°C; R_F 0.5 (petroleum ether–ethyl acetate, 3:1); ν_{max} ($CHCl_3$) 3423 (w), 3053 (s), 2985 (m), 1741 (m), 1662 (m), 1542 (m), 1485 (m), 1440 (m), 1424 (m), 1264 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.76–7.73 (2H, m, *ortho*-H aromatics), 7.59–7.19 (12H, m, aromatics), 6.65 (1H, d, J=7.5 Hz, N*H*), 5.14 (1H, dt,J=7.5 and 5.5 Hz, NHC*H*CO), 3.79 (3H, s, CO_2CH_3), 3.34 (1H, dd, J=14.0 and 5.5 Hz, CH_AH_BAr), 3.27 (1H, dd, J=14.0 and 5.5 Hz, CH_AH_BAr); δ_C (67.5 MHz, $CDCl_3$) 172.0 (CO_2CH_3), 166.8 (N*C*O), 140.6, 140.0, 134.8, 133.8 (*C*=CH), 131.8, 129.7, 128.7, 128.6, 127.3, 126.9, 126.8, 126.7 (C=*C*H), 53.5 (NH*C*HCO), 52.5 (CO_2CH_3), 37.5 (CH_2Ar); *m/z* (CI, NH_3) 360 ($M+H^+$, 100%), 238 (10), 208 (10), 167 (10), 122 (10), 105 (10). Found: $M+H^+$, 360.1589. $C_{23}H_{21}NO_3$ requires for $M+H^+$, 360.1600.

3.10.8. Methyl *N*-benzoyl-β-phenylphenylalaninate 32. White solid; mp 134–136°C; R_F 0.1 (dichloromethane–toluene, 10:1); ν_{max} ($CHCl_3$) 3437 (m), 3065 (w), 3031 (w), 2955 (w), 2247 (m), 1739 (s), 1666 (s), 1514 (s), 1484 (s), 1451 (m), 1360 (m), 1227 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.61–7.54 (2H, m, *ortho*-H aromatics), 7.50–7.18 (13H, m, aromatics), 6.40 (1H, br d, J=8.5 Hz, N*H*), 5.60 (1H, t, J=8.5 Hz, NHC*H*CO), 4.60 (1H, d, J=8.5 Hz, Ph_2CH), 3.54 (3H, s, CO_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 171.3 (CO_2CH_3), 166.2 (*C*ON), 140.0, 139.4 (*C*=CH), 128.5, 127.2, 127.1, 24.1 (C=*C*H), 52.8 (CO_2CH_3), 39.3 (NCH_2CO); *m/z* (CI, NH_3) 360 ($M+H^+$, 100%), 194 (100), 183 (60), 167 (40), 122 (40), 105 (70). Found: $M+H^+$, 360.1594. $C_{23}H_{21}NO_3$ requires for $M+H^+$, 360.1600.

3.10.9. Methyl *N*-benzoyl-(9*H*-fluoren-9-yl)glycinate 33. Orange solid; mp 154–156°C; R_F 0.5 (petroleum ether–ethyl acetate, 1:1); ν_{max} ($CHCl_3$) 3434 (w), 3023 (w), 1742 (m), 1665 (s), 1513 (s), 1483 (m), 1448 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.82–7.64 (3H, m, aromatics), 7.48–7.23 (10H, m, aromatics), 5.99 (1H, d, J=9.0 Hz, N*H*), 5.70 (1H, dd, J=9.0 and 3.5 Hz, NHC*H*CO), 4.72 (1H, d, J=3.5 Hz, NHCHC*H*Ar), 3.79 (3H, s, CO_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 171.5 (CO_2CH_3), 167.3 (*C*ON), 142.8, 142.2, 141.1, 141.0, 133.8 (*C*=CH), 131.6, 128.4, 128.0, 127.6, 127.4, 126.8, 126.7, 124.8, 124.7, 120.2, 119.8 (C=*C*H), 54.0 (NH*C*HCO), 52.6 (CO_2CH_3), 49.2 (NHCH*C*HAr$_2$); *m/z* (CI, NH_3) 358 ($M+H^+$, 100%), 326 (10), 236 (10), 194 (20), 162 (10), 122 (10), 105 (20). Found: $M+H^+$, 358.1429. $C_{23}H_{19}NO_3$ requires for $M+H^+$, 358.1443.

3.11. Photolysis of dimethyl 2-(*N*-benzoylamino)-malonate 35

A mixture of malonate **35**[37] (4.55 g, 18.1 mmol), di-*tert*-butyl peroxide (5.29 g, 6.6 ml, 36.2 mmol) and toluene (8.33 g, 9.6 ml, 90.5 mmol) in benzene (184 ml) was photolysed for 12 h using a 400 W lamp. After evaporation in vacuo, the crude product was isolated as an orange oil (8.13 g). A sample (0.98 g, 12.0% of the crude mass) was purified by column chromatography (silica; petroleum ether–ethyl acetate, 2:1) to afford 1,2-diphenylethane (0.211 g), methyl 2-(*N*-benzoylamino)-2-benzylmalonate **36** [0.098 g, 0.817 g upon scale up, 13%, (58% based on recovered malonate)], methyl *N*-benzoylphenylalaninate **11a** [0.017 g, 0.142 g scaled, 3%, (12%)] and starting malonate **35** (0.42 g, scaled up to 3.53 g, 78%).

3.11.1. Dimethyl 2-(*N*-benzoylamino)-2-benzylmalonate 36. Colourless oil; R_F 0.4 (petroleum ether–ethyl acetate, 2:1); ν_{max} ($CHCl_3$) 3419 (m), 3030 (w), 2955 (m), 1744 (s), 1665 (s), 1511 (s), 1480 (s), 1441 (m), 1316 (m), 1284 (s), 1219 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.77–7.74 (2H, m, aromatics), 7.54–7.41 (3H, m, aromatics), 7.25–7.20 (4H, m, aromatics), 7.02–6.98 (2H, m, aromatic and N*H*), 3.84 (6H, s, 2×CO_2CH_3), 3.78 (2H, s, CH_2Ph); δ_C (67.5 MHz, $CDCl_3$) 168.0 (CO_2CH_3), 166.2 (Ph*C*ON), 135.0, 133.3 (*C*=CH), 132.1, 129.8, 128.6, 128.4, 127.3, 127.1 (C=*C*H), 67.4 (CO*C*CO), 53.6 (CO_2CH_3), 38.1 (CH_2Ph); *m/z* (CI, NH_3) 342 ($M+H^+$, 100%), 220 (10), 105 (20). Found: $M+H^+$, 342.1342. $C_{19}H_{19}NO_5$ requires for $M+H^+$, 342.1341.

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