The Preparation of a New "Safety Catch" Ester Linker for Solid-Phase Synthesis

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A new "safety catch" linker for esters has been synthesized on polystyrene resin. This 2-*tert*-butoxyphenol resin **10** may be acylated to give a relatively stable ester that will allow nucleophilic chemistry without reaction at the linking ester group. Removal of the *tert*-butyl group with acid unmasks a highly reactive 2-hydroxyphenyl ester that reacts readily with nucleophiles to cause release of the product from the resin. This sequence has been exemplified by acylating the resin with various bromo acids, carrying out nucleophilic displacements with thiols, phenols, or amines, activating the ester with trifluoroacetic acid and cleaving from the resin with amines to give the (nucleophile) substituted carboxamides in high yield and purity. Kinetic studies with a model ester revealed half-lives for reaction with morpholine of 119 h for the *tert*-butoxyphenyl ester and 1 min for the corresponding phenol.

Introduction

The ester group is one of the most common types of linker used in solid-phase synthesis, linking a substrate to a polymeric support.[1] The types of ester used vary in their reactivity toward nucleophiles from the extremely stable Merrifield[2] and Wang[3] esters to Kaiser's oximino esters used to promote peptide aminolysis.[4] Others, such as polystyrylmethylthiophenoxy esters,[5] are known, but their degree of reactivity has not been quantified beyond the anecdotal. We were interested in designing an ester that would be stable to nucleophiles during the course of a synthesis, but would then be capable of activation to a highly reactive state at the end of a synthesis when release from the resin was required, that is a so-called "safety catch" linker.

The concept of safety catch linkers has been explored widely; for example, Kenner[6] developed a peptide synthesis by coupling amino acids to a sulfonamide resin as a stable acyl sulfonamide that deprotonates in basic conditions and is then stable toward nucleophilic attack. Subsequent N-alkylation of the sulfonamide using diazomethane produces a readily cleavable acyl derivative. This concept was extended later by Ellman's group, who used iodomethane or iodoacetonitrile to activate the sulfonamide linker.[7] The whole concept of safety catch linkers is discussed in James' review.[1]

Aryl esters are reactive toward nucleophiles, but several groups have sought to reduce this reactivity by imposing steric hindrance on the ester group. Thus, ortho benzyloxy[8] and phenacyloxy[9] groups reduce reactivity markedly. Conversely, the introduction of *o*-hydroxy groups into aryl esters increases the reactivity by some degree due to anchimeric assistance of the hydroxy group during reaction with nucleophiles, possibly by stabilization of the tetrahedral intermediate. Cowell and Jones[10] and Merrifield et al.[11] have both, therefore, explored protected *o*-hydroxyphenyl esters as safety catch linkers. The first group used the benzyloxyphenyl ester and released the free phenol by hydrogenolysis, while Merrifield used the *tert*-butoxyphenyl ester and activated proteolytically with trifluoroacetic acid (TFA). He also made mention of application of these latter esters in cyclic peptide synthesis on solid phase, but with no great success and with no details given of the type of linker employed.[11]

We wish to report our sucessful synthesis of a resin-linker-*tert*-butoxyphenol system that is capable of being esterified, is moderately stable to nucleophiles, and that may be activated with TFA to give an extremely reactive *o*-hydroxyphenyl ester which is cleaved rapidly by nucleophiles. For convenience, we have called this "BuPhe" resin. The use of this resin to make simple chemical libraries will also be described.

Results and Discussion

The 2-*tert*-butoxyphenol **3** may be prepared in large quantities from catechol by the route shown in Scheme 1, this being a modification of Merrifield's method.[11] Reaction of **3** (Scheme 2) with diazotized 4-amino benzene sulfonic acid gave a water-soluble azo derivative that, in

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(3) Wang, S.-W. *J. Am. Chem. So.c* **1973**, *95*, 1328.
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(5) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867.
(6) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636−7.
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(8) Jones, J. H.; Young, G. T. *J. Chem. Soc. C* **1968**, 436−41.
(9) Trudelle, Y. *J. Chem. Soc., Chem. Commun.* **1971**, 639−41.
(10) Cowell, R. D.; Jones, J. H. *J. Chem Soc. C* **1971**, 1082−1090.
(11) Mitchell, A. R.; Altaf-Ur Rahman; Merrifield, R. B. *Peptides* **1990**, 39−40; Giralt, E., Andreu, D., Eds.; Escom Science Publishers BV: Leiden, The Netherlands, 1991.

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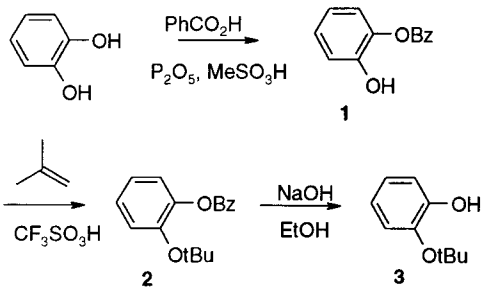
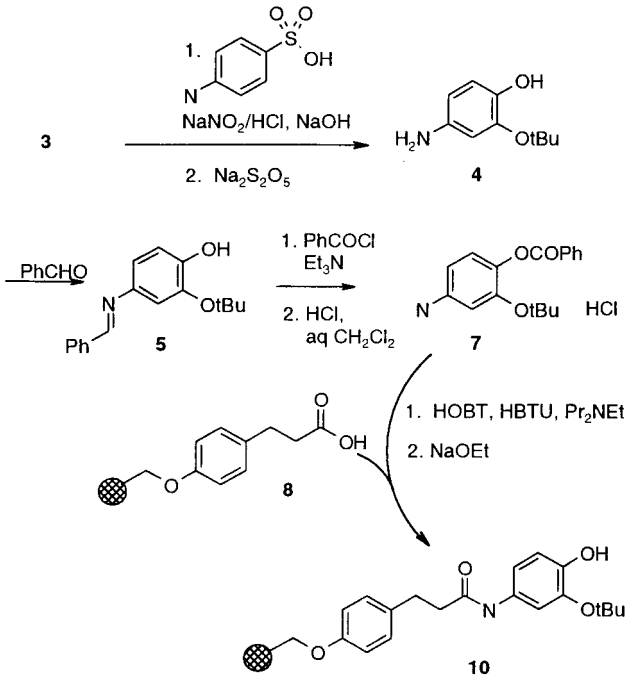
Scheme 1



Scheme 2



situ, was reduced with sodium dithionite to give the amine **4**. This could be extracted from the reaction mixture directly, but it proved advantageous to include benzaldehyde in order to form the Schiff base **5**, in situ, and provide better extraction of the imine, which was also more stable than the aminophenol. Benzoylation, followed by hydrolysis of the imine, gave very pure protected aniline **7**, directly suitable for coupling to the resin bound acid **8**.

This acid **8** was easily prepared from chloromethylpolystyrene and ethyl 4-hydroxyphenyl propionate, followed by hydrolysis with sodium hydroxide. After the aniline **7** was coupled to this resin, the benzoate **9** was converted to free phenol **10** ("BuPhe" resin) using sodium methoxide in methanol/THF. When chloromethylpolystyrene with a loading of 3.6 mmol/g was used, the resulting resin contained approximately 1.8 mmol phenol/g.

Esters of the BuPhe resin **12** could be prepared (Scheme 3) using either acid chlorides or carboxylic acids coupled with 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). Various bromoesters of the resin were prepared, and these were then allowed to react with thiols, phenols, or amines to give the corresponding thioethers, ethers, or amines **13** (X = S, O, N), without cleavage of the ester bond. Activation with TFA to give the phenol **14** was followed by nucleophilic cleavage from the resin using amines, the amide

Scheme 3

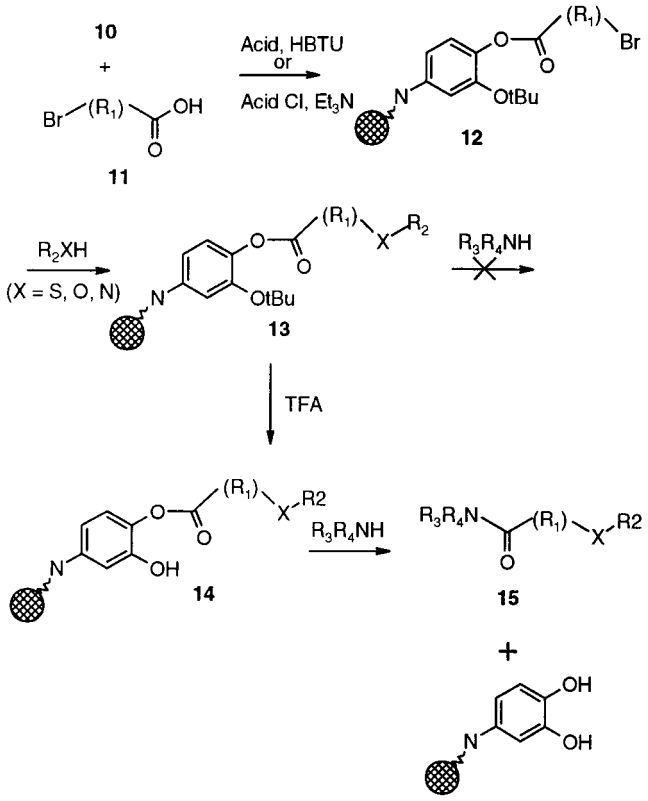
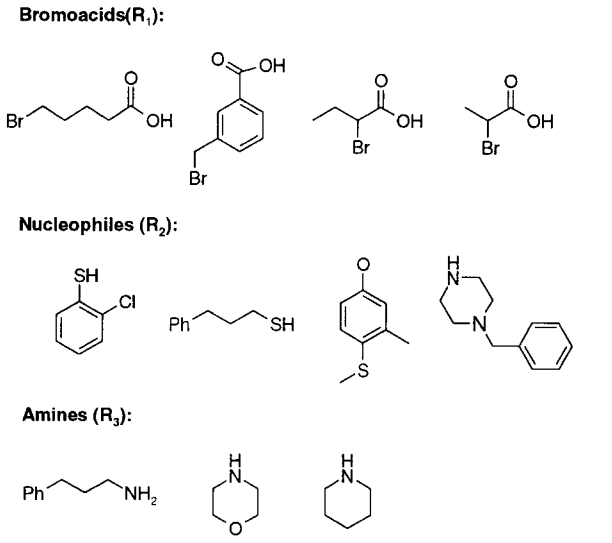


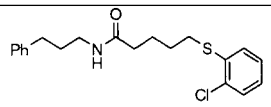
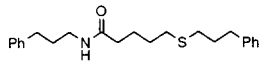
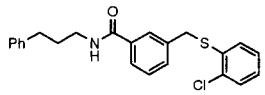
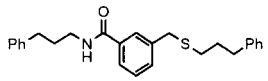
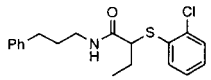
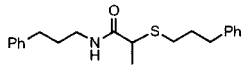
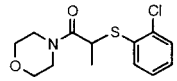
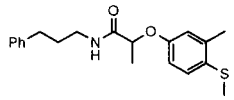
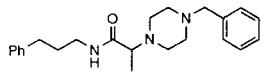
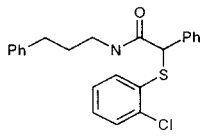
Table 1. Building Blocks Used



products **15** being very pure, typically better than 90%, without any need for purification.

Examples of the building blocks used are shown in Table 1, and as shown in Table 2, the synthesis works with α- and ω-haloesters, along with esters containing a benzyl halide, although reaction of alkanethiols with the unreactive ω-haloesters causes an unacceptably high degree of ester cleavage. Both primary and secondary amines may be used to cleave the activated esters, but anilines do not work under the conditions studied. In many cases, the aminolysis could be performed using a sub-equivalent amount of amine (relative to the loading of ester on the resin), leading to complete loss of amine from the reaction solution; alternatively, a slight excess could be used, followed by treatment of unreacted amine

Table 2. Sample Library

		Crude Yield (%)	Crude Purity (%)	Pure Yield (%)
15a		67	94	63
15b		No Reaction		-
15c		83	65	51
15d		90	94	-[a]
15e		62	88	59
15f		75	97	-[a]
15g		100	90	88
15h		39	73	15
15i		>100	52	69
15j		79	75	50

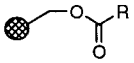
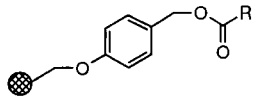
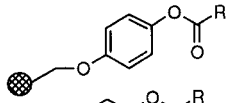
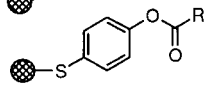
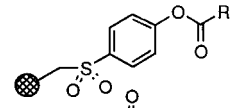
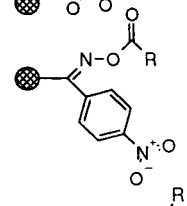
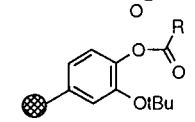
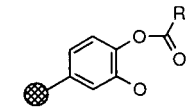
[a] Not purified.

with a scavenger resin[12] such as isocyanatomethyl polystyrene.

Kinetic Studies. To assess more accurately the relative reactivities of our esters, we decided to quantify the reactivity of a series of known esters. To this end, a series of resin bound 4-methoxyphenylacetic esters **16** was prepared (Table 3) and the rate of aminolysis was measured using a 50-fold excess of piperidine. The formation of 4-methoxyphenylacetyl piperidide was quantified using HPLC, using standard solutions for calibration, to determine reaction rate and half-life. Because of the large excess of nucleophile the reactions were assumed to have pseudo-first-order kinetics and were analyzed using the Enzfitter program developed for enzyme kinetics.[13] This allowed calculation of a half-life.

The reactivity of resin-bound esters toward nucleophilic cleavage varies widely, as shown in Table 3. Merrifield esters **16a** are completely inert to the reaction conditions used, and Wang esters **16b** are little different. Various aryl esters show greater reactivity, the degree depending on the electronic character of the resin-phenol link, the most reactive studied being the strongly electron-withdrawing sulfone **16e**, which is 300 times more reactive than the ether **16c**, with the thioether **16d** having intermediate reactivity. The sulfone shows similar reactivity to the ester of Kaiser's oxime **16f**, and both of these are very synthetically useful solid-phase active ester systems, although it would not be possible to do any nucleophilic chemistry on their derivatives without causing cleavage from the resin.

Table 3. Kinetic Studies: Rate of Reaction of Resin-Bound Esters with Morpholine

Resin (R=4-methoxyphenyl)	Name	Half Life (Hr
	Merrifield **(16a)**	No Reaction
	Wang **(16b)**	No Reaction
	Phenoxy **(16c)**	50
	Phenylthio **(16d)**	3.9
	Phenylsulphonyl **(16e)**	0.17
	Kaiser Oxime **(16f)**	0.17
	'BuPhe' - **(16g)** (Non Activated)	119
	'BuPhe' - **(16h)** (Activated)	0.02

The BuPhe resin derivative **16g** is relatively resistant to attack by piperidine, while the corresponding phenol **16h** is more reactive by many orders of magnitude. Useful chemistry can thus be performed without ester cleavage, followed by nucleophilic release from the resin after activation by TFA. We have illustrated this principle above by creating several simple libraries from bromoesters, performing the nucleophilic displacement of the bromine without loss from the resin and then removing the *tert*-butyl group and cleaving the products as amides in very high yield and purity. The residual resin is a catechol and, therefore, cannot be realkylated and reused.

The balance of reactivity of the BuPhe resin esters in the activated vs nonactivated states is governed critically by the electronic nature of the linking group. Thus, the nonactivated ester, with an electron neutral (σ 0) acylamino group in the para position to the phenol group, is 700 times less reactive than the sulfone resin **16e**, with the electron-withdrawing (σ 0.72) group in the same position. It would be possible to make the nonactivated ester more resistant to nucleophilic attack by adding either another ortho substituent, or another electron-

(12) Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101.

(13) Leatherbarrow, R. J 1987 *Enzfitter*, Elsevier Biosoft. For a review, see: Leatherbarrow, R. J. *Trends in Biochemical Science* **1990**, 455−8.

donating group in the ring, but in both cases this would also reduce the reactivity of the ester after activation. We are currently looking at further uses for esters of BuPhe resin.

Experimental Section

^{1}H NMR spectra were determined at 300 MHz, and ^{13}C NMR spectra of resins were determined at 400 MHz as gels using a magic angle spinning probe (Bruker). Mass spectra were determined using positive ion electrospray, and HRMS was also performed using electrospray ionization (Quattro), calibrated with PEG 200/400/600, and looking at peaks within 10 ppm. Evaporations were performed on a rotary evaporator. For resin products combustion analysis proved satisfactory and reproducible for N, S, and halogens, but C and H were too variable to be useful.

2-Hydroxyphenyl Benzoate (1). A mixture of catechol (22 g, 0.20 mol) and benzoic acid (48 g, 0.40 mol) was mixed with polyphosphoric acid (500 g), heated 30 min on a steam bath, and then poured into 1 L of H_2O. The resulting solid was collected, slurried with saturated $NaHCO_3$ (200 mL) twice, and washed with H_2O (2 × 200 mL). After drying, the product was recrystallized from toluene to give 19.6 g (36%) of **1** as a white solid. Mp: 130 °C. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.70; H, 4.81. MS: 215 $(M + H)^+$. ^{1}H NMR (DMSO): δ 6.8 (m, 1H), 7.0 (m, 1H), 7.15 (m, 2H), 7.6 (m, 2H), 7.7 (m, 1H), 8.15 (m, 2H), 9.7 (s, 1H) ppm.

The very viscous polyphosphoric acid mixture is difficult to stir on a large scale and may be substituted by Eaton's reagent (10% P_2O_5 in $MeSO_3H$) using 40 mL/g of catechol and stirring for 3 h at ambient temperature. A similar work up gives a rather oily product which is best purified by flash chromatography using CH_2Cl_2 to give a 35−40% yield of product.

2-*tert*-Butoxyphenyl Benzoate (2). The phenol **1** (21.4 g, 0.10 mol) was dissolved in 200 mL of CH_2Cl_2 and cooled to −40 °C under an argon atmosphere. Isobutene (56 g, 1.0 mol) was added over 1 h and the mixture cooled to −50 °C. Trifluoromethanesulfonic acid (0.5 mL) was added carefully (mild exotherm) and the reaction stirred for 2.5 h at −45 to −50 °C. Triethylamine (Et_3N, 0.8 mL) was then added to quench the reaction, and it was allowed to warm to rt overnight. Evaporation of the solvent gave the product **2** as an oil (27 g, 100%), which was not purified. A small sample was purified on silica gel using 10% EtOAc/isohexane to give pure **2** as a colorless oil that crystallized on standing. Mp: 63 °C. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.01; H, 6.66. MS: 271 $(M + H)^+$. ^{1}H NMR (DMSO): δ 1.2 (s, 9H), 7.1−7.3 (m, 4H), 7.6−7.8 (m, 3H), 8.1 (d, 2H) ppm.

2-*tert*-Butoxyphenol (3). The ester **2** (27 g, 0.10 mol) was dissolved in EtOH (240 mL), and aqueous NaOH (40%, 14 mL) was added (slight exotherm). The solution was refluxed 45 min, 15 mL of water added, and then the mixture was refluxed a further 5 h. After cooling, the suspension was diluted with 30 mL of water and the solution evaporated to a dark oil. This was shaken with water (220 mL) and isohexane (220 mL) with the pH adjusted to 9 with AcOH. The extracts were dried ($MgSO_4$) and evaporated. The resulting oil was purified on a 70 g silica gel column using 5−10% EtOAc/isohexane, giving 15.3 g (92%) of pure **3** (alternatively the product may be distilled, bp 60 °C/0.4 mmHg). Overall yield was 33% from catechol. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.53. MS: 167 $(M + H)^+$. ^{1}H NMR (DMSO): δ 1.3 (s, 9H), 6.7 (m, 1H), 6.8−7.8 (m, 3H), 8.6 (s, 1H) ppm.

4-Amino-2-*tert*-butoxyphenol, Benzaldehyde Imine (5). A mixture of sulfanilic acid (57.15 g, 0.33 mol), Na_2CO_3 (17.49 g, 0.165 mol), and H_2O (600 mL) was stirred and cooled to 0 °C. $NaNO_2$ (22.77 g, 0.33 mol) was added, followed by 5.5 M HCl (165 mL), added below the liquid surface over 30 min at 4−9 °C. After being stirred for a further 30 min at 0 °C, the reaction mixture was poured into a (previously prepared and cooled to 0 °C) solution of 2-*tert*-butoxyphenol (50.0 g, 0.30 mol) in 10% NaOH (375 mL). After 5 min at 0 °C, the deep red solution was stirred for a further 1 h and allowed to warm to rt. At this stage, if desired, the reaction could be purged with argon and kept overnight before proceeding. Aqueous NaOH solution (40%, 50 mL) was now added, the reaction heated to 90 °C, and $Na_2S_2O_4$ (126.3 g, 0.726 mol) added portionwise at a rate to control both exotherm and effervescence until the red color was discharged (sometimes slightly more or less than the above amount). After cooling, the pH was adjusted to 7 with a little HCl, benzaldehyde (30.5 mL, 0.30 mol) was added, and the mixture stirred vigorously for 30 min. The resulting imine was extracted into CH_2Cl_2 (1 × 400 mL, 2 × 200 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give **5** as a crude brown solid, wt 57.14 g, 71% yield. The product proved too unstable to purify but MS showed a peak at 270 $(M + H)^+$, and ^{1}H NMR ($CDCl_3$) showed the expected peaks at δ 1.46 (s, 9H), 5.73 (s, 1H), 6.97 (m, 3H), 7.45 (m, 3H), 7.90 (m, 2H), 8.44 (s, 1H) ppm.

4-Amino-2-*tert*-butoxyphenyl Benzoate, Benzaldehyde Imine (6). Phenol **5** (57.0 g, 0.21 mol) was dissolved in CH_2Cl_2 (550 mL) and cooled to 0 °C. Et_3N (87.6 mL, 0.63 mol) was added, followed by dropwise addition of benzoyl chloride (26.4 mL, 0.21 mol) in CH_2Cl_2 (100 mL) over 1 h. The reaction was then allowed to warm to rt. After 1 h, the reaction was poured into H_2O (1 L) with rapid stirring for 30 min, the CH_2Cl_2 layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 250 mL). The combined extracts were dried and evaporated to give a light brown solid, 80.09 g (>100% yield). This was dissolved in the minimum amount of CH_2Cl_2 and passed down a column of alumina (ICN Alumina N, Ak. I), 175 mm bed on a 70 mm diameter column. Elution with 5% EtOAc/isohexane, followed by evaporation, gave a yellow solid, wt 61.15 g (78% yield). MS: 374 $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H), 6.97 (dd, 1H), 7.04 (d, 1H), 7,20 (d, 1H), 7.47 (m, 5H), 7.62 (m, 1H), 7.92 (m, 2H), 8.22 (m, 2H), 8.46 (s, 1H) ppm.

4-Amino-2-*tert*-butoxyphenyl Benzoate (7). The imine **6** (61.08 g, 0.164 mol) was dissolved in CH_2Cl_2 (620 mL) and the mixture stirred vigorously with a paddle stirrer. HCl (2 M, 620 mL) was added and the stirring continued for 1.25 h, adding a further 400 mL of CH_2Cl_2 after 45 min. Vigorous mixing of the two layers was essential. The white solid that separated was collected, washed with EtOAc (3 × 100 mL), sucked as dry as possible, and then dried under vacuum at rt to give **7** as an almost white solid, wt 38.63 g (73% yield). MS: 286 $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9H), 7.03 (dd, 1H), 7.23 (s, 1H), 7.34 (d, 1H), 7.61 (t, 2H), 7.77 (t, 1H), 8.12 (d, 2H) ppm. The product did not analyze well, and so a portion was converted to the free base using $NaHCO_3$/EtOAc extraction, and the resulting solid was analyzed. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.35; H, 6.61; N, 4.92.

4-(Carboxyethyl)phenoxymethyl Polystyrene (8). Chloromethylpolystyrene resin (Polymer Labs, 150−300 μm, 3.47 mmol/g, 20 g, 69.4 mmol) was shaken in DMF (200 mL), and ethyl 3-(4-hydroxyphenyl)propionate (16.85 g, 87 mmol) was added, followed by NaOMe (5.06 g, 94 mmol). The mixture was shaken 24 h at 50 °C, cooled, and filtered. The resin was washed with DMF (3 × 200 mL), THF (1 × 200 mL), 50% aqueous THF (3 × 200 mL), THF (3 × 200 mL), MeOH (3 × 200 mL), and Et_2O (3 × 200 mL) before drying under vacuum. The product weighed 29.54 g (95% theoretical) with no detectable Cl by microanalysis.

This resin was suspended in THF (300 mL), 10% aqueous NaOH (40 mL, 0.10 mol) was added, and the mixture was shaken 18 h at 40 °C. After cooling, the mixture was filtered, and the resin was washed with THF (3 × 300 mL), 50% aqueous THF (2 × 300 mL), 1:1 THF/2 M HCl (2 × 300 mL), 50% aqueous THF (2 × 300 mL), THF (3 × 300 mL), MeOH (3 × 300 mL), and Et_2O (3 × 300 mL) before drying under vacuum to give 29.18 g resin (theory 29.02 g). FT-IR ($CHCl_3$ gel): C═O 1713 cm^{-1}. ^{13}C NMR ($CDCl_3$): δ 29.79, 35.79, 69.84, 157.38, 179.06 ppm.

4-(Polystyrylmethoxy)phenylpropionic Acid (4-Benzoyloxy-3-*tert*-butoxy)anilide (9). The resin **8** (50 g, 0.09 mol) was swollen in dry *N*-methylpyrrolidone (NMP, 400 mL) under an argon atmosphere, HBTU (37.5 g, 0.10 mol), HOBT (13.4 g, 0.10 mol), and DIPEA (33.9 mL, 25.15 g, 0.20 mol)

were added, and the mixture was shaken for 1 h at 50 °C. The aniline hydrochloride **7** (31.8 g, 0.10 mol) was then added and shaking continued for 20 h at 50 °C. After cooling, the reaction was filtered and the product washed with NMP/H_2O (90/10, 2 × 400 mL), THF (3 × 400 mL), 50% aqueous THF (3 × 400 mL), THF (3 × 400 mL), MeOH (3 × 400 mL), and Et_2O (3 × 400 mL) before drying under vacuum. The whole procedure was then repeated (double coupling) and resulted in a pale beige resin, wt 73.9 g (theory 73.9 g). FT-IR: C═O 1686 and 1732 cm^{-1}. Anal. N calcd as 2.04% for 1.46 mmol/g, found 1.91%, equals 1.37 mmol/g. ^{13}C NMR ($CDCl_3$): δ 28.5, 30.4, 35.7, 68.8, 80.3, 114.5, 115.0, 122.3, 136.2, 140.6, 146.9, 157.2, 165.1, 171.1 ppm.

4-(Polystyrylmethoxy)phenylpropionic Acid (4-Hydroxy-3-*tert*-butoxy)anilide (10) "BuPhe" Resin. The resin **9** (73.9 g, 0.09 mol) was shaken with THF (1200 mL), and saturated NaOMe in MeOH (76 mL) was added over 0.5 h. The reaction was stirred for 4 h and filtered, and the product was washed with 50% aqueous THF (3 × 400 mL), THF/1 M HCl (50/50, 3 × 400 mL), 50% aqueous THF (3 × 400 mL), THF (3 × 400 mL), MeOH (3 × 400 mL), and Et_2O (3 × 400 mL) before drying under vacuum. The light brown resin weighed 65.45 g (theory 64.64 g). FT-IR ($CHCl_3$ gel): C═O 1660 cm^{-1}, OH 3520 cm^{-1}. Anal. for N calcd as 2.41% for 1.72 mmol/g, found, 2.12%, equals 1.55 mmol/g. ^{13}C NMR ($CDCl_3$): δ 29.4, 30.6, 35.7, 69.8, 80.6, 114.4, 114.6, 115.5, 116.0, 129.1, 141.7, 145.0, 146.4, 157.2, 171.1 ppm.

General Procedure for Coupling of BuPhe Resin with Bromoacids. A typical procedure is as follows using 2-bromopropionic acid:

(a) Via the Acid Chloride. The resin **10** (2.8 g, 5.0 mmol) was stirred in CH_2Cl_2 (35 mL) under an argon atmosphere, and Et_3N (2.78 mL, 2.02 g, 20 mmol) was added, followed by 2-bromopropionyl chloride (2.02 mL, 3.43 g, 20 mmol), in CH_2Cl_2 (15 mL) added over 30 min (exotherm), keeping the temp below 25 °C. The mixture was shaken for 6 h at rt, filtered, and washed with CH_2Cl_2 (3 × 30 mL), THF (3 × 30 mL), 50% aqueous THF (3 × 30 mL), THF (3 × 30 mL), MeOH (3 × 30 mL), and Et_2O (3 × 30 mL), before drying under vacuum to give a light brown free flowing resin, wt 3.7 g. Microanalysis gave N, 1.8%, Cl, trace, Br, 10.8%, from which the loading was 1.35 mmol/g (theory 1.35). FT-IR: OH absent, C═O 1804 cm^{-1}. ^{13}C NMR (THF-d_8): δ 20.8, 29.1, 31.4, 36.4, 40.7, 70.6, 80.6, 113.9, 115.4, 122.9, 130.0, 134.4, 138.0, 138.8, 148.3, 158.4, 168.6, 171.2 ppm.

(b) Via the Acid. 2-Bromopropionic acid (25.56 mL, 43.45 g, 0.284 mol) was stirred in CH_2Cl_2 (400 mL) under an argon atmosphere. Diisopropylcarbodiimide (3.88 mL, 35.9 g, 0.284 mol) was added slowly, keeping the temperature below 10 °C, and the mixture was then shaken 2 h. The resin **10** (40 g, 56.8 mmol) was added to the mixture, followed by 4-(dimethylamino)pyridine (DMAP, 1.73 g, 0.14 mmol), and the reaction was shaken for 24 h at rt. The resin was filtered and then washed with DMF (3 × 300 mL), THF (3 × 300 mL), 50% aqueous THF (3 × 300 mL), THF (3 × 300 mL), MeOH (3 × 300 mL), and Et_2O (3 × 300 mL) before drying under vacuum to give a light brown free-flowing resin, wt 47.67 g. Microanalysis gave N, 1.59%, Br, 8.89%, from which the loading was 1.12 mmol/g (theory 1.19). FT-IR, ^{13}C NMR both as **(a)**.

BuPhe Resin, Ester with 2-(2-Chlorophenylthio)propionic Acid 13 (R_1 = CHMe, R_2XH = 2-Cl-C_6H_4SH). The resin **12** (R1 = CHMe, 1.0 g, 1.24 mmol) was added to a prestirred mixture of 2-chlorothiophenol (2.89 g, 2.0 mmol), diisopropylethylamine (320 μL, 240 mg, 1.86 mol), and KI (206 mg, 1.86 mmol) in NMP (10 mL) under an argon atmosphere and the reaction shaken for 24 h at rt. The resin was filtered, washed with NMP (3 × 15 mL), THF (3 × 15 mL), 50% aqueous THF (3 × 15 mL), THF (3 × 15 mL), MeOH (3 × 15 mL), and Et_2O (3 × 15 mL) before drying under vacuum to give a light yellow-brown free-flowing resin, wt 1.20 g. Microanalysis gave N, 1.6%, Br, 0%, S, 3.2%, Cl, 3.7% from which the mean loading was 1.06 mmol/g (theory 1.07). FT-IR (CH_2Cl_2 gel): C═O 1737 cm^{-1}. ^{13}C NMR ($CDCl_3$): δ 15.8, 29.1, 41.5, 44.3, 113.9, 115.4, 123.1, 126.3, 129.4, 130.0, 130.7, 133.7, 134.3, 136.3, 138.5, 140.3, 146.1, 148.4, 158.4, 170.5, 171.2 ppm.

2-(2-Chlorophenylthio)propionic Acid Morpholide 15g (R_1 = CHMe, X = S, R_2 = 2-Cl-Ph, R_3 = $(CH_2)_2O(CH_2)_2$, R_4 = H). The resin **13** (R_1 = CHMe, R_2XH = 2-Cl-C_6H_4SH, 1.20 g, 1.27 mmol) was treated with 10% trifluoroacetic acid (TFA) in CH_2Cl_2 (25.0 mL) and triisopropylsilane (TIPS, 600 μL) for 0.5 h. The resin was filtered and washed with CH_2Cl_2 (2 × 15 mL), 10% Et_3N in THF (2 × 15 mL), and THF (3 × 15 mL), suspended in THF (15 mL), and morpholine (1.0 mL, 11.5 mmol) was added. After shaking for 18 h, the suspension was filtered and evaporated to give 365 mg of crude product (100% yield), 90% pure by HPLC, purified by flash chromatography (CH_2Cl_2) to give 319 mg (88%) of pure product. A portion of this was triturated with isohexane, when white crystals were formed; they were collected, washed, and dried. Anal. Calcd for $C_{13}H_{16}ClNO_2S$: C, 54.64; H, 5.64; N, 4.90; S, 11.22. Found: C, 54.53; H, 5.65; N, 4.75; S, 11.20. MS: 286 $(M + H)^+$. ^1H NMR: δ 1.4 (d, 3H), 3.3−3.7 (m, 8H), 4.1 (q, 1H), 7.15 (m, 2H), 7.4 (dd, 1H), 7.5 (dd, 1H) ppm.

2-(4-Methylthio-3-methylphenoxy)propionic Acid (3-Phenylpropyl)amide (15h, R_1 = CHMe, X = O, R_2 = 4-MeS-3-Me-Ph, R_3 = $Ph(CH_2)_3$, R_4 = H). Under argon, cesium carbonate (1.076 g, 3.3 mmol) and 4-(methylthio)-3-methylphenol (254 mg, 1.65 mmol) were shaken in dry NMP (10 mL) for 1 h. Resin **13** (R = CHMe) (500 mg, 0.55 mmol) was added and the mixture shaken for 5 h. The resin was filtered, washed with H_2O (3 × 20 mL), THF (3 × 20 mL), and MeOH (3 × 20 mL), and dried to give a brown resin, wt 445 mg. Anal. Calcd for 1.02 mmol/g: N, 1.42; Br, absent; S, 3.26. Found: N, 1.81; Br, <0.3; S, 1.41; corresponding to 0.44 mmol/g (some cleavage from resin).

This resin (365 mg, ca. 0.16 mmol) was shaken with TFA/CH_2Cl_2 (5 mL of 10%) and TIPS (150 μL) for 30 min and washed with CH_2Cl_2 (3 × 10 mL), 1 M Et_3N/CH_2Cl_2 (3 × 10 mL) and THF (3 × 10 mL). DMSO (5 mL) was added, followed by 3-phenylpropylamine (217 μL, ca. 3 equiv based on original resin), and the reaction was shaken for 18 h at 50 °C. The mixture was filtered, washed with DMSO (10 mL), and evaporated to give 86 mg (39%) of crude product, 73% pure by HPLC. This was purified by flash chromatography (gradient of 2−10% EtOAc/isohexane) to give 26 mg of product (15%) as a brown oil. MS: 344 $(M + H)^+$. HRMS: calcd 344.1684, found 344.1696 (+3.4 ppm). ^1H NMR ($CDCl_3$): δ 1.5 (d, 3H), 1.85 (m, 2H), 2.32 (s, 3H), 2.4 (s, 3H), 2.55 (t, 2H), 3.3 (m, 2H), 4.65 (m, 1H), 6.4 (br s, 1H), 6.75 (m, 2H), 7.1−7.3 (m, 6H) ppm.

2-[1-(4-Benzyl)piperazinyl]propionic Acid (3-Phenylpropyl)amide 15i (R1 = CHMe, X = 1-(4-Benzyl)piperazine, R_3 = $Ph(CH_2)_3$, R_4 = H). Under argon, DIPEA (144 uL, 0.825 mmol) was added to a mixture of resin **13** (R = CHMe) (500 mg, 0.55 mmol), KI (137 mg, 0.825 mmol), and 1-benzylpiperazine (144 μL, 0.825 mmol) in dry NMP (5 mL). The reaction mixture was shaken for 18 h at rt, washed with NMP (3 × 10 mL), 50% aqueous THF (3 × 10 mL), THF (3 × 10 mL), and MeOH (3 × 10 mL), and dried to give 520 mg of resin. Anal. Calcd for 1.0 mmol/g: N, 4.20; Br absent. Found: N, 4.51; Br, <0.3.

This resin (300 mg, ca. 0.30 mmol) was shaken in 10% TFA/CH_2Cl_2 (5 mL) and TIPS (150 μL) for 30 min. The resin was filtered and then washed with CH_2Cl_2 (3 × 10 mL), 1 M Et_3N in CH_2Cl_2 (3 × 10 mL), and THF (3 × 10 mL). THF (5 mL) was added to the resin, followed by 3-phenylpropylamine (150 μL, ca. 2 equiv), and the reaction mixture was shaken at 50 °C for 18 h. The resin was filtered and then washed with THF (10 mL), and the solution was evaporated to give 165 mg of crude product, 52% pure by HPLC. Purification by flash chromatography (20% EtOAc/isohexane) gave 80 mg of the desired product (69% yield) as a colorless oil. MS: 366 $(M + H^+)$. HRMS: calcd 366.2525, found 366.2553 (+2.1 ppm). ^1H NMR ($CDCl_3$): δ 1.2 (d, 3H), 1.85 (m, 2H), 2.5−2.7 (m, 10H), 3.0 (q, 1H), 3.3 (m, 2H), 3.5 (s, 2H), 7.1−7.4 (m, 11H) ppm.

Compounds 15a,c−f,j (Table 2). These compounds were all made by the method described for **15g**, from resins prepared as described for **13**, in order to define the general applicability

of the reaction. **15d** and **15f** were essentially pure after the reaction and were only characterized by MS; **15a**, **15c**, **15d,** and **15j** were purified and characterized by NMR and HRMS.

15a. Mp: 59−60 °C. HRMS: calcd 362.1345, found 362.1316 (−8.1 ppm). ^{1}H NMR ($CDCl_3$): δ 1.6−1.9 (m, 6H), 2.15 (m, 2H), 2.6 (m, 2H), 2.95 (m, 2H), 3.3 (m, 2H), 5.4 (br, 1H), 7.05−7.4 (m, 9H).

15c. Mp: 98−100 °C. HRMS: calcd 396.1189, found 396.1188 (−0.2 ppm). ^{1}H NMR ($CDCl_3$): δ 1.95 (m, 2H), 2.75 (m, 2H), 3.5 (m, 2H), 4.15 (s, 2H), 6.05 (br, 1H), 7.1−7.6 (m, 13H).

15e. Mp: 71−72 °C. HRMS: calcd 348.1189, found 348.1198 (+2.6 ppm). ^{1}H NMR ($CDCl_3$): δ 1.1 (m, 3H), 1.75 (m, 2H), 1.9 (m, 1H), 2.05 (m, 1H), 2.5 (t, 2H), 3.2 (m, 2H), 3.75 (m, 1H), 6.7 (br, 1H), 7.05−7.4 (m, 9H).

15j. Waxy solid. HRMS: calcd 396.1189, found 396.1198 (+2.3 ppm). ^{1}H NMR ($CDCl_3$): d 1.75 (m, 2H), 2.5 (m, 2H), 3.3 (m, 2H), 5.05 (s, 1H), 6.9 (br s, 1H), 7.0−7.5 (m, 14H).

Kinetic Experiments. Esters of the various resins with 4-methoxyphenylacetic acid were prepared by the following generic method:

4-Methoxyphenylacetic acid (2.66 g, 16.0 mmol) in DMF (15 mL) and CH_2Cl_2 (40 mL) was treated, over 10 min at 0−5 °C, with a solution of diisopropylcarbodiimide (1.21 mL, 2.66 g, 8.0 mmol) in CH_2Cl_2 (5 mL). After 30 min, 4-dimethylaminopyridine (49 mg, 0.40 mmol) and *N*-methylmorpholine (440 μL, 404 mg, 4.0 mmol) were added, and the solution wasadded to the resin (4.0 mmol), pre-swelled in CH_2Cl_2. The mixture was shaken for 16 h and then filtered and washed with DMF (2 × 50 mL), MeOH (2 × 40 mL), and Et_2O (2 × 40 mL), before drying under vacuum.

Kinetic Analysis. The ester resin (40 μmol) was allowed to swell in THF (1 mL), and piperidine (175 μL, 2 mmol, 50 equiv) was added. The mixture was shaken under an argon atmosphere at rt, and aliquots of 20 μL were taken at intervals. These were added to an internal standard (140 μL of a 0.55% solution of 4-benzyloxybenzyl alcohol in MeOH), and an HPLC analysis was performed using MeCN (+0.1% TFA) and water (+0.1% TFA) in a gradient from 25 to 62% organic phase over 5 min (C_{18} column: Spherisorb ODS2) and detection at 275 nm. The degree of reaction was calculated and half-life estimated using the Enzfitter program[13] (or this may be done manually), assuming "pseudo-first-order" kinetics due to the large excess of piperidine employed.

Hydroxyphenoxymethyl Polystyrene Resin. Chloromethyl polystyrene (Polymer Labs, 3.6 mmol/g, 150−300 μm, 1% DVB: 70 g) was stirred in dry DMF (350 mL) and treated with quinol monotetrahydropyranyl ether (108.5 g, 0.56 mol) followed by careful addition (5 min) of NaOMe (30.1 g, 0.56 mol). The mixture was stirred for 18 h at 55 °C under argon, cooled, and filtered. The product was washed with 50% aqueous DMF (4 × 200 mL), DMF (2 × 200 mL), THF (4 × 400 mL), and Et_2O (4 × 200 mL) before drying under vacuum to give 111.5 g of resin. Anal.: Cl, <0.3%. ^{13}C NMR ($CDCl_3$): δ 18.9, 25.2, 30.4, 61.9, 70.9, 97.2, 115.4, 117.6, 151.1, 153.8 ppm.

The above resin (109 g) was stirred for 24 h in a mixture of THF (750 mL), MeOH (330 mL), and *p*-toluenesulfonic acid (2 g) and then filtered. The product was washed with THF (3 × 500 mL), MeOH (3 × 500 mL), and Et_2O (3 × 300 mL) before drying under vacuum. Yield: 76 g. ^{13}C NMR (THF-d_8): δ 70.1, 115.3, 151.5, 152.0 ppm.

Hydroxyphenylthiomethyl Polystyrene Resin. Chloromethyl polystyrene (Polymer Labs, 3.6 mmol/g, 150−300 μm, 1% DVB: 395 g) was stirred with DMF (5 L) and added to a solution of 4-mercaptothiophenol (474 g, 3.76 mol) in DMF (2.2 L). Et_3N (430 mL, 3.1 mol) was added (exotherm to 35 °C) and the mixture stirred for 72 h at rt. The product was filtered, washed with DMF (4 × 2 L), THF (4 × 1.5 L), 50% aqueous THF (4 × 1.5 L), THF (4 × 2.5 L), and MeOH (4 × 2.5 L), and dried under vacuum. Yield: 520 g. Anal.: S, 9.1; Cl, 0; corresponds to 2.56 mm/g. ^{13}C NMR (THF-d_8): δ 40.0, 115.5, 157.3 ppm.

Note: A similar resin is now available from Novabiochem.

Hydroxyphenylsulfonylmethyl Polystyrene Resin. The above resin (200 g) was stirred in CH_2Cl_2 (2.5 L) for 15 min at 15 °C, and then peracetic acid (39%, 437 mL) was added dropwise, keeping the temperature below 25 °C. After the addition the reaction was filtered and washed with AcOH (3 × 2.5 L), CH_2Cl_2/AcOH (4:1, 3 × 1.5 L), CH_2Cl_2 (3 × 1.5 L), THF (5 × 1.5 L), and *t*-BuOMe (3 × 1.5 L) before drying under vacuum. Yield 197 g. Anal.: S, 7.4%; corresponds to 2.08 mm/g. ^{13}C NMR (THF-d_8): δ 40.0, 62.0, 114.7, 161.5 ppm.

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Supporting Information Available: ^{13}C NMR spectra for compounds **8**−**10**, **12**, **13**, **15i**, and the hydroxy resins; ^{1}H NMR spectra for compounds **1**−**3**, **5**−**7**, and **15a**,**c**,**e**,**g**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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