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Enantiomeric enrichment of α-amino acid derivatives: recrystallization of *N*-Fmoc α-amino acid *tert*-butyl esters

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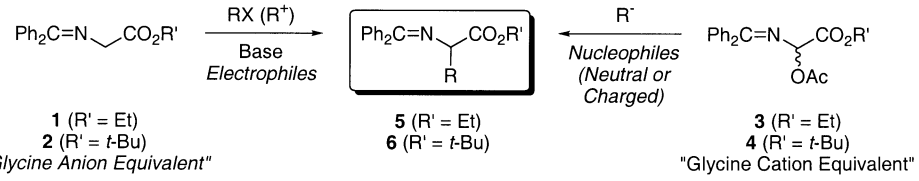
Abstract—The optical purity of products derived from enantioselective reactions of the benzophenone imine of glycine *tert*-butyl esters can often be improved by conversion to the *N*-Fmoc α-amino acid *tert*-butyl esters followed by simple recrystallization.

1. Introduction

New methods for the synthesis of natural and unnatural α-amino acids have been developed by numerous research groups over the past quarter century.[1,2] Since 1978 we have been interested in the use of Schiff bases for the synthesis of α-amino acids by Phase-Transfer Catalysis (PTC)[3–5] and other synthetic routes. The use of benzophenone imines of α-amino acid esters for the synthesis of first racemic and then of optically active α-amino acids will be reviewed and then a new method for the enantiomeric enrichment of these products will be described.

The benzophenone imines of glycine alkyl esters can serve as either glycine anion or glycine cation equivalents in the preparation of α-monoalkyl amino acid derivatives (Scheme 1). Thus, reaction of **1** with base and an electrophile yields the monoalkyl derivative **5** *via* the Schiff base ester enolate. A key feature of this methodology is the *selective monoalkylation* of the starting benzophenone imine substrates, which is due to the considerable decrease in acidity of the monoalkylated product [**5**, *R*=Me, pKa, (DMSO)=22.8] in comparison with the starting substrate [**1**, pKa (DMSO)=18.7].[6] The complementary Schiff base acetate **3**, which is readily prepared from **1**, can be reacted with various neutral or charged nucleophiles (e.g. organocopper reagents, organoboranes/ArOK, active methylene anions/Pd(0), vinyl organometallics/Pd(0), active aromatics/$TiCl_4$, vinyl silanes/$TiCl_4$).[7,8] Products containing the benzophenone imine group are typically more stable to hydrolysis and chromatography than their aldimine counterparts.[1] However, since the benzophenone imine is removed under mildly acidic aqueous conditions, care must be taken to avoid acids or long residence times on chromatography columns.

The solid-phase synthesis of unnatural α-amino acids and peptides, termed 'Unnatural Peptide Synthesis' ('UPS'), using the benzophenone imines of resin-bound glycinates, was reported in 1996 as a part of our academic-industrial collaboration with the laboratory of Dr William L. Scott at the Lilly Research Laborarories.[9] UPS involves the room-temperature introduction of an amino acid side-chain by a three-step sequence during a normal solid-phase peptide synthesis (SPPS) (Scheme 2). The resin-bound N-terminal glycine residue (**7**) is activated as the benzophenone imine to form **8**, the side-chain is introduced by deprotonation and reaction with an electrophile to yield **9**, and then the imine is



Scheme 1. Glycine anion and cation equivalents for the synthesis of α-amino acids.

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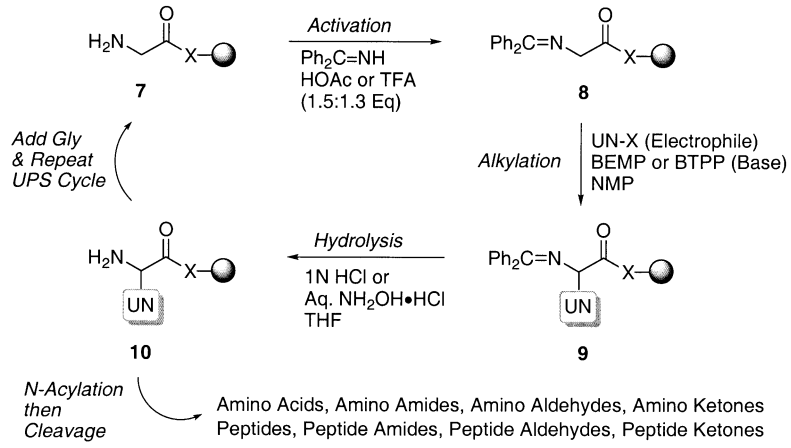


Scheme 2. Unnatural amino acid and peptide synthesis.

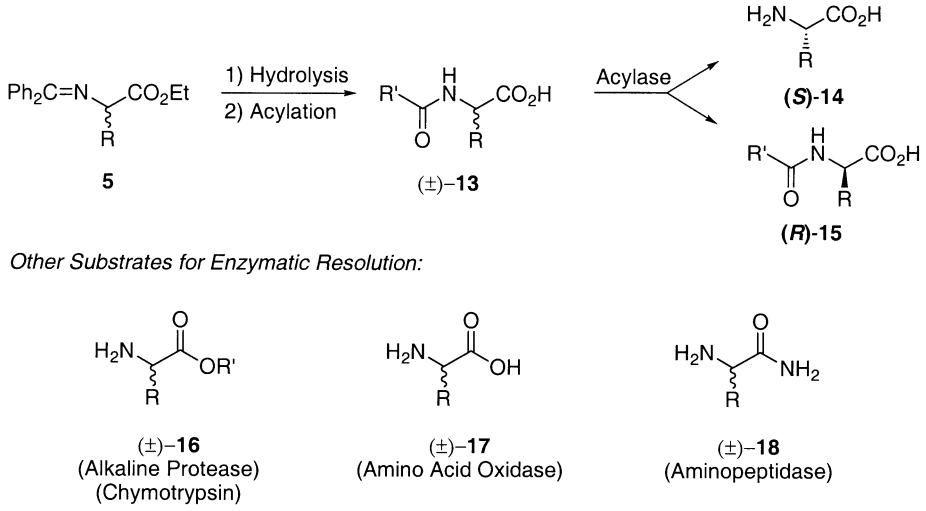
selectively removed by hydrolysis or transimination to give the resin-bound product **10**. Product **10** can then either be subjected to another UPS cycle or it can be cleaved from the resin.[10]

Since solid-phase synthesis already involves a second phase, use of normal PTC-type reaction conditions with a heterogeneous base was expected to be problematic. The neutral, organic-soluble Schwesinger bases, BEMP (**11**) and BTPP (**12**) (Scheme 3),[11] employed in the alkylation step, function similar to typical PTC base systems. Because these sterically hindered bases do not react with alkyl halides at an appreciable rate, both the electrophile and the base can be present from the beginning of the alkylation step.

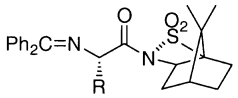
Scheme 3. Schwesinger bases: strong, neutral, organic-soluble bases.

As noted in Scheme 2, a number of different types of amino acid- or peptide-derived products are available by UPS methodology. Relatively unreactive alkylating agents can be used by increasing the stoichiometry of the base and alkyl halide or by using an in situ Finkelstein reaction for conversion to the more reactive alkyl halide.[9c] α,α-Dialkylation can be accomplished either by alkylation of an aldimine-activated monoalkylated substrate[9b] or by a tandem procedure involving normal UPS monoalkylation of the benzophenone imine of a glycine substrate followed by a direct second alkylation with stronger base (KHMDS) under anhydrous conditions.[9d] Michael addition of substrates **8** leads to various glutamic acid derivatives.[9e] Different resins can be used for the preparation of amino amides or peptide amides (Rink resin)[9g] or amino aldehydes, amino ketones, peptide aldehydes or peptide ketones (Weinreb amide resin).[9f] A resin-bound glycine cation equivalent (**9**, Un=OAc) can be reacted with organoboranes to give a variety of α-substituted amino acid derivatives.[7h]

The preparation of optically active α-alkyl amino acids from the benzophenone imines of glycine derivatives has been accomplished in three major ways: enzymatic resolution, the use of chiral auxiliaries, and enantioselective



Scheme 4. Enzymatic resolution of alkylation products.



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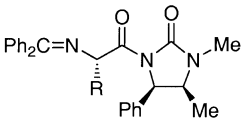


20

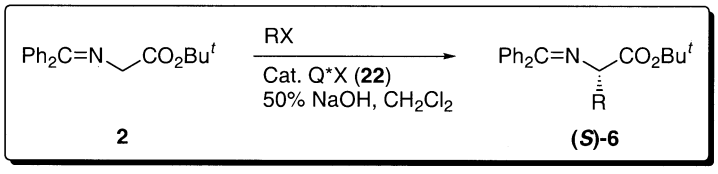
Scheme 5. Products from the alkylation of benzophenone imines containing chiral auxiliaries.

synthesis involving a chiral catalyst or reagent. Each of these methods will be discussed below.

Although classical resolutions[12] can and certainly have been used for the preparation of optically active α-amino acids from derivatives prepared by various synthetic routes from compounds such as **1** or **3**, the use of enzymatic resolution will be the focus of this discussion. Långström and co-workers prepared ^{11}C-labeled L-amino acids for positron emission tomography (PET) studies by racemic alkylation of the benzophenone imine of glycine *tert*-butyl ester (**2**) followed by hydrolysis to the amino acid and then selective destruction of the D-amino acid using D-amino acid oxidase.[13] Because of the short half-life of ^{11}C (20.4 min), syntheses involving this isotope need to be both very rapid and efficient. In 1989 the Whitesides group reported the kinetic resolution of unnatural amino acid derivatives prepared by racemic alkylation of **1** and other amino acid anion equivalents (Scheme 4).[14] Enantioselective hydrolysis of racemic *N*-acyl amino acids (**13**) was accomplished using acylase I. Such enzymatic resolutions provide access to each of the enantiomers of the amino acid, the hydrolyzed product (*S*)-**14** and the unreacted starting substrate (*R*)-**15**. The groups of Imperiali,[15] Pirrung,[16] Long,[17] and others[18] have reported enzymatic resolutions of various amino acid derivatives (**13**, **16**, and **17**). Groups at DSM Research and the University of Amsterdam have used enzymatic resolution of α-amino amides as a route to the enriched (*S*)-**14** and unreacted (*R*)-**18**.[2j,19]

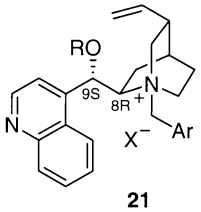
Use of either an ester or an amide chiral auxiliary in conjunction with nitrogen activation with the benzophenone imine has been reported by a number of groups. Two of these systems, which have been used with considerable success (**19** and **20**), will be discussed here (Scheme 5). Alkylation of substrate **19** (*R*=H), which contains the Oppolzer sultam auxiliary, to give products **19**, has been reported by the groups of Chassaing[20] and Roques.[21] Palladium-catalyzed allylations of **19** (*R*=H) were accomplished by the de Meijere[22] and Salaün groups.[22a] Pleixats reported use of phase-transfer catalyzed conditions, which avoid the use of the normal low-temperature, anhydrous conditions that often require use of HMPA or another additive, for the alkylation of **19** (*R*=H).[23] More recently, the Nájera group has made use of substrate **20** (*R*=H), which contains an ephedrine-derived imidazolidinone chiral auxiliary, for both alkylations and Michael additions using several different base systems as a route to products **20**.[24]

The final major route to prepare optically active α-amino acids from the benzophenone imines of glycine alkyl esters involves enantioselective reactions, in which the chiral control is used either as a catalyst or a reagent (Scheme 6). In 1989 we reported the catalytic enantioselective alkylation of imine **2** using the pseudoenantiomeric catalysts, **21a** (from cinchonine, CnOH) or **22a** (from cinchonidine,



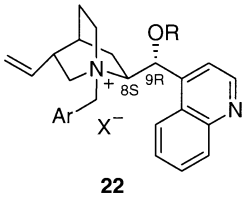
2 **(*S*)-6**

Pseudoenantiomeric *Cinchona* Alkaloid-Derived Phase-Transfer Catalysts:



21

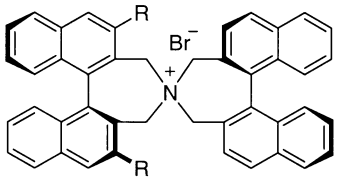
Cinchonine-derived
21a (R=H, Ar=Ph)
21b (R=Allyl, Ar=Ph)
21c (R=H, Ar=9-An)
21d (R=Allyl, Ar=9-An)



22

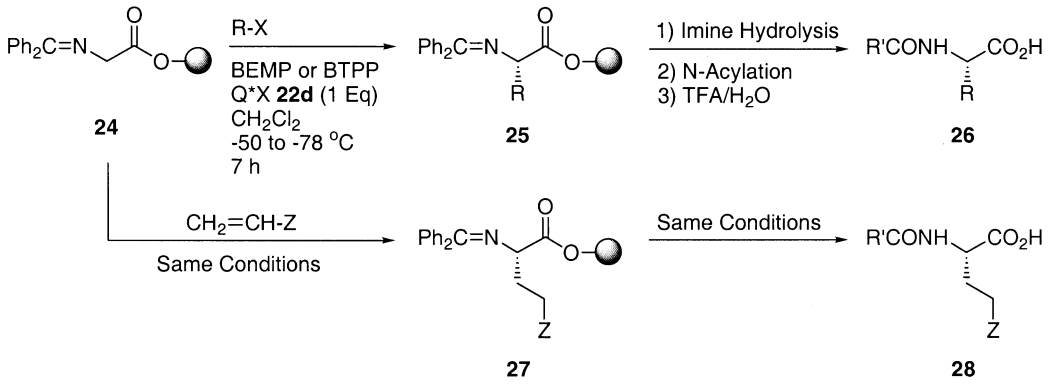
Cinchonidine-derived
22a (R=H, Ar=Ph)
22b (R=Allyl, Ar=Ph)
22c (R=H, Ar=9-An)
22d (R=Allyl, Ar=9-An)

BINAP-Derived Phase-Transfer Catalyst:



23 (R = β-Np)
Gives Products **(*R*)-6**

Scheme 6. Enantioselective phase-transfer catalysis.



Scheme 7. Enantioselective reactions of a resin-bound glycine derivative.

CdOH), derived from the *Cinchona* alkaloids (Scheme 6).[25] Even though only modest enantioselectivities (up to 66% ee) by today's standards were achieved using these first generation catalysts, it was possible to increase the optical purity of some of these products by a simple recrystallization or by enzymatic resolution of the partially enriched derivatives (see beginning of Results and Discussion Section). A second generation of catalysts (**21b** and **22b**), in which the free hydroxyl group of the original *Cinchona*-quat catalysts were O-alkylated, gave enantioselectivities of up to 81%.[26]

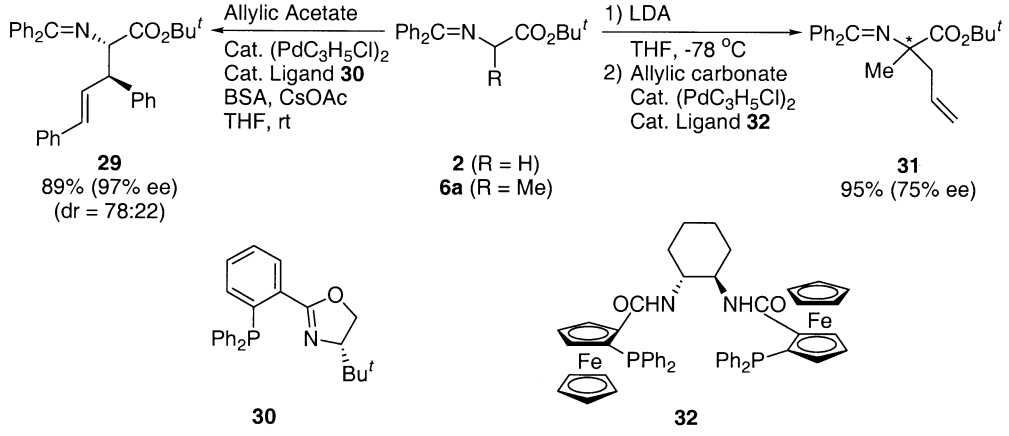
A further major improvement in catalyst design was reported simultaneously in late 1997 by the Lygo[27] and Corey[28] groups. Enantioselectivites of 91–94% were obtained for the model benzylation reaction by introduction of the *N*-9-anthracenylmethyl group into either the catalysts containing a free hydroxyl group (**21c** and **22c**),[27] which are converted to the active O-alkylated catalysts in situ during the PTC alkylation reaction, or the O-allylated catalysts (**22d**[28] or **21d**[29]). The highest enantioselectivities reported for these two related catalyst systems were 94% ee using the Lygo catalyst **22c** (with benzyl bromide)[27] and 99.5% ee using the Corey catalyst **22d** (with either *n*-hexyl iodide or benzhydryl bromide).[28] Reactions developed using these catalyst systems include: alkylations,[27,28a,b,30] Michael additions,[28b,c] and aldol reactions.[28d]

We showed that it was possible to carry out catalytic enantioselective alkylations[29] and Michael additions[31] under homogeneous reaction conditions by using the Schwesinger bases BEMP (**11**) or BTPP (**12**) together with *Cinchona*-derived quats **21d** or **22d**. In this case, the highest enantioselectivity (97% ee) was obtained using isobutyl bromide.

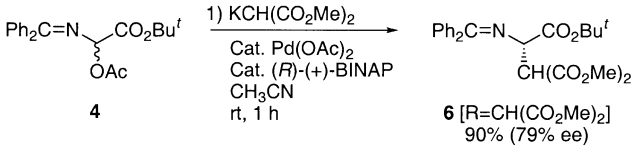
The Maruoka group recently reported use of a BINAP-derived catalyst (**23**) for the catalytic enantioselective alkylation of substrate **2**.[32] Excellent enantioselectivity (96% ee) was obtained with only 1 mol% of catalyst at 0°C in 30 min for the model benzylation reaction. Recently this group has reported a dramatic rate enhancement of the alkylation reaction using ultrasonic irradiation (methylation in 8 h with stirring or in 1 h with ultrasound).[32c]

The solid-phase enantioselective alkylation[33] and Michael addition[31] of resin-bound glycinate **24** was accomplished using the *Cinchona*-derived reagents **21d** and **22d** together with the Schwesinger bases BEMP (**11**) and BTPP (**12**) (Scheme 7). In this case the model benzylation with **22d** gave product in 76% ee. The highest enantioselectivity achieved was 89% using methallyl bromide.

Polymer-supported *Cinchona*-derived catalysts similar in structure to catalysts **21a** and **22a** have recently been reported by the Nájera group.[34] Alkylation of the benzophenone imine of glycine isopropyl ester gave up to 90% ee for the alkylation with benzyl bromide. Other active alkylating agents gave enantioselectivites from 24–64%.



Scheme 8. Catalytic enantioselective allylic substitution using Pd(0) and a chiral ligand.



Scheme 9. Catalytic enantioselective reaction of a glycine cation equivalent with malonate anion.

The catalytic enantioselective allylic substitutions of **2** using Pd(0) and a chiral phosphine ligand have been studied by a number of groups. With the exception of the two cases discussed below (Scheme 8), the enantioselectivites have only been modest with this type of reaction. The Williams group reported the allylation of **2** with a diphenyl-substituted allylic acetate in the presence of the phosphorous-containing oxazole ligand **30** as a route to allylated product **29** (97% ee).[35] Considerably lower enantioselectivites with the parent allyl acetate imply that the choice of the electrophilic partner is important in obtaining high inductions in these reactions. Recently, the groups of Hou and Dai have shown that allylic allylation of the alanine-derived imine **6a** using a ferrocene ligand with planar chirality (**32**) gives 75% ee of the α,α-dialkylated product **31**.[36] These results are promising since such optically active α,α-dialkylated systems are typically difficult to prepared from benzophenone imine-containing starting substrates.

We reported a catalytic enantioselective synthesis involving a glycine cation equivalent in conjunction with a novel (2-aza-π-allyl)palladium intermediate as a route to optically active β-carboxyaspartic acid derivatives (Scheme 9).[7g,37] Reaction of **4** with malonate anion for one hour at room temperature in the presence of catalytic Pd(0) and the chiral bisphosphine ligand BINAP gave product **6** [*R*=$CH(CO_2Me)_2$] in 79% ee (see beginning of Results and Discussion Section for the use of recrystallization to improve the optical purity of this product). The reaction was optimized for substrate ester, imine, and leaving group; base, solvent, counterion, and additive; and steric factors in the nucleophilic partner. The level of induction was shown to be sensitive to the nature of the nucleophile.

2. Results and discussion

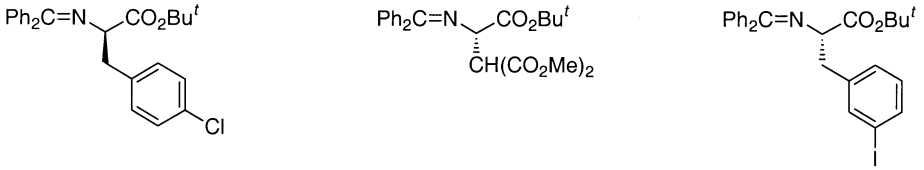
The enantioselective syntheses outlined above demonstrate that it is now possible to prepare a variety of types of unnatural α-amino acid derivatives with moderate to high enantioselectivities from substrates **2** and **4**. One potential problem in these syntheses is the need to enrich product enantiomers to optically pure products. The Imperiali group[15] and others[18b] have used enantioselective PTC reactions followed by enzymatic resolution of product derivatives to achieve this goal.

We[7g,25] and others[15b,38,39] have shown that in some cases it is possible to recrystallize a partially enriched product to an optically pure one. Two notable successes in this regard as well as one failure are shown in Scheme 10. Enantioselective PTC alkylation of **2** with 4-chlorobenzyl bromide using the first generation catalyst **21a** yielded (*R*)-**6** in 66% ee. A single recrystallization gave racemic crystals and nearly optically pure product in the filtrate.[25] In the complementary catalytic enantioselective synthesis involving palladium-catalyzed coupling of malonate anion with the glycine cation equivalent **4** (Scheme 9), the initial product was obtained in 79% ee. Again a single recrystallization gave a highly enriched product, in this case as crystalline product (*S*)-**6**.[7g] Unfortunately, not all cases work so well! As noted by Pirrung and Krishnamurthy, phenylalanine analogs with unsymmetrical substitutions are often non-crystalline.[16b] An example is shown in Scheme 10; the benzophenone imine of 3-iodophenylalanine *tert*-butyl ester (*S*)-**6b** is an oil, so it is not possible to enrich this product by simple recrystallization.

We now report that it is often possible to achieve enantiomeric enrichment by recrystallization of the *N*-Fmoc α-amino acid *tert*-butyl esters (**33**). These products are readily prepared from the benzophenone derivatives **6** by mild hydrolysis with aqueous citric acid followed by *N*-acylation with FmocCl (Scheme 11 and Table 1). Enantiomeric excesses were determined by chiral HPLC.[40]

Several representative products **6** obtained by catalytic enantioselective alkylation (**6a**–**6e**) or Michael addition (**6g**–**6j**) of the benzophenone imine of glycine *tert*-butyl ester (**2**) as well as the product **6f**, derived from glycine cation equivalent **4**, were chosen for recrystallization studies (Table 1). Following conversion into the Fmoc *tert*-butyl esters **6**, the products were recrystallized. In many cases the crystals obtained were highly enriched in the major enantiomer (**6a**–**6c**, **6f**, **6h**, and **6j**). In other cases the enriched major enantiomer was contained in the filtrate (**6d** and **6e**). The mixed glutamate ester (**6g**) was an oil, so its optical purity could not be improved. In one case (**6i**), the crystals obtained on repeated recrystallization were of constant %ee.

The orthogonal nature of the Fmoc and *tert*-butyl ester

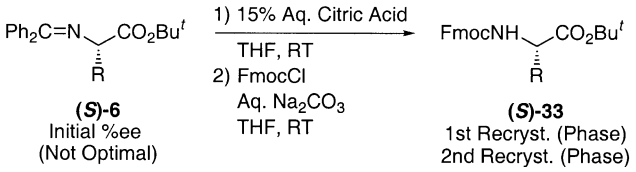


(*R*)-6 (R=4-$ClC_6H_4CH_2$)
95% (66% ee)
One Recryst:
61% (>99% ee)
(16.8 g)

(*S*)-6 [R=$CH(CO_2Me)_2$]
90% (79% ee)
One Recryst:
62% (95.5% ee)
(2.65 g)

(*S*)-6b
91% (63% ee)
Oil

Scheme 10. Enantiomeric enrichment by recrystallization of Schiff base *tert*-butyl esters.



Scheme 11. Imine hydrolysis of **6** followed by conversion to the *N*-Fmoc α-amino acid *tert*-butyl esters (**33**).

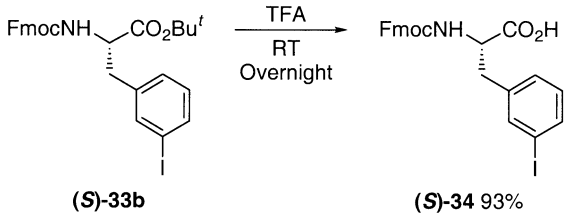
groups allows for differential deprotection of derivatives **33**. For example, the Fmoc *tert*-butyl ester of 3-iodophenylalanine [(*S*)-**33b**] was converted into Fmoc-3-iodophenylalanine [(*S*)-**34**] in 93% yield by treatment with TFA (Scheme 12).

The benzophenone imines of glycine esters are proving to be important starting materials for the synthesis of optically enriched α-amino acid derivatives. The new method for the enantiomeric enrichment of the Fmoc *tert*-butyl derivatives reported here provides another option for the preparation of optically active α-amino acid derivatives of high purity.

3. Experimental

3.1. General methods

The starting alkylated products **6a**–**6e** and **6g**–**6j** were prepared from **2**.[40] Product **6f** was prepared from **4**.[41] NMR analyses were performed on a GE 300 MHz spectrometer; δ is in ppm relative to TMS as internal standard in the indicated solvent. Elemental analyses were performed by Midwest Microlab of Indianapolis, IN. High resolution mass spectrometry data were obtained with a Kratos MS80 high resolution mass spectrometer with chemical ionization.



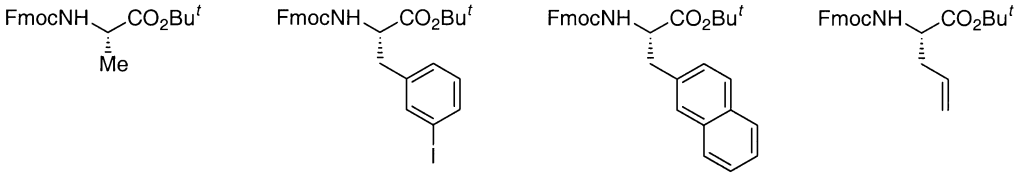
Scheme 12. Hydrolysis of (*S*)-**33b** to yield *N*-Fmoc-3-iodophenylalanine (**34**).

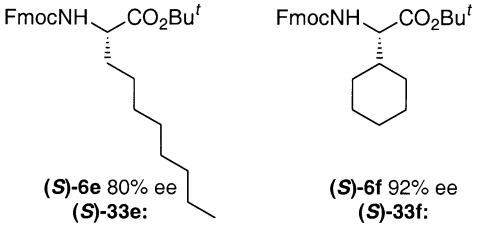
3.2. General procedure for the hydrolysis of the alkylated benzophenone imine (6)

The alkylated product **6** (150–300 mg) was dissolved in THF (6 mL) and 15% aqueous citric acid (3 mL) was added. The reaction mixture was stirred at room temperature

Table 1. Enantioselectivities of substrates **6** and recrystallized products **33**

Alkylation Products:





Michael Addition Products:

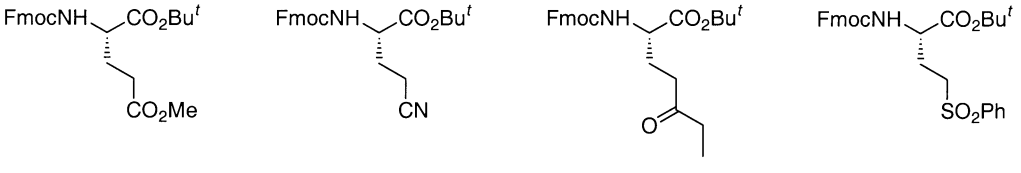


Table 2. Initial %ee of Products (*S*)-**6** and recrystallization yields and %ee of Products (*S*)-**33**

		Yield (%ee) of (*S*)-**33** following recrystallization					
		1st recrystallization		2nd recrystallization		3rd recrystallization	
Product (R Group)	%ee (*S*)-**6**	Filtrate[a]	Crystals[a]	Filtrate[a]	Crystals[a]	Filtrate[a]	Crystals[a]
6a (Me)	83	12 (24)	88 (91)	8 (34)	92 (96)	10 (60)	90 (100)
6b (3-I-PhCH$_2$)	63	26 (22)	74 (93)	7 (14)	93 (>98)	–	–
6c (2-Naphthylmethyl)	71	12 (16)	88 (93)	9 (32)	91 (>99)	–	–
6d (Allyl)	84	80 (>98)	20 (26)	–	–	–	–
6e (*n*-Octyl)	80	40 (93)	60 (71)	–	–	–	–
6f (Cyclohexyl)	92	14 (46)	86 (>99)	–	–	–	–
6g[b] (CH$_2$CH$_2$CO$_2$Me)	82	–	–	–	–	–	–
6h (CH$_2$CH$_2$CN)	76	19 (12)	81 (91)	20 (78)	80 (95)	–	–
6i (CH$_2$CH$_2$COEt)	65	18 (65)	82 (65)	(65)	(65)	(65)	(65)
6j (CH$_2$CH$_2$SO$_2$Ph)	70	22 (24)	78 (83)	–	–	–	–

[a] Yield (ee).
[b] Oil.

overnight, then made basic with saturated aqueous K_2CO_3 and extracted with ethyl acetate (3×10 mL) followed by drying of the extracts ($MgSO_4$). Concentration under reduced pressure gave the crude amino acid *tert*-butyl esters, which were used in the next step without further purification.

3.3. General procedure for the conversion of the amino *tert*-butyl esters to the *N*-Fmoc amino acid *tert*-butyl esters (33)

The crude amino ester was dissolved in THF (6 mL) and 10% aqueous Na_2CO_3 (6 mL) was added, followed by FmocCl (9-fluorenylmethyl chloroformate) (1.0 equiv). The reaction mixture was stirred at room temperature overnight. The aqueous layer was then extracted with EtOAc (3×10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography to remove benzophenone and excess of reagents. The purified product was then crystallized from the indicated solvent (Table 2). The enantiomeric excess was determined by chiral HPLC (isocratic) using the conditions specified in each case: column, mobile phase (ranges used), flow rate (ranges used), detection wavelength, retention times. Table 2 lists the initial %ee of products (*S*)-**6** and the recrystallization yields and %ee of products (*S*)-**33**.

3.3.1. 1,1-Dimethylethyl *N*-[9H-fluoren-9-ylmethoxy)-carbonyl]-L-alaninate 33a. (*R*=Me): Pentane/Et_2O, Mp. 89–90°C; ^{1}H NMR ($CDCl_3$, δ) 1.40 (d, 3 H, *J*=6.6 Hz); 1.48 (s, 9 H); 4.20–4.30 (m, 2 H); 4.38 (d, 2 H, *J*=7.4 Hz); 5.37 (d, 1H, *J*=6.6 Hz); 7.32 (td, 2 H, *J*=7.4 and 1.5 Hz); 7.40 (t, 2 H, *J*=7.4 Hz); 7.61 (d, 2 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 18.8, 27.9, 47.1, 50.1, 66.8, 81.8, 119.8, 125.0, 126.9, 127.6, 141.2, 143.8, 143.9, 155.5, 172.2. Anal. calcd for $C_{22}H_{25}NO_4$: C 71.91, H 6.86, N 3.81; found: C 72.07, H 6.89, N 3.77. Chiracel OD, hexane/i-PrOH (85:15), 1.0 mL/min, 254 nm, retention times: *R* (minor) 8.53 min, *S* (major) 20.83 min.

3.3.2. 1,1-Dimethylethyl *N*-[(9H-fluoren-9-ylmethoxy)-carbonyl]-3-iodo-L-phenylalaninate 33b. (*R*=3-I-$C_6H_4CH_2$): Pentane/Et_2O, Mp. 86–88°C; ^{1}H NMR ($CDCl_3$, δ) 1.43 (s, 9 H); 3.04 (d, 2 H, *J*=5.1 Hz); 4.22 (t, 1 H, *J*=7.0 Hz); 4.34 (dd, 1 H, *J*=10.3 and 7.4 Hz); 4.44–4.53 (m 2 H); 5.32 (d, 1H, *J*=8.1 Hz); 7.02 (t, 1 H, *J*=7.4 Hz); 7.11 (d, 1 H, *J*=7.4 Hz); 7.33 (td, 2 H, *J*=7.4 and 1.5 Hz); 7.41 (t, 2 H, *J*=7.4 Hz); 7.54–7.59 (m, 4 H); 7.77 (d, 2 H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, δ): 27.9, 37.9, 47.2, 55.0,.9, 82.7, 94.2, 119.9, 125.1, 127.0, 16138.6, 141.3, 143.8, 155.4, 170.1. Anal. calcd for $C_{28}H_{28}INO_4$: C 59.06, H 4.96, N 2.46; found: C 59.00, H 4.95, N 2.39. Chiracel OD, hexane/i-PrOH (70:30), 1.0 mL/min, 254 nm, retention times: *R* (minor) 7.68 min, *S* (major) 23.47 min.

3.3.3. 1,1-Dimethylethyl (α*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]-2-naphthalenepropanoate 33c. (*R*= 2-Naphthylmethyl): Pentane/Et_2O, Mp. 104–105°C; ^{1}H NMR ($CDCl_3$, δ) 1.41 (s, 9 H); 3.27 (d, 2 H, *J*=5.9 Hz); 4.20(t, 1 H, *J*=7.0 Hz); 4.32 (dd, 1 H, *J*=10.3 and 6.6 Hz); 4.43 (dd, 1 H, *J*=10.3 and 7.4 Hz); 4.65 (q, 1 H, *J*=5.9 Hz); 5.32 (d, 1H, *J*=8.1 Hz); 7.24–7.32 (m, 3 H); 7.39 (t, 2 H, *J*=7.4 Hz); 7.44–7.47 (m, 2 H); 7.56 (t, 2 H, *J*=6.6 Hz); 7.62 (s, 1 H); 7.75–7.83 (m 5 H); ^{13}C NMR ($CDCl_3$, δ): 27.9, 38.5, 47.1, 55.2, 66.8, 82.3, 119.9, 124.9, 125.0, 125.6, 125.8, 126.0, 126.9, 127.4, 127.6, 128.0, 128.1, 132.4, 133.3, 133.6, 141.2, 143.7, 143.8, 155.5, 170.5. Anal. calcd for $C_{32}H_{31}NO_4$: C 77.87, H 6.33, N 2.84; found: C 77.92, H 6.37, N 2.92. Chiracel OD, hexane/i-PrOH (75:25), 1.0 mL/min, 254 nm, retention times: *R* (minor) 9.15 min, *S* (major) 21.52 min.

3.3.4. 1,1-Dimethylethyl (2*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]-4-pentenoate 33d. (*R*=Allyl): Pentane/Et_2O, Mp. 81–82°C; ^{1}H NMR ($CDCl_3$, δ) 1.48 (s, 9 H); 2.46–2.62 (m, 2 H); 4.23 (t, 1H, *J*=7.0 Hz); 4.32–4.40 (m, 3 H); 5.15 (d, 2 H, *J*=12.5 Hz); 5.36 (d, 1H, *J*=8.1 Hz); 5.67–5.78 (m, 1 H); 7.31 (t, 2 H, *J*=7.0 Hz); 7.40 (t, 2 H, *J*=7.4 Hz); 7.60 (d, 2 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 27.8, 36.8, 47.0, 53.5, 66.8, 81.9, 118.7, 119.7, 124.9, 126.8, 127.4, 132.2, 141.1, 143.7, 143.8, 155.5, 170.6. Anal. calcd for $C_{24}H_{27}NO_4$: C 73.26, H 6.92, N 3.56; found: C 73.00, H 6.87, N 3.33. Chiracel OD, hexane/i-PrOH (85:15), 1.0 mL/min, 254 nm, retention times: *R* (minor) 6.84 min, *S* (major) 12.89 min.

3.3.5. 1,1-Dimethylethyl (2*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]decanoate 33e. (*R*=n-Octyl): Hexane, Mp. 61–63°C; ^{1}H NMR ($CDCl_3$, δ) 0.88 (t, 3 H, *J*=6.6 Hz); 1.27–1.83 (m, 23 H); 4.21–4.29 (m, 2 H); 4.38 (d, 2 H, *J*=7.4 Hz); 5.30 (d, 1H, *J*=8.1 Hz); 7.31 (t, 2 H, *J*=7.4 Hz); 7.40 (t, 2 H, *J*=7.4 Hz); 7.60 (d, 2 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 14.0, 22.6, 24.9, 27.9, 29.1, 29.2, 29.3, 31.7, 32.7, 47.2, 54.3, 66.8, 81.8, 119.9, 125.0, 126.9, 127.6, 141.2, 143.8, 143.9, 155.8, 171.8. Anal. calcd for $C_{29}H_{39}NO_4$: C 74.81, H 8.44, N 3.01; found: C 74.65, H 6.36, N 3.11. Chiracel OD, hexane/i-PrOH (85:15), 1.0 mL/min, 254 nm, retention times: *R* (minor) 6.94 min, *S* (major) 15.48 min.

3.3.6. 1,1-Dimethylethyl (α*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]cyclohexaneacetate 33f. (*R*=Cyclohexyl): Pentane/Et_2O, Mp. 104–105°C; ^{1}H NMR ($CDCl_3$, δ) 1.01–1.28 (m, 6 H); 1.48 (s, 9 H); 1.60–1.78 (m, 5 H); 4.15–4.25 (m, 2 H); 4.34–4.45 (m, 2 H); 5.30 (d, 1H, *J*=8.8 Hz); 7.32 (t, 2 H, *J*=7.4 Hz); 7.40 (t, 2 H, *J*=7.4 Hz); 7.61 (d, 2 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 26.0, 27.9, 28.0, 29.3, 41.3, 47.2, 59.0, 66.8, 81.9, 119.9, 125.0, 127.0, 127.6, 141.3, 143.8, 143.9, 156.1, 171.1. Anal. calcd for $C_{27}H_{33}NO_4$: C 74.45, H 7.64, N 3.22; found: C 74.10, H 7.94, N 3.13. Chiracel OD, hexane/i-PrOH (85:15), 1.0 mL/min, 254 nm, retention times: *R* (minor) 6.33 min, *S* (major) 8.99 min.

3.3.7. 1,1-Dimethylethyl 5-methyl *N*-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-glutamate 33g. (*R*=$CH_2CH_2CO_2Me$): Hexane and Hexane/Et_2O; ^{1}H NMR ($CDCl_3$, δ) 1.46 (s, 9 H); 1.81–2.42 (m, 4 H); 3.68 (s, 3 H); 4.18–4.31 (m, 2 H); 4.39 (d, 2 H, *J*=7.0 Hz); 5.42 (d, 1H, *J*=7.5 Hz); 7.28–7.7.44 (m, 4 H); 7.60 (d, 2 H, *J*=7.3 Hz); 7.76 (d, 2 H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, δ): 27.3, 27.5, 29.7, 46.8, 51.2, 53.5, 66.6, 81.7, 119.5, 124.7, 126.6, 127.3, 140.9, 143.4, 143.6, 155.7, 170.7, 172.7. HRMS *m/z* calcd for $C_{25}H_{30}NO_6$ 440.2073 for ($M+H^+$), found 440.2088. Chiracel OD, hexane/i-PrOH (85:15), 1.0 mL/min, 254 nm, retention times: *R* (minor) 12.41 min, *S* (major) 19.35 min.

3.3.8. 1,1-Dimethylethyl 4-cyano-(2*S*)-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]butanoate 33h. (*R*=CH_2CH_2CN): Pentane/Et_2O, Mp. 61–62°C; ^{1}H NMR ($CDCl_3$, δ) 1.48 (s, 9 H); 1.92–2.01 (m, 1 H); 2.21–2.40 (m, 3 H); 4.22 (t, 1 H, *J*=6.3 Hz); 4.25–4.54 (m, 3 H); 5.38 (d, 1H, *J*=6.6 Hz); 7.33 (t, 2 H, *J*=7.0 Hz); 7.42 (t, 2 H, *J*=7.4 Hz); 7.59 (d, 2 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, δ): 13.5, 27.9, 28.9, 47.2, 53.3, 66.9, 83.3, 120.0, 124.9, 125.0, 127.1, 127.7, 141.3, 143.5, 143.7, 155.9, 169.8. Anal. calcd for $C_{24}H_{26}N_2O_4$: C 70.92, H 6.45, N 6.89; found: C 70.20, H 6.44, N 6.83. Chiracel OD, hexane/i-PrOH (60:40), 1.0 mL/min, 254 nm, retention times: *R* (minor) 8.46 min, *S* (major) 14.33 min.

3.3.9. 1,1-Dimethylethyl (2*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]-5-oxoheptanoate 33i. (*R*=CH_2CH_2COEt): Pentane/Et_2O, Mp.78–80°C; ^{1}H NMR ($CDCl_3$, δ) 1.06 (t, 3 H, *J*=7.4 Hz); 1.47 (s, 9 H); 1.83–1.97 (m, 1 H); 2.09–2.21 (m, 1 H); 2.40–2.61 (m, 4 H); 4.22 (t, 1 H, *J*=7.0 Hz); 4.38 (d, 2 H, *J*=6.6 Hz); 5.39 (d, 1H, *J*=8.1 Hz); 7.31 (t, 2 H, *J*=7.4 Hz); 7.40 (t, 2 H, *J*=7.7 Hz); 7.58–7.61 (m, 2 H); 7.77 (d, 2 H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, δ): 7.5, 26.3, 27.7, 35.6, 37.7, 46.9, 53.7, 66.6, 81.8, 119.7, 124.8, 126.7, 127.4, 141.8, 143.5, 143.7, 155.8, 171.0, 209.9. Anal. calcd for $C_{26}H_{31}NO_5$: C 71.37, H 7.14, N 3.20; found: C 71.35, H 7.21, N 3.13. Chiracel OD, hexane/i-PrOH (80:20), 1.0 mL/min, 254 nm, retention times: *R* (minor) 9.92 min, *S* (major) 19.66 min.

3.3.10. 1,1-Dimethylethyl (2*S*)-[[(9H-fluoren-9-ylmethoxy)-carbonyl]amino]-4(phenylsulfonyl)butanoate 33j. (*R*=$CH_2CH_2SO_2Ph$): Pentane/Et_2O, Mp. 91–92°C; ^{1}H NMR ($CDCl_3$, δ) 1.44 (s, 9 H); 1.99–2.11 (m, 1 H); 2.28–2.40 (m, 1 H); 2.99–3.10 (m, 1 H); 3.14–3.25 (m, 1 H); 4.18 (t, 1 H, *J*=6.6 Hz); 4.24–4.31 (m, 1 H); 4.37 (d, 2 H, *J*=7.4 Hz); 5.37 (d, 1H, *J*=7.4 Hz); 7.31 (td, 2 H, *J*=7.4 and 2.2 Hz); 7.40 (t, 2 H, *J*=7.4 Hz); 7.53–7.58 (m, 4 H); 7.66 (t, 1 H, *J*=7.4 Hz); 7.77 (d, 2 H, *J*=8.1 Hz); 7.90 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 26.1, 27.9, 47.1, 52.5, 52.9, 67.1, 83.2, 119.9, 125.0, 127.1, 127.6, 128.0, 129.3, 133.8, 138.9, 141.3, 143.6, 143.7, 155.8, 169.9. Anal. calcd for $C_{29}H_{31}NO_6S$: C 66.77, H 5.99, N 2.69; found: C 66.57, H 6.03, N 2.73. Baker Bond DNBPG (Covalent), hexane/i-PrOH/$EtNMe_2$ (97:3:0.2), 1.0 mL/min, 254 nm, retention times: *S* (major) 50.26 min, *R* (minor) 53.27 min.

3.4. Hydrolysis of the benzophenone imine of 3-iodophenylalanine *tert*-butyl ester (4b) to form *N*-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-iodo-L-phenylalanine (34)

TFA (0.5 mL) was added to the Fmoc-ester product **33b** (240 mg, 0.42 mmol) and the reaction mixture was stirred at room temperature overnight. Concentration under reduced pressure gave the crude Fmoc-protected amino acid (**34**), which was recrystallized from ethyl acetate. Yield (200 mg, 0.39 mmol, 93%). ^{1}H NMR ($CDCl_3$, δ) 3.02–3.22 (m, 2 H); 4.22 (t, 1 H, *J*=6.6 Hz); 4.36–4.51 (m, 2 H); 4.50–4.65 (m, 1 H); 5.22 (d, 1H, *J*=7.4 Hz); 7.03 (t, 1 H, *J*=7.4 Hz); 7.12 (d, 1 H, *J*=7.4 Hz); 7.32 (app.t, 2 H, *J*=7.4 Hz); 7.41 (t, 2 H, *J*=7.4 Hz); 7.54–7.62 (m, 4 H); 7.78 (d, 2 H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, δ): 34.9, 45.3, 53.6, 64.5, 92.6, 118.3, 123.7, 125.5, 126.0, 127.1, 128.6, 133.7, 136.4, 138.9, 139.3, 142.2, 154.5, 171.5. HRMS *m/z* calcd for $C_{24}H_{20}INO_4$ 513.0396, Found 513.0440.

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References

1. For a review about the preparation of optically active α-amino acids from the benzophenone imines of glycine derivatives, see: O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3–15.
2. For selected recent reviews concerning the synthesis of α-amino acids, see: (a) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215–250. (b) Bouifraden, S.; Drouot, C.; El Hadrami, M.; Guenoun, F.; Lecointe, L.; Mai, N.; Paris, M.;

Pothion, C.; Sadoune, M.; Sauvagnat, B.; Amblard, M.; Aubagnac, J. L.; Calmes, M.; Chevallet, P.; Daunis, J.; Enjalbal, C.; Fehrentz, J. A.; Lamaty, F.; Lavergne, J. P.; Lazaro, R.; Rolland, V.; Roumestant, M. L.; Viallefont, P.; Vidal, Y.; Martinez, J. *Amino Acids* **1999**, *16*, 345–379. (c) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621–631. (d) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. (e) Beller, M.; Eckert, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1010–1027. (f) Kawabata, T.; Fuji, K. *J. Synth. Org. Chem. Japan* **2000**, *58*, 1095–1099. (g) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523–1535. (h) Yao, S. L.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435–2448. (i) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689–2697. (j) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197–4212. (k) Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184–201.

3. (a) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641–2644. (b) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625–4628.
4. O'Donnell, M. J. Asymmetric Phase-Transfer Reactions. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; 2nd ed., Wiley-VCH: New York, 2000; Chapter 10; pp 727–755.
5. For a review concerning amino acid and peptide synthesis using phase-transfer catalysis, see: O'Donnell, M. J.; Esikova, I. A.; Mi, A.; Shullenberger, D. F.; Wu, S. In *In Phase-Transfer Catalysis*, Halpern, M. E., Ed.; ACS Symposium Series 659, American Chemical Society: Washington, DC, 1997; Chapter 10; pp 124–135.
6. O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520–8525.
7. For synthetic studies of glycine cation equivalents (**3** or **4**) from the author's laboratory, see: (a) O'Donnell, M. J.; Bennett, W. D.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695–698. (b) O'Donnell, M. J.; Falmagne, J.-B. *Tetrahedron Lett.* **1985**, *26*, 699–702. (c) O'Donnell, M. J.; Falmagne, J.-B. *Chem. Commun.* **1985**, 1168–1169. (d) O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389–5401. (e) O'Donnell, M. J.; Yang, X.; Li, M. *Tetrahedron Lett.* **1990**, *31*, 5135–5138. (f) O'Donnell, M. J.; Li, M.; Bennett, W. D.; Grote, T. *Tetrahedron Lett.* **1994**, *35*, 9383–9386. (g) O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A.; Kubiak, C. P.; Yang, F.; Stanley, G. G. *J. Org. Chem.* **1997**, *62*, 3962–3975. (h) O'Donnell, M. J.; Delgado, F.; Drew, M. D.; Pottorf, R. S.; Zhou, C.; Scott, W. L. *Tetrahedron Lett.* **1999**, *40*, 5831–5835.
8. For synthetic reactions of glycine cation equivalents (**3** or **4**) reported by others, see: (a) King III, G. A.; Sweeny, J. G.; Iacobucci, G. A. *J. Agric. Food Chem.* **1991**, *39*, 52–56. (b) Kozhushkov, S. I.; Brandl, M.; Yufit, D. S.; Machinek, R.; de Meijere, A. *Liebigs Ann./Recueil* **1997**, 2197–2204. (c) Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1997**, *38*, 3385–3386. (d) Clark, B. P.; Harris, J. R. *Synth. Commun.* **1997**, *27*, 4223–4234. (e) Brandl, M.; Kozhushkov, S. I.; Bräse, S.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 453–457. (f) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, 3105–3115.
9. Reports of unnatural amino acid and peptide synthesis (UPS) from the author's laboratory: (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070–6071. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695–3698. (c) O'Donnell, M. J.; Lugar, C. W.; Pottorf, R. S.; Zhou, C.; Scott, W. L.; Cwi, C. L. *Tetrahedron Lett.* **1997**, *38*, 7163–7166. (d) Griffith, D. L.; O'Donnell, M. J.; Pottorf, R. S.; Scott, W. L.; Porco, Jr., J. A. *Tetrahedron Lett.* **1997**, *38*, 8821–8824. (e) Domínguez, E.; O'Donnell, M. J.; Scott, W. L. *Tetrahedron Lett.* **1998**, *39*, 2167–2170. (f) O'Donnell, M. J.; Drew, M. D.; Pottorf, R. S.; Scott, W. L. *J. Comb. Chem.* **2000**, *2*, 172–181. (g) Scott, W. L.; Delgado, F.; Lobb, K.; Pottorf, R. S.; O'Donnell, M. *J. Tetrahedron Lett.* **2001**, *42*, 2073–2076.
10. For the alkylation of soluble, PEG polymer-supported benzophenone imines of glycine, see: (a) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 821–824. (b) Sauvagnat, B.; Kulig, K.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Comb. Chem.* **2000**, *2*, 134–142.
11. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.
12. For recent lead references concerning resolutions, see: (a) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2349–2354. (b) Collet, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3239–3241. (c) Collet, A. *Enantiomer* **1999**, *4*, 157–172. (d) Maier, N. M.; Franco, P.; Lindner, W. *J. Chromatogr. A* **2001**, *906*, 3–33.
13. Antoni, G.; Långström, B. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 125–143.
14. Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354–6364.
15. (a) Imperiali, B.; Prins, T. J.; Fisher, S. L. *J. Org. Chem.* **1993**, *58*, 1613–1616. (b) Torrado, A.; Imperiali, B. *J. Org. Chem.* **1996**, *61*, 8940–8948.
16. (a) Pirrung, M. C.; Krishnamurthy, N. *J. Org. Chem.* **1993**, *58*, 954–956. (b) Pirrung, M. C.; Krishnamurthy, N. *J. Org. Chem.* **1993**, *58*, 957–958.
17. Huang, X.; Long, E. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1937–1940.
18. (a) Knittel, J. J.; He, X. Q. *Pept. Res.* **1990**, *3*, 176–181. (b) Kise, Jr., K. J.; Bowler, B. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3319–3324. (c) Harada, N.; Nishiyama, S.; Sato, K.; Tsukada, H. *Appl. Radiat. Isotopes* **2000**, *52*, 845–850.
19. (a) Schoemaker, H. E.; Boesten, W. H. J.; Kaptein, B.; Roos, E. C.; Broxterman, Q. B.; van den Tweel, W. J. J.; Kamphuis, J. *Acta Chem. Scand.* **1996**, *50*, 225–233. (b) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677–680. (c) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717–720. (d) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127–1135. (e) Péter, A.; Olajos, E.; Casimir, R.; Tourwé, D.; Broxterman, Q. B.; Kaptein, B.; Armstrong, D. W. *J. Chromatogr. A* **2000**, *871*, 105–113.
20. (a) Josien, H.; Martin, A.; Chassaing, G. *Tetrahedron Lett.* **1991**, *32*, 6547–6550. (b) Josien, H.; Chassaing, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1351–1354. (c) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J.-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586–1601. (d) Martin, A.; Chassaing, G.; Vanhove, A. *Isotopes Environ. Health Stud.* **1996**, *32*, 15–19. (e) Sagan, S.; Josien,

H.; Karoyan, P.; Brunissen, A.; Chassaing, G.; Lavielle, S. *Bioorg. Med. Chem.* **1996**, *4*, 2167–2178.
21. (a) Liu, W.-Q.; Roques, B. P.; Garbay-Jaureguiberry, C. *Tetrahedron: Asymmetry* **1995**, *6*, 647–650. (b) Soleilhac, J.-M.; Cornille, F.; Martin, L.; Lenoir, C.; Fournié-Zaluski, M.-C.; Roques, B. P. *Anal. Biochem.* **1996**, *241*, 120–127. (c) Blommaert, A. G. S.; Dhôtel, H.; Ducos, B.; Durieux, C.; Goudreau, N.; Bado, A.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 647–658. (d) Liu, W.-Q.; Roques, B. P.; Garbay, C. *Tetrahedron Lett.* **1997**, *38*, 1389–1392.
22. (a) Voigt, K.; Stolle, A.; Salaün, J.; de Meijere, A. *Synlett* **1995**, 226–228. (b) Zindel, J.; de Meijere, A. *J. Org. Chem.* **1995**, *60*, 2968–2973.
23. López, A.; Pleixats, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1967–1977.
24. (a) Guillena, G.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3935–3938. (b) Guillena, G.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 7310–7322.
25. O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.
26. O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507–4518.
27. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385–1388. (c) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389–1392. (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671–8674.
28. (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347–5350. (c) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097–1100. (d) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.
29. O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775–8778.
30. Lemaire, C.; Guillouet, S.; Plenevaux, A.; Brihaye, C.; Aerts, J.; Luxen, A. *J. Labelled Compd. Radiopharm.* **1999**, *42*, S113–S115.
31. O'Donnell, M. J., Delgado, F., Domínguez, E., de Blas, J., Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821–828.
32. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229. (c) Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500–1502. (d) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339–8342.
33. O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347–6362.
34. Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281.
35. Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1515–1518.
36. You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933–1934.
37. Yamaguchi, M.; Ohba, K.; Tomonaga, H.; Yamagishi, T. *J. Mol. Catal. A-Chem.* **1999**, *140*, 255–258.
38. (a) Imperiali, B.; Fisher, S. L. *J. Org. Chem.* **1992**, *57*, 757–759. (b) Imperiali, B.; Roy, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 12083–12084. (c) Imperiali, B.; Roy, R. S. *J. Org. Chem.* **1995**, *60*, 1891–1894.
39. Tohdo, K.; Hamada, Y.; Shioiri, T. *Synlett* **1994**, 247–249.
40. (a) For the preparation and HPLC analysis of **6a**, **6c**, **6d**, and **6e**, see: Ref. 29. These products were made using BTPP as base under non-optimal conditions for maximizing the enantioselectivity. (b) Compound **6b** was prepared in 91% yield according to the procedure described in Ref. 29, using BTPP as base under non-optimal conditions for maximizing the enantioselectivity. Chiral HPLC analysis conditions for **6b**: Whelk-01, hexane/i-PrOH (95:5), 1.0 mL/min, 254 nm. (c) For the preparation and HPLC analysis of **6g**, **6h**, **6i**, and **6j**, see: Ref. 31. These products were made using BTPP as base under non-optimal conditions for maximizing the enantioselectivity.
41. O'Donnell, M. J., Drew, M. D., Delgado, F., Zhou, C. Unpublished Results. Chiral HPLC analysis conditions for **6f**: Whelk-01, hexane/i-PrOH (95:5), 1.0 mL/min, 254 nm, retention times: (*R*) 4.25 min, (*S*) 4.76 min.