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Enantioselective Solid-Phase Synthesis of α-Amino Acid Derivatives

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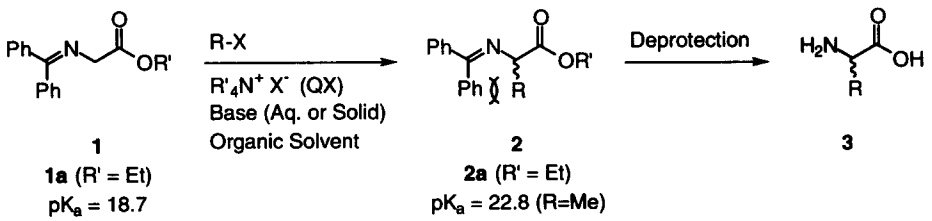
Abstract: Wang-resin bound derivatives of glycine Schiff base esters are alkylated in the presence of quaternary ammonium salts derived from cinchonidine or cinchonine using phosphazene bases to give either enantiomer of the product α-amino acid derivatives in 51-89% ee.
Keywords: Amino acids and derivatives, Enantiocontrol, Phase transfer, Solid-phase synthesis.

Background

We have been interested for some time in the use of Schiff bases for the synthesis of amino acid derivatives by Phase-Transfer Catalysis (PTC).[1] The benzophenone imines of glycine esters are effective for both the large and small scale preparation of these important compounds. The development of this field since our first publications in 1978 will be reviewed and then a new application, the enantioselective synthesis of α-amino acid derivatives using a resin-bound glycine with phase-transfer techniques, will be described.

Racemic α-Amino Acid Synthesis by Phase-Transfer Catalysis (PTC)

Initial studies in the PTC alkylation of the benzophenone imines of glycine esters (**1**) or aminoacetonitrile involved reaction with an alkyl halide in a two-phase system consisting of an organic solvent (toluene or methylene chloride) and an aqueous (e.g. 50% aq. NaOH, "liquid-liquid PTC") or solid base (KOH, KOH/K_2CO_3, or K_2CO_3, "solid-liquid PTC") with either a full equivalent ("ion-pair extraction") or a catalytic amount ("phase-transfer catalysis") of an achiral quaternary ammonium halide (Scheme 1).[2,3] The reactions,



Scheme 1. Synthesis of α-Amino Acids by Phase-Transfer Catalysis.

which are generally conducted at room temperature (refluxing acetonitrile when K_2CO_3 is used as base), yield racemic products **2**, which are readily deprotected to the racemic α-amino acids (**3**). In addition to chemo- and regioselectivity for the α-alkylation product, the alkylation is also frequentioselective; that is, it gives the monoalkylated product in preference to the dialkylated one.[1] This is a consequence of $A_{1,3}$ strain in the monoalkyl product, which causes the active methine product **2** to be considerably less acidic than the active

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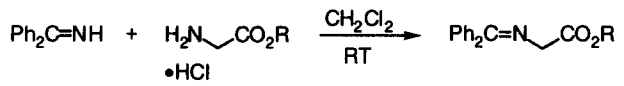
methylene starting substrate **1**, thereby avoiding a second deprotonation/alkylation step (acidities in Scheme 1 were determined in DMSO).[4] An added and important consequence of this acid-weakening effect is that, provided a mild base system is chosen, it should be possible to carry out an enantioselective monoalkylation of **1** *without racemization* of the optically active product **2** under basic reaction conditions.

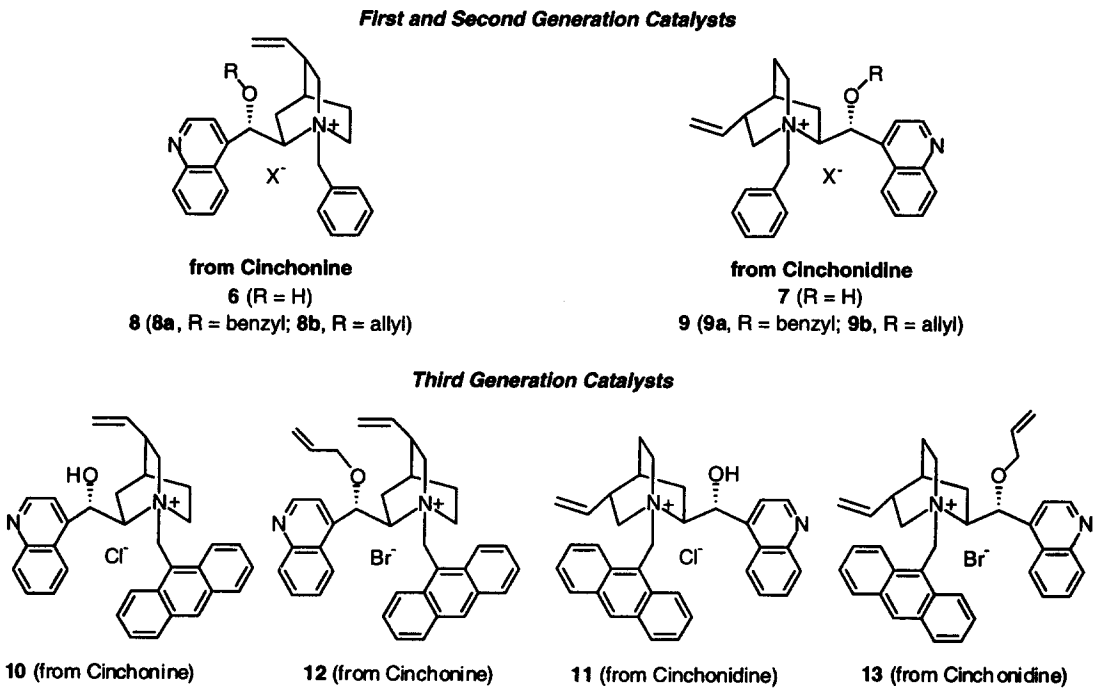
The benzophenone imines of glycine esters or aminoacetonitrile (as well as higher amino acids) are conveniently prepared by a room-temperature transimination reaction involving benzophenone imine and the corresponding amine derivative as its salt (Scheme 2).[5] The benzophenone imine is a versatile protecting group



Scheme 2. Transimination as a Mild Procedure for Preparing Schiff Base Derivatives of Amino Acids.

for primary amines because it is relatively stable in non-acidic conditions, it can be subjected to flash chromatography, it has a UV chromophore for easy detection (TLC, HPLC), and it can be removed either with mild acid or by hydrogenolysis.

Catalytic Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis

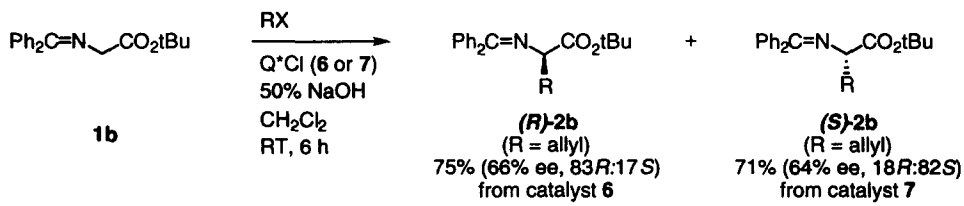


Scheme 3. Three Generations of Chiral, Non-Racemic PTC Catalysts Derived from the *Cinchona* Alkaloids.

Although it is often possible to resolve the racemic products obtained with achiral catalysts, it is more desirable to control the stereochemistry at the newly formed α-center in these PTC alkylations. This can be accomplished either by use of a chiral auxiliary[6] or with a chiral catalyst such as a chiral, non-racemic quaternary ammonium salt. The latter method, enantioselective phase-transfer catalysis, would likely be a method of choice, especially for large-scale synthesis, provided that inexpensive chiral catalysts were available for the synthesis of either product enantiomer and that these chiral control elements yielded products of high enantiomeric purity.

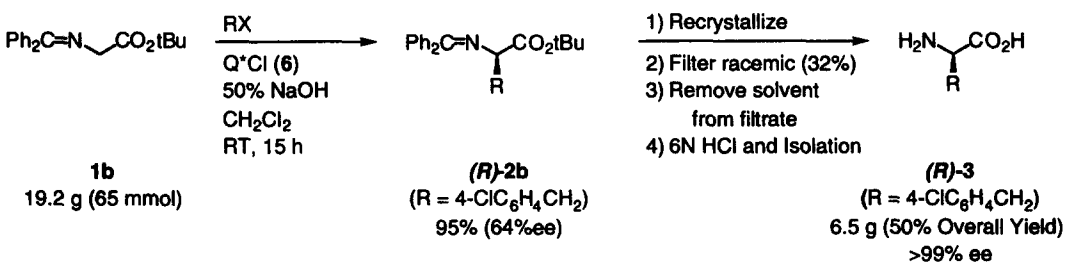
Quaternary ammonium catalysts derived from the *cinchona* alkaloids, cinchonine and cinchonidine, have been effective in PTC alkylations as well as in other PTC reactions.[7,8] Three generations of these catalysts, which will be described in the paragraphs below, are depicted in Scheme 3 above. Although the two parent alkaloids are diastereomers, the two are often termed pseudoenantiomers, because normally the catalyst prepared from one alkaloid gives one enantiomer as the major product while the other alkaloid-derived catalyst yields the other enantiomer in excess.

The first catalytic, enantioselective synthesis of α-amino acid derivatives involving PTC was reported in 1989 (Scheme 4).[9,10] This involved a room temperature alkylation of the benzophenone imine of glycine *t*-butyl



Scheme 4. Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives using "First Generation" PTC Catalysts.

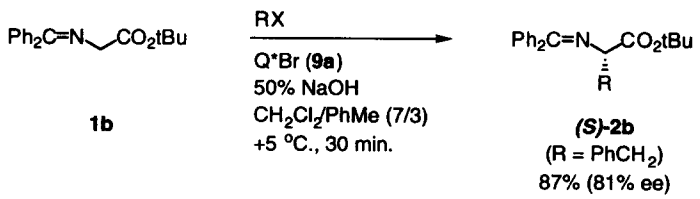
ester (**1b**) in a liquid-liquid PTC reaction using 50% aq. NaOH and methylene chloride with the first generation *N*-alkyl *cinchona* salts (**6** or **7**), developed earlier by the Merck group.[11] While the levels of stereocontrol in this process were only moderate (up to 66% ee, 83:17 ratio of enantiomers), it is possible in certain cases to obtain optically pure products from these reactions by a simple recrystallization of the crude product to remove racemic crystals. This is demonstrated by the "large-scale" synthesis of optically pure 4-chlorophenylalanine,



Scheme 5. "Large-Scale" Room-Temperature Synthesis of an Optically Pure Amino Acid by Chiral PTC.

an interesting non-natural amino acid, in 50% overall chemical yield from Schiff base substrate **1b** (Scheme 5).[12] Imperiali and coworkers have also used enzymatic resolution of optically enriched derivatives obtained from the catalytic enantioselective PTC alkylation of **1b** to give optically pure products.[13,14]

The second generation of catalysts, the *N*-alkyl-*O*-alkyl cinchona-derived salts (**8** or **9**) were reported in 1994.[15] It was shown that these catalysts are formed by *in-situ* *O*-alkylation of catalysts **6** or **7** during the PTC alkylation reaction. Alternatively, new catalysts **8** or **9** can be independently prepared from the parent alkaloids by sequential *N*- and then *O*-alkylation, thus providing a second site for catalyst modification. X-Ray crystallography of **9a** verified the structure of this new catalyst and reaction studies (Scheme 6) optimized the



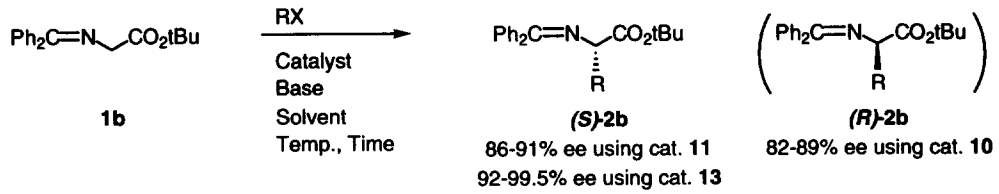
Scheme 6. Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives with "Second Generation" PTC Catalysts.

reaction system.[1,15,16] A mixed solvent system (CH_2Cl_2/PhMe 7/3) gave slightly higher (typically a few % ee) inductions than pure methylene chloride. Lower temperatures also improved the levels of induction, with a lower limit of about +5 °C due to solubility of the aqueous base. While stirring rates did not generally affect the enantioselectivity, faster and more efficient stirring did increase the reaction rate substantially. Other model studies showed that generally the chloride salts give slightly higher enantioselectivities than the bromide salts. Finally, the *O*-allyl group was shown to be the optimal oxygen substituent in these second generation catalysts.

The above studies set the stage for the development of the third generation of chiral PTC catalysts (Scheme 3, **10** – **13**), which were reported independently by the Lygo (catalysts **10** and **11**)[17] and Corey (catalyst **13**)[18a] groups in late 1997 (Scheme 7). The 9-anthracenylmethyl group was introduced as a very effective nitrogen substituent in these catalysts.

Catalysts reported by the Lygo group,[17] which involved the free OH catalysts **11** or **10**, are likely converted to the active *O*-alkyl catalysts by *in-situ* *O*-alkylation, providing either the *S*-enantiomer product (***(S)*-2b**) in 86-91% ee using catalyst **11** or the *R*-enantiomer product (***(R)*-2b**) in 82-89% ee from catalyst **10**. The reaction involves 50% aq. KOH as base in toluene at room temperature for 3-18 hours. Alkylation with the α-haloester, *t*-butyl iodoacetate, gave only modest enantioselectivities (72 and 67% ee, respectively).

The system reported by the Corey group[18] uses catalyst **13** for preparation of the alkylation products ***(S)*-2b** in very high enantioselectivities (92-99.5% ee). This involves a solid-liquid PTC reaction with $CsOH \bullet H_2O$ as base in methylene chloride at –60 to –78 °C for 18-36 hours. A variety of different alkyl halides (methyl, *n*-alkyl, allyl, propargyl, benzyl, α,ω-dihaloalkanes and Michael acceptors) gave excellent results. In addition, X-ray structures of the catalyst **13** as well as the ion-pair of *p*-nitrophenoxide and the cation **13** led to a proposed structure for the ion-pair of the enolate from **1b** and the quaternary salt cation **13**.



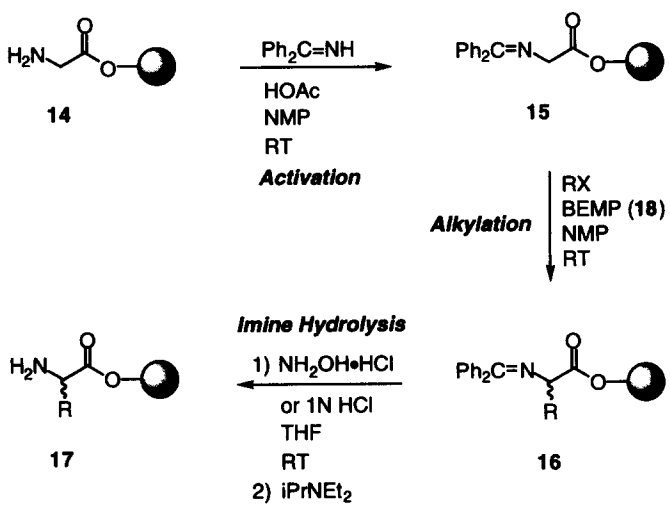
Conditions for Benzylation ($PhCH_2Br$) to form *(S)*-2b (R = $PhCH_2$) using catalyst 11 or 13:

Lygo, Catalyst **11** (Ref. 17)	Corey, Catalyst **13** (Ref. 18)
50% KOH	$CsOH•H_2O$
CH_2Cl_2	CH_2Cl_2
RT, 18 h	-78 °C, 23 h
68% (to amino acid)	87% (to ***(S)*-2b**)
91% ee (95.5:4.5)	94% ee (97:3)

Scheme 7. Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives with "Third Generation" PTC Catalysts.

Solid-Phase Synthesis of α-Amino Acids and Peptides by "Unnatural Peptide Synthesis" (UPS)

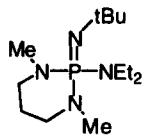
A related program in our laboratory, which was begun in 1995 in collaboration with Dr. William L. Scott of Eli Lilly and Company, has focused on the solid-phase synthesis of unnatural amino acids and peptides, termed "Unnatural Peptide Synthesis" ("UPS").[19-26] The methodology involves introduction of an unnatural amino acid side chain during a normal Solid-Phase Peptide Synthesis (SPPS) (Scheme 8). The three key steps are: activation



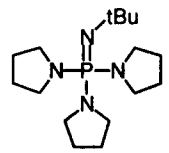
Scheme 8. Solid-Phase Synthesis of α-Amino Acid Derivatives by "UPS."

of an *N*-terminal glycine residue as the benzophenone imine, deprotonation and alkylation of the resulting active methylene compound (**15**), and then imine hydrolysis to free the *N*-terminal amino residue for further reactions. The organic soluble, non-ionic Schwesinger bases (Scheme 9)[27] used in this chemistry function similarly to

typical phase-transfer base systems in that they do not react with alkyl halides, therefore they can be added together with the electrophile at the start of the reaction. In addition, since only a small amount of the anion is generated and then trapped by reaction with the alkyl halide, these reactions can be conducted at room temperature.



18 (BEMP)



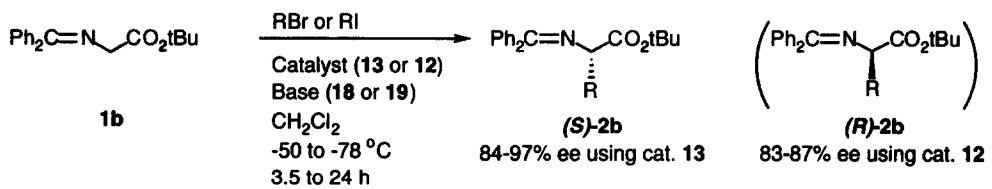
19 (BTPP)

Scheme 9. Schwesinger Bases: Strong, Neutral, Organic-Soluble Bases.

In addition to the monoalkylation studies described above, several other types of solid-phase UPS reactions have been reported from our laboratories. Resin-bound α,α-dialkylated amino acid or peptide products are available by alkylation of a resin-bound monoalkylated aldimine derivative.[28] Alternatively, a tandem dialkylation procedure from a resin-bound glycine derivative involving an initial UPS step followed by a second alkylation using the stronger base KHMDS at –40 °C also leads to α,α-dialkylated amino acid products.[29] Conjugate additions of **15** with a variety of Michael acceptors have also been described.[30]

Homogeneous Catalytic Enantioselective Synthesis of α-Amino Acids

A homogeneous catalytic enantioselective synthesis of α-amino acid derivatives has been reported recently.[31] The very effective third generation catalyst **13**, described earlier by Corey,[18] or its pseudoenantiomer **12**, were used in conjunction with the Schwesinger bases BEMP (**18**, for active halides) or the slightly stronger base BTPP (**19**, for non-active halides). The reaction was carried out in methylene chloride at either –78 °C (for active halides) or at –40 to –50 °C (for non-active halides). With the exception of isobutyl bromide, which gave a 97% ee in 24 hours with catalyst **13**, the other reactions only took from 3.5 to 7 hours. As in the earlier Lygo studies,[17] enantioselectivities were, in general, higher with catalyst **13** (84-97% ee) than with its pseudoenantiomer **12** (83-87% ee) and the α-halo ester, *t*-butyl bromoacetate, gave the lowest level of induction (56% ee).

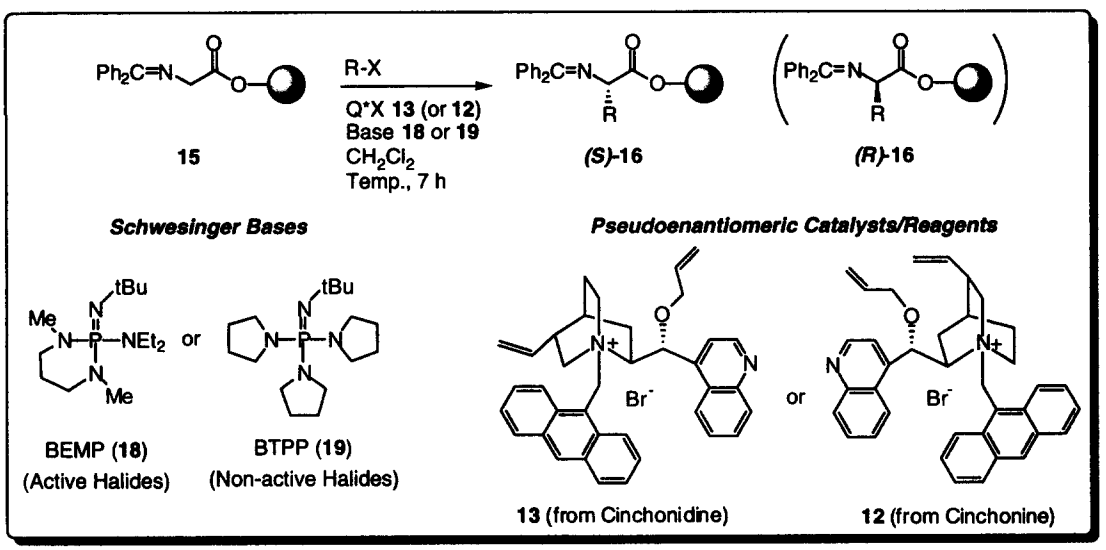


Scheme 10. Homogeneous Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives.

Results and Discussion

We were interested in combining various principles discussed in the previous Background Section in order to realize an enantioselective synthesis of α-amino acid derivatives on solid-phase.[32] Such a methodology would be very useful for the rapid preparation of optically active amino acids or related derivatives in a combinatorial fashion.[24-26] It was reasoned that the homogeneous system outlined previously in Scheme 10 utilizing BEMP or BTPP (**18** and **19**, Scheme 9) in combination with the very effective third-generation catalysts (**13** and **12**, Scheme 3) might well provide an ideal system for the solid-phase enantioselective alkylation study. The Wang resin was chosen for initial experiments since the majority of our solid-phase efforts to date have utilized this support.[20b,28-30] We report here the results of our preliminary studies.

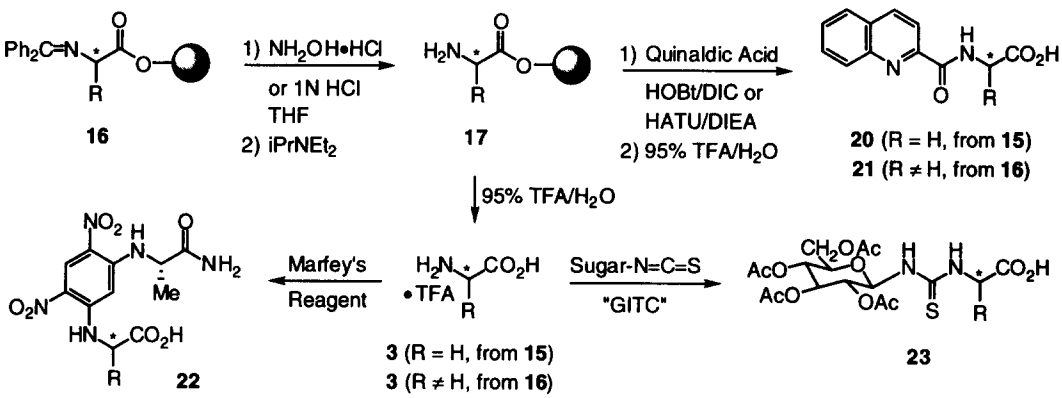
Two model alkylations were chosen for the study of the enantioselective alkylation of the Wang-resin bound benzophenone imine of glycine (**15**) (Scheme 11). Benzylation with benzyl bromide represents an alkylation using an active alkyl halide while ethylation with ethyl iodide is an alkylation involving a less reactive, normal primary alkyl halide.



Scheme 11. Enantioselective Solid-Phase Synthesis of α-Amino Acid Derivatives.

Two complementary analytical methods were used in these studies (Scheme 12), requiring that each reaction be run in duplicate. The first method involved imine hydrolysis of the alkylated resin-bound product (**16**), neutralization, *N*-acylation of the resin-bound primary amine **17** and then cleavage of the product from the resin with TFA. The resulting *N*-quinaldoylated acid product (**20**, from unreacted starting material and **21**, from alkylated product) was weighed to determine mass recovery yield and then subjected to reverse-phase HPLC on an achiral C_{18} column to determine product purity and conversion. The quinaldoylated products were further analyzed by low- and high-resolution mass spectrometry.

The second analytical method (Scheme 12), used to measure the level of enantioselectivity, involved hydrolysis of the resin-bound imine product (**16**), neutralization and then hydrolysis from the resin using TFA.



Scheme 12. Imine Hydrolysis, Cleavage from the Resin and Derivatization of Optically Active α-Amino Acid Products.

The resulting free amino acid product (**3**) was weighed to determine mass recovery yield. Then an aliquot was reacted with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate ("glucose isothiocyanate," "GITC") to make the diastereomeric glucose thiourea ("GTU") derivatives (**23**), which were analyzed by achiral HPLC.[33-35] In the case of aspartic acid (**3**, R = CH_2CO_2H), derivatization was accomplished using Marfey's reagent [*N*α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide] and the resulting product (**22**, R = CH_2CO_2H) was analyzed by HPLC.[36] These methods for determining enantioselectivities by conversion of the products into diastereomers for analysis proved, in general, to be considerably faster for the wide variety of amino acids analyzed than the use of chiral HPLC analysis of the enantiomeric products.[37]

The initial experiment (Table 1) involved benzylation (5 eq. $PhCH_2Br$) of the Wang-resin bound benzophenone imine of glycine (**15**) using a catalytic amount (0.1 equivalent) of the quaternary ammonium salt **13** in methylene chloride at –78 °C for seven hours using BEMP (5 eq.) as base. Both mass recovery (92%) and HPLC purity (3% **20**; 95% **21**, R = $PhCH_2$-) were good, however, the level of enantioselectivity was only 44% ee. Reaction with the less active ethyl iodide (10 eq. of both base (BTPP) and ethyl iodide at –78 °C) using a catalytic amount of **13** resulted in incomplete conversion of starting material to product (79% mass recovery; 39% **20**; 61% **21**, R = Et) and a similar level of enantioselection (46% ee) in the product α-amino butyric acid. Further

Table 1. Enantioselective Alkylation of **15** with Different Amounts of Quaternary Salt **13**.

RX	13 (eq.)	Yield (20+21) (%)	% 20 (HPLC)	% 21 (HPLC)	Yield 3 (%)	% ee
$PhCH_2Br$	0.1	92	3	95	91	44
"	0.5	98	3	93	92	72
"	1.0	97	3	95	93	76
"	2.0	94	2	96	94	77
EtI	0.1	79	39	61	103	46
"	0.5	89	11	89	98	74
"	1.0	94	5	95	103	77
"	2.0	95	3	97	98	81

experiments (Table 1) involved using varying equivalents of quaternary salt **13** (0.1, 0.5, 1.0, and 2.0 eq.) to measure the effect of the amount of catalyst on enantioselectivity with both alkyl halides and, for ethyl iodide, the extent of conversion. We were gratified to see a substantial improvement in enantioselection (up to 77% ee for benzylation and 81% ee for ethylation using 2 eq. of **13**) as well as high conversion of starting material to product in the ethylation reaction.

The "optimal conditions" chosen for further study use 1.0 equivalent of quaternary salt **13** with 5.0 equivalents of both base (BEMP) and active alkyl halide at –78 °C in methylene chloride for a reaction time of seven hours. For less reactive alkyl halides, 1.0 equivalent of **13** and 10.0 equivalents of both base (BTPP) and less reactive or hindered alkyl halide were used at –40 to –50 °C (acetonitrile/dry ice slush) in methylene chloride for seven hours. These "optimal conditions" involve a full equivalent of the quaternary salt **13**, which now serves as a chiral reagent rather than a chiral catalyst. Although not formally a catalytic process, these resin-bound alkylations using a full equivalent of the quaternary ammonium salt **13** are not problematic, since the solid-phase reactions are typically run on small-scale (40 μmol) and the chiral reagent/catalyst **13** is easily prepared[18a] in two steps from an inexpensive starting material (cinchonidine), available from the chiral pool.[38] Additionally, the pseudoenantiomeric reagent/catalyst **12** is prepared[31] (see experimental) from cinchonine.[38] Finally, since the enantioselective alkylation can also be carried out in homogeneous solution with **1b** as starting substrate using a catalytic amount of **13** or **12**,[31] the two methods are complementary.

In a second set of experiments, the effect of temperature on the enantioselective alkylation was probed (Table 2). Alkylations with benzyl bromide were conducted at five different temperatures: –78 °C, –40 °C, –20 °C, 0 °C, and ambient temperature. As expected, the best enantioselectivity (76% ee) was obtained at –78 °C However, it is significant that *considerable induction (51% ee) occurs at room temperature.* Selectivities similar to those observed with benzyl bromide were obtained with ethyl iodide at both –78 °C and at ambient temperature. However, as noted in Table 1, substantial amounts of starting material (as the quinaldoylated derivative, **20**) were still observed. This confirms that reactions with the less reactive or hindered halides need to be run at slightly higher temperature (–40 to –50 °C).

Table 2. Enantioselective Alkylation of **15** with Quaternary Salt **13** at Different Temperatures.

RX	Temperature (°C)	Yield (20+21) (%)	% 20 (HPLC)	% 21 (HPLC)	Yield 3 (%)	% ee
$PhCH_2Br$	-78	97	1	96	96	76
"	-40	95	1	97	95	71
"	-20	96	0	99	98	60
"	0	97	1	98	98	61
"	RT	97	0	98	96	51

With these preliminary studies completed, attention was turned to conducting the enantioselective alkylation of the resin-bound glycine Schiff base **15** with a variety of different alkyl halides (Table 3). Inductions ranged from 51-89% ee for 17 different alkyl halides to yield the *(S)*-amino acid products using quaternary salt **13**. Lower inductions (55-67% ee for 3 different alkyl halides) were observed with the quaternary salt **12** to form the *(R)*-amino acid products. The lower enantioselectivities observed with the cinchonine-derived reagent (**12**) compared with the cinchonidine-derived salt (**13**) are consistent with the earlier report by Lygo[17] (Scheme 7,

compare catalysts **11** and **10**) as well as our own observations with the homogeneous system (Scheme 10, compare catalysts **13** and **12**).[31]

Table 3. Enantioselective Alkylation of Resin-Bound Glycine Substrate **15** with Different Alkyl Halides.

Cmpd.	R-X	Base	T (°C)	Yield 21 (%) (a)	% 21 (HPLC)	Yield 3 (%)	% ee *S* (*R*)
a	Me-I	BEMP	-78	98	96	99	86
b	Et-I	BTPP	-40	98	93	96	77 (60)
c	nOctyl-I	BTPP	-40	96 (b)	88	99	80
d	Allyl-Br	BEMP	-78	99	94	97	83 (67)
e	$(CH_3)_2CHCH_2$-I	BTPP	-40	70 (c)	25	61	80
f	CH_2=C(Me)CH_2-Br	BEMP	-78	100	60	94	89
g	$PhCH_2$-Br	BEMP	-78	100	96	96	76 (55)
h	4-$MeC_6H_4CH_2$-Br	BEMP	-78	83	97	97	80
i	4-$NCC_6H_4CH_2$-Br	BEMP	-78	89	97	72	67
j	4-$CF_3C_6H_4CH_2$-Br	BEMP	-78	99	95	100	72
k	4-$FC_6H_4CH_2$-Br	BEMP	-78	92	95	94	74
l	4-$BrC_6H_4CH_2$-Br	BEMP	-78	98	96	97	80
m	4-$O_2NC_6H_4CH_2$-Br	BEMP	-78	97	96	86	61
n	4-$PhC_6H_4CH_2$-Br	BEMP	-78	95	99	100	85
o	2-(Bromomethyl)naphthalene	BEMP	-78	93	98	99	51
p	Ph_2CH-Br	BTPP	-40	87	95	78	60
q	$tBuO_2CCH_2$-Br	BEMP	-78	99	96	98	57

a. Using the optimized conditions for alkylation, there was, except where noted otherwise, typically 1-3% of **20** in the quinaldoylated product (**21**). This small amount of unreacted starting material resulted from incomplete mixing and resin adhering to the sides and top of the reaction vessel. b. With octyl iodide, 10% unreacted starting material (**20**) was observed. c. With isobutyl iodide, 70% unreacted starting material (**20**) was observed.

The enantioselectivities observed in the alkylation of the resin-bound benzophenone imine of glycine (**15**) to form the *(S)*-amino acid products are less than their homogeneous counterparts (Scheme 10)[31] by an average of 13.5% ee (range of 1% ee to 28% ee less effective for 14 cases). In the homogeneous case, isobutyl iodide gave the highest induction observed (97% ee),[31] however, on resin an 80% ee was obtained in the product with only a 25% chemical yield and considerable unreacted starting material (70%) was observed (Table 3, entry e). Interestingly, the structurally similar but considerably more reactive methallyl bromide (Table 3, entry f) gave the highest enantioselectivity observed on-resin (89% ee). In the case of diphenylmethyl bromide (Table 3, compound p), the alkylation product was obtained in 60% ee on resin. As in the other cases, a poor selectivity was observed in the solid-phase alkylation using *t*-butyl bromoacetate (Table 3, entry q, 57% ee). The chiral induction in these reactions is presumed to originate from preferential alkyation of one face of a chiral ion-pair between the enolate anion of **15** and the cation of the *cinchona*-derived quaternary ammonium salt (**12** or **13**). A working model for such a chiral ion-pair in solution was proposed recently by Corey and coworkers.[18a]

In summary, an enantioselective alkylation of a resin-bound glycine imine has been developed. The enantioselectivities observed are remarkable considering that no optimization of perhaps two of the most important variables, the resin and its linker, has been attempted. Future studies will address these points.

Experimental

***O*(9)-Allyl-*N*-9-anthracenylmethylcinchoninium bromide.** To a suspension of cinchonine (2.0 g, 6.8 mmol) in toluene (20 mL) was added 9-(chloromethyl)anthracene (1.62 g, 7.14 mmol). The reaction mixture was refluxed for 24 h and then cooled to room temperature. The solid was collected by filtration to afford 2.40 g of the desired *N*-9-anthracenylmethylcinchoninium chloride as a light yellow solid. Concentration of the filtrate and crystallization from CH_2Cl_2/Et_2O afforded an additional 0.43 g of the product as a light yellow solid (80% combined yield). This product was used directly in the next step.

To a suspension of the above crude product (3.0 g, 5.76 mmol) in CH_2Cl_2 (25 mL) was added allyl bromide (1.52 mL, 17.55 mmol) and 50% aqueous NaOH (3.0 mL, 28.5 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during which time all of the solids dissolved. The mixture was diluted with water (30 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give an orange solid. The solid was suspended in ether, stirred overnight and filtered to give crude product. Recrystallization from $EtOH/Et_2O$ (the ether was added dropwise until the solution of the product in EtOH turned cloudy) afforded 2.92 (84%) of the product as a light orange solid. ^1H NMR (300 MHz, CD_3OD) δ 1.17-1.27 (m, 1 H); 1.63-1.71 (m, 1 H);1.78-1.87 (m, 2 H); 2.26-2.34 (m, 1 H); 2.58 (app. t, 1 H, J = 12.1 Hz); 2.83 (app. q, 1 H, J = 11.0 Hz); 3.21 (app. t, 1 H, J = 11.4 Hz); 4.25 (app. t, 1 H, J = 11.0 Hz); 4.36-4.56 (m, 4 H); 5.07 (d, 1 H, J = 17.7 Hz); 5.21 (d, 1H, J = 10.7 Hz); 5.61 (d, 1 H, J = 10.7 Hz); 5.71 (d, 1 H, J = 17.7 Hz); 5.91-6.15 (m, 3 H); 6.39-6.42 (m, 1 H); 6.91 (bs, 1 H); 7.60-7.67 (m, 2 H); 7.70-7.75 (m, 1 H); 7.81-7.86 (m, 1 H); 7.93-7.97 (m, 3 H); 8.18-8.26 (m, 3 H); 8.34 (d, 1 H, J = 9.6 Hz); 8.62 (m, 1 H); 8.86 (d, 1 H, J = 9.6 Hz); 8.88 (s, 1 H); 9.04 (d, 1 H, J = 5.2 Hz); m.p. 142-144 °C.; HRMS (FAB^+): calcd. for $C_{37}H_{37}N_2O^+$: 525.2906, found 525.2902.

Alkylation of the Benzophenone Imine of Gly-Wang-Resin. Method A (Reactive Alkyl Halides). The benzophenone imine of Wang resin (**15**) (40 μmol, 89 mg, substitution = 0.45 mmol/g), was weighed into a 3-4 mL capacity test tube. 2mL of dry dichloromethane was added, followed by the catalyst (24 mg, 40 μmol, 1 eq.) and the alkyl halide (0.2 mmol, 5 eq.). The reaction mixture was cooled to -78 °C and BEMP (58 μL, 0.2 mmol, 5 eq.) was added, and the reaction mixture was maintained at -78 °C for 7 h with gentle stirring (magnetic stirring and manual agitation) under argon. The resin was then collected by filtration into a fritted glass vial, washed with dichloromethane (6 x 1.5 mL), and subsequent steps were carried out directly in the fritted glass vial.

Method B (Unreactive Alkyl Halides). The benzophenone imine of Wang resin (**15**) (40 μmol, 89 mg, substitution = 0.45 mmol/g), was weighed into a 3-4 mL capacity test tube. 2mL of dry dichloromethane was added, followed by the catalyst (24 mg, 40 μmol, 1 eq.) and the alkyl halide (0.4 mmol, 10 eq.). The reaction mixture was cooled to -40 °C (CH_3CN/dry ice slush; this bath gave a temperature from –40 to –50 °C) and BTPP (122 μL, 0.4 mmol, 10 eq.) was added, and the reaction mixture was maintained at -40 °C for 7 h with gentle stirring (magnetic stirring and manual agitation) under argon. The resin was then collected by filtration into a fritted glass vial, washed with dichloromethane (6 x 1.5 mL), and subsequent steps were carried out directly in the fritted glass vial.

Imine Hydrolysis. Method A (compounds **17a-17o** and **17q**). The resin-bound imine product **16** (40 μmol) was washed with THF and then THF/H_2O (3:1) (3 x 1.5-2 mL each). 1 N $NH_2OH{\cdot}HCl$/THF (1:2) (1.5-2 mL) was added to the resin and the suspension was mixed by rotation for 5 h at room temperature. The reaction

mixture was filtered, washed with NMP (5 x 1.5-2 mL), and then neutralized with 10 % DIEA/NMP (3 x 1.5-2 mL each). This was followed by washing with NMP (10 x 1.5-2 mL).

Method B (compound **17p**). The resin bound imine product **16** (40 μmol) was washed with THF and then THF/H_2O (3:1) (3 x 1.5-2 mL each). 1 N HCl/THF (1:2) (1.5-2 mL) was added, the RV top capped and mixed for 4 h at ambient temperature. The reaction was filtered and the resin washed 3x with THF and then neutralized with 10% DIEA/NMP (3x). This was followed by washing 3x each with NMP, CH_2Cl_2, and NMP.

***N*-Acylation.** Method A (to form resin-bound precursors to products **21a-21m** and **21q**). To the resin bound amino acid **17** (40 μmol), NMP (1.20 mL) was added followed by a 1 M solution of quinaldic acid in NMP (200 μL, 5 eq), 1 M solution of HOBt•H_2O in NMP (200 μL, 5 eq) and DIC (31 μL, 5 eq) and the suspension was mixed by rotation for 18 h at room temperature. The reaction was filtered and washed with NMP, THF, and then CH_2Cl_2 (3 x 1.5-2 mL each).

Method B (to form resin-bound precursors to products **21n-21p**). To the resin bound amino acid **17** (40 μmol), NMP (0.50 mL) was added followed by a 1 M solution of quinaldic acid in NMP (400 μL, 10 eq), 1M solution of HATU in NMP (520 μL, 13 eq) and DIEA (91 μL, 13 eq) and the suspension was mixed by rotation for 18 h at room temperature. The reaction was filtered and washed with NMP, THF, and then CH_2Cl_2 (3 x 1.5-2 mL each).

Table 4. High Resolution Mass Spectra (FAB^+) for Compounds **21**.

Compound	R-	Calculated		Found
21a	Me-	$C_{13}H_{13}N_2O_3$	245.0926	245.0932
21b	Et-	$C_{14}H_{15}N_2O_3$	259.1083	259.1092
21c	nOctyl-	$C_{20}H_{27}N_2O_3$	343.2022	343.2012
21d	Allyl-	$C_{15}H_{15}N_2O_3$	271.1083	271.1090
21e	$(CH_3)_2CHCH_2$-	$C_{16}H_{18}N_2O_3$	a	a
21f	CH_2=C(Me)CH_2-	$C_{16}H_{17}N_2O_3$	285.1239	285.1240
21g	$PhCH_2$-	$C_{19}H_{17}N_2O_3$	321.1239	321.1243
21h	4-$MeC_6H_4CH_2$-	$C_{20}H_{19}N_2O_3$	335.1396	335.1404
21i	4-$NCC_6H_4CH_2$-	$C_{20}H_{16}N_3O_3$	346.1192	346.1193
21j	4-$CF_3C_6H_4CH_2$-	$C_{20}H_{16}F_3N_2O_3$	389.1113	389.1108
21k	4-$FC_6H_4CH_2$-	$C_{19}H_{16}FN_2O_3$	339.1145	339.1137
21l	4-$BrC_6H_4CH_2$-	$C_{19}H_{16}BrN_2O_3$	399. 0344	399.0329
21m	4-$O_2NC_6H_4CH_2$-	$C_{19}H_{16}N_3O_5$	366.1090	366.1082
21n	4-$PhC_6H_4CH_2$-	$C_{25}H_{21}N_2O_3$	397.1552	397.1543
21o	(2-Naphthyl)methyl-	$C_{23}H_{19}N_2O_3$	371.1396	371.1382
21p	Ph_2CH-	$C_{25}H_{20}N_2O_3$	396.1474	396.1477
21q	HO_2CCH_2-	$C_{14}H_{13}N_2O_5$	289.0824	289.0836

a. Only the low resolution mass spectrum was obtained for product **21e**, since it contained considerable starting material. Calc. 286, Found (M+1) 287.

Product Cleavage from the Resin to Prepare Products 21 or 3. To the resin-bound product (40 μmol), 95% TFA/H_2O (1.5-2 mL) was added and the reaction was mixed by rocking for 4 h. The reaction mixture was filtered into a tared vial and the resin washed with TFA/H_2O (3 x 1.5-2 mL) and then CH_2Cl_2 (3 x 1.5-2 mL). The solvent was removed under reduced pressure and the residue was dried *in vacuo*. See Table 4 for the mass spectral data obtained for products **21**.

HPLC Analysis. Quantities of **20** and **21** were determined by HPLC on a Varian 9010/9050 system using a Nova-Pak C_{18} column (150 x 3.9 mm) with mobile phases of 0.1% (v/v) TFA/H_2O (A) and 0.08% (v/v) TFA/CH_3CN (B) and a gradient of 0–100% B in 20 min at a flow rate of 1 mL/min with UV detection at 220 nm.

A Hewlett-Packard 1100 Series HPLC was used to analyze the GITC amino acids derivatives (**23**) and the Marfey's derivative **22**. A Zorbax SB-C_{18} column (4.6 x 75 mm, 3.5 μ particle size) was eluted with CH_3CN/H_2O gradients containing 0.1% TFA at 1 mL/min (for gradients, see footnote of Table 5). The products were detected at 250 nm (GTU derivatives **23**) or 340 nm (Marfey's derivatives **22**).

Table 5. HPLC Analysis of Amino Acid GTU Derivatives **23** and Marfey's Derivative **22**.

Cmpd.	R-	Gradient (a)	Ret. Time (min.) (S)	(R)	Δt	% ee (S:R)
(S)-**23a**	Me-	C	15.53	17.28	1.75	86 (93:7)
(S)-**23b**	Et-	A	12.61	14.04	1.43	77 (88.5:11.5)
(R)-**23b**	Et-	A	12.61	14.04	1.43	60 (20:80)
(S)-**23c**	nOctyl-	B	30.32	31.04	0.72	80 (90:10)
(S)-**23d**	Allyl-	A	14.92	16.10	1.18	83 (91.5:8.5)
(R)-**23d**	Allyl-	A	14.92	16.10	1.18	67 (16.5:83.5)
(S)-**23e**	$(CH_3)_2CHCH_2$-	A	19.02	19.94	0.92	80 (90:10)
(S)-**23f**	CH_2=C(Me)CH_2-	A	17.37	18.32	0.95	89 (94.5:5.5)
(S)-**23g**	$PhCH_2$-	A	20.62	21.50	0.88	76 (88:12)
(R)-**23g**	$PhCH_2$-	A	20.62	21.50	0.88	55 (22.5:77.5)
(S)-**23h**	4-$MeC_6H_4CH_2$-	B	22.53	23.30	0.77	80 (90:10)
(S)-**23i**	4-$NCC_6H_4CH_2$-	B	19.54	20.30	0.76	67 (83.5:16.5)
(S)-**23j**	4-$CF_3C_6H_4CH_2$-	B	25.33	26.10	0.77	72 (86:14)
(S)-**23k**	4-$FC_6H_4CH_2$-	B	21.26	22.07	0.81	74 (87:13)
(S)-**23l**	4-$BrC_6H_4CH_2$-	B	24.06	24.91	0.85	80 (90:10)
(S)-**23m**	4-$O_2NC_6H_4CH_2$-	B	21.27	22.16	0.89	61 (80.5:19.5)
(S)-**23n**	4-$PhC_6H_4CH_2$-	B	26.48	27.15	0.67	85 (92.5:7.5)
(S)-**23o**	(2-Naphthyl)methyl-	B	24.84	25.67	0.83	51 (75.5:24.5)
(S)-**23p**	Ph_2CH-	B	25.43	26.02	0.59	60 (80:20)
(S)-**22**	HO_2CCH_2-	D	7.08	8.28	1.20	57 (78.5:21.5)

a. Gradient A = 20-25% CH_3CN over 9 min. then 25-50 % CH_3CN over 20 min. Gradient B = 20-25% CH_3CN over 9 min. then 25-60 % CH_3CN over 26 min. Gradient C = 15-30% CH_3CN over 25 min. Gradient D = 20-25% CH_3CN over 15 min.

GITC Derivatization and Analysis Procedure. For HPLC analysis, the crude amino acids **3** (racemic or optically active reaction products) were derivatized with GITC by a slightly modified method of Nimura et al.[33a] A 1 mg sample of amino acid was dissolved in 1 mL of 50% (v/v) aqueous acetonitrile containing 0.4% (w/v) triethylamine. For the very hydrophobic amino acids, 90% CH_3CN was used instead. A 250 μL aliquot of this amino acid solution was mixed with 500 μL of a solution of 0.2% (w/v) GITC in acetonitrile and the resulting mixture was allowed to stand at room temperature for 90 min.[34] For the amino acids with aromatic side chains, 0.100 mL of a 0.25% (w/v) solution of ethanolamine in CH_3CN was added to scavenge excess GITC.[35] After 10 min., 10-15 μL of TFA was added and a 5 μL aliquot was injected directly into the HPLC.

Marfey's Reagent Derivatization and Analysis of Aspartic Acid. A modification of the procedure of Fujii, *et al*[36] was used to derivatize aspartic acid. The product was dissolved in methanol to a 2 mg/mL concentration, a 0.125 mL aliquot was placed in a sample vial, dried *in vacuo* for 2-3 h, the residue was dissolved in 0.25 mL of 1 M $NaHCO_3$ and then 100 mL of 1% Marfey's reagent in CH_3CN was added. This solution was sonicated for 60 min at 37 °C. Reactions were quenched by addition of 0.25 mL of 1 M HCl and 5-10 μL of product **22** was analyzed by HPLC.

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27. Abbreviations: BEMP = 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; BTPP = *t*-butylimino-tri(pyrrolidino)phosphorane; KHMDS = potassium bis(trimethylsilyl)amide; NMP = 1-methyl-2-pyrrolidinone; DIEA = diisopropylethyl amine; HOBt = 1-hydroxybenzotriazole; DIC = diisopropyl carbodiimide; HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TFA = trifluoroacetic acid.

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37. We and others have measured enantioselectivities of the optically active Schiff base alkylation products **2b** with a variety of chiral HPLC methods. See: (a) Reference 9. (b) Reference 13a. (c) Reference 18a. (d) Reference 31. (e) Lee, W. *Anal. Lett.* **1997,** *30*, 2791-2799. (f) Lee, W. *Bull. Korean Chem. Soc.* **1998,** *19*, 715-717.

38. The price of 0.1 mole of the parent alkaloids, cinchonidine and cinchonine (see Scheme 3 for structures), is $15.60 and $16.00, respectively (Aldrich Chemical Company Catalog Handbook of Fine Chemicals, 1998-1999).