The Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis with Achiral Schiff Base Esters

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ABSTRACT
The development and application of chiral phase-transfer catalysis (PTC) for the enantioselective synthesis of optically active α-amino acid derivatives using achiral Schiff base esters developed in the author's laboratory and by others is reviewed. Phase-transfer catalysts derived from the *Cinchona* alkaloids have been exploited as inexpensive and attractive organocatalysts in the chiral PTC process. The recent evolution and use of these and other catalytic systems is described.

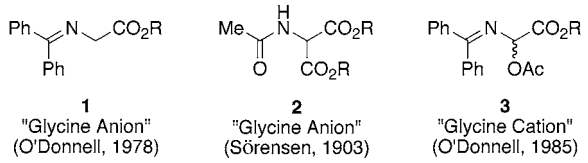
1. Introduction

The ever-increasing demand for enantiomerically enriched compounds has led to the rapid development of a variety of asymmetric transformations. Catalytic asymmetric processes are especially attractive in this regard since they allow for the use of substoichiometric amounts of the chiral control element, which is often the most expensive reagent in the process.[1] Chiral phase-transfer catalysis (PTC) offers further advantages because it typically involves mild conditions, simple reaction procedures, safe and inexpensive reagents and solvents, the use of organocatalysts (catalysts without metals), and the possibility of conducting reactions on either a small or large scale.[2] The preparation of optically active α-amino acid derivatives[3] by chiral PTC with achiral Schiff base esters, developed in the author's laboratory and by others, represents the most successful use of this methodology to date and will serve as the focus of this Account.

2. Background: Racemic Syntheses and Starting Material Preparation

The benzophenone imines of glycine alkyl esters (**1**) were introduced from our laboratory in 1978[4] as a practical alternative to diethylacetamidomalonate (**2**), the starting material for the classical 1903 Sörensen method for the synthesis of racemic α-amino acids (Scheme 1).[5] In the past 25 years, substrates **1** have been used in numerous syntheses of both racemic and optically active α-amino acids.[6] The complementary glycine cation equivalent **3**, readily available from **1**, can be reacted with various nucleophilic partners. This section outlines the early development of racemic syntheses using **1** and **3**.

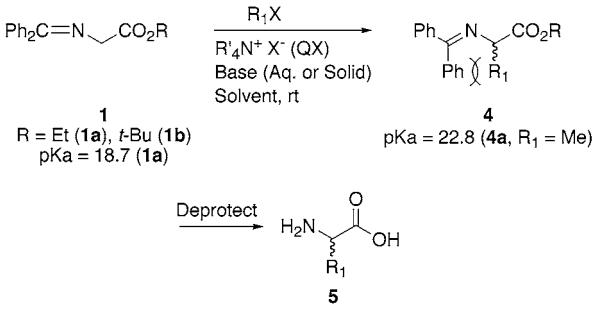
Scheme 1. Acyclic Glycine Derivatives for α-Amino Acid Synthesis



1 "Glycine Anion" (O'Donnell, 1978) **2** "Glycine Anion" (Sörensen, 1903) **3** "Glycine Cation" (O'Donnell, 1985)

Our efforts in the preparation of α-amino acids by PTC date from 1978, when the first general synthesis of racemic α-amino acids was reported (Scheme 2):[4,6]

Scheme 2. PTC for the Preparation of α-Amino Acid Derivatives

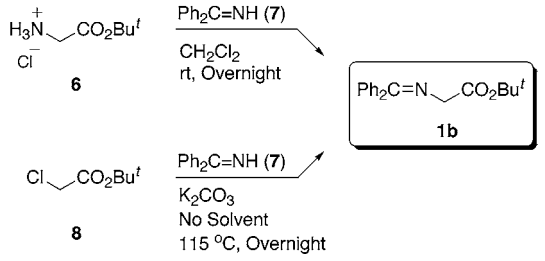


1 R = Et (**1a**), *t*-Bu (**1b**) pKa = 18.7 (**1a**) **4** pKa = 22.8 (**4a**, R_1 = Me) **5**

A key feature of this methodology is the *selective monoalkylation* of the starting substrates **1**, due to the considerable difference in acidity [pK_a(DMSO)] between starting substrates **1** and monoalkylated products **4**.[7] Additionally, this acid-weakening effect is crucial for the stereoselective introduction of an alkyl group to form **4** without concomitant racemization of the newly created stereogenic center under the basic reaction conditions.

The starting benzophenone imines of glycine alkyl esters **1** are readily prepared by several routes (Scheme 3). Transimination of the glycine alkyl ester salt (**6**) with benzophenone imine (**7**) is a convenient procedure for the preparation of various benzophenone imine derivatives.[8] A method that is adaptable to the large-scale synthesis of **1b** involves reaction of *tert*-butyl chloroacetate with benzophenone imine in the presence of base without solvent.[9]

Scheme 3. Syntheses of the Benzophenone Imine of Glycine *tert*-Butyl Ester



6 **1b** **8**

Marty O'Donnell was born in Williams, Iowa, in 1946. He received his B.S. degree in chemistry from the University of Iowa in 1968 and his Ph.D. in 1973 from Yale with Professor K. B. Wiberg and completed a postdoctoral fellowship with Professor Léon Ghosez at the Université Catholique de Louvain in Belgium. He started at IUPUI in 1975 and was promoted to full professor in 1984. His research interests include the development of new synthetic methodology for amino acids and peptides, combinatorial chemistry and solid-phase organic synthesis, and asymmetric synthesis using phase-transfer catalysis as well as organometallic catalysis.

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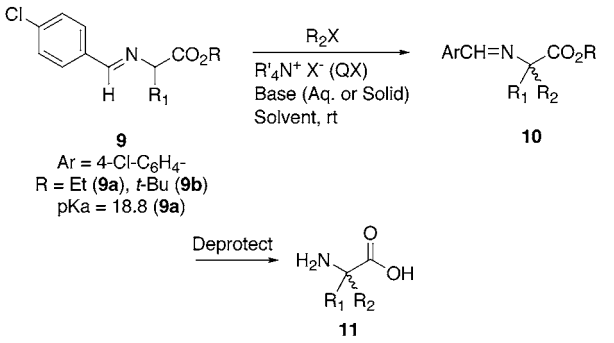
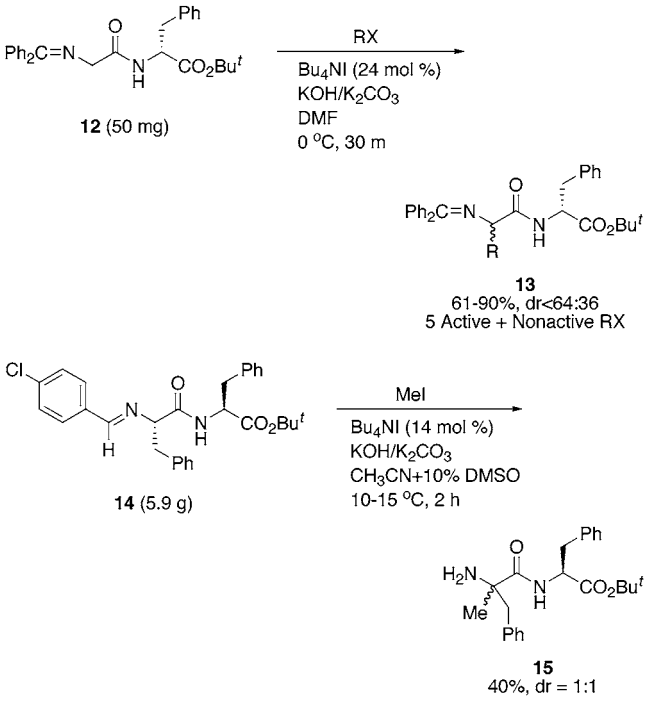
The preparation of racemic α,α-dialkylated α-amino acids by PTC was reported in 1982 in collaboration with the group of Professor L. Ghosez at the Université Catholique de Louvain in Belgium (Scheme 4).[10]

Scheme 4. PTC for the Preparation of α,α-Dialkylamino Acid Derivatives



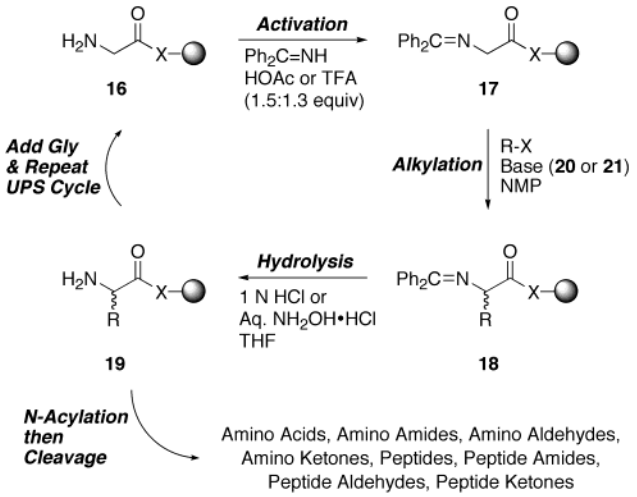
Selective alkylation of Schiff base dipeptide esters **12** and **14** on the N-terminal carbon with retention of configuration at the C-terminal α-carbon using solid–liquid PTC gave both diastereomeric products (Scheme 5).[11]

Scheme 5. N-Terminal Functionalization of Peptides by PTC



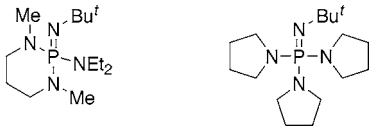
In collaboration with Dr. William L. Scott of Eli Lilly and Company in Indianapolis, we reported the solid-phase synthesis of unnatural amino acids and peptides, termed "unnatural peptide synthesis" ("UPS"), in 1996 (Scheme 6):[12]

Scheme 6. Unnatural Amino Acid and Peptide Synthesis (UPS)



UPS involves the introduction of an amino acid side chain during a normal solid-phase peptide synthesis (SPPS, "Merrifield synthesis") by adding a new cycle of three steps. First, the N-terminal amino acid residue is activated as the benzophenone imine (for monoalkylation of an N-terminal glycine) or the aldimine (for dialkylation of an N-terminal monoalkylated residue; not shown). Second, deprotonation and alkylation/Michael addition of the activated substrate is accomplished with an organic-soluble, nonionic phosphazene base ("Schwesinger base", **20** or **21**, Scheme 7)[13] together with an appropriate electrophile.

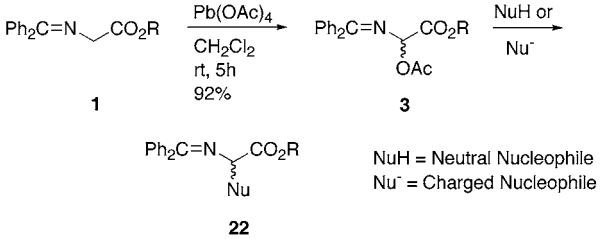
Scheme 7. Schwesinger Bases for UPS or Homogeneous Solution-Phase Reactions



Third and finally, mild hydrolysis of the imine functionality gives resin-bound product, which can be cleaved from the solid support or subjected to further UPS cycles, SPPS, or solid-phase organic synthesis (SPOS).

The benzophenone imines of glycine alkyl esters also function as starting materials for the preparation of the α-acetoxy derivatives **3**, which serve as glycine cation equivalents. Substrates **3** react with various neutral or charged nucleophiles to give monosubstituted amino acid derivatives (Scheme 8).[6,14]

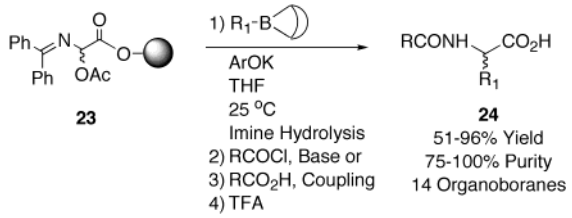
Scheme 8. Preparation and Reactions of a Glycine Cation Equivalent



Representative products **22** include α-heteroatom-substituted derivatives, aryl and vinyl glycines, and α-amino acids containing a β-quaternary center.

The organoborane alkylation of resin-bound acetate **23** yields several amino acid structural types not readily available by the complementary anionic equivalent (Scheme 9).[15]

Scheme 9. Organoborane Alkylation of a Resin-Bound Glycine Cation Equivalent

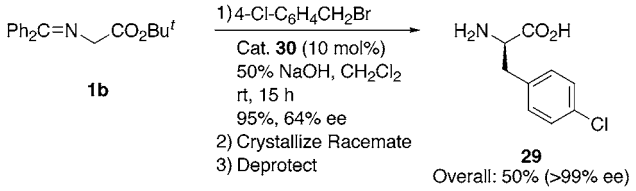


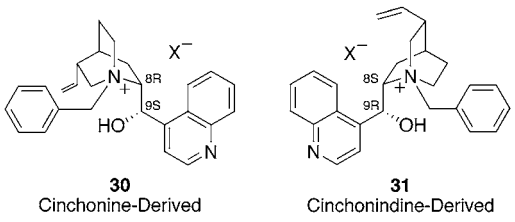
3. Evolution of Enantioselective PTC with *Cinchona* Alkaloids

The *Cinchona* alkaloids (Figure 1) have enjoyed a rich history in science, medicine, and chemistry.[16,17] Catalysts derived from cinchonine (**25**) and cinchonidine (**27**) have been used extensively in chiral PTC because the parent alkaloids are inexpensive, are readily available in both pseudoenantiomeric forms, and can be easily converted to effective phase-transfer catalysts.[2,6]

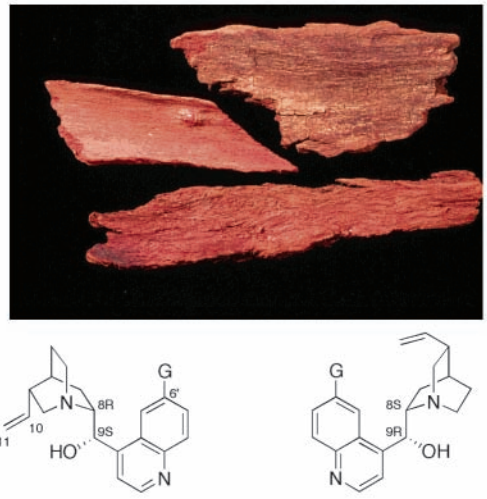
Monoalkylation to α-Substituted Amino Acid Derivatives. In 1984, the Merck group reported the use of the quaternerized derivatives (**30** and **31**) of cinchonine and cinchonidine as chiral phase-transfer catalysts for the highly enantioselective alkylation of an indanone derivative.[18] In 1989, we reported the catalytic enantioselective alkylation of our acyclic substrate **1b** using these "first generation catalysts" (Scheme 10).[19] Although by today's standards the enantioselectivities were moderate (66% ee), it was often possible to obtain optically pure α-amino acids by recrystallization of the enriched products obtained from the chiral PTC reaction.

Scheme 10. Enantioselective Alkylation by PTC with First Generation Catalysts





In 1994, we made a significant improvement in the enantioselectivity by proposing that the active catalyst in chiral PTC alkylations was formed by in situ *O*-alkylation

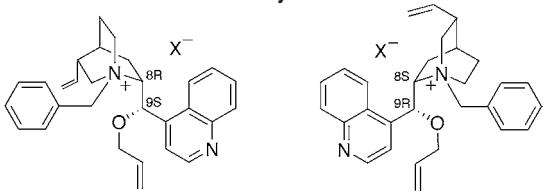


Cinchonine (**25**) (G = H) $19/0.1 mole
Quinidine (**26**) (G = OMe) $130/0.1 mole
Cinchonidine (**27**) (G = H) $18/0.1 mole
Quinine (**28**) (G = OMe) $85/0.1 mole

FIGURE 1. *Cinchona* plant and bark with structures and prices of the *Cinchona* alkaloids. Reproduced with permission of the Wellcome Trust Library.

of the *Cinchona* quaternary ammonium salt.[20] The best catalyst (81% ee) for these second generation catalysts contained the *O*-allyl group (**32** or **33**, Scheme 11**)**. Further studies showed that a mixed solvent system (70/30 PhMe/CH_2Cl_2) was optimal.[21]

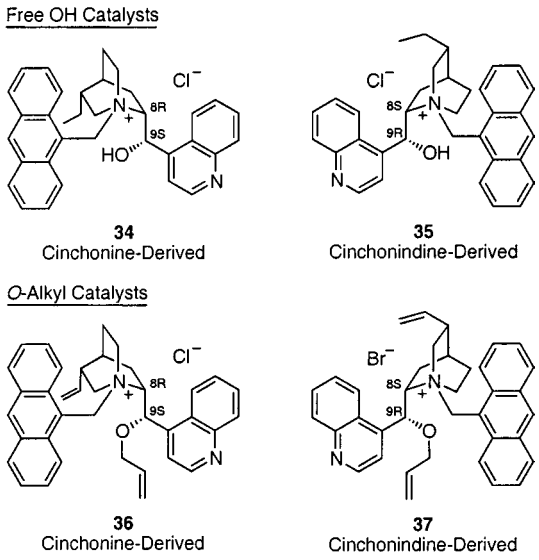
Scheme 11. Second Generation *Cinchona*-Derived Phase-Transfer Catalysts



These studies set the stage for a further major catalyst improvement, reported simultaneously in 1997 by the

Lygo[22] and Corey[23] groups. These third generation catalysts (Scheme 12) contained the *N*-9-anthracenylmethyl group with either a free OH (**34** or **35**), converted in situ to the active *O*-alkyl catalyst, or an *O*-allyl group (**37**). In the Lygo system, slightly higher enantioselectivites (~3%) were obtained using the 10,11-dihydro derivative (**35**).

Scheme 12. Third Generation *Cinchona*-Derived Phase-Transfer Catalysts



Corey et al. rationalized the origin of the enantioselectivity based on the structure of the key ion pair between the enolate of **1b** and catalyst **37** (Figure 2, the cation of **37** is in approximately the same orientation as depicted in Scheme 12).[23] In this case, the alkyl halide would approach the ion pair from the back right (dashed arrow), leading to the observed (*S*)-product.

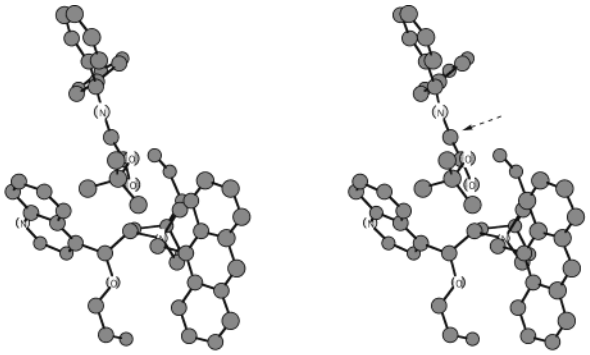
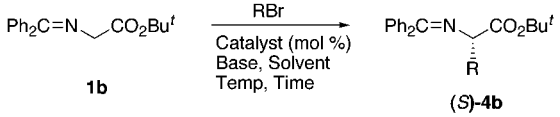


FIGURE 2. Stereoview of the ion pair between the enolate of **1b** and **37**.

We showed that it was possible to conduct these reactions in homogeneous solution with Schwesinger bases (**20** or **21**) and catalyst **37** or its pseudoenantiomer **36**.[24] Table 1 compares the reaction conditions, yields, and enantioselectivities for the three systems.

Table 1. Alkylations with Third Generation *Cinchona*-Derived Phase-Transfer Catalysts

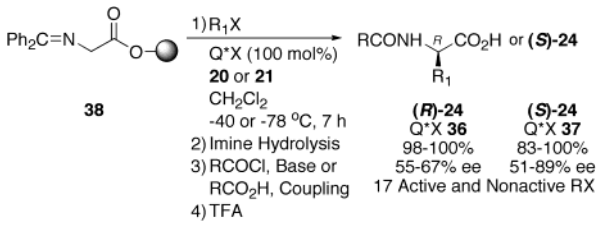


Comparison of Benzylation Leading to Product (*S*)-**4b** (R = CH_2Ph)

Lygo	Corey	O'Donnell
Heterogeneous	Heterogeneous	Homogeneous
Cat. **35** (10 mol%)	Cat. **37** (10 mol%)	Cat. **37** (10 mol%)
50% KOH, PhMe	$CsOH•H_2O$, CH_2Cl_2	BEMP (**20**), CH_2Cl_2
rt, 18 h	-78 °C, 23 h	-78 °C, 7 h
94% ee (32:1)	94% ee (32:1)	91% ee (21:1)
68% CY (after imine hydrol)	87% CY	88% CY
Ref. 22	Ref. 23	Ref. 24

We also reported the enantioselective solid-phase alkylation of **38** with both active (benzylic, allylic, α-halo esters) and nonactive (1-haloalkanes) alkyl halides (Scheme 13).[25]

Scheme 13. Enantioselective Alkylation of a Resin-Bound Glycine Derivative



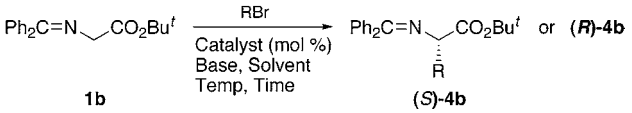
4. Further Developments in Enantio- and Diastereoselective PTC

A number of major research efforts have been mounted for further development and application of stereoselective PTC reactions to prepare α-amino acids. This section focuses on selected aspects of this chemistry with coverage mainly since our 2001 review.[6] While further significant achievements have been realized recently, advancement in the field has often been made on an empirical basis. For this reason, in addition to brief discussions, the following sections use reaction schemes to highlight important variables. These include substrate and catalyst structures, base, solvent(s), temperature, time, chemical yield, stereochemical yield, and number and types of electrophiles used. Subtle changes in one or more of these variables often lead to major improvements in the levels of selectivity. Important trends are noted, and in the final section, a summary of recent applications demonstrates use of this methodology in a variety of synthetic arenas. Except for our own studies (section 5), reports of metal-containing catalysts or substrates will not be discussed. Stereoselective reactions involving Schiff base derivatives of α-amino acids containing chiral auxiliaries and enzymatic resolutions of racemic or optically enriched products derived from Schiff base esters also will not be covered.[6]

Catalyst Development for Monoalkylations. Corey et al. reported in *Organic Syntheses* a preparation of catalyst **37**[26,27] and its use in catalytic Michael additions (see Scheme 28).

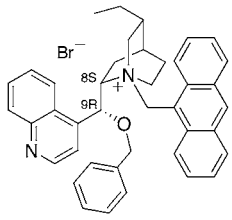
The general reaction used for the majority of recent monoalkylation studies discussed below is shown in Scheme 14. Key variables and results are given with each catalyst.

Scheme 14. General Reaction Used for Catalyst Development Studies

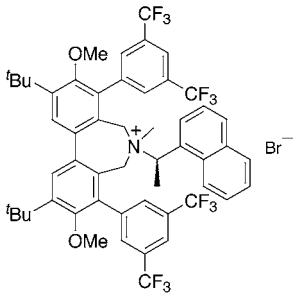


A recent study from the Lygo group of the in situ generation and use of catalysts from the parent alkaloid (**27**), which gave results comparable to those obtained with preformed catalyst, was applied to the generation and screening of a catalyst library of 20 members to yield optimal catalyst **39**.[28] A second library (40 members) of catalysts was prepared from simple chiral amines and conformationally dynamic biphenyls. Optimized catalyst **40**, derived from α-methylnaphthylamine, gave impressive results in the test benzylation reaction (97% ee, 1 mol % **40**) (Scheme 15).

Scheme 15. Lygo Phase-Transfer Catalysts



39 (10 mol%)
9M Aq.KOH + KBr
PhMe/CH_2Cl_2 (7:3)
0 °C, 4-18 h
98% ee (*S*)
3-Bromo-2-methylpropene

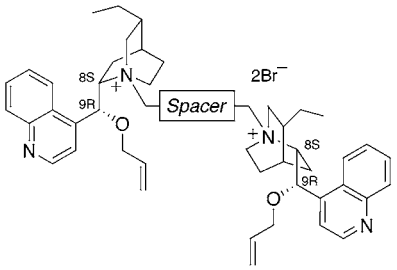


40 (1 mol%)
15M Aq. KOH, PhMe
0 °C, 1-2 h
71-100% 89-97% ee (*R*)
6 Active RX

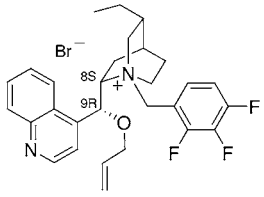
The groups of Jew and Park reported dimeric (and trimeric) catalysts with a spacer group between the *Cinchona* alkaloid units.[29] Catalyst **41a** gave excellent enantioselectivites with both active and nonactive alkyl halides. A study of electronic factors in the *Cinchona*-derived catalysts led to catalyst **42**, in which fluoro substituents on the *N*-benzylic group play an important role (Scheme 16). This catalyst was also used for dialkylation of imino ester substrates (see Scheme 25).

The Nájera group[3e] also reported dimeric-type catalysts (**43**).[30] Interestingly, an unexpected reversal in the sense of enantioselectivity when the base system was changed

Scheme 16. Jew and Park Phase-Transfer Catalysts



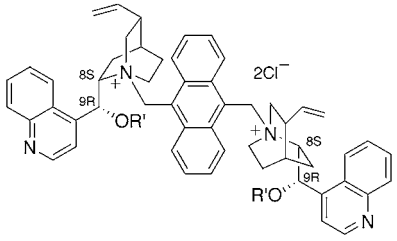
41 (5 mol%)
50% Aq.KOH
PhMe/$CHCl_3$ (7:3)
-20 °C, 4-12 h
81-94%, 97->99% ee (*S*)
6 Active & Nonactive RX



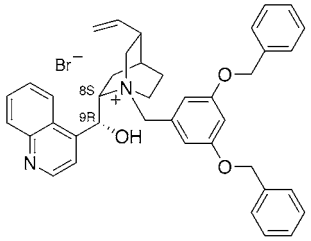
42 (10 mol%)
50% Aq.KOH
PhMe/$CHCl_3$ (7:3)
-20 °C, 3-18 h
60-96%, 94->99% ee (*S*)
12 Active & Nonactive RX
Dialkylation (Scheme 25)

from KOH to NaOH with catalyst **44** was reported (Scheme 17).

Scheme 17. Nájera Phase-Transfer Catalysts



43 (5 mol%)
(R' = H or Allyl)
50% Aq. KOH
PhMe/$CHCl_3$ (7:3)
-20 °C, 9-18 h
60-95%, 32-90% ee (*S*)
6 Active + Nonactive RX

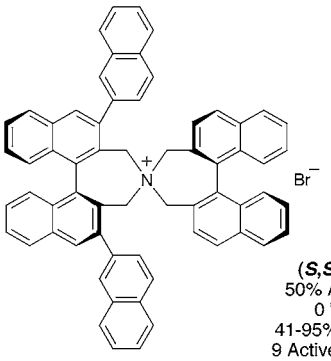


44 (10 mol%)
50% Aq. KOH, 66% ee (*S*)
50% Aq. NaOH, 40% ee (*R*)

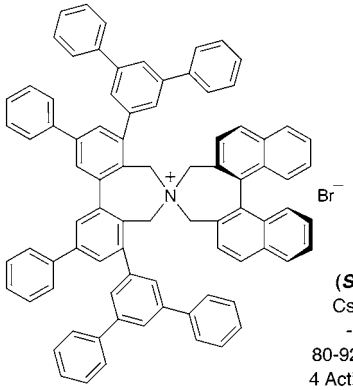
The Maruoka group has developed several structurally rigid, C_2-symmetric, chiral spiro ammonium salts derived from (*S*)- or (*R*)-1,1′-bi-2-naphthol derivatives (Scheme 18).[31] Such catalysts are more stable to the basic reaction conditions in PTC than β-hydrogen-containing quaternary ammonium salts, which can be degraded by in situ Hofmann elimination. Consequently, catalyst loadings (0.2−1 mol %) are often less than with normal quaternary ammonium salts. While these catalysts are expected to be expensive (they are not derived from the chiral pool and often require multistep syntheses), they have been effec-

tive in a wide range of chemical transformations. Dialkylations (see Scheme 27), as well as peptide alkylations and aldol reactions (see Schemes 31 and 33, respectively), will be discussed later.

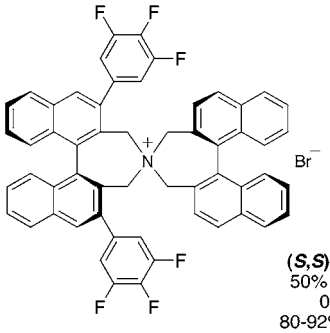
Scheme 18. Maruoka Phase-Transfer Catalysts



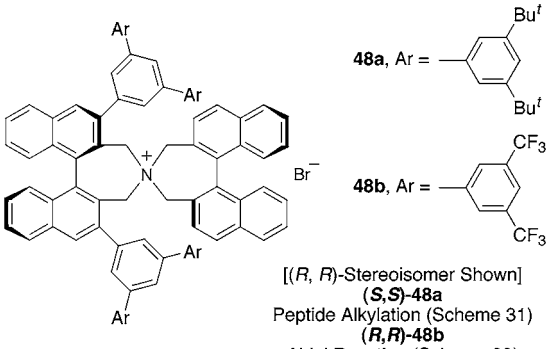
(*S,S*)-45 (1 mol%)
50% Aq. KOH, PhMe
0 °C, 0.5-10 h
41-95%, 90-96% ee (*R*)
9 Active + Nonactive RX



(*S,S*)-46 (1 mol%)
CsOH•H_2O, PhMe
-15 °C, 15-19 h
80-92%, 93-94% ee (*R*)
4 Active + Nonactive RX



(*S,S*)-47 (0.2-1 mol%)
50% Aq. KOH, PhMe
0 °C, 1.5-24 h
80-92%, 96-99% ee (*R*)
13 Active + Nonactive RX
Dialkylation (Scheme 27)

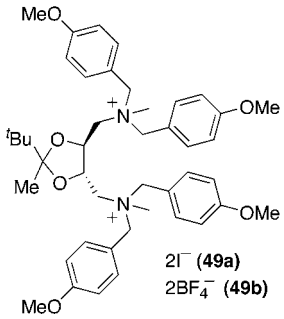


48a, Ar = 3,5-di-*t*-Bu-phenyl
48b, Ar = 3,5-di-CF$_3$-phenyl

[(*R, R*)-Stereoisomer Shown]
(*S,S*)-48a
Peptide Alkylation (Scheme 31)
(*R,R*)-48b
Aldol Reaction (Scheme 33)

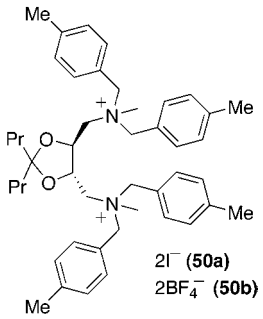
The Shibasaki group reported the preparation and evaluation of a library of more than 40 two-center tartrate-derived catalysts for alkylation of **1b** with active alkyl halides (optimal catalyst **49a**) and Michael additions (optimal catalyst **50**, Scheme 19). An interesting counterion effect, in which BF_4^- gave higher reactivity and selectivity, was reported recently.[32]

Scheme 19. Shibasaki Phase-Transfer Catalysts



$2I^-$ **(49a)**
$2BF_4^-$ **(49b)**

(*S,S*)-49 (10 mol%)
CsOH•H_2O
PhMe/CH_2Cl_2 (7:3)
-70 °C, 22-60 h
71-92%, 80-93% ee (*R*)
Active RX

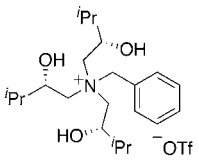


$2I^-$ **(50a)**
$2BF_4^-$ **(50b)**

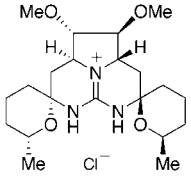
(*S,S*)-50
Michael Addition

Scheme 20 shows other catalysts for the enantioselective PTC alkylations of **1b**. The Takabe group developed a series of C_3-symmetric amine-based chiral PTC catalysts (**51**),[33] while Nagasawa et al. reported C_2-symmetric pentacyclic guanidine-based catalysts (**52**).[34]

Scheme 20. Other Phase-Transfer Catalysts



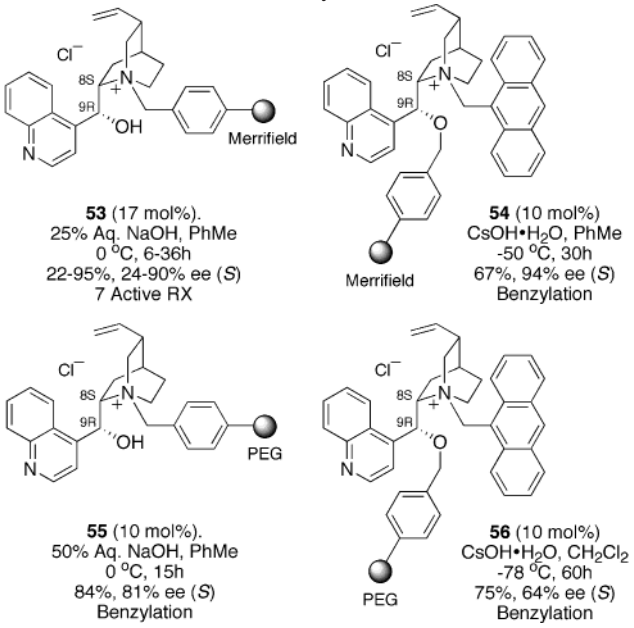
51 (1 mol%)
50% Aq, KOH, PhMe
0 °C, 12 h
55%, 58% ee (*S*)
Benzylation



52 (30 mol%)
1M Aq. KOH, CH2Cl2
0 °C, 40-160 h
55-85%, 76-90% ee (*R*)
Active + Nonactive RX

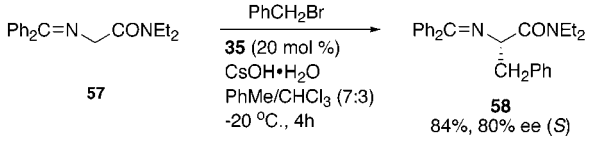
Several groups have developed polymer-bound phase-transfer catalysts.[35−37] Advantages for such resin-bound catalysts include simplified product purification and catalyst recovery by filtration and the potential for catalyst recycling. Studies of Merrifield- (**53** and **54**) and soluble PEG-bound catalysts (**55** and **56**), the role of spacers and different sites of attachment between support and catalyst, liquid−liquid or solid−liquid reaction systems, and micellar conditions[38] were reported (Scheme 21).

Scheme 21. Polymer-Bound *Cinchona*-Derived Phase-Transfer Catalysts



Ramachandran et al. achieved the alkylation of the benzophenone imine of glycinamide (**57**) under chiral PTC conditions (Scheme 22).[39] N,N-Disubstituted glycinamides gave higher enantioselectivities than their N-monosubstituted counterparts. Calculations predicted the correct absolute configuration of the products.

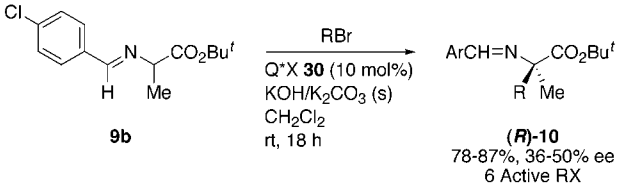
Scheme 22. Alkylation of Glycinamide Derivatives by Enantioselective PTC



Alkylation To Form α,α-Disubstituted Amino Acid Derivatives. The construction of compounds containing quaternary stereogenic centers (carbons with four different non-hydrogen groups) by catalytic enantioselective processes continues to be challenging.[40] The nonproteinogenic α,α-disubstituted amino acids are significant targets as enzyme inhibitors and for incorporation into peptides to induce conformational restriction and increase both enzymatic and chemical stablity.[3]

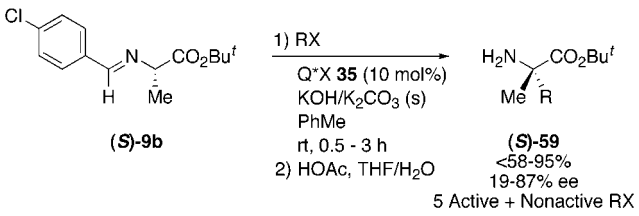
We obtained α,α-dialkylamino acids in up to 50% ee by room-temperature enantioselective solid/liquid PTC alkylation of the 4-chlorobenzaldehyde imine of alanine *tert*-butyl ester (**9b**) with first generation catalysts in 1992 (Scheme 23).[41]

Scheme 23. Catalytic Enantioselective Synthesis of α,α-Dialkylamino Acid Derivatives by PTC



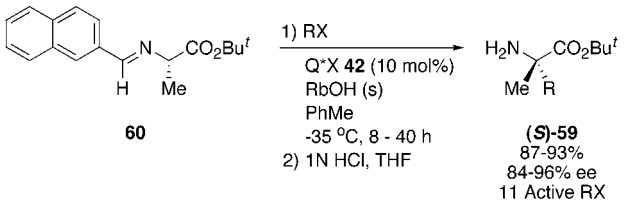
Catalyst **35** gave improved enantioselectivities with active halides. The loss of selectivity with other electrophiles (*n*-BuI, $ICH_2CO_2Bu^t$) was attributed to competing, nonselective background alkylation (Scheme 24).[42]

Scheme 24. α,α-Dialkylamino Acid Derivatives by Enantioselective PTC with Catalyst 35



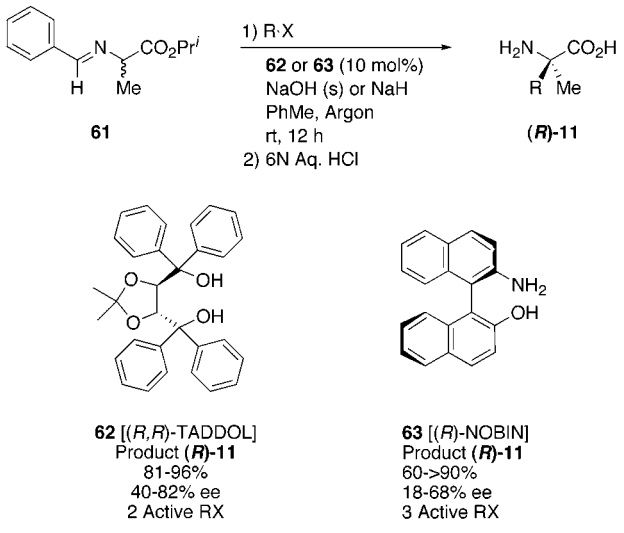
Catalyst **42** gave impressive selectivities with active halides in the dialkylation reaction. Improved enantioselectivity was achieved with a bulky aldimine substituent, the stronger base rubidium hydroxide, and lower reaction temperature (Scheme 25).[43]

Scheme 25. α,α-Dialkylamino Acid Derivatives by Enantioselective PTC with Catalyst 42



Anions from TADDOL or NOBIN were used as chiral bases in PTC dialkylations. These catalysts function as chelating agents for the sodium cation, which makes the resulting ion pair soluble in toluene and provides a rigid complex between the chiral ligand and the substrate in the transition state for the alkylation (Scheme 26).[44]

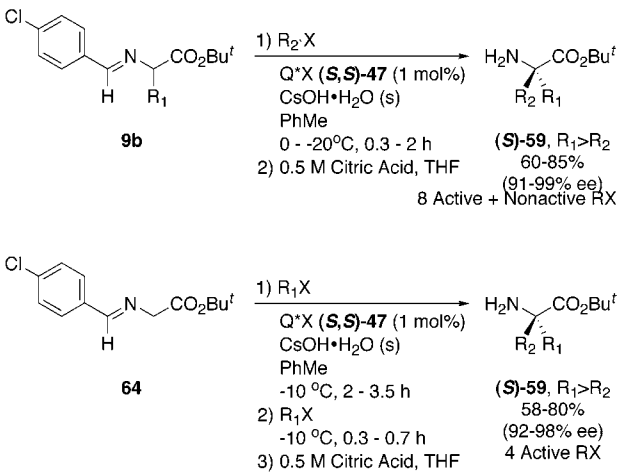
Scheme 26. α,α-Dialkylamino Acid Derivatives by Enantioselective PTC with Catalyst 62 or 63



Catalyst **47** was used for preparation of α,α-dialkylamino acid derivatives from either monoalkyl substrate **9b** or, by two sequential alkylations, from glycine precursor **64**.

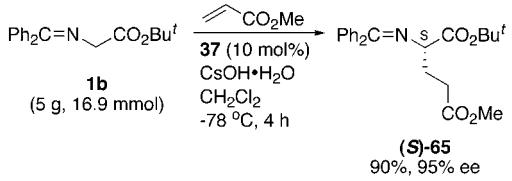
The latter reaction provides an attractive one-pot synthesis of these compounds from a glycine precursor (Scheme 27).[45]

Scheme 27. α,α-Dialkylamino Acid Derivatives by Enantioselective PTC with Catalyst 47



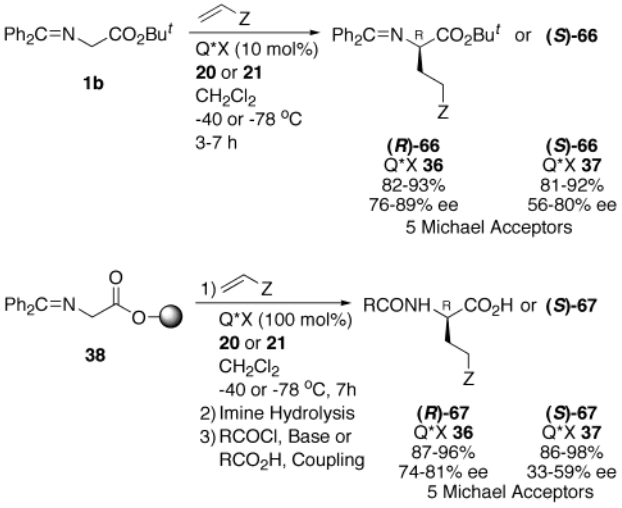
Michael Additions. Michael additions with glycine anion equivalents provide a convenient route to glutamic acid derivatives.[3,46] Michael addition of **1b** and methyl acrylate using catalyst **37** was reported (Scheme 28).[26]

Scheme 28. Catalytic Enantioselective Michael Addition by PTC



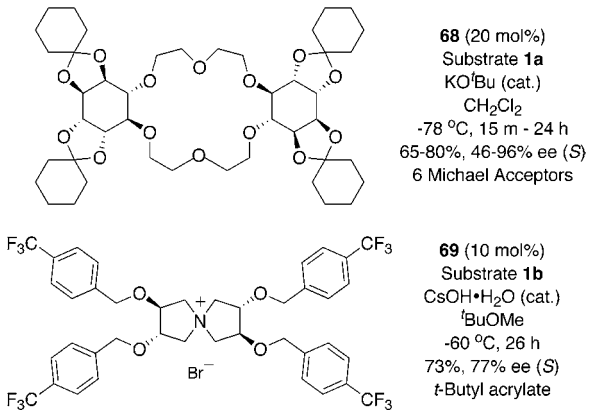
In 2001, we reported the enantioselective Michael addition (with Schwesinger bases **20** or **21**) of **1b** under homogeneous conditions or with resin-bound glycinate **38** (Scheme 29).[47] This extends the types of optically active products accessible by our UPS methodology (see earlier Schemes 6, 9, and 13).

Scheme 29. Enantioselective Michael Additions in Homogeneous Solution and on Solid Phase



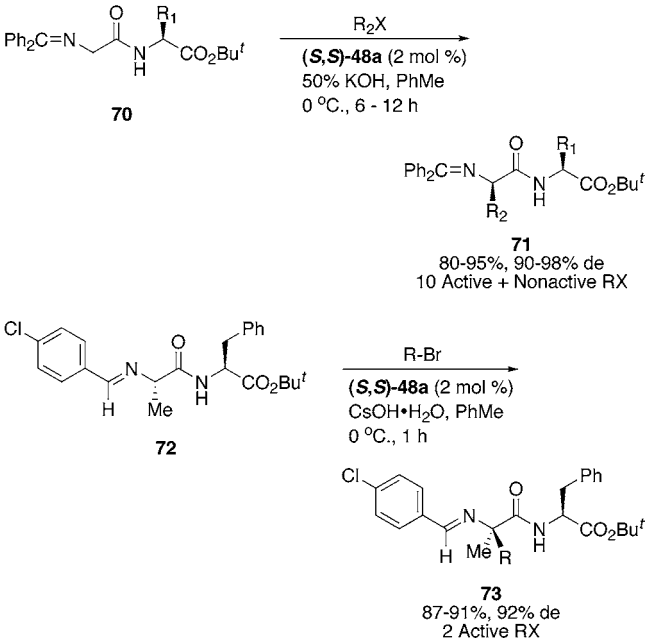
Akiyama et al. demonstrated that crown ether **68**, prepared from *chiro*-inositol, was an effective catalyst,[48] as was spiro catalyst **69** from the groups of Arai and Nishida (Scheme 30).[49]

Scheme 30. Other Michael Addition Catalysts



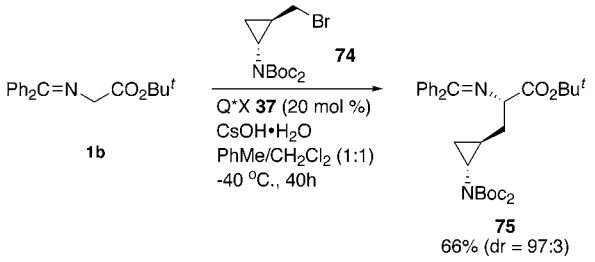
Reactions Involving Multiple Stereogenic Centers. An impressive stereoselective N-terminal functionalization of peptide derivatives was achieved recently (Scheme 31).[31f] A number of interesting studies for the preparation of di-, tri-, and tetrapeptides were reported (see **102** in Table 2).

Scheme 31. Stereoselective N-Terminal Functionalization of Peptides



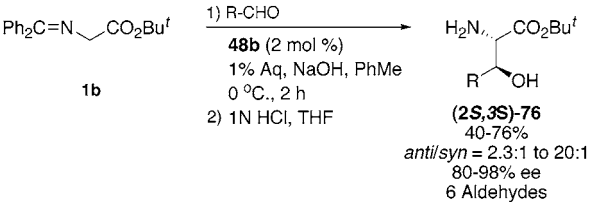
Diastereoselective chiral PTC with chiral, nonracemic electrophile **74** was used by Armstrong et al. to prepare **75**, a component of Belactosin A. Optimization studies led to the highly stereoselective formation of the product, which contains three stereogenic centers (Scheme 32).[50]

Scheme 32. Cyclopropylalanine Derivatives by Enantioselective PTC



Directed asymmetric aldol reaction by PTC, which creates two new stereogenic centers, gave anti diastereomers of β-hydroxy-α-amino acids (Scheme 33).[31g] The Molinski group reported sparteine-mediated aldol reactions of **1b**, which gave reversed diastereoselectivity in THF vs toluene (~2:1 in both cases) with moderate levels of enantioselectivity (≤60% ee).[51]

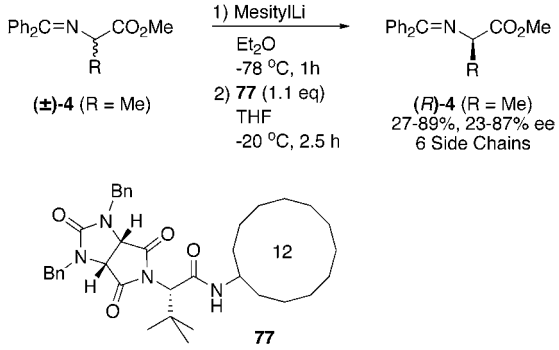
Scheme 33. Directed Asymmetric Aldol Reaction by Chiral PTC



5. Related Research

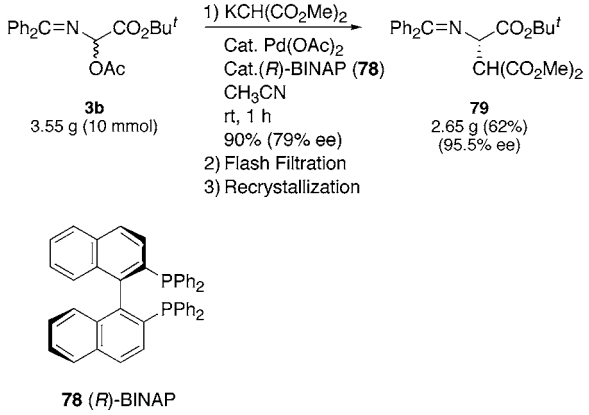
The Yamamoto group has reported an asymmetric protonation ("deracemization") of the anion of **4** with a chiral amide. Such an approach provides a route to optically active α-amino acids from their racemic counterparts, as well as a potential route from L- to D-amino acids (Scheme 34)[52]

Scheme 34. Asymmetric Protonation of the Enolate from (±)-4



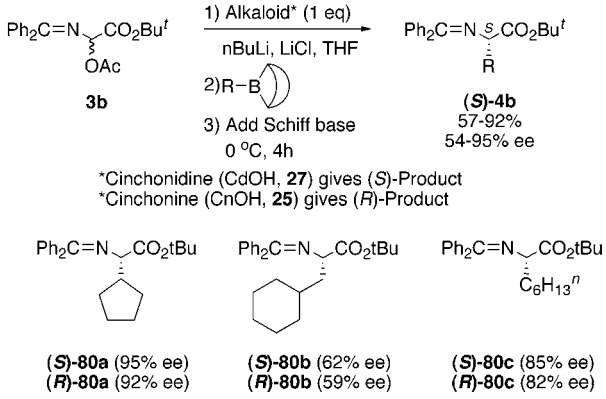
Several reactions of glycine cation equivalent **3** from our group that involve either metal-containing catalysts or reagents are outlined below. The enantioselective coupling of malonate anion to **3b** with a palladium/BINAP catalyst pair gave the protected β-carboxyaspartic acid derivative **79** (Scheme 35).[53]

Scheme 35. Enantioselective Reaction of a Glycine Cation Equivalent with Malonate Anions



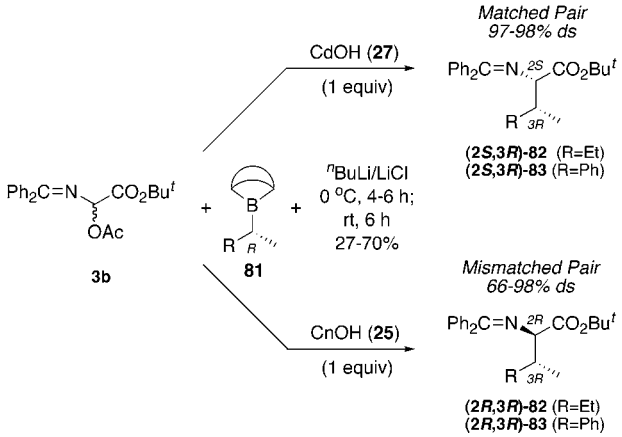
Organoborane alkylations of **3b**, originally reported from our laboratory in 1985 as a route to racemic α-amino acids,[15] have recently been extended to the preparation of the optically active derivatives. The parent *Cinchona* alkaloids (**25** and **27**, Figure 1) serve a dual role in these reactions, first as chiral base and then as chiral proton source. The overall transformation involves boron-mediated carbon−carbon bond construction followed by enantioselective protonation of the final boron enolate intermediate (Scheme 36).[54]

Scheme 36. Enantioselective Synthesis of α-Amino Acids via Organoboranes



When chiral, nonracemic organoboranes (**81**) are used in conjunction with the *Cinchona* alkaloids in the boron alkylation reaction, optically active β-substituted α-amino acids are formed by a process involving a final diastereoselective protonation (Scheme 37).[55]

Scheme 37. *β*-Substituted α-Amino Acids by a Diastereoselective Boron Alkylation



6. Applications

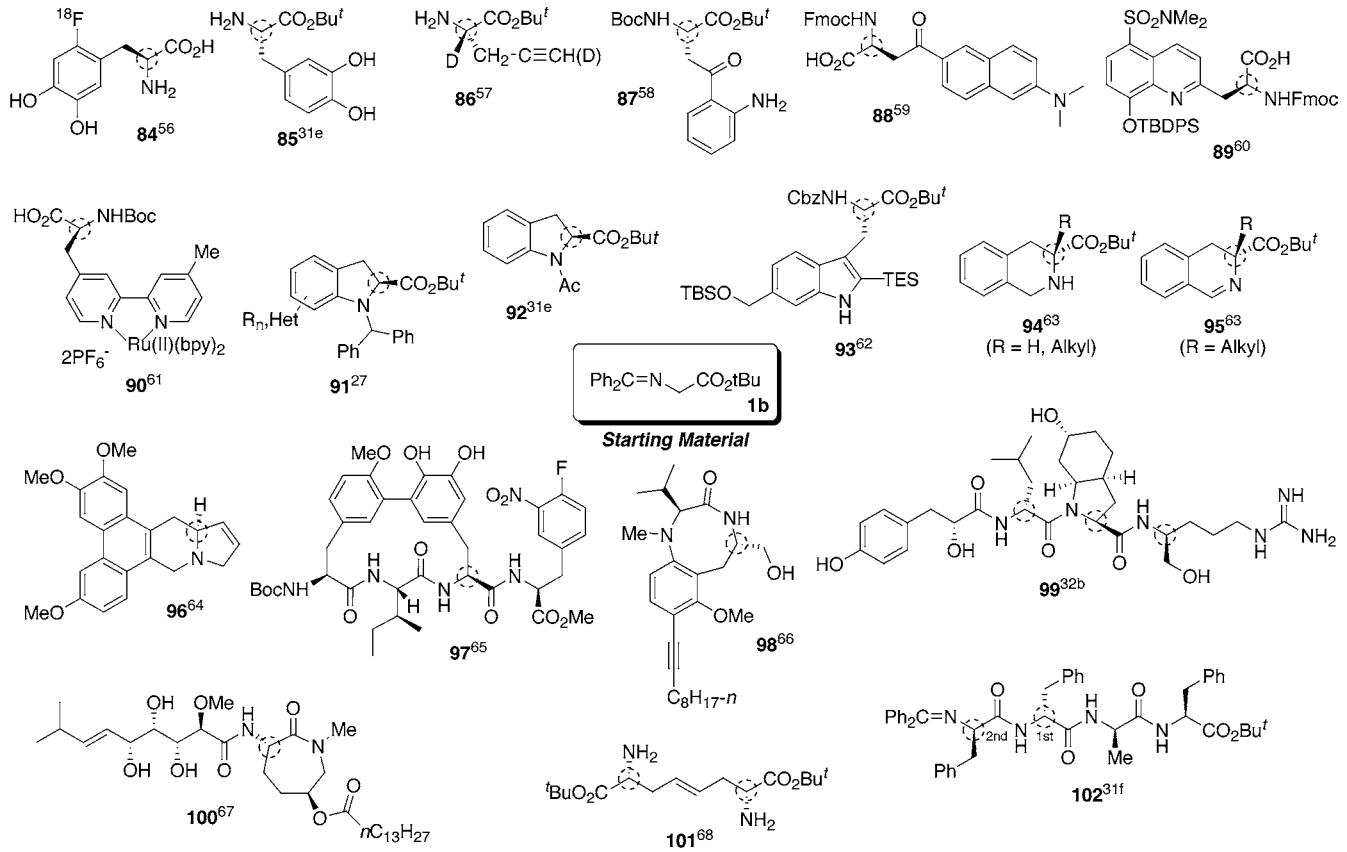
Table 2 summarizes recent applications of the benzophenone imine of glycine *tert*-butyl ester (**1b**) in a number of other chiral PTC alkylation studies. Several additional acyclic α-amino acids derivatives have been prepared by catalytic enantioselective alkylations (**84**−**90**). Such alkylations have also been used in syntheses to prepare heterocyclic products (**91**−**96**) or in the total syntheses of more complex targets (**97**−**100**). Further products containing multiple stereocenters are also highlighted (**101**−**102**).

7. The Future

The benzophenone imine of glycine *tert*-butyl ester (**1b**), together with a variety of different chiral phase-transfer catalysts, is being widely used for the synthesis of optically active α-amino acid targets. Additionally, other related substrates and reactions have provided access to other products. Further careful and systematic studies are still needed to understand the details of the chiral inductions observed and to account for the subtle role played by the many variables in these complex systems. Such an in-depth appreciation will allow for the design of cost-effective reaction systems that lead to high chemical and stereochemical yields. This area will continue its rapid growth in importance as new catalysts, reagents, and reaction types and conditions are explored and as the methodology finds further application in the total syntheses of complex molecules.

I am indebted to all of my co-workers and collaborators whose intellectual and experimental contributions have made our program possible. The financial support of the National Institutes of Health (Grant GM 28193) and Eli Lilly and Company is gratefully acknowledged. Finally, I thank my family for their continued love and understanding.

Table 2. Products Prepared by Catalytic, Enantio- or Diastereoselective PTC Reactions of 1b[a]



[a] Stereogenic center(s) prepared in reaction(s) circled.

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