Asymmetric Phase-Transfer Catalysis Utilizing Chiral Quaternary Ammonium Salts: Asymmetric Alkylation of Glycine Imines

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ABSTRACT

O-Alkyl *N*-anthracenylmethyl derivatives of *Cinchona* alkaloids can function as enantioselective phase-transfer catalysts. By employing these catalysts in the asymmetric alkylation of glycine imines, one can generate a range of α-amino acid derivatives with high levels of enantiomeric excess. It is also possible to generate the catalysts in situ from commercially available chiral amines, which offers the opportunity to evaluate libraries of related structures. This latter approach has been successfully applied to a series of biphenyl quaternary ammonium salts resulting in the development of a new highly selective catalyst and opening up the potential of further expanding the range of α-amino acid derivatives that can be prepared.

Phase-Transfer Catalysis

Phase-transfer catalysts (PTCs) are chemical agents that facilitate the transfer of a molecule or ion from one reaction phase to another and in doing so can greatly accelerate the rate of heterogeneous (polyphasic) reaction processes.[1−3] The simplest examples of these processes are "normal" biphasic phase-transfer reactions in which the catalyst facilitates reaction by solublizing a reagent or substrate ion in the organic phase (Figure 1).

The most commonly used PTCs in reactions of this type are quaternary ammonium salts, and it has been shown that a number of subtly distinct mechanistic schemes are operative in these systems.[4] These variations relate to whether the ion exchange process takes place mainly in the aqueous phase (as implied in Figure 1), the interfacial region, or the organic phase. Irrespective of the mechanistic detail, these processes often offer a number of advantages over homogeneous alternatives:

• The reactivity of the reagent anion (Y^-) in the organic phase is usually enhanced since the Q^+Y^- ion pair tends to have greater charge separation and reduced hydration compared to aqueous solutions of the precursor salt

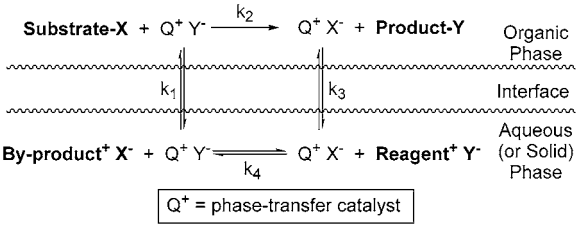

FIGURE 1.

(Reagent$^+$Y$^-$). Consequently intrinsic reaction rates (k_2) tend to be significantly higher than those obtained in homogeneous media.

• PTC reaction processes are generally more selective (less side reactions) than homogeneous reactions due to controlled delivery of the reagent into the substrate-containing phase.

• The reaction conditions are usually compatible with a wide variety of (water-immiscible) organic solvents. This allows the opportunity to select a solvent that is optimal for recovery or reuse or both in prior or subsequent synthetic steps. In addition, it is sometimes possible to utilize the substrate itself as the organic phase, thus eliminating the need for any organic solvent.

• The biphasic nature of these processes greatly simplifies reagent and byproduct separation and hence product isolation. This makes PTC reactions highly attractive alternatives to processes that use polar, water-miscible solvents.

• The catalysts (quaternary ammonium salts) are usually inexpensive and are biodegradable.

Because of these advantages, phase-transfer reactions have been recognized as "green" alternatives to many homogeneous reaction processes, and they have found widespread application in synthetic organic chemistry.[1−3,5] In the last 25 years, increasing attention has focused on the development of asymmetric phase-transfer processes.[6] Our own work in this area has centered around the use of *Cinchona* alkaloid derived quaternary ammonium salts in enantioselective C−C and C−O bond forming processes,[7] and in this Account, we present aspects of this work that relate to the asymmetric synthesis of α-amino acids.

Alkylation of Glycine Imines

The application of chiral PTCs to the asymmetric alkylation of glycine imine ester **4** was first reported by O'Donnell in 1989.[8] *N*-Benzyl derivatives of the *Cinchona* alkaloids were employed for this process, typically leading to enantioselectivities in the range 42−66% ee. This study also demonstrated that the diastereoisomeric catalysts **1** and **2** (derived from cinchonine and cinchonidine respectively) were enantiocomplimentary in the sense that they led to selectivity for opposite enantiomers of the product and that the *tert*-butyl ester imine **4** was the optimal substrate. It was later demonstrated that *O*-alkylation of these catalysts occurred during the reaction and that this, coupled with careful optimization of the reaction condi-

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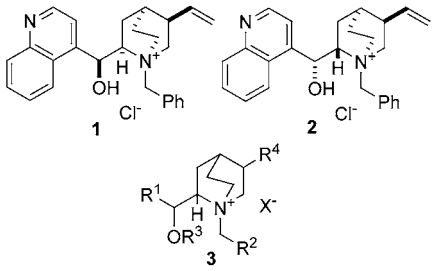


tions, could lead to significantly higher enantioselectivities (up to 81% ee).[9,10]

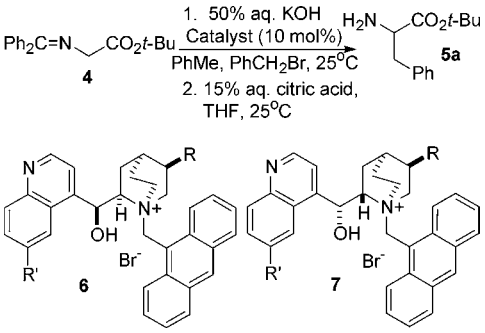
Our own work in this area started in 1994[11] when we initiated a study designed to probe the role of the various groups attached to the quinuclidine core in catalysts such as **1** and **2**. For this purpose, a series of chiral quaternary ammonium salts **3** were constructed,[11−13,14] and their efficacy in the phase-transfer alkylation of imine **4** was investigated. This study demonstrated that the *N*-anthracenylmethyl derivatives gave significantly improved levels of enantioselectivity compared with the corresponding *N*-benzyl salts. Subsequent investigations demonstrated that this was also the case for *Cinchona* alkaloid derived catalysts and that the salts derived from cinchonine and cinchonidine (**6b** and **7b**) gave rise to higher levels of enantioselectivity than those from quinidine and quinine (**6c** and **7c**) (Table 1).[15,16]

Quaternary ammonium salts **6b** and **7b** were found to undergo rapid *O*-benzylation under the alkylation conditions (Scheme 1), and identical levels of enantioselectivity were obtained with prealkylated salts. This suggests that the *O*-benzyl ethers of **6** and **7** are the catalysts that are responsible for the selectivities observed during the formation of **5a** (Table 1).

Interestingly when quaternary ammonium salts **6b** and **7b** were employed in reactions involving other alkyl halides, similar levels of enantioselectivity were obtained (Table 2). Since it is likely that *O*-alkylation of the (pre)-catalyst is occurring in each case, these observations suggest that the nature of the *O*-alkyl group has little effect on the enantioselectivity of these phase-transfer reactions. This finding is consistent with similar observations made during the study of quaternary ammonium salts **3**.[13]

Reaction via an ion-pair arrangement **A** (Figure 2) would account for the enantioselectivities obtained with quaternary ammonium salts **3**, **6**, and **7**.[17,18] In this arrangement, the Re-face of the enolate carbon is blocked by the quinoline ring of the quaternary ammonium salt, so preferential reaction via the Si-face would be expected. Molecular modeling studies within our group[13,19] suggest that such an ion pair could be favored, but alternative ion pairs (e.g., **B)** are also possible and may in part be responsible for some loss of selectivity during the alkylation reaction. Inspection of the structure in ion-pair **B** suggested that it should be less favored due to the increased charge separation required to accommodate the bulky *tert*-butyl group in the "groove" between the quinoline and anthracene rings. It also appeared that increasing the size of the vinyl substituent might assist in further

Table 1. *C*-Benzylation of Glycine Imine 4 Using *N*-Anthracenylmethyl Derivatives of *Cinchona* Alkaloids



catalyst	R	R′	% yield	% ee
6a	H	H	75	85 (*R*)
6b	CH=CH$_2$	H	73	86 (*R*)
6c	CH=CH$_2$	OMe	56	78 (*R*)
7a	H	H	77	85 (*S*)
7b	CH=CH$_2$	H	68	91 (*S*)
7c	CH=CH$_2$	OMe	53	83 (*S*)

Scheme 1

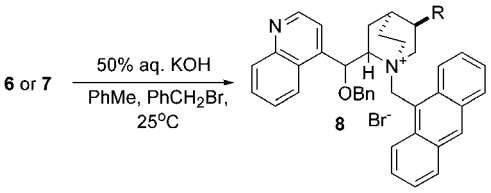
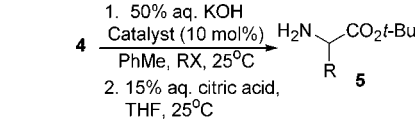


Table 2. Amino Acid Ester Synthesis Utilizing Cinchonine- and Cinchonidine-Derived Catalysts 6b and 7b



RX	catalyst	% yield	% ee
PhCH$_2$Br	**6b**	63	89 (*R*)
	7b	68	91 (*S*)
CH$_2$=CHCH$_2$Br	**6b**	62	88 (*R*)
	7b	76	88 (*S*)
n-BuI	**6b**	56	87 (*R*)
	7b	42	88 (*S*)

destabilizing ion-pair **B**. Such a modification, however, would only be expected to have an effect for cinchonidine-derived catalysts because the diastereoisomeric cinchonine-derived salts possess a different spatial arrangement of the vinyl group (Figure 3).

On the basis of this reasoning the alkylation of glycine imine **4** using quaternary ammonium salts **8a** and **8b** was investigated. The results obtained (Table 3) appear to support the above discussion. Quaternary ammonium salt **8b**, derived from dihydrocinchonidine, gives improved levels of enantioselectivity compared with the corresponding cinchonidine-derived salt **7b** (Tables 1 and 2). In contrast, salt **8a** gives no improvement compared with **6b** suggesting this that type of modification does not benefit cinchonine-derived catalysts.

Throughout the development of these asymmetric phase-transfer alkylation reactions, emphasis has been

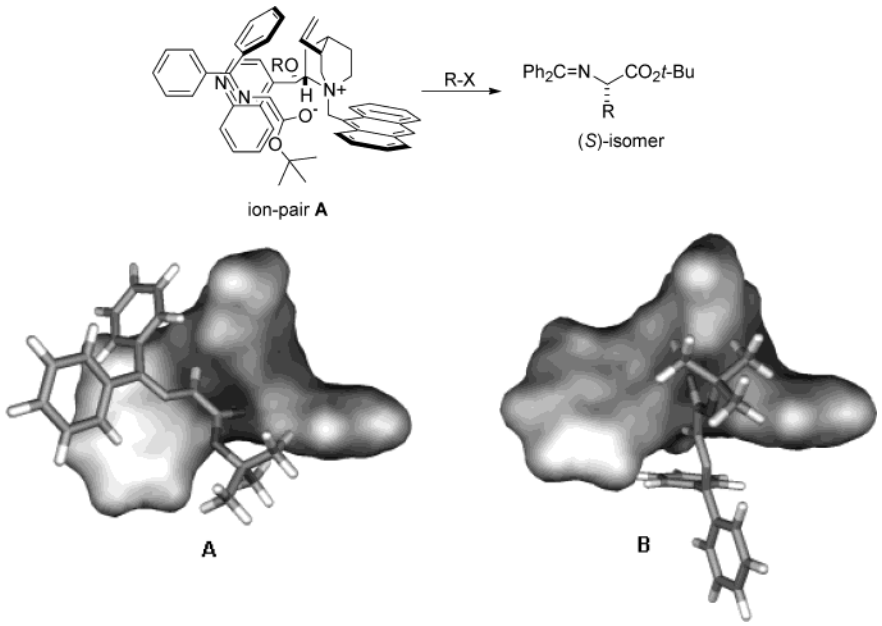


FIGURE 2. Possible ion-pair arrangements (solvent-accessible surface of the quaternary ammonium ion is shown).

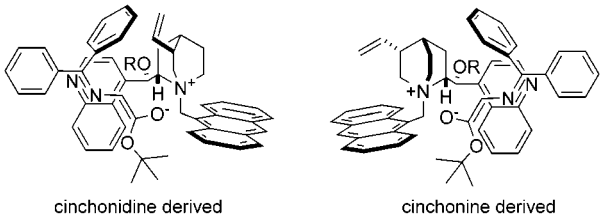
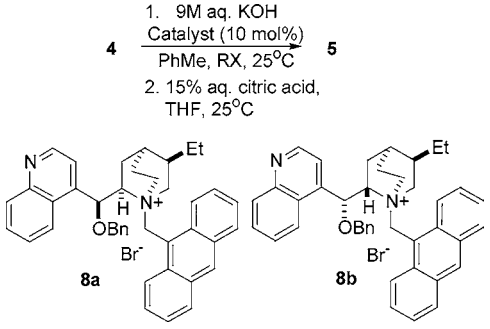


FIGURE 3. Possible favored ion-pair arrangements for cinchonine- and cinchonidine-derived catalysts.

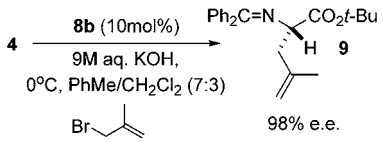
Table 3. Amino Acid Ester Synthesis Utilizing Catalysts 8a and 8b



RX	catalyst	% yield	% ee
$PhCH_2Br$	**8a**	77	86 (*R*)
	8b	85	94 (*S*)
4-Br−$C_6H_4CH_2Br$	**8b**	80	94 (*S*)
(2-naphthyl)CH_2Br	**8b**	83	93 (*S*)
CH_2=$CHCH_2Br$	**8b**	87	92 (*S*)
CH_2=$C(CH_3)CH_2Br$	**8b**	78	94 (*S*)
n-BuI	**8b**	78	93 (*S*)

placed on developing chemistry that is as environmentally benign as possible. Thus the reactions reported have been performed at ambient temperature using nonchlorinated solvents and aqueous base. Under these conditions, it has proved possible to generate a range of L-amino acid esters in good overall yields and with enantioselectivities typically in the range 92−94% ee (Table 3).

Scheme 2

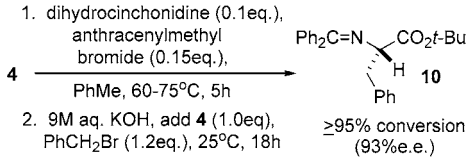


In most instances, this level of selectivity is sufficient because the products, or simple derivatives thereof, can be crystallized to high levels of enantiomeric purity.[20] However, if required it is possible to further improve the enantioselectivity of a given reaction by careful optimization of the reaction conditions. For example, Table 3, entry 6, can be improved to 98% ee (Scheme 2) simply by using a mixed solvent system in conjunction with cooling to 0 °C.[21]

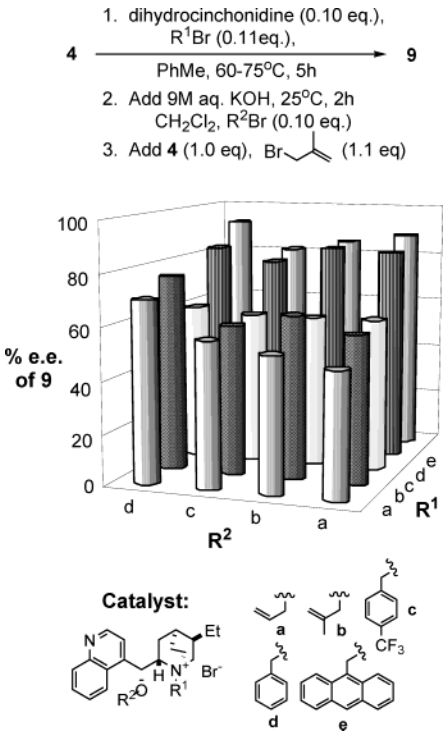
The studies outlined above have identified a series of quaternary ammonium salts that are highly effective for the asymmetric phase-transfer alkylation of glycine imine **4**. The *N*-anthracenylmethyl derivatives of either cinchonine (salt **6b)** or dihydrocinchonidine are effective in most cases; however, since these salts usually undergo modification (*O*-alkylation) under the reaction conditions, it is sometimes advantageous to use premade *O*-alkyl derivatives. In general, we have found that benzyl ethers (e.g., **8b**) serve this purpose well, but it should be noted that the *O*-allyl derivative of *N*-anthracenylmethylcinchonidinium bromide has also proved highly successful in reactions of this type. This latter catalyst was first reported by the Corey group in 1997[22] who demonstrated that it could deliver high enantioselectivity in the alkylation of imine **4** when used in conjunction with $CsOH{\cdot}H_2O$ at −78 °C. More recently, the same catalyst has also been shown to be effective under homogeneous conditions in conjunction with a phosphazene base.[23]

Since the first reports concerning the use of *N*-anthracenylmethyl derivatives of *Cinchona* alkaloids in the asymmetric alkylation of imine **4**,[15,22] a number of other

Scheme 3. In Situ Generation of Chiral Phase-Transfer Catalyst 8b



Scheme 4. Screening of Quaternary Ammonium Salts Generated in Situ from Dihydrocinchonidine

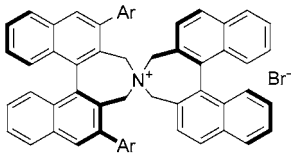


N-arylmethyl derivatives of *Cinchona* alkaloids have been shown to give high enantioselectivities (>90% ee) in this type of reaction process.[24] Thus, to facilitate the identification of an optimal catalyst for a given alkylation process, a means of rapidly screening a range of candidate structures would be useful. One such approach has recently been reported.[21] This approach is based on the observation that it is possible to couple the phase-transfer alkylation reaction with a *N*-quaternization step.[9,13] In this way, the phase-transfer catalysts can be generated from the parent alkaloids in situ (Scheme 3). Asymmetric alkylations performed in this way give similar yields and enantioselectivities to those employing premade catalysts.

With the use of a slight modification of this procedure, it has proved possible to employ simple laboratory automation for the rapid generation and screening of libraries of chiral quaternary ammonium salts (Scheme 4).[21] This approach opens up the possibility of screening large libraries of chiral quaternary ammonium salts and should be applicable to a wide range of hydroxide-mediated phase-transfer reaction processes. To exploit this technology further, we have recently sought to develop a nonalkaloid template that will allow a diverse set of chiral quaternary ammonium salts to be generated using simple chiral amine precursors. Initial studies in this area have employed biphenyls **11**, which are readily prepared from commercially available 2-*tert*-butyl-5-methylphenol. Coupling of **11** with a series of secondary amines allowed the generation of a diverse range of quaternary ammonium salts. A library of 40 salts generated in this way was tested in the phase-transfer alkylation of imine **4**, resulting in enantioselectivities from −30% to 91% ee (Scheme 5).[25]

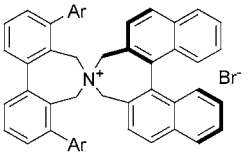
The range of enantioselectivities obtained in this study demonstrates that substantial diversity in catalyst performance can be obtained using this approach. In addition, this study resulted in the identification of a promising new catalyst, **12g**. Further studies involving this catalyst have shown that it is capable of delivering high levels of enantioselectivity in the alkylation of imine **4** (Table 4) and is effective at relatively low loadings (1 mol %).[25]

Quaternary ammonium salt **12g** bears some structural similarity with spirobinaphthyl quaternary ammonium salts (e.g., **13** and **14**) developed by the Maruoka group.[26]



Ar = 3,4,5-trifluorophenyl

13



Ar = 2-naphthyl

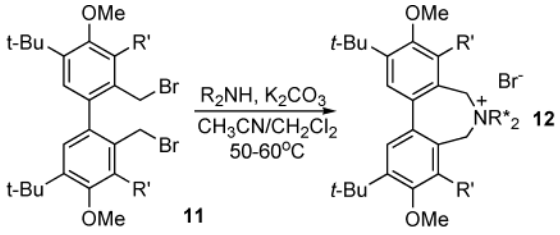
14

These latter catalysts have been shown to be extremely effective in the asymmetric alkylation of amino acid derived imines, but to date no model has been reported to account for the enantioselectivities observed. Despite the structural similarities, the lack of a spirobicyclic ring system in **12g**, coupled with additional degrees of freedom associated with the α-methylnaphthylamine unit, suggests that any ion pairs involving **12g** will be significantly different from those involving **13** and **14**.

Comparison of **12g** with the dihydrocinchonidine-derived catalyst **8b** in the asymmetric alkylation of a series of different glycine imine esters suggests that the former catalyst may tolerate a wider range of imine substrates (Table 5). In particular, the high enantioselectivity obtained using catalyst **12g** in conjunction with a benzhydryl imine ester (Table 5, entry 4) suggests that this may be a means of expanding the range of α-amino acid derivatives available via this methodology.[27]

All of the phase-transfer alkylations discussed above involve the use of aqueous hydroxide to effect the deprotonation of imine **4**. In principle, this could be initiated by extraction of hydroxide ion into the organic phase via ion pairing with the chiral quaternary ammonium salt.

Scheme 5. Asymmetric *C*-Benzylation of Imine 4 Using a Library of Quaternary Ammonium Salts Generated from Biphenyl Precursors 11



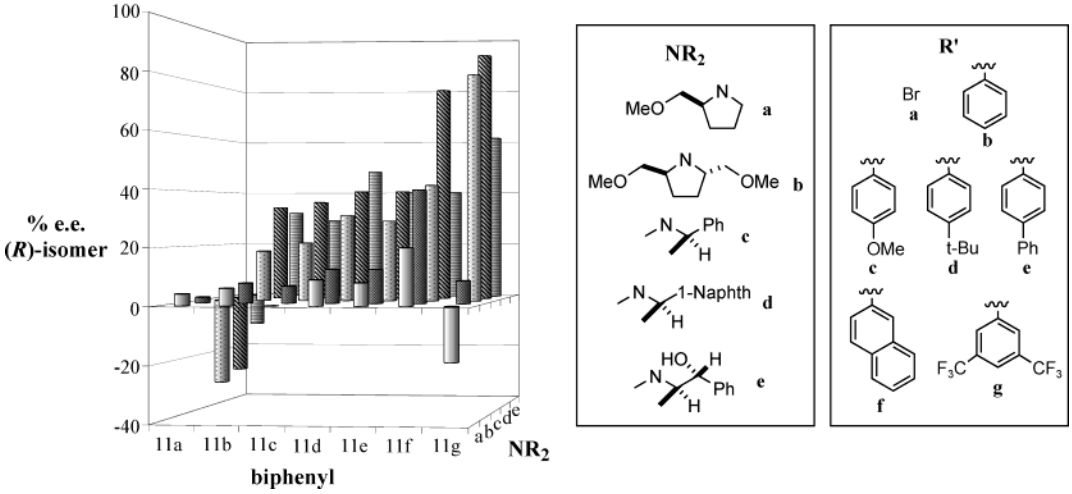
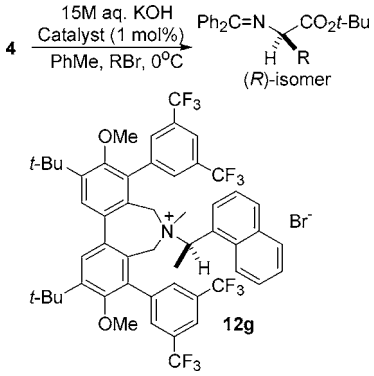


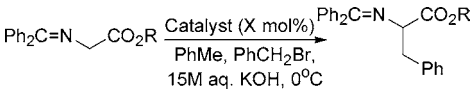
Table 4. Amino Acid Imine Ester Synthesis Utilizing α-Methylnaphthylamine-Derived Catalyst 12g



RBr	% yield	% ee
$PhCH_2Br$	89	97
(2-naphthyl)CH_2Br	97	96
$CH_2{=}CHCH_2Br$	83	94
$CH_2{=}C(CH_3)CH_2Br$	100	95
$CH_2{=}C(Br)CH_2Br$	77	93
$HCCCH_2Br$	71	89

However, a number of studies have suggested that quaternary ammonium salts do not efficiently transport hydroxide ion into an organic solvent.[28] Moreover, studies into the kinetics of phase-transfer reactions involving *N*-benzyl derivatives of *Cinchona* alkaloids suggest that direct deprotonation of imine **4** by hydroxide at the interface is most likely and that the quaternary ammonium ion then transports the imine enolate into the organic phase.[9] Studies involving the corresponding *N*-anthracenylmethyl salts (**6b**, **8b**) suggest that they probably act in the same way and that the deprotonation/alkylation sequence occurs as shown in Figure 4.

Table 5. *C*-Benzylation of Glycine Imine Esters Using Catalysts 8b and 12g



R	catalyst	% yield	% ee
t-Bu	**8b** (10 mol %)	90	93 (*S*)
	12g (1 mol %)	89	97 (*R*)
Ph_2CH	**8b** (10 mol %)	96	63 (*S*)
	12g (1 mol %)	95	92 (*R*)
$PhCH_2$	**8b** (10 mol %)	68	79 (*S*)
	12g (1 mol %)	86	86 (*R*)
Et	**8b** (10 mol %)	63	87 (*S*)
	12g (1 mol %)	88	55 (*R*)

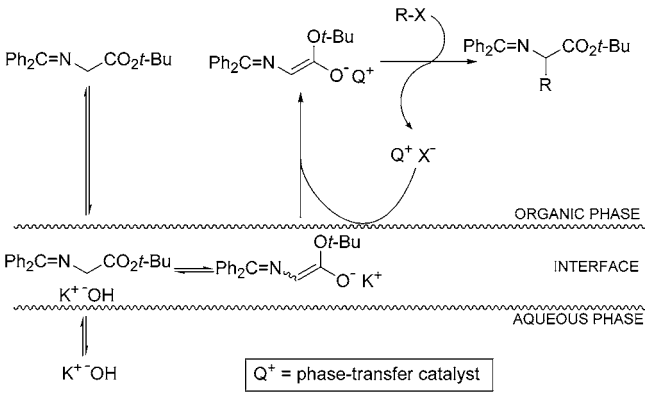
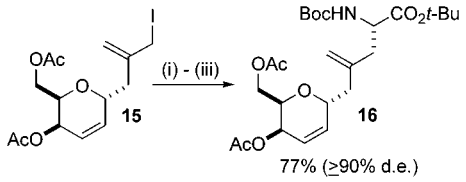


FIGURE 4. Phase-transfer alkylation of imine **4**.

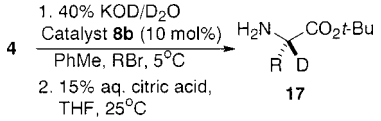
If this scheme is correct, then only low levels of hydroxide ion should be present in the organic phase and the asymmetric alkylation ought to tolerate hydroxide sensitive functionality in the electrophile (R−X). This indeed appears to be the case; for example, iodide **15** has

Scheme 6



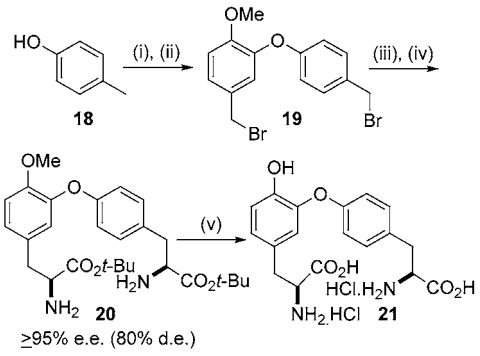
(i) **4, 8b** (10 mol%), 9M aq. KOH, PhMe, RT; (ii) 15% aq. citric acid, THF, RT; (iii) Boc_2O, Et_3N, CH_2Cl_2, 0 °C-RT

Table 6. Enantioselective Synthesis of α-Deuterated α-Amino Acid Esters



RBr	% ^2H	% yield	% ee
$PhCH_2Br$	≥94	90	94
4-Br−$C_6H_4CH_2Br$	≥95	80	95
(2-naphthyl)CH_2Br	≥95	84	94
CH_2=$CHCH_2Br$	≥95	92	92
CH_2=$C(CH_3)CH_2Br$	≥95	70	96

Scheme 7. Synthesis of Isodityrosine 21



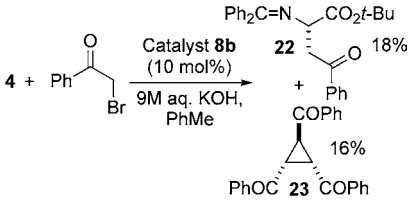
(i) 2-bromo-4-methylanisole, pyridine, CuO, K_2CO_3, reflux (86%); (ii) NBS, AIBN, CCl_4, hν, reflux, (79%); (iii) **4** (2 eq.), **7b** (0.2 eq.), 50% aq. KOH, PhMe, RT; (iv) 15% aq. citric acid, THF, RT (65% from **19**); (v) TfOH, TFA, PhSMe, -5°C; aq. HCl (87%).

been converted into the *C*-glycopeptide intermediate **16** in good overall yield and with no evidence of acetate hydrolysis (Scheme 6).[29]

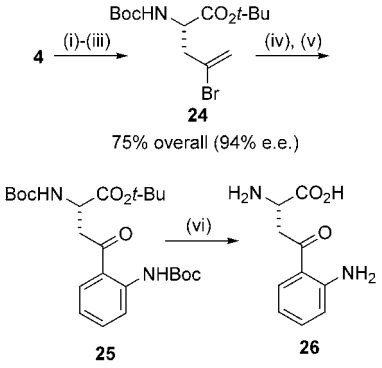
Another potentially useful feature of the liquid−liquid phase-transfer alkylation reaction is that the imine **4** undergoes rapid H/D exchange if KOD/D_2O is used as the aqueous phase. This provides a simple and efficient means of preparing labeled amino acid esters (Table 6).[30]

The scope of this methodology has been further developed for the synthesis of naturally occurring amino acids. For example, during the course of the synthesis of isodityrosine **21** (Scheme 7), it was demonstrated that a double alkylation involving reaction of dibromide **19** with two molecules of imine **4** could be employed in the stereoselective construction of the key amino ester intermediate **20**.[31] Studies involving a number of other dibromides suggest that this approach can be used for the stereoselective construction of a wide range of bis-amino acids.[32]

Scheme 8



Scheme 9. Synthesis of L-Kynurenine



(i) 2,3-dibromopropene, 9M aq. KOH, PhMe, CH_2Cl_2, **8b** (10 mol%), RT; (ii) 15% aq. citric acid, THF, RT; (iii) Boc_2O, Et_3N, RT; (iv) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, PhMe, EtOH, reflux; (v) O_3, CH_2Cl_2, -78°C; Et_3N, RT (84% from 24); (vi) CF_3CO_2H, $CHCl_3$, reflux (62%).

Although the liquid−liquid phase-transfer reaction conditions have proved extremely convenient to use and are compatible with a wide range of alkylating agents, alkylations involving α-haloketones (e.g., α-bromoacetophenone) generally result in low yields of the desired product **22** (Scheme 8). This appears to be because α-bromoketones are prone to hydrolysis and also readily participate in a base-mediated self-condensation, leading to the formation of cyclopropyl ketone byproducts such as **23**.[33]

In some cases, these problems can be overcome by careful optimization of the reaction conditions. This approach has been demonstrated during the development of an enantioselective synthesis of the fluorescent amino acid 6-(2-dimethylaminonaphthoyl)alanine.[34]

An alternative solution involving the use of a masked α-halocarbonyl compound has also been reported.[35] This approach involved the enantioselective alkylation of imine **4** with 2,3-dibromopropene. Subsequent imine hydrolysis and *N*-protection then provided the versatile α-amino acid derivative **24** in high enantiomeric excess. The vinyl bromide function present in **24** served as a convenient handle for the introduction of a range of aryl groups, and subsequent oxidative cleavage of the alkene then revealed the required keto function. This strategy has been exploited in the enantioselective synthesis of L-kynurenine **26** (Scheme 9).[35]

Conclusion

Although this Account, by necessity, has focused on work carried out in our group, it is important to note that

research groups throughout the world have made major contributions to this area of chemistry. This combined effort has helped to establish asymmetric phase-transfer catalysis as a powerful tool for the construction of a wide range of natural and unnatural α-amino acids.[10,36] In addition, chiral quaternary ammonium salts have proved to be effective in a number of other highly enantioselective phase-transfer reaction processes.[2,6] Key challenges in this field lie in the further expansion of the chemistry that can be performed using this type of catalysis and in the further optimization of the reactions already possible.

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