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PTC in OPRD: An Illustrative Overview

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Abstract:

Illustrative examples of phase transfer catalysis (PTC) are compiled, albeit arbitrarily, to demonstrate its applicability to organic process research and development (OPRD), which covers eleven types of reactions: (1) ether formation, (2) ester formation, (3) hydrolytic removal of *O*-acetyl and *O*-silyl groups, (4) ester hydrolysis, (5) one-pot transesterification, (6) inorganic anionic species-mediated oxidation, (7) activation of KF for the fluoride-elicited nucleophilic displacement, (8) dichlorocarbene generation, (9) C−C bond formation in racemic synthesis, (10) asymmetric C−C bond formation in enantioselective synthesis of α-amino acids and α-hydroxy acids, and (11) enantio- and diasterocontrolled nitroaldol reactions.

Introduction

This mini-review article is intended to illustrate intrinsic versatility of phase transfer catalysis (PTC) in organic process research development (OPRD), in particular, when it is challenged by the need to build multifunctional, architecturally complex molecules.[1] Thus, to demonstrate the way that PTC impacts OPRD in addressing such synthetic issues, the following reactions will be discussed with illustrative examples while they have been chosen at the author's discretion, though: (1) ether formation by *O*-alkylation of hydroxy groups, (2) ester formation by *O*-alkylation of carboxylic acid groups and by *O*-acylation of hydroxy groups, (3) hydrolytic removal of *O*-acetyl and *O*-silyl protecting groups to release the parent hydroxy groups, (4) hydrolysis of esters to carboxylic acids, (5) one-pot transesterification to exchange *O*-alkyl groups in esters, (6) oxidation employing inorganic anionic species: MnO_4^- and ClO^-, (7) activation of KF for the fluoride-elicited nucleophilic displacement leading to amination, (8) dichlorocarbene generation for *gem*-dichlorocyclopropanation of olefins and for isonitrile formation from primary amines, (9) generation of stabilized carbanions for C−C bond formation in racemic synthesis, (10) asymmetric C−C bond formation in the enantioselective synthesis of α-amino acids and α-hydroxy acids, and (11) asymmetric nitroaldol reactions leading to diastereo- and enantioselective construction of 1,2-nitro alcohols and derivatives thereof. This cross section of the reactions that have benefited from PTC would help readers to gain insight into what difference PTC can make in OPRD.

Ether Formation. Williamson ether synthesis ($R^1O^- + R^2X \rightarrow R^1OR^2$) is usually conducted under anhydrous homogeneous conditions using polar aprotic solvents, such as THF and DMF. It is because prior formation of alkoxide (RO^-) is required through the agency of moisture-sensitive strong bases (M^+B^-), such as NaH, LDA, LHMDS, and KHMDS: $R^1OH + M^+B^- \rightarrow R^1O^-M^+ + BH$. However, the deprotonation of hydroxy groups may be performed in a biphasic aqueous/organic mixture when an aqueous solution of alkali metal hydroxide (M^+OH^-), such as NaOH, is used in combination with a phase transfer catalyst (Q^+X^-). Under such PTC conditions, the hydroxide anion (OH^-) is captured by the lipophilic cation (Q^+) to give a new ion pair (Q^+OH^-): $M^+OH^- + Q^+X^- \rightarrow Q^+OH^- + M^+X^-$. Because of its substantial lipophilicity, the newly generated hydroxide vehicle (Q^+OH^-) can penetrate into the organic phase, where it is "naked" (free from hydration) and as such, is reactive enough to deprotonate the alcoholic hydroxy group involved: $Q^+OH^- + R^1OH \rightarrow R^1O^-Q^+ + H_2O$. The alkoxide species thus generated (RO^-Q^+) is so lipophilic that it remains in the organic phase, participating in the *O*-alkylation that leads to ether formation with regeneration of the catalyst (Q^+X^-): $R^1O^-Q^+ + R^2X \rightarrow R^1OR^2 + Q^+X^-$. In addition, now that a water-immiscible solvent is used as the organic phase, adoption of PTC conditions should facilitate product isolation.

Its termini being differentiated, (*S*)-3-*O*-benzyl-glycerol (**4**) can serve as a chiral glycerol equivalent; hence, it has found a range of applications in the synthesis of single enantiomers of chiral drug candidates, such as (*S*)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine (HPMPC, **5**) of antiviral activity (Scheme 1).[2] Preparation of (*S*)-**4** commenced with $NaIO_4$-mediated glycol cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**);[3] the split aldehyde was then reduced with $NaBH_4$ to give (*R*)-1,2-*O*-isopropylidene-glycerol (**2**). To effect its *O*-benzylation, **2** was treated with a biphasic mixture of excess BnCl (Bn = $PhCH_2$) and 50% aqueous NaOH solution in the presence of $Bu_3(Bn)NBr$. The reaction mixture was stirred with heating at 100 °C for several hours until the reaction went to completion although $Bu_3(Bn)NBr$ has propensity for Hofmann elimination at elevated temperatures: $Bu_3(Bn)NBr + NaOH \rightarrow EtCH{=}CH_2 + Bu_2(Bn)N + NaBr + H_2O$. On phase separation, the organic layer containing (*R*)-1,2-*O*-isopropylidene-glycerol-3-benzyl ether (**3**) was exposed to aqueous H_2SO_4 solution at 100 °C to hydrolyze the acetonide moiety of **3** to (*S*)-diol (**4**). After all Bn_2O and any BnCl, and some BnOH were extracted into petroleum ether, the aqueous mixture was made alkaline, saturated with NaCl, and extracted with AcOEt to isolate (*S*)-**4**. Finally, fractional distillation separated the residual BnOH

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(1) (a) For a comprehensive treatise on PTC, see: Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994. (b) Halpern, M. E. Benefits and Challenges of Applying Phase-Transfer Catalysis Technology in the Pharmaceutical Industry. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Deckker: New York, 1999; pp 283–298..

(2) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R., II; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 1457.

(3) Golding, B. T.; Ioannou, P. V. *Synthesis* **1977**, 423.

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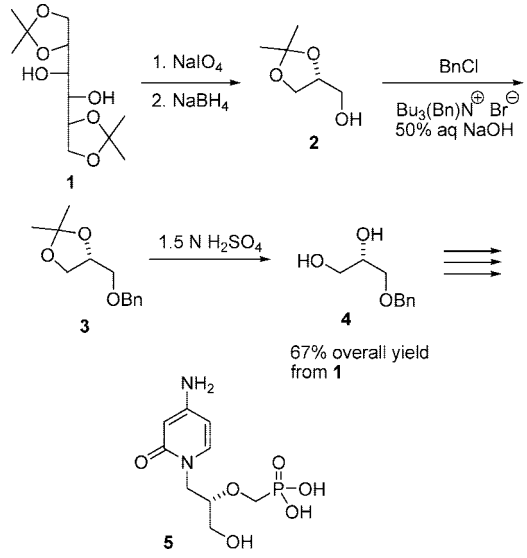
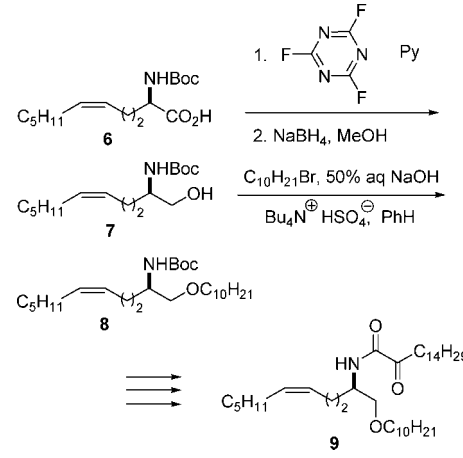
Scheme 1. **Benzyl ether formation**



Scheme 2. **Formation of long-chain aliphatic ether**



from (*S*)-**4** to a substantial degree and afforded (*S*)-**4** in 67% overall yield from **1**. While (*S*)-**4** thus obtained was contaminated with a little BnOH (about 3%), its preparation was accomplished expeditiously without isolation of the intermediate (*R*)-**3**.

Except for its susceptibility to Hofmann elimination, $Bu_3(Bn)NBr$ should be the quaternary ammonium salt of choice in conducting *O*-alkylative benzylation under PTC conditions because it remains immortal (unchanged) throughout the reaction via self-regeneration:[4] in the case of the *O*-benzylation of **2**, its derived alkoxide may react with $Bu_3(Bn)NBr$ to give the desired **3** and Bu_3N; the latter may undergo *N*-alkylation in situ with the externally added BnCl, which leads to regeneration of $Bu_3(Bn)NX$ (X = Cl or Br).

O-Alkylation under PTC conditions was also used to advantage in assembling long-chain *N*-Boc-2-amino ether (**8**), an advanced synthetic intermediate for a pancreatic lipase inhibitor of an α-ketoamide type (**9**), which featured the following two structural traits: (1) an *N*-acyl-2-amino ether backbone mimicking the structure of triglyceride, a substrate of pancreatic lipase, and (2) a highly electrophilic α-keto carbonyl function to trap the serine hydroxy group located in the active site of the enzyme (Scheme 2).[5] On treatment with cyanuric fluoride in pyridine (Py), *N*-Boc-2-amino-5-undecenoic acid (**6**), prepared from D-glutamic acid, was converted to the corresponding acid fluoride, which was reduced with $NaBH_4$ in MeOH to give 2-amino alcohol (**7**). When **7** was treated with decyl bromide in a biphasic mixture of benzene and 50% aqueous NaOH solution in the presence of catalytic Bu_4NHSO_4, it underwent *O*-alkylation to give ether (**8**) in a satisfactory yield. At this juncture, it should be noted that the Boc-protected primary amine function in **7** did not undergo *N*-alkylation, surviving the *O*-alkylation conditions unaffected.[6]

Decyl bromide is a less reactive alkylating agent than BnCl and what is worse, unlike the preceding example, Bu_4NHSO_4 is devoid of the same alkyl group ($C_{10}H_{21}$) as incorporated in the ether product; hence, no self-protection against the eliminative decomposition. Actually, these unfavorable conditions notwithstanding, the ether formation proceeded uneventfully with **7** by the catalysis of Bu_4NHSO_4; such successful results may be ascribed to the highly lipophilic nature of **7** compared to glycerol-based **2**.

Ester Formation. Being susceptible to saponification (alkaline hydrolysis), esters are difficult to prepare by *O*-alkylation of carboxylate anions generated in aqueous basic media. However, when it is conducted in a biphasic mixture (water-immiscible organic solvent/aqueous alkaline solution) under PTC conditions, ester formation becomes a predominant event, as exemplified by successful conversion of carboxylic acid (**11**) to benzyl ester (**12**) (Scheme 3).[7] On treatment with $NaIO_4$ in $CCl_4/MeCN/H_2O$ in the presence of catalytic $RuCl_3$, verbenone (**10**), prepared from (+)-α-pinene by allylic oxidation, underwent oxidative cleavage at its enone function to give keto acid (**11**) in 94% yield with concomitant loss of CO_2. When **11** was treated with BnCl in a biphasic mixture of CH_2Cl_2 and an aqueous K_2CO_3 solution in the presence of Et_4NCl, **12** was obtained in 72% yield. With its carboxylic acid function being protected as the benzyl ester, **12** could be converted to (1*R*,3*S*)-*N*-Boc-3-amino-2,2-dimethylcyclobutane-1-carboxylic acid (**13**), a proteinogenic amino acid surrogate designed to mimic backbone and side chain conformations of peptides, by the following three-step functional group manipulations: (1) haloform reaction (NaBrO, dioxane/H_2O; 83% yield) on the methyl ketone functionality, (2) Curtius rearrangement [$(PhO)_2P(O)N_3$, Et_3N, *tert*-BuOH; 58% yield] on the resulting carboxylic acid, and (3) catalytic hydrogenolysis (H_2, catalytic Pd/C, AcOEt; 79% yield) of the benzyl ester.

If phase transfer catalysts of a quaternary ammonium type for ester formation needed to possess the same attributes as those

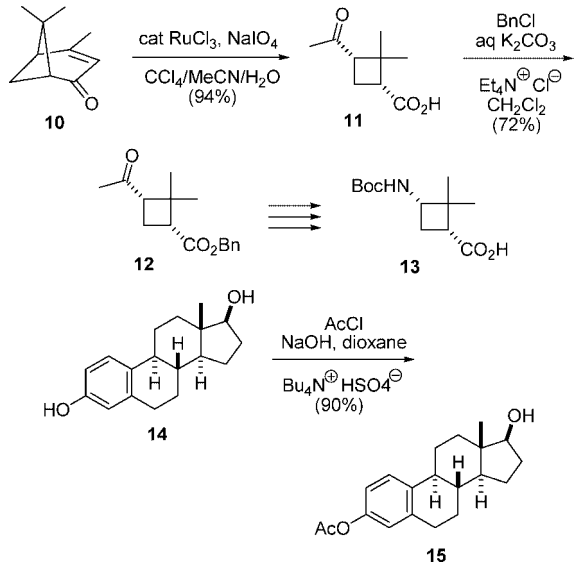
(4) Drs. M. Halpern and J. Pesti, appointed editors of this special issue, kindly shared with the author these informative comments and allowed him to add them to this article.

(5) Chiou, A.; Markidis, T.; Constantinou-Kokotou, V.; Verger, R.; Kokotos, G. *Org. Lett.* **2000**, *2*, 347.

(6) For the combined use of quaternary ammonium salt and crown ether in a biphasic aqueous/organic mixture to form ether between secondary alcohol and mesylate, see: Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 857.

(7) Burgess, K.; Li, S.; Rebenspies, J. *Tetrahedron Lett.* **1997**, *38*, 1681.

Scheme 3. **Ester formation and chemoselective acylation of phenol**

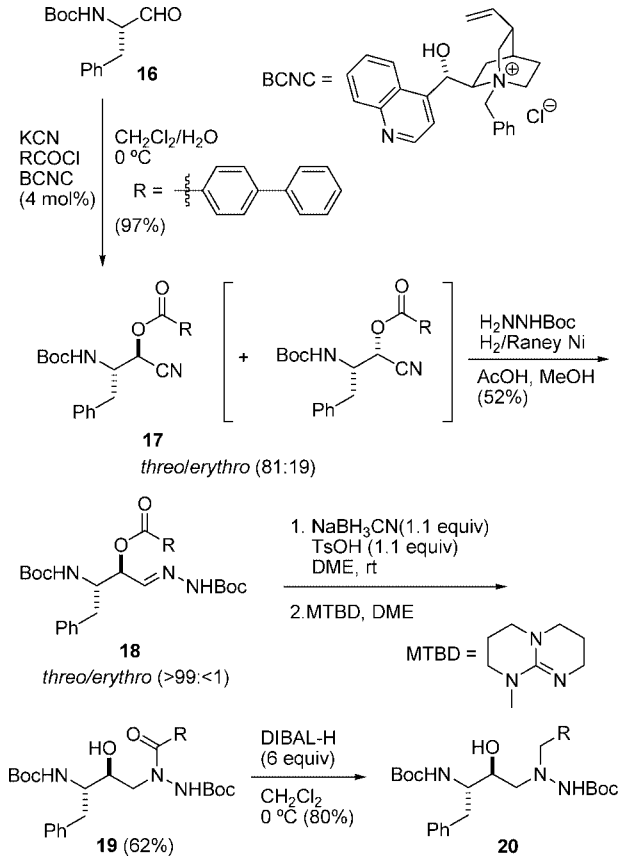


for ether formation, they should be equipped with the alkyl group (R^2) that may appear in the ester product ($R^1CO_2R^2$).[4] However, contrary to such extrapolation, it was Et_4NCl, but not benzyl(trialkyl)ammonium salt, that was employed as the phase transfer catalyst in the benzyl ester formation with **11**. It is because carboxylate anions are not so reactive to undergo *O*-ethylation by Et_4NCl; in addition, neither carboxylate (RCO_2^-) nor carbonate (CO_3^{2-}) is basic enough to induce Hofmann elimination with Et_4NCl. From a viewpoint of process development, it is noteworthy that the PTC conditions applied were so mild as to render the ester formation in question free from epimerization or racemization; in fact, this experimental result seems phenomenal when it is considered that **11** and **12** are both stereochemically labile due to the thermodynamically unfavorable *cis*-relationship between the carboxyl (COOR; R = H for **11**, Bn for **12**) and acetyl (COMe) groups in each of them.

Another method for ester formation, *O*-acylation, can also benefit from PTC in terms of chemoselectivity (Scheme 3):[8] When β-estradiol (**14**) was treated with AcCl in a biphasic mixture of powdered NaOH and dioxane in the presence of catalytic Bu_4NHSO_4, its phenolic hydroxy group at the C3 position underwent acetylation selectively to give acetate (**15**) in 90% yield, with its aliphatic 17-hydroxy function being unaffected. At this juncture, it is worthy of commentary that the PTC conditions mentioned above worked well also in the *O*-acylation of highly hindered phenols, such as 2,6-di-*tert*-buyl-4-methylphenol.[8]

When cyanohydrin formation in a biphasic aqueous/organic mixture is coupled with PTC-promoted *O*-acylation, a hydroxy group arising from the kinetically favored event can be trapped as an ester before thermodynamic equilibrium is established between the stereoisomers of cyanohydrin. This ingenious synthetic maneuver was successfully implemented in building hydroxyethylhydrazine (**20**), a common precursor to aza-dipeptide isosters of potent HIV protease inhibitory activity, as

Scheme 4. **Trapping cyanohydrin by in situ *O*-acylation**

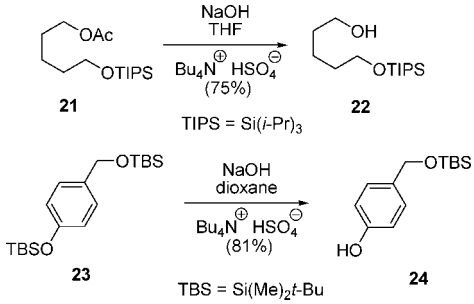


outlined in Scheme 4:[9] When *N*-Boc L-phenylalanine aldehyde (**16**) was treated with KCN in a biphasic CH_2Cl_2/H_2O mixture in the presence of 4-phenylbenzoyl chloride and *N*-benzyl cinchoninium chloride (BCNC; 4 mol %), cyanohydrin ester (**17**) was produced as a 81:19 mixture of its *threo* and *erythro* isomers in 97% yield. The diastereomeric mixture of **17** thus obtained was subjected, without purification, to catalytic reduction (Raney Ni, H_2, AcOH, MeOH) concomitant with formation of hydrazone with $H_2N-NHBoc$. On crystallization, *threo*-hydrazone (**18**) of >98% de was isolated in 52% yield, which was then reduced with $NaBH_3CN$ in DME in the presence of *p*-TsOH. When the resulting hydrazine derivative was treated with 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in DME, the *O*-acyl to *N*-acyl migration took place to give *N*-acyl-*N*′-Boc-hydrazine (**19**) in 62% overall yield. Eventually, reduction with DIBAL-H in CH_2Cl_2 gave **20** in 80% yield, which was then converted to HIV protease inhibitors of the aza-dipeptide isoster structure via removal of the two Boc protecting groups followed by acylation of both amine and hydrazine nitrogen atoms.

Hydrolysis of *O*-acetate, *O*-silyl ether and ester. Because of its intrinsic nature of mildness, PTC can impart subtle chemoselectivity to hydrolytic deprotection, such as *O*-deacylation ($R^1OCOR^2 \rightarrow R^1OH$),[10] *O*-desilylation ($R^1OSiR^2R^3R^4 \rightarrow R^1OH$),[11] and ester hydrolysis ($R^1CO_2R^2 \rightarrow R^1CO_2H$).[12] When ω-acetoxyalkyl triisopropylsilyl (TIPS) ether (**21**) was exposed

(8) Illi, V. O. *Tetrahedron Lett.* **1979**, 2431.
(9) Fässler, A.; Bold, G.; Steiner, H. *Tetrahedron Lett.* **1998**, *39*, 4925.
(10) Crouch, R. D.; Burger, J. S.; Zietek, K. A.; Cadwallader, A. B.; Bedison, J. E.; Smielewska, M. M. *Synlett* **2003**, 991.
(11) Crouch, R. D.; Stieff, M.; Frie, J. L.; Cadwallader, A. B.; Bevis, D. C. *Tetrahedron Lett.* **1999**, *40*, 3133.

Scheme 5. **Selective hydrolytic removal of *O*-acetyl and *O*-silyl protections**



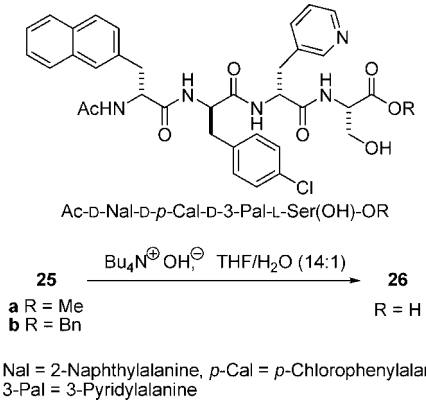
to a biphasic mixture of powdered NaOH and THF in the presence of Bu_4NHSO_4 (0.5 equiv), selective *O*-deacetylation took place to give α,ω-glycol with mono-TIPS protection (**22**) in 75% yield, the TIPS ether function surviving the hydrolysis unaffected (Scheme 5).[10]

When using the PTC conditions similar to those mentioned above, a phenolic silyl ether could be deprotected in preference to an aliphatic one (Scheme 5):[11] When 4-hydroxybenzylalcohol bis-TBS ether (**23**) was treated with a biphasic mixture of powdered NaOH and dioxane in the presence of Bu_4NHSO_4 (0.5 equiv), phenol (**24**) was obtained in 81% yield with its aliphatic *O*-TBS ether being untouched. Besides the demonstrated chemoselectivity (ester versus silyl ether in **21** and aromatic versus aliphatic silyl ether in **23**), the PTC conditions applied to the biphasic solid/liquid mixture would provide operational simplicity in product isolation due to no need for aqueous workup.

Basic hydrolysis is a common means to deprotect C-terminal carboxylic esters of peptides; however, it is often plagued with the following inconveniences: (1) limited solubility of peptide esters in an aqueous or organic medium and (2) deterioration in the stereochemical integrity of chiral α-carbons. Indeed, to circumvent such problems, one can use *O*-benzyl ester as a protection of the C-terminal carboxylic acid because the *O*-benzyl group can be removed by catalytic reduction in place of basic hydrolysis. However, when Ac-D-Nal-D-*p*-Cal-D-3-Pal-L-Ser(OH)-OBn (**25b**) was subjected to catalytic hydrogenolysis, it turned out that the C-terminal deprotection suffered from three serious drawbacks:[12a] (1) slow reaction, (2) considerable epimerization, and (3) partial reduction of the pyridine ring of the D-3-Pal residue.

To resolve this conundrum, an investigation into application of Bu_4NOH, an efficacious vehicle of hydroxide anions, to basic hydrolysis of C-terminal esters was made, as outlined in Scheme 6.[12a] When Ac-D-Nal-D-*p*-Cal-D-3-Pal-L-Ser(OH)-OMe (**25a**) was treated with Bu_4NOH (1.5–2 equiv) in THF/H_2O (33:1) at −5 °C, ester hydrolysis proceeded cleanly, giving the desired acid (**26**) in 82% yield, with its DDDD-diastereomer being formed in not more than 1.7% yield. The Bu_4NOH-mediated hydrolysis of polypeptide C-terminal esters can provide the following

Scheme 6. **Hydrolysis of peptide C-terminal esters**



advantages over the traditional procedures: (1) Because of the solubilizing effect caused by Bu_4NOH, hydrolysis proceeds even with polypeptide esters insoluble in common organic solvents or in water.[12b] (2) The stereogenic centers at the α-position of the C-terminal esters would suffer from little epimerization, if any.[12a]

Transesterification. Transesterification is a method to produce new esters by changing alcoholic moieties of esters from one to another: $RCO_2R^1 + R^2OH \rightarrow RCO_2R^2 + R^1OH$. The reaction reaches equilibrium so swiftly that it is not so easy a task to isolate the transesterified product (RCO_2R^2) in a pure state. Thus, to shift the reaction equilibrium in a forward direction as much as possible, the incoming alcohol (R^2OH) is often used in excess amounts in the presence of an acid or base catalyst.[13] However, to overcome such a mechanistic limitation, two-step but one-pot procedures were designed in which an ester hydrolysis step was telescoped into an *O*-alkylative esterification step.

Such preparatively intriguing operations were implemented when ester hydrolysis and *O*-alkylation of the resulting carboxylate were conducted in sequence using the common phase transfer catalyst, as depicted in (Scheme 7).[14] As part of a process development program to produce loracarbef (**30**), a carbacepharosporin antibiotic, a practical method to convert methyl ester (**27**) to 4-nitrobenzyl ester (**29**) had to be devised such that the carboxylic acid functionality could be released without affecting the vulnerable carbacepharosporin skeleton later in the synthesis of **30**.[15] To meet such a developmental requirement, a one-pot procedure for transesterification was developed using a single phase transfer catalyst for dual purposes: ester hydrolysis and re-esterification via *O*-alkylation of the resulting carboxylate.[14] When **27** was treated with 5 M aqueous NaOH solution in a biphasic CH_2Cl_2/H_2O mixture at pH 13.2 in the presence of catalytic Bu_4NBr (0.15 equiv) at ambient temperature, it was converted to sodium carboxylate (**28**) in 1–2 h. On completion of the hydrolysis, the mixture was adjusted to pH 7–8 with 5 M aqueous HCl solution and

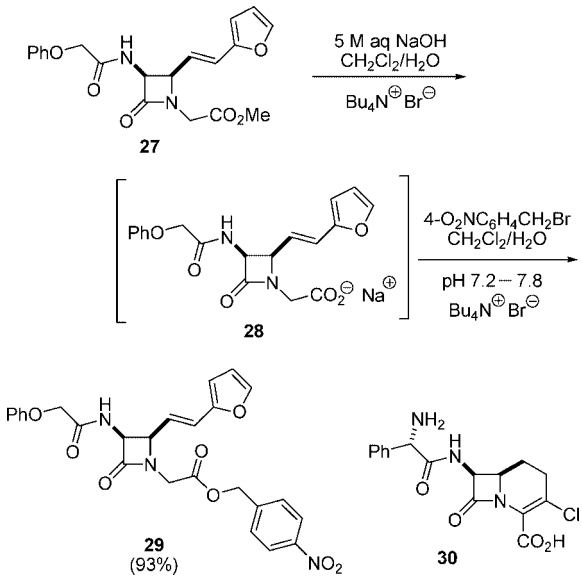
(12) (a) Abdel-Magid, A. F.; Cohen, J. H.; Maryanoff, C. A.; Shah, R. D.; Villani, F. J.; Zhang, F. *Tetrahedron Lett.* **1998**, *39*, 3391. (b) Abdel-Magid, A. F.; Bos, M. E.; Eggmann, U.; Maryanoff, C. A.; Scott, L.; Thaler, A.; Villani, F. J. Solution Phase Synthesis of the Pulmonary Surfactant KL$_4$: A 21 Amino Acid Synthetic Protein. In *Chemical Process Research: The Art of Practical Organic Synthesis*; Abdel-Magid, A. F., Ragan, J. A., Eds.; ACS Symposium Series 870; American Chemical Society: Washington, DC, 2004; pp 181–197.

(13) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790.

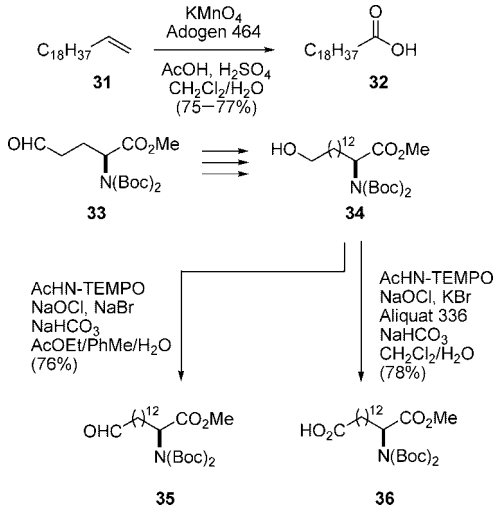
(14) Doecke, C. W.; Staszak, M. A.; Luke, W. D. *Synthesis* **1991**, 985.

(15) Astleford, B. A.; Weigel, L. O. Resolution Versus Stereoselective Synthesis in Drug Development: Some Case Histories. In *Chirality in Industry II: Developments in the Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons: Chichester, 1997; pp 99–117..

Scheme 7. **One-pot transesterification**



Scheme 8. **Oxidative conversion with olefinic and alcoholic derivatives**



then exposed to 4-nitrobenzylbromide at ambient temperature for 12 h to produce 4-nitrobenzyl ester (**29**) in 93% overall yield; the sensitive β-lactam moiety remained unaffected throughout the alkaline hydrolysis of methyl ester (**27**) and the *O*-alkylation of sodium carboxylate (**28**).[16]

Oxidation. Besides the displacement reactions discussed above, activation of inorganic anionic species for oxidation in biphasic media accounted for the early successes of PTC applied to functional group manipulations, as exemplified by the classical permanganate-mediated olefinic cleavage (Scheme 8):[17] When 1-eicosene (**31**) was exposed to $KMnO_4$ in a biphasic mixture of CH_2Cl_2/H_2O containing 9 M aqueous H_2SO_4 solution and AcOH in the presence of Adogen 464 [$Me(C_{8-10}H_{17-21})_3NCl$, 6% w/w], the oxidation went to completion at ambient temperature in 18 h. On aqueous workup followed by crystallization, nonadecanoic acid (**32**) was obtained in 75–77% yield.

PTC has made a difference when it was applied to oxidation of alcohols wherein stoichiometric NaOCl was employed in combination with catalytic 4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy free radical (AcHN-TEMPO) (Scheme 8).[18] When *N*,*N*-di-Boc-ω-hydroxy α-amino acid ester (**34**), prepared from methyl (*S*)-*N*,*N*-di-Boc-2-amino-5-oxopentanoate (**33**), was treated with an aqueous solution of NaOCl (1.1 equiv) and $NaHCO_3$ (2.9 equiv) in a biphasic mixture of PhMe/AcOEt/H_2O in the presence of AcHN-TEMPO (2 mol %) and NaBr at –6 °C for 1 h, oxidation terminated at an aldehyde stage and *N*,*N*-di-Boc-ω-formyl-α-amino acid ester (**35**) was obtained in 76% yield. In contrast, when **34** was exposed to an aqueous solution of NaOCl (2.5 equiv) and AcHN-TEMPO (1 mol %) in a biphasic mixture of CH_2Cl_2/H_2O containing $NaHCO_3$ (2.9 equiv) and KBr in the presence of Aliquat 336 [$Me(C_8H_{17})_3NCl$, 5 mol %] at 0 °C for 15 min, the oxidation went to a stage of carboxylic acid to afford ω-carboxy-α-amino acid (**36**) in 78% yield.[19]

Activation of Fluoride. Being a hard base,[20] fluoride anion (F^-) binds with alkali metal cations (M^+), such as K^+ and Cs^+, so tightly as to form salts (M^+F^-) that are reluctant to participate in nucleophilic substitution. Thus, to strip M^+F^- of M^+ and thereby to enhance the reactivity of F^- towards nucleophilic substitution, crown ethers [$(OCH_2CH_2)_m$] are often employed which possess fit-sized cavities tailored to capture the metallic counteractions (M^+); for instance, 18-crown-6 [$(OCH_2CH_2)_m$, $m = 6$], accommodating K^+ in its central cavity, is suited for the activation of KF, as illustrated by structure (**37**) in Scheme 9.

It should be of practical and economical advantage if crown ethers [cyclic polyglymes; $(OCH_2CH_2)_m$] can be replaced with monomethylpolyglymes [$Me(OCH_2CH_2)_nOH$] in activating F^- towards nucleophilic substitution by stripping M^+ off M^+F^-. In fact, when KF is in contact with monomethyltriglyme [TGME; $Me(OCH_2CH_2)_nOH$, $n = 3$], K^+ may become almost under siege of TGME, as illustrated by structure (**38**) in Scheme 9, to deliver a fluoride-vehicle soluble in an organic phase; this speculation opened a practical avenue to a TGME-assisted fluoride-catalyzed amination process as outlined in Scheme 9.[21]

When 2-chloroimidazole (**39**) was treated with amine (**40**) in TGME in the presence of spray-dried KF (0.3 equiv), lutidine, and H_2O (1% w/w), amination proceeded via 2-fluoroimidazole (**41**) at 120 °C, where inclusion of lutidine was essential to prevent urea (**43**) from being formed. The reaction went to completion in 2 h to provide 2-aminoimidazole (**42**) in 87%

(16) For another example of transesterification under phase transfer catalysis, see: O'Donnell, M. J.; Cook, G. K.; Rusterholz, D. B. *Synthesis* **1991**, 989.

(17) Lee, D. G.; Shannon, E. L.; Chang, V. S. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. VII, pp 397–400..

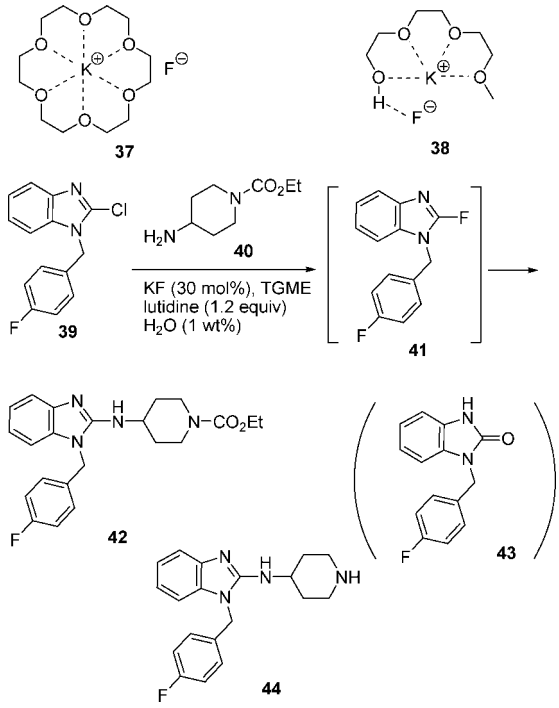
(18) Markidis, T.; Kokotos, G. *J. Org. Chem.* **2002**, *67*, 1685.

(19) (a) For the influence of Aliquat 336 on the oxidation mediated by stoichiometric NaOCl and catalytic 4-MeO-TEMPO, see: Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) For the selective oxidation of a primary hydroxy group without affecting a secondary one by TEMPO-assisted NaOCl-mediated oxidation in the presence of catalytic Bu_4NCl, see: Siedelecka, R.; Skarzewski, J.; Młochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177.

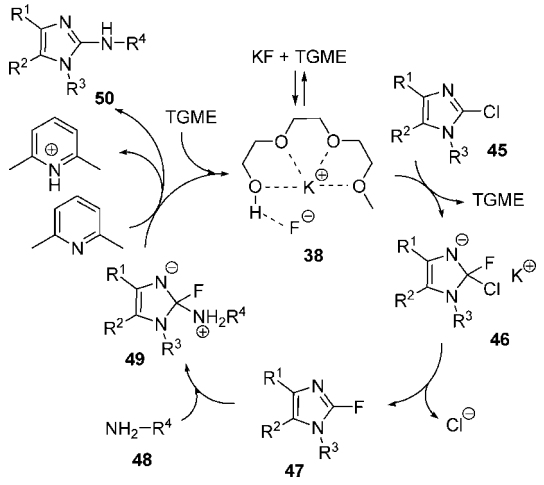
(20) For prediction of reaction courses based on the theory of hard and soft acids and bases (HSAB), see: Dörwald, F. Z. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*; Wiley-VCH: Weinheim, 2005.

(21) Senanayake, C. H.; Hong, Y.; Xiang, T.; Wilkinson, H. S.; Bakale, R. P.; Jurgens, A. R.; Pippert, M. F.; Butler, H. T.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 6875.

Scheme 9. **Fluoride-assisted amination of 2-chloroimidazole**



Scheme 10. **The plausible mechanism of the fluoride-assisted amination**

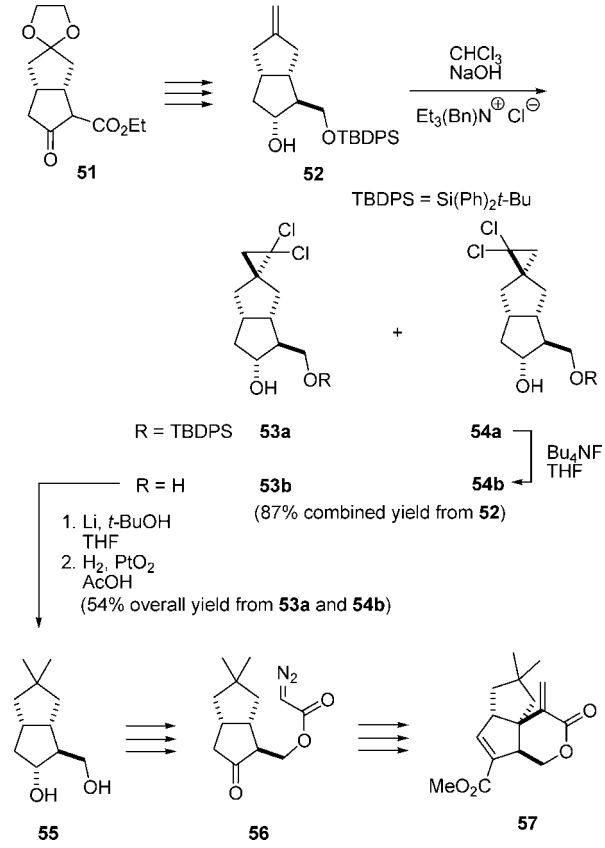


yield, which was a penultimate precursor to norastemizole (**44**), a potent antihistamine drug.

The fluoride-mediated amination is assumed to proceed as depicted in Scheme 10:[22] In contact with KF, TGME captures it to form the activated fluoride vehicle (**38**), which helps to add fluoride to 2-chloroimidazole (**45**). When chloride leaves the resulting tetrahedral adduct (**46**), 2-fluoroimidazole (**47**) is generated with its C−F bond being ready for further conversion to a C−N bond. Amine (**48**) subsequently attacks **47** to form adduct (**49**), which collapses to 2-aminoimidazole (**50**) with the help of lutidine; the released fluoride participates in the next cycle of the reaction sequence after complexation with TGME.

(22) Senanayake, C. H. Practical Catalytic Processes for Large-Scale Manufacture of Antihistamine Norastemizole and β-Agonist (*R*,*R*)-Formotrol. In 4th International Conference on Organic Process Research & Development, Kowloon, Hong Kong, March 18–21, 2001, Scientific Update: Mayfield, U.K., 2001.

Scheme 11. **Cyclopropanation with dichlorocarbene**

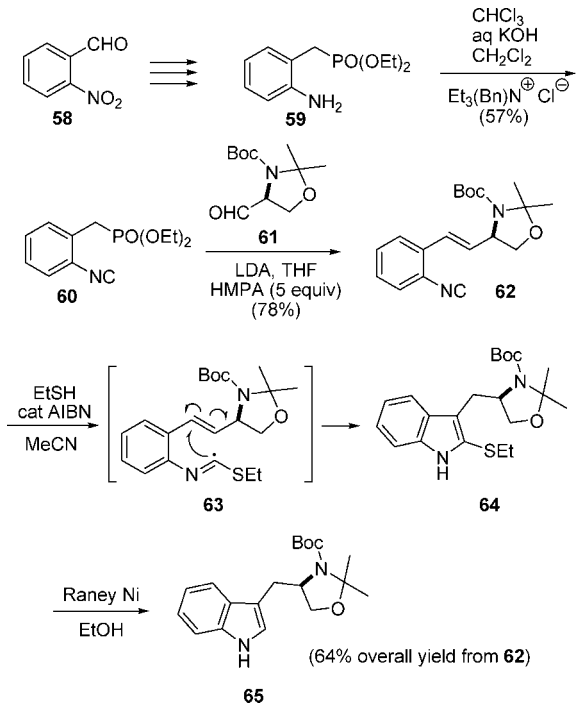


Generation of Dichlorocarbene. Indeed, carbene (**:**CH_2) in itself is too reactive a species to isolate; however, it can be generated in a stabilized form of its metallic complex (carbenoid) by treating CH_2I_2 with Zn−Cu couple in ether.[23] In contrast, dichlorocarbene (**:**CCl_2) can be generated under metal-free conditions by exposing $CHCl_3$ to an aqueous hydroxide solution in the presence of a phase transfer catalyst.[24] Because of operational simplicity in generating dichlorocarbene under PTC conditions, the ensuing 1,1-dichlorocyclopropanation of alkenes would serve as a preparative substitute for the carbenoid-mediated direct cyclopropanation, provided that the 1,1-dichlorocyclopropane produced can be converted to a bare cyclopropane unit by reductive dechlorination, as exemplified in Scheme 11.[25]

When chiral nonracemic bicyclo[3.3.0]octane (**52**) possessing an *exo*-methylene group, prepared from β-keto ester (**51**), was treated with a biphasic mixture of powdered KOH and $CHCl_3$ in the presence of catalytic $Bn(Et)_3NCl$ at ambient temperature, *gem*-dichlorocyclopropanation took place and went to completion in 15 min to give a mixture of **53a** and **54a**. On treatment with Bu_4NF in THF, a mixture of diol (**53b**) and **54b** was obtained in a combined overall yield of 87% from *exo*-olefin (**52**). When the mixture of **53b** and **54b** was subjected to perdechlorination (Li, *tert*-BuOH, THF) followed by hydrogenolytic scission of the cyclopropane ring (catalytic Pt, AcOH),

(23) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Charette, A. B.; Beauchemin, A. *Organic Reactions*; Wiley & Sons: New York, 2001; Vol. 58, pp1–415.
(24) (a) Ma$_{\text{s}}$kosza, M.; Wawrzyniewcz, M. *Tetrahedron Lett.* **1969**, 4659. (b) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.
(25) Mori, K.; Tsuji, M. *Tetrahedron* **1988**, *44*, 2835.

Scheme 12. **Preparation of isonitrile and its application to indole synthesis**

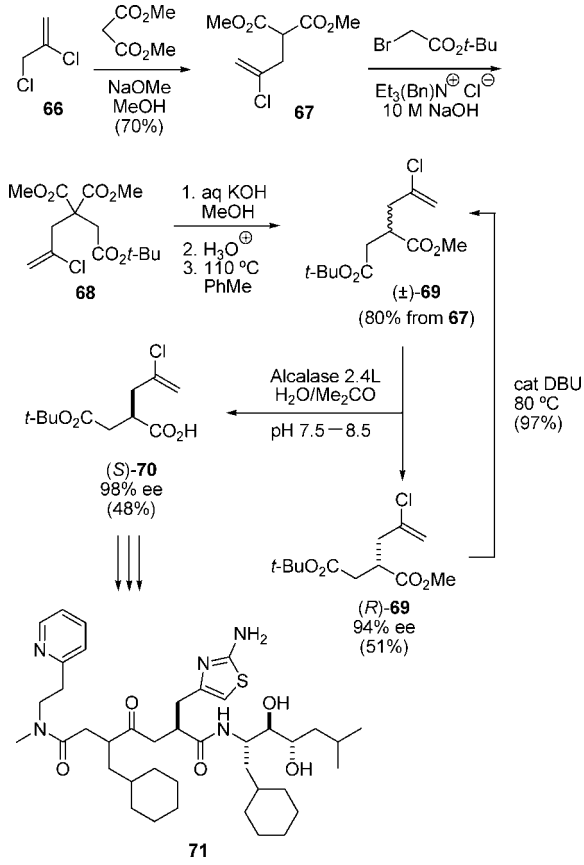


7,7-dimethyl-bicyclo[3.3.0]octane (**55**) was isolated as a single stereoisomer in 54% overall yield. Diol (**55**) was then converted to (−)-pentalenolactone E methyl ester (**57**) via esterification with diazoacetic acid, $Rh_2(OAc)_4$-catalyzed carbene insertion with **56**, methoxycarbonylation, and methylenation.[26]

Isonitrile (R−N═C**:**), indispensable for Ugi four-component reaction,[27] is often prepared from formamide (R−NHCHO) by dehydration using Ph_3P, CCl_4, and Et_3N.[28] However, it can be produced more conveniently by generating dichlorocarbene (**:**CCl_2) from $CHCl_3$ and an aqueous hydroxide solution under PTC conditions in the presence of primary amine (R−NH_2); the dichlorocarbene thus formed is inserted into the N-H bond to give dichloromethyl amine (R−NH−$CHCl_2$) incipiently, which then collapses to isonitrile (R−N═C**:**) via 2-fold elimination of HCl.[28]

When an isonitrile function, prepared from an aniline derivative under the above-mentioned PTC conditions, is allowed to engage with an *ortho*-situated vinyl moiety in a radical reaction, the 3-substituted indole structure can be constructed, as delineated in Scheme 12:[30] When diethyl (2-aminobenzyl)phosphonate (**59**), prepared from 2-nitrobenzaldehyde (**58**), was reacted with dichlorocarbene generated from $CHCl_3$ (2.5 equiv) under PTC conditions [50% aqueous KOH solution/CH_2Cl_2 (1:1), Et_3(Bn)NCl (2 mol %), heating at reflux],

Scheme 13. **Malonate synthesis**

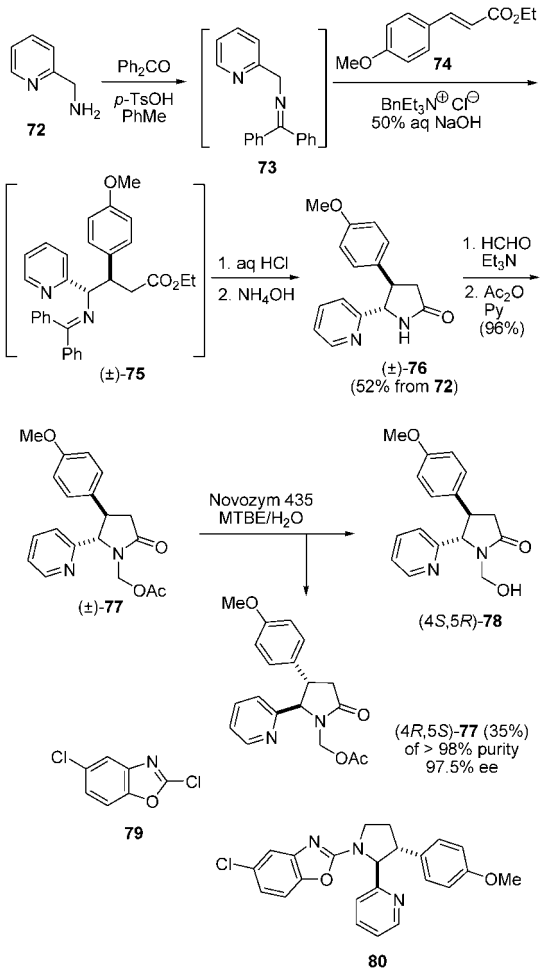


isonitrile (**60**) was obtained in 57% yield. On the Horner-Wadsworth-Emmons condensation (LDA, HMPA, THF, −78 °C) with Garner's aldehyde (**61**), **60** was converted to 2-isocyanostyrene (**62**), a penultimate precursor for the indole ring construction, in 78% yield. When **62** was treated with EtSH in MeCN in the presence of catalytic AIBN, the radical cyclization proceeded by way of **63**. The resulting 2-ethylthioindole (**64**) was subjected, without purification, to Raney Ni-mediated desulfurization to deliver 3-substituted indole (**65**), its overall yield from **62** being 62%.

C−C Bond Formation for Racemic Synthesis. Resolution is still a viable option to access single enantiomers as long as the racemic compounds to be resolved are easy to access. Thus, racemic synthesis may benefit from PTC that helps an easy-to-handle aqueous base to generate a stabilized carbanion and allow it to participate in C−C bond formation in situ, as illustrated in Scheme 13:[31] To effect the second alkylation of dimethyl (2-chloro-2-propenyl)malonate [**67**; prepared by NaOMe-mediated alkylation of dimethyl malonate with 2,3-dichloropropene (**66**) in 70% yield] under solvent-free phase transfer conditions, a mixture of **67** and *tert*-butyl bromoacetate (1.0 equiv) was added to 10 M aqueous NaOH solution (10.2 equiv) in the presence of $Bn(Et)_3NCl$ (0.4 mol %) at temperatures below 15 °C. When the resulting biphasic mixture was stirred at ambient temperature overnight, dialkylated malonate (**68**) was produced quantitatively. On separation from the aqueous phase, crude **68** was moved forward, without purifica-

(26) For ring expansion of pyranose to septanose via dihalocyclopropanation, see: Ganesh, V. G.; Jayaraman, N. *J. Org. Chem.* **2007**, *72*, 5500.
(27) (a) Domling, A.; Ugi, I. *Angew.Chem., Int. Ed.* **2000**, *39*, 3168. (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.
(28) Amato, F.; Marcaccini, S. *Organic Syntheses*; Wiley & Sons: New York, 2005; *Vol 82*, pp 18–21..
(29) (a) Gokel, G. W.; Widera, R. P.; Weber, W. P. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, pp 232–235. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew.Chem., Int. Ed. Engl.* **1972**, *11*, 530.
(30) Tokuyama, H.; Watanabe, M.; Hayashi, Y.; Kurokawa, T.; Peng, G.; Fukuyama, T. *Synlett* **2001**, 1403.
(31) Beaulieu, P. L.; Gillard, J.; Bailey, M.; Beaulieu, C.; Duceppe, J.-S.; Lavallée, P.; Wernic, D. *J. Org. Chem.* **1999**, *64*, 6622.

Scheme 14. **Michael addition of 2-aminopyridine Schiff base**



tion, to the next monosaponification step that employed KOH in a homogeneous MeOH/H_2O mixture at temperatures below 15 °C. After acidification, the resulting monoacid was extracted into toluene (PhMe), and the PhMe solution was heated to reflux to induce decarboxylation, which afforded (±)-succinate (**69**) in 80% overall yield from **67**.

When (±)-**69** was treated with Alcalase 2.4 L (Subtilisin Carlsberg, 0.02 w/w) in aqueous acetone at pH 7.2–8.1 at ambient temperature for 71 h, kinetic resolution took place, its methyl ester moiety undergoing (*S*)-selective hydrolysis.[31] Simple acid–base extraction allowed the hydrolyzed (*S*)-acid (**70**) of 98% ee and the unaffected (*S*)-ester (**69**) of 94% ee to be isolated in 48% and 51% yield, respectively; (*S*)-**70** was then incorporated into BILA 2157 BS (**71**), a potent specific inhibitor of human rennin, while oily (*S*)-**69** was heated neat to 80 °C in the presence of catalytic DBU for 24 h to regenerate (±)-**69** in 97% yield.

PTC is also effective for Michael reactions with C−C bond formation wherein stabilized carbanions are added to electron-deficient olefinis (Scheme 14):[32] On *p*-TsOH-catalyzed condensation with benzophenone in PhMe, 2-(aminomethyl)pyridine (**72**) was converted to the Schiff base (**73**). To the PhMe solution of crude **73** were added ethyl 4-methoxycinnamate (**74**), $Bn(Et)_3NCl$ (5 mol %), and 50% aqueous solution of NaOH; the resulting biphasic mixture was stirred at ambient temperature for 19 h to furnish (±)-**75**. On acidic hydrolysis of the benzophenone imine with 12 M aqueous HCl solution, basification with 15 M aqueous NH_3 solution permitted spontaneous cyclization of a lactam ring at ambient temperature in 18 h. Extractive workup followed by crystallization afforded (±)-*trans*-2-pyrrolidinone (**76**, *trans*/*cis* = 93:7) as a crystalline solid in 52% overall yield from **72**.

To effect *N*-hydroxymethylation, **76** was treated with 37% aqueous CH_2O in THF in the presence of Et_3N at ambient temperature for 4 days. On *O*-acetylation with Ac_2O in Py, crude (±)-*trans*-1-acetoxymethyl-2-pyrrolidinone (**77**) was obtained in 96% yield. When the crude (±)-**77** thus secured was treated with Novozyme 435 (immobilized on acrylic resin) in a mixture of H_2O and MTBE for 10 days, enantioselective hydrolysis proceeded to 60% conversion at which point the unaffected (4*R*,5*S*)-**77** exhibited 97.5% ee. A solution of the left-over (4*R*,5*S*)-**77** and the digested (4*S*,5*R*)-**78** in CH_2Cl_2 was then washed with 1.0 M aqueous H_3PO_4 solution to hydrolyze (4*S*,5*R*)-**78** to (4*S*,5*R*)-**76**, with (4*R*,5*S*)-**77** remaining unaffected. The resulting (4*S*,5*R*)-pyrrolidinone (**76**) was extracted into the aqueous phase as its salt with H_3PO_4. In contrast, (4*R*,5*S*)-1-acetoxymethylpyrrolidinone (**77**) remained dissolved in the CH_2Cl_2 phase even after its salt formation with H_3PO_4 because of much lower solubility of the salt in the aqueous phase. On concentration of the CH_2Cl_2 solution, (4*R*,5*S*)-**77** of >98% purity (HPLC) was obtained in 97.5% ee and 35% yield from (±)-**77**. Eventually, (4*R*,5*S*)-**77** thus resolved was converted to BIRZ-227 (**80**), an LTB_4 biosynthesis inhibitor, via three-step reactions: (1) hydrolytic removal of the *N*-acetoxymethyl group with concentrated aqueous NH_3 solution in MeOH, (2) BH_3-mediated reduction of the lactam functionality, and (3) coupling reaction to substitute the resulting pyrrolidine for the chloride at the 2-position in 2,5-dichlorobenzoxazole (**79**).

Asymmetric C−C Bond Formation. With chiral nonracemic phase transfer catalysts that can dictate the stereochemical course of C−C bond formation, it is possible to build new stereogenic centers of defined absolute configuration directly, as illustrated in Scheme 15:[33] When aldimine Schiff base of alanine ethyl ester (**81**) was treated with *p*-bromobenzyl bromide in a biphasic mixture of PhMe and $CsOH \cdot H_2O$ in the presence of catalytic (*S*)-biphenyl-based ammonium bromide (**82**) (1 mol %) at 0 °C for 10 h, asymmetric alkylation proceeded with high enantioselectivity to deliver (*R*)-α-(*p*-bromobenzyl)alanine ethyl ester (**83**) of 90% ee in 86% yield after citric acid-catalyzed hydrolysis of the aldimine protection.[34–36]

On treatment with 3,5-dichlorophenyl isocyanate in DMSO in the presence of Na_2CO_3, (*R*)-**83** participated in urea formation

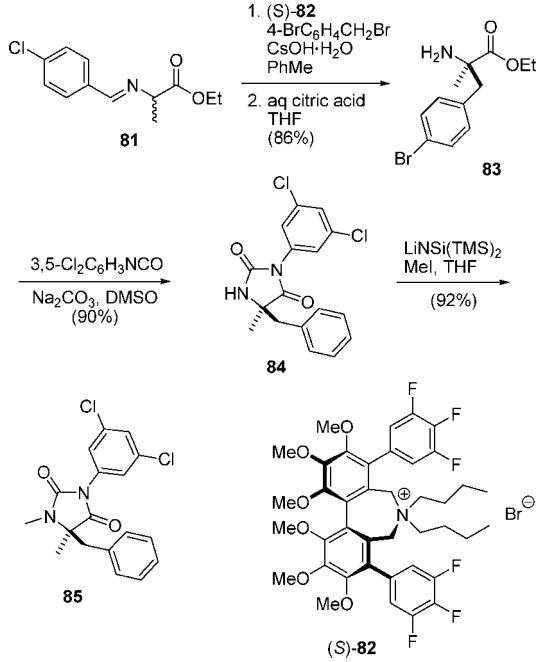
(32) Yee, N. K.; Nummy, L. J.; Byrne, D. P.; Smith, L. L.; Roth, G. P. *J. Org. Chem.* **1998**, *63*, 326.

(33) Han, A.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555.

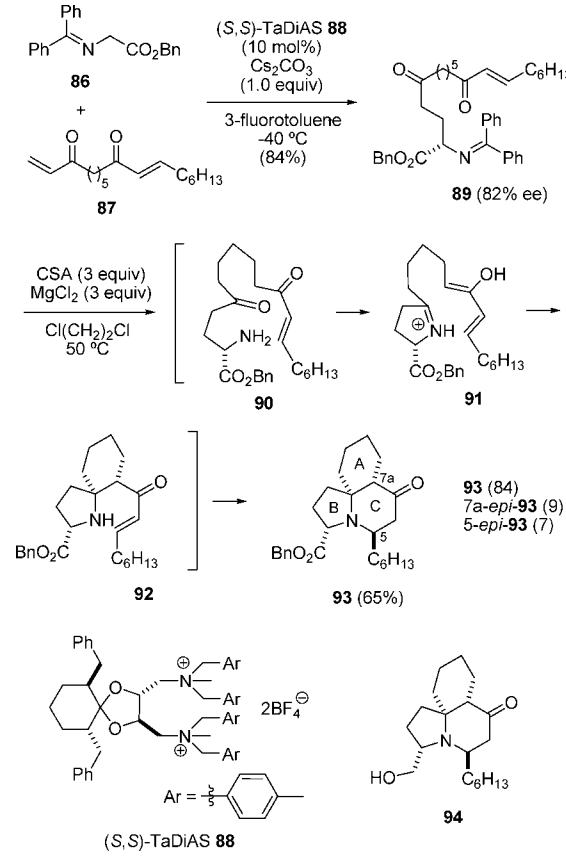
(34) (a) For the related work from Maruoka's labs that deserves noticing from a viewpoint of practicality, see Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549. (b) Ooi, T.; Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K. *Tetrahedron: Asymmetry* **2006**, *17*, 603.

(35) For the stereoselective synthesis of α-amino acid derivatives by asymmetric alkylation of Schiff base esters under PTC, see O'Donnell, M. *Acc. Chem. Res.* **2004**, *37*, 506. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (d) Ikunaka, M. *Organic Process Res.Dev.* **2007**, *11*, 495.

Scheme 15. **Asymmetric alkylation of alanine ethyl ester Schiff base**



Scheme 16. **Asymmetric Michael addition of glycine benzyl ester Schiff base**



with its primary amine, which was followed by spontaneous cyclization leading to hydantoin (**84**) in 90% yield. Finally, *N*-methylation [$LiN(TMS)_2$, MeI, THF, 0 °C–ambient temperature] provided BIRT-377 (**85**) in 92% yield, a cell adhesion inhibitor blocking the interaction between lymphocyte function-associated antigen (LFA)-1 and intracellular cell adhesion antigen (ICAM)-1.[37]

When enantioselective alkylation of Schiff base esters under asymmetric PTC is adapted to Michael reactions, it becomes possible to pave a concise tandem way for (+)-cylindricine A (**94**), a tricyclic alkaloid isolated from a marine ascidian named *Clavelina cylindrica* (Scheme 16):[38] When benzophenone Schiff base of benzyl glycinate (**86**) was added to dienone (**87**) in a biphasic mixture of Cs_2CO_3 and 3-fluorotoluene in the presence of (*S*,*S*)-TaDiAS (**88**; 10 mol %), a tartrate-derived two-center phase transfer catalyst,[39] at −40 °C for 66 h, α-monoalkylated glycine derivative (**89**) of 82% ee was produced in 84% isolated yield.

On exposure to camphorsulfonic acid (CSA) and $MgCl_2$ in 1,2-dichloroethane at 50 °C for 12 h, **89** underwent tandem cyclization via (1) removal of the benzophenone imine protection from **89** to release the primary amine in **90**, (2) formation of intramolecular imine with the δ-situated ketone in **91**, (3) intramolecular Mannich reaction (**91** → **92**), and (4) aza-Michael addition (**92** → **93**). As a result, a mixture of tricyclic products evolved which consisted of **93** (the *cis*-fused AC ring and β-oriented C5-pentyl group), 7a-*epi*-**93** (the *trans*-fused AC ring and β-oriented C5-pentyl group), and 5-*epi*-**93** (the *cis*-fused AC ring and α-oriented C5-pentyl group) in a ratio of 84:9:7. From this mixture was isolated the desired **93** in 65% yield while 7a-*epi*-**93** could be isomerized to **93** under basic conditions. Finally, **93** was converted to (+)-cylindricine A (**94**) in 31% overall yield by two transformations: (1) deprotection of the benzyl ester by catalytic hydrogenolysis and (2) conversion of the released carboxylic acid to an alcohol function by $NaBH_4$-mediated reduction of the derived mixed anhydride without affecting the ketone functionality.

Besides α-amino acid Schiff base esters, 2-diphenylmethoxy-2′,5′-dimethoxyacetophenone (**95**), a synthetic equivalent to a glycolic acid ester,[40] also underwent asymmetric alkylation in a biphasic liquid/solid mixture in the presence of cinchonidinium bromide (**97**), as outlined in Scheme 17:[41] When **95** was treated with 4-pivaloyloxybenzylbromide (**96**) in a biphasic mixture of $CsOH \cdot H_2O$ and hexane/CH_2Cl_2 (1:1) in the presence of **97** (10 mol %) at −40 °C for 24 h, the (*S*)-configured alkylation product (**98**) was obtained in 83% ee and 95% yield. On

(36) For the stability of a cinchona-alkaloid-derived phase transfer catalyst under biphasic alkaline conditions for the asymmetric alkylation of *tert*-butyl gycinate-benzophenone Schiff base, see : Patterson, D. E.; Xie, S.; Jones, L. A.; Osterhout, M. H.; Henry, C. G.; Roper, T. D. *Organic Process Res.Dev.* **2007**, *11*, 624.

(37) For process development of a key intermediate for LFA-1 inhibitors of the more elaborate structure, see : Frutos, R. P.; Eriksson, M.; Wang, X-J.; Byrne, D.; Varsolona, R.; Johnson, M. D.; Nummy, L.; Krishnamurthy, D.; Senanayake, C. H. *Org.Process Res. Dev.* **2005**, *9*, 137.

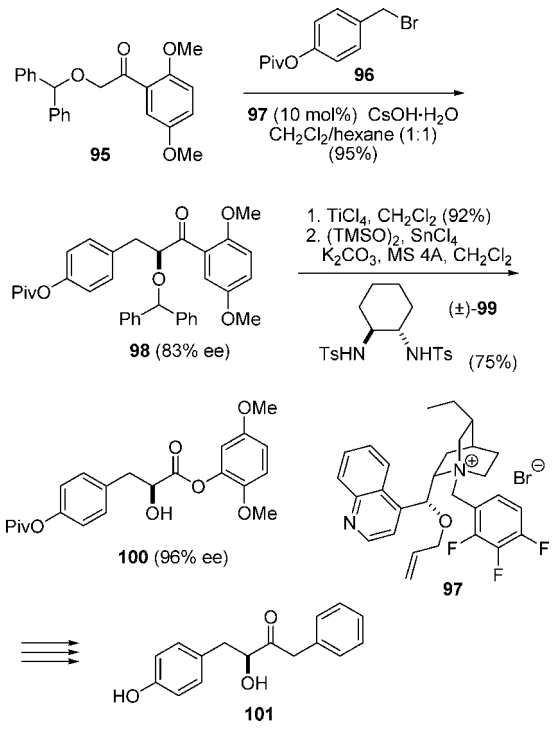
(38) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.

(39) (a) For the development of asymmetric two-center phase transfer catalysts and their applications, see : Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743. (b) Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino, T.; Shibasaki, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5433. (c) Ohshima, T. *Chem.Pharm. Bull.* **2004**, *52*, 1031.

(40) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470.

(41) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2006**, *71*, 8651.

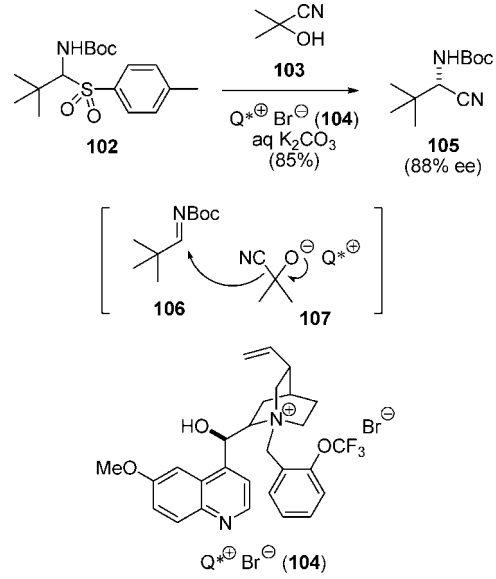
Scheme 17. **Asymmetric alkylation of 2-diphenylmethoxy-2′,5′-dimethoxyacetophenone**



treatment with $TiCl_4$ in CH_2Cl_2 at −78 °C, the diphenylmethyl group was removed from **98** in 92% yield; Baeyer–Villiger oxidation under Shibasaki's conditions [bis(trimethylsilyl)peroxide, (±)-*trans*-*N*,*N*′-bis(*p*-toluenesulfonyl)-1,2-cyclohexanediamine (**99**), $SnCl_4$, 4 Å molecular sieves, CH_2Cl_2, 0 °C] provided (*S*)-α-hydroxy carboxylic acid 2,5-dimethoxyphenyl ester (**100**) in 83% yield. Recrystallization from Et_2O elevated the enantiomeric purity of **100** to 96% ee at the cost of its isolated yield, the overall yield for the Baeyer–Villiger oxidation and recrystallization diminishing to 75%. The glycolic acid ester (**100**) thus obtained was converted to kurasoin A (**101**), a protein farnesyltransferase inhibitor, via finely tuned four-step reactions: (1) Weinreb amide formation [$AlMe_3$, NH(OMe)Me·HCl, CH_2Cl_2, ambient temperature; 92%], (2) *O*-silylation (Et_3SiCl, imidazole, DMF, ambient temperature; 91% yield), (3) ketone formation ($PhCH_2MgCl$, THF, 0 °C; 82% yield), (4) *O*-desilylation followed by hydrolysis of pivalate ester in one pot [Bu_4NF, THF, 0 °C; LiOH, H_2O_2, H_2O; 65% overall yield].[42]

In the enantioselective alkylation discussed above, enantiotopic faces of nucleophiles, such as enolates generated from alanine Schiff base ester (**81**), glycine Schiff base ester (**86**), and 2,2′,5′-trialkoxyacetophenone (**95**), have been differentiated with the help of the chiral nonracemic ammonium salts used, (*S*)-biphenyl-based (**82**), (*S*,*S*)-TaDiS (**88**), and cinchonidinium (**97**), respectively. Furthermore, such asymmetric chiral phase transfer catalysts should differentiate between enantiotopic faces of electrophiles that may participate in C−C bond formation with achiral nucleophiles. For instance, when a cyanide ion (CN^-) can be added to a prochiral imine function (C═N double bond) with its enantiotopic face selection under the influence of a chiral nonracemic phase transfer catalyst, asymmetric Strecker synthesis would result which leads to enantioselective formation of α-amino nitrile, a versatile precursor to α-amino acid derivatives, as illustrated in Scheme 18.[43]

Scheme 18. **Asymmetric Strecker synthesis**

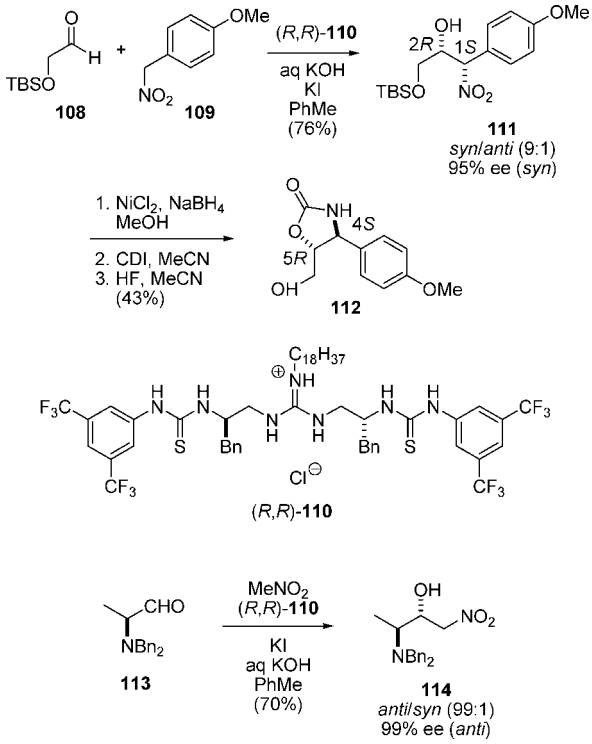


When *N*-Boc protected α-amido sulfone (**102**) was treated with acetone cyanohydrin (**103**) in a biphasic mixture of 50% aqueous K_2CO_3 solution and PhMe in the presence of quinine-derived $Q^{*+}Br^-$ (**104**) (10 mol %) at −20 °C for 42 h, *N*-Boc protected α-amino nitrile (**105**), a penultimate precursor to (*S*)-*tert*-leucine, was produced in 85% ee and 88% yield. In this asymmetric Strecker reaction, $Q^{*+}Br^-$ (**104**) exerted differentiation between enantiotopic faces of *N*-Boc protected imine (**106**) generated in situ from **102**, wherein a cyanide anion was transferred from a lipophilic ion pair (**107**) [preformed from **103** and **104**] to **106** under the influence of chirality of **104**.[44]

Two contiguous stereogenic centers can be established simultaneously in their absolute sense when an enantiotopic face of an electrophile is connected properly with that of an entering nucleophile within a highly ordered transition state in which a chiral nonracemic phase transfer catalyst is firmly involved. To put this synthetic maneuver into play, asymmetric bifunctional catalyst [(*R*,*R*)-(**110**)] was designed and built by incorporating three functional modules in it (Scheme 19):[45] (1) a central guanidinium base [−HNC(C═NH−)NH−] equipped with a long aliphatic chain ($C_{18}H_{37}$), (2) two chiral spacers flanking the central guanidinium group which were both derived from (*R*)-D-phenylalanine [(*R*)-D-Phe], and (3) two terminally situated thiourea groups [−HN(C═S)NHAr] each of which is tethered to the (*R*)-D-Phe-derived chiral spacer. When 4-methoxy-α-nitrotoluene (**109**) was treated with *O*-TBS-protected hydroxyacetaldehyde (**108**) in a biphasic mixture

(42) For the enantioselective synthesis of *tertiary* α-hydroxy carboxylic acids under asymmetric PTC, see: Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3839.
(43) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869.
(44) For another example of asymmetric Strecker Synthesis, see: Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.
(45) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643.

Scheme 19. **Stereocontrolled nitroaldol reactions**



of PhMe/H_2O (1:1) containing KOH (10 mol %) and KI (50 mol %)[46] in the presence of (*R*,*R*)-**110** (10 mol %) at 0 °C for 48 h, the nitroaldol (Henry) reaction proceeded with high enantio- and diastereoselectivity to afford (1*S*,2*R*)-*syn*-nitro alcohol (**111**) of 95% ee in a *syn*/*anti* ratio of (9:1) and 76% yield (Scheme 19).[47] On reduction with $NaBH_4$ in the presence of $NiCl_2$ in MeOH at 0 °C, the resulting 1,2-amino alcohol was subjected to cyclic carbamate formation (CDI, MeCN, 80 °C); eventually, *O*-desilylation (HF, MeCN, 0 °C) gave (4*S*,5*R*)-*epi*-cytoxazone (**112**),[48] a type-2 cytokine selective inhibitor, in a three-step overall yield of 43%.[49]

Being highly lipophilic in its nature, (*R*,*R*)-**110** may well function as a chiral surfactant rather than as an ordinary phase transfer catalyst, fulfilling the following three separate tasks in a highly coordinated manner:[47,48] (1) (*R*,*R*)-**110** captures and stabilizes the nitronate anion derived from **109** by hydrogen bonding with its guanidinium moiety; (2) (*R*,*R*)-**110** also traps aldehyde (**108**) by hydrogen bonding with its thiourea functionality such that the carbonyl function in **108** is activated toward the nucleophilic attack by the nitronate anion that is locked in the central space of (*R*,*R*)-**110**; and (3) (*R*,*R*)-**110** allows the nitronate anion generated from **109** to add to the activated carbonyl group of **108** with the least steric repulsion under the influence of chirality of its (*R*)-D-Phe-derived spacer(s).

The guanidinium−thiourea bifunctional catalyst [(*R*,*R*)-(**110**)] proved to be also effective in adding a $MeNO_2$-derived nucleophile to *N*-protected α-amino aldehydes with high diastereoselectivity:[50] For instance, when *N*,*N*-di-Bn (*S*)-alanine aldehyde (**113**) was treated with $MeNO_2$ in a biphasic mixture of PhMe/H_2O (1:1) containing KOH (20 mol %) and KI (50 mol %)[46] in the presence of (*R*,*R*)-**110** (10 mol %) at 0 °C for 24 h, (2*S*,3*S*)-*anti*-*N*,*N*-di-Bn-1-nitro-3-aminobutan-2-ol (**114**) of 99% ee was obtained in an *anti*/*syn* ratio of (99:1) and 70% yield.[51]

Indeed, recent progress in asymmetric PTC is remarkable as demonstrated by the above-discussed examples;[33,38,41,43,45,47] however, its adaptation to industrial production still remains a challenge because little knowledge is available about how to conduct asymmetric PTC reactions on scale while the industrial use of achiral quaternary ammonium salts has numerous track records.[3,12,14,21,31,32] Such circumstances notwithstanding, the key to the industrial success of asymmetric PTC processes should be durability of asymmetric catalysts employed,[36] as was discussed in the context of ether and ester formation.

Conclusions

To demonstrate versatility of PTC, select examples of its application have been discussed in the setting of building multifunctional, architecturally complex organic compounds. Although this mini-review article is meant to be illustrative rather than comprehensive, such case studies would help readers to hold the view that biphasic reactions conducted under PTC conditions should give the following advantages over homogeneous ones: (1) facile isolation of products,[3,31,32] (2) chemoselectivity due to attenuated or amplified reactivity of reagents,[5,8,10,11] (3) protection of susceptible organic molecules against contact with destructively reactive reagents by phase separation,[7,9,14] (4) activation of inorganic anionic species, such as OH^-,[12] MnO_4^-,[17] ClO^-,[18] and F^-,[21] by forming specific vehicles soluble in organic media, (5) convenient generation of active species otherwise difficult to prepare, such as dichlorocarbene (**:**CCl_2)[25] and isonitrile (R−N═C**:**),[30] and (6) stereoselective C−C bond formation under mild conditions using an easy-to-handle set of reagents.[33,38,41,43,47,50] In conclusion, the real potential of PTC should lie in its ability to re-engineer reaction conditions themselves such that the desired products be produced selectively and isolated with minimum effort; and as such, its salient power should not be limited to asymmetric synthesis,

(46) It was reported in ref 51 that, in the absence of KI, the enantiomeric purity of the nitroaldol products deteriorated via the retro-nitroaldol process and that the chloride counteranion in (*R*,*R*)-**110** must have been exchanged for iodide in situ in the presence of KI.

(47) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894.

(48) Grajewska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 803.

(49) For other reactions under asymmetric PTC by which two contiguous stereogenic centers are built under control of their absolute configuration, such as aldol reaction of glycinate Schiff base, Mannich reaction of glycinate Schiff base, and conjugate addition of nitroalkanes to alkylidenemalonates, see, respectively: Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685. (b) Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (c) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790.

(50) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144.

(51) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem.- Asian J.* **2007**, 1150.

which is indeed a critical issue to be addressed in modern process chemistry, though.[52]

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(52) (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.