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Phase-Transfer Catalysis

Recent Developments in Asymmetric Phase-Transfer Reactions

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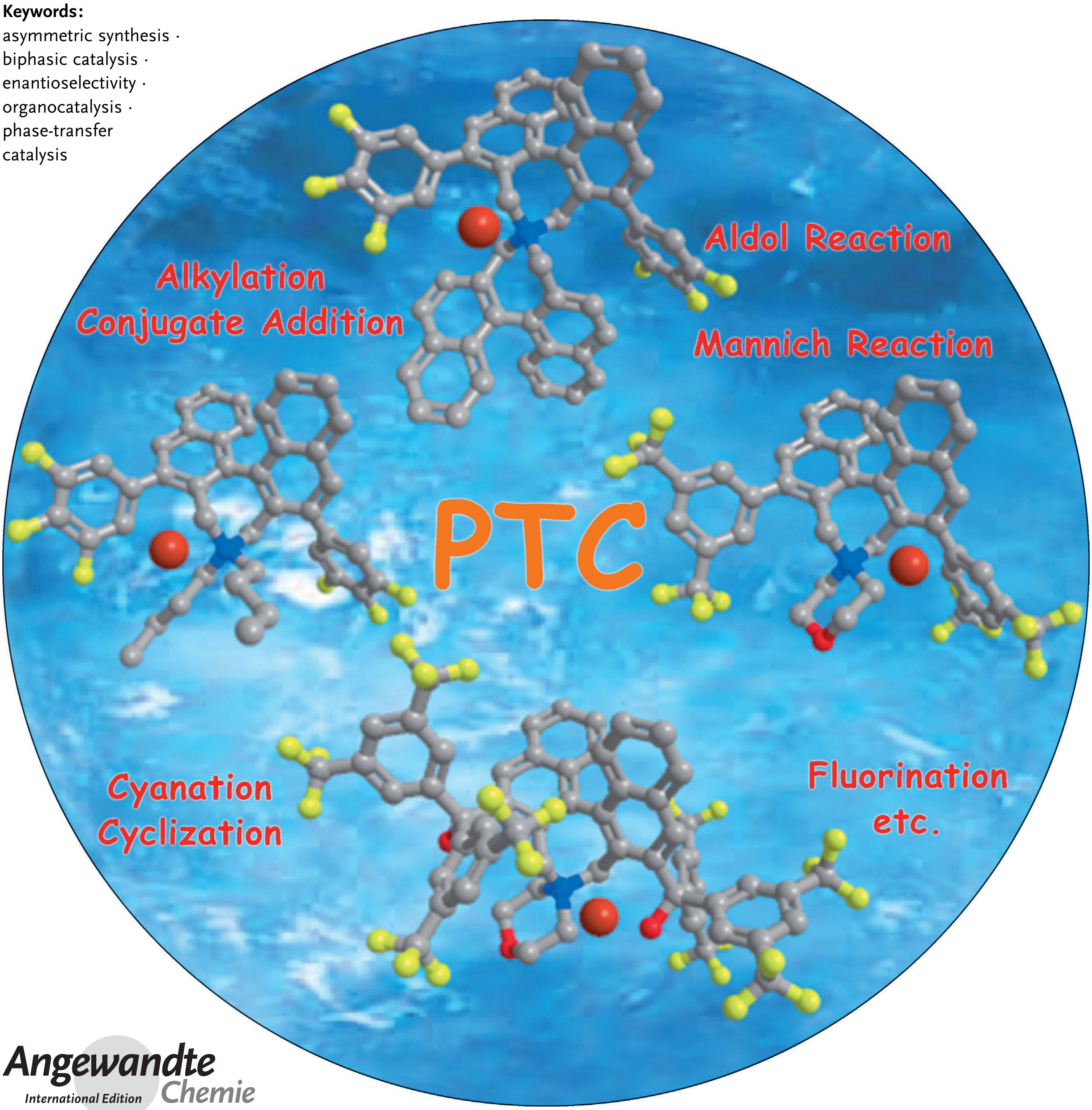

Phase-transfer catalysis has been recognized as a powerful method for establishing practical protocols for organic synthesis, because it offers several advantages, such as operational simplicity, mild reaction conditions, suitability for large-scale synthesis, and the environmentally benign nature of the reaction system. Since the pioneering studies on highly enantioselective alkylations promoted by chiral phase-transfer catalysts, this research field has served as an attractive area for the pursuit of "green" sustainable chemistry. A wide variety of asymmetric transformations catalyzed by chiral onium salts and crown ethers have been developed for the synthesis of valuable organic compounds in the past several decades, especially in recent years.

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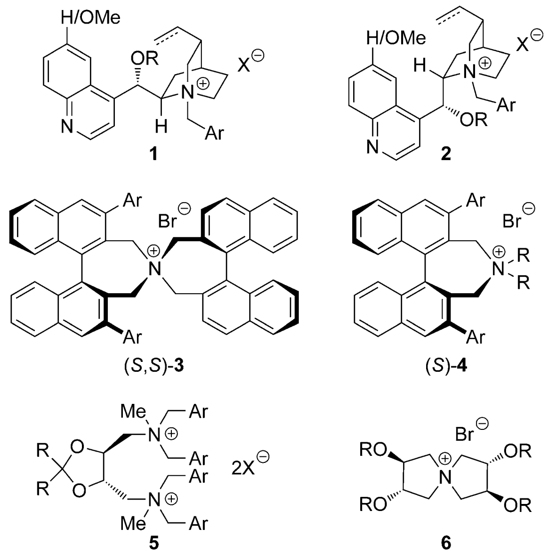
1. Introduction

Phase-transfer catalysis has long been recognized as a versatile method for organic synthesis in both industry and academia, as it features simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations in process chemistry.[1] Asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, nonracemic catalysts has become a topic of great scientific interest, particularly in the last 20 years. Notable achievements have been made recently that have resulted in it being feasible to perform various bond-forming reactions under mild phase-transfer-catalyzed conditions.[2] In 2007, we summarized the progress of asymmetric phase-transfer reactions as a review in this Journal, covering the literature until 2005.[3] Various types of natural and non-natural product derived chiral phase-transfer catalysts were introduced, and the structures of representative catalysts are summarized in Scheme 1. The catalytic ability of these catalysts was compared in the asymmetric alkylation of *N*-(diphenylmethylene)glycine ester, which was developed by O'Donnell[2,3] as a benchmark reaction. Since the publication of the review, these privileged chiral phase-transfer catalysts have been utilized for a wide variety of transformations, and some of them have been applied to the efficient asymmetric synthesis of biologically active compounds. Furthermore, newly designed chiral phase-transfer catalysts have been developed and used in asymmetric reactions. This Review focuses on more recent progress in asymmetric phase-transfer reactions, between 2006 and the middle of 2012, showcasing the various synthetic applications of phase-transfer reactions.



Scheme 1. Representative chiral phase-transfer catalysts.

2. Alkylation

2.1. C–C Bond Formation

2.1.1. Asymmetric Synthesis of α-Amino Acids

Phase-transfer alkylation using a chiral catalyst and a prochiral protected glycine derivative is a particularly attractive method for the preparation of optically active α-amino acids. Various types of chiral phase-transfer catalysts

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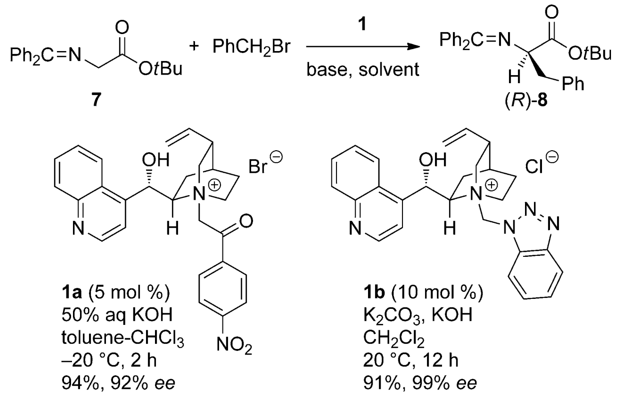
have been applied to the reaction, and several practical reaction systems have already been developed.[2,3] Nowadays, this reaction has become one of the benchmark reactions for examining the performance of new phase-transfer catalysts.

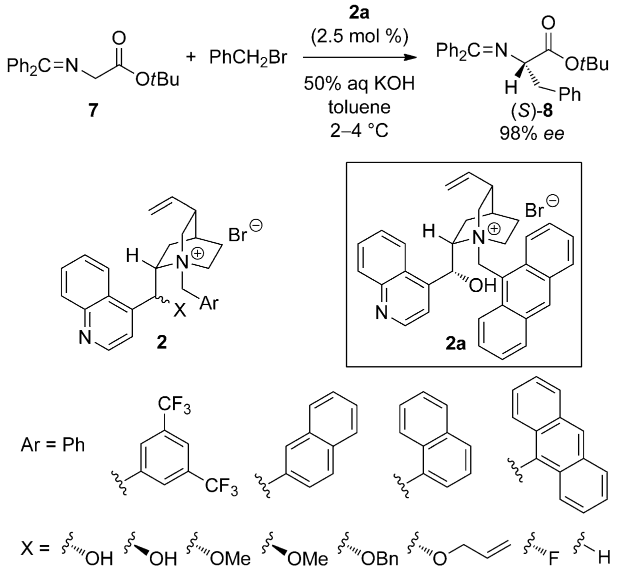
The successful design of cinchona alkaloid derived phase-transfer catalysts[2] formed the basis for the development of cinchonine-derived catalysts possessing an aryl ketone (**1a**)[4] and a benzotriazole (**1b**)[5] moiety (Scheme 2). The application of these catalysts to the asymmetric benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **7** as a benchmark reaction produced the phenylalanine derivative **8** with high enantioselectivity.



Scheme 2. A new family of cinchonine-derived catalysts.

Systematic study of the structure–activity/selectivity relationship of the catalyst for cinchonidine-derived phase-transfer catalysts **2** in the asymmetric benzylation of **7** by Denmark and Weintraub led to the observation that the Lygo–Corey type catalyst **2a** gave the highest enantioselectivity (Scheme 3).[6]

Park and co-workers summarized the effect of a series of dimeric and trimeric quaternary ammonium salts of type **9** derived from cinchona alkaloids on the asymmetric alkylation of **7** (Scheme 4).[7] The dimeric catalyst **9a** was found to be one of the most effective catalysts for the reaction.



Scheme 3. Study of the structure–activity/selectivity relationship for cinchonidine-derived catalysts.

A new family of trimeric and dimeric catalysts **10**[8] and **11**[9] based on the design of the dimeric and trimeric catalysts by Park and co-workers were also developed. The asymmetric benzylation of **7** with these catalysts afforded the product **8** with moderate to good enantioselectivity (Scheme 5).

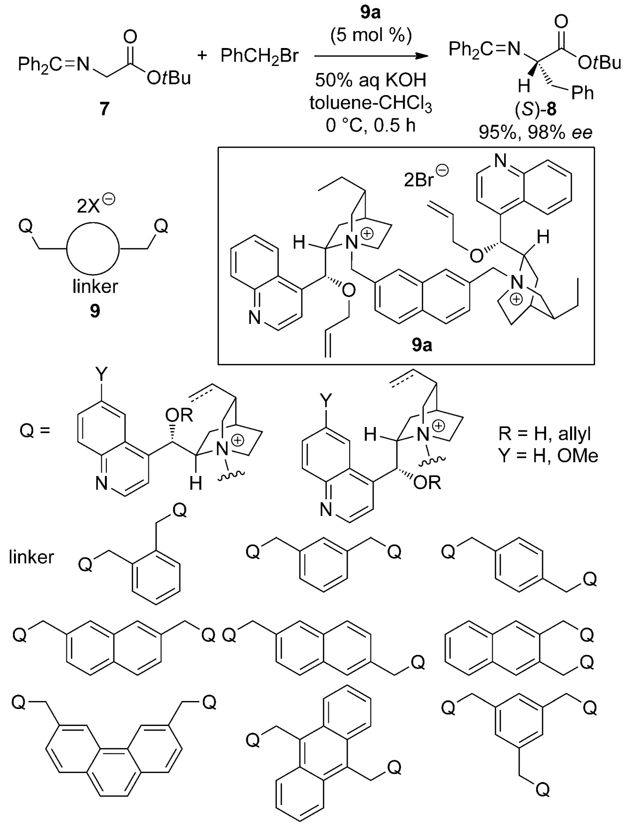
Shirakawa and Shimizu demonstrated a new approach for the design of chiral phase-transfer catalysts by making use of the inherently chiral calix[4]arene backbone (**12a**).[10] Although the enantioselectivity of the obtained product **8** was very low, this is a valuable example of the application of the inherently chiral calix[4]arene as a chiral catalyst (Scheme 6).

Other types of quaternary ammonium salts were also developed as chiral phase-transfer catalysts and applied to the asymmetric alkylation of **7** (Scheme 7). Although tartaric acid derived N-spiro derivative **13**[11] afforded the alkylation products with good enantioselectivity, the other catalysts **14**,[12] **15**,[13] and **16**[14] resulted in low to moderate enantioselectivities.

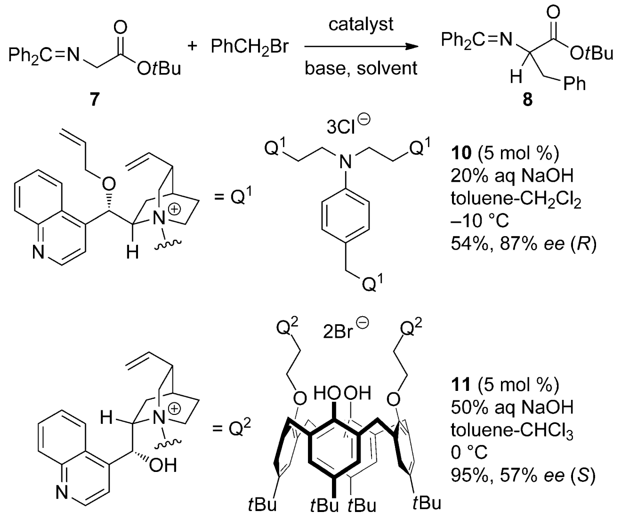
Denmark et al. developed novel quaternary ammonium salts of type **17** and investigated the catalyst structure–activity/selectivity relationship systematically in the benzylation of **7** (Scheme 8).[15] This strategy for the design of the catalyst allows for the introduction of four different groups, and more than 160 catalysts were prepared by this approach.

Seiji Shirakawa received his PhD (2004) from Kyoto University with Prof. Keiji Maruoka, and was a postdoctoral fellow in the research groups of Prof. James L. Leighton at Columbia University (2004–2005) and Prof. Shū Kobayashi at the University of Tokyo (2005–2007). He was appointed assistant professor at Nihon University in 2007, and since 2009 has been an associate professor at Kyoto University. He has received the Sanyo Chemical Industries Award in Synthetic Organic Chemistry, Japan (2009) and the Chemical Society of Japan Presentation Award (2010).

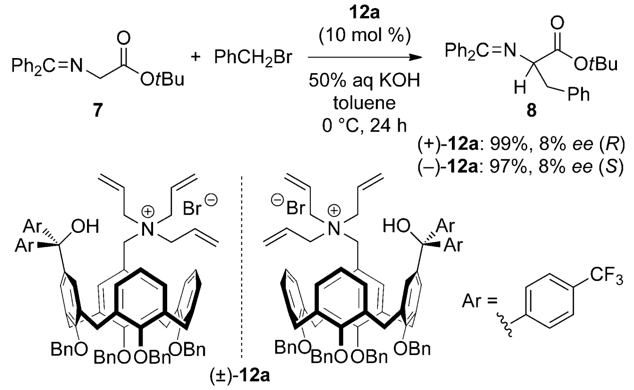
Keiji Maruoka received his PhD (1980) from the University of Hawaii with Prof. Hisashi Yamamoto. He then became an assistant professor at Nagoya University and associate professor there in 1990. He then moved to Hokkaido University as a full professor (1995), and since 2000 has been a professor at Kyoto University. His research focuses on organic synthesis with designer organocatalysts. His awards include the Chemical Society of Japan Award (2007), Arthur C. Cope Scholar Award (2011), Medal with Purple Ribbon (2011), and Humboldt Research Award (2011).



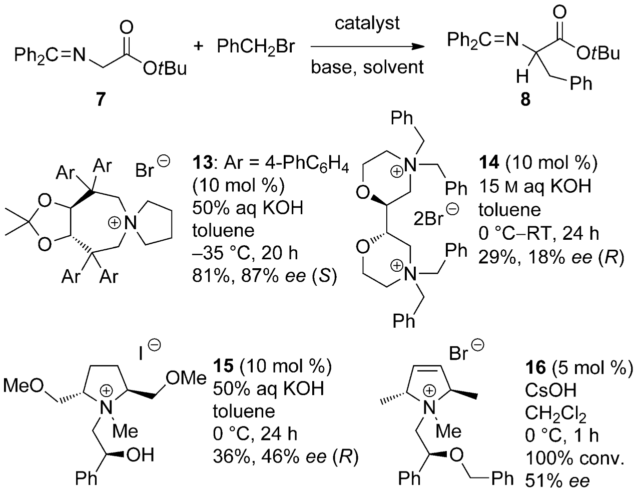
Scheme 4. A series of dimeric and trimeric quaternary ammonium salts.



Scheme 5. A new family of dimeric catalysts.



Scheme 6. Novel design of a chiral phase-transfer catalyst with an inherently chiral calix[4]arene backbone. Bn = benzyl.

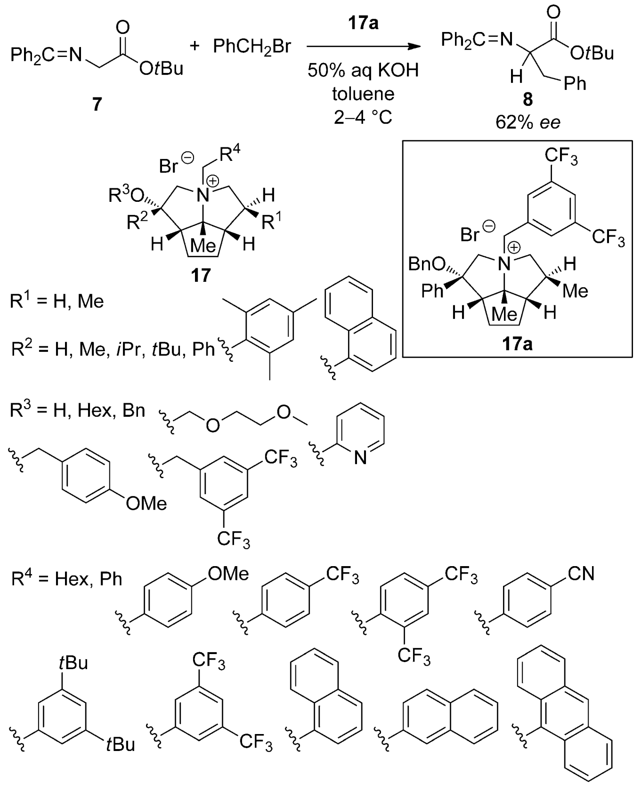


Scheme 7. Novel chiral quaternary ammonium salts for the asymmetric alkylation of **7**.

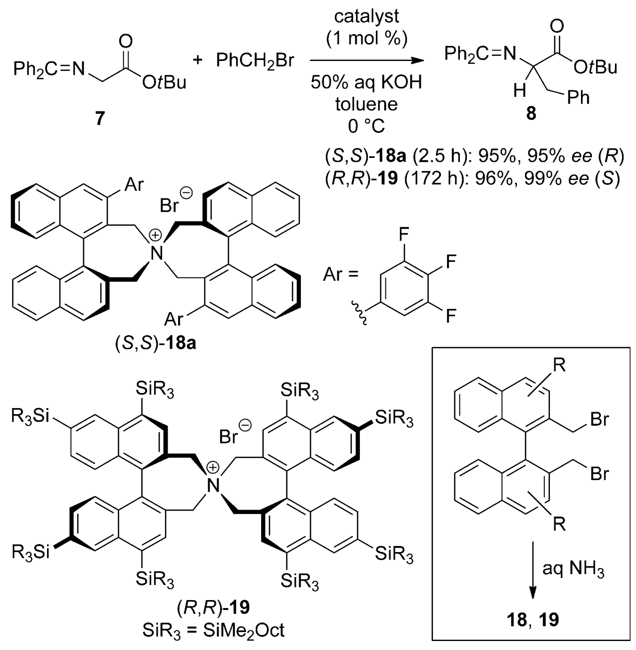
These catalysts exhibited a wide range of activity and to a lesser degree enantioselectivity. The trend of the catalyst structure–activity/selectivity relationship was discussed in detail. This information is very useful for the design of novel chiral phase-transfer catalysts.

Based on the design of our first generation catalysts, namely, binaphthyl-modified chiral phase-transfer catalysts of type **3** (Scheme 1), which is now commercially available as the "Maruoka catalyst",[2,3] symmetrical catalysts **18a**[16] and **19**[17] were developed for the highly enantioselective alkylation of **7** (Scheme 9). These symmetrical catalysts could be prepared from a single binaphthyl subunit, and aqueous ammonia used as a very economical nitrogen source.

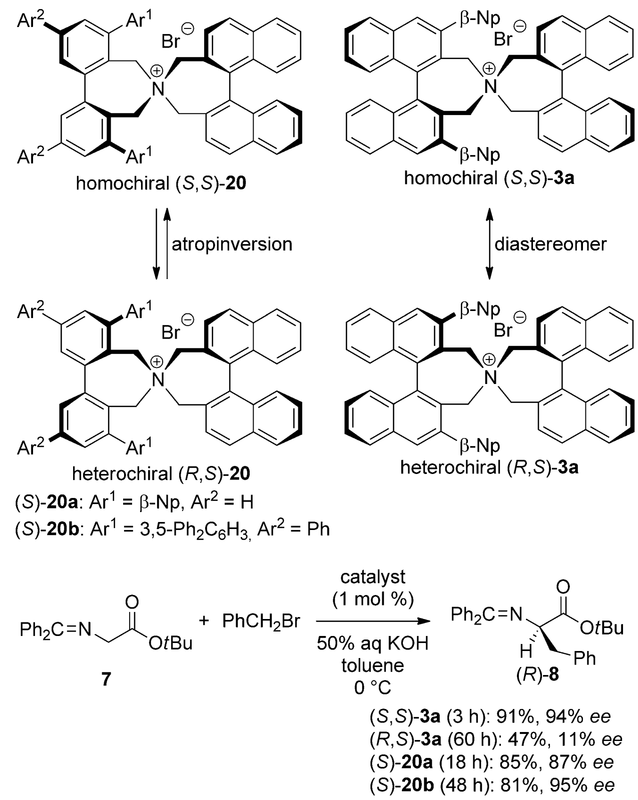
Although the conformationally rigid, N-spiro structure created by the two chiral binaphthyl subunits represents a characteristic feature of **3**, it also imposes limitations on the catalyst design because of the imperative use of two different chiral binaphthyl moieties. Accordingly, we developed a new C_2-symmetric chiral quaternary ammonium bromide **20** with an achiral, conformationally flexible biphenyl subunit (Scheme 10).[18] The phase-transfer benzylation of **7** with catalyst (*S*)-**20a** containing a β-naphthyl group at the 3,3′-position of the flexible biphenyl moiety proceeded smoothly at 0°C to afford the corresponding alkylation product **8** in 85% yield and 87% *ee* after 18 h (Scheme 10). The origin of the observed chiral efficiency could be ascribed to the considerable difference between the catalytic activity of the rapidly equilibrated, diastereomeric homo- and heterochiral



Scheme 8. A systematic investigation of the structure–activity/selectivity relationship for novel quaternary ammonium salts **17**.



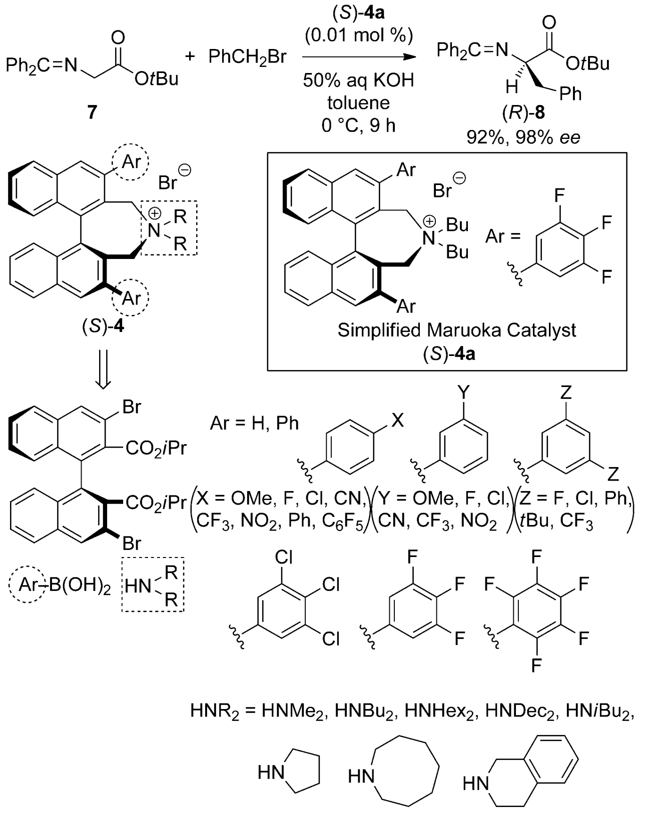
Scheme 9. Symmetrical binaphthyl-modified catalysts.



Scheme 10. Conformationally flexible chiral phase-transfer catalysts.

catalysts: homochiral (*S*,*S*)-**20a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce **8** with high enantiomeric excess, whereas heterochiral (*R*,*S*)-**20a** displays low reactivity and stereoselectivity. Supportive evidence for this hypothesis was that the benzylation with 1 mol% of conformationally rigid, heterochiral (*R*,*S*)-**3a** under similar conditions proceeded slowly and, even after 60 h, gave rise to **8** in 47% yield and 11% *ee* (Scheme 10). This unique phenomenon provides a powerful strategy for the molecular design of chiral catalysts: the requisite chirality can be provided by the simple binaphthyl moiety, and an additional structural requirement for fine-tuning the reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure; this certainly obviates the need for two chiral units and should be an advantage in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. In fact, quaternary ammonium bromide possessing a sterically demanding substituent such as (*S*)-**20b** can be easily prepared, and the benzylation of **7** with (*S*)-**20b** as a catalyst gave **8** in 81% yield and 95% *ee*.

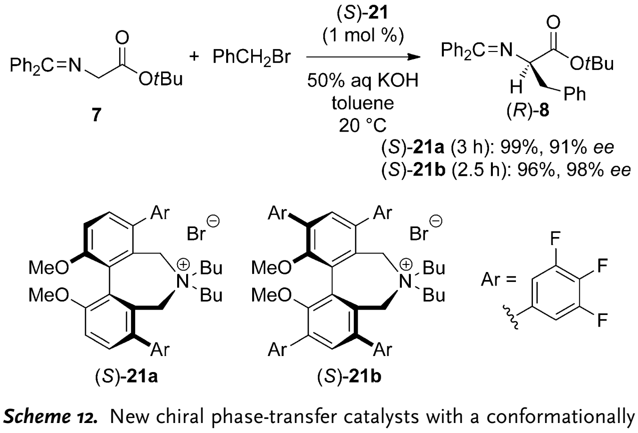
We chose the basic structure **4** as a simplified version of our first generation chiral phase-transfer catalyst **3**. As the catalyst (*S*)-**4** can be readily prepared from three components (Scheme 11), a chiral binaphthyl part, an arylboronic acid ($ArB(OH)_2$), and a secondary amine (R_2NH), the appropriate modification of the $ArB(OH)_2$ and R_2NH portions should give a series of newly designed catalysts. Hence, we studied the substituent effects of Ar and R moieties in detail by using combinatorial chemistry, as variation of these groups would allow facile generation of large libraries of structures. As a result, we discovered that chiral quaternary ammonium bromide **4a** with a 3,4,5-trifluorophenyl group (as Ar) and flexible straight-chain alkyl groups (R) instead of a rigid binaphthyl moiety functions as a chiral high-performance phase-transfer catalyst. In the case of R = Bu, we call this the



Scheme 11. Combinatorial design of simplified binaphthyl-modified catalysts.

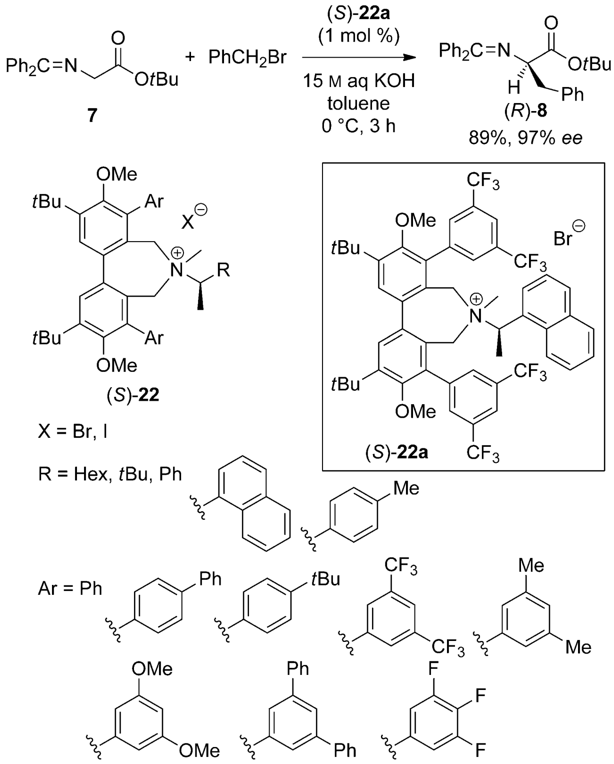
“simplified Maruoka catalyst”. Most notably, the asymmetric alkylation of glycine derivative **7** with benzyl bromide proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01 mol% of the simplified Maruoka catalyst (*S*)-**4a** to afford the benzylation product **8** with excellent enantioselectivity (Scheme 11).[19]

The structure of the highly efficient catalyst **4a** formed the basis for the preparation of new chiral phase-transfer catalysts of type **21** with a conformationally fixed biphenyl core. The enantioselectivity obtained with catalyst (*S*)-**21b** exhibited an unexpected temperature effect, and the asymmetric alkylation of **7** at room temperature (20 °C) gave higher enantiomeric excess than that at 0 °C (Scheme 12).[20]



Scheme 12. New chiral phase-transfer catalysts with a conformationally fixed biphenyl core.

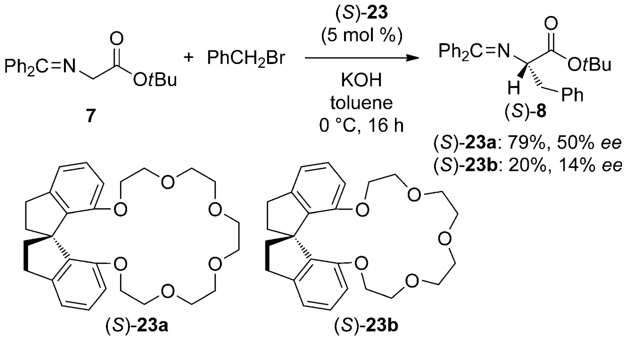
Lygo et al. constructed a library of quaternary ammonium salts of type **22** through the reaction of commercially available chiral secondary amines and a series of conformationally flexible biphenyl units. Screening of the library in the asymmetric benzylation of **7** led to the identification of the highly effective catalyst (*S*)-**22a**, which exhibited impressive catalytic activity and enantioselectivity (Scheme 13).[21]



Scheme 13. Chiral phase-transfer catalysts with a chiral secondary amine and a biphenyl unit.

Takizawa and co-workers developed novel spiro chiral crown ethers **23** for the asymmetric alkylation of **7**. These catalysts promoted asymmetric benzylation in the presence of solid KOH to give product **8** with low to moderate enantioselectivity (Scheme 14).[22]

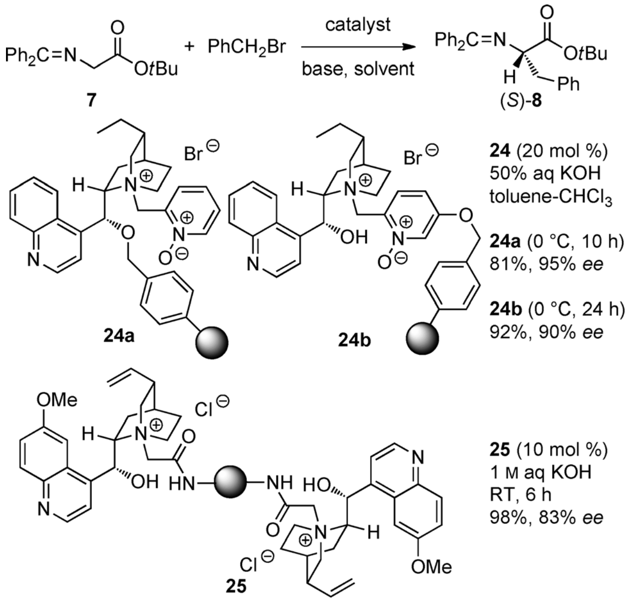
The importance of the development of polymer-supported catalysts is evident, since the enantioselective synthesis of α-



Scheme 14. Spiro chiral crown ethers.

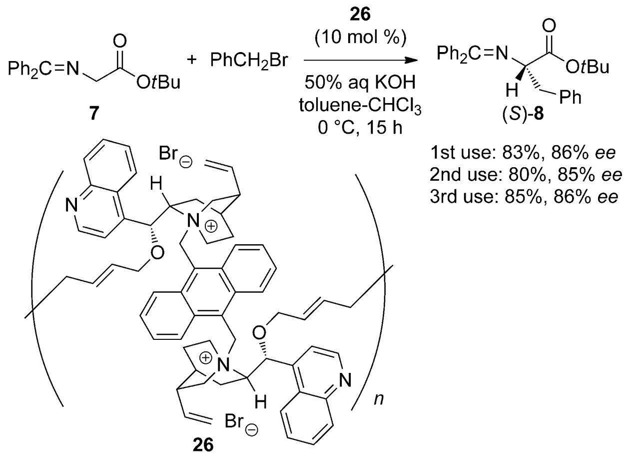
amino acids with easily available and reusable chiral catalysts offers clear advantages for large-scale synthesis.

Based on the successful design of a cinchona alkaloid derived catalyst possessing a pyridine-*N*-oxide moiety,[2o] polymer-supported catalysts **24a**[23] and **24b**[24] were prepared and applied to the highly enantioselective alkylation of **7** (Scheme 15). The water-soluble polyethylene glycol (PEG) supported dimeric catalyst **25** was also developed and the catalyst was applied to the asymmetric alkylation of **7** in aqueous media without the use of any organic solvents (Scheme 15).[25]



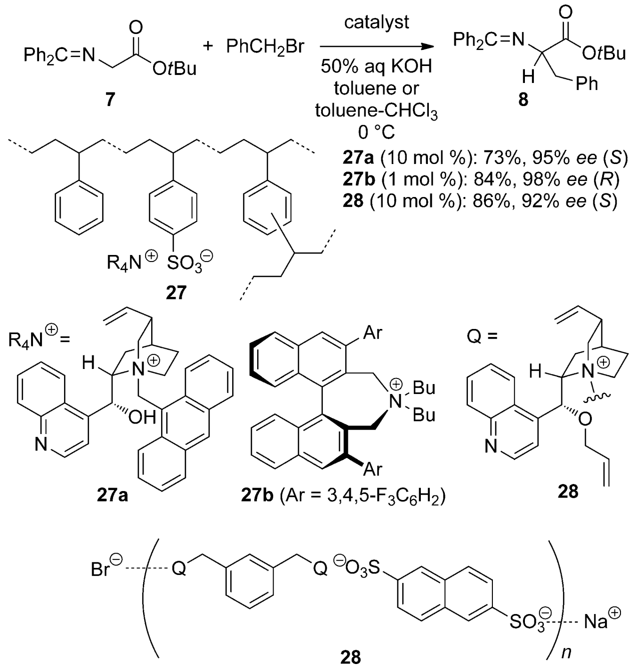
Scheme 15. Polymer-supported chiral phase-transfer catalysts.

Itsuno et al. developed a novel type of polymeric catalyst **26** based on the successful design of dimeric catalysts derived from the cinchona alkaloid (Scheme 16).[26] The polymeric catalyst was applied to the asymmetric benzylation of **7**, and the catalyst could be reused without loss of reactivity and selectivity.



Scheme 16. A novel type of polymeric catalyst.

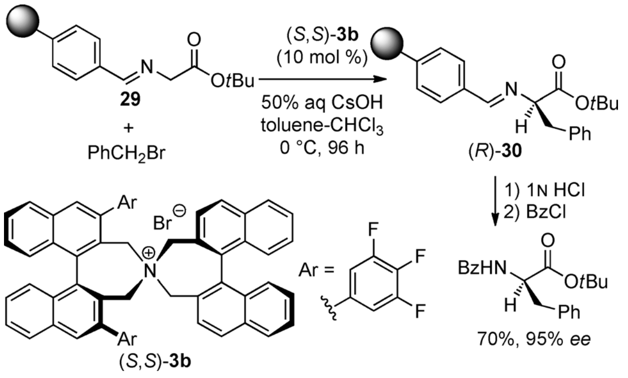
The same research group reported a new type of immobilization method involving the ionic bonding of sulfonate groups to a polymer. Polymer-supported chiral quaternary ammonium salts **27a** and **27b** were readily prepared by reaction of the sulfonated polymer with the corresponding chiral ammonium salt. The polymeric catalysts were applied to the alkylation of **7** and reused without loss of reactivity or selectivity (Scheme 17).[27] These findings led to the development of a novel main-chain ionic chiral polymer catalyst **28** with a quaternary ammonium sulfonate repeating unit (Scheme 17).[28]



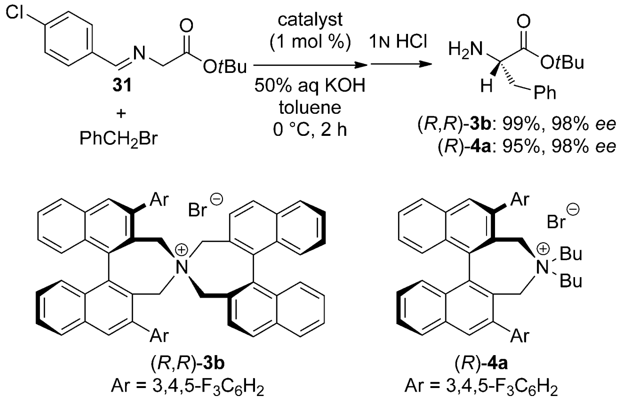
Scheme 17. Novel approaches to polymer catalysts.

Solid-phase synthesis, in which polymer-bound substrates are utilized, has some advantages over liquid-phase synthesis, such as easy purification and application to combinatorial chemistry. Park and co-workers utilized the Merrifield resin supported glycine Schiff base **29** for asymmetric alkylation under phase-transfer conditions. Considering the sensitivity of the enantioselectivity to the ester groups, an aldimine linker was chosen and the asymmetric alkylation was performed with 10 mol% (*S*,*S*)-**3b**. The *N*-benzoyl-α-amino acid *tert*-butyl ester could be isolated after treating the solid-bound product **30** with aqueous hydrochloric acid and protection with benzoyl chloride (Scheme 18).[29]

The selective monoalkylation of glycine *tert*-butyl ester aldimine Schiff base **31** has been realized in high chemical yield and excellent enantioselectivity under mild liquid–liquid phase-transfer conditions in the presence of binaphthyl-modified chiral quaternary ammonium bromides **3b** and **4a** (Scheme 19).[30] This reaction demonstrates that **31** can be used as a cost-effective substrate for the preparation of optically active α-amino acid derivatives by chiral phase-transfer catalysis.



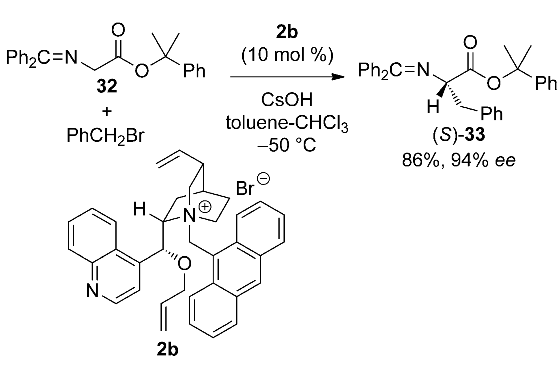
Scheme 18. Solid-phase synthesis of an α-amino acid. Bz = benzoyl.



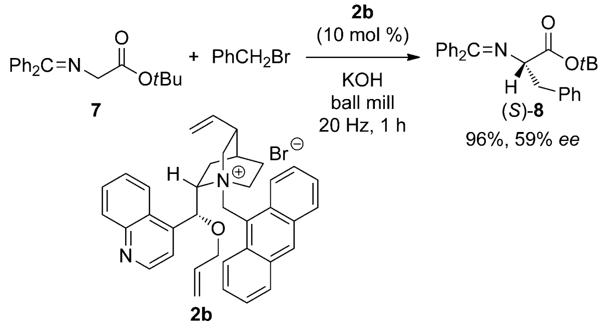
Scheme 19. Highly enantioselective monoalkylation of glycine *tert*-butyl ester aldimine.

The enantioselective phase-transfer alkylation of the cumyl ester of glycine benzophenone imine **32** provides an attractive alternative to the analogous *tert*-butyl ester **7** (Scheme 20).[31] The cumyl ester can be easily cleaved from the alkylation product **33** by hydrogenolysis without acid treatment.

The asymmetric alkylation of **7** in a ball mill in the absence of solvents was promoted by catalyst **2b** in the presence of solid KOH. This reaction produced the alkylation product with moderate enantioselectivity (Scheme 21).[32]

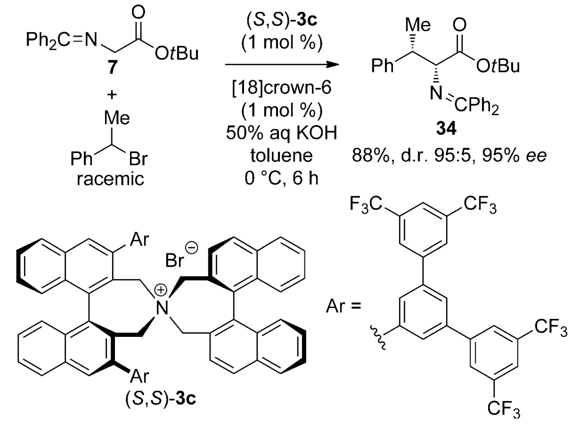


Scheme 20. Alkylation of a cumyl ester of glycine benzophenone imine.



Scheme 21. Asymmetric phase-transfer alkylation in a ball mill.

We have demonstrated that phase-transfer catalysis with chiral quaternary ammonium salt (*S*,*S*)-**3c** and [18]crown-6 creates a new opportunity for the asymmetric alkylation of **7**. This combination involves an efficient kinetic resolution of racemic secondary alkyl halides, thereby giving a straightforward entry to enantiomerically enriched *syn*-β-alkyl-α-amino acid derivatives, such as **34** (Scheme 22).[33]

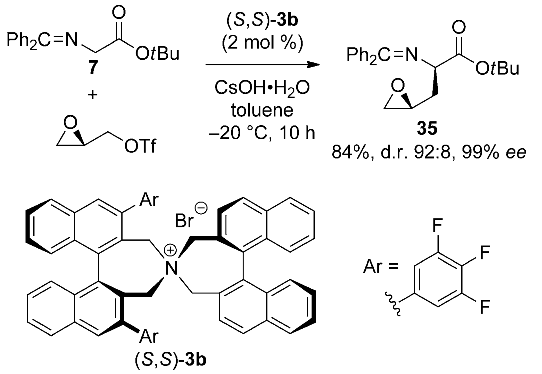


Scheme 22. Kinetic resolution of a racemic secondary alkyl halide by phase-transfer alkylation.

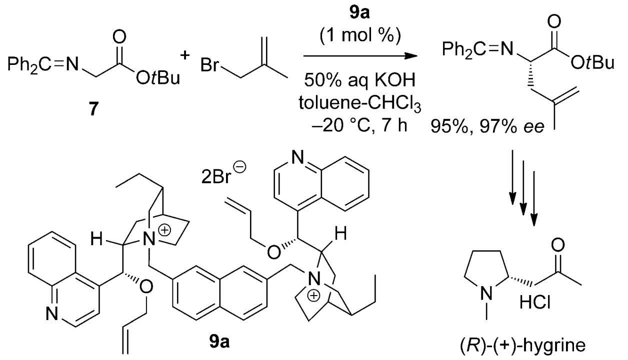
We also reported the asymmetric alkylation of **7** with alkyl sulfonates, especially with epoxy sulfonates as notable examples, under phase-transfer conditions. The asymmetric reaction of **7** with chiral epoxy triflates furnished γ,δ-epoxy-α-amino acid esters, such as **35**, with high stereoselectivity (Scheme 23).[34]

Park and co-workers applied their dimeric dihydrocinchonidinium salt **9a** to the synthesis of the hygrine hydrochloride salt. Asymmetric methallylation of **7** was chosen as a key step and the synthesis was completed in 12 steps in an overall 29 % yield. They also succeeded in determining the absolute configuration of the (+)-hygrine as *R* (Scheme 24).[35]

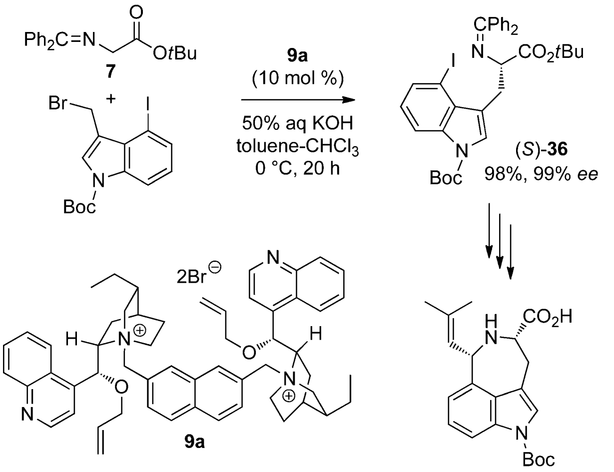
Park and co-workers also reported an enantioselective synthesis of (−)-*cis*-clavicipitic acid by the asymmetric phase-transfer alkylation of **7**. The key intermediate **36** was obtained with high enantioselectivity by phase-transfer alkylation in the presence of catalyst **9a** (Scheme 25).[36]



Scheme 23. Asymmetric alkylation with epoxy triflate. Tf = trifluoromethanesulfonyl.

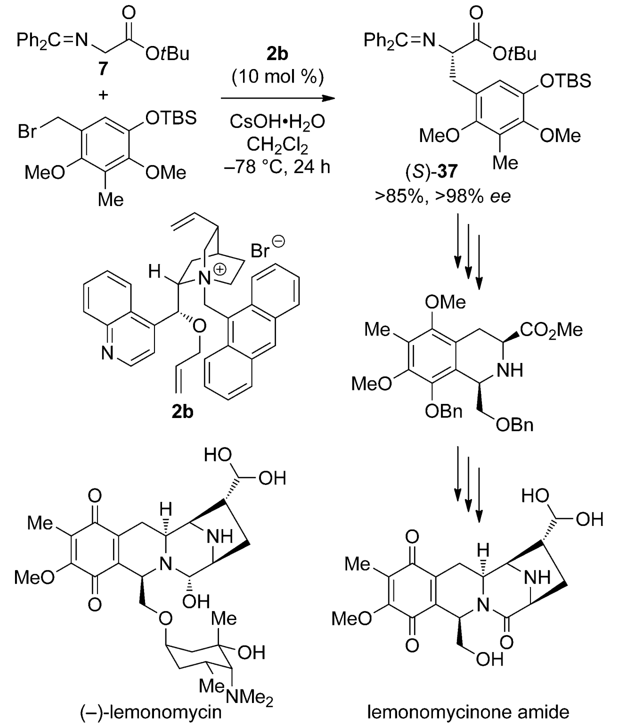


Scheme 24. Total synthesis of (+)-hygrine.



Scheme 25. Enantioselective synthesis of (−)-*cis*-clavicipitic acid. Boc = *tert*-butoxycarbonyl.

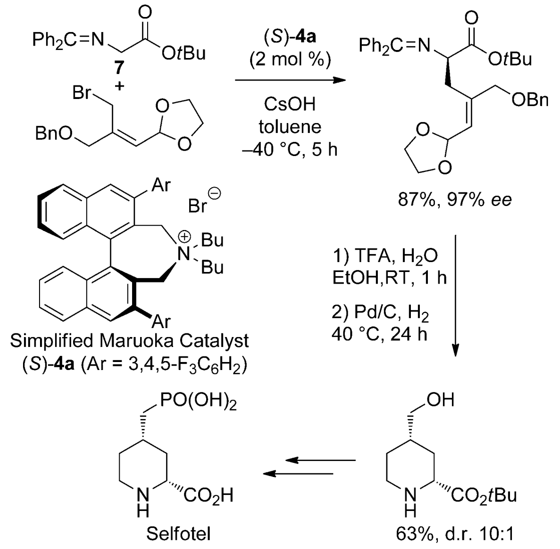
Zhu and co-workers reported an efficient asymmetric synthesis of lemonomycinone amide in their synthetic study on (−)-lemonomycin (Scheme 26).[37] The enantioselective alkylation of **7** with 5-*tert*-butyldimethylsilyloxy-2,4-dimethoxy-3-methylbenzyl bromide in the presence of the Lygo–Corey type catalyst **2b** afforded the key intermediate **37** with high enantioselectivity.



Scheme 26. Efficient asymmetric synthesis of lemonomycinone amide. TBS = *tert*-butyldimethylsilyl.

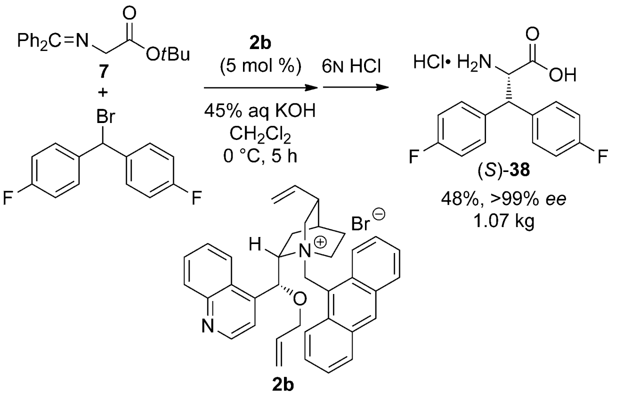
An asymmetric synthesis of cyclic amino acids having piperidine structures was realized starting from glycine derivative **7** through the combination of asymmetric phase-transfer alkylation and subsequent reductive amination. The synthetic utility of this method was highlighted by the asymmetric synthesis of Selfotel (CGS-19755), which is a potent NMDA receptor antagonist (Scheme 27).[38]

GlaxoSmithKline successfully applied the Lygo–Corey type catalyst **2b** to the asymmetric synthesis of the potential



Scheme 27. Asymmetric synthesis of Selfotel. TFA = trifluoroacetic acid.

drug 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine **38** by phase-transfer alkylation (Scheme 28).[39] The addition order of the catalyst or base was found to be extremely critical for their experiments on a kilogram scale.



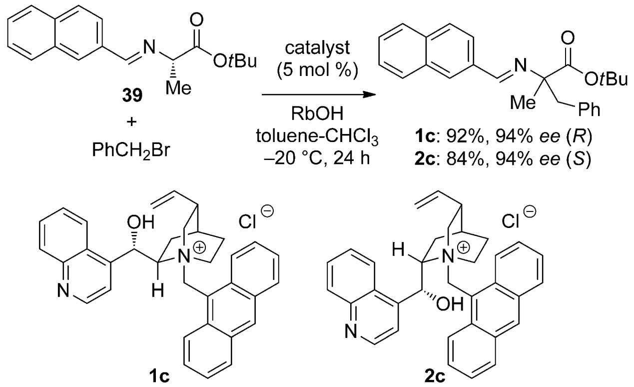
Scheme 28. Large-scale synthesis of α-amino acid **38**.

2.1.2. *Asymmetric Synthesis of α,α-Dialkyl α-Amino Acids*

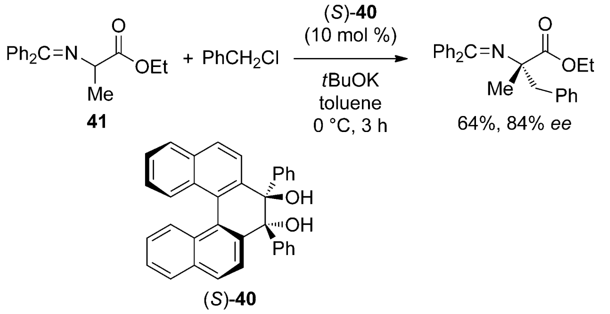
Nonproteinogenic, chiral α,α-dialkyl-α-amino acids with stereochemically stable quaternary carbon centers have been significant synthetic targets not only because they were shown to be effective enzyme inhibitors but also because they are indispensable for the elucidation of enzyme mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation, and phase-transfer catalysis has made unique contributions.[2,3]

Based on previous studies by Jew, Park et al.,[40] Nájera and co-workers reported the asymmetric alkylation of 2-naphthylaldimine alanine *tert*-butyl ester **39** in the presence of cinchona alkaloid derived quaternary ammonium salts **1c** and **2c**. The alkylations of **39** in the presence of the strong base rubidium hydroxide (RbOH) at −20°C led to the highest enantioselectivities (Scheme 29).[41]

Kitamura et al. developed binaphthyl-modified diol catalyst **40** for the asymmetric benzylation of *N*-(diphenylmethylene)alanine ester **41** in the presence of sodium *tert*-butoxide. The use of benzyl chloride and its slow addition were essential to obtain high enantioselectivity in this reaction (Scheme 30).[42]

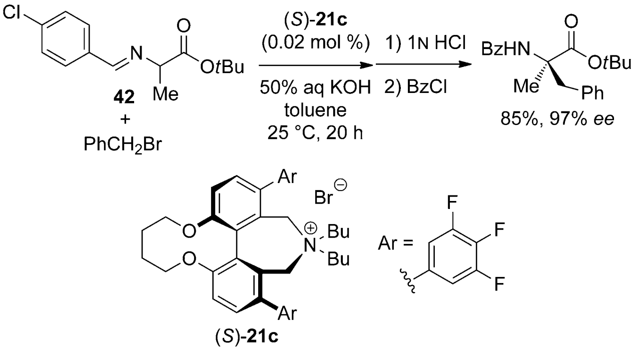


Scheme 29. Asymmetric alkylation of alanine derivative **39** by cinchona alkaloid derived catalysts.



Scheme 30. A binaphthyl-modified diol catalyst.

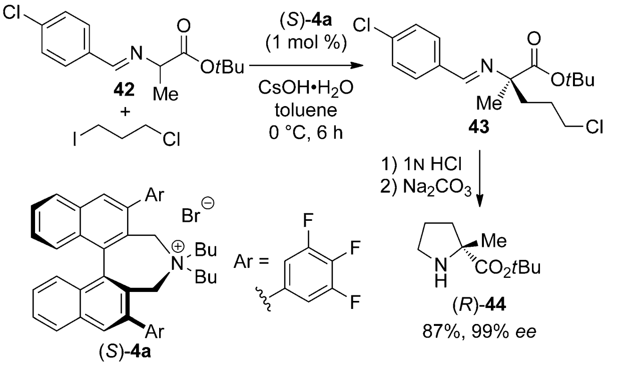
We have successfully designed very powerful chiral phase-transfer catalyst (*S*)-**21c** with a conformationally fixed biphenyl core for the asymmetric alkylation of an alanine derivative **42** (Scheme 31).[43] A remarkable feature of the catalyst system is that the reaction proceeds under mild reaction conditions (KOH as base, room temperature) with an extremely low catalyst loading (0.02 mol%).



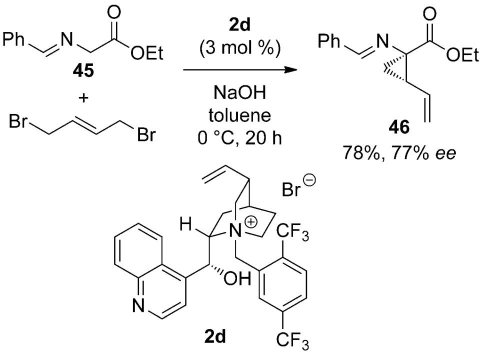
Scheme 31. Practical synthesis of α,α-dialkyl-α-amino acid with low catalyst loading under mild reaction conditions.

The catalytic asymmetric synthesis of various cyclic α-amino acid derivatives with tetrasubstituted α-carbon atoms has been accomplished by phase-transfer C-alkylation of α-alkyl-amino acid derivatives and subsequent intramolecular N-alkylation. For example, treatment of **42** with a dihaloalkane under phase-transfer conditions in the presence of the simplified Maruoka catalyst (*S*)-**4a** gave the corresponding alkylated product **43**. Hydrolysis of the imine and subsequent treatment with Na_2CO_3 facilitated intramolecular ring closure to give the α-methylproline *tert*-butyl ester **44** with excellent enantioselectivity (Scheme 32).[44]

A Merck research group reported a concise asymmetric synthesis of 1-amino-2-vinylcyclopropanecarboxylic acid derivative **46** as a key intermediate in the preparation of many inhibitors of the hepatitis C virus. Stereoselective cyclopropanation of a glycine derivative **45** was effected by



Scheme 32. Asymmetric synthesis of a cyclic α-alkyl amino acid derivative.



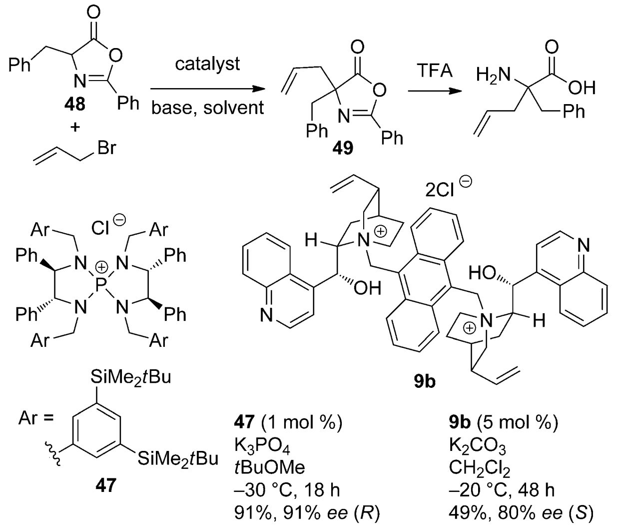
Scheme 33. Asymmetric synthesis of 1-amino-2-vinylcyclopropane-carboxylic acid.

treatment with *trans*-1,4-dibromo-2-butene in the presence of catalyst **2d** (Scheme 33).[45]

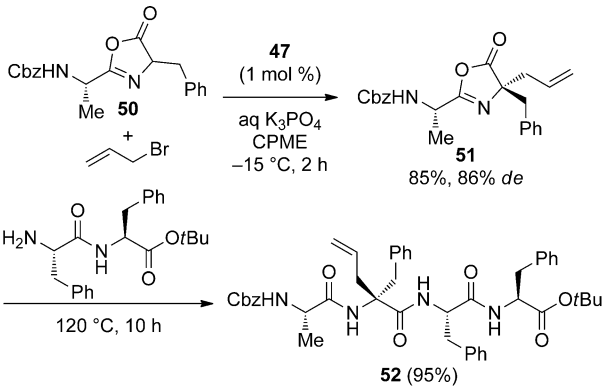
Ooi and co-workers successfully demonstrated that the P-spiro chiral tetraaminophosphonium salt **47** can function as an effective catalyst for the highly enantioselective alkylation of azlactones, such as **48**, derived from α-amino acids. The resulting alkylated azlactone **49** can be readily converted into the corresponding α,α-dialkyl-α-amino acid by acidic hydrolysis (Scheme 34).[46] This study led Nájera and co-workers to investigate the alkylation in the presence of dimeric cinchonidinium salt **9b** (Scheme 34).[47]

Ooi and co-workers developed a novel method for the synthesis of peptides containing quaternary stereogenic carbon centers based on the synthetic strategy for α,α-dialkyl-α-amino acids from azlactones shown in Scheme 34. Stereoselective alkylation of C-terminal azlactone **50** derived from a dipeptide occurred with high efficiency by using a chiral tetraaminophosphonium salt **47** as a phase-transfer catalyst, and the alkylated azlactone product **51** could be employed directly for peptide ligation to give growing peptides such as **52** (Scheme 35).[48] Cyclopentyl methyl ether (CPME) is the solvent of choice to achieve high chemical yield and high selectivity.

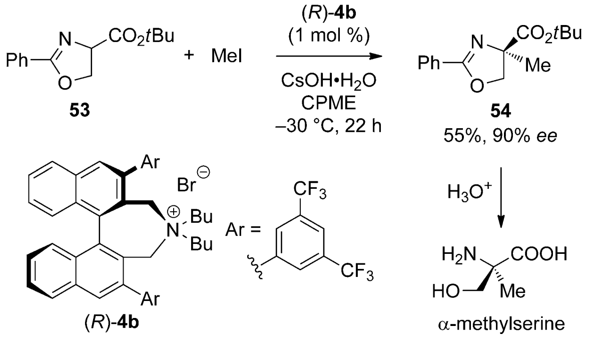
On the basis of previous studies by Jew, Park et al.,[49] we reported a highly enantioselective methylation of phenyloxazoline *tert*-butyl ester **53** by using (*R*)-**4b** as a catalyst to furnish α-methylserine derivative **54** (Scheme 36).[50]



Scheme 34. Asymmetric alkylation of an azlactone.



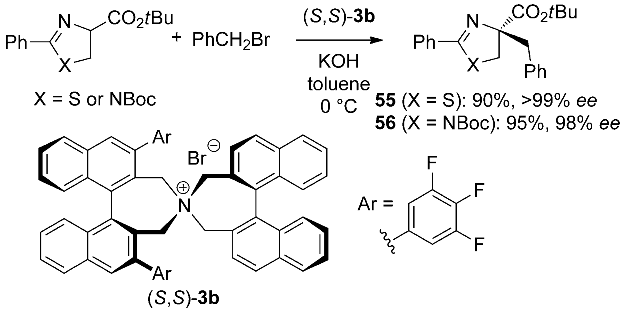
Scheme 35. Asymmetric quaternization of a peptide backbone. Cbz = benzyloxycarbonyl.



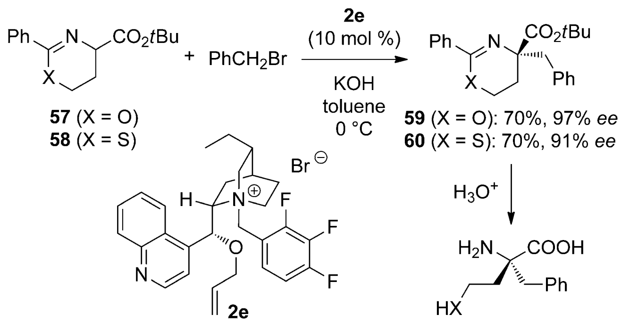
Scheme 36. Asymmetric synthesis of an α-methylserine.

The synthetic strategy for α-alkyl serines in Scheme 36 was applied to the asymmetric synthesis of α-alkyl cysteine derivatives, such as **55**,[51] and α-alkyl-α,β-diaminopropionic acid derivatives, such as **56**[52] (Scheme 37).

Furthermore, Park and co-workers applied the synthetic strategy to the synthesis of α-alkylhomoserine and α-alkylhomocysteine derivatives, such as **59** and **60**, through the use



Scheme 37. Asymmteric synthesis of α-alkyl cysteine and α-alkyl-α,β-diaminopropionic acid.



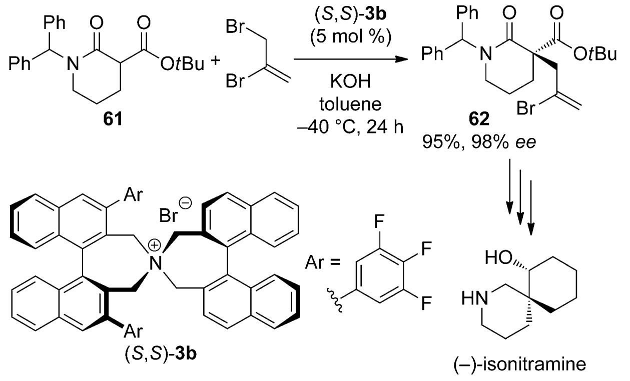
Scheme 38. Asymmetric synthesis of an α-alkylhomoserine and α-alkylhomocysteine.

of substrates **57** and **58** with a six-membered ring and catalyst **2e** (Scheme 38).[53]

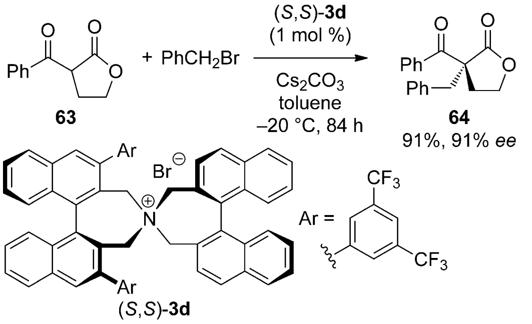
2.1.3. Other Alkylations

Park et al. reported the highly enantioselective alkylation of α-*tert*-butoxycarbonyllactam **61** catalyzed by (*S*,*S*)-**3b** for the construction of a β-quaternary chiral piperidine core system. The synthetic method could be applied to the enantioselective synthesis of key intermediate **62** for the total synthesis of (−)-isonitramine (Scheme 39).[54]

The highly enantioselective alkylation of α-acyl-γ-butyrolactone **63** has been achieved in the presence of (*S*,*S*)-**3d**. The resulting α-alkylated keto lactone **64** serves as a valuable chiral building block in organic synthesis (Scheme 40).[55]

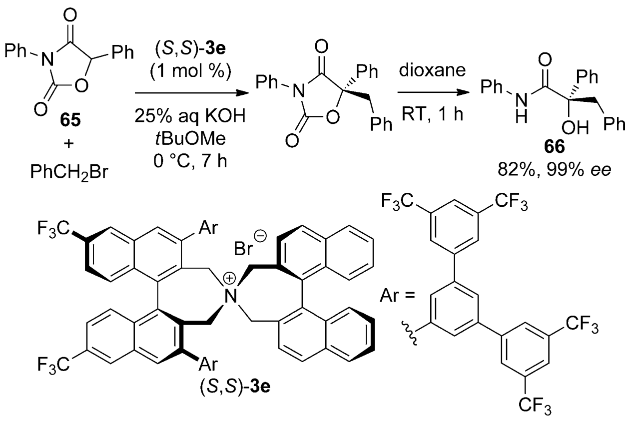


Scheme 39. Asymmetric alkylation of an α-*tert*-butoxycarbonyllactam.



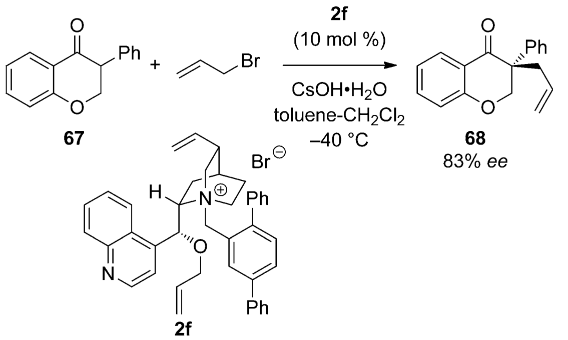
Scheme 40. Asymmetric alkylation of an α-acyl-γ-butyrolactone.

We reported the highly enantioselective alkylation of 3,5-diaryloxazolidin-2,4-diones, such as **65**, under mild phase-transfer conditions in the presence of catalyst (*S*,*S*)-**3e**. This method allows a wide range of *tert*-α-hydroxy-β-aryl carboxylic acid derivatives, such as **66**, to be readily obtained in good yield and high enantiomeric excess (Scheme 41).[56]



Scheme 41. Asymmetric synthesis of a *tert*-α-hydroxy-β-aryl carboxylic acid.

Scheidt and co-workers reported the asymmetric alkylation of isoflavanone **67** catalyzed by a cinchonidine-derived catalyst **2f** to obtain alkylated isoflavanone **68** possessing a quaternary carbon center with good enantioselectivity (Scheme 42).[57]

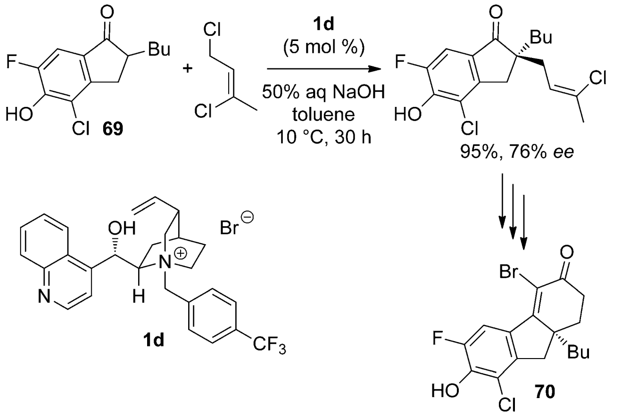


Scheme 42. Asymmetric alkylation of an isoflavanone.

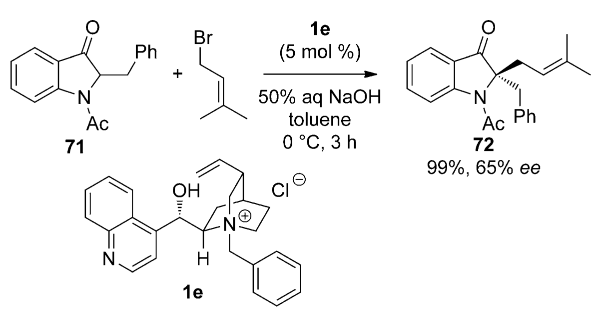
A group at Merck reported an efficient asymmetric synthesis of **70**, an estrogen receptor β-modulator, by asymmetric alkylation of an indanone derivative **69** with catalyst **1d** (Scheme 43).[58] The synthesis was accomplished in 34% yield over eight steps from commercially available 2-fluoroanisole.

The asymmetric alkylation of 2-substituted indolin-3-one **71** in the presence of catalyst **1e** was reported by Kawasaki and co-workers. The reaction gave a 2,2-disubstituted indolin-3-one **72** with moderate enantioselectivity (Scheme 44).[59]

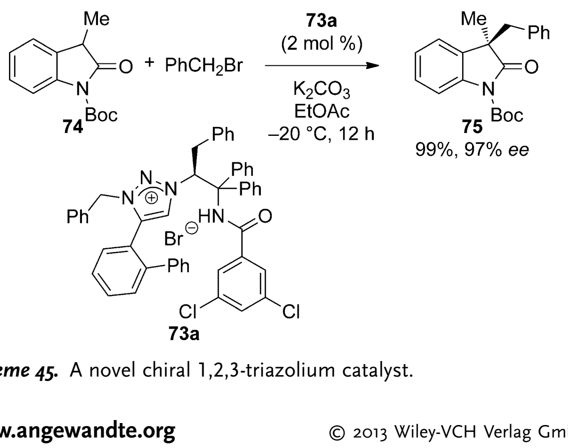
The novel chiral 1,2,3-triazolium **73a** was designed by Ooi and co-workers, and its potential as a phase-transfer catalyst has been demonstrated in the asymmetric alkylation of 3-substituted oxindoles, such as **74**, to give the alkylation products, such as **75**, with high enantioselectivity (Scheme 45).[60] The amide moiety of the catalyst **73a** is crucial for obtaining high enantioselectivity.



Scheme 43. Asymmetric synthesis of the estrogen receptor β-modulator **70**.



Scheme 44. Asymmetric alkylation of a 2-substituted indolin-3-one.

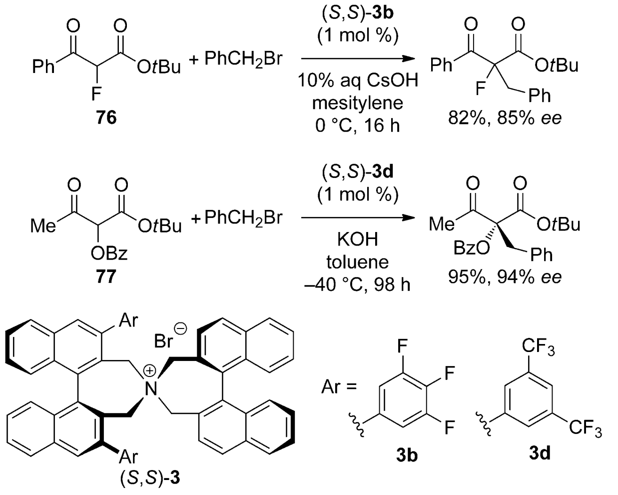


Scheme 45. A novel chiral 1,2,3-triazolium catalyst.

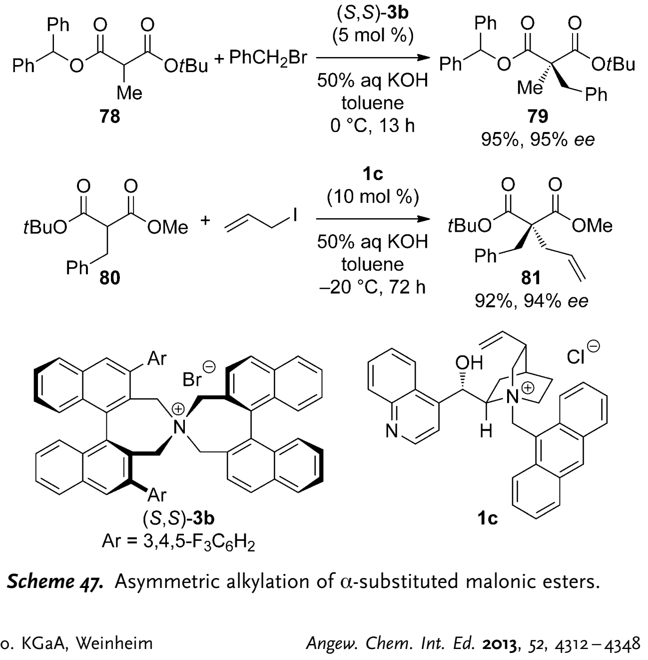
As a complementary approach to the asymmetric fluorination and hydroxylation of α-alkyl-β-keto esters, the highly enantioselective alkylation of α-fluoro- and α-benzoyloxy-β-keto esters **76**[61] and **77**[62] was realized by using N-spiro chiral ammonium salts (*S*,*S*)-**3b** and **3d** as catalysts (Scheme 46).

The research groups of Park and Itoh independently reported the asymmetric alkylation of α-substituted malonic esters through the discrimination of two different ester moieties (Scheme 47). Park and co-workers employed the malonic ester **78** with a binaphthyl-modified catalyst (*S*,*S*)-**3b** to obtain α,α-dialkylmalonate **79** with high enantioselectivity.[63] Itoh, in contrast, used the malonic ester **80** with a cinchonine-derived catalyst **1c** to give alkylation product **81**.[64]

Park and co-workers reported the highly enantioselective monoalkylation of a malonamic ester by the use of **82** as a key

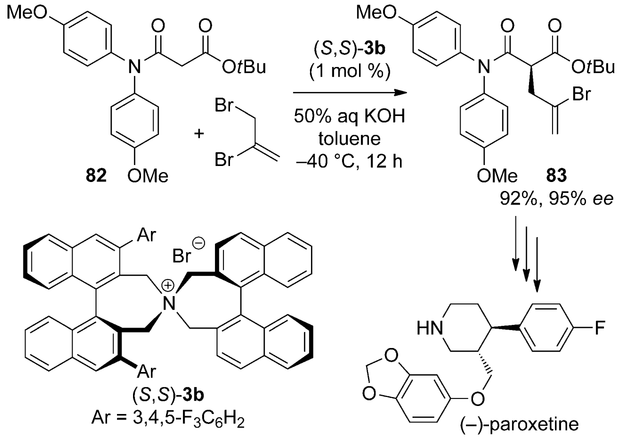


Scheme 46. Asymmetric alkylation of α-fluoro- and α-benzoyloxy-β-keto esters.



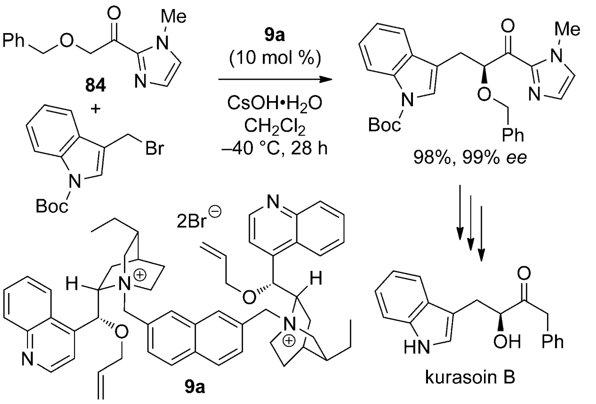
Scheme 47. Asymmetric alkylation of α-substituted malonic esters.

substrate. This synthetic method could be applied to the enantioselective synthesis of key intermediate **83** for the synthesis of (−)-paroxetine (Scheme 48).[65]



Scheme 48. Asymmetric monoalkylation of a malonamic ester.

Andrus et al. reported the highly enantioselective alkylation of 2-acylimidazole **84** with dimeric dihydrocinchonidinium catalyst **9a**. This method was applied to the efficient enantioselective synthesis of kurasoin B (Scheme 49).[66]

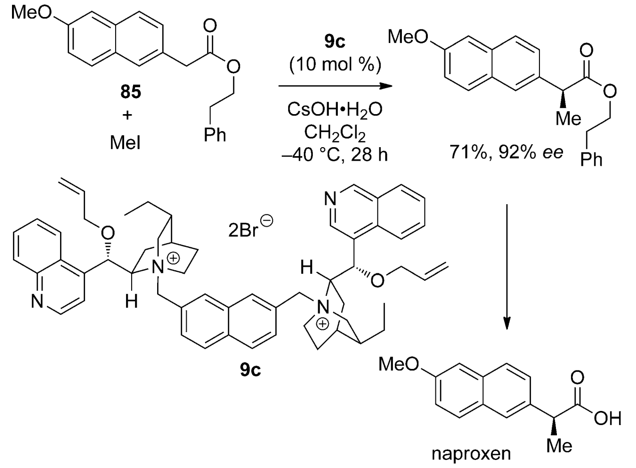


Scheme 49. Asymmetric alkylation of an acylimidazole.

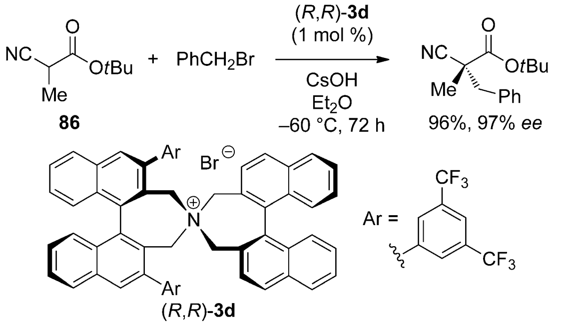
The same research group also reported the enantioselective alkylation of aryl acetates, such as **85**. This method was highlighted by the efficient enantioselective synthesis of naproxen (Scheme 50).[67]

The highly enantioselective alkylation of cyanoacetates, such as **86**, was achieved by Itoh et al. through the use of N-spiro chiral ammonium salt (*S*,*S*)-**3d** (Scheme 51).[68]

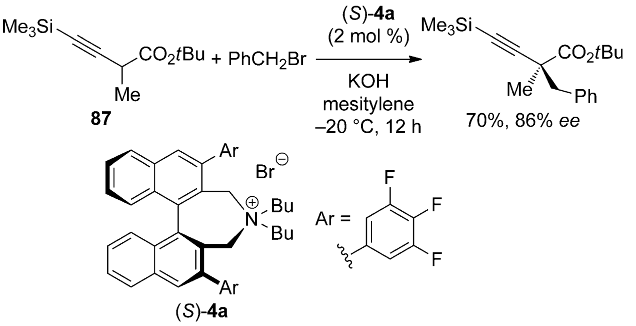
We demonstrated the ability of α-alkyl-α-alkynyl esters, such as **87**, to undergo highly enantioselective alkylation under phase-transfer conditions, thereby furnishing α-chiral acetylenes with an all-carbon quaternary center. A detailed investigation of this reaction system revealed the formation of an allenyl ester prior to the alkylation (Scheme 52).[69]



Scheme 50. Asymmetric alkylation of an aryl acetate.

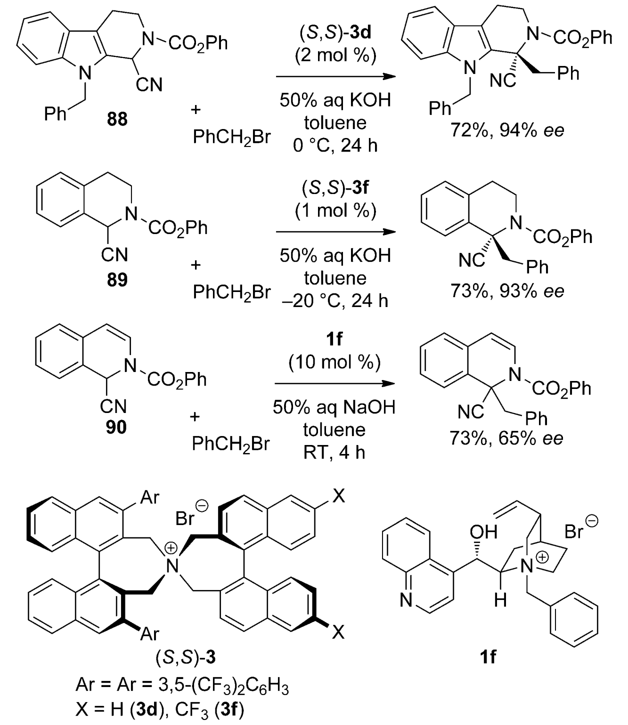


Scheme 51. Asymmetric alkylation of a cyanoacetate.



Scheme 52. Asymmetric alkylation of α-alkyl-α-alkynyl esters.

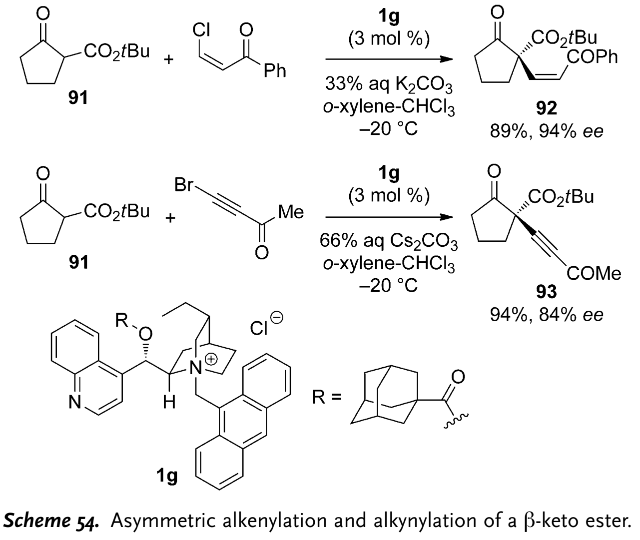
The efficient catalytic asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines has been achieved through asymmetric alkylation of 1-cyanotetrahydro-β-carboline **88** by using the binaphthyl-modified N-spiro-type chiral phase-transfer catalyst (*S*,*S*)-**3d**.[70] This reaction is a valuable example of highly enantioselective alkylations at the α-carbon atom of a cyano group under phase-transfer conditions that are otherwise difficult. This method was applied to the highly enantioselective alkylation of 1-cyanotetrahydroisoquinoline **89** to obtain 1,1-disubstituted tetrahydroisoquinolines.[71] The asymmetric alkylation of dihydroisoquinoline **90** with cinchonine-derived catalyst was reported by Rozwadowska and co-workers (Scheme 53).[72]



Scheme 53. Asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines and isoquinolines.

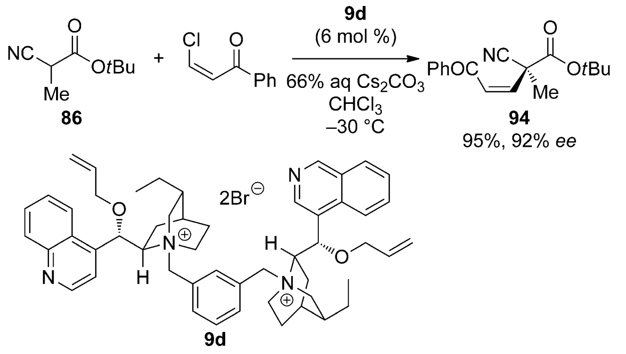
2.1.4. Alkenylation and Alkynylation

Jørgensen and co-workers reported the asymmetric alkenylation of β-keto esters, such as **91**, catalyzed by dihydrocinchonine-derived phase-transfer catalyst **1g** containing a 1-adamantoyl group. Activated β-haloalkenes were utilized as the vinyl sources, which participate in the substitution reaction through an addition/elimination sequence. A *Z*-configured double bond could be incorporated into the product **92** by starting from a (*Z*)-vinyl halide (Scheme 54).[73] The same strategy was successfully applied to the asymmetric alkynylation of β-keto esters to afford the alkynylation product **93**.[74]



Scheme 54. Asymmetric alkenylation and alkynylation of a β-keto ester.

Jørgensen and co-workers also reported the asymmetric alkenylation of cyanoacetates, such as **86**, in the presence of dimeric catalyst **9d**. The reaction occurred efficiently to give product **94** with high enantioselectivity (Scheme 55).[75]

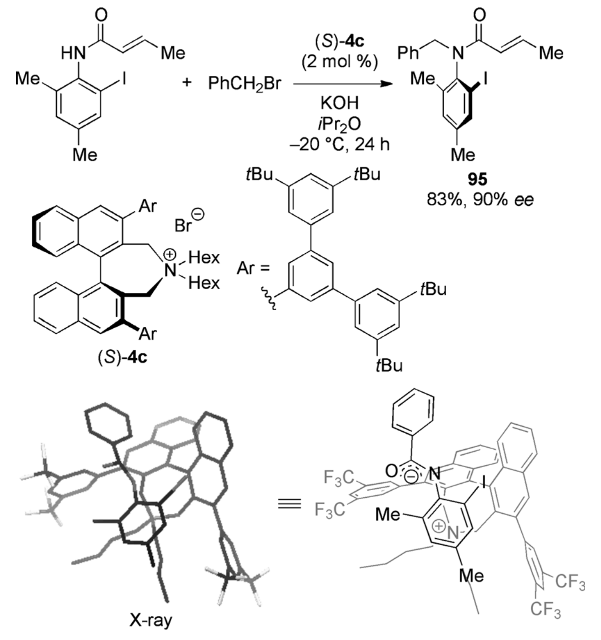


Scheme 55. Asymmetric alkenylation of a cyanoacetate.

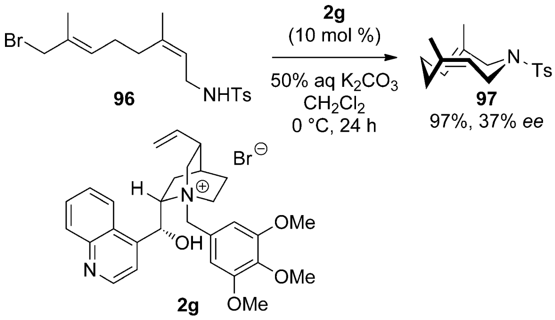
2.2. C–N Bond Formation

The asymmetric synthesis of axially chiral *o*-iodoanilides, such as **95**, which are useful chiral building blocks, was achieved through N-alkylations catalyzed by the chiral quaternary ammonium salt (*S*)-**4c** under phase-transfer conditions (Scheme 56).[76] The structure of the transition state of the reaction is discussed on the basis of the X-ray crystal structure of ammonium anilide.

The enantioselective synthesis of a planar chiral organonitrogen cycle **97** was examined by Tomooka et al. through the use of the cinchonidine-derived chiral phase-transfer catalyst **2g** (Scheme 57).[77] The intramolecular face-selective cyclization of **96** gave a planar chiral compound **97** with moderate enantioselectivity.



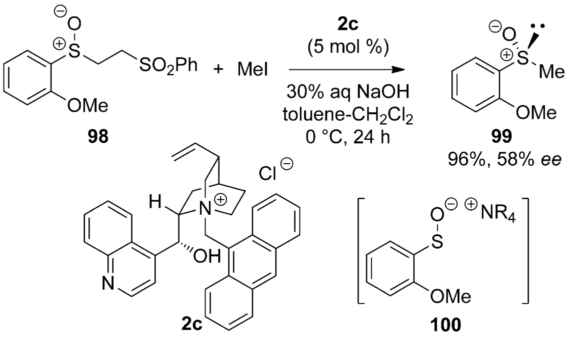
Scheme 56. Catalytic asymmetric synthesis of an axially chiral *o*-iodoanilide and X-ray crystal structure of an ammonium anilide.



Scheme 57. Catalytic asymmetric synthesis of a planar chiral organonitrogen compound.

2.3. C—S Bond Formation

Perrio and co-workers reported a conceptually new approach to chiral sulfoxides based on asymmetric phase-transfer alkylations with catalyst **2c**. For example, *o*-anisyl methyl sulfoxide **99** was produced with moderate enantioselectivity by the asymmeteric methylation of **98** via intermediate **100** (Scheme 58).[78]



Scheme 58. Asymmetric synthesis of a chiral sulfoxide.

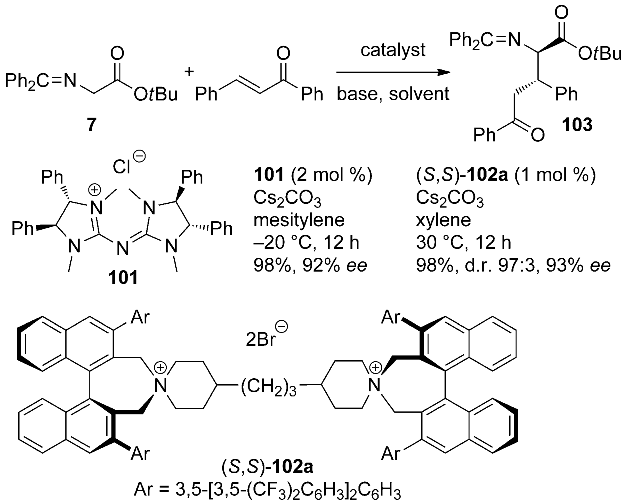
3. Conjugate Addition

3.1. C—C Bond Formation

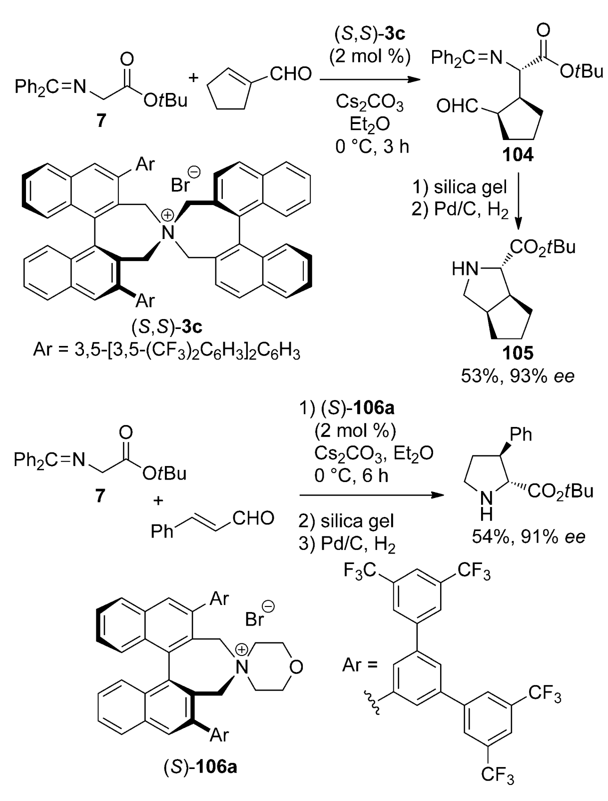
3.1.1. Asymmetric Synthesis of α-Amino Acid Derivatives

The enantioselective conjugate addition of glycine derivatives by means of chiral phase-transfer catalysis has led to the synthesis of various functionalized α-alkyl-α-amino acids.

Tan and co-workers developed the new chiral pentanidium catalyst **101**, which was successfully applied to the enantioselective conjugate addition of glycine benzophenone imine *tert*-butyl ester (**7**) to α,β-unsaturated carbonyl compounds (Scheme 59).[79] This efficient reaction gave product **103** as a single diastereomer with high enantioselectivity. Ma and co-workers also carried out a highly enantioselective conjugate addition with the same reaction by using a newly designed binaphthyl-modified bisammonium salt **102a** (Scheme 59).[80]



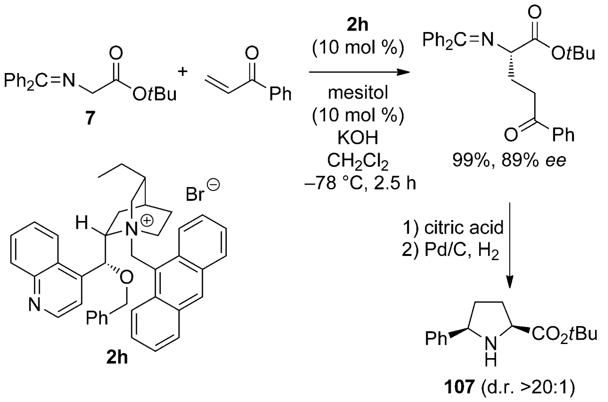
Scheme 59. Enantioselective conjugate addition of glycine benzophenone imine *tert*-butyl ester to an α,β-unsaturated carbonyl compound.



Scheme 60. Efficient asymmetric synthesis of cyclic amino acids.

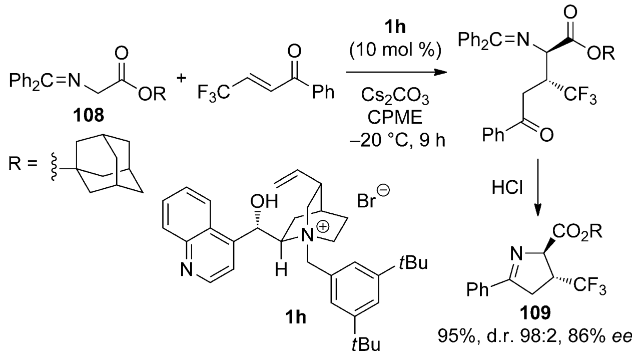
The efficient asymmetric synthesis of bicyclic amino acid **105** as a core structure of telaprevir, a hepatitis C virus protease inhibitor, has been accomplished by the phase-transfer-catalyzed stereoselective conjugate addition of **7** to cyclopent-1-enecarbaldehyde (Scheme 60).[81a] The hydrolysis of conjugate adduct **104** and a subsequent intramolecular formation of an imine gave a precursor, which was reduced by catalytic hydrogenation to furnish the target bicyclic amino acid **105**. This method can be applied to the asymmetric synthesis of 3-substituted prolines.[81b]

Lygo et al. reported a highly stereoselective three-step sequence for the enantioselective synthesis of *cis*-5-substituted proline esters, such as **107**. The sequence features an asymmetric conjugate addition of **7** to vinyl ketones in the presence of catalyst **2h**, followed by acid-catalyzed imine exchange and catalytic hydrogenation (Scheme 61).[82]



Scheme 61. Asymmetric synthesis of a *cis*-5-substituted proline.

The same strategy was used by Shibata and co-workers for the asymmetric synthesis of β-trifluoromethylpyrroline carboxylates, such as **109**. The use of the bulky adamantyl glycinate **108** with catalyst **1h** led to the product with high stereoselectivity (Scheme 62).[83]

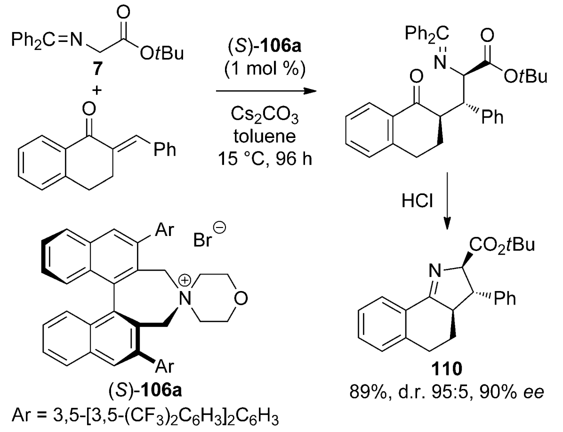


Scheme 62. Asymmetric synthesis of a β-trifluoromethyl-pyrroline carboxylate.

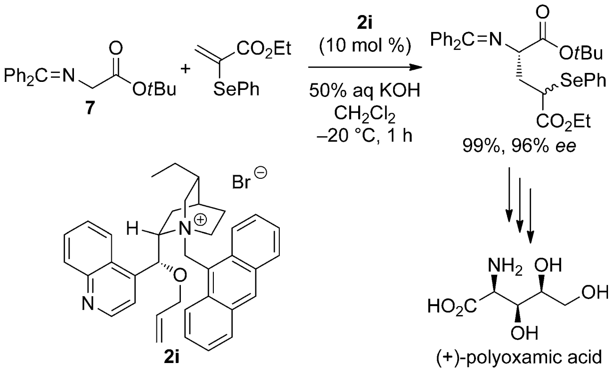
The asymmetric synthesis of tricyclic compounds, such as **110**, containing three adjacent stereocenters was also achieved by using the same strategy. The chiral phase-transfer catalyst (*S*)-**106a** was effective for delivering the target product with high stereoselectivity (Scheme 63).[84]

Park and co-workers reported an efficient enantioselective synthesis of (+)-polyoxamic acid by the phase-transfer-catalyzed conjugate addition of **7** in the presence of catalyst **2i**. (+)-Polyoxamic acid was obtained in 7 steps and 46% overall yield (Scheme 64).[85]

Shibasaki and co-workers achieved the short total synthesis of (+)-cylindricine C by the asymmetric phase-transfer conjugate addition of glycine ester **111** in the presence of tartrate-derived bisammonium salt **5a**. The Michael acceptor **112** was designed to include the appropriate functionalities for the following acid-catalyzed tandem cyclization (Scheme 65).[86]

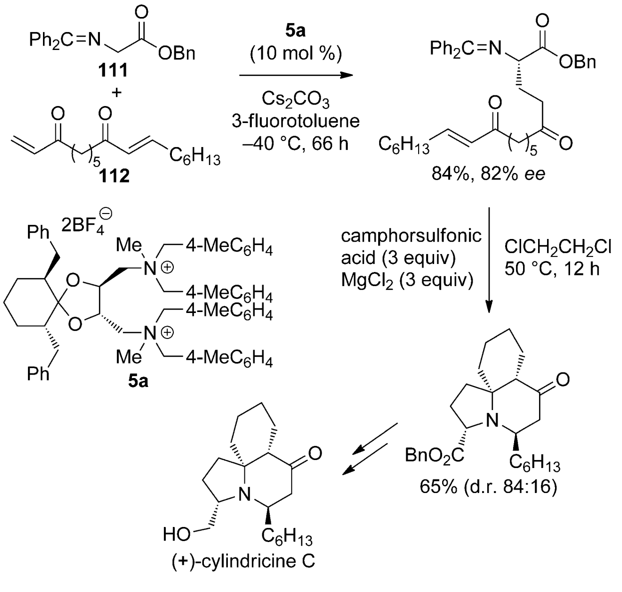


Scheme 63. Asymmetric synthesis of a tricyclic compound.



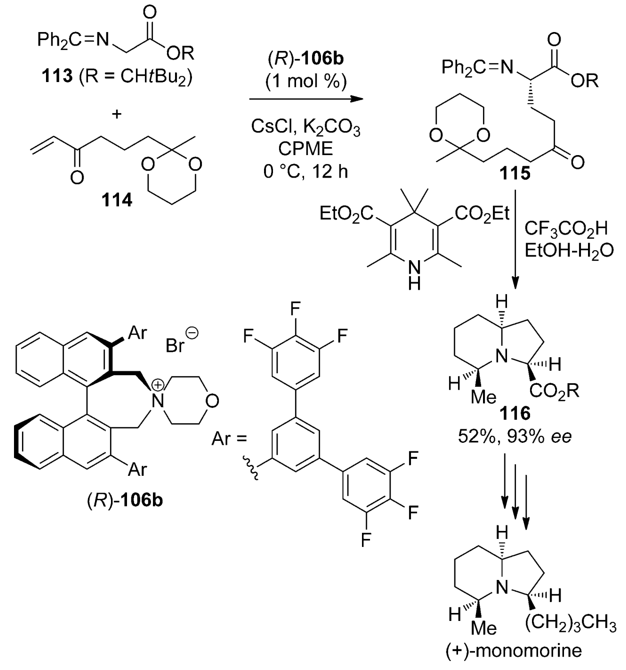
Scheme 64. Enantioselective synthesis of (+)-polyoxamic acid.

We reported the asymmetric conjugate addition of a glycine ester for the efficient asymmetric synthesis of



Scheme 65. Short synthesis of (+)-cylindricine C.

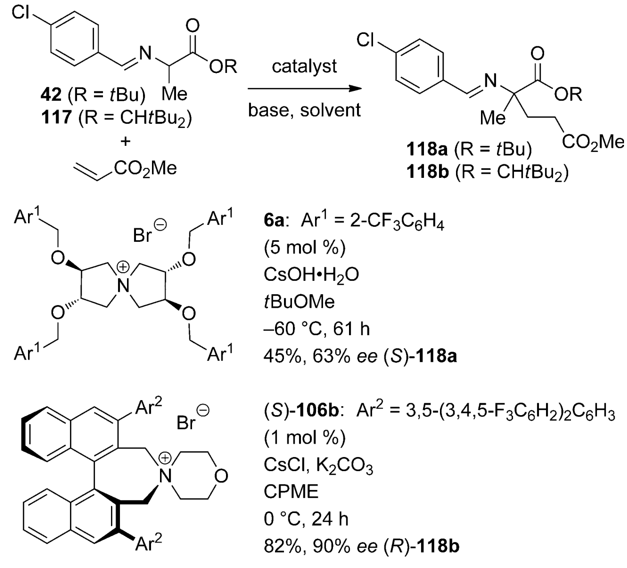
pyrrolidine, hexahydropyrrolizine, and octahydropyrrolizine core structures. For example, treatment of glycine ester **113** with the α,β-enone **114** under phase-transfer conditions in the presence of catalyst (*R*)-**106b** gave the corresponding conjugate adduct **115**. Intramolecular reductive amination of **115** and subsequent acetal hydrolysis followed by reductive amination was effected with the Hantzsch ester and trifluoroacetic acid in aqueous ethanol to furnish the octahydropyrrolizine core structure **116** with excellent enantioselectivity in a one-pot reaction. This product was transformed into (+)-monomorine in three additional steps (Scheme 66).[87]



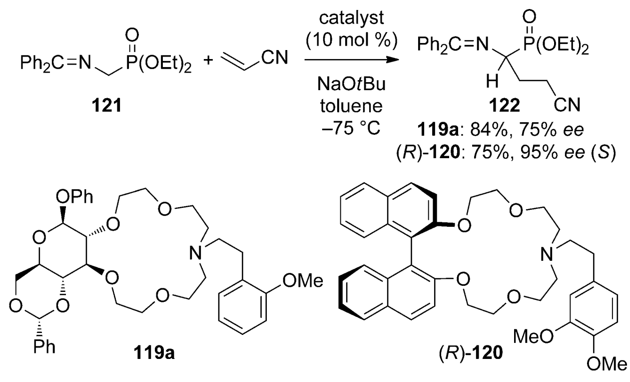
Scheme 66. Efficient enantioselective synthesis of (+)-monomorine.

Arai et al. and our research group independently reported the catalytic asymmetric conjugate addition of alanine derivatives to methyl acrylate (Scheme 67). Arai et al. examined the reaction of alanine *tert*-butyl ester **42** in the presence of tartrate-derived N-spiro phase-transfer catalyst **6a**, which gave the corresponding α,α-dialkyl-α-amino acid derivative **118a** with moderate enantioselectivity.[88] We employed the alanine ester **117** and catalyst (*S*)-**106b** to obtain the product **118b** with high enantioselectivity. In this reaction, the combination of K_2CO_3 and a catalytic amount of CsCl as bases is essential to promote the reaction efficiently.[89]

Jászay et al. reported the asymmetric conjugate addition of an α-aminophosphonate derivative **121** to acrylonitrile catalyzed by chiral azacrown ethers **119a**[90] and **120**[91] in the presence of sodium *tert*-butoxide. The binaphthyl-modified azacrown ether **120** was effective for the reaction and gave the conjugate adduct **122** with high enantioselectivity (Scheme 68).



Scheme 67. Asymmetric conjugate addition of alanine derivatives.

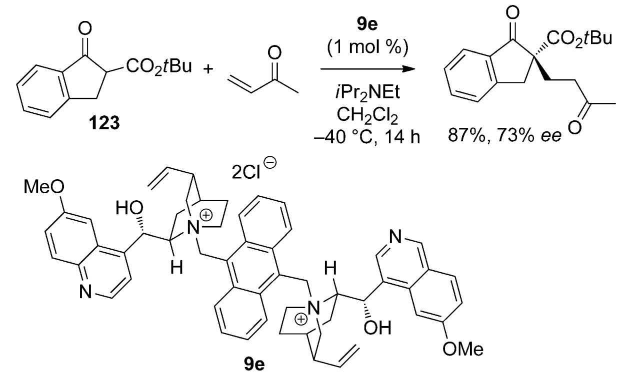


Scheme 68. Asymmetric conjugate addition of an α-aminophosphonate.

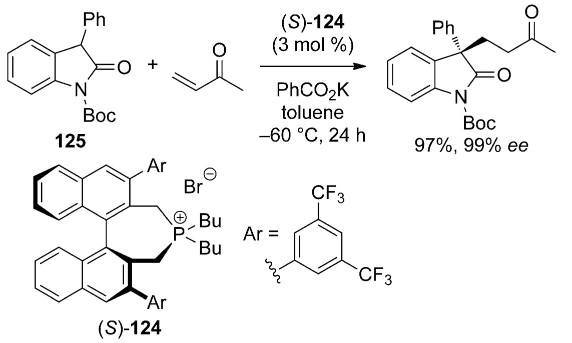
3.1.2. Other Conjugate Additions

Nájera and co-workers reported the asymmetric conjugate addition of β-keto ester **123** to methyl vinyl ketone in the presence of the dimeric catalyst **9e**. In this reaction, diisopropylethylamine was employed as a base (Scheme 69).[92]

In contrast to the broad synthetic utility of chiral quaternary tetraalkylammonium salts in asymmetric phase-transfer catalysis, chiral quaternary tetraalkylphosphonium salts have not been regarded as reliable phase-transfer catalysts because of the facile formation of the corresponding ylides under basic conditions. Indeed, catalytic asymmetric synthesis with chiral quaternary tetraalkylphosphonium salts used as the phase-transfer catalysts remains poorly studied. We have successfully developed a highly efficient, enantioselective conjugate addition of 3-phenyloxindole **125** to methyl vinyl ketone that occurs with exceptionally high enantioselectivity in the presence of chiral phosphonium salt (*S*)-**124** under phase-transfer conditions (Scheme 70).[93] In this reaction, potassium benzoate was used as a relatively mild base.



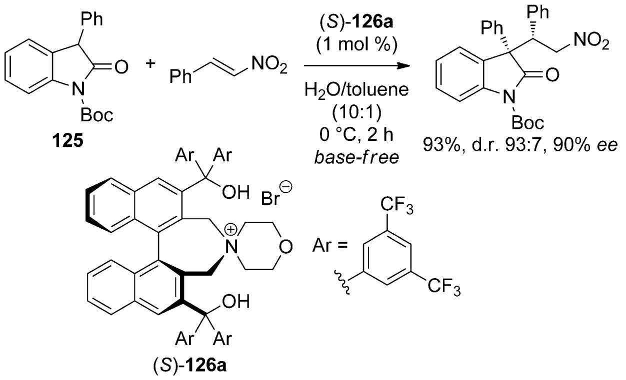
Scheme 69. Asymmetric conjugate addition of a β-keto ester.



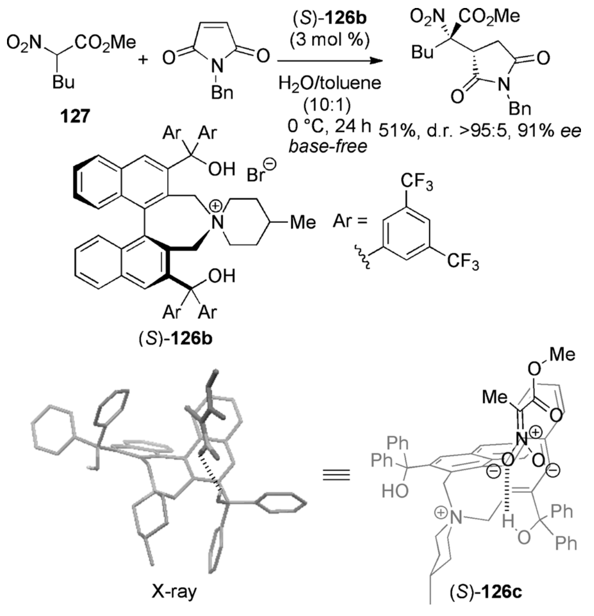
Scheme 70. A chiral tetraalkylphosphonium salt as a phase-transfer catalyst for the asymmetric conjugate addition of a 3-phenyloxyindole.

Although quaternary ammonium salts are generally believed to require base additives to act as catalysts in phase-transfer reactions, we discovered that the enantioselective phase-transfer conjugate addition of 3-phenyloxindole **125** to β-nitrostyrene proceeded smoothly with both high diastereo- and enantioselectivity in the presence of a chiral bifunctional ammonium bromide (*S*)-**126a** under neutral conditions in a water-rich solvent (Scheme 71).[94]

This attractive base-free neutral phase-transfer reaction system could be applied to the highly stereoselective conjugate addition of α-substituted nitroacetates, such as **127**, to maleimides in the presence of a chiral bifunctional ammonium bromide (*S*)-**126b** (Scheme 72).[95] The reaction does not work well under ordinary phase-transfer conditions in aqueous basic solutions, such as aqueous KOH, K_2CO_3, and $PhCO_2K$, and under homogeneous water-free reaction conditions. Hence, the highly enantioselective conjugate addition was only achieved when the reaction was performed under base-free neutral phase-transfer conditions. In this study, we carried out an X-ray diffraction analysis of the ammonium nitronate (*S*)-**126c** to gain insight into the structure of the intermediate (Scheme 72). Very importantly, the hydrogen-bonding interactions between the hydroxy group in the binaphthyl unit and the anionic oxygen atom of nitro group is clearly observed in the crystal structure.



Scheme 71. Asymmetric conjugate addition of a 3-phenyloxindole under neutral phase-transfer conditions.

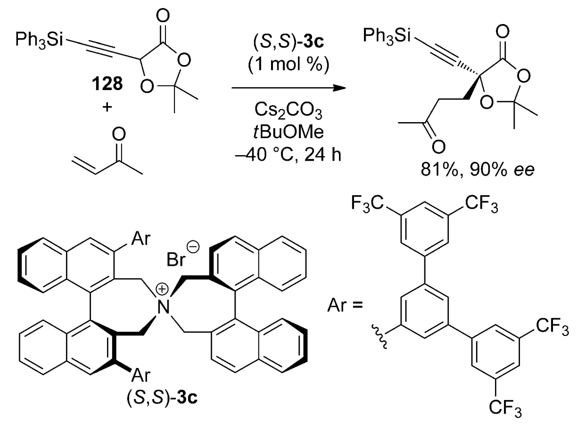


Scheme 72. Asymmetric conjugate addition of an α-substituted nitroacetate under neutral phase-transfer conditions, and the X-ray crystal structure of (*S*)-**126c**.

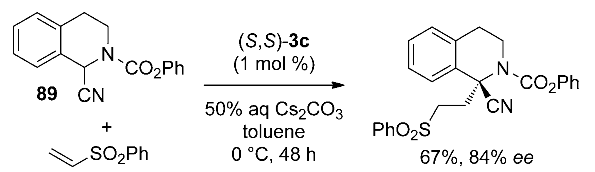
We reported the highly enantioselective conjugate addition of 5-(triphenylsilyl)ethynyl-1,3-dioxolan-4-one **128** to methyl vinyl ketone using phase-transfer catalyst (*S*,*S*)-**3c** (Scheme 73).[69b]

We have also succeeded in the asymmetric conjugate addition of 1-cyanotetrahydroisoquinoline **89** to vinyl sulfone in the presence of catalyst (*S*,*S*)-**3c** to produce a 1,1-disubstituted tetrahydroisoquinoline (Scheme 74).[71]

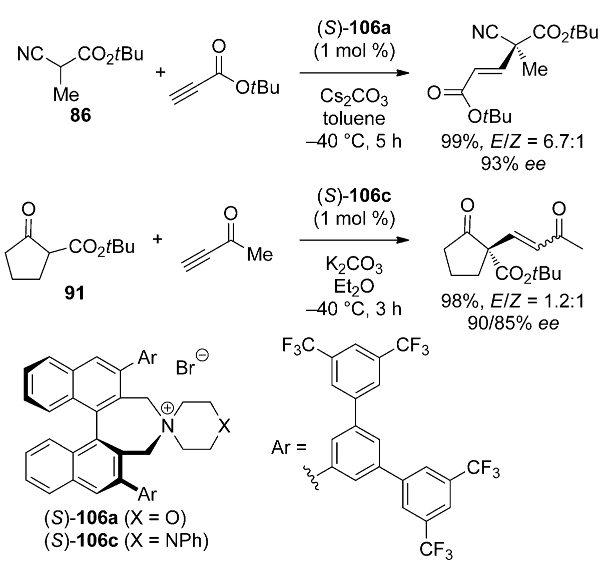
The asymmetric conjugate addition of α-substituted cyanoacetates to acetylenic esters under phase-transfer conditions is quite challenging, because of the difficulty in controlling the stereochemistry of the product. We have developed highly enantioselective conjugate additions of α-alkyl-α-cyanoacetates, such as **86**, to acetylenic esters catalyzed by (*S*)-**106a** (Scheme 75).[96] In this asymmetric transformation, an all-carbon quaternary stereocenter can be constructed with high enantiomeric purity. This reaction was extended to the highly enantioselective conjugate addition of



Scheme 73. Asymmetric conjugate addition of a 5-(triphenylsilyl)-ethynyl-1,3-dioxolan-4-one.



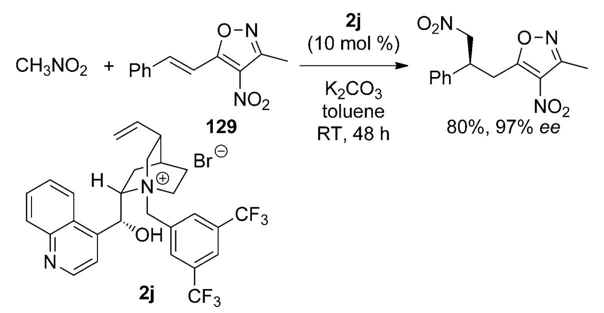
Scheme 74. Asymmetric conjugate addition of a 1-cyanotetrahydroisoquinoline.



Scheme 75. Asymmetric conjugate addition to an acetylenic ester and a ketone.

β-keto esters, such as **91**, to acetylenic ketones catalyzed by (*S*)-**106c** (Scheme 75).[97]

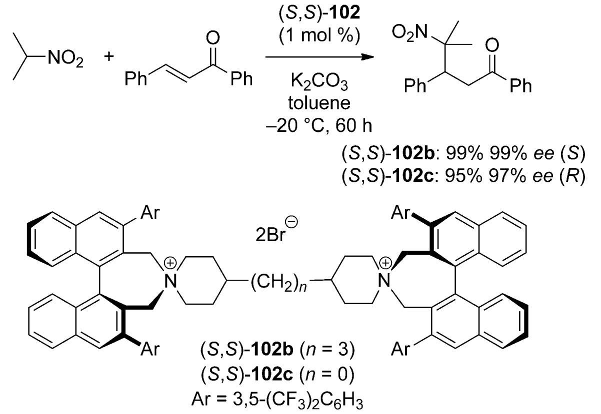
4-Nitro-5-styrylisoxazoles, such as **129**, were used as masked α,β-unsaturated carboxylic acids in the asymmetric conjugate addition to nitroalkanes. The 4-nitroisoxazole core acts as an activator of the conjugated alkene and a latent carboxylate functionality. The reaction proceeded with high enantioselectivity in the presence of cinchonidine-derived catalyst **2j** at room temperature (Scheme 76).[98]



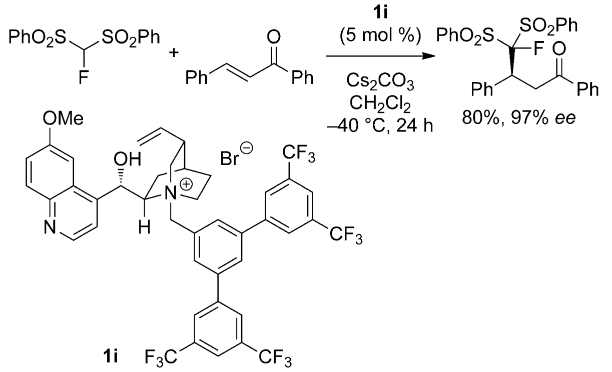
Scheme 76. Asymmetric conjugate addition to a 4-nitro-5-styrylisoxazole.

N-Spiro quaternary ammonium salts (*S*,*S*)-**102b** and (*S*,*S*)-**102c** with different lengthed alkyl spacers were used as phase-transfer catalysts in the conjugate addition of 2-nitropropane to chalcone, and an intriguing reversal of enantioselectivity was observed (Scheme 77).[99]

Shibata and co-workers reported the highly enantioselective conjugate addition of 1-fluorobis(phenylsulfonyl)methane, as a synthetic equivalent of a monofluoromethide species, to chalcone catalyzed by quinidine-derived catalyst **1i** with a sterically demanding substituent (Scheme 78).[100]

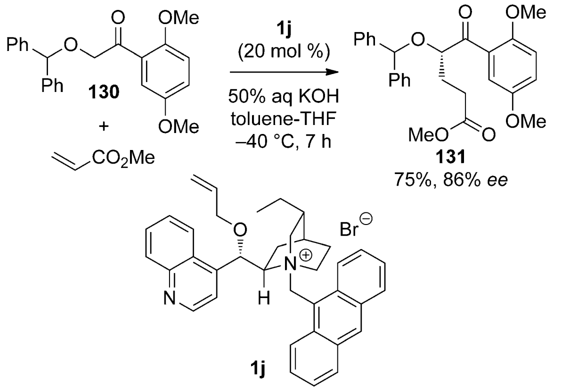


Scheme 77. Reversal of the enantioselectivity by tuning the conformational flexibility of the catalyst.



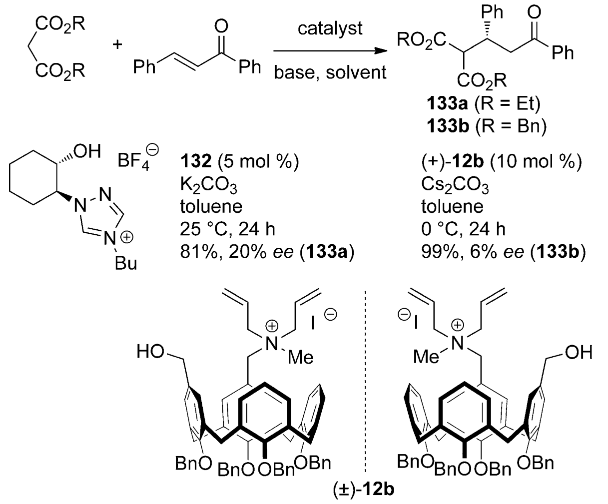
Scheme 78. Asymmetric conjugate addition of 1-fluorobis(phenylsulfonyl)methane to chalcone.

Andrus and Ye reported the phase-transfer-catalyzed asymmetric conjugate addition by using diphenylmethyloxy-2,5-dimethoxyacetophenone **130** as a key substrate. The reaction was promoted by catalyst **1j** to give conjugate adduct **131** with good enantioselectivity (Scheme 79).[101]



Scheme 79. Asymmetric conjugate addition of diphenylmethyloxy-2,5-dimethoxyacetophenone.

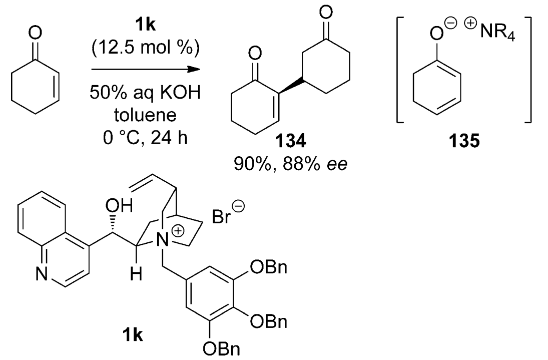
The novel chiral phase-transfer catalysts **132**[102] and **12b**[103] were applied to the asymmetric conjugate addition of malonates to chalcone, with the products **133** being obtained with low enantioselectivity (Scheme 80).



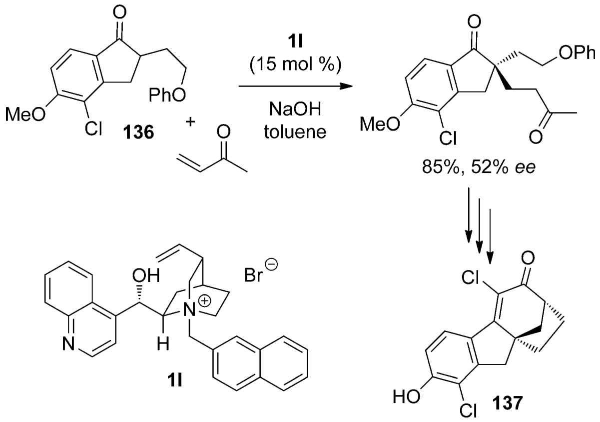
Scheme 80. Novel chiral phase-transfer catalysts for asymmetric conjugate addition.

Bella and co-workers reported the asymmetric dimerization of cyclohexenone catalyzed by cinchonine-derived catalyst **1k**. The reaction proceeded via intermediate **135** to give dimerization product **134** with good enantioselectivity (Scheme 81).[104]

A research group at Merck reported a practical asymmetric synthesis of **137**, an estrogen receptor β-selective agonist, by asymmetric conjugate addition of an indanone derivative **136** in the presence of catalyst **1l** (Scheme 82).[105]



Scheme 81. Asymmetric dimerization of cyclohexenone.



Scheme 82. Practical asymmetric synthesis of estrogen receptor β-selective agonist **137**.

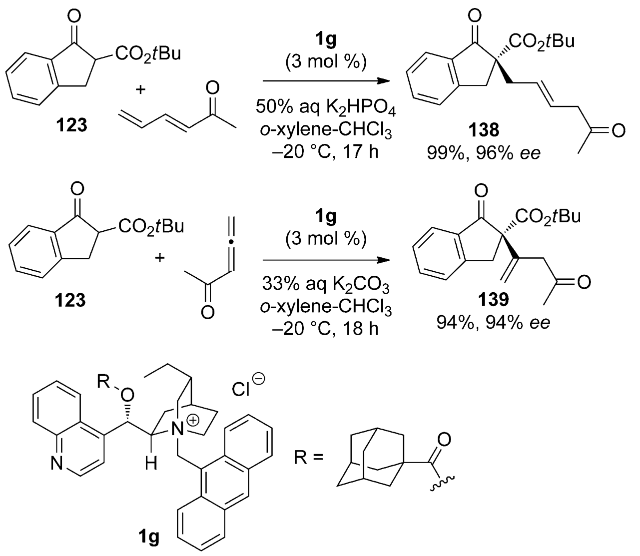
The challenges addressed here involved scaling the asymmetric phase-transfer reaction to a 44 mol (14 kg) scale.

The asymmetric 1,6-addition of β-ketoesters, such as **123**, to dienes possessing an electron-withdrawing substituent was described by Jørgensen and co-workers. The reaction was efficiently promoted by catalyst **1g** to give the 1,6-adduct **138** with high enantioselectivity (Scheme 83).[106] The highly enantioselective conjugate addition of β-ketoesters to electron-deficient allenes was also developed to obtain conjugate adducts such as **139** (Scheme 83).[107]

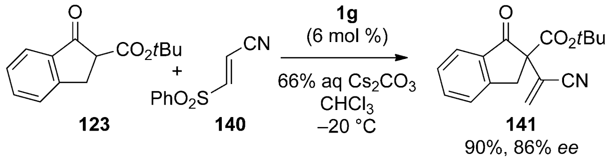
Jørgensen and co-workers also reported the asymmetric conjugate addition of β-ketoester **123** to **140**, which has a sulfone as a leaving group. The reaction was promoted by catalyst **1g** to give product **141** arising from a conjugate addition and subsequent elimination of sulfone (Scheme 84).[108]

3.2. C−N Bond Formation

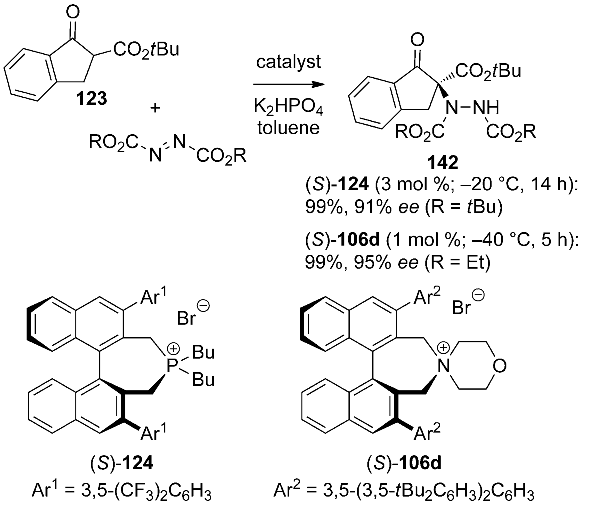
The highly enantioselective amination of β-ketoesters, such as **123**, can be achieved by using quaternary phosphonium (**124**)[109] or ammonium (**106d**)[110] salts as catalysts. In the reaction, azodicarboxylates were employed as an electrophile to obtain the amination product **142** (Scheme 85).



Scheme 83. Asymmetric conjugate additions of a β-ketoester to diene- and allene-carbonyl compounds.



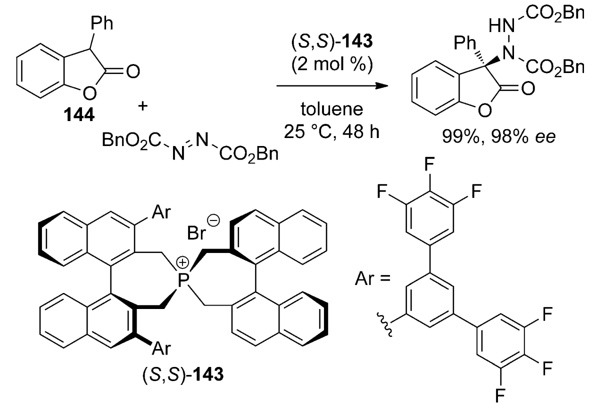
Scheme 84. Asymmetric conjugate addition/elimination strategy.



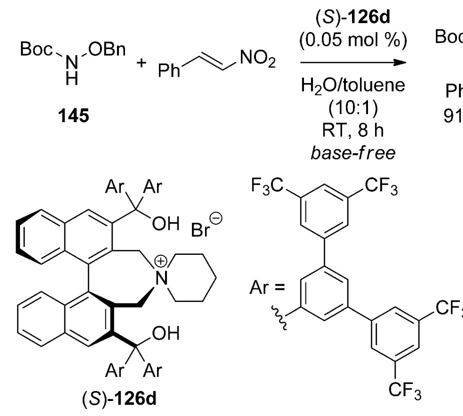
Scheme 85. Asymmetric amination of a β-ketoester.

Ma and co-workers reported a highly enantioselective amination of benzofuranones, such as **144**, catalyzed by quaternary phosphonium salt (*S*,*S*)-**143** under base-free homogeneous conditions (Scheme 86).[111]

We have successfully developed a highly efficient catalytic asymmetric amination of nitroolefins under neutral phase-transfer conditions in the presence of a chiral bifunctional tetraalkylammonium bromide (*S*)-**126d** in a water-rich solvent. In the reaction, *tert*-butylbenzyloxycarbamate (**145**) was used as a nucleophile to achieve a high yield and enantioselectivity with low catalyst loading (0.05 mol%) of **126d** (Scheme 87).[112]

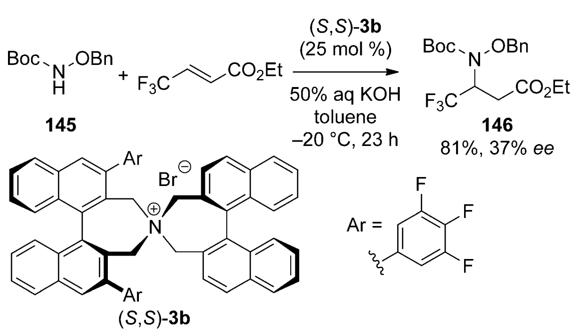


Scheme 86. Asymmetric amination of a benzofuranone.



Scheme 87. Asymmetric amination of a nitroolefin.

Gröger and co-workers reported a similar asymmetric amination by using *tert*-butylbenzyloxycarbamate (**145**) under basic conditions with catalyst (*S*,*S*)-**3b**. The desired amination product **146** was obtained with moderate enantioselectivity (Scheme 88).[113]

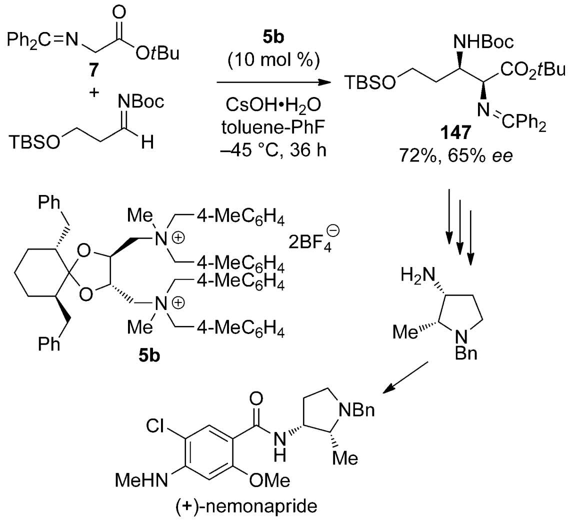


Scheme 88. Asymmetric conjugate amination.

4. Mannich Reaction

4.1. C–C Bond Formation

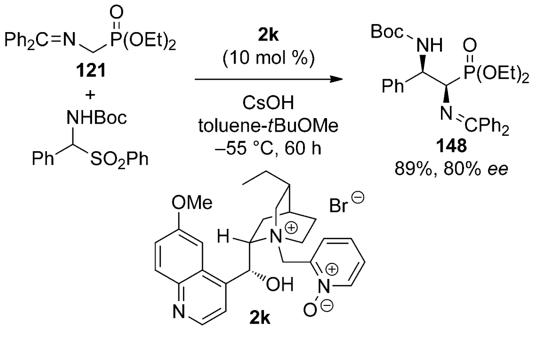
Shibasaki and co-workers reported the asymmetric Mannich reaction of glycine benzophenone imine *tert*-butyl ester **7** with *N*-*tert*-butoxycarbonyl (*N*-Boc) imines catalyzed by tartrate-derived bisammonium salt **5b**. This method could be applied to the enantioselective synthesis of key intermediate **147** for the synthesis of (+)-nemonapride (Scheme 89).[86b]



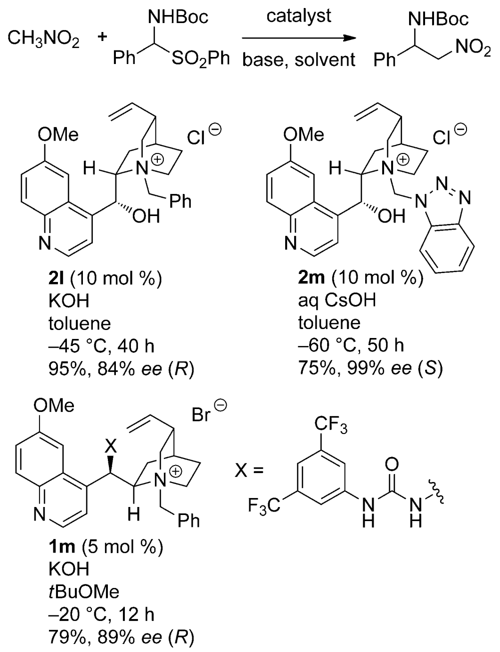
Scheme 89. Asymmetric Mannich reaction of glycine benzophenone imine *tert*-butyl ester.

An asymmetric Mannich reaction of the α-aminophosphonate derivative **121** with *N*-Boc-imines, generated in situ from α-amido sulfones, was reported by Bernardi and co-workers. The reaction was promoted by catalyst **2k** to afford the α,β-diaminophosphonic acid derivatives, such as **148**, with good enantioselectivities (Scheme 90).[114]

The research groups of Bernardi[115] and Palomo[116] independently reported a phase-transfer-catalyzed aza-Henry reaction. α-Amido sulfones were used to generate reactive *N*-carbamoylimines in situ, and aza-Henry reactions of not only aromatic imines but also aliphatic imines were successful (Scheme 91). The unprotected hydroxy group on *N*-benzylquininium chloride **2l** was found to be crucial to obtain high enantioselectivities. Other types of cinchona alkaloid derived phase-transfer catalysts such as **2m**[117] and **1m**[118] were subsequently applied to the reaction to give products with high enantioselectivity (Scheme 91).

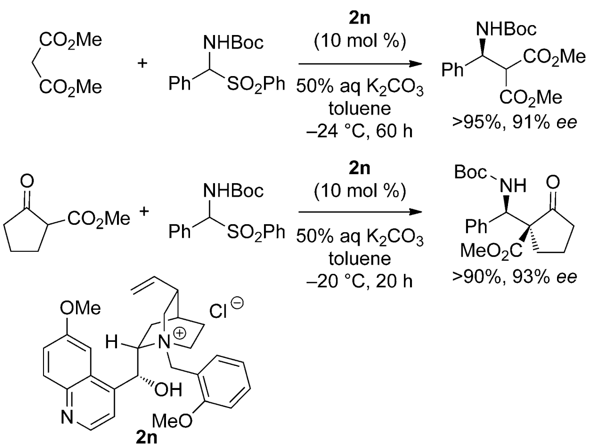


Scheme 90. Asymmetric Mannich reaction of an α-aminophosphonate.



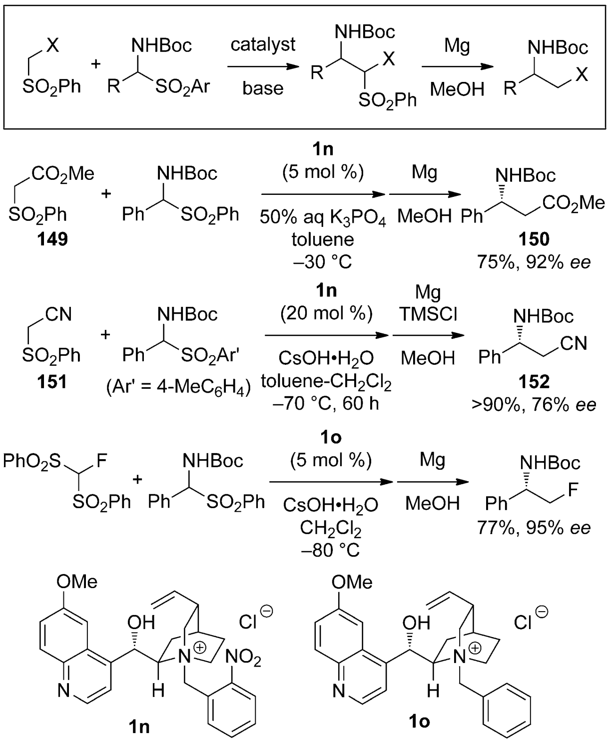
Scheme 91. Asymmetric aza-Henry reaction.

Bernardi, Ricci, and co-workers reported highly enantioselective Mannich reactions of malonates and β-ketoesters with in situ generated *N*-Boc-imines catalyzed by **2n** (Scheme 92).[119]



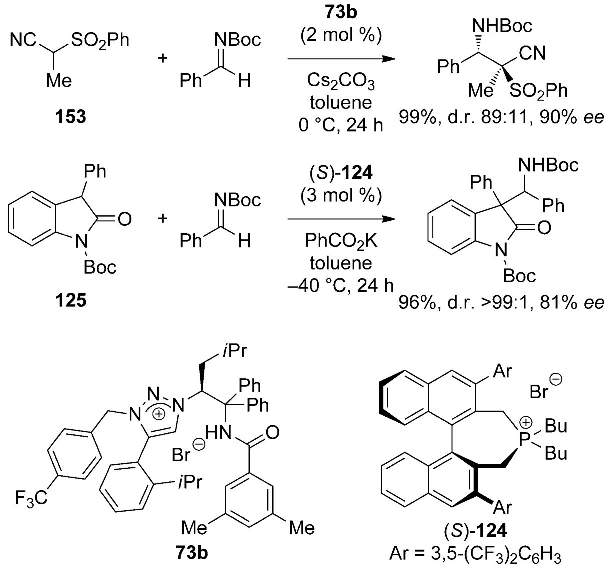
Scheme 92. Asymmetric Mannich reactions with malonate and β-ketoesters.

As a consequence of their strong electron-withdrawing nature, sulfonyl groups are able to stabilize a carbanion at the α position, and the α-substituted sulfones have been used for the generation of various nucleophilic species. Furthermore, the sulfonyl group of the products resulting from nucleophilic additions with the α-substituted sulfone can be easily



Scheme 93. Asymmetric Mannich reactions with α-substituted sulfones.

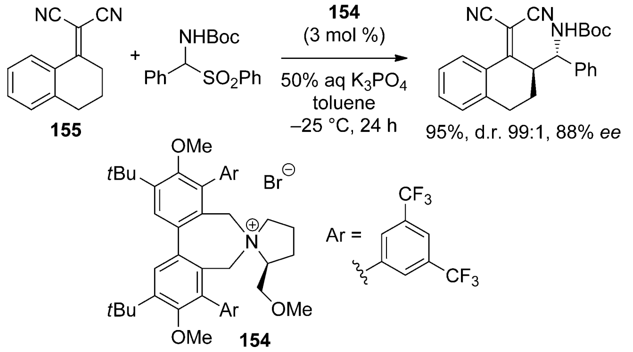
removed. Bernardi, Ricci, and co-workers used this strategy to develop an asymmetric Mannich reaction of sulfonylacetate **149** to obtain β-aminoesters (Scheme 93).[120] For example, the reaction of sulfonylacetate **149** and the in situ generated *N*-Boc-imine of benzaldehyde in the presence of catalyst **1n** under phase-transfer conditions gave the Mannich product. Subsequent treatment of the crude product with magnesium powder in methanol gave the β-aminoester **150** with high enantioselectivity. Palomo and co-workers used the sulfonyl acetonitrile **151** as a synthetic equivalent of acetonitrile to obtain product **152** (Scheme 93).[121] Shibata, Toru, and co-workers used the same strategy for a highly enantioselective monofluoromethylation by using 1-fluorobis(phenylsulfonyl)methane with catalyst **1o** (Scheme 93).[122]



Scheme 94. Asymmetric Mannich reactions with an α-substituted cyanosulfone and a 3-substituted oxindole.

Highly enantioselective Mannich reactions of α-substituted cyanosulfones such as **153** catalyzed by **73b** (Scheme 94),[123] and 3-substituted oxindoles such as **125** catalyzed by (*S*)-**124** were also reported (Scheme 94).[93]

Niess and Jørgensen reported an asymmetric vinylogous Mannich reaction of dicyanoalkylidenes with in situ generated *N*-Boc-imines, such as **155**, catalyzed by **154** under phase-transfer conditions (Scheme 95).[124]

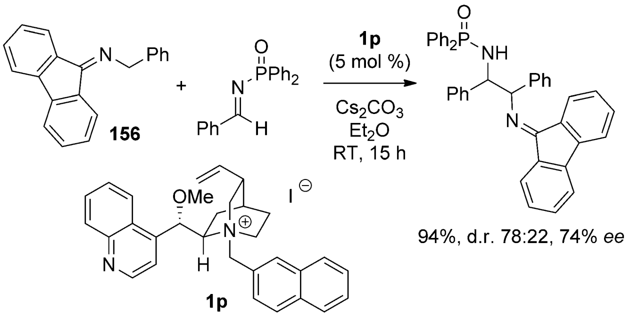


Scheme 95. Asymmetric vinylogous Mannich reaction.

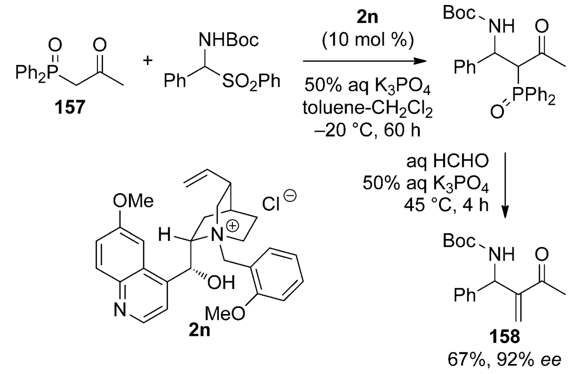
Kobayashi and co-workers reported the asymmetric Mannich reaction of aminoalkane derivative with *N*-diphenylphosphinylimine. 9-Fluorenylindene was selected as a protecting and activating group for the aminoalkane, and the asymmetric reaction of **156** with catalyst **1p** gave the product with moderate stereoselectivity (Scheme 96).[125]

Optically active β-amino-α-methylene derivatives (aza-Morita–Baylis–Hillman adducts), such as **158**, were prepared by using a one-pot protocol involving the enantioselective Mannich reaction of **157** catalyzed by **2n**, followed by a Horner olefination (Scheme 97).[126]

Jørgensen and co-workers reported an asymmetric monofluorovinylation through an enantioselective Mannich reaction of α-fluoro-β-keto-benzothiazolesulfone, such as **159**, with in situ generated *N*-benzyloxycarbonylimine (*N*-Cbz-



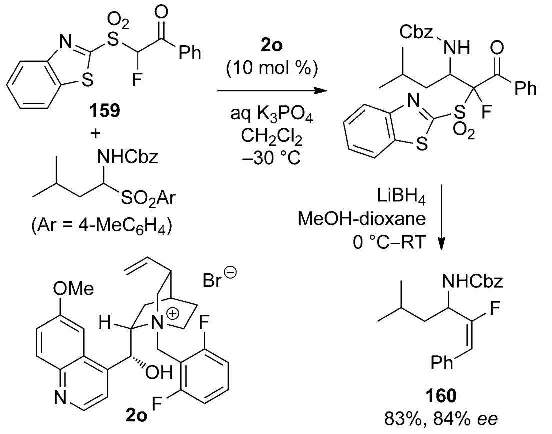
Scheme 96. Asymmetric Mannich reaction of an aminoalkane.



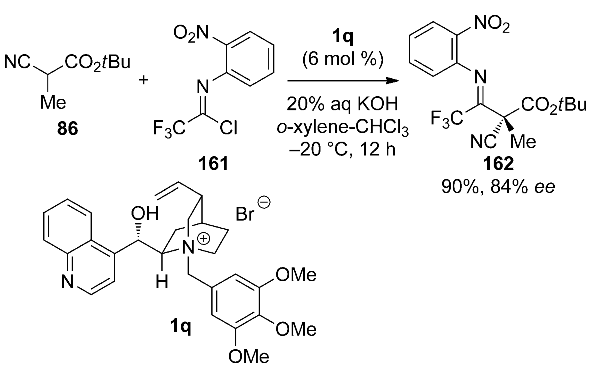
Scheme 97. Asymmetric synthesis of a β-amino-α-methylene derivative.

imine) in the presence of catalyst **2o**. Reduction of the Mannich product with $LiBH_4$ gave (*E*)-**160** with good enantioselectivity (Scheme 98).[127]

Jørgensen and co-workers also reported the enantioselective substitution of α-alkyl-α-cyanoacetates by imidoyl chloride **161**. For example, the reaction with α-methyl α-cyanoacetate **86** and imidoyl chloride **161** in the presence of catalyst **1q** under phase-transfer conditions afforded optically active ketimine **162** with good enantioselectivity (Scheme 99).[128]



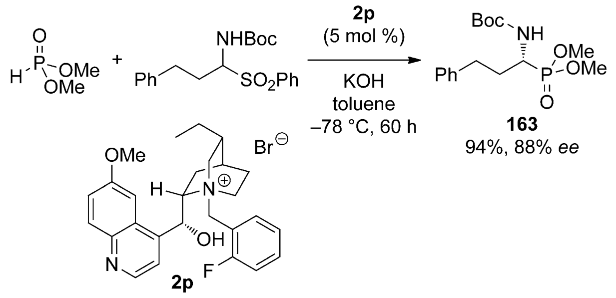
Scheme 98. Asymmetric monofluorovinylation.



Scheme 99. Enantioselective substitution of an α-alkyl-α-cyanoacetate by an imidoyl chloride.

4.2. C–P Bond Formation

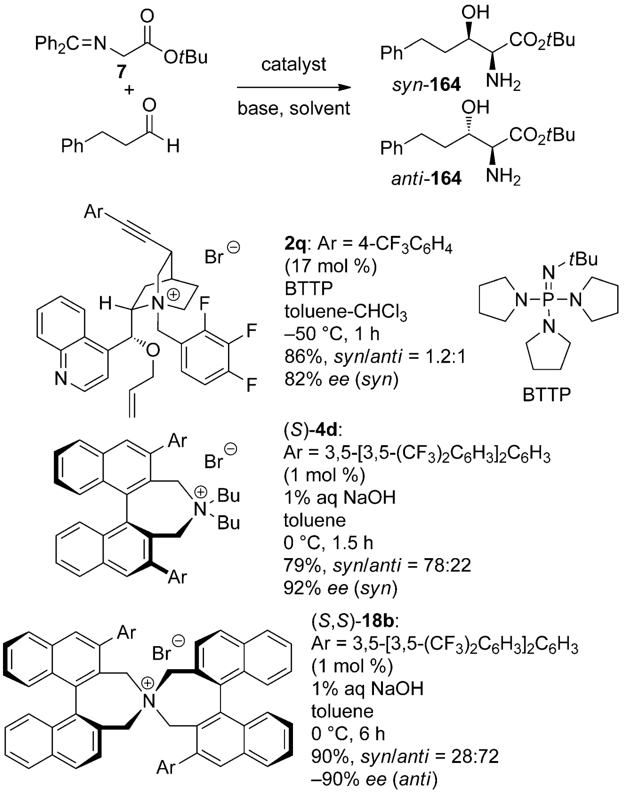
Bernardi, Ricci, and co-workers reported an asymmetric hydrophosphonylation of in situ generated *N*-Boc-imines catalyzed by **2p** for the synthesis of α-aminophosphonate derivatives such as **163** (Scheme 100).[129]



Scheme 100. Asymmetric hydrophosphonylation of an imine.

5. Aldol Reaction

Phase-transfer-catalyzed enantioselective direct aldol reactions of glycine donors with aldehyde acceptors provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids, which are extremely important chiral units, especially from a pharmaceutical viewpoint.

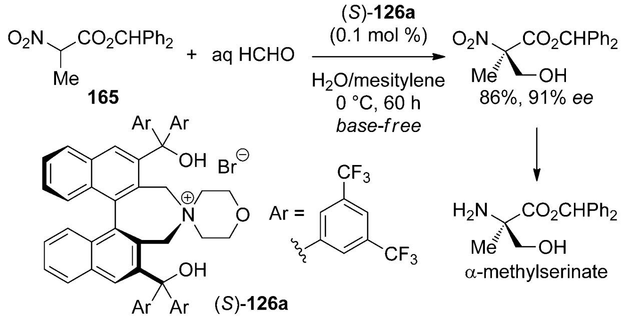


Scheme 101. Asymmetric aldol reaction of glycine benzophenone imine *tert*-butyl ester.

Castle and co-workers prepared novel cinchona alkaloid derived quaternary ammonium salt **2q**, and investigated its efficacy for the preparation of β-hydroxy-α-amino acids from an asymmetric aldol reaction of glycine derivative **7**. The aldol reaction was preformed in the presence of BTTP as an organic base under homogeneous conditions to give the *syn*-aldol product **164** with modest diastereoselectivity and good enantioselectivity (Scheme 101).[130]

We examined the effect of simplified catalyst (*S*)-**4d** on the asymmetric aldol reaction of **7**. The reaction gave the aldol product **164** with *syn* selectivity and high enantioselectivity (Scheme 101).[19b] This result is complementary to the *anti*-selective asymmetric aldol reaction with spiro-type (first generation-type) catalyst (*S,S*)-**3c**, as reported previously.[131] The symmetrical catalyst (*S,S*)-**18b** was also applied to the direct aldol reaction of **7**, and gave the product **164** with *anti* selectivity and high enantioselectivity (Scheme 101).[16]

We reported the hitherto difficult, highly enantioselective aldol reaction of α-substituted nitroacetates, such as **165**, with aqueous formaldehyde for the synthesis of α-alkyl serine derivatives under base-free neutral phase-transfer conditions with low catalyst loading (0.1 mol%) of (*S*)-**126a** (Scheme 102).[132]



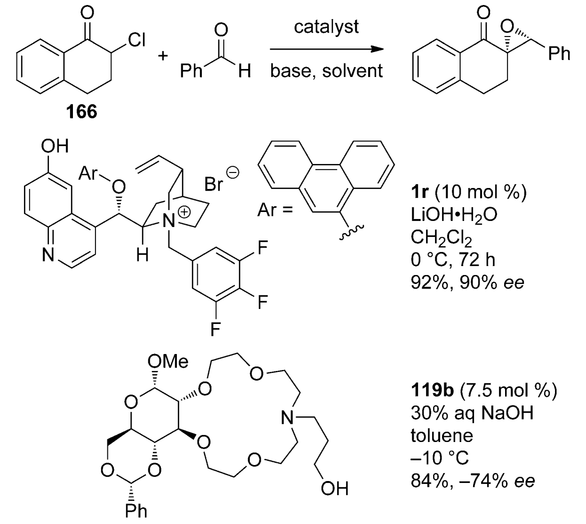
Scheme 102. Asymmetric aldol reaction of an α-substituted nitroacetate with aqueous formaldehyde under base-free neutral conditions.

6. Darzens Reaction

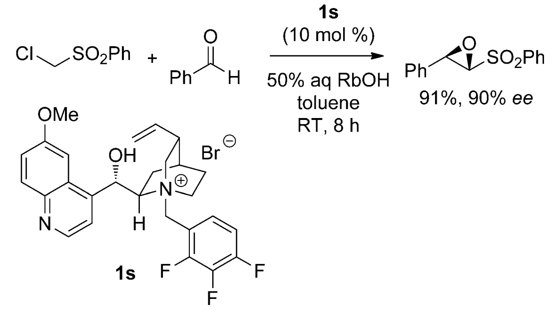
The Darzens reaction is one of the most powerful methods for synthesizing α,β-epoxycarbonyl and related compounds.

Deng and co-workers reported a highly enantioselective Darzens reaction of α-chloro ketones, such as **166**, and aldehydes catalyzed by **1r** (Scheme 103).[133] The phenanthracenyl group in the 9-position and hydroxy group in the 6′-position of catalyst **1r** were important to obtain high enantioselectivity. Bakó et al. also reported an asymmetric Darzens reaction with chiral azacrown ether **119b**, with the product being obtained with moderate enantioselectivity (Scheme 103).[134]

Jew, Jeong, and co-workers reported a highly enantioselective Darzens reaction of chloromethyl phenyl sulfone and aldehydes in the presence of catalyst **1s** (Scheme 104).[135]



Scheme 103. Asymmetric Darzens reaction of an α-chloro ketone and an aldehyde.



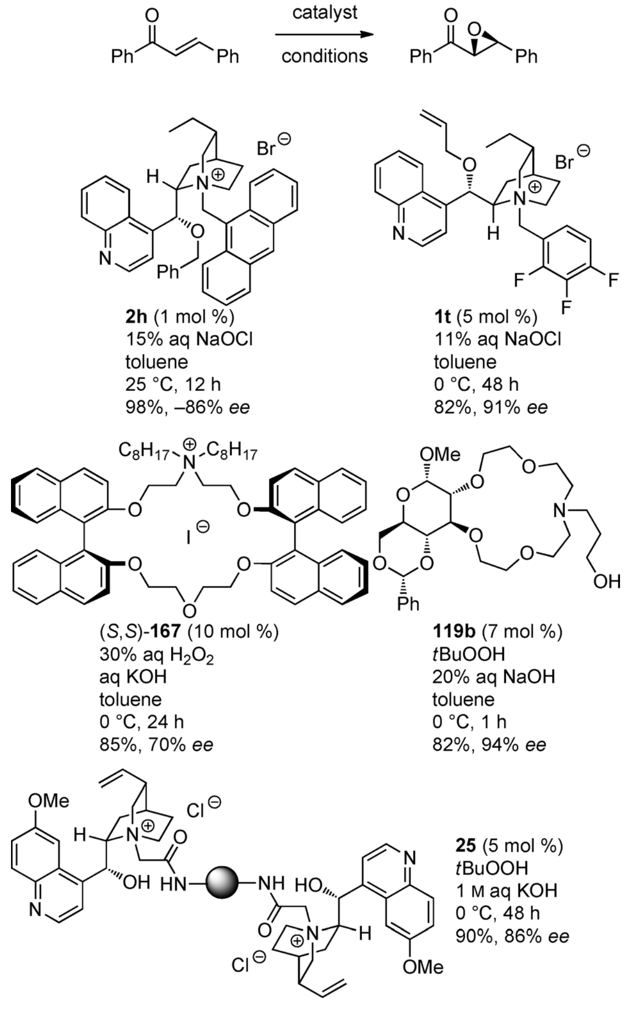
Scheme 104. Asymmetric Darzens reaction of chloromethyl phenyl sulfone with an aldehyde.

7. Cyclization

7.1. Epoxidation

The catalytic asymmetric epoxidation of electron-deficient olefins, particularly α,β-unsaturated ketones, has been the subject of numerous investigations, and a number of useful methods have been developed. Among these, the method involving chiral phase-transfer catalysis occupies a unique place because of its practical advantages, and it allows the highly enantioselective epoxidation of *trans*-α,β-unsaturated ketones, particularly of chalcone.

Lygo et al. reported the asymmetric epoxidation of α,β-unsaturated ketones with aqueous NaOCl in the presence of catalyst **2h** under mild conditions at room temperature (Scheme 105).[136] A highly enantioselective epoxidation of chalcones catalyzed by **1t** was reported by Park, Jeong, and co-workers.[137] Hori et al. designed the phase-transfer catalyst (*S,S*)-**167** containing a quaternary ammonium salt moiety and a crown ether moiety.[138] The ability of the catalyst was demonstrated in the asymmetric epoxidation of α,β-unsaturated ketones, with the epoxides being obtained with moderate enantioselectivity. Bakó and co-workers reported the



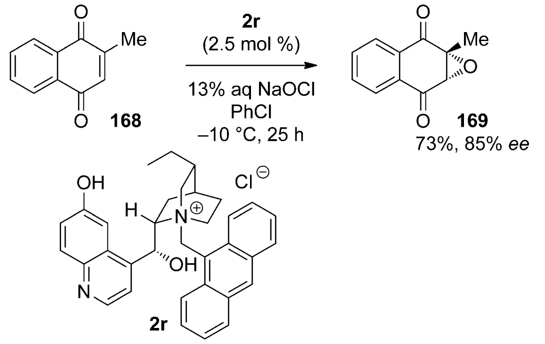
Scheme 105. Asymmetric epoxidation of chalcone.

asymmetric epoxidation of chalcones catalyzed by chiral azacrown ether **119b**.[139] Wang et al. applied the polymer-supported catalyst **25** to the asymmetric epoxidation of chalcones.[140]

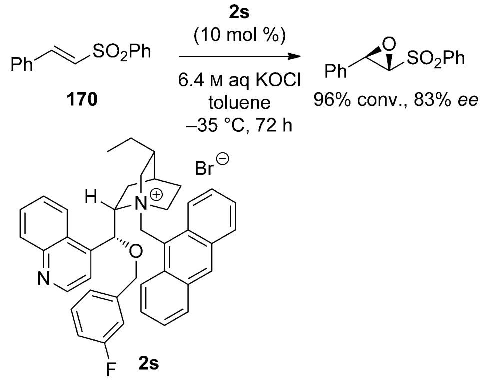
In contrast to *trans*-enone substrates, enantiocontrol in the epoxidation of *cis*-enones is still a difficult task, and successful examples are limited to the epoxidation of naphthoquinones. Berkessel et al. reported the asymmetric epoxidation of naphthoquinone **168** catalyzed by **2r**. The reaction gave the epoxidation product **169** containing a quaternary carbon center with good enantioselectivity (Scheme 106).[141]

A research group at Pfizer reported the scalemic asymmetric epoxidation of α,β-unsaturated sulfones, such as **170**. Among the screening of several parameters, they examined the effect of the ether moiety of the dihydrocinchonidinium salt, which led to the use of (3-fluorophenyl)methyl ether **2s** as the optimal catalyst (Scheme 107).[142]

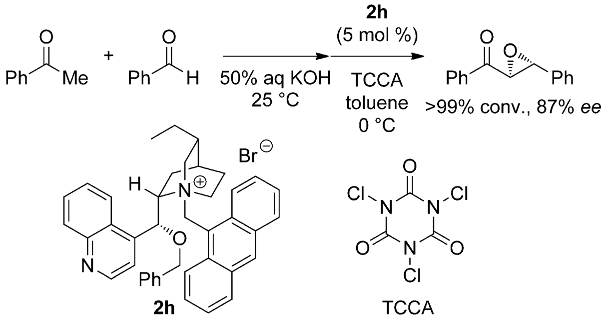
A one-pot Claisen–Schmidt condensation/asymmetric epoxidation procedure was developed by Wang and Liang (Scheme 108).[143] The method allows α,β-epoxy ketones to be obtained with high enantioselectivity simply from an aldehyde and a ketone under mild conditions.



Scheme 106. Asymmetric epoxidation of a naphthoquinone.



Scheme 107. Asymmetric epoxidation of an α,β-unsaturated sulfone.

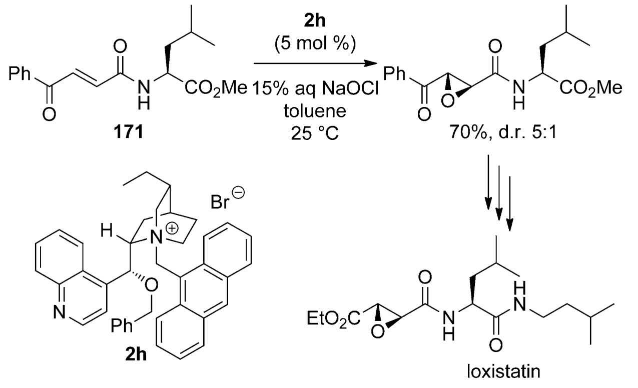


Scheme 108. One-pot Claisen–Schmidt condensation/asymmetric epoxidation procedure.

Lygo et al. utilized a chiral phase-transfer-catalyzed epoxidation in the stereoselective synthesis of loxistatin. In the key step of the synthesis, a stereoselective epoxidation of the enone **171** bearing a leucine ester moiety was employed. The diastereomeric ratio was highly dependent on the phase-transfer catalyst, and they succeeded in achieving moderate diastereoselectivity by using catalyst **2h** (Scheme 109).[144]

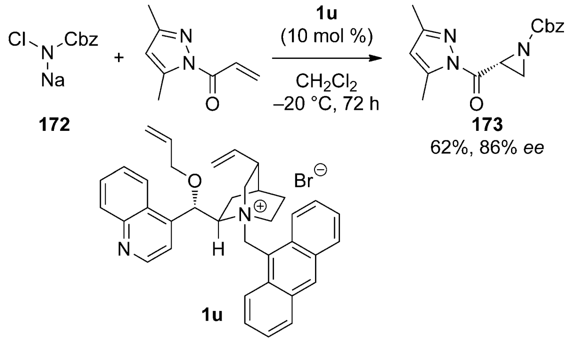
7.2. Aziridination

Chiral aziridines have been used as chiral auxiliaries, chiral ligands, and chiral building blocks for the preparation of biologically active compounds. Minakata et al. reported



Scheme 109. Stereoselective synthesis of loxistatin.

a method for the asymmetric aziridination of electron-deficient olefins with *N*-chloro-*N*-sodium carbamate **172**. The reaction was promoted by cinchonine-derived catalyst **1u** to afford **173** with good enantioselectivity (Scheme 110).[145]



Scheme 110. Asymmetric aziridination of an electron-deficient olefin.

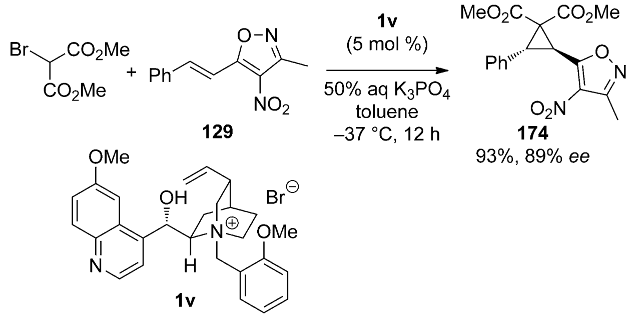
7.3. Cyclopropanation

Adamo and co-workers reported an asymmetric cyclopropanation of 4-nitro-5-styrylisoxazoles, such as **129**, with 2-bromomalonate in the presence of catalyst **1v**; the reaction gave the highly substituted cyclopropane **174** with high enantioselectivity (Scheme 111).[146]

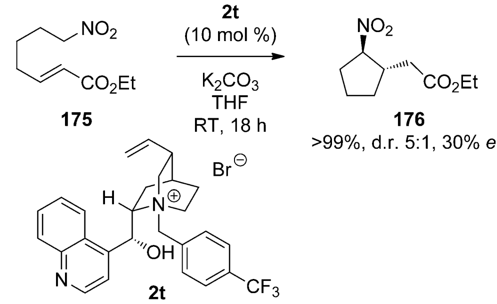
7.4. Other Cyclizations

Cobb and co-workers reported the intramolecular enantioselective conjugate addition of **175** to obtain five-membered γ-nitro ester **176**. The reaction was promoted efficiently by catalyst **2t** to afford the product **176** with moderate enantioselectivity (Scheme 112).[147]

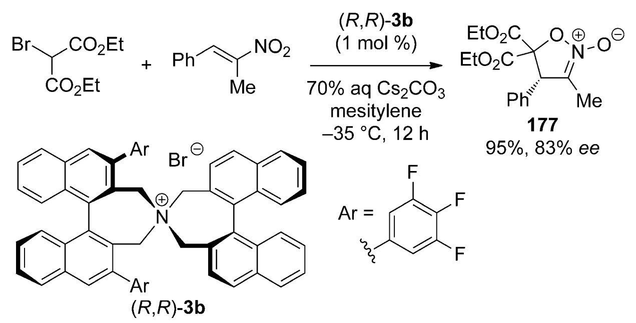
The catalytic asymmetric synthesis of isooxazoline-*N*-oxides, such as **177**, has been accomplished by asymmetric phase-transfer conjugate addition of bromomalonate to nitroolefins and subsequent ring-closing O-alkylation. Of the binaphthyl-modified quaternary ammonium salts tested, catalyst **3b** afforded the highest enantioselectivity (Scheme 113).[148]



Scheme 111. Asymmetric cyclopropanation of a 4-nitro-5-styrylisoxazole.



Scheme 112. Intramolecular enantioselective conjugate addition.

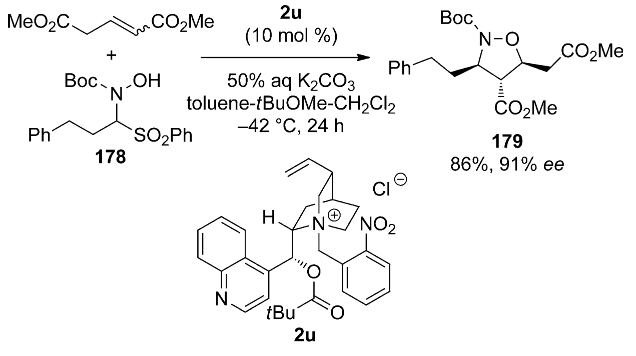


Scheme 113. Asymmetric synthesis of an isooxazoline-*N*-oxide.

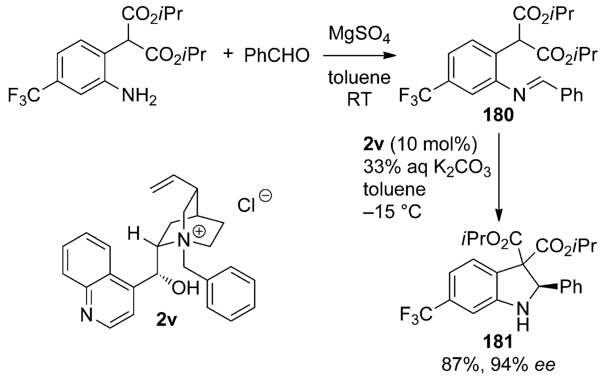
Fini, Bernardi, and co-workers developed an asymmetric [3+2] cycloaddition of nitrone, generated in situ from **178**, and glutaconate. The reaction was promoted by catalyst **2u** to give isoxazolidine **179** with high enantioselectivity (Scheme 114).[149]

Smith and co-workers have described a catalytic asymmetric 6π electrocyclization under phase-transfer conditions. Treatment of an in situ generated *N*-aryl imine **180** with K_2CO_3 in the presence of catalyst **2v** afforded the cyclized product **181** in good yield and high enantioselectivity (Scheme 115).[150]

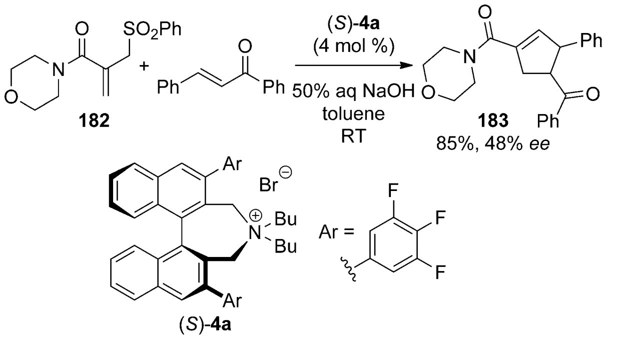
Brière and co-workers reported the asymmetric [3+2] cycloaddition of allylic sulfone **182** and chalcone under phase-transfer conditions. The reaction was promoted by the simplified Maruoka catalyst (*S*)-**4a** to give product **183** with moderate enantioselectivity (Scheme 116).[151]



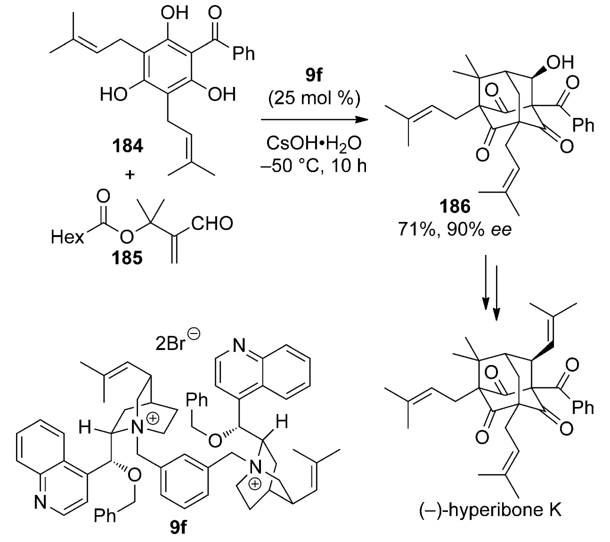
Scheme 114. Asymmetric [3+2] cycloaddition of a nitrone.



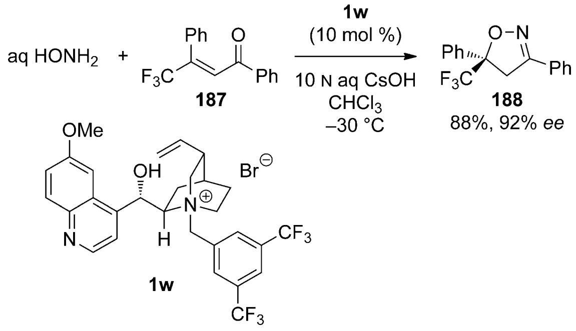
Scheme 115. Asymmetric 6π electrocyclization.



Scheme 116. Asymmetric [3+2] cycloaddition of an allylic sulfone.



Scheme 117. Asymmetric total synthesis of hyperibone K.



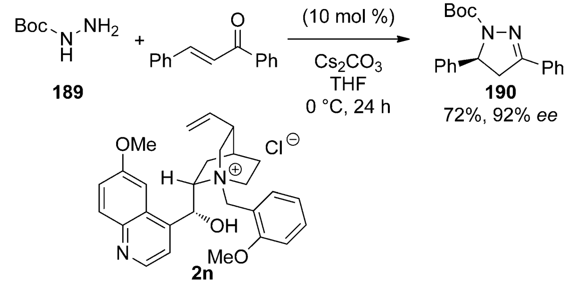
Scheme 118. Asymmetric synthesis of a trifluoromethyl-substituted 2-isoxazoline.

Porco Jr. and co-workers achieved the asymmetric total synthesis of hyperibone K by an elegant enantioselective alkylative dearomatization/annulation of compound **184** with α-acetoxyenal **185**. The reaction was promoted by dimeric catalyst **9f** to afford the adamantane **186** with high enantioselectivity. The product **186** was transformed to (−)-hyperibone K in two additional steps (Scheme 117).[152]

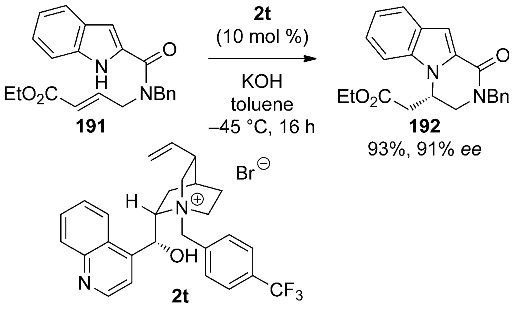
Shibata and co-workers reported the asymmetric synthesis of trifluoromethyl-substituted 2-isoxazoline **188** by an enantioselective conjugate addition of hydroxylamine to enone **187** in the presence of catalyst **1w** and subsequent intramolecular formation of the imine (Scheme 118).[153]

Brière and co-workers developed a method for the straightforward enantioselective synthesis of 3,5-diaryl pyrazolines, such as **190**, by phase-transfer-catalyzed conjugate addition of *N*-Boc-hydrazine **189** to chalcones in the presence of catalyst **2n** and subsequent intramolecular formation of the imine (Scheme 119).[154]

A highly enantioselective approach to indol-derived tricyclic compounds, such as **192**, was developed by Bandini et al. through a phase-transfer-catalyzed intramolecular aza-conjugate addition of **191** in the presence of catalyst **2t** (Scheme 120).[155]

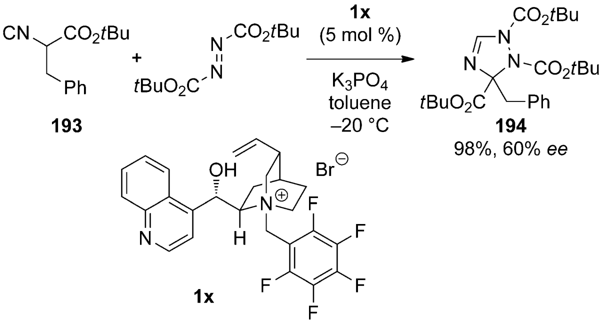


Scheme 119. Asymmetric synthesis of a 3,5-diaryl pyrazoline.



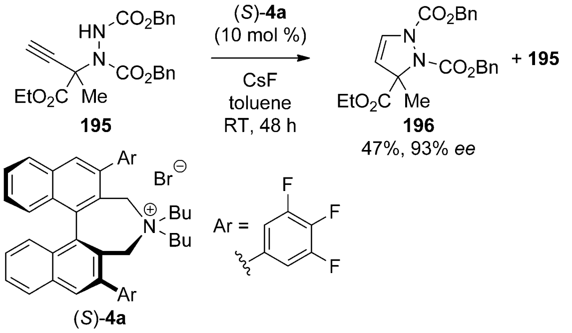
Scheme 120. Asymmetric intramolecular aza-conjugate addition.

Jørgensen and co-workers reported an asymmetric synthesis of 1,2,4-triazolines, such as **194**, from isocyano esters and azodicarboxylate. The reaction of isocyano ester **193** and di-*tert*-butylazodicarboxylate in the presence of catalyst **1x** under phase-transfer conditions gave the 1,2,4-triazoline **194** in high yield and moderate enantioselectivity (Scheme 121).[156]



Scheme 121. Asymmetric synthesis of a 1,2,4-triazoline.

Maity and Lepore reported the kinetic resolution of racemic β-alkynyl hydrazines, such as **195**, by phase-transfer-catalyzed cyclization. For example, racemic β-alkynyl hydrazine **195** was treated with CsF in the presence of simplified Maruoka catalyst (*S*)-**4a** to obtain azaproline **196** with high enantioselectivity (Scheme 122).[157] Half of the substrate **195** was recovered in a highly enantioenriched form.

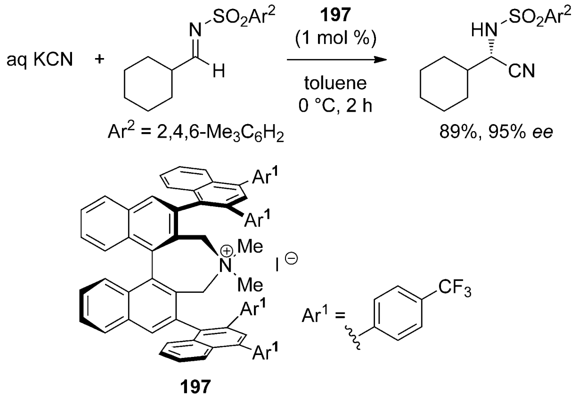


Scheme 122. Kinetic resolution of a racemic β-alkynyl hydrazine.

8. Cyanation

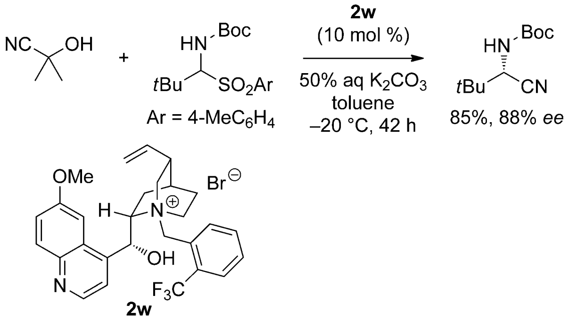
8.1. Strecker Reaction

The catalytic asymmetric cyanation of imines, the Strecker reaction, is one of the most direct and useful methods for the asymmetric synthesis of α-amino acids and their derivatives. Numerous recent efforts in this field have resulted in the establishment of highly efficient and general protocols, although the use of either alkyl metal cyanide or anhydrous hydrogen cyanide generally at low temperature is inevitable. In this regard, we report on the first example of a phase-transfer-catalyzed, highly enantioselective Strecker reaction of aldimines by using aqueous KCN; the chiral quaternary ammonium salts **197** bearing a tetranaphthyl backbone were found to be remarkably efficient catalysts (Scheme 123).[158]



Scheme 123. Asymmetric Strecker reaction of an aldimine with aqueous KCN.

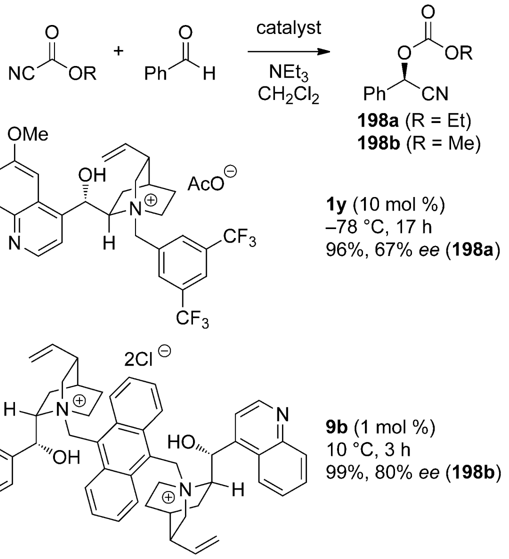
Herrera, Rich et al. utilized acetone cyanohydrin as a cyanide source for the phase-transfer-catalyzed Strecker reaction in the presence of catalyst **2w**. The intermediacy of the conjugate base of acetone cyanohydrin was suggested, since the use of potassium cyanide as the cyanide source led to a lower enantioselectivity (Scheme 124).[159]



Scheme 124. Asymmetric Strecker reaction with acetone cyanohydrin.

8.2. Cyanation of Aldehyde

The enantioselective cyanoformylation of aldehydes was reported by Feng and co-workers. The reaction of ethyl cyanoformate and aldehydes with triethylamine in the presence of of quinidine-derived catalyst **1y** led to cyanoformylation product **198a** with moderate enantioselectivity (Scheme 125).[160] Same type of reaction but using methyl cyanoformate and dimeric catalyst **9b** was also reported by Chinchilla, Nájera et al. (Scheme 125).[161]

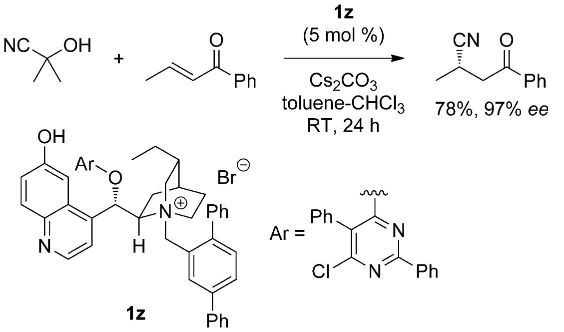


Scheme 125. Asymmetric cyanoformylation of an aldehyde.

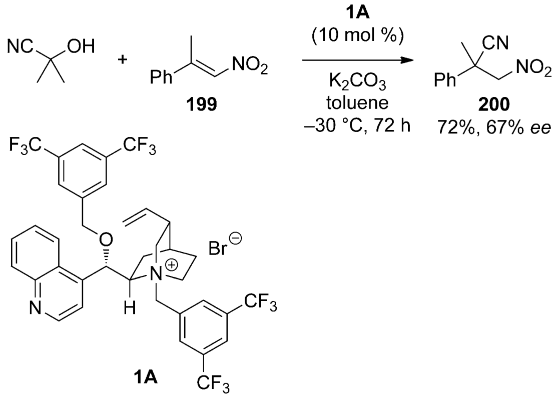
8.3. Conjugate Cyanation

Deng and co-workers developed a highly enantioselective conjugate cyanation of α,β-unsaturated ketones catalyzed by **1z**, which possesses a 6-chloro-2,5-diphenylpyrimidin-4-yl moiety (Scheme 126).[162] The hydroxy group at the 6′-posision of catalyst **1z** was important to obtain high enantioselectivity.

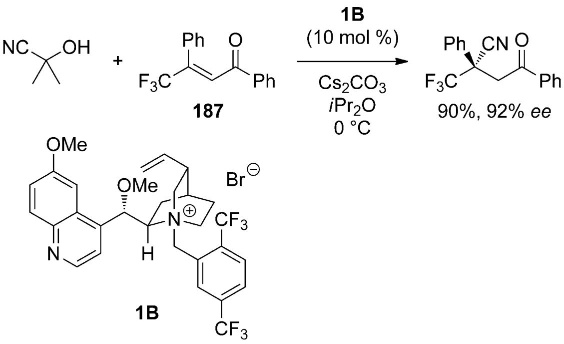
Fochi, Ricci, and co-workers reported the asymmetric conjugate cyanation of β,β-disubstituted nitroolefins, such as **199**. The reaction of acetone cyanohydrin and nitroolefin **199** in the presence of catalyst **1A** afforded the product **200** with moderate enantioselectivity (Scheme 127).[163]



Scheme 126. Asymmetric conjugate cyanation of an α,β-unsaturated ketone.



Scheme 127. Asymmetric conjugate cyanation of a β,β-disubstituted nitroolefin.



Scheme 128. Asymmetric conjugate cyanation of a β-aryl-β-trifluoromethyl-substituted enone.

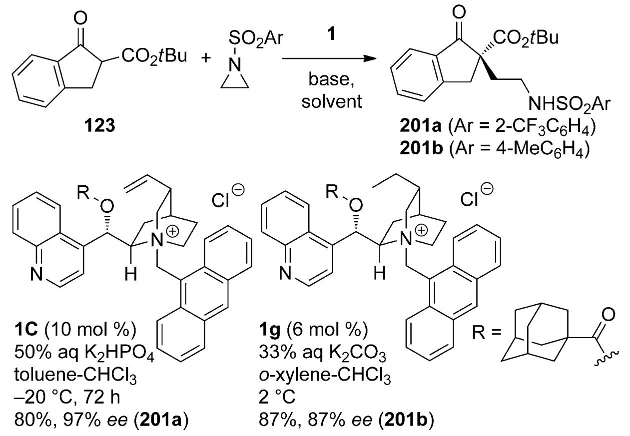
The highly enantioselective conjugate cyanation of β-aryl-β-trifluoromethyl-substituted enones, such as **187**, in the presence of catalyst **1B** was reported by Shibata and co-workers (Scheme 128).[164]

9. Ring-Opening Reaction

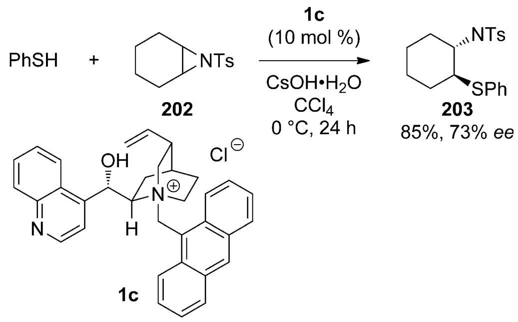
The research groups of Dixon[165] and Jørgensen[166] independently reported the asymmetric ring-opening reaction of aziridines with β-ketoesters (Scheme 129). The reaction of β-ketoester **123** and *N*-sulfonylaziridine catalyzed by **1C** or **1g** under phase-transfer conditions gave the product **201** with high enantioselectivity.

Hou and co-workers reported the asymmetric desymmetrization of *meso*-aziridines with thiols under phase-transfer conditions. The reaction of thiophenol and *N*-tosylaziridine **202** catalyzed by cinchonidine-derived ammonium salt **1f** afforded product **203** with moderate enantioselectivity (Scheme 130).[167]

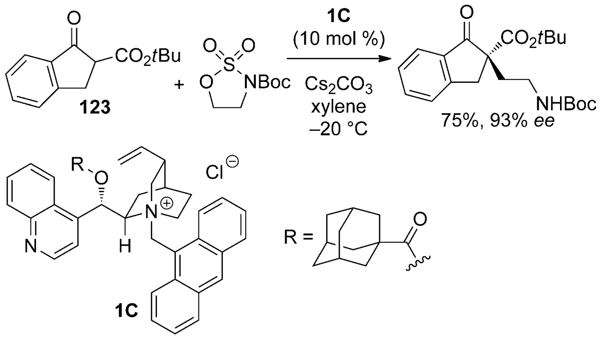
A subsequent study by Dixon and co-workers led to a highly enantioselective ring-opening reaction of cyclic sulfamidate with β-ketoesters, such as **123**, in the presence of catalyst **1C** (Scheme 131).[168]



Scheme 129. Asymmetric ring-opening reaction of an aziridine.



Scheme 130. Asymmetric desymmetrization of a *meso*-aziridine. Ts = toluene-4-sulfonyl.

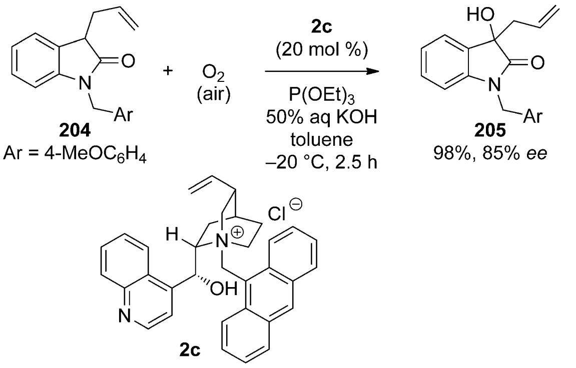


Scheme 131. Asymmetric ring-opening reaction of a cyclic sulfamidate.

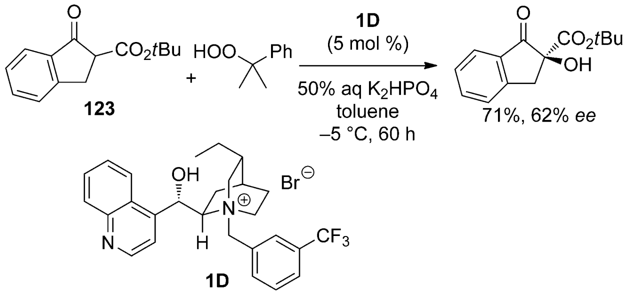
10. Hydroxylation

Itoh and co-workers reported the asymmetric hydroxylation of 3-substituted oxindoles, such as **204**, with molecular oxygen used as an oxidant. The reaction of oxindole **204** was promoted by catalyst **2c** in air to give hydroxylation product **205** with good enantioselectivity (Scheme 132).[169]

Meng and co-workers reported the asymmetric hydroxylation of β-ketoesters, such as **123**, with cumene hydroperoxide in the presence of catalyst **1D** under phase-transfer conditions (Scheme 133).[170]



Scheme 132. Asymmetric hydroxylation of a 3-substituted oxindole.

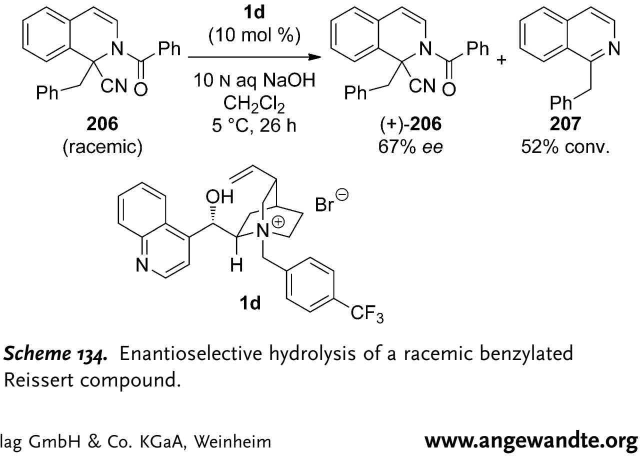


Scheme 133. Asymmetric hydroxylation of a β-ketoester.

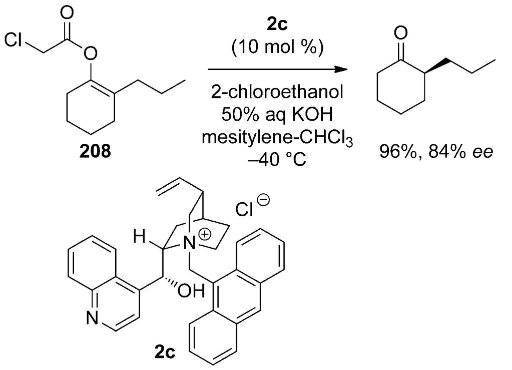
11. Hydrolysis

Frisch and Jørgensen reported the enantioselective hydrolysis of benzylated Reissert compound **206** under phase-transfer conditions. Treatment of racemic compound **206** with aqueous NaOH solution in the presence of cinchonine-derived ammonium salt **1d** led to enantioselective hydrolysis occurring at the benzoyl group on the nitrogen atom of compound **206**. Half of the starting compound **206** was recovered in an enantioenriched form together with 1-benzylisoquinoline (**207**), formed as a result of hydrolysis (Scheme 134).[171]

Tokunaga and co-workers reported the asymmetric hydrolysis of enol esters, such as **208**, in the presence of catalyst **2c** under the phase-transfer conditions with aqueous KOH. The mechanism of this reaction was discussed and the



Scheme 134. Enantioselective hydrolysis of a racemic benzylated Reissert compound.



Scheme 135. Asymmetric hydrolysis of an enol ester.

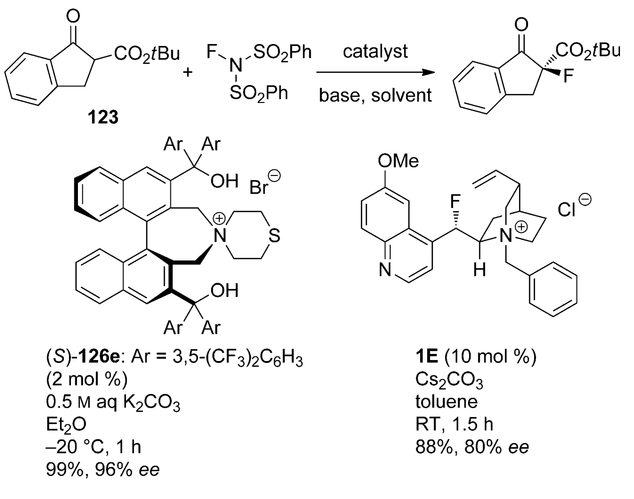
enantioselective step of this reaction was proposed to be protonation of the ammonium enolate (Scheme 135).[172]

12. Fluorination

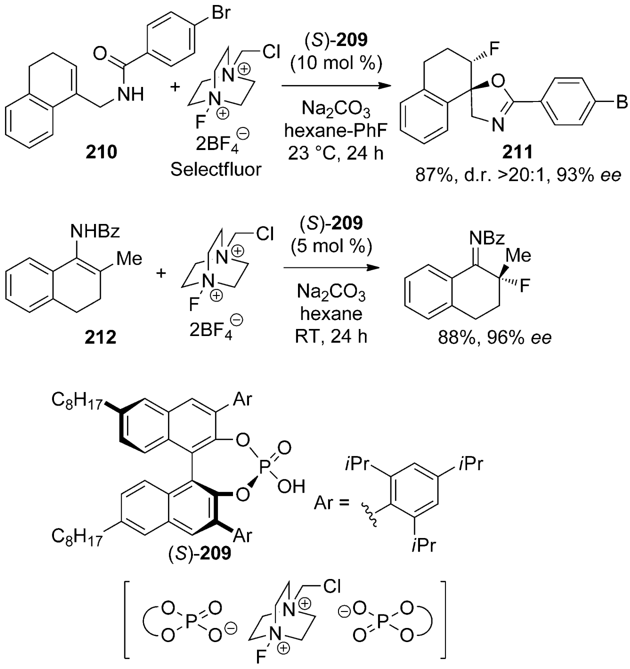
Organic molecules containing fluorine atoms have attracted much attention because they often show different properties from the parent compounds because of the unique properties of the carbon–fluorine bond. Replacement of a hydrogen atom in bioactive compounds with a fluorine atom is now a common strategy in the field of medicinal chemistry. For this reason, an efficient method for the direct enantioselective construction of fluorinated stereogenic carbon centers is extremely important.

We developed a highly enantioselective fluorination of β-keto esters, such as **123**, with *N*-fluorobenzenesulfonimide under mild phase-transfer conditions by employing the chiral bifunctional ammonium bromide **126e** as the key catalyst (Scheme 136).[173] The same reaction was also examined with 9-fluorinated quinidine-derived catalyst **1E** (Scheme 136).[174]

Toste and co-workers described the new concept of an anionic phase-transfer catalyst, whereby a chiral phosphate catalyst was used in the asymmetric fluorination of alkenes. They used selectfluor as a versatile cationic fluorinating agent, which would normally be insoluble in nonpolar organic solvents. They hypothesized that lipophilic, bulky chiral phosphate anions, such as the conjugate base of (*S*)-**209**, could exchange with the tetrafluoroborate anions associated with selectfluor to bring the reagent into solution. The resulting chiral ion pair could then mediate an asymmetric fluorination of an organic substrate in solution (Scheme 137). Based on this hypothesis, they examined the asymmetric fluorocyclization of **210** in the presence of catalyst (*S*)-**209** and sodium carbonate, and the target product **211** was obtained with high stereoselectivity (Scheme 137).[175] This reaction system was also applied to the highly enantioselective fluorination of enamides such as **212** (Scheme 137).[176]



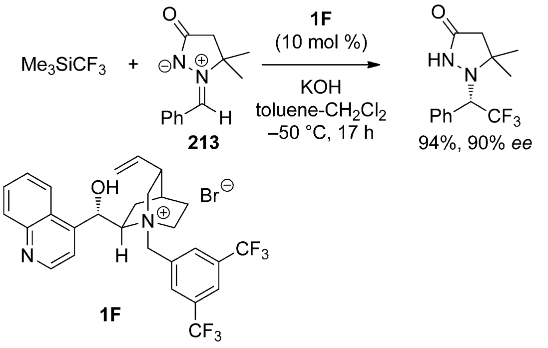
Scheme 136. Asymmetric fluorination of a β-keto ester.



Scheme 137. New concept of an anionic phase-transfer catalyst.

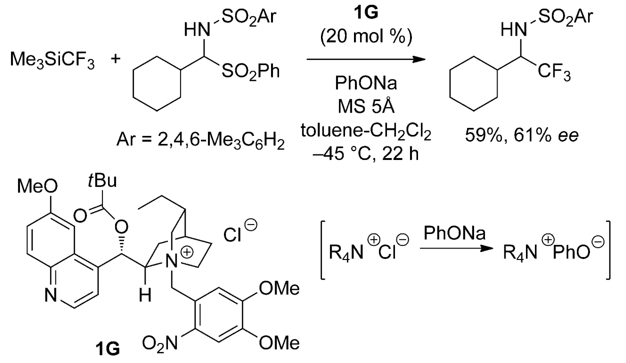
13. Trifluoromethylation

Shibata and co-workers reported the highly enantioselective trifluoromethylation of azomethine imines, such as **213**, with trimethyl(trifluoromethyl)silane in the presence of catalyst **1F** (Scheme 138).[177]



Scheme 138. Asymmetric trifluoromethylation of an azomethine imine.

Bernardi et al. reported the asymmetric trifluoromethylation of in situ generated imine in the presence of catalyst **1G** and sodium phenoxide. The ammonium phenoxide was generated as the active catalytic species by the reaction of ammonium chloride **1G** with sodium phenoxide (Scheme 139).[178]



Scheme 139. In situ generation of ammonium phenoxides.

14. Summary and Outlook

Recent progress in asymmetric phase-transfer reactions reported between 2006 and middle of 2012 have been summarized in this Review. The structure–activity/selectivity relationship of several chiral quaternary ammonium salts as catalysts was investigated systematically in the asymmetric alkylation of a glycine derivative. The systematic accumulation of such knowledge will allow an even more rational design of the catalyst for selective chemical synthesis in both a reliable and practical manner. A wide variety of highly enantioselective transformations catalyzed mainly by cinchona alkaloid or binaphthyl-derived quaternary ammonium salts were later introduced, and some of these reactions have been applied to the asymmetric synthesis of biologically active compounds, including natural products. Furthermore, pharmaceutical companies have demonstrated the practicability of asymmetric phase-transfer reactions in the large-scale preparation of drugs, and the practicability of asymmetric phase-transfer reactions has widely been recognized in both industry and academia. Further industrial applications of asymmetric phase-transfer reactions will appear in the next decades. Several new-types of catalysts have been developed and applied successfully to highly enantioselective transformations. Continuous efforts should be made toward the design and development of conceptually new catalysts, as well as understanding the relationship between the structure of the catalyst and its stereocontrolling ability. Another interesting development is the hitherto unknown base-free neutral phase-transfer reaction system for asymmetric conjugate addition and aldol reactions. The reactions are promoted efficiently by a chiral bifunctional ammonium bromide under neutral conditions in a water-rich biphasic solvent and produce important compounds. The new concept of anionic phase-transfer catalysis by using a chiral phosphate catalyst has been demonstrated in asymmetric fluorinations. The development of a conceptually new reaction system and reaction mode will open up further possibilities in asymmetric phase-transfer catalysis.

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