CHIRAL PHASE-TRANSFER CATALYSIS (CPTC) BY MODIFIED CINCHONA ALKALOIDS

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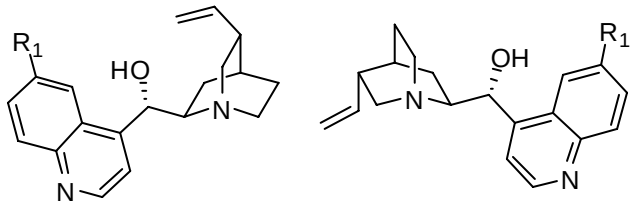
INTRODUCTION

Phase-transfer catalysis (PTC) involves the use of environmentally benign organocatalysts, mild reaction conditions, and simple experimental procedures that are insensitive to air/moisture and amenable to large-scale processes.[1] Furthermore, the use of inexpensive inorganic bases such as NaOH in place of expensive moisture-sensitive hydride, alkoxide and amide bases makes PTC an attractive option for both laboratory and industrial processes. Although PTC has been applied extensively in a

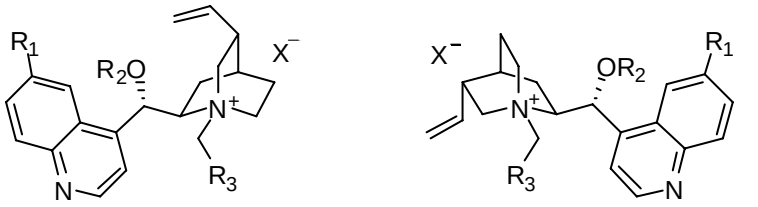


Cinchonidine: R_1 = H
Quinidine: R_1 = OMe

Cinchonine: R_1 = H
Quinine: R_1 = OMe

Figure 1. Cinchona Alkaloids

variety of organic transformations, only recently have significant advances in chiral phase-transfer catalysis (CPTC) been made. The cinchona alkaloids have served as the primary source of effective chiral phase-transfer catalysts (Figure 1). These inexpensive, commercially available alkaloids can be transformed to active quaternary ammonium salt catalysts in one or two steps (Figure 2).[2] Furthermore,



Cinchonidine-derived catalysts

Cinchonine-derived catalysts

R_1 = H, OMe
R_2 = H, Allyl, Benzyl
R_3 = Benzyl, Anthracenylmethyl
X^- = Counterion (usually Br^-)

Figure 2. Cinchona-derived chiral phase-transfer catalysts

the alkaloids are available as pseudoenantiomers that can achieve similar levels of asymmetric induction with opposite senses of enantioselectivity.[1] If basic conditions are employed in PTC, an interfacial

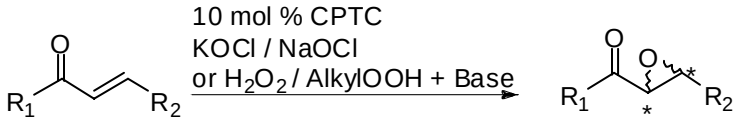
mechanism is implicated for sufficiently lipophilic quaternary ammonium catalysts.[3] The interfacial mechanism involves formation of a contact ion pair between the quaternary ammonium cation and the anionic organic nucleophile that is generated at the interface by an inorganic base. The quaternary ammonium cation transfers the anionic organic nucleophile into the organic phase, where it can react with the organic electrophile.[4] Described in this report are various C─C, C─N and C─O bond-forming CPTC methods that use modified cinchona alkaloid catalysts.

ASYMMETRIC REACTIONS OF MODIFIED CINCHONA PHASE-TRANSFER CATALYSTS

The Epoxidation of Electron-Deficient Olefins

Unlike the Sharpless epoxidation of allylic alcohols, no generally applicable method has been developed for asymmetric epoxidation of electron-deficient olefins such as α,β-unsaturated ketones. Instead, a wide variety of methodologies are available including CPTC methods (Scheme 1).[5] The use of cinchona-derived catalysts for the asymmetric epoxidation of chalcones and quinones was first reported by Wynberg in 1976 in excellent yields but modest enantioselectivities (<62.5:37.5 er).[6] In 1997, Lygo and coworkers achieved considerable enhancements in enantioselectivity (84.5:15.5─94:6 er) for the epoxidation of chalcones using NaOCl as the oxidant and an *O*-benzylated *N*-anthracenylmethyl cinchona-derived catalyst.[7] Inexplicably, the non-*O*-alkylated catalyst induced opposite senses of enantioselectivity depending on whether NaOCl or alkaline H_2O_2 was used as the oxidant.[7] In 1999, Corey used a similar *O*-benzylated *N*-anthracenylmethyl catalyst under solid-liquid PTC conditions employing KOCl as the oxidant to achieve excellent enantioselectivities (95.5:4.5─99.25:0.75 er) for the epoxidation of chalcone derivatives. Based on the observation that the epoxidation of β-alkylidene-α-tetralones results in a decrease in enantioselectivity, Corey proposed a transition-state model in which the phenyl attached to the carbonyl carbon is out of conjugation with the carbonyl group.[8] Modified

Scheme 1. Epoxidation of *trans*-enones



R_1= Ph, *t*-Bu
R_2 = Hexyl, Ph

85:15 - 98-2 er

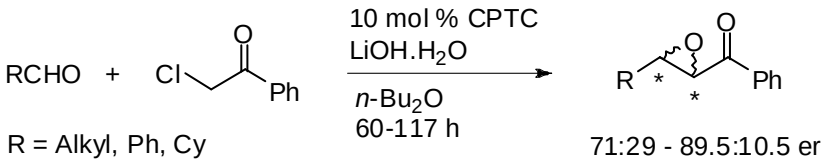
cinchona catalysts with a free hydroxyl group require H_2O_2 or an alkyl peroxide as the oxidant to achieve high enantioselectivity, whereas the *O*-alkylated catalysts require hypochlorite as the oxidant.[9] While hydrogen bonding between the catalyst's free hydroxyl and the oxidant may be involved in H_2O_2 or alkyl peroxide based systems (in contrast to the hypochlorite anion-based model proposed by Corey),

no clear contact ion pair model has been proposed. Lygo has successfully extended the hypochlorite-based system to achieve the enantioselective oxidization of allylic alcohols directly to epoxy ketones.[10] More recently, the presence of surfactants such as 1 mol % of Span-20 has been shown to considerably enhance enantioselectivity.[11] Adam and coworkers explored the epoxidation of isoflavones using alkyl peroxides as the oxidant. A hydrogen-bonding transition-state model involving the ether-oxygen of the isoflavone and the hydroxyl of the catalyst was proposed.[12] While modified cinchona alkaloid catalysts have been successfully employed in the asymmetric epoxidation of *trans*-enones, the epoxidation of *cis*-enones remains a major challenge.[13]

Darzens Reaction

The Darzens reaction is a powerful C─C bond-forming reaction that involves an aldol reaction between a ketone and an α-halo organic species bearing an electron-withdrawing group (Scheme 2). An intramolecular cyclization yields an epoxide with the generation of two stereogenic centers. Although the Darzens reaction has been known for over a hundred years, the development of enantioselective variants are a challenge.[14] Current protocols are limited to the stoichiometric use of chiral auxiliaries, or external ligands.[14] Metal-based catalytic methods are often ineffective due to the formation of stable

Scheme 2. Darzens reaction



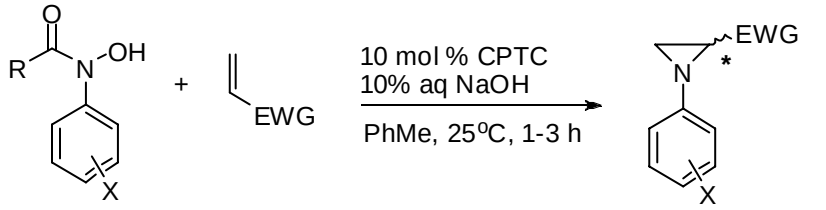
metal salts.[14] The use of cinchona-derived catalysts, however, has the potential to achieve high degrees of diastereoselectivity and enantioselectivity, as demonstrated by Arai and coworkers in the reaction of cyclic and acyclic α-chloroketones with alkyl and aryl aldehydes (71:29─89.5:10.5 er).[15,16] For the reaction involving acyclic α-chloroketones, the presence of aldol products in the reaction mixture suggested that the enantioselectivity was a result of the kinetic resolution of a single *anti*-aldolate stereoisomer.[16] Curiously, no aldol products for the reaction involving cyclic α-chloroketones were observed suggesting the formation of a chiral ammonium enolate complex.

Aziridination

Aziridines are versatile substrates for a variety of ring-cleavage and ring-expansion reactions. The enantioselective syntheses of aziridines by cinchona derived phase-transfer catalysts utilize both cyclic and acyclic α,β-unsaturated ketones as starting materials. Interestingly, the aziridination of both *t*-butyl acrylate with aryl hydroxamic acids, and of 2-(phenylsulfanyl)-2-cycloalkenones with ethyl-

nosyloxycarbamate, forms the same enantiomer regardless of which pseudoenantiomer of the cinchona-derived catalyst is employed.[17,18] However, modification of the *N*-alkyl group of the cinchona catalyst permits the synthesis of both enantiomers with moderate to excellent enantioselectivity (Scheme 3).[19]

Scheme 3. Synthesis of aryl aziridines



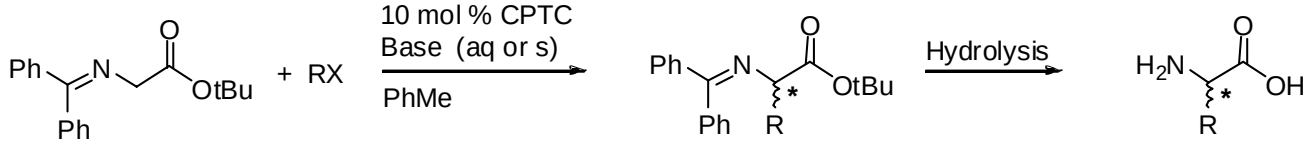
EWG = CO_2t-Bu, CO_2Me, Ph, SOPh
R = *t*-Bu, Ph
X = H, OMe, Cl, Br, Me, NO_2

71.5:28.5 - 97.5:2.5 er

Alkylation, Vinylation, and Alkynylation Reactions

Glycine imine *t*-butyl esters can be efficiently alkylated with alkyl halides under CPTC conditions to afford optically active α-amino acid precursors in high yields and good to excellent enantioselectivity (Scheme 4). Additionally, the conditions can be regulated either to achieve selective monoalkylation or to facilitate dialkylation.[20] The first example of glycine imine ester alkylation using modified cinchona catalysts was reported by O'Donnell in 1989 with moderate levels of enantioselectivity (71:29─83:17 er).[21] It was later realized that the cinchona-based catalysts underwent efficient *O*-alkylation with the organic halide electrophile under the basic conditions of the reaction.[20]

Scheme 4. Alkylation of glycine imine ester

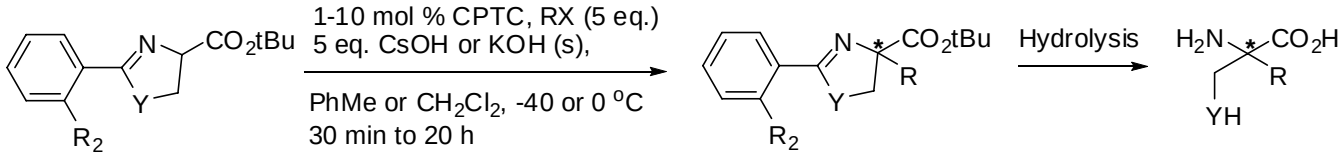


R = Alkyl, Allyl, Propargyl, Benzyl
X = Cl, Br, I

However, because the enantioselectivity is similar to that obtained using pre-alkylated catalysts, the *O*-alkylation of the catalyst does not appear to affect the catalyst's selectivity. In 1997, both Corey and Lygo developed similar *N*-anthracenylmethyl catalysts that were used to realized significant levels of enantioselectivity in comparison to the first-generation *N*-benzylated catalysts.[22,23] Both investigators proposed similar contact ion pair models to account for the observed asymmetric induction and reasoned that the additional rigidity and sterics due to the anthracenylmethyl group were responsible for the improved enantioselectivity.[22,23] This α-alkylation methodology has been applied in the synthesis of

optically active α-alkyl serines and cysteines (Scheme 5).[24,25] In addition, because the hydroxide base is not transported into the organic media, the tolerance of base-sensitive functionality in the electrophile has been demonstrated.[26] While a variety of points are present on the cinchona alkaloid motif for mounting the catalyst on a solid support, attachment at the hydroxyl of the alkaloid best preserves the enantioselectivity of the catalyst.[27]

Scheme 5. Synthesis of α-alkyl serines and cysteines

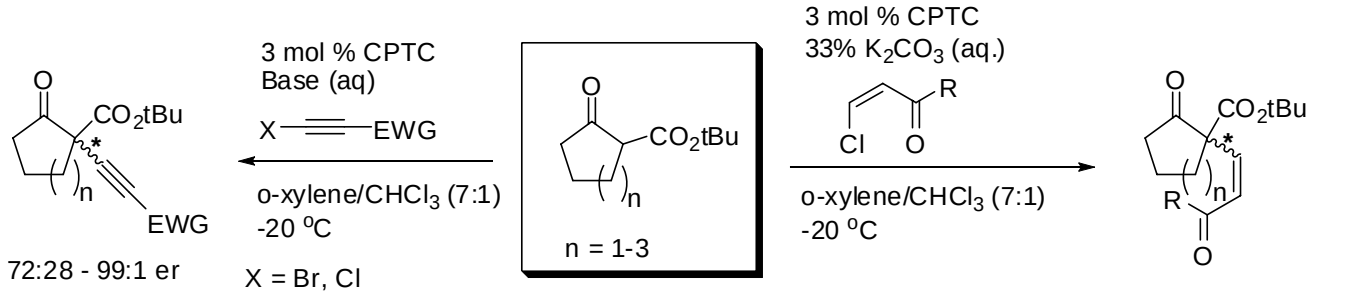


Y = S, O
R_1 = Alkyl, Allyl, Propargyl, Benzyl
X = I, Br
R_2 = H, Ph

83.5:16.5 -99.5-0.5 er

Jørgensen and coworkers developed an enantioselective vinylation of cyclic β-ketoesters with electron-deficient (*E)*- and (*Z)*-alkenes via an addition-elimination mechanism. The methodology allows substituted products with the retention of the double bond configuration (Scheme 6).[28] In addition, products containing tri-substituted alkenes can be attained. However, only moderate enantioselectivity was observed for acyclic β-ketoesters (<70:30 er) using this methodology. Jørgensen extended this reaction to synthesize α-alkynyl substituted cyclic β-ketoesters with a broad scope of electron-deficient alkynes (Scheme 6).[29]

Scheme 6. Alkynylation and vinylation



72:28 - 99:1 er

X = Br, Cl
EWG = COMe, COPh, SO_2-*p*-tolyl, CO_2Allyl

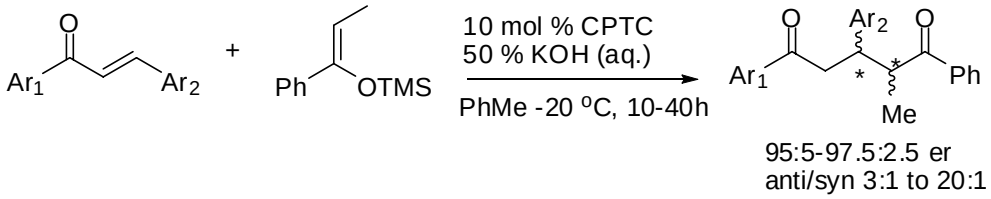
R = Ph, Benzyl, Alkyl, OEt

86:14 - >95:5 Z/E
87.5:12 - 97.5:2.5 er

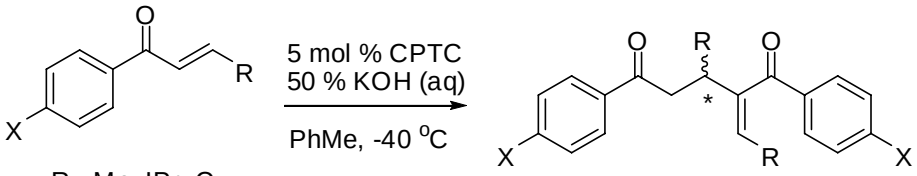
Michael Additions

The Michael addition of acyclic and cyclic α,β-unsaturated ketones with electron-deficient cyclic and acyclic alkenes, malonates and trimethylsilyl enol ethers can be achieved by modified cinchona catalysts with moderate to good enantioselectivity (Scheme 7).[30-32] Additionally, the dimerization of cyclic and acyclic α,β-unsaturated ketones that have γ-protons can be accomplished with excellent enantioselectivity to afford useful 1,5-diketone adducts that may be difficult to obtain by other methods (Scheme 8).[33,34]

Scheme 7. Michael addition



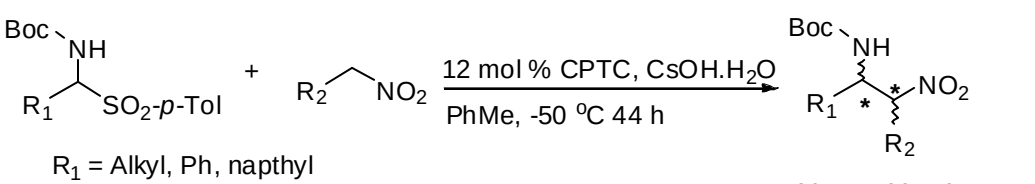
Scheme 8. Dimerization of acyclic enones



Nitro-Mannich (Aza-Henry) And Mannich Reactions

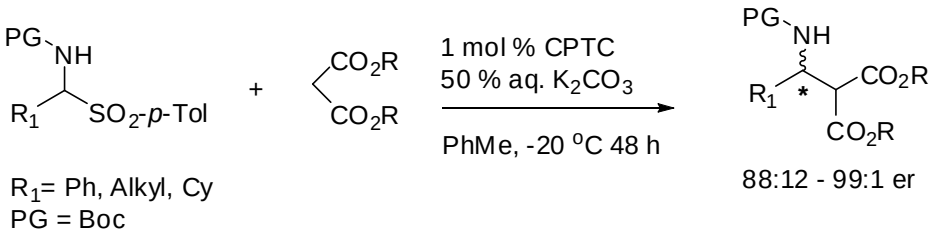
The aza-Henry or nitro-Mannich reaction is a useful C─C bond-forming event that generates β-nitro amines, which are useful precursors for the synthesis of vicinal di-amines and β-substituted α-amino acids. Under solid-liquid PTC conditions, α-amidosulfones bearing aliphatic and aromatic groups can be converted *in situ* to active azamethine compounds that can react with nitroalkanes to form primarily *syn* adducts (75:25─95:5 *syn/anti*) with good enantioselectivity (Scheme 9).[35,36] The Mannich reaction involving α-amidosulfones and malonates in the presence of a hydroxyl-containing modified cinchona catalyst yields good to excellent enantioselectivity (Scheme 10).[38] Subsequent decarboxylation

Scheme 9. Nitro-Mannich reaction



and hydrolysis affords enantiomerically enriched β-amino acid derivatives.

Scheme 10. Mannich reaction



CONCLUSION

The modified cinchona catalysts have dominated and revolutionalized the development of the CPTC field. They have demonstrated the possibility of achieving highly enantioselective transformations under phase-transfer conditions for a variety of C─C, C─O and C─N bond-forming reactions. The asymmetric alkylation of cyclic and acyclic enolates using modified cinchona alkaloids allows access to enantiomerically pure unnatural amino acids and synthetically useful adducts containing quaternary stereogenic centers. Additionally, the asymmetric epoxidation of *trans*-enones such as chalcones has been achieved with excellent enantioselectivities. While the epoxidation of *cis*-enones has generally been a challenge for these catalysts, there are examples where good enantioselectivity has been accomplished.[12] Highly enantioselective Michael, Mannich, and aziridination reactions have also been developed under CPTC conditions. More recently, the use of cinchona-derived catalysts has been extended to α-fluorination and Strecker reactions.[39,40] It is evident from the considerable development of CPTC methods in the recent years that more synthetically useful transformations will continue to be applied and investigated under phase-transfer conditions. The tolerance of base-sensitive functionality in the electrophile is a particularly promising area for further investigation. Unfortunately while a variety of highly enantioselective methodologies have been developed, there remains a considerable deficiency in our understanding of the mode of stereoinduction by the modified cinchona alkaloid catalysts. Further insight by thoroughly investigating substrate scope, performing kinetic studies and computational modeling of contact ion pairs may aid in the rational design of more efficient catalysts that tolerate a broader scope of substrates.

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