Design of Chiral Ammonium Betaines and Their Functions as Organic Base and Nucleophilic Catalysts

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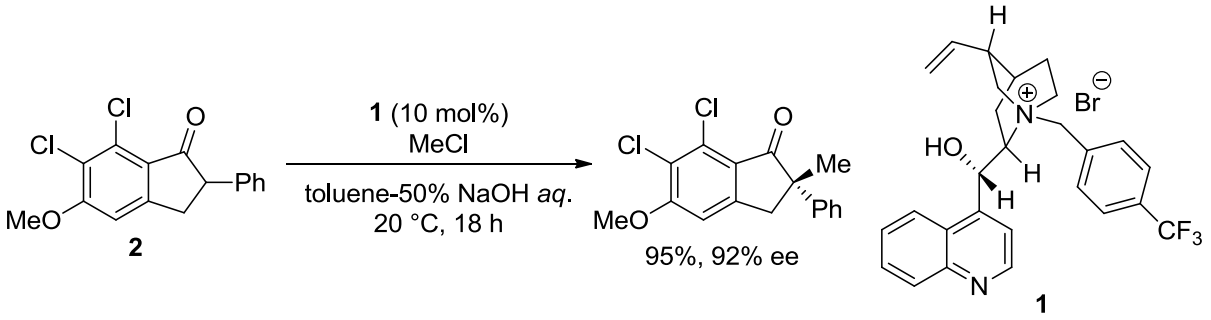
Chapter 1

General Introduction and Summary

1 .1 Pioneering Works on Chiral Ammonium Salts

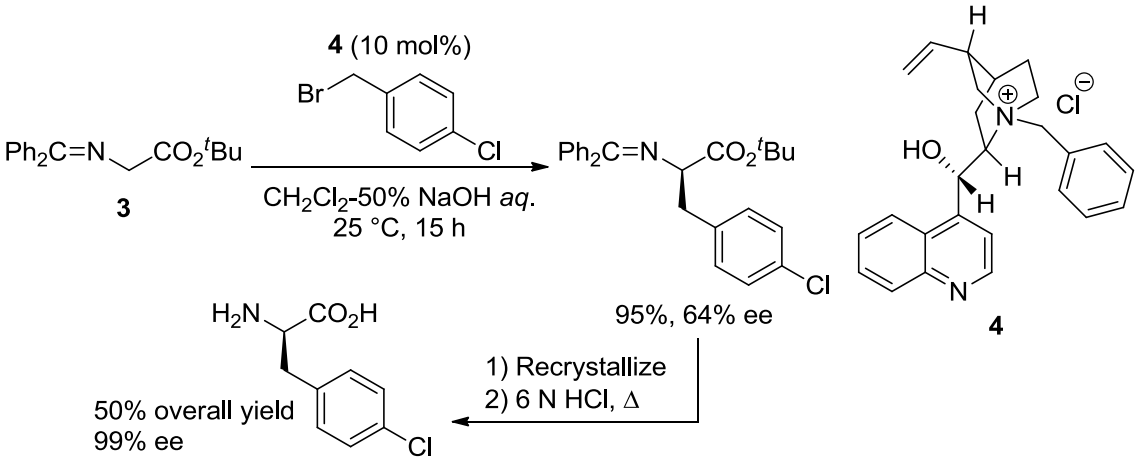
Chiral tetraalkylammonium salts which promote stereoselective carbon-carbon or carbon-heteroatom bond formations as organocatalysts have attracted a particular interest. They are especially investigated as phase-transfer catalysts under liquid-liquid or liquid-solid biphasic conditions. In 1984, the Merck research group reported a first effective chiral phase-transfer catalyst, (*N*-(*p*-trifluoromethyl)benzyl)-cinchoninium bromide **1**, for asymmetric methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone **2** (Scheme 1).[1]

Scheme 1. Asymmetric Methylation Catalyzed by a Cinchoninium salt



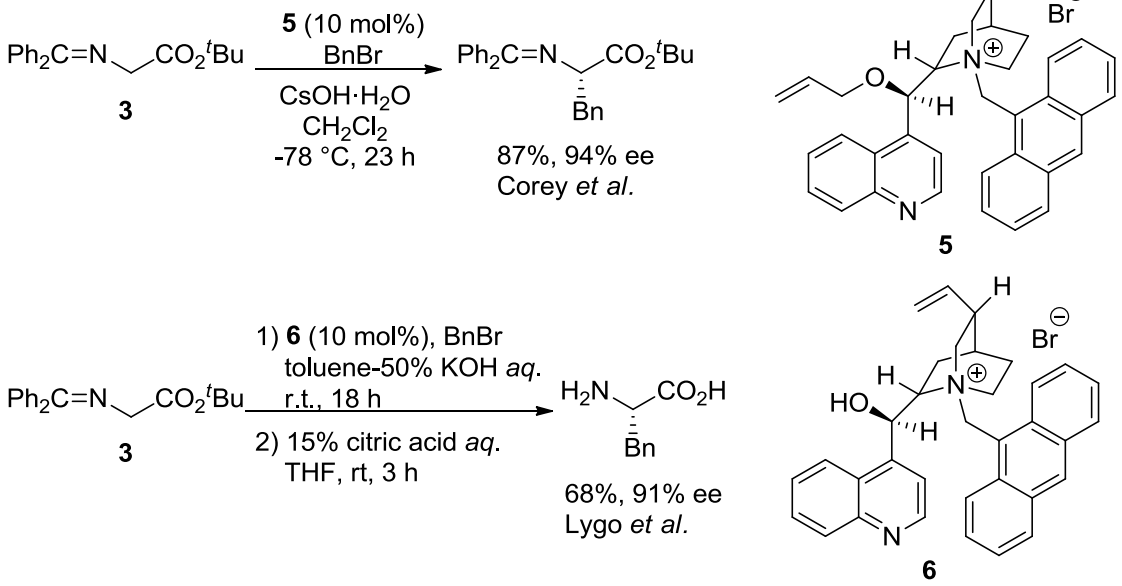
Thereafter, practical efficient asymmetric α-amino acid syntheses with alkylation of glycine Schiff base **3** catalyzed by cinchona alkaloid derived ammonium salts were introduced by O'Donnell in 1989 (Scheme 2).[2]

Scheme 2. Practical Efficient Asymmetric α-Amino Acid Syntheses



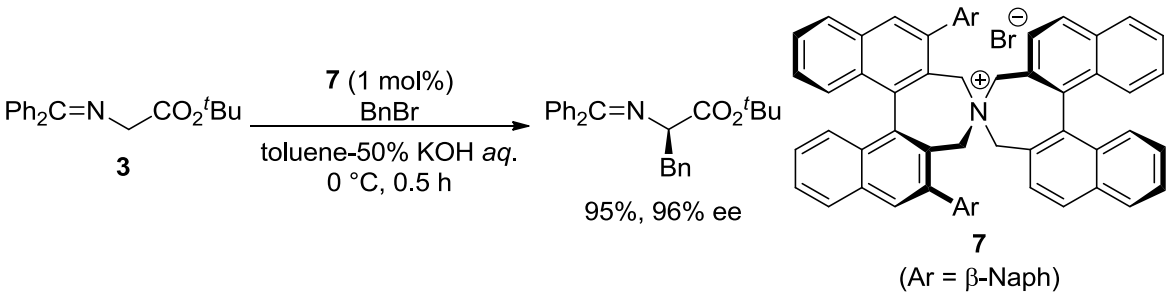
In 1997, Corey and Lygo independently disclosed that *N*-(9-anthracenylmethyl)-cinchonidinium salt induced extremely high enantioselectivity in the alkylation of glycine Schiff base **3** (Scheme 3).[3,4] In consequence, initial investigations of efficient chiral ammonium salts as organocatalysts were practically limited to natural products derivatives, such as cinchona alkaloids.

Scheme 3. *N*-(9-Anthracenylmethyl)-Cinchonidinium Salts



In this context, Maruoka developed a *N*-spiro C_2-symmetric chiral ammonium salt as an effective phase-transfer catalyst for the benzylation of glycine Schiff base **3**. Only 1 mol% of (*S*)-BINOL derived ammonium salt **7** smoothly promoted the reaction at 0 ºC and produced (*R*)-phenylalanine derivatives up to 96% ee in 95% yield (Scheme 4).[5] These reports have accelerated the research on the use of chiral ammonium salts as chiral phase-transfer catalysts.

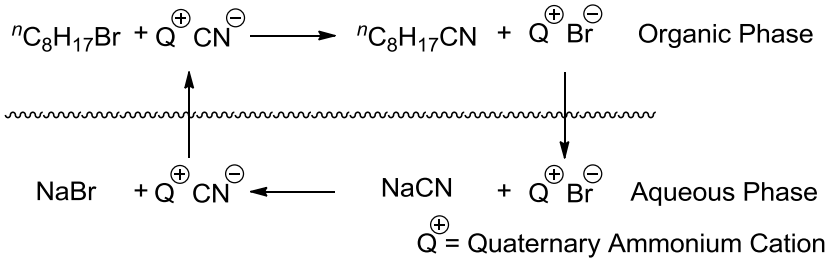
Scheme 4. Chiral Ammonium Salt Based on Binaphthyl Units



1.2 General Mechanisms and Applications of Ammonium Salts Catalyzed Phase-Transfer Reactions

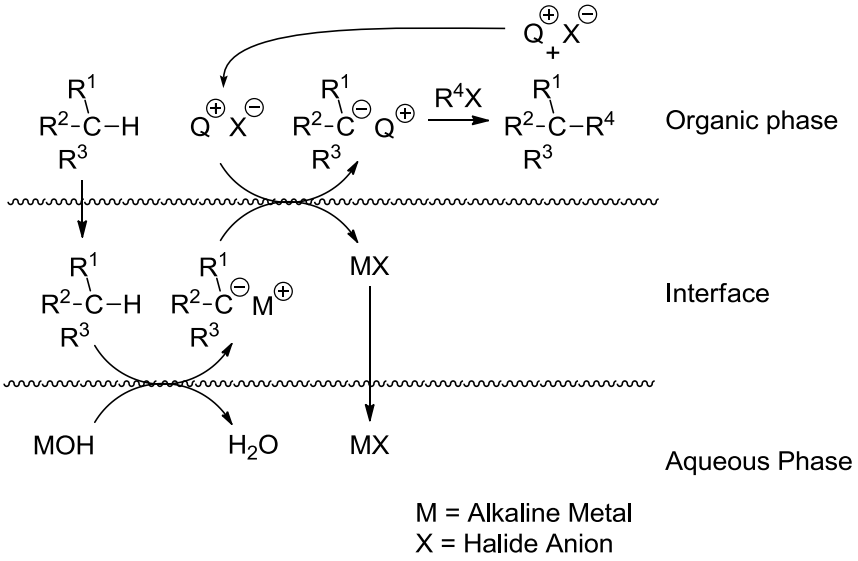
The mechanism of chiral ammonium salts catalyzed phase-transfer reactions are classified into two categories: (1) extraction mechanism,[6] (2) interfacial mechanism.[7] Extraction mechanism was suggested by Starks in 1971. For example, in the reaction of 1-bromooctane and sodium cyanide, ion exchange between sodium cyanide and an ammonium bromide produces an organic-soluble ammonium cyanide in an aqueous phase. Then, the ammonium cyanide further reacts with 1-bromooctane to form the nonanenitrile and regenerate an ammonium bromide in an organic phase. The regenerated ammonium salt transfers to the aqueous phase to exchange its anion with sodium cyanide again (Figure 1).

Figure 1. Extraction Mechanism of Ammonium Salts



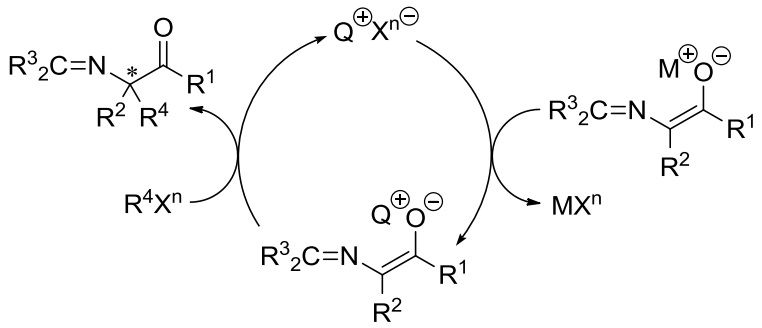
On the other hand, Makosza recommended interfacial mechanism (Figure 2). A metal hydroxide deprotonate an active methane, methylene or methine compound in interfacial area, and then the generated metal carbanion is extracted as an ammonium carbanion into organic phase. The ammonium carbanion reacts with electrophile to form the product in concomitant regeneration of the catalyst in organic phase. Since chiral quaternary ammonium salts, possessing highly hydrophobic organic structure, are restricted from transfer into aqueous phase, the interfacial mechanism seems to be commonly applicable to the asymmetric reactions.

Figure 2. Interfacial Mechanism of Ammonium Salts



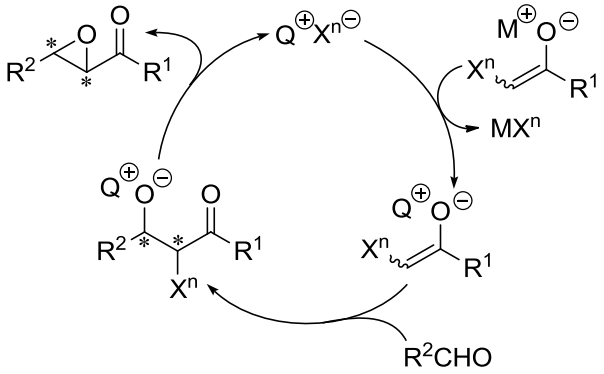
Asymmetric alkylation of active methylene or methine compounds catalyzed by chiral ammonium salts occupies the central position in the field of asymmetric phase-transfer catalysis. Notably, the stereoselective alkylation of amino acid derived Schiff base has attracted much attention due to the utility of the products, which are converted into both natural and unnatural α-alkyl-α-amino acid and related compounds by simple derivatization.[8,9,10] Since the absolute configuration of products is controlled by chiral ammonium cations, both L- and D-amino acids are easily prepared by switching the absolute configuration of ammonium cation moiety (Figure 3). In addition, alkylation of other active methylene or methine compounds, such as 1,3-dicarbonyl, α-hetero carbonyl, α-unsaturated carbonyl compounds, are extensively studied,[8,11] and Jørgensen disclosed alkenylation, alkynylation, and S_NAr reactions of 1,3-dicarbonyl compounds.[12]

Figure 3. Alkylation of Schiff Base



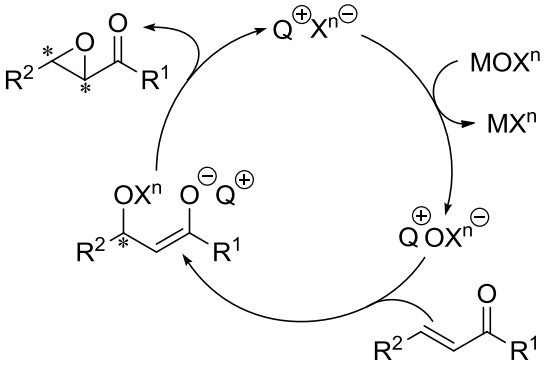
The Darzens condensation, which involves the 1,2-addition of nucleophile to aldehyde and subsequent alkylation of alkoxide, is one of the most powerful method for α,β-epoxycarbonyl syntheses. The absolute stereochemistry of the products are determined in the 1,2-addition step of a chiral ammonium enolate to aldehyde to give an aldol-type adduct (Figure 3).[13] Since the first report by Shioiri and Arai in 1998,[14] catalytic asymmetric Darzens reactions have been demonstrated in heterogeneous conditions catalyzed by chiral ammonium salts.[8]

Figure 4. Asymmetric Darzens Condensation



α,β-Epoxycarbonyl compounds can also be synthesized by the epoxidation of α,β-unsaturated carbonyl compounds. The chiral ammonium salts catalyzed epoxidation with sodium hypochlorite or metal peroxide, which is generated from inorganic base and hydrogen peroxide, under liquid-liquid biphasic conditions has been elaborated on account of its advantage including commercial availability of reagents and operational simplicity.[8] In this reaction, there are two stereoselective bond-forming steps, conjugate addition of peroxide to α,β-unsaturated carbonyl compounds and intramolecular attack of ammonium enolate to oxygen atom (Figure 5).

Figure 5. Asymmetric Epoxidation

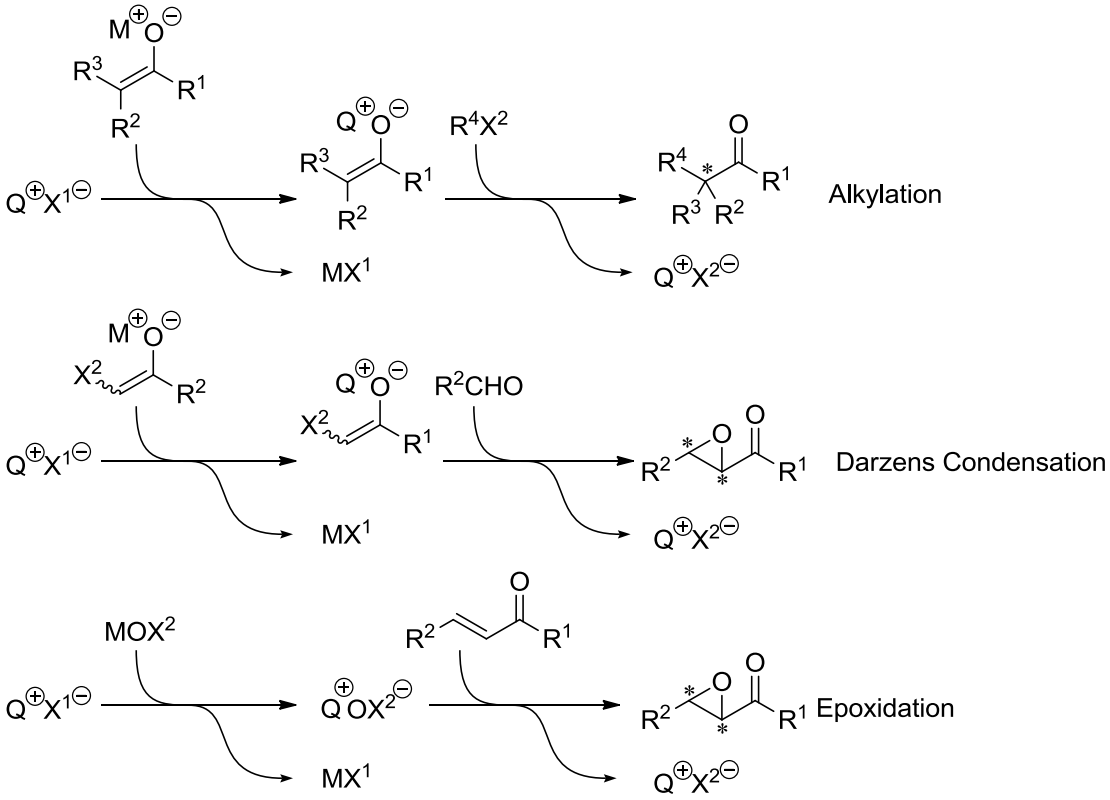


Furthermore, chiral tetraalkylammonium salts have been applied to various asymmetric reactions, such as conjugate additions, aldol and related reactions, Mannich and related reactions, Never rearrangements, Horner-Wadsworth-Emmons Reactions, cyclopropanations, aziridinations, oxidations, reductions, fluorinations, sulfenylations, cyanations, under biphasic conditions.[8,10e,10l,10o,11c,15]

1.3 Ammonium Salts Possessing Functionalized Anions

Ammonium salts consist of two components, an ammonium cation part and an anion part. When ammonium salt catalysts act as phase-transfer catalysts under biphasic conditions, functions of an ammonium cation such as stereocontrolling ability are the subject of interest; however reports on utilization of a function of anion part are restricted. The reason is that anion parts are delivered outside of the reaction system via ion-exchange process with metal salts, and do not participate in bond-forming steps (Figure 6).

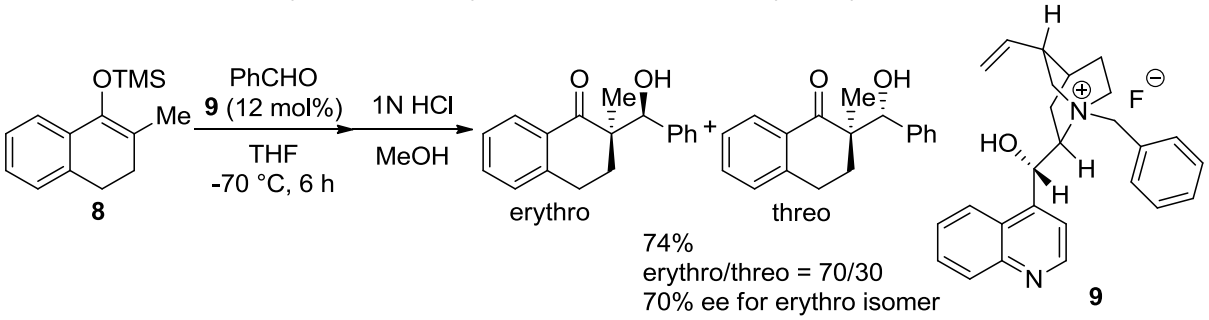
Figure 6. Reaction Mechanism under Biphasic Conditions



In this context, much effort have been paid for ammonium salts with functionalized anions, and Lewis basic ammonium fluorides or ammonium bifluorides have been used as organocatalysts under homogeneous conditions. Since chiral ammonium fluorides can generate nonracemic ammonium nucleophiles from silyl nucleophiles due to the affinity of fluoride ions to silicon atoms, there are some examples of the asymmetric reactions with silyl enolate,[16,17] silyl nitronates,[16,18] Ruppert-Prakash reagents (trifluoromethyltrimethylsilane),[16,19] alkoxysilanes,[20] or silylacetylene[21] as nucleophile

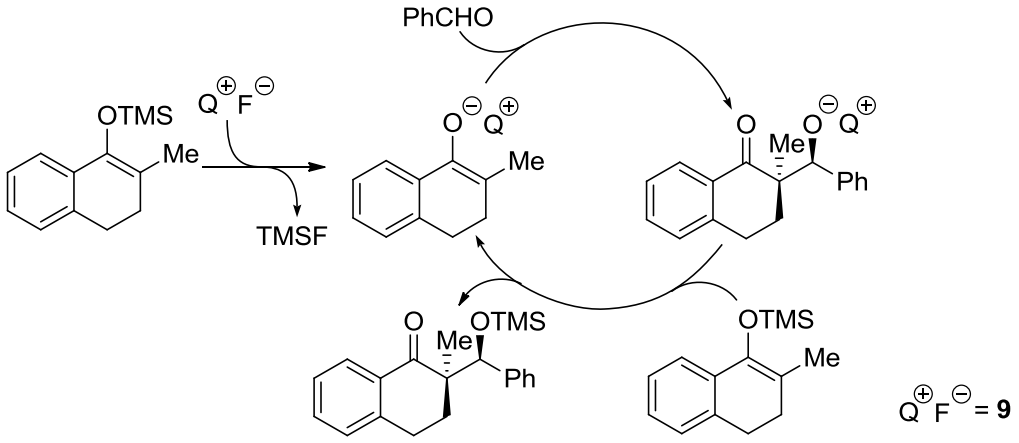
precursors. In 1993, Shioiri demonstrated first example of a chiral ammonium fluoride catalyzed asymmetric Mukaiyama-aldol reaction of silyl enol ether of 2-methyl-1-tetralone **8** with benzaldehyde (Scheme 5).[22]

Scheme 5. Asymmetric Mukaiyama-Aldol Reaction Catalyzed by Ammonium Fluoride



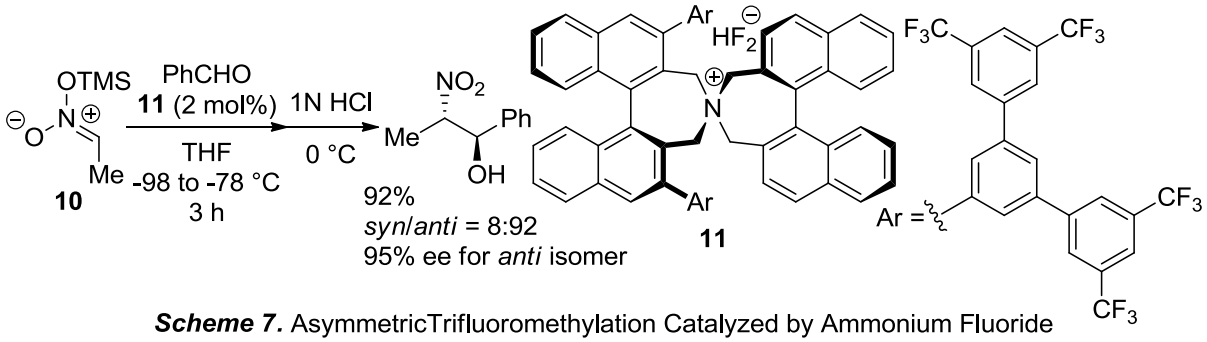
The mechanism of the ammonium fluoride **9** catalyzed Mukaiyama-aldol reaction is proposed as shown below (Figure 7). Ammonium enolates and trimethylsilyl fluoride are formed from ammonium fluoride **9** and silyl enol ether by the attack of fluoride ion on silicon atom. Next, ammonium alkoxide is constructed through the asymmetric 1,2-addition of ammonium enolate to benzaldehyde. Finally, nucleophilic attack of the ammonium alkoxide occurs on silicon atom of other silyl enol ether to produce Mukaiyama-aldol adduct, simultaneously generating ammonium enolate for next bond-formation.

Figure 7. Reaction Mechanism of Ammonium Fluoride Catalyzed Mukaiyama-Aldol Reaction

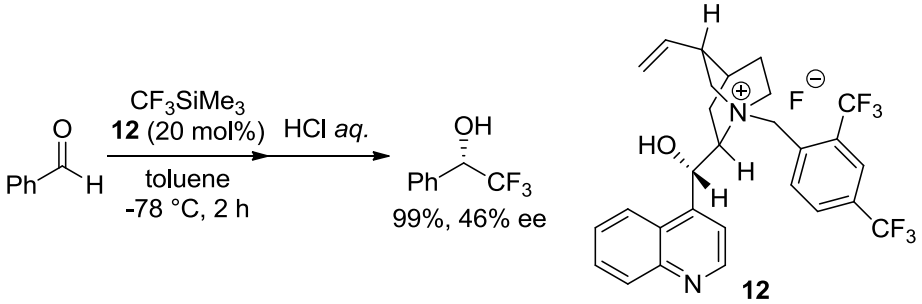


Maruoka demonstrated nitroaldol reaction of silyl nitronate **10** with aldehydes catalyzed by C_2-symmetric quaternary ammonium bifluoride **11** (Scheme 6).[23] Kobayashi and Iseki presented an example of the catalytic asymmetric trifluoromethylation of aldehydes and ketones with Ruppert-Prakash reagents mediated by chiral quaternary ammonium fluorides **12** (Scheme 7).[24] Lawrence disclosed asymmetric reduction of ketones with trialkoxysilane catalyzed by quininium fluorides **13** (Scheme 8).[20]

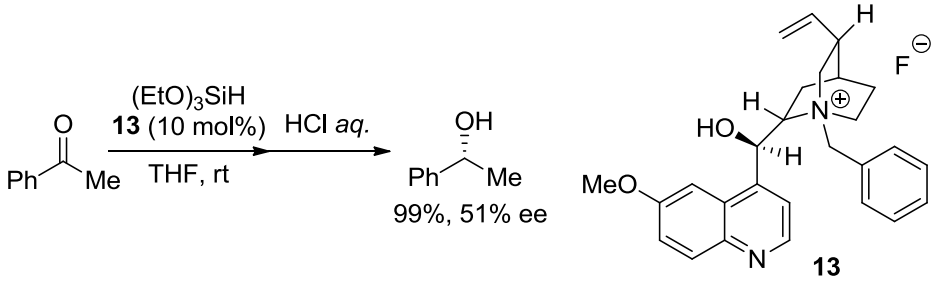
Scheme 6. Asymmetric Nitroaldol Reaction Catalyzed by Ammonium Bifluoride



Scheme 7. AsymmetricTrifluoromethylation Catalyzed by Ammonium Fluoride

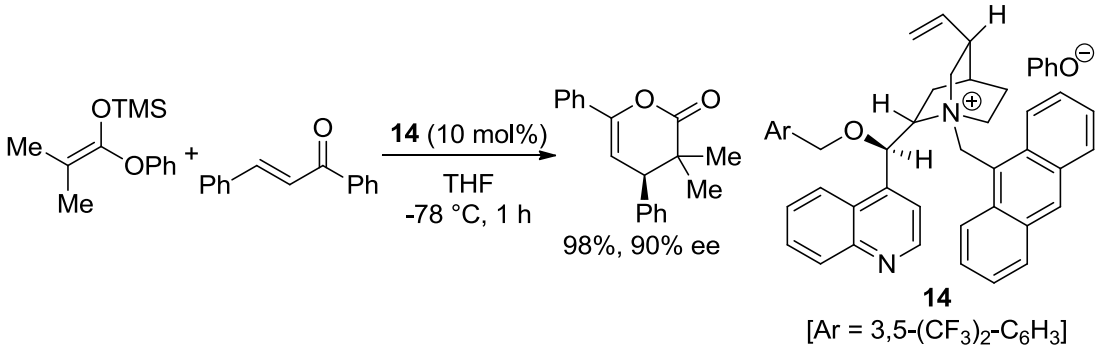


Scheme 8. Asymmetric Reduction Catalyzed by Ammonium Fluoride



Moreover, Mukaiyama reported that chiral ammonium phenoxides derived from cinchona alkaloids were effectively employed as a catalyst for the asymmetric reactions of silyl enolate or Ruppert-Prakash reagents.[16,25] In 2006, Mukaiyama demonstrated a convenient one-pot preparation of 3,4-dihydropyran-2-ones by chiral quaternary ammonium phenoxides catalyzed enantioselective tandem Michael addition-lactonization with ketene silyl acetals and α,β-unsaturated ketones (Scheme 9).[26]

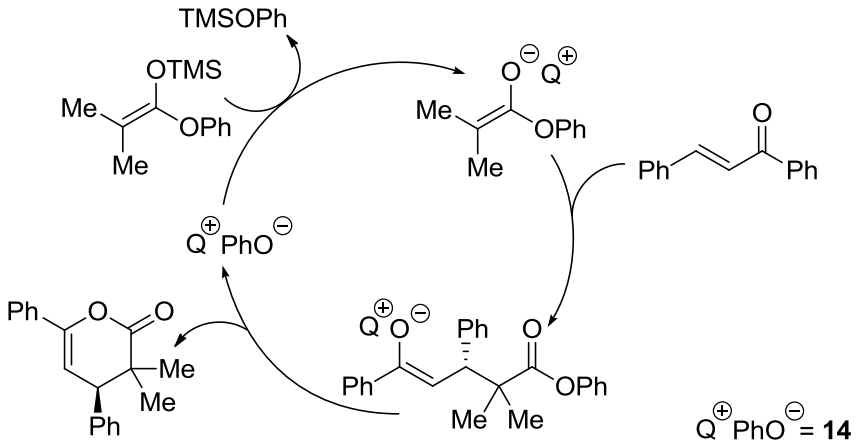
Scheme 9. Ammonium Phenoxide Catalyzed Tandem Michael Addition and Lactonization



Possible mechanism is suggested that ketene silyl acetals are activated by nucleophilic attack of the phenoxide ion of the ammonium salt to the silicon center for producing ammonium enolates and trimethylsilyl ether of phenol, and ammonium enolate reacts with chalcone to afford Michael-type

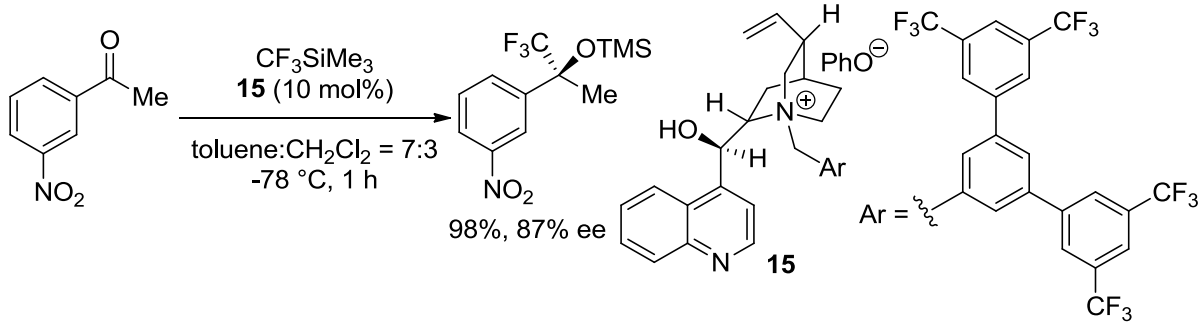
intermediate. Eventually, 3,4-dihydropyran-2-ones are produced via transesterification and ammonium phenoxides are formally regenerated (Figure 8).

Figure 8. Reaction Mechanism of Scheme 9



Additionally, Mukaiyama utilized ammonium phenoxides **15** for highly enantioselective trifluoromethylation of 3-nitro-acetophenone with Ruppert-Prakash reagents (Scheme 10).[27]

Scheme 10. Ammonium Phenoxide Catalyzed Trifluoromethylation

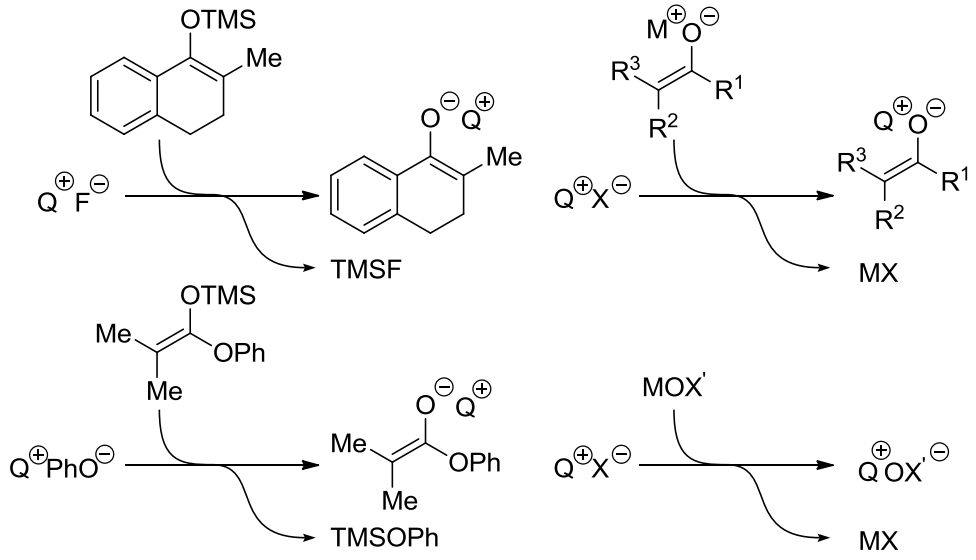


It is fair to say that chiral tetraalkylammonium salts possessing functionalized anion, such as fluoride, bifluoride, or phenoxides, were utilized as an activator of silicon in the development of the various asymmetric reactions with silyl nucleophiles.

2.1 Chiral Ammonium Betaine in Asymmetric Catalyses

Chiral tetraalkylammonium salts have been continuously investigated over the last three decades, and their applications to asymmetric catalysis are more than 100 examples. In the phase-transfer catalyses, capability of ammonium cations have been well documented;[8] however, the role of counter ions have seldom been addressed. A few examples, ammonium fluorides, bifluorides, phenoxides, have been reported as organocatalysts possessing utilizable anion under homogeneous conditions.[16,18] Although the functional anions are feasible to activate silyl nucleophiles as Lewis base, the anionic parts are delivered outside of the catalytic cycle as inactive silyl compounds (Figure 9a) and thus do not participate in the bond-forming steps (Figure 9b).

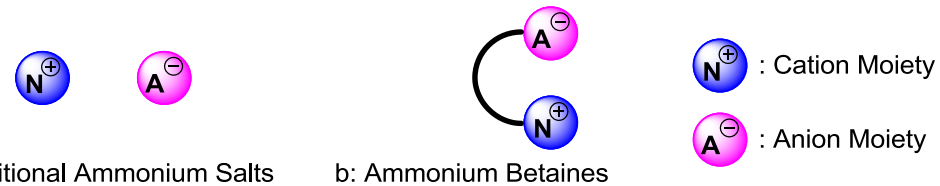
Figure 9. Mechanism of Generation of Ammonium Enolates



a: Nucleophilic Activation Prosess b: Ion-Exchange Process

In this way, participation of anionic parts to reaction cycle including a bond-forming step have been restricted, and thus potential of chiral ammonium salts, which consists of both cationic parts and anionic parts, have been veiled yet. One of the reasons is that traditional chiral ammonium salts are intermolecular ion pair, which are composed of independent, unconstrained cationic and anionic parts, therefore this type of ammonium salts are easily uncoupled and formed another new ion pair (Figure 10a). On the other hand, intramolecular ion-pair type ammonium salts, which can be called ammonium betaines, could allow its anion moiety to work as functional group because they have quaternary ammonium cation moiety and organic anion moiety in the same molecules (figure 10b).

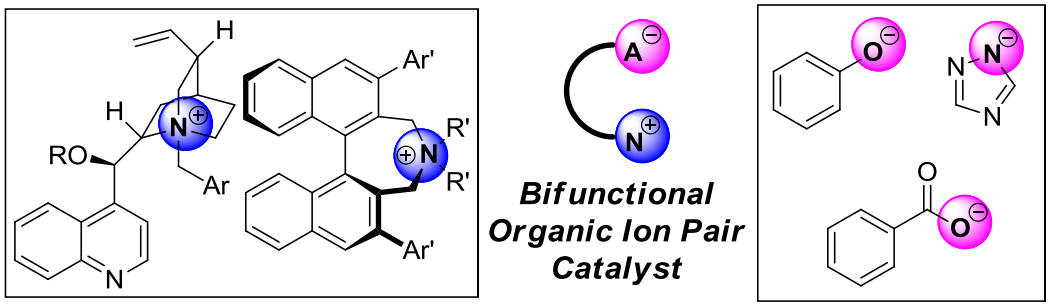
Figure 10. Ammonium Betaine



a: Traditional Ammonium Salts (Intermolecular Type Ion Pair) b: Ammonium Betaines (Intramoleculer Type Ion Pair)

In fact, ammonium cations are capable of controlling anionic nucleophiles via ionic interaction in various asymmetric reactions and organic anions exhibit Brønsted or Lewis basicity. Since ammonium betaines can give a chance to utilize both functional groups in a reaction system, it could be expected that intrinsic features of ammonium salts are uncovered by the study toward development of ammonium betaines as bifunctional organic ion pair catalyst (Figure 11).

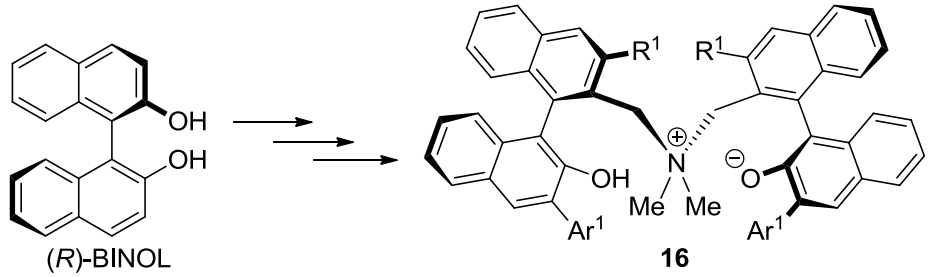
Figure 11. Ammonium Betaine as Bifunctional Catalyst



2.2.1 Pseudo C_2-Symmetric Ammonium Betaine as Bifunctional Organic Base Catalyst (Chapter 2)

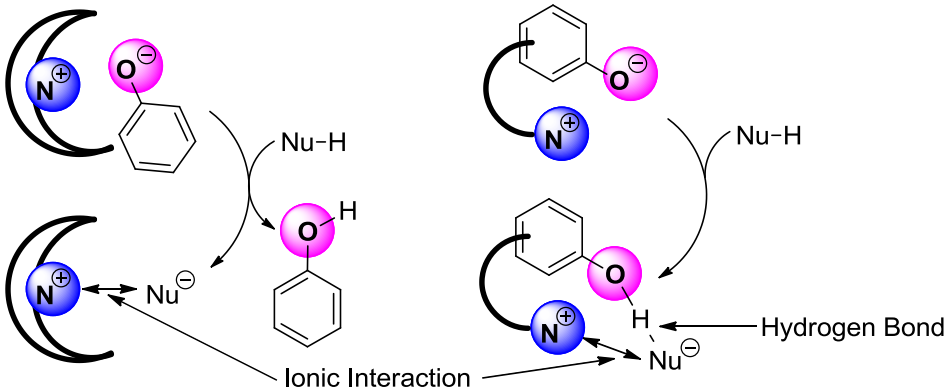
Newly designed pseudo C_2-symmetric ammonium betaines **16**, which are regarded as an intramolecular-type ammonium aryloxide, were synthesized from optically active (*R*)-BINOL (Figure 12).

Figure 12. Synthesis of C_2-Symmetric Ammonium Betaine



Since chiral ammonium betaines **16** are possessing Brønsted basic aryloxides, their ability as bifunctional organic base catalysts were initially evaluated. In the case of intermolecular-type ion pair, an ammonium cation forms ion pair with the anionic nucleophile after the deprotonation of nucleophilic reagents by an aryloxide as a Brønsted base. During this process, anion moiety is transformed into arylhydroxide, a conjugate acid. Since arylhydroxide is non-ionic molecule, they hardly contact to reaction intermediates at bond-forming steps (Figure 13a). On the other hand, since ammonium betaine have both ammonium cation and aryloxide in the same molecules, arylhydroxide, which is formed from the reaction of anion moiety with nucleophilic reagents, are situated close to ammonium cations at bond-forming steps. Thus, the nucleophilic anion could be precisely recognized and controlled by hydrogen bond assisted ionic interaction (Figure 13b).

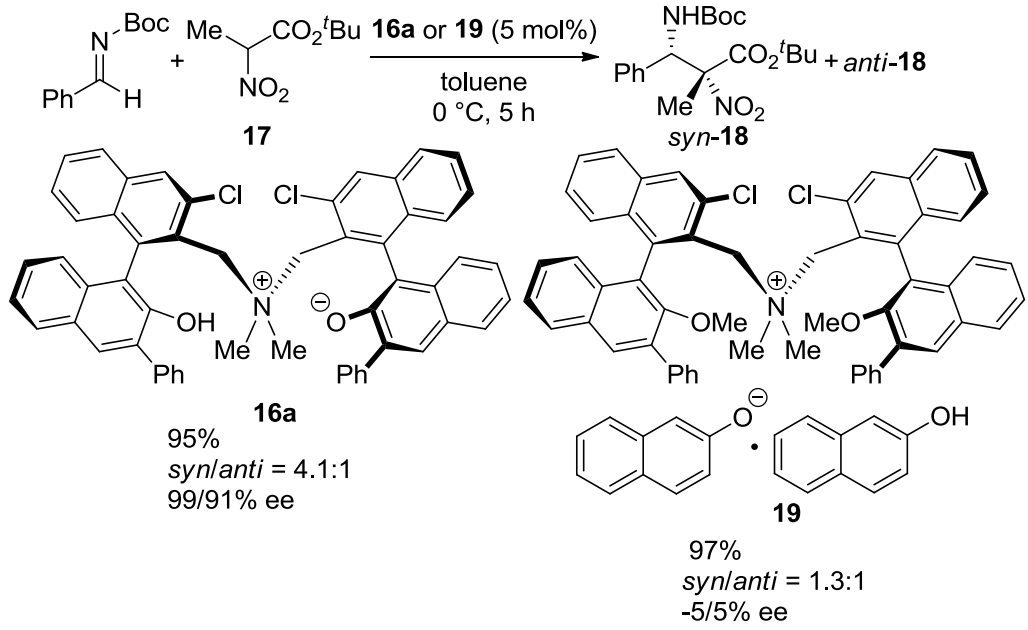
Figure 13. Intermolecular Ammonium Salt vs. Ammonium Betaine



a: Intermolecular Anmonium Salt b: Ammonium Betaine

To evaluate the ability of ammonium betaines **16** as a chiral organic base catalyst, direct Mannich-type reaction of α–nitro carboxylate **17** with imines was selected.[28] Chiral ammonium betaine **16a** catalyzed asymmetric Mannich-type reaction resulted in high catalytic performance with excellent enantioselectivity (95%, *syn*/*anti* = 4.1:1, 99% ee for *syn* isomer). An intermolecular ammonium salt **19**, which has similar ammonium cation unit to **16a**, catalyzed direct Mannich-type reaction smoothly to furnish the product **18** with very low stereoselectivities. So it was uncovered that the intramolecular ion pair structure of ammonium betaine is crucial for inducing high stereoselectivity (Scheme 11).

Scheme 11. Asymmetric Mannich-Type Reaction Catalyzed by Chiral Ammonium Betaine

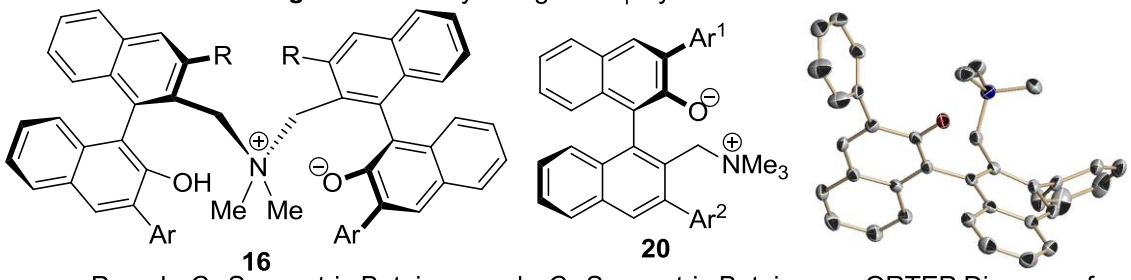


2.2.2 Application of Simplified C_1-Symmetric Ammonium Betaine (Chapter 3)

It was disclosed that ammonium betaines performed as chiral bifunctional organic base catalysts. Although pseudo C_2-symmetric ammonium betaines **16** possessed two hydrogen-bonding sites, one hydroxide and one aryloxide, the actual role of two hydroxyl groups in reaction intermediate had been

unclear (Figure 14a). To obtain insight into the intermediate of the stereoselective bond-formation, simplified C_1-symmetric ammonium betaines of type **20**, which consist of mono-binaphthyl unit and a hydrogen-bonding site, were newly designed and synthesized. It was expected to be capable of modifying the environment around the quaternary ammonium center by introducing unsymmetrical substituents (Ar^1, Ar^2) to the three positions of each naphthyl rings (Figure 14b). Additionally, the three-dimensional molecular structure of **20a** (Ar^1, Ar^2 = Ph) was unequivocally determined by single-crystal X-ray diffraction analysis, and revealed intramolecular ion pair structure of ammonium betaine (Figure 15c).

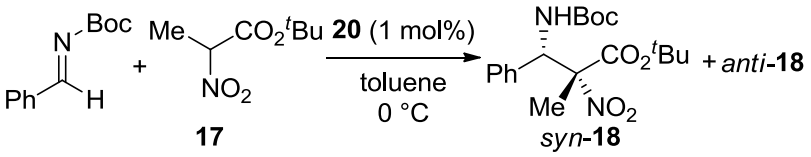
Figure 14. Newly Designed C_1-Symmetric Betaine

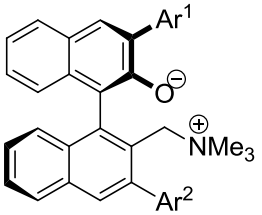


a: Pseudo C_2-Symmetric Betaine b: C_1-Symmetric Betaine c: ORTEP Diagram of **20a** (Ar^1, Ar^2 = Ph)

The ability of C_1-symmetric ammonium betaines **20** as bifunctional organic base catalysts was compared with pseudo C_2-symmetric ammonium betaines **16** in the asymmetric direct Mannich-type reactions of α–nitro carboxylate **17** with imines (Scheme 12).[28] Use of **20a**, whose three-dimensional structure was determined, afforded the desired product **18** in 92% yield with 90% ee. Modification of substituents Ar^1, Ar^2 resulted in enhancement of both diastereo- and enantioselectivity in this reaction system. With **20b** (Ar^1 = *p*-^{t}Bu-C_6H_4, Ar^2 = Cl), the desired product **18** was obtained in 98% yield with *syn*/*anti* = 3.2:1 and 95% ee (*syn* isomer). Since similar result with the pseudo C_2-symmetric ammonium betaines **16b** catalyzed direct Mannich-type reaction was observed, it disclosed the ability of simplified C_1-symmetric ammonium betaines **20**, possessing a hydrogen-bonding site, as bifunctional organic base catalysts.

Scheme 12. C_1-Symmetric Ammonium Betaine Catalyzed Mannich-Type Reaction





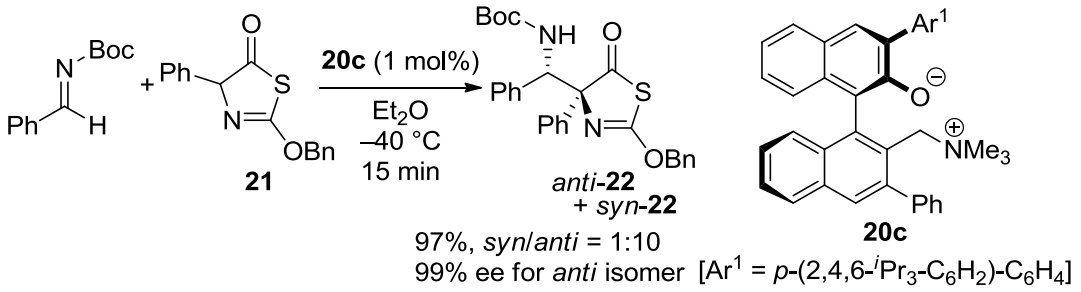
	20a	**20b**
	10 h, 92%	8 h, 98%
	syn/*anti* = 2.1:1	3.2:1
	90% ee for *syn* isomer	95% ee

20a (Ar^1, Ar^2 = Ph)
20b (Ar^1 = *p*-^{t}Bu-C_6H_4, Ar^2 = Cl)

Further, the applications of ammonium betaines as chiral bifunctional organic base catalysts were expanded to asymmetric direct Mannich-type reaction of thiazol-5(*4H*)-one **21**[29] with imine.

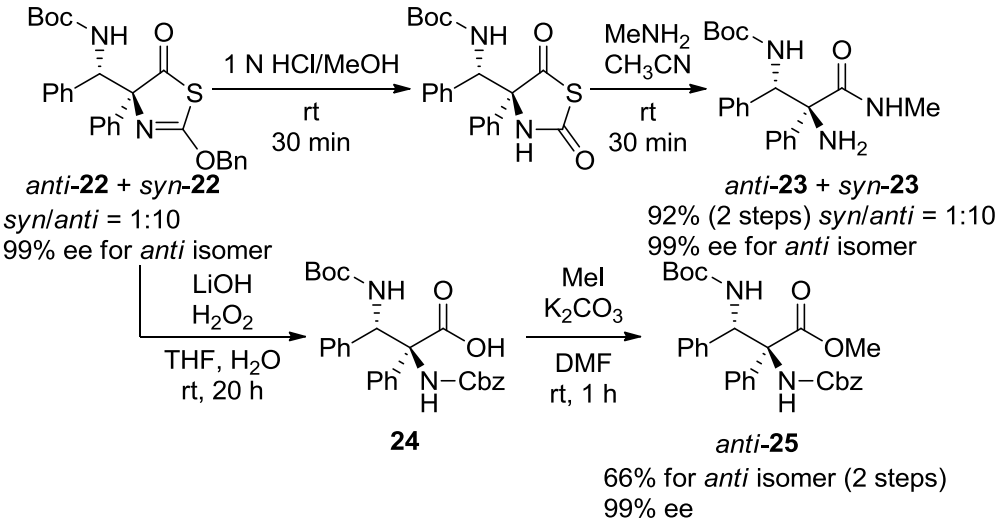
Use of **20c**, which has sterically congested aryl substituent, *p*-(2,4,6-$^{i}Pr_3$-C_6H_2)-C_6H_4, at the three position on the naphthyl ring of aryloxide side, afforded the Mannich adduct **22** in 97% yield with *syn*/*anti* = 1:10 and 99% ee (*anti* isomer) (Scheme 13).

Scheme 13. Asymmetric Mannich-Type Reaction of Thiazol-5-(*4H*)-one



The Mannich adducts **22** was converted into the corresponding α,β-diamino amide **23** via acidic hydrolysis with hydrochloric acid in methanol and ring opening reaction with methylamine to give **23** in 92% yield. The product **22** was further transformed into α,β-diamino acid **24**, which is bearing different protecting groups on the each amines, under the influence of lithium hydroxides and hydrogen peroxides. It is noteworthy that no racemizaton was detected by HPLC analysis of **23** and **25** (Scheme 14).

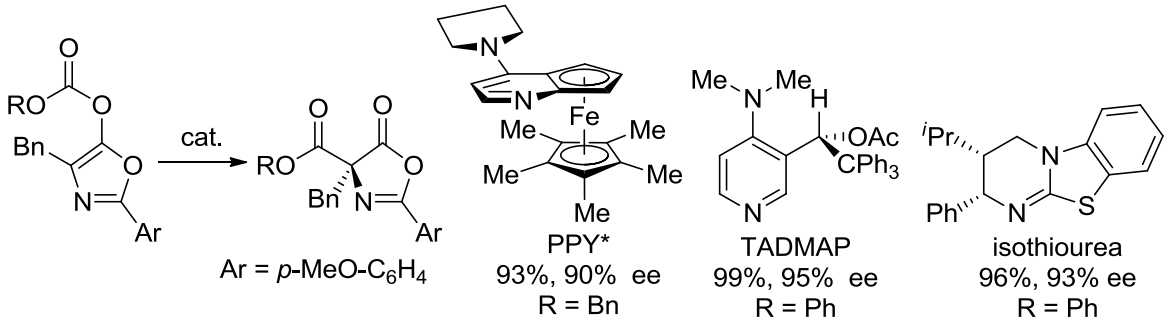
Scheme 14. Derivatization of Mannich Adduct



2.3.1 Chiral Ammonium Betaine as Ionic Nucleophilic Catalyst (Chapter 4)

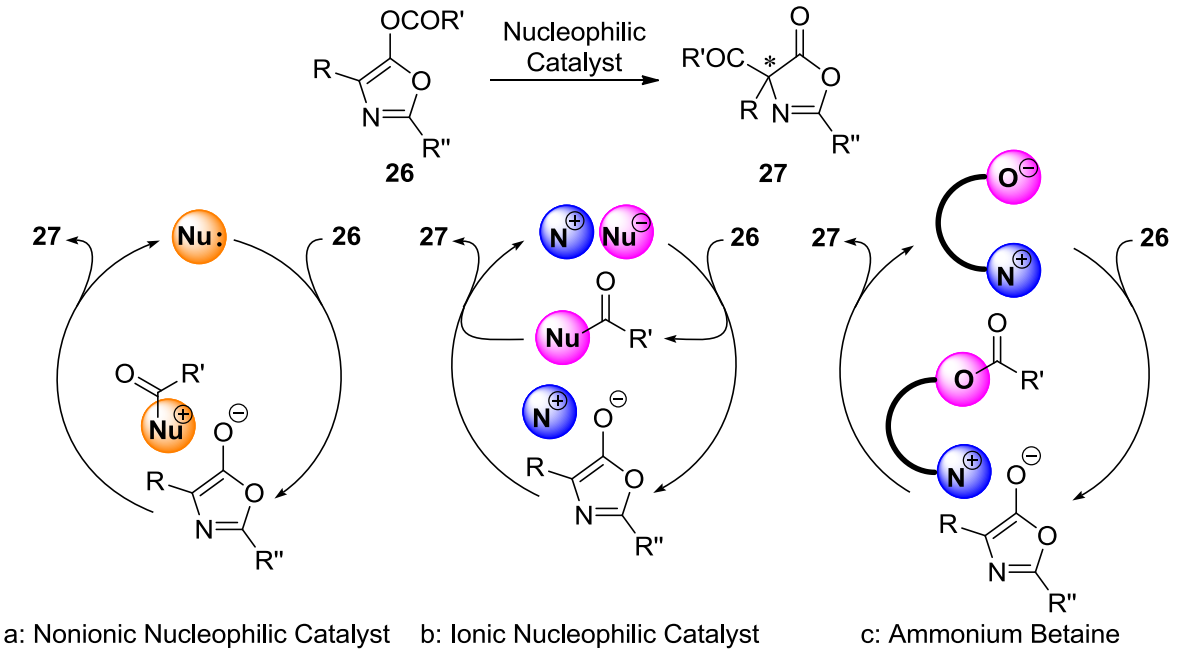
Chiral ammonium betaines had been applied as bifunctional organic base, which are capable of recognizing nucleophiles with double interaction, ionic interaction and hydrogen bond, to asymmetric direct Mannich-type reaction. Further, since the available functionality of aryloxides are not only Brønsted basicity but also Lewis basicity, chiral ammonium betaines were utilized as ionic nucleophilic catalysts.[30,31] The acyl transfer reactions of *O*-acylated azlactones, which are called Steglich reaction,[32] are promoted by nucleophilic catalysts.[33,34] Fu[34a] disclosed that PPY* induced high enantioselectivity in this reaction in 1998, and Vedejs[34b] and Smith[34g] reported asymmetric Steglich reactions catalyzed by TMDMAP and chiral isothiourea derivative, respectively (Scheme 15).

Scheme 15. Steglich Reaction Catalyzed by Nucleophilic Catalyst



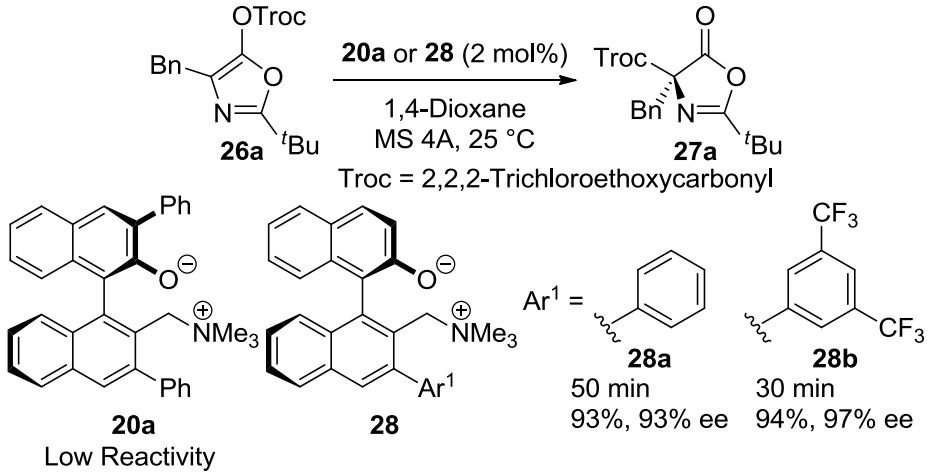
Applications of traditional nonionic nucleophilic catalysts, such as pyridine or isothiourea derivative to acyl transfer reactions had been investigated. However, the reports on acyl transfer reactions promoted by ionic nucleophilic catalysts had never been described despite of their higher nucleophilicity than nonionic nucleophilic catalysts. The reason of this situation is following. To accelerate the acyl transfer reactions, catalysts are required to promote two reactions, which are nucleophilic attack of catalysts to *O*-acylated azlactone **26** as initial steps and C-C bond formation steps (Figure 15). In the case of the nonionic nucleophilic catalysts, reaction intermediate generated by nucleophilic attack of catalysts to **26** is ion pair, which is composed of cationic acylated catalyst and an azlactone enolate. Thus, C-C bond formation is pseudo intramolecular reaction in the ion pair of highly reactive acylating reagent and enolate, where acyl transfer reactions proceed smoothly (Figure 15a). On the other hand, ionic nucleophilic catalysts could rapidly attack to acylating reagent. However, the C-C bond formation is intermolecular reaction between azlactone enolate bearing ammonium ion and acylated anionic part of the catalyst, which is nonionic, low reactive acylation reagents. Since it is difficult to promote this C-C bond-forming step, the development of acyl transfer reactions promoted by ionic nucleophilic catalysts are restricted (Figure 15b). In the case of ammonium betaines, since C-C bond formations are pseudo intramolecular reaction of ammonium ion possessing acylating site and azlactone enolate, acyl transfer reaction would proceed smoothly (Figure 15c).

Figure 15. Reaction Mechanism of Steglich Reacction



Unfortunately, ammonium betaines **20a** catalyzed Steglich reaction resulted in low reactivity. Significantly, dramatic improvement of the catalytic activity was observed under the influence of **28a** whose phenyl group was removed from *ortho*-position of aryloxides. Further, use of **28b**, which has 3,5-$(CF_3)_2$-C_6H_3 as an electron-withdrawing group at the three position of naphthyl ring, afforded the corresponding products in 94% yield with 97% ee (Scheme 16).

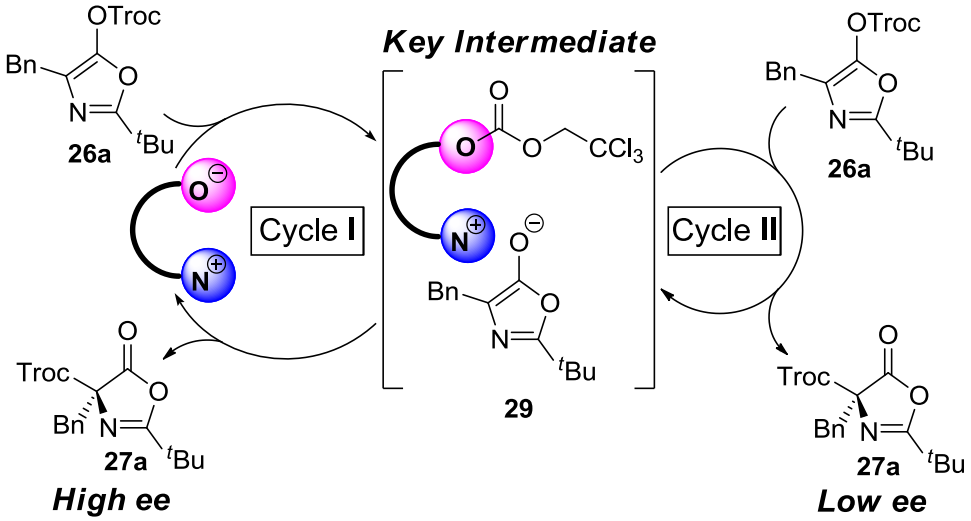
Scheme 16. Chiral Ammonium Betaine Catalyzed Steglich Reaction



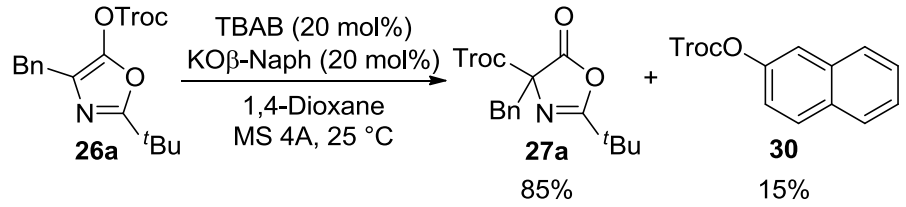
The enantioselectivities depended on substrate concentration to catalyst in this reaction. The reaction under low substrate concentration (slow addition of a substrate solution to a catalyst solution) resulted in high enantioselectivity. On the other hand, under high substrate concentration (addition of catalyst to a substrate solution) low enantioselectivity was observed. These results suggested that there are two reaction pathways shown below (Figure 16). The Cycle I is pseudo intramolecular reaction of the key intermediate **29**, which is generated by nucleophilic attack of aryloxide to **26a**. The Cycle II is intermolecular reaction between the key intermediate **29** as ammonium enolates and **26a** as acylating reagents. In addition, it was anticipated that Cycle II is

competitive with Cycle I under high substrate concentration conditions. The Steglich reaction catalyzed by tetrabutylammonium β-naphthoxide resulted in the formation of the desire product in 85% yield and 2,2,2-trichloroethoxycarbonyl-β-naphthoxide **30**, which are acylated anion moiety of the catalyst, in 15% yield. This result revealed that **26a** is capable of serving as an acylating reagent (Scheme 17). Because the reaction under low substrate concentration showed higher enantioselectivity than that under high substrate concentration, it was proposed that pseudo intramolecular reaction of the key intermediate **29** (Cycle I) is crucial for obtaining highly enantioselective product **27**.

Figure 16. Possible Reaction Pathways for Chiral Ammonium Betaine Catalyzed Steglich Reaction



Scheme 17. Tetra Butyl Ammonium β-Naphthoxide Catalyzed Steglich Reaction

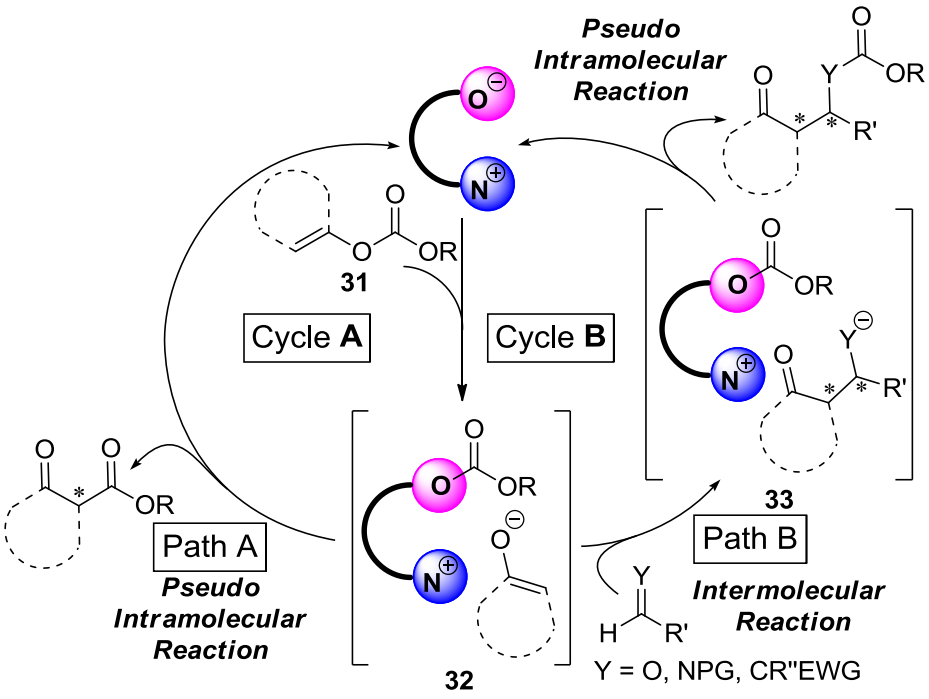


2.3.2 Development of New Reaction System Catalyzed by Ammonium Betaine as Ionic Nucleophilic Catalyst (Chapter 5)

The application of asymmetric Steglich reaction catalyzed by ammonium betaine was demonstrated. Existence of two reaction pathways, ***pseudo intramolecular*** acyl transfer reaction and ***intermolecular*** acyl transfer reaction, was disclosed. Thus, reaction intermediate **32**, which is generated by nucleophilic attack of betaine to vinylic carbonate **31**, could react with various electrophiles. In other ward, there are two reaction pathways, pseudo intramolecular reaction of the intermediate **32** (Figure 18, Path A), and intermolecular reaction of **32** with electrophile (Figure 18, Path B). Since this intermolecular reaction seems to be specific pathway of ammonium betaine catalyzed acyl transfer reaction, it gives an opportunity to develop new reaction system. The actual working hypothesis is following: (1) intermolecular reaction of **32** with electrophile, such as aldehydes,

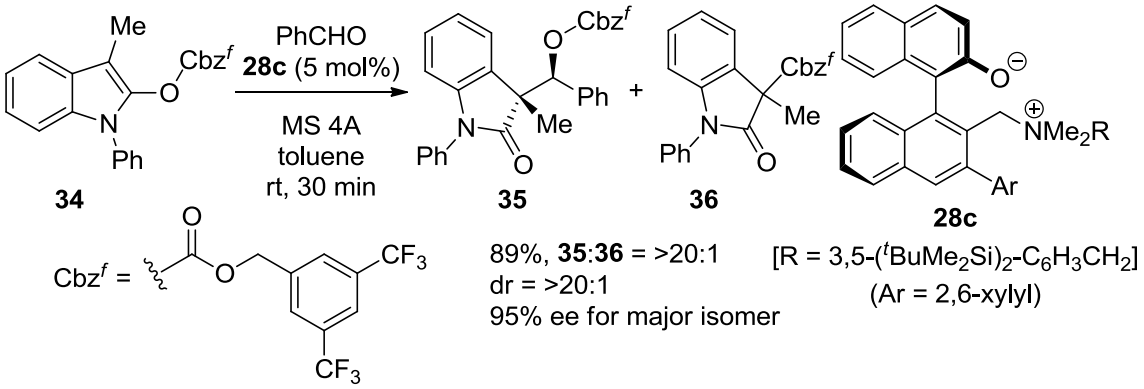
imines, or α,β-unsaturated carbonyl compounds; (2) subsequent pseudo intramolecular acyl transfer reaction of the second intermediate **33** (Figure 18 Cycle B).

Figure 17. Intramolecular Reaction vs. Intermolecular Reaction



Asymmetric aldol reactions of oxindole are powerful approach for enantioselective construction of oxindole derivatives containing a quaternary stereocenter at the C-3 position.[35] However, asymmetric catalytic aldol reactions of oxindoles with aldehydes or ketones remains largely unexplored due to instability of oxindole aldol adducts, which easily undergo racemization via retro aldol reaction.[35] Since ammonium betaine catalyzed aldol-type reactions of oxindole derived vinylic carbonate **34** with aldehydes would produce acyl protected oxindole aldol adduct, no racemization of products should occur. Indeed, chiral ammonium betaine **28c** catalyzed asymmetric aldol-type reaction of vinylic carbonate **34** with benzaldehyde showed the high catalytic activity and stereoselectivity (89%, dr = >20:1, 95% ee for major isomer). On the other hand, use of DMAP, which is the most popular nucleophilic catalyst, produced only migration product **36** (12 h, 96%).

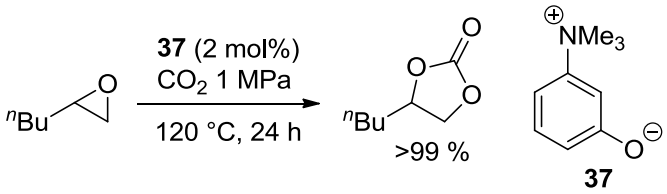
Scheme 18. Ammonium Betaine Catalyzed Aldol-Type Reaction



2.4 Other Ammonium Betaines Catalysts

Quite recently, after author's report, another achiral ammonium betaine catalyst has been developed. Sakai successfully applied ammonium betaine **37** as bifunctional organocatalysts to activation of carbon dioxide and epoxides for producing cyclic carbonate (Scheme 19).[36]

Scheme 19. Ammonium Betaine Activated CO_2



3 Conclusion

Although chiral tetraalkylammonium salts have attracted considerable attraction as asymmetric catalysts, intramolecular ion pair type ammonium salts as chiral organocatalysts had remained unexplored. However, the author focused on ammonium betaines and revealed their capability as chiral bifunctional organic base and nucleophilic catalysts. The author also emphasized that this study would be a new approach toward the developments of ammonium salts as asymmetric catalysts.

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Chapter 2

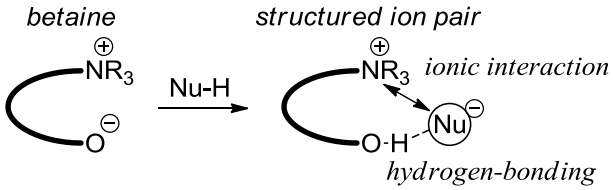
Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric Mannich-type Reaction of α-Nitrocarboxylates

Abstract: A chiral ammonium betaine, an intramolecular ion-pairing quaternary ammonium aryloxide **3d**, has been designed and its vast potential as an enantioselective organic base catalyst has been successfully demonstrated in the highly enantioselective direct Mannich-type reaction of α-substituted α-nitrocarboxylates **6** with various *N*-Boc imines **5**. The present study provides a conceptually new approach toward the design of bifunctional, chiral quaternary ammonium salts and their utilizations as a homogeneous organic molecular catalyst.

Introduction

A betaine, historically regarded as *N*,*N*,*N*-trimethylglycine, can be chemically defined as a neutral compound with an onium ion center bearing no hydrogen atom and an anionic moiety that is not adjacent to the cationic site. If the onium center consists of a nitrogen atom, it is classified as a quaternary ammonium salt.[1] In contrast to intermolecular ion-pairing ammonium salts, a quaternary ammonium betaine possessing an anion as its embedded functionality is inherently amenable to modification of the entire structure of the organic ion-pair. Additionally, an ammonium betaine containing a basic anion could be capable of deprotonating a pronucleophile (Nu-H) to furnish an onium ion as its conjugate acid form (Figure 1). The acidic proton thus generated could direct the counterionic nucleophile at a defined position through the hydrogen-bonding interaction, thereby rendering a structured intermolecular ion pair. Although these properties of an ammonium betaine, in combination with an appropriate chiral scaffold, would offer a new approach to homogeneous catalysis of bifunctional[2] chiral onium salts, research in this direction has remained elusive. Herein, we report the design of chiral quaternary ammonium betaines of type **3** (Scheme 1) and demonstrate its potential as an enantioselective organic base catalyst[3] in a direct Mannich-type reaction.[4]

Figure 1. Ammonium Betaine as a Structural Platform to Induce Bifunctional Catalysis



Results and Discussion

1. Asymmetric Direct Mannich-Type Reaction of α-Nitrocarboxylates Catalyzed by Chiral Ammonium Betaines

First, we synthesized quaternary ammonium chloride **1** as a precursor and sought an appropriate condition for the preparation of chiral ammonium betaine **2** possessing an aryloxy moiety as a basic functionality. Treatment of **1** with anhydrous tripotassium phosphate in acetone afforded **2** as a bench stable, yellowish solid as shown in Scheme 1.[5] In order to evaluate the performance of **2** as an organic base catalyst, author selected α-substituted α-nitrocarboxylate **6** as a suitable pronucleophile and examined its Mannich-type reaction with *N*-Boc aldimines based on a recent efficient protocol for the asymmetric synthesis of α-substituted α,β-diamino acids.[6] Thus, an initial attempt was made by treating *tert*-butyl 2-nitropropionate (**6a**) with benzaldehyde-derived *N*-Boc imine **5a** in the presence of **2** (5 mol%) in toluene at 0 ˚C for 20 h. This revealed that **2** was indeed able to act as a catalyst, though its activity and stereoselectivity were insufficient (entry 1 in Table 1). Encouraged by this observation, author next assembled the betaines of type **3** with the expectation that the C_2-symmetric its conjugate acid would induce a high level of stereocontrol.[7] Interestingly, while **3a** did not improve enantioselectivity despite the increase in catalytic activity (93% yield in 10 h) (entry 2),

incorporation of phenyl substituents at the *ortho* position of the aryloxy moiety (**3b**) resulted in remarkable enantioselectivity (entry 3). Further, the introduction of substituents to the other *ortho* position of the binaphthyl component (R^1) was found to be associated with improvement of diastereoselectivity, and the use of chloro-substituted **3d** led to the preferential formation of a *syn*-isomer with almost complete enantiocontrol (entries 4 and 5). It should be noted that the catalyst loading can be reduced to 1 mol% without any detrimental effect on the stereoselectivity (entry 6). Meanwhile, the importance of the zwitterionic nature of **3d** for stereocontrol was clearly demonstrated by comparing it with intermolecular ion-pairing chiral quaternary ammonium 2-naphthoxide **4**.[8] Although a similar reaction rate was induced by **4**, the loss of stereoselectivity implies the crucial role of the proximal phenolic proton as a hydrogen-bonding donor in forming the expected structured ion pair (entry 7).[9]

Scheme 1. Chiral Ammonium Betaines **2** and **3**

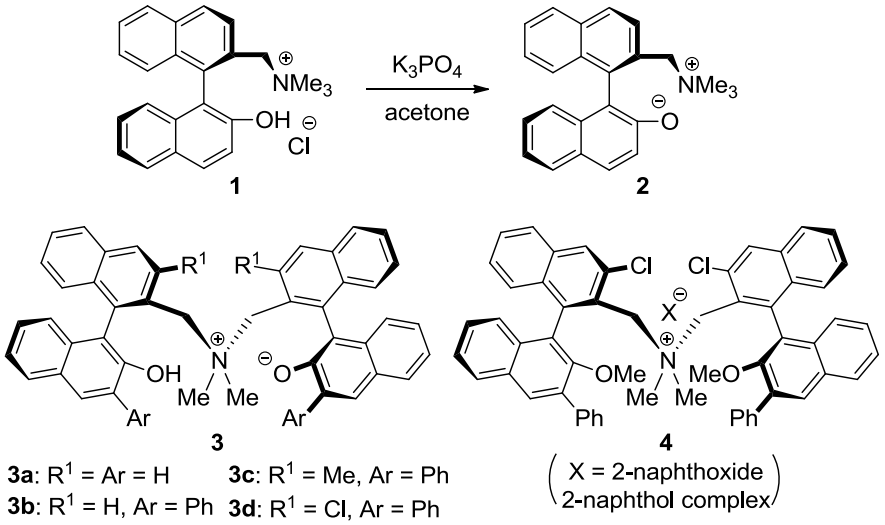
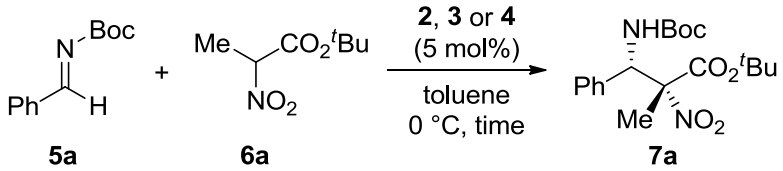


Table 1. Effect of the Catalyst Structure on the Reactivity and Stereoselectivity of the Direct Mannich-type Reaction of *tert*-Butyl 2-Nitoropropionate (**6a**).



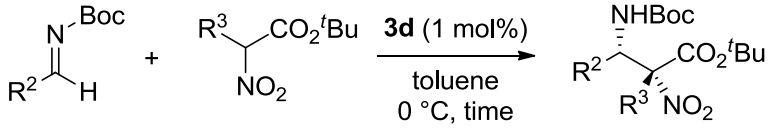
entry	catalyst	time (h)	yield[b] (%)	d.r.[c] (*syn:anti*)	ee[d] (%)
1	**2**	20	40	1:1.2	12/18
2	**3a**	10	93	1:1	-24/16
3	**3b**	8.5	93	1:1	98/95
4	**3c**	2	91	2.0:1	99/90
5	**3d**	5	95	4.1:1	99/91
6[e]	**3d**	8	97	3.9:1	99/93
7	**4**	5	97	1.3:1	-5/5

[a]Unless otherwise noted, the reaction of **5a** (1.1 equiv.) and **6a** (0.1 mmol) in toluene (0.2 mL) was conducted in the presence of catalyst (5 mol%) at 0 °C for the given reaction time. [b]Isolated yield. [c]Determined by ^{1}H-NMR analysis of the crude reaction mixtures. [d]Determined by chiral HPLC analysis using a chiral column (DAICEL

Chiralpak AD-H) with hexane-isopropyl alcohol (10/1) as solvent. Absolute and relative configurations were determined by comparison with literature data after derivatization.[6b] [e]1 mol% of the catalyst was used

With the information on the catalytic and chiral efficiencies of **3d** at hand, the scope of this direct Mannich-type reaction was explored. The representative results are summarized in Table 2. Generally, 1 mol% of **3d** was sufficient for a smooth reaction in toluene at 0 ˚C, giving **7** in excellent chemical yield. The trend of the stereochemical outcome was the *syn*-selectivity and the rigorous enantiocontrol observed for both diastereomers. With aromatic *N*-Boc imines, the present system tolerated the incorporation of both electron-withdrawing and electron-donating substituents including the methoxycarbonyl group (entries 1-5). A near-identical level of reactivity and selectivity was attained in the reactions with imines derived from furfural and 1-naphthaldehyde (entries 6 and 7). Moreover, aliphatic aldehyde-derived imines appeared to be good Mannich acceptors albeit certain decrease in the diastereoselectivity was detected (entries 8 and 9). As evident from the result of the reaction with α-nitrobutanoate, other α-nitrocarboxylates bearing different α-substituents could also be employable as pronucleophiles (entry 10).

Table 2. Substrate Scope of Chiral Ammonium Betaine **3d**-Catalyzed Direct Mannich-type Reaction.



5 **6** **7**

entry	R^2	R^3	time (h)	yield[b] (%)	d.r.[c] (*syn:anti*)	ee[d] (%)
1	*p*-Cl-C_6H_4	Me	8	>99	3.6:1	99/91
2	*p*-Br-C_6H_4		6	96	3.8:1	99/92
3	*p*-MeO-C_6H_4		9	96	5.0:1	99/72
4	*p*-MeOCO-C_6H_4		3	95	4.4:1	99/92
5	*o*-Me-C_6H_4		10	91	5.2:1	98/93
6	furyl		6	>99	4.4:1	99/96
7[e]	1-naphthyl		15	96	3.8:1	98/91
8[e]	$PhCH_2CH_2$		10	91	2.0:1	97/92
9[e]	$CH_3(CH_2)_7$		11	97	2.2:1	99/91
10[e]	Ph	Et	24	93	3.2:1	99/87

[a]Unless otherwise specified, the reaction of **5** (1.1 equiv.) with **6** (0.2 mmol) was carried out in toluene (0.4 mL) under the influence of **3d** (1 mol%) at 0 ˚C for the given reaction time. [b]Isolated yield. [c]Determined by ^{1}H-NMR analysis of the crude reaction mixtures. [d]Determined by chiral HPLC analysis using a chiral column, see the Supporting Information for details. [e]1.5 equiv. of **5** was used.

Summary

In summary, author has devised a chiral ammonium betaine as a highly enantioselective organic base catalyst in the direct Mannich-type reaction of α-substituted α-nitrocarboxylates with various *N*-Boc imines. Author believes the chemistry described here represents a new direction for the

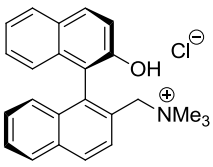
design of bifunctional, chiral quaternary ammonium salts and their utilization as homogeneous organic molecular catalysts. Intensive research in this direction is underway in our laboratory.

Experimental

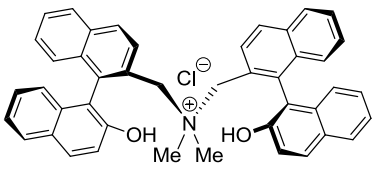
General Information: Infrared spectra were recorded on a JASCO FT/IR-230 or JASCO FT/IR-300E spectrometer. ^{1}H NMR spectra were recorded on a Varian INOVA-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance ($(CD_3)_2SO$; 2.50 ppm, CD_3OD; 3.31 ppm) or Me_4Si resonance (0.0 ppm; $CDCl_3$, $(CD_3)_2CO$) as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian INOVA-500 (126 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance ($CDCl_3$; 77.16 ppm, $(CD_3)_2SO$; 39.5 ppm, CD_3OD; 49.0 ppm) or Me_4Si resonance (0.0 ppm; $(CD_3)_2CO$) as the internal standard. Optical rotations were measured on a JASCO DIP-1000 polarimeter. The high resolution mass spectra were conducted at the Research Center for Materials Science, Graduate School of Science, Nagoya University. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40-50 μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns (ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK AD-H (AD-H) or CHIRALCEL OD-H (OD-H)).

Toluene was supplied from Kanto Chemical Co., Inc. as "Dehydrated solvent system". Aromatic and heteroaromatic imines,[10] aliphatic imines,[11] and nitroacetates[12] were prepared by following the literature procedure. Other simple chemicals were purchased and used as such.

Characterization of Betaine Precursors 1, 3:

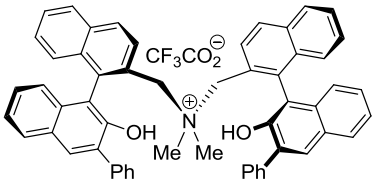


1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (1H, br), 7.87 (1H, d, J = 8.5 Hz), 7.82-71 (3H, m), 7.61 (1H, d, J = 8.5 Hz), 7.48 (1H, d, J = 8.5 Hz), 7.44 (1H, t, J = 8.5 Hz), 7.23 (1H, d, J = 8.5 Hz), 7.22 (1H, t, J = 8.5 Hz), 7.10 (1H, t, J = 8.5 Hz), 7.07 (1H, t, J = 8.5 Hz), 6.65 (1H, d, J = 8.5 Hz), 4.43 (1H, d, J = 13.0 Hz), 4.31 (1H, d, J = 13.0 Hz), 2.65 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 139.2, 134.1, 133.8, 132.8, 130.8, 130.0, 128.7, 128.5, 128.4, 128.1, 127.8, 127.7, 127.3, 127.0, 124.7, 123.7, 123.3, 119.4, 115.2, 67.6, 52.9; IR (KBr): 3384, 3171, 1623, 1508, 1475, 1434, 1344, 1299, 1274, 1233, 974, 878, 825, 763 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{24}NO^+$ ([M-Cl]$^+$) 342.1858. Found 342.1871.

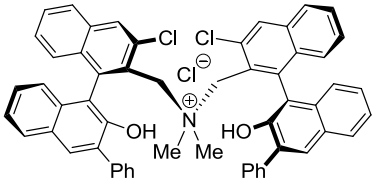


3a·HCl: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (2H, br), 7.74 (2H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.5 Hz), 7.48 (2H, d, J = 8.5 Hz), 7.43 (2H, t, J = 8.5 Hz), 7.34 (2H, t, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 7.30-7.20 (6H, m), 7.13 (2H, t, J = 8.5 Hz), 7.00 (2H, t, J = 8.5 Hz), 6.53 (2H, d, J = 8.5 Hz), 4.66 (2H, d, J = 12.5 Hz), 3.86 (2H, d, J = 12.5 Hz), 2.36 (6H, brs); ^{13}C NMR

(175 MHz, $(CD_3)_2CO$) δ 155.0, 141.0, 134.9, 134.4, 133.7, 130.3, 129.8, 129.6, 129.3, 128.9, 128.6, 128.5, 128.1, 127.6, 127.4, 124.9, 123.4_5, 123.4_2, 120.3, 115.8, 66.6, 50.0; IR (KBr): 3165, 3058, 1623, 1507, 1475, 1434, 1344, 1274, 977, 820 cm^{-1}; HRMS (FAB) Calcd for $C_{44}H_{36}NO_2^+$ ($[M\text{-}Cl]^+$) 610.2746. Found 610.2736.

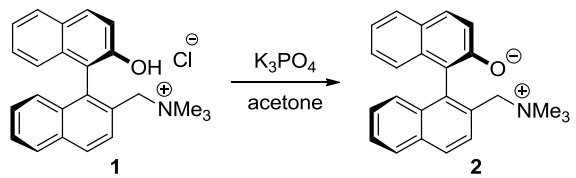


3b·CF_3CO_2H: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.5 Hz), 7.71 (2H, d, J = 8.5 Hz), 7.68 (2H, d, J = 8.5 Hz), 7.57 (2H, s), 7.51 (2H, d, J = 8.5 Hz), 7.50 (2H, t, J = 8.5 Hz), 7.32-7.22 (12H, m), 7.18-7.12 (6H, m), 6.68 (2H, d, J = 8.5 Hz), 4.56 (2H, d, J = 13.0 Hz), 4.22 (2H, d, J = 13.0 Hz), 2.57 (6H, s), O-H protons were not found due to broadening; ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (q, $J_{F\text{-}C}$ = 37.2 Hz), 148.4, 137.1, 136.3, 134.4, 132.8, 132.4, 130.8, 130.2, 129.8, 129.5, 129.2, 129.1, 128.9, 128.6_4, 128.5_9, 128.2, 128.0, 127.7, 127.2, 127.0, 125.2, 124.5, 123.8, 116.4_5, 116.3_6 (q, $J_{F\text{-}C}$ = 292.3 Hz), 66.5, 50.0; IR (KBr): 3390, 3059, 1678, 1498, 1476, 1425, 1206, 1138, 1072, 1029, 768, 705 cm^{-1}; HRMS (FAB) Calcd for $C_{56}H_{44}NO_2^+$ ($[M\text{-}CF_3CO_2]^+$) 762.3372. Found 762.3366.



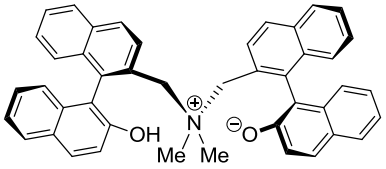
3d·HCl: Although NMR analysis gave broad spectrum at room temperature, it can be improved at 100 ˚C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 ˚C) δ 8.63 (2H, brs), 8.28 (2H, s), 8.04 (2H, d, J = 8.5 Hz), 8.03 (2H, s), 8.00 (2H, d, J = 8.5 Hz), 7.65 (2H, t, J = 8.5 Hz), 7.57 (4H, d, J = 8.5 Hz), 7.47 (4H, t, J = 8.5 Hz), 7.42 (2H, d, J = 8.5 Hz), 7.40 (2H, t, J = 8.5 Hz), 7.30 (2H, t, J = 8.5 Hz), 7.21 (2H, t, J = 8.5 Hz), 7.20 (2H, t, J = 8.5 Hz), 6.62 (2H, d, J = 8.5 Hz), 4.77 (2H, d, J = 13.5 Hz), 4.61 (2H, br), 2.66 (6H, brs); ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 ˚C) δ 149.7, 141.1, 137.2, 134.3, 132.1, 131.8, 131.7, 131.1, 129.2, 129.0, 128.9, 128.2_5, 128.1_6, 128.1, 127.6, 127.1, 127.0, 126.8, 126.6, 123.9, 123.4, 116.8, 65.4, 50.5, two carbons were not found probably due to overlapping; IR (KBr): 3405, 3056, 1619, 1472, 1427, 1259, 1199, 1006, 899, 750 cm^{-1}; HRMS (FAB) Calcd for $C_{56}H_{42}Cl_2NO_2^+$ ($[M\text{-}Cl]^+$) 830.2593. Found 830.2592.

Preparation and Characterization of Betaine 2, 3a:



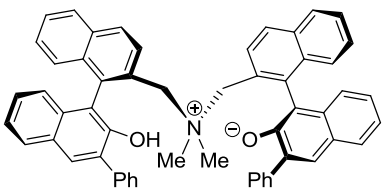
Preparation of Ammonium betaine 2: A solution of ammonium chloride **1** in acetone was treated with an excess amount of anhydrous K_3PO_4 and filtered with the aid of ethyl acetate. The filtrate was concentrated by rotary evaporation. The residual solid was dissolved to trifluoroethanol and the solution thus obtained was filtered through a syringe filter (porous size: 0.45 μm). After concentration, the residual solid was washed with Et_2O on a funnel and dried under vacuum to afford chiral ammonium betaine **2** as a yellowish solid. **2:** ^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (1H, d, J =

8.5 Hz), 7.97 (1H, d, J = 8.5 Hz), 7.80 (1H, d, J = 8.5 Hz), 7.74_2 (1H, d, J = 8.5 Hz), 7.73_6 (1H, d, J = 8.5 Hz), 7.53 (1H, td, J = 8.5, 1.0 Hz), 7.46 (1H, d, J = 8.5 Hz), 7.30 (1H, td, J = 8.5, 1.0 Hz), 7.18 (1H, d, J = 8.5 Hz), 7.08-7.02 (2H, m), 6.59-6.54 (1H, m), 4.53 (1H, d, J = 13.0 Hz), 4.28 (1H, d, J = 13.0 Hz), 2.89 (9H, s); ^{13}C NMR (126 MHz, CD_3OD) δ 163.2, 143.6, 136.4, 136.2, 134.9, 131.2, 130.9, 129.4, 129.3, 129.0, 128.9, 128.4, 127.9, 127.5, 127.3, 126.3, 124.9, 123.6, 121.6, 116.8, 69.6, 53.8; IR (KBr): 3398, 1623, 1508, 1475, 1434, 1344, 1274, 1233, 975, 878, 826, 763 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{24}NO^+$ ($[M+H]^+$) 342.1858. Found 342.1849.

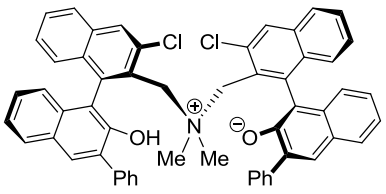


3a: Prepared by similar procedure for the preparation of **2**. ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.06-7.56 (4H, br), 7.63 (2H, br), 7.56-6.75 (14H, br), 7.47 (2H, br), 6.44 (2H, br), 4.50 (2H, br), 4.04 (2H, br), 2.36 (6H, br), O-H proton was not found probably due to broadening; ^{13}C NMR analysis gave broad spectrum and it was not assignable; IR (KBr): 3057, 2923, 1621, 1473, 1346, 1274, 1146, 869, 820, 749 cm^{-1}; HRMS (FAB) Calcd for $C_{44}H_{36}NO_2^+$ ($[M+H]^+$) 610.2736. Found 610.2746.

For the preparation of **3b-d**, the following, rather convenient procedure was also applicable: A solution of ammonium salt **3**·HCl or **3**·CF_3CO_2H in ethyl acetate was treated with 0.1 M aqueous $NaHCO_3$ and phases were separated. The organic phase was dried over Na_2SO_4 and filtered. All volatiles were removed by evaporation and residual solid was washed with Et_2O on a funnel. The solid was dried under reduced pressure to afford the ammonium betaine **3** as a yellow solid.

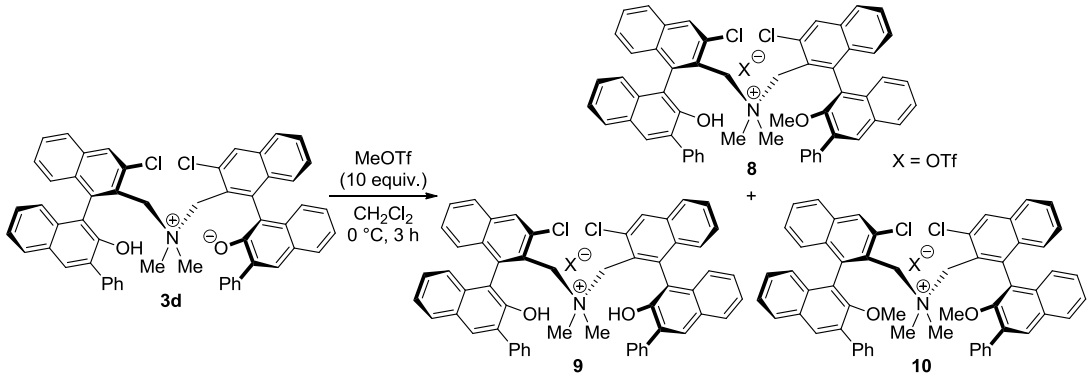


3b: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.94 (2H, d, J = 8.5 Hz), 7.79 (2H, d, J = 8.5 Hz), 7.78 (2H, d, J = 8.5 Hz), 7.63 (2H, s), 7.54 (2H, t, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.30 (2H, t, J = 8.5 Hz), 7.21 (4H, d, J = 8.5 Hz), 7.09 (2H, t, J = 8.5 Hz), 7.05-6.96 (8H, m), 6.61 (2H, d, J = 8.5 Hz), 4.79 (2H, d, J = 13.0 Hz), 4.38 (2H, d, J = 13.0 Hz), 2.79 (6H, s), O-H proton was not found probably due to broadening; ^{13}C NMR analysis gave broad spectrum and it was not assignable; IR (KBr): 3374, 3052, 1686, 1601, 1421, 1200, 1030, 819, 767, 704 cm^{-1}; HRMS (FAB) Calcd for $C_{56}H_{44}NO_2^+$ ($[M+H]^+$) 762.3372. Found 762.3366.



3d: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.10 (1H, br), 7.97 (1H, br), 7.95 (1H, brd, J = 7.5 Hz), 7.87 (2H, br), 7.80 (2H, br), 7.69 (1H, br), 7.64 (1H, br), 7.59 (2H, br), 7.45 (3H, br), 7.24 (1H, br), 7.14 (3H, br), 7.03 (5H, br), 6.90 (6H, br), 6.45 (1H, br), 5.18 (1H, br), 4.91 (1H, d, J = 13.5 Hz), 4.71 (1H, br), 4.70 (1H, d, J = 13.5 Hz), 3.15 (3H, brs), 2.35 (3H, s), O-H proton was not found probably due to broadening; ^{13}C NMR analysis gave broad spectrum and it was not assignable; IR (KBr): 3435, 3054, 1611, 1494, 1469, 1424, 1005, 849, 791, 748 cm^{-1}; HRMS (FAB) Calcd for $C_{56}H_{42}Cl_2NO_2^+$ ($[M+H]^+$) 830.2593. Found 830.2592. $[\alpha]^{25}_D$ -104.1 (c = 0.36, MeOH).

In order to obtain compelling evidence to support the betaine structure of **3d**, author performed the direct monomethylation of **3d** as shown below.



Direct Monomethylation of Ammonium Betaine 3d: To a solution of methyl trifluoromethanesulfonate (17 μL, 0.15 mmol) in 100 μL of CH_2Cl_2 was added a solution of **3d** (11.0 mg, 0.013 mmol) in 400 μL of CH_2Cl_2 dropwise at 0 ˚C. The reaction mixture was stirred for 3 h and poured into ice-cooled water. Extractive workup was performed with chloroform and the organic phase was dried over Na_2SO_4. Purification on silica gel column chromatography gave a mixture of ammonium salts (10.9 mg).

FAB-MS spectrum (Chart S1) of the mixture showed one major peak corresponding to **8** (*m*/*z* = 844) and two minor peaks corresponding to **9** (*m*/*z* = 830), **10** (*m*/*z* = 858), respectively. This result clearly indicated the predominant presence of ammonium betaine **3d** in the solution used for the reaction. Further information was obtained from ^{1}H NMR spectra taking at 100 ˚C (Chart S2) and the ratio of ammonium salts was assigned to be **8**/**9**/**10** = 75/17/8. **8:** ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 ˚C) δ 8.60 (1H, br), 8.31 (2H, s), 8.17 (1H, s), 8.09 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 8.5 Hz), 8.04 (1H, d, *J* = 8.5 Hz), 8.03 (1H, s), 7.97 (1H, d, *J* = 8.5 Hz), 7.66 (2H, t, *J* = 8.5 Hz), 7.60-7.56 (4H, m), 7.51-7.37 (9H, m), 7.29 (1H, t, *J* = 8.5 Hz), 7.25 (1H, t, *J* = 8.5 Hz), 7.22-7.16 (2H, m), 7.07 (1H, d, *J* = 8.5 Hz), 6.84 (1H, br), 6.61 (1H, br), 4.82-4.68 (2H, m), 4.60 (2H, br), 2.79 (6H, s), 2.64 (3H, s).

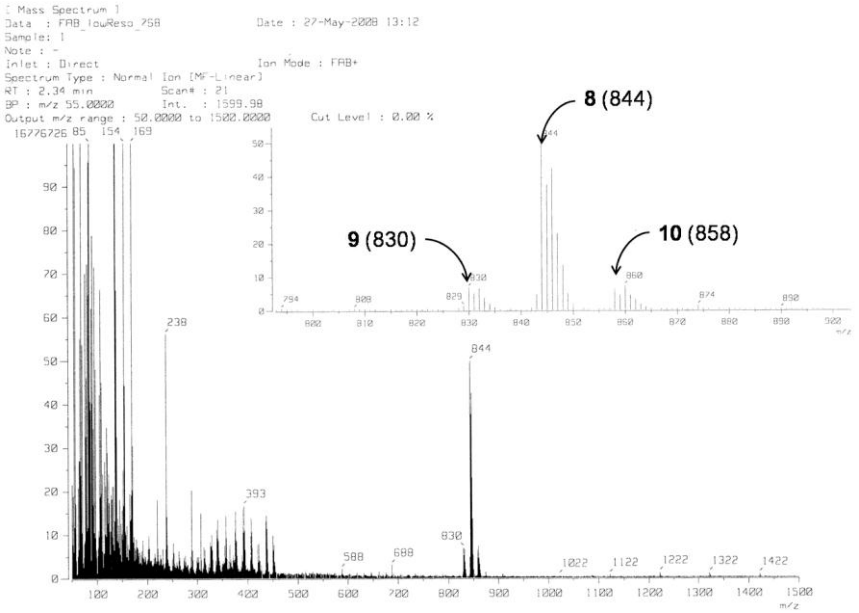


Chart S1. FAB-MS (NBA) spectrum.

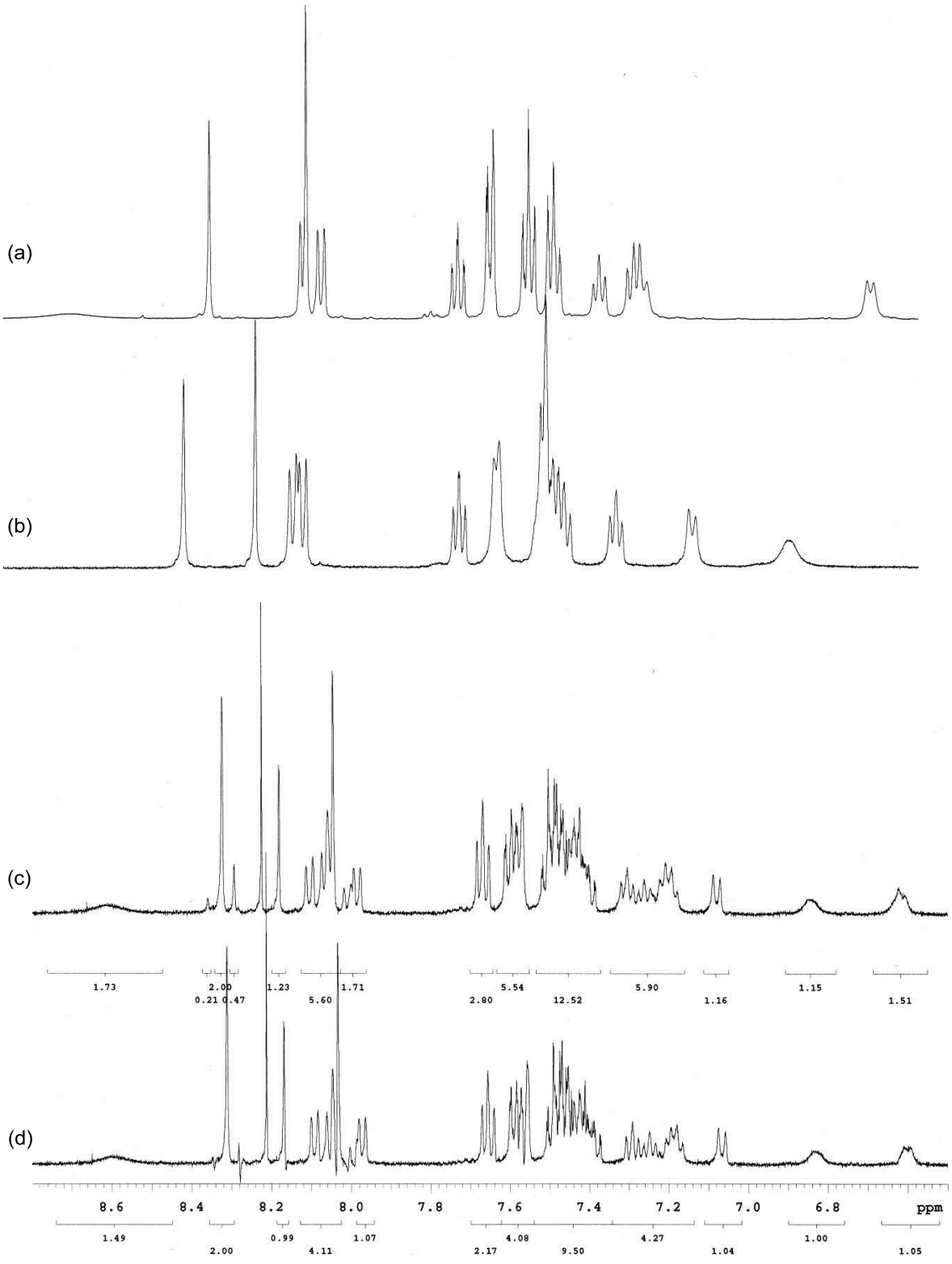
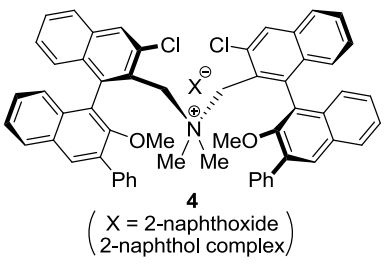
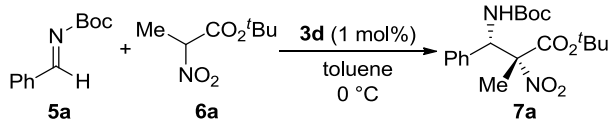


Chart S2. Expansion of aromatic region of ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 ˚C) spectra of ammonium salts. (a) ^{1}H NMR spectrum of **9**. (b) ^{1}H NMR spectrum of **10**. (c) ^{1}H NMR spectrum of a mixture of **8**, **9**, and **10**. (d) Expecting ^{1}H NMR spectrum of **8**, which was made by subtraction of spectrum {(c)-(a)-(b)}.



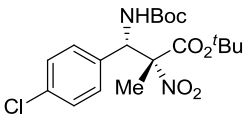
4
(X = 2-naphthoxide
2-naphthol complex)

4: Prepared from the corresponding ammonium hydroxide according to the literature procedure.[8] Although NMR analysis gave broad spectrum at room temperature, it can be improved at 100 ˚C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 ˚C) δ 8.34 (2H, s), 8.16 (2H, s), 8.07 (2H, d, J = 8.5 Hz), 8.05 (2H, d, J = 8.5 Hz), 7.69 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz), 7.65_5 (2H, t, J = 8.5 Hz), 7.61-7.54 (6H, m), 7.47-7.37 (10H, m), 7.32 (2H, t, J = 8.5 Hz), 7.26 (2H, t, J = 8.5 Hz), 7.17 (2H, t, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.04 (2H, s), 6.83 (2H, br), 4.88 (2H, b), 4.74 (2H, d, J = 13.5 Hz), 2.81 (6H, s), 2.59 (6H, s); ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 ˚C) δ 137.0, 133.9, 132.0_3, 131.9_7, 130.9, 130.1, 129.9, 129.4, 128.5_3, 128.4_5, 128.3_8, 128.3_1, 127.8, 127.2, 127.0, 126.8_8, 126.8_2, 126.6, 126.1, 125.8, 125.7, 125.4, 125.1, 124.6, 124.3, 123.3, 121.9, 118.1, 108.3, 65.2, 59.5, 50.8, five carbons were not found; IR (KBr): 3056, 1627, 1496, 1459, 1402, 1220, 901, 849, 750 cm^{-1}; HRMS (FAB) Calcd for $C_{58}H_{46}Cl_2NO_2^+$ ([M-(2-naphthoxide·2-naphthol)]$^+$) 858.2906. Found 858.2911.

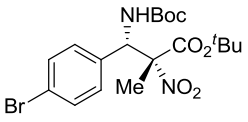


5a **6a** **7a**

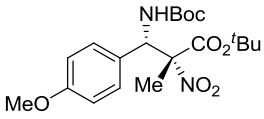
Representative Procedure for Catalytic Asymmetric Mannich-type Reaction of α-Nitrocarboxylates 6a: To a dried test tube was weighted betaine **3d** (1.66 mg, 0.002 mmol) under an argon atmosphere. The catalyst was dissolved into toluene (400 μL) at room temperature. *tert*-Butyl 2-nitropropionate **6a** (35.0 mg 0.2 mmol) was added at 0 ˚C. Benzaldehyde-derived *N*-Boc imine **5a** (45.2 mg, 0.22 mmol) was introduced dropwise and the stirring was continued for the indicated time under the conditions. The reaction mixture was poured into ice-cooled 1 N aqueous HCl and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and filtered. All volatiles were removed by evaporation and the diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. Purification of the residue by column chromatography on silica gel gave **7a** as a mixture of diastereomers (97%, *syn*:*anti* = 3.9:1), whose enantiomeric excesses were determined by HPLC analysis (*syn*/*anti* = 99% ee/93% ee). **7a:** HPLC: AD-H, Hexane (H)/Isopropyl alcohol (IPA) = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.8 min (major *anti* isomer; (2*S*,3*S*)), 13.2 min (major *syn* isomer; (2*R*,3*S*)), 18.5 min (minor *syn* isomer; (2*S*,3*R*)), 19.3 min (minor *anti* isomer; (2*R*,3*R*)). Absolute and relative configurations were determined by comparison with literature data after derivatization.[6b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (3H, m), 7.26-7.22 (2H, m), 6.57 (1H, d, J = 10.5 Hz), 5.38 (1H, d, J = 10.5 Hz), 1.71 (3H, s), 1.53 (9H, s), 1.41 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 154.7, 135.5, 128.8, 128.4, 96.6, 85.3, 80.2, 59.0, 28.5, 27.8, 21.7, one carbon was not found probably due to overlapping; IR (KBr): 3452, 2978, 1742, 1583, 1556, 1370, 1352, 1314, 754, 704 cm^{-1}; HRMS (FAB) Calcd for $C_{19}H_{29}N_2O_6^+$ ([M+H]$^+$) 381.2026. Found 381.2042.



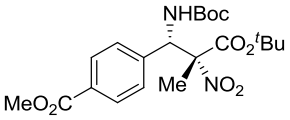
7b: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 14.4 min (major *anti* isomer), 15.5 min (major *syn* isomer), 28.0 min (minor *anti* isomer), 29.7 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 6.54 (1H, d, J = 10.0 Hz), 5.35 (1H, d, J = 10.0 Hz), 1.71 (3H, s), 1.52 (9H, s), 1.41 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 154.6, 134.9, 134.0, 129.8, 129.0, 96.4, 85.6, 80.5, 58.4, 28.4, 27.8, 21.6; IR (liq. film): 3453, 2980, 2934, 1746, 1714, 1596, 1557, 1370, 1346, 844, 759 cm^{-1}; HRMS (FAB) Calcd for $C_{19}H_{28}ClN_2O_6^+$ ([M+H]$^+$) 415.1636. Found 415.1653.



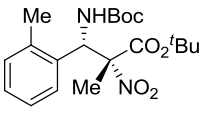
7c: HPLC: AD-H, H/Ethanol (EtOH) = 30:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.8 min (major *anti* isomer), 15.3 min (major *syn* isomer), 22.9 min (minor *anti* isomer), 37.6 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 6.53 (1H, d, J = 10.0 Hz), 5.33 (1H, d, J = 10.0 Hz), 1.70 (3H, s), 1.52 (9H, s), 1.40 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 154.6, 134.6, 132.0, 130.1, 123.1, 96.4, 85.6, 80.5, 58.5, 28.4, 27.8, 21.6; IR (liq. film): 3454, 2979, 2933, 1746, 1715, 1557, 1487, 1369, 1346, 1166, 1011, 843 cm^{-1}; HRMS (FAB) Calcd for $C_{19}H_{28}BrN_2O_6^+$ ([M+H]$^+$) 459.1131. Found 459.1122.



7d: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 14.7 min (major *anti* isomer), 16.2 min (major *syn* isomer), 28.4 min (minor *anti* isomer), 30.7 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (2H, d, J = 9.0 Hz), 6.84 (2H, d, J = 9.0 Hz), 6.51 (1H, d, J = 10.0 Hz), 5.32 (1H, d, J = 10.0 Hz), 3.78 (3H, s), 1.69 (3H, s), 1.52 (9H, s), 1.40 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 160.4, 155.2, 130.1, 128.0, 114.7, 97.4, 85.8, 80.7, 59.1, 55.9, 29.0, 28.3, 22.2; IR (liq. film): 3458, 2979, 2935, 1745, 1721, 1584, 1557, 1486, 1254, 1166, 845 cm^{-1}; HRMS (FAB) Calcd for $C_{20}H_{31}N_2O_7^+$ ([M+H]$^+$) 411.2131. Found 411.2124.

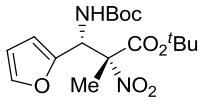


7e: HPLC: AD-H, H/IPA = 3:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.8 min (major *anti* isomer), 8.3 min (major *syn* isomer), 13.9 min (minor *syn* isomer), 24.8 min (minor *anti* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 9.0 Hz), 7.34 (2H, d, J = 9.0 Hz), 6.58 (1H, d, J = 10.0 Hz), 5.44 (1H, d, J = 10.0 Hz), 3.91 (3H, s), 1.72 (3H, s), 1.53 (9H, s), 1.40 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 165.2, 154.6, 140.4, 130.7, 130.0, 128.5, 96.3, 85.6, 80.5, 58.8, 52.3, 28.4, 27.8, 21.6; IR (liq. film): 3454, 2980, 1726, 1558, 1486, 1370, 1347, 1283, 1166, 843, 734 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{31}N_2O_8^+$ ([M+H]$^+$) 439.2080. Found 439.2080.

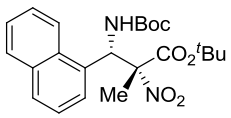


7f: HPLC: AD-H, H/IPA/EtOH = 98:1:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.5 min (major *anti* isomer), 14.1 min (minor *anti* isomer), 14.8 min (minor *syn* isomer), 16.3 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.12 (3H, m), 7.08 (1H, d, J = 7.5

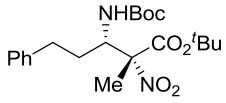
Hz), 6.54 (1H, d, *J* = 10.0 Hz), 5.84 (1H, d, *J* = 10.0 Hz), 2.52 (3H, s), 1.63 (3H, s), 1.53 (9H, s), 1.40 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 154.8, 136.9, 134.9, 130.9, 128.5, 127.2, 126.3, 97.2, 85.2, 80.0, 53.6, 28.5, 27.7, 20.5, 20.2; IR (liq. film): 3457, 2979, 2933, 1746, 1717, 1558, 1486, 1369, 1256, 842, 734 cm^{-1}; HRMS (FAB) Calcd for $C_{20}H_{31}N_2O_6^+$ ([M+H]$^+$) 395.2182. Found 395.2184.



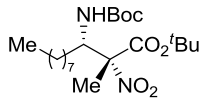
7g: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.2 min (major *anti* isomer), 11.2 min (major *syn* isomer), 12.8 min (minor *anti* isomer), 15.3 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, brd, *J* = 2.0 Hz), 6.32 (1H, dd, *J* = 3.5, 2.0 Hz), 6.30 (1H, brd, *J* = 3.5 Hz), 6.23 (1H, d, *J* = 10.5 Hz), 5.56 (1H, d, *J* = 10.5 Hz), 1.79 (3H, s), 1.50 (9H, s), 1.43 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 154.7, 149.5, 142.9, 110.7, 109.4, 95.8, 85.4, 80.5, 53.3, 28.4, 27.7, 21.0; IR (KBr): 3449, 2982, 2938, 1721, 1561, 1491, 1394, 1369, 1302, 1234, 1143, 840 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{27}N_2O_7^+$ ([M+H]$^+$) 371.1818. Found 371.1828.



7h: HPLC: OD-H, H/EtOH = 49:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.8 min (minor *anti* isomer), 9.3 min (major *syn* isomer), 10.0 min (minor *syn* isomer), 10.8 min (major *anti* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, d, *J* = 8.0 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.82 (1H, d, *J* = 8.0 Hz), 7.59 (1H, t, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 9.5 Hz), 6.54 (1H, d, *J* = 9.5 Hz), 1.56 (9H, s), 1.44 (3H, s), 1.39 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 154.8, 133.7, 132.7, 132.1, 129.4, 129.2, 127.1, 126.0, 125.8, 124.9, 123.0, 97.8, 85.4, 80.2, 52.3, 28.5, 27.8, 21.6; IR (liq. film): 3455, 2979, 2933, 1746, 1714, 1557, 1486, 1370, 1258, 1166, 846 cm^{-1}; HRMS (FAB) Calcd for $C_{23}H_{30}N_2O_6^+$ ([M]$^+$) 430.2104. Found 430.2105.

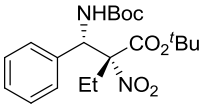


7i: HPLC: AD-H, H/EtOH = 30:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.0 min (major *syn* isomer), 11.5 min (major *anti* isomer), 12.1 min (minor *anti* isomer), 14.6 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m), 7.22-7.16 (3H, m), 5.53 (1H, d, *J* = 11.0 Hz), 4.35 (1H, td, *J* = 11.0, 2.5 Hz), 2.79-2.73 (1H, m), 2.68-2.61 (1H, m), 1.91-1.83 (1H, m), 1.75 (3H, s), 1.67-1.59 (1H, m), 1.47 (9H, s), 1.46 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 155.6, 141.1, 128.6, 128.5, 126.3, 96.8, 85.0, 80.0, 55.1, 33.1, 32.4, 28.5, 27.7, 21.1; IR (liq. film): 3453, 2979, 2933, 1745, 1721, 1604, 1556, 1495, 1369, 1346, 1167, 842 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{33}N_2O_6^+$ ([M+H]$^+$) 409.2339. Found 409.2321.



7j: HPLC: AD-H, H/IPA = 49:1, flow rate = 0.5 mL/min, λ = 254 nm, 9.4min (major *syn* isomer), 12.8 min (major *anti* isomer), 19.2 min (minor *anti* isomer), 23.9 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (1H, d, *J* = 11.0 Hz), 4.27 (1H, td, *J* = 11.0, 2.5 Hz), 1.80 (3H, s), 1.70-1.62 (1H, m), 1.61-1.53 (1H, m), 1.48 (9H, s), 1.44 (9H, s), 1.41-1.20 (12H,

m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 155.5, 97.0, 84.8, 79.7, 55.3, 31.9, 30.7, 29.5, 29.3, 29.2, 28.4, 27.7, 26.0, 22.7, 21.2, 14.2; IR (liq. film): 3453, 2927, 2856, 1747, 1722, 1556, 1493, 1369, 1345, 1169, 843 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{41}N_2O_6^+$ ([M+H]$^+$) 417.2965. Found 417.2974.



7k: HPLC: AD-H, H/EtOH = 30:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.0 min (major *syn* isomer), 9.7 min (major *anti* isomer), 10.9 min (minor *anti* isomer), 12.7 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **7a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (3H, m), 7.23-7.16 (2H, m), 6.55 (1H, d, J = 10.5 Hz), 5.39 (1H, d, J = 10.5 Hz), 2.08 (1H, quin, J = 7.5 Hz), 1.95 (1H, quin, J = 7.5 Hz), 1.56 (9H, s), 1.42 (9H, s), 1.07 (3H, t, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 154.7, 135.7, 128.9, 127.9, 100.4, 85.3, 80.2, 59.1, 28.6, 28.5, 28.0, 9.1, one carbon was not found probably due to overlapping; IR (liq. film): 3454, 2979, 2936, 1746, 1721, 1556, 1486, 1369, 1252, 1167, 843 cm^{-1}; HRMS (FAB) Calcd for $C_{20}H_{31}N_2O_6^+$ ([M+H]$^+$) 395.2182. Found 395.2184.

Reference

(1) (a) Jones, R. A. *Quaternary Ammonium Salts: Their use in Phase-Transfer Catalysis*; Academic Press: London, UK, 2001. (b) *Asymmetric Phase Transfer Catalysis*; Maruoka, K., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(2) Review of bifunctional metal catalysis: Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269 and references therein.

(3) Reviews of organocatalysis: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267.

(4) For reviews on organocatalyzed Mannich-type reactions, see: (a) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.

(5) Chiral ammonium betaine **2** can also be prepared by passing a solution of **1** in methanol through the ion-exchange resin [Amberlyst A-26 (OH)] followed by evaporation. Thus, once **1** is converted to the corresponding ammonium hydroxide, it would immediately undergo neutralization to liberate H_2O, forming intramolecular ion-pairing **2**. Author also confirmed that **1** itself could not catalyze the present Mannich-type reaction at all.

(6) (a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.

(7) Chiral ammonium betaines **3b-d** can also be readily prepared by treatment of their precursors with 0.1 M aqueous solution of $NaHCO_3$. See the experimental section.

(8) **4** was prepared from the corresponding ammonium hydroxide according to the literature

procedure: Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian J.* **2007**, *2*, 123.
(9) For the catalysis of intermolecular ion-pairing, chiral quaternary ammonium phenoxide, see ref 8 and references therein.
(10)Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(11)Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.
(12)Kornblum, N.; Blackwood, R. K. *Org. Synth. Coll. Vol.* **1963**, *4*, 454.

Chapter 3

Flexible Synthesis, Structural Determination, and Synthetic Application of a New C_1-Symmetric Chiral Ammonium Betaine

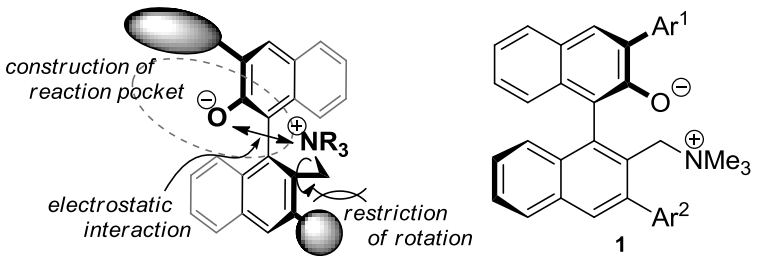
Abstract: A C_1-symmetric chiral ammonium betaine **1** has been developed, and its intramolecular ion-pairing structure in solid state and its catalytic perfomance to achieve the highly stereoselective Mannich-type reactions are revealed.

Introduction

Chiral ammonium betaine had been a previously unexplored structural motif in asymmetric catalysis despite its inherent potential as a bifunctional onium salt catalyst.[1] Recently, our group uncovered its capability to function as a chiral organic base catalyst by the development of pseudo C_2-symmetric chiral quaternary ammonium aryloxides; these betaines can be applied to the catalytic, highly enantioselective direct Mannich-type reaction of α-nitrocarboxylates.[2] Although the C_2-symmetric nature of the catalyst played a crucial role in inducing a high level of stereocontrol, it made it difficult to verify the three-dimensional structure and to pursue rational yet flexible manipulations of the catalyst. This situation prompted us to devise structurally simplified C_1-symmetric chiral quaternary ammonium aryloxides in order to create a basis for further investigating the potential applicability of betaines as a chiral organic base catalyst. Here author describes the synthesis and an unequivocal structural determination of a chiral C_1-symmetric ammonium betaine **1** and its successful application to the highly stereoselective direct Mannich-type reaction (Figure 1).[3]

Our prime concern for consolidating the structural features of the pseudo C_2-symmetric chiral ammonium betaine into a single binaphthyl unit leads to the design concept for the differently 3,3'-substituted **1**, which has the following characteristics: (1) the *ortho*-substituent of aryloxide (Ar^1) would create an effective chiral environment around the reaction sphere; (2) the aromatic group at the *ortho*-position of the alkylammonium moiety (Ar^2) could restrict the free rotation of the pendant cation; (3) the intramolecular electrostatic interaction regulates the direction of the cationic site, which would eventually affect the position of a nucleophilic anion (Fig. 1). To prove the validity of this approach toward developing the C_1-symmetric betaine, establishment of a reliable and flexible synthetic route to **1** was required.

Figure 1. Design concept for C_1-symmetric ammonium betaine **1**



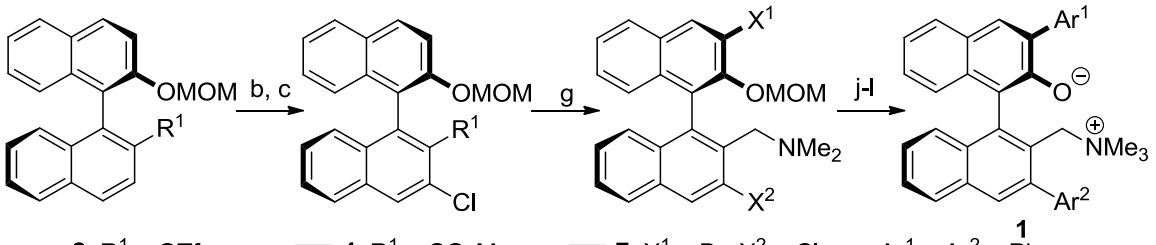
Results and Discussion

2. Flexible Synthesis of a New C_1-Symmetric Chiral Ammonium Betaine

As shown in Scheme 1, author initially prepared **2** from commercially available (*R*)-1,1'-bi-2-naphthol in the usual manner, and methoxycarbonylation of the triflate moiety yielded **3**. Then, selective *ortho*-metallation and subsequent chlorination were realized, giving rise to **4** in 51% yield. After simple reduction of the ester, the primary alcohol was brominated to **5**. The generated benzylic bromide was used for the alkylation of dimethylamine, and the sequential MOM-directed lithiation-bromination resulted in the formation of the key intermediate **7** (83%) for the introduction of different substituents to the 3 and 3' positions. Indeed, when **7** was subjected to the Suzuki-Miyaura coupling conditions, only the aryl bromide functionality participated in the reaction and thus various

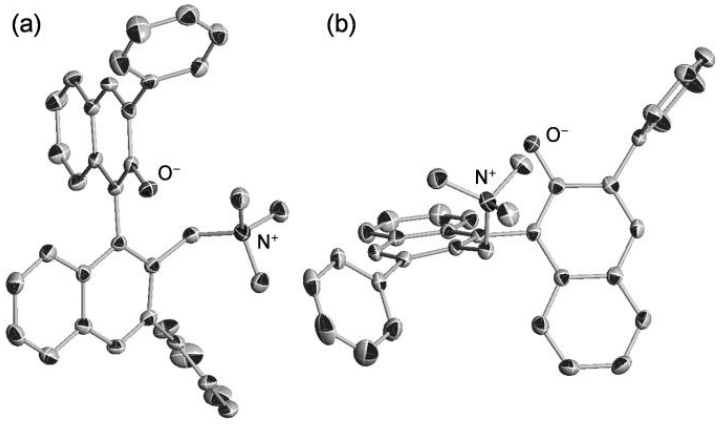
aromatic substituents (Ar^1) could be selectively installed. In the consecutive cross-coupling of **8** with another boric acid [$Ar^2B(OH)_2$], employment of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-phos) as a ligand turned out to be essential to achieve a synthetically satisfactory chemical yield.[4] Quaternization of the tertiary amine moiety of **9** with MeI and deprotection of the MOM group gave ammonium salt, which was treated with 0.1 M $NaHCO_3$ aqueous solution to afford the requisite chiral ammonium betaine **1**. Single crystal X-ray diffraction analysis of **1a** revealed its three-dimensional molecular appearance (Fig. 2).[5] Importantly, the tetraalkylammonium cation moiety turns in the same direction as the oxygen of the aryloxide anion, thereby revealing the intramolecular ion-pairing structure.

Scheme 1 Flexible synthetic route to **1**



(a) CO (1 atm), $Pd(OAc)_2$, dppp, $^iPr_2NEt$, MeOH, DMSO, 80 °C, 71%; (b) LTMP, $B(O^iPr)_3$, THF, -78 °C-rt; (c) $CuCl_2$, $KF{\cdot}2H_2O$, THF, H_2O, rt, 51% (2 steps); (d) $LiAlH_4$, Et_2O, 0 °C; (e) NBS, Me_2S, 0 °C, 92% (2 steps); (f) Me_2NH *aq*., MeCN, rt; (g) ^{n}BuLi, THF, then $(BrF_2C)_2$, -78 °C-rt, 83% (2 steps); (h) $Pd(OAc)_2$, PPh_3, $Ar^1B(OH)_2$, K_3PO_4, THF, 65 °C, 73-79%; (i) Pd_2dba_3, S-phos, $Ar^2B(OH)_2$, K_3PO_4, DMF, 100 °C, 44-98% (except **8b**); (j) MeI, rt; (k) HCl, MeOH, 40 °C, (l) $NaHCO_3$ *aq*., 71-82% (3 steps). dppp: 1,3-diphenylphosphinopropane, LTMP: lithium 2,2,6,6-tetramethylpiperidide, NBS: *N*-bromosuccinimde, dba: dibenzylideneacetone, S-phos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, Mes = 2,4,6-trimethylphenyl, Tip = 2,4,6-triisopropylphenyl

Figure 2. ORTEP diagrams of 1a: (a) top view (b) front view. All hydrogen atoms, and solvent molecules are omitted for clarity. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.

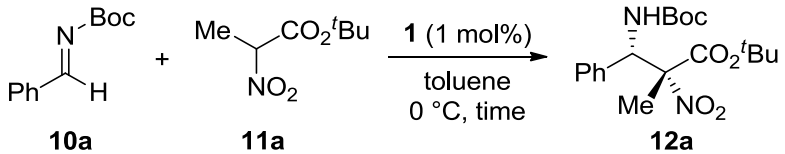


3. Asymmetric Direct Mannich-Type Reaction of α-Nitrocarboxylates Catalyzed by Chiral Ammonium Betaines

With the flexible synthetic scheme and precise structural information in hand, author sets out to evaluate the structure-activity relationship of these C_1-symmetric ammonium betaines as a chiral organic base catalyst in order to demonstrate the effectiveness of the present molecular design. For this purpose, author chose the direct Mannich-type reaction of α-nitrocarboxylates **11** with *N*-Boc imines **10** (see Table schemes), mainly for the following two reasons: 1) this catalytic asymmetric protocol represents one of the simplest strategies to access variable precursors of α-tetrasubstituted α,β-diamino acids that are potentially valuable intermediates of biologically active, functionalized molecules; however, only a handful of effective catalyst systems have been reported in literatures;[6,7] 2) such an investigation offers an appropriate opportunity for evaluating the validity of having consolidated the structural features of our initially devised, pseudo C_2-symmetric chiral ammonium betaine into **1**; this would strengthen the basis for pursuing further molecular design of this type of ammonium betaines. Herein, author reports a set of results of this study.

Initially, the reaction of *tert*-butyl 2-nitropropionate (**11a**) with benzaldehyde-derived *N*-Boc imine **10a** was conducted in the presence of a catalytic amount of **1a** (1 mol%) in toluene at 0 ºC. Smooth bond formation occurred and after 10 h of stirring, the desired Mannich adduct **12a** was obtained in 92% yield. Although its diastereomeric ratio was relatively low (*syn*/*anti* = 2.1:1), the enantiomeric excess of the major *syn* isomer was determined to be 90% ee (Table 1, entry 1). It was of interest that the replacement of the phenyl substituent of the naphthyl unit bearing a pendent ammonium cation moiety (Ar^2) by the sterically less demanding chloride atom slightly improved the stereoselectivities (entry 2). Notably, the steric bulkiness of the aromatic nuclei at the 3 position of the aryloxylate unit (Ar^1) was revealed to have significant influence on the catalytic performance of **1**. For instance, the use of **1c** possessing a 4-*tert*-butylphenyl group as Ar^1 led to an improvement in both the diastereo- and enantioselectivities (entry 3), whereas a substantial decrease in catalytic efficiency and stereoselectivities was observed when 3,5-di-*tert*-butylphenyl-substituted **1d** was tested (entry 4). Consequently, the most stereoselective catalyst **1c** was selected for further investigations.

Table 1. Effect of substituent on each naphthyl group of chiral ammonium betaine **1**[a]



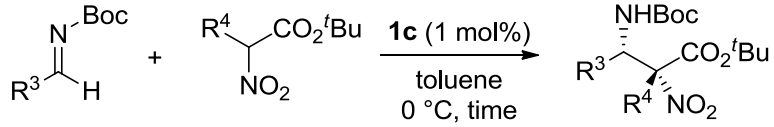
10a **11a** **12a**

Entry	**1**	Time (h)	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	ee (%)[d]
1	**1a**	10	92	2.1:1	90
2	**1b**	8	89	2.6:1	93
3	**1c**	8	98	3.2:1	95
4	**1d**	36	91	1.6:1	47

[a] Reactions were carried out with 0.22 mmol of **10a**, 0.2 mmol of **11a**, and 0.002 mmol of **1** in 0.4 mL of toluene at 0 ºC under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of crude mixture. [d] Enantiomeric excess was analyzed by chiral HPLC. Absolute configuration was assigned based on the previous report.[2]

Since the optimal structure of **1** as a catalyst was thus identified, author next examined the applicability of the present method. As shown in Table 2, a series of aromatic *N*-Boc imines with substituents having different electronic properties could be employed, and the general trend of selectivity was the moderate diastereocontrol and the rigorous enantiofacial discrimination for the major *syn* isomer (entries 1-5). It should be added that the incorporation of the *ortho* substituent seemed to be associated with a higher diastereoselectivity (entry 5). This system also tolerated heteroaromatic imines such as 2-furylaldehyde-derived one, in which the highest level of enantioselectivity was attained (entry 7). Moreover, *tert*-butyl 2-nitrobutanoate (**11b**) appeared to be a suitable pro-nucleophile for the **1c**-catalyzed direct Mannich-type protocol (entry 8).

Table 2. Scope of substrate for **1c**-catalyzed Mannich-type reaction of α-nitrocarboxylates with *N*-Boc imines[a]



10 **11** **12**

Entry	R^3	R^4	**11**	Time (h)	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	ee (%)[d]
1	*p*-Br−C_6H_4	Me	**11a**	6	95	3.1:1	93
2	*p*-Cl−C_6H_4	Me	**11a**	6	99	2.8:1	95
3	*p*-CO_2Me−C_6H_4	Me	**11a**	3	97	2.8:1	94
4	*p*-MeO−C_6H_4	Me	**11a**	9	99	3.8:1	95
5	*o*-Me−C_6H_4	Me	**11a**	12	90	5.9:1	90
6[e]	1-Naph	Me	**11a**	15	99	4.4:1	92
7	2-furyl	Me	**11a**	6	99	2.3:1	96
8[e]	Ph	Et	**11b**	24	99	2.1:1	94

[a] Reactions were carried out with 0.22 mmol of **10**, 0.2 mmol of **11**, and 0.002 mmol of **1c** in 0.4 mL of toluene at 0 ºC under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of crude mixture. [d] Enantiomeric excess was analyzed by chiral HPLC. [e] 1.5 equiv of **10** was used.

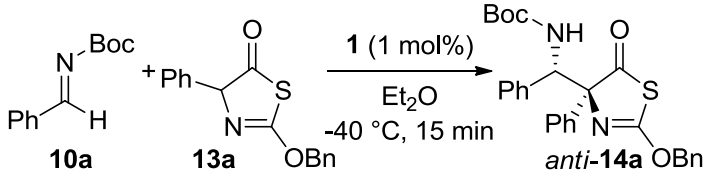
4. Asymmetric Direct Mannich-Type Reaction of 2-benzyloxythiazol-5(4*H*)-ones Catalyzed by Chiral Ammonium Betaines

During our continuous efforts to explore the scope and limitations of **1** as an organic base catalyst, author was interested in its performance in the direct Mannich-type reaction of 2-benzyloxythiazol-5(4*H*)-ones[8] (**13**, scheme shown in Table 3) as a new class of amino acid-derived nucleophiles because the following notable advantages were expected: (1) the enolate generated from the sulfur-containing heterocycle could exert prominent nucleophilicity, and its beneficial consequence would be the accommodation of α-aryl substituents; (2) the reaction products could be readily derivatized into the corresponding differently protected α-tetrasubstituted α,β-diamino acids[2,6,7] through mild oxidative cleavage of the thiazolone moiety.

Initial attempt was made by treating phenylglycine-derived **13a** with benzaldehyde *N*-Boc imine **10a** in the presence of **1a** (1 mol%) in Et_2O at −40 °C. As assumed, the reaction was completed within 15

min to furnish the desired **14a** in a near quantitative yield with an *anti*/*syn* ratio of 4.7:1.[9] Fortunately, the enantiomeric excess of the major *anti* isomer was found to be 99% ee (entry 1 in Table 3). Here, replacement of the phenyl group (Ar^2, cation side) with smaller chloro functionality (**1b**) or hindered *p*-*tert*-butylphenyl moiety (**1e**) led to decrease in the diastereoselectivity (entries 2 and 3). On the other hand, as the steric demand of Ar^1 (aryloxide side) was increased, a substantial improvement in diastereoselectivity was observed without any detrimental effect on the reactivity and enantioselectivity (entries 4 and 5). Consequently, chiral ammonium betaine **1h** possessing a phenyl group as Ar^2 and *p*-(2,4,6-triisopropylphenyl)phenyl group as Ar^1 was identified as an optimal catalyst for achieving high levels of relative and absolute stereocontrol (entry 6).

Table 3. Optimization of catalyst structure[a]

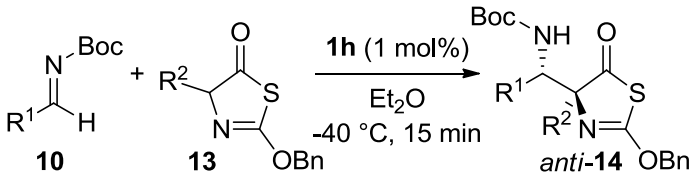


entry	**1**	yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	**1a**	97	4.7:1	99
2	**1b**	95	2.1:1	99
3	**1e**	91	4.5:1	99
4	**1f**	96	5.7:1	99
5	**1g**	94	6.4:1	99
6	**1h**	97	10:1	99

[a] See experomental for details. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR of crude mixture. [d] Enantiomeric excess of major *anti* isomer was indicated and it was analyzed by chiral HPLC.

The results of further experiments to probe the substrate scope by using **1h** are summarized in Table 4. Generally, 1 mol% of the catalyst was sufficient for rapid bond-formation under mild conditions, giving **14** in high yield. The stereochemical outcome was scarcely affected by the electronic properties of the substituents of aromatic *N*-Boc imines (entries 1-5), and hetero- and fused-aromatic imines were also tolerated (entries 6 and 7). Since the α-aryl substituent of the nucleophilic component (**13**) could be variable with similar degree of stereocontrol (entry 8), this direct Mannich-type protocol provide a reliable entry to optically active α-tetrasubstituted α,β-diamino acids bearing α,β-diaryl side chains, a potentially useful chiral building block not accessible so far in a catalytic enantioselective manner.[10] Moreover, α-alkyl-substituted thiazol-5(4*H*)-ones such as **13c** were employable, although a decrease in the diastereoselectivity seemed to be inevitable (entry 9).

Table 4. Substrate scope[a]



entry	R^3	R^4	**13**	yield (%)[b]	d.r. (*syn:anti*)[c]	ee (%)[d]	**14**
1	*p*-F−C_6H_4	Ph	**13a**	92	1:15	99	**14b**
2	*p*-Br−C_6H_4	Ph	**13a**	90	1:11	98	**14c**
3	*p*-Me−C_6H_4	Ph	**13a**	92	1:10	99	**14d**
4	*m*-Br−C_6H_4	Ph	**13a**	95	1:12	99	**14e**
5	*m*-MeO−C_6H_4	Ph	**13a**	93	1:10	99	**14f**
6[e]	3-furyl	Ph	**13a**	97	1:11	97	**14g**
7	β-Naph	Ph	**13a**	96	1:10	97	**14h**
8	Ph	*p*-Cl−C_6H_4	**13b**	96	1:11	99	**14i**
9[f]	Ph	$PhCH_2$	**13c**	88	1:2.7	92	**14j**

[a] See experomental for details. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR of crude mixture. [d] Enantiomeric excess of major *anti* isomer was indicated and it was analyzed by chiral HPLC. [e] Reaction was performed at -60 °C for 1 h. [f] 0 °C, 14 h

5. Derivatizations of Mannich Adduct to α-Tetrasubstituted α,β-Diamino Acid

The product derivatizations illustrated in Scheme 2 clearly demonstrate the synthetic utility of the present system. As expected, thiazolone ring of **14a** was readily cleaved with in situ generated LiOOH under mild conditions, directly producing the corresponding differently protected α-tetrasubstituted α,β-diamino acid. Subsequent esterification followed by chromatographic separation of diastereomers gave the stereochemically homogeneous ester *anti*-**15** (66% in 2 steps). It should be noted that this process involves the one-pot conversion of the intermediary benzyloxy thiocarbonyl moiety into the common carbobenzyloxy (Cbz) group, highlighting the unique property of 2-alkoxythiazol-5(4*H*)-ones.[11] Meanwhile, treatment of **14a** with 1 M hydrochloric acid in methanol afforded *N*-carboxythio anhydride **16** and its single crystal X-ray diffraction analysis enabled the assignment of the absolute configuration of the major *anti*-isomer (Fig. 3).[12] Further, simple exposure of **16** to methylamine in acetonitrile furnished α,β-diamino acid amide **17** without loss of stereochemical integrity.

Scheme 2 Derivatization of **14a** to α-aryl-α,β-diamino acid ester **15** and amide **17**. [*1 A mixture of diastereomers (*anti*/*syn* = 10:1) and 99% ee for major *anti* isomer.]

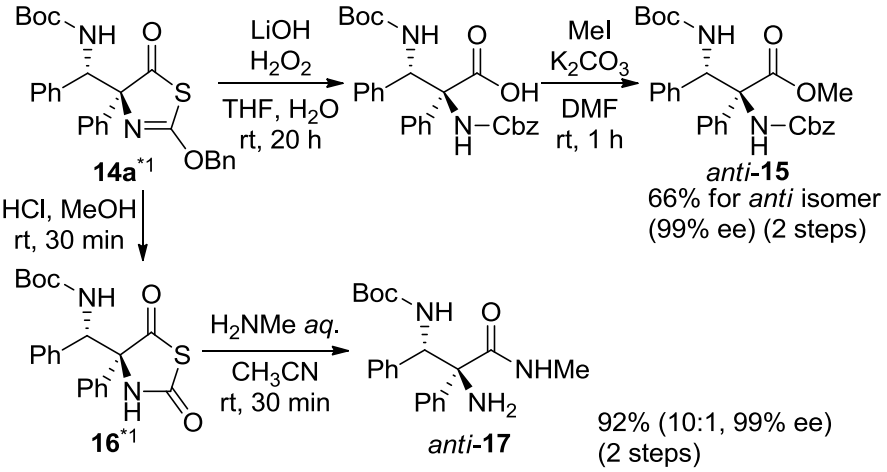
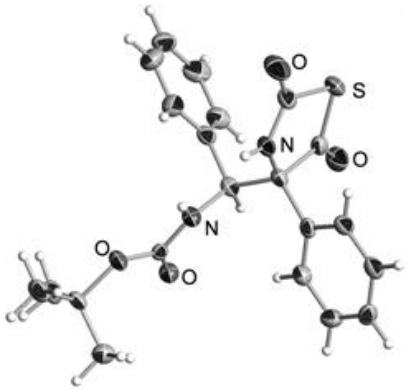


Figure 3. ORTEP diagram of *anti*-**16**. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.



Summary

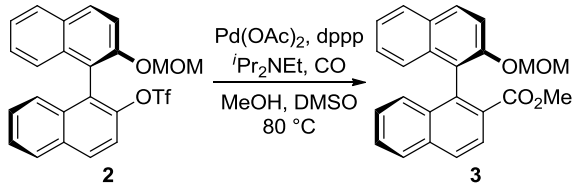
In conclusion, author has presented a reliable yet flexible synthesis and a complete structural determination of a new C_1-symmetric chiral ammonium betaine, and its ability as an organic base catalyst has been demonstrated by successfully applying it to the development of the highly stereoselective direct Mannich-type reactions. The synthetic value of the Mannich adducts **14** has been revealed by simple derivatization processes that offer a facile and stereoselective way to the differently protected α-tetrasubstituted α,β-diamino acids and their derivatives bearing α,β-diaryl side chains. Author believes that the structural features of C_1-symmetric chiral quaternary ammonium aryloxides provide a new platform for cultivating the potential functions of the betaines as a bifunctional chiral organic molecular catalyst through taking full advantage of the intramolecular ion-pairing structure.

Experimental

General Information: Infrared spectra were recorded on a JASCO FT/IR-300E spectrometer. ^{1}H NMR spectra were recorded on a Varian Mercury-300BB (300 MHz), a Varian INOVA-500 (500 MHz) or Varian INOVA-700 (700 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2SO$; 2.50 ppm, CD_3OD; 3.31 ppm, C_6D_6; 7.16 ppm] or Me_4Si resonance (0.0 ppm; $CDCl_3$, $(CD_3)_2CO$) as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian INOVA-500 (126 MHz) or a Varian INOVA-700 (175 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2CO$; 29.84 ppm, $(CD_3)_2SO$; 39.51 ppm, CD_3OD; 49.00 ppm, $CDCl_3$; 77.16 ppm, C_6D_6; 128.06 ppm]. Optical rotations were measured on a JASCO DIP-1000 polarimeter. The high resolution mass spectra were conducted on JEOL JMS-700 (MStation). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40-50 μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK AD-H (AD-H) or CHIRALPAK IA (IA)].

Toluene, THF, Et_2O, and CH_2Cl_2 were supplied from Kanto Chemical Co., Inc. as "Dehydrated solvent system". Aromatic and heteroaromatic imines,[13] nitroacetates,[14] and 2-alkoxythiazol-5(4*H*)-ones[8] were prepared by following the literature procedure. Other simple chemicals were purchased and used as such.

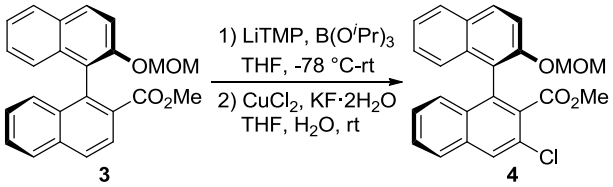
Preparation and Characterization of C_1-Symmetric Chiral Ammonium Betaine 1:



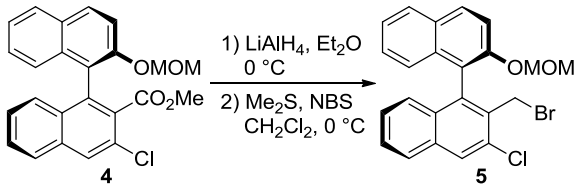
2 **3**

Representative procedure for preparation of 3[15]: A solution of **2**[16] (6.5 g, 14.0 mmol), $Pd(OAc)_2$ (472.5 mg, 2.1 mmol), and dppp (948.6 mg, 2.31 mmol) in DMSO (70.0 mL) was evacuated and backfilled with argon. Then, ^{i}Pr$_2$NEt (10.6 mL, 62.0 mmol) and MeOH (28.0 mL) were added and the mixture was stirred for 24 h at 80 °C. After being cooled to room temperature, the resulting mixture was poured into H_2O and extracted with ethyl acetate (EA) twice. The combined organic extracts were washed with H_2O twice and brine, and dried over Na_2SO_4. Evaporation of volatiles and subsequent purification of the residue by column chromatography on silica gel [hexane (H)/EA = 20:1-5:1 as eluent] afforded **3** (3.7 g, 9.94 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 8.5 Hz), 7.98 (1H, d, J = 8.5 Hz), 7.94 (1H, d, J = 8.5 Hz), 7.92 (1H, d, J = 8.5 Hz), 7.85 (1H, d, J = 8.5 Hz), 7.55 (1H, d, J = 8.5 Hz), 7.51 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.32 (1H, d, J = 8.5 Hz), 7.31 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.26 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.17 (1H, ddd, J = 8.5, 6.5, 1.5 Hz),

6.97 (1H, d, J = 8.5 Hz), 5.05 (1H, d, J = 6.5 Hz), 4.96 (1H, d, J = 6.5 Hz), 3.46 (3H, s), 3.08 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 151.8, 137.3, 135.2, 134.0, 133.1, 129.6, 129.5, 128.9, 128.0_5, 128.0_2, 127.8_4, 127.7_9, 126.7, 126.5, 126.2, 125.2, 124.0, 123.5, 116.5, 94.9, 55.9, 51.9, one carbon was not found probably due to overlapping; IR (neat): 3060, 2950, 1727, 1333, 1278, 1241, 1150, 1035, 1014, 908, 768, 732 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{20}O_4$ ($[M+H]^+$) 372.1362. Found 372.1364.

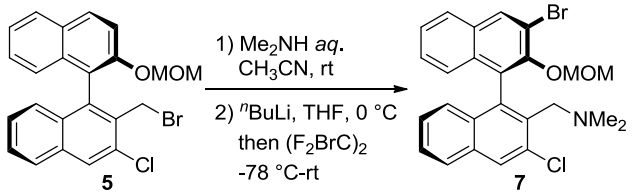


Representative procedure for preparation of 4: $B(O^iPr)_3$ (5.7 mL, 25.0 mmol) and a solution of **3** (3.7 g, 10.0 mmol) in THF (10.0 mL) were sequentially introduced to a THF solution of lithium 2,2,6,6-tetramethylpiperidine (LiTMP) (ca. 1 M, 20 mL, 20.0 mmol) at −78 °C. The resulting reaction mixture was allowed to warm to room temperature without removing cooling bath and poured into saturated NH_4Cl aqueous solution. The aqueous phase was extracted with EA twice and the combined organic extracts were washed with brine. After drying over Na_2SO_4 and filtration, the organic phase was concentrated under vacuum. The residual solid was mixed with $CuCl_2$ (2.7 g, 20.0 mmol) and $KF{\cdot}2H_2O$ (941.3 mg, 10.0 mmol), and the whole materials were dissolved into 80% aqueous THF (30.0 mL). After degassing process, the mixture was stirred overnight. The resulting mixture was quenched by the addition of saturated NH_4Cl aqueous solution and extracted with EA twice. The combined organic phasees were washed with brine and dried over Na_2SO_4. Filtration and concentration were performed, and the crude product was purified by column chromatography on silica gel (H/EA = 20:1-5:1 as eluent) to give **4** (2.1 g, 5.1 mmol, 51%) as a white solid. **4:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.84 (1H, d, J = 8.5 Hz), 7.83 (1H, d, J = 8.5 Hz), 7.56 (1H, d, J = 8.5 Hz), 7.51 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.33 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.28 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.25 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.24 (1H, d, J = 8.5 Hz), 7.07 (1H, d, J = 8.5 Hz), 5.11 (1H, d, J = 7.0 Hz), 5.02 (1H, d, J = 7.0 Hz), 3.31 (3H, s), 3.22 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 153.0, 135.3, 134.1, 133.7, 132.7, 131.3, 130.6, 129.3, 128.0, 127.8_1, 127.7_9, 127.6, 127.4, 127.1, 127.0, 126.8, 125.6, 124.2, 120.2, 116.0, 94.9, 56.0, 52.0; IR (neat): 3060, 2951, 1737, 1280, 1243, 1137, 1072, 1034, 1014, 909, 733 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{19}O_4Cl$ ($[M+H]^+$) 406.0972. Found 406.0980.



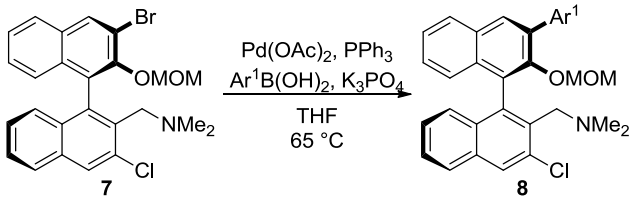
Representative procedure for preparation of 5: To a suspension of $LiAlH_4$ (174.6 mg, 4.6 mmol) in Et_2O (23.0 mL) was added **4** (934.0 mg, 2.3 mmol) portionwise at 0 °C and the reaction mixture was

stirred for 1 h at 0 °C. The reaction was quenched by the sequential treatment with H_2O (174.6 μL), 15% NaOH aqueous solution (174.6 μL), and H_2O (523.8 μL). After being stirred for 1 h at room temperature, this mixture was filtered through a pad of Celite and the filtrate was concentrated. Without further purification, this crude was used for the subsequent bromination. To a suspension of NBS (2.0 g, 11.5 mmol) in CH_2Cl_2 (11.5 mL) was added Me_2S (845.0 μL, 11.5 mmol) dropwise at 0 °C and the yellow mixture was stirred for 10 min at 0 °C. The crude alcohol was added portionwise at 0 °C. The reaction mixture was stirred for 24 h at 0 °C and poured into saturated $NaHCO_3$ aqueous solution. Extractive workup was performed with $CHCl_3$ and the combined extracts were dried over Na_2SO_4. Removal of volatiles and purification of the residue by column chromatography on silica gel (H/EA = 50:1-5:1 as eluent) furnished **5** (840.4 mg, 1.9 mmol, 83% in two steps) as a white solid. **5:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, s), 8.01 (1H, d, J = 8.5 Hz), 7.89 (1H, d, J = 8.5 Hz), 7.81 (1H, d, J = 8.5 Hz), 7.64 (1H, d, J = 8.5 Hz), 7.47 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.36 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.24 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.22 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.11 (1H, d, J = 8.5 Hz), 6.96 (1H, d, J = 8.5 Hz), 5.15 (1H, d, J = 7.0 Hz), 5.00 (1H, d, J = 7.0 Hz), 4.51 (1H, d, J = 10.0 Hz), 4.39 (1H, d, J = 10.0 Hz), 3.17 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 137.3, 133.9, 133.5, 132.5, 132.2, 131.9, 130.7, 129.7, 128.5, 128.1, 127.6, 127.2, 127.0, 126.8, 125.4, 124.5, 120.5, 116.2, 95.0, 56.1, 30.0, one carbon was not found probably due to overlapping; IR (neat): 2954, 1593, 1508, 1243, 1149, 1071, 1034, 1014, 992, 907, 749 cm^{-1}; HRMS (FAB) Calcd for $C_{23}H_{18}O_2ClBr$ ([M+H]$^+$) 440.0179. Found 440.0179.



Representative procedure for preparation of 7: Bromide **5** (220.0 mg, 0.5 mmol) was treated with 50% aqueous Me_2NH (262.0 μL, 2.5 mmol) in MeCN (5.0 mL) for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$ twice. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Residual crude product of **6** was satisfactory pure in NMR for the next reaction. To a solution of the crude **6** in THF (5.0 mL) was added a solution of ^{n}BuLi in hexane (1.6 M, 780.0 μL, 1.25 mmol) dropwise at 0 °C and the solution was stirred for 30 min. After being cooled to −78 °C, the reaction mixture was treated with 1,2-dibromo-1,1,2,2-tetrafluoroethane (188.0 μL, 1.5 mmol). The resulting reaction mixture was warmed to room temperature, diluted with saturated NH_4Cl aqueous solution, and extracted with EA twice. The organic extracts were dried, filtered, and concentrated. The residual solid was purified by column chromatography on silica gel (H/EA = 20:1-2:1 as eluent) to give **7** (201.7 mg, 0.4 mmol, 83% in two steps) as a yellow highly viscous liquid. **7:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, s), 8.06 (1H, s), 7.81_2 (1H, d, J = 8.5 Hz), 7.80_6 (1H, d, J = 8.5 Hz), 7.46 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.41 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.24 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.22 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.11 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 8.5 Hz), 4.77 (1H, d, J = 5.5 Hz), 4.56 (1H, d, J =

5.5 Hz), 3.73 (1H, d, *J* = 13.0 Hz), 3.12 (1H, d, *J* = 13.0 Hz), 2.58 (3H, s), 1.83 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 135.3, 135.2, 134.2, 133.2, 133.1_3, 133.0_8, 132.1, 131.5, 129.7, 128.8, 127.2, 127.1, 126.8, 126.7, 126.5, 126.1, 117.4, 98.9, 59.2, 56.6, 45.7, two carbons were not found probably due to overlapping; IR (neat): 2939, 2817, 2766, 1160, 1002, 970, 930, 749 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{24}NO_2BrCl^+$ ($[M+H]^+$) 486.0659. Found 486.0667.



Representative procedure for preparation of 8: To a test tube were placed **7** (48.5 mg, 0.1 mmol), *p*-(2,4,6- *i*Pr$_3$-C$_6$H$_2$)-C$_6$H$_4$B(OH)$_2$ (**B1**, 48.6 mg, 0.15 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (2.6 mg, 0.01 mmol), and K_3PO_4 (84.9 mg, 0.4 mmol). After the addition of THF (0.35 mL), evacuation and refill with argon were repeated three times and the reaction mixture was stirred for 18 h at 65 °C. The reaction mixture was filtered through a pad of Celite at room temperature. The concentrated filtrate was purified by column chromatography on silica gel (H/EA = 20:1-2:1 as eluent) to afford **8h** (50.6 mg, 0.74 mmol, 74%) as a white solid.

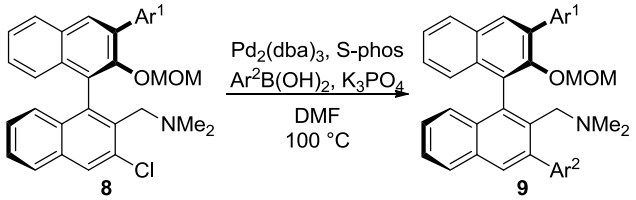
8a (Ar^1 = Ph)**:** 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.97 (1H, s), 7.89 (1H, d, *J* = 8.5 Hz), 7.79 (1H, d, *J* = 8.5 Hz), 7.71 (2H, d, *J* = 7.5 Hz), 7.46 (2H, t, *J* = 7.5 Hz), 7.43 (1H, dt, *J* = 8.5, 4.0 Hz), 7.41-7.35 (2H, m), 7.24-7.19 (3H, m), 7.09 (1H, d, *J* = 8.5 Hz), 4.23 (1H, d, *J* = 6.0 Hz), 4.19 (1H, d, *J* = 6.0 Hz), 3.76 (1H, d, *J* = 13.0 Hz), 3.37 (1H, d, *J* = 13.0 Hz), 2.17 (3H, s), 1.94 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 139.0, 136.4, 135.2, 134.3, 133.4, 133.2, 132.1, 131.0, 130.8, 129.7, 129.6, 128.6, 128.4, 128.0_8, 128.0_6, 127.6, 127.5, 127.0, 126.7, 126.6, 126.4, 126.2, 125.3, 98.4, 59.5, 55.9, 45.8; IR (neat): 2939, 2766, 1158, 996, 976, 933, 751 cm^{-1}; HRMS (FAB) Calcd for $C_{31}H_{29}NO_2Cl^+$ ($[M+H]^+$) 482.1887. Found 482.1902.

8f (Ar^1 = *p*-^{t}Bu-C$_6$H$_4$)**:** 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.97 (1H, s), 7.89 (1H, d, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.64 (2H, d, *J* = 8.5 Hz), 7.49 (2H, d, *J* = 8.5 Hz), 7.44 (1H, dt, *J* = 8.0, 4.0 Hz), 7.39 (1H, t, *J* = 8.0 Hz), 7.23-7.19 (3H, m), 7.07 (1H, d, *J* = 8.0 Hz), 4.25 (1H, d, *J* = 6.0 Hz), 4.20 (1H, d, *J* = 6.0 Hz), 3.73 (1H, d, *J* = 13.5 Hz), 3.36 (1H, d, *J* = 13.5 Hz), 2.16 (3H, s), 1.94 (6H, s), 1.37 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 150.6, 136.5, 136.0, 135.2, 135.0, 134.3, 133.3, 133.2, 132.2, 131.0, 130.8, 129.1, 128.4, 128.1, 128.0, 127.7, 127.0, 126.7, 126.6, 126.3, 126.2, 125.5, 125.3, 98.4, 59.5, 55.8, 45.8, 34.7, 31.5; IR (neat): 2962, 2764, 1457, 1391, 1158, 1078, 998, 976, 837, 750 cm^{-1}; HRMS (FAB) Calcd for $C_{35}H_{37}NO_2Cl^+$ ($[M+H]^+$) 538.2513. Found 538.2488.

8g (Ar^1 = *p*-(2,4,6-Me$_3$-C$_6$H$_2$)-C$_6$H$_4$)**:** 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (1H, s), 8.05 (1H, s), 7.92 (1H, d, *J* = 8.0 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.77 (2H, d, *J* = 8.0 Hz), 7.44 (1H, ddd, *J* = 8.0, 5.5, 3.0 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 7.28-7.19 (5H, m), 7.10 (1H, d, *J* = 8.0 Hz), 6.97 (2H, s), 4.27 (1H, d, *J* = 6.0 Hz), 4.24 (1H, d, *J* = 6.0 Hz), 3.79 (1H, d, *J* = 13.0 Hz), 3.38 (1H, d, *J* = 13.0 Hz), 2.34 (3H, s), 2.26 (3H, s), 2.05 (6H, s), 1.94 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 140.3,

138.8, 137.2, 136.8, 136.3, 136.0, 135.3, 135.0, 134.3, 133.4, 133.2, 132.1, 131.0, 130.9, 129.7, 129.5, 128.5, 128.3, 128.1, 128.0, 127.6, 127.0, 126.7_2, 126.6_7, 126.4, 126.3, 125.3, 98.4, 59.5, 56.0, 45.8, 21.2, 20.9; IR (neat): 2938, 2765, 1454, 1389, 1158, 998, 975, 842, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{40}H_{39}NO_2Cl^+$ ($[M+H]^+$) 600.2669. Found 600.2686.

8h (Ar^1 = *p*-(2,4,6- *i*Pr_3-C_6H_2)-C_6H_4)**:** 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (1H, s), 8.06 (1H, s), 7.93 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.76 (2H, d, *J* = 8.0 Hz), 7.45 (1H, ddd, *J* = 8.0, 5.5, 2.5 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 7.25-7.20 (2H, m), 7.22 (1H, ddd, *J* = 8.0, 6.5, 1.5 Hz), 7.09_4 (1H, d, *J* = 8.0 Hz), 7.08_6 (2H, s), 4.26 (1H, d, *J* = 5.5 Hz), 4.24 (1H, d, *J* = 5.5 Hz), 3.81 (1H, d, *J* = 13.0 Hz), 3.38 (1H, d, *J* = 13.0 Hz), 2.96 (1H, sept, *J* = 7.0 Hz), 2.69 (2H, sept, *J* = 7.0 Hz), 2.32 (3H, s), 1.93 (6H, s), 1.32 (6H, d, *J* = 7.0 Hz), 1.10_3 (6H, d, *J* = 7.0 Hz), 1.09_9 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 148.1, 146.6, 140.1, 137.2, 136.9, 136.3, 135.4, 135.0, 134.4, 133.4, 133.3, 132.1, 131.0, 130.9, 130.0, 129.3, 128.5, 128.1, 128.0, 127.6, 127.1, 126.7_4, 126.6_8, 126.3_4, 126.3_2, 125.4, 120.7, 98.5, 59.5, 56.0, 45.8, 34.4, 30.5, 24.3_4, 24.2_8, 24.2; IR (neat): 2959, 2766, 1458, 1362, 1158, 1077, 998, 976, 844, 753 cm^{-1}; HRMS (FAB) Calcd for $C_{46}H_{51}NO_2Cl^+$ ($[M+H]^+$) 684.3608. Found 684.3624.



Representative procedure for preparation of 9: To a test tube were placed **8h** (68.4 mg, 0.1 mmol), $PhB(OH)_2$ (24.4 mg, 0.2 mmol), Pd_2dba_3 (4.58 mg, 0.005 mmol), S-phos (8.21 mg, 0.02 mmol), and K_3PO_4 (84.9 mg, 0.4 mmol). After the addition of DMF (0.2 mL), evacuation and refill with argon were repeated three times and the reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was filtered through a pad of Celite at room temperature and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (H/EA = 20:1-2:1 as eluent) to give **9h** (71.4 mg, 0.098 mmol, 98%) as a white solid.

9a (Ar^1 = Ph, Ar^2 = Ph)**:** 44% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.88 (1H, d, *J* = 8.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.80 (1H, s), 7.72 (2H, d, *J* = 7.5 Hz), 7.49 (2H, d, *J* = 7.5 Hz), 7.46 (2H, t, *J* = 7.5 Hz), 7.44-7.33 (4H, m), 7.42 (2H, t, *J* = 7.5 Hz), 7.26-7.17 (4H, m), 4.29 (1H, d, *J* = 5.5 Hz), 4.21 (1H, d, *J* = 5.5 Hz), 3.52 (1H, d, *J* = 13.0 Hz), 3.33 (1H, d, *J* = 13.0 Hz), 2.26 (3H, s), 1.55 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 143.1, 142.2, 139.3, 136.3, 135.4, 134.4, 134.0, 132.9, 132.5, 130.8, 130.4, 129.7, 129.6, 129.5, 129.4, 128.5, 127.9, 127.8, 127.7, 127.4, 127.2, 127.1, 126.6, 126.0, 125.9, 125.8, 125.1, 98.4, 58.6, 55.9, 44.9; IR (neat): 2929, 2853, 2762, 1454, 1157, 993, 971, 934, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{37}H_{34}NO_2^+$ ($[M+H]^+$) 524.2590. Found 524.2573.

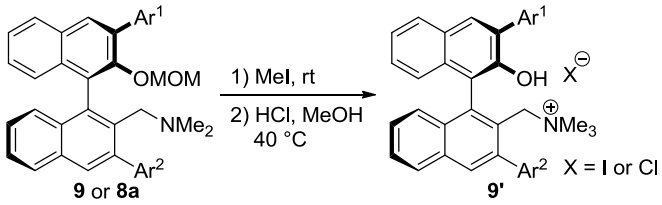
9c (Ar^1 = Ph, Ar^2 = *p*-^{t}Bu-C_6H_4)**:** 71% yield. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.88 (1H, d, *J* = 8.4 Hz), 7.84 (1H, d, *J* = 8.4 Hz), 7.82 (1H, s), 7.72 (2H, d, *J* = 8.4 H), 7.48-7.34 (9H, m), 7.26-7.18 (4H, m), 4.28 (1H, d, *J* = 5.6 Hz), 4.19 (1H, d, *J* = 5.6 Hz), 3.54 (1H, brd, *J* = 11.2 Hz), 3.36

(1H, brd, J = 11.2 Hz), 2.25 (3H, s), 1.55 (6H, s), 1.39 (9H, s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.8, 149.3, 142.0, 139.8, 139.2, 136.3, 135.3, 134.2, 133.8, 132.6, 132.3, 130.7, 130.1, 129.5_1, 129.4_5, 129.3, 129.2, 128.3, 127.7, 127.6, 127.2, 127.0_1, 126.9_8, 125.7, 125.6_2, 125.5_9, 124.9, 124.3, 98.2, 58.4, 55.8, 44.8, 34.5, 31.4; IR (neat): 2961, 2762, 1456, 1158, 994, 973, 751 cm^{-1}; HRMS (FAB) Calcd for $C_{41}H_{42}NO_2^+$ ($[M+H]^+$) 580.3216. Found 580.3215.

9f (Ar^1 = p-^{t}Bu-C_6H_4, Ar^2 = Ph)**:** 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.87 (1H, d, J = 8.5 Hz), 7.84 (1H, d, J = 8.5 Hz), 7.80 (1H, s), 7.66 (2H, d, J = 8.0 Hz), 7.48_7 (2H, d, J = 8.0 Hz), 7.47_9 (2H, d, J = 8.0 Hz), 7.42 (2H, t, J = 8.0 Hz), 7.42-7.34 (3H, m), 7.26 (1H, d, J = 8.5 Hz), 7.23 (1H, t, J = 8.5 Hz), 7.20 (1H, t, J = 8.5 Hz), 7.17 (1H, d, J = 8.5 Hz), 4.32 (1H, d, J = 5.5 Hz), 4.21 (1H, d, J = 5.5 Hz), 3.51 (1H, d, J = 13.5 Hz), 3.34 (1H, d, J = 13.5 Hz), 2.25 (3H, s), 1.54 (6H, s), 1.37 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 150.2, 143.1, 142.2, 136.3, 135.3, 134.5, 133.8, 132.9, 132.5, 130.9, 130.3, 129.6, 129.4_2, 129.3_9, 129.2, 127.9, 127.8, 127.7, 127.2, 127.1, 126.6, 125.9, 125.8, 125.4, 125.0, 98.4, 58.6, 55.9, 44.9, 34.7, 31.5, two carbons were not found probably due to overlapping; IR (neat): 2960, 2813, 2761, 1463, 1158, 994, 972, 837, 751 cm^{-1}; HRMS (FAB) Calcd for $C_{41}H_{42}NO_2^+$ ($[M+H]^+$) 580.3216. Found 580.3243.

9g (Ar^1 = p-(2,4,6-Me_3-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.91 (1H, d, J = 8.5 Hz), 7.86 (1H, d, J = 8.5 Hz), 7.81 (1H, s), 7.78 (2H, d, J = 8.0 Hz), 7.49 (2H, d, J = 8.0 Hz), 7.45-7.38 (4H, m), 7.36 (1H, t, J = 8.5 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.26-7.20 (4H, m), 7.19 (1H, d, J = 8.5 Hz), 6.97 (2H, s), 4.33 (1H, d, J = 5.5 Hz), 4.26 (1H, d, J = 5.5 Hz), 3.54 (1H, d, J = 13.0 Hz), 3.35 (1H, d, J = 13.0 Hz), 2.35 (3H, s), 2.34 (3H, s), 2.05 (6H, s), 1.55 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 143.1, 142.3, 140.2, 138.9, 137.6, 136.8, 136.3, 136.1, 135.4, 134.4, 134.0, 132.9, 132.5, 130.9, 130.3, 129.8, 129.6, 129.4, 128.3, 127.9_2, 127.8_7, 127.7, 127.2, 127.1, 126.6, 126.0, 125.9_3, 125.8_7, 125.1, 98.5, 58.6, 56.1, 45.0, 21.2, 20.9, two carbons were not found probably due to overlapping; IR (neat): 2932, 2853, 2763, 1455, 1157, 994, 972, 842, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{46}H_{44}NO_2^+$ ($[M+H]^+$) 642.3372. Found 642.3376

9h (Ar^1 = p-(2,4,6-iPr$_3$-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, s), 7.91 (1H, d, J = 8.5 Hz), 7.86 (1H, d, J = 8.5 Hz), 7.81 (1H, s), 7.76 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.43 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.42 (2H, t, J = 8.0 Hz), 7.40 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.36 (1H, t, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.24 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.22 (1H, ddd, J = 8.5, 6.5, 1.5 Hz), 7.18 (1H, d, J = 8.5 Hz), 7.08 (2H, s), 4.33 (1H, d, J = 5.5 Hz), 4.27 (1H, d, J = 5.5 Hz), 3.55 (1H, d, J = 13.0 Hz), 3.35 (1H, d, J = 13.0 Hz), 2.96 (1H, sept, J = 7.0 Hz), 2.70 (2H, sept, J = 7.0 Hz), 2.40 (3H, s), 1.54 (6H, s), 1.32 (6H, d, J = 7.0 Hz), 1.11 (6H, d, J = 7.0 Hz), 1.10 (6H, d, J = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 148.1, 146.7, 143.1, 142.3, 139.9, 137.5, 137.0, 136.3, 135.5, 134.4, 134.0, 132.9, 132.5, 130.9, 130.3, 129.9, 129.6, 129.5, 129.4_5, 129.3_6, 127.9, 127.6, 127.2, 126.6, 126.0, 125.9_2, 125.8_8, 125.1, 120.7, 98.5, 58.6, 56.1, 45.0, 34.4, 30.5, 24.4, 24.3, 24.2, two carbons were not found probably due to overlapping; IR (neat): 2959, 2867, 2762, 1459, 1362, 1157, 1073, 994, 972, 935, 844, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{52}H_{56}NO_2^+$ ($[M+H]^+$) 726.4311. Found 726.4317.



Representative procedure for preparation of 9': Amine **9h** was dissolved into MeI (1.0 mL) at room temperature and the solution was stirred for 6 h. After removal of excess MeI, the residual solid was treated with 1 M HCl methanolic solution (1.0 mL) at 40 °C for 12 h. The concentrated crude solid was purified by column chromatography on silica gel (H/EA = 1:1 then $CHCl_3$/MeOH = 1:0-5:1 as eluent) to give **9'h** quantitatively.

9'a (Ar^1 = Ph, Ar^2 = Ph)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.74 (1H, brs), 8.13 (1H, d, *J* = 7.7 Hz), 8.12 (1H, s), 8.09 (1H, s), 8.04 (1H, d, *J* = 7.7 Hz), 7.69 (2H, d, *J* = 7.7 Hz), 7.68-7.64 (3H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.54 (1H, t, *J* = 7.7 Hz), 7.51 (2H, t, *J* = 7.7 Hz), 7.45 (1H, t, *J* = 7.7 Hz), 7.43 (1H, t, *J* = 7.7 Hz), 7.41 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.28 (1H, d, *J* = 7.7 Hz), 6.94 (1H, d, *J* = 7.7 Hz), 4.89 (1H, br), 4.45 (1H, br), 2.54 (9H, brs); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.0, 140.9, 140.8, 138.9, 137.6, 133.7, 132.4, 131.8, 131.5, 131.0, 130.9, 129.6, 129.1, 128.7, 128.3, 127.9, 127.8, 127.6, 127.5, 127.0, 126.9, 126.5, 124.5, 123.4, 123.1, 117.7, 64.3, 53.5, two carbons were not found probably due to overlapping; IR (neat): 3055, 2930, 1620, 1486, 1427, 1327, 1238, 1216, 1189, 1127, 1029, 899, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{36}H_{32}NO^+$ ($[M-X]^+$) 494.2484. Found 494.2493.

9'b (Ar^1 = Ph, Ar^2 = Cl)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.80 (1H, brs), 8.47 (1H, s), 8.11 (1H, d, *J* = 7.7 Hz), 8.10 (1H, s), 8.03 (1H, d, *J* = 7.7 Hz), 7.69 (1H, t, *J* = 7.7 Hz), 7.67 (2H, d, *J* = 7.7 Hz), 7.50 (2H, t, *J* = 7.7 Hz), 7.46 (1H, t, *J* = 7.7 Hz), 7.42 (1H, t, *J* = 7.7 Hz), 7.39 (1H, t, *J* = 7.7 Hz), 7.31 (1H, t, *J* = 7.7 Hz), 7.23 (1H, d, *J* = 7.7 Hz), 6.75 (1H, br), 4.83 (1H, br), 4.47 (1H, br), 2.98 (9H, brs); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.0, 140.7, 137.5, 134.4, 132.5, 132.1, 131.7, 131.2_1, 131.1_8, 129.3_2, 129.2_9, 129.0, 128.4, 128.3, 128.2, 127.7, 127.3, 127.1, 127.0, 126.6, 124.7, 123.5, 122.7, 116.8, 64.8, 53.5; IR (neat): 3186, 3049, 2928, 1620, 1484, 1427, 1183, 1125, 882, 749 cm^{-1}; HRMS (FAB) Calcd for $C_{30}H_{27}NOCl^+$ ($[M-X]^+$) 452.1781. Found 452.1788.

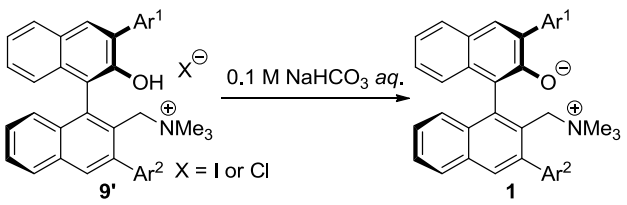
9'e (Ar^1 = Ph, Ar^2 = *p*-^{t}Bu-C_6H_4)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.72 (1H, br), 8.12 (1H, s), 8.11 (1H, d, *J* = 7.7 Hz), 8.04 (1H, d, *J* = 7.7 Hz), 7.70 (2H, d, *J* = 7.7 Hz), 7.65 (1H, t, *J* = 7.7 Hz), 7.64 (2H, d, *J* = 7.7 Hz), 7.59 (2H, d, *J* = 7.7 Hz), 7.51 (2H, t, *J* = 7.7 Hz), 7.46-7.39 (4H, m), 7.35 (1H, t, *J* = 7.7 Hz), 7.27 (1H, d, *J* = 7.7 Hz), 6.93 (1H, d, *J* = 7.7 Hz), 4.89 (1H, br), 4.46 (1H, br), 2.53 (9H, s), 1.46 (9H, s); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.4, 149.9, 140.8, 138.8, 137.9, 137.6, 133.8, 132.4, 131.8, 131.5, 130.9, 130.8, 129.3, 129.1, 129.0, 128.3, 127.9, 127.7, 127.6, 127.0, 126.8, 126.4, 125.4, 124.8, 123.4, 123.1, 117.7, 64.4, 53.6, 34.0, 30.7; IR (neat): 3381, 2961, 1621, 1487, 1192, 1128, 890, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{40}H_{40}NO^+$ ($[M-X]^+$) 550.3110. Found 550.3098.

9'f (Ar^1 = *p*-^{t}Bu-C_6H_4, Ar^2 = Ph)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.71 (1H, brs), 8.13 (1H, d,

J = 7.7 Hz), 8.12 (1H, s), 8.08 (1H, s), 8.02 (1H, d, *J* = 7.7 Hz), 7.70-7.61 (7H, m), 7.54 (1H, t, *J* = 7.7 Hz), 7.53 (2H, d, *J* = 7.7 Hz), 7.44 (1H, t, *J* = 7.7 Hz), 7.40 (1H, t, *J* = 7.7 Hz), 7.35 (1H, t, *J* = 7.7 Hz), 7.28 (1H, d, *J* = 7.7 Hz), 6.93 (1H, d, *J* = 7.7 Hz), 4.88 (1H, br), 4.44 (1H, br), 2.54 (9H, brs), 1.38 (9H, s); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.1, 149.6, 140.9, 140.8, 139.0, 134.6, 133.7, 132.2, 131.6, 131.5, 131.0, 130.8, 129.6, 128.7_3, 128.7_0, 128.3, 128.2, 127.9, 127.6, 127.5, 126.9, 126.8, 126.5, 124.6, 124.5, 123.4, 123.0, 117.7, 64.3, 53.5, 33.9, 30.7; IR (neat): 3055, 2960, 1618, 1484, 1447, 1401, 1237, 1128, 1027, 899, 753 cm^{-1}; HRMS (FAB) Calcd for $C_{40}H_{40}NO^+$ ([M-X]$^+$) 550.3104. Found 550.3105.

9'g (Ar^1 = *p*-(2,4,6-Me_3-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.80 (1H, brs), 8.19 (1H, s), 8.14 (1H, d, *J* = 7.7 Hz), 8.13 (1H, s), 8.07 (1H, d, *J* = 7.7 Hz), 7.79 (2H, d, *J* = 7.7 Hz), 7.67 (2H, d, *J* = 7.7 Hz), 7.66 (1H, t, *J* = 7.7 Hz), 7.63 (2H, t, *J* = 7.7 Hz), 7.54 (1H, t, *J* = 7.7 Hz), 7.45 (1H, t, *J* = 7.7 Hz), 7.42 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.29 (1H, d, *J* = 7.7 Hz), 7.25 (2H, d, *J* = 7.7 Hz), 6.96_4 (2H, s), 6.95_6 (1H, d, *J* = 7.7 Hz), 4.90 (1H, br), 4.54 (1H, br), 2.56 (9H, brs), 2.30 (3H, s), 2.05 (6H, s); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.0, 140.9, 140.8, 139.4, 138.9, 137.9, 135.8, 135.5, 134.7, 133.7, 132.3, 131.5, 131.0_3, 130.9_8, 129.6, 129.0, 128.7, 128.6, 128.4, 128.3, 127.9, 127.6, 127.5_3, 127.4_7, 127.0, 126.9, 126.5, 124.5, 123.4, 123.2, 117.8, 64.3, 53.5, 20.1, 19.9, one carbon was not found probably due to overlapping; IR (neat): 3012, 2922, 1615, 1482, 1434, 1236, 1126, 1004, 847, 753 cm^{-1}; HRMS (FAB) Calcd for $C_{45}H_{42}NO^+$ ([M-X]$^+$) 612.3266. Found 612.3293.

9'h (Ar^1 = *p*-(2,4,6-*i*Pr_3-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 8.85 (1H, brs), 8.22 (1H, s), 8.14 (1H, d, *J* = 7.7 Hz), 8.13 (1H, s), 8.08 (1H, d, *J* = 7.7 Hz), 7.78 (2H, d, *J* = 7.7 Hz), 7.67 (2H, d, *J* = 7.7 Hz), 7.66 (1H, t, *J* = 7.7 Hz), 7.63 (2H, t, *J* = 7.7 Hz), 7.54 (1H, t, *J* = 7.7 Hz), 7.45 (1H, t, *J* = 7.7 Hz), 7.42 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.31-7.26 (3H, m), 7.10 (2H, s), 6.95 (1H, d, *J* = 7.7 Hz), 4.89 (1H, br), 4.59 (1H, br), 2.95 (1H, sept, *J* = 7.0 Hz), 2.71 (2H, sept, *J* = 7.0 Hz), 2.56 (9H, brs), 1.29 (6H, d, *J* = 7.0 Hz), 1.10 (12H, d, *J* = 7.0 Hz); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 80 °C) δ 150.0, 147.2, 145.7, 140.9_2, 140.8_6, 139.2, 138.8, 136.1, 135.8, 133.7, 132.4, 131.5, 131.0, 129.6, 129.0, 128.7, 128.6, 128.4, 128.3, 127.9, 127.6, 127.5, 127.0, 126.9, 126.5, 124.6, 123.4, 123.1, 119.8, 117.8, 64.3, 53.5, 33.1, 29.3_7, 29.3_6, 23.6, 23.4, two carbons were not found probably due to overlapping; IR (neat): 2959, 2868, 1618, 1469, 1361, 1217, 1128, 1005, 877, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{51}H_{54}NO^+$ ([M-X]$^+$) 696.4205. Found 696.4221.



Representative procedure for preparation of 1: A solution of **9'h** (ca. 0.1 mmol) in EA (5.0 mL) was washed with 0.1 M $NaHCO_3$ aqueous solution (20.0 mL) three times. The resulting yellow organic phase was dried over Na_2SO_4, filtered, and concentrated to furnish crude betaine. Washing it with ether on a funnel followed by drying under vacuum afforded **1h** as a yellow powder (57.0 mg,

0.082 mmol, 82%).

1a (Ar^1 = Ph, Ar^2 = Ph)**:** 74% yield (3 steps). ^{1}H NMR (700 MHz, CD_3OD) δ 7.95 (br), 7.94 (br), 7.90 (br), 7.82 (br), 7.72 (d, *J* = 7.7 Hz), 7.67 (br), 7.58 (br), 7.53 (t, *J* = 7.7 Hz), 7.48 (br), 7.38 (br), 7.26 (d, *J* = 7.7 Hz), 7.11 (br), 6.98 (br), 6.63 (br), 5.10 (d, *J* = 14.0 Hz), 4.98 (br), 4.94 (d, *J* = 14.0 Hz), 4.45 (br), 2.63 (br), 2.34 (br); IR (KBr): 3025, 1605, 1582, 1487, 1424, 1391, 1227, 969, 887, 759 cm^{-1}; HRMS (FAB) Calcd for $C_{36}H_{32}NO^+$ ($[M+H]^+$) 494.2484. Found 494.2477.

1b (Ar^1 = Ph, Ar^2 = Cl)**:** 76% yield (3 steps). ^{1}H NMR (300 MHz, CD_3OD) δ 8.22 (br), 7.95 (br), 7.93 (br), 7.87 (br), 7.76 (br), 7.72 (br), 7.59 (t, *J* = 7.5 Hz), 7.40 (t, *J* = 7.5 Hz), 7.29 (t, *J* = 7.5 Hz), 7.09 (br), 6.62 (br), 6.51 (br), 4.98-4.76 (br), 4.41 (br), 3.08 (br), 2.83 (br); IR (KBr): 3021, 1608, 1583, 1487, 1421, 1281, 1150, 975, 880, 748 cm^{-1}; HRMS (FAB) Calcd for $C_{30}H_{27}NOCl^+$ ($[M+H]^+$) 452.1781. Found 452.1784.

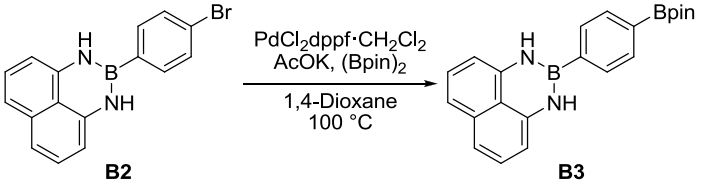
1e (Ar^1 = Ph, Ar^2 = *p*-^{t}Bu-C_6H_4)**:** 72% yield (3 steps). ^{1}H NMR (700 MHz, CD_3OD) δ 8.55 (br), 7.97 (d, *J* = 8.4 Hz), 7.96 (br), 7.92 (br), 7.87 (br), 7.81 (br), 7.76 (br), 7.70 (br), 7.68 (d, *J* = 8.4 Hz), 7.64 (br), 7.58 (br), 7.57 (d, *J* = 8.4 Hz), 7.45 (d, *J* = 8.4 Hz), 7.44-7.36 (m), 7.36-7.32 (m), 7.30 (br), 7.22 (br), 7.16 (br), 7.04 (br), 6.77 (br), 6.68 (br), 5.16 (d, *J* = 14.7 Hz), 5.10 (d, *J* = 14.7 Hz), 4.38 (d, *J* = 14.7 Hz), 2.63 (brs), 2.35 (brs), 1.40 (s); IR (KBr): 2961, 1609, 1486, 1416, 1386, 1224, 889, 750 cm^{-1}; HRMS (FAB) Calcd for $C_{40}H_{40}NO^+$ ($[M+H]^+$) 550.3110. Found 550.3105.

1f (Ar^1 = *p*-^{t}Bu-C_6H_4, Ar^2 = Ph)**:** 78% yield (3 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (br), 7.96 (br), 7.94 (br), 7.90 (br), 7.82 (br), 7.75 (br), 7.71 (d, *J* = 7.5 Hz), 7.67 (br), 7.58 (br), 7.54 (t, *J* = 7.5 Hz), 7.49 (br), 7.43 (d, *J* = 7.5 Hz), 7.38 (br), 7.28 (br), 7.10 (br), 6.98 (br), 6.63 (br), 5.10 (d, *J* = 13.0 Hz), 5.04-4.91 (br), 4.45 (br), 2.62 (br), 2.34 (br), 1.36 (s); IR (KBr): 3025, 2959, 1607, 1583, 1486, 1425, 1203, 1151, 891, 831, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{40}H_{40}NO^+$ ($[M+H]^+$) 550.3110. Found 550.3113.

1g (Ar^1 = *p*-(2,4,6-Me_3-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** 81% yield (3 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 7.99 (br), 7.97 (br), 7.96 (br), 7.92 (br), 7.85 (br), 7.77 (br), 7.69 (br), 7.59 (br), 7.50 (br), 7.39 (br), 7.29 (br), 7.14 (d, *J* = 7.5 Hz), 7.06 (br), 7.01 (br), 6.92 (s), 6.66 (br), 5.13 (d, *J* = 14.0 Hz), 5.03 (br), 4.95 (d, *J* = 14.0 Hz), 4.47 (br), 2.66 (br), 2.37 (br), 2.30 (s), 2.04 (s); IR (KBr): 3023, 1606, 1581, 1483, 1425, 1389, 1279, 1150, 1003, 835, 745 cm^{-1}; HRMS (FAB) Calcd for $C_{45}H_{42}NO^+$ ($[M+H]^+$) 612.3266. Found 612.3237.

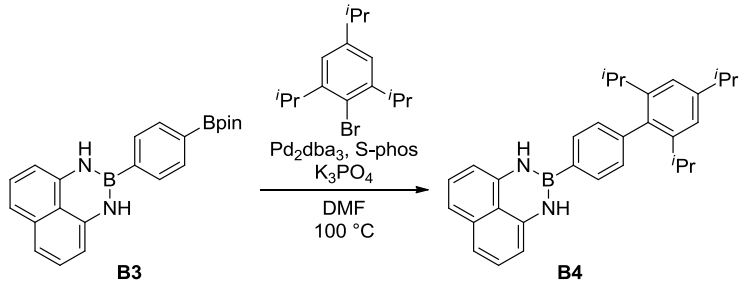
1h (Ar^1 = *p*-(2,4,6-*i*Pr_3-C_6H_2)-C_6H_4, Ar^2 = Ph)**:** 82% yield (3 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (br), 7.96 (br), 7.93 (br), 7.82 (br), 7.79 (br), 7.68 (br), 7.59 (br), 7.57 (br), 7.51 (br), 7.41 (br), 7.31 (br), 7.18 (d, *J* = 8.0 Hz), 7.06 (s), 7.02 (br), 6.73 (br), 6.67 (br), 5.13 (d, *J* = 14.5 Hz), 5.04 (br), 4.93 (d, *J* = 14.5 Hz), 4.45 (br), 2.92 (sept, *J* = 7.0 Hz), 2.78 (br), 2.67 (br), 2.37 (br), 1.29 (d, *J* = 7.0 Hz), 1.09 (d, *J* = 7.0 Hz); IR (KBr): 3020, 2958, 1605, 1581, 1468, 1426, 1389, 1203, 838, 747 cm^{-1}; HRMS (FAB) Calcd for $C_{51}H_{54}NO^+$ ($[M+H]^+$) 696.4205. Found 696.4221.

Preparation of Boronic Acid B1:



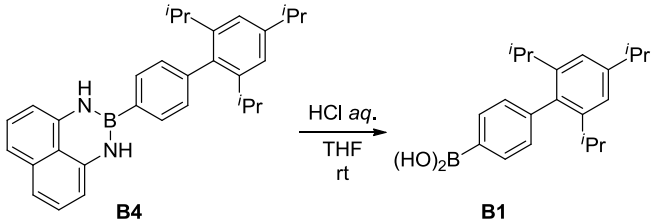
B2 **B3**

Conversion of B2 to B3: Title compound was prepared from known intermediate **B2**[17] according to the literature procedure.[18] **B3:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 7.5 Hz), 7.63 (2H, d, J = 7.5 Hz), 7.12 (2H, t, J = 7.5 Hz), 7.04 (2H, d, J = 7.5 Hz), 6.39 (2H, d, J = 7.5 Hz), 6.03 (2H, s), 1.36 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 136.5, 134.5, 130.8, 127.7, 120.0, 118.0, 106.2, 84.1, 25.0, the boron-bound carbons were not detected due to quadrupolar relaxation; IR (KBr): 3424, 3372, 2979, 1600, 1528, 1392, 1360, 1321, 1235, 1141, 1094, 768 cm^{-1}.



B3 **B4**

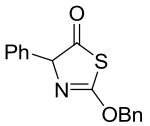
Conversion of B3 to B4: Title compound was prepared according to the procedure for the synthesis of **9**. **B4:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (2H, d, J = 7.5 Hz), 7.27 (2H, d, J = 7.5 Hz), 7.14 (2H, t, J = 7.5 Hz), 7.08 (2H, s), 7.06 (2H, d, J = 7.5 Hz), 6.41 (2H, d, J = 7.5 Hz), 6.08 (2H, s), 2.95 (1H, sept, J = 7.0 Hz), 2.60 (2H, sept, J = 7.0 Hz), 1.32 (6H, d, J = 7.0 Hz), 1.10 (12H, d, J = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 146.5, 143.3, 141.3, 136.9, 136.5, 131.3, 129.9, 127.8, 120.7, 120.0, 117.9, 106.1, 34.4, 30.5, 24.4, 24.2, the boron-bound carbon was not detected due to quadrupolar relaxation; IR (KBr): 3419, 2959, 2867, 2586, 1588, 1525, 1466, 1399, 1361, 1319, 1260, 1089, 1005, 818 cm^{-1}; HRMS (FAB) Calcd for $C_{31}H_{35}N_2B^+$ ([M+H]$^+$) 446.2899, Found 446.2896.



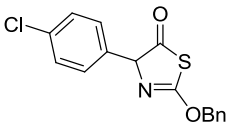
B4 **B1**

Conversion of B4 to B1: Title compound was prepared according to the literature procedure.[17] **B1:** ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.94 (2H, d, J = 8.0 Hz), 7.18 (2H, br), 7.17 (2H, d, J = 8.0 Hz), 7.11 (2H, s), 2.95 (1H, sept, J = 7.0 Hz), 2.60 (2H, sept, J = 7.0 Hz), 1.29 (6H, d, J = 7.0 Hz), 1.06 (12H, d, J = 7.0 Hz); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 148.7, 147.0, 143.9, 138.1, 134.8, 129.8, 121.2, 35.1, 31.0, 24.5, 24.4, the boron-bound carbon was not detected due to quadrupolar relaxation; IR (KBr): 3387, 2961, 2869, 1705, 1609, 1461, 1359, 1259, 1102, 1005 cm^{-1}.

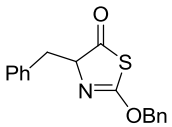
Characterization of 2-Alkoxythiazol-5(4*H*)-one 13: A series of 2-Alkoxythiazol-5(4*H*)-one **13** was prepared by following the literature method.[8]



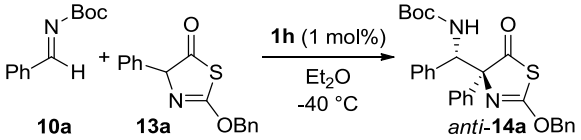
11a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.45 (2H, m), 7.43-7.38 (3H, m), 7.38-7.32 (3H, m), 7.27-7.24 (2H, m), 5.60 (1H, s), 5.57 (1H, d, J = 12.0 Hz), 5.52 (1H, d, J = 12.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 162.2, 135.1, 134.8, 128.9$_2$, 128.8$_7$, 128.8$_4$, 128.7$_7$, 128.7, 126.8, 83.6, 71.5; IR (neat): 1752, 1631, 1454, 1368, 1247, 1196, 1092, 1068, 908, 753 cm^{-1}; HRMS (FAB) Calcd for $C_{16}H_{14}NO_2S^+$ ([M+H]$^+$) 284.0745. Found 284.0749.



11b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 7.5 Hz), 7.44-7.37 (3H, m), 7.31 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.5 Hz), 5.57 (1H, d, J = 12.0 Hz), 5.56 (1H, s), 5.51 (1H, d, J = 12.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.1, 162.4, 135.0, 134.7, 133.2, 129.0, 128.9$_3$, 128.8$_6$, 128.7, 128.1, 82.8, 71.6; IR (neat): 1733, 1633, 1488, 1455, 1246, 1193, 1085, 1013, 903, 741 cm^{-1}; HRMS (FAB) Calcd for $C_{16}H_{13}NO_2SCl^+$ ([M+H]$^+$) 318.0356. Found 318.0355.

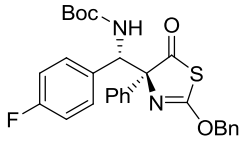


11c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (5H, m), 7.26-7.19 (3H, m), 7.15-7.12 (2H, m), 5.42 (1H, d, J = 12.0 Hz), 5.33 (1H, d, J = 12.0 Hz), 4.77 (1H, dd, J = 7.0, 4.5 Hz), 3.25 (1H, dd, J = 13.5, 4.5 Hz), 3.05 (1H, dd, J = 13.5, 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.0, 160.8, 135.9, 135.2, 129.9, 128.7, 128.6, 128.3, 127.0, 81.6, 71.1, 38.7, one carbon was not found probably due to overlapping; IR (neat): 1728, 1635, 1496, 1454, 1245, 1209, 1108, 1030, 905, 740 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{16}NO_2S^+$ ([M+H]$^+$) 298.0902. Found 298.0902.

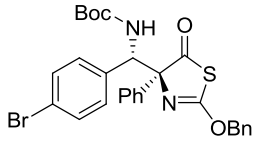


Representative procedure for catalytic asymmetric Mannich-type reaction of 2-alkoxythiazol-5(4*H*)-one: To a solution of **1h** (1.39 mg, 0.002 mmol) and **11a** (56.7 mg, 0.20 mmol) in Et_2O (2 mL) was added benzaldehyde *N*-Boc imine **10a** (45.2 mg, 0.22 mmol) at −40 °C under argon atmosphere. After 15 min of stirring, a 0.5 M solution of trifluoroacetic acid in toluene (20.0 μL) was introduced to the reaction mixture. The resulting solution was poured into ice-cooled 1 M HCl aqueous solution and the aqueous phase was extracted with EA twice. The combined organic phases were washed with brine and dried over Na_2SO_4. After concentration to give the crude residue, the diastereomeric ratio of the product was determined by ^{1}H NMR analysis (500 MHz). Silica gel column chromatography using H/EA solvent system (H/EA = 10:1-5:1 as eluent) afforded **14a** (94.9 mg) as a mixture of diastereomers in 97% yield (*anti*/*syn* = 10:1) and the enantiomeric excess was measured by HPLC analysis. **14a:** HPLC: AD-H, H/EtOH = 32:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.3 min (minor *anti* isomer), 5.7 min (major *anti* isomer), 6.4 min (major *syn* isomer), 24.4 min (minor *syn* isomer), Absolute and relative configurations were assigned by derivatization to **16** (see below); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.69-7.64 (2H, m), 7.58 (2H, d, J = 7.5 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.40-7.31 (5H, m),

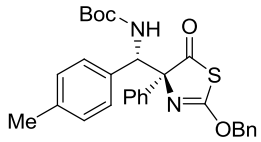
7.31-7.26 (3H, m), 6.42 (1H, d, J = 10.0 Hz), 5.82 (1H, d, J = 12.0 Hz), 5.78 (1H, d, J = 12.0 Hz), 5.72 (1H, d, J = 10.0 Hz), 1.18 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 206.4, 161.9, 155.6, 138.4, 137.1, 136.6, 129.8, 129.7, 129.5, 129.3, 129.1, 128.7, 128.6, 127.5, 94.2, 79.3, 72.5, 61.4, 28.4, one carbon was not found probably due to overlapping; IR (neat): 3438, 3017, 2979, 1712, 1635, 1494, 1367, 1217, 1169, 1076, 755 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{29}N_2O_4S^+$ ($[M+H]^+$) 489.1848. Found 489.1866.



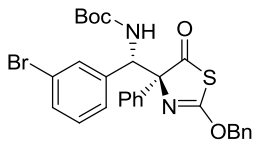
14b: HPLC: AD-H, H/2-propanol (IPA) = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.4 min (major *anti* isomer), 9.6 min (minor *anti* isomer), 15.0 min (minor *syn* isomer), 29.1 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.68-7.64 (2H, m), 7.60 (2H, d, J = 7.0 Hz), 7.51 (2H, t, J = 7.0 Hz), 7.46 (1H, t, J = 7.0 Hz), 7.42-7.30 (5H, m), 7.05 (2H, t, J = 8.5 Hz), 6.45 (1H, d, J = 9.5 Hz), 5.83 (1H, d, J = 12.0 Hz), 5.78 (1H, d, J = 12.0 Hz), 5.71 (1H, d, J = 9.5 Hz), 1.18 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 206.4, 163.0 (d, J_{F-C} = 262.5 Hz), 162.1, 155.5, 136.9, 136.6, 134.6 (d, J_{F-C} = 3.8 Hz), 131.8 (d, J_{F-C} = 8.4 Hz), 129.7, 129.5$_8$, 129.5$_6$, 129.3, 129.1, 127.4, 115.4 (d, J_{F-C} = 21.4 Hz), 94.1, 79.4, 72.6, 60.7, 28.3; IR (neat): 3439, 2978, 1714, 1635, 1510, 1393, 1367, 1226, 1161, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{28}N_2O_4SF^+$ ($[M+H]^+$) 507.1754. Found 507.1766.



14c: HPLC: IA, H/IPA = 32:1, flow rate = 0.5 mL/min, λ = 254 nm, 7.7 min (minor *anti* isomer), 8.0 min (major *anti* isomer), 10.6 min (minor *syn* isomer), 23.0 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, C_6D_6) for major *anti* isomer δ 7.77 (2H, d, J = 7.5 Hz), 7.19 (2H, t, J = 7.5 Hz), 7.15-7.06 (8H, m), 6.76 (2H, d, J = 8.5 Hz), 5.97 (1H, d, J = 9.5 Hz), 5.46 (1H, d, J = 9.5 Hz), 5.08 (1H, d, J = 12.0 Hz), 4.91 (1H, d, J = 12.0 Hz), 1.22 (9H, s); ^{13}C NMR (126 MHz, C_6D_6) for major *anti* isomer δ 204.5, 162.8, 154.8, 136.8, 136.4, 135.5, 131.4, 130.8, 129.0$_0$, 128.9$_7$, 128.9$_1$, 128.8$_7$, 126.8, 122.3, 93.1, 79.6, 71.5, 60.5, 28.2, one carbon was not found probably due to overlapping; IR (neat): 3436, 3016, 2979, 1712, 1634, 1488, 1368, 1217, 1166, 1074, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{28}N_2O_4SBr^+$ ($[M+H]^+$) 569.0936. Found 569.0935.

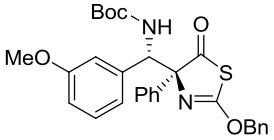


14d: HPLC: AD-H, H/IPA/EtOH = 93:2:5, flow rate = 0.5 mL/min, λ = 210 nm, 10.5 min (minor *anti* isomer), 11.1 min (major *anti* isomer), 14.5 min (minor *syn* isomer), 15.9 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.67-7.64 (2H, m), 7.58 (2H, d, J = 7.5 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.45 (1H, d, J = 7.5 Hz), 7.40-7.34 (3H, m), 7.22 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 6.37 (1H, d, J = 10.0 Hz), 5.82 (1H, d, J = 12.0 Hz), 5.78 (1H, d, J = 12.0 Hz), 5.67 (1H, d, J = 10.0 Hz), 2.29 (3H, s), 1.18 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 206.4, 161.8, 155.5, 138.1, 137.2, 136.6, 135.5, 129.7, 129.6, 129.5, 129.3, 129.2, 129.0, 128.9, 127.4, 94.3, 79.2, 72.4, 61.2, 28.4, 21.2; IR (neat): 3438, 3011, 2978, 1714, 1635, 1494, 1367, 1226, 1168, 1072, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{29}H_{31}N_2O_4S^+$ ($[M+H]^+$) 503.2005. Found 503.1993.

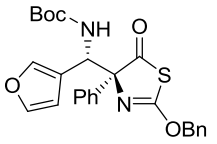


14e: HPLC: IA, H/IPA/EtOH = 98.5:0.5:1, flow rate = 0.5 mL/min, λ = 210

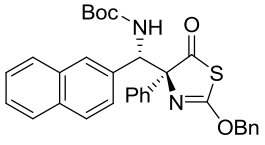
nm, 14.5 min (minor *anti* isomer), 16.2 min (major *anti* isomer), 18.5 min (major *syn* isomer), 23.6 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, C_6D_6) for major *anti* isomer δ 7.77 (2H, d, J = 8.0 Hz), 7.57 (1H, s), 7.23-7.14 (6H, m), 7.14-7.08 (3H, m), 7.01 (1H, d, J = 7.5 Hz), 6.60 (1H, t, J = 7.5 Hz), 6.06 (1H, d, J = 9.5 Hz), 5.54 (1H, d, J = 9.5 Hz), 5.11 (1H, d, J = 11.5 Hz), 5.04 (1H, d, J = 11.5 Hz), 1.21 (9H, s); ^{13}C NMR (126 MHz, C_6D_6) for major *anti* isomer δ 204.6, 162.9, 154.8, 140.2, 136.3, 135.2, 131.9, 131.3, 129.9, 129.1, 129.0, 128.9$_3$, 128.8$_7$, 126.9, 122.3, 93.1, 79.7, 71.9, 60.7, 28.2, two carbons were not found probably due to overlapping; IR (neat): 3434, 3014, 2978, 1714, 1634, 1493, 1367, 1225, 1166, 1074, 755 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{28}N_2O_4SBr^+$ ([M+H]$^+$) 569.0936. Found 569.0911.



14f: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.5 min (minor *anti* isomer), 11.4 min (major *anti* isomer), 15.5 min (minor *syn* isomer), 20.5 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.67-7.65 (2H, m), 7.56 (2H, d, J = 7.5 Hz), 7.48 (2H, t, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.40-7.32 (3H, m), 7.22 (1H, t, J = 7.5 Hz), 7.09 (1H, s), 6.93 (1H, d, J = 7.5 Hz), 6.86 (1H, d, J = 7.5 Hz), 6.52 (1H, d, J = 10.0 Hz), 5.82 (1H, d, J = 12.0 Hz), 5.79 (1H, d, J = 12.0 Hz), 5.72 (1H, d, J = 10.0 Hz), 3.80 (3H, s), 1.18 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 206.4, 161.8, 160.2, 155.6, 140.0, 137.1, 136.4, 129.7, 129.6, 129.5, 129.2, 129.0, 128.9, 127.5, 122.1, 115.6, 114.1, 94.2, 79.2, 72.5, 61.5, 55.6, 28.4; IR (neat): 3440, 3014, 2978, 1713, 1636, 1493, 1257, 1219, 1174, 1072, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{29}H_{31}N_2O_5S^+$ ([M+H]$^+$) 519.1954. Found 519.1974.

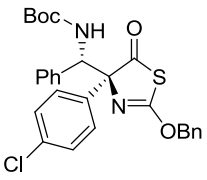


14g: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.6 min (major *anti* isomer), 11.7 min (minor *anti* isomer), 20.7 min (minor *syn* isomer), 33.7 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, C_6D_6) for major *anti* isomer δ 7.78 (2H, d, J = 7.5 Hz), 7.18 (2H, t, J = 7.5 Hz), 7.16-7.05 (6H, m), 7.02 (1H, s), 6.91 (1H, s), 6.09 (1H, d, J = 10.0 Hz), 5.99 (1H, s), 5.32 (1H, d, J = 10.0 Hz), 5.09 (1H, d, J = 12.0 Hz), 4.99 (1H, d, J = 12.0 Hz), 1.22 (9H, s); ^{13}C NMR (126 MHz, C_6D_6) for major *anti* isomer δ 204.8, 162.7, 154.8, 143.0, 141.3, 136.3, 135.5, 128.9, 128.7, 128.6, 126.9, 122.8, 110.2, 93.5, 79.4, 71.4, 53.8, 28.2, two carbons were not found probably due to overlapping; IR (neat): 3430, 2978, 1723, 1636, 1495, 1367, 1256, 1223, 1166, 1072, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{26}H_{27}N_2O_5S^+$ ([M+H]$^+$) 479.1641. Found 479.1632.

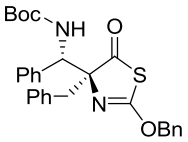


14h: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.1 min (minor *anti* isomer), 11.8 min (major *anti* isomer), 16.5 min (minor *syn* isomer), 54.4 min (major *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, CD_3OD) for major *anti* isomer δ 7.79-7.71 (3H, m), 7.70-7.64 (3H, m), 7.50-7.24 (11H, m), 5.81 (1H, s), 5.69 (1H, d, J = 11.5 Hz), 5.66 (1H, d, J = 11.5 Hz), 1.19 (9H, s), N-H proton was not found probably due to deuteration; ^{13}C NMR (126 MHz, CD_3OD) for major *anti* isomer δ 207.0, 162.6, 157.1, 137.5, 136.8,

135.8, 134.3, 134.1, 129.8, 129.7, 129.6, 129.4, 129.1, 128.6, 128.5, 127.7, 127.4, 127.3, 127.2, 94.5, 80.6, 72.8, 62.3, 28.5, two carbons were not found probably due to overlapping; IR (neat): 3426, 2977, 1712, 1634, 1494, 1392, 1367, 1255, 1176, 1072, 751 cm^{-1}; HRMS (FAB) Calcd for $C_{32}H_{31}N_2O_4S^+$ ($[M+H]^+$) 539.2005. Found 539.1997.

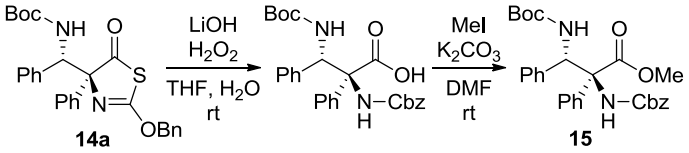


14i: HPLC: AD-H, H/EtOH = 32:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.8 min (minor *anti* isomer), 7.3 min (major *anti* isomer), 9.4 min (major *syn* isomer), 16.4 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.68 (2H, d, *J* = 9.0 Hz), 7.58 (2H, d, *J* = 7.0 Hz), 7.50 (2H, t, *J* = 7.0 Hz), 7.45 (1H, t, *J* = 7.0 Hz), 7.39 (2H, d, *J* = 9.0 Hz), 7.36 (2H, d, *J* = 7.0 Hz), 7.32-7.28 (3H, m), 6.55 (1H, d, *J* = 10.5 Hz), 5.82 (1H, d, *J* = 12.0 Hz), 5.78 (1H, d, *J* = 12.0 Hz), 5.67 (1H, d, *J* = 10.5 Hz), 1.19 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 206.3, 162.0, 155.6, 138.0, 136.5, 136.1, 134.9, 129.8, 129.6_3, 129.5_6, 129.5, 129.4, 129.0, 128.7, 93.8, 79.4, 72.6, 61.8, 28.3, one carbon was not found probably due to overlapping; IR (neat): 3433, 3033, 2978, 1714, 1634, 1491, 1367, 1227, 1166, 1095, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{28}N_2O_4SCl^+$ ($[M+H]^+$) 523.1458. Found 523.1446.



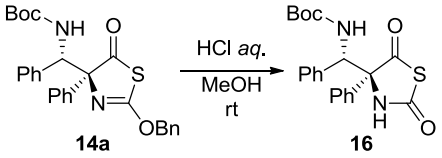
14j: HPLC: AD-H, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.1 min (minor *anti* isomer), 10.8 min (major *anti* isomer), 14.7 min (major *syn* isomer), 28.4 min (minor *syn* isomer), Absolute and relative configurations were assigned on the analogy of **14a**; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 7.52-7.32 (6H, m), 7.24-7.16 (7H, m), 7.14-7.08 (2H, m), 6.76 (1H, d, *J* = 10.0 Hz), 5.64 (1H, d, *J* = 12.0 Hz), 5.61 (1H, d, *J* = 12.0 Hz), 5.24 (1H, d, *J* = 10.0 Hz), 3.48 (1H, d, *J* = 13.0 Hz), 3.28 (1H, d, *J* = 13.0 Hz), 1.43 (9H, s); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) for major *anti* isomer δ 208.3, 161.9, 156.2, 138.6, 136.7, 135.6, 131.5, 129.7, 129.5, 129.3, 128.7, 128.5, 127.6, 93.7, 79.7, 72.0, 60.9, 42.6, 28.6, two carbons were not found probably due to overlapping; IR (neat): 3426, 3032, 2979, 1715, 1633, 1495, 1367, 1218, 1166, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{29}H_{31}N_2O_4S^+$ ($[M+H]^+$) 503.2005. Found 503.1992.

Derivatization of 14a:

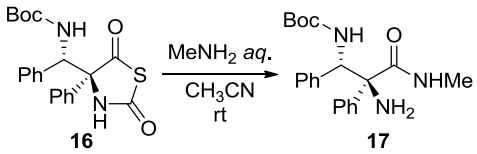


Procedure for derivatization of 14a to 15: A solution of **14a** (*anti*/*syn* = 10:1, 99% ee for *anti* isomer) (24.9 mg, 0.0533 mmol) in THF (5.3 mL) was treated with 30% H_2O_2 aqueous solution (315.0 μL) and a 1.0 M LiOH aqueous solution (530.0 μL, 0.53 mmol) at room temperature for 20 h. Then, a saturated aqueous solution of Na_2SO_3 was added until peroxides were completely reduced. The resulting mixture was acidified with 2 M $KHSO_4$ aqueous solution and extracted with EA twice. The organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude carboxylic acid. In the presence of K_2CO_3 (29.3 mg, 0.212 mmol), MeI (7 μL, 0.106 mmol) was

added to a solution of the obtaining acid in DMF (0.18 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether twice. After concentration of the organic extracts, purification of the residue by column chromatography on silica gel (H/EA = 10:1-3:1 as eluent) gave diastereomerically pure **15** as a white solid (17.8 mg, 0.0353 mmol, 66% in two steps) without loss of the enantiomeric purity. **15:** HPLC: AD-H, H/EtOH = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.9 min (major isomer), 8.1 min (minor isomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 8.5 Hz), 7.51 (2H, d, *J* = 7.5 Hz), 7.43-7.30 (8H, m), 7.25-7.20 (3H, m), 7.12 (2H, dd, *J* = 7.5, 2.0 Hz), 6.41 (1H, s), 6.22 (1H, d, *J* = 8.5 Hz), 5.22 (1H, d, *J* = 12.5 Hz), 5.07 (1H, d, *J* = 12.5 Hz), 3.71 (3H, s), 1.37 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 156.2, 156.1, 138.8, 136.3_0, 136.2_8, 128.7, 128.6, 128.5, 128.3, 127.9, 127.4, 127.3, 79.4, 70.6, 67.4, 59.0, 53.9, 28.6; IR (neat): 3395, 2978, 1713, 1504, 1455, 1366, 1269, 1168, 1053, 730 cm^{-1}; $[\alpha]_D^{28}$ -45.4° (c = 0.55, $CHCl_3$); HRMS (FAB) Calcd for $C_{29}H_{33}N_2O_6^+$ ($[M+H]^+$) 505.2339. Found 505.2331.



Preparation of 16 from 14a: Treatment of **14a** (*anti*/*syn* = 10:1, 99% ee for *anti* isomer) with 1 M HCl methanolic solution at room temperature for 30 min followed by purification by silica gel column chromatography (H/EA = 5:1-1:1 as eluent) furnished **16** as a white solid. **16:** ^{1}H NMR (500 MHz, CD_3OD) for major *anti* isomer δ 7.68 (2H, d, *J* = 7.5 Hz), 7.46 (2H, t, *J* = 7.5 Hz), 7.41 (1H, t, *J* = 7.5 Hz), 7.39-7.34 (3H, m), 7.32 (2H, d, *J* = 7.5 Hz), 6.93 (1H, d, *J* = 9.5 Hz), 5.82 (1H, br), 1.23 (9H, s) , a N-H proton was not found probably due to deuteration; ^{13}C NMR (126 MHz, CD_3OD) for major *anti* isomer δ 199.5, 167.2, 156.8, 137.7, 136.7, 130.2, 129.9, 129.8, 129.5, 127.4, 82.7, 81.0, 60.9, 28.4, one carbon was not found probably due to overlapping; IR (neat): 3292, 2979, 1710, 1685, 1523, 1395, 1245, 1161, 1065, 753 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{23}N_2O_4S^+$ ($[M+H]^+$) 399.1379. Found 399.1383.



Conversion of 16 to 17: To a solution of **16** (*anti*/*syn* = 10:1) obtained as above in MeCN was added 40% aqueous solution of $MeNH_2$ at room temperature and the mixture was stirred for 30 min. After concentration to remove all volatiles, **17** was isolated by silica gel column chromatography ($CHCl_3$/MeOH = 1:0-5:1 as eluent) in 92% yield (two steps) without loss of the enantiomeric purity. **17:** HPLC: IA, H/EtOH = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.5 min (major *syn* isomer), 16.5 min (minor *syn* isomer), 21.5 min (major *anti* isomer), 25.4 min (minor *anti* isomer); ^{1}H NMR (500 MHz, CD_3OD) for major *anti* isomer δ 7.75 (2H, d, *J* = 7.5 Hz), 7.41 (2H, d, *J* = 7.5 Hz), 7.38-7.30 (4H, m), 7.27 (2H, t, *J* = 7.5 Hz), 6.13 (1H, s), 2.50 (3H, s), 1.27 (9H, s), N-H protons were not found probably due to deuteration; ^{13}C NMR (126 MHz, CD_3OD) for major *anti* isomer δ 176.0,

157.6, 142.2, 140.4, 129.5, 129.3, 129.0, 128.6, 128.3, 127.6, 80.2, 68.7, 59.6, 28.7, 26.3; IR (neat): 3363, 2978, 1693, 1653, 1520, 1496, 1411, 1365, 1248, 1168, 881, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{28}N_3O_3^+$ ($[M+H]^+$) 370.2131. Found 370.2115.

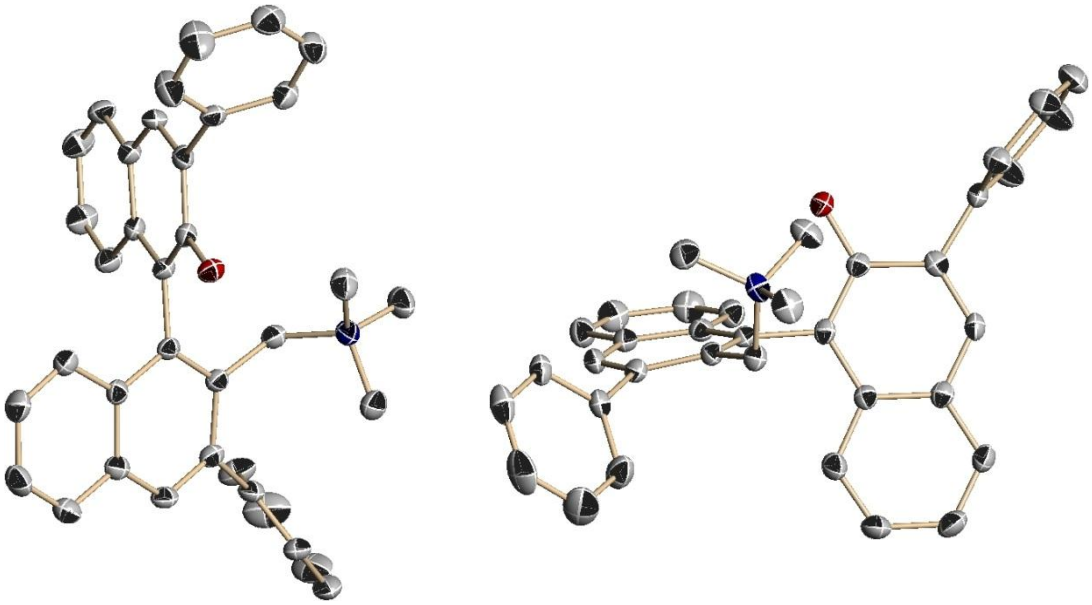
Crystallographic Structure Determination:

Recrystallization of 1a: Recrystallization of **1a** was achieved by using MeOH/toluene solvent system at −15 °C.

The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 153 K on a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on F^2 by using SHELXTL.[19] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions and isotropic thermal parameters refined. The crystallographic data were summarized in the following table.

Table S1. Crystal data and structure refinement for **1a**·2MeOH·H_2O.

Empirical formula	C38 H41 N O4	
Formula weight	575.72	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.552(5) Å	α = 90°.
	b = 9.827(5) Å	β = 109.875(11)°.
	c = 14.569(7) Å	γ = 90°.
Volume	1555.4(13) $Å^3$	
Z	2	
Density (calculated)	1.229 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	616	
Crystal size	0.60 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.49 to 28.39°.	
Index ranges	-15<=h<=15, -13<=k<=12, -14<=l<=19	
Reflections collected	11719	
Independent reflections	6478 [R_{int} = 0.0329]	
Completeness to theta = 28.39°	98.7 %	
Absorption correction	None	
Max. and min. transmission	0.9922 and 0.9543	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6478 / 1 / 399	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1157	
R indices (all data)	R1 = 0.0593, wR2 = 0.1216	
Largest diff. peak and hole	0.291 and -0.234 e.$Å^{-3}$	



(a) Top view (b) Front view

Figure S1. Molecular structure of **1a**. All hydrogen atoms and solvent molecules are omitted for clarity. Blue = nitrogen, red = oxygen, black = carbon. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.

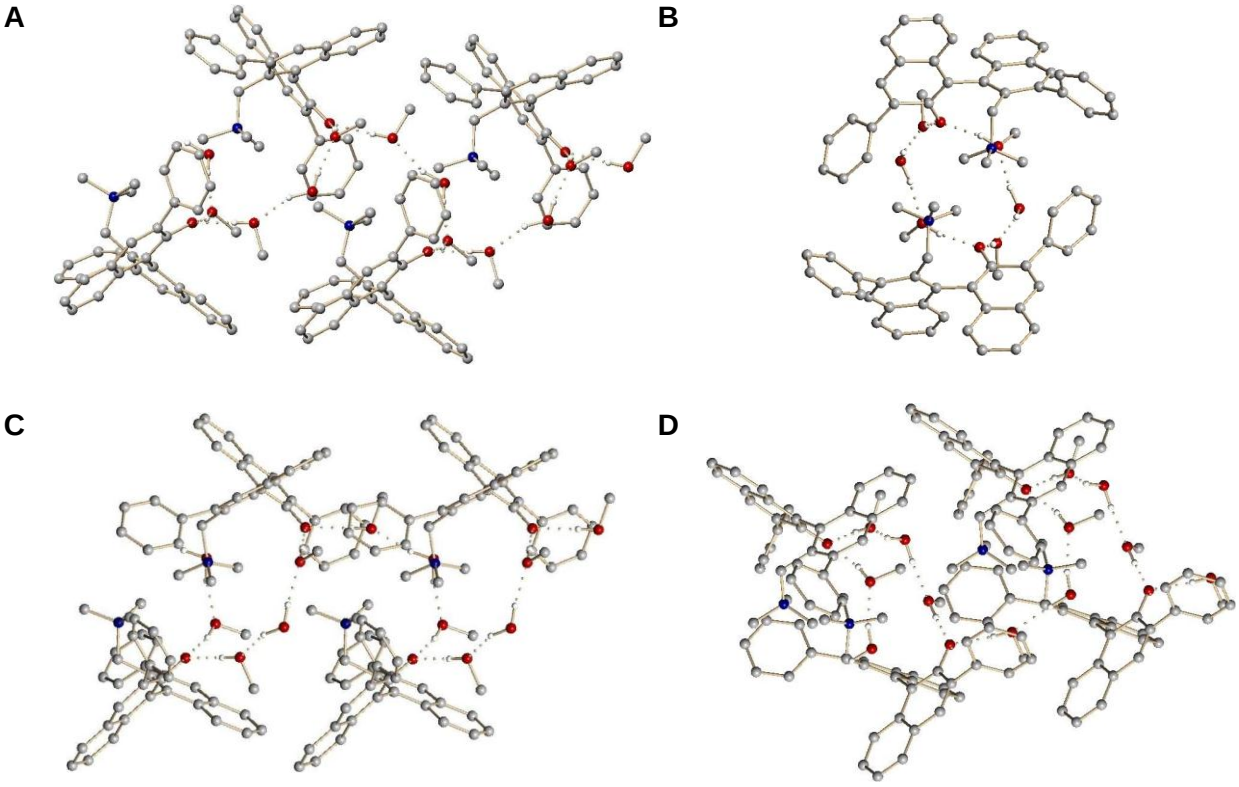


Figure S2. Packing model of **1a**. All hydrogen atoms except O-H protons are omitted for clarity. Blue = nitrogen, red = oxygen, black = carbon. The molecules form helical hydrogen-bonding network (···H-O-H···O(Me)-H···O^{-}(**1a**) ···H-O(Me) ···H-O-H···).

Recrystallization of *anti*-16: Recrystallization of *anti*-**16** was achieved by using CD_3OD as a solvent at room temperature.

The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 153 K on a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on F^2 by using SHELXTL.[19] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to nitrogen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions and isotropic thermal parameters refined. The crystallographic data were summarized in the following table.

Table S2. Crystal data and structure refinement for *anti*-**16**.

Empirical formula	C21 H22 N2 O4 S1	
Formula weight	398.47	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 11.7097(16) Å	α = 90°.
	b = 16.840(2) Å	β = 90°.
	c = 21.042(3) Å	γ = 90°.
Volume	4149.2(10) $Å^3$	
Z	8	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	0.184 mm^{-1}	
F(000)	1680	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.55 to 28.33°.	
Index ranges	-15<=h<=15, -22<=k<=12, -28<=l<=27	
Reflections collected	31771	
Independent reflections	10322 [R_{int} = 0.0696]	
Completeness to theta = 28.33°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9641 and 0.9468	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10322 / 0 / 527	
Goodness-of-fit on F^2	1.084	
Final R indices [I>2sigma(I)]	R1 = 0.0627, wR2 = 0.1196	
R indices (all data)	R1 = 0.0824, wR2 = 0.1277	
Absolute structure parameter	0.01(7)	
Largest diff. peak and hole	0.430 and -0.224 e.$Å^{-3}$	

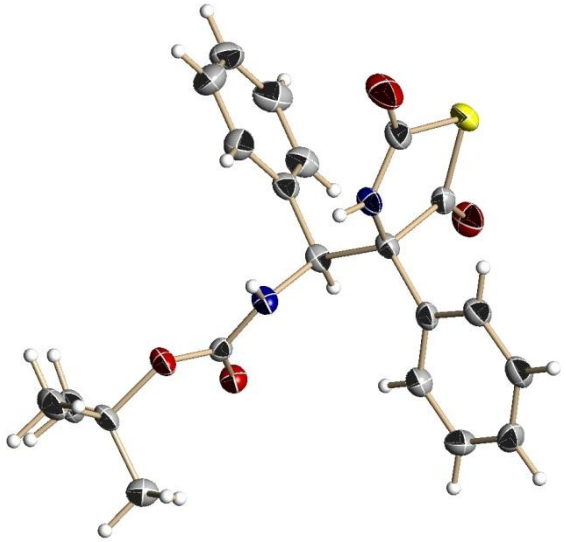


Figure S3. Molecular structure of *anti*-**16**. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.

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(1) Shibasaki, M.; Kanai, M. in *New Frontiers in Asymmetric Catalysis*, eds. Mikami, K.; Lautens, M. John Wiley & Sons, Inc., Hoboken, 2007, 383.

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(4) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.*, **2004**, *43*, 1871.

(5) Crystal data for **1a**·2MeOH·H_2O (CCDC 744059): $C_{36}H_{31}NO{\cdot}2CH_4O{\cdot}H_2O$ (MW 575.72), monoclinic, $P2_1$, a = 11.552(5), b = 9.827(5), c = 14.569(7) Å, β = 109.875(11)º, V = 1555.4(13) $Å^3$, Z = 2, T = 153(2) K, Independent reflections 6478 [R_{int} = 0.0329], R1(R_w) = 0.0496 (0.1157) (I > 2σ (I)), GOF = 1.032.

(6) (a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (d) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094. (e) Puglisi, A.; Raimondi, L.; Benaglia, M.; Bonsignore, M.; Rossi, S. *Tetrahedron Lett.* **2009**, *50*, 4340.

(7) (a) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. (b) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (c) Kim, H.; Chin, J. *Org. Lett.* **2009**, *11*, 5258. (d) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876.

(8) Lin, Y.; Andersen, K. K. *Eur. J. Org. Chem.*, 2002, 557.
(9) The reaction with the betaine precursor **1a**·HCl was very sluggish under the identical conditions.
(10)For non-enantioselective examples, see: (a) Wang, Y.; Zhu, Y.; Chen, Z.; Mi, A.; Hu W.; Doyle, M. P. *Org. Lett.*, **2003**, *5*, 3923. (b) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose B. J.; Kozlowski, M. C. *J. Am. Chem. Soc.*, **2008**, *130*, 15794.
(11)It is known that the deprotection of α,α-disubstituted oxazol-5-one requires harsh conditions due to the high stability of amide protective group in the ring-opening product. For examples, see: (a) ref 7a. (b) Uraguchi, D.; Asai, Y.; Seto Y.; Ooi, T. *Synlett*, **2009**, 658.
(12)Crystal data for *anti*-**13** (CCDC 744058): $C_{21}H_{22}N_2O_4S$ (MW 398.47), Orthorhombic, $P2_12_12_1$, a = 11.7097(16), b = 16.840(2), c = 21.042(3) Å, V = 4149.2(10) $Å^3$, Z = 8, T = 153(2) K, Independent reflections 10322 [R_{int} = 0.0696], Flack parameter 0.01(7), R1(R_w) = 0.0627 (0.1196) ($I > 2\sigma$ (I)), GOF = 1.084.
(13)Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **2002**, *124*, 12964.
(14)Kornblum, N.; Blackwood, R. K. *Org. Synth. Coll. Vol.* **1963**, *4*, 454.
(15)Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.*, **1993**, *34*, 1615.
(16)Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.*, **2007**, *129*, 2410.
(17)Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.*, **2007**, *129*, 758.
(18)Powell, N. A.; Ciske, F. L.; Cai, C.; Holsworth, D. D.; Mennen, K.; Van Huis, C. A.; Jalaie, M.; Day, J.; Mastronardi, M.; McConnell, P.; Mochalkin, I.; Zhang, E.; Ryan, M. J.; Bryant, J.; Collard, W.; Ferreira, S.; Gu, C.; Collins, R.; Edmunds, J. J. *Bioorg. Med. Chem.*, **2007**, *15*, 5912.
(19)Sheldrick, G. M. SHELXTL 5.1, Bruker AXS Inc., Madison, Wisconsin, 1997.

Chapter 4

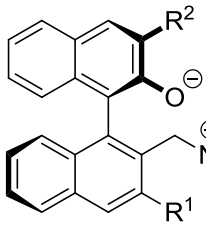
Chiral Ammonium Betaines as an Ionic Nucleophilic Catalyst

Abstract: The chiral ammonium betaine **1** has been successfully applied to the asymmetric Steglich rearrangement as an ionic nucleophilic catalyst. The catalyzed reaction results in record levels of product enantioselectivity, and has a broad substrate scope.

Introduction

Asymmetric nucleophilic catalysis has been extensively studied over the last several decades and plays an increasingly important role in modern asymmetric synthesis.[1] The general definitive feature of this catalysis is that a Lewis basic catalyst reacts with a substrate to give a reactive ionic intermediate through the formation of a new covalent bond, which will be eventually cleaved by the elimination of the catalyst. With this respect, an anionic molecule could function as a potentially more nucleophilic catalyst for initiating the reaction, compared to the commonly utilized, electronically neutral molecules, but it generates a rather stable intermediate bearing no charge (*vide infra*). Hence, research toward exploiting the reactivity of anionic molecules for the development of new type of nucleophilic catalysis, i.e., enantioselective ionic nucleophilic catalysis, has met with limited success.[2,3]

Author recently introduced intramolecular ion-pairing chiral ammonium betaine of type **1** as a new yet intriguing structural motif of organic base catalysts.[4,5] The basic character of its anionic site, aryloxylate, and the hydrogen-bonding capability of its conjugate acid, arylhydroxide, appeared to be the key features for realizing highly enantioselective Mannich-type reactions. Given that the aryloxylate functionality has a nucleophilic character as well, author envisioned that **1** could be evolved into a chiral nucleophilic catalyst having its own characteristics through appropriate structural manipulations.[6]

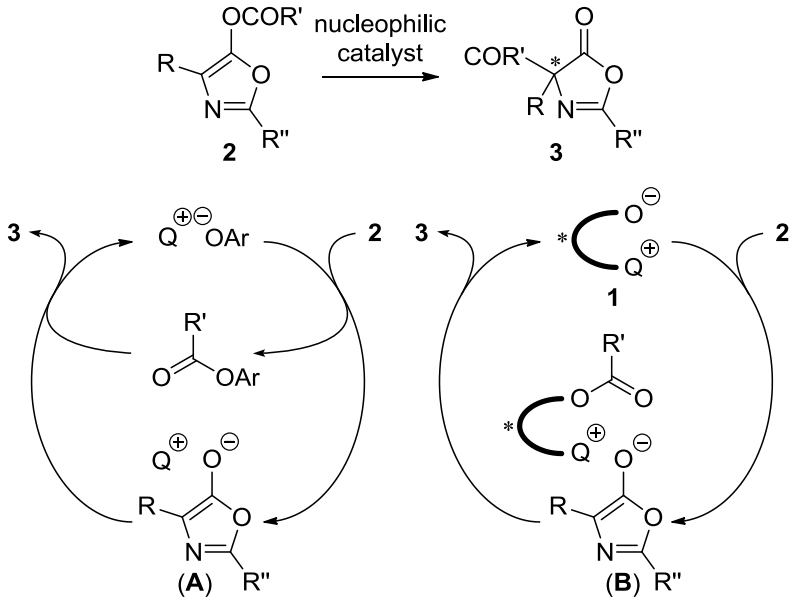


1

1a: $R^1 = R^2 = Ph$
1b: $R^1 = Ph$, $R^2 = H$
1c: $R^1 = p\text{-}CF_3\text{-}C_6H_4$, $R^2 = H$
1d: $R^1 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$, $R^2 = H$

Acyl transfer reactions by means of nucleophilic catalysts are the fundamental molecular transformation in synthetic organic chemistry. Among these reactions, the Steglich rearrangement,[7] which is the rearrangement of 5-oxazolyl carbonate into 4-carboxyazlactones, offers an attractive process to establish a tetrasubstituted stereocenter, and also serves as a model system to evaluate the efficiency of chiral nucleophilic catalysts (Figure 1) ever since the Fu's pioneering study with a synthetic DMAP analogue.[8,9] However, the use of an ionic nucleophile such as onium aryloxylate (Q^+OAr^-) in this reaction has been encumbered, probably due to the presumed low reactivity of the in situ generated, electronically neutral aryl ester (R'COOAr) toward onium enolate (**A**) in their coupling event (left-cycle). On the other hand, in the betaine catalysis, the rate-limiting carbon-carbon bond formation would proceed in a *pseudo-intramolecular* manner, and the unique intermediary ion pair (**B**) could have the potential to not only circumvent the reactivity impediment but also induce an unprecedented level of stereocontrol (right-cycle). Herein, author presents the highly enantioselective Steglich rearrangement using chiral ammonium betaines as ionic nucleophilic catalysts.

Figure 1. Working hypothesis for the Steglich rearrangement withan onium aryloxide (Q^+OAr^-) as an ionic nucleophilic catalyst.
Left-cycle: with a conventional intermolecular onium salt,
Right-cycle: with an intramolecular onium salt such as chiral ammonium betaine of type **1**.

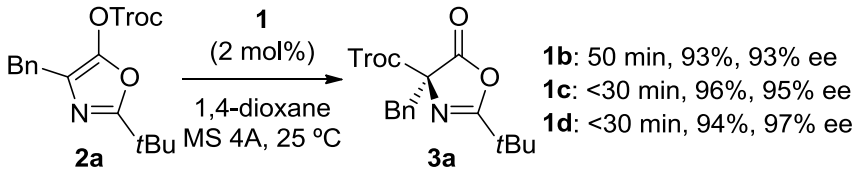


Results and Discussion

6. Asymmetric Stglich Reaction Catalyzed by Chiral Ammonium Betaines

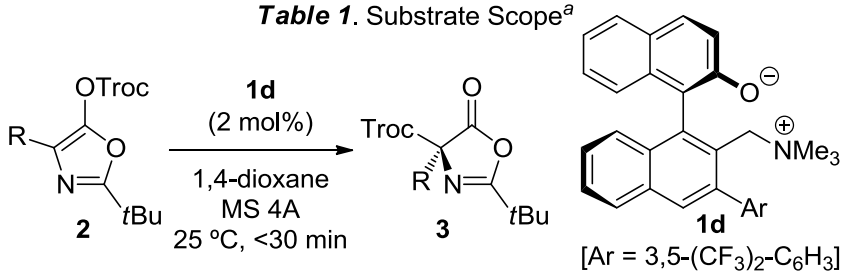
The reaction was generally conducted by the addition of a 1,4-dioxane solution of 2-*tert*-butyl-4-benzyl-5-oxazolyl 2,2,2-trichloroethyl carbonate (**2a**) to a stirred mixture of **1** (2 mol%) and powdered 4 Å molecular sieves[10] in 1,4-dioxane at 25 ºC.[11] Since an initial attempt with **1a**[4] as a catalyst showed its ineffectiveness in terms of both reactivity and stereoselectivity, author prepared **1b** lacking a substituent at the 3-position of the aryloxylate moiety (R^2) for primarily releasing the inherent nucleophilicity of the aryloxy anion. As expected, the rearrangement in the presence of **1b** proceeded cleanly to give the desired product **3a** in 93% yield, and fortunately, the enantiomeric excess was determined to be 93% ee (Scheme 1).[12] It is worthy to note that the characteristic yellow color of betaine **1b** instantaneously lightened with the addition of one drop of a solution of **2a**, which implies the formation of an intermolecular ion pair **B**. Indeed, the analysis of this mixture by ESI-MS method showed a peak corresponding to acylated **1b** (*m*/*z* = 592), thus corroborating our conjecture. After a while, without the addition of **2a**, the original yellow color gradually returned, indicating the regeneration of betaine **1b**, which was also verified by the detection of protonated **1b** (*m*/*z* = 418) in the MS measurement. This unique phenomenon would support the validity of the proposed reaction mechanism and that the carbon-carbon bond formation is the rate-limiting step in this catalysis.[9a] Interestingly, the installation of electron-withdrawing aromatic functionality such as the *p*-trifluoromethylphenyl (**1c**) or 3,5-bis(trifluoromethyl)phenyl (**1d**) group to the naphthyl unit possessing a pendent ammonium cation (R^1) led to the enhancement of catalytic efficiency, which was visually associated with the fact that the mixture retained its yellow color throughout the reaction. The enantioselectivity was synchronously improved to 95% ee and 97% ee, respectively.

Scheme 1. Chiral Ammonium Betaine **1**-Catalyzed Steglich Rearrangement



With the optimized catalyst structure in hand, the general applicability of the asymmetric catalysis of the Steglich rearrangement by **1d** was investigated using a series of amino acid-derived enol carbonates **2**; the representative examples are listed in Table 2. Substrates with simple alkyl, substituted benzylic, or functionalized alkyl side chains were efficiently transformed into the corresponding 4-(2,2,2-trichloroethoxycarbonyl)oxazolones **3** in high chemical yields with uniformly excellent and record levels of enantioselectivity (entries 1-10). It should be emphasized that enol carbonates bearing a sterically demanding α-substituent such as valine-derived one, a challenging substrate so far, can be well-accommodated by simply increasing the reaction temperature to 40 ºC (entry 5).

Table 1. Substrate Scope[a]



entry	R	**3**	Yield[b] (%)	ee[c] (%)
1	CH_3	**3b**	99	96
2	CH_3CH_2	**3c**	99	96
3	$CH_3(CH_2)_3$	**3d**	96	96
4	$(CH_3)_2CHCH_2$	**3e**	97	97
5[d]	$(CH_3)_2CH$	**3f**	94	95
6	*p*-CH_3O−$C_6H_4CH_2$	**3g**	98	97
7	*p*-Cl−$C_6H_4CH_2$	**3h**	97	96
8	*o*-F−$C_6H_4CH_2$	**3i**	96	95
9	$CH_3O(CH_2)_2$	**3j**	91	94
10	$CH_3S(CH_2)_2$	**3k**	95	96

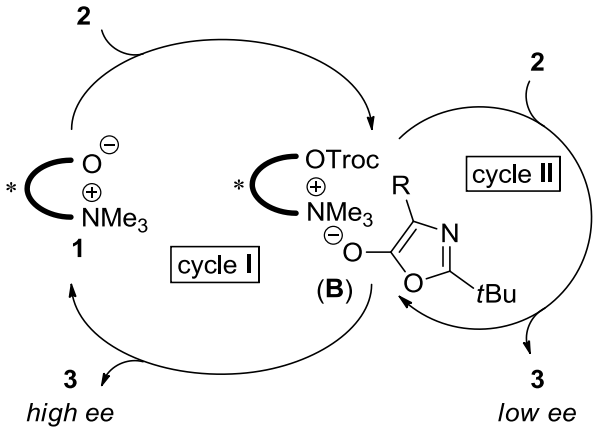
[a]Unless otherwise noted, the reactions were performed on 0.25 mmol scale in 2.5 mL of 1,4-dioxane with MS 4A at 25 ºC. See Supporting Information for further details. [b]Isolated yields were reported. [c]Enantiomeric excesses were determined by chiral stationary phase HPLC. Absolute configurations of **3b**-**k** were assigned on the analogy of **3a**. [d]The reaction was carried out at 40 ºC.

7. Mechanistic Study of the Asymmtric Steglich Reaction Catalyzed by Ammonium Betaines

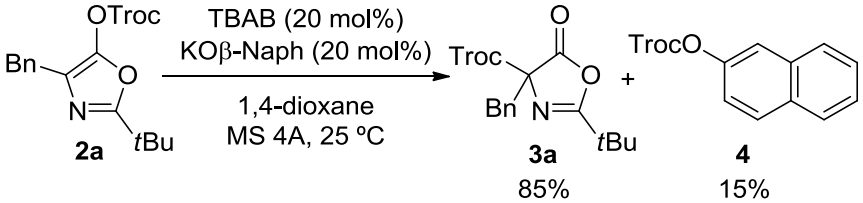
In the present system, the stereoselectivity was strongly dependent on substrate concentration, and it was of critical importance to maintain a low concentration of **2** for achieving an excellent enantiomeric excess. In fact, enantioselectivity was decreased to 87% ee when the reaction was performed by adding **1d** to a solution of **2a** under otherwise identical conditions. This observation

could provide an additional mechanistic clue to the **1d**-catalyzed Steglich rearrangement, that is, the existence of two reaction pathways. One is highly stereoselective pseudo-intramolecular bond formation (Figure 2, cycle I) and the other is less stereoselective intermolecular reaction of the chiral ammonium enolate **B** with **2** (cycle II). In order to assess the involvement of cycle II, the reactivity of **2** as an acyl transfer reagent toward ammonium enolate was evaluated by the following experiment (Scheme 2). The rearrangement of **2a** was carried out in a similar manner under the influence of in situ generated, intermolecular ion-pairing tetrabutylammonium β-naphthoxide (20 mol%),[13] which afforded **3a** in 85% yield together with 2,2,2-trichloroethyl β-naphthyl carbonate (**4**, 15% yield). The concomitant isolation of **4**, with amount comparable to that of the catalyst used, clearly indicates that **3a** was mainly produced through the reaction of **2a**-derived tetrabutylammonium enolate with **2a** itself. Therefore, chiral ammonium enolate **B** could also react with **2**, and this intermolecular bond-forming process would compete with the pseudo-intramolecular reaction of **B**. This is probably the origin of the concentration dependence of stereoselectivity, and the addition of substrate to a catalyst solution is crucial to allow predominant participation of the pseudo-intramolecular process that essentially relies on the intramolecular ion-pairing nature of **1**.

Figure 2. Possible reaction pathways for chiral ammonium betaine **1**-catalyzed Steglich rearrangement.



Scheme 2. In Situ Generated TBAOβ-Naph-Catalyzed Reaction of **2a**



Summary

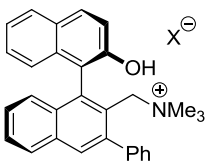
In conclusion, a nucleophilic property of chiral ammonium betaines has been revealed and has been successfully applied for realizing the highly enantioselective Steglich rearrangement. This unraveled yet attractive function of ammonium betaines as ionic nucleophilic catalysts opens a door to a new avenue for the development of asymmetric nucleophilic catalysis.

Experimental

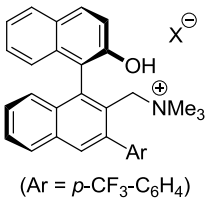
General Information: Infrared spectra were recorded on a JASCO FT/IR-300E spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) or Varian INOVA-700 (700 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2SO$: 2.50 ppm, CD_3OD: 3.31 ppm, C_6D_6: 7.16 ppm] or Me_4Si resonance (0.00 ppm; $CDCl_3$) as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet, br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz) or a Varian INOVA-700 (176 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2SO$: 39.51 ppm, $CDCl_3$: 77.16 ppm]. ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (−64.0 ppm) resonance as the external standard. Optical rotations were measured on a JASCO DIP-1000 polarimeter. The high resolution mass spectra were conducted on JEOL JMS-700 (MStation). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40-50 μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK AD-H (AD-H), CHIRALPAK AS-H (AS-H) or CHIRALCEL OJ-H (OJ-H)].

1,4-Dioxane was freshly distilled from sodium metal prior to use. Betaine precursors **1b·HX**[4] and *O*-acylated azlactones **3**[9a] were prepared by following the literature procedure. Powdered molecular sieves 4A was supplied from Merck. Other simple chemicals were purchased and used as such.

Characterization of Betaine Precursors 1·HX (X = Cl or I):



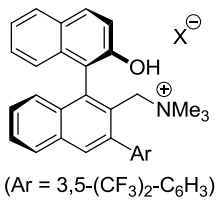
1b·HX (X = Cl or I): ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 10.13 (1H, brs), 8.10 (1H, d, *J* = 7.7 Hz), 8.08 (1H, s), 8.07 (1H, d, *J* = 7.7 Hz), 7.98 (1H, d, *J* = 7.7 Hz), 7.65 (2H, d, *J* = 7.7 Hz), 7.63 (2H, tt, *J* = 7.7, 1.4 Hz), 7.62 (1H, t, *J* = 7.7 Hz), 7.54 (1H, d, *J* = 7.7 Hz), 7.53 (1H, tt, *J* = 7.7, 1.4 Hz), 7.40 (1H, t, *J* = 7.7 Hz), 7.38-7.32 (2H, m), 7.20 (1H, d, *J* = 7.7 Hz), 6.98 (1H, d, *J* = 7.7 Hz), 4.89 (1H, br), 4.30 (1H, br), 2.52 (9H, s); ^{13}C NMR (176 MHz, $(CD_3)_2SO$, 80 °C) δ 152.9, 140.7, 140.6, 139.6, 133.5, 133.0, 131.2, 130.5, 129.6, 128.7, 128.1, 127.9, 127.8, 127.5_2, 127.4_6, 127.0, 126.6_0, 126.5_6, 123.9, 122.9, 122.8, 118.2, 115.7, 64.4, 53.5, one carbon was not found probably due to overlapping; IR (KBr) 3176, 1622, 1509, 1474, 1434, 1343, 1276, 1147, 1029, 900, 768 cm^{-1}; HRMS (FAB) Calcd for $C_{30}H_{28}NO^{+}$ ($[M-X]^{+}$) 418.2171, Found 418.2153.



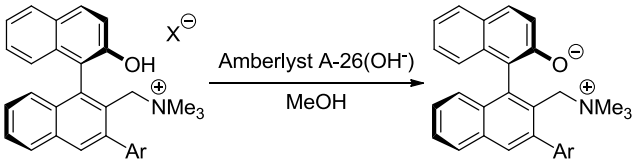
(Ar = *p*-CF_3-C_6H_4)

1c·HX (X = Cl or I): ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 10.08 (1H, brs), 8.12 (1H, s), 8.11 (1H, d, *J* = 7.7 Hz), 8.08 (1H, d, *J* = 7.7 Hz), 7.99 (1H, d, *J* = 7.7 Hz), 7.94 (2H, d, *J* = 7.7 Hz), 7.89 (2H, d, *J* = 7.7 Hz), 7.65 (1H, t, *J* = 7.7 Hz), 7.53 (1H, d, *J* = 7.7 Hz), 7.42 (1H, t, *J* = 7.7 Hz), 7.37 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.21 (1H, d, *J* = 7.7 Hz), 7.01 (1H, d, *J* = 7.7 Hz), 4.83 (1H, br),

4.36 (1H, br), 2.56 (9H, s); ^{13}C NMR (176 MHz, $(CD_3)_2SO$, 80 °C) δ 152.8, 144.9, 141.6, 140.1, 139.2, 133.4, 133.0, 131.4, 131.0, 130.6, 130.5, 128.1$_5$ (q, J_{F-C} = 32.2 Hz), 128.1$_3$, 127.9, 127.8$_8$, 127.7, 127.1, 126.9, 126.7, 125.5, 123.8 (q, J_{F-C} = 271.0 Hz), 123.3, 122.8, 118.2, 115.5, 64.1, 53.3; ^{19}F NMR (376 MHz, $(CD_3)_2SO$) δ −61.8; IR (KBr) 3058, 1619, 1483, 1323, 1274, 1167, 1126, 1065, 1017, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{31}H_{27}F_3NO^+$ ($[M-X]^+$) 486.2045, Found 486.2042.

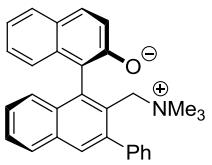


1d·HX (X = Cl or I): ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 80 °C) δ 10.12 (1H, brs), 8.35 (2H, brs), 8.20 (1H, s), 8.17 (1H, s), 8.13 (1H, d, J = 7.7 Hz), 8.08 (1H, d, J = 7.7 Hz), 7.98 (1H, d, J = 7.7 Hz), 7.67 (1H, t, J = 7.7 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.45 (1H, t, J = 7.7 Hz), 7.39-7.34 (2H, m), 7.21 (1H, d, J = 7.7 Hz), 7.07 (1H, d, J = 7.7 Hz), 4.69 (1H, d, J = 14.7 Hz), 4.32 (1H, br), 2.57 (9H, s); ^{13}C NMR (176 MHz, $(CD_3)_2SO$, 80 °C) δ 152.9, 143.4, 140.2, 137.7, 133.3, 133.0, 131.7$_5$, 131.7$_1$, 130.8 (q, J_{F-C} = 33.4 Hz), 130.7, 130.4, 128.1, 127.9$_4$, 127.9$_1$, 127.8$_5$, 127.2, 127.1, 126.7, 123.1, 122.8$_1$ (q, J_{F-C} = 274.0 Hz), 122.8$_0$, 121.3, 118.3, 115.4, 64.2, 53.3, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $(CD_3)_2SO$) δ −62.0; IR (KBr) 3060, 1622, 1470, 1434, 1372, 1281, 1137, 1010, 898, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{32}H_{26}F_6NO^+$ ($[M-X]^+$) 554.1919, Found 554.1923.

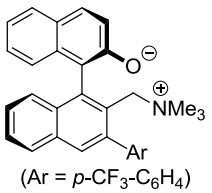


1·HX (X = Cl or I) **1**

Preparation of Ammonium Betaine 1: Ammonium betaine **1** was prepared by passage of a methanolic solution of the corresponding ammonium halide **1**·HX (X = Cl or I) through a column of ion exchange resin Amberlyst A-26 OH form. The solution was concentrated by rotary evaporation and residual solid was washed with Et_2O on a funnel. The solid thus obtained was dried under reduced pressure to afford the ammonium betaine **2** as a yellow solid and used for the asymmetric Steglich rearrangement without further purification.

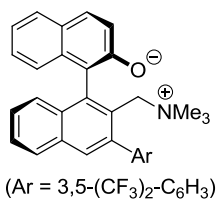


1b: ^{1}H NMR (400 MHz, CD_3OD) δ 8.00-7.88 (brm), 7.79 (d, J = 8.7 Hz), 7.70-7.43 (brm), 7.35 (br), 7.24 (br), 7.16 (br), 7.08 (br), 7.02 (br), 6.74 (brd, J = 6.4 Hz), 6.66 (br), 5.11 (d, J = 13.3 Hz), 4.99 (d, J = 13.3 Hz), 4.32 (d, J = 13.3 Hz), 2.57 (br), 2.32 (br); IR (KBr) 3365, 3030, 1609, 1587, 1494, 1462, 1422, 1367, 1245, 759 cm^{-1}; HRMS (FAB) Calcd for $C_{30}H_{28}NO^+$ ($[M+H]^+$) 418.2171, Found 418.2153; $[\alpha]^{26}_D$ +17.3 (c = 0.95, MeOH).



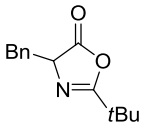
1c: ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (br), 7.99 (br), 7.91 (br), 7.83 (br), 7.76 (br), 7.57 (br), 7.41 (br), 7.34 (br), 7.19 (br), 7.13 (br), 7.05 (br), 6.80 (br), 6.69 (br), 4.98 (br), 4.36 (d, J = 11.4 Hz), 2.61 (br), 2.38 (br); ^{19}F NMR (376 MHz, CD_3OD) δ −65.5; IR (KBr) 3411, 3038, 1613, 1463, 1423, 1369, 1325, 1168, 1125, 1065, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{31}H_{27}F_3NO^+$ ($[M+H]^+$) 486.2045, Found 486.2038; $[\alpha]^{26}_D$

−16.4 (c = 0.33, MeOH).

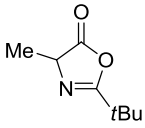


1d: ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (br), 8.42 (br), 8.12 (s), 8.02 (d, J = 8.2 Hz), 7.97 (s), 7.79 (d, J = 9.2 Hz), 7.73 (d, J = 6.9 Hz), 7.58 (br), 7.38 (br), 7.32 (br), 7.20 (br), 7.04 (br), 6.69 (br), 4.98 (br), 4.78 (br), 4.44 (br), 2.61 (br), 2.42 (br); ^{19}F NMR (376 MHz, CH_3OH) δ −65.6; IR (KBr) 3374, 3048, 1611, 1589, 1466, 1423, 1371, 1280, 1181, 1139, 751 cm^{-1}; HRMS (FAB) Calcd for $C_{32}H_{26}F_6NO^+$ ($[M+H]^+$) 554.1919, Found 554.1932; $[\alpha]^{23}_D$ −64.9 (c = 0.21, MeOH).

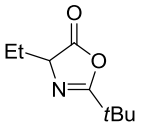
Characterization of Azlactones 5:



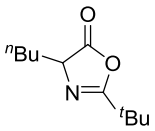
5a[14]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.19 (3H, m), 7.19-7.14 (2H, m), 4.47 (1H, t, J = 5.0 Hz), 3.27 (1H, dd, J = 13.7, 5.0 Hz), 3.18 (1H, dd, J = 13.7, 5.0 Hz), 1.06 (9H, s).



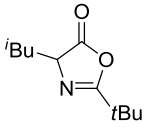
5b[15]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1H, q, J = 7.8 Hz), 1.47 (3H, d, J = 7.8 Hz), 1.29 (9H, s).



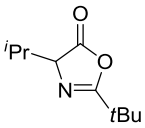
5c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (1H, t, J = 6.0 Hz), 1.98 (1H, dqd, J = 13.8, 7.6, 6.0 Hz), 1.86 (1H, dqd, J = 13.8, 7.6, 6.0 Hz), 1.29 (9H, s), 0.94 (3H, t, J = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 172.0, 65.8, 34.3, 26.9, 24.5, 8.9; IR (neat) 2975, 1823, 1667, 1461, 1291, 1165, 1110, 1086, 1041, 893 cm^{-1}; HRMS (FAB) Calcd for $C_9H_{16}NO_2^+$ ($[M+H]^+$) 170.1181, Found 170.1182.



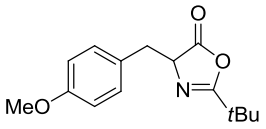
5d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (1H, t, J = 6.2 Hz), 1.98-1.85 (1H, m), 1.84-1.71 (1H, m), 1.47-1.14 (4H, m), 1.29 (9H, s), 0.91 (3H, t, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 171.8, 64.9, 34.3, 31.0, 26.9, 26.6, 22.4, 13.9; IR (neat) 2962, 1821, 1668, 1461, 1367, 1260, 1167, 1044, 893, 758 cm^{-1}; HRMS (FAB) Calcd for $C_{11}H_{20}NO_2^+$ ($[M+H]^+$) 198.1494, Found 198.1494.



5e[16]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (1H, dd, J = 8.0, 6.2 Hz), 1.95 (1H, nonet, J = 6.9 Hz), 1.74 (1H, ddd, J = 14.0, 6.9, 6.2 Hz), 1.57 (1H, ddd, J = 14.0, 8.0, 6.9 Hz), 1.28 (9H, s), 0.98 (3H, d, J = 6.9 Hz), 0.96 (3H, d, J = 6.9 Hz).

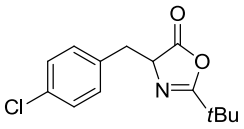


5f[17]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, d, J = 4.6 Hz), 2.28 (1H, sept-d, J = 6.9, 4.6 Hz), 1.29 (9H, s), 1.05 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.9 Hz).

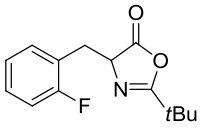


5g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 4.44 (1H, t, J = 5.0 Hz), 3.76 (3H, s), 3.21 (1H, dd, J = 14.0, 5.0 Hz), 3.12 (1H, dd, J = 14.0, 5.0 Hz), 1.08 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 171.8, 158.9, 131.1, 126.6, 113.7, 66.0, 55.4, 36.0, 34.0, 26.5; IR (neat) 2974, 1817, 1669, 1612,

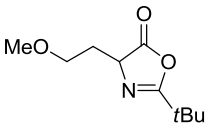
1513, 1249, 1178, 1096, 1027, 894 cm^{-1}; HRMS (FAB) Calcd for $C_{15}H_{20}NO_3^+$ ($[M+H]^+$) 262.1443, Found 262.1444.



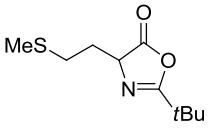
5h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.2 Hz), 4.46 (1H, t, J = 5.0 Hz), 3.25 (1H, dd, J = 14.2, 5.0 Hz), 3.14 (1H, dd, J = 14.2, 5.0 Hz), 1.09 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 172.2, 133.3, 133.2, 131.4, 128.5, 65.6, 36.2, 34.1, 26.6; IR (neat) 2975, 1817, 1669, 1493, 1266, 1161, 1092, 1053, 1025, 894 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{17}ClNO_2^+$ ($[M+H]^+$) 266.0948, Found 266.0952.



5i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, tdd, J = 7.3, 5.5, 1.8 Hz), 7.20 (1H, td, J = 7.8, 1.8 Hz), 7.10-6.99 (2H, m), 4.49 (1H, t, J = 5.5 Hz), 3.37 (1H, dd, J = 14.0, 5.5 Hz), 3.15 (1H, dd, J = 14.0, 5.0 Hz), 1.11 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 172.2, 161.4 (d, $J_{F\text{-}C}$ = 250.6 Hz), 131.8 (d, $J_{F\text{-}C}$ = 3.9 Hz), 129.2 (d, $J_{F\text{-}C}$ = 7.7 Hz), 124.1 (d, $J_{F\text{-}C}$ = 3.9 Hz), 122.2 (d, $J_{F\text{-}C}$ = 16.5 Hz), 115.5 (d, $J_{F\text{-}C}$ = 22.3 Hz), 65.1, 34.1, 30.3, 26.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9; IR (neat) 2976, 1819, 1669, 1494, 1456, 1233, 1106, 1055, 894, 758 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{17}FNO_2^+$ ($[M+H]^+$) 250.1243, Found 250.1238.

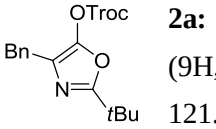


5j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (1H, dd, J = 5.9, 5.0 Hz), 3.51-3.40 (2H, m), 3.27 (3H, s), 2.27-2.12 (2H, m), 1.30 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 172.4, 67.8, 61.8, 58.8, 34.4, 30.6, 26.9; IR (neat) 2976, 1823, 1666, 1481, 1458, 1293, 1170, 1109, 1051, 895 cm^{-1}; HRMS (FAB) Calcd for $C_{10}H_{18}NO_3^+$ ($[M+H]^+$) 200.1287, Found 200.1281.

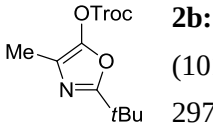


5k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (1H, t, J = 6.8 Hz), 2.63 (2H, t, J = 6.8 Hz), 2.22 (1H, dq, J = 14.4, 6.8 Hz), 2.09 (3H, s), 2.08 (1H, dq, J = 14.4, 6.8 Hz), 1.29 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 172.4, 63.1, 34.3, 29.8, 29.7, 26.8, 15.0; IR (neat) 2975, 1818, 1664, 1481, 1366, 1297, 1255, 1160, 1070, 894 cm^{-1}; HRMS (FAB) Calcd for $C_{10}H_{18}NO_2S^+$ ($[M+H]^+$) 216.1058, Found 216.1049.

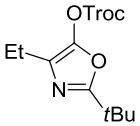
Characterization of *O*-Acylated Azlactones 2 (Troc = 2,2,2-trichloroethoxycarbonyl):



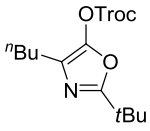
2a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m), 4.70 (2H, s), 3.81 (2H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 150.5, 145.3, 137.4, 129.0, 128.5, 126.6, 121.3, 93.5, 77.8, 34.0, 31.7, 28.4; IR (neat) 2973, 1796, 1673, 1565, 1455, 1370, 1282, 1215, 1147, 1046, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{19}Cl_3NO_4^+$ ($[M+H]^+$) 406.0380, Found 406.0399.



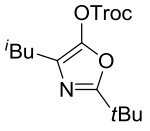
2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (2H, s), 2.06 (3H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 150.8, 145.0, 118.3, 93.6, 77.9, 33.9, 28.4, 10.3; IR (neat) 2974, 1797, 1682, 1565, 1460, 1376, 1281, 1216, 1176, 1120, 1049, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{11}H_{15}Cl_3NO_4^+$ ($[M+H]^+$) 330.0067, Found 330.0071.



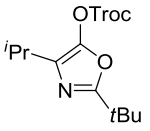
2c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (2H, s), 2.45 (2H, q, J = 7.5 Hz), 1.35 (9H, s), 1.19 (3H, t, J = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 151.1, 144.3, 123.7, 93.7, 77.9, 34.0, 28.4, 18.5, 12.4; IR (neat) 2974, 1797, 1674, 1565, 1462, 1371, 1278, 1213, 1170, 1120, 1053, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{12}H_{17}Cl_3NO_4^+$ ([M+H]$^+$) 344.0223, Found 344.0209.



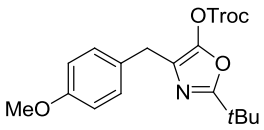
2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (2H, s), 2.40 (2H, t, J = 8.0 Hz), 1.58 (2H, tt, J = 8.0, 7.5 Hz), 1.35 (9H, s), 1.34 (2H, sext, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 151.1, 144.6, 122.6, 93.7, 77.9, 34.0, 30.1, 28.4, 24.8, 22.6, 14.0; IR (neat) 2963, 1797, 1674, 1566, 1462, 1371, 1281, 1215, 1167, 1121, 1044, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{21}Cl_3NO_4^+$ ([M+H]$^+$) 372.0536, Found 372.0553.



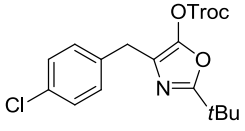
2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (2H, s), 2.26 (2H, d, J = 7.0 Hz), 1.98 (1H, nonet, J = 7.0 Hz), 1.35 (9H, s), 0.91 (6H, d, J = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 151.0, 145.3, 121.8, 93.7, 77.8, 34.0, 33.8, 28.4, 27.6, 22.4; IR (neat) 2962, 1797, 1674, 1566, 1463, 1370, 1282, 1217, 1170, 1123, 1045, 828 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{21}Cl_3NO_4^+$ ([M+H]$^+$) 372.0536, Found 372.0521.



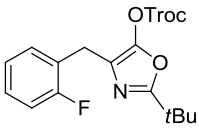
2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (2H, s), 2.80 (1H, sept, J = 6.9 Hz), 1.34 (9H, s), 1.22 (6H, d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 151.3, 143.4, 127.5, 93.7, 77.9, 34.0, 28.5, 25.8, 21.0; IR (neat) 2972, 1797, 1666, 1567, 1462, 1371, 1281, 1215, 1147, 1126, 1042, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_4^+$ ([M+H]$^+$) 358.0380, Found 358.0376.



2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, d, J = 8.7 Hz), 6.82 (2H, d, J = 8.7 Hz), 4.72 (2H, s), 3.77 (3H, s), 3.75 (2H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 158.4, 150.6, 145.2, 130.0, 129.4, 121.7, 113.9, 93.5, 77.9, 55.3, 34.0, 30.9, 28.4; IR (neat) 2971, 1794, 1672, 1611, 1561, 1512, 1459, 1369, 1247, 1215, 1176, 1146, 1038, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{18}H_{21}Cl_3NO_5^+$ ([M+H]$^+$) 436.0485, Found 436.0478.

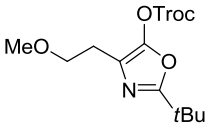


2h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.7 Hz), 7.18 (2H, d, J = 8.7 Hz), 4.75 (2H, s), 3.77 (2H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 150.6, 145.3, 135.9, 132.5, 130.4, 128.7, 120.9, 93.4, 77.9, 34.0, 31.0, 28.4; IR (neat) 2974, 1795, 1673, 1564, 1492, 1370, 1284, 1215, 1147, 1046, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{18}Cl_4NO_4^+$ ([M+H]$^+$) 439.9990, Found 439.9999.

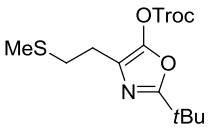


2i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, t, J = 7.8 Hz), 7.20 (1H, dt, J = 7.8, 5.9 Hz), 7.06 (1H, t, J = 7.8 Hz), 7.02 (1H, dd, J = 9.2, 7.8 Hz), 4.74 (2H, s), 3.84 (2H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 161.1 (d, $J_{F\text{-}C}$ = 249.6 Hz), 150.5, 145.3, 131.0 (d, $J_{F\text{-}C}$ = 3.9 Hz), 128.5 (d, $J_{F\text{-}C}$ = 8.7 Hz), 124.5 (d, $J_{F\text{-}C}$ = 16.4 Hz), 124.1 (d, $J_{F\text{-}C}$ = 2.9 Hz), 120.1, 115.3 (d, $J_{F\text{-}C}$ = 22.3 Hz), 93.4, 77.9, 34.0, 28.4, 24.7 (d, $J_{F\text{-}C}$ = 3.9 Hz); ^{19}F NMR

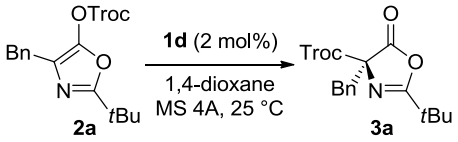
(376 MHz, $CDCl_3$) δ −119.4; IR (neat) 2975, 1798, 1675, 1566, 1493, 1456, 1371, 1281, 1215, 1149, 1116, 1047, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{18}Cl_3FNO_4^+$ ($[M+H]^+$) 424.0285, Found 424.0300.



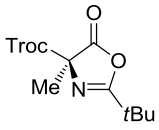
2j: ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (2H, s), 3.61 (2H, t, J = 6.9 Hz), 3.33 (3H, s), 2.72 (2H, t, J = 6.9 Hz), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 150.8, 145.5, 119.6, 93.6, 77.9, 70.3, 58.7, 34.0, 28.4, 25.9; IR (neat) 2974, 1797, 1678, 1565, 1461, 1371, 1284, 1216, 1166, 1118, 1051, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_5^+$ ($[M+H]^+$) 374.0329, Found 374.0332.



2k: ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (2H, s), 2.79-2.68 (4H, m), 2.11 (3H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 150.8, 145.2, 120.8, 93.6, 77.9, 34.0, 32.3, 28.4, 25.3, 15.6; IR (neat) 2973, 1797, 1675, 1565, 1439, 1370, 1280, 1213, 1176, 1136, 1047, 827 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_4S^+$ ($[M+H]^+$) 390.0100, Found 390.0085.

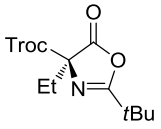


Representative Procedure for Catalytic Asymmetric Steglich Rearrangement of *O*-Acylated Azlactone 2: A test tube was charged with a magnetic stirrer bar and MS 4A (100 mg) under argon atmosphere. The MS 4A was then dried with heat gun under reduced pressure for 5 minutes and the test tube was refilled with argon. Ammonium betaine **1d** (2.77 mg, 0.005 mmol) and 1,4-dioxane (1.0 mL) were added to the test tube successively under argon atmosphere at 25 °C. To the yellow mixture was added a solution of **2a** (101.7 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) over 15 min (Dropwise addition was maintained for this period to avoid completely discoloring the reaction mixture to white.). Upon completion of the addition, the reaction mixture was further stirred for 10 min and a 0.5 M solution of trifluoroacetic acid in toluene (20.0 μL) was introduced. The whole mixture was filtered with $CHCl_3$ to remove MS 4A and the filtrate was concentrated. The crude residue was purified by silica gel column chromatography using hexane (H)/ethyl acetate (EA) solvent system (H/EA = 50:1-5:1 as eluent) to afford **3a** (95.6 mg) in 94% yield and the enantiomeric excess of **3a** was measured by HPLC analysis (97% ee). **3a:** HPLC: AS-H, H/isopropyl alcohol (IPA) = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.0 min (minor isomer: (*R*)), 9.8 min (major isomer: (*S*)), Absolute configuration was assigned by derivatization to **6** (see below); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (3H, m), 7.20-7.12 (2H, m), 4.91 (1H, d, J = 11.9 Hz), 4.75 (1H, d, J = 11.9 Hz), 3.56 (1H, d, J = 14.0 Hz), 3.50 (1H, d, J = 14.0 Hz), 1.03 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 174.0, 164.3, 132.5, 130.7, 128.4, 127.9, 94.1, 76.7, 75.0, 39.1, 34.2, 26.3; IR (neat) 2976, 1826, 1769, 1667, 1496, 1456, 1219, 1095, 905, 790 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{19}Cl_3NO_4^+$ ($[M+H]^+$) 406.0380, Found 406.0377; $[\alpha]^{25}_D$ −7.7 (c = 1.75, MeOH).

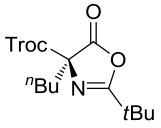


3b: HPLC: OJ-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.0 min (minor

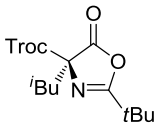
isomer), 10.8 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (1H, d, J = 12.1 Hz), 4.71 (1H, d, J = 12.1 Hz), 1.72 (3H, s), 1.32 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 174.6, 164.6, 94.0, 75.0, 72.3, 34.6, 26.7, 19.9; IR (neat) 2978, 1828, 1766, 1666, 1452, 1304, 1218, 1126, 1043, 911 cm^{-1}; HRMS (FAB) Calcd for $C_{11}H_{15}Cl_3NO_4^+$ ($[M+H]^+$) 330.0067, Found 330.0052; $[\alpha]^{23}_D$ −97.7 (c = 1.04, $CHCl_3$).



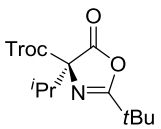
3c: HPLC: AS-H, H/IPA = 199:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.6 min (minor isomer), 9.1 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, d, J = 11.9 Hz), 4.73 (1H, d, J = 11.9 Hz), 2.29 (1H, dq, J = 14.7, 7.6 Hz), 2.22 (1H, dq, J = 14.7, 7.6 Hz), 1.33 (9H, s), 0.87 (3H, t, J = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 174.4, 164.4, 94.1, 76.5, 74.9, 34.6, 26.9, 26.7, 7.4; IR (neat) 2978, 1824, 1770, 1664, 1461, 1368, 1218, 1061, 903, 796 cm^{-1}; HRMS (FAB) Calcd for $C_{12}H_{17}Cl_3NO_4^+$ ($[M+H]^+$) 344.0223, Found 344.0219; $[\alpha]^{25}_D$ −66.5 (c = 1.07, $CHCl_3$).



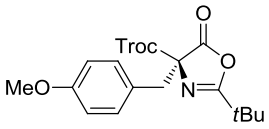
3d: HPLC: AD-H, H/IPA = 199:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.4 min (major isomer), 10.1 min (minor isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, d, J = 12.1 Hz), 4.73 (1H, d, J = 12.1 Hz), 2.25 (1H, ddd, J = 13.7, 12.2, 5.0 Hz), 2.15 (1H, ddd, J = 13.7, 11.7, 5.0 Hz), 1.36 (2H, sext, J = 7.3 Hz), 1.33 (9H, s), 1.30-1.05 (2H, m), 0.90 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 164.5, 94.1, 76.0, 74.9, 34.6, 32.9, 26.8, 25.1, 22.4, 13.8, one carbon was not found probably due to overlapping; IR (neat) 2963, 1827, 1769, 1666, 1461, 1368, 1216, 1067, 903, 793 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{21}Cl_3NO_4^+$ ($[M+H]^+$) 372.0536, Found 372.0522; $[\alpha]^{23}_D$ −55.7 (c = 1.12, $CHCl_3$).



3e: HPLC: AS-H, H/IPA = 199:1, flow rate = 0.5 mL/min, λ = 210 nm, 7.9 min (minor isomer), 8.2 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, d, J = 12.1 Hz), 4.71 (1H, d, J = 12.1 Hz), 2.36 (1H, dd, J = 14.4, 5.7 Hz), 2.03 (1H, dd, J = 14.4, 7.5 Hz), 1.69-1.55 (1H, m), 1.33 (9H, s), 0.96 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 174.2, 164.6, 94.1, 75.6, 75.0, 41.5, 34.6, 26.7, 24.5, 24.0, 22.8; IR (neat) 2964, 1826, 1769, 1663, 1459, 1368, 1201, 1066, 902, 789 cm^{-1}; HRMS (FAB) Calcd for $C_{14}H_{21}Cl_3NO_4^+$ ($[M+H]^+$) 372.0536, Found 372.0521; $[\alpha]^{25}_D$ −82.8 (c = 1.35, $CHCl_3$).

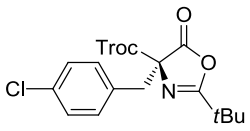


3f: HPLC: AS-H, H/IPA = 199:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.4 min (minor isomer), 8.7 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, d, J = 12.1 Hz), 4.78 (1H, d, J = 12.1 Hz), 2.77 (1H, sept, J = 6.9 Hz), 1.33 (9H, s), 1.07 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 173.8, 164.3, 94.2, 79.8, 74.9, 34.6, 33.4, 26.9, 17.2, 16.2; IR (neat) 2976, 1823, 1771, 1658, 1462, 1369, 1210, 1152, 1056, 906 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_4^+$ ($[M+H]^+$) 358.0380, Found 358.0376; $[\alpha]^{27}_D$ −40.2 (c = 0.97, $CHCl_3$).

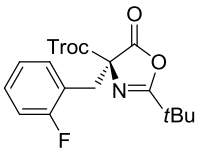


3g: HPLC: AS-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.8 min (minor isomer), 14.4 min (major isomer), Absolute configuration was

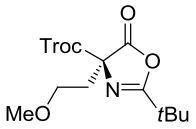
assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (2H, d, J = 8.9 Hz), 6.80 (2H, d, J = 8.9 Hz), 4.90 (1H, d, J = 11.9 Hz), 4.74 (1H, d, J = 11.9 Hz), 3.76 (3H, s), 3.50 (1H, d, J = 14.2 Hz), 3.44 (1H, d, J = 14.2 Hz), 1.07 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 174.0, 164.4, 159.3, 131.7, 124.4, 113.8, 94.1, 74.9, 55.4, 38.4, 34.2, 26.4, one carbon was not found probably due to overlapping; IR (neat) 2978, 1825, 1768, 1663, 1612,1514, 1217, 1077, 906, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{18}H_{21}Cl_3NO_5^+$ ([M+H]$^+$) 436.0485, Found 436.0494; $[\alpha]^{22}_D$ +8.3 (c = 1.50, $CHCl_3$).



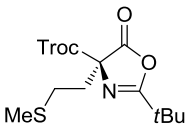
3h: HPLC: AS-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.9 min (minor isomer), 12.3 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.7 Hz), 7.10 (2H, d, J = 8.7 Hz), 4.90 (1H, d, J = 11.9 Hz), 4.74 (1H, d, J = 11.9 Hz), 3.52 (1H, d, J = 14.0 Hz), 3.46 (1H, d, J = 14.0 Hz), 1.07 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 173.8, 164.1, 134.0, 132.0, 131.1, 128.5, 94.0, 76.4, 75.0, 38.4, 34.3, 26.4; IR (neat) 2977, 1826, 1768, 1665, 1493, 1369, 1218, 1093, 907, 757 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{18}Cl_4NO_4^+$ ([M+H]$^+$) 439.9990, Found 439.9972; $[\alpha]^{23}_D$ +14.1 (c = 1.14, $CHCl_3$).



3i: HPLC: AS-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.6 min (minor isomer), 10.3 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, tdd, J = 8.0, 5.0, 1.4 Hz), 7.18 (1H, td, J = 8.0, 1.4 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.03 (1H, dd, J = 9.2, 8.0 Hz), 4.87 (1H, d, J = 11.9 Hz), 4.77 (1H, d, J = 11.9 Hz), 3.73 (1H, d, J = 13.9 Hz), 3.51 (1H, d, J = 13.9 Hz), 1.05 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 174.0, 164.1, 161.5 (d, $J_{F\text{-}C}$ = 252.6 Hz), 132.3 (d, $J_{F\text{-}C}$ = 2.9 Hz), 129.8 (d, $J_{F\text{-}C}$ = 8.7 Hz), 124.1 (d, $J_{F\text{-}C}$ = 3.9 Hz), 120.0 (d, $J_{F\text{-}C}$ = 15.5 Hz), 115.6 (d, $J_{F\text{-}C}$ = 22.3 Hz), 94.0, 76.2, 75.0, 34.3, 32.0, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9; IR (neat) 2976, 1827, 1769, 1665, 1494, 1457, 1234, 1116, 995, 905 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{18}Cl_3FNO_4^+$ ([M+H]$^+$) 424.0285, Found 424.0265; $[\alpha]^{20}_D$ −2.0 (c = 1.13, MeOH).



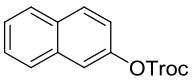
3j: HPLC: AS-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.3 min (minor isomer), 12.4 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (1H, d, J = 11.9 Hz), 4.67 (1H, d, J = 11.9 Hz), 3.45 (1H, ddd, J = 9.6, 5.5, 3.0 Hz), 3.38 (1H, ddd, J = 11.4, 9.6, 3.0 Hz), 3.22 (3H, s), 2.66 (1H, ddd, J = 14.7, 11.4, 5.5 Hz), 2.49 (1H, dt, J = 14.7, 3.0 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 174.9, 164.7, 94.1, 75.0, 73.5, 67.1, 58.8, 34.7, 32.8, 26.8; IR (neat) 2977, 1827, 1768, 1660, 1461, 1218, 1135, 1029, 905, 790 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_5^+$ ([M+H]$^+$) 374.0329, Found 374.0315; $[\alpha]^{26}_D$ −102.1 (c = 1.01, $CHCl_3$).



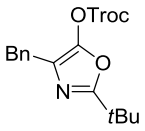
3k: HPLC: AS-H, H/IPA = 99:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.5 min (minor isomer), 11.4 min (major isomer), Absolute configuration was assigned on the analogy of **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, d, J = 11.9 Hz), 4.73 (1H, d, J = 11.9 Hz), 2.69-2.41 (4H, m), 2.07 (3H, s), 1.33 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.6, 164.3, 94.0, 75.0, 74.7, 34.7, 31.7, 28.1, 26.8, 15.0; IR (neat) 2977, 1825, 1767, 1659,

1437, 1368, 1203, 1092, 904, 792 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{19}Cl_3NO_4S^+$ ($[M+H]^+$) 390.0100, Found 390.0103; $[\alpha]^{24}_D$ −114.3 (c = 1.04, $CHCl_3$).

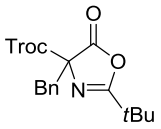
Procedure for Tetrabutylammonium β-Naphthoxide-Catalyzed Rearrangement: A test tube was charged with a magnetic stirrer bar and MS 4A (100 mg) under argon atmosphere. MS 4A was dried with heat gun under reduced pressure for 5 minutes and the test tube was refilled with argon. Tetrabutylammonium bromide (16.62 mg, 0.05 mmol), potassium β-naphthoxide (9.11 mg, 0.05 mmol) and 1,4-dioxane (1.0 mL) were added to the test tube successively under argon atmosphere at 25 °C.[18] Then, a solution of **2a** (101.7 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) was added dropwise over 3 min. Upon completion of the addition, the reaction mixture was further stirred for 10 min and a 0.5 M solution of trifluoroacetic acid in toluene (200.0 μL) was introduced. The resulting mixture was filtered with $CHCl_3$ to remove MS 4A and the filtrate was concentrated. The NMR yields were determined by 400 MHz ^{1}H NMR analysis (C_6D_6) of the crude residue containing mesitylene (26.5 mg, 0.22 mmol) as an internal standard (**3a:** 85%, **4:** 15%).



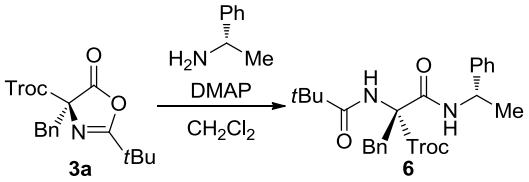
4: ^{1}H NMR (400 MHz, C_6D_6) δ 7.52-7.46 (2H, m), 7.43 (1H, dd, *J* = 6.0, 3.6 Hz), 7.42 (1H, d, *J* = 9.1 Hz), 7.22-7.11 (3H, m), 4.48 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 148.5, 133.7, 131.8, 129.9, 127.9$_5$, 127.9$_2$, 127.0, 126.3, 120.2, 118.1, 94.3, 77.3; IR (neat) 2279, 1775, 1229, 1051, 956, 812, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_9Cl_3O_3^+$ ($[M]^+$) 317.9617, Found 317.9619.



2a: ^{1}H NMR (400 MHz, C_6D_6) δ 7.25 (2H, d, *J* = 7.6 Hz), 7.09 (2H, t, *J* = 7.6 Hz), 6.98 (1H, t, *J* = 7.6 Hz), 4.19 (2H, s), 3.75 (2H, s), 1.20 (9H, s).



3a: ^{1}H NMR (400 MHz, C_6D_6) δ 7.14-7.09 (2H, m), 7.01-6.93 (3H, m), 4.40 (1H, d, *J* = 12.1 Hz), 4.02 (1H, d, *J* = 12.1 Hz), 3.60 (1H, d, *J* = 13.7 Hz), 3.55 (1H, d, *J* = 13.7 Hz), 0.91 (9H, s).



Procedure for Derivatization of 3a to 6: To a solution of **3a** (95.6 mg, 0.235 mmol) in CH_2Cl_2 (800 μL) were added (*S*)-(–)-α-methylbenzylamine (33.5 μL, 0.26 mmol) and *N*,*N*-dimethylaminopyridine (2.4 mg, 0.02 mmol) at room temperature. After being stirred for 60 h, the reaction mixture was concentrated. The crude residue was purified by silica gel column chromatography (H/EA = 2:1 as eluent) and subsequent recrystallization (H/$CHCl_3$ solvent system at −15 °C) afforded stereochemically pure amide **6** (41.2 mg, 0.0078 mml) in 33% yield. **6:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (8H, m), 7.14 (1H, s), 7.12-7.05 (2H, m), 6.49 (1H, d, *J* = 7.2 Hz), 5.07 (1H, quin, *J* = 7.2 Hz), 4.77 (1H, d, *J* = 11.9 Hz), 4.59 (1H, d, *J* = 11.9 Hz), 3.91 (1H, d, *J* = 14.2 Hz), 3.51 (1H, d, *J* = 14.2 Hz), 1.57 (3H, d, *J* = 7.2 Hz), 1.16 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 169.2, 164.5,

141.9, 134.4, 130.2, 129.0, 128.4, 128.0, 127.7, 126.2, 94.0, 75.5, 66.4, 50.2, 39.5, 38.8, 27.4, 21.7; IR (neat) 3393, 3359, 2962, 1759, 1683, 1640, 1538, 1504, 1219, 1192, 1048, 907, 758 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{30}Cl_3N_2O_4^+$ ($[M+H]^+$) 527.1271, Found 527.1257.

Crystallographic Structure Determination:

Recrystallization of 6: Recrystallization of **6** was performed by using H/$CHCl_3$ solvent system at −15 °C.

The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 153 K on a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on F^2 by using SHELXTL.[19] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to nitrogen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions and isotropic thermal parameters refined. The crystallographic data were summarized in the following table.

Table S1. Crystal Data and Structure Refinement for **6** (CCDC 772979).

Empirical formula	$C_{25}H_{29}Cl_3N_2O_4$	
Formula weight	527.85	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.0175(12) Å	α = 90°.
	b = 11.0369(14) Å	β = 90°.
	c = 24.289(3) Å	γ = 90°.
Volume	2685.4(6) $Å^3$	
Z	4	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.374 mm^{-1}	
F(000)	1104	
Crystal size	0.40 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.68 to 28.29°.	
Index ranges	-13<=h<=10, -14<=k<=14, -23<=l<=32	
Reflections collected	20206	
Independent reflections	6672 [R_{int} = 0.0410]	
Completeness to theta = 28.29°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9636 and 0.8649	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6672 / 0 / 319	
Goodness-of-fit on F^2	1.093	
Final R indices [I>2sigma(I)]	R_1 = 0.0580, wR_2 = 0.1187	

R indices (all data)	$R_1 = 0.0706$, $wR_2 = 0.1246$
Absolute structure parameter	-0.02(6)
Largest diff. peak and hole	0.535 and -0.311 e.Å^{-3}

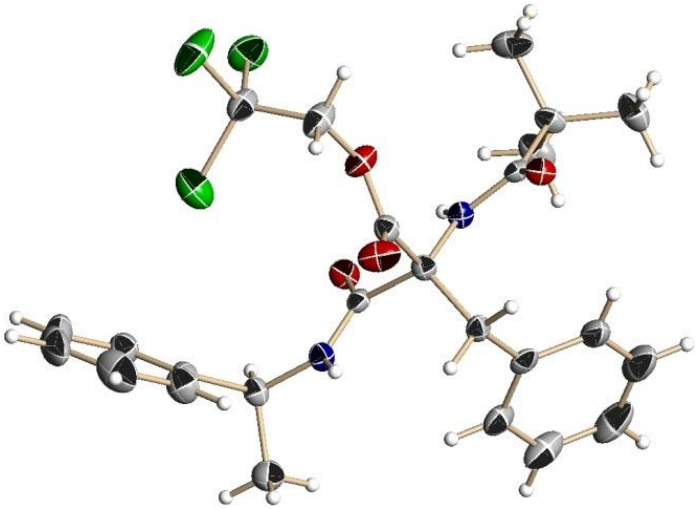


Figure S1. Molecular structure of **6**. Blue = nitrogen, red = oxygen, green = chlorine, black = carbon. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.

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(8) For review, see: Moyano, A.; El-Hamdouni, N.; Atlamsani, A. *Chem. Eur. J.* **2010**, *16*, 5260.

(9) (a) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. (c) Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332. (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (e) Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769. (f) Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 2626. (g) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914.

(10)The addition of molecular sieves 4A was crucial for avoiding protonation of reactive ammonium enolate by a small amount (<5%) of water which was contaminated from slightly hygroscopic onium salt **1**

(11)Under the representative conditions, author also attempted the reactions of benzyl and phenyl carbonate derivatives with **1d** as a catalyst, which gave unsatisfactory results: benzyl carbonate analogue of **2a**; [a low conversion (40 ºC for 30 min)]; phenyl carbonate analogue of **2a** [76% yield with 83% ee (25 ºC for 30 min)].

(12)Absolute configuration of **3a** was determined by X-ray diffraction analysis after derivatization (CCDC 772979). See Supporting Information for details.

(13)The generation of tetrabutylammonium β-naphthoxide in solution was confirmed by ^{1}H NMR analysis.

(14)Hugener, M.; Heimgartner, H. *Helv. Chim. Acta.* **1995**, *78*, 1863.

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(18)The generation of tetrabutylammonium β-naphthoxide in solution was confirmed by ^{1}H NMR analysis. The purification of tetrabutylammonium β-naphthoxide thus prepared turned out to be rather unsuccessful so far.

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Chapter 5

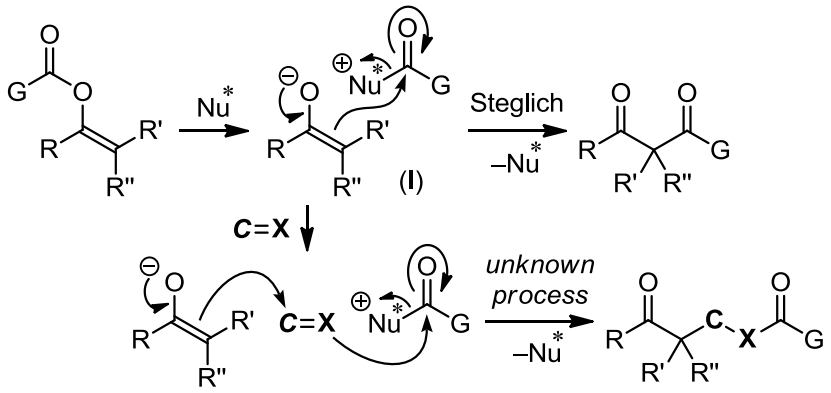
Ionic Nucleophilic Catalysis of Chiral Ammonium Betaines for Highly Stereoselective Aldol Reaction from Oxindole-Derived Vinylic Carbonates

Abstract: A new strategy for developing stereoselective bond-forming reactions is introduced, which simultaneously utilizes vinylic esters as an enolate precursor and an acylating agent for the coupling with electrophiles by taking advantage of the ionic nucleophilic catalysis of chiral ammonium betaines. Its synthetic utility is clearly demonstrated by establishing a highly diastereo- and enantioselective aldol reaction from oxindole-derived vinylic carbonates.

Introduction

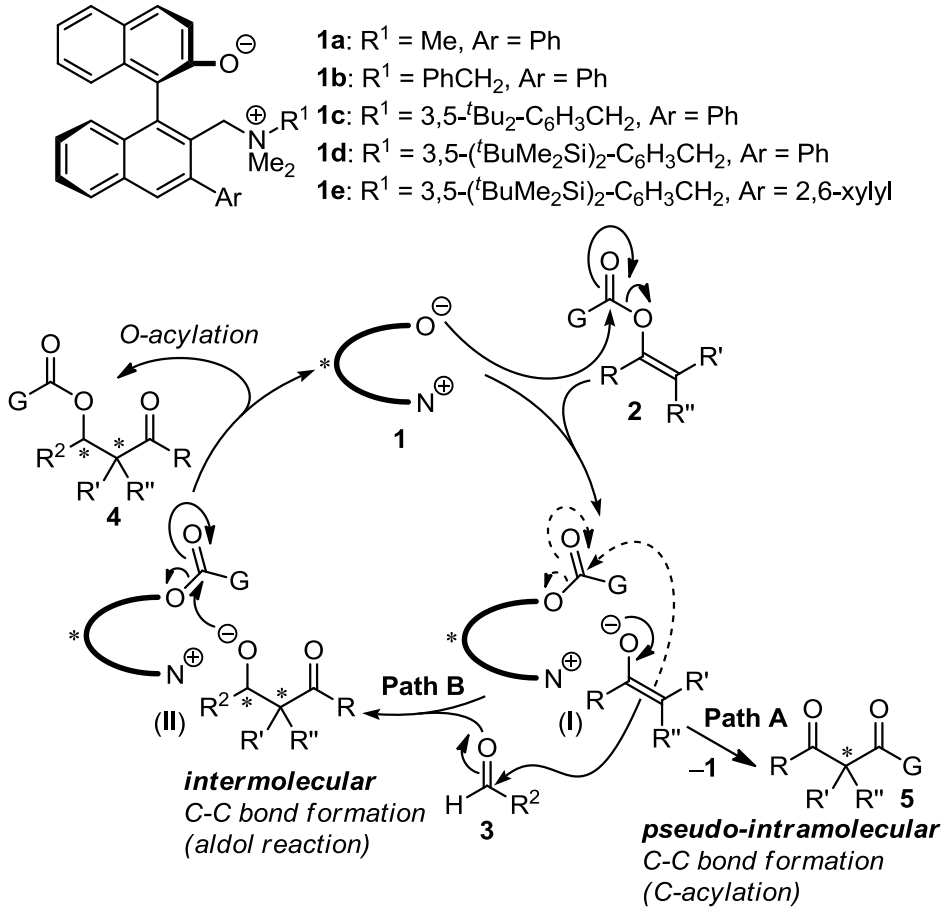
Vinylic esters (carbonates) represent one of the universal structural motifs encountered in natural products and are also important and reactive synthetic intermediates.[1-3] Looking at the primary structure, it is comprised of activated ester and electron-rich olefin moieties (Fig. 1).

Figure 1. Working hypothesis (G = alkyl, alkoxy)



While there have been numerous applications of the activated ester component as a mild and efficient acylating reagent,[2] the olefin component has been comparatively underutilized in organic synthesis other than for use as monomers in the preparation of several polymers and copolymers in academia and industries.[3] In the arena of asymmetric catalysis, the latent reactivity of the olefinic functionality has been harnessed in the employment of vinylic esters as an enolate precursor or surrogate for facilitating otherwise difficult stereoselective bond-forming processes.[4-7] Among the synthetically valuable transformations based on this strategy, chiral nucleophilic catalyst-mediated, enantioselective Steglich-type rearrangements are unique in view of realizing simultaneous utilization of the acyl and enolate moieties of substrates, i.e., 5-oxazolyl carbonates.[8-10] The mechanism of this reaction involves the generation of chiral enolate **I** through the attack of the catalyst (Nu*) to vinylic esters (carbonates) and subsequent stereoseletive acyl transfer within the ion pair **I**. On the other hand, if an external electrophile (*C*=X) such as carbonyl compounds or electron-deficient olefins could be inserted into **I** to forge two new bonds in a sequential manner, it would greatly expand the potential of the asymmetric nucleophilic catalysis. However, this possibility remains unexplored probably due to the stringent difficulty associated with extending precise catalyst control over the reactivity of **I** and the stereochemistry of the initial C-C bond formation. Herein, author reports our own approach to this problem based on the characteristic features of the ionic nucleophilic catalysis of chiral ammonium betaines **1**,[8h,11] which leads to achieve a highly diastereo- and enantioselective aldol reaction from oxindole-derived vinylic carbonates. The key for establishing this new system is the appropriate structure and reactivity of aryl carbonates of type **I** possessing ammonium enolate (Fig. 2), which enables the selective enolate addition to aldehyde and subsequent acyl transfer, thusderivatizing the stereochemically homogeneous product with judicious incorporation of the two functional groups of the vinylic carbonate origin.

Figure 2. The structures of chiral ammonium betaines **1** and the mechanism on their catalysis with vinylic esters



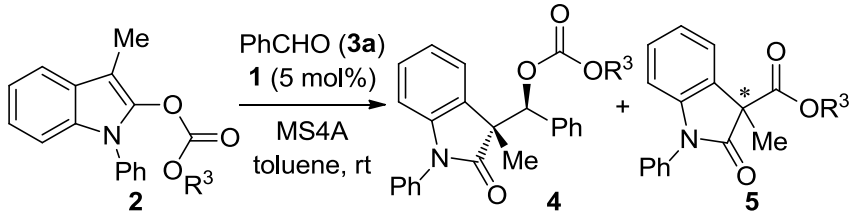
As illustrated in Figure 2, the reaction of chiral ammonium betaine **1** with vinylic ester **2** smoothly generates the intermediate **I** and the following pseudo-intramolecular attack of this transient enolate to the aryl ester moiety of the pairing ammonium ion gives usual Steglich product (Path A). Considering the moderate acyl transfer ability of the ammonium ion, however, author envisaged that the ammonium enolate **I** could react with an external electrophile such as aldehyde **3** to afford the corresponding ammonium alkoxide **II** (Path B), which would be rapidly *O*-acylated to furnish a fully protected aldol adduct **4** with regeneration of the betaine catalyst **1**. Author further expected that this unique catalytic pathway involving the intermolecular C-C bond formation could be selectively guided by the appropriate structural modification of **1**. To examine this hypothesis, oxindole-derived vinylic carbonate **2** was selected as a model substrate. Although the oxindole core and the related structural frameworks, particularly those having a quaternary carbon stereocenter, are commonly found in biologically relevant molecules,[12] the catalytic asymmetric aldol reaction of oxindoles has been poorly studied and only a few protocols were developed by use of highly reactive carbonyl compounds as requisite electrophiles.[13] This is probably because the aldol adducts of oxindoles are relatively unstable under basic conditions and are prone to undergo retro-aldol reaction. In fact, Bencivenni et al. recently addressed this problem and introduced an *O*-protection procedure for the ease of analysis and eventual product manipulations. With this respect, our approach would be generically advantageous for in situ derivatization of the desired aldol adduct in such a stable form.

Results and Discussion

8. Ionic Nucleophilic Catalysis of Chiral Ammonium Betaines for Highly Stereoselective Aldol Reaction

The actual investigation was initiated by carrying out the reaction of *O*-trichloroethoxycarbonyl enolate **2a** with benzaldehyde **3a** in the presence of chiral ammonium betaine **1a** and molecular sieves 4A in toluene.[14] Near complete consumption of the starting **2a** was observed within 30 min and the desired aldol adduct **4a** was obtained as a mixture of diastereomer in a ratio of 6:1 in 77% yield with concomitant yet considerable formation of Steglich-product **5a** (**4a**:**5a** = 8:1). The enantiomeric excess of the major isomer of **4a** was determined to be 34% ee (Table 1, entry 1). As anticipated, the structural modification of the catalyst had beneficial impact on the product distribution as well as the stereoselectivity and, interestingly, the installation of 3,5-disubstituted benzyl group on the nitrogen atom of **1** resulted in their dramatic improvements (entries 3 and 4). The aromatic substituent on the binaphthyl backbone (Ar) also affected each selectivity and 2,6-xylyl group was found to be optimal (entry 5). In addition, author reasoned that the structure of the carbonate substituent of **2** (R^3) would be a critical parameter for improving the reaction profile because the parent structure of **1** is modified by the acyl transfer from **2** in serving as a chiral component of the ammonium enolate at the C-C bond-forming stage (Fig. 2, **I** → **II**). Indeed, incorporation of benzyl group (**2b**) enhanced the enantioselectivity to 92% ee albeit with decrease in catalyst turnover (entry 6). Additional electronic tuning by introducing a trifluoromethy substituent (**2c**) delivered sufficient reaction efficiency and even higher selectivities (entry 7). Eventually, use of 3,5-bis(trifluoromethyl)benzyl-substituted **2d** in combination with the catalyst **1e** led to virtually complete discrimination of the reaction pathway with excellent levels of setereoselectivity (entry 8). Importantly, attempted reaction of **2d** with DMAP (5 mol%) as a representative nucleophilic catalyst under otherwise identical conditions gave rise to the corresponding Steglich product **5d** exclusively (12 h, 96% yield), illustrating the distinct feature of the ionic nucleophilic catalysis of chiral ammonium betaines of type **1**.

Table 1. Optimization of the Conditions for the Reaction of Vinylic Carbonate **2** and Benzaldehyde **3a** with Chiral Ammonium Betaines **1**[a]



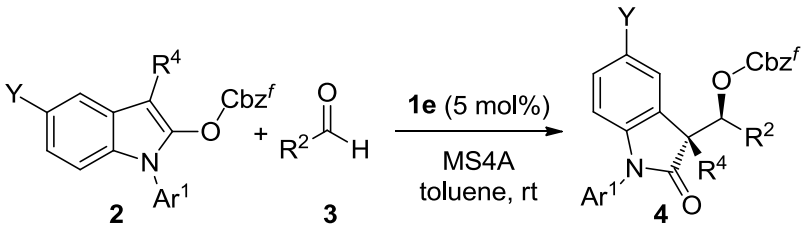
entry	**1**	R	**2**	yield[b] (%)	dr[c]	**4**:5[c]	ee[d] (%)	**4**
1	**1a**	Cl_3CCH_2	**2a**	77	6:1	8:1	34	**4a**
2	**1b**	Cl_3CCH_2	**2a**	67	7:1	4:1	39	**4a**
3	**1c**	Cl_3CCH_2	**2a**	79	15:1	15:1	71	**4a**
4	**1d**	Cl_3CCH_2	**2a**	82	15:1	11:1	78	**4a**
5	**1e**	Cl_3CCH_2	**2a**	86	≥20:1	13:1	89	**4a**
6[e]	**1e**	$PhCH_2$	**2b**	51	≥20:1	≥20:1	92	**4b**

7	**1e**	4-CF_3–$C_6H_4CH_2$	**2c**	88	≥20:1	≥20:1	93	**4c**
8	**1e**	3,5-$(CF_3)_2$–$C_6H_4CH_2$	**2d**	89	≥20:1	≥20:1	95	**4d**

[a] Unless otherwise noted, reactions were performed on 0.1 mmol scale with 2.0 equiv of **3** and 5 mol% of **1** in toluene (2.0 mL) for 0.5 h at rt. [b] Isolated yield. [c] The diastereomeric ratio and the product distribution were determined by ^{1}H NMR (400 MHz) analysis of crude aliquot. [d] Enantiomeric excess of major isomer was indicated, which was analyzed by chiral stationary phase HPLC. Absolute configurations of **4a-d** were assigned by analogy to **4e** (Scheme 1). [e] The reaction time was 12 h.

With the optimized conditions in hand, further experiments were conducted to explore the scope of this new stereoselective aldol reaction of oxindoles catalyzed by **1e**. As seen from the representative results summarized in Table 2, the present system nicely accommodated a range of simple aromatic aldehydes, including fused and heteroaromatic ones, and the corresponding aldol adducts were obtained uniformly with excellent diastereo- and enantioselectivities (entries 1-6). The structure of vinylic carbonates **2** can also be variable with regard to the C(5) and C(3) substituents without loss in stereocontrol (entries 7-10). It should be noted that comparable reactivity and selectivity were observed in the reaction with vinylic carbonate **2i** bearing a *p*-methoxyphenyl group on the nitrogen atom (entry 11).

Table 2. Substrates Generality (Cbzf = 3,5-$(CF_3)_2$-$C_6H_3CH_2$)[a]



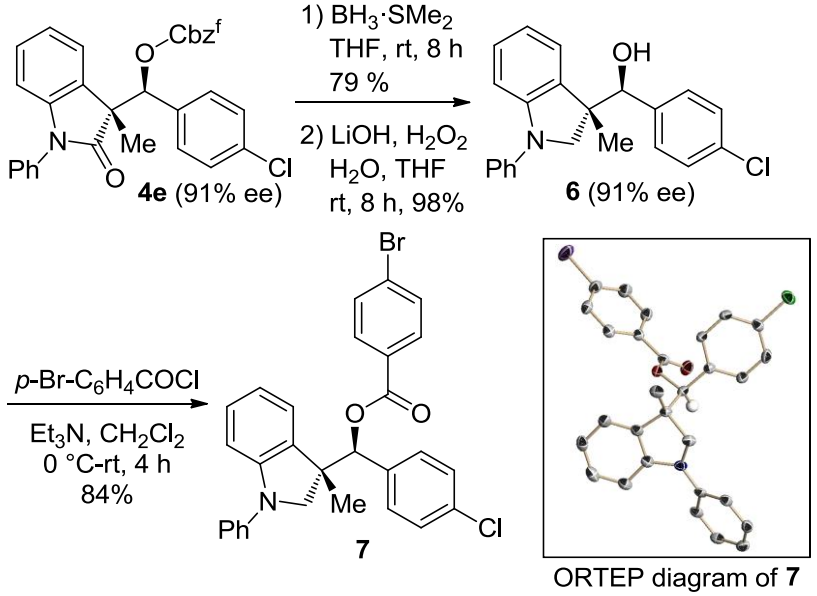
2d: R^4 = Me, Y = H, Ar^1 = Ph **2g**: R^4 = Et, Y = H, Ar^1 = Ph
2e: R^4 = Me, Y = Br, Ar^1 = Ph **2h**: R^4 = Bn, Y = H, Ar^1 = Ph
2f: R^4 = Me, Y = MeO, Ar^1 = Ph **2i**: R^4 = Me, Y = H, Ar^1 = PMP

entry	**2**	R^2 (**3**)	yield[b] (%)	dr[c]	ee[d] (%)	**4**
1	**2d**	4-Cl-C_6H_4 (**3b**)	96	≥20:1	91	**4e**
2	**2d**	4-Me-C_6H_4 (**3c**)	87	≥20:1	96	**4f**
3	**2d**	3-Br-C_6H_4 (**3d**)	95	14:1	90	**4g**
4	**2d**	3-MeO-C_6H_4 (**3e**)	90	≥20:1	93	**4h**
5	**2d**	1-naphthyl (**3g**)	73	≥20:1	95	**4i**
6	**2d**	2-thienyl (**3h**)	91	≥20:1	96	**4j**
7	**2e**	**3a**	90	≥20:1	96	**4k**
8	**2f**	**3a**	87	≥20:1	94	**4l**
9	**2g**	**3a**	89	18:1	92	**4m**
10	**2h**	**3a**	87	18:1	92	**4n**
11	**2i**	**3a**	94	≥20:1	93	**4o**

[a] Reactions were performed on 0.1 mmol scale with 2.0 equiv of **3** and 5 mol% of **1e** in toluene (2.0 mL) for 0.5 h at rt. [b] Isolated yield. [c] The diastereomeric ratio was determined by ^{1}H NMR (400 MHz) analysis of crude aliquot. [d] Enantiomeric excess of major isomer was indicated, which was determined by chiral HPLC analysis. Absolute configuration of **4e** was determined by X-ray crystallographic analysis of its derivative (Scheme 1), see Supporting Information for details. Absolute configurations of **4f-q** were assigned by analogy to **4e**.

Absolute configuration of **4e** was determined by X-ray diffraction analysis after conversion into the corresponding indoline derivative **7** (Scheme 1). The reduction of the carbonyl moiety of **4e** by treatment with $BH_3 \cdot SMe_2$ in THF followed by hydrolysis using LiOOH afforded secondary alcohol **6**. Subsequent acylation with *p*-bromobenzoyl chloride furnished **7** in good yield, which was recrystallized from hexane/EtOH solvent system at room temperature (see ORTEP diagram in Scheme 1).

Scheme 1. Absolute Configuration Determination



Summary

In conclusion, author has introduced a new strategy for developing stereoselective carbon-carbon bond-forming reactions, which relies on the salient features of chiral ammonium betaines as an ionic nucleophilic catalyst in exploiting binary reactivity of vinylic esters (carbonates) for the coupling with electrophiles. This enables the establishment of the highly stereoselective aldol reaction of oxindole-derived vinylic carbonates with simple aldehydes. The present approach significantly expands the scope of the asymmetric ionic nucleophilic catalysis of chiral ammonium betaines and also offers an unprecedented opportunity of utilizing both reactive subunits of vinylic esters in reaction development.

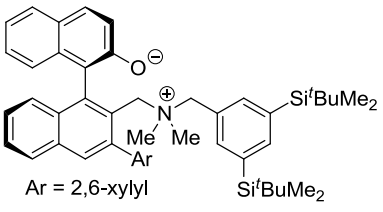
Experimental

General Information: Infrared spectra were recorded on a Shimazu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance [CD_3OD: 3.31 ppm] or Me_4Si resonance (0.00 ppm; $CDCl_3$, $(CD_3)_2CO$) as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet, br = broad) and

coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2CO$: 29.84 ppm, CD_3OD: 49.00 ppm, $CDCl_3$: 77.16 ppm]. ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (−64.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on PSQ60AB (spherical, av. 55 μm; Fuji Silysia Chemical ltd.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK AD-3 (AD-3), CHIRALPAK IA (IA), CHIRALPAK IC-3 (IC-3), or CHIRALPAC IC (IC)].

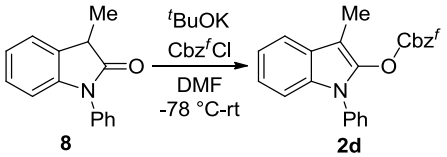
Toluene was supplied from Kanto Chemical Co., Inc. as "Dehydtated" and further purified by passing through neutral alumina under nitrogen atmosphere. Betaine **1**,[8h,11c] *N*-aryl oxindoles **8**[15], and chloroformate[16] were prepared by following the literature procedure. Powdered molecular sieves 4A was supplied from Merck. Other simple chemicals were purchased and used as such.

Characterization of Betaine 1e:



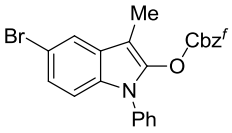
1e: ^1H NMR (400 MHz, CD_3OD) δ 7.91 (1H, d, J = 8.2 Hz), 7.82-7.63 (3H, m), 7.67 (1H, s), 7.59 (1H, br), 7.53 (1H, t, J = 7.3 Hz), 7.32 (1H, br), 7.28-6.96 (7H, m), 6.95 (1H, br), 6.52 (1H, br), 4.18 (1H, d, J = 12.1 Hz), 4.05 (1H, d, J = 12.1 Hz), 3.95 (1H, d, J = 11.5 Hz), 3.88 (1H, d, J = 11.5 Hz), 2.75 (3H, brs), 2.48 (3H, brs), 2.35 (3H, brs), 1.94 (3H, brs), 0.81 (18H, s), 0.29 (12H, s); ^{13}C NMR (101 MHz, CD_3OD) δ 166.3, 147.3, 143.7, 141.4, 140.3, 140.0, 138.7, 138.0, 136.7, 136.2, 135.7, 134.2, 131.3, 129.8, 129.5, 129.3, 129.2, 128.9, 128.8$_7$, 127.7, 127.4, 126.9, 126.1, 125.7, 122.2, 121.1, 117.7, 72.7, 63.9, 51.7, 26.9, 21.6, 21.4, 17.7, -6.0, four carbons were not found probably due to overlapping; IR (film) 2953, 2926, 2855, 1589, 1462, 1422, 1362, 1248, 826 cm^{-1}; HRMS (ESI) Calcd for $C_{50}H_{64}NOSi_2^+$ ($[M+H]^+$) 750.4521, Found 750.4511; $[\alpha]^{19}_D$ +65.6 (c = 1.49, MeOH).

Preparation and Characterization of Vinylic Carbonate 2:

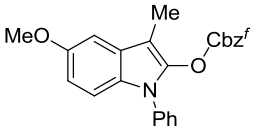


Representative procedure for preparation of 2d: A solution of ^{t}BuOK in THF (1.0 M, 2.2 ml, 2.2 mmol) was added to a solution of the *N*-phenyl oxindole 8 (446.5 mg, 2.0 mmol) in DMF (10.0 mL) dropwise at −60 °C and the solution was stirred for 30 min. To a reaction mixture was introduced 3,5-bis(trifluoromethyl)benzyl chloroformate (735.8 mg, 2.4 mmol). The resulting mixture was warmed to room temperature, diluted with a 1N HCl aqueous solution, and extracted with ethyl acetate (EA) twice.

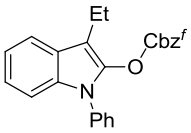
The combined organic extracts were washed with brine, and dried over Na_2SO_4. After evaporation of volatiles, purification of the residue by column chromatography on silica gel (hexane (H)/$CHCl_3$ = 20:1-1:1 as eluent) and following recrystallization from hexane at −40 °C to give **2d** (661.2 mg, 1.3 mmol, 67%) as a colorless crystal. **2d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.73 (2H, s), 7.61-7.56 (1H, m), 7.39 (2H, t, J = 7.5 Hz), 7.33 (2H, d, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 7.24-7.16 (3H, m), 5.21 (2H, s), 2.25 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 138.4, 136.9, 135.5, 133.0, 132.3 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.5, 128.5, 127.7, 126.9, 126.7, 123.1 (q, $J_{F\text{-}C}$ = 277.7 Hz), 122.9 (m), 122.7, 120.6, 119.2, 110.2, 98.5, 68.9, 7.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (film) 1767, 1503, 1456, 1366, 1277, 1252, 1225, 1175, 1130, 887, 843 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{18}F_6NO_3^+$ ($[M+H]^+$) 494.1185, Found 494.1186.



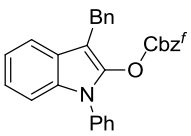
2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.73 (2H, s), 7.70 (1H, d, J = 2.1 Hz), 7.39 (2H, t, J = 7.5 Hz), 7.34-7.27 (3H, m), 7.26 (1H, dd, J = 8.7, 2.1 Hz), 7.07 (1H, d, J = 8.7 Hz), 5.21 (2H, s), 2.21 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 139.1, 136.7, 135.1, 132.3 (q, $J_{F\text{-}C}$ = 33.9 Hz), 131.7, 129.6, 128.5, 128.4, 128.1, 126.8, 125.5, 123.1 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.0 (m), 121.8, 113.7, 111.8, 98.3, 69.1, 7.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (film) 1769, 1503, 1445, 1362, 1281, 1217, 1204, 1165, 1140, 1126, 893 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{17}BrF_6NO_3^+$ ($[M+H]^+$) 572.0291, Found 572.0293.



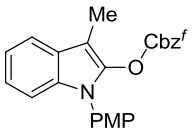
2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.74 (2H, s), 7.38 (2H, t, J = 7.5 Hz), 7.31 (2H, d, J = 7.5 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.13 (1H, d, J = 9.2 Hz), 7.02 (1H, d, J = 2.0 Hz), 6.83 (1H, dd, J = 9.2, 2.0 Hz), 5.22 (2H, s), 3.88 (3H, s), 2.22 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 152.2, 138.7, 136.9, 135.7, 132.2 (q, $J_{F\text{-}C}$ = 33.9 Hz), 129.5, 128.5, 128.0, 127.6, 127.1, 126.6, 123.1 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.9 (m), 112.4, 111.2, 101.4, 98.4, 68.9, 56.1, 7.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (film) 1769, 1281, 1229, 1202, 1165, 1126, 895 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{20}F_6NO_4^+$ ($[M+H]^+$) 524.1291, Found 524.1293.



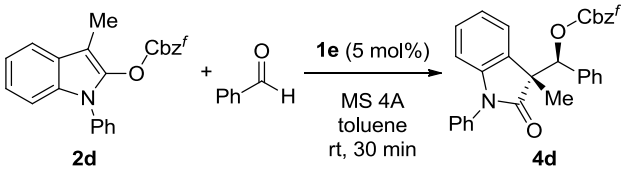
2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.72 (2H, s), 7.65-7.60 (1H, m), 7.40-7.31 (4H, m), 7.28 (1H, t, J = 7.1 Hz), 7.24-7.14 (3H, m), 5.19 (2H, s), 2.73 (2H, q, J = 7.7 Hz), 1.28 (3H, t, J = 7.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 137.9, 136.9, 135.5, 133.2, 132.2 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.5, 128.6, 127.7, 126.9, 125.9, 123.1 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.9 (m), 122.6, 120.5, 119.4, 110.3, 104.7, 68.9, 16.4, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (film) 1771, 1628, 1603, 1503, 1458, 1362, 1279, 1217, 1130, 891 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{20}F_6NO_3^+$ ($[M+H]^+$) 508.1342, Found 508.1344.



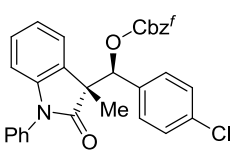
2h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, s), 7.65 (2H, s), 7.46 (1H, d, J = 7.8 Hz), 7.40-7.32 (4H, m), 7.32-7.20 (6H, m), 7.19-7.08 (3H, m), 5.05 (2H, s), 4.09 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 139.9, 138.9, 136.7, 135.4, 133.2, 132.2, (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.5, 128.8, 128.6, 128.5, 127.9, 127.0, 126.2, 126.0, 123.1 (q, $J_{F\text{-}C}$ = 277.1 Hz), 122.9 (m), 122.8, 120.8, 119.6, 110.3, 101.8, 68.9, 29.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (film) 1782, 1499, 1456, 1281, 1263, 1211, 1171, 1114, 876, 843 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{22}F_6NO_3^+$ ($[M+H]^+$) 570.1498, Found 570.1500.



2i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.76 (2H, s), 7.60-7.54 (1H, m), 7.24 (2H, d, J = 9.1 Hz), 7.20-7.10 (3H, m), 6.90 (2H, d, J = 9.1 Hz), 5.22 (2H, s), 3.82 (3H, s), 2.24 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 152.3, 138.7, 137.0, 135.5, 132.2 (q, $J_{F\text{-}C}$ = 34.2 Hz), 128.4, 128.1, 126.5, 123.1 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.8 (m), 122.5, 120.4, 119.1, 114.6, 110.1, 98.0, 68.9, 55.5, 7.3, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.5 ; IR (film) 1771, 1516, 1458, 1277, 1254, 1213, 1171, 1123, 891, 831 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{20}F_6NO_4^+$ ([M+H]$^+$) 524.1291, Found 524.1294.

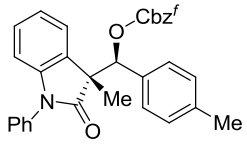


Representative Procedure for Catalytic Asymmetric Aldol-Type Reaction of Vinylic Carbonate 2d: A test tube was charged with a magnetic stirrer bar and MS 4A (100 mg) under argon atmosphere. The MS 4A was then dried with heat gun under reduced pressure for 5 minutes and the test tube was refilled with argon. Vinylic carbonate **2d** (49.3 mg, 0.1 mmol), benzaldehyde (21.2 mg, 0.2 mmol) and toluene (2.0 mL) were added to the test tube successively under argon atmosphere at room temperature. After addition of **1e** (3.75 mg, 0.005 mmol) as solid, the reaction mixture was stirred for 30 min and a 0.5 M solution of trifluoroacetic acid in toluene (50.0 μL) was introduced. The whole mixture was passed through a pad of celite by the aid of EA to remove MS 4A and the filtrate was concentrated. Diastereomeric ratio was analyzed by 400 MHz NMR of the crude residue (dr = >20:1). The crude mixture was purified by silica gel column chromatography using H/EA solvent system (H/EA = 10:1-5:1 as eluent) to afford **4d** (53.4 mg 0.089 mmol) in 89% yield and the enantiomeric excess of **4d** was measured by HPLC analysis (95% ee). **4d:** HPLC: AD-3, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 20.1 min (minor diastereomer), 36.0 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.71 (2H, s), 7.47 (2H, t, J = 7.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.36-7.30 (3H, m), 7.30-7.18 (5H, m), 6.99 (1H, t, J = 7.8 Hz), 6.74 (1H, d, J = 7.8 Hz), 6.71 (1H, d, J = 7.3 Hz), 6.00 (1H, s), 5.16 (1H, d, J = 13.5 Hz), 5.12 (1H, d, J = 13.5 Hz), 1.52 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 153.6, 144.2, 137.8, 135.0, 134.4, 132.1 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.7, 129.0, 128.9, 128.7, 128.3, 128.1, 127.9, 127.7, 126.7, 125.4, 123.2 (q, $J_{F\text{-}C}$ = 276.4 Hz), 122.5, 109.6, 83.6, 67.9, 52.2, 20.4, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1755, 1721, 1611, 1504, 1371, 1279, 1246, 1175, 1132, 970 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{24}F_6NO_4^+$ ([M+H]$^+$) 600.1604, Found 600.1604.

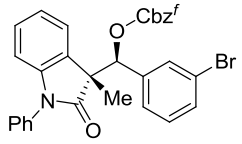


4e: HPLC: AD-3, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.4 min (minor diastereomer), 13.1 min (major diastereomer), Absolute configuration was assigned by derivatization to **6** (see below); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.72 (2H, s), 7.48 (2H, t, J = 7.6 Hz), 7.40 (1H, t, J = 7.6 Hz), 7.32 (2H, d, J = 8.7 Hz), 7.27 (2H, d, J = 7.6 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.17 (2H, d, J = 8.7 Hz), 7.01 (1H, t, J = 7.5 Hz), 6.76 (1H, d, J = 7.5 Hz), 6.74 (1H, d, J = 7.5 Hz), 5.96 (1H, s), 5.17 (1H, d, J = 13.3 Hz), 5.13 (1H, d, J = 13.3 Hz), 1.51 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 153.6, 144.2, 137.6, 135.0, 134.3, 133.6, 132.1 (q,

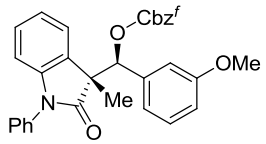
$J_{F\text{-}C}$ = 34.2 Hz), 129.8, 129.1, 128.9, 128.6, 128.4, 128.0, 126.7, 125.2, 123.2 (q, $J_{F\text{-}C}$ = 276.1 Hz), 122.6, 122.5$_6$ (m), 109.8, 82.9, 68.0, 52.0, 20.3, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.5; IR (liq. film) 1755, 1721, 1611, 1503, 1371, 1279, 1244, 1175, 1132, 970 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{23}ClF_6NO_4^+$ ([M+H]$^+$) 634.1214, Found 634.1216.



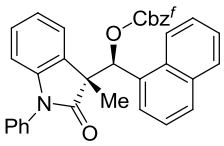
4f: HPLC: AD-3, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 25.6 min (minor diastereomer), 38.5 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, s), 7.70 (2H, s), 7.47 (2H, t, *J* = 7.5 Hz), 7.39 (1H, t, *J* = 7.5 Hz), 7.30 (2H, d, *J* = 7.5 Hz), 7.21 (1H, t, *J* = 7.6 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 7.12 (2H, d, *J* = 8.5 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 6.76 (1H, d, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 5.97 (1H, s), 5.15 (1H, d, *J* = 13.3 Hz), 5.11 (1H, d, *J* = 13.3 Hz), 2.37 (3H, s), 1.49 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 153.6, 144.2, 138.8, 137.8, 134.5, 132.1 (q, $J_{F\text{-}C}$ = 34.2 Hz), 132.0, 129.7, 129.0, 128.8, 128.6, 128.3, 127.9, 127.6, 126.8, 125.6, 123.2 (q, $J_{F\text{-}C}$ = 275.8 Hz), 122.4, 109.6, 83.6, 67.8, 52.2, 21.4, 20.5, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.5; IR (liq. film) 1753, 1719, 1611, 1503, 1371, 1277, 1244, 1173, 1130, 968, 907 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{26}F_6NO_4^+$ ([M+H]$^+$) 614.1761, Found 614.1762.



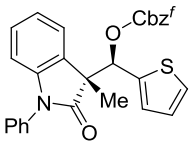
4g: HPLC: IA, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 17.4 min (minor isomer), 35.3 min (major isomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, s), 7.74 (2H, s), 7.49 (2H, t, *J* = 7.5 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.37 (1H, s), 7.28 (2H, d, *J* = 7.5 Hz), 7.22 (1H, t, *J* = 7.7 Hz), 7.21 (1H, t, *J* = 7.8 Hz), 7.17 (1H, d, *J* = 7.8 Hz), 7.03 (1H, t, *J* = 7.7 Hz), 6.76 (1H, d, *J* = 7.7 Hz), 6.73 (1H, d, *J* = 7.7 Hz), 5.94 (1H, s), 5.19 (1H, d, *J* = 13.3 Hz), 5.13 (1H, d, *J* = 13.3 Hz), 1.52 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 153.6, 144.2, 137.6, 137.3, 134.3, 132.1$_3$, 132.1$_3$ (q, $J_{F\text{-}C}$ = 34.2 Hz), 130.7, 129.8, 129.7, 128.9, 128.5, 128.4, 128.0, 126.7, 126.4, 125.2, 123.2 (q, $J_{F\text{-}C}$ = 278.0 Hz), 122.6, 122.5$_9$ (m), 122.3, 109.8, 82.7, 68.1, 52.0, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1753, 1719, 1611, 1503, 1369, 1277, 1244, 1175, 1130, 940, 907 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{23}BrF_6NO_4^+$ ([M+H]$^+$) 678.0709, Found 678.0714.



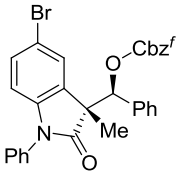
4h: HPLC: AD-3, H/EtOH (Et) = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 12.5 min (minor diastereomer), 33.1 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.72 (2H, s), 7.47 (2H, t, *J* = 7.5 Hz), 7.39 (1H, t, *J* = 7.5 Hz), 7.28 (2H, d, *J* = 7.5 Hz), 7.25 (1H, t, *J* = 7.8 Hz), 7.20 (1H, t, *J* = 7.8 Hz), 7.00 (1H, t, *J* = 7.8 Hz), 6.90 (1H, d, *J* = 7.8 Hz), 6.85 (1H, d, *J* = 7.8 Hz), 6.78 (1H, d, *J* = 7.8 Hz), 6.75 (1H, d, *J* = 7.8 Hz), 6.72 (1H, s), 5.97 (1H, s), 5.17 (1H, d, *J* = 13.3 Hz), 5.13 (1H, d, *J* = 13.3 Hz), 3.71 (3H, s), 1.53 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 159.2, 153.6, 144.2, 137.8, 136.5, 134.4, 132.1 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.7, 129.2, 129.0, 128.7, 128.3, 128.0, 126.7, 125.5, 123.2 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.5 (m), 122.4, 120.0, 114.9, 112.9, 109.6, 83.5, 68.0, 55.3, 52.2, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1753, 1719, 1611, 1497, 1371, 1277, 1242, 1173, 1130, 968, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{26}F_6NO_5^+$ ([M+H]$^+$) 630.1710, Found 630.1704.



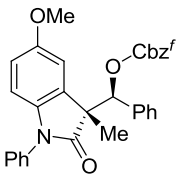
4i: HPLC: AD-3, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 22.2 min (major isomer), 39.4 min (minor isomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (1H, d, J = 7.8 Hz), 7.89 (2H, d, J = 7.8 Hz), 7.79 (1H, s), 7.64 (2H, s), 7.58 (1H, t, J = 7.8 Hz), 7.54-7.36 (8H, m), 7.21 (1H, t, J = 7.8 Hz), 6.99 (1H, s), 6.95 (1H, t, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz), 6.68 (1H, d, J = 7.8 Hz), 5.10 (1H, d, J = 13.3 Hz), 5.03 (1H, d, J = 13.3 Hz), 1.44 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 153.5, 144.3, 137.7, 134.6, 133.6, 132.0 (q, $J_{F\text{-}C}$ = 33.9 Hz), 131.9, 131.4, 129.8, 129.0, 128.9, 128.7, 128.4, 127.9, 126.8, 126.7, 126.6, 126.2, 126.0, 124.7, 123.7, 123.1 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.5 (m), 122.2, 109.7, 79.0, 67.9, 53.2, 20.9, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1755, 1717, 1611, 1503, 1369, 1277, 1256, 1175, 1130, 966, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{36}H_{26}F_6NO_4^+$ ([M+H]$^+$) 650.1761, Found 650.1759.



4j: HPLC: IA, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.3 min (minor diastereomer), 26.8 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.73 (2H, s), 7.47 (2H, t, J = 7.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.33-7.27 (3H, m), 7.22 (1H, t, J = 7.8 Hz), 7.03 (1H, t, J = 7.8 Hz), 7.02-6.96 (2H, m), 6.91 (1H, d, J = 6.9 Hz), 6.76 (1H, d, J = 7.8 Hz), 6.27 (1H, s), 5.18 (2H, s), 1.59 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 153.6, 144.2, 137.7, 137.4, 134.4, 132.1 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.7, 128.9, 128.8$_6$, 128.3, 127.9, 127.0, 126.8, 126.7, 125.9, 125.2, 123.2 (q, $J_{F\text{-}C}$ = 278.3 Hz), 122.7, 122.5 (m), 109.7, 80.3, 68.1, 52.3, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1755, 1719, 1611, 1503, 1371, 1277, 1242, 1173, 1128, 966, 907 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{22}F_6NO_4S^+$ ([M+H]$^+$) 606.1168, Found 606.1164.

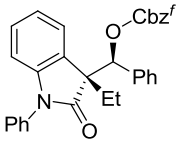


4k: HPLC: AD-3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 10.7 min (minor diastereomer), 16.6 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.71 (2H, s), 7.47 (2H, t, J = 7.5 Hz), 7.44-7.35 (4H, m), 7.33 (1H, dd, J = 8.4, 1.8 Hz), 7.29-7.21 (4H, m), 6.76 (1H, d, J = 1.8 Hz), 6.64 (1H, d, J = 8.4 Hz), 5.99 (1H, s), 5.16 (1H, d, J = 13.0 Hz), 5.12 (1H, d, J = 13.0 Hz), 1.49 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 153.5, 143.3, 137.7, 134.6, 134.1, 132.1 (q, $J_{F\text{-}C}$ = 33.5 Hz), 131.5, 130.9, 129.9, 129.3, 128.7, 128.6, 128.3, 128.0, 127.6, 126.6, 123.2 (q, $J_{F\text{-}C}$ = 277.1 Hz), 122.5 (m), 115.1, 111.1, 83.3, 68.0, 52.3, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.5; IR (liq. film) 1755, 1722, 1503, 1360, 1277, 1242, 1173, 1130, 968, 907 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{23}BrF_6NO_4^+$ ([M+H]$^+$) 678.0709, Found 678.0711.

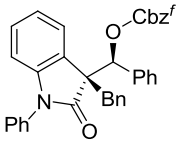


4l: HPLC: IC, H/IPA/Et = 87:9:4, flow rate = 1.0 mL/min, λ = 210 nm, 11.8 min (major diastereomer), 23.5 min (minor diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.71 (2H, s), 7.46 (2H, t, J = 7.8 Hz), 7.40-7.32 (4H, m), 7.32-7.24 (4H, m), 6.74 (1H, dd, J = 8.7, 2.4 Hz), 6.68 (1H, d, J = 8.7 Hz), 6.27 (1H, d, J = 2.4 Hz), 6.01 (1H, s), 5.16 (1H, d, J = 14.0 Hz), 5.12 (1H, d, J = 14.0 Hz), 3.69 (3H, s), 1.50 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 155.7, 153.6, 137.8, 137.6, 135.0, 134.7, 132.1 (q, $J_{F\text{-}C}$ = 33.9 Hz), 130.1, 129.7, 129.1, 128.1, 128.0$_9$, 127.9, 127.7, 126.5, 123.2 (q, $J_{F\text{-}C}$ = 277.4 Hz),

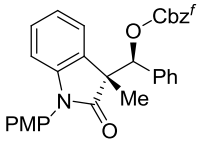
122.5 (m), 113.5, 112.3, 110.1, 83.5, 67.9, 55.8, 52.5, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1753, 1715, 1503, 1364, 1277, 1248, 1173, 1130, 968, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{26}F_6NO_5^+$ ([M+H]$^+$) 630.1710, Found 630.1710.



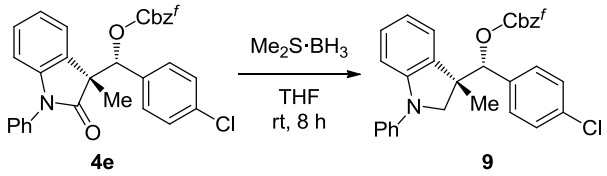
4m: HPLC: IA, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 16.0 min (minor diastereomer), 38.8 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.03 (3H, s), 7.51 (2H, t, J = 7.4 Hz), 7.44 (1H, t, J = 7.4 Hz), 7.40-7.31 (3H, m), 7.29-7.22 (5H,m), 7.05 (1H, t, J = 7.5 Hz), 6.85 (1H, d, J = 7.5 Hz), 6.68 (1H, d, J = 7.5 Hz), 6.02 (1H, s), 5.37 (1H, d, J = 13.4 Hz), 5.31 (1H, d, J = 13.4 Hz), 2.30 (1H, dq, J = 14.3, 7.3 Hz), 1.80 (1H, dq, J = 14.3, 7.3 Hz), 0.62 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 176.9, 154.4, 146.0, 140.1, 136.5, 135.7, 132.2 (q, $J_{F\text{-}C}$ = 33.5 Hz), 130.4, 129.5, 129.4, 128.9, 128.6, 128.5, 127.7, 126.1, 124.3 (q, $J_{F\text{-}C}$ = 276.3 Hz), 123.1, 122.9 (m), 109.7, 83.9, 68.5, 58.2, 27.8, 8.4, two carbons were not found probably due to overlapping; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −64.9; IR (liq. film) 1755, 1717, 1611, 1501, 1464, 1373, 1277, 1240, 1173, 1130, 1074, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{26}F_6NO_4^+$ ([M+H]$^+$) 614.1761, Found 614.1757.



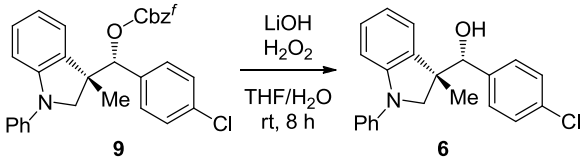
4n: HPLC: AD-3, H/IPA/Et = 90:5:5, flow rate = 1.0 mL/min, λ = 210 nm, 21.1 min (minor diastereomer), 31.8 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.04 (2H, s), 8.03 (1H, s), 7.45-7.37 (8H, m), 7.11 (2H, t, J = 7.5 Hz), 7.07-6.99 (4H, m), 6.86 (2H, d, J = 7.5 Hz), 6.83 (2H, d, J = 7.5 Hz), 6.32 (1H, d, J = 7.5 Hz), 6.24 (1H, s), 5.39 (1H, d, J = 13.3 Hz), 5.34 (1H, d, J = 13.3 Hz), 3.63 (1H, d, J = 12.8 Hz), 3.07 (1H, d, J = 12.8 Hz); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 176.2, 154.5, 145.6, 140.1, 136.5, 135.9, 135.4, 132.2 (q, $J_{F\text{-}C}$ = 33.5 Hz), 131.0, 130.2, 129.6, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 127.6, 127.4, 127.3$_6$, 126.9, 124.3 (q, $J_{F\text{-}C}$ = 276.3 Hz), 123.0 (m), 122.7, 109.4, 83.5, 68.5, 59.2, 40.7; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −64.9; IR (liq. film) 1753, 1717, 1611, 1495, 1373, 1277, 1240, 1173, 1132, 966, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{38}H_{28}F_6NO_4^+$ ([M+H]$^+$) 676.1917, Found 676.1921.



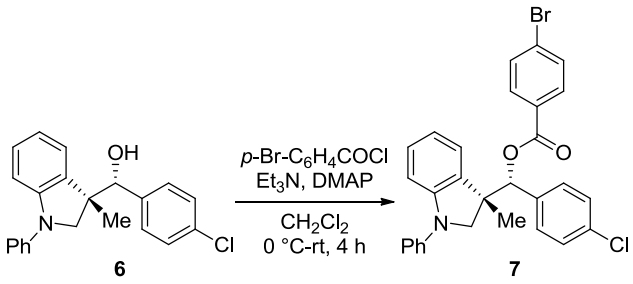
4o: HPLC: AD-3, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 10.6 min (minor diastereomer), 25.1 min (major diastereomer), Absolute configuration was assigned on the analogy of **4e**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.72 (2H, s), 7.40-7.29 (3H, m), 7.23-7.12 (5H, m), 7.02-6.94 (3H, m), 6.70 (1H, d, J = 8.5 Hz), 6.68 (1H, d, J = 8.5 Hz), 6.00 (1H, s), 5.17 (1H, d, J = 13.7 Hz), 5.13 (1H, d, J = 13.7 Hz), 3.84 (3H, s), 1.51 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 159.4, 153.6, 144.7, 137.8, 135.1, 132.1 (q, $J_{F\text{-}C}$ = 34.2 Hz), 128.9, 128.8$_5$, 128.7, 128.1, 127.9, 127.7, 127.0, 125.3, 123.2 (q, $J_{F\text{-}C}$ = 277.1 Hz), 122.5 (m), 122.3, 115.0, 109.5, 83.6, 67.9, 55.6, 52.1, 20.4, one carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4; IR (liq. film) 1753, 1717, 1611, 1514, 1371, 1277, 1244, 1171, 1130, 968, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{26}F_6NO_5^+$ ([M+H]$^+$) 630.1710, Found 630.1710.



Preparation of 9 from 4e: 4e (dr = 20:1, 91% ee for major isomer) (55.2 mg, 0.087 mmol) was treated with $BH_3{\cdot}SMe_2$ (25 μL, 0.26 mmol) in THF (440 μL) under argon atmosphere for 8 h at 30 ºC. The reaction mixture was diluted with a saturated $NaHCO_3$ aqueous solution and extracted with EA twice. The combined extracts were dried over Na_2SO_4 and filtrated. Removal of volatiles and purification of the residue by column chromatography on silica gel (H/EA = 50:1-10:1 as eluent) furnished **8** (42.8 mg, 0.069 mmol, 79%) as a colorless oil. **9:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.76 (2H, s), 7.26-7.18 (3H, m), 7.08 (1H, t, J = 7.8 Hz), 7.01 (2H, d, J = 8.2 Hz), 6.93-6.86 (4H, m), 6.81 (2H, d, J = 7.8 Hz), 6.77 (1H, t, J = 7.8 Hz), 5.56 (1H, s), 5.18 (1H, d, J = 13.0 Hz), 5.13 (1H, d, J = 13.0 Hz), 3.95 (1H, d, J = 10.5 Hz), 3.72 (1H, d, J = 10.5 Hz), 1.55 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 146.8, 143.0, 137.8, 134.7, 134.1, 134.0, 132.2 (q, $J_{F\text{-}C}$ = 34.2 Hz), 129.1, 128.8, 128.0, 127.9$_5$, 127.8$_6$, 124.3, 123.2 (q, $J_{F\text{-}C}$ = 276.7 Hz), 122.6 (m), 121.2, 119.0, 117.3, 109.1, 83.8, 68.0, 60.3, 47.9, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.5; IR (liq. film) 1751, 1591, 1501, 1391, 1279, 1258, 1175, 1134, 966 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{25}ClF_6NO_3^+$ ([M+H]$^+$) 620.1422, Found 620.1417.



Procedure for derivatization of 9 to 6: A solution of **9** (42.8 mg, 0.069 mmol) in THF (7 mL) was added a 30% H_2O_2 aqueous solution (400 μL) and a 1.0 M LiOH aqueous solution (690 μL 0.69 mmol) at room temperature for 8 h. Then, a saturated aqueous solution of Na_2SO_3 was added until peroxides were completely reduced. The resulting mixture was extracted with EA twice and the combined organic extracts were dried over Na_2SO_4. After concentration of the organic phase, purification of the residue by column chromatography on silica gel (H/EA = 10:1-8:1 as eluent) afforded **5** (23.4 mg 0.067 mmol, 97%) without loss of the enantiomeric purity. **6:** HPLC: IC-3, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 13.1 min (major isomer), 15.4 min (minor isomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, t, J = 8.2 Hz), 7.17 (1H, d, J = 7.3 Hz), 7.08 (1H, t, J = 7.3 Hz), 7.05 (2H, d, J = 8.2 Hz), 6.96 (2H, d, J = 8.2 Hz), 6.94 (1H, d, J = 7.3 Hz), 6,92 (1H, t, J = 7.3 Hz), 6.89 (2H, d, J = 8.2 Hz), 6.79 (1H, t, J = 7.3 Hz), 4.66 (1H, s), 3.91 (1H, d, J = 10.3 Hz), 3.65 (1H, d, J = 10.3 Hz), 2.17 (1H, br), 1.49 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 143.3, 138.9, 135.6, 133.4, 129.1, 128.3, 128.2$_9$, 127.6, 124.3, 121.2, 118.9, 117.5, 108.8, 78.6, 60.7, 48.8, 21.2; IR (liq. film) 3414, 3057, 2868, 1589, 1499, 1481, 1387, 1327, 1279, 1179, 1090, 1013, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{21}ClNO^+$ ([M+H]$^+$) 350.1306, Found 350.1305.



Procedure for derivatization of 6 to 7: A solution of **6** (22.4 mg, 0.064 mmol) in CH_2Cl_2 (7 mL) was added a Et_3N (22 μL, 0.16 mmol), 4-bromobenzoyl chloride (30.9 mg, 0.14 mmol) and DMAP (1.59 mg, 0.013 mmol) at 0 ºC. The resulting mixture was warmed to room temperature and stirred for 4 hours. Then, the reaction mixture was diluted a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ twice. The combined extracts were dried over Na_2SO_4 and filtrated. Removal of volatiles and purification of the residue by column chromatography on silica gel (H/EA = 50:1-10:1 as eluent) furnished **7** (42.8 mg, 0.054 mmol, 84%) as a white solid. **6:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.24 (2H, t, J = 7.9 Hz), 7.13 (1H, d, J = 7.9 Hz), 7.09 (1H, t, J = 7.9 Hz), 7.02 (2H, d, J = 7.9 Hz), 6.96-6.88 (4H, m), 6.85 (2H, d, J = 7.9 Hz), 6.77 (1H, t, J = 7.9 Hz), 5.93 (1H, s), 4.03 (1H, d, J = 10.1 Hz), 3.82 (1H, d, J = 10.1 Hz), 1.57 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 147.0, 143.0, 135.4, 134.0, 133.9, 132.0, 131.2, 129.1, 128.9, 128.7, 128.6, 128.1, 127.8, 124.5, 121.3, 118.9, 117.4, 108.8, 80.4, 60.9, 47.9, 22.3; IR (liq. film) 2968, 2930, 1722, 1589, 1501, 1483, 1389, 1263, 1092, 1011, 908 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{24}BrClNO_2^+$ ($[M+H]^+$) 532.0673, Found 572.0674.

Crystallographic Structure Determination:

Recrystallization of 7: Recrystallization of **7** was performed by using H/Et solvent system at room temperature.

The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 153 K on a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on F^2 by using SHELXTL.[17] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to nitrogen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions and isotropic thermal parameters refined. The crystallographic data were summarized in the following table.

Table S1. Crystal Data and Structure Refinement for **7** (CCDC 772979).

Empirical formula	$C_{29}H_{23}BrClNO_2$	
Formula weight	532.84	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.1197(19) Å	α = 90°.
	b = 19.421(6) Å	β = 90°.
	c = 20.604(6) Å	γ = 90°.
Volume	2448.7(12) $Å^3$	
Z	4	
Density (calculated)	1.445 Mg/m^3	
Absorption coefficient	1.815 mm^{-1}	
F(000)	1088	
Crystal size	0.30 x 0.30 x 0.10 mm^3	
Theta range for data collection	1.44 to 28.35°.	
Index ranges	-8<=h<=6, -25<=k<=25, -25<=l<=27	
Reflections collected	18102	
Independent reflections	6067 [R(int) = 0.0528]	
Completeness to theta = 28.35°	99.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.8393 and 0.6120	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6067 / 0 / 308	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R_1 = 0.0438, wR_2 = 0.0915	
R indices (all data)	R_1 = 0.0645, wR_2 = 0.1106	
Absolute structure parameter	-0.002(9)	
Largest diff. peak and hole	0.497 and -0.320 e.$Å^{-3}$	

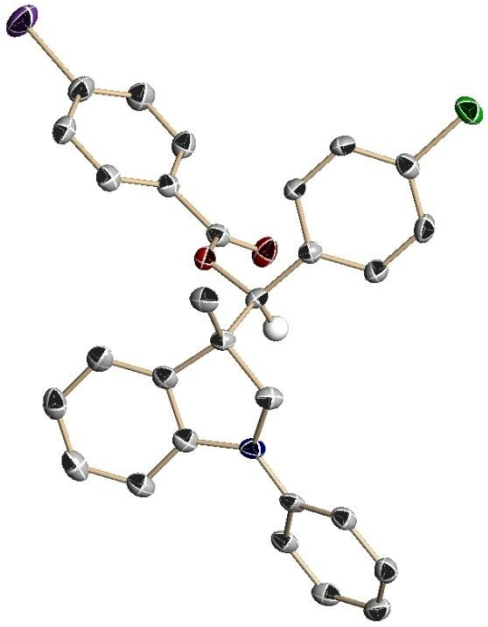


Figure S1. Molecular structure of **7**. White = hydrogen, blue = nitrogen, red = oxygen, green = chlorine, black = carbon, purple = bromine. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level.

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