Strategy for Vinylogous Nitronate Generation for Highly Selective Aza-Henry Reactions Catalyzed by Chiral Ammonium Betaine

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ビニロガスニトロナートの生成に立脚した
キラルアンモニウムベタインを触媒とする
高選択的アザ Henry 反応

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Chapter 1

General Introduction and Summary

1.1 Asymmetric Synthesis of Nitro Compounds[1]

Nitro compounds have been recognized as important building blocks which provide valuable functionalized organic molecules because nitro group could be transformed to various functional group. Nef reaction, reduction, or nucleophilic substitution reaction are used for this purpose.

Therefore nitro compounds have been seen as an important intermediate to synthesize mutifunctionalized complex organic compounds. In this regards, many researchers have focused on development of synthetic methodology for chiral nitro compounds. Among them, Henry reaction, aza-Henry reaction and Michael addition to nitroolefins are the most widely used examples.

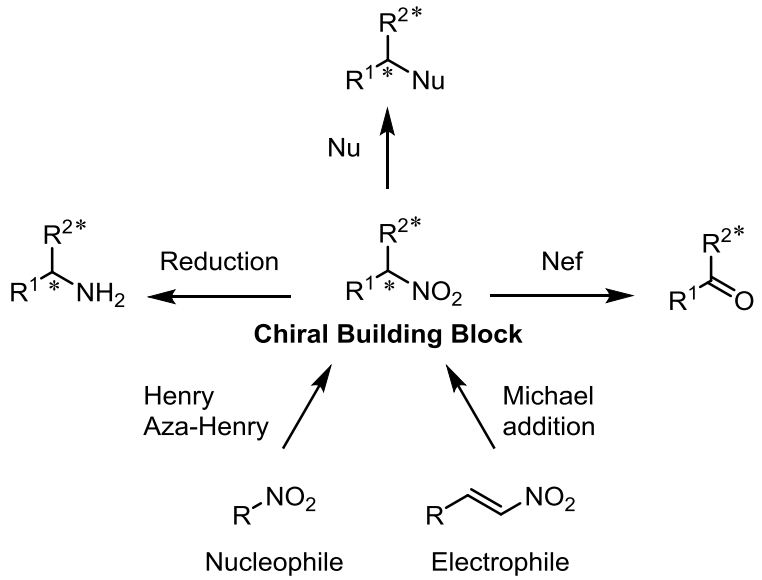
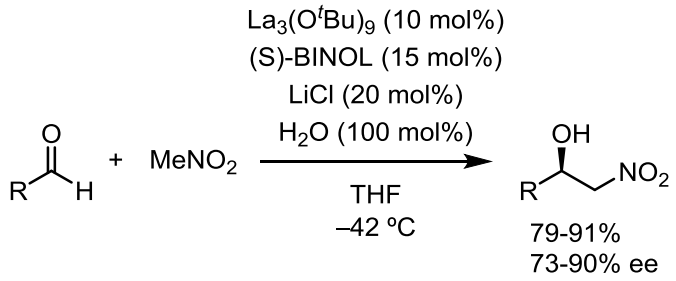


Figure 1. Chiral Nitro Compounds as Building Block[1]

1.1.1 Henry Reaction

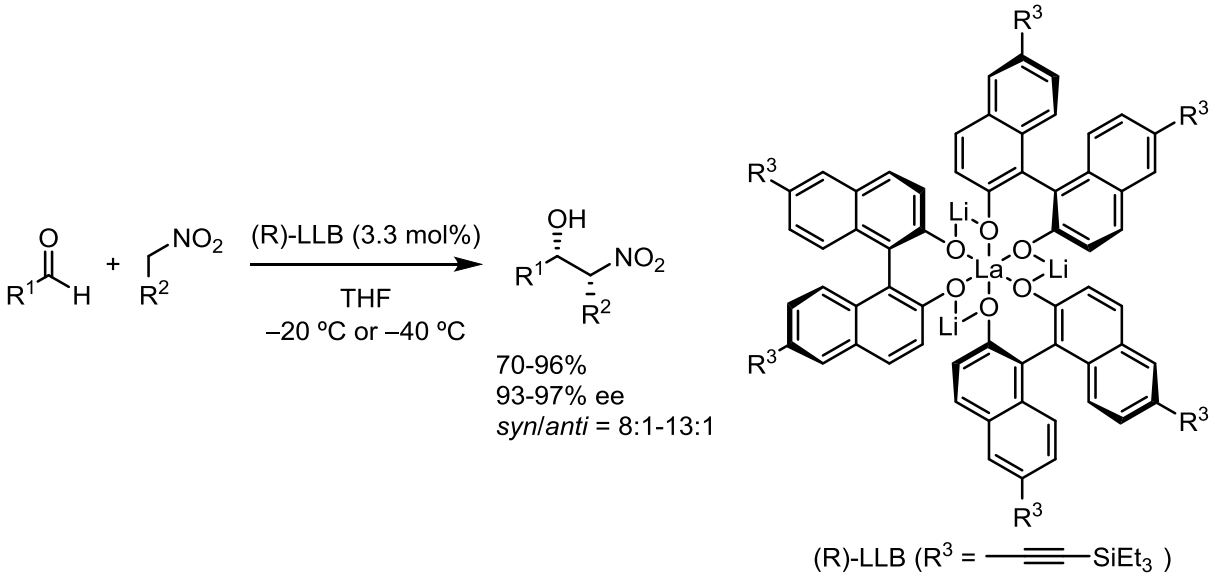
Henry reaction, first discovered in 1895,[2] is one of the classical named C-C bond forming reaction. Henry reaction has been regarded as a efficient method for the synthesis of 1,2-nitroalcohol, which could be a versatile intermediate to provide bioactive compounds such as β-amino alcohols and α-hydroxy carboxylic acids.[1,3] According to importance of reaction product, Henry reaction have been attracted great attention.[3]

In 1992, Shibasaki and co-workers reported first enantioselective catalytic Henry reaction. In their seminal work, it was found that LLB, which is optically active La-alkoxide generated from $La_3(OtBu)_9$, chiral binaphthol and LiCl can promote could promote Henry reaction with good enantioselectivity(Scheme 1).[4a]



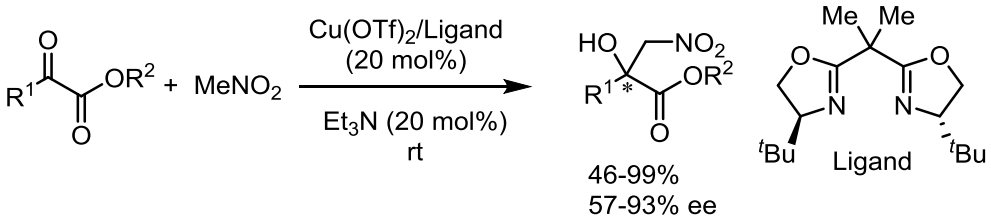
Scheme 1. LLB Catalyzed Stereoselective Henry Reaction[4a]

Owing to their continual effort to expand scope of reaction using this catalytic system, the same group reported Henry reaction of various nitroalkanes(Scheme 2).[4c] It is found that the Introduction of two TES-substituted alkynyl groups to 6- and 6'- position of binaphthol was important. Reaction products were obtained in not only high enantioselectivity but excellent *syn*-selectivity.



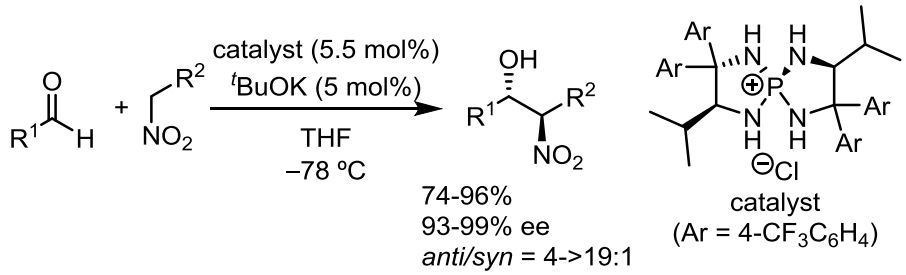
Scheme 2. Substituted LLB Catalyzed Stereoselective Henry Reaction of various nitroalkanes[4c]

Moreover, chiral Cu-bis(oxazoline) system could also catalyze Henry reaction. In 2002, Jørgensen group achieved enantioselective Henry reaction of nitromethanes with various α-keto ester using bis(oxazoline)-complex with triethylamine(Scheme 3).[5] This reaction demonstrated for the first time that ketone, which has lower reactivity than aldehydes, could react in catalytic stereoselective Henry reaction.



Scheme 3. Cu-BOX Complex Catalyzed Enantioselective Henry Reaction with Ketoesters[5]

Chiral organocatalyst could also catalyze Henry reaction. In 1994, Najera et al. revealed first organocatalytic enantioselective Henry reaction using chiral guanidine.[6] Although enantioselectivity is not high(up to 54% ee), this report demonstrated the possibility of asymmetric Henry reaction catalyzed by small organic molecules. In 2007, Ooi et al. reported highly stereoselective Henry reaction catalyzed by chiral tetraaminophosphonium salt(Scheme 4).[7] This is the first example to provide Henry adduct with excellent *anti*-selectivity.



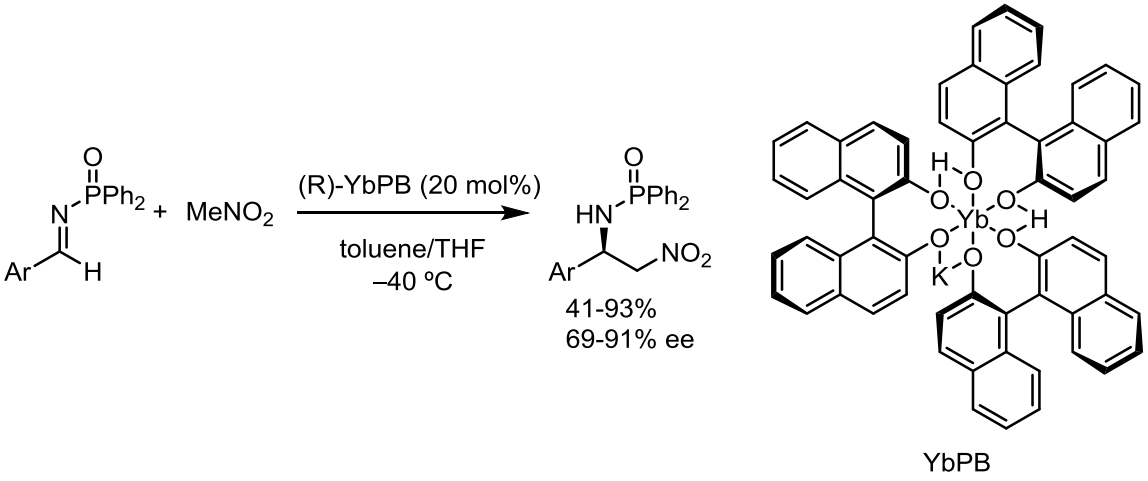
Scheme 4. Anti-selective Enantioselective Henry Reaction[7]

Still Henry reaction continues to attract attention to develop new methodologies. There are much more methodologies using metal- or organocatalyst which provide Henry adduct in high enantio- and diastereoselectivity[1a,3]. In the past, many reaction system could be applied only to the reaction of nitromethane. By contrast, recently many reaction using nitroalkanes other than nitromethane have been reported.

1.1.2 Aza-Henry Reaction

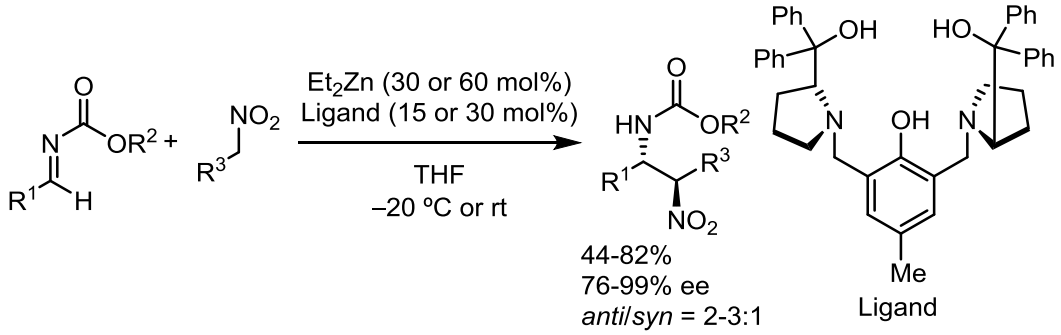
Aza-Henry reaction has also been regarded as a powerful and useful method in organic synthesis. This reaction provide β-nitroamines which could be transformed to 1,2-vicinal diamine or α-amino acids.[1,8]

In many cases, catalytic system which promoted Henry reaction could also have been applied to aza-Henry reaction. For example, first catalytic asymmetric Aza-Henry reaction was achived by Shibasaki's heterometallic complexes(Scheme 5).[9] In contrast to Henry reaction, YbPB, prepared from $Yb(O^iPr)_3$, KO^tBu and chiral binahthol was the best catalyst for stereoselective aza-Henry reaction. Shibasaki and co-workers surveyed composition of the catalyst and it is found that $Yb(O^iPr)_3$: KO^tBu:binaphthol = 1:1:3 was the best composition.



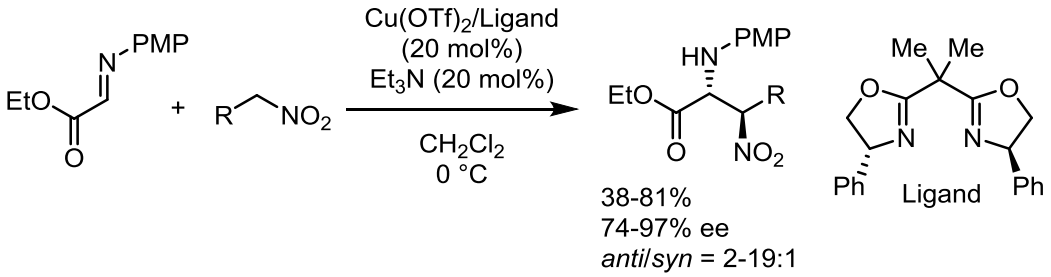
Scheme 5. YbPB Catalyzed Enantioselective Aza-Henry Reaction[9]

Trost group have also reported stereoselective catalytic aza-Henry reactions to carbamate-protected imines using dinuclear Zn catalyst(Scheme 6).[10] This catalytic system could be applied to the reaction of several nitroalkane to provide aza-Henry adduct with low diastereoselectivity. It is noteworthy that Trost's Zinc dinuclear catalyst could catalyze aza-Henry reaction of α,β-unsaturated imines.



Scheme 6. Zinc Complex Catalyzed Stereoselective Aza-Henry Reaction[10]

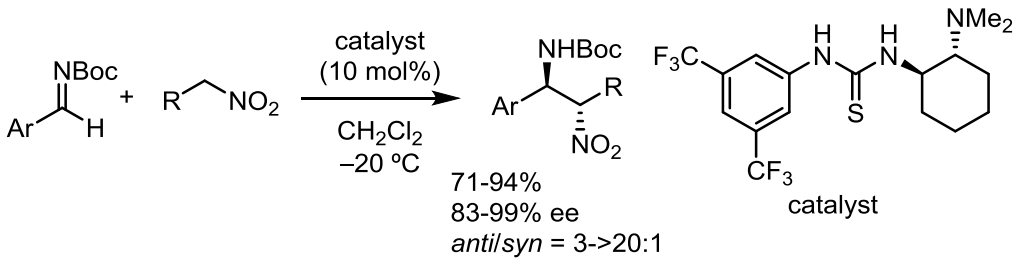
In 2001, Jørgensen et al. demonstrated their Cu complex could coordinated to α-imino esters. First they reported Cu-catalyzed aza-Henry reaction of trimethylsilyl nitronate[11a]. Although this reaction could proceeded without base, very low temperature was needed. Following this report, Jørgensen group developed asymmetric aza-Henry reaction of nitroalkanes to α-imino esters catalyzed by Cu complex. It is noted that this reaction could be performed under ambient temperature with good stereoselectivity(Scheme 7).[11b]



Scheme 7. Cu-BOX Complex Catalyzed Stereoselective Aza-Henry Reaction with α-Imino Esters[11b]

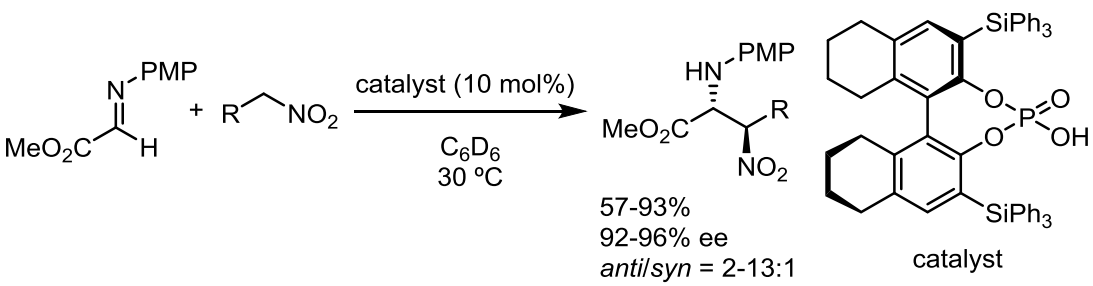
As is the case in Henry reaction, a number of highly stereoselective organocatalytic aza-Henry reaction have been investigated.

The first aza-Henry reaction catalyzed by organocatalyst was reported by Takemoto and co-workers in 2004. It had been already demonstrated that bifunctional thiourea catalyst with tertially amino group, which is generally called Takemoto catalyst, could promote asymmetric Michael addition to nitroolefins.[12] Based on this observation, they applied this catalytic system to aza-Henry reaction to N-diphenylphosphinoyl imines. Subsequently, same group reported that stereoselectivity was increased by using N-Boc aldimines instead(Scheme 8).[13]



Scheme 8. Stereoselective Aza-Henry Reaction Catalyzed by Takemoto Catalyst[13]

It is also appeared that Brønsted acid could catalyze aza-Henry reaction. Rueping reported that chiral phosphoric acid could activate nitro-mannich reaction (Scheme 9).[14] This is the first organocatalytic aza-Henry reaction using α-Imino Esters. It is also supposed that corresponding diamino acid esters could be important synthetic blocks.

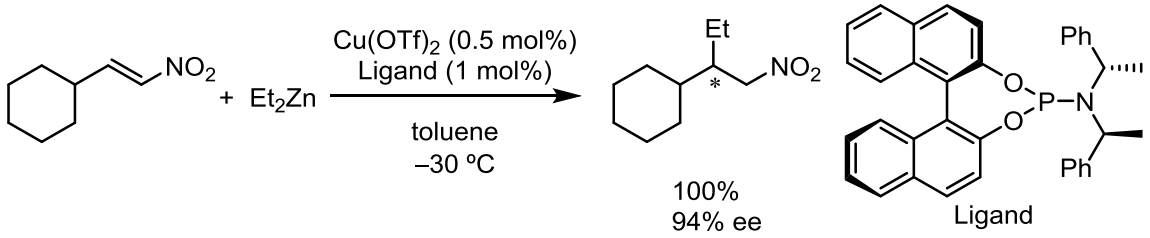


Scheme 9. Chiral Phosphoric Acid Catalyzed Stereoselective Aza-Henry Reaction with α-Imino Esters[14]

These catalytic methodologies described above prompted many researchers to develop novel asymmetric aza-Henry reaction to improve efficiency, stereoselectivity with wide substrate scope. Consequently various asymmetric reaction have still been developed.[8]

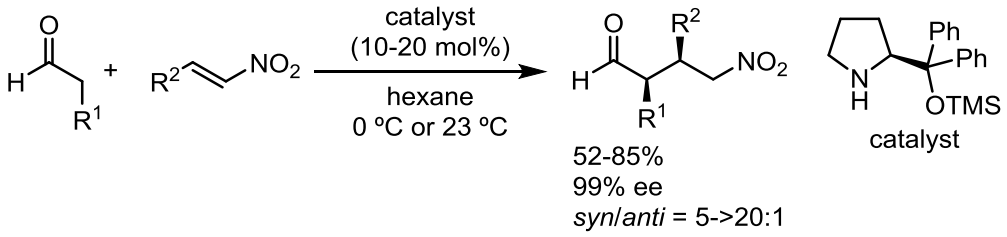
1.1.3 Michael Addition to Nitroolefins

Asymmetric conjugate addition to nitoolefins have been recognized as a powerful method to construct enantioenriched nitro compounds. Actually, many efficient catalytic systems have been reported.[15] Especially, numerous efforts have been devoted to the development of conjugate additions of dialkylzinc to nitroolefins. In 1995, Seebach et al. reported highly stereoselective conjugate addition using stoichiometric Ti-TADDOLate with up to 90% ee.[16] And then, in 1998, Sewald group discovered asymmetric conjugate addition to nitroolefins catalyzed by chiral Cu complex(up to 86% ee).[17] Afterward Alexakis and co-workers improved stereoselectivity(Scheme 10)[18]. It is also noted that this reaction system needs only 0.5 mol% Cu salt and 1 mol% ligand.



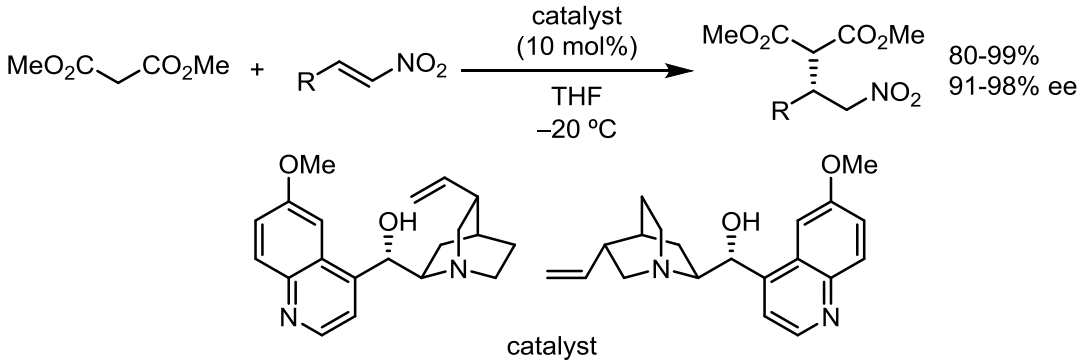
Scheme 10. Cu-Catalyzed Asymmetric Conjugate Addition to Nitroolefin[18]

Numerous organocatalytic processes have also been investigated. Among them, first proline-type catalyst gained much attention. Barbas III et al. reported asymmetric conjugate addition to nitroalkenes using chiral pyrrolidine catalyst in good enantioselectivity(up to 91% ee).[19] This report prompted other researchers to investigate greater reaction using pyrrolidine derivatives. In 2005, Hayashi and co-workers achieved highly stereoselective Michael reaction of aldehydes and nitroalkenes(Scheme 11)[20]. According to their report, introduction of a siloxy group improved catalyst activity due to increased solubility.



Scheme 11. Asymmetric Conjugate Addition of Aldehydes to Nitroolefins[20]

It is known that *cinchona* alkaloids derivatives could function as a bifunctinal catalyst. Alcohol or phenol moiety of alkaloids could work as an acid to activate electrophile and tertially amino group interact nucleophile. Deng et al. realized highly enantioselective enantioselective asymmetric conjugate addition to nitroolefins under the catalysis of quinidine or quinine(Scheme 12).[21] Following this work, Deng group have reported several related asymmetric Michael additions.[22]



Scheme 12. Asymmetric Conjugate Addition of Malonates to Nitroolefins[21]

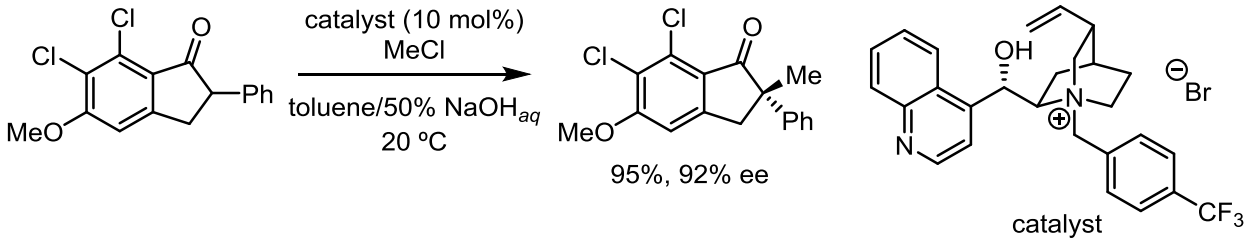
In this section the author introduced leading examples of asymmetric conjugate addition to nitroolefins. Nitroolefins have been regarded as the most highly reactive Michael acceptor due to its electronic property. Moreover, nitroolefins are often described “synthetic chameleon” due to its utility as synthetic synthon.[23] Therefore many researchers focused their attention on development of reaction using nitroolefins and a number of catalytic reaction with various nucleophile other than described here have been known.[1a,14]

1.2 Chiral Ammonium Salts

Chiral quaternary ammonium salts have been recognized as catalysts to promote stereoselective bond forming reactions. Chiral quaternary ammonium salts are very unique catalysts to control reactive anionic intermediate and attract great interest.

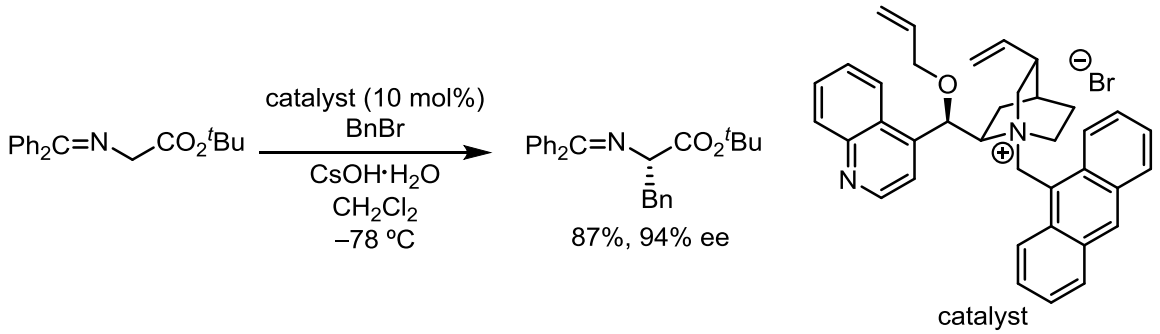
1.2.1. Pioneering Study on Chiral Ammonium Salts as phase-transfer catalysts

A number of reaction using chiral ammonium salts as a phase-transfer catalysts have been developed.[24] In 1984, the pioneering study was reported by Merck research group. In this report, a cinchoninium salt was used as a phase-transfer catalyst to promote asymmetric methylation reaction of indanone derivative(Scheme 13).[25]

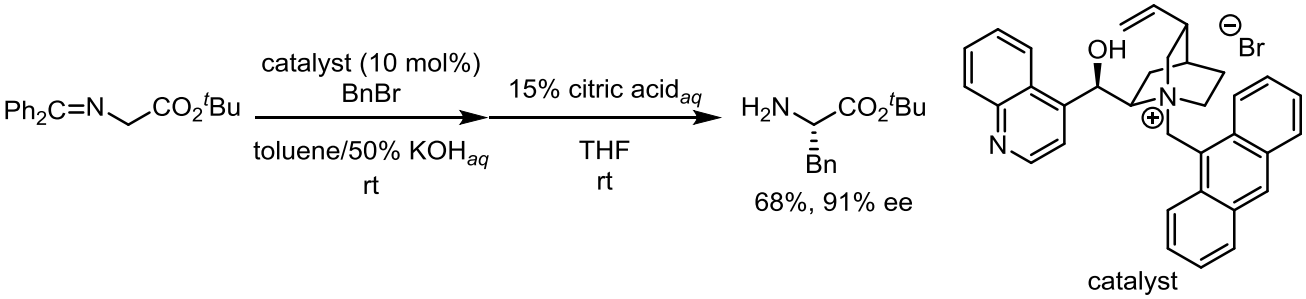


Scheme 13. Asymmetric Methylation Catalyzed by a Cinchoninium Salt[25]

Afterwards, several reactions catalyzed by ammonium salts derived from *cinchona* alkaloids have been developed. In 1997, Corey group[26] and Lygo group[27] independently developed asymmetric phase-transfer alkylation of Schiff base to synthesize α-amino acids(Scheme 14,15).

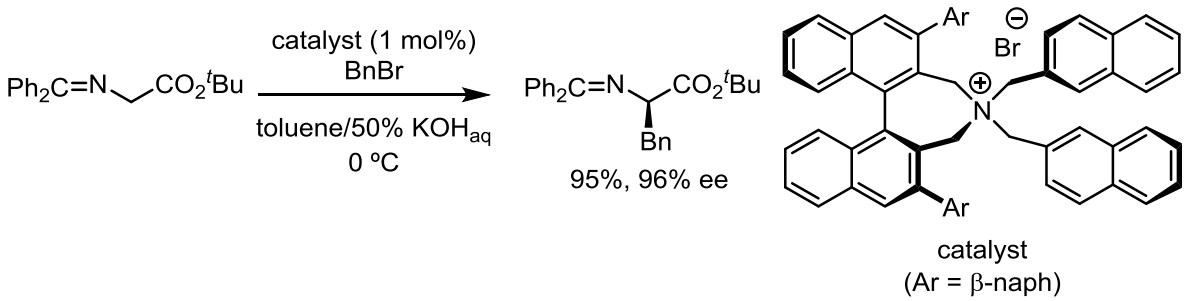


Scheme 14. Asymmetric Alkylation of Schiff Base by Corey Group[26]



Scheme 15. Asymmetric Alkylation of Schiff Base by Lygo group[27]

In 1999, Maruoka and co-workers developed a novel *N*-spiro chiral ammonium salt as a catalyst for asymmetric phase-transfer benzylation reaction of Schiff base(Scheme 16).[28] In contrast to previous catalysts, this catalyst could be derived from binaphthol, which is not natural alkaloid derivatives. Maruoka et al suggested that BINOL derivatives could be modified easily unlike in case with of *cinchona* alkaloid derivatives. This catalytic system realized much lower catalyst loading with high stereoselectivity.



Scheme 16. Asymmetric Alkylation of Schiff Base by Maruoka Group[28]

1.2.2. General Mechanism of Reaction Catalyzed by Phase-Transfer Catalysts

Phase-transfer reaction catalyzed by chiral quaternary ammonium salts are supposed to follow interfacial mechanism(Figure 2).[29] First of all, base(MOH) deprotonate an active methane, methylene or methine in interfacial area to form corresponding metal enolate(M^+C^-). And then carbanion species are extracted from interface into organic phase due to the action of chiral ammonium ion(Q^+X^-). The ammonium carbanion(Q^+C^-) reacts with electrophile(RX) to provide reaction product in organic phase.

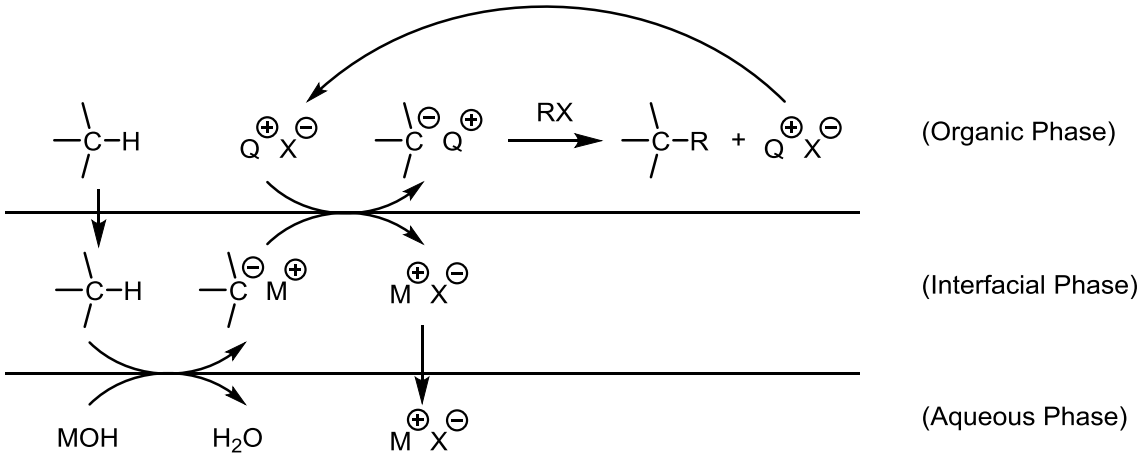
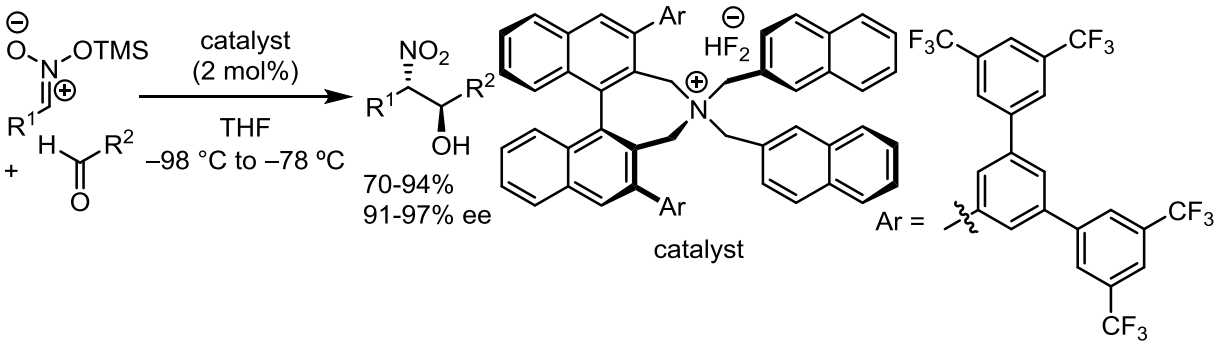


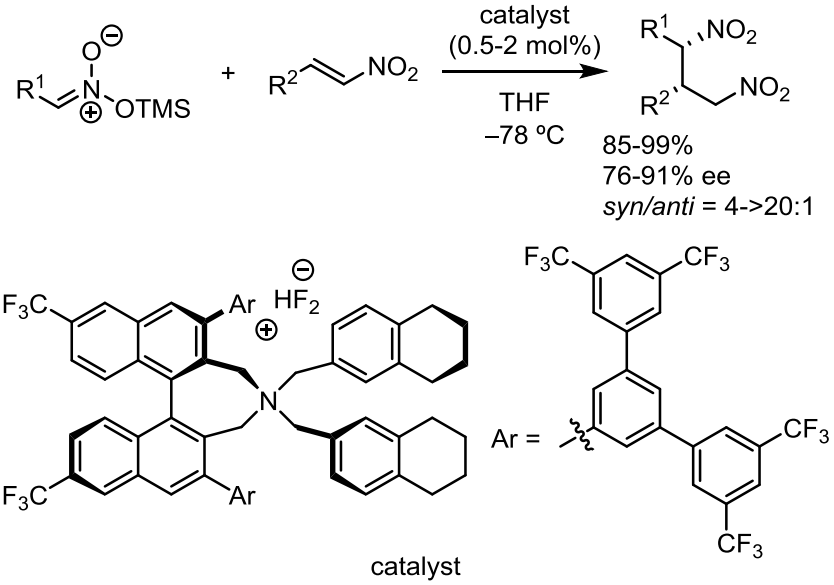
Figure 2. Proposed Interfacial Mechanism of Phase-Transfer Catalysts[29]

1.2.3. Chiral Ammonium Salts with Functionalized Anion

In many cases, studies on chiral ammonium salts have focused on function of ammonium cation. As described in section **1.2.2.**, anion of catalysts are not involved in bond formation step because anion are transferred outside of reaction systems via ion-exchange process. Therefore it is very difficult to develop chiral ammonium salts with functionalized anion as a phase-transfer catalyst. One of the successful examples is reaction catalyzed by chiral ammonium fluoride or bifluorides[30]. For example, Maruoka et al. reported asymmetric Henry reaction and Michael addition of silyl nitronates catalyzed by quaternary ammonium bifluoride(Scheme 17, 18).[31,32] In these reactions, first anion moiety of catalyst, fluoride or bifluoride anion attack to silyl nitronate to form corresponding ammonium nitronate.

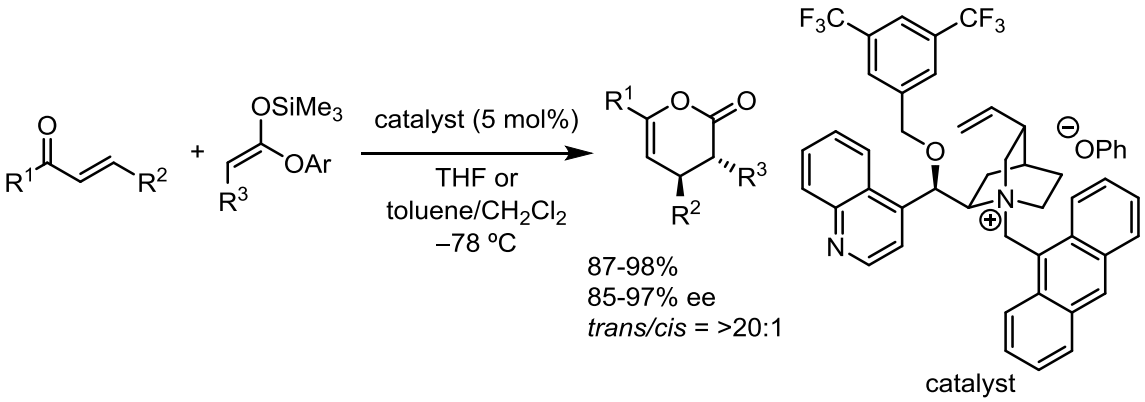


Scheme 17. Asymmetric Henry Reaction of Silyl Nitronates[31]



Scheme 18. Asymmetric Henry Reaction of Silyl Nitronates[32]

In addition, Mukaiyama developed chiral ammonium phenoxide catalyzed asymmetric reactions of silyl enolates(Scheme 19).[33] Along with the reaction of ammonium fluoride or bifluorides, in this reaction, anion moiety of the catalyst could function as a lewis base to activate silyl-protected nucleophile. Nucleophillic attack of phenoxide anion could give ammonium enolate intermediate.



Scheme 19. Asymmetric Aldol Reaction of Silyl Enolates[33]

Reactions described in this section demonstrated that anion moiety of ammonium salts could function as an activator to provide reactive nucleophilic ion pair.

1.2.4. Chiral Ammonium Betaine

As described above, numerous studies on intermolecular chiral ammonium salts have been reported. On the other hand, our research group focused on intramolecular chiral ammonium salts, which can be called chiral ammonium betaine.

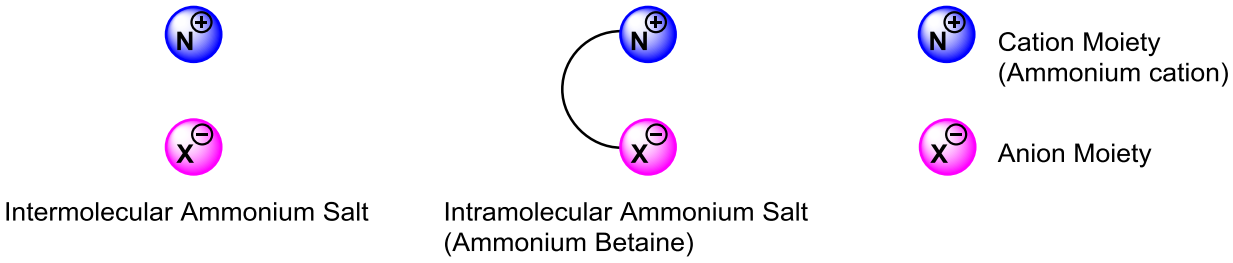
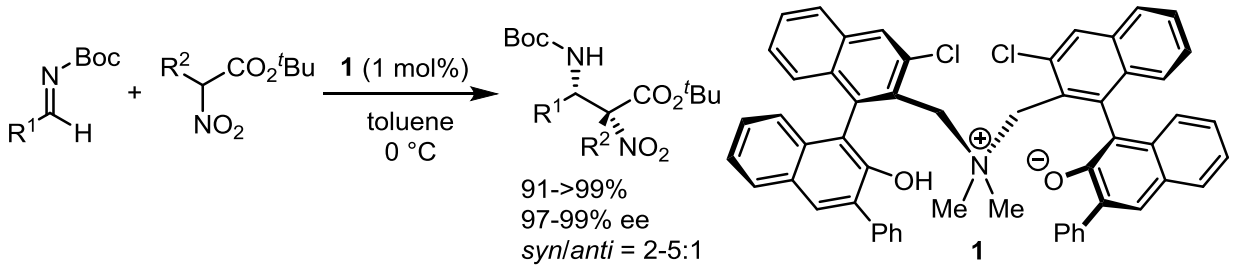


Figure 3. Structural Difference between Intermolecular Ammonium Salt and Ammonium Betaine

In contrast with intermolecular ammonium salts, ammonium betaine enable anion moiety to be involved in bond forming process. Since ammonium betaine has its cation moiety and anion moiety in the same molecules anion of the catalyst would not proceed ion-exchange process.

Based on this assumption, our research group designed chiral ammonium betaine **1**. It is found that chiral ammonium betaine could function as an organic base catalyst to promote highly stereoselective Mannich-type reaction(Scheme 20).[34]



Scheme 20. Asymmetric Mannich-Type Reaction Catalyzed by Chiral Ammonium Betaine[34]

In this reaction, first ammonium betaine deprotonate nucleophilic reagent and ammonium cation form ion pair with corresponding anionic nucleophile. At the same time, conjugate acid of anion moiety, aryl hydroxide is located close to ammonium cation. Therefore nucleophilic anion is precisely controlled by hydrogen bond and ionic interaction. In the case of intermolecular ammonium salt, after the deprotonation, conjugate acid of anion is delivered outside of the reaction system(Figure 4).

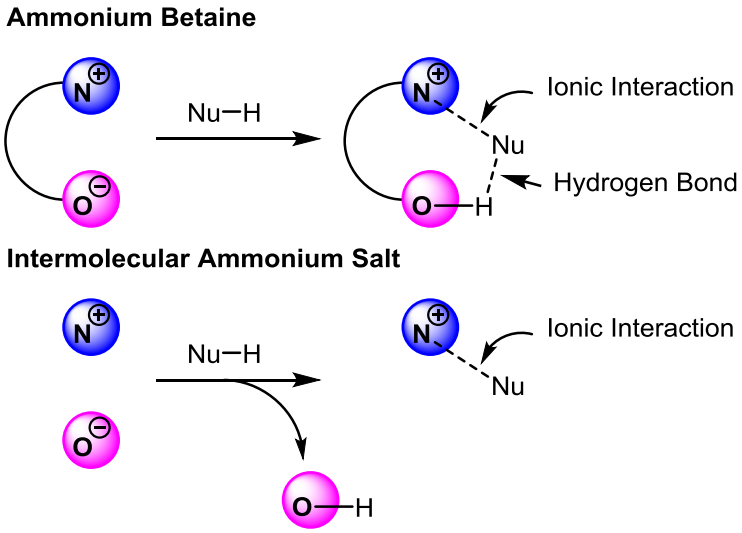
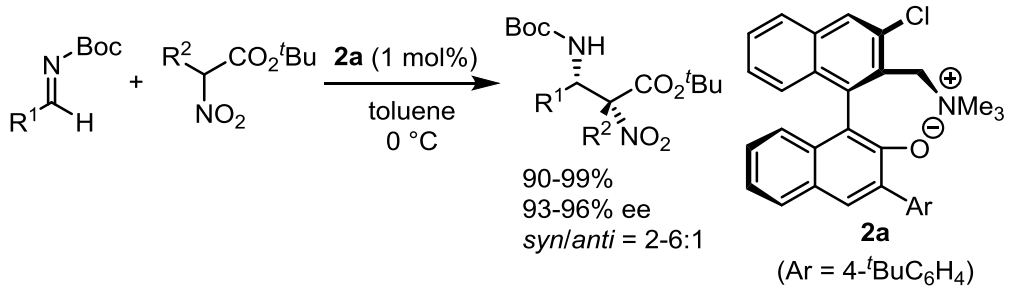


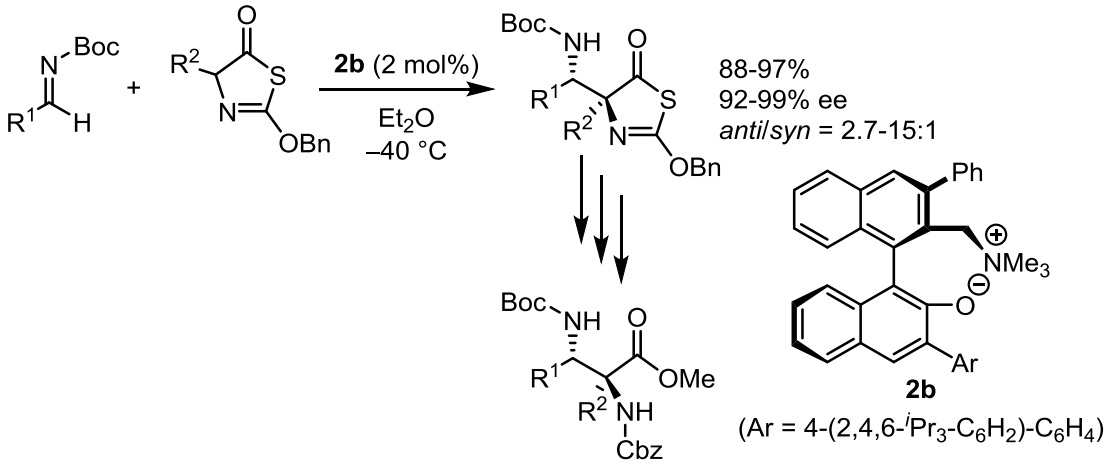
Figure 4. Concept of Ammonium Betaines as a Bifunctional Catalyst

Following this report, our group discovered that simplified C_1-symmetric chiral quartenary ammonium betaines **2** could also function as bifunctional organic base catalysts. It is demonstrated that reaction catalyzed by this new ammonium betaine **2** provide adduct in similar efficiency and stereoselectivity to the reaction catalyzed by **1**(Scheme 21).[35] This new ammonium betaine have much advantage from the aspect of catalyst synthesis. This catalyst could be modified more easily.



Scheme 21. Asymmetric Mannich-Type Reaction Catalyzed by Simplified Chiral Ammonium Betaine[35]

Moreover, asymmetric Mannich-type reaction of thiazol-5(4H)-one catalyzed by ammonium betaine **2** was reported(Scheme 22).[36] Reaction adduct were obtained with high enantio- and diastereoselectivity. In addition, reaction product could be derivatized to α,β-diamino acid derivatives.



Scheme 22. Asymmetric Mannich-Type Reaction Catalyzed by Simplified Chiral Ammonium Betaine[36]

Moreover, Aryl oxides, anionic part of chiral ammonium betaine, have Lewis basicity. Therefore chiral ammonium betaine is also expected to work as a chiral nucleophilic catalyst(Figure 5).

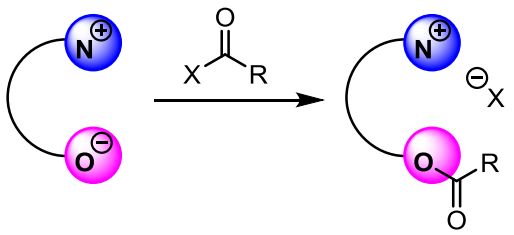
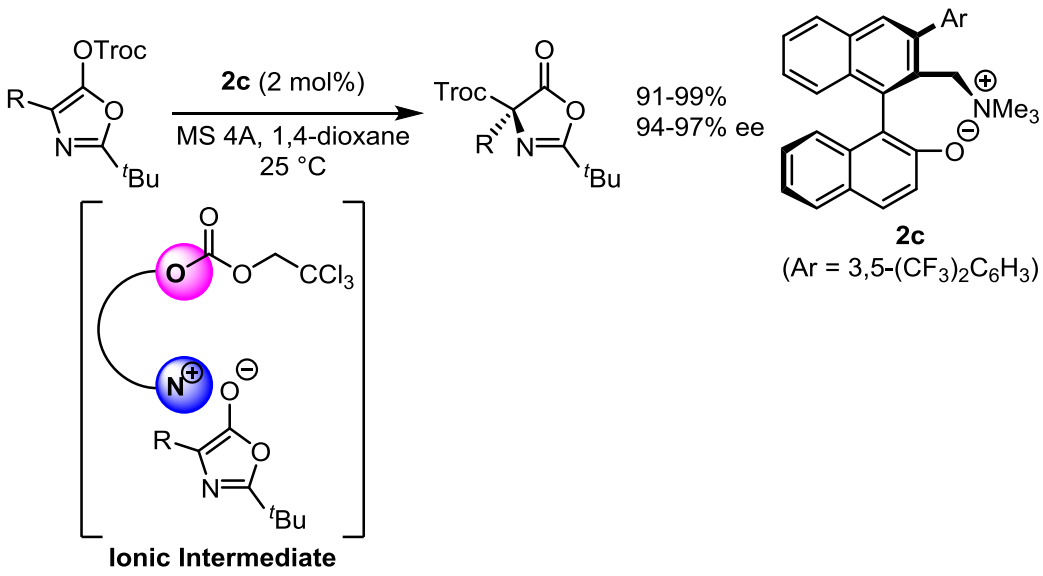


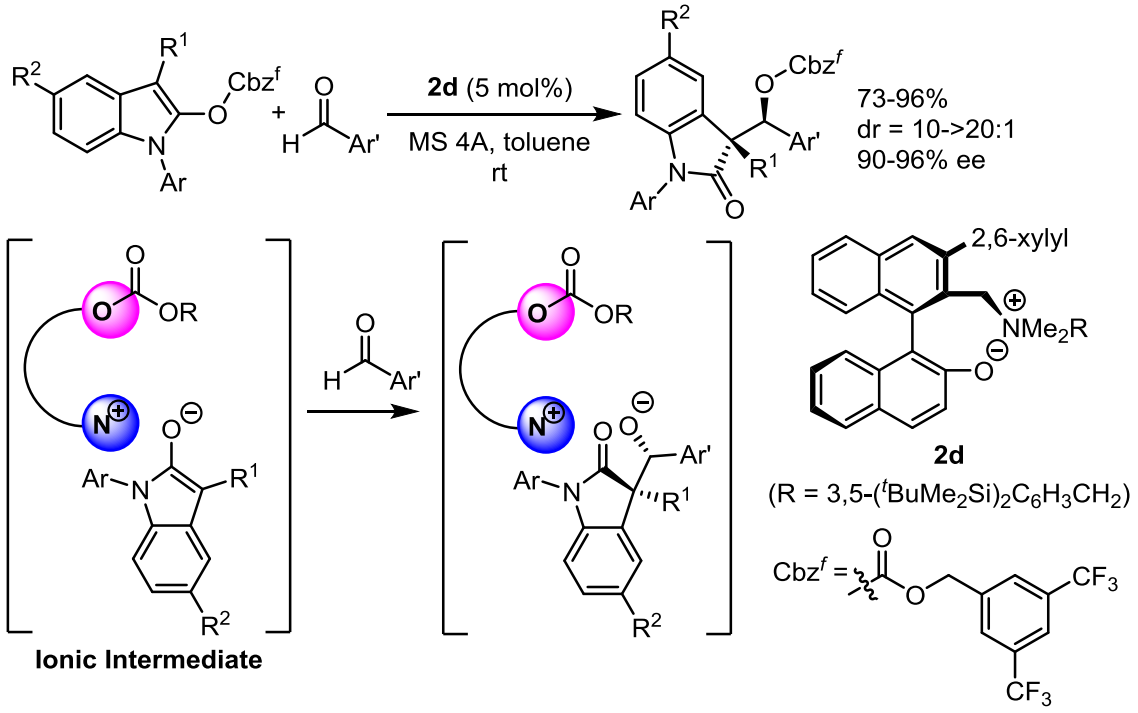
Figure 5. Concept of Ammonium Betaines as an Ionic Nucleophilic Catalyst

Based on this assumption, our research group developed asymmetric Steglich reaction(Scheme 23).[37] In this report, it is discovered that the enantioselectivity depended on substrate concentration to the catalyst. Under low concentration, nucleophilic anion of corresponding ionic intermediate could react with acyl moiety of the intermediate(pseudo intramolecular reaction). By contrast, under high concentration, anion of intermediate could also react with unreacted substrate.



Scheme 23. Asymmetric Steglich Reaction Catalyzed by Chiral Ammonium Betaine[37]

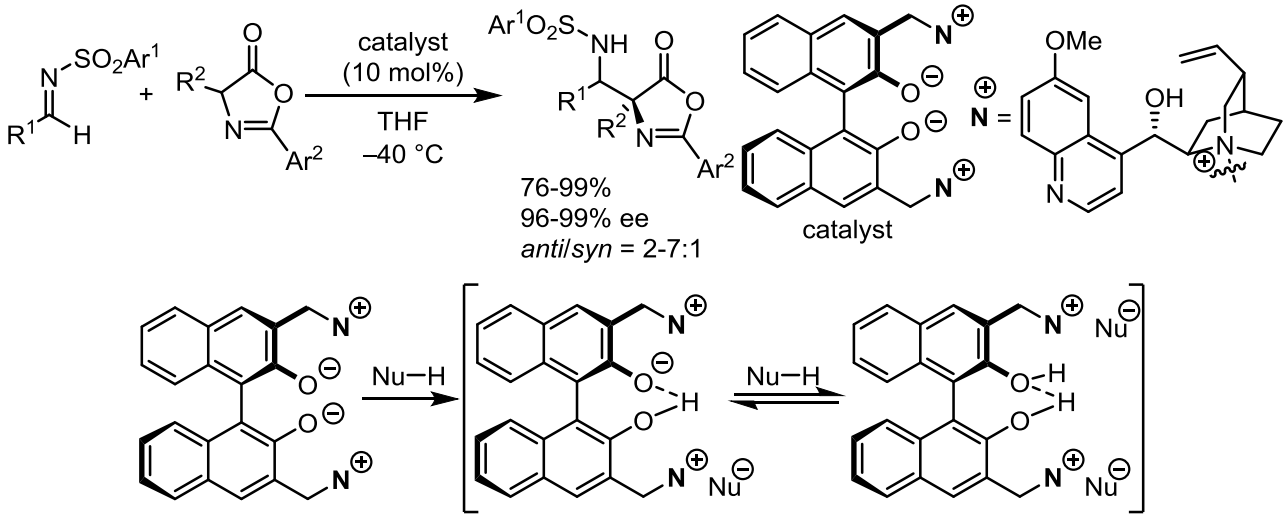
The result of the Steglich reaction indicated that corresponding ionic intermediate could react with various electrophile. Based on this assumption, our research group developed aldol reaction of vinylic carbonates using chiral ammonium betaine(Scheme 24).[38] In a similar fashion to the steglich reaction, ionic intermediate was formed by the nucleophilic attack of the catalyst. The corresponding intermediate react with aldehydes to provide another intermediate.



Scheme 24. Asymmetric Aldol Reaction of Vinylic Carbonates Catalyzed by Chiral Ammonium Betaine[38]

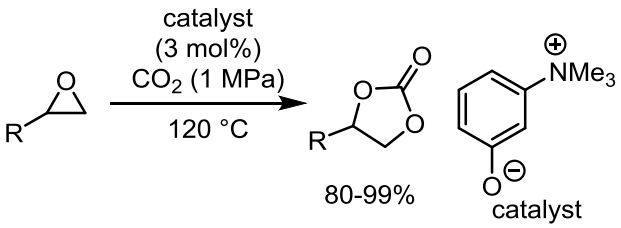
1.2.5. Other Ammonium Betaines as organic catalyst

Recently several research groups also focus their attention on ammonium betaines. Gong et al. developed bis(betaine) as asymmetric base catalyst for Mannich reaction of azlactones(Scheme 25).[39] Gong supposed that bis(betaine) would deprotonate to form ion pair with anionic nucleophile. They suggested that coressponding ion pair could activate electrophile due to its acidity through a hydrogen-bonding interaction.

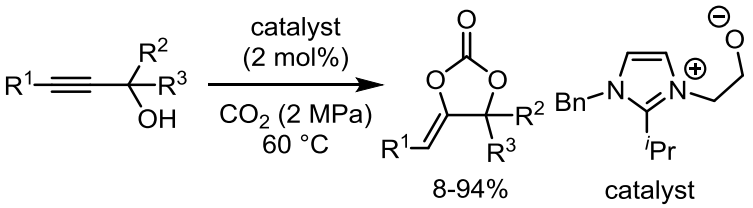


Scheme 25. Asymmetric Mannich Reaction of Azlactones Catalyzed by Bis(Betaine)[39]

On the other hand, several groups respectively developed reaction using ammonium betaines(Scheme 26,27).[40, 41] In these reports, anion moiety of catalyst function as a lewis base. Nucleophilic attack of the catalyst to carbon dioxide to give corresponding ion pair, and then the ammonium carbonate react with substrates to provide desired adduct.

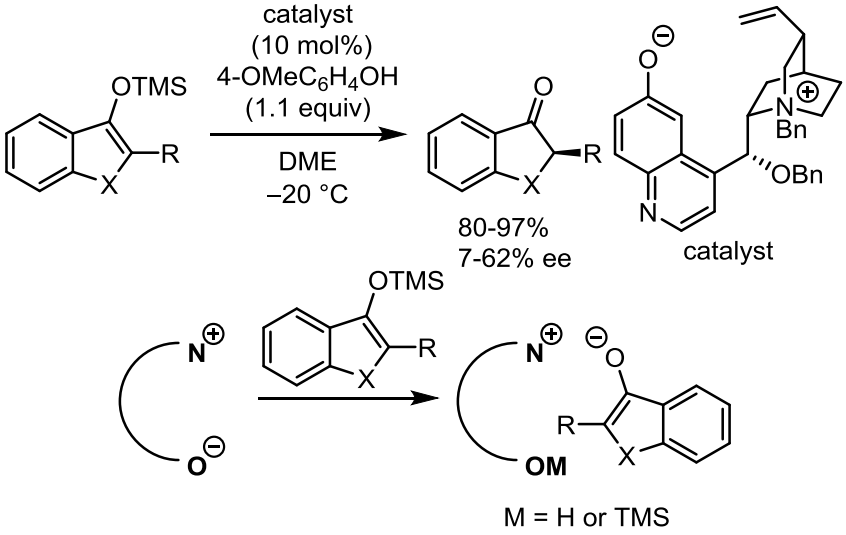


Scheme 26. Synthesis of Cyclic Carbonate Using Ammonium betaine[40]



Scheme 27. Synthesis of Cyclic Carbonate using Imidazolium Betaine[41]

Levacher et al. have reported asymmetric protonation of silyl enol ether catalyzed by Betaines derived from *cinchona* alkaloids(Scheme 28).[42] According to the report, aryloxide moiety of this catalyst could also function as a Lewis base. Levacher and co-workers assumed that corresponding enolate interact with ammonium cation, and then protonated by the aryl alcohol to provide desired product with modest stereoselectivity..



Scheme 28. Asymmetric Protonation of Silyl Enolates Catalyzed by Betaine Derived from *Cinchona* Alkaloid[42]

1.3 Nucleophilic Nitro Compounds which possesses alkene moiety

As described in section **1.1.**, a numerous asymmetric catalytic reaction using substrates which contain nitro functionality have been reported. On the other hand, olefin group could also be converted to other functional group such as reduction, oxidation, addition or various reaction catalyzed by transition metal(Figure 6). Therefore chiral nitro compounds possessing olefin functionality would also be most attractive building block for highly functionalized molecules.

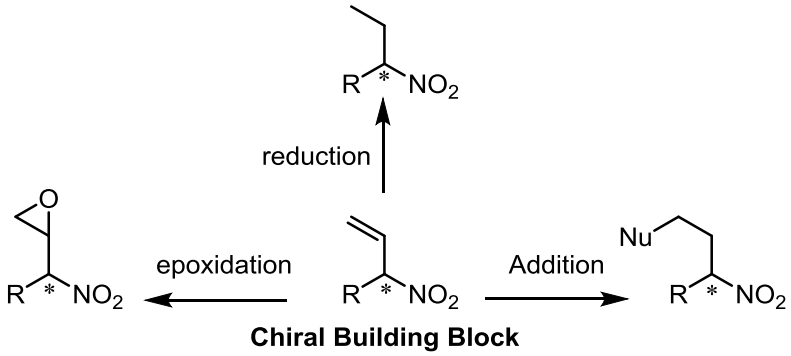
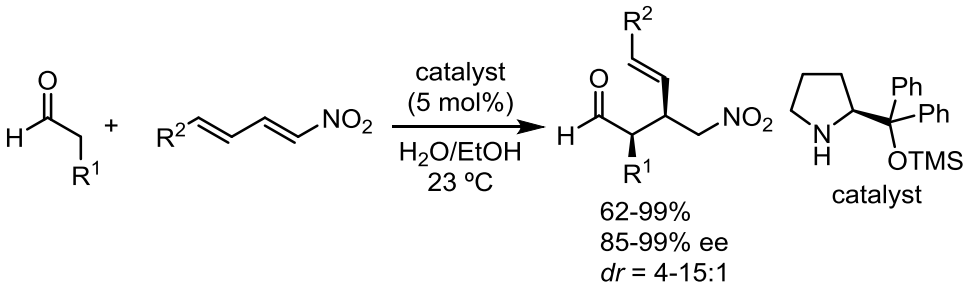


Figure 6. Reactivity of Chiral Nitro Compounds with alkene moiety

By the reasons described above, asymmetric conjugate reaction of nitrodiene would be a good reaction which constructs useful chiral building block. Actually, several research group developed catalytic asymmetric conjugated addition using nitrodienes[43]. For example, Alexakis et al. reported stereoselective conjugate addition of carbonyl compounds to nitrodienes catalyzed by proline-type catalyst(Scheme 29).[44]



Scheme 29. Asymmetric Conjugate addition to Nitrodienes[44]

1.3.1 Vinylogous Nitronate

On the other hand, the author focused his attention on vinylogous nitronates. This nucleophiles are expected to be generated from nitroalkanes with olefin under basic condition and provide chiral nitro compounds with alkene. However, approach to use this nucleophiles have been unexplored. By contrast, vinylogous enolates, which could be generated from α,β-unsaturated carbonyl compounds under basic conditions, are widely used as nucleophile for catalytic asymmetric reaction.[45] Actually, numerous methodologies have been reported with excellent stereoselectivity such as vinylogous aldol reaction by Terada group,[46] vinylogous Mannich reaction by Shibasaki group,[47] and vinylogous Mukaiyama-Michael reaction by Schnider group.[48] It is also noted that in many cases

reaction of vinylogous enolates provide γ-adduct selectively.

It is expected that vinylogous nitronates would also be generated from α,β-unsaturated nitroolefins based on observation on vinylogous enolates. However, in fact it is found that under basic condition γ-proton of α,β-unsaturated nitroolefins could not deprotonated to provide vinylogous nitronate(Figure 7).

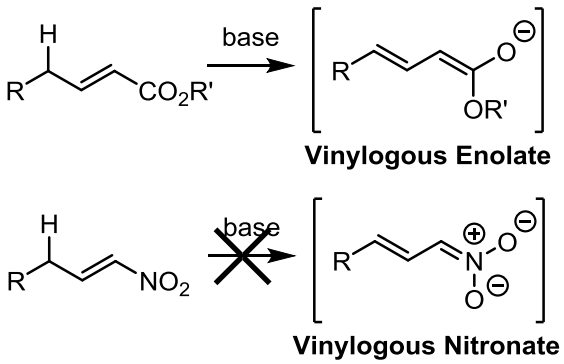


Figure 7. Trial to Vinylogous Nitronate Generation

1.3.2. New Strategy for vinylogous nitronate generation

As a solution to this, the author suggest new strategy for vinylogous nitronate generation. The author hypothesized that nitroolefin which possess substituent on cis position of nitro group could generate vinylogous nitronate under the presence of base due to steric repulsion between nitro group and substituent. It is assumed that this steric repulsion would be relieved with the generation of vinylogous nitronate(Figure 8). In other words, steric repulsion enabled the nitroolefins to be converted to vinylogous nitronate.

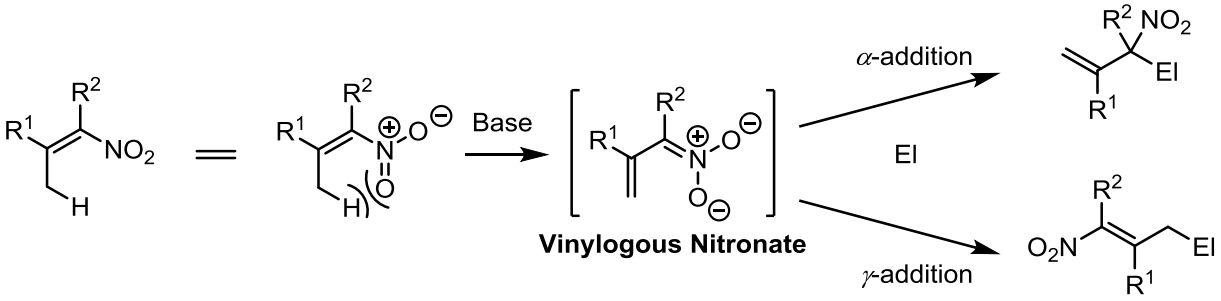
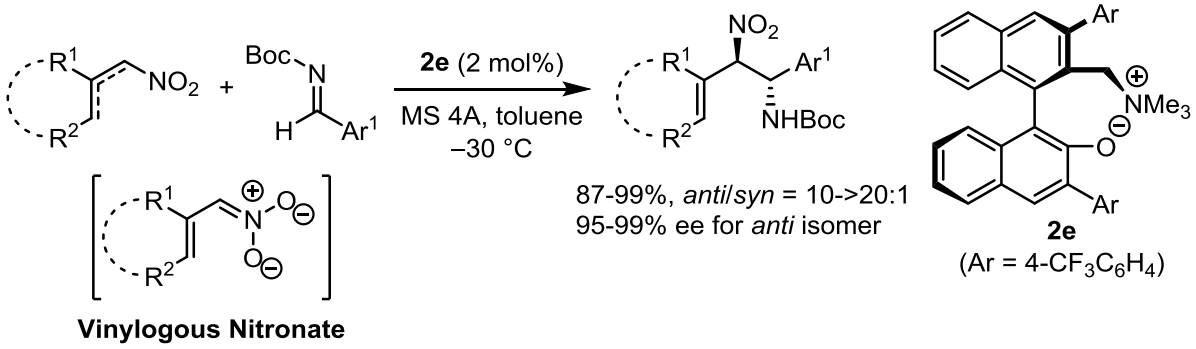


Figure 8. Working hypothesis of vinylogous nitronate generation

1.3.3. Nitroolefins as a Nucleophilic Component for Highly Stereoselective Aza-Henry Reaction under the Catalysis of Chiral Ammonium Betaines (Chapter 2)

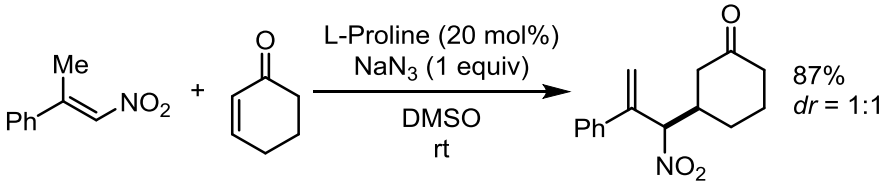
β,β-disubstituted nitroolefins were chosen as model precursor to provide vinylogous nitronates based on hypothesis described above. The author assumed that chiral ammonium betaine could deprotonate to generate vinylogous nitronates and the corresponding nucleophile would react with *N*-Boc aldimines to give aza-Henry adducts with high enantioselectivities. By optimization of the reaction condition and the catalyst structure, as expected, reaction products were obtained in excellent stereoselectivity with wide range of both substrates under

the catalysis of chiral ammonium betaine **2e**. It is also found that this reaction proceeded with >95% α-selectivity(Scheme 30).

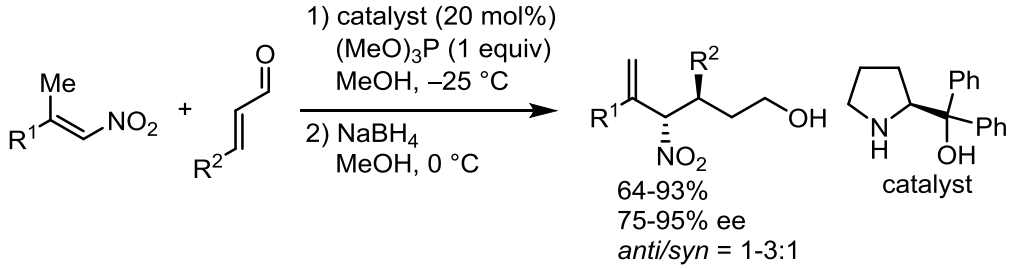


Scheme 30. Stereoselective Aza-Henry Reaction of β,β-Disubstituted Nitroolefins

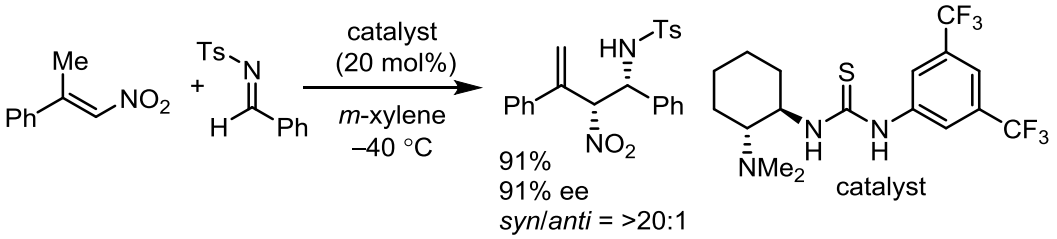
On the other hand, it is already known that same nitroolefins could be used as nucleophile under the catalysis of nucleophilic catalyst. In 2007, Shi and other group developed cross double-Michael reaction(Scheme 31).[49a] In general, reaction using nitroolefins catalyzed by Lewis base provide polymer of nitroolefins as byproduct. However this nitroolefin could proceeded in the desired reaction because the steric hinderance of β-substituent of nitroolefins inhibit polymerization of nitroolefins. Following this finding, several groups have developed reaction using β,β-disubstituted nitroolefins under the presence of nucleophilic catalyst(Scheme 32, 33, 34).[49]



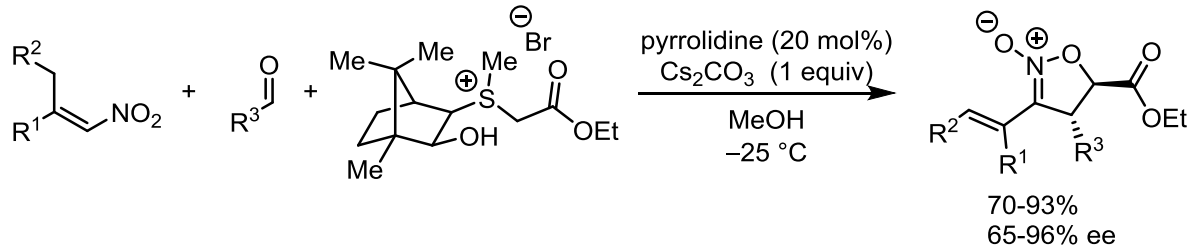
Scheme 31. Cross Double-Michael Reaction of β,β-Disubstituted Nitroolefins[49a]



Scheme 32. Enantioselective Cross Double-Michael Reaction of β,β-Disubstituted Nitroolefins[49b]

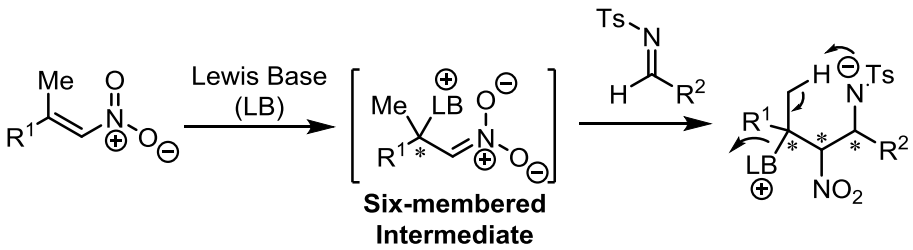


Scheme 33. Stereoselective Morita-Baylis-Hillman-type Reaction of β,β-Disubstituted Nitroolefins by Xu[49c]



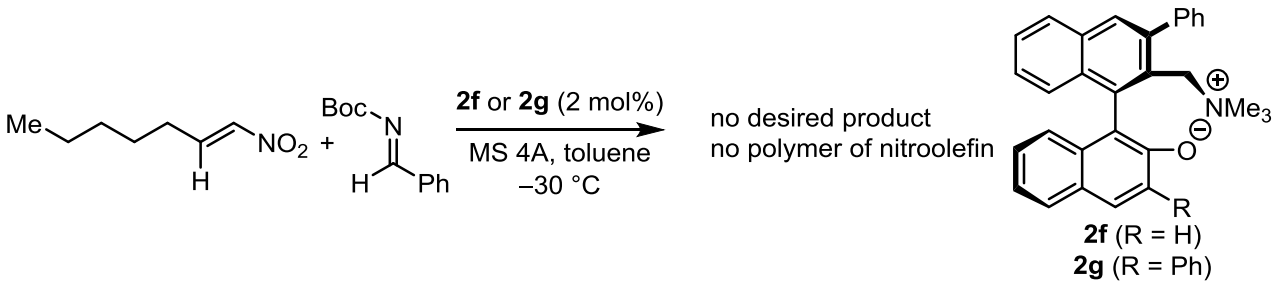
Scheme 34. One-Pot Asymmetric Synthesis of Isoxazoline-*N*-Oxide[49d]

Xu suggested in their report that reaction proceeded via six-membered intermediate and following intramolecular proton transfer would provide reaction product(Scheme 35).



Scheme 35. Reaction mechanism suggested by Xu[49c]

Therefore author conducted several control experiment to confirm that reaction proceeded via vinylogous nitronates. For example, it is found that reaction of β-monosubstituted nitroolefin provided neither reaction product nor polymer of nitroolefin(Scheme 36). This result indicated that ammonium betaine would not function as a nucleophilic catalyst. It is also demonstrated by this result that using β,β-disubstituted nitroolefins as substrates is necessary.



Scheme 36. Control Experiment

1.3.4. Vinylogy in Nitronates: Utilization of α-Aryl Conjugated Nitroolefins as a Nucleophile for Highly Stereoselective Aza-Henry Reaction (Chapter 3)

As described in section **1.3.3.**, reaction of β,β-disubstituted nitroolefins provided only α-adduct. The author became interested in regioselectivity of aza-Henry reaction using α,β-disubstituted nitroolefins. In analogy with β,β-disubstituted nitroolefins, α,β-disubstituted nitroolefins could generate vinylogous nitronate under the presence of chiral ammonium betaine due to steric hinderance of substrate(Figure 9). The α-substituent of the corresponding vinylogous nitronates are expected to affect regioselectivity.

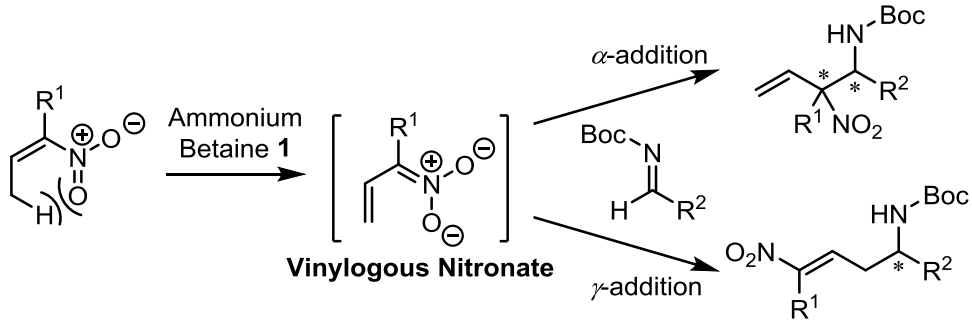
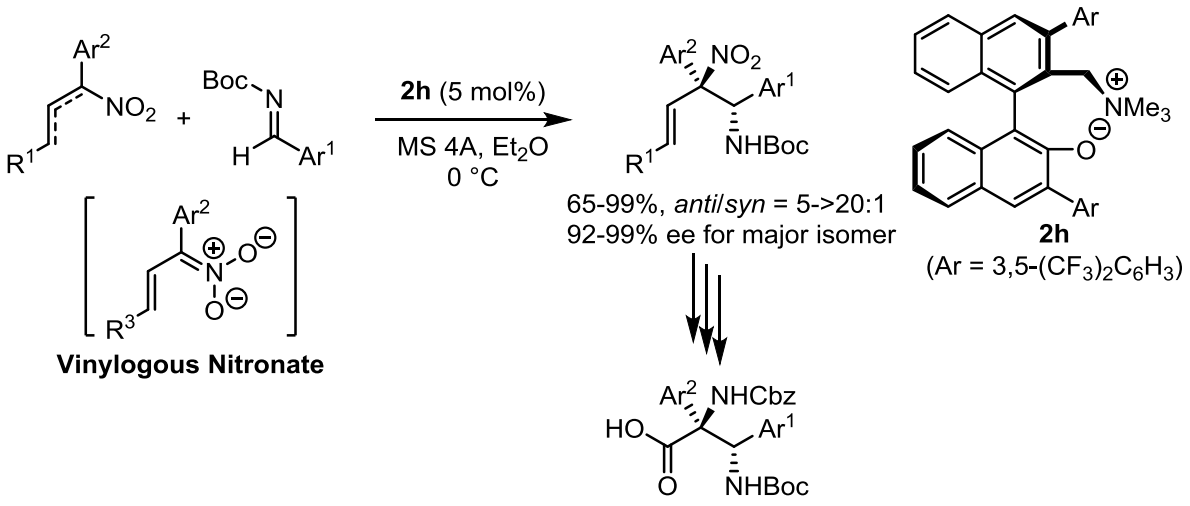


Figure 9. Working Hypothesis of Reaction of α,β-Disubstituted Nitroolefins

As assumed above, it is found that α,β-disubstituted nitroolefins are converted to vinylogous nitronates under the catalysis of chiral ammonium betaine **2h**. Moreover, reaction products were easily converted to α,β-diamino acids(Scheme 37). As is the case with reaction of β,β-disubstituted nitroolefins, corresponding intermediate provide α-adduct selectively. The result of reaction suggested that vinylogous nitronate generated by this strategy could react only α-position.



Scheme 37. Stereoselective Aza-Henry Reaction of α,β-Disubstituted Nitroolefins

1.3.5. Chiral Ammonium Betaine-Catalyzed Highly Stereoselective Aza-Henry Reaction of a-Aryl Nitromethanes with Aromatic N-Boc Imines (Chapter 4)

The fact that vinylogous nitronates were generated from β,β-disubstituted nitroolefins(section **1.3.3.**) prompted author to apply the catalytic system to aza-Henry reaction of α-aryl nitromethanes. The author assumed that chiral ammonium betaine deprotonates α-arylnitromethanes to produce α-aryl nitronates due to structural similarity(Figure 10).

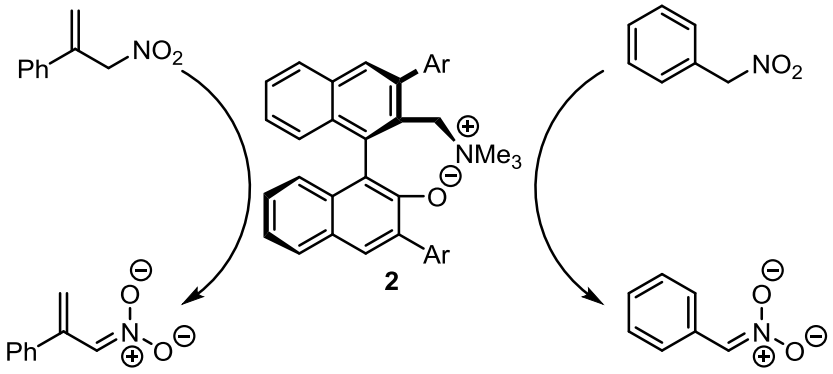
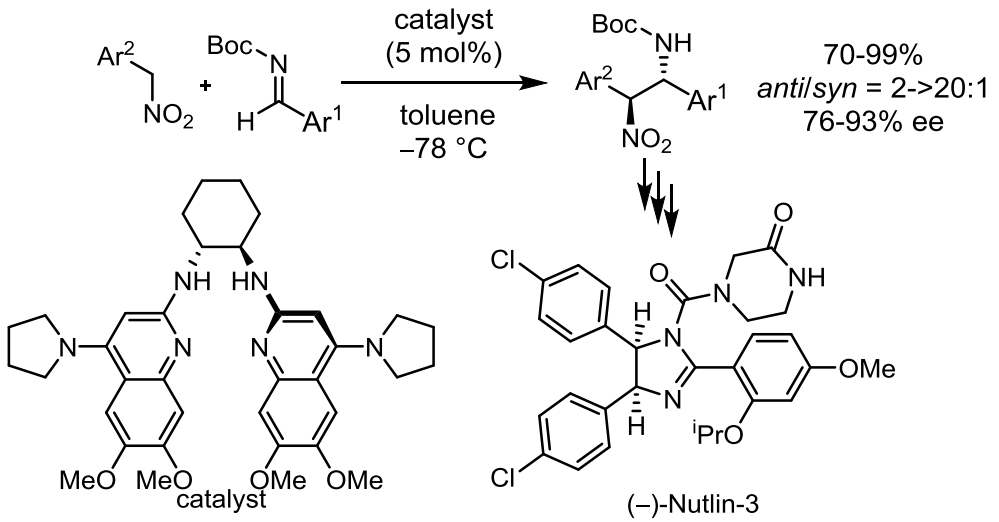


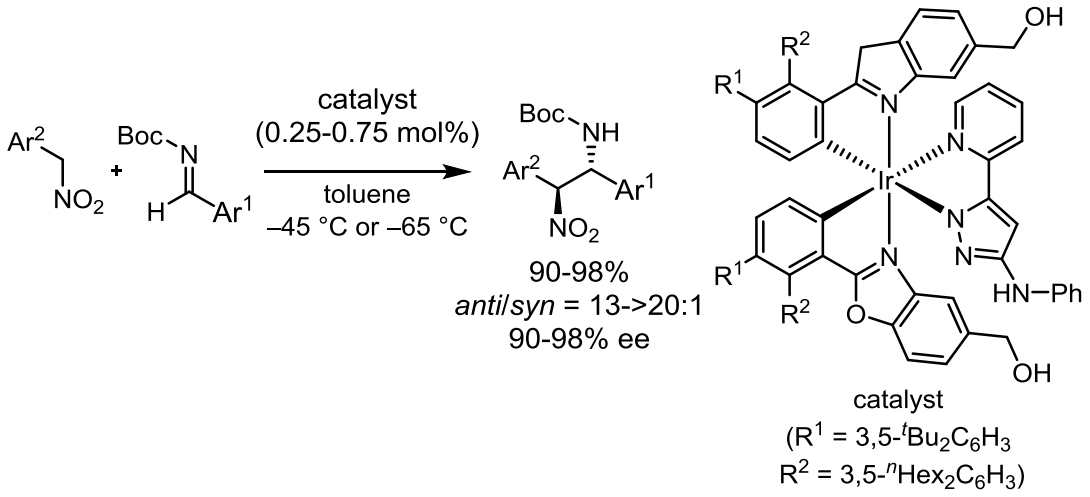
Figure 10. Working hypothesis of reaction of α-aryl nitromethanes

Desired products of this reaction could be synthetic precursor of 1,2-diarylethylenediamines. Chiral 1,2-diarylethylenediamines are recognized as an important building block which are contained in various bioactive compounds such as (-)-nutrin-3. Therefore asymmetric syntheses of 1,2-diarylethylenediamines have attracted interest. Johnston et al. reported aza-Henry reaction of α-aryl nitromethanes using chiral bisamidine catalyst(Scheme 38).[50] In their report, reaction product were acutually derivatized to (-)-nutrin-3.



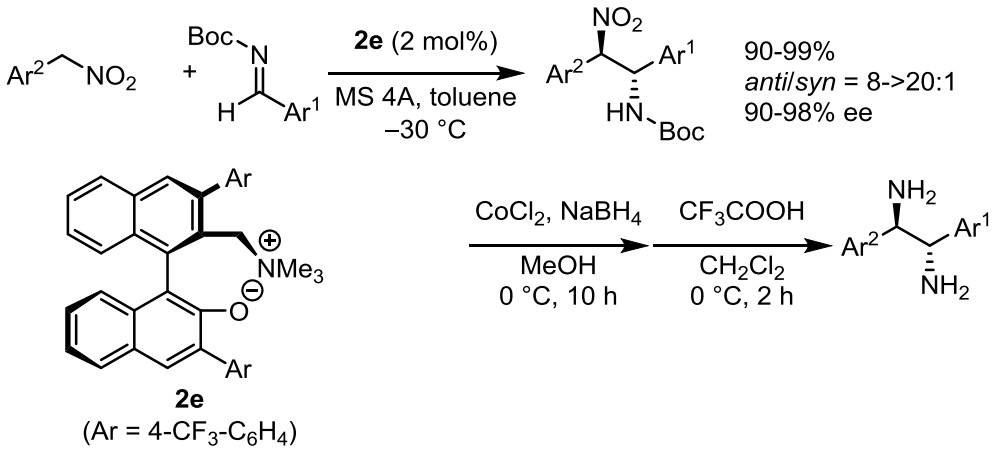
Scheme 38. Stereoselective Aza-Henry Reaction of α-Aryl Nitromethanes by Johnston et al.[50]

Moreover, it was demonstrated that reaction product were obtained under the presence of Ir-templated chiral base catalyst(Scheme 39).[51] However development of asymmetric reaction with broadly scope is still needed.



Scheme 39. Stereoselective Aza-Henry Reaction of α-Aryl Nitromethanes catalyzed by Ir-templated base[51]

After considerable optimization of catalyst structure and reaction condition, author discovered that chiral ammonium betaine **2e** catalyzed aza-Henry reaction in almost quantitative yields and excellent stereoselectivity. It is also confirmed that reaction could apply to gram-scale reaction without loss of reaction efficiency and stereoselectivity. Synthetic utility of this reaction have been clearly demonstrated through the derivatization of reaction product to chiral 1,2-diarylethylenediamines(Scheme 40).



Scheme 40. Stereoselective Aza-Henry Reaction of α-Aryl Nitromethanes

1.4. Summary

In this thesis, author demonstrated that vinylogous nitronates could generate by use of steric repulsion of substrates under the catalysis of chiral ammonium betaine. These studies also disclosed that vinylogous nitronates react at α-position even if the nitronates have a α-substituent. These are the first example to utilize vinylogous nitronates as a nucleophile in asymmetric reaction. The author emphasizes that vinylogous nitronates would be a novel useful intermediate to provide chiral building block.

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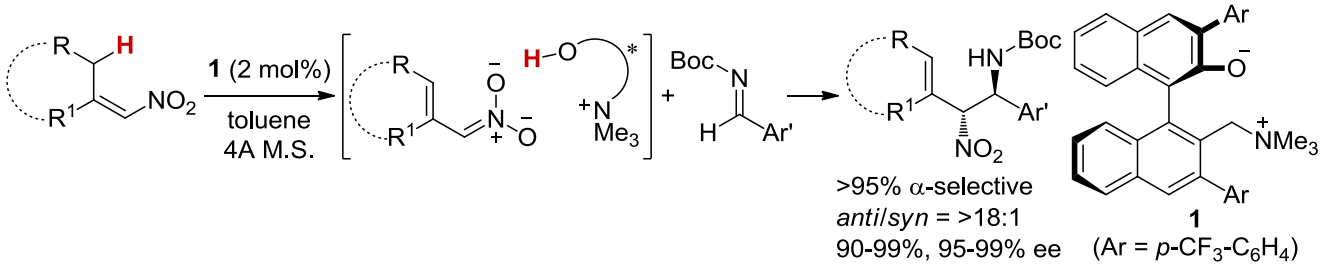
Chapter 2

Nitroolefins as a Nucleophilic Component for Highly Stereoselective Aza-Henry Reaction under the Catalysis of Chiral Ammonium Betaines

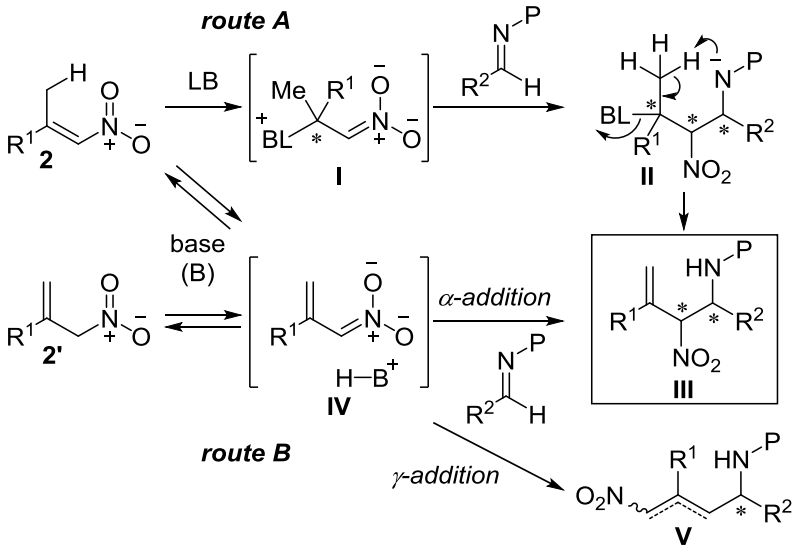
Abstract:



Vinylogous nitronate was successfully generated from β,β-disubstituted nitroolefins for achieving a highly regio-, diastereo-, and enantioselective aza-Henry reaction under the influence of chiral ammonium betaine of type **1** as an organic base catalyst. The present approach greatly expands the synthetic utility of nitroolefins in the development of carbon-carbon bond-forming reactions.

2.1. Introduction

Catalytic stereoselective syntheses of nitro compounds are recognized as an important process to provide valuable chiral building blocks for the construction of biologically relevant, complex organic molecules.[1] This is largely due to the utility of the nitro group as a masked functionality to be transformed to a variety of other useful functional groups, which is well described by the term, synthetic chameleon.[2] Accordingly, numerous efforts have been devoted to the development of reliable methodologies for the catalytic stereocontrolled assembly of nitro-containing carbon frameworks. In this endeavour, the addition of carbon or heteroatom nucleophiles to nitroolefins featuring a highly electron-deficient conjugate system has been extensively studied, demonstrating the versatility of nitroolefins as a reactive Michael acceptor.[3] In sharp contrast, however, there are few known applications of nitroolefins as a nucleophilic component.[4-6] Although the Morita-Baylis-Hillman (MBH) reaction is one of the representative bond-forming processes for utilizing an electron-deficient conjugate system as a nucleophile,[7] it is difficult to accommodate nitroolefins by avoiding concomitant polymerization because of their extremely electrophilic character; hence, only limited examples of non-stereoselective reactions have appeared in literatures.[4] In 2007, Shi and co-workers reported a new approach to overcome this problem by introducing ß,ß-disubstituted nitroolefins as a requisite nucleophile.[5a] The steric hindrance created by the additional ß-alkyl substituent would be instrumental in suppressing undesired homooligomerization. Thus, Lewis base (LB)-catalyzed double Michael reaction between ß,ß-disubstituted nitroolefins and enones or enoates was realized in moderate to good chemical yield albeit with poor diastereoselectivity. Following this stimulating disclosure, ß,ß-disubstituted nitroolefins **2** have been used for achieving enantioselective aza-MBH-type reactions with bifunctional thiourea catalyst.[6] This study by Xu et al. proposed that another role of a ß-alkyl substituent would be to effectively deliver a proton to the intermediary amide ion **II** in an intramolecular fashion to furnish the final product **III** with concurrent regeneration of the LB catalyst (Scheme 1, route A). Apart from these LB-catalyzed protocols, which involve the generation of nitronate **I** by virtue of the electrophilic character of nitroolefins, there is another possible way of employing this class of nitroolefins as a nucleophile (route B). Considering the relatively high acidity of the γ-proton of **2**, treating **2** with an appropriate base would afford vinylogous nitronate **IV**.[8,9] However, experimental and computational studies conducted by Shi's group suggested that the addition of nitronate **IV** to enones would be energetically unfavorable,[5a] and the synthetic potential of this approach has been largely unexplored, leaving the intrinsic reactivity at α- and γ-position of the extended nitronate virtually unknown. Here, we communicate the first example of the latter reaction system (route B) by establishing an aza-Henry reaction[10] of nitronate **IV** with high regio-, enantio-, and diastereoselectivity under the influence of the chiral ammonium betaine of type **1** as a base catalyst.[11,12]



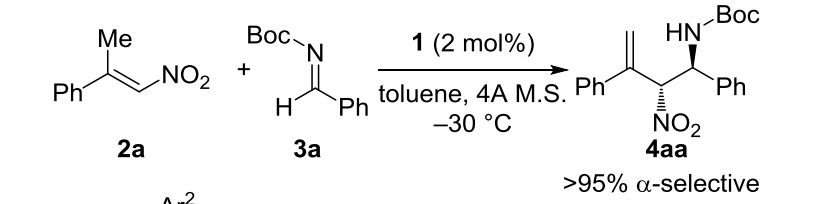
Scheme 1. Two possible reaction routes for the aza-Henry reaction of ß,ß-disubstituted nitroolefins **2** with *N*-protected imines.

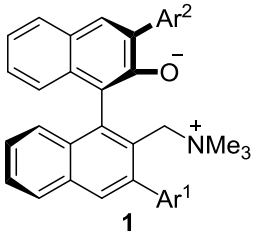
2.2. Results and Discussion

Initially, axially chiral ammonium betaine **1a** was applied as catalyst to the reaction of ß,ß-disubstituted nitroolefin **2a** with *N*-Boc imine **3a** in toluene containing molecular sieves 4Å (4A M.S.) at –30 °C. After 24 h of stirring, the expected aza-Henry adduct **4aa** was indeed obtained in 77% isolated yield with almost complete regio- and diastereoselectivities (Table 1, entry 1). Fortunately, the enantiomeric excess of *anti*-**4aa** was determined to be 97% ee. When the more nucleophilic catalyst **1b**,[13] which lacks a substituent at the 3-position of the aryloxylate moiety (Ar^2), was used as a catalyst under otherwise identical conditions, the bond formation occurred sluggishly to afford **4aa** in only 20% yield with low stereoselectivity (entry 2).[14] This intriguing result strongly suggests that **1** functions as an organic base to catalyze the reaction through route B and also reveals the importance of Ar^2 for attaining high reactivity and stereoselectivity. Meanwhile, the ^{1}H NMR (400 MHz) analysis of the crude mixture obtained from the initial attempt with **1a** showed that the remaining nitroolefin was substantially contaminated by non-conjugated **2a'** (**2a**:**2a'** = 3.3:1).[15] This observation prompted us to separately prepare the ß,γ-unsaturated nitroolefin **2a'** for comparing the initial rate of reactions with **2a**, an equimolar mixture of both nitroolefins, and **2a'** as a substrate (entries 3-5, respectively). The isolated yield of **4aa**, which was determined after 1 h of stirring, gradually increased as the content of **2a'**, whereas the stereoselectivity was retained at the same level. Therefore, **2a'** having acidic α-protons is more frequently converted to the product **4aa**, confirming the operation of base catalysis in the present system. It should be noted that isomerization of the nitroolefin was again observed in this trial, and the ratio of **2a** to **2a'** in the crude residue was determined to be 6.4:1 (entry 3), 5.8:1 (entry 4), and 4.0:1 (entry 5). Consequently, the aza-Henry reaction proceeded via vinylogous nitronate **IV**, through which competitive isomerization of the starting nitroolefins took place. Furthermore, because the treatment of the

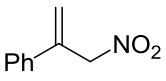
ß-monosubstituted nitroolefin such as 1-nitrohept-1-ene with **3a** under the influence of **1a** or **1b** in a similar manner led to the formation of neither an aza-MBH adduct nor a polymer of the nitroolefin, the possibility of route A involving the initial conjugate addition of **1** to **2** could be ruled out, and the presence of the two ß-substituents in **2** appeared to be crucial for the generation of the requisite nitronate **IV**. We then turned our attention to the structural modification of chiral ammonium betaine **1** for improving the reactivity and selectivity profiles. Although the structures of the aromatic groups attached to the binaphthyl backbone (Ar^1 and Ar^2) had marginal effects on stereoselectivity, **1e** possessing two *para*-trifluoromethylphenyl substitutions at the 3-positions of both naphthyl units was identified as an optimal catalyst in terms of catalytic efficiency (entries 1 and 6-8).

Table 1. Optimization of catalyst structure and determination of the reaction pathway for the ammonium betaine-catalyzed stereoselective aza-Henry reaction[a]





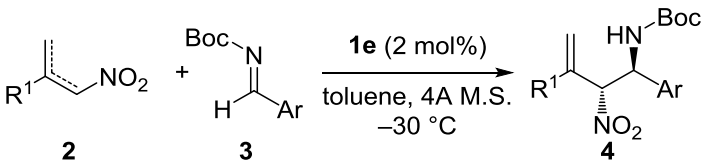
1a: $Ar^1 = Ar^2$ = Ph
1b: Ar^1 = Ph, Ar^2 = H
1c: Ar^1 = *p*-CF_3-C_6H_4, Ar^2 = Ph
1d: Ar^1 = Ph, Ar^2 = *p*-CF_3-C_6H_4
1e: $Ar^1 = Ar^2$ = *p*-CF_3-C_6H_4



entry	1	time [h]	yield[b] [%]	dr[c] [anti/syn]	ee[d] [%]
1	**1a**	24	77	>20:1	97/–
2	**1b**	24	20	1:1	32/26
3	**1a**	1	38	>20:1	96/–
4[e]	**1a**	1	40	>20:1	96/–
5[f]	**1a**	1	57	>20:1	96/–
6	**1c**	24	87	>20:1	95/–
7	**1d**	24	70	17:1	96/95
8	**1e**	24	90	>20:1	99/–

[a] Unless otherwise noted, reactions were performed with 0.11 mmol of **2a** and 0.10 mmol of **3a** in the presence of **1** (2 mol%) in 0.5 mL of toluene with 4A M.S. at –30 °C. See Supporting Information for further details. [b] The isolated yields were reported. [c] Diastereomeric ratios (dr) were determined by ^{1}H NMR (400 MHz) analysis of crude aliquot. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute and relative configuration was determined by X-ray crystallographic analysis after derivatization. See Supporting Information. [e] An equimolar mixture of **2a** and **2a'** was used instead of pure **2a**. [f] β,γ-Unsaturated nitroolefin **2a'** was used instead of **2a**.

Table 2. Scope of nitroolefins **2** and *N*-Boc imines **3**[a]



2 **3** **4**

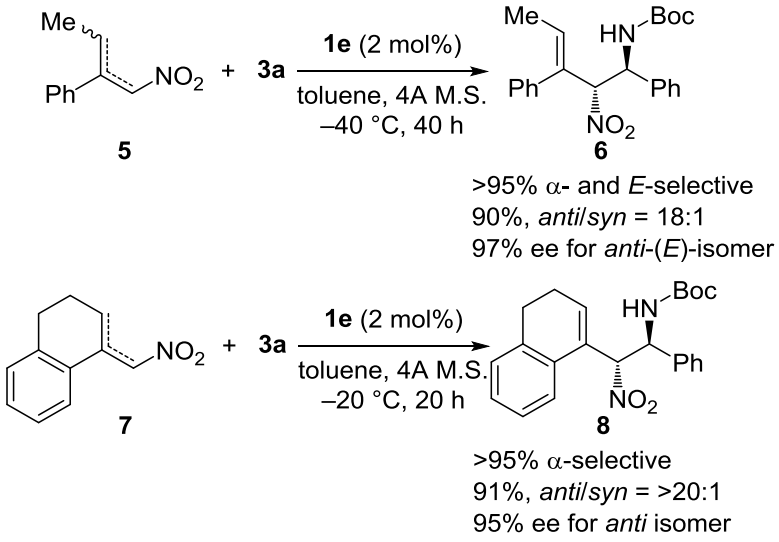
anti/*syn* = >20:1
>95% α-selective

entry	R^1 [2]		Ar [3]		time [h]	yield[b] [%]	ee[c] [%]	prod. [4]
1	Ph	**2a**	*o*-F–C_6H_5	3b	24	93	98	**4ab**
2	Ph	**2a**	*o*-MeO–C_6H_5	3c	27	93	96	**4ac**
3	Ph	**2a**	*m*-MeO–C_6H_5	3d	24	99	98	**4ad**
4	Ph	**2a**	*p*-MeO–C_6H_5	3e	29	99	98	**4ae**
5	Ph	**2a**	*p*-Me–C_6H_5	3f	30	91	98	**4af**
6	Ph	**2a**	*p*-Br–C_6H_5	3g	23	99	99	**4ag**
7	Ph	**2a**	2-furyl	3h	24	92	96	**4ah**
8	*o*-F–C_6H_5	**2b**	Ph	3a	24	87	98	**4ba**
9[d]	*m*-Cl–C_6H_5	**2c**	Ph	3a	18	96	98	**4ca**
10[d]	*p*-Br–C_6H_5	**2d**	Ph	3a	15	93	98	**4da**
11	*p*-Me–C_6H_5	**2e**	Ph	3a	22	91	98	**4ea**
12	2-naphthyl	**2f**	Ph	3a	25	90	99	**4fa**
13[e]	Me	**2g**	Ph	3a	28	90	95	**4ga**

[a] Unless otherwise noted, reactions were performed with 0.11 mmol of **2** and/or **2'** and 0.10 mmol of **3** in the presence of **1** (2 mol%) in 0.5 mL of toluene with 4A M.S. at –30 °C. See Supporting Information for further details. [b] The isolated yields were reported. [c] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute and relative configurations of **4** were assigned by analogy to **4aa**. [d] 0.12 mmol of **2** was used. [e] Reaction was performed at –40 °C. A diastereomeric mixture of **4ga** was obtained in the *anti*/*syn* ratio of 10:1.

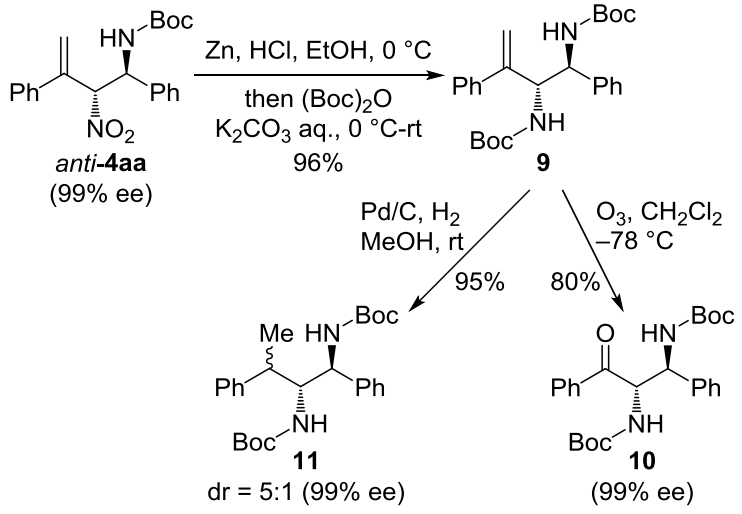
Experiments to evaluate the substrate scope of this unique asymmetric aza-Henry protocol revealed the excellent stereocontrolling ability of the chiral ammonium betaine **1e** (Table 2). With regard to the aromatic imine electrophiles **3**, the incorporation of *ortho*-, *meta*-, and *para*-substituents of different electronic properties was tolerated (entries 1-6), and the heteroaromatic imine **3h** derived from 2-furylaldehyde also appeared to be a good candidate (entry 7). The ß-aromatic substituent (R^1) of the nitroolefin nucleophiles **2** could be variable with rigorous relative and absolute stereocontrols (entries 8-12). Moreover, aliphatic nitroolefin such as **2g** was employable as a nucleophilic component and underwent smooth addition to **3a** at –40 °C to give **4ga** in 90% yield with

95% ee albeit with a slight loss of the diastereoselectivity (entry 13).



Scheme 2. γ-Substituted nitroolefins as a nucleophilic component.

The generality of the present system was further demonstrated through the application to γ-substituted nitroolefins. For instance, reaction of an isomeric mixture of nitroolefin **5** with **3a** in the presence of **1e** proceeded with similar efficiency to afford the corresponding adduct **6** in an almost stereochemically pure form in 90% yield (Scheme 2). In addition, excellent levels of diastereo- and enantioselectivity were also attained with carbocyclic nitroolefin **7** as a substrate.



Scheme 3. Derivatization of the aza-Henry adduct *anti*-**4aa**.

The densely functionalized nitro compounds **4** can be readily derivatized into useful chiral building blocks, as exemplified in Scheme 3. The selective reduction of the nitro group of *anti*-**4aa** (99% ee) with zinc metal and hydrochloric acid in ethanol followed by the protection of the resulting primary

amino functionality furnished the unsaturated *anti*-1,2-diamine derivative **9** in 96% yield. The subsequent ozonolysis of the remaining double bond afforded stereochemically homogeneous *anti*-α,β-diamino ketone **10**, whereas its simple hydrogenation produced a diastereomeric mixture of the saturated 1,2-diamine derivative **11** bearing three consecutive stereogenic carbon centers without the loss of enantiomeric excess.

2.3. Conclusions

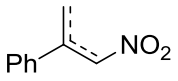
In conclusion, we successfully utilized ß,ß-disubstituted nitroolefins as a synthetically relevant nucleophile through the generation of the corresponding chiral vinylogous nitronate under the base catalysis of chiral ammonium betaines. The reactivity and selectivity of this key intermediate have been clearly visualized for the first time by achieving a highly regio-, diastereo-, and enantioselective aza-Henry reaction with *N*-Boc imines under mild conditions. The present approach greatly expands the scope of the carbon-carbon bond-forming processes involving nitroolefins.

2.4. Experimental Section

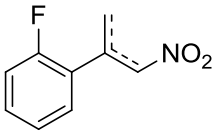
General Information: Infrared spectra were recorded on a SHIMADZU IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance [$(CD_3)_2CO$: 2.05 ppm, $(CD_3)_2SO$: 2.50 ppm, and CD_3OD: 3.31 ppm] or tetramethylsilane (0.00 ppm) resonance ($CDCl_3$) as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, 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, $(CD_3)_2SO$: 39.52 ppm, CD_3OD: 49.00 ppm, and $CDCl_3$: 77.16 ppm]. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive (ESI), JEOL JMS-700 (FAB), JEOL JMS-T100GCV (EI), or Bruker Daltonics micrOTOF-QII (ESI) Mass Spectrometers. 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 PSQ60AB (spherical, 40-50 μm; FUJI SILYSIA Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK IA (IA), CHIRALPAK AD-H (AD-H), CHIRALPAK AD-3 (AD-3), or CHIRALPAK AS-H (AS-H)].

Toluene was freshly distilled from sodium metal prior to use. Betaine precursors[11c], imines[16], and nitroolefins[17] were prepared by following the literature procedure. Powdered 4Å molecular sieves (4A M.S.) was supplied by Merck & Co., Inc. Other simple chemicals were purchased and used as such.

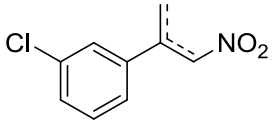
Characterization of Nitroolefins:



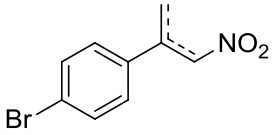
2a: The synthesis was performed by following the literature procedure.[3c] Physical data for **2a** are identical with reported one[3c] and the data for **2a'** are following. **2a':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (2H, m), 7.40-7.32 (3H, m), 5.83 (1H, s), 5.54 (1H, s), 5.37 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 136.9, 129.0, 128.9, 125.9, 121.9, 79.7; IR (neat) 1549, 1371, 926, 916, 781 cm^{-1}; HRMS (ESI) Calcd for $C_9H_9N_1Na_1O_2^+$ ([M+Na]$^+$) 186.0525. Found 186.0530.



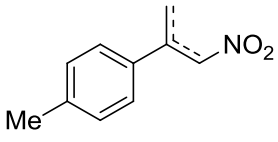
2b: The synthesis was performed by following the literature procedure.[3c] **2b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, tdd, J = 8.0, 1.6 Hz, $J_{F\text{-}H}$ = 5.0 Hz), 7.30 (1H, td, J = 8.0, 1.6 Hz), 7.22 (1H, q, J = 1.6 Hz), 7.21 (1H, td, J = 8.0, 1.6 Hz), 7.15 (1H, ddt, $J_{F\text{-}H}$ = 11.0 Hz, J = 8.0, 1.6 Hz), 2.61 (3H, t, J = 1.6 Hz, $J_{F\text{-}H}$ = 1.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $J_{F\text{-}C}$ = 254.5 Hz), 145.8, 138.4, 131.7 (d, $J_{F\text{-}C}$ = 8.7 Hz), 129.3 (d, $J_{F\text{-}C}$ = 1.9 Hz), 126.6 (d, $J_{F\text{-}C}$ = 12.6 Hz), 124.8 (d, $J_{F\text{-}C}$ = 3.9 Hz), 116.7 (d, $J_{F\text{-}C}$ = 22.3 Hz), 19.6 (d, $J_{F\text{-}C}$ = 2.9 Hz); IR (neat) 1514, 1487, 1449, 1341, 1209, 827, 758 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8F_1N_1Na_1O_2^+$ ([M+Na]$^+$) 204.0431. Found 204.0441. **2b':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (2H, m), 7.16 (1H, td, J = 8.0, 1.4 Hz), 7.08 (1H, ddd, $J_{F\text{-}H}$ = 12.0 Hz, J = 8.0, 0.8 Hz), 5.73 (1H, s), 5.66 (1H, s), 5.36 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (d, $J_{F\text{-}C}$ = 251.6 Hz), 134.8, 130.6 (d, $J_{F\text{-}C}$ = 8.7 Hz), 130.4 (d, $J_{F\text{-}C}$ = 2.9 Hz), 125.6, 125.4 (d, $J_{F\text{-}C}$ = 13.5 Hz), 124.8 (d, $J_{F\text{-}C}$ = 3.8 Hz), 116.1 (d, $J_{F\text{-}C}$ = 22.3 Hz), 80.1; IR (neat) 1551, 1489, 1452, 1371, 1213, 935, 829, 762 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8F_1N_1Na_1O_2^+$ ([M+Na]$^+$) 204.0431. Found 204.0432.



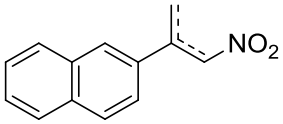
2c: The synthesis was performed by following the literature procedure.[3c] Physical data for **2c** are identical with reported one[3c] and the data for **2c'** are following. **2c':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, m), 7.36-7.27 (3H, m), 5.84 (1H, s), 5.59 (1H, s), 5.34 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 137.0, 135.0, 130.2, 129.0, 126.3, 124.1, 123.3, 79.4; IR (neat) 1549, 1371, 930, 880, 822, 789 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8Cl_1N_1Na_1O_2^+$ ($[M+Na]^+$) 220.0136. Found 220.0130.



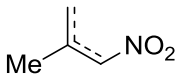
2d: The synthesis was performed by following the literature procedure.[3c] Physical data for **2d** are identical with reported one[3d] and the data for **2d'** are following. **2d':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 8.7 Hz), 7.31 (2H, d, J = 8.7 Hz), 5.82 (1H, s), 5.57 (1H, s), 5.34 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1, 135.9, 132.1, 127.6, 123.1, 122.7, 79.5; IR (neat) 1551, 1489, 1371, 1007, 928, 831 cm^{-1}; HRMS (ESI) Calcd for $C_9H_8Br_1N_1Na_1O_2^+$ ($[M+Na]^+$) 263.9631. Found 263.9627.



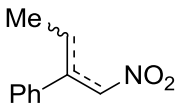
2e: The synthesis was performed by following the literature procedure.[3c] Physical data for **2e** are identical with reported one[3c] and the data for **2e'** are following. **2e':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, J = 8.2 Hz), 7.18 (2H, d, J = 8.2 Hz), 5.79 (1H, s), 5.48 (1H, s), 5.35 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 137.8, 134.0, 129.7, 125.8, 121.0, 80.0, 21.3; IR (neat) 1551, 1516, 1371, 922, 824 cm^{-1}; HRMS (ESI) Calcd for $C_{10}H_{11}N_1Na_1O_2^+$ ($[M+Na]^+$) 200.0682. Found 200.0690.



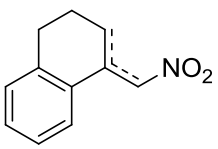
2f: The synthesis was performed by following the literature procedure.[3c] Physical data for **2f** are identical with reported one[3c] and the data for **2f'** are following. **2f':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.80 (4H, m), 7.60 (1H, dd, J = 8.7, 2.0 Hz), 7.54-7.47 (2H, m), 5.98 (1H, s), 5.64 (1H, s), 5.48 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 134.2, 133.4, 133.3, 128.8, 128.5, 127.8, 126.8$_2$, 126.8$_0$, 125.1, 123.7, 122.4, 79.8; IR (neat) 1549, 1373, 926, 891, 858, 817, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{11}N_1Na_1O_2^+$ ($[M+Na]^+$) 236.0682. Found 236.0691.



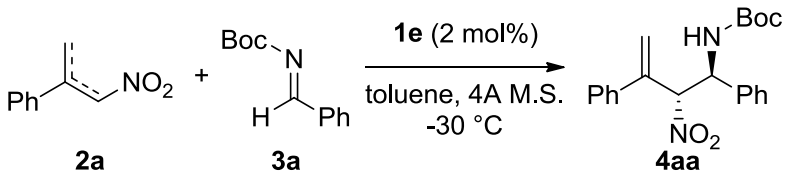
2g: The synthesis was performed by following the literature procedure.[3b] Physical data for **2g** are identical with reported one[3b] and the data for **2g'** are following. **2g':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, s), 5.18 (1H, s) , 4.90 (2H, s), 1.89 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 120.9, 82.3, 20.4; IR (neat) 1549, 1429, 1375, 1314, 1196, 920, 760 cm^{-1}; HRMS (EI) Calcd for $C_4H_7N_1O_2$ ($[M]^+$) 101.0477. Found 101.0477.



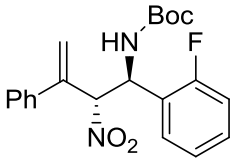
5: The synthesis was performed following the literature procedure.[3a] Physical data for **5'** are identical with reported one[3a] and assignment of **5** is difficult because it is formed in a small amount and inseparable from **5'**.



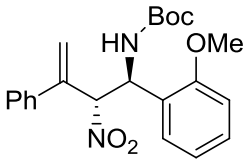
7: The synthesis was performed following the literature procedure.[3a] Physical data for **7'** are identical with reported one[3a] and assignment of **7** is difficult because it is formed in a small amount and inseparable from **7'**.



Representative Procedure for Catalytic Asymmetric Aza-Henry Reaction of β,β-Disubstituted Nitroolefins 2: A magnetic stirrer bar and 4A M.S. (10 mg) was placed in an oven-dried test tube under argon (Ar) atmosphere. The 4A M.S. was dried with a heat gun under reduced pressure for 5 min and the test tube was refilled with Ar. Chiral ammonium betaine **1e** (1.26 mg, 0.0020 mmol) and toluene (0.50 mL) were added to the test tube successively under Ar at 25 °C. After the mixture was cooled to –30 °C, nitroolefin **2a** (17.9 mg, 0.11 mmol) and benzaldehyde-derived *N*-Boc imine **3a** (20.5 mg, 0.10 mmol) were introduced sequentially. The reaction mixture was stirred for 24 h and poured into ice-cooled 1 *N* aqueous HCl. The aqueous phase was extracted with ethyl acetate (EA) twice. The combined organic phases were 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 (*anti*/*syn* = >20:1). Purification of the residue by column chromatography on silica gel (hexane (H)/EA = 3:1 as eluent) gave **4aa** as a mixture of diastereomers (33.2 mg, 90%), whose enantiomeric excesses were determined by HPLC analysis (99% ee for *anti* isomer). **4aa:** HPLC: AS-H, H/2-propanol (IPA) = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.3 min (1*S*, 2*R*), 20.4 min (minor enantiomer of *syn* isomer), 28.0 min (1*R*, 2*S*), 48.0 min (major enantiomer of *anti* isomer). Absolute and relative configurations were determined by X-ray crystallographic analysis after derivatization to **12** (see below). ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.47-7.26 (10H, m), 5.93 (1H, s), 5.78 (1H, d, J = 10.1 Hz), 5.71 (1H, s), 5.52 (1H, br), 4.82 (1H, br), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 141.1, 139.9, 137.7, 129.1, 128.9, 128.8, 128.6, 127.3, 126.9, 120.4, 92.3, 80.5, 57.0, 28.3; IR (film) 2978, 2930, 1684, 1556, 1497, 1406, 1395, 1366, 1252, 1159, 1016, 775 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{25}N_2O_4^+$ ([M+H]$^+$) 369.1814. Found 369.1812.

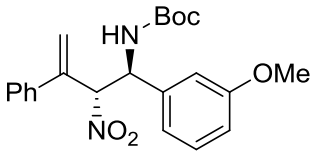


4ab: HPLC: AD-H, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 10.4 min (minor enantiomer of *anti* isomer), 12.3 min (minor enantiomer of *syn* isomer), 19.7 min (major enantiomer of *syn* isomer), 26.3 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.47-7.26 (7H, m), 7.11 (1H, t, J = 8.0 Hz), 7.07 (1H, dd, $J_{F\text{-}H}$ = 11.4 Hz, J = 8.0 Hz), 5.98 (1H, s), 5.91 (1H, d, J = 10.5 Hz), 5.74 (1H, s), 5.70 (1H, t, J = 10.5 Hz), 5.05 (1H, d, J = 10.5 Hz), 1.37 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.2 (d, $J_{F\text{-}C}$ = 249.7 Hz), 154.5, 140.9, 139.9, 131.3, 130.7 (d, $J_{F\text{-}C}$ = 8.7 Hz), 128.9, 128.6, 126.8, 124.8, 124.4 (d, $J_{F\text{-}C}$ = 11.6 Hz), 120.2, 116.2 (d, $J_{F\text{-}C}$ = 21.3 Hz), 91.0, 80.5, 54.5 (d, $J_{F\text{-}C}$ = 9.7 Hz), 28.3; IR (neat) 2978, 2932, 1697, 1555, 1491, 1393, 1366, 1159, 1016, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{24}F_1N_2O_4^+$ ([M+H]$^+$) 387.1720. Found 387.1725.

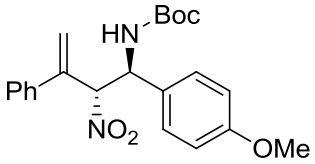


4ac: HPLC: AD-3, H/IPA/EtOH = 185:14:1, flow rate = 0.5 mL/min, λ = 254 nm, 21.8 min (major enantiomer of *anti* isomer), 25.6 min (minor enantiomer of *syn* isomer), 29.3 min (minor enantiomer of *anti* isomer), 46.7 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz,

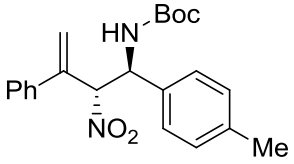
$CDCl_3$) *anti* isomer δ 7.48-7.25 (7H, m), 6.91 (1H, t, *J* = 7.8 Hz), 6.89 (1H, d, *J* = 8.2 Hz), 6.08 (1H, d, *J* = 10.5 Hz), 6.02 (1H, s), 5.73 (1H, s), 5.66 (1H, t, *J* = 10.5 Hz), 5.46 (1H, d, *J* = 10.5 Hz), 3.88 (3H, s), 1.37 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 157.2, 154.7, 141.0, 140.6, 131.6, 130.2, 128.8, 128.3, 126.6, 124.6, 121.4, 119.6, 111.3, 90.5, 79.9, 56.7, 55.6, 28.4; IR (film) 3447, 2976, 2932, 1715, 1553, 1489, 1366, 1283, 1242, 1161, 1020, 754 cm^{-1}; HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_5^+$ ($[M+H]^+$) 399.1920. Found 399.1906.



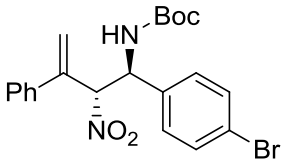
4ad: HPLC: AD-H, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 18.4 min (minor enantiomer of *syn* isomer), 27.9 min (major enantiomer of *syn* isomer), 38.5 min (major enantiomer of *anti* isomer), 57.8 min (minor enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.46-7.34 (5H, m), 7.24 (1H, t, *J* = 8.0 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 6.86-6.81 (2H, m), 5.93 (1H, s), 5.76 (1H, d, *J* = 9.6 Hz), 5.70 (1H, s), 5.53 (1H, br), 4.79 (1H, br), 3.77 (3H, s), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.0, 154.5, 141.1, 139.9, 139.3, 130.2, 128.9, 128.6, 126.9, 120.4, 119.2, 114.1, 113.3, 92.2, 80.5, 57.0, 55.4, 28.3; IR (film) 2976, 2932, 1699, 1555, 1493, 1366, 1261, 1161, 1043, 777 cm^{-1}; HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_5^+$ ($[M+H]^+$) 399.1920. Found 399.1906.



4ae: HPLC: AD-3, H/IPA = 93:7, flow rate = 1.0 mL/min, λ = 210 nm, 22.3 min (minor enantiomer of *anti* isomer), 28.0 min (minor enantiomer of *syn* isomer), 36.1 min (major enantiomer of *syn* isomer), 46.3 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.45-7.33 (5H, m), 7.24 (2H, d, *J* = 8.7 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 5.92 (1H, s), 5.75 (1H, d, *J* = 10.0 Hz), 5.70 (1H, s), 5.45 (1H, br), 4.79 (1H, br), 3.77 (3H, s), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 159.8, 154.5, 141.1, 140.0, 129.8, 128.9, 128.5$_4$, 128.5$_0$, 126.9, 120.3, 114.4, 92.5, 80.4, 56.6, 55.4, 28.3; IR (film) 3391, 2982, 2934, 1686, 1553, 1508, 1364, 1294, 1248, 1157, 833, 775 cm^{-1}; HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_5^+$ ($[M+H]^+$) 399.1920. Found 399.1906.

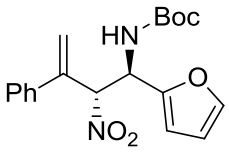


4af: HPLC: AD-3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 25.2 min (minor enantiomer of *anti* isomer), 26.9 min (minor enantiomer of *syn* isomer), 37.7 min (major enantiomer of *syn* isomer), 45.7 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.46-7.33 (5H, m), 7.20 (2H, d, *J* = 8.0 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 5.93 (1H, s), 5.75 (1H, d, *J* = 9.2 Hz), 5.70 (1H, s), 5.49 (1H, br), 4.77 (1H, br), 2.31 (3H, s), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 141.1, 140.0, 138.6, 134.7, 129.7, 128.9, 128.5, 127.1, 126.9, 120.3, 92.4, 80.4, 56.9, 28.3, 21.2; IR (film) 3387, 2978, 2926, 1699, 1553, 1514, 1364, 1288, 1248, 1161, 775 cm^{-1}; HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_4^+$ ($[M+H]^+$) 383.1971. Found 383.1986.

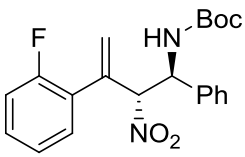


4ag: HPLC: AD-3, H/IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 26.0 min (minor enantiomer of *anti* isomer), 29.0 min (minor enantiomer of *syn* isomer), 40.3 min (major enantiomer of *syn* isomer), 51.1 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.44 (2H, d, *J* = 8.2 Hz), 7.43-7.34 (5H, m), 7.19 (2H, d, *J* = 8.2 Hz), 5.87 (1H, s), 5.75 (1H,

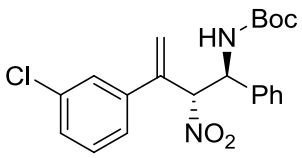
br), 5.70 (1H, s), 5.43 (1H, br), 4.84 (1H, br), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 140.9, 139.5, 136.7, 132.2, 129.1, 129.0, 128.7, 126.9, 122.8, 120.5, 92.0, 80.8, 56.5, 28.3; IR (film) 3389, 2980, 2926, 1686, 1551, 1516, 1489, 1362, 1288, 1248, 1157, 1013 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{24}Br_1N_2O_4^+$ ([M+H]$^+$) 447.0919. Found 447.0927.



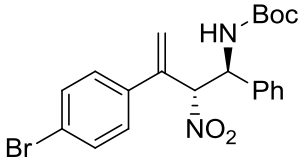
4ah: HPLC: AD-H, H/EtOH = 97:3, flow rate = 1.0 mL/min, λ = 237 nm, 14.8 min (major enantiomer of *syn* isomer), 16.6 min (minor enantiomer of *syn* isomer), 21.3 min (minor enantiomer of *anti* isomer), 38.0 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.44-7.32 (6H, m), 6.30 (2H, s), 5.86 (1H, d, J = 9.6 Hz), 5.83 (1H, s), 5.69 (1H, s), 5.68 (1H, br), 4.93 (1H, d, J = 9.1 Hz), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.4, 149.7, 142.8, 140.6, 139.6, 128.9, 128.6, 126.8, 120.0, 110.7, 108.8, 90.3, 80.6, 50.6, 28.3; IR (film) 2978, 2930, 1699, 1557, 1408, 1393, 1368, 1254, 1163, 1013 cm^{-1}; HRMS (FAB) Calcd for $C_{19}H_{23}N_2O_5^+$ ([M+H]$^+$) 359.1607. Found 359.1619.



4ba: HPLC: AD-3, H/IPA/EtOH = 89:4:7, flow rate = 0.2 mL/min, λ = 210 nm, 55.6 min (minor enantiomer of *syn* isomer), 63.1 min (minor enantiomer of *anti* isomer), 70.6 min (major enantiomer of *syn* isomer), 73.6 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.37-7.26 (7H, m), 7.15 (1H, t, J = 8.0 Hz), 7.11 (1H, dd, J_{F-H} = 11.0 Hz, J = 8.0 Hz), 6.15 (1H, s), 5.74 (1H, s), 5.71 (1H, d, J = 11.0 Hz), 5.55 (1H, br), 4.96 (1H, br), 1.38 (9H, s); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) *anti* isomer δ 160.6 (d, J_{F-C} = 249.6 Hz), 155.5, 139.6, 137.6, 131.5 (d, J_{F-C} = 2.9 Hz), 131.3 (d, J_{F-C} = 8.7 Hz), 129.5, 129.2, 128.5, 128.1 (d, J_{F-C} = 15.5 Hz), 125.3 (d, J_{F-C} = 2.9 Hz), 124.5, 116.6 (d, J_{F-C} = 22.3 Hz), 93.4, 79.7, 57.6 28.5; IR (film) 2978, 2930, 1697, 1557, 1489, 1393, 1366, 1250, 1161, 799, 758 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{24}F_1N_2O_4^+$ ([M+H]$^+$) 387.1720. Found 387.1725.

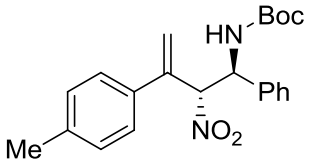


4ca: HPLC: AD-3, H/EtOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 12.6 min (minor enantiomer of *syn* isomer), 15.2 min (major enantiomer of *syn* isomer), 16.4 min (minor enantiomer of *anti* isomer), 32.0 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.39 (1H, s), 7.39-7.26 (8H, m), 5.99 (1H, s), 5.73 (1H, s), 5.70 (1H, br), 5.52 (1H, br), 4.78 (1H, br), 1.37 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 141.8, 140.1, 137.5, 134.8, 130.2, 129.2, 128.9, 128.7, 127.2, 125.0, 121.5, 92.0, 80.7, 57.1, 28.3, one carbon was not found probably due to overlapping; IR (film) 2978, 2930, 1699, 1557, 1497, 1366, 1248, 1163, 795 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{24}Cl_1N_2O_4^+$ ([M+H]$^+$) 403.1425. Found 403.1433.

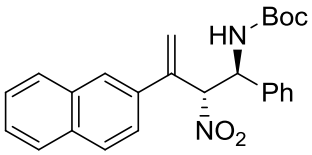


4da: HPLC: AD-3, H/IPA = 93:7, flow rate = 1.0 mL/min, λ = 210 nm, 20.8 min (major enantiomer of *anti* isomer), 24.5 min (minor enantiomer of *syn* isomer), 29.8 min (minor enantiomer of *anti* isomer), 38.1 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.50 (2H, d, J = 7.8 Hz), 7.36-7.24 (7H, m), 5.94 (1H, s), 5.74 (1H, br), 5.70 (1H, s), 5.50 (1H, br), 4.80 (1H, br), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 140.2, 138.7, 137.5,

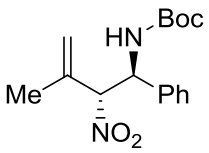
132.0, 129.2, 128.9, 128.6, 127.2, 122.8, 121.1, 92.2, 80.7, 57.0, 28.3; IR (film) 2978, 2930, 1699, 1555, 1489, 1366, 1248, 1163, 1011, 833, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{24}Br_1N_2O_4^+$ ($[M+H]^+$) 447.0919. Found 447.0909.



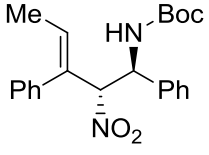
4ea: HPLC: AD-3, H/EtOH = 197:3, flow rate = 1.0 mL/min, λ = 254 nm, 29.5 min (major enantiomer of *syn* isomer), 34.0 min (minor enantiomer of *syn* isomer), 39.1 min (minor enantiomer of *anti* isomer), 60.1 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.36-7.26 (7H, m), 7.19 (2H, d, J = 8.2 Hz), 5.87 (1H, s), 5.76 (1H, d, J = 9.6 Hz), 5.67 (1H, s), 5.51 (1H, br), 4.82 (1H, br), 2.37 (3H, s), 1.36 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 140.9, 138.6, 137.8, 137.0, 129.6, 129.1, 128.8, 127.3, 126.8, 119.6, 92.4, 80.4, 57.0, 28.3, 21.3; IR (film) 3391, 2978, 2926, 1682, 1551, 1514, 1366, 1290, 1248, 1155, 826, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_4^+$ ($[M+H]^+$) 383.1971. Found 383.1972.



4fa: HPLC: AD-3, H/EtOH = 98:2, flow rate = 1.0 mL/min, λ = 267 nm, 42.7 min (major enantiomer of *syn* isomer), 47.0 min (minor enantiomer of *anti* isomer), 59.0 min (major enantiomer of *anti* isomer), 68.2 min (minor enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.90-7.81 (4H, m), 7.57-7.47 (3H, m), 7.36-7.26 (5H, m), 6.03 (1H, s), 5.91 (1H, d, J = 10.0 Hz), 5.83 (1H, s), 5.60 (1H, br), 4.82 (1H, br), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.6, 141.0, 137.7, 137.3, 133.3, 133.1, 129.1, 128.8, 128.7, 128.4, 127.8, 127.3, 126.8, 126.7, 125.9, 124.8, 120.6, 92.3, 80.5, 57.3, 28.3; IR (film) 2978, 2930, 1699, 1555, 1503, 1366, 1250, 1163, 752 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{27}N_2O_4^+$ ($[M+H]^+$) 419.1971. Found 419.1952.

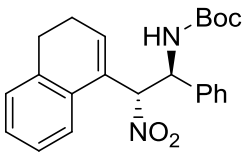


4ga: HPLC: AD-3, H/EtOH = 99:1, flow rate = 1.0 mL/min, λ = 223 nm, 30.9 min (minor enantiomer of *anti* isomer), 32.3 min (minor enantiomer of *syn* isomer), 37.4 min (major enantiomer of *anti* isomer), 50.4 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.40-7.25 (5H, m), 5.40 (1H, br), 5.35 (1H, s), 5.30 (1H, s), 5.26 (1H, d, J = 10.0 Hz), 4.83 (1H, br), 1.94 (3H, s), 1.38 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.7, 137.9, 137.4, 129.1, 128.8, 127.2, 122.0, 96.4, 80.6, 54.3, 28.3, 17.9; IR (film) 3402, 2981, 2925, 1684, 1546, 1520, 1368, 1292, 1250, 1168, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{16}H_{23}N_2O_4^+$ ($[M+H]^+$) 307.1658. Found 307.1656.



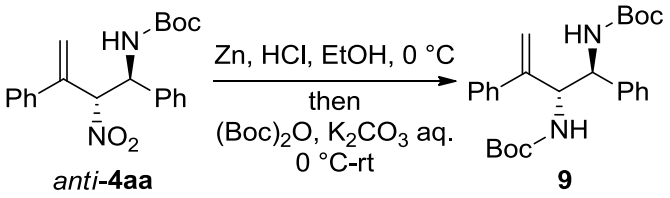
6: Geometry of the double bond was determined by NOE experiments on degree of enhancement of the peak areas of the *ortho*-protons of left phenyl group upon irradiation of the methyl signal and the peak areas of protons next to nitrogen atoms upon irradiation of the signal for olefinic proton. HPLC: IA, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 35.0 min (minor *syn* isomer), 41.9 min (major *syn* isomer), 50.5 min (minor *anti* isomer), 64.2 min (major *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] *anti* isomer δ 7.74 (1H, d, J = 9.6 Hz), 7.48-7.22 (8H, m), 7.14 (2H, d, J = 6.9 Hz), 6.40 (1H, q, J = 6.9 Hz), 5.65 (1H, d,

J = 11.4 Hz), 5.08 (1H, dd, *J* = 9.6, 11.4 Hz), 1.56 (3H, d, *J* = 6.9 Hz), 1.36 (9H, s); ^{13}C NMR [101 MHz, $(CD_3)_2SO$] *anti* isomer δ 154.4, 138.8, 136.0, 133.5, 132.7, 128.9, 128.5, 128.4, 128.1, 127.8, 127.6, 95.5, 78.7, 54.3, 28.1, 15.0; IR (neat) 2978, 2930, 1699, 1553, 1495, 1456, 1364, 1250, 1163, 1017, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_4Na^+$ ([M+Na]$^+$) 405.1785. Found 405.1781.

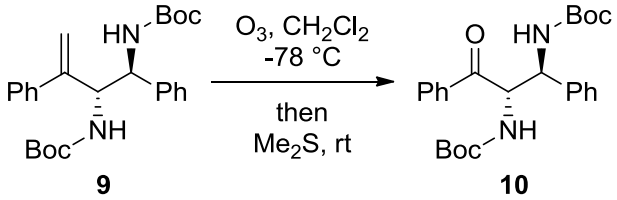


8: HPLC: AD-3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 12.1 min (minor *anti* isomer), 16.1 min (major *anti* isomer), 18.7 min (minor *syn* isomer), 25.6 min (major *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.46 (1H, d, *J* = 7.8 Hz), 7.39-7.15 (8H, m), 6.76 (1H, t, *J* = 4.6 Hz), 5.93 (1H, d, *J* = 10.1 Hz), 5.62 (1H, br), 4.92 (1H, br), 2.73 (2H, dd, *J* = 7.1, 8.9 Hz), 2.46-2.26 (2H, m), 1.32 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.6, 137.7, 136.4, 133.1, 132.9, 129.0, 128.8, 128.2, 127.8, 127.3, 127.0, 122.1, 89.4, 80.4, 56.2, 28.2, 27.6, 23.2, one carbon was not found probably due to overlapping; IR (film) 2976, 2933, 1699, 1553, 1491, 1365, 1252, 1163, 1020, 758 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{26}N_2O_4Na^+$ ([M+Na]$^+$) 417.1785. Found 417.1783.

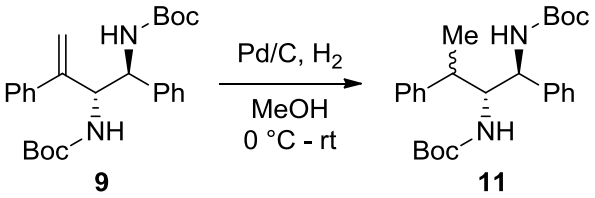
Derivatization of the Aza-Henry Adduct 4aa:



Procedure for Derivatization of 4aa to 9: Zinc powder (130.8 mg, 2.0 mmol) was added to a solution of **4aa** (36.8 mg, 0.10 mmol) in 0.48 M HCl/EtOH (4.2 mL) at 0 °C. After 5 min of stirring, a saturated aqueous solution of K_2CO_3 was added to the mixture and then $(Boc)_2O$ (25.3 μL, 0.11 mmol) was introduced dropwise. The mixture was stirred at room temperature for 12 h. EtOH was removed by evaporation and the residue was extracted with EA twice. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by column chromatography on silica gel (H/EA = 3:1 as eluent) gave **9** in 96% yield. **9:** HPLC: AD-3, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 243 nm, 50.8 min (minor enantiomer), 66.5 min (major enantiomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, J = 7.3 Hz), 7.38-7.15 (6H, m), 7.08 (2H, d, J = 7.3 Hz), 5.48 (1H, br), 5.26 (1H, s), 5.17 (1H, d, J = 9.6 Hz), 4.81 (1H, br), 4.80 (1H, s), 4.74 (1H, d, J = 9.6 Hz), 1.45 (9H, s), 1.40 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 155.0, 147.1, 139.9, 137.8, 128.8, 128.2, 128.1, 127.6, 127.1, 127.0, 114.6, 80.3, 79.8, 57.4, 56.3, 28.4, one carbon was not found probably due to overlapping; IR (film) 3398, 2978, 2930, 1682, 1518, 1366, 1292, 1246, 1165, 1001, 874, 756 cm^{-1}; HRMS (FAB) Calcd for $C_{26}H_{35}N_2O_4^+$ ($[M+H]^+$) 439.2597. Found 439.2583.



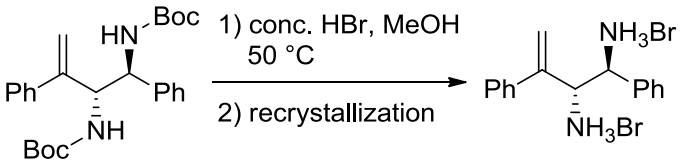
Ozonolysis of 9: O_3 was passed through a solution of **9** (43.8 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at –78 °C for 2 h and then excess O_3 was removed by bubbling of O_2. Me_2S (73.4 μL, 1.0 mmol) was added to the mixture and the solution was allowed to warm up to room temperature. After 2 h of standing, all volatiles were evaporated and purification of the residue by column chromatography on silica gel (H/EA = 3:1 as eluent) gave **10** in 80% yield. **10:** HPLC: AD-3, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 18.4 min (major enantiomer), 26.6 min (minor enantiomer). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.08 (2H, d, J = 7.8 Hz), 7.66 (1H, t, J = 7.8 Hz), 7.54 (2H, t, J = 7.8 Hz), 7.36 (2H, d, J = 7.3 Hz), 7.28 (1H, t, J = 7.3 Hz), 7.22 (2H, t, J = 7.3 Hz), 6.77 (1H, d, J = 8.0 Hz), 6.24 (1H, d, J = 8.0 Hz), 5.76 (1H, t, J = 8.0 Hz), 5.24 (1H, t, J = 8.0 Hz), 1.33 (9H, s), 1.31 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 156.2, 155.3, 137.1, 134.8, 134.2, 129.1, 129.0, 128.5, 128.0, 126.8, 80.5, 79.9, 58.8, 57.5, 28.5, 28.4; IR (film) 3385, 2976, 2928, 1674, 1518, 1341, 1250, 1229, 1161, 1005, 871, 758 cm^{-1}; HRMS (FAB) Calcd for $C_{25}H_{33}N_2O_5^+$ ($[M+H]^+$) 441.2389. Found 441.2398.



9 **11**

Hydrogenation of 9: To a solution of **9** (43.8 mg, 0.10 mmol) in MeOH (2.5 mL) was added 10 % Pd/C (10.0 mg) at 0 °C under Ar and then the atmosphere was replaced with H_2 (balloon). After 1 h of stirring at room temperature, the reaction mixture was filtered through a pad of Celite for removing Pd/C and concentration of the filtrate was performed. The residue was purified by column chromatography on silica gel (H/EA = 3:1 as eluent) to afford **11** quantitatively in the diastereomeric ratio of 5:1. **11:** ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 100 °C) *major* isomer δ 7.35-7.12 (10H, m), 7.07 (1H, br), 5.13 (1H, br), 4.27 (1H, t, *J* = 10.0 Hz), 4.11 (1H, td, *J* = 10.0, 5.0 Hz), 3.20 (1H, qd, *J* = 6.9, 5.0 Hz), 1.37 (9H, s), 1.28 (3H, d, *J* = 6.9 Hz), 1.17 (9H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$, 100 °C) *major* isomer δ 154.4, 154.0, 142.2, 141.4, 127.8, 127.4, 127.2, 126.9, 125.9, 125.6, 77.4, 77.2, 57.3, 56.5, 27.8, 27.5, 18.5, one carbon was not found probably due to overlapping; IR (film) 3362, 2974, 2932, 1693, 1497, 1366, 1169, 1009 cm^{-1}; HRMS (FAB) Calcd for $C_{26}H_{37}N_2O_4^+$ ([M+H]$^+$) 441.2753. Found 441.2757.

Determination of Absolute Configuration of the Aza-Henry Adduct 4aa:



9 **12**

Deprotection of 9 Derived from 4aa and Recrystallization of 12: A solution of **9** (40.0 mg, 0.09 mmol) in MeOH (1.0 mL) was treated with *conc.* aqueous HBr (23.0 μL, 0.2 mmol) at 50 °C for 12 h. The resulting mixture was concentrated *in vacuo* to give crude residue mostly containing dihydrobromide **12**. A single crystal of **12**, which is suitable for X-ray and other spectroscopic analyses, was obtained by recrystallization from H/EA/MeOH solvent system at room temperature. Absolute and relative configurations of **12** were determined to be (1*S*, 2*R*) by X-ray diffraction analysis (see below). ^{1}H NMR (400 MHz, CD_3OD) δ 7.70-7.64 (4H, m), 7.63-7.56 (3H, m), 7.54-7.43 (3H, m), 6.06 (1H, s), 5.99 (1H, s), 4.91 (2H, s), six protons were not found due to deuteration; ^{13}C NMR (101 MHz, CD_3OD) δ 143.4, 139.0, 132.9, 132.1, 131.2, 130.4, 130.3, 129.6, 128.1, 121.9, 58.2, 56.6; IR (film) 2922, 2853, 1501, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{19}N_2^+$ ([M+H–2Br]$^+$) 239.1543. Found 239.1543.

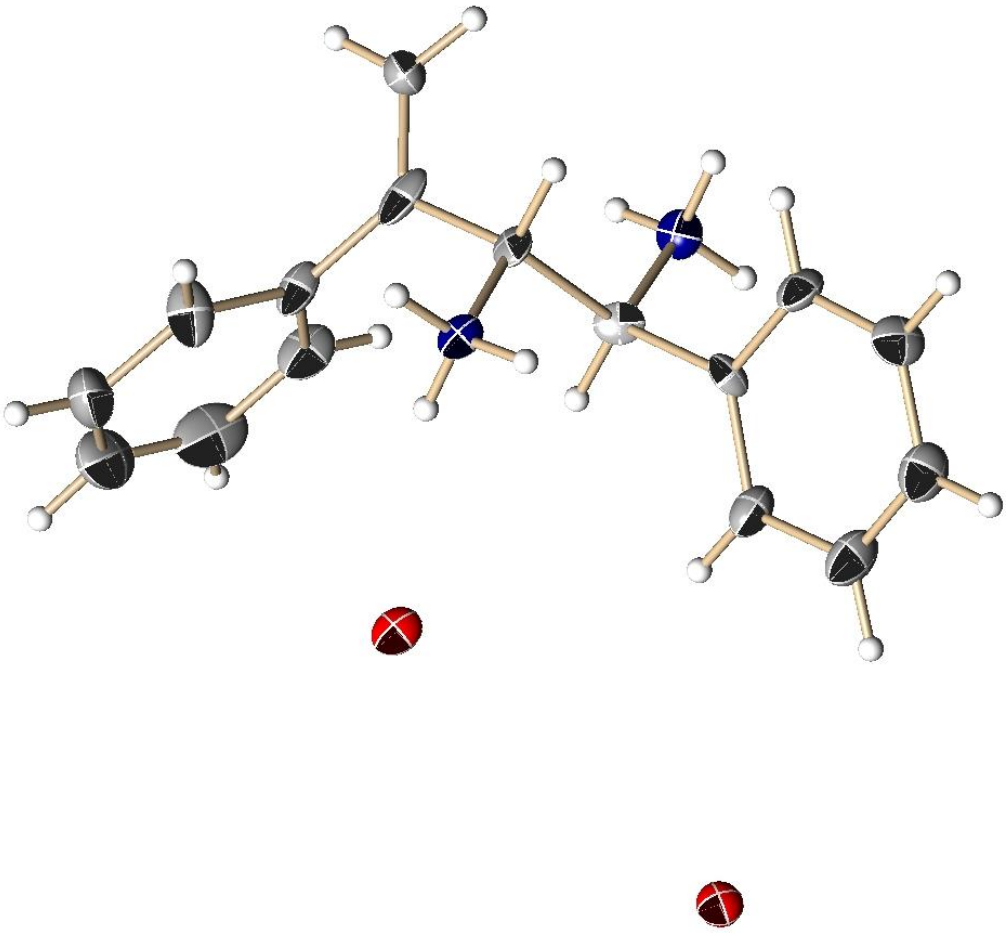


Figure S1. ORTEP diagram of **12**. Blue = nitrogen, red = bromine, gray = carbon.

Crystallographic Structure Determination:

The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 153 K on a Brucker 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[18]. All non-hydrogen atoms were refined with anisotropic displacement parameters and the hydrogen atoms were placed in calculated positions. The crystallographic data were summarized in the following table.

Table S1. Crystal data and structure refinement for **12**. (CCDC 881694)

Empirical formula	$C_{16}H_{20}Br_2N_2$	
Formula weight	400.16	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.890(8) Å	α = 106.82(2)°.
	b = 6.888(9) Å	β = 94.94(2)°.
	c = 11.317(15) Å	γ = 100.70(2)°.
Volume	427.0(9) $Å^3$	
Z	1	
Density (calculated)	1.556 Mg/m^3	
Absorption coefficient	4.739 mm^{-1}	
F(000)	200	
Crystal size	0.22 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.90 to 28.38°.	
Index ranges	-6<=h<=7, -9<=k<=7, -14<=l<=14	
Reflections collected	2964	
Independent reflections	2464 [R(int) = 0.0385]	
Completeness to theta = 28.38°	95.5 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2464 / 3 / 183	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R_1 = 0.0595, wR_2 = 0.1659	
R indices (all data)	R_1 = 0.0612, wR_2 = 0.1672	
Absolute structure parameter	0.02(3)	
Largest diff. peak and hole	2.693 and -2.515 e.$Å^{-3}$	

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(15) When the reaction was conducted with triethylamine as a base at room temperature, the formation of a trace amount of **4aa** was observed albeit with concomitant isomerization of **2a** to **2a'**.

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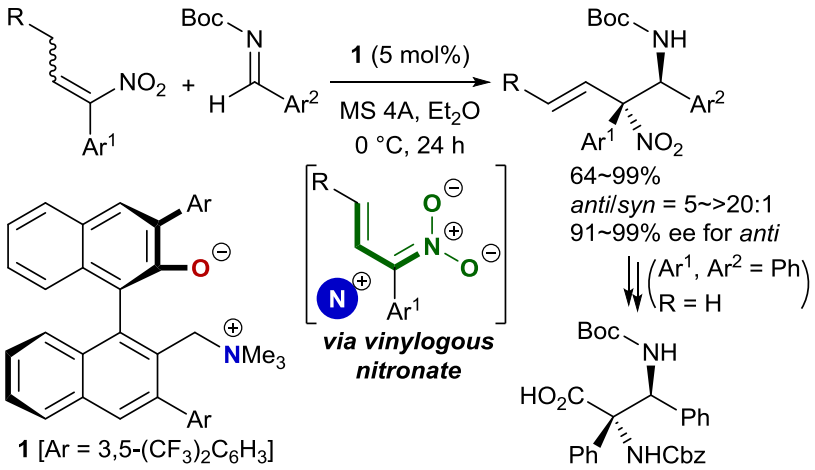
Chapter 3

Vinylogy in Nitronates:
Utilization of α-Aryl Conjugated Nitroolefins as a Nucleophile for Highly Stereoselective Aza-Henry Reaction

Abstract:



Vinylogous reactivity of α,β-disubstituted nitroolefins was uncovered through the facile generation of the corresponding α-substituted vinylogous nitronates and their use for the development of a highly diastereo- and enantioselective aza-Henry reaction with N-Boc aldimines under the catalysis of chiral ammonium betaines. The novel vinylogous nitronates undergo the stereoselective bond formation at the sterically encumbered α-position exclusively, allowing the construction of contiguous tertiary-quaternary stereogenic carbon centers.

3.1. Introduction

The principle of vinylogy was originally defined by Reynold C. Fuson in 1935 for both electrophiles and nucleophiles.[1] Interposing double bond(s) between an activating group and a parent reactive site of a substrate produces a conjugate π-system, through which the inherent electronic effects propagate, often shifting the reactive site. The extended conjugate system brings about multiple selectivity issues depending on the mode of transformations, but it also imparts additional yet useful functional handle to the products. Accordingly, a wide variety of studies into exploiting the characteristics of this principle in synthetic reaction development has recently been performed, leading to the establishment of highly selective catalytic methodologies.[2,3] However, most of the existing methods employ substrates bearing carbonyl-based activating groups and the potential utility of vinylogous reactivity associated with other functionalities such as nitro and sulfonyl groups is largely unexplored.[4] In particular, while simple nitronates of nitroalkanes have found extensive use as nucleophiles, especially in asymmetric catalysis, vinylogous nitronates remain underutilized in stereoselective transformations primarily because of the difficulty in selectively deprotonating the γ-carbon of nitroolefins using standard bases.[5] In 2012, we disclosed a highly stereoselective aza-Henry reaction of vinylogous nitronates generated from β,β-disubstituted nitroolefins with chiral ammonium betaine of type **1** as a catalyst, wherein the β-substituted vinylogous nitronate predominantly reacted at the sterically more *accessible* α-position with *N*-Boc aldimines.[6–11] It was assumed that the steric repulsion between the *cis*-oriented substituents, the nitro and alkyl groups, on the C=C moiety of the parent nitroolefin (allylic 1,3-strain[12]) would be relieved upon abstraction of the γ–proton, assisting the generation of the requisite vinylogous nitronate (Fig. 1). This notion led us to become interested in utilizing α,β-disubstituted nitroolefins **2** as the nucleophilic component, which feature similar steric congestion that would benefit the facile generation of the corresponding α-substituted vinylogous nitronates under the influence of **1**. Here, we report the realization of this possibility through the development of a highly diastereo- and enantioselective aza-Henry reaction of **2** with *N*-Boc imines **3** catalyzed by appropriately modified chiral ammonium betaine **1**. Notably, the novel vinylogous nitronate generated *in situ* from **2** undergoes bond formation at the sterically more *encumbered* α-position exclusively, thereby enabling the construction of adjacent tertiary-quaternary stereogenic carbon centers.

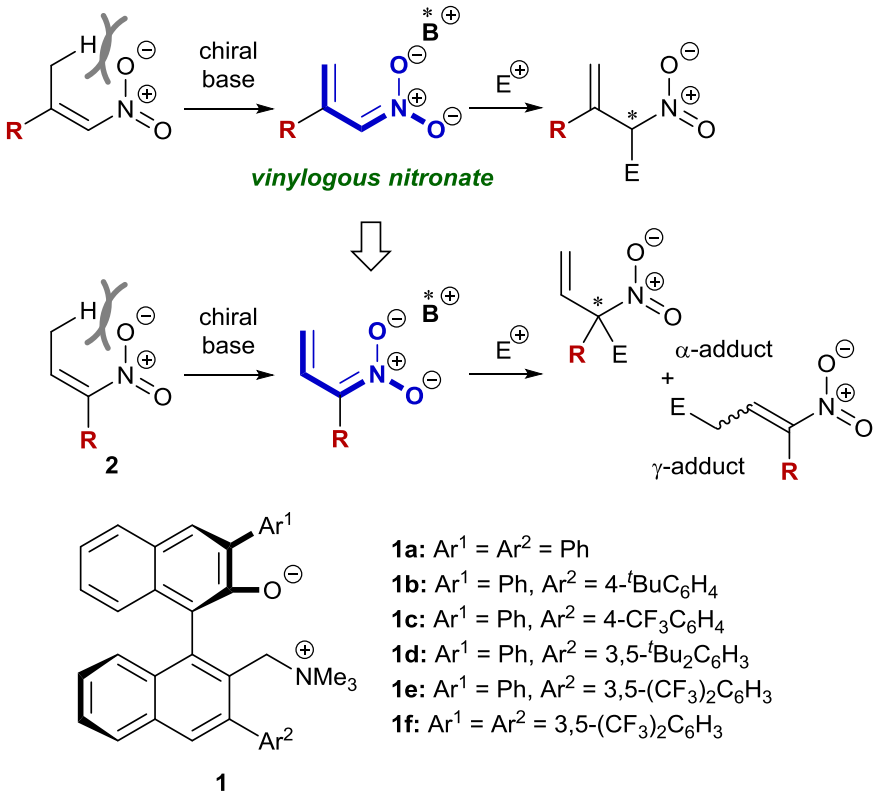


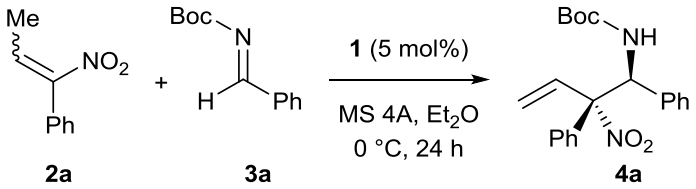
Figure 1. Generation of Vinylogous Nitronates from Conjugated Nitroolefins and Structures of C_1-Symmetric Chiral Ammonium Betaine **1**.

3.2. Results and Discussion

2-Phenyl-1-nitroprop-1-ene (**2a**, *E*/*Z* = 1:10) was selected as a model pronucleophile to assess the validity of our hypothesis on the applicability of α,β-disubstituted nitroolefins as precursors for α-substituted vinylogous nitronates. Thus, an initial attempt was made by treating **2a** with *N*-Boc benzaldimine (**3a**) in the presence of 4A molecular sieves (MS 4A) and chiral ammonium betaine **1a** (5 mol%) in Et_2O at 0 ºC (Table 1, entry 1).[13] Although the rate was insufficient, bond formation took place within 24 h of stirring; intriguingly, ^{1}H NMR (400 MHz) analysis of the crude mixture showed product signals corresponding only to aza-Henry adduct **4a** that was formed through the exclusive α-addition of the expected vinylogous nitronate to **3a** despite the significant steric constraints. It should be noted that the *E*/*Z* ratio of the recovered **2a** was virtually unchanged. This observation suggested that the vinylogous nitronate was generated from both isomers, probably because the relief of the allylic 1,3-strain through the deprotonation of the γ-carbon could be appreciated by either geometrical isomer.[14] Since a promising level of stereoselectivity was attained with betaine **1a** as the catalyst, we pursued the optimization of **1** by altering the structural features of the aryl appendages at the 3,3'-positions of the binaphthyl backbone (Ar^1 and Ar^2). As revealed in Table 1 (entries 2-6), introduction of electron-deficient substituents such as a trifluoromethyl group, rather than a sterically demanding alkyl group, to the aromatic nucleus had a positive impact on the catalytic efficiency and stereocontrolling ability of **1** (entries 2,4 vs 3,5). Eventually, compounds **1f** possessing 3,5-bis(trifluoromethyl)phenyl groups as Ar^1 and Ar^2 was identified as the optimal catalyst that allowed the

production of **4a** in 90% yield with rigorous stereochemical control of the vicinal tertiary-quaternary stereocenters (entry 6).

Table 1 Effect of Substituents at 3-Position of Each Naphthyl Unit of Chiral Ammonium Betaine **1**[a]



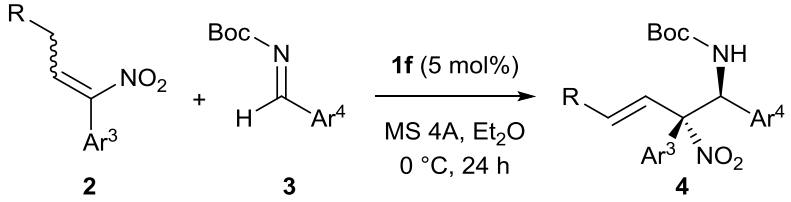
2a **3a** **4a**

Entry	**1**	Yield (%)[b]	d.r. (*anti*/*syn*)[c]	ee (%)[d]
1	**1a**	21	13:1	77
2	**1b**	trace	-	-
3	**1c**	52	15:1	87
4	**1d**	52	14:1	87
5	**1e**	69	19:1	90
6	**1f**	90	>20:1	96

[a] Reactions were carried out with 0.11 mmol of **2a**, 0.10 mmol of **3a**, and 0.005 mmol of **1** in 0.3 mL of Et_2O with 100 mg of MS 4A at 0 ºC under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^1H NMR (400 MHz) analysis of crude aliquots. [d] Enantiomeric excesses of product **4a** were analyzed by chiral HPLC using DAICEL CHIRALPAK IA with a hexane/2-propanol solvent system. Absolute and relative stereochemistries of **4a** were determined by comparison with known α,β-diamino acid after derivatization (Scheme 1).

With the optimized reaction conditions in hand, the substrate generality of this asymmetric aza-Henry protocol was investigated and the representative results are summarized in Table 2. As the electrophilic component, various *N*-Boc aromatic aldimines **3** were employable irrespective of their steric and electronic attributes (entries 1-9). When an electron-withdrawing group was introduced at the *para*-position of the aromatic ring, certain decrease in chemical yield was detected, while high diastereoselectivity and excellent enantioselectivity were generally observed (entries 2 and 4). The imines **3i** and **3j** derived from 1-naphthyl- and 2-furylaldehydes, respectively, were also amenable to this catalytic system, although diastereoselectivity was moderate in the reaction with **3j** (entries 8 and 9). With respect to nitroolefin nucleophile **2**, varying the α-aromatic substituent subtly affected the efficiency and stereocontrol (entries 10-12). Furthermore, elongation of the β-alkyl chain was tolerated, which suggested the smooth generation of the vinylogous nitronates from 1-nitro-1-phenylbutene (**2e**) and 1-nitro-1-phenyloctene (**2f**) under the present conditions, leading to afford the aza-Henry adducts **4n** and **4o** in high yield in an essentially stereochemically pure form (entries 13 and 14).

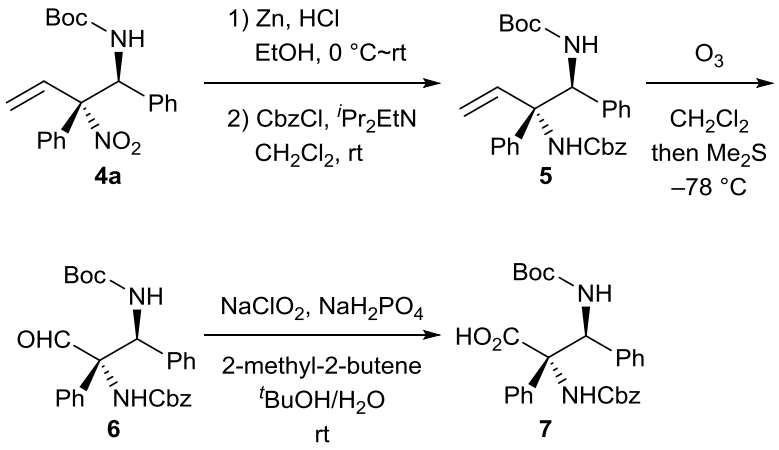
Table 2 Substrate Scope in **1f**-Catalyzed Aza-Henry Reaction of α,β-Disubstituted Nitroolefins **2** with *N*-Boc Imines **3**[a]



Entry	R, Ar^3 (**2**)	Ar^4 (**3**)	Yield (%)[b]	d.r. (*anti*/*syn*)[c]	ee (%)[d]	Prod (**4**)
1	H, Ph (**2a**)	4-MeC_6H_4 (**3b**)	82	>20:1	92	**4b**
2	H, Ph (**2a**)	4-FC_6H_4 (**3c**)	64	>20:1	96	**4c**
3	H, Ph (**2a**)	4-ClC_6H_4 (**3d**)	97	15:1	93	**4d**
4	H, Ph (**2a**)	4-$CF_3C_6H_4$ (**3e**)	70	>20:1	99	**4e**
5	H, Ph (**2a**)	3-BrC_6H_4 (**3f**)	80	13:1	93	**4f**
6	H, Ph (**2a**)	3-$MeOC_6H_4$ (**3g**)	94	16:1	94	**4g**
7	H, Ph (**2a**)	2-FC_6H_4 (**3h**)	91	>20:1	96	**4h**
8	H, Ph (**2a**)	1-naphthyl (**3i**)	66	14:1	91	**4i**
9	H, Ph (**2a**)	2-furyl (**3j**)	68	5:1	94	**4j**
10	H, 4-MeC_6H_4 (**2b**)	Ph (**3a**)	85	>20:1	95	**4k**
11	H, 4-FC_6H_4 (**2c**)	Ph (**3a**)	73	10:1	92	**4l**
12	H, 3-$MeOC_6H_4$ (**2d**)	Ph (**3a**)	99	18:1	98	**4m**
13	Me, Ph (**2e**)	Ph (**3a**)	90	>20:1	99	**4n**
14	$Me(CH_2)_6$, Ph (**2f**)	Ph (**3a**)	86	>20:1	98	**4o**

[a] Reactions were carried out with 0.11 mmol of **2**, 0.10 mmol of **3**, and 0.005 mmol of **1f** in 0.3 mL of Et_2O with 100 mg of MS 4A at 0 °C under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^1H NMR (400 MHz) analysis of crude mixtures. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute and relative configurations of aza-Henry adducts **4** were assigned by analogy to **4a**.

The absolute stereochemistry of the major diastereomer of **4a** was determined by derivatization into known α,β-diamino acid **7** (Scheme 1). Reduction of the nitro functionality of **4a** followed by protection of the resulting primary amine with benzyl chloroformate (CbzCl) afforded differentially protected chiral diamine **5** in good yield. Its vinyl group was oxidatively cleaved via ozonolysis to give α,β-diamino aldehyde **6** and subsequent Pinnick oxidation of the aldehyde moiety furnished α,β-diamino acid **7**. The conservation of the enantiomeric excess in **7** was confirmed by chiral HPLC analysis of its methyl ester[15] and the absolute configuration was assigned as 1*S*,2*S* by comparison with the literature data.[7b]



Scheme 1. Derivatization of **4a** to the Corresponding α,β-Diamino Acid **7** to Determine Its Absolute and Relative Configuration

3.3. Conclusions

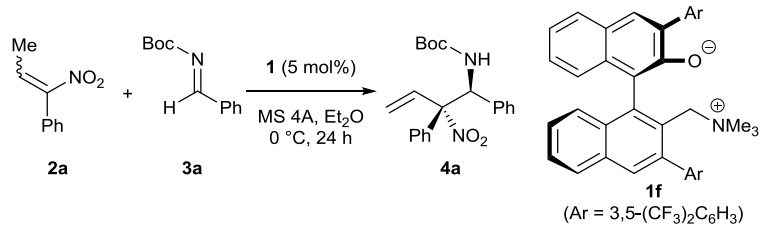
In conclusion, we have demonstrated the feasibility and synthetic utility of catalytically generating α-substituted vinylogous nitronates from α,β-disubstituted nitroolefins through the development of a highly stereoselective aza-Henry reaction using chiral ammonium betaines as organic base catalysts. The relief of the steric repulsion between *cis*-oriented substituents of the nitroolefins appeared to assist the facile generation of the vinylogous nitronates, which reacted with *N*-Boc aldimines at the sterically more congested α-position exclusively, thus establishing the contiguous tertiary-quaternary stereocenters. We believe that the present study significantly expands the potential of the vinylogous reactivity of nitroolefins and its utilization for developing selective carbon-carbon bond-forming reactions.

3.4. Experimental Section

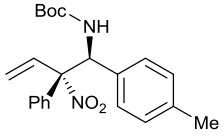
General Information: Infrared spectra were recorded on a SHIMADZU IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0.00 ppm) resonance as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, 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 ($CDCl_3$: 77.16 ppm). The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive (ESI). 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 IA (IA), CHIRALPAK IC (IC), CHIRALPAK ID-3 (ID-3), CHIRALPAK IF-3 (IF-3), CHIRALPAK AD-3 (AD-3), CHIRALPAK AZ-3 (AZ-3), CHIRALPAK AD-H (AD-H), and CHIRALCEL OD-3 (OD-3) with hexane (H), 2-propanol (IPA), and ethanol (EtOH) as eluent].

Diethylether (Et_2O) was supplied from Kanto Chemical Co., Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. Betaines[6,7b], nitro olefins[14], and *N*-Boc imines[15] were prepared by following the literature procedure. Powdered 4Å molecular sieves (MS 4A) was supplied by NACALAI TESQUE, INC. Other simple chemicals were purchased and used as such.

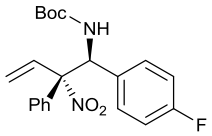
Experimental Section:



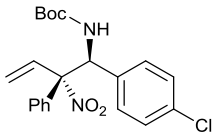
Representative Procedure for Catalytic Asymmetric Aza-Henry Reaction: A magnetic stirrer bar and MS 4A (100.0 mg) were placed in an oven-dried test tube under argon (Ar) atmosphere. The MS 4A was dried with a heat gun under reduced pressure for 5 min and the test tube was refilled with Ar. Chiral ammonium betaine **1f** (3.83 mg, 0.0050 mmol) and Et_2O (0.30 mL) were added to the test tube successively under Ar at 25 °C. After the mixture was cooled to 0 °C, nitroolefin **2a** (17.9 mg, 0.11 mmol) and benzaldehyde-derived *N*-Boc imine **3a** (20.5 mg, 0.10 mmol) were introduced to the tube sequentially. The reaction mixture was stirred for 24 h and then, poured into ice-cooled 1 *N* hydrochloric acid. The aqueous phase was extracted with ethyl acetate (EA) twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. All volatiles were removed by evaporation to afford the crude residue, which was analyzed by ^{1}H NMR (400 MHz) to determine the diastereomeric ratio (*anti*/*syn* = >20:1). Purification of the residue by column chromatography on silica gel ($H/CHCl_3$ = 1:2 as eluent) gave **4a** as a mixture of diastereomers (33.2 mg, 90%), whose enantiomeric excesses were determined by HPLC analysis (96% ee for *anti* isomer). **4a:** HPLC: IA, H/IPA = 98:2, flow rate = 0.3 mL/min, λ = 210 nm, 22.0 min (1*S*, 2*S*), 23.2 min (1*R*, 2*R*), 25.5 min (minor diastereomer), 27.6 min (minor diastereomer). Absolute and relative configurations were assigned by the derivatization to **7** (see below). ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.60–7.39 (3H, m), 7.39–7.30 (3H, m), 7.30–7.28 (4H, m), 6.44 (1H, d, J = 9.6 Hz), 6.15 (1H, dd, J = 17.4, 11.0 Hz), 5.64 (1H, d, J = 9.6 Hz), 5.37 (1H, d, J = 11.0 Hz), 4.64 (1H, d, J = 17.4 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 136.7, 136.0, 135.0, 129.0, 128.8, 128.7, 127.4, 121.4, 101.9, 80.2, 59.3, 28.4, two carbon atoms were not found probably due to overlapping; IR (film) 3447, 2976, 1713, 1547, 1479, 1366, 1312, 1294, 1159, 1057, 945 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{24}N_2O_4Na^+$ ($[M+Na]^+$) 391.1628. Found 391.1626.



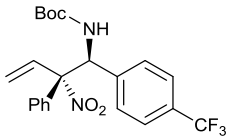
4b: HPLC: AD-3, H/IPA = 98:2, flow rate = 0.3 mL/min, λ = 210 nm, 27.1 min (minor enantiomer of major diastereomer), 29.5 min (major enantiomer of major diastereomer), 32.2 min (minor diastereomer), 37.2 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.44–7.37 (3H, m), 7.24–7.19 (2H, m), 7.16 (2H, d, J = 9.4 Hz), 7.13 (2H, d, J = 9.2 Hz), 6.40 (1H, d, J = 9.6 Hz), 6.17 (1H, dd, J = 17.4, 11.0 Hz), 5.60 (1H, d, J = 9.6 Hz), 5.36 (1H, d, J = 11.0 Hz), 4.63 (1H, d, J = 17.4 Hz), 2.34 (3H, s), 1.33 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 138.5, 136.1, 135.1, 133.6, 129.5, 129.0, 128.7, 128.5, 127.4, 121.3, 102.0, 80.1, 59.0, 28.4, 21.3; IR (film) 3449, 2974, 1713, 1547, 1483, 1366, 1310, 1290, 1165, 941 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_4Na^+$ ($[M+Na]^+$) 405.1785. Found 405.1786.



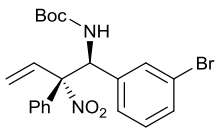
4c: HPLC: ID-3, H/IPA = 97:3, flow rate = 0.2 mL/min, λ = 210 nm, 30.1 min (minor enantiomer of major diastereomer), 32.2 min (major enantiomer of major diastereomer), 39.6 min (minor diastereomer), 51.2 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.45–7.39 (3H, m), 7.26–7.16 (4H, m), 7.05 (2H, dd, J_{H-H} = 7.6 Hz, J_{F-H} = 7.6 Hz), 6.39 (1H, brd, J = 9.8 Hz), 6.14 (1H, dd, J = 17.4, 11.0 Hz), 5.62 (1H, d, J = 9.8 Hz), 5.40 (1H, d, J = 11.0 Hz), 4.67 (1H, d, J = 17.4 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 162.8 (d, J_{F-C} = 251.6 Hz), 155.1, 135.7, 134.8, 132.5, 130.4 (d, J_{F-C} = 8.7 Hz), 129.1, 128.8, 127.3, 121.7, 115.8 (d, J_{F-C} = 22.3 Hz), 101.8, 80.4, 58.7, 28.4; IR (film) 3449, 2980, 1711, 1605, 1547, 1479, 1366, 1294, 1225, 1161, 849 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_4F_1Na^+$ ([M+Na]$^+$) 409.1534. Found 409.1535.



4d: HPLC: AZ-3, H/EtOH = 98:2, flow rate = 0.2 mL/min, λ = 224 nm, 31.0 min (major enantiomer of major diastereomer), 36.0 min (minor enantiomer of major diastereomer), 41.4 min (minor diastereomer), 43.8 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.45–7.39 (3H, m), 7.33 (2H, d, J = 8.7 Hz), 7.24–7.15 (4H, m), 6.38 (1H, d, J = 9.4 Hz), 6.14 (1H, dd, J = 17.4, 11.0 Hz), 5.61 (1H, d, J = 9.4 Hz), 5.40 (1H, d, J = 11.0 Hz), 4.67 (1H, d, J = 17.4 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.0, 135.6, 135.3, 134.7, 130.0, 129.2, 129.0, 128.8, 127.3, 121.8, 101.7, 80.5, 58.7, 28.4, one carbon atom was not found probably due to overlapping; IR (film) 3451, 2980, 1713, 1549, 1483, 1344, 1163, 1092, 1015, 947, 849 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}{}^{35}Cl_1N_2O_4Na^+$ ([M+Na]$^+$) 425.1239. Found 425.1239.

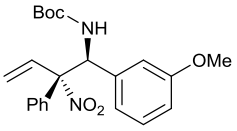


4e: HPLC: IA, H/IPA = 98:2, flow rate = 0.5 mL/min, λ = 221 nm, 12.1 min (major enantiomer of major diastereomer), 15.4 min (minor diastereomer), 16.4 min (minor diastereomer), 17.9 min (minor enantiomer of major diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.62 (2H, d, J = 8.2 Hz), 7.46–7.41 (3H, m), 7.39 (2H, d, J = 8.2 Hz), 7.24–7.17 (2H, m), 6.43 (1H, d, J = 9.6 Hz), 6.13 (1H, dd, J = 17.4, 10.8 Hz), 5.70 (1H, d, J = 9.6 Hz), 5.43 (1H, d, J = 10.8 Hz), 4.71 (1H, d, J = 17.4 Hz), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 140.8, 135.4, 134.5, 130.9 (q, J_{F-C} = 33.2 Hz), 129.3, 129.2, 128.9, 127.3, 125.8 (q, J_{F-C} = 3.9 Hz), 124.0 (q, J_{F-C} = 276.1 Hz), 122.1, 101.5, 80.6, 59.0, 28.4; IR (film) 3464, 2976, 1711, 1620, 1551, 1479, 1323, 1163, 1125, 1069, 947, 853 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{23}N_2O_4F_3Na^+$ ([M+Na]$^+$) 459.1502. Found 459.1501.

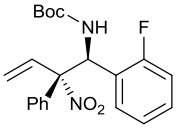


4f: HPLC: IA, H/IPA/EtOH = 96:2:2, flow rate = 0.2 mL/min, λ = 214 nm, 25.7 min (major enantiomer of major diastereomer), 28.2 min (minor enantiomer of major diastereomer), 29.3 min (minor diastereomer), 31.0 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.47 (1H, dt, J = 7.3, 1.6 Hz), 7.45–7.35 (4H, m), 7.23 (1H, t, J = 7.8 Hz), 7.22–7.15 (3H, m), 6.38 (1H, d, J = 9.6 Hz), 6.16 (1H, dd, J = 17.4, 10.8 Hz), 5.60 (1H, d, J = 9.6 Hz), 5.43 (1H, d, J = 10.8 Hz), 4.69 (1H, d, J = 17.4 Hz), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.0, 139.0, 135.5, 134.7, 131.9$_3$, 131.8$_8$, 130.4, 129.2, 128.8, 127.3, 122.8, 122.0, 101.6, 80.5, 58.8, 28.4, one carbon atom was not found probably due to overlapping; IR (film) 3453, 2976,

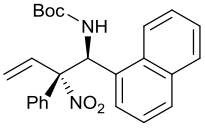
1713, 1547, 1470, 1410, 1339, 1288, 1161, 1059, 947, 839 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_4{}^{79}Br_1Na^+$ ($[M+Na]^+$) 469.0733. Found 469.0735.



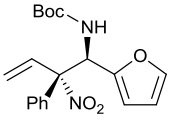
4g: HPLC: IA, H/IPA = 98:2, flow rate = 0.5 mL/min, λ = 210 nm, 15.6 min (major enantiomer of major diastereomer), 17.4 min (minor enantiomer of major diastereomer), 18.9 min (minor diastereomer), 35.0 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.47–7.37 (3H, m), 7.26 (1H, t, J = 8.0 Hz), 7.24–7.17 (2H, m), 6.85 (1H, t, J = 5.5 Hz), 6.79 (1H, s), 6.40 (1H, d, J = 10.1 Hz), 6.20 (1H, dd, J = 17.4, 11.0 Hz), 5.61 (1H, d, J = 10.1 Hz), 5.37 (1H, d, J = 11.0 Hz), 4.64 (1H, d, J = 17.4 Hz), 3.79 (3H, s), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 159.7, 155.1, 138.1, 136.0, 135.0, 129.8, 129.0, 128.7, 127.4, 121.4, 120.9, 114.7, 113.9, 101.8, 80.2, 59.2, 55.4, 28.4; IR (film) 3431, 2976, 1711, 1601, 1547, 1479, 1342, 1256, 1157, 1038, 947, 862 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_5Na^+$ ($[M+Na]^+$) 421.1734. Found 421.1729.



4h: HPLC: ID-3, H/EtOH = 95:5, flow rate = 0.1 mL/min, λ = 210 nm, 46.6 min (minor enantiomer of major diastereomer), 50.4 min (major enantiomer of major diastereomer), 53.6 min (minor diastereomer), 56.2 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.47–7.38 (3H, m), 7.38–7.29 (1H, m), 7.29–7.19 (3H, m), 7.16 (1H, t, J = 7.1 Hz), 7.09 (1H, t, J_{H-H} = 7.1 Hz, J_{F-H} = 11.4 Hz), 6.43 (1H, d, J = 9.6 Hz), 6.10 (1H, d, J = 9.6 Hz), 6.06 (1H, ddd, J = 17.2, 10.7, 3.0 Hz), 5.40 (1H, d, J = 10.7 Hz), 4.64 (1H, d, J = 17.2 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.2 (d, J_{F-C} = 251.6 Hz), 155.0, 134.7 (d, J_{F-C} = 5.8 Hz), 130.5 (d, J_{F-C} = 8.7 Hz), 129.1, 128.8, 128.7, 127.5, 125.1, 124.5 (d, J_{F-C} = 12.6 Hz), 122.4, 115.8 (d, J_{F-C} = 23.2 Hz), 102.1, 80.4, 51.9, 28.4, one carbon atom was not found probably due to overlapping; IR (film) 3449, 2932, 1713, 1549, 1481,1344, 1298, 1229, 1157, 1057, 839 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_4F_1Na^+$ ($[M+Na]^+$) 409.1534. Found 409.1535.

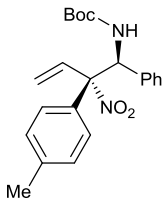


4i: HPLC: OD-3, H/IPA = 98:2, flow rate = 0.3 mL/min, λ = 210 nm, 18.9 min (major enantiomer of major diastereomer), 35.2 min (minor enantiomer of major diastereomer), minor diastereomers were not assigned. Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 8.20 (1H, d, J = 8.5 Hz), 7.87 (2H, t, J = 8.5 Hz), 7.57–7.40 (7H, m), 7.38–7.35 (2H, m), 6.72 (1H, d, J = 9.6 Hz), 6.69 (1H, d, J = 9.6 Hz), 5.79 (1H, dd, J = 17.4, 10.8 Hz), 5.22 (1H, d, J = 10.8 Hz), 4.58 (1H, d, J = 17.4 Hz), 1.32 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.2, 136.2, 135.0, 133.8, 133.7, 131.7, 129.5, 129.1$_2$, 129.0$_7$, 128.8, 127.6, 126.8, 126.0, 125.9, 125.4, 123.7, 122.0, 103.1, 80.0, 52.4, 28.4; IR (film) 2926, 1713, 1549, 1487, 1368, 1325, 1165, 1067 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{26}N_2O_4Na^+$ ($[M+Na]^+$) 441.1785. Found 441.1783.

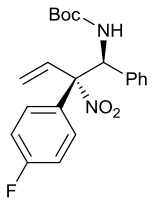


4j: HPLC: AD-3, H/EtOH = 98:2, flow rate = 0.5 mL/min, λ = 210 nm, 12.7 min (major enantiomer of major diastereomer), 13.9 min (minor diastereomer), 15.7 min (minor diastereomer), 17.7 min (minor enantiomer of major diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.45–7.31 (5H, m), 7.24–7.15 (2H, m), 6.40–6.26 (3H, m), 6.06 (1H, d, J = 10.5 Hz), 5.84 (1H, d, J = 10.5 Hz), 5.46 (1H, d, J = 10.5 Hz), 4.867 (1H, d, J = 17.4 Hz), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.0, 150.3, 142.7, 134.9,

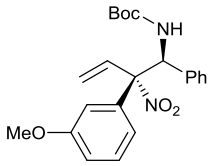
134.5, 129.0, 128.7, 127.1, 122.0, 110.7, 109.5, 101.1, 80.4, 53.6, 28.3; IR (film) 3431, 2976, 1713, 1551, 1485, 1366, 1329, 1231, 1155, 1013, 949, 870 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{22}N_2O_5Na^+$ ($[M+Na]^+$) 381.1421. Found 381.1420.



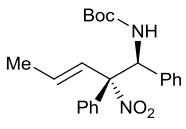
4k: HPLC: IA, H/IPA = 95:5, flow rate = 0.5 mL/min, λ = 210 nm, 10.3 min (major enantiomer of major diastereomer), 10.9 min (minor enantiomer of major diastereomer), 11.6 min (minor diastereomer), 12.7 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.38–7.29 (3H, m), 7.27–7.22 (2H, m), 7.21 (2H, d, J = 8.2 Hz), 7.10 (2H, d, J = 8.2 Hz), 6.43 (1H, d, J = 9.9 Hz), 6.14 (1H, dd, J = 17.3, 10.9 Hz), 5.60 (1H, d, J = 9.9 Hz), 5.36 (1H, d, J = 10.9 Hz), 4.66 (1H, d, J = 17.3 Hz), 2.38 (3H, s), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 139.0, 136.8, 136.2, 132.1, 129.4, 128.8, 128.7, 127.3, 121.3, 101.7, 80.2, 59.2, 28.4, 21.2, one carbon atom was not found probably due to overlapping; IR (film) 3447, 2970, 1713, 1547, 1483, 1366, 1310, 1292, 1169, 1057, 843 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_4Na^+$ ($[M+Na]^+$) 405.1785. Found 405.1787.



4l: HPLC: IC, H/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 10.5 min (major enantiomer of major diastereomer), 13.0 min (minor diastereomer), 14.0 min (minor diastereomer), 18.7 min (minor enantiomer of major diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.39–7.31 (3H, m), 7.26–7.18 (4H, m), 7.10 (2H, t, $J_{H–H}$ = 8.7 Hz, $J_{F–H}$ = 8.7 Hz), 6.38 (1H, d, J = 9.8 Hz), 6.16 (1H, dd, J = 17.2, 11.0 Hz), 5.60 (1H, d, J = 9.8 Hz), 5.39 (1H, d, J = 11.0 Hz), 4.65 (1H, d, J = 17.2 Hz), 1.35 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 162.8 (d, $J_{F–C}$ = 253.5 Hz), 155.1, 136.4, 136.0, 130.9 (d, $J_{F–C}$ = 2.9 Hz), 129.5 (d, $J_{F–C}$ = 8.7 Hz), 128.9, 128.8, 128.6, 128.5, 121.5, 115.7 (d, $J_{F–C}$ = 22.3 Hz), 101.4, 80.4, 59.3, 28.4; IR (film) 3453, 2978, 1709, 1605, 1549, 1514, 1485, 1312, 1236, 1169, 1055, 943, 837 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_4F_1Na^+$ ($[M+Na]^+$) 409.1534. Found 409.1535.

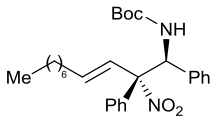


4m: HPLC: IF-3, H/IPA/EtOH = 94:2:4, flow rate = 0.5 mL/min, λ = 210 nm, 11.0 min (minor enantiomer of major diastereomer), 12.1 min (major enantiomer of major diastereomer), 13.2 min (minor diastereomer), 13.8 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.38–7.29 (4H, m), 7.27–7.22 (2H, m), 6.94 (1H, dd, J = 8.2, 2.3 Hz), 6.83–6.74 (2H, m), 6.44 (1H, d, J = 9.6 Hz), 6.13 (1H, dd, J = 17.3, 10.9 Hz), 5.62 (1H, d, J = 9.6 Hz), 5.38 (1H, d, J = 10.9 Hz), 4.73 (1H, d, J = 17.3 Hz), 3.81 (3H, s), 1.34 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 159.8, 155.1, 136.7, 136.3, 135.8, 129.7, 128.8, 128.7, 121.4, 119.6, 114.8, 113.1, 101.8, 80.2, 59.2, 55.5, 28.4, one carbon atom was not found probably doe to pverlapping; IR (film) 3443, 2978, 1703, 1601, 1547, 1487, 1352, 1288, 1227, 1167, 1030, 949 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_5Na^+$ ($[M+Na]^+$) 421.1734. Found 421.1733.



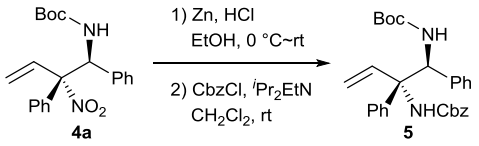
4n: HPLC: AZ-3, H/IPA = 98:2, flow rate = 0.3 mL/min, λ = 210 nm, 21.5 min (minor enantiomer of major diastereomer), 25.3 min (major enantiomer of major diastereomer), 29.4 min (minor diastereomer), 31.6 min (minor diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.44–7.30 (6H, m),

7.28–7.16 (4H, m), 6.42 (1H, d, *J* = 9.6 Hz), 5.78 (1H, dd, *J* = 15.8, 3.2 Hz), 5.61 (1H, d, *J* = 9.6 Hz), 5.03 (1H, sextet, *J* = 9.0 Hz), 1.67 (3H, d, *J* = 6.4 Hz), 1.33 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 136.9, 135.9, 133.5, 129.4, 128.8, 128.7_4, 128.6_9, 128.6_0, 127.4, 101.9, 80.1, 59.5, 28.4, 18.3, one carbon atom was not found probably due to overlapping; IR (film) 3451, 2972, 1713, 1547, 1479, 1366, 1292, 1161, 1047, 970, 843 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{26}N_2O_4Na^+$ ($[M+Na]^+$) 405.1785. Found 405.1785.



4o: HPLC analysis was performed after reduction of the nitro group. HPLC (*amine*): IA, H/IPA = 98:2, flow rate = 0.3 mL/min, λ = 210 nm, 35.6 min (minor enantiomer of major diastereomer), 42.2 min (minor diastereomer), 47.6 min (minor diastereomer), 56.7 min (major enantiomer of major diastereomer). Absolute and relative configurations were assigned on the analogy of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.44–7.37 (3H, m), 7.37–7.30 (3H, m), 7.28–7.16 (4H, m), 6.43 (1H, d, *J* = 10.1 Hz), 5.75 (1H, d, *J* = 16.0 Hz), 5.61 (1H, d, *J* = 10.1 Hz), 5.02 (1H, dt, *J* = 16.0, 6.8 Hz), 1.98 (2H, q, *J* = 6.8 Hz), 1.34 (9H, s), 1.31–1.17 (10H, m), 0.87 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.1, 138.6, 136.9, 135.9, 128.7, 128.6, 128.3, 127.4, 102.0, 80.1, 59.6, 32.5, 31.9, 29.1, 28.6, 28.4, 22.8, 14.2, three carbons were not found probably due to overlapping; IR (film) 3453, 2922, 1713, 1547, 1483, 1425, 1391, 1256, 1161, 972 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{38}N_2O_4Na^+$ ($[M+Na]^+$) 489.2724. Found 489.2725.

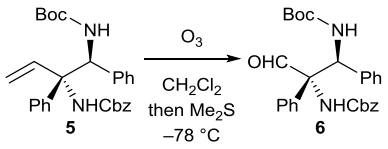
Derivatization of 4a:



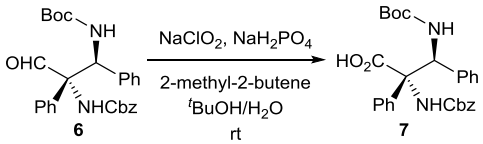
Conversion of Nitroalkane 4a to Boc-Protected Amine 5: 4a (36.8 mg, 0.10 mmol) was taken in HCl/EtOH/H_2O (666.7 μL, 3.0 M, 2.0 mmol, EtOH/H_2O = 1:2) and Zn powder (130.8 mg, 2.0 mmol) was introduced to the solution portionwise. The mixture was stirred for 12 h at ambient temperature. The reaction mixture was diluted with water and the aqueous phase was extracted with EA twice. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration, the resulting residue was purified by column chromatography on silica gel (H/EA = 1:1 as eluent) to afford the corresponding amine **S1** in 90% yield (30.5 mg, 0.090 mmol). **Amine S1:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 7.8 Hz), 7.34 (2H, t, *J* = 7.8 Hz), 7.30–7.22 (4H, m), 7.19 (2H, brd, *J* = 6.9 Hz), 6.42 (1H, dd, *J* = 17.4, 10.8 Hz), 5.66 (1H, brd, *J* = 6.9 Hz), 5.09 (1H, d, *J* = 6.9 Hz), 5.04 (1H, d, *J* = 10.8 Hz), 4.93 (1H, d, *J* = 17.4 Hz), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 144.4, 143.7, 138.9, 128.4_4, 128.3_7, 127.8, 127.4, 127.0, 126.2, 113.4, 79.3, 62.9, 62.0, 28.3; IR (film) 3318, 2976, 1703, 1585, 1514, 1366, 1248, 1169, 995 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{27}N_2O_4^+$ ($[M+H]^+$) 339.2067. Found 339.2065.

The amine **S1** (30.5 mg, 0.090 mmol) was dissolved into CH_2Cl_2 (0.90 mL) and ^{i}Pr$_2$EtN (39.6 μL, 0.23 mmol) and benzyl chloroformate (19.3 μL, 0.14 mmol) were added sequentially. The reaction mixture was stirred for 24 h and poured to water. The mixture was then extracted with $CHCl_3$ twice and the combined organic extracts were washed with brine. Organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was

purified by silica gel column chromatography (H/EA = 5/1 as eluent) to afford **5** in 56% yield (23.6 mg, 0.050 mmol). **5:** ^{1}H NMR (400 MHz, acetone) δ 7.48 (1H, d, J = 8.2 Hz), 7.42–7.38 (3H, m), 7.38–7.28 (5H, m), 7.28–7.21 (1H, m), 7.21–7.11 (5H, m), 6.67 (1H, s), 6.08 (1H, dd, J = 17.4, 10.5 Hz), 5.38 (1H, d, J = 8.7 Hz), 5.19–5.09 (3H, m), 5.03 (1H, d, J = 12.4 Hz), 4.84 (1H, d, J = 17.4 Hz), 1.30 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 155.4, 140.6, 137.8, 137.5, 136.6, 128.7, 128.5, 128.4$_1$, 128.3$_6$, 127.7, 127.6, 127.5, 126.7, 116.4, 80.1, 66.9, 66.5, 62.3, 28.5; IR (film) 3354, 2970, 1715, 1699, 1489, 1456, 1364, 1246, 1165 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{32}N_2O_4Na^+$ ([M+Na]$^+$) 495.2254. Found 495.2248.



Ozonolysis of the Double Bond in 5: Ozone gas was generated from pure oxygen by using OZM-300SW (Blowerman co. jp.) and was passed through a solution of **5** in CH_2Cl_2 (0.50 mL) at –78 °C for 1 h. Consumption of **5** was monitored by TLC and then, the passing gas was exchanged with pure oxygen. After a while, dimethyl sulfide (36.7 μL) was added to the solution and the mixture was allowed to warm up to room temperature. All volatiles were removed by evaporation to afford the crude residue, which was purified by column chromatography on silica gel (H/EA = 5:1 as eluent) to give **6** (19.0 mg, 80%). **6:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s), 7.48–7.31 (11H, m), 7.27–7.18 (3H, m), 7.09 (2H, d, J = 7.8 Hz), 6.14 (1H, s), 5.96 (1H, d, J = 9.6 Hz), 5.24 (1H, d, J = 12.6 Hz), 5.08 (1H, d, J = 12.6 Hz), 1.37 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 156.5, 156.2, 129.5, 129.0, 128.9, 128.8, 128.5, 128.3, 128.2, 127.5, 127.1, 79.8, 74.4, 67.5, 56.7, 28.5, two carbon atoms were not found probably due to overlapping; IR (film) 3372, 2978, 1711, 1697, 1506, 1456, 1365, 1248, 1165, 1067 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{30}N_2O_5Na^+$ ([M+Na]$^+$) 497.2047. Found 497.2047.



Pinnick Oxidation of 6: To a solution of **6** in ^{t}BuOH/H_2O (0.45/0.35 mL) were added $NaClO_2$ (10.9 mg, 0.12 mmol), NaH_2PO_4 (24.0 mg, 0.20 mmol), and 2-methyl-2-butene (42.5 μL, 0.40 mmol) at room temperature with stirring. After being stirred for 1 h, the reaction mixture was diluted with brine and the aqueous phase was extracted with EA twice. Organic phases were dried over Na_2SO_4, filtered, and concentrated. The residual material was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 5:1 as eluent) to give **7** (12.0 mg, 61%), whose enantiomeric excess was determined by HPLC analysis after derivatizing to the corresponding methyl ester (97% ee).[1a] **7:** HPLC (methyl ester): AD-H, H/EtOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 7.4 min (1*S*, 2*S*), 8.6 min (1*R*, 2*R*), 27.2 min (minor diastereomer), 40.5 min (minor diastereomer). Absolute and relative

configurations were assigned by comparison with the literature data.[1a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, br), 7.50 (2H, brd, J = 6.4 Hz), 7.42–7.20 (11H, m), 7.15 (2H, t, J = 7.3 Hz), 6.57 (1H, br), 6.31 (1H, br), 5.21 (1H, d, J = 12.4 Hz), 5.05 (1H, d, J = 12.4 Hz), 1.32 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 157.1, 156.6, 138.0, 136.4, 136.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.3, 80.8, 67.3, 28.5, two carbon atoms were not found probably due to overlapping; IR (film) 3368, 2926, 1713, 1667, 1497, 1368, 1248, 1163, 1051, 885 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{30}N_2O_6Na^+$ ($[M+Na]^+$) 513.1996. Found 513.2009.

Notes and References

(1) Fuson, R. C. *Chem. Rev.* 1934, **16**, 1.

(2) (a) Csákÿ, A. G.; de la Herrána, G.; Murcia, M. C. *Chem. Soc. Rev.* 2010, **39**, 4080. (b) Biju, A. T. *ChemCatChem* 2011, **3**, 1847. (c) Silva, E. M. P.; Silva, A. M. S. *Synthesis* 2012, **44**, 3109.

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(7) (a) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* 2008, **130**, 10878. (b) Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun.* 2010, **46**, 300. (c) Uraguchi, D.; Koshimoto, K.; Sanada, C.; Ooi, T. *Tetrahedron: Asymmetry* 2010, **21**, 1189. (d) Uraguchi, D.; Oyaizu, K.; Noguchi, H,; Ooi, T. *Chem. Asian J.* 2015, **10**, doi: 10.1002/asia.201402943.

(8) (a) Uraguchi, D.; Koshimoto, K.; Miyake, S.; Ooi, T. *Angew. Chem. Int. Ed.* 2010, **49**, 5567. (b) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* 2012, **134**, 6972.

(9) (a) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z. *Angew. Chem. Int. Ed.* 2012, **51**, 4085. (b) Claraz, A.; Landelle, G.; Oudeyer, S.; Levacher, V. *Eur. J. Org. Chem.* 2013, 7693. (c) Wang, Y.-B.; Sun, D.-S.; Zhou, H.; Zhang, W.-Z.; Lu, X.-B. *Green Chem.* 2014, **16**, 2266.

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(11) Review on enantioselective methodologies using *N*-carbamoyl-imines, see: Vesely, J.; Rios, R. *Chem. Soc. Rev.* 2014, **43**, 611.

(12) Hoffmann, R. W. *Chem. Rev.* 1989, **89**, 1841.

(13) The addition of MS 4A was effective to improve catalytic efficiency probably because of suppressing protonation of the ammonium nitronate by a small amount (<5%) of water, which was contaminated from slightly hygroscopic onium salt **1**.14 There would be a similar degree of steric repulsion between methyl and phenyl groups in *E*-**2a** to that between methyl and nitro groups in *Z*-**2a**.15 See Electronic supplementary information (ESI) for details.

(14) Asaro, F.; Pitacco, G.; Valentin, E. *Tetrahedron* 1987, **43**, 3279.

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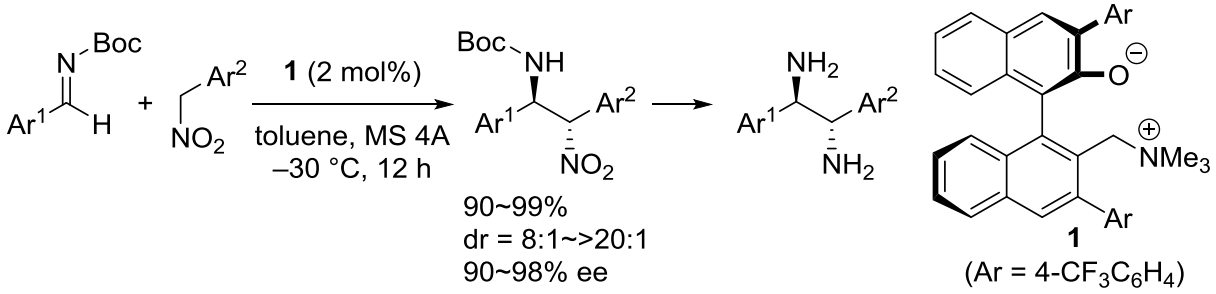
Chapter 4

Chiral Ammonium Betaine-Catalyzed Highly Stereoselective Aza-Henry Reaction of a-Aryl Nitromethanes with Aromatic *N*-Boc Imines

Abstract:



A highly stereoselective aza-Henry reaction of α-aryl nitromethanes with aromatic N-Boc imines was established by using C_1-symmetric chiral ammonium betaine as a bifunctional organic base catalyst. Various substituted aryl groups for both imines and nitromethanes were tolerated in the reaction, and a series of precursors for the synthesis of unsymmetrical anti-1,2-diaryl ethylenediamines were provided.

4.1. Introduction

Largely as a straightforward route to optically active vicinal diamines and α-amino carbonyl compounds, the asymmetric aza-Henry reaction has been the subject of numerous investigations over the past decades, and a number of highly stereoselective catalytic methodologies have been elaborated.[1,2] Among these, coupling of α-aryl nitromethanes with aromatic imines offers an attractive tool for the construction of symmetric and unsymmetric chiral 1,2-diarylethylenediamine skeletons through simple reduction of the nitro functional group. However, despite the significant relevance of this class of diamines to the core structures of various therapeutic agents as well as chiral ligands and catalysts,[3] the available synthesis protocols are extremely limited; the recent contribution from Johnston's group utilizing Bis(AMidine) catalysis represents the only successful example known to date.[4,5] In conjunction with our continuous efforts to expand the potential of C_1-symmetric chiral ammonium betaines of type **1** as a bifunctional organic base catalyst,[6-11] we report herein our approach to this problem; that is, the relative and absolute stereochemistry of the coupling between α-aryl nitromethanes and *N*-Boc arylaldimines can be precisely controlled under the efficient catalysis of **1**, thereby giving rapid access to structurally diverse 1,2-diarylethylenediamine derivatives.[12]

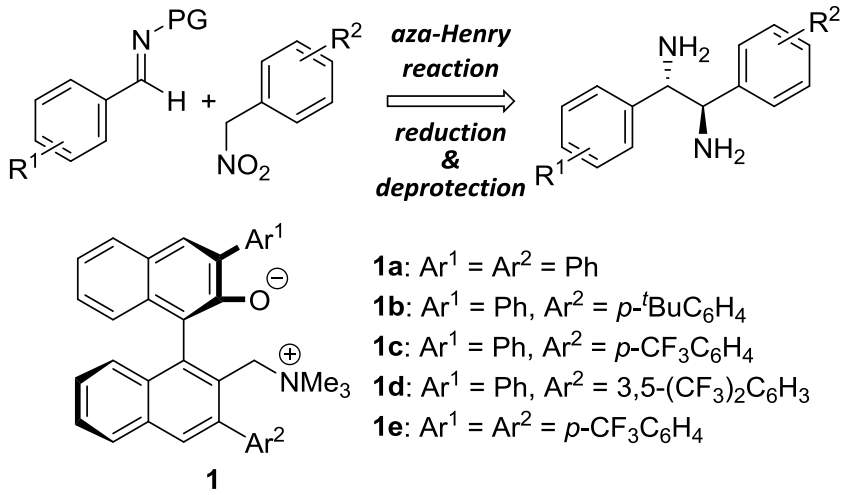


Figure 1. Aza-Henry Route to 1,2-Diarylethylenediamines and Structures of C_1-Symmetric Chiral Ammonium Betaine **1**.

4.2. Results and Discussion

We initially conducted the aza-Henry reaction of α-phenyl nitromethane (**3a**) with benzaldehyde-derived *N*-Boc imine **2a** in toluene in the presence of chiral ammonium betaine **1a** (2 mol%) and molecular sieves 4A (MS 4A) at –30 °C.[13] Bond formation was completed within 24 h, and the desired adduct **4aa** was isolated in quantitative yield as a diastereomeric mixture (*anti*/*syn* = 5:1). Fortunately, the enantiomeric excess of the major *anti*-isomer was revealed to be 86% by chiral stationary-phase HPLC analysis (Table 1, entry 1). We then focused our investigation on the effect of 3,3'-substituents in the binaphthyl backbone (Ar^1 and Ar^2) on the selectivity profile. The electronic property rather than the steric demand of the pendent aromatic nuclei appeared important in relative and absolute stereocontrol as the introduction of a 4-trifluoromethylphenyl group at the 3-position of the naphthyl

unit with the methylenetrimethylammonium appendage at the 2-position (Ar^2) led to significant improvement of both diastereo- and enantioselectivity (entry 2 vs. 3). Installation of a more electron-deficient but bulky aromatic substituent such as the 3,5-bis(trifluoromethyl)phenyl group did not have positive impact on the stereochemical outcome (entry 4). Eventually, chiral ammonium betaine **1e** bearing 4-trifluoromethylphenyl groups on both the naphthyl units exhibited high catalytic activity and excellent enantiocontrolling ability (entry 5).[14]

Table 1. Effect of Substituents at 3-Position of Each Naphthyl Unit of Chiral Ammonium Betaine 1.[a]

2a **3a** *anti*-**4aa** *syn*-**4aa**

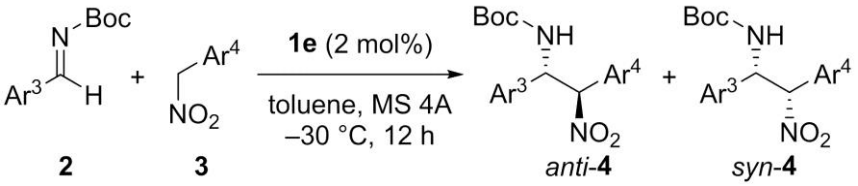
Entry	**1**	Time [h]	Yield [%][b]	d.r. [*anti*/*syn*][c]	ee [%][d]
1	**1a**	24	99	5:1	86/88
2	**1b**	24	99	7:1	79/87
3	**1c**	24	92	15:1	94/91
4	**1d**	24	98	7:1	79/96
5	**1e**	12	97	11:1	98/95

[a] Reactions were carried out with 0.1 mmol of **2a**, 0.11 mmol of **3a**, and 0.002 mmol of **1** in 0.5 mL of toluene with 100 mg of MS 4A at –30 °C under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^{1}H NMR (400 MHz) analysis of crude aliquots. [d] Enantiomeric excesses of products **4** were analyzed by chiral HPLC using DAICEL CHIRALCEL AD-3 with a hexane/ethanol solvent system. Absolute and relative stereochemistries of anti- and syn-**4aa** were determined by a single crystal X-ray diffraction analysis of its derivative (Scheme 1) and an epimerization experiment (Scheme 2).

With the optimal catalyst structure in hand, we explored the substrate generality of the **1e**–catalyzed stereoselective aza-Henry reaction; the representative results are summarized in Table 2. With various substituted aromatic *N*-Boc imines **2**, consistent yet high levels of stereocontrol were possible (entries 1–5). It is worth noting, however, that a subtle decrease in both diastereo- and enantioselectivity was observed with imines having halide substituents, while the stereoselectivity was enhanced when methyl- and methoxy-substituted imines were employed. Fused and heteroaromatic imines were also tolerated in the reaction, but at a slight expense of diastereoselectivity (entries 6 and 7). The present catalytic system was applicable to a range of α-aryl nitromethanes **3**, where the effect induced by the electronic properties of the aryl substituents on the selectivity was opposite to that observed with substituted imines **2** (entries 8–12); incorporation of electron-withdrawing groups into the aromatic moiety of **3** was beneficial, whereas the attachment of electron-donating groups was unpreferable. In addition, 1-(2-naphthyl)nitromethane (**3g**) was found to be a good candidate, and the corresponding aza-Henry adduct **4ag** was obtained quantitatively with a diastereomeric ratio of 10:1 and 97% ee for the *anti*-isomer (entry 13). As expected, arbitrary combinations of imine electrophiles and α-aryl nitromethane nucleophiles were well accommodated and excellent stereoselectivities were consistently obtained (entries 14–17).[15] Finally, the scalability of this protocol was demonstrated by the reaction of **2a** with **3a** on a gram scale under otherwise

standard conditions, which afforded **4aa** with a comparable degree of efficiency and stereocontrol (entry 18). The subsequent recrystallization afforded 0.8 g of the essentially stereochemically pure *anti*-**4aa**.

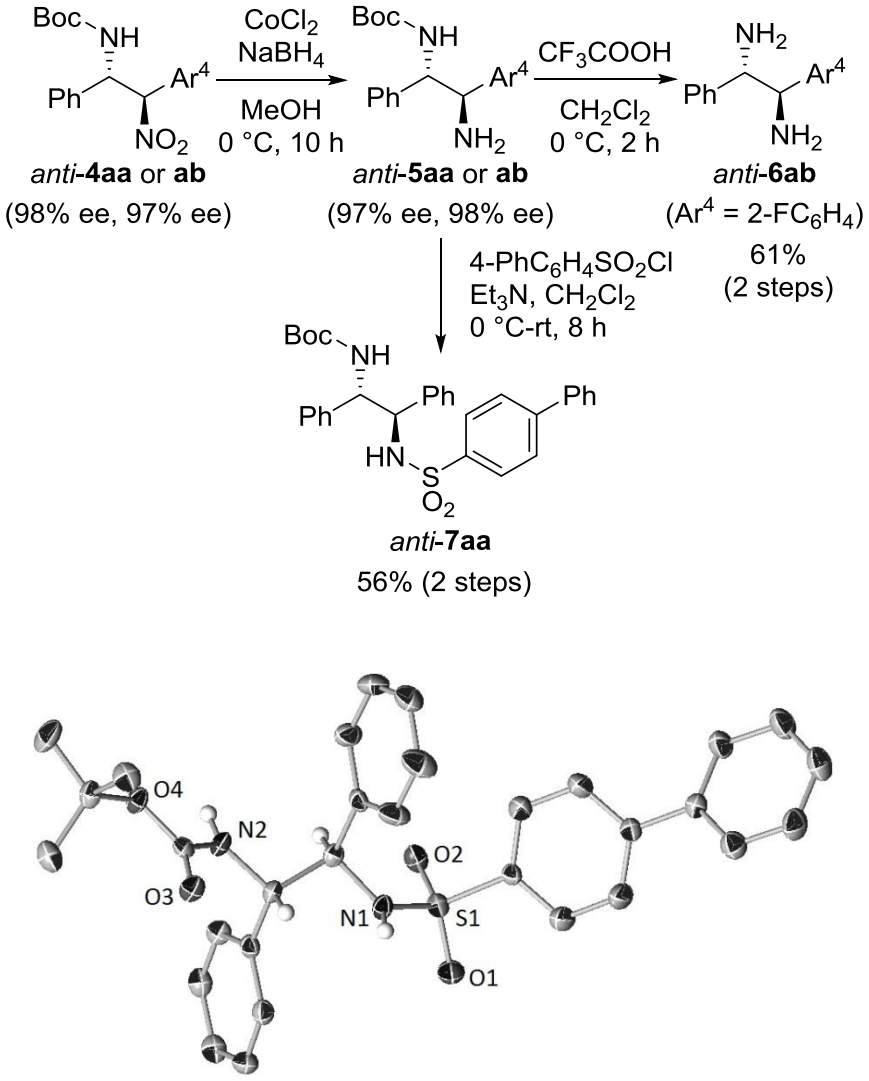
Table 2. Substrate Scope in **1e**-Catalyzed Aza-Henry Reaction of α-Aryl Nitromethane **3** with N-Boc Imines **2**.[a]



Entry	Ar^3 (**2**)	Ar^4 (**3**)	Yield [%][b]	d.r. [*anti*/*syn*][c]	ee [%][d]	Prod (**4**)
1	*o*-FC_6H_4 (**2b**)	Ph (**3a**)	99	11:1	93/91	**4ba**
2	*m*-$MeOC_6H_4$ (**2c**)	Ph (**3a**)	98	16:1	96/94	**4ca**
3	*p*-BrC_6H_4 (**2d**)	Ph (**3a**)	99	10:1	93/80	**4da**
4	*p*-MeC_6H_4 (**2e**)	Ph (**3a**)	99	12:1	97/96	**4ea**[e]
5	*p*-$MeOC_6H_4$ (**2f**)	Ph (**3a**)	92	19:1	97/95	**4fa**[e]
6	2-naphthyl (**2g**)	Ph (**3a**)	99	8:1	95/97	**4ga**[e]
7	2-furyl (**2h**)	Ph (**3a**)	99	10:1	93/92	**4ha**
8	Ph (**2a**)	*o*-FC_6H_4 (**3b**)	92	>20:1	97/95	**4ab**
9	Ph (**2a**)	*m*-$MeOC_6H_4$ (**3c**)	99	9:1	96/90	**4ac**
10	Ph (**2a**)	*p*-BrC_6H_4 (**3d**)	98	12:1	98/93	**4ad**
11	Ph (**2a**)	*p*-MeC_6H_4 (**3e**)	99	8:1	95/95	**4ae**
12	Ph (**2a**)	*p*-$MeOC_6H_4$ (**3f**)	99	8:1	90/91	**4af**
13	Ph (**2a**)	2-naphthyl (**3g**)	99	10:1	97/96	**4ag**
14	*o*-FC_6H_4 (**2b**)	*o*-FC_6H_4 (**3b**)	91	>20:1	98/94	**4bb**
15	*o*-FC_6H_4 (**2b**)	*p*-BrC_6H_4 (**3d**)	92	17:1	96/89	**4bd**
16	*p*-$MeOC_6H_4$ (**2f**)	*o*-FC_6H_4 (**3b**)	91	>20:1	98/94	**4fb**
17	*p*-$MeOC_6H_4$ (**2f**)	*p*-BrC_6H_4 (**3d**)	90	>20:1	93/90	**4fd**
18[f]	Ph (**2a**)	Ph (**3a**)	99	11:1	97/97	**4aa**

[a] Unless otherwise noted, reactions were carried out with 0.1 mmol of **2**, 0.11 mmol of **3**, and 0.002 mmol of **1e** in 0.5 mL of toluene with 100 mg of MS 4A at –30 °C under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^{1}H NMR (400 MHz) analysis of crude mixtures. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute and relative configurations of aza-Henry adducts **4** were assigned by analogy to **4aa**, **4ea**, **4fa**, and **4ga**. [e] Absolute and relative configurations of anti-isomers were determined by comparison to literature data.[4] [f] The reaction was performed with 3.5 mmol of **2a**, 3.85 mmol of **3a**, and 0.07 mmol of **1d** in 17.5 mL of toluene with 3.5 g of MS 4A at –30 °C under argon atmosphere.

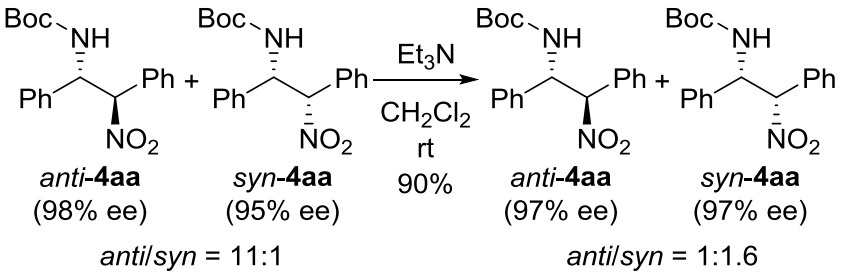
Product **4** could be readily derivatized into the corresponding 1,2-diarylethylenediamines by the two-step sequence exemplified in Scheme 1. Reduction of the nitro functionality of *anti*-**4ab** by $CoCl_2$/$NaBH_4$, followed by deprotection under acidic conditions, furnished a differently substituted diamine *anti*-**6ab** in 61% yield (2 steps). Meanwhile, intermediate *anti*-**5aa** derived from *anti*-**4aa** was converted to the 4-phenylbenzenesulfonamide derivative *anti*-**7aa**; X-ray diffraction analysis of its single crystal prepared by recrystallization from a 1,4-dioxane/diethyl ether solvent system at room temperature allowed us to assign the absolute stereochemistry of *anti*-**4aa** to be 1*S*,2*R*.[16]



Scheme 1. Derivatization of anti-**4ab** to the Corresponding 1,2-Diarylethylenediamine anti-**6ab**, Determination of Absolute and Relative Stereochemistry of Aza-Henry Adduct **4aa**, and ORTEP Diagram of anti-**7aa** (Ellipsoids displayed at 50% probability. A solvent molecule (1,4-dioxane) and calculated hydrogen atoms except for those attached to stereogenic carbon atoms are omitted for clarity.).

For further understanding the stereochemical outcome of the catalysis of chiral ammonium betaine **1e**, the absolute stereochemistry of the minor isomer was determined. A diastereomeric mixture of **4aa** (dr = 11:1, 98% ee/95% ee) was treated with a stoichiometric amount of triethylamine at room temperature to facilitate epimerization at the stereogenic carbon attached to the nitro group (Scheme 2). The resulting nearly equal mixture of *anti*- and *syn*-**4aa** was analyzed by chiral HPLC, showing an enantiomeric excess of 97% for both diastereomers. Namely, epimerization with the weak organic base affected only the diastereomeric ratio but not the enantiomeric ratio. This result clearly indicates that the minor diastereomer *syn*-**4aa** has 1*S*,2*S* configuration and is indeed diastereomeric to *anti*-**4aa** at the carbon connected to the nitro group. This strongly suggests that the chiral

ammonium betaine **1e** rigorously discriminates the prochiral faces of *N*-Boc aldimines **2** in the carbon-carbon bond-forming event.



Scheme 2. Epimerization of Aza-Henry Adduct **4aa** for Determination of Absolute Stereochemistry of syn-**4aa**.

4.3. Conclusions

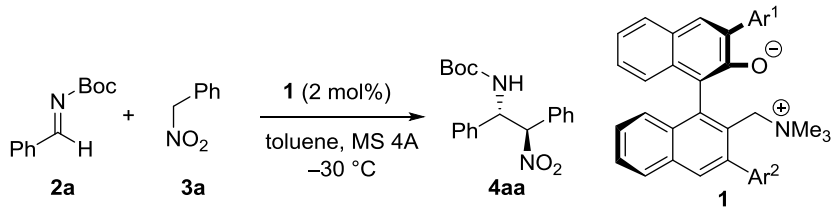
In conclusion, a highly stereoselective aza-Henry reaction of α-aryl nitromethanes with aromatic imines was achieved under the catalysis of chiral ammonium betaine **1e**. This simple and broadly useful protocol would be appreciated in the practical synthesis of non-racemic *anti*-1,2-diarylethylenediamines.

4.4. Experimental Section

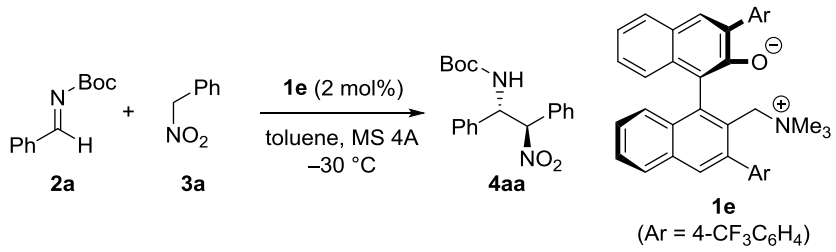
General Information: Infrared spectra were recorded on a SHIMADZU IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0.00 ppm) resonance as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, 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 ($CDCl_3$: 77.16 ppm). The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive (ESI). 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 PSQ60AB (spherical, 40-50 μm; FUJI SILYSIA Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK IA (IA), CHIRALPAK IC (IC), CHIRALPAK AD-3 (AD-3), and CHIRALPAK AZ-3 (AZ-3) with hexane (H), 2-propanol (IPA), and ethanol (EtOH) as eluent].

Toluene was supplied from Kanto Chemical Co., Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. Betaines[7b,7d], nitro compounds[17], and *N*-Boc imines[18] were prepared by following the literature procedure. Powdered 4Å molecular sieves (MS 4A) was supplied by Merck & Co., Inc. Other simple chemicals were purchased and used as such.

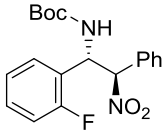
Structural Optimization of the Ammonium Betaine (Table S1)



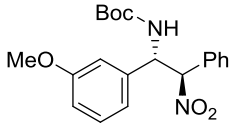
entry	Ar^1	Ar^2	time [h]	yield [%]	d.r.	ee [%]
1	Ph	Ph	24	99	5:1	86/88
2	Ph	*p*-$CF_3C_6H_4$	24	92	15:1	94/91
3	*p*-$CF_3C_6H_4$	Ph	26	94	5:1	90/90
4	Ph	*p*-^{t}BuC_6H_4	24	99	7:1	79/87
5	*p*-^{t}BuC_6H_4	Ph	22	99	4:1	86/93
6	Ph	3,5-$(CF_3)_2C_6H_3$	24	98	7:1	79/96
7	3,5-$(CF_3)_2C_6H_3$	Ph	22	83	6:1	75/90
8	Ph	3,5-$(^t$Bu$)_2C_6H_3$	23	99	2:1	45/84
9	3,5-$(^t$Bu$)_2C_6H_3$	Ph	23	99	12:1	–32/37
10	*p*-$CF_3C_6H_4$	*p*-$CF_3C_6H_4$	12	97	11:1	98/95



Representative Procedure for Catalytic Asymmetric Aza-Henry Reaction: A magnetic stirrer bar and MS 4A (100.0 mg) was placed in an oven-dried test tube under argon (Ar) atmosphere. The MS 4A was dried with a heat gun under reduced pressure for 5 min and the test tube was refilled with Ar. Chiral ammonium betaine **1** (1.26 mg, 0.0020 mmol) and toluene (0.50 mL) were added to the test tube successively under Ar at 25 °C and the catalyst solution was stirred for 30 min. After the mixture was cooled to –30 °C, arylnitromethane **3a** (15.1 mg, 0.11 mmol) and benzaldehyde-derived *N*-Boc imine **2a** (20.5 mg, 0.10 mmol) were introduced to the tube sequentially. The reaction mixture was stirred for 12 h and then, poured into ice-cooled 1 *N* hydrochloric acid. The aqueous phase was extracted with ethyl acetate (EA) twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. All volatiles were removed by evaporation to afford the crude residue which was analyzed by ^{1}H NMR (400 MHz) for determining the diastereomeric ratio (*anti*/*syn* = 11:1). Purification of the residue by column chromatography on silica gel (H/EA = 3:1 as eluent) gave **4aa** as a mixture of diastereomers (33.2 mg, 97%), whose enantiomeric excesses were determined by HPLC analysis (98% ee for *anti* isomer, 95% ee for *syn* isomer). **4aa:** HPLC: AD-3, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 20.3 min (1*S*,2*R*), 23.3 min (1*R*,2*S*), 24.3 min (1*R*,2*R*), 41.1 min (1*S*,2*S*). ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.60–7.54 (2H, m), 7.46–7.15 (8H, m), 5.78 (1H, brd, J = 9.2 Hz), 5.68 (1H, br), 4.86 (1H, br), 1.25 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.4, 137.7, 131.6, 130.3, 129.2, 129.0, 128.9, 128.1, 127.3, 94.4, 80.6, 56.8, 28.2; IR (film) 3397, 2978, 2928, 1684, 1547, 1518, 1364, 1292, 1250, 1165, 756 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{22}N_2O_4Na^+$ ([M+Na]$^+$) 365.1472. Found 365.1470.

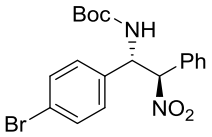


4ba: HPLC: IC, H/EtOH = 19:1, flow rate = 0.5 mL/min, λ = 210 nm, 11.1 min (major enantiomer of *anti* isomer), 12.0 min (minor enantiomer of *anti* isomer), 13.6 min (minor enantiomer of *syn* isomer), 16.4 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.63 (2H, t, J = 3.7 Hz), 7.48–7.26 (5H, m), 7.13 (1H, t, J = 8.8 Hz), 7.11 (1H, t, J = 8.8 Hz), 5.87 (2H, br), 5.11 (1H, br), 1.21 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.3 (d, $J_{F\text{-}C}$ = 249.6 Hz), 154.3, 131.5, 131.3, 130.8 (d, $J_{F\text{-}C}$ = 8.7 Hz), 130.4, 128.9, 124.9 (d, $J_{F\text{-}C}$ = 2.9 Hz), 124.3 (d, $J_{F\text{-}C}$ = 12.6 Hz), 116.3 (d, $J_{F\text{-}C}$ = 21.3 Hz), 93.5, 80.4, 54.1, 28.1, one carbon atom was not found probably due to overlapping; IR (film) 3404, 2972, 2922, 1703, 1543, 1514, 1491, 1366, 1283, 1169 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{21}FN_2O_4Na^+$ ([M+Na]$^+$) 383.1378. Found 383.1376.

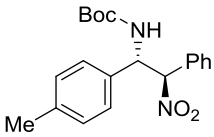


4ca: HPLC: AD-3, H/EtOH = 94:6, flow rate = 1.0 mL/min, λ = 210 nm, 24.4 min (major enantiomer of *anti* isomer), 28.5 min (minor enantiomer of *syn* isomer), 39.5 min (major enantiomer of *syn* isomer), 43.9 min (minor enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*

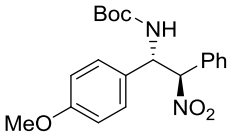
isomer δ 7.57 (2H, d, J = 8.4 Hz), 7.48–7.36 (3H, m), 7.30 (1H, t, J = 8.4 Hz), 6.93 (1H, d, J = 8.4 Hz), 6.88 (1H, s), 6.86 (1H, d, J = 8.4 Hz), 5.76 (1H, brd, J = 8.7 Hz), 5.67 (1H, br), 4.83 (1H, br), 3.79 (3H, s), 1.25 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.0, 154.3, 139.2, 131.6, 130.3$_2$, 130.2$_6$, 128.9, 119.2, 114.2, 113.3, 94.4, 80.5, 56.6, 55.4, 28.2, one carbon atom was not found probably due to overlapping; IR (film) 3389, 2982, 2926, 1682, 1549, 1520, 1364, 1283, 1265, 1165, 1038 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{24}N_2O_5Na^+$ ([M+Na]$^+$) 395.1577. Found 395.1577.



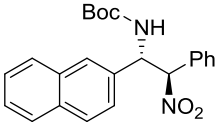
4da: HPLC: AD-3, H/EtOH = 85:15, flow rate = 0.5 mL/min, λ = 210 nm, 15.3 min (major enantiomer of *anti* isomer), 20.6 min (minor enantiomer of *anti* isomer), 21.3 min (minor enantiomer of *syn* isomer), 40.6 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.53 (2H, d, J = 7.8 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.45–7.30 (3H, m), 7.23 (2H, d, J = 8.4 Hz), 5.75 (1H, br), 5.60 (1H, br), 4.89 (1H, br), 1.26 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.4, 136.7, 132.2, 131.3, 130.5, 129.1, 128.8, 122.9, 94.0, 80.8, 56.1, 28.2, one carbon atom was not found probably due to overlapping; IR (film) 3387, 2982, 2930, 1682, 1547, 1518, 1364, 1288, 1248, 1161, 1013, 822 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{21}N_2O_4{}^{79}BrNa^+$ ([M+Na]$^+$) 443.0577. Found 443.0577.



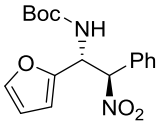
4ea[4a]**:** HPLC: IA, H/IPA/EtOH = 92:5:3, flow rate = 1.0 mL/min, λ = 210 nm, 12.9 min (minor enantiomer of *syn* isomer), 14.2 min (1*S*,2*R*), 16.5 min (1*R*,2*S*), 29.6 min (major enantiomer of *syn* isomer). Analytical and spectral data were in agreement with the literature data.[4] Absolute and relative configurations were assigned from published data.[4] ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.58 (2H, dd, J = 7.8, 1.8 Hz), 7.46–7.35 (3H, m), 7.24 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J = 8.2 Hz), 5.75 (1H, brd, J = 8.7 Hz), 5.64 (1H, br), 4.82 (1H, br), 2.33 (3H, s), 1.24 (9H, s).



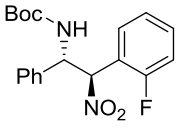
4fa[4a]**:** HPLC: AD-3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 34.0 min (minor enantiomer of *syn* isomer), 37.5 min (1*S*,2*R*), 50.9 min (1*R*,2*S*), 69.6 min (major enantiomer of *syn* isomer). Analytical and spectral data were in agreement with the literature data.[4] Absolute and relative configurations were assigned from published data.[4] ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.57 (2H, d, J = 8.2 Hz), 7.46–7.36 (3H, m), 7.27 (2H, d, J = 11.0 Hz), 6.87 (2H, d, J = 11.0 Hz), 5.75 (1H, d, J = 9.2 Hz), 5.61 (1H, br), 4.85 (1H, br), 3.79 (3H, br), 1.25 (9H, s).



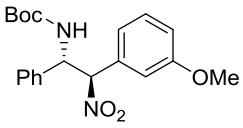
4ga[4a]**:** HPLC: AD-3, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 19.1 min (minor enantiomer of *syn* isomer), 24.2 min (major enantiomer of *anti* isomer), 26.5 min (minor enantiomer of *anti* isomer), 37.9 min (major enantiomer of *syn* isomer). Analytical and spectral data were in agreement with the literature data.[4] Absolute and relative configurations were assigned from published data.[4] ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.88–7.79 (4H, m), 7.61 (2H, dd, J = 7.3, 1.8 Hz), 7.50 (2H, m), 7.48–7.39 (4H, m), 5.90 (2H, br), 4.94 (1H, br), 1.25 (9H, s).



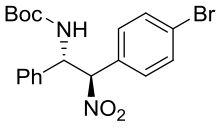
4ha: HPLC: IC, H/IPA = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 18.7 min (major enantiomer of *anti* isomer), 28.6 min (minor enantiomer of *anti* isomer), 34.3 min (minor enantiomer of *syn* isomer), 40.2 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.54 (2H, d, J = 11.4 Hz), 7.45–7.31 (4H, m), 6.34 (2H, s), 5.83 (2H, br), 4.91 (1H, br), 1.26 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.2, 149.8, 143.0, 131.3, 130.3, 128.9, 128.0, 110.8, 108.8, 92.6, 80.6, 50.5, 28.1; IR (film) 3393, 2978, 2924, 1686, 1547, 1516, 1368, 1283, 1260, 1165, 1011, 800 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{20}N_2O_5Na^+$ ([M+Na]$^+$) 355.1264. Found 355.1263.



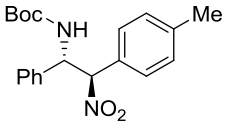
4ab: HPLC: AD-3, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.1 min (minor enantiomer of *anti* isomer), 19.1 min (major enantiomer of *anti* isomer), 22.7 min (minor enantiomer of *syn* isomer), 26.4 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.80 (1H, t, J = 8.2 Hz), 7.45–7.30 (6H, m), 7.24 (1H, t, J = 8.2 Hz), 7.13 (1H, t, J = 8.2 Hz), 6.21 (1H, d, J = 9.8 Hz), 5.73 (1H, br), 4.88 (1H, d, J = 9.8 Hz), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.9 (d, $J_{F\text{-}C}$ = 252.6 Hz), 154.2, 137.3, 132.0 (d, $J_{F\text{-}C}$ = 8.7 Hz), 129.3, 129.2, 129.1, 127.3, 124.9 (d, $J_{F\text{-}C}$ = 2.9 Hz), 119.3 (d, $J_{F\text{-}C}$ = 12.6 Hz), 115.6 (d, $J_{F\text{-}C}$ = 23.2 Hz), 86.0, 80.5, 56.4 28.1; IR (film) 3387, 2976, 2930, 1694, 1553, 1512, 1360, 1296, 1252, 1153 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{21}FN_2O_4Na^+$ ([M+Na]$^+$) 383.1378. Found 383.1377.



4ac: HPLC: AD-3, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 29.4 min (minor enantiomer of *anti* isomer), 32.4 min (minor enantiomer of *syn* isomer), 35.4 min (major enantiomer of *syn* isomer), 38.2 min (major enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.42–7.28 (6H, m), 7.16–7.08 (2H, m), 6.96 (1H, dd, J = 8.2, 2.3 Hz), 5.75 (1H, br), 5.69 (1H, br), 4.91 (1H, br), 3.82 (3H, s), 1.26 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 159.9, 154.4, 137.7, 132.9, 129.9, 129.2, 128.9, 127.3, 121.3, 116.4, 113.8, 94.3, 80.5, 56.6, 55.5, 28.2; IR (film) 3395, 2980, 2934, 1682, 1545, 1518, 1364, 1290, 1263, 1155, 1047 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{24}N_2O_5Na^+$ ([M+Na]$^+$) 395.1577. Found 395.1576.

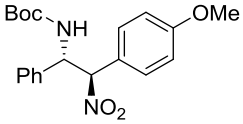


4ad: HPLC: IA, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.3 min (minor enantiomer of *syn* isomer), 18.9 min (major enantiomer of *anti* isomer), 28.4 min (minor enantiomer of *anti* isomer), 52.0 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.54 (2H, d, J = 8.7 Hz), 7.46 (2H, d, J = 8.7 Hz), 7.40–7.13 (5H, m), 5.75 (1H, br), 5.63 (1H, br), 4.88 (1H, br), 1.27 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 137.2, 132.1, 130.6$_2$, 130.5$_8$, 129.2, 129.0, 127.3, 124.8, 93.7, 80.7, 56.8, 28.2; IR (film) 3395, 2976, 2924, 1684, 1549, 1520, 1366, 1292, 1248, 1167 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{21}N_2O_4{}^{79}BrNa^+$ ([M+Na]$^+$) 443.0577. Found 443.0576.

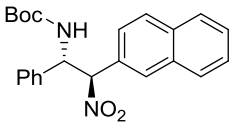


4ae: HPLC: IA, H/IPA/EtOH = 92:5:3, flow rate = 1.0 mL/min, λ = 210 nm, 13.1 min (minor enantiomer of *syn* isomer), 15.4 min (major enantiomer of *anti* isomer), 17.9 min (minor enantiomer of *anti* isomer), 28.1 min (major enantiomer of *syn* isomer). Absolute and

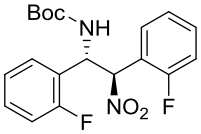
relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.45 (2H, d, J = 8.2 Hz), 7.40–7.28 (5H, m), 7.20 (2H, d, J = 8.2 Hz), 5.72 (1H, br), 5.65 (1H, br), 4.89 (1H, br), 2.36 (3H, s), 1.26 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.5, 140.4, 137.8, 129.6, 129.1, 128.8, 128.7, 127.3, 94.2, 80.4, 56.7, 28.2, 21.4, one carbon atom was not found probably due to overlapping; IR (film) 3385, 2978, 2926, 1688, 1549, 1518, 1366, 1290, 1250, 1169 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{24}N_2O_4Na^+$ ($[M+H]^+$) 379.1628. Found 379.1627.



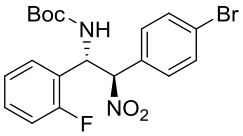
4af: HPLC: AD-3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 230 nm, 26.8 min (minor enantiomer of *syn* isomer), 46.8 min (major enantiomer of *anti* isomer), 67.3 min (minor enantiomer of *anti* isomer), 78.7 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.50 (2H, d, J = 8.7 Hz), 7.38–7.28 (5H, m), 6.92 (2H, d, J = 8.7 Hz), 5.72 (1H, brd, J = 9.6 Hz), 5.64 (1H, br), 4.88 (1H, br), 3.82 (3H, s), 1.27 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.1, 154.5, 137.8, 130.4, 129.1, 128.8, 127.3, 123.7, 114.3, 94.0, 80.5, 56.7, 55.5, 28.2; IR (film) 3397, 2976, 2934, 1684, 1549, 1514, 1369, 1290, 1248, 1169, 1032 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{24}N_2O_5Na^+$ ($[M+Na]^+$) 395.1577. Found 395.1577.



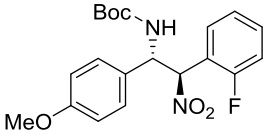
4ag: HPLC: AD-3, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 16.0 min (minor enantiomer of *syn* isomer), 32.2 min (major enantiomer of *anti* isomer), 35.9 min (major enantiomer of *syn* isomer), 47.1 min (minor enantiomer of *anti* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 8.03 (1H, s), 7.92–7.83 (3H, m), 7.69 (1H, dd, J = 8.7, 1.8 Hz), 7.55 (1H. t, J = 3.6 Hz), 7.42–7.32 (5H, m), 5.97 (1H, brd, J = 9.6 Hz), 5.79 (1H, brt, J = 9.6 Hz), 4.83 (1H, brd, J = 9.6 Hz), 1.16 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 154.4, 134.9, 133.4, 133.3, 131.6, 129.2, 129.0, 128.9, 128.3, 127.8, 126.8, 126.7, 124.5, 94.3, 80.6, 56.9, 28.2, one carbon atom was not found probably due to overlapping; IR (film) 3389, 2968, 2916, 1688, 1547, 1520, 1364, 1294, 1254, 1169, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{24}N_2O_4Na^+$ ($[M+Na]^+$) 415.1628. Found 415.1626.



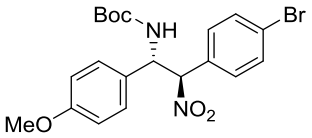
4bb: HPLC: AD-3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 17.0 min (minor enantiomer of *anti* isomer), 29.1 min (minor enantiomer of *syn* isomer), 38.3 min (major enantiomer of *anti* isomer), 51.2 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.83 (1H, t, $J_{H\text{-}H}$ = 6.6 Hz, $J_{F\text{-}H}$ = 6.6 Hz), 7.49–7.30 (3H, m), 7.24 (1H, t, J = 7.3 Hz), 7.20–7.06 (3H, m), 6.33 (1H, d, J = 10.5 Hz), 5.85 (1H, t, J = 10.5 Hz), 5.18 (1H, brd, J = 10.5 Hz), 1.21 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.3 (d, $J_{F\text{-}C}$ = 245.8 Hz), 161.0 (d, $J_{F\text{-}C}$ = 253.5 Hz), 154.3, 132.0 (d, $J_{F\text{-}C}$ = 7.7 Hz), 131.3, 131.0 (d, $J_{F\text{-}C}$ = 9.7 Hz), 129.0, 125.0 (d, $J_{F\text{-}C}$ = 2.9 Hz), 124.8 (d, $J_{F\text{-}C}$ = 3.9 Hz), 124.1 (d, $J_{F\text{-}C}$ = 11.6 Hz), 119.2 (d, $J_{F\text{-}C}$ = 13.6 Hz), 116.4 (d, $J_{F\text{-}C}$ = 22.3 Hz), 115.6 (d, $J_{F\text{-}C}$ = 21.3 Hz), 85.0, 80.5, 54.0, 28.1; IR (film) 3339, 2980, 2932, 1703, 1557, 1493, 1368, 1277, 1236, 1161, 1016 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{20}F_2N_2O_4Na^+$ ($[M+Na]^+$) 401.1283. Found 401.1281.



4bd: HPLC: AD-3, H/EtOH = 90.5:9.5, flow rate = 0.5 mL/min, λ = 210 nm, 21.2 min (major enantiomer of *anti* isomer), 24.5 min (minor enantiomer of *syn* isomer), 25.9 min (minor enantiomer of *anti* isomer), 35.1 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.56 (2H, d, J = 8.2 Hz), 7.51 (2H, d, J = 8.2 Hz), 7.46–7.28 (2H, m), 7.13 (2H, m), 5.82 (2H, br), 5.08 (1H, brd, J = 6.4 Hz), 1.24 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.3 (d, $J_{F\text{-}C}$ = 239.0 Hz), 154.3, 132.1, 131.3, 131.0 (d, $J_{F\text{-}C}$ = 8.7 Hz), 130.6, 130.5, 125.0, 124.9, 123.9 (d, $J_{F\text{-}C}$ = 14.5 Hz), 116.4 (d, $J_{F\text{-}C}$ = 22.3 Hz), 92.9, 80.7, 54.1, 28.1; IR (film) 3429, 2970, 1705, 1547, 1491, 1368, 1283, 1169, 1013 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{20}FN_2O_4{}^{79}BrNa^+$ ([M+Na]$^+$) 461.0483. Found 461.0482.

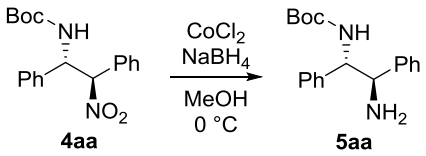


4fb: HPLC: AD-3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 18.6 min (minor enantiomer of *anti* isomer), 23.4 min (minor enantiomer of *syn* isomer), 33.5 min (major enantiomer of *anti* isomer), 46.6 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.79 (1H, t, $J_{H\text{-}H}$ = 7.3 Hz, $J_{F\text{-}H}$ = 7.3 Hz), 7.40 (1H, td, $J_{H\text{-}H}$ = 7.3 Hz, $J_{F\text{-}H}$ = 7.3 Hz), 7.30 (2H, d, J = 8.7 Hz), 7.23 (1H, t, J = 7.3 Hz), 7.12 (1H, dd, $J_{F\text{-}H}$ = 9.2 Hz, $J_{H\text{-}H}$ = 7.3 Hz), 6.89 (2H, d, J = 8.7 Hz), 6.17 (1H, d, J = 10.5 Hz), 5.65 (1H, br), 4.86 (1H, brd, J = 7.3 Hz), 3.80 (3H, s), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.9 (d, $J_{F\text{-}C}$ = 252.6 Hz), 160.0, 154.2, 131.9 (d, $J_{F\text{-}C}$ = 8.7 Hz), 129.4, 129.2, 128.5, 124.8 (d, $J_{F\text{-}C}$ = 3.8 Hz), 119.4 (d, $J_{F\text{-}C}$ = 12.6 Hz), 115.6 (d, $J_{F\text{-}C}$ = 21.3 Hz), 114.6, 86.1, 80.4, 56.0, 55.4, 28.1; IR (film) 3387, 2978, 2930, 1692, 1553, 1512, 1364, 1296, 1240, 1163, 1032 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{23}FN_2O_5Na^+$ ([M+Na]$^+$) 413.1483. Found 413.1484.

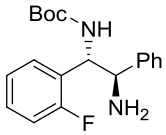


4fd: HPLC: AD-3, H/IPA = 80:20, flow rate = 1.0 mL/min, λ = 254 nm, 13.3 min (minor enantiomer of *syn* isomer), 14.9 min (major enantiomer of *anti* isomer), 31.1 min (minor enantiomer of *anti* isomer), 46.7 min (major enantiomer of *syn* isomer). Absolute and relative configurations were assigned on the analogy of **4aa**, **4ea**, and **4fa**. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.54 (2H, d, J = 8.7 Hz), 7.45 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 5.73 (1H, brd, J = 9.2 Hz), 5.56 (1H, brt, J = 9.2 Hz), 4.81 (1H, br), 3.80 (3H, s), 1.27 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.0, 154.4, 132.0, 130.7, 130.6, 129.2, 128.5, 124.7, 114.6, 93.8, 80.7, 56.4, 55.4, 28.2; IR (film) 3408, 2980, 2930, 1682, 1547, 1512, 1368, 1292, 1238, 1163, 1013 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{23}N_2O_5{}^{79}BrNa^+$ ([M+Na]$^+$) 473.0683. Found 473.0683.

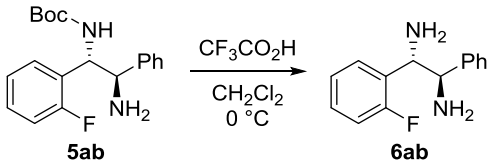
Derivatization and Determination of Absolute Configuration:



Reduction of Nitro Group: To a solution of **4aa** (34.2 mg, 0.10 mmol) in MeOH (0.40 mL) was added $CoCl_2$ (13.0 mg, 0.10 mmol) at room temperature. Portionwise addition of $NaBH_4$ (56.7 mg, 1.50 mmol) to the mixture was performed at 0 °C. The reaction mixture was then stirred for 10 h and poured into a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with EA twice. The combined organic phases were dried over Na_2SO_4 and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (H/EA = 2:1 as eluent) to give **5aa** in 91% (28.4 mg, 0.091 mmol). **5aa:** HPLC: IC, H/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 25.7 min (minor enantiomer of *syn* isomer), 31.5 min (major enantiomer of *anti* isomer), 37.3 min (major enantiomer of *syn* isomer), 47.3 min (minor enantiomer of *anti* isomer). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) *anti* isomer δ 7.40–7.10 (10H, m), 4.56 (1H, t, J = 2.2 Hz), 3.99 (1H, d, J = 2.2 Hz), 1.73 (2H, br), 1.19 (9H, s); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) *anti* isomer δ 154.5, 143.9, 141.4, 127.8, 127.7, 127.6, 127.5, 126.9, 126.6, 77.6, 60.8, 59.6, 28.1; IR (film) 3385, 2976, 2926, 1682, 1512, 1290, 1248, 1164, 989 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{25}N_2O_2^+$ ($[M+H]^+$) 313.1911. Found 313.1908.

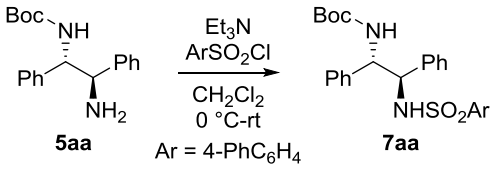


5ab: HPLC: AZ-3, H/EtOH = 96:4, flow rate = 0.5 mL/min, λ = 210 nm, 40.5 min (major enantiomer of *syn* isomer), 43.5 min (minor enantiomer of *syn* isomer), 52.2 min (major enantiomer of *anti* isomer), 72.4 min (minor enantiomer of *anti* isomer). ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.35–7.17 (4H, m), 7.14–6.97 (5H, m), 5.47 (1H, br), 4.84 (1H, br), 4.53 (1H, d, J = 1.7 Hz), 1.53 (2H. br), 1.31 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 160.6 (d, $J_{F\text{-}C}$ = 248.7 Hz), 155.1, 139.3, 129.6 (d, $J_{F\text{-}C}$ = 13.5 Hz), 129.0 (d, $J_{F\text{-}C}$ = 8.7 Hz), 128.4, 128.3 (d, $J_{F\text{-}C}$ = 3.9 Hz), 127.7, 127.5, 124.2 (d, $J_{F\text{-}C}$ = 2.9 Hz), 115.3 (d, $J_{F\text{-}C}$ = 23.2 Hz), 79.5, 59.7, 53.8, 28.4; IR (film) 3393, 2972, 2924, 1694, 1585, 1487, 1454, 1366, 1290, 1250, 1223, 1167, 1078, 1020 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{24}FN_2O_2^+$ ($[M+H]^+$) 331.1816. Found 331.1813.



Removal of Boc Group: Trifluoroacetic acid (0.15 mL) was added to a solution of **5ab** (33.0 mg, 0.10 mmol) in CH_2Cl_2 (0.15 mL) at 0 °C. The reaction mixture was stirred for 2 h and then, poured into an ice-cooled 1 *N* aqueous solution of NaOH. The aqueous phase was extracted with chloroform twice. The combined organic extracts were dried over Na_2SO_4 and filtered. After removal of all volatiles, purification by column chromatography

on silica gel (H/EA = 1:3 as eluent) was performed to give **6ab** in 86% (19.8 mg, 0.086 mmol). **6ab:** ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.39–7.21 (7H, m), 7.13 (1H, t, J = 7.3 Hz), 7.05 (1H, dd, J = 10.6, 8.7 Hz), 4.36 (1H, d, J = 7.3 Hz), 4.11 (1H, d, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 161.0 (d, $J_{F\text{-}C}$ = 249.6 Hz), 142.6, 130.1 (d, $J_{F\text{-}C}$ = 13.5 Hz), 128.9 (d, $J_{F\text{-}C}$ = 8.7 Hz), 128.7 (d, $J_{F\text{-}C}$ = 4.8 Hz), 128.5, 127.8, 127.6, 124.4 (d, $J_{F\text{-}C}$ = 2.9 Hz), 115.6 (d, $J_{F\text{-}C}$ = 23.2 Hz), 62.0, 56.3; IR (film) 3391, 3283, 3059, 3022, 1730, 1582, 1487, 1454, 1381, 1279, 1227, 1103, 1028cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{16}FN_2^+$ ($[M+H]^+$) 231.1292. Found 231.1292.



Sulfonylation of Amino Group of *anti*-5aa: To a solution of **5aa** (31.2 mg, 0.10 mmol) and Et_3N (41.8 μL, 0.30 mmol) in dichloromethane (1.0 mL) was added 4-$PhC_6H_4SO_2Cl$ (30.3 mg, 0.12 mmol) at 0 °C. The reaction mixture was stirred for 8 h at room temperature and then, poured into an ice-cooled 1 *N* hydrochloric acid. The aqueous phase was extracted with chloroform twice and the combined organic phases were dried over Na_2SO_4. After filtration and concentration, the crude residue was purified by column chromatography on silica gel (H/EA = 3:1 as eluent) to give **7aa** in 62% (32.8 mg, 0.062 mmol). **Recrystallization of *anti*-7aa:** Single crystals of *anti*-**7aa** suitable for X-ray diffraction analysis were obtained by recrystallization by using a 1,4-dioxane/ether solvent system at room temperature. **7aa:** ^{1}H NMR (400 MHz, $CDCl_3$) *anti* isomer δ 7.64 (2H, d, J = 8.0 Hz), 7.52-7.36 (7H, m), 7.28-7.17 (3H, m), 7.10 (1H, t, J = 8.0 Hz), 7.02 (2H, t, J = 8.0 Hz), 6.82 (2H, brd, J = 8.0 Hz), 6.66 (2H, d, J = 8.0 Hz), 5.64 (1H, brd, J = 7.8 Hz), 5.37 (1H, br), 4.96 (1H, br), 4.83 (1H, dd, J = 7.8, 3.2 Hz), 1.43 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *anti* isomer δ 155.7, 145.4, 139.5, 138.7, 136.7, 136.2, 129.1, 128.6, 128.5, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4_1, 127.3_7, 80.4, 62.1, 59.6, 28.4, one carbon atom was not found probably due to overlapping; IR (film) 3381, 3302, 2980, 2928, 1682, 1522, 1329, 1290, 1252, 1155, 1015 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{32}N_2O_4SNa^+$ ($[M+Na]^+$) 551.1975. Found 551.1976.

Crystallographic Structure Determination: The single crystal, obtained by the procedure described above, was mounted on MicroMesh. Data of X-ray diffraction were collected at 113 K on a Rigaku VariMax with Saturn diffractometer with fine-focus sealed tube Mo/Kα radiation (λ = 0.71075 Å). An absorption correction was made using Crystal Structure. 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.

Table S1. Crystal data and structure refinement for *anti*-**7aa**·1,4-dioxane complex (CCDC 1018060).

Empirical formula	C31 H32 N2 O4 S, C4 H8 O2
Formula weight	616.75
Temperature	113(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 5.3335(13) Å α = 90°
	b = 30.147(8) Å β = 91.575(4)°.
	c = 9.989(3) Å γ = 90°
Volume	1605.5(7) $Å^3$
Z	2
Density (calculated)	1.276 Mg/m^3
Absorption coefficient	0.149 mm^{-1}
F(000)	656.0
Crystal size	0.200 x 0.050 x 0.010 mm^3
Theta range for data collection	3.387 to 27.459°
Index ranges	–6<=h<=6, –39<=k<=39, –11<=l<=12
Reflections collected	13359
Independent reflections	7186 [R(int) = 0.0428]
Completeness to theta = 25.242°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.999 and 0.996
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7186 / 1 / 408
Goodness-of-fit on F^2	0.949
Final R indices [I>2sigma(I)]	R_1 = 0.0490, wR_2 = 0.1066
R indices (all data)	R_1 = 0.0789, wR_2 = 0.1320
Absolute structure parameter	0.06(6)
Largest diff. peak and hole	0.482 and –0.292 e.$Å^{-3}$

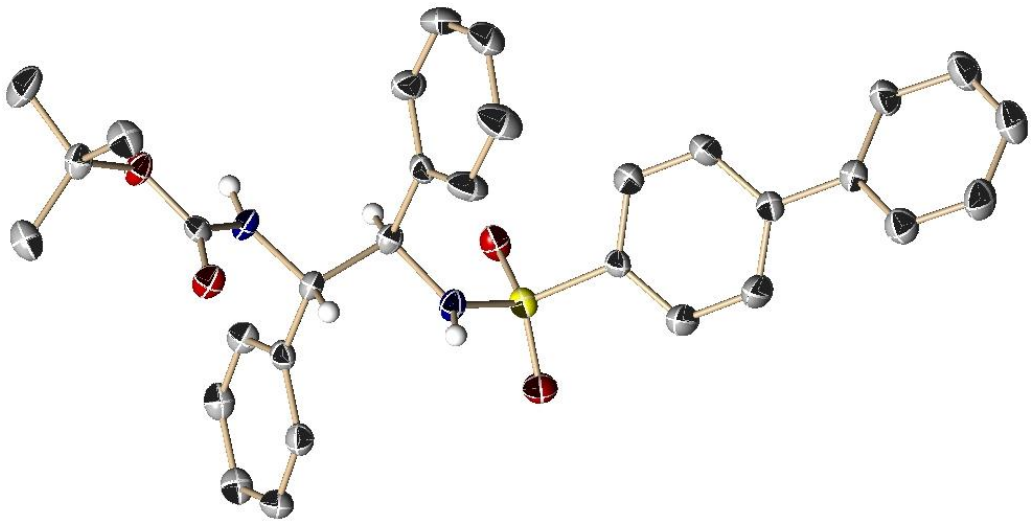


Fig. S1. Molecular structure of *anti*-**7aa**. The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level. A solvent molecule (1,4-dioxane) and calculated hydrogen atoms except for those attached to stereogenic carbon atoms are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon.

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(13) The addition of MS 4A is crucial for attaining reproducibility and high enantioselectivity probably because a small amount (<5%) of water from slightly hygroscopic **1** would be incorporated into a hydrogen-bonding network in the transition state, causing a substantial decrease in enantioselectivity. The reaction between **2a** and **3a** with **1a** as a catalyst in the absence of MS 4A afforded the adduct **4aa** in 99% yield with diastereomeric ratio of 5:1 and the enantiomeric excess of the major isomer was determined to be 69%.

(14) Additional data of structural optimization of the catalyst are included in Supporting Information.

(15) Although the present protocol could be applied to aliphatic *N*-Boc aldimines, enantioselectivity significantly dropped. For example, reaction of nonanal-derived imine **2** (Ar^3 = $(CH_2)_7Me$) with **3a** under the optimized conditions gave the corresponding adduct **4** (Ar^3 = $(CH_2)_7Me$, Ar^4 = Ph) in 64% yield with diastereomeric ratio of 11:1 and enantiomeric excess of the major isomer was determined to be 34%.

(16) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1018060. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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List of Publications

Chapter 2 Nitroolefins as a Nucleophilic Component for Highly Stereoselective Aza-Henry Reaction under the Catalysis of Chiral Ammonium Betaines
Uraguchi, D.; Oyaizu. K; Ooi, T. *Chem. Eur. J.* **2012**, *18*, 8306.

Chapter 3 Vinylogy in Nitronates: Utilization of α-Aryl Conjugated Nitroolefins as a Nucleophile for Highly Stereoselective Aza-Henry Reaction
Uraguchi, D.; Oyaizu. K; Ooi, T. *Chem. Commun. in press*

Chapter 4 Chiral Ammonium Betaine-Catalyzed Highly Stereoselective Aza-Henry Reaction of a-Aryl Nitromethanes with Aromatic *N*-Boc Imines
Uraguchi, D.; Oyaizu. K; Noguchi, H.; Ooi, T. *Chem. Asian. J.* DOI: 10.1002/asia.201402943

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