主論文

Development of Hitherto Difficult Asymmetric Transformations Utilizing Chiral 1,2,3-Triazolium Catalysts

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Chapter 1 Introduction and General Summary

1.1 Chiral Carbonyl Compounds

Chiral carbonyl compounds are ubiquitous motif in natural products and are attractive targets in medicinal chemistry. Additionally, chiral carbonyl compounds can be utilized as a chiral building block because carbonyl group can be easily transformed into various functional groups (Figure 1).

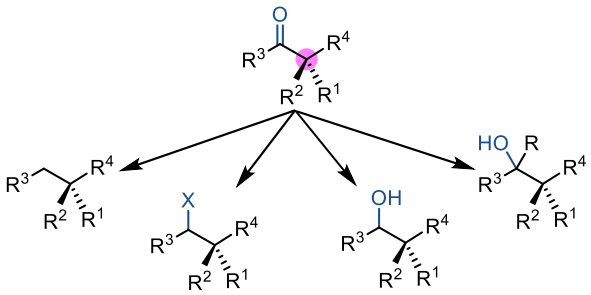
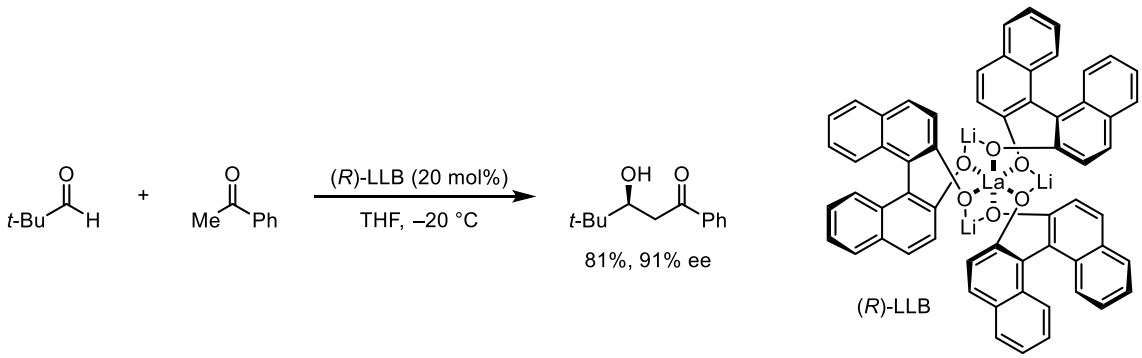


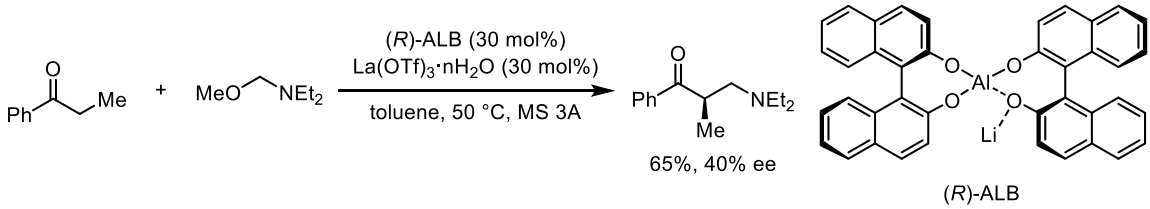
Figure 1. Derivatizations of Carbonyl Compound

Catalytic asymmetric reactions of enolates or enaimines with electrophiles are one of the most fundamental yet efficient transformations to provide chiral carbonyl compounds, and a great number of successful examples has been reported. In particular, Aldol reaction, Michael reaction and Mannich reaction are the fundamental and important reactions in this reaction system, so a lot of reactions between enolates or enaimines and aldehydes, ketones, imines or olefins have been reported. For instance, Shibasaki *et al.* developed first catalytic asymmetric cross-aldol reaction in 1997 by using $LaLi_3$ tris(binaphthoxide) complex (LLB) as a bifunctional catalyst which exhibits both Lewis acidity and Brønsted basicity (Scheme 1).[1]

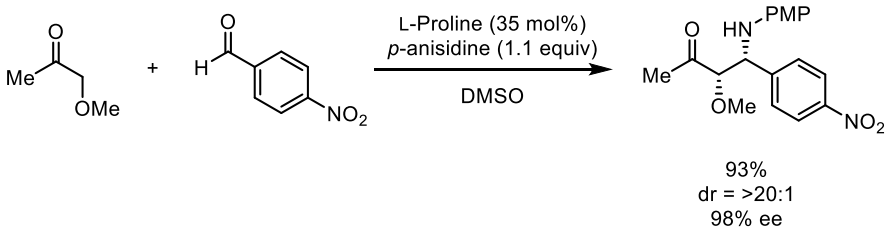


Scheme 1.

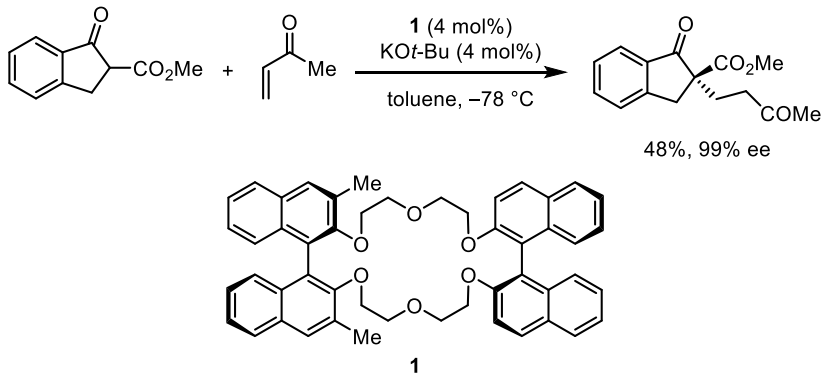
Furthermore, Shibasaki *et al.* developed asymmetric direct Mannich reaction of propiophenone with aminomethyl ether under the cooperative catalysis of an AlLibis(binaphthoxide) complex (ALB) and Lanthanum(III) Trifluoromethanelsulfonate in 1999 (Scheme 2).[2a] While this reaction is a first example of catalytic asymmetric direct Mannich reaction, enantioselectivity did not reach to satisfactory level. Following this report, List successfully realized highly diastereo- and enantioselective three component direct Mannich reaction by using proline as a catalyst in 2001 (Scheme 3).[2b] Cram *et al.* also contributed this area. They developed chiral crown ether complex catalyzed asymmetric Michael reaction and succeeded to give enantioenriched product (Scheme 4).[3]



Scheme 2.



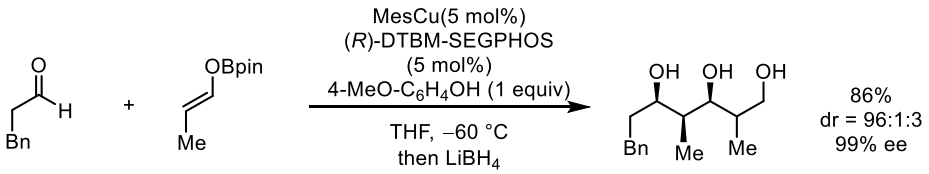
Scheme 3.



Scheme 4.

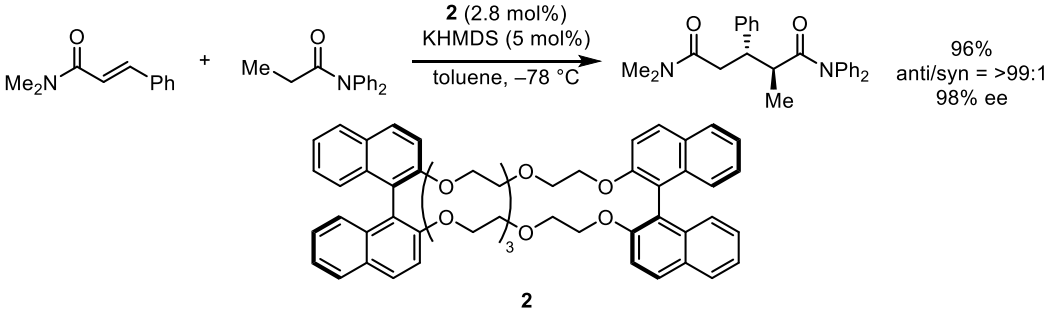
These pioneering works on the asymmetric transformations of carbonyl compounds have attracted the attention of chemists in the world. Then, this research area have been rapidly developed and a great number of reactions have been reported until now.

More challenging transformations of carbonyl compounds have been recently achieved based on the development of appropriate catalytic system. For example, Kanai *et al*. reported copper catalyzed asymmetric iterative and domino cross-aldol reaction between an aldehyde and a boron enol ether (Scheme 5).[4] This reaction enables the double, triple and quadruple aldol reaction and can provide enantio- and diastereomerically enriched 1,3-polyols in one-pot.



Scheme 5.

Kobayashi *et al.* developed catalytic asymmetric direct Michael reaction of simple amides as a nucleophile (Scheme 6).[5] This is a first successful example of direct catalytic asymmetric reactions of amides. The generation of enolate from simple amides usually requires the use of stoichiometric strong base due to the high pK_a value of α-proton. In the present system, an intermediate, which generates via the addition of enolate to Michael accepter, acts as strong Brønsted base for deprotonation from α-carbon of amide, enabling the promotion of catalytic cycles.



2

Scheme 6.

Following the above-mentioned pioneering works, about 17,000 reports concerning the catalytic asymmetric reaction of carbonyl nucleophiles. However, over 90% of these transformations are categorized into nucleophilic addition to aldehydes, ketones, imines, or electron-deficient olefins as an electrophile. In other words, the chemistry of carbonyl transformations has progressed based on the design and application of a wide variety of carbonyl nucleophiles, and the scope of electrophiles has been investigated within quite limited range.

In this context, the author took up the challenge to develop the asymmetric reactions of carbonyled nucleophiles with previously unutilized or inapplicable electrophiles. Especially, the author developed the hitherto difficult catalytic asymmetric substitution-type reactions of carbonyl compounds. These transformations would open a way to difficult-to-access chiral compounds.

1.2 Asymmetric Substitution

Nucleophilic substitution is one of the most fundamental, yet powerful methods for construction of carbon-carbon or carbon-heteroatom bond. The electron rich nucleophile selectively attacks on the α-carbon of the halide (or pseudo halide) and forms the new single bond with the disconnection of carbon-halogen bond. However, there are some problems in this type of transformations. The most crucial one is that the use of stoichiometric Brønsted bases is inevitable to trap the acids, which concomitantly generate in the substitution reactions. As a solution for this problem, the author considered that the asymmetric phase-transfer catalysis using chiral cationic catalysts with aqueous or solid inorganic base would be effective platform.

1.2.1 Phase-Transfer Catalyst

The quaternary ammonium and phosphonium salts can promote carbon-carbon or carbon-heteroatom bond formations under liquid-liquid or liquid-solid biphasic conditions. Concerning the mechanism of phase-transfer catalyzed alkylation reactions, Starks proposed the extraction pathway.[6] In this mechanistic scenario, ammonium bromide transfers from the organic phase to aqueous phase and extracts hydroxide ion as a counter ion to organic phase. Then, ammonium hydroxide [$Q^+ \cdot OH^-$] acts as Brønsted base to generate the anionic species from substrate, leading to the formation of key ionic intermediate [$Q^+ \cdot R^-$]. This intermediate reacts with halide to close the catalytic cycle, giving rise to the product with the concomitant regeneration of ammonium bromide [$Q^+ \cdot Br^-$] (Figure 2).

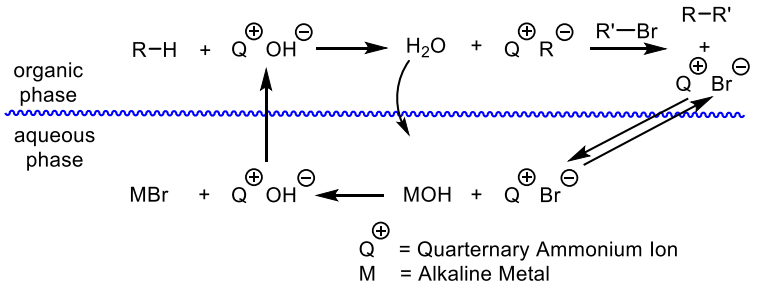
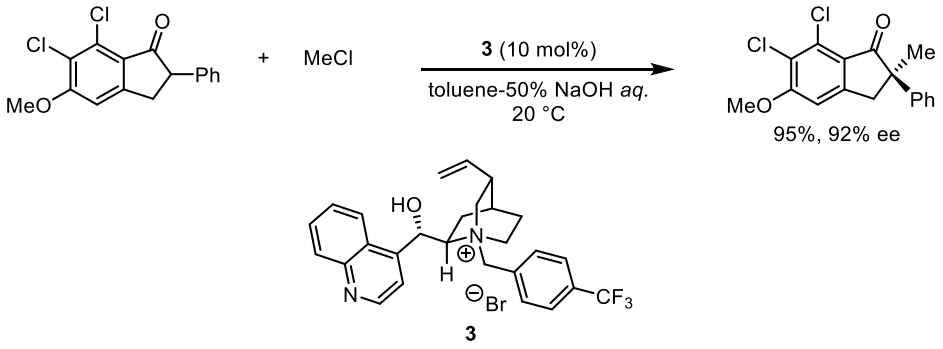


Figure 2. Extraction Mechanism for Phase-Transfer Catalyzed Alkylation of R–H.

Chiral non-racemic quaternary ammonium ions have been exploited as an asymmetric phase transfer catalyst for the stereocontrol in reactions of anionic intermediates, such as enolates. In 1984, the first asymmetric phase-transfer catalysis using a chiral quaternary ammonium salt was reported by Merck group.[7] Highly enantioselective methylation of an 1-indanone-derived enolate was achieved by using a cinchona alkaloid-based chiral ammonium bromide **3** as a catalyst under biphasic condition (Scheme 7). This pioneering work clearly demonstrated the effectiveness of asymmetric phase-transfer catalysis and attracted much attentions from organic chemists.



Scheme 7.

1.2.1.1 Hydrogen Bond Assists Ability of Phase-Transfer Catalyst

Conventional chiral quaternary onium ions interact with anionic species only via electrostatic attractive force. The electrostatic interaction is non-orbital and non-oriented, thus making the distance and direction between cation and anion highly fluctuated. As the design of chiral phase transfer catalyst, the introduction of hydrogen bond-donor site is effective, which allows the formation of structurally well-defined, contact ion pair.[8] In addition, hydrogen bond-donor site could contribute to accelerate the bond-forming events because such bifunctional catalysts can coordinate not only the anionic nucleophiles but also the electrophiles, thus promoting the reactions through pseudo-intramolecular transition structures (Figure 3).

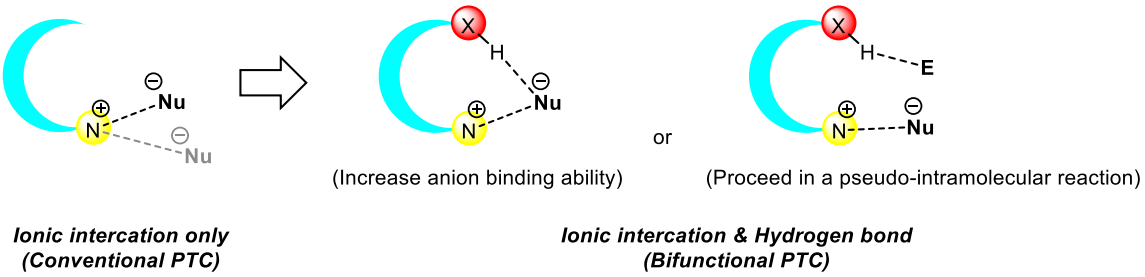
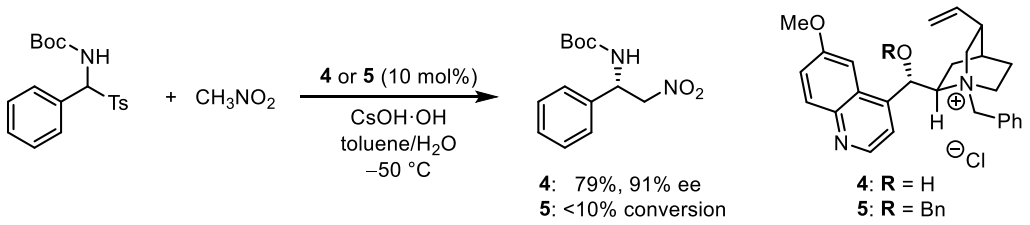


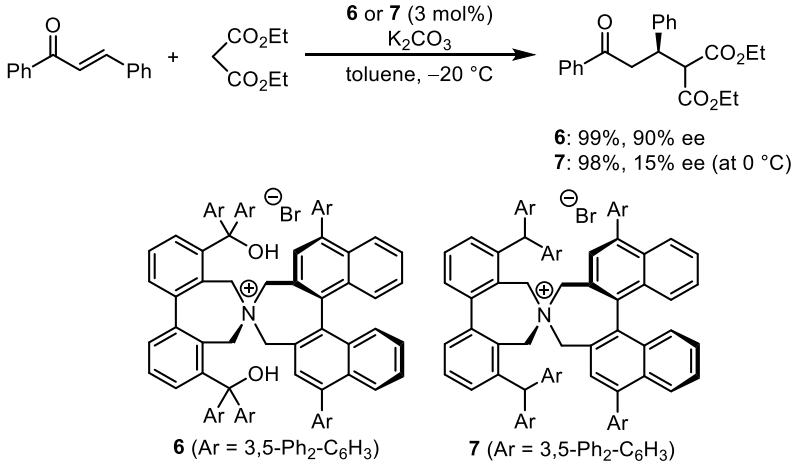
Figure 3. Comparison of Conventional PTC and Bifunctional PTC

For an example on bifunctional phase-transfer catalysts, Palomo reported catalytic enantioselective aza-Henry reaction using cinchona alkaloid derivatives as a phase-transfer catalyst.[9] Noteworthy is that the catalyst **4** having free hydroxyl group gave the desired Henry adduct in good yield with high enantioselectivity, while *O*-alkylated catalyst **5** was shown to be inactive in this reaction (conversion was <10%) (Scheme 8).



Scheme 8.

Maruoka *et al.* developed highly enantioselective Michael reaction of malonates to calcone derivatives using bifunctional chiral phase-transfer catalyst **6**.[10] As same with Palomos' work, free hydroxyl group was proven to be crucial for the high level of asymmetric induction. The enantiomeric excess was dramatically dropped when catalyst was switched to ammonium bromide **7**, which lacks hydroxyl groups (Scheme 9). These studies unambiguously showed the importance of hydrogen-bonding functionality for the promotion and/or stereocontrol of asymmetric reactions.



Scheme 9.

1.2.1.2 Chiral 1,2,3-Triazolium Salts

1,4-Disubstituted 1,2,3-triazole have shown to behave as amide bond mimics, where the N(3) atoms of triazoles act as hydrogen bond acceptors and the polarized C(5) protons act as hydrogen bond donors (Figure 4).[11] Furthermore, 1,4-disubstituted 1,2,3-triazoles can be synthesized easily by the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes with organic azides. With these unique and attractive features of 1,2,3-triazoles in mind, our research group interested in the application of 1,2,3-triazole derivatives for the the design of new bifunctional phase-transfer catalysts.

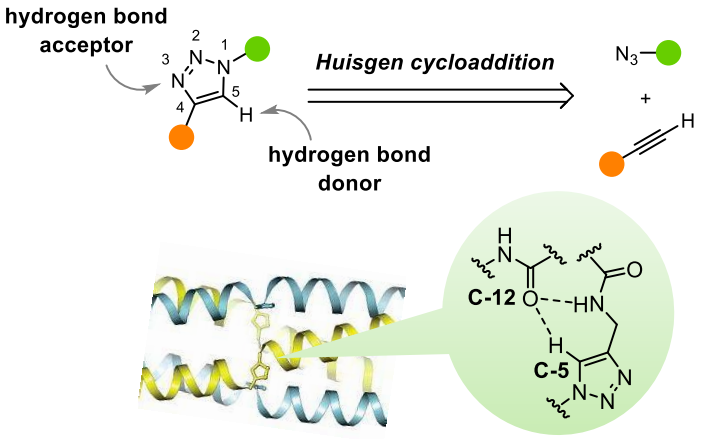


Figure 4. Feature of 1,2,3-Triazoles

The 1,2,3 triazoles can be easily converted into the 1,2,3-triazolium salts through *N*-alkylation reaction with alkyl halides. An advantage of this conversion is the significant improvement of anion-binding ability which stemmed from the increased acidity of C-5 proton (Figure 5). Recently, the remarkable hydrogen-bonding ability of triazolium ion has been exploited in the area of supramolecular chemistry.[12]

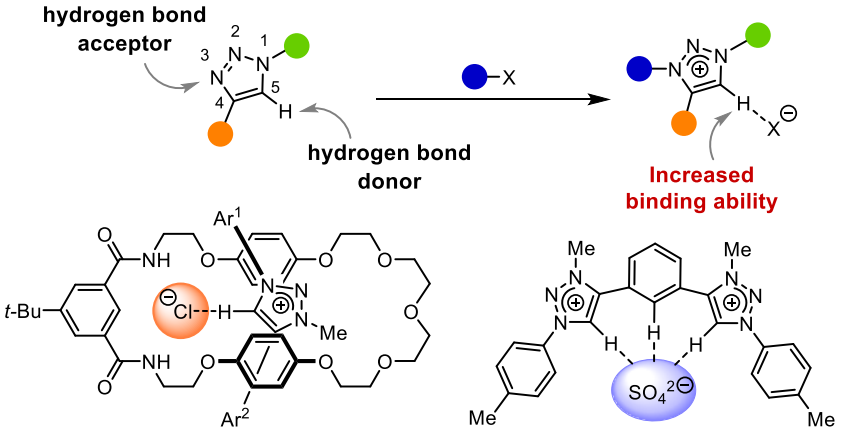


Figure 5. Supramolecules Having 1,2,3-Triazolium Ions

The first problem in the design of chiral 1,2,3-triazolium catalysts was how to combine triazole core with chiral molecular structure. If cyclic chiral structure is employed, catalyst skeleton will be rigid, but it should become difficult to synthesize. On the other hand, the use of acyclic chiral structure allows the simplification of its synthesis. However, flexible acyclic framework make the transition structures rather fluctuated, thus being unfavorable for stereocontrol. To eliminate this dilemma, second hydrogen bond-donating site such as amido functionality was introduced to the catalyst molecules, leading to the formation of rigid pseudo cyclic structure through the double hydrogen bond between triazole ion and anion (Figure 6).

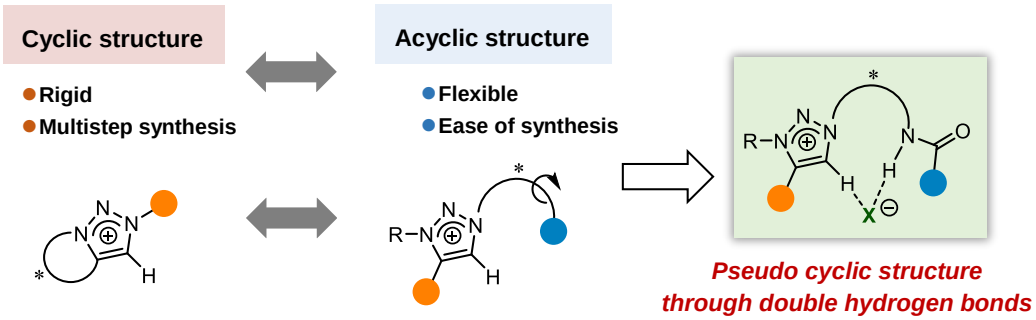
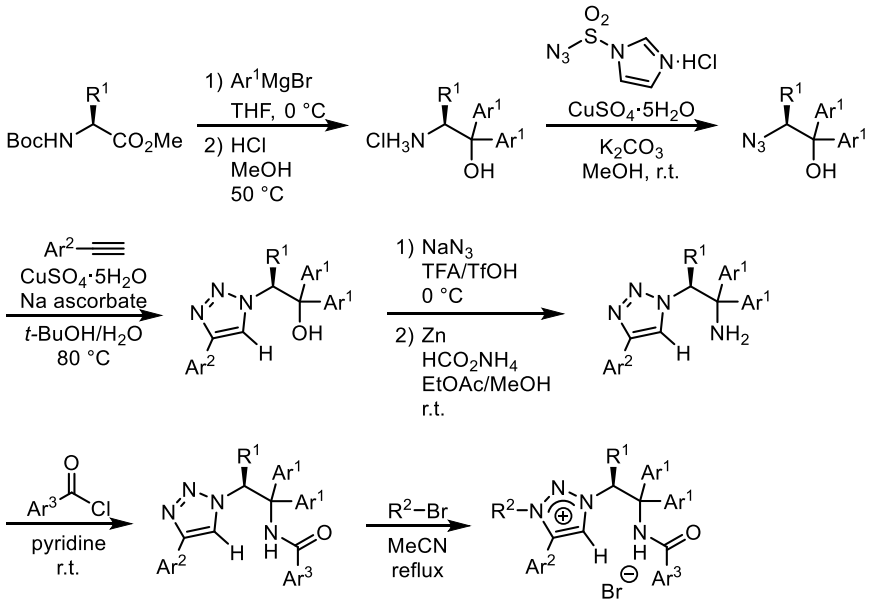


Figure 6. Design of Chiral 1,2,3-Triazolium Catalyst

Based on this concept, our group established synthetic method for the chiral 1,2,3-triazolium salts from *N*-Boc amino acid esters.[13] According to the literature procedure, geminal aromatic groups were introduced to *N*-Boc amino acid esters by the addition of the corresponding Grignard reagents, and the Boc group was removed by the treatment with 1N HCl in methanol at 50 °C. The amino group of the resulting amino alcohol hydrochloride was converted to azide moiety by the reaction with imidazole-1-sulfonyl azide hydrochloride and the catalytic amount of copper sulfate. Then, the Huisgen cycloaddition of resulting azide alcohol with aryl acetylene was conducted to produce 1,2,3-triazole. The tertialy hydroxyl group was then replaced by the azide moiety through the reaction with sodium azide in the mixed solvent of trifluoroacetic acid and trifluoromethanesulfonic acid (TfOH). Subsequent reduction of azide moiety furnished the amino compounds containing the triazole skeleton. Finally, after the treatment of amino compounds with benzoyl chloride derivative, the resulting product was alkylated with benzylic halide to give the chiral 1,2,3-triazolium salts (Scheme 10).



Scheme 10.

After the ion exchange process, the three dimensional molecular structure of chiral 1,2,3-triazolium chloride was revealed by X-ray diffraction analysis.[13] As expected, counter ion appeared to be interacted with the C(5) proton of triazolium ion and the amido N-H proton through the double hydrogen bonds. Furthermore, the conformation of catalyst was fixed via the formation of the pseudo-cyclic structure (Figure 7).

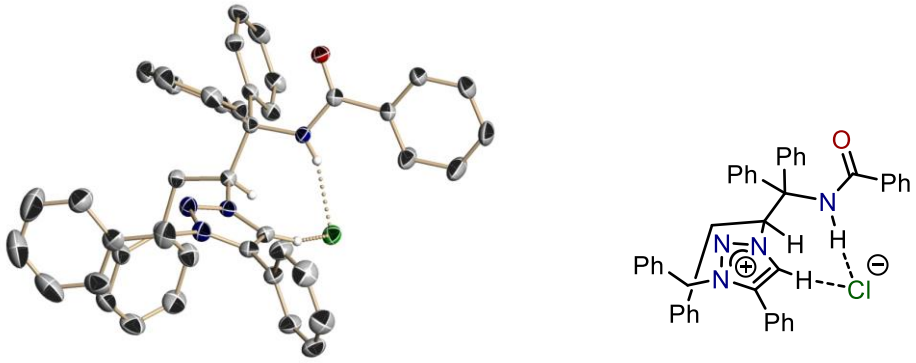
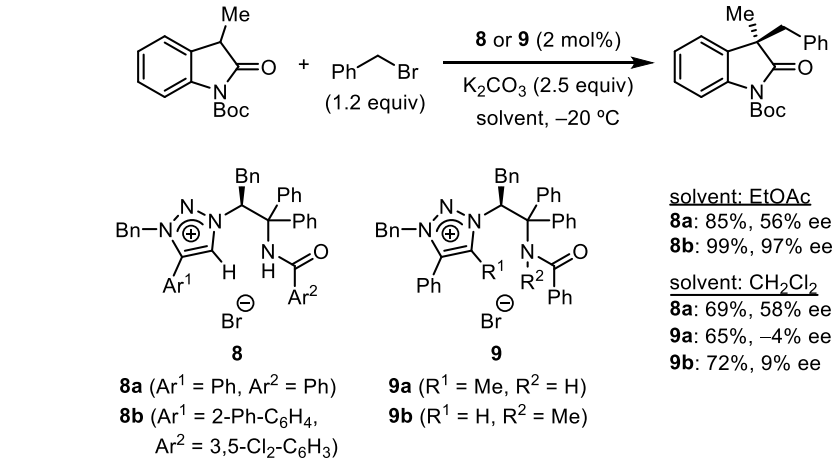


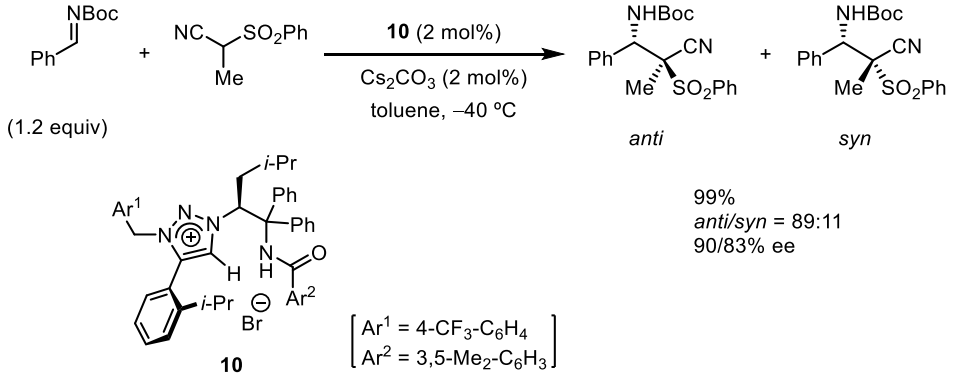
Figure 7. Three Dimensional Molecular Structure of Chiral 1,2,3-Triazolium Chloride

This type of chiral 1,2,3-triazolium salts has powerful potential as an organic catalyst. As a first successful demonstration, our group applied the newly developed chiral 1,2,3-triazolium salts for catalytic asymmetric phase-transfer alkylation of oxindoles.[13] In this reaction, triazolium salt **8b** possessing *o*-biphenyl substituent on C-4 position of triazole ring and 3,5-dichloro-benzoyl group on amide nitrogen exhibited the highest performance, promoting the reaction with high efficiency and excellent enantioselectivity. On the other hand, the reaction using the structurally similar catalysts **9a** or **9b**, bearing a methyl group instead of a C(5) proton or an amide proton, induced negligible enantioselectivity. These results showed that the double hydrogen bond-donating ability of the triazolium ion was essential for asymmetric induction (Scheme 11). In addition, the investigation of the scope of substrates revealed that the enantioselectivities in the alkylations of oxindoles were sensitive not on the structure of oxindoles but on alkyl halides. This tendency was unique in asymmetric phase-transfer catalysis because chiral cationic catalysts generally interact with anionic nucleophiles and thus are favorable for the recognition of their stereochemistry. In other words, enantioselectivities in conventional asymmetric phase-transfer catalysis seemed to highly depend on the structure of nucleophiles. This information implied that chiral triazolium ions could coordinate to alkyl halides in the transition states and have a potential for the recognition of the stereochemistries of electrophiles.



Scheme 11.

Similar implication was gained from catalytic asymmetric Mannich-type reactions of α-cyano α-sulfonyl carbanions using chiral 1,2,3-triazolium salts **10**.[14] Under the optimized reaction conditions, the Mannich additions proceeded with uniformly moderate diastereoselectivities and excellent enantioselectivities. The X-ray crystallographic analyses of both two diastereomeric products showed that the sterechemistires derived from cyanoesters were opposite in two diastereomers and the stereocenters derived from imines have same absolute configuration. This result strongly indicated that 1,2,3-triazolium catalyst almost completely discriminated the prochiral face of *N*-Boc imine (Scheme 12).



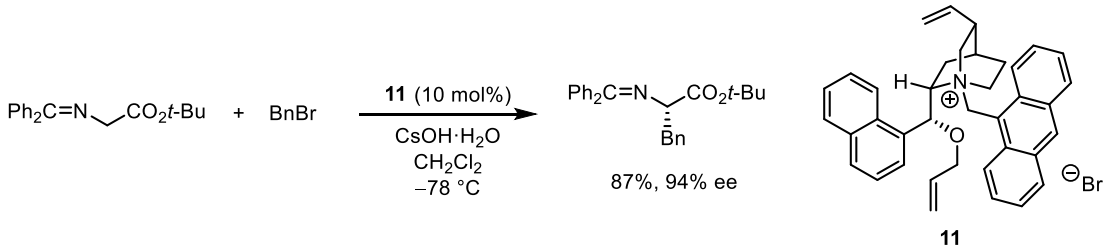
Scheme 12.

From these results in mind, the author envisioned that chiral 1,2,3-triazolium salts would be effective for the development of carbon–carbon and carbon–heteroatom bond-forming reactions, especially the asymmetric reactions involving the discrimination of the stereochemistry of electrophiles.

1.2.2 Asymmetric Substitution of Chiral Electrophiles

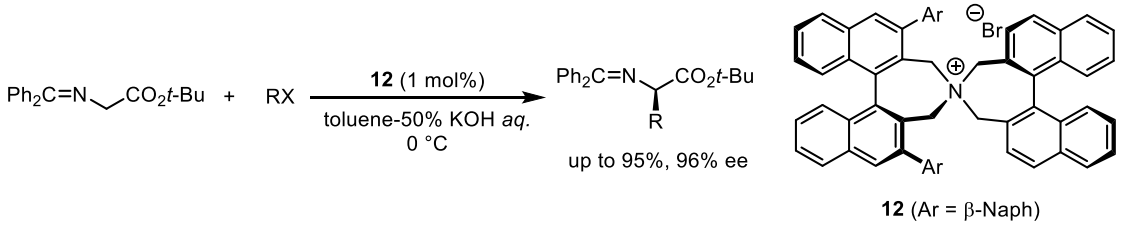
1.2.2.1 Preface: Asymmetric Phase-Transfer Alkylation with Primary Alkyl Halides

There have been many reports on the catalytic asymmetric reactions of enolates with primary halides. A representative reaction is catalytic asymmetric α-alkylation of glycine Schiff base. In 1997, Corey group reported a first successful example, in which cinchonidine-derived chiral ammonium bromide **11** promoted the benzylation of glycine imine to produce the phenylalanine derivative with high enantioselectivity (Scheme 13).[15] A critical problem of cinchonidine or cinchonine-derived catalysts is the instability of ammonium ions under basic conditions; theses quaternary ammonium ions easily decompose through Hoffmann elimination.



Scheme 13.

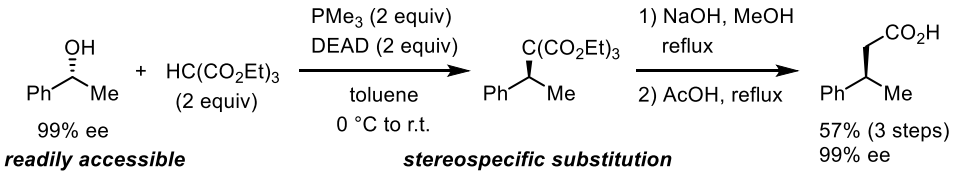
Hoffmann elimination of quaternary ammonium ions is triggered by the deprotonation from β-carbon of ammonium nitrogen. Thus, lack of β-proton would lead to the prevention of catalyst decomposition. With this idea, Maruoka group developed 1,1′-bi-2-naphthol (BINOL)-derived C_2-symmetric chiral ammonium salts of type **12**.[16] The performance of these new catalysts was clearly manifested through their application for asymmetric alkylation of glycine Schiff base. Only in the presence of 1 mol% of catalyst **12**, alkylations with primary alkyl halides smoothly proceeded to give the corresponding alkylated products uniformly in excellent yield with excellent enatioselectivity (Scheme 14).



Scheme 14.

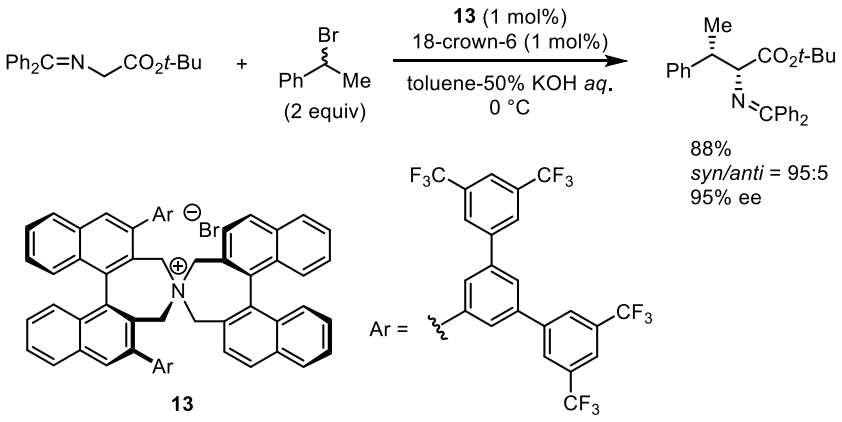
1.2.2.2 Asymmetric Substitution at Trisubstituted Chiral Carbons

Carbon–carbon bond formation through direct substitution at the chiral carbon center is powerful transformations for constructing chiral organic molecular frameworks. It is well known that nucleophilic substitution at the trisubstituted chiral carbon of optical active secondary pseudo halides with carbon nucleophiles in basic conditions smoothly proceed with complete stereospecificity in stereoinvertive manner. For example, Hillier *et al.* reported the substitution of optically pure secondary alcohol with diethyl malonate; this Mitsunobu reaction proceeded with complete stereoinvertive to construct a tertiary stereocenter in optically pure form (Scheme 15).[17]



Scheme 15.

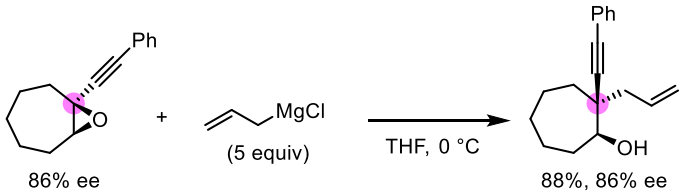
The alkylations of prochiral enolates with secondary (pseudo)alkyl halides provide a direct and efficient way to access contiguous stereocenters. When racemic halides are used as an electrophile, the reaction involves a formidable challenge in terms of stereocontrol, that is the simultaneous achievement of the discrimination of prochiral face of enolate and the kinetic resolution of secondary halides. To date, there has been only a single successful example, highlighting the difficulty of such multiple stereocontrols. Maruoka *et al.* discovered that the reaction of glycine Schiff base with racemic secondary benzylic bromide proceeded in enantio- and diastereoselective manner by using BINOL-derived ammonium salt **13** having extended aromatic substituents at 3,3′-positions (Scheme 16).[18]



Scheme 16.

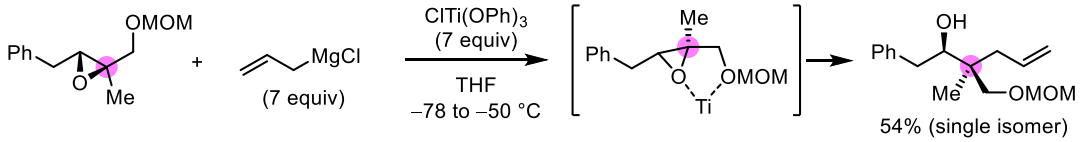
1.2.2.3 Asymmetric Substitution at Tetrasubstituted Chiral Carbons

As was different from reactions with secondary alkyl halides or pseudo halides, asymmetric substitution at the tetrasubstituted chiral carbon has remained almost unexplored, primarily because of the difficulty associated with the preparation of enantiomerically pure tertiary pseudo halides as well as the difficulty for the direct substitution at their sterically hindered carbons. As one of a few successful examples, the stereospecific ring-opening reaction of the optically active epoxide with Grignard reagents was reported by Taber *et al.* (Scheme 17).[19] In this case, a key to realize regioselective and stereospecific opening would be the neighboring stabilizing effect by alkynyl group.



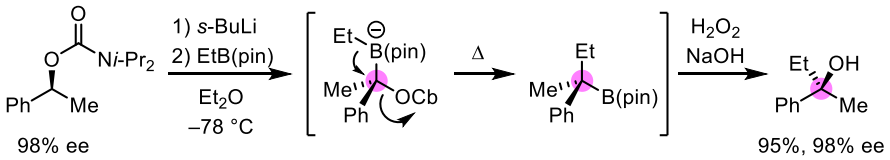
Scheme 17.

Tanaka *et al.* also reported a stereospecific ring-opening reaction of 2,2,3-trisubstituted epoxides with Grignard reagents (Scheme 18).[20] By using titanium (IV) complex, complete regioselectivity was achieved via the chelation of titanium with two Lewis basic oxygens of substrates.



Scheme 18.

Recently, Aggarwal group developed stereospecific 1,2-metallate rearrangement of boronate complexes (Scheme 19).[21] The key step of this transformation can be regarded as S_N2 substitution at tetrasubstituted chiral carbon.



Scheme 19.

In the above mentioned stereospecific reactions, only the simple organometallic reagents, such as Grignard reagents, were used as a nucleophile, and there has been no example of substitution at tetrasubstituted chiral carbon with more functionalized nucleophiles, such as enolates. There has been also no report of the catalytic stereoselective substitution of racemic tertiary (pseudo) halides.

While it is unprecedented transformation, the direct stereoselective substitution at tetrasubstituted chiral carbons with α,α-disubstituted enolates would provide an efficient method to produce difficult-to-construct contiguous all-carbon quaternary stereocenters (Figure 8).

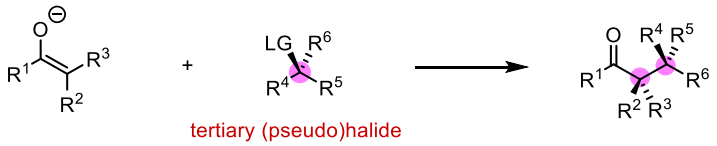
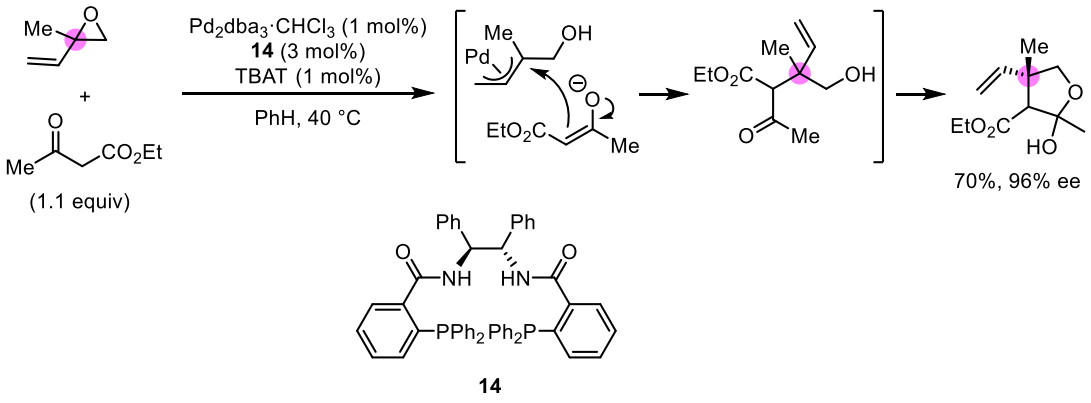


Figure 8. Stereoselective Transformation of α,α-Disubstituted Enolates with Tertiary (Pseudo)Halide to Construct Contiguous All-Carbon Quaternary Stereocenters

In contrast to the difficulty of direct asymmetric substitution at tetrasubstituted carbon, Tsuji–Trost allylic substitution through the π-allyl transition metal intermediates enables the facile asymmetric indirect substitution at tetrasubstituted chiral carbons. For instance, Trost *et al.* developed highly enantioselective allylic alkylation of vinylepoxides with β-ketoesters by using chiral palladium catalyst (Scheme 20).[22] This chiral palladium shielded the *Re* face of allyl moiety of the intermediate, thus allowing the nucleophilic addition of enolates on the *Si* face and resulting in the stereoselective construction of tetrasubstituted chiral carbons. The stereochemistry of another chiral carbon of products, that was α-carbon of β-ketoesters, could not be controlled probably due to the rapid epimerization.



Scheme 20.

1.2.2.4 Catalytic Ring-Opening Alkylation of Racemic 2,2-Disubstituted Aziridines with 3-Substituted Oxindoles: Chapter 2

In the above mentioned situation, the author started his research for the development of catalytic asymmetric substitution at the tetrasubstituted chiral carbon with prochiral α,α-disubstituted enolates, and selected 2,2-disubstituted aziridine as an electrophile. The aziridines has high reactivity because of its ring strain, and the reactivity could be further improved by introducing the electron withdrawing group on nitrogen. The aromatic substituents at C-2 position would enhance the regioselectivity by the neighboring effect (Figure 9).

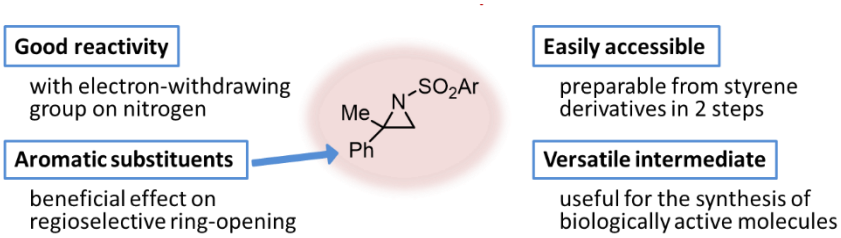
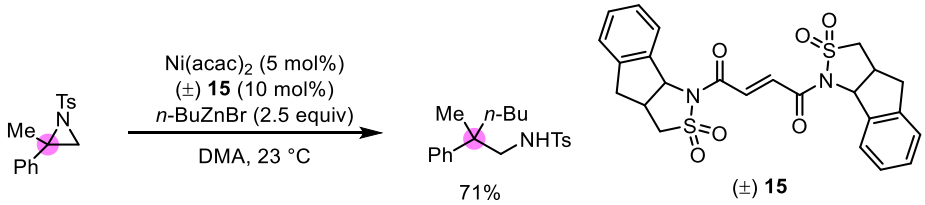


Figure 9. Characteristics of 2,2-Disubstituted Aziridine.

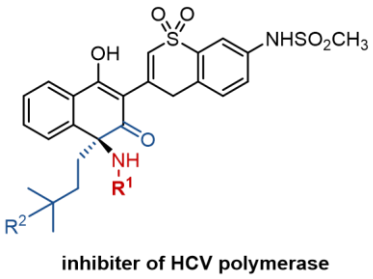
Doyle group developed the nickel catalyzed regioselective ring opening of 2,2-disubstituted aziridines with alkyl zinc reagents while this reaction is not asymmetric transformation (Scheme 21).[23]



Scheme 21.

1.2.3 Carbon-Nitrogen Bond Formation

Chiral α-aminocarbonyl compounds are common structural motif in natural products and are attractive targets in medicinal chemistry. In terms of the application of α-aminocarbonyl compounds for pharmaceuticals, not only the organic frameworks around carbonyl group, but also the substituents on nitrogen have significant impact probably because amino groups often act as binding functionalities in bioorganic systems. For instance, the substituents on nitrogen are of particular importance for the biological activity of aminonaphthalenone derivatives, which is potent HCV therapeutics.[24] As shown in Figure 10, compared to the aminonapthalenones having *N*-benzoyl or other electron-withdrawing groups, *N*-benzyl derivatives showed much higher activity. Therefore, the strategy for the asymmetric bond-formation between carbonyl compounds and a variety of amine derivatives is highly desirable.



inhibiter of HCV polymerase

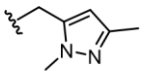
R^1	R^2	IC_{50} (nM)	EC_{50} (nM)
COPh	H	108	ND
CO_2Me	H	25	210
$CONH_2$	H	27	576
SO_2Me	H	24	69
CH_2Ph	H	19	34
CH_2Ph	Me	10	17
	Me	5	15

Figure 10. Effect of Substituents on Nitrogen for The Biological Activity.

The most straightforward way to access such chiral compounds is the direct introduction of non-protected amines into the α-position of carbonyl group. However, this simple scheme is an unrealized transformation because of inherent electronegativity both of carbonyl α-carbon and nitrogen atom. Therefore, the use of electrophilic reagents is essential for the realization of such α-amination of carbonyl compounds (Figure 11).

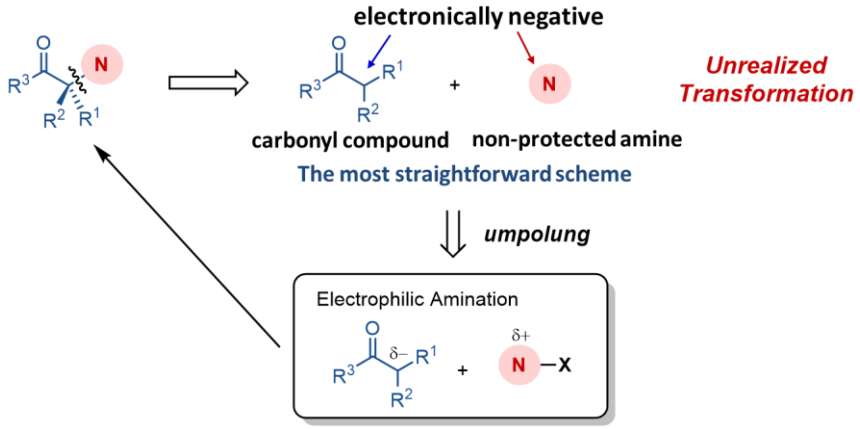
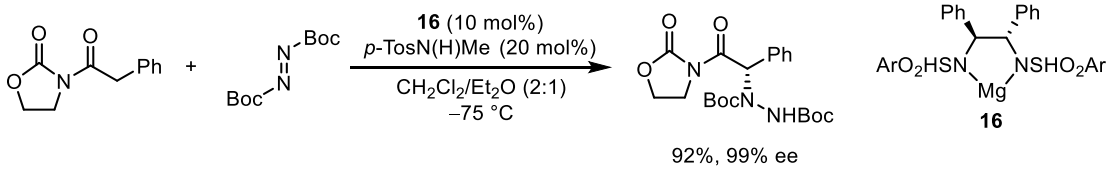


Figure 11. Strategy for Straightforward Access to Chiral α-Aminocarbonyl Compounds.

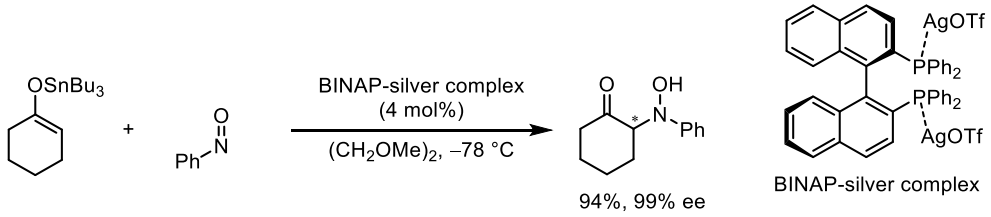
1.2.3.1 Formal Synthesis of α-Aminocarbonyl Compounds

To date, a great number of asymmetric carbon–nitrogen bond-forming reactions at α-position of carbonyl compounds have been reported. Almost all of these reactions was achieved based on the use of one of three reagents; azodicarboxylates, nitroso compounds, or azidoiodinane. In 1997, Evans *et al.* reported an initial successful example for asymmetric α-hydrazination of *N*-acyloxazolidinones with azodicarboxylates. They achieved high enantioselectivity by the use of the magnesium bis(sulfonamide) complex **16** as a catalyst (Scheme 22).[25]



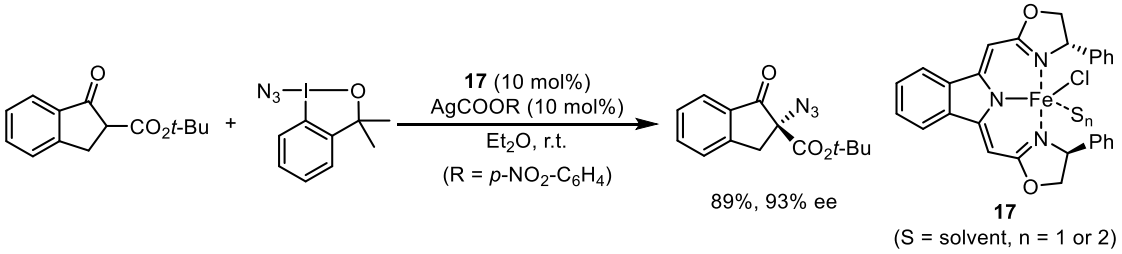
Scheme 22.

For α-aminohydroxylation of carbonyl compounds with nitroso compounds, Yamamoto *et al.* reported a pioneering work. They found that tin enlates regio- and enantioselectively attacked at nitrogen of nitrosoarenes under the influence of BINAP-silver complex to afford the corresponding chiral α-hydroxylaminocarbonyl compounds (Scheme 23).[26]



Scheme 23.

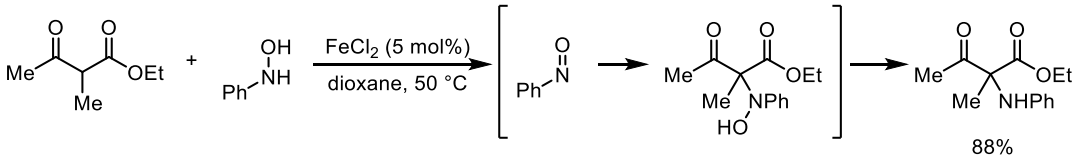
A single example for asymmetric α-azidation of carbonyl compounds was presented by Gade *et al.* in 2013. In particular, they developed iron catalyzed enantioselective α-azidation of β-keto esters and oxindoles by using T-shaped iodine(III) compound as an azido-transfer reagent (Scheme 24).[27]



Scheme 24.

These C–N bond-forming reactions with three types of electrophilic nitrogen sources have been efficient methodology for the asymmetric synthesis of chiral α-aminocarbonyl compounds. However, the reactions with these nitrogen sources require the following reductive N–N or N–O bond cleavages under relatively harsh conditions to give target α-aminocarbonyl compounds, inevitably reducing the synthetic efficiency and the functional group compatibility. In addition, the substituents on α-amino groups should be limited to alkoxycarbonyl or aryl groups. So, when the compounds with alkyl or related substituted α-amino group were required, other new strategy should be developed.

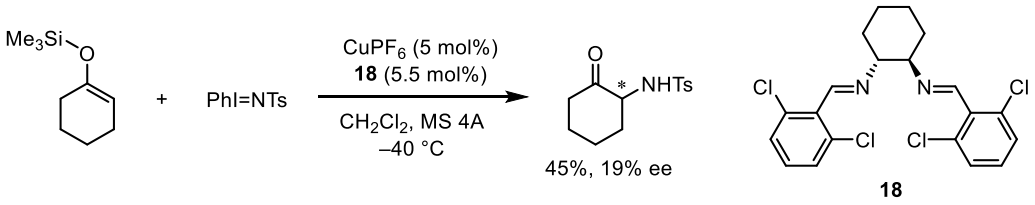
Recently, Murru and Srivastava *et al.* developed iron catalyzed non-stereoselective direct α-amination of carbonyl compounds with hydroxylamines. Although they showed any evidence to prove the reaction mechanism, this amination would proceed through the cascade of aerobic oxidation of hydroxylamines, *N*-nitoroso aldol of carbonyl, and N–O bond cleavage (Scheme 25).[28]



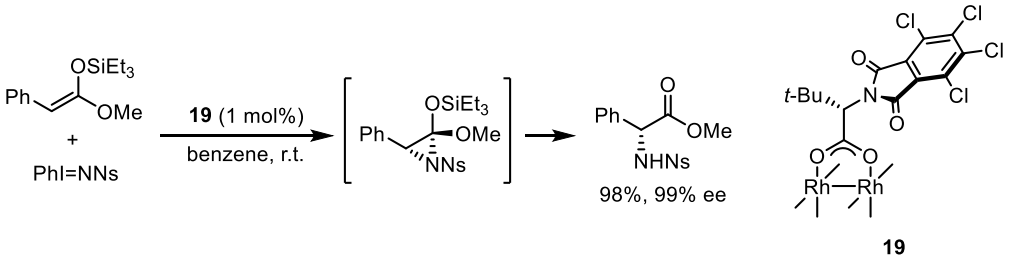
Scheme 25.

1.2.3.2 Asymmetric α-Amination of Silyl Enol Ethers or Ketene Silyl Acetals

Asymmetric α-amination of silyl enol ethers or ketene silyl acetals have been developed. Adam and co-workers reported copper-catalyzed asymmetric α-amination of silyl enol ethers with *N*-(tosylimino)iodobenzene (Scheme 26).[29] Hashimoto *et al.* achieved highly enantioselective α-amination of ketene silyl acetales by using dimeric chiral Rh catalyst **19** (Scheme 27).[30] These reactions of silyl enols ether and ketene silyl acetals proceeded through the formation of intermediary aziridines, followed by the ring-opening processes to afford the corresponding *N*-sulfonyl α-aminocarbonyl compounds.

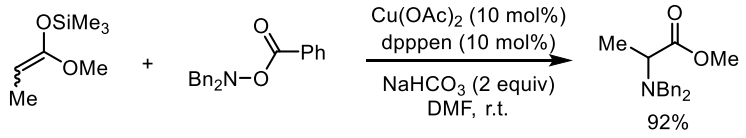


Scheme 26.



Scheme 27.

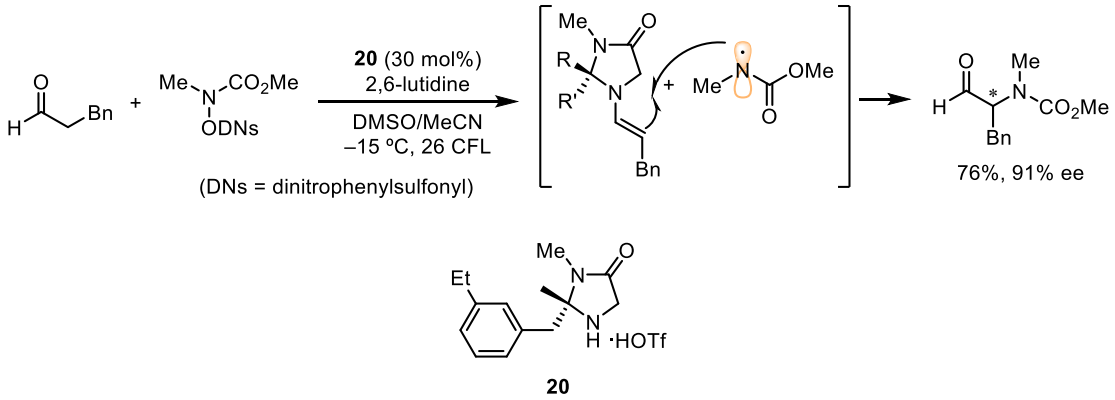
While this reaction is not asymmetric transformation, α-amination of silyl acetals with *O*-benzoyl hydroxylamine has been reported by Miura group. In this reaction, non-protected amines could be introduced at α-position of carbonyl compounds (Scheme 28).[31]



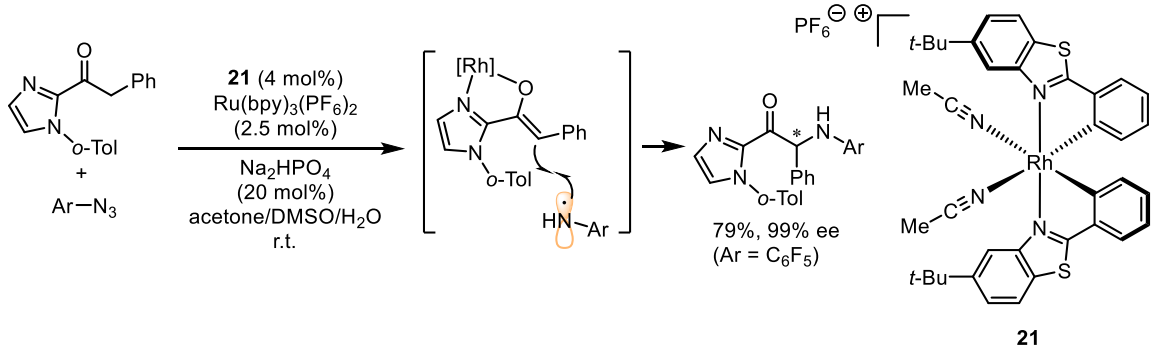
Scheme 28.

1.2.3.3 Photocatalytic Asymmetric α-Amination

Recently, Prof. MacMillan made an excellent contribution on the topic of asymmetric amination via a combination of photoredox with organocatalysis (Scheme 29).[32] They discovered that electrophilic nitrogen-centered radical could be generated from this substrate bearing a photo-labile leaving group, and it undergo the enantioselective coupling with chiral emamines. Prof. Meggers also developed photocatalytic direct α-amination. They found that the asymmetric coupling of enolate with nitrogen-centered radicals generated from electron-deficient azides could be realized by using chiral rhodium complex **21** and photosensitizer under the visible light irradiation (Scheme 30).[33] Although MacMillans' and Meggers' protocols allow the direct access to α-aminocarbonyl compounds, the scope of the substituents on α-amino groups was quite limited.



Scheme 29.



Scheme 30.

1.2.3.4 A Modular Strategy for the Direct Catalytic Asymmetric α-Amination of Carbonyl Compounds: Chapter 3

As described in section **1.2.3.1** to **1.2.3.3**, the structural diversity of substituents on nitrogen is quite limited in the previously reported asymmetric aminations. Therefore, the author focused on the development of asymmetric amination, especially being applicable for the introduction of a wide variety of amino groups, and selected hydroxyl amines as a nitrogen source because *N*-substituted hydroxylamines are readily available. Actually, various monosubstituted hydroxylamines could be synthesized from oxims or nitrobenzens in one step (Figure 12).

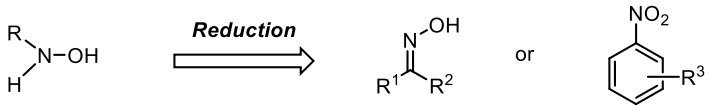
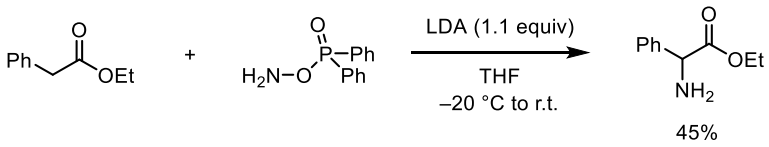


Figure 12. Synthesis of *N*-Substituted Hydroxyl Amines

Hydroxylamines have been classically utilized as electrophilic nitrogen source based on the optimization of their reactivity by changing substituent on oxygen. For example, Boche's group realized direct amination using *O*-diphenylphosphinyl hydroxylamine as nitrogen source (Scheme 31).[34] However, these reactions required strong nucleophile such as metal enolates. The conversion of phosphoryl group into more electron-withdrawing group, such as sulfonyl group, could improve the electrophilicity, but these derivatives are thermally labile and are known to easily decompose.[35] Therefore, it would be difficult to apply these pre-activated hydroxylamines into asymmetric direct α-amination of carbonyl compounds.



Scheme 31.

As a solution of this problem, the author developed a new strategy for the *in-situ* activation of hydroxylamines by using trichloroacetonitrile.[36] Activation of hydroxyl group by the treatment with trichloroacetonitrile has been exploited in various transformations, such as glycosylation[37] or alkylation.[38] The author envisioned that *O*-addition of hydroxylamines to trichloroacetonitrile would smoothly proceed under mild basic conditions and the resulting *O*-trichloroacetimino hydroxylamines could act as an electrophilic nitrogen source for asymmetric amination (Figure 13).

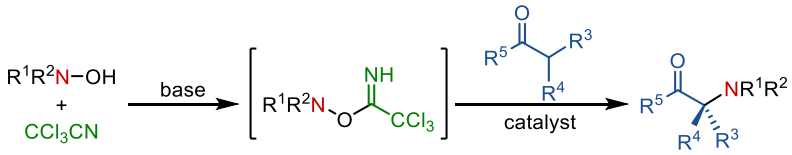
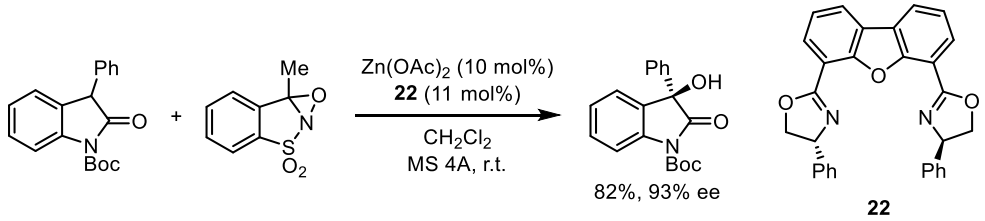


Figure 13. Reaction Design of Direct α-Amination via *In-Situ* Generation of Electrophilic Nitrogen Source

1.2.4 Carbon-Oxygen Bond Formation

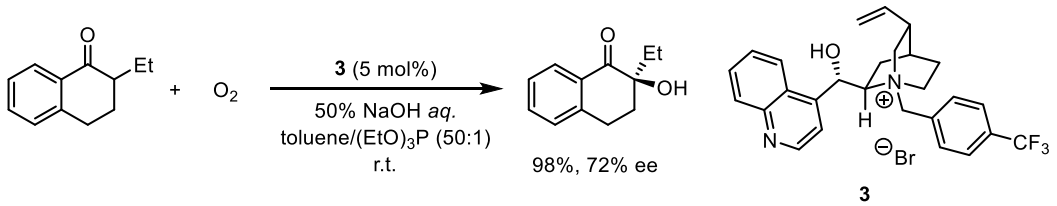
1.2.4.1 Asymmetric α-Hydroxylation of Carbonyl Compounds

α-Hydroxycarbonyl compounds are common structural core of many biologically active compounds and serve as versatile synthetic intermediates. One of the most efficient and straightforward synthesis of α-hydroxycarbonyl compounds is asymmetric α-hydroxylation of carbonyls by the use of electrophilic oxygenating agents. To date, there has been a wide variety of successful examples using efficient catalysts and appropriate oxygenating reagents, such as dimethyldioxirane, oxaziridine, nitrosoarene, molecular oxygen and alkyl hydroperoxide. For example, Shibata and Toru *et al.* reported enantioselective α-hydroxylation of oxindoles with oxaziridine (Scheme 32).[39] While the reactivity of these oxaziridines is attractive, the requirement of tedious pre-preparation should be problematic.



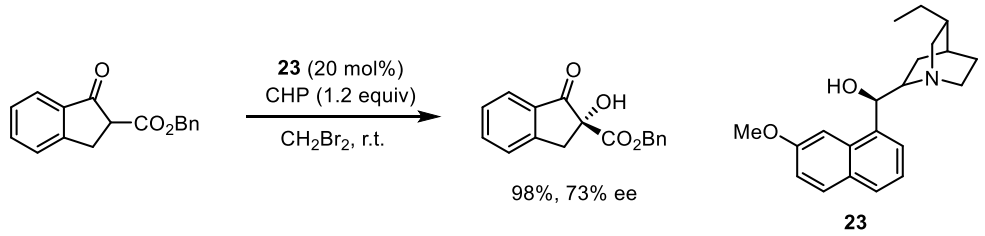
Scheme 32.

Shioiri *et al.* reported first asymmetric α-hydroxylation of cyclic ketones with molecular oxygen as an oxidant (Scheme 33).[40] This reaction required excess amount of reductant to prevent the peroxide-initiated undesired reaction.



Scheme 33.

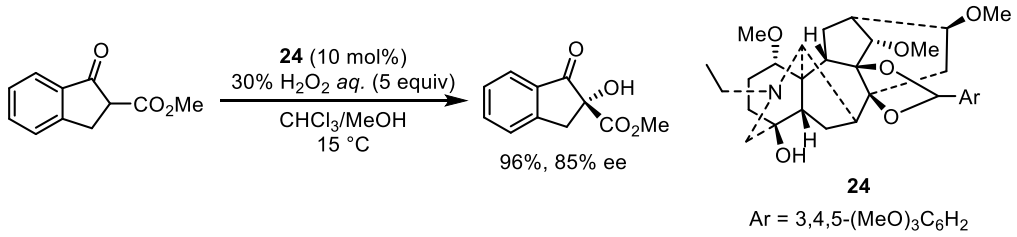
Alkyl hydroperoxides, such as cumene hydroperoxide (CHP), were used as an oxidant for asymmetric α-hydroxylations. An example is shown in Scheme 34.[41]



Scheme 34.

1.2.4.2 Asymmetric α-Hydroxylation of Carbonyl Compounds by Using Hydrogen Peroxide as an Oxidant

Hydrogen peroxide is inexpensive and safe-to-handle oxidant, but its reactivity as an electrophile is usually insufficient. In fact, there has be no successful report, except a single contribution by Meng and con-workers, on asymmetric hydroxylation with hydrogen peroxide. Very recently, Meng *et al.* reported the asymmetric α-hydroxylation of indanone-derived β-ketoesters with hydrogen peroxide as an electrophilic oxygen source (Scheme 35).[42] However, this reaction unfortunately suffered from a narrow substrate scope and unsatisfactory level of enantioselectivity.



Scheme 35.

1.2.4.3 *In Situ* Electrophilic Activation of Hydrogen Peroxide for Catalytic Asymmetric α-Hydroxylation of 3-Substituted Oxindoles: Chapter 4

The author expected that *in situ* electrophilic activation of hydrogen peroxide by the use of trichloroacetonitrile can be also applied for the realization of asymmetric hydroxylation. The treatment of hydrogen peroxide with trichloroacetonitrile is known to furnish the peroxy trichloroacetimidic acid under mild basic condition.[43] This peroxyimidic acid would also react with catalytically generated chiral enolates of carbonyl compounds as same as the amination in section **1.2.3.4**. As a result, chiral 1,2,3-triazolium salt-catalyzed highly enantioselective α-hydroxylation of oxindoles was achieved through the optimization of reaction parameters (Chapter 4).

1.3 Conclusion

In this theme, highly hitherto difficult asymmetric transformations were achieved by the use of unique electrophiles or electrophilic activation under the chiral 1,2,3-triazolium catalysis. The first catalytic asymmetric direct substitution at the tetrasubstituted chiral carbon has been achieved by the use of 2,2,-disubstituted aziridines as a tertiary pseudo halides. This powerful method enables the construction of contiguous all-carbon quaternary stereocenters which is the most challenging objectives in asymmetric synthesis. Furthermore, the novel catalytic asymmetric carbon–heteroatom bond-forming reactions have been developed utilizing unique electrophilic activation of hydroxyl amines and hydrogen peroxide by the use of trichloroacetonitrile. The author hopes that these strategies would have a large ripple effect in pharmaceutical chemistry and material science that aim to create new functions based on molecular structure.

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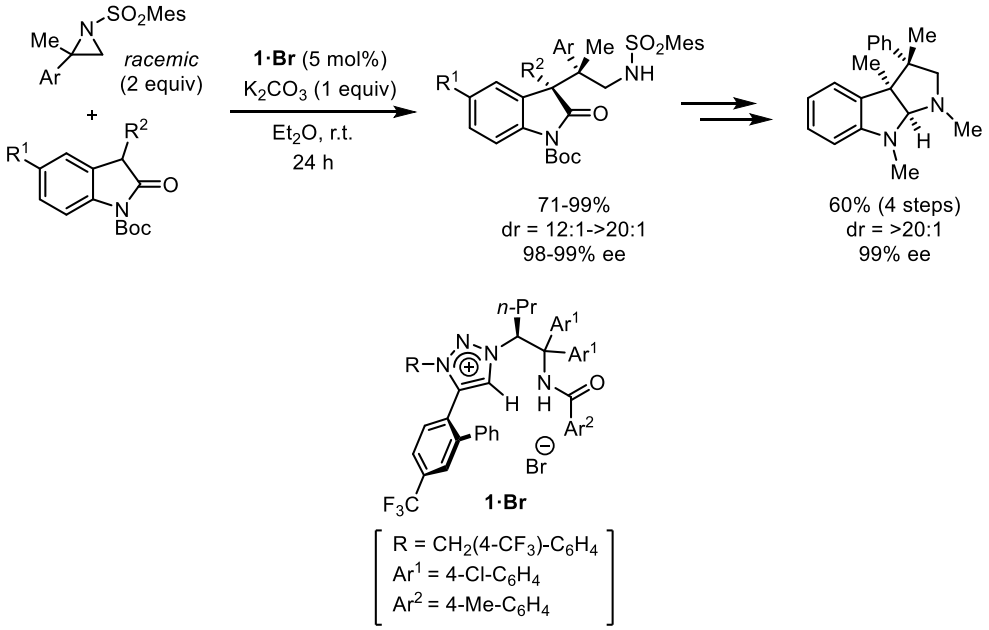
Chapter 2

Catalytic Ring-Opening Alkylation of Racemic 2,2-Disubstituted Aziridines with 3-Substituted Oxindoles



Abstract:

A highly diastereo- and enantioselective ring-opening alkylation of racemic 2,2-disubstituted aziridines with 3-substituted oxindoles is achieved under the catalysis of a chiral 1,2,3-triazolium salt. This reaction represents a hitherto unknown, catalytic stereoselective carbon−carbon bond formation through direct substitution at the tetrasubstituted chiral carbon.

1. Introduction

Carbon–carbon bond formation through direct substitution at the chiral carbon center is one of the most fundamental and powerful transformations for constructing chiral organic molecular frameworks. In particular, stereospecific or stereoselective nucleophilic substitution at the trisubstituted chiral carbon of secondary (pseudo)halides, epoxides, and aziridines with carbon nucleophiles has been the subject of extensive research.[1,2] In contrast, asymmetric substitution at the tetrasubstituted chiral carbon remains a formidable pursuit, primarily because of the stringent difficulties associated with the preparation of enantiomerically pure tertiary (pseudo)halides and stereospecific carbon–carbon bond-forming substitution at their sterically congested chiral carbons. While several stereospecific reactions such as ring opening of optically active epoxides[3-5] and 1,2-metallate rearrangement of boronate complexes[6] have been reported, stereoselective direct substitution reactions at the tetrasubstituted chiral carbon are entirely unknown, and so are catalyst-controlled systems.[7] Here, the author discloses the first successful example of such a transformation, that is, asymmetric ring-opening alkylation of racemic 2,2-disubstituted aziridines with 3-substituted oxindoles catalyzed by chiral 1,2,3-triazolium salts.[8] This catalytic protocol offers a robust strategy for the highly diastereo- and enantioselective construction of contiguous all-carbon quaternary stereocenters.[9,10]

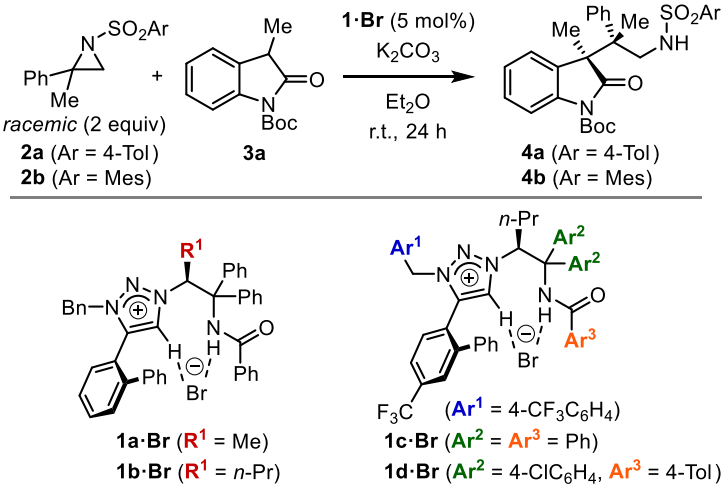
2. Result and Discussion

2.1. Optimization of the Reaction Conditions

N-Activated aziridines are regarded versatile pseudohalides, and their catalytic asymmetric ring-opening reactions with carbon nucleophiles provide useful tools for the synthesis of various nitrogen-containing biologically active compounds.[11-13] In consideration of the prominent reactivity of such aziridines, the author attempted the reaction of racemic *N*-sulfonyl 2-methyl-2-phenylaziridine **2** with 3-methyloxindole **3a** (Table 1). Thus, **3a** was treated with 2 equiv of racemic *N* -tosyl aziridine **2a** in the presence of *L*-alanine-derived chiral 1,2,3-triazolium bromide **1a·Br**[14] (5 mol%) and K_2CO_3 (1 equiv) in Et_2O at room temperature for 24 h. The ring-opening substitution occurred exclusively at the fully substituted carbon to give alkylation product **4a**, which had adjacent quaternary chiral carbons, in 78% yield (entry 1). Although the diastereoselectivity was low, each diastereomer of **4a** was obtained in a highly enantioenriched form. Notably, the identity of *N*-sulfonyl substituent was important for stereocontrol, and slightly higher diastereoselectivity was attained in the reaction with *N*-mesitylsulfonyl aziridine **2b** without compromising on the enantioselectivity (entry 2). From this preliminary information, the structural modification of the modular chiral triazolium ion **1** was conducted in order to improve the catalytic efficiency and stereocontrolling ability. A systematic evaluation of the effect of individual substituent structures revealed that the *L*-norvaline-derived

triazolium ion possessing strongly electron-withdrawing trifluoromethyl groups at the triazolium C(4) phenyl ring and the N(3) benzylic appendage (**1c**) allowed the reaction to proceed smoothly with a high level of diastereoselectivity as well as complete enantiocontrol (entries 3 and 4). Further tuning of the electronic and steric attributes of **1** led to the identification of triazolium bromide **1d·Br** as the optimal catalyst, which efficiently promoted bond formation between **3a** and **2b** to afford **4b** quantitatively with near-perfect diastereo- and enantioselectivity (entry 5). The relative and absolute stereochemistry of the alkylation product **4b** was unequivocally determined by X-ray crystallographic analysis.[15]

Table 1. Optimization of Reaction Conditions[a]



entry	1	2	% yield[b]	dr[c]	% ee[d]
1	1a	2a	78	2:1	94/92
2	1a	2b	88	3.7:1	95/80
3	1b	2b	56	4.4:1	93/86
4	1c	2b	95	16:1	99/nd
5	1d	2b	99	>20:1	99/nd

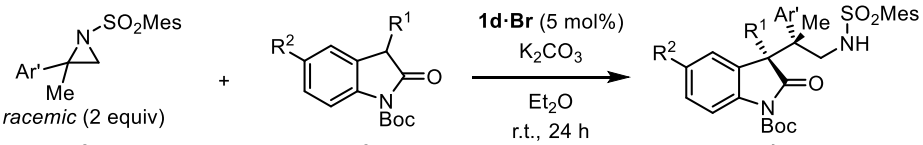
[a] Reactions were carried out with 0.20 mmol of **2**, 0.10 mmol of **3a**, and 0.10 mmol of K_2CO_3 in the presence of **1** (5.0 mol%) in Et_2O (1.0 mL) at room temperature for 24 h. [b] Isolated yield based on the amount of **3a**. [c] Determined by ^1H NMR analysis of crude reaction mixture. [d] Determined by chiral HPLC analysis. nd = not determined.

2.2. Substrate Scope

Experiments were then conducted to probe the substrate scope of this unprecedented catalytic, highly stereoselective ring-opening alkylation of 2,2-disubstituted aziridines. The representative results are summarized in Table 2. With regard to aziridine **2**, incorporation of both electron-donating

and electron-withdrawing groups onto aryl substituents was tolerated, and good-to-excellent diastereo- and enantioselectivities were uniformly observed (entries 1-7). Moreover, functionalized and fused aromatic systems were also accommodated (entries 8 and 9). Not only 3-methyl-oxindole **3a** but also other alkyl-substituted oxindoles could be employed as the nucleophilic reacting partner, and the corresponding alkylation products were obtained with almost complete stereoselectivities, although considerable decrease in the reactivity was inevitable, probably because of the increased steric hindrance (entries 10 and 11). This ring-opening alkylation was also applicable to oxindoles with substituents having different electronic properties on the aromatic nuclei (entries 12-14).

Table 2. Substrate Scope[a]

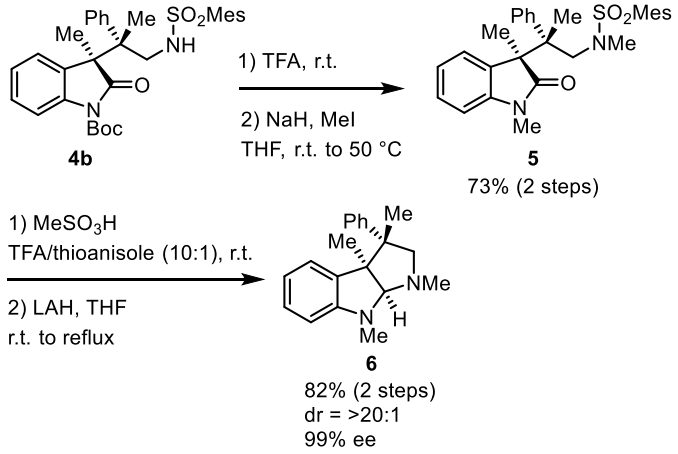


entry	**2** (Ar')	**3** (R^1, R^2)	4	% yield[b]	dr[c]	% ee[d]
1	**2c** (3-MeC_6H_4)	**3a** (Me, H)	4c	92	>20:1	99
2	**2d** (3-$MeOC_6H_4$)	3a	4d	98	19:1	99
3[e]	**2e** (3-ClC_6H_4)	3a	4e	87	>20:1	99
4[e]	**2f** (3-BrC_6H_4)	3a	4f	81	11:1	98
5[e,f]	**2g** (4-MeC_6H_4)	3a	4g	82	14:1	99
6	**2h** (4-ClC_6H_4)	3a	4h	92	>20:1	99
7	**2i** (4-BrC_6H_4)	3a	4i	96	16:1	99
8	**2j** (4-*t*-$BuO_2CC_6H_4$)	3a	4j	87	>20:1	99
9	**2k** (2-Naph)	3a	4k	97	>20:1	99
10	**2b** (Ph)	**3b** (Et, H)	4l	71	>20:1	99
11[e,f]	2b	**3c** (Bn, H)	4m	80	>20:1	99
12	2b	**3d** (Me, Me)	4n	84	>20:1	99
13	2b	**3e** (Me, OMe)	4o	88	12:1	99
14[g]	2b	**3f** (Me, F)	4p	71	12:1	99

[a] Unless otherwise noted, reactions were carried out with 0.20 mmol of **2**, 0.10 mmol of **3**, and 0.10 mmol of K_2CO_3 in the presence of **1d·Br** (5.0 mol%) in Et_2O (1.0 mL) at room temperature for 24 h. [b] Isolated yield based on the amount of **3**. [c] Determined by ^1H NMR analysis of crude reaction mixture. [d] Enantiomeric excesses of the major diastereomer were indicated, which were determined by chiral HPLC analysis. [e] Performed with 10 mol% of **1d·Br**. [f] Conducted at 10 °C for 48 h. [g] With 2.2 equiv of aziridine **2**.

3. Derivatization

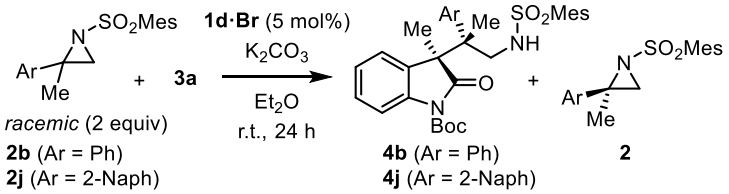
The synthetic utility of this catalytic protocol was clearly demonstrated by its application to the concise asymmetric synthesis of a pyrrolidinoindoline derivative, which is the ubiquitous core structure of a wide array of biologically relevant natural products.[16] As exemplified in Scheme 1, removal of the *N*-Boc group of **4b** (dr = >20:1, 99% ee) by treatment with trifluoroacetic acid, followed by the methylation of both oxindole and sulfonylamide nitrogens, furnished **5**. Subsequent desulfonylation was effected by the exposure of **5** to methanesulfonic acid in trifluoroacetic acid/thioanisole (10:1), and the following reductive cyclization gave rise to the stereochemically pure pyrrolidinoindoline derivative **6** bearing vicinal all-carbon quaternary stereocenters, in good yield.



Scheme 1. Synthesis of Pyrrolidinoindoline Derivative **6** from **4b**.

4. Mechanistic Investigation

In the present catalytic asymmetric ring-opening substitutions, the starting aziridines **2** were recovered in optically active form. For instance, after the reaction of racemic aziridine **2b** with oxindole **3a** under the optimized conditions, **2b** was recovered with 76% ee (99% recovery yield based on the amount of **3a**) (Scheme 2).



4b: 99%, dr = >20:1, 99% ee, **2b**: 99% recovery, 76% ee, *S* = 17
4j: 97%, dr = >20:1, 99% ee, **2j**: 99% recovery, 76% ee, *S* = 17

Scheme 2. Enantiomeric Excess of Recovered Aziridines **2**.[17]

In the reaction of 2-naphthyl- substituted aziridine **2j** with **3a**, enantiomerically enriched **2j** (76% ee) was also obtained, and the absolute configuration of the major enantiomer was assigned to be *R* by single-crystal X-ray diffraction analysis (Figure 1). The relative and absolute stereochemistry of the corresponding alkylation product **4j** was established simultaneously. This information confirmed that (*S*)-aziridine was preferentially consumed and that the ring-opening substitution would mainly proceed in a stereoinvertive manner.[18,19]

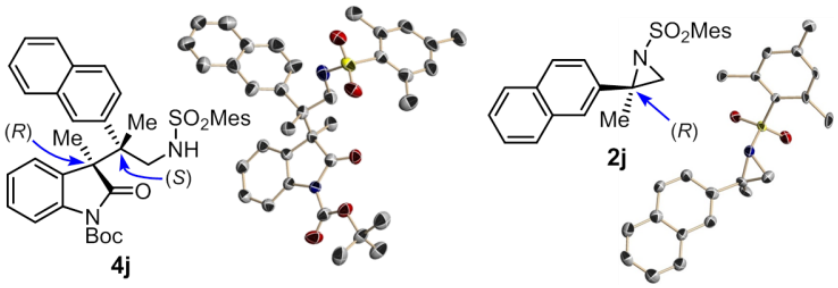


Figure 1. ORTEP Diagrams of Product **4j** and Recovered **2j**. (calculated hydrogens are omitted for clarity)

To gain further insight into the reaction profiles, the author performed kinetic experiments, which uncovered that the present catalytic ring-opening alkylation had pseudo-first-order dependence on the catalyst **1d·Br** and zero-order dependence on both aziridine **2** and oxindole **3**. When the amount of K_2CO_3 was increased, the reaction exhibited first-order kinetics.[15] In addition, the alkylation did not take place at all in the absence of **1d·Br**. These findings clearly indicate that the rate-limiting step is not carbon–carbon bond formation. In phase-transfer reaction of solid–liquid biphasic system without additional water, the process on the surface of solid particle, that is the formation of potassium enolate in the present case, is usually slow compared to the processes in organic phase.[20] As a consequence, ion-exchange for the generation of the requisite chiral triazolium enolate **A** from the corresponding potassium enolate and either **1d·Br** (initial process) or the intermediary triazolium amide **B** (main process) becomes turnover-limiting step of the catalytic cycle (Figure 2).

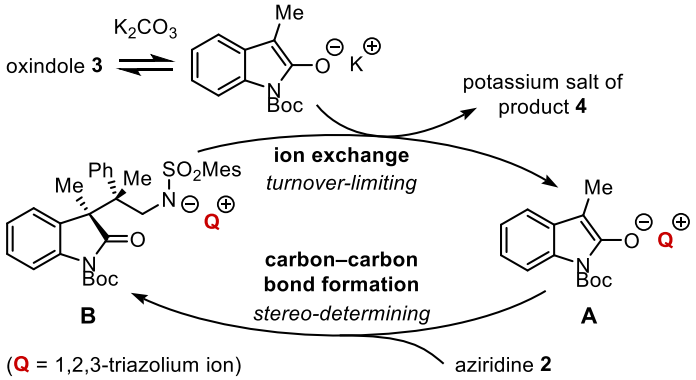


Figure 2. Main Processes in Catalytic Cycle.

The author then examined the relationship between the ee of the catalyst **1d·Br** and the ee of the product **4b** and observed a pronounced positive nonlinear effect.[15, 21] This phenomenon strongly suggests that more than one triazolium ion is involved in the stereo-determining alkylation transition state, although the precise structure remains open for discussion.

5. Conclusion

In conclusion, a highly diastereo- and enantioselective ring-opening alkylation of racemic 2,2-disubstituted aziridines with 3-substituted oxindoles have been developed by using an appropriately modified chiral 1,2,3-triazolium salt as the requisite catalyst. This method represents the first catalytic, stereoselective carbon-carbon bond-forming reaction through direct substitution at a tetrasubstituted chiral carbon and should find fruitful applications in the rapid assembly of densely substituted chiral organic molecules, particularly those having contiguous all-carbon quaternary stereocenters. Further mechanistic studies to fully elucidate the transition state structure are the focus of ongoing investigations.

6. 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 (C_6D_6; 7.16 ppm) or the tetramethylsilane (0.0 ppm) resonance as the internal standard [$(CD_3)_2CO$ and $CDCl_3$]. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept =septet, m = multiplet, and 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 as the internal standard [$(CD_3)_2CO$; 29.84 ppm, $CDCl_3$; 77.16 ppm, and C_6D_6; 128.06 ppm]. ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (–64.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on PSQ60AB (spherical, av. 55 μm; Fuji Silysia Chemical ltd.) and Silica gel 60 (Merck 1.09385.9929, 230-400 mesh). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALCEL OJ-3 (OJ3), CHIRALCEL OZ-3 (OZ3), CHIRALPAK AD-3 (AD3), CHIRALPAK ID-3 (ID3), and CHIRALPAK IE-3 (IE3)] with hexane (Hex), isopropyl alcohol (IPA) and ethanol (EtOH) as eluent.

All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by passing through neutral alumina under nitrogen atmosphere. 1,2,3-Triazolium salts **1·X** were synthesized by following the literature methods.[8a] Other simple chemicals were purchased and used as such.

Additional Experimental Data and Discussion:

(A) Initial Rate Kinetics

General Procedure for Kinetic Experiments:

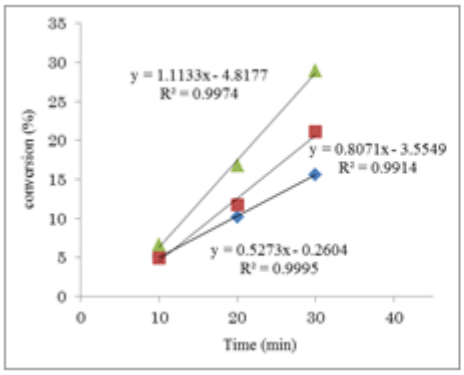
[**2b**] = 0.2 M, [**3a**] = 0.1 M, [**1d·Br**] = 0.005 M, [K_2CO_3] = 0.1 mmol, [anisole] = 0.25 M.

A solution of **1d·Br** (4.76 mg, 0.005 mmol), aziridine **2b** (63.1 mg, 0.20 mmol), and oxindole **3a** (24.7 mg, 0.10 mmol) in Et_2O (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. To this solution was added K_2CO_3 (13.8 mg, 0.10 mmol) and the mixture was stirred at room temperature. After stirring for 10, 20, or 30 min, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and the extractive work-up was performed with $CHCl_3$. After evaporation to remove solvent, the residue was dissolved into C_6D_6 (1 mL). To this solution was added anisole (27.2 μL, 0.25 mmol) as an internal standard. The sample thus prepared was analyzed by ^1H NMR at room temperature. The yield of product **4b** was measured by comparison of the integrated area of the methyl protons of anisole.

Note: Taking out the aliquots of the reaction mixture from liquid–solid biphasic system to analyze the conversion at the first stage of the reaction (10 min) caused an error of the following reaction rate, probably due to the deviation of the relative amount of K_2CO_3 salt. Therefore, the author analyzed the conversion at recorded times by quenching each reaction experiments. The reproducibility of data was confirmed by performing all experiments twice.

Kinetics on catalyst 1d·Br:

[**2b**] = 0.2 M, [**3a**] = 0.1 M, [**1d·Br**] = 0.003 ~ 0.007 M, [K_2CO_3] = 0.1 mmol.

(a) 

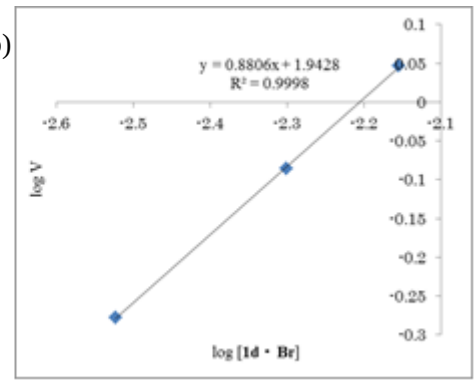
(b) 

Figure S1. (a) Initial Rate Kinetics (catalyst) (b) Kinetics on Catalyst **1d·Br**

initial rate

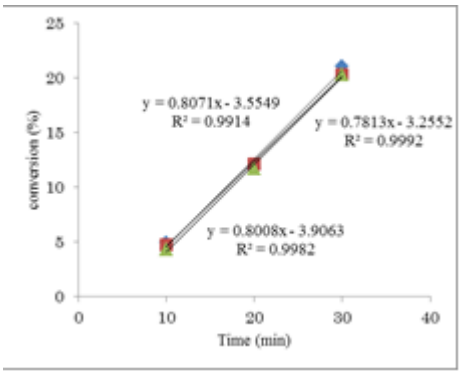
0.003 M: 0.0088 Ms^{-1}, 0.005 M: 0.0135 Ms^{-1}, 0.007 M: 0.0186 Ms^{-1}

Pseudo-first-order dependence on the concentration of catalyst **1d·Br**

Kinetics on aziridine 2b:

[**2b**] = 0.2 ~ 0.3 M, [**3a**] = 0.1 M, [**1d·Br**] = 0.005 M, [K_2CO_3] = 0.1 mmol.

(a)



(b)

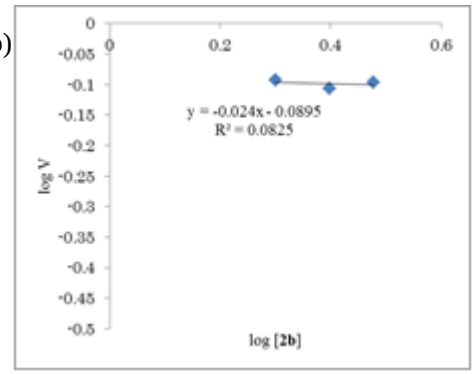


Figure S2. (a) Initial Rate Kinetics (aziridine) (b) Kinetics on Aziridine **2b**

initial rate

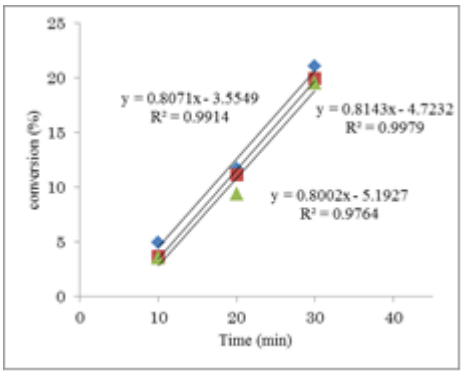
0.20 M: 0.0135 Ms^{-1}, 0.25 M: 0.0130 Ms^{-1}, 0.30 M: 0.0133 Ms^{-1}

Zero-order dependence on the concentration of aziridine **2b**

Kinetics on oxindole 3a:

[**2b**] = 0.2 M, [**3a**] = 0.1 ~ 0.2 M, [**1d·Br**] = 0.005 M, [K_2CO_3] = 0.1 mmol.

(a)



(b)

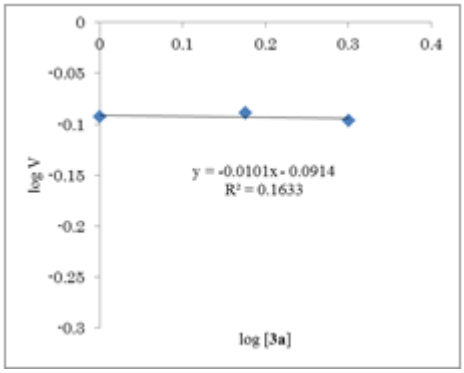


Figure S3. (a) Initial Rate Kinetics (oxindole) (b) Kinetics on Oxindole **3a**

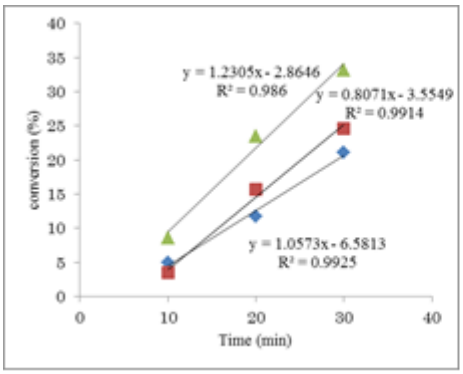
initial rate

0.10 M: 0.0135 Ms^{-1}, 0.15 M: 0.0135 Ms^{-1}, 0.20 M: 0.0137 Ms^{-1}

Zero-order dependence on the concentration of oxindole **3a**

Kinetics on K_2CO_3:

[**2b**] = 0.2 M, [**3a**] = 0.1M, [**1d·Br**] = 0.005 M, [K_2CO_3] = 0.1 ~ 0.15 mmol.

(a) 

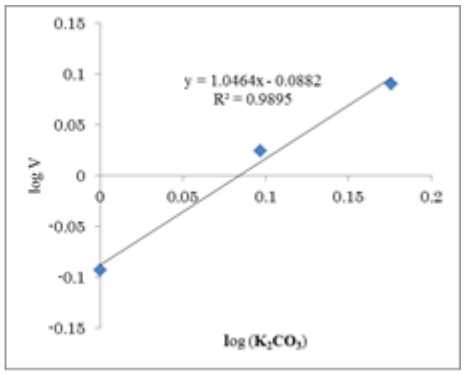
(b) 

Figure S4. (a) Initial Rate Kinetics (base) (b) Kinetics on K_2CO_3

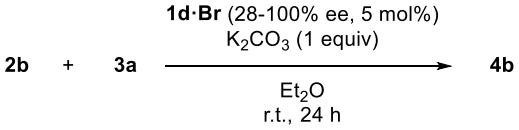
initial rate

0.10 mmol: 0.0135 Ms^{-1}, 0.125 mmol: 0.0176 Ms^{-1}, 0.15 mmol: 0.0205 Ms^{-1}

First-order dependence on the amount of K_2CO_3

These definitive data clearly indicated that the rate-limiting step is not carbon–carbon bond formation between oxindole-derived chiral triazolium enolate with aziridine but ion-exchange process for the generation of the requisite enolate.

(B) Nonlinear Effect



entry	ee (%) of **1d·Br**	yield (%) of **4b**	ee (%) of **4b**
1	28	92	45
2	37	84	68
3	48	92	87
4	68	96	98
5	77	80	94
6	100	97	99

Table S1. Asymmetric Amplification

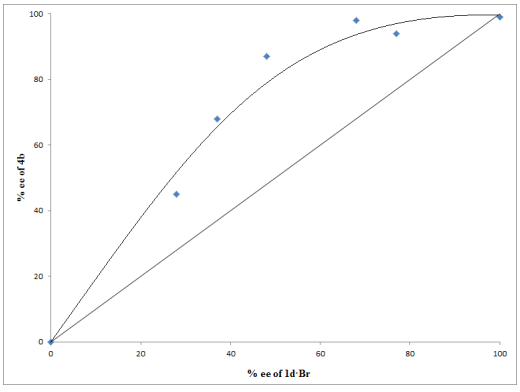
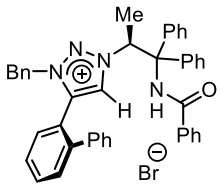


Figure S5. Nonlinear Effect

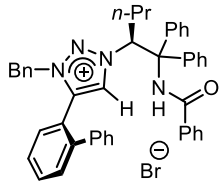
The data of Table S1 and the graph of Figure S5 demonstrated a pronounced positive nonlinear effect, which suggested that more than one catalyst is involved in the stereo-determining step.

Experimental Section:

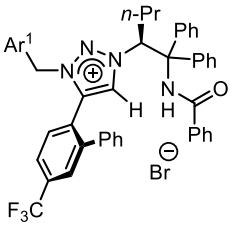
Characterization of 1,2,3-Triazolium Salt 1▪Br



1a·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (1H, brs), 8.65 (1H, brs), 8.20 (2H, d, *J* = 6.9 Hz), 7.87-7.82 (3H, m), 7.64 (1H, t, *J* = 7.6 Hz), 7.45-7.29 (8H, m), 7.27-7.22 (2H, m), 7.20-7.14 (4H, m), 7.03-6.97 (4H, m), 6.91-6.84 (4H, m), 6.55 (2H, d, *J* = 7.8 Hz), 4.85 (2H, s), 1.63 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 142.9, 140.3, 139.9, 138.5, 135.3, 133.7, 132.9, 132.4, 132.0, 131.9, 131.1, 130.2, 129.9, 129.4, 129.2, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.2, 120.3, 69.4, 65.9, 55.2, 15.8, two peaks for aromatic carbons were not found probably due to overlapping; IR 3221, 2934, 1672, 1520, 1275, 1148, 746, 702 cm^{-1}; HRMS (ESI) Calcd for $C_{43}H_{37}N_4O^+$ ([M]$^+$) 625.2962. Found 625.2969.; $[\alpha]_D^{22}$ = –44.3 (c = 1.0, MeOH).

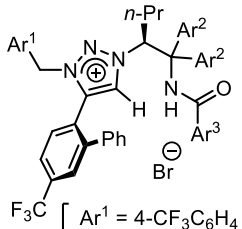


1b·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (1H, brs), 8.51 (1H, brs), 8.20 (2H, d, *J* = 6.2 Hz), 7.79 (2H, brs), 7.66 (2H, td, *J* = 7.7, 1.2 Hz), 7.51-7.35 (9H, m), 7.30-7.15 (9H, m), 7.07 (2H, t, *J* = 7.6 Hz), 6.85 (2H, d, *J* = 7.1 Hz), 6.64 (2H, d, *J* = 7.5 Hz), 5.07 (2H, brs), 2.13-2.07 (1H, m), 1.90-1.81 (1H, m), 1.33-1.25 (1H, m), 0.84-0.75 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 142.8, 140.6, 138.6, 133.7, 133.1, 132.4, 132.2, 131.9, 130.8, 130.6, 129.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.6, 128.4, 128.3, 128.3, 127.8, 127.7, 127.4, 120.3, 70.4, 69.1, 55.8, 31.9, 19.3, 13.7, three peaks for aromatic carbons were not found probably due to overlapping; IR 3235, 2932, 1674, 1485, 1285, 1146, 748, 704 cm^{-1}; HRMS (ESI) Calcd for $C_{45}H_{41}N_4O^+$ ([M]$^+$) 653.3275. Found 653.3270.; $[\alpha]_D^{22}$ = –27.7 (c = 1.0, MeOH).



[Ar^1 = 4-$CF_3C_6H_4$]

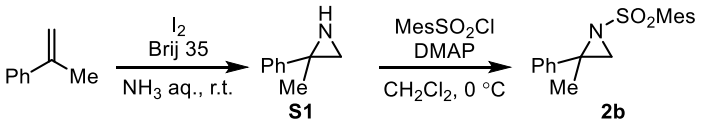
1c·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (1H, brs), 8.42 (1H, brs), 8.09 (2H, d, J = 7.3 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.70 (1H, s), 7.55 (2H, d, J = 6.8 Hz), 7.48-7.29 (15H, m), 7.17 (2H, t, J = 7.8 Hz), 7.11 (1H, brs), 6.89 (2H, d, J = 8.0 Hz), 6.82 (2H, d, J = 7.6 Hz), 5.69 (1H, brs), 5.37 (1H, d, J = 15.3 Hz), 2.16-2.10 (1H, m), 1.60-1.57 (1H, m), 1.25-1.19 (1H, m), 0.81-0.73 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 143.4, 141.6, 140.0, 137.3, 137.0, 134.5 (q, $J_{C\text{-}F}$ = 33.9 Hz), 134.0, 133.5, 132.3, 132.0 (q, $J_{C\text{-}F}$ = 32.9 Hz), 129.7, 129.5, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 128.0, 127.4 (q, J = 2.9 Hz), 126.1 (q, $J_{C\text{-}F}$ = 3.9 Hz), 125.7 (q, $J_{C\text{-}F}$ = 2.9 Hz), 125.5 (q, $J_{C\text{-}F}$ = 276 Hz), 123.3 (q, $J_{C\text{-}F}$ = 277 Hz), 69.7, 68.7, 56.1, 32.7, 19.4, 13.6, three peaks for aromatic carbons were not found probably due to overlapping; IR 3026, 2934, 1674, 1485, 1325, 1130, 752, 706 cm^{-1}; HRMS (ESI) Calcd for $C_{47}H_{39}N_4OF_6^+$ ([M]$^+$) 789.3023. Found 789.3015.; $[\alpha]_D^{22}$ = –25.1 (c = 0.4, MeOH).



[Ar^1 = 4-$CF_3C_6H_4$
Ar^2 = 4-ClC_6H_4
Ar^3 = 4-Tol]

1d·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (1H, brs), 8.18 (1H, brs), 8.04 (2H, d, J = 8.0 Hz), 7.79 (1H, d, J = 8.0 Hz), 7.73 (1H, s), 7.56 (2H, brs), 7.48 (2H, d, J = 8.2 Hz), 7.36-7.32 (4H, m), 7.24-7.14 (9H, m), 6.88-6.83 (4H, m), 5.49 (1H, brs), 5.22 (1H, d, J = 15.3 Hz), 2.34, (3H, s), 2.05-1.96 (1H, m), 1.62 (1H, br), 1.24 (1H, br), 0.82-0.70 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 143.6, 143.1, 140.1, 139.5, 137.2, 134.8, 134.8 (q, $J_{C\text{-}F}$ = 33.9 Hz), 134.5, 134.1, 133.6, 133.0, 132.3 (q, $J_{C\text{-}F}$ = 32.9 Hz), 130.9, 130.3, 130.1, 129.6, 129.4, 129.4, 129.3, 128.8, 128.6, 128.3, 128.0, 127.6, 126.2 (q, $J_{C\text{-}F}$ = 3.9 Hz), 125.6 (q, $J_{C\text{-}F}$ = 3.9 Hz), 123.5, 123.4 (q, $J_{C\text{-}F}$ = 278 Hz), 123.2 (q, $J_{C\text{-}F}$ = 278 Hz), 69.6, 68.2, 55.9, 32.2, 21.6, 19.3, 13.6, one peak for aromatic carbon was not found probably due to overlapping; IR 3026, 2934, 2361, 1674, 1325, 1132, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{48}H_{39}N_4OF_6Cl_2^+$ ([M]$^+$) 871.2400. Found 871.2390.; $[\alpha]_D^{22}$ = –17.2 (c = 1.0, MeOH).

Preparation and Characterization of 2,2-Disubstituted Aziridines 2:

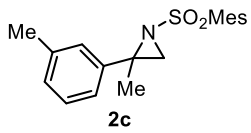


To a solution of I_2 (5.08 g, 20 mmol) and Brij 35 (0.60 g) in NH_3 aq. (30 mL) was added α-methylstyrene (1.30 mL, 10 mmol), and the reaction mixture was stirred for 2 h at room temperature. The resulting solution was diluted with a saturated aqueous solution of Na_2SO_3 and EtOAc. The extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 1:1 as eluent) to afford **S1** (915 mg, 6.9 mmol, 69% yield) as a yellow liquid. **S1**: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.36 (2H, d, J = 7.3 Hz), 7.31 (2H, t, J = 7.3 Hz), 7.22 (1H, t, J = 7.3 Hz), 1.94 (2H, s), 1.60 (3H, s), 0.63 (1H, br).

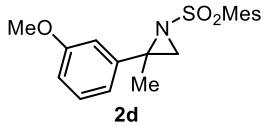
To a solution of **S1** (915 mg, 6.9 mmol) in CH_2Cl_2 (15 mL) were added 2-mesitylenesulfonyl chloride (1.51 g, 6.9 mmol), and *N*,*N*-dimethyl-4-aminopyridine (0.84 g, 6.9 mmol), at 0 ºC, and the whole reaction mixture was stirred for 3 h at the same temperature. The mixture was then diluted with water and the extractive work-up was conducted with $CHCl_3$. The organic extracts were dried over Na_2SO_4, filtered , and concentrated. Purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 30:1 as eluent) gave **2b** (631 mg, 2.0 mmol, 29% yield) as a white solid.

2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, J = 7.3 Hz), 7.33 (2H, t, J = 7.3 Hz), 7.28 (1H, t, J = 7.3 Hz), 6.96 (2H, s), 3.02 (1H, s), 2.71 (6H, s), 2.54 (1H, s), 2.30 (3H, s), 2.06 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 141.3, 139.7, 135.1, 131.9, 128.5, 127.8, 126.6, 51.1, 42.0, 23.3, 21.1, 21.0; IR 3152, 2938, 1314, 1121, 1105, 1024, 862, 800, 775 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{22}NO_2S^+$ ($[M+H]^+$) 316.1366. Found 316.1366.; HPLC conditions for the recovered aziridine **2b** (Scheme 1), OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 13.2 min (major), 14.5 min (minor); $[\alpha]_D^{22}$ = –22.0 (c = 3.5, $CHCl_3$, 76% ee).



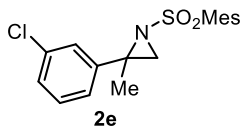
2c

2c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, td, J = 7.1, 1.4 Hz), 7.18 (1H, s), 7.17 (1H, dd, J = 7.1 1.4 Hz), 7.08 (1H, d, J = 7.1 Hz), 6.95 (2H, s), 2.99 (1H, s), 2.71 (6H, s), 2.53 (1H, s), 2.33 (3H, s), 2.30 (3H, s), 2.04 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 141.3, 139.8, 138.2, 135.2, 131.9, 128.5, 128.4, 127.4, 123.7, 51.2, 41.9, 23.3, 21.6, 21.1, one peak for mehtyl carbon was not found probably due to overlapping; IR 2940, 2920, 1601, 1452, 1321, 1038, 905, 719 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{24}NO_2S^+$ ($[M+H]^+$) 330.1522. Found 330.1522.



2d

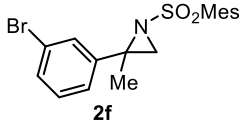
2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, t, J = 9.4 Hz), 6.97 (1H, dd, J = 9.4, 0.9 Hz), 6.96 (2H, s), 6.93 (1H, t, J = 0.9), 6.81 (1H, dd, J = 9.4, 0.9 Hz), 3.79 (3H, s), 3.01 (1H, s), 2.72 (6H, s), 2.51 (1H, s), 2.30 (3H, s), 2.05 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 143.1, 142.8, 139.8, 135.1, 131.9, 129.6, 118.9, 113.4, 112.3, 55.3, 51.1, 42.0, 23.3, 21.1, 20.9; IR 2967, 2918, 1601, 1315, 1111, 905, 698 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{24}NO_3S^+$ ($[M+H]^+$) 346.1471. Found 346.1472.



2e

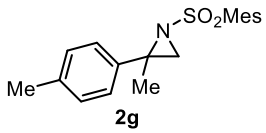
2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, t, J = 1.4 Hz), 7.30-7.28 (3H, m), 6.97 (2H, s), 3.01 (1H, s), 2.71 (6H, s), 2.50 (1H, s), 2.31 (3H, s), 2.04 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 143.0, 139.8, 134.9, 134.4, 132.0,

129.9, 128.0, 126.9, 124.9, 50.1, 42.0, 23.3, 21.1, 20.6; IR 3472, 3148, 1599, 1314, 1130, 1053, 878 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{21}NO_2SCl^+$ ($[M+H]^+$) 350.0976. Found 350.0977.



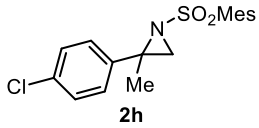
2f

2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, t, J = 1.8 Hz), 7.40 (1H, dt, J = 7.8, 1.8 Hz), 7.33 (1H, dt, J = 7.8, 1.8 Hz), 7.20 (1H, t, J = 7.8 Hz), 6.97 (2H, s), 3.01 (1H, s), 2.71 (6H, s), 2.50 (1H, s), 2.31 (3H, s), 2.04 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 143.0, 139.8, 134.9, 132.0, 130.9, 130.2, 129.9, 125.4, 122.6, 50.1, 42.0, 23.3, 21.2, 20.6; IR 3144, 2943, 1601, 1315, 1144, 876, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{21}NO_2SBr^+$ ($[M+H]^+$) 394.0471. Found 394.0472.



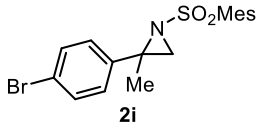
2g

2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.2 Hz), 7.13 (2H, d, J = 8.2 Hz), 6.95 (2H, s), 2.99 (1H, s), 2.70 (6H, s), 2.53 (1H, s), 2.33 (3H, s), 2.30 (3H, s), 2.03 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 140.0, 138.3, 137.5, 135.2, 131.9, 129.2, 126.6, 51.0, 42.1, 23.3, 21.2, 21.1, one peak for mehtyl carbon was not found probably due to overlapping; IR 3028, 2938, 1603, 1319, 1157, 820, 692 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{24}NO_2S^+$ ($[M+H]^+$) 330.1522. Found 330.1536.



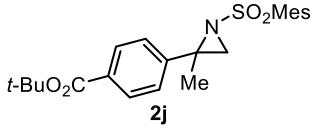
2h

2h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, dd, J = 6.1, 2.8 Hz), 7.29 (2H, dd, J = 6.1, 2.8 Hz), 6.96 (2H, s), 3.00 (1H, s), 2.70 (6H, s), 2.51 (1H, s), 2.30 (3H, s), 2.03 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 139.8, 139.7, 135.0, 133.6, 131.9, 128.7, 128.1, 50.2, 42.0, 23.3, 21.1, 20.8; IR 3159, 2943, 2633, 1317, 1148, 868, 696 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{21}NO_2SCl^+$ ($[M+H]^+$) 350.0976. Found 350.0978.



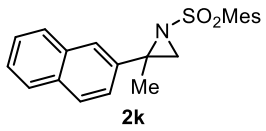
2i

2i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, dd, J = 6.7, 1.8 Hz), 7.26 (2H, dd, J = 6.7, 1.8 Hz), 6.96 (2H, s), 3.00 (1H, s), 2.70 (6H, s), 2.50 (1H, s), 2.31 (3H, s), 2.03 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 140.4, 139.7, 134.9, 131.9, 131.6, 128.4, 121.8, 50.2, 42.0, 23.3, 21.1, 20.7; IR 3275, 2932, 1321, 1161, 1055, 872, 723 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{21}NO_2SBr^+$ ($[M+H]^+$) 394.0471. Found 394.0468.



2j

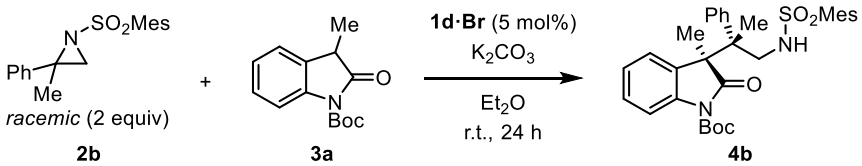
2j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, dt, J = 8.7, 1.8 Hz), 7.43 (2H, dt, J = 8.7, 1.8 Hz), 6.96 (2H, s), 3.03 (1H, s), 2.71 (6H, s), 2.52 (1H, s), 2.31 (3H, s), 2.06 (3H, s), 1.59 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 145.7, 143.0, 139.8, 135.0, 132.0, 131.5, 129.7, 126.5, 81.3, 50.5, 42.1, 28.3, 23.3, 21.2, 20.6; IR 2976, 1721, 1452, 1300, 1049, 858, 569 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{29}NO_4NaS^+$ ($[M+Na]^+$) 438.1710. Found 438.1710.



2k

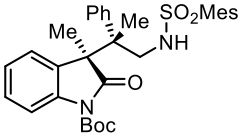
2k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.79 (4H, m), 7.51-7.45 (3H, m), 6.96 (2H, s), 3.09 (1H, s), 2.73 (6H, s), 2.66 (1H, s), 2.30 (3H, s), 2.15 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 139.8, 138.7, 135.2, 133.1, 132.8, 131.9, 128.4, 128.1, 127.8, 126.5, 126.4, 125.6, 124.6, 51.2, 42.1, 23.3, 21.2, 20.9; IR 3472, 2932, 2658, 1314, 1130, 935, 854, 696 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{24}NO_2S^+$ ([M+H]$^+$) 366.1522. Found 366.1523.; HPLC conditions for the recovered aziridine **2j** (Scheme 1), AD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.9 min (*S*), 8.1 min (*R*) ; $[\alpha]_D^{22}$ = +11.5 (c = 1.5, $CHCl_3$, 76% ee).

General Procedure for 1d·Br-Catalyzed Asymmetric Ring-Opening Alkylation of 2,2-Disubstituted Aziridines 2 with Oxindole 3:



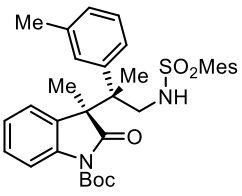
A solution of **1d·Br** (4.76 mg, 0.005 mmol), aziridine **2b** (63.1 mg, 0.20 mmol), and oxindole **3a** (24.7mg, 0.10 mmol) in Et_2O (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. To this solution was added K_2CO_3 (13.8 mg, 0.10 mmol) and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and the extractive work-up was performed with $CHCl_3$. After drying over Na_2SO_4, filtration, and removal of solvent, the resulting crude residue was purified by column chromatography (Hex/$CHCl_3$/EtOAc = 8:2:1 as eluent) to afford **4b** (55.7 mg, 0.10 mmol, 99% yield) as a white solid.

Characterization of Alkylation Products 4:



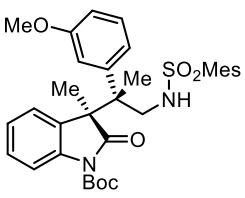
4b

4b: ^{1}H NMR (400 MHz, C_6D_6) δ 7.97 (1H, d, *J* = 7.8 Hz), 6.96-6.90 (2H, m), 6.83 (2H, t, *J* = 7.6 Hz), 6.63 (1H, td, *J* = 7.8, 1.0 Hz), 6.58 (2H, s), 6.54 (2H, d, *J* = 7.6 Hz), 6.03 (1H, d, *J* = 7.6 Hz), 4.26 (1H, dd, *J* = 8.7, 5.5 Hz), 3.90 (1H, dd, *J* = 12.4, 8.7 Hz), 3.71 (1H, dd, *J* = 12.4, 5.5 Hz), 2.59 (6H, s), 1.91 (3H, s), 1.42 (9H, s), 1.24 (3H, s), 1.05 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 177.0, 149.4, 141.8, 140.3, 139.6, 139.4, 134.5, 132.1, 130.7, 128.5, 127.3, 125.1, 123.3, 114.7, 83.3, 54.1, 47.4, 46.8, 28.0, 23.2, 20.7, 18.9, 18.5, two peaks for aromatic carbons were not found probably due to overlapping; IR 2978, 2371, 1732, 1605, 1479, 1348, 1153, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{38}N_2O_5NaS^+$ ([M+Na]$^+$) 585.2394. Found 585.2390.; HPLC ID3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 40.7 min (major isomer of major diastereomer), 63.8 min (minor isomer of major diastereomer), 73.8 min (minor diastereomer), 78.6 min (minor diastereomer).



4c

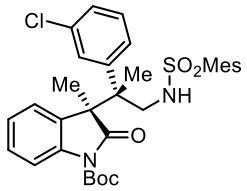
4c: ^{1}H NMR (400 MHz, C_6D_6) δ 7.95 (1H, brd, *J* = 6.0 Hz), 6.94 (1H, t, *J* = 8.0 Hz), 6.83-6.77 (2H, m), 6.65 (1H, t, *J* = 7.6 Hz), 6.58 (2H, s), 6.44 (1H, brd, *J* = 7.4 Hz), 6.35 (1H, s), 6.12 (1H, brd, *J* = 6.9 Hz), 4.35-4.19 (1H, m), 3.88 (1H, dd, *J* = 12.4, 8.7 Hz), 3.70 (1H, dd, *J* = 12.4, 4.6 Hz), 2.58 (6H, s), 1.92 (3H, s), 1.91 (3H, s), 1.41 (9H, s), 1.30 (3H, s), 1.07 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.9, 149.4, 141.7, 140.4, 139.5, 139.2, 137.2, 134.5, 134.4, 132.1, 130.8, 128.9, 128.5, 125.3, 125.1, 123.2, 114.6, 83.2, 54.1, 47.5, 46.8, 27.9, 23.1, 21.5, 20.7, 18.8, 18.5, one peak for aromatic carbon was not found probably due to overlapping; IR 3319, 2978, 1730, 1605, 1479, 1290, 847, 652 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_5NaS^+$ ([M+Na]$^+$) 599.2550. Found 599.2549.; HPLC ID3, Hex/IPA = 19:1, flow rate = 0.5 mL/min, λ = 210 nm, 70.5 min (major isomer of major diastereomer), 106 min (minor isomer of major diastereomer), 124 min (minor diastereomer), 132 min (minor diastereomer).



4d

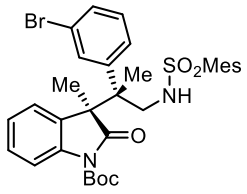
4d: ^{1}H NMR (400 MHz, C_6D_6) δ 7.93 (1H, d, *J* = 8.2 Hz), 6.93 (1H, td, *J* = 7.8, 1.4 Hz), 6.78 (1H, t, *J* = 7.8 Hz), 6.66 (1H, t, *J* = 7.3 Hz), 6.59-6.56 (3H, m), 6.28 (1H, brs), 6.25 (1H, d, *J* = 7.3 Hz), 6.19 (1H, d, *J* = 7.8 Hz), 4.42 (1H, dd, *J* = 8.7, 4.8 Hz), 3.85 (1H, dd, *J* = 12.5, 8.7 Hz), 3.70 (1H, dd, *J* = 12.5, 4.8 Hz), 3.19 (3H, s), 2.58 (6H, s), 1.92 (3H, s), 1.41 (9H, s), 1.33 (3H, s), 1.08 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.8, 159.5, 149.4, 141.8, 140.9, 140.4, 139.5, 134.4, 132.1, 130.8, 128.9, 128.5, 125.1, 123.3, 120.3, 114.7, 114.1, 113.3, 83.2, 54.5, 54.0, 47.7, 46.9, 27.9, 23.1, 20.7, 18.8, 18.5; IR 3315, 2978, 1730, 1602, 1290, 1147, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_6NaS^+$ ([M+Na]$^+$) 615.2499. Found 615.2495.; HPLC ID3, Hex/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 16.1 min (major isomer of major diastereomer),

18.5 min (minor isomer of major diastereomer), 21.5 min (minor diastereomer), 23.8 min (minor diastereomer).



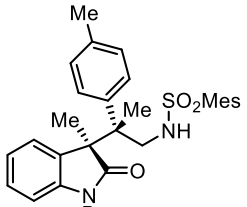
4e

4e: ^{1}H NMR (400 MHz, C_6D_6) δ 7.92 (1H, d, J = 8.2 Hz), 6.93 (1H, td, J = 8.2, 1.4 Hz), 6.89 (1H, dd, J = 7.8, 1.4 Hz), 6.70-6.66 (2H, m), 6.57 (2H, s), 6.48 (1H, t, J = 7.8 Hz), 6.24 (1H, brd, J = 7.3 Hz), 6.18 (1H, brd, J = 6.9 Hz), 4.32 (1H, dd, J = 7.8, 6.2 Hz), 3.71 (1H, dd, J = 12.7, 7.8 Hz), 3.58 (1H, dd, J = 12.7, 6.2 Hz), 2.54 (6H, s), 1.91 (3H, s), 1.42 (9H, s), 1.19 (3H, s), 0.99 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.4, 149.3, 142.0, 141.8, 140.3, 139.5, 134.0, 132.2, 130.2, 128.9, 128.8, 127.4, 125.8, 124.9, 123.4, 114.9, 83.4, 53.9, 47.5, 46.8, 27.9, 23.1, 20.7, 18.2, 18.1, two peaks for aromatic carbons were not found probably due to overlapping; IR 3273, 2980, 1730, 1605, 1477, 1147, 750, 583 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{37}N_2O_5NaSCl^+$ ([M+Na]$^+$) 619.2004. Found 619.2004.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 17.2 min (major isomer of major diastereomer), 25.3 min (minor isomer of major diastereomer), 28.3 min (minor diastereomer), 35.0 min (minor diastereomer).



4f

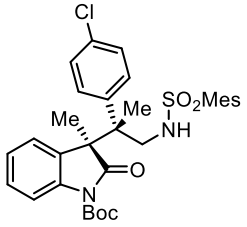
4f: ^{1}H NMR (400 MHz, C_6D_6) δ 7.92 (1H, d, J = 8.2 Hz), 7.04 (1H, d, J = 8.0 Hz), 6.96 (1H, t, J = 8.2 Hz), 6.86-6.80 (1H, m), 6.70 (1H, t, J = 7.8 Hz), 6.57 (2H, s), 6.42 (1H, t, J = 8.2 Hz), 6.24 (2H, brd, J = 6.2 Hz), 4.41 (1H, dd, J = 7.8, 6.2 Hz), 3.71 (1H, dd, J = 12.7, 7.8 Hz), 3.57 (1H, dd, J = 12.7, 6.2 Hz), 2.54 (6H, s), 1.92 (3H, s), 1.43 (9H, s), 1.20 (3H, s), 1.00 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.4, 149.3, 142.1, 142.0, 140.3, 139.5, 134.1, 132.3, 131.4, 130.4, 130.2, 129.2, 128.8, 126.3, 124.9, 123.4, 122.4, 114.9, 83.4, 53.9, 47.5, 46.8, 27.9, 23.1, 20.7, 18.2, 18.2; IR 3273, 2978, 1732, 1605, 1477, 1150, 754, 536 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{37}N_2O_5NaSBr^+$ ([M+Na]$^+$) 663.1499. Found 663.1500.; HPLC OD3, Hex/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 30.1 min (major isomer of major diastereomer), 33.0 min (minor diastereomer), 38.4 min (minor isomer of major diastereomer), 62.9 min (minor diastereomer).



4g

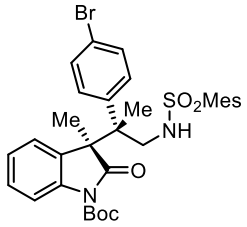
4g: ^{1}H NMR (400 MHz, C_6D_6) δ 7.98 (1H, d, J = 8.2 Hz), 6.95 (1H, td, J = 8.2, 1.4 Hz), 6.69 (2H, d, J = 7.8 Hz), 6.64 (1H, td, J = 7.8, 0.9 Hz), 6.59 (2H, s), 6.49 (2H, d, J = 7.8 Hz), 6.11 (1H, d, J = 7.8 Hz), 4.37 (1H, dd, J = 8.7, 5.0 Hz), 3.89 (1H, dd, J = 12.8, 8.7 Hz), 3.73 (1H, dd, J = 12.8, 5.0 Hz), 2.60 (6H, s), 2.03 (3H, s), 1.92 (3H, s), 1.42 (9H, s), 1.26 (3H, s), 1.07 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 177.1, 149.5, 141.8, 140.3, 139.6, 136.7, 136.3, 134.6, 132.1, 130.8, 128.7, 128.5, 125.2, 123.3, 114.7, 83.2, 54.1, 47.4, 46.5, 27.9, 23.2, 20.8, 20.7, 19.0, 18.6, one peak for aromatic carbon was not found probably due to overlapping; IR 3283, 2978, 2359, 1730, 1605, 1292, 1152, 754,

658 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_5NaS^+$ ($[M+Na]^+$) 599.2550. Found 599.2573.; HPLC OD3, Hex/EtOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 10.9 min (minor diastereomer), 11.5 min (major isomer of major diastereomer), 13.1 min (minor isomer of major diastereomer), 16.7 min (minor diastereomer).



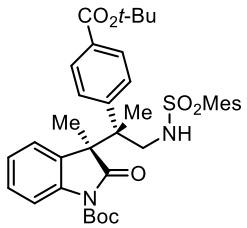
4h

4h: ^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (1H, d, *J* = 8.0 Hz), 6.95 (1H, t, *J* = 8.0 Hz), 6.75 (2H, d, *J* = 7.8 Hz), 6.68 (1H, t, *J* = 7.8 Hz), 6.54 (2H, s), 6.29-6.20 (3H, m), 4.63 (1H, dd, *J* = 7.4, 6.8 Hz), 3.74 (1H, dd, *J* = 12.9, 7.4 Hz), 3.63 (1H, dd, *J* = 12.9, 6.8 Hz), 2.52 (6H, s), 1.93 (3H, s), 1.39 (9H, s), 1.25 (3H, s), 1.03 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.5, 149.1, 142.1, 140.3, 139.6, 138.0, 134.2, 133.2, 132.1, 130.3, 129.3, 128.7, 125.0, 123.5, 114.8, 83.4, 53.9, 47.6, 46.6, 27.9, 23.1, 20.7, 18.5, 18.3, one peak for aromatic carbon was not found probably due to overlapping; IR 3273, 2978, 1730, 1605, 1290, 1148, 750, 536 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{37}N_2O_5NaSCl^+$ ($[M+Na]^+$) 619.2004. Found 619.2003.; HPLC OD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 15.0 min (minor diastereomer), 17.6 min (major isomer of major diastereomer), 21.4 min (minor isomer of major diastereomer), 31.7 min (minor diastereomer).



4i

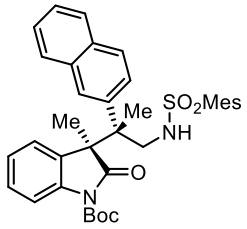
4i: ^{1}H NMR (400 MHz, C_6D_6) δ 7.88 (1H, d, *J* = 8.0 Hz), 6.94 (1H, td, *J* = 8.0, 0.9 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.66 (1H, td, *J* = 8.0, 0.9 Hz), 6.54 (2H, s), 6.22-6.16 (3H, m), 4.48 (1H, dd, *J* = 7.3, 6.9 Hz), 3.72 (1H, dd, *J* = 13.3, 7.3 Hz), 3.61 (1H, dd, *J* = 13.3, 6.9 Hz), 2.52 (6H, s), 1.93 (3H, s), 1.40 (9H, s), 1.21 (3H, s), 1.00 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.5, 149.1, 142.1, 140.3, 139.6, 138.5, 134.2, 132.1, 130.7, 130.3, 129.6, 128.7, 125.0, 123.4, 121.5, 114.8, 83.4, 53.8, 47.5, 46.6, 27.9, 23.1, 20.8, 18.4, 18.3; IR 3279, 2978, 1732, 1605, 1290, 1055, 750, 536 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{37}N_2O_5NaSBr^+$ ($[M+Na]^+$) 663.1499. Found 663.1497.; HPLC ID3, Hex/IPA/EtOH = 92:5:3, flow rate = 1.0 mL/min, λ = 210 nm, 16.2 min (major isomer of major diastereomer), 22.8 min (minor isomer of major diastereomer), 25.0 min (minor diastereomer), 27.4 min (minor diastereomer).



4j

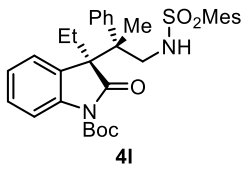
4j: ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.56 (1H, d, *J* = 8.0 Hz), 7.53 (2H, d, *J* = 8.2 Hz), 7.29 (1H, td, *J* = 8.0, 1.4 Hz), 7.10 (1H, td, *J* = 8.0, 0.9 Hz), 6.92 (2H, s), 6.87 (1H, brd, *J* = 7.3 Hz), 6.68 (2H, br), 5.76 (1H, t, *J* = 6.9 Hz), 3.80 (1H, dd, *J* = 13.1, 6.9 Hz), 3.72 (1H, dd, *J* = 13.1, 6.9 Hz), 2.44 (6H, s), 2.29 (3H, s), 1.59 (3H, s), 1.57 (9H, s), 1.47 (3H, s), 1.46 (9H, s); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 177.2, 165.9, 149.3, 145.0, 143.0, 140.8, 140.1, 135.1, 132.7, 131.2, 131.2, 129.5, 129.0, 128.6, 126.0, 124.4, 115.2, 84.0, 81.4, 54.8, 48.1, 48.0, 28.5, 28.2,

23.2, 21.1, 18.9, 18.7; IR 3289, 2978, 1711, 1605, 1292, 1150, 752, 538 cm^{-1}; HRMS (ESI) Calcd for $C_{37}H_{46}N_2O_7NaS^+$ ($[M+Na]^+$) 685.2918. Found 685.2916.; HPLC OD3, Hex/EtOH = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 20.0 min (minor diastereomer), 22.0 min (major isomer of major diastereomer), 27.2 min (minor isomer of major diastereomer), 35.2 min (minor diastereomer).



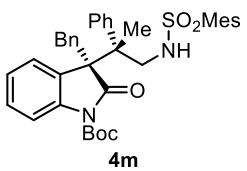
4k

4k: ^{1}H NMR (400 MHz, C_6D_6) δ 7.88 (1H, d, *J* = 8.2 Hz), 7.49 (1H, d, *J* = 7.8 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.24-7.18 (4H, m), 6.94 (1H, td, *J* = 8.2, 1.4 Hz), 6.63-6.56 (2H, m), 6.50 (2H, s), 6.19 (1H, brd, *J* = 5.0 Hz), 4.33 (1H, br), 3.91 (1H, dd, *J* = 12.6, 8.0 Hz), 3.85 (1H, dd, *J* = 12.6, 5.7 Hz), 2.51 (6H, s), 1.90 (3H, s), 1.43 (3H, s), 1.25 (9H, s), 1.12 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.7, 149.2, 141.8, 140.4, 139.5, 136.9, 134.4, 133.1, 132.6, 132.1, 130.7, 128.7, 128.6, 127.5, 127.2, 126.4, 126.0, 125.3, 125.1, 123.3, 114.8, 83.1, 54.2, 47.8, 47.0, 27.7, 23.1, 20.7, 18.9, 18.5, one peak for aromatic carbon was not found probably due to overlapping; IR 3273, 2978, 1730, 1605, 1344, 1148, 746, 534 cm^{-1}; HRMS (ESI) Calcd for $C_{36}H_{40}N_2O_5NaS^+$ ($[M+Na]^+$) 635.2550. Found 635.2552.; HPLC OD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 18.8 min (minor diastereomer), 23.0 min (minor isomer of major diastereomer), 27.6 min (major isomer of major diastereomer), 50.0 min (minor diastereomer).



4l

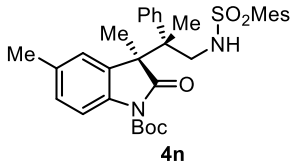
4l: ^{1}H NMR (400 MHz, C_6D_6) δ 7.98 (1H, d, *J* = 8.0 Hz), 6.95 (1H, td, *J* = 8.0, 1.4 Hz), 6.92 (1H, t, *J* = 7.3 Hz), 6.83 (2H, t, *J* = 7.5 Hz), 6.66 (1H, t, *J* = 7.5 Hz), 6.59 (2H, s), 6.54 (2H, br), 6.06 (1H, brd, *J* = 7.3 Hz), 4.26 (1H, dd, *J* = 8.7, 5.0 Hz), 3.88 (1H, dd, *J* = 12.4, 8.7 Hz), 3.75 (1H, dd, *J* = 12.4, 5.0 Hz), 2.60 (6H, s), 2.05 (1H, qd, *J* = 13.2, 6.9 Hz), 1.91 (3H, s), 1.45 (1H, qd, *J* = 13.2, 6.9 Hz), 1.40 (9H, s), 1.30 (3H, s), 0.25 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, C_6D_6) δ 176.4, 149.3, 141.8, 141.5, 139.6, 139.5, 134.5, 132.1, 128.6, 127.2, 125.3, 123.3, 114.7, 83.3, 60.2, 47.5, 47.3, 27.9, 24.4, 23.2, 20.7, 19.1, 9.5, three peaks for aromatic carbons were not found probably due to overlapping; IR 3283, 2978, 1730, 1605, 1296, 1152, 754, 660 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_5NaS^+$ ($[M+Na]^+$) 599.2550. Found 599.2550.; HPLC ID3, Hex/EtOH = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 23.8 min (major isomer of major diastereomer), 31.9 min (minor isomer of major diastereomer), 34.2 min (minor diastereomer), 41.9 min (minor diastereomer).



4m

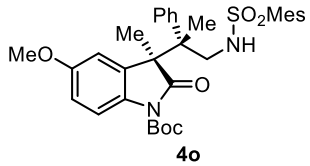
4m: ^{1}H NMR (400 MHz, C_6D_6) δ 7.69 (1H, d, *J* = 8.0 Hz), 6.97 (1H, t, *J* = 7.3 Hz), 6.89 (2H, t, *J* = 7.8 Hz), 6.81 (1H, td, *J* = 8.0, 1.4 Hz), 6.77-6.63 (8H, m), 6.60 (2H, s), 6.20 (1H, brd, *J* = 7.3 Hz), 4.43 (1H, dd, *J* = 8.7, 5.0 Hz), 4.23 (1H, dd, *J* = 12.5, 8.7 Hz), 3.92 (1H, dd, *J* = 12.5, 5.0 Hz), 3.45 (1H, d, *J* = 12.8 Hz), 2.83 (1H, d, *J* = 12.8 Hz), 2.64 (6H, s), 1.91 (3H, s), 1.34 (9H, s), 1.31 (3H, s); ^{13}C NMR

(101 MHz, C_6D_6) δ 176.1, 149.0, 141.8, 141.2, 139.8, 139.6, 135.7, 134.7, 132.2, 130.7, 128.6, 127.4, 126.7, 126.3, 122.7, 114.6, 83.2, 61.0, 47.6, 38.2, 27.9, 23.2, 20.7, 19.5, four peaks for aromatic carbons and one peak for aliphatic carbon were not found probably due to overlapping; IR 3292, 2980, 1730, 1605, 1252, 1032, 748, 654 cm^{-1}; HRMS (ESI) Calcd for $C_{38}H_{42}N_2O_5NaS^+$ ([M+Na]$^+$) 661.2707. Found 661.2702.; HPLC ID3, Hex/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.5 min (major isomer of major diastereomer), 21.1 min (minor diastereomer), 28.9 min (minor isomer of major diastereomer), 53.1 min (minor diastereomer).



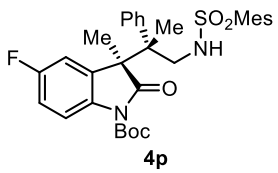
4n

4n: ^{1}H NMR (400 MHz, C_6D_6) δ 7.90 (1H, d, J = 8.2 Hz), 6.93 (1H, t, J = 7.4 Hz), 6.83 (2H, t, J = 7.4 Hz), 6.77 (1H, dd, J = 8.2, 1.4 Hz), 6.59 (2H, s), 6.54 (2H, d, J = 7.4 Hz), 5.89 (1H, brs), 4.39-4.31 (1H, m), 3.92 (1H, dd, J = 12.6, 8.5 Hz), 3.70 (1H, dd, J = 12.6, 5.0 Hz), 2.59 (6H, s), 1.93 (3H, s), 1.91 (3H, s), 1.42 (9H, s), 1.27 (3H, s), 1.09 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 177.1, 149.5, 141.8, 139.6, 139.5, 138.0, 134.4, 132.6, 132.1, 130.7, 129.0, 127.3, 125.9, 114.5, 83.1, 54.1, 47.4, 46.8, 28.0, 23.2, 20.9, 20.7, 18.9, 18.6, two peaks for aromatic carbons were not found probably due to overlapping; IR 3291, 2978, 1728, 1605, 1304, 1055, 750, 656 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_5NaS^+$ ([M+Na]$^+$) 599.2550. Found 599.2544.; HPLC AD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 22.6 min (minor diastereomer), 28.8 min (minor isomer of major diastereomer), 36.4 min (major isomer of major diastereomer), 44.2 min (minor diastereomer).



4o

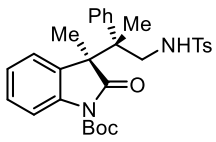
4o: ^{1}H NMR (400 MHz, C_6D_6) δ 7.96 (1H, d, J = 8.7 Hz), 6.92 (1H, t, J = 7.3 Hz), 6.85 (2H, t, J = 7.3 Hz), 6.61-6.58 (5H, m), 5.62 (1H, brs,) 4.40 (1H, dd, J = 8.7, 5.0 Hz), 4.00 (1H, dd, J = 12.8, 8.7 Hz), 3.73 (1H, dd, J = 12.8, 5.0 Hz), 3.15 (3H, s), 2.61 (6H, s), 1.92 (3H, s), 1.45 (9H, s), 1.22 (3H, s), 1.06 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 177.2, 156.2, 149.6, 141.8, 139.5, 139.5, 134.5, 133.5, 132.1, 132.0, 127.3, 115.6, 113.7, 111.5, 83.2, 54.9, 54.4, 47.2, 46.8, 28.0, 23.2, 20.7, 19.0, 18.9, two peaks for aromatic carbons were not found probably due to overlapping; IR 3283, 2978, 1726, 1605, 1277, 1150, 748, 656 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{40}N_2O_6NaS^+$ ([M+Na]$^+$) 615.2499. Found 615.2497.; HPLC ID3, Hex/EtOH = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 35.1 min (major isomer of major diastereomer), 43.5 min (minor diastereomer), 48.3 min (minor diastereomer), 51.3 min (minor isomer of major diastereomer).



4p

4p: ^{1}H NMR (400 MHz, C_6D_6) δ 7.82 (1H, dd, J = 9.1, $J_{F\text{-}H}$ = 4.6 Hz), 6.91 (1H, t, J = 7.4 Hz), 6.82 (2H, t, J = 7.4 Hz), 6.63-6.58 (3H, m), 6.48 (2H, d, J = 7.4 Hz), 5.70 (1H, brd, J = 6.4 Hz), 4.26 (1H, dd, J = 8.7, 5.0 Hz), 3.89 (1H, dd, J = 12.6, 8.7 Hz), 3.62 (1H, dd, J = 12.6, 5.0 Hz), 2.59 (6H,

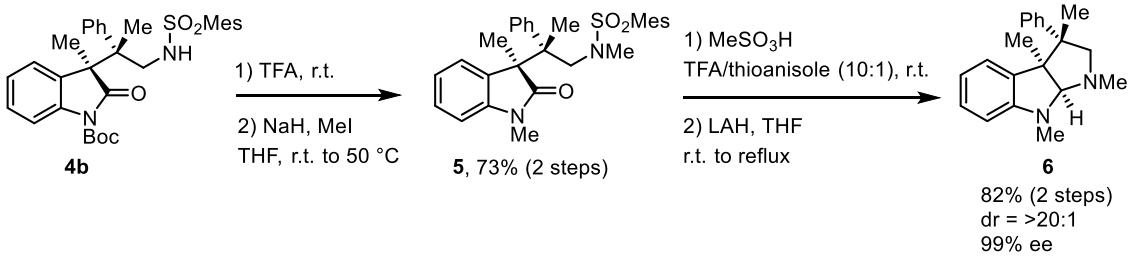
s), 1.92 (3H, s), 1.42 (9H, s), 1.16 (3H, s), 0.93 (3H, s); ^{13}C NMR (101 MHz, C_6D_6) δ 176.6, 159.3 (d, $J_{F\text{-}C}$ = 247.7 Hz), 149.4, 141.9, 139.6, 139.0, 136.1, 134.5, 132.6 (d, $J_{F\text{-}C}$ = 7.7 Hz), 132.1, 127.6, 115.9 (d, $J_{F\text{-}C}$ = 6.8 Hz), 114.9 (d, $J_{F\text{-}C}$ = 23.2 Hz), 112.8 (d, $J_{F\text{-}C}$ = 25.2 Hz), 83.6, 54.3, 47.1, 46.7, 27.9, 23.2, 20.7, 18.9, 18.4, two peaks for aromatic carbons were not found probably due to overlapping; ^{19}F NMR (376 MHz, C_6D_6) δ –118.4; IR 3286, 2980, 1732, 1605, 1477, 1152, 754, 658 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{37}N_2O_5FNaS^+$ ([M+Na]$^+$) 603.2299. Found 603.2296.; HPLC IE3, H/EtOH = 19:1, flow rate = 1.0 mL/min, λ = 220 nm, 38.7 (major isomer of major diastereomer), 42.1 min (minor isomer of major diastereomer), 48.1 (minor diastereomer), 50.4 min (minor diastereomer).



4a

4a: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.74 (2H, d, J = 8.2 Hz), 7.60 (1H, d, J = 8.0 Hz), 7.41 (2H, d, J = 8.2 Hz), 7.25 (1H, td, J = 8.0, 1.4 Hz), 7.17 (1H, t, J = 7.3 Hz), 7.09 (2H, t, J = 7.5 Hz), 7.01 (1H, td, J = 7.7, 0.9 Hz), 6.82 (2H, d, J = 7.3 Hz), 6.63 (1H, d, J = 7.3 Hz), 5.78 (1H, brt, J = 6.6 Hz), 3.85 (1H, dd, J = 12.8, 5.6 Hz), 3.74 (1H, dd, J = 12.8, 7.8 Hz), 2.44 (3H, s), 1.53 (3H, s), 1.52 (9H, s), 1.45 (3H, s); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 177.5, 149.4, 143.7, 140.6, 140.0, 139.0, 131.4, 130.4, 129.0, 128.9, 128.2, 127.9, 127.7, 126.0, 124.0, 114.8, 83.8, 54.8, 48.2, 47.6, 28.1, 21.4, 19.0, 18.7; IR 3300, 2978, 1734, 1477, 1290, 1060, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{34}N_2O_5NaS^+$ ([M+Na]$^+$) 557.2081. Found 557.2080.; HPLC OZ3, H/IPA/EtOH = 92:5:3, flow rate = 0.5 mL/min, λ = 210 nm, 48.8 (minor diastereomer), 59.1 min (minor diastereomer), 65.5 min (major isomer of major diastereomer), 89.0 min (minor isomer of major diastereomer).

Derivatization of 4b to Pyrrolidinoindoline 6



The alkylated product **4b** (169 mg, 0.30 mmol, dr = >20:1.0, 99% ee) was placed in a test tube and dissolved into trifluoroacetic acid (TFA) (0.3 mL). The resulting solution was stirred for 2.5 h at room temperature. After cooling to 0 °C, the reaction mixture was poured onto ice and the aqueous solution thus obtained was neutralized by NaOH. The aqueous phase was extracted with EtOAc and the organic phase was dried over Na_2SO_4. Filtration and concentration of the organic phase gave crude material. This crude material was dissolved into THF (3.0 mL), and NaH (36 mg, 0.9 mmol) was carefully introduced into the solution under Ar at 0 °C. After stirring for 30 min at room temperature, methyl iodide (0.050 mL, 0.9 mmol) was added to the solution and whole reaction

mixture was stirred for 12 h at 50 °C. The mixture was then diluted with water and the extractive workup was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 3:1 as eluent) to afford **5** (108 mg, 0.22 mmol, 73% yield for 2 steps) as a white solid.

5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, t, J = 7.8 Hz), 7.16-7.11 (4H, m), 6.99-6.96 (3H, m), 6.90 (2H, t, J = 7.8 Hz), 6.58 (1H, d, J = 7.8 Hz), 4.41 (1H, d, J = 14.1 Hz), 3.68 (1H, d, J = 14.1 Hz), 2.71 (3H, s), 2.65 (6H, s), 2.32 (3H, s), 2.11 (3H, s), 1.33 (6H, s).

To a solution of **5** (108 mg, 0.22 mmol) in TFA (0.2 mL) and thioanisole (0.02 mL) was added $MeSO_3H$ (0.02 mL, 0.33 mmol) and the resulting solution was stirred for 6 h at room temperature. After cooling to 0 °C, the reaction mixture was poured onto ice and the aqueous solution thus obtained was neutralized by NaOH. The aqueous phase was extracted with EtOAc and the organic phase was dried over Na_2SO_4. Filtration and concentration of the organic phase gave crude material. To a solution of this crude material in THF (4.4 mL) was carefully added $LiAlH_4$ (83 mg, 2.2 mmol) and the mixture was refluxed for 2 h. After cooling to 0 °C, the reaction was quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (3.2 g 10 mmol), and the resulting suspension was vigorously stirred overnight at room temperature. The mixture was filtered with the aid of EtOAc and the filtrates were concentrated. Purification of the crude residue by column chromatography (Hex/EtOAc = 1:1 as eluent) furnished **6** (52.6 mg, 0.18 mmol, 82% yield for 2 steps, dr = >20:1.0, 99% ee) as a white solid. **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, dd, J = 8.0, 1.4 Hz), 7.35 (2H, t, J = 8.0 Hz), 7.24 (1H, td, J = 8.0, 1.4 Hz), 7.13 (1H, td, J = 7.6, 1.4 Hz), 7.11 (1H, dd, J = 7.6, 1.1 Hz), 6.71 (1H, td, J = 7.8, 1.1 Hz), 6.43 (1H, d, J = 8.0 Hz), 4.02 (1H, s), 3.50 (1H, d, J = 8.9 Hz), 3.08 (1H, d, J = 8.9 Hz), 2.92 (3H, s), 2.73 (3H, s), 1.32 (3H, s), 0.95 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 145.6, 133.4, 128.3, 128.2, 127.1, 126.3, 123.7, 117.0, 106.5, 102.4, 66.4, 58.3, 51.3, 43.0, 35.2, 26.4, 26.0; IR 2926, 1605, 1491, 1240, 1022, 908, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{25}N_2^+$ ($[M+H]^+$) 293.2012. Found 293.2007.; HPLC OJ3, H/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 10.6 min (major), 14.0 min (minor).

Crystallographic Structure Determination:

Recrystallization of 1a·Cl, 4b, 4j, 2j, and 6: A single crystal of **1a·Cl** was obtained from toluene at room temperature. Single crystals of **4b** and **4j** were obtained from CH_2Cl_2/Et_2O solvent system at room temperature. A single crystal of **2j** was obtained from Et_2O/Hex solvent system at room temperature. A single crystal of **6** was obtained from Hex at room temperature. The single crystals thus obtained were mounted on CryoLoop. Data of X-ray diffraction were collected at 133 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 *F2* by using SHELXTL.[22] All non-hydrogen atoms were refined with anisotropic displacement parameters.

Hydrogen atoms bonded to oxygen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions. The crystallographic data were summarized in **Tables S2, S3, S4, S5,** and **S6.**

Table S2. Crystal Data, Structure Refinement for **1a·Cl**.

Empirical formula	C43 H37 Cl N4 O	
Formula weight	661.22	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 11.727(3) Å	α= 81.252(4)°.
	b = 11.746(3) Å	β= 72.971(4)°.
	c = 15.471(4) Å	γ = 60.415(4)°.
Volume	1772.0(7) $Å^3$	
Z	2	
Density (calculated)	1.239 Mg/m^3	
Absorption coefficient	0.147 mm^{-1}	
F(000)	696	
Crystal size	0.50 x 0.40 x 0.20 mm^3	
Theta range for data collection	1.99 to 28.42°.	
Index ranges	-13<=h<=15, -13<=k<=15, -20<=l<=18	
Reflections collected	12521	
Independent reflections	10248 [R(int) = 0.0285]	
Completeness to theta = 28.42°	96.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10248 / 3 / 885	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0801, wR2 = 0.2197	
R indices (all data)	R1 = 0.0831, wR2 = 0.2225	
Absolute structure parameter	0.14(8)	
Largest diff. peak and hole	1.860 and -0.398 e.$Å^{-3}$	

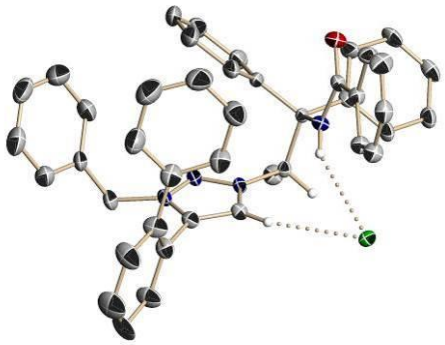


Figure S6. Molecular Structure of Ion-Paired Ligand **1a·Cl**. Calculated hydrogen atoms are omitted for clarity.
Blue = nitrogen, red = oxygen, green = chlorine, black = carbon.

Table S3. Crystal Data, Structure Refinement for **4b**.

Empirical formula	C32 H38 N2 O5 S	
Formula weight	562.70	
Temperature	103(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P_21_21_21	
Unit cell dimensions	a = 6.4319(16) Å	α= 90°.
	b = 16.382(4) Å	β= 90°.
	c = 27.793(7) Å	γ = 90°.
Volume	2928.4(13) $Å^3$	
Z	4	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	0.154 mm^{-1}	
F(000)	1200	
Crystal size	0.30 x 0.02 x 0.02 mm^3	
Theta range for data collection	3.18 to 27.48°.	
Index ranges	-8<=h<=8, -21<=k<=21, -36<=l<=31	
Reflections collected	23968	
Independent reflections	6696 [R(int) = 0.1223]	
Completeness to theta = 27.48°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9969 and 0.9553	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	6696 / 0 / 369
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0933, wR2 = 0.2105
R indices (all data)	R1 = 0.1421, wR2 = 0.2481
Absolute structure parameter	-0.29(16)
Largest diff. peak and hole	0.721 and -0.402 e.$Å^{-3}$

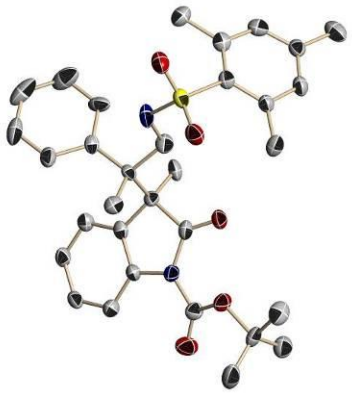


Figure S7. Molecular Structure of **4b**. All calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon.

Table S4. Crystal Data, Structure Refinement for **4k**.

Empirical formula	C36 H41 N2 O5 S	
Formula weight	613.77	
Temperature	293(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P_21_21_21	
Unit cell dimensions	a = 6.493(2) Å	α= 90°.
	b = 16.778(6) Å	β= 90°.
	c = 30.179(11) Å	γ = 90°.
Volume	3288(2) $Å^3$	
Z	4	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.143 mm^{-1}	
F(000)	1308	
Crystal size	0.30 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.16 to 27.37°.	
Index ranges	-8<=h<=8, -19<=k<=21, -38<=l<=38	

Reflections collected	26453
Independent reflections	7433 [R(int) = 0.0952]
Completeness to theta = 27.37°	99.6 %
Max. and min. transmission	0.9929 and 0.9584
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7433 / 0 / 405
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0784, wR2 = 0.1907
R indices (all data)	R1 = 0.1011, wR2 = 0.2145
Absolute structure parameter	0.06(13)
Largest diff. peak and hole	0.726 and -0.540 e.$Å^{-3}$

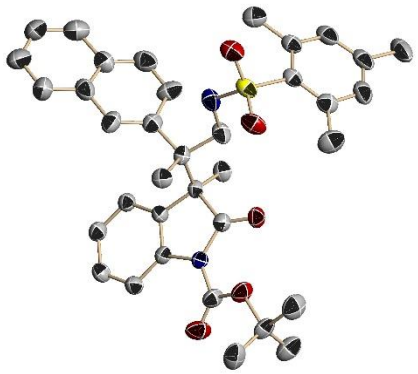


Figure S8. Molecular Structure of **4k**. All calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon.

Table S5. Crystal data and structure refinement for **2k**.

Empirical formula	C32 H38 N2 O5 S	
Formula weight	562.70	
Temperature	103(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P_21_21_21	
Unit cell dimensions	a = 6.4319(16) Å	α= 90°.
	b = 16.382(4) Å	β= 90°.
	c = 27.793(7) Å	γ = 90°.
Volume	2928.4(13) $Å^3$	
Z	4	

Density (calculated)	1.276 Mg/m^3
Absorption coefficient	0.154 mm^{-1}
F(000)	1200
Crystal size	0.30 x 0.02 x 0.02 mm^3
Theta range for data collection	3.18 to 27.48°.
Index ranges	-8<=h<=8, -21<=k<=21, -36<=l<=31
Reflections collected	23968
Independent reflections	6696 [R(int) = 0.1223]
Completeness to theta = 27.48°	99.8 %
Absorption correction	Empirical
Max. and min. transmission	0.9969 and 0.9553
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6696 / 0 / 369
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0933, wR2 = 0.2105
R indices (all data)	R1 = 0.1421, wR2 = 0.2481
Absolute structure parameter	-0.29(16)
Largest diff. peak and hole	0.721 and -0.402 $e.Å^{-3}$

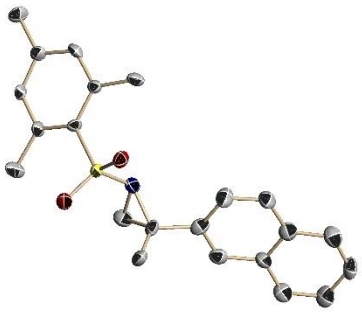


Figure S9. Molecular Structure of **2k**. All calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, black = carbon.

Table S6. Crystal data and structure refinement for **6**.

Empirical formula	C20 H24 N2
Formula weight	292.41
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system	Rhombohedral
Space group	R3

Unit cell dimensions	a = 21.290(6) Å	α= 90°.
	b = 21.290(6) Å	β= 90°.
	c = 9.790(4) Å	γ = 120°.
Volume	3843(2) $Å^3$	
Z	9	
Density (calculated)	1.137 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	1422	
Crystal size	0.30 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.91 to 28.34°.	
Index ranges	-28<=h<=24, -27<=k<=28, -13<=l<=12	
Reflections collected	7069	
Independent reflections	3315 [R(int) = 0.0528]	
Completeness to theta = 28.34°	87.6 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9934 and 0.9803	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3315 / 1 / 203	
Goodness-of-fit on F^2	1.169	
Final R indices [I>2sigma(I)]	R1 = 0.0748, wR2 = 0.1857	
R indices (all data)	R1 = 0.0973, wR2 = 0.1931	
Largest diff. peak and hole	0.235 and -0.220 $e.Å^{-3}$	

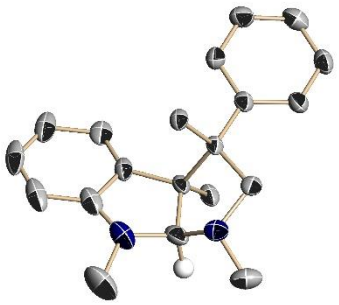


Figure S10. Molecular Structure of **6**. All calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, black = carbon.

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(15) For detailes, see the Supporting Information.

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(19) As a control experiment, the reaction of **3a** with 1 equiv of **2b** under otherwise identical conditions with those described in Table 2 was conducted, which resulted in the formation of diastereomeric mixture of **4b** (dr = 4:1) in 60% yield with 97% ee for major diastereomer. This result also indicated that the kinetic resolution of aziridine **2** was operative in the present asymmetric ring-opening alkylation.

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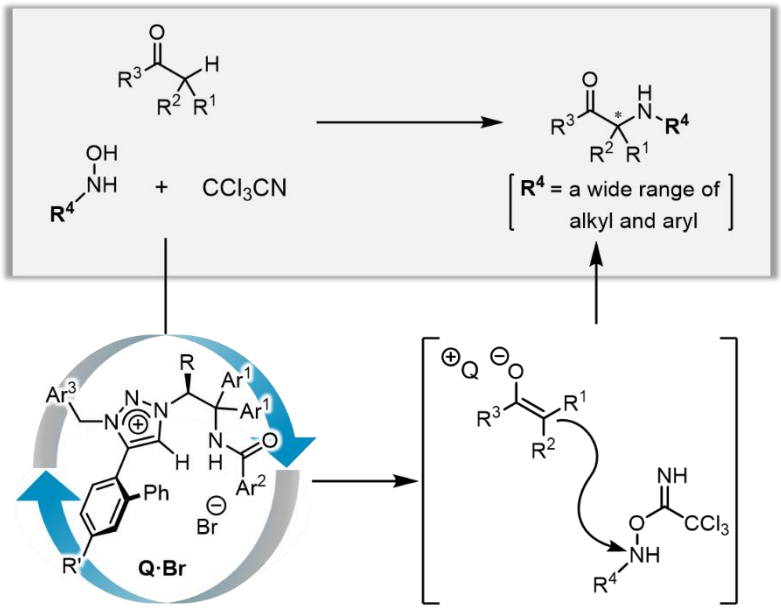
Chapter 3

A Modular Strategy for the Direct Catalytic Asymmetric α-Amination of Carbonyl Compounds



Abstract:

Direct catalytic methods for the stereoselective introduction of various non-protected amines at the carbon atom adjacent to a carbonyl group remain elusive in synthetic chemistry, despite offering the most straightforward entry to chiral α-aminocarbonyl compounds. Here, the author demonstrates that the *in situ* activation of hydroxylamines with trichloroacetonitrile enables a direct transfer of their amine moieties to the C-3 position of oxindoles with rigorous enantiocontrol under the catalysis of chiral 1,2,3-triazolium salts. This protocol provides a powerful and practical means to access optically active 3-aminooxindoles with a wide array of alkyl and aryl substituents on nitrogen. Other carbonyl compounds, such as β-ketoesters and α-cyanoesters, can also be directly transformed into the corresponding α-aminocarbonyls with high enantioselectivity.

1. Introduction

The development of general methods for the stereoselective construction of chiral aminocarbonyls with sufficient structural variation of the nitrogen substituents represents an enduring challenge in chemical synthesis.[1-4] Among the manifold of transformations that are conceivable for the assembly of chiral α-aminocarbonyls, the catalytic asymmetric α-amination of carbonyl compounds is one of the most efficient and straightforward methods and a multitude of stereoselective C–N bond-forming reactions has been reported.[5] However, the direct enantioselective installation of a diverse range of non-protected amines onto carbonyl α-carbons still remains unrealized.[6-8] The main obstacle to achieve this goal stems from the structural and functional-group requirements for electrophilic nitrogen sources to be competent to forge a C–N bond yet compatible with the respective catalytic system. In fact, only few reagents, such as azodicarboxylates,[9-11] nitroso arenes[12,13] and carbonyls,[14] azidoiodinanes,[15] or sulfonyloxycarbamates[16] have been used for implementing the asymmetric amination strategies. Consequently, subsequent reductive N–N or N–O bond cleavage and/or deacylation are necessary to generate unmasked amine functionalities. Very recently, utilizing electron-acceptor-substituted aryl aminyl radicals generated from the corresponding aryl azides, direct asymmetric α-amination of 2-acyl imidazoles was achieved.[17] In all of above-mentioned approaches, the scope of substituents on nitrogen is strictly limited by the nature of the electrophilic nitrogen sources, which renders it difficult to directly introduce various amines at the α-carbon atom of carbonyls with rigorous stereocontrol in a single synthetic operation.

The author designed a modular strategy for the catalytic asymmetric α-amination of carbonyl compounds based on the use of hydroxylamines as an amine source.[18] Although hydroxylamines themselves are nucleophilic, their derivatives containing *O*-electron-withdrawing substituents, such as benzoyl or phosphinyl groups, have classically been employed as electrophilic nitrogen sources in α-amination reactions.[19] The problem associated with this type of methodology is the insufficient reactivity of *O*-substituted hydroxylamines, which only react with highly nucleophilic organometallic species.[20] The introduction of a strongly electron-withdrawing substituent on oxygen, e.g. a sulfonyl group, would enhance the electrophilicity, but this class of hydroxylamines is thermally labile and decomposes immediately at room temperature.[21] The new approach is to activate simple hydroxylamines *in situ* via the treatment with trichloroacetonitrile under mildly basic conditions,[22,23] where phase-transfer catalysis of chiral onium salts can be operative.[24] The author speculated that the hydroxylamine nitrogen atom of an *in situ*-formed *O*-trichloroacetimino hydroxylamine would be sufficiently electrophilic to engage in bond connection with a catalytically generated chiral onium enolate of the carbonyl compound, thereby allowing the stereocontrolled transfer of the amine component. Here, the author disclosed the realization of a highly enantioselective α-amination of several carbonyl compounds, namely, oxindoles, β-ketoesters, and α-cyanoesters, based on this strategy using chiral 1,2,3-triazolium salts as requisite catalysts. Considering the structural diversity

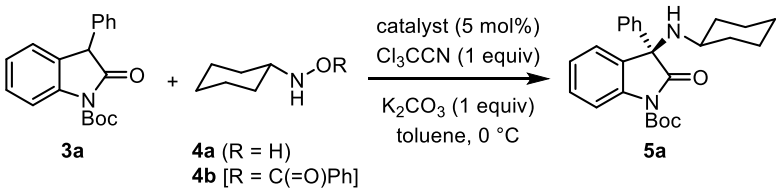
of the readily available hydroxylamines, this protocol provides a powerful and practical tool for the straightforward synthesis of optically active α-aminocarbonyls with a wide array of alkyl and aryl substituents on nitrogen.

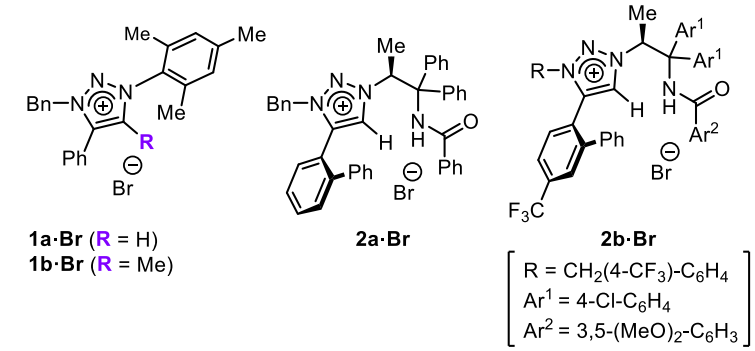
2. Result and Discussion

2.1. Optimization of the Reaction Conditions

Initially, the author focused on assessing the viability of the α-amination of oxindoles by using *N*-substituted hydroxylamines as the amine source in combination with trichloroacetonitrile. For this purpose, *N*-Boc-3-phenyloxindole (**3a**) and *N*-cyclohexylhydroxylamine (**4a**) were selected as model substrates because the asymmetric incorporation of a bulky *N*-alkylamino group at the α-carbon atom relative to the carbonyl group remains unexplored. An initial experiment was carried out by treating **3a** with **4a** and trichloroacetonitrile in the presence of powdered potassium carbonate and a catalytic amount of tetrabutylammonium bromide or benzyltrimethylammonium bromide in toluene at 0 °C. However, these common phase-transfer catalysts proved to be inactive for the targeted C–N bond formation, and the starting materials were recovered together with several unidentified products (entries 1 and 2, Table 1). In contrast, the reaction using 1,2,3-triazolium bromide **1a·Br** as a catalyst under otherwise identical conditions afforded the desired 3-aminooxindole **5a**, albeit in very low yield (entry 3). Since the structurally similar catalyst **1b·Br**, bearing a methyl instead of a hydrogen substituent at the C-5 carbon, did not induce any reactivity (entry 4), the author presumed that the hydrogen bond donating ability of the triazolium ion was essential for promoting this amination. Encouraged by the feasibility of a direct transfer of the amine component of *N*-cyclohexylhydroxylamine, chiral 1,2,3-triazolium bromides of type **2·Br** that feature ample structural modularity[25] were applied to the amination with the aim of enhancing the reactivity and achieving absolute stereocontrol. Indeed, *L*-alanine-derived catalyst **2a·Br** afforded **5a** in significantly increased yield with an excellent level of enantiocontrol. A subsequent pertinent modification of the triazolium structure allowed us to identify **2b·Br** as the optimal catalyst, which delivered **5a** in critically improved yield with virtually complete stereochemical control (entry 6). It should be noted that the **2b·Br**-catalyzed reaction did not afford any product in the absence of trichloroacetonitrile (entry 7). In addition, the amination did not proceed when *O*-benzoyl hydroxylamine **4b** was used as the sole electrophilic nitrogen source (entry 8). These results corroborate the critical importance of the combined use of hydroxylamine and trichloroacetonitrile in order to promote the stereoselective direct α-amination of **3a**.

Table 1. Optimization of Reaction Conditions[a]





Entry	Catalyst	**4**	Yield (%)[b]	ee (%)[c]
1[d]	*n*-Bu_4N·Br	**4a**	0	–
2[d]	$BnNMe_3$·Br	**4a**	0	–
3[d]	**1a·Br**	**4a**	10	–
4[d]	**1b·Br**	**4a**	0	–
5	**2a·Br**	**4a**	41	96
6	**2b·Br**	**4a**	80	99
7[e]	**2b·Br**	**4a**	0	–
8[e]	**2b·Br**	**4b**	0	–

[a] Unless otherwise noted, the following reaction conditions were used: 0.10 mmol of **3a**, 0.15 mmol of **4**, 0.10 mmol of Cl_3CCN, and 0.10 mmol of K_2CO_3 in the presence of catalyst (5.0 mol%) in toluene (1.0 mL) at 0 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Performed using 10 mol% of catalyst. [e] Performed in the absence of Cl_3CCN.

2.2. Studies on Reactive Intermediate

An NMR spectroscopic analysis was conducted to confirm the *in situ* generation of an *O*-imino hydroxylamine. When trichloroacetonitrile and hydroxylamine **4a** were mixed (1:1 ratio) in toluene-d_8 at room temperature, the immediate disappearance of the peaks corresponding to the starting materials and the formation of imino hydroxylamine were observed by ^1H and ^{13}C NMR analyses (Figure 1). The formation of the imino hydroxylamine was also verified by the analysis using electrospray ionization mass spectrometry (ESI-MS).

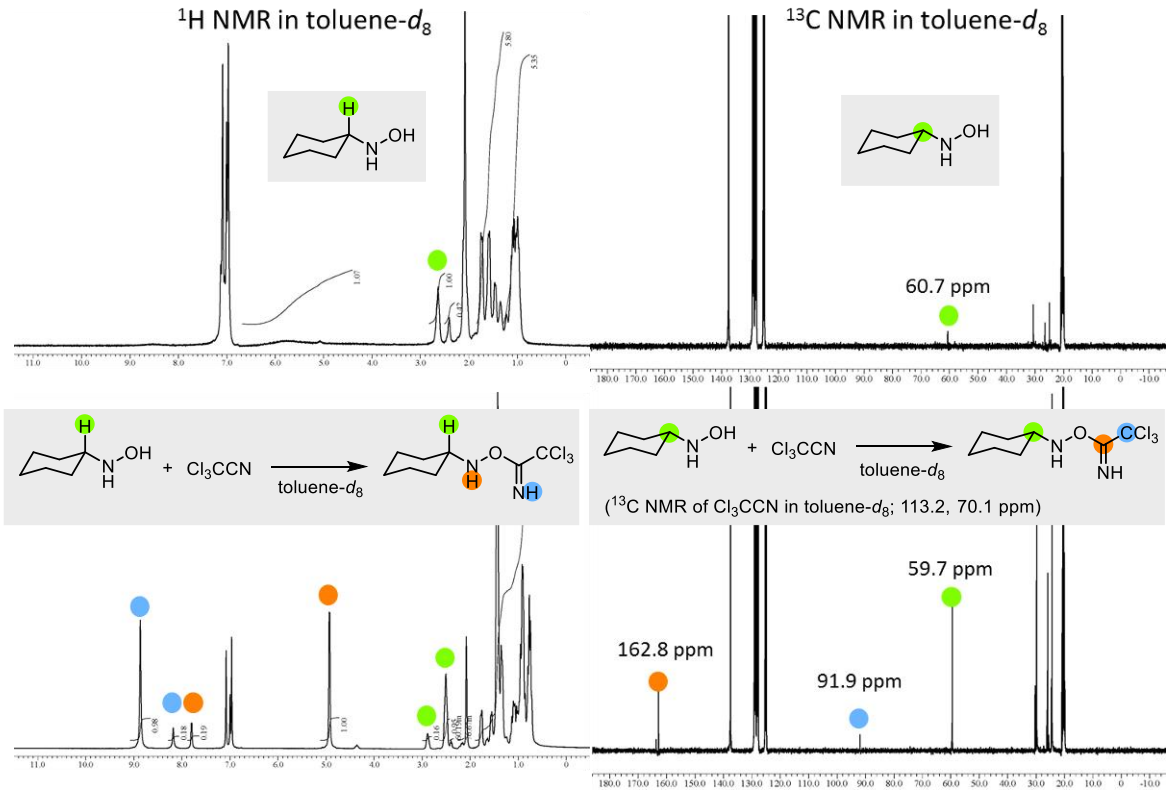


Figure 1. ^{1}H and ^{13}C NMR Spectra of a Mixture of Hydroxylamine **4a** and Trichloroacetonitrile.

NMR spectra shown in Figures 1 indicated that imino hydroxylamine was formed as a mixture of two isomers. Similarly, the treatment of *N*-benzylhydroxylamine with trichloroacetonitrile in toluene-d_8 resulted in the formation of two isomers, both of which proton–proton couplings between amino NH and benzylic CH_2 were clearly observed. This information suggested that both two isomers were generated through the bond connection between oxygen atom, not nitrogen atom, of hydroxylamine and the cyano carbon of trichloroacetonitrile. In fact, when *N*-cyclohexyl-*O*-methylhydroxylamine was treated with trichloroacetonitrile in toluene-d_8, the formation of the corresponding *N*-imino hydroxylamine was not detected at all (Scheme 1).

Scheme 1. The Reaction of *N*-Cyclohexyl-*O*-Methylhydroxylamine and Trichloroacetonitrile.

From these results, the observation of two isomers would stem from the potential existence of the geometrical isomers of the imino double bond or the rotational isomers of the C–O bond (Figure. 2).[26]

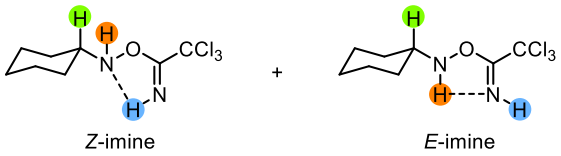
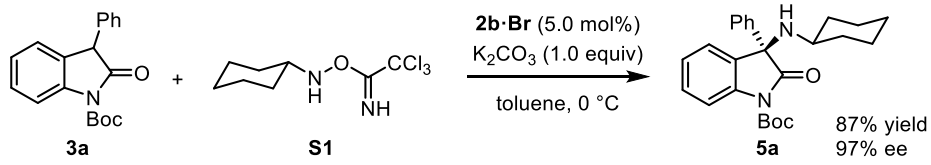


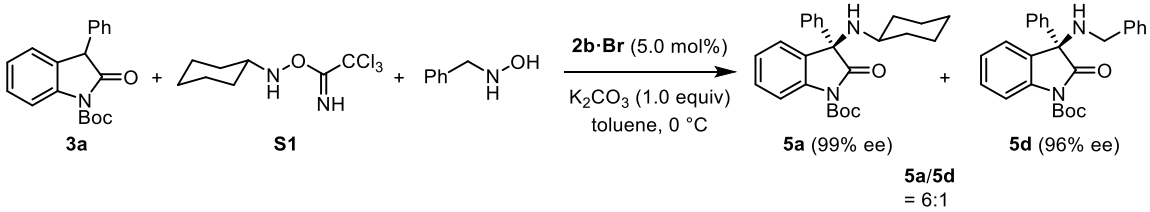
Figure 2. The Geometrical Isomers of an *O*-Imino Hydroxylamine.

Even though the *O*-imino hydroxylamine could be purified by chromatography on silica gel, it was not stable enough to be stored. However more importantly, when the isolated imino hydroxylamine was used immediately for the asymmetric amination under the influence of **2b·Br**, **5a** was produced with similarly high efficiency and enantiopurity (Scheme 2). This result unambiguously demonstrated that the imino hydroxylamine was an actual reactive intermediate.



Scheme 2. α-Amination of Oxindole with *O*-imino hydroxylamine.

To investigate whether the formation of *O*-imino hydroxylamine from hydroxylamine and trichloroacetonitrile is reversible, a control experiment was conducted, in which a 1:1 mixture of purified *N*-cyclohexyl *O*-trichloroacetimino hydroxylamine (**S1**) and *N*-benzylhydroxylamine was subjected to **2b·Br**-catalyzed amination reaction of *N*-Boc-3-phenyloxindole (**3a**) in the absence of trichloroacetonitrile (Scheme 3). ^{1}H NMR analysis of the crude product revealed the formation of a 6:1 mixture of 3-(*N*-cyclohexyl)aminooxindole (**5a**) and 3-(*N*-benzyl)aminooxindole (**5d**), indicating that imino hydroxylamine would undergo the retro reaction to regenerate the corresponding hydroxylamine and trichloroacetonitrile.



Scheme 3. Cross-Over Experiment.

2.3. Substrate Scope

The author next explored the scope of this asymmetric α-amination protocol with regard to hydroxylamines (**4**). As illustrated in Figure. 3, a wide range of amines could be directly introduced at the C-3 carbon of oxindole **3a** from the parent hydroxylamines in a highly stereoselective fashion.

Not only sterically hindered *N*-cycloalkyl hydroxylamines, but also *N*-benzylic and other simple alkyl-substituted hydroxylamines could be used as viable amine sources, producing the corresponding 3-aminooxindoles (**5b**-**5h**) with uniformly excellent enantioselectivity. For the reactions with *N*-isopropyl, allylic, and alkoxycarbonylmethyl hydroxylamines, an increased catalyst loading was required to obtain **5i**, **5j**, and **5k** in satisfactory yield. Furthermore, the direct incorporation of unmasked aniline derivatives was possible with comparable degrees of efficiency and selectivity, where 1,2,3-triazolium salt **2a·Br** proved to be a superior catalyst, and various functional groups on the aryl moiety, e.g. bromine, ester, or nitrile, were tolerated well (**5l**-**5o**). It should be noted that **2c·Br**, a *L*-leucine-derived analogue of **2c·Br**, exhibited higher catalytic activity in the reaction with a hydroxylamine bearing a 4-vinylphenyl substituent on nitrogen, which afforded the desired product **5p** with high optical purity in a synthetically useful yield. With respect to oxindoles, the incorporation of aromatic substituents with different electronic properties at the 3-position was amenable to the **2a·Br**-catalyzed amination (**5q**-**5u**). 3-Alkyl-oxindoles could also be used as carbonyl nucleophiles in the catalysis using **2c·Br**, thus furnishing the corresponding 3-aminooxindoles **5v-5z** in generally high yield with excellent enantiomeric excess. Additionally, this catalytic system was able to accommodate 5-substituted oxindoles, and the corresponding aminations proceeded cleanly to yield **5Aa** and **5Ab** in a highly enantio-enriched form.

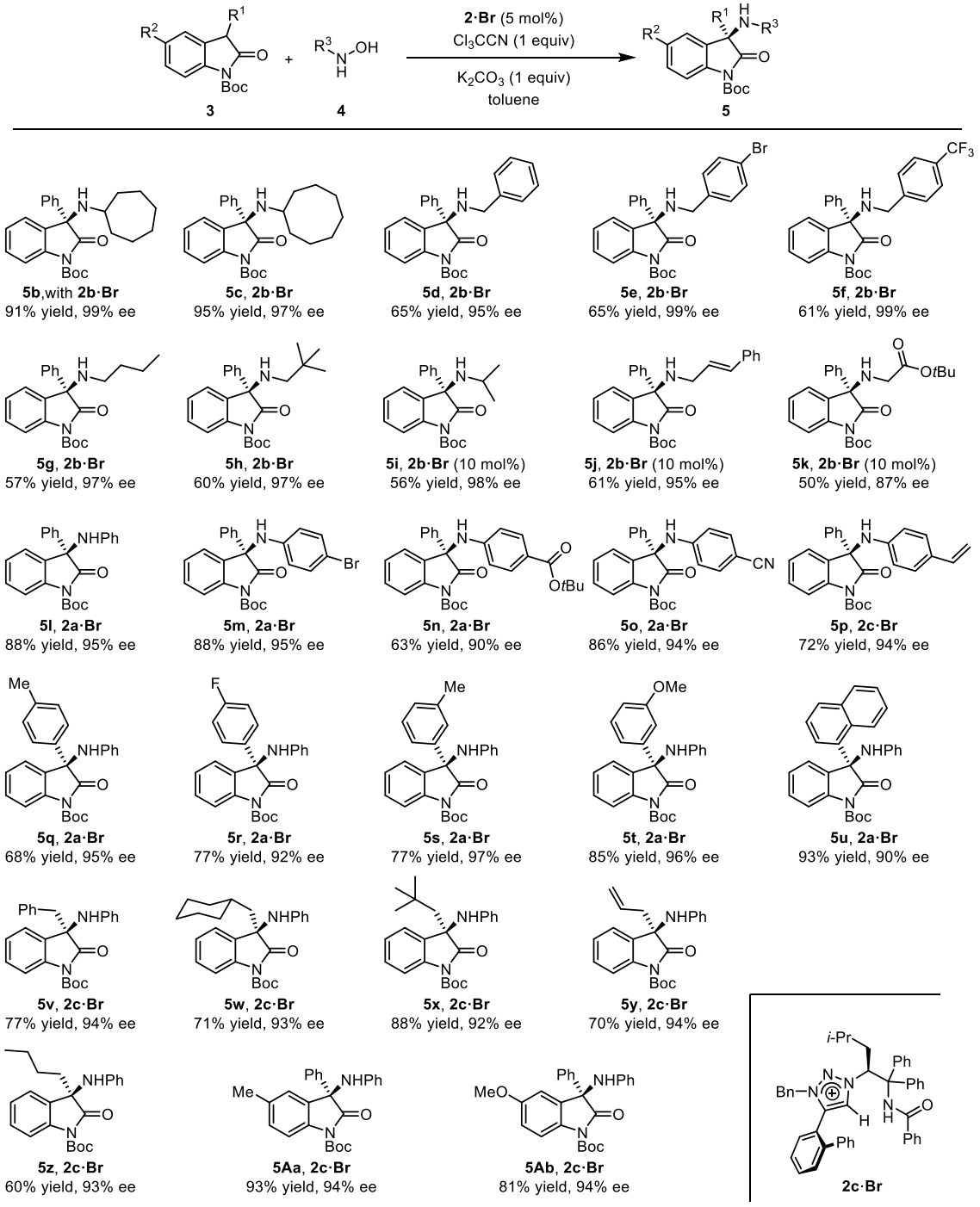
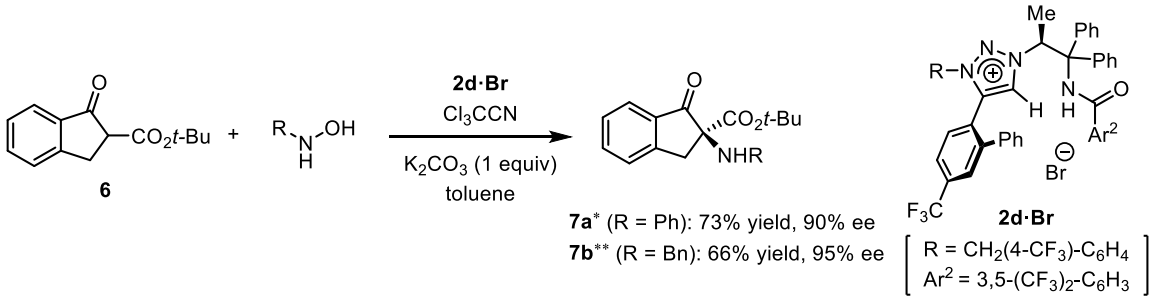


Figure 3. Substrate Scope

Isolated yield and enantiomeric excess are given below each product; for further experimental details, see Experimental Section. All yields are isolated yields and enantiomeric excesses were determined by HPLC analysis.

In the presence of the suitable catalyst **2d·Br**, 1-indanone derivative **6** also underwent smooth amination with *N*-phenylhydroxylamine or *N*-benzylhydroxylamine to produce α-amino β-ketoester **7a** or **7b** with high enantioselectivity (Scheme 4).

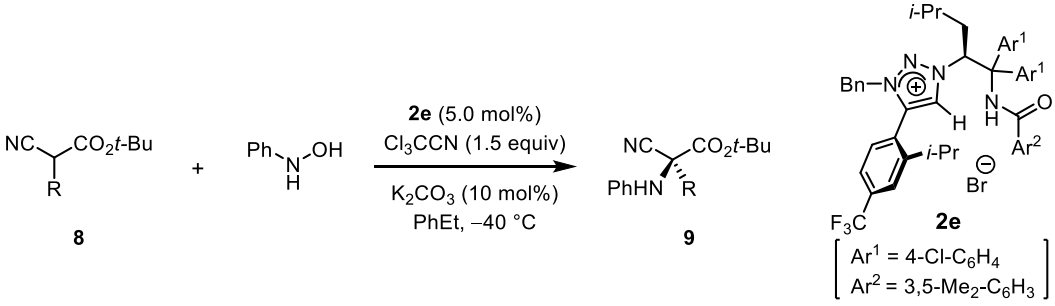


Scheme 4. Direct Asymmetric Amination of 1-Indanone Derivative.

* Reactions was carried out with 0.10 mmol of **6**, 0.15 mmol of hydroxyl amine, 0.10 mmol of Cl_3CCN, and 0.10 mmol of K_2CO_3 in the presence of catalyst (5.0 mol%) in toluene (1.0 mL) at 0 °C for 24 h. ** Reactions was carried out with 0.10 mmol of **6**, 0.35 mmol of hydroxyl amine, 0.30 mmol of Cl_3CCN, and 0.10 mmol of K_2CO_3 in the presence of catalyst (10.0 mol%) in toluene (1.0 mL) at 20 °C for 24 h.

Moreover, a series of cyanoesters **8** could be directly aminated under the conditions optimized for this type of acyclic substrates to give the corresponding aminoesters **9a**-**9e** in uniformly good yield with high enantiomeric excess (Table 2).

Table 2. Scope of direct asymmetric aminations of cyanoesters [a]

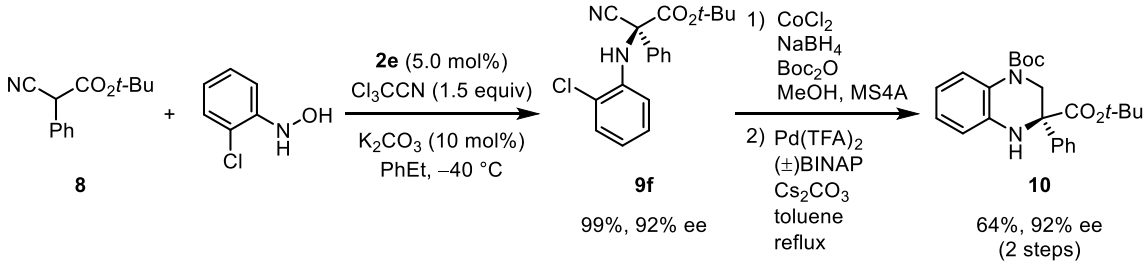


Entry	R	**9**	Yield (%)[b]	ee (%)[c]
1	Ph	**9a**	97	92
2	4-Me-C_6H_4	**9b**	67	90
3	4-MeO-C_6H_4	**9c**	91	94
4[d]	4-F-C_6H_4	**9d**	63	87
5	2-Naph	**9e**	63	89

[a] Unless otherwise noted, the following reaction conditions were used: 0.10 mmol of **3a**, 0.15 mmol of hydroxylamine, 0.15 mmol of Cl_3CCN, and K_2CO_3 (10 mol%) in the presence of catalyst (5.0 mol%) in ethylbenzene saturated with water (3.0 mL) at -40 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Reaction was carried out in ethylbenzene saturated with water (1.0 mL)

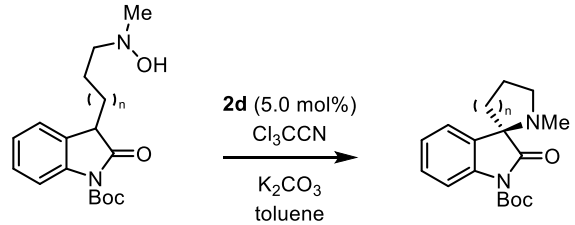
3. Derivatization and Application

The author examined the application of this catalytic protocol to the concise asymmetric synthesis of a tetrahydroquinoxaline derivative, which chiral ring system is found in potential therapeutics such as promising anti HIV agents. The reaction of α-phenyl cyanoester with *N*-2-chlorophenylhydroxylamine provided enantioenriched α-amino α-cyanoester **9f**. Then, reduction of the nitrile moiety by the treatment with sodium borohydride under the cobalt catalysis, followed by the palladium catalyzed C-N coupling, furnished tetrahydroquinoxaline derivative **10** without loss of stereochemical integrity (Scheme 5).[27]



Scheme 5. Synthesis of Tetrahydroquinoxaline Derivative **9f** from **10**.

The present method was further applied to asymmetric intramolecular C–N bond formations. An attempted reaction of oxindole **11a**, containing an *N*-hydroxylaminopropyl side chain, merely afforded trace amounts of 5-membered cyclic product **12a**, most likely due to the ready protonation of the oxindole enolate intermediate by the amino N-H functionality. As expected, treatment of **11b**, bearing a *N*-hydroxyl-*N*-methylamino group, with catalyst **2d·Br** induced a facile intramolecular ring closure to furnish pyrrolidinyl spirooxindole **12b** of high enantiomeric purity, which is of particular importance as a key structural motif in several natural alkaloids with distinct bioactivity profiles.[28] Chiral piperidinyl spirooxindole **12c** was also obtained with a good level of enantiocontrol in the reaction of **11c** having one carbon-elongated side chain (Scheme 6).



11a (R^1 = H, n = 1)
11b (R^1 = Me, n = 1)
11c (R^1 = Me, n = 2)

12a (R^1 = H, n = 1): trace
12b (R^1 = Me, n = 1): 64% yield, 97% ee
12c (R^1 = Me, n = 2): 66% yield, 88% ee

Scheme 6. Asymmetric Intramolecular Aminations.

4. Conclusion

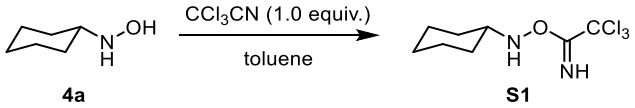
In conclusion, a new strategy have been developed for the direct incorporation of structurally diverse non-protected amines at the carbon atom adjacent to a carbonyl group with high levels of enantiocontrol in a single synthetic operation. This system is based on the *in situ* activation of readily available hydroxylamines by trichloroacetonitrile under mild conditions that are compatible with the phase-transfer catalysis of chiral 1,2,3-triazolium salts. The author anticipates that this modular and operationally simple method, which provides access to optically active α-aminocarbonyl compounds, will find numerous applications in chemical synthesis.

5. 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), JEOL JNM-ECZ400S (400 MHz) and JEOL JNM-ECA600II (600 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance (toluene-d_8; 2.08 ppm) or the tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept =septet, m = multiplet, and br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz), JEOL JNM-ECZ400S (101 MHz) and JEOL JNM-ECA600II (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$; 77.16 ppm, toluene-d_8; 20.43 ppm). ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) and JEOL JNM-ECZ400S (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (–64.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive (ESI). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on Silica gel 60 (Merck 1.09385.9929, 230-400 mesh), CHROMATOREX DIOL MB100-40/75 (spherical, 40~75 μm; Fuji Silysia Chemical ltd.), CHROMATOREX NH DM2035 (spherical, 60 μm; Fuji Silysia Chemical ltd.) and CHROMATOREX COOH MB100-40/75 (spherical, 40~75 μm; Fuji Silysia Chemical ltd.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALCEL OZ-3 (OZ3), CHIRALPAK AD-3 (AD3), CHIRALPAK IC-3 (IC3), CHIRALPAK ID-3 (ID3), CHIRALPAK IE-3 (IE3) and CHIRALPAK IF-3 (IF3)] with hexane (Hex), isopropyl alcohol (IPA) and ethanol (EtOH) as eluent.

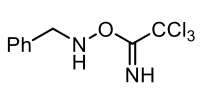
All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. Dichloromethane (CH_2Cl_2), 1,2-dichloroethane ($ClCH_2CH_2Cl$), diethyl ether (Et_2O), and tetrahydrofuran (THF) were supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by both A2 alumina and Q5 reactant using a GlassContour solvent dispensing system. 1,2,3-Triazolium salts **1·Br** and **2·Br** were synthesized by following the literature methods.[25] Other simple chemicals were purchased and used as such.

Pre-preparation and characterization of *O*-trichloroacetimino hydroxylamines:



4a **S1**

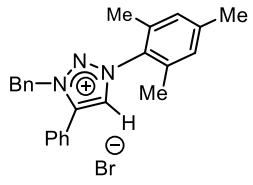
To a solution of **4a** (13.8 mg, 0.12 mmol) in toluene (1.0 mL) was added trichloroacetonitrile (12 μL, 0.12 mmol), and the resulting solution was stirred for 30 min at room temperature. After the solvent was removed, the resulting crude residue was purified by column chromatography on CHROMATOREX DIOL (Hex/EtOAc = 10:1 as eluent) to afford **S1** (24.7 mg, 0.095 mmol, 79% yield). **S1**: ^{1}H NMR for major isomer (400 MHz, toluene-d_8) δ 8.87 (1H, brs), 4.93 (1H, brd, J = 4.0 Hz), 2.51 (1H, br), 1.64-1.25 (5H, m), 1.13-0.72 (5H, m); ^{13}C NMR for major isomer (101 MHz, toluene-d_8) δ 162.8, 92.0, 59.5, 29.9, 26.0, 24.4; IR 3238, 3208, 2932, 2853, 1672, 1452, 1302, 1157, 1078, 926, 885, 795 cm^{-1}; HRMS (ESI) Calcd for $C_8H_{14}N_2OCl_3^+$ ([M+H]$^+$) 259.0166. Found 259.0166.



S2

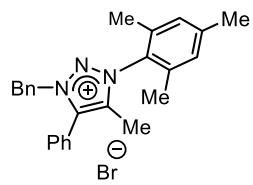
S2: ^{1}H NMR for major isomer (400 MHz, toluene-d_8) δ 8.75 (1H, brs), 7.13 (1H, t, J = 7.2 Hz), 7.07-7.03 (2H, m), 6.89 (2H, dd, J = 6.4, 2.4 Hz), 5.18 (1H, t, J = 6.0 Hz), 3.49 (2H, d, J = 6.0 Hz); ^{13}C NMR for major isomer (101 MHz, toluene-d_8) δ 162.0, 135.4, 129.3, 128.3, 91.7, 56.2, one peak for aromatic carbon was not found probably due to overlapping.; IR 3200, 3032, 2918, 2359, 1719, 1676, 1454, 1298, 1072, 914, 872, 795 cm^{-1}; HRMS (ESI) Calcd for $C_9H_{10}N_2OCl_3^+$ ([M+H]$^+$) 266.9853. Found 266.9849.

Characterization of 1,2,3-triazolium salts



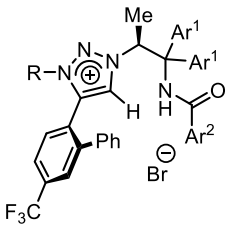
1a·Br

1a·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s), 7.98 (2H, d, J = 7.2 Hz), 7.58-7.51 (3H, m), 7.35-7.27 (3H, m), 7.12 (2H, d, J = 7.6 Hz), 7.02 (2H, s), 6.08 (2H, s), 2.34 (3H, s), 2.16 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.4, 134.4, 131.9, 131.8, 131.3, 131.2, 130.4, 129.8, 129.5, 129.4, 129.2, 128.2, 121.5, 56.5, 21.2, 18.0; IR 3649, 3389, 3028, 2982, 2359, 2180, 1607, 1454, 1186, 1020, 922, 723 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{24}N_3^+$ ([M]$^+$) 354.1965. Found 354.1962.



1b·Br

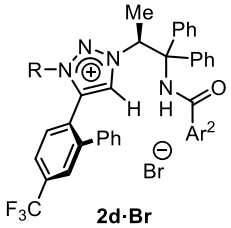
1b·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, dd, J = 6.8, 2.4 Hz), 7.51-7.47 (3H, m), 7.24-7.16 (3H, m), 7.01-6.99 (4H, m), 5.94 (2H, s), 2.30 (3H, s), 2.17 (3H, s), 2.06 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 140.9, 139.1, 135.0, 131.9, 131.7, 130.8, 129.9, 129.6, 129.2, 129.1, 128.3, 121.8, 56.8, 21.1, 17.8, 9.1, one peak for aromatic carbon was not found probably due to overlapping; IR 3647, 3389, 3032, 2918, 2172, 1827, 1607, 1447, 1331, 1055, 924, 725 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{26}N_3^+$ ([M]$^+$) 368.2121. Found 368.2120.



2b·Br

R = CH_2(4-CF_3)-C_6H_4
Ar^1 = 4-Cl-C_6H_4
Ar^2 = 3,5-$(MeO)_2$-C_6H_3

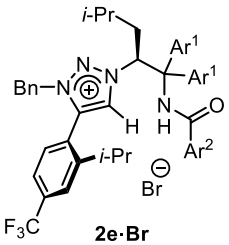
2b·Br: $[\alpha]_D^{25}$ = –11.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (1H, brs), 8.87 (1H, brs), 7.97 (1H, d, J = 8.0 Hz), 7.92 (1H, q, J = 6.8 Hz), 7.79 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 7.6 Hz), 7.70 (1H, s), 7.52 (2H, d, J = 8.0 Hz), 7.34 (2H, s), 7.33 (2H, d, J = 7.4 Hz), 7.28 (1H, t, J = 7.4 Hz), 7.10 (2H, t, J = 7.6 Hz), 7.01 (2H, d, J = 8.0 Hz), 6.88 (2H, d, J = 7.2 Hz), 6.80 (2H, brs), 6.75 (2H, d, J = 8.0 Hz), 6.58 (1H, t, J = 2.2 Hz), 5.11 (1H, d, J = 14.6 Hz), 5.02 (1H, d, J = 14.6 Hz), 3.83 (6H, s), 1.65 (3H, d, J = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 161.0, 144.0, 139.2, 137.9, 137.0, 135.4, 134.8 (q, $J_{C\text{-}F}$ = 33.8 Hz), 134.2, 133.8, 133.6, 133.1, 132.8, 132.5 (q, $J_{C\text{-}F}$ = 33.8 Hz), 130.7, 130.1, 129.5, 129.4, 129.4, 128.7, 128.6, 127.9, 127.6, 126.3 (q, $J_{C\text{-}F}$ = 3.9 Hz), 125.3, 123.8, 123.4 (q, $J_{C\text{-}F}$ = 277 Hz), 123.1 (q, $J_{C\text{-}F}$ = 277 Hz), 106.1, 105.5, 68.7, 65.5, 56.3, 55.2, 15.7, one peak for aromatic carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0, –63.1; IR 3211, 3011, 2963, 2839, 2253, 1674, 1593, 1493, 1323, 1130, 826, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{47}H_{37}N_4O_3F_6Cl_2^+$ ([M]$^+$) 889.2141. Found 889.2125.



2d·Br

R = CH_2(4-CF_3)-C_6H_4
Ar^2 = 3,5-$(CF_3)_2$-C_6H_3

2d·Br: $[\alpha]_D^{23}$ = –42.7 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (1H, brs), 9.72 (1H, brs), 8.75 (2H, s), 8.13 (1H, brm), 7.97 (1H, brs), 7.83 (2H, d, J = 7.2 Hz), 7.70 (1H, q, J = 6.8 Hz), 7.69 (1H, s), 7.60 (1H, d, J = 8.0 Hz), 7.46 (2H, d, J = 8.0 Hz), 7.34 (2H, t, J = 7.6 Hz), 7.27 (1H, t, J = 7.8 Hz), 7.20 (2H, t, J = 6.6 Hz), 7.09-7.04 (4H, m), 6.98 (2H, brs), 6.92 (2H, d, J = 7.2 Hz), 6.81 (2H, d, J = 8.0 Hz), 5.08 (1H, d, J = 14.6 Hz), 5.01 (1H, d, J = 14.6 Hz), 1.79 (3H, d, J = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 143.7, 139.4, 139.1, 137.2, 135.8, 134.7 (q, $J_{C\text{-}F}$ = 33.8 Hz), 134.5, 133.3, 133.2, 133.1, 132.3 (q, $J_{C\text{-}F}$ = 33.8 Hz), 131.7 (q, $J_{C\text{-}F}$ = 33.8 Hz), 129.8, 129.4, 129.2, 129.2, 128.9, 128.7, 128.3, 128.1, 127.8, 127.3, 126.2 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.4 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.5 (q, $J_{C\text{-}F}$ = 274 Hz), 123.3 (q, $J_{C\text{-}F}$ = 274 Hz), 123.1 (q, $J_{C\text{-}F}$ = 274 Hz), 69.8, 65.9, 55.1, 15.8, three peaks for aromatic carbons were not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4, –63.0, –63.3; IR 3219, 3022, 2359, 2210, 1682, 1526, 1450, 1325, 1277, 1126, 1016, 908, 845, 731 cm^{-1}; HRMS (ESI) Calcd for $C_{47}H_{33}N_4OF_{12}^+$ ([M]$^+$) 897.2457. Found 897.2438.



2e·Br

Ar^1 = 4-Cl-C_6H_4
Ar^2 = 3,5-Me_2-C_6H_3

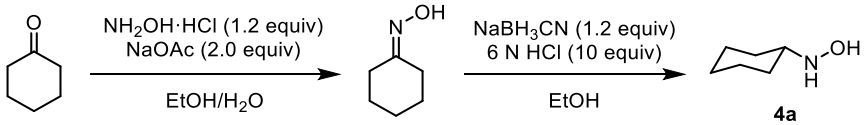
2e·Br: $[\alpha]_D^{28}$ = –45.4 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (1H, brs), 8.80 (1H, brs), 7.80 (2H, s), 7.76 (2H, br), 7.69 (1H, br), 7.64-7.59 (2H, m), 7.37 (2H, d, *J* = 8.4 Hz), 7.35-7.26 (8H, m), 7.05 (1H, s), 6.77 (2H, d, *J* = 7.2 Hz), 5.41 (1H, br), 5.30 (1H, brd, *J* = 15.2 Hz), 2.36-2.25 (1H, m), 2.31 (6H, s), 2.08 (1H, brt, 16.8 Hz), 1.88 (1H, dd, *J* = 14.4, 9.6 Hz), 1.33-1.23 (1H, m), 1.16 (3H, d, *J* = 6.4 Hz), 1.01 (3H, d, *J* = 6.8 Hz), 0.83 (3H, d, *J* = 6.8 Hz), 0.77 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 150.0, 138.9, 138.9, 138.2, 134.7 (q, $J_{C\text{-}F}$ = 33.2 Hz), 134.6, 134.1, 133.9, 133.8, 133.0, 132.9, 132.1, 130.3, 130.1, 129.9, 129.3, 128.7, 128.5, 127.9, 125.7, 123.7, 123.4, 123.3, 123.3 (q, $J_{C\text{-}F}$ = 273 Hz), 69.0, 68.8, 56.3, 38.0, 31.0, 25.6, 23.5, 23.1, 22.0, 21.0, one peak for aromatic carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.1; IR 3229, 3019, 2965, 2357, 1674, 1607, 1495, 1327, 1267, 1132, 1096, 1013, 839, 758 cm^{-1}; HRMS (ESI) Calcd for $C_{46}H_{46}N_4OF_3Cl_2^+$ ($[M]^+$) 797.2995. Found 797.2980.

Preparation and characterization of substrates

Synthesis of 3-substituted oxindoles 3:

N-Boc oxindoles were synthesized by following the literature methods.[29] These *N*-Boc oxindoles are known compounds, and their characterization date were in agreement with those reported in the literature.

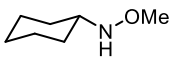
Synthesis of *N*-alkyl hydroxylamines:



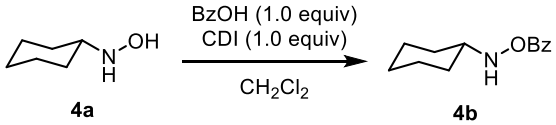
4a

To a solution of cyclohexanone (1.0 mL, 10 mmol) and hydroxylammonium chloride (0.83 g, 12 mmol) in ethanol (10 mL) and water (10 mL) was added sodium acetate (1.64 g, 20 mmol). The solution was stirred until ketone was consumed. The solvent was removed under vacuum, and the residue was diluted with water and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration and removal of solvent afforded oxime that was used for the next reaction without further purification. The crude oxime was suspended with ethanol (20 mL). Then, sodium cyanoborohydride (0.75 g, 12 mmol) was added to this mixture followed by the dropwise addition of a 6 N MeOH solution of HCl (16 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was poured into water and the whole mixture was neutralized with KOH pellet at 0 °C. The extractive work-up was performed with EtOAc, and the organic extracts were washed with brine and dried over Na_2SO_4. Evaporation to remove the solvent and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 3:1 to 1:1 as eluent) furnished **4a** (0.52 g, 4.5 mmol, 45%

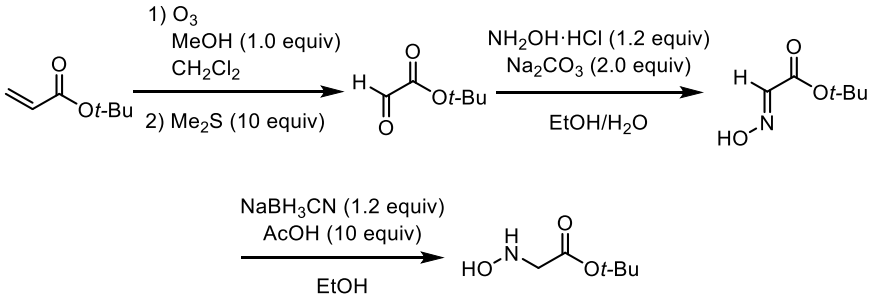
yield) as a white solid. **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, brs), 2.84-2.79 (1H, m), 1.92-1.62 (5H, m), 1.33-1.06 (5H, m).



N-Cyclohexyl-*O*-methylhydroxylamine was synthesized by following the above described method with *O*-methylhydroxylamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, brs), 3.54 (3H, s), 2.84 (1H, tt, *J* = 10.6, 3.8 Hz), 1.88-1.84 (2H, m), 1.77-1.73 (2H, m), 1.65-1.60 (1H, m), 1.33-1.05 (5H, m).



To a solution of carbonyldiimidazole (CDI) (0.16 g, 1.0 mmol) in CH_2Cl_2 (2.0 mL) was added benzoic acid (0.12 g, 1.0 mmol) at room temperature and the mixture was stirred for 30 min. Then, **4a** (0.11 g, 1.0 mmol) was introduced and the stirring was kept for additional 6 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. Extractive work-up was performed with EtOAc, and the organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 3:1 as eluent) gave **4b** (0.18 g, 0.82 mmol, 82% yield) as a colorless oil. **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, dd, *J* = 7.8, 1.2 Hz), 7.58 (1H, td, *J* = 7.8, 1.2 Hz), 7.46 (2H, t, *J* = 7.8 Hz), 3.09-3.03 (1H, m), 2.02-1.91 (2H, m), 1.82-1.79 (2H, m), 1.71-1.50 (1H, m), 1.38-1.18 (5H, m).



To a solution of *tert*-butyl acrylate (2.9 mL, 20 mmol) in CH_2Cl_2 (70 mL) was added MeOH (20 mmol, 0.85 mL) and the reaction flask was cooled to –78 °C. Then, ozone was bubbled into this solution for 30 min at the same temperature. The mixture was treated with dimethyl sulfide (200 mmol, 14.8 mL) to reduce the remaining ozone, and the whole reaction mixture was stirred for 12 h at room temperature. The resulting mixture was concentrated and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 5:1 as eluent) afforded *tert*-butyl glyoxylate (2.34 g, 18 mmol, 90% yield) as a colorless oil.

To a solution of *tert*-butyl glyoxylate (2.34 g, 18 mmol) and hydroxylammonium chloride (1.53 g, 22 mmol) in ethanol (18 mL) and water (18 mL) was added sodium carbonate (3.82 g, 36 mmol). The

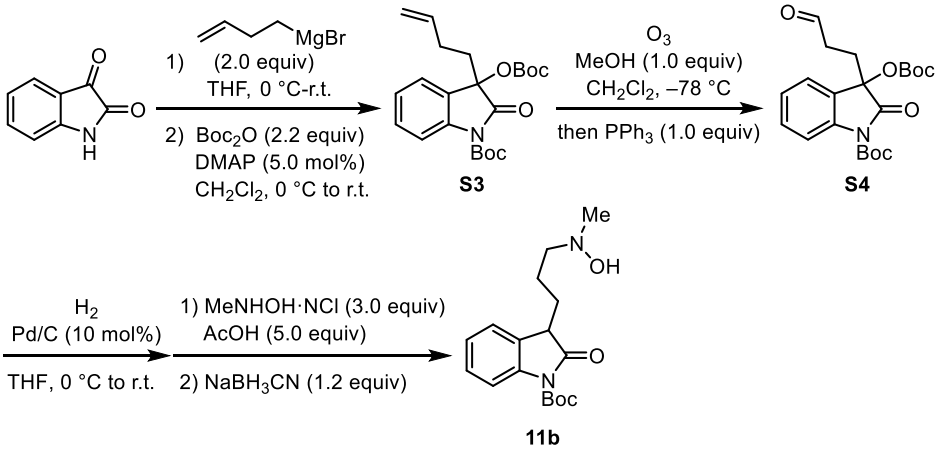
whole reaction solution was stirred for 6 h and then, the solvent was removed under vacuum. The residue was diluted with water and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 3:1 as eluent) furnished the corresponding oxime (2.44 g, 16.8 mmol, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (1H, brs), 7.47 (1H, s), 1.54 (9H, s).

This oxime (1.45 g, 10 mmol) was then suspended with ethanol (20 mL). Then, sodium cyanoborohydride (0.75 g, 12 mmol) was added to this mixture followed by the dropwise addition of acetic acid (5.7 mL, 100 mmol). After stirring for 12 h, the reaction mixture was poured into water and the whole mixture was neutralized with a saturated aqueous solution of $NaHCO_3$. The solvent was removed under vacuum and extractive work-up was performed with EtOAc. The organic extracts were dried over Na_2SO_4, and the solvents were evaporated. The crude residue was purified by column chromatography on silica gel (Hex/EtOAc = 2:1 as eluent) to give the corresponding hydroxylamine (0.35 g, 2.4 mmol, 24% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (2H, brs), 3.58 (2H, s), 1.50 (9H, s).

Synthesis of *N*-aryl hydroxylamines:

N-Aryl hydroxylamines were synthesized by following the literature methods.[30] These hydroxylamines are known compounds, and their characterization date were in agreement with those reported in the literature.

Synthesis of oxindole 11b for asymmetric intramolecular amination:

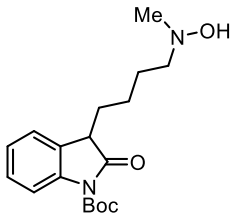


A solution of 1-butenyl magnesium bromide (1.0 M in THF, 20 mL, 20 mmol) was added to a stirred suspension of isatin (1.47 g, 10 mmol) in THF (50 mL) at 0 °C under argon, and this mixture was stirred at room temperature until isatin was consumed. The resulting mixture was diluted with a saturated aqueous solution of NH_4Cl and the extractive work-up was performed with EtOAc. After

drying over Na_2SO_4, filtration, and removal of solvent, the crude product was used for the next step without further purification. To a solution of the crude material in CH_2Cl_2 (50 mL) were added $(Boc)_2O$ (5.1 mL, 22 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (61 mg, 0.5 mmol) at room temperature and the mixture was stirred for 3 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the combined organic layers were washed with water and brine, and then dried over Na_2SO_4. Evaporation to remove the solvents and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 3:1 as eluent) afforded **S3** (3.0 g, 7.5 mmol, 75% yield) as an orange solid. **S3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 7.6 Hz), 7.38 (1H, td, *J* = 8.0, 1.2 Hz), 7.31 (1H, dd, *J* = 7.0, 1.2 Hz), 7.19 (1H, t, *J* = 7.4 Hz), 5.68 (1H, ddt, *J* = 17.2, 10.4, 6.2 Hz), 4.94 (1H, dd, *J* = 17.2, 1.6 Hz), 4.92 (1H, dd, *J* = 10.4, 1.6 Hz), 2.15-1.98 (4H, m), 1.66 (9H, s), 1.35 (9H, s).

To a solution of **S3** in CH_2Cl_2 (40 mL) was added MeOH (0.32 mL, 7.5 mmol) and the reaction flask was cooled to –78 °C. Then, ozone was bubbled into the reaction solution for 30 min with stirring at the same temperature. Triphenylphosphine (2.0 g, 7.5 mmol) was added to reduce the remaining ozone, and the whole mixture was stirred for additional 30 min at room temperature. After concentration of the reaction mixture, the crude residue was purified by column chromatography on silica gel (Hex/EtOAc = 3:1 as eluent) to give **S4** (1.5 g, 3.7 mmol, 49% yield) as a pale yellow oil. **S4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, s), 7.87 (1H, d, *J* = 8.0 Hz), 7.37 (1H, t, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 7.2 Hz), 7.18 (1H, t, *J* = 7.8 Hz), 2.41 (2H, t, *J* = 7.8 Hz), 2.00 (2H, t, *J* = 7.8 Hz), 1.65 (9H, s), 1.33 (9H, s).

Pd/C (39 mg, 0.37 mmol) was added to a solution of **S4** in THF (15 mL) at 0 °C, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 24 h at room temperature. After the filteration to remove Pd/C, *N*-methylhydroxylamine (0.93 g, 11.1 mmol) and acetic acid (1.05 mL, 18.5 mmol) were successively added to the resulting solution, and the mixture was stirred for 2 h at room temperature. Then, sodium cyanoborohydride (0.28 g, 4.5 mmol) was added and the stirring was maintained for additional 3 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, evaporation of the solvents and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 2:1 as eluent) furnished **11b** (0.58 g, 1.8 mmol, 49% yield) as a white solid. **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.4 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 7.24 (1H, d, *J* = 7.2 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 3.62 (1H, brt, *J* = 5.8 Hz), 2.63 (2H, t, *J* = 7.2 Hz), 2.56 (3H, s), 2.12-1.96 (2H, m), 1.71-1.43 (2H, m), 1.64 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 149.3, 140.2, 128.2, 127.8, 124.4, 123.7, 115.0, 84.3, 61.6, 48.3, 45.7, 28.9, 28.2, 23.2; IR 3308, 2980, 2253, 1728, 1609, 1464, 1350, 1290, 1146, 912, 843, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{25}N_2O_4^+$ ($[M+H]^+$) 321.1809. Found 321.1805.



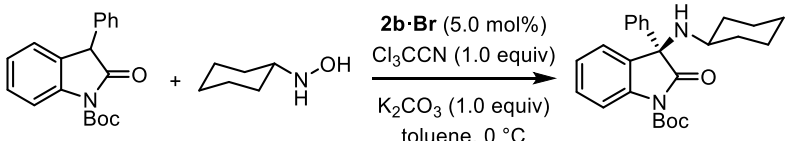
11c

Oxindole **11c** was prepared by the same procedure using 1-pentenyl magnesium bromide instead of 1-butenyl magnesium bromide.

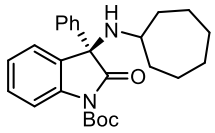
11c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, J = 8.0 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.23 (1H, d, J = 7.6 Hz), 7.15 (1H, t, J = 7.6 Hz), 6.71 (2H, br), 3.55 (1H, brt, J = 5.6 Hz), 2.67-2.55 (2H, m), 2.59 (3H, s), 2.06-1.93 (2H, m), 1.69-1.56 (2H, m), 1.64 (9H, s), 1.43-1.34 (2H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3, 149.4, 140.2, 128.2, 127.9, 124.4, 123.8, 115.0, 84.4, 61.8, 48.6, 46.0, 31.2, 28.2, 27.2, 23.5; IR 3242, 2936, 1726, 1609, 1464, 1350, 1292, 1148, 1094, 843, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{27}N_2O_4^+$ ([M+H]$^+$) 335.1965. Found 335.1960.

V. Representative procedure for catalytic asymmetric α-amination and characterization of products

Procedure for catalytic asymmetric α-amination of oxindoles and characterization of amination products 5:

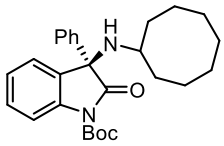


A solution of **2b·Br** (4.85 mg, 0.005 mmol), oxindole **3a** (30.9 mg, 0.10 mmol), hydroxylamine **4a** (17.3 mg, 0.15 mmol), and K_2CO_3 (13.8 mg, 0.10 mmol) in toluene (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. Then, the resulting mixture was cooled to 0 °C. After the introduction of trichloroacetonitrile (10 μL, 0.10 mmol) into the reaction flask, the stirring was kept for 24 h at the same temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the crude residue was purified by column chromatography on CHROMATOREX NH (Hex/EtOAc = 30:1 as eluent) to afford **5a** as a colorless oil (32.5 mg, 0.080 mmol, 80% yield, 99% ee). **5a**: $[\alpha]_D^{24}$ = +68.5 (c = 1.3, $CHCl_3$) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, dd, J = 8.0, 2.0 Hz), 7.43 (2H, dd, J = 8.2, 1.8 Hz), 7.34 (1H, td, J = 7.2, 1.2 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.30-7.23 (3H, m), 7.17 (1H, td, J = 8.2, 1.2 Hz), 2.36-2.30 (1H, m), 2.17 (1H, brs), 1.76-1.45 (5H, m), 1.64 (9H, s), 1.19-1.01 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 149.3, 141.7, 139.5, 130.4, 129.2, 128.7, 128.2, 126.3, 126.0, 124.6, 115.4, 84.6, 69.4, 53.3, 35.8, 35.1, 28.3, 25.8, 25.3, 25.1; IR 3327, 2928, 2853, 1767, 1728, 1607, 1472, 1342, 1287, 1146, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{31}N_2O_3^+$ ([M+H]$^+$) 407.2329. Found 407.2327.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.8 min (minor isomer), 14.2 min (major isomer).



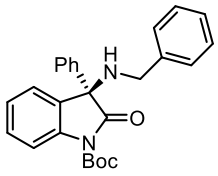
5b

5b: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +59.3 (c = 1.0, $CHCl_3$) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 8.4 Hz), 7.43 (2H, dt, *J* = 8.0, 1.6 Hz), 7.33 (1H, dt, *J* = 7.8, 1.2 Hz), 7.31-7.22 (4H, m), 7.17 (1H, t, *J* = 7.6 Hz), 2.58-2.52 (1H, m), 2.16 (1H, brs), 1.80-1.72 (1H, m), 1.64 (9H, s), 1.58-1.12 (11H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 149.3, 141.7, 139.6, 130.3, 129.2, 128.7, 128.2, 126.4, 126.1, 124.6, 115.3, 84.6, 69.7, 55.1, 37.2, 36.5, 28.7, 28.4, 28.3, 24.1, 23.8; IR 3325, 2926, 2855, 1765, 1728, 1605, 1464, 1342, 1285, 1146, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{33}N_2O_3^+$ ($[M+H]^+$) 421.2486. Found 421.2486.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.0 min (minor isomer), 12.5 min (major isomer).



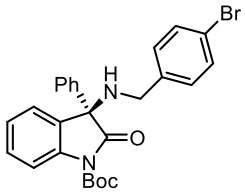
5c

5c: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +52.4 (c = 1.3, $CHCl_3$) for 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 7.6 Hz), 7.44 (2H, d, *J* = 6.8 Hz), 7.33 (1H, dt, *J* = 8.2, 1.0 Hz), 7.31-7.22 (4H, m), 7.16 (1H, td, *J* = 7.4, 1.2 Hz), 2.58-2.52 (1H, m), 2.15 (1H, brs), 1.75-1.22 (13H, m), 1.64 (9H, s), 1.10-1.01 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 149.3, 141.7, 139.6, 130.4, 129.2, 128.7, 128.1, 126.4, 126.1, 124.6, 115.3, 84.6, 69.8, 53.8, 34.2, 33.8, 28.2, 27.6, 27.2, 25.9, 23.9, 23.5; IR 3321, 2918, 1765, 1728, 1605, 1466, 1342, 1285, 1146, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{35}N_2O_3^+$ ($[M+H]^+$) 435.2642. Found 435.2640.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.0 min (minor isomer), 13.3 min (major isomer).



5d

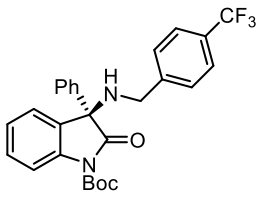
5d: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{23}$ = +11.5 (c = 1.2, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 8.0 Hz), 7.48 (2H, d, *J* = 7.2 Hz), 7.38 (2H, t, *J* = 8.0 Hz), 7.34-7.22 (8H, m), 7.20 (1H, t, *J* = 7.6 Hz), 3.63 (1H, d, *J* = 12.2 Hz), 3.46 (1H, d, *J* = 12.2 Hz), 2.54 (1H, brs), 1.66 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 149.2, 140.6, 139.8, 139.8, 129.7, 129.5, 128.8, 128.5, 128.4, 128.4, 127.3, 126.3, 125.4, 125.1, 115.5, 84.8, 69.9, 48.5, 28.3; IR 3318, 3030, 2978, 1763, 1730, 1605, 1466, 1342, 1287, 1148, 1001, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{27}N_2O_3^+$ ($[M+H]^+$) 415.2016. Found 415.2017.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.3 min (major isomer), 14.0 min (minor isomer).



5e

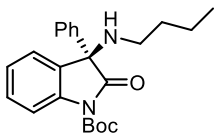
5e: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{23}$ = +41.0 (c = 1.0, $CHCl_3$) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.0 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.8 Hz), 7.38-7.25 (5H, m), 7.19 (1H, t, *J* = 8.0 Hz), 7.18 (2H, d, *J* = 8.0 Hz), 3.59 (1H, d, *J* = 12.0 Hz), 3.42 (1H, d, *J* = 12.0 Hz), 2.52, (1H, brs), 1.66 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 149.2, 140.5, 139.9, 138.9, 131.5, 130.1, 129.6, 129.5, 128.9, 128.5, 126.3,

125.4, 125.1, 121.1, 115.5, 84.9, 69.9, 47.9, 28.3; IR 3325, 3057, 2980, 2930, 1730, 1605, 1466, 1342, 1287, 1148, 1011, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_3Br^+$ ($[M+H]^+$) 493.1121. Found 493.1121.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.2 min (*S*), 9.2 min (*R*).



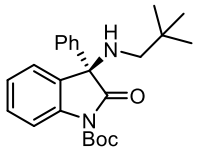
5f

5f: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{23}$ = +50.0 (c = 1.0, $CHCl_3$) for 99% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, dd, *J* = 8.6, 1.2 Hz), 7.54 (2H, d, *J* = 7.6 Hz), 7.48 (2H, d, *J* = 7.6 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 7.36 (2H, td, *J* = 7.3, 1.2 Hz), 7.31 (1H, d, *J* = 7.2 Hz), 7.29 (1H, t, *J* = 6.8 Hz), 7.19 (1H, t, *J* = 7.0 Hz), 3.71 (1H, d, *J* = 13.2 Hz), 3.52 (1H, d, *J* = 13.2 Hz), 2.57 (1H, brs), 1.67 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 149.2, 143.9, 140.3, 139.8, 129.6, 129.5 (q, J_{F-C} = 32.3 Hz), 129.4, 128.9, 128.6, 128.5, 126.3, 125.4, 125.2, 124.3 (q, J_{F-C} = 273 Hz), 115.6, 85.0, 69.9, 48.0, 28.3, one peak for aromatic carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.3; IR 3318, 3059, 2982, 2934, 1732, 1607, 1468, 1323, 1248, 1123, 1018, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{25}N_2O_3F_3Na^+$ ($[M+Na]^+$) 505.1709. Found 505.1707.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.3 min (major isomer), 8.3 min (minor isomer).



5g

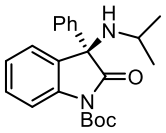
5g: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +68.6 (c = 0.8, $CHCl_3$) for 97% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 8.0 Hz), 7.42 (2H, dd, *J* = 8.2, 1.2 Hz), 7.33 (1H, td, *J* = 8.4, 1.6 Hz), 7.31-7.25 (4H, m), 7.17 (1H, t, *J* = 7.6 Hz), 2.44 (1H, dt, *J* = 10.8, 6.8 Hz), 2.24 (1H, brs), 2.22 (1H, dt, *J* = 10.8, 6.8 Hz), 1.64 (9H, s), 1.50-1.40 (2H, m), 1.36-1.25 (2H, m), 0.84 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 149.3, 140.8, 139.8, 130.0, 129.2, 128.8, 128.3, 126.3, 125.4, 124.9, 115.4, 84.7, 69.9, 43.9, 32.7, 28.3, 20.4, 14.1; IR 3389, 3053, 2932, 1771, 1603, 1464, 1344, 1287, 1142, 1003, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{29}N_2O_3^+$ ($[M+H]^+$) 381.2173. Found 381.2171.; HPLC IF3, Hex/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.2 min (minor isomer), 6.7 min (major isomer).



5h

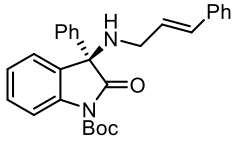
5h: Reaction was carried out with 5 M K_2CO_3 *aq.* in toluene (0.5 mL) at room temperature. Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{23}$ = +104.4 (c = 0.8, $CHCl_3$) for 97% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 8.0 Hz), 7.47 (2H, dt, *J* = 8.2, 1.4 Hz), 7.32 (1H, td, *J* = 7.6, 1.6 Hz), 7.30-7.23 (4H, m), 7.16 (1H, td, *J* = 7.3, 1.2 Hz), 2.30 (1H, d, *J* = 10.6 Hz), 2.22 (1H, brs), 1.85 (1H, d, *J* = 10.6 Hz), 1.66 (9H, s), 0.88 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 149.3, 141.4, 139.7, 130.3, 129.1, 128.8, 128.2, 126.2, 125.4, 124.9, 115.3, 84.7, 69.9, 55.3, 31.6, 28.3, 27.7; IR 3327, 3057, 2953, 1730, 1607, 1470, 1342, 1285, 1148, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_3Na^+$

([M+Na]$^+$) 417.2149. Found 417.2153.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 4.1 min (minor isomer), 4.8 min (major isomer).



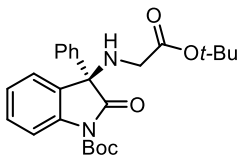
5i

5i: Reaction was carried out with 5 M K_2CO_3 *aq.* in toluene (0.5 mL) at room temperature. Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +72.3 (c = 1.2, $CHCl_3$) for 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 8.0 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 7.36-7.22 (5H, m), 7.18 (1H, td, *J* = 7.6, 1.2 Hz), 2.73 (1H, sept, *J* = 6.0 Hz), 2.16 (1H, brs), 1.64 (9H, s), 1.01 (3H, d, *J* = 6.0 Hz), 0.88 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 149.3, 141.6, 139.6, 130.2, 129.3, 128.7, 128.2, 126.3, 126.1, 124.7, 115.4, 84.6, 69.5, 46.0, 28.3, 25.5, 24.7; IR 3329, 3059, 2974, 1767, 1607, 1476, 1342, 1285, 1146, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{27}N_2O_3^+$ ([M+H]$^+$) 367.2016 Found 367.2016.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.6 min (minor isomer), 8.0 min (major isomer).



5j

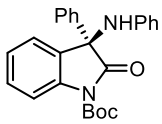
5j: Reaction was carried out with 5 M K_2CO_3 *aq.* in toluene (0.5 mL) at room temperature. Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +56.9 (c = 1.2, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 8.8 Hz), 7.45 (2H, d, *J* = 7.6 Hz), 7.36 (2H, t, *J* = 7.6 Hz), 7.33-7.25 (7H, m), 7.21 (2H, t, *J* = 7.6 Hz), 6.37 (1H, d, *J* = 16.2 Hz), 6.21 (1H, ddd, *J* = 16.2, 7.2, 5.6 Hz), 3.26 (1H, dd, *J* = 13.6, 7.2 Hz), 3.18 (1H, dd, *J* = 13.6, 5.6 Hz), 2.46 (1H, brs), 1.59 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 149.1, 140.6, 139.9, 137.0, 131.9, 129.5, 128.8, 128.6, 128.3, 127.8, 127.6, 126.5, 126.3, 125.5, 125.0, 115.5, 84.7, 69.5, 46.9, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3318, 3024, 2980, 1730, 1605, 1466, 1342, 1287, 1148, 968, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{28}N_2O_3Na^+$ ([M+Na]$^+$) 463.1992. Found 463.1993.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 12.5 min (major isomer), 17.7 min (minor isomer).



5k

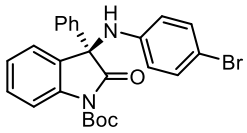
5k: Reaction was carried out with 5 M K_2CO_3 *aq.* in toluene (0.5 mL) at room temperature. Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{24}$ = +63.6 (c = 1.4, $CHCl_3$) for 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.4 Hz), 7.45 (2H, dd, *J* = 8.6, 1.4 Hz), 7.36-7.25 (5H, m), 7.17 (1H, t, *J* = 7.4 Hz), 3.20 (2H, s), 2.83 (1H, brs), 1.65 (9H, s), 1.42 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 170.7, 149.2, 139.8, 139.6, 129.6, 129.6, 128.8, 128.4, 126.5, 125.4, 125.1, 115.5, 84.8, 81.7, 68.6, 46.6, 28.2, 28.2; IR 3333, 3063, 2980, 1730, 1607, 1477, 1369, 1246, 1148, 1001, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{30}N_2O_5Na^+$ ([M+Na]$^+$) 461.2047. Found

461.2045.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.0 min (major isomer), 16.0 min (minor isomer).



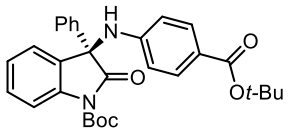
5l

5l: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +10.2 (c = 0.8, $ClCH_2CH_2Cl$) for 94% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 8.0 Hz), 7.51-7.49 (2H, m), 7.41-7.33 (5H, m), 7.19 (1H, t, *J* = 7.2 Hz), 7.01 (2H, t, *J* = 8.0 Hz), 6.69 (1H, t, *J* = 7.4 Hz), 6.34 (2H, d, *J* = 7.2 Hz), 4.62 (1H, brs), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 149.3, 144.7, 140.0, 139.4, 129.7, 129.2, 129.1, 129.0, 126.9, 125.4, 125.1, 119.4, 115.8, 115.5, 84.8, 68.1, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3395, 3055, 2982, 1730, 1601, 1501, 1342, 1287, 1146, 1003, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{24}N_2O_3Na^+$ ($[M+Na]^+$) 423.1679. Found 423.1674.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 7.6 min (minor isomer), 9.4 min (major isomer).



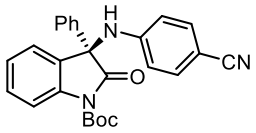
5m

5m: Purified by column chromatography on silica gel; $[\alpha]_D^{22}$ = +31.1 (c = 1.0, acetone) for 95% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 8.4 Hz), 7.48-7.45 (2H, m), 7.40 (1H, td, *J* = 8.4, 1.2 Hz), 7.37-7.33 (4H, m), 7.21 (1H, t, *J* = 7.0 Hz), 7.10 (2H, d, *J* = 9.0 Hz), 6.23 (2H, d, *J* = 9.0 Hz), 4.62 (1H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 149.2, 143.8, 139.5, 139.4, 132.0, 130.0, 129.3, 129.1, 128.7, 126.8, 125.3, 125.2, 117.1, 115.9, 111.5, 85.0, 68.0, 28.2; IR 3397, 3057, 2980, 1732, 1595, 1493, 1341, 1287, 1146, 908, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{23}N_2O_3BrNa^+$ ($[M+Na]^+$) 501.0784. Found 501.0785.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.6 min (minor isomer), 11.7 min (major isomer).



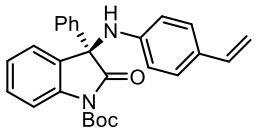
5n

5n: Purified by column chromatography on silica gel; $[\alpha]_D^{24}$ = +16.1 (c = 1.0, acetone) for 90% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.4 Hz), 7.67 (2H, d, *J* = 8.4 Hz), 7.48-7.46 (2H, m), 7.42 (1H, td, *J* = 7.8, 1.2 Hz), 7.37-7.35 (4H, m), 7.21 (1H, td, *J* = 7.6, 1.2 Hz), 6.30 (2H, d, *J* = 8.4 Hz), 4.95 (1H, s), 1.62 (9H, s), 1.51 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 165.8, 149.2, 148.3, 139.4, 139.2, 131.2, 130.1, 129.3, 129.3, 128.4, 126.9, 125.2, 122.4, 115.9, 113.7, 85.0, 80.1, 67.6, 28.4, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3366, 3061, 2978, 1732, 1605, 1476, 1341, 1288, 1148, 1007, 770 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{32}N_2O_5Na^+$ ($[M+Na]^+$) 523.2203. Found 523.2204.; HPLC OD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.6 min (major isomer), 9.2 min (minor isomer).



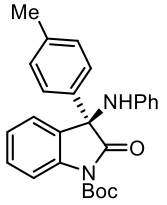
5o

5o: Purified by column chromatography on CHROMATOREX DIOL; $[\alpha]_D^{23}$ = +45.6 (c = 1.0, acetone) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.0 Hz), 7.47-7.43 (3H, m), 7.38-7.34 (4H, m), 7.29 (2H, d, *J* = 8.6 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 6.33 (2H, d, *J* = 8.6 Hz), 5.07 (1H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 149.1, 148.1, 139.2, 138.6, 133.6, 130.3, 129.5, 127.8, 126.8, 125.3, 125.1, 119.9, 116.1, 114.5, 101.2, 85.3, 67.4, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3360, 3059, 2982, 2216, 1732, 1605, 1516, 1464, 1337, 1285, 1146, 910, 827, 756 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{23}N_3O_3Na^+$ ([M+Na]$^+$) 448.1632. Found 448.1632.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 12.2 min (minor isomer), 27.3 min (major isomer).



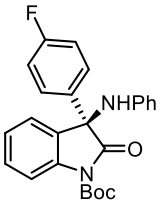
5p

5p: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +15.0 (c = 1.2, acetone) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 8.8 Hz), 7.50-7.47 (2H, m), 7.42-7.34 (5H, m), 7.20 (1H, d, *J* = 7.6 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 6.52 (1H, dd, *J* = 17.3, 11.0 Hz), 6.30 (2H, d, *J* = 8.0 Hz), 5.46 (1H, d, *J* = 17.3 Hz), 4.99 (1H, d, *J* = 11.0 Hz), 4.67 (1H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 149.3, 144.5, 139.8, 139.4, 136.5, 129.8, 129.2, 129.1, 129.1, 129.0, 127.3, 126.9, 125.3, 125.1, 115.8, 115.2, 110.6, 84.8, 68.0, 28.2; IR 3402, 3057, 2980, 1730, 1609, 1516, 1476, 1342, 1287, 1146, 829, 731 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 449.1836. Found 449.1838.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.4 min (minor isomer), 17.1 min (major isomer).



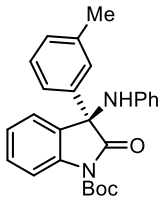
5q

5q: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +6.9 (c = 1.1, $ClCH_2CH_2Cl$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 8.8 Hz), 7.41-7.36 (4H, m), 7.19 (1H, t, *J* = 7.6 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 7.01 (2H, t, *J* = 7.6 Hz), 6.68 (1H, td, *J* = 7.6, 0.8 Hz), 6.32 (2H, d, *J* = 8.4 Hz), 4.60 (1H, s), 2.33 (3H, s), 1.60 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 149.3, 144.8, 139.3, 139.0, 137.0, 129.8, 129.6, 129.2, 126.8, 125.3, 125.0, 119.3, 115.7, 115.2, 84.7, 67.8, 28.2, 21.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3395, 3053, 2982, 1728, 1603, 1503, 1464, 1342, 1285, 1146, 910, 841, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 437.1836. Found 437.1839.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.5 min (minor isomer), 11.1 min (major isomer).



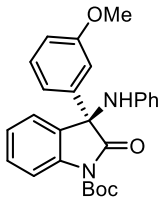
5r

5r: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = –10.1 (c = 0.8, acetone) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, d, J = 8.8 Hz), 7.48 (2H, dd, J = 9.0, $J_{F\text{-}H}$ = 5.2 Hz), 7.41 (1H, td, J = 8.6, 1.2 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.20 (1H, t, J = 8.0 Hz), 7.04 (2H, dd, J = 9.0, $J_{F\text{-}H}$ = 8.8 Hz), 7.02 (2H, t, J = 7.6 Hz), 6.71 (1H, t, J = 7.2 Hz), 6.35 (2H, d, J = 7.6 Hz), 4.53 (1H, brs), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 163.1 ($J_{F\text{-}C}$ = 250 Hz), 149.2, 144.5, 139.4, 135.6 ($J_{F\text{-}C}$ = 2.8 Hz), 129.9, 129.2, 129.0 ($J_{F\text{-}C}$ = 8.7 Hz), 128.9, 125.3, 125.2, 119.6, 116.1 ($J_{F\text{-}C}$ = 22.2 Hz), 115.9, 115.5, 85.0, 67.5, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –112.6; IR 3393, 3053, 1732, 1603, 1504, 1464, 1342, 1287, 1148, 812, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{23}N_2O_3FNa^+$ ([M+Na]$^+$) 441.1585. Found 441.1583.; HPLC IF3, Hex/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.8 min (minor isomer), 10.8 min (major isomer).



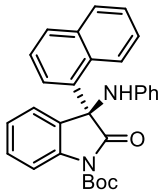
5s

5s: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +13.8 (c = 1.2, 1,2-dichloroethane) for 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 8.4 Hz), 7.41-7.37 (2H, m), 7.35 (1H, s), 7.24-7.22 (2H, m), 7.19 (1H, t, J = 7.6 Hz), 7.17-7.14 (1H, m), 7.01 (2H, t, J = 8.0 Hz), 6.69 (1H, t, J = 7.2 Hz), 6.33 (2H, dd, J = 8.0, 1.2 Hz), 4.61 (1H, brs), 2.33 (3H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 149.3, 144.7, 139.9, 139.4, 139.0, 129.8, 129.7, 129.2, 129.1, 129.0, 127.4, 125.4, 125.0, 123.9, 119.3, 115.7, 115.3, 84.8, 68.0, 28.2, 21.7; IR 3404, 3051, 2982, 1730, 1601, 1501, 1476, 1341, 1285, 1144, 1001, 910, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 437.1836. Found 437.1834.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.1 min (minor isomer), 8.0 min (major isomer).



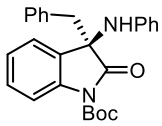
5t

5t: Purified by column chromatography on silica gel; $[\alpha]_D^{22}$ = +17.2 (c = 0.8, 1,2-dichloroethane) for 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, J = 8.6, 1.2 Hz), 7.41-7.36 (2H, m), 7.26 (1H, t, J = 8.0 Hz), 7.18 (1H, td, J = 7.2, 1.2 Hz), 7.08 (1H, t, J = 2.2 Hz), 7.03 (2H, t, J = 8.2 Hz), 7.00 (1H, dd, J = 8.2, 1.2 Hz), 6.87 (1H, dd, J = 8.4, 2.2 Hz), 6.69 (1H, t, J = 7.4 Hz), 6.34 (2H, dd, J = 8.2, 1.2 Hz), 4.62 (1H, brs), 3.77 (3H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 160.1, 149.3, 144.7, 141.5, 139.4, 130.1, 129.8, 129.2, 129.0, 125.3, 125.1, 119.4, 119.1, 115.7, 115.4, 114.2, 113.0, 84.8, 68.0, 55.5, 28.2; IR 3397, 3053, 2980, 1730, 1601, 1501, 1464, 1341, 1246, 1144, 1049, 908, 839, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_4Na^+$ ([M+Na]$^+$) 453.1785. Found 453.1786.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.1 min (minor isomer), 14.8 min (major isomer).



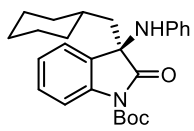
5u

5u: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +12.2 (c = 0.8, acetone) for 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (1H, dd, *J* = 8.8, 1.6 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.87 (1H, dd, *J* = 6.6, 3.0 Hz), 7.84 (1H, d, *J* = 8.0 Hz), 7.51-7.43 (3H, m), 7.39 (1H, td, *J* = 7.8, 1.2 Hz), 7.35 (1H, t, *J* = 8.0 Hz), 7.28 (1H, dd, *J* = 7.2, 1.2 Hz), 7.13 (1H, td, *J* = 7.2, 1.6 Hz), 7.03 (2H, td, *J* = 8.0, 1.2 Hz), 6.75 (1H, t, *J* = 7.4 Hz), 6.44 (2H, d, *J* = 8.0 Hz), 4.72 (1H, brs), 1.57 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 149.4, 143.9, 139.6, 135.1, 134.7, 130.7, 130.5, 130.0, 129.4, 129.0, 126.8, 126.6, 126.4, 125.9, 125.6, 125.2, 125.0, 120.1, 117.0, 115.6, 84.6, 70.0, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3387, 3051, 2980, 1728, 1601, 1503, 1464, 1339, 1287, 1144, 1084, 908, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 473.1836. Found 473.1839.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.2 min (minor isomer), 7.5 min (major isomer).



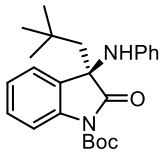
5s

5v: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +11.5 (c = 1.2, $CHCl_3$) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 8.0 Hz), 7.29-7.25 (2H, m), 7.17-7.13 (2H, m), 7.08 (2H, t, *J* = 7.2 Hz), 6.96 (2H, t, *J* = 7.8 Hz), 6.78 (2H, d, *J* = 7.6 Hz), 6.66 (1H, t, *J* = 7.2 Hz), 6.23 (2H, d, *J* = 7.6 Hz), 4.48 (1H, brs), 3.24 (2H, s), 1.53 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 148.6, 144.8, 139.2, 132.5, 130.3, 129.4, 129.3, 128.1, 127.9, 127.5, 124.8, 123.9, 119.4, 115.4, 115.2, 84.2, 66.2, 48.2, 28.1; IR 3387, 3030, 2980, 1790, 1732, 1601, 1497, 1344, 1288, 1146, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 437.1836. Found 437.1834.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.3 min (minor isomer), 9.8 min (major isomer).



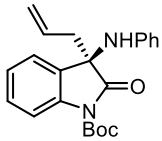
5w

5w: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +11.0 (c = 0.7, $CHCl_3$) for 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.0 Hz), 7.37 (1H, td, *J* = 8.0, 1.2 Hz), 7.31 (1H, d, *J* = 7.2 Hz), 7.17 (1H, t, *J* = 7.6 Hz), 6.95 (2H, td, *J* = 8.0, 1.2 Hz), 6.65 (1H, t, *J* = 7.4 Hz), 6.19 (2H, dd, *J* = 7.8, 1.2 Hz), 4.25 (1H, brs), 1.90 (2H, d, *J* = 5.6 Hz), 1.61 (9H, s), 1.58-1.41 (5H, m), 1.26-0.84 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 149.3, 144.9, 139.3, 129.4, 129.4, 129.2, 125.0, 124.0, 119.5, 115.6, 115.5, 84.5, 65.0, 49.2, 35.0, 34.7, 32.9, 28.2, 26.2, 26.2, 26.1; IR 3391, 3053, 2922, 1730, 1601, 1464, 1344, 1288, 1146, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{32}N_2O_3Na^+$ ([M+Na]$^+$) 443.2305. Found 443.2309.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.5 min (major isomer), 7.4 min (minor isomer).



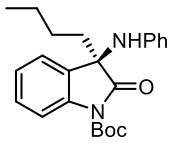
5x

5x: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +10.2 (c = 1.4, $CHCl_3$) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.2 Hz), 7.38-7.34 (2H, m), 7.16 (1H, t, *J* = 7.0 Hz), 6.95 (2H, td, *J* = 7.8, 1.2 Hz), 6.67 (1H, t, *J* = 7.4 Hz), 6.21 (2H, d, *J* = 8.0 Hz), 4.16 (1H, brs), 2.18 (1H, d, *J* = 13.4 Hz), 2.11 (1H, d, *J* = 13.4 Hz), 1.59 (9H, s), 0.72 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 149.3, 144.7, 139.7, 129.6, 129.2, 129.1, 125.1, 124.7, 119.9, 116.4, 115.6, 84.4, 64.7, 54.7, 31.3, 30.8, 28.2; IR 3393, 3053, 2955, 1728, 1601, 1477, 1344, 1285, 1144, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_3Na^+$ ([M+Na]$^+$) 417.2149. Found 417.2144.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.6 min (minor isomer), 7.3 min (major isomer).



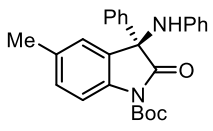
5t

5y: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = –13.0 (c = 0.8, $CHCl_3$) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.8 Hz), 7.36 (1H, td, *J* = 7.8, 1.2 Hz), 7.29 (1H, d, *J* = 6.8 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 6.97 (2H, t, *J* = 8.0 Hz), 6.66 (1H, t, *J* = 7.2 Hz), 6.20 (2H, d, *J* = 8.4 Hz), 5.72 (1H, dddd, *J* = 14.8, 11.6, 8.2, 6.8 Hz), 5.22 (1H, d, *J* = 14.8 Hz), 5.22 (1H, d, *J* = 11.6 Hz), 4.40 (1H, brs), 2.69 (1H, dd, *J* = 13.0, 6.8 Hz), 2.60 (1H, dd, *J* = 13.0, 8.2 Hz), 1.63 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 149.3, 144.8, 138.8, 130.0, 129.4, 129.3, 129.1, 125.0, 123.8, 121.7, 119.4, 115.7, 115.0, 84.7, 64.0, 45.7, 28.2; IR 3393, 3053, 2980, 1730, 1603, 1477, 1344, 1288, 1146, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{24}N_2O_3Na^+$ ([M+Na]$^+$) 387.1679. Found 387.1680.; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.2 min (minor isomer), 8.0 min (major isomer).



5u

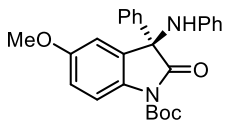
5z: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = –22.8 (c = 0.8, acetone) for 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.36 (1H, td, *J* = 7.6, 1.2 Hz), 7.30 (1H, dd, *J* = 6.6, 1.2 Hz), 7.17 (1H, t, *J* = 7.4 Hz), 6.96 (2H, t, *J* = 8.2 Hz), 6.65 (1H, t, *J* = 7.4 Hz), 6.21 (2H, d, *J* = 8.8 Hz), 4.32 (1H, brs), 1.98-1.93 (2H, m), 1.63 (9H, s), 1.30-1.05 (4H, m), 0.83 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 149.3, 145.1, 139.2, 129.4, 129.3, 129.3, 125.0, 123.8, 119.4, 115.6, 115.2, 84.7, 65.0, 41.7, 28.3, 24.8, 22.7, 13.9; IR 3389, 3053, 2932, 1730, 1603, 1464, 1344, 1287, 1142, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{28}N_2O_3Na^+$ ([M+Na]$^+$) 403.1992. Found 403.1985.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.0 min (major isomer), 6.8 min (minor isomer).



5Aa

5Aa: Purified by column chromatography on silica gel; $[\alpha]_D^{23}$ = +29.9 (c = 1.3, 1,2-dichloroethane) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 8.8 Hz), 7.50 (2H, dd, *J* = 7.8, 2.2 Hz), 7.38-7.33 (3H, m), 7.20 (1H, s), 7.19 (1H, d, *J* = 6.8 Hz), 7.02 (2H, t, *J* = 8.0 Hz), 6.70 (1H, t, *J* = 7.4 Hz), 6.35 (2H, d, *J* = 8.0 Hz), 4.61 (1H, s), 2.32 (3H, s), 1.60 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 149.3,

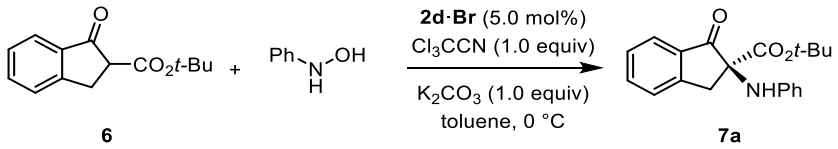
144.8, 140.1, 136.9, 134.8, 130.3, 129.2, 129.2, 129.1, 128.9, 126.8, 125.8, 119.3, 115.6, 115.3, 84.6, 68.1, 28.2, 21.3; IR 3404, 3055, 2980, 1730, 1601, 1489, 1333, 1298, 1152, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 437.1836. Found 437.1833.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.7 min (minor isomer), 9.5 min (major isomer).



5Ab

5Ab: Purified by column chromatography on silica gel; $[\alpha]_D^{22}$ = +25.1 (c = 0.9, 1,2-dichloroethane) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 9.2 Hz), 7.50 (2H, dd, *J* = 7.8, 2.4 Hz), 7.38-7.34 (3H, m), 7.02 (2H, t, *J* = 7.8 Hz), 6.95 (1H, d, *J* = 2.4 Hz), 6.91 (1H, dd, *J* = 9.0, 3.0 Hz), 6.70 (1H, t, *J* = 7.4 Hz), 6.36 (2H, d, *J* = 8.8 Hz), 4.61 (1H, s), 3.76 (3H, s), 1.60 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 157.3, 149.4, 144.7, 140.0, 132.6, 130.5, 129.3, 129.2, 129.0, 126.8, 119.4, 116.8, 115.3, 114.7, 111.2, 84.6, 68.3, 55.7, 28.2; IR 3399, 3057, 2980, 1728, 1601, 1487, 1369, 1277, 1150, 731 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_4Na^+$ ([M+Na]$^+$) 453.1785. Found 453.1789.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.3 min (minor isomer), 11.1 min (major isomer).

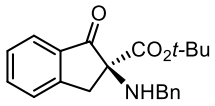
Procedure for catalytic asymmetric α-amination of 1-indanone derivative and characterization of amination product 7:



6 **7a**

A solution of **2d·Br** (4.88 mg, 0.005 mmol), 1-indanone derivative **6** (23.2 mg, 0.10 mmol), *N*-phenylhydroxylamine (16.4 mg, 0.15 mmol), and K_2CO_3 (13.8 mg, 0.10 mmol) in toluene (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. Then, the resulting mixture was cooled to 0 °C. After the introduction of trichloroacetonitrile (10 μL, 0.10 mmol) into the reaction flask, the stirring was kept for 24 h at the same temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the crude residue was purified by column chromatography on CHROMATOREX NH (Hex/EtOAc = 30:1 as eluent) to afford **7a** as a colorless oil (22.6 mg, 0.073 mmol, 73% yield, 90% ee). **7a**: $[\alpha]_D^{22}$ = +72.1 (c = 1.1, acetone) for 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 8.0 Hz), 7.68 (1H, t, *J* = 7.6 Hz), 7.53 (1H, d, *J* = 8.0 Hz), 7.44 (1H, t, *J* = 7.4 Hz), 7.14 (2H, dd, *J* = 8.0, 7.2 Hz), 6.75 (1H, td, *J* = 7.2, 1.2 Hz), 6.55 (2H, d, *J* = 8.0 Hz), 5.13 (1H, brs), 4.00 (1H, d, *J* = 17.0 Hz), 3.43 (1H, d, *J* = 17.0 Hz), 1.23 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.6, 153.0, 145.4, 136.2, 134.2, 129.4, 128.1, 126.6, 125.2, 118.9, 114.6, 83.3, 71.9, 38.8, 27.6; IR 3385, 3053, 2978, 1715, 1603, 1504, 1369, 1263, 1150, 937, 745 cm^{-1}; HRMS (ESI)

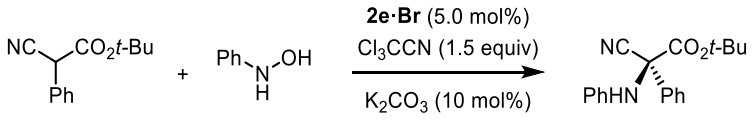
Calcd for $C_{20}H_{21}NO_3Na^+$ ([M+Na]$^+$) 346.1414. Found 346.1410.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.8 min (*S*), 9.9 min (*R*).



7b

7b: The reaction was carried out with **2d·Br** (10 mol%), *N*-benzylhydroxylamine (3.5 equiv.), trichloroacetonitrile (3.0 equiv.), and K_2CO_3 (1.0 equiv.) in toluene at 20 °C for 24 h. Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{26}$ = +10.3 (c = 2.1, acetone) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* = 7.6 Hz), 7.63 (1H, t, *J* = 7.2 Hz), 7.48 (1H, d, *J* = 7.2 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.35 (2H, d, *J* = 7.4 Hz), 7.30 (2H, t, *J* = 7.4 Hz), 7.24 (1H, t, *J* = 7.4 Hz), 3.80 (1H, d, *J* = 11.6 Hz), 3.74 (1H, d, *J* = 17.2 Hz), 3.73 (1H, d, *J* = 11.6 Hz), 3.21 (1H, d, *J* = 17.2 Hz), 2.79 (1H, br), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 169.7, 153.3, 139.9, 135.7, 134.7, 128.6, 128.4, 127.9, 127.3, 126.4, 125.0, 82.8, 73.8, 48.9, 37.5, 28.0; IR 3339, 3030, 2978, 2359, 1713, 1607, 1454, 1369, 1250, 1150, 1028, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{24}NO_3^+$ ([M+H]$^+$) 338.1751. Found 338.1750.; HPLC OZ3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 6.6 min (minor isomer), 10.1 min (major isomer).

Procedure for catalytic asymmetric α-amination of cyanoesters and characterization of amination products 9:

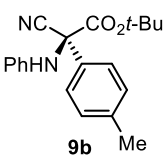


8 **9a**

A solution of **2e·Br** (4.39 mg, 0.005 mmol), *N*-phenylhydroxylamine (16.4 mg, 0.15 mmol), and K_2CO_3 (1.4 mg, 0.010 mmol) in ethylbenzene saturated with water[31] (3.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. The resulting mixture was cooled to 0 °C. After the introduction of trichloroacetonitrile (15 μL, 0.15 mmol), the stirring was kept for further 15 min at the same temperature. The mixture was then cooled to –40 °C, and cyanoester **8** (21.7 mg, 0.10 mmol) was added. After stirring at –40 °C for 24 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, and the extractive work-up was performed with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography on CHROMATOREX NH (Hex/EtOAc = 30:1 as eluent) to afford **9a** as a colorless oil (29.9 mg, 0.097 mmol, 97% yield, 92% ee). **9a**: $[\alpha]_D^{26}$ = +71.7 (c = 1.0, CH_2Cl_2) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, dd, *J* = 8.0, 2.0 Hz), 7.42-7.37 (3H, m), 7.12 (2H, t, *J* = 8.0 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.58 (2H, dd, *J* = 8.6, 1.0 Hz), 5.25 (1H, brs), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 142.3, 134.9, 129.6, 129.2, 126.3, 119.8, 116.9, 115.3, 86.2, 63.7, 27.5, one peak for aromatic carbon was not found probably due to overlapping; IR 3374, 3055, 2982, 2237,

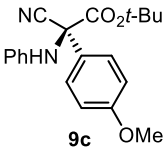
1748, 1605, 1506, 1371, 1258, 1150, 835, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{20}N_2O_2Na^+$ ($[M+Na]^+$) 331.1417. Found 331.1417.; HPLC ID3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 8.5 min (*R*), 9.4 min (*S*).

Comparison of the optical rotation with literature data revealed that the absolute configuration of **9a** was *S* ($[\alpha]_D^{26}$ = +71.2 (c = 1.0, CH_2Cl_2) for 92% ee; lit. (*S*)-**9a**[32]: $[\alpha]_D^{20}$ = +41 (*c* = 1.0, CH_2Cl_2) for 59% ee).



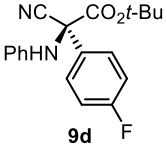
9b

9b: Purified by column chromatography on CHROMATREX NH; $[\alpha]_D^{27}$ = +25.5 (c = 1.0, CH_2Cl_2) for 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 8.0 Hz), 7.19 (2H, d, *J* = 8.0 Hz), 7.12 (2H, dd, *J* = 8.0, 7.2 Hz), 6.78 (1H, tt, *J* = 7.2, 0.8 Hz), 6.59 (2H, dd, *J* = 8.0, 0.8 Hz), 5.20 (1H, brs), 2.35 (3H, s), 1.40 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 142.4, 139.5, 131.8, 129.9, 129.2, 126.2, 119.7, 117.0, 115.3, 86.0, 63.5, 27.5, 21.2; IR 3383, 3055, 2980, 2236, 1744, 1603, 1503, 1368, 1271, 1258, 1144, 1044, 826, 745 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{22}N_2O_2Na^+$ ($[M+Na]^+$) 345.1573. Found 345.1575.; HPLC AD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 11.8 min (minor isomer), 18.6 min (major isomer).



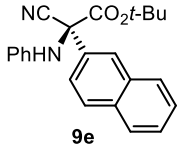
9c

9c: Purified by column chromatography on CHROMATREX NH; $[\alpha]_D^{26}$ = +21.4 (c = 1.0, CH_2Cl_2) for 94% ee; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 9.0 Hz), 7.13 (2H, t, *J* = 7.8 Hz), 6.91 (2H, d, *J* = 9.0 Hz), 6.78 (1H, t, *J* = 7.8 Hz), 6.60 (2H, d, *J* = 7.8 Hz), 5.18 (1H, brs), 3.81 (3H, s), 1.40 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 160.4, 142.4, 129.2, 127.6, 126.6, 119.7, 117.0, 115.3, 114.5, 86.0, 63.2, 55.4, 27.5; IR 3383, 3053, 2980, 2241, 1746, 1605, 1506, 1371, 1254, 1148, 831, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{22}N_2O_3Na^+$ ($[M+Na]^+$) 361.1523. Found 361.1521.; HPLC IC3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 9.3 min (minor isomer), 10.4 min (major isomer).



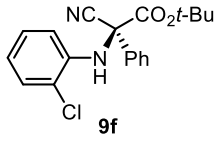
9d

9d: This reaction was carried out in ethylbenzene saturated with water (0.1 M). Purified by column chromatography on CHROMATREX NH; $[\alpha]_D^{27}$ = +36.7 (c = 1.0, CH_2Cl_2) for 87% ee; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (2H, dd, *J* = 8.4, J_{F-H} = 5.7 Hz), 7.14 (2H, t, *J* = 7.8 Hz), 7.10 (2H, dd, J_{F-H} = 9.0, *J* = 8.4 Hz), 6.80 (1H, t, *J* = 7.8 Hz), 6.57 (2H, d, *J* = 7.8 Hz), 5.25 (1H, brs), 1.41 (9H, s); ^{13}C NMR (151MHz, $CDCl_3$) δ 164.6, 163.3 (d, J_{F-C} = 249 Hz), 142.0, 130.7 (d, J_{F-C} = 2.9 Hz), 129.3, 128.3 (d, J_{F-C} = 8.8 Hz), 120.0, 116.6, 116.3 (d, J_{F-C} = 22.0 Hz), 115.4, 86.5, 63.1, 27.5; IR 3372, 3055, 2984, 2239, 1748, 1605, 1506, 1371, 1260, 1148, 833, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{19}N_2O_2FNa^+$ ($[M+Na]^+$) 349.1323. Found 349.1323.; HPLC AD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 10.4 min (minor isomer), 17.4 min (major isomer).



9e

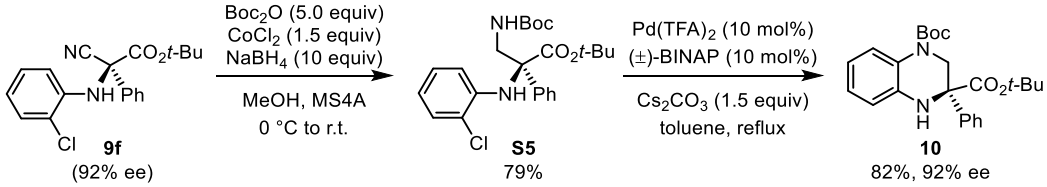
9e: Purified by column chromatography on CHROMATREX NH; $[\alpha]_D^{27}$ = +26.9 (c = 1.0, CH_2Cl_2) for 89% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, d, *J* = 1.2 Hz), 7.90-7.84 (3H, m), 7.72 (1H, dd, *J* = 8.8, 2.2 Hz), 7.56-7.52 (2H, m), 7.10 (2H, dd, *J* = 7.6, 7.2 Hz), 6.77 (1H, t, *J* = 7.2 Hz), 6.62 (2H, d, *J* = 7.6 Hz), 5.35 (1H, brs), 1.38 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 142.3, 133.7, 133.2, 132.3, 129.3, 129.2, 128.6, 127.8, 127.2, 126.9, 126.4, 123.0, 119.9, 116.9, 115.4, 86.4, 63.9, 27.5; IR 3381, 3055, 2982, 2237, 1746, 1605, 1506, 1371, 1260, 1148, 824, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{22}N_2O_2Na^+$ ([M+Na]$^+$) 381.1573. Found 381.1572.; HPLC AD3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 16.9 min (minor isomer), 27.4 min (major isomer).



9f

9f: Purified by column chromatography on CHROMATOREX NH; $[\alpha]_D^{26}$ = +124.5 (c = 1.0, CH_2Cl_2) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, dd, *J* = 8.0, 2.4 Hz), 7.43-7.39 (3H, m), 7.31 (1H, dd, *J* = 8.0, 1.6 Hz), 6.96 (1H, td, *J* = 7.8, 1.6 Hz), 6.71 (1H, td, *J* = 7.8, 1.6 Hz), 6.43 (1H, dd, *J* = 8.4, 1.6 Hz), 6.10 (1H, brs), 1.40 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 138.6, 134.3, 129.7, 129.5, 129.3, 127.5, 126.2, 120.8, 119.9, 116.5, 114.6, 86.6, 63.3, 27.5; IR 3383, 3067, 2982, 2241, 1748, 1597, 1501, 1371, 1275, 1150, 1038, 835, 745 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{19}N_2O_2ClNa^+$ ([M+Na]$^+$) 365.1027. Found 365.1026.; HPLC AD3, Hex/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 8.5 min (minor isomer), 10.3 min (major isomer).

Derivatization of 9f to tetrahydroquinoxaline 10:

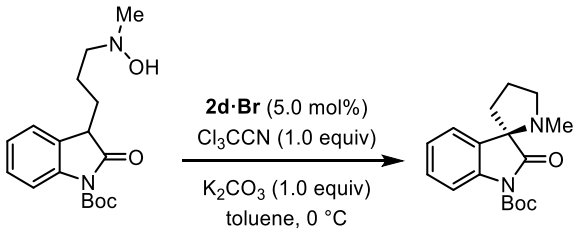


A solution of **9f** (34.3 mg, 0.10 mmol), cobalt(II) chloride anhydride (19.5 mg, 0.15 mmol), $(Boc)_2O$ (114 μL, 0.50 mmol) and *molecular sieve*s 4A (100 mg) in dry methanol (3.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. Then, sodium borohydride (37.8 mg, 1.0 mmol) was cautiously added to this solution at 0 °C. The mixture was stirred at room temperature for 5 h and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The extractive work-up was performed with EtOAc, and the combined organic extracts were washed with 0.2 M aqueous solution of EDTA·2Na. After drying over Na_2SO_4, filtration, and removal of solvent, the crude residue was purified by column chromatography on silica gel (Hex/EtOAc = 30:1 as eluent) to afford **S5** as a clear oil (35.3 mg, 0.079 mmol, 79% yield). **S5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, dd, *J* = 8.0, 1.6 Hz), 7.33 (2H, t, *J* = 7.6 Hz), 7.30-7.26 (2H, m), 6.78 (1H, td, *J* = 8.0, 1.2 Hz), 6.57 (1H, td, *J* = 7.6,

1.6 Hz), 6.27 (1H, brs), 6.08 (1H, dd, *J* = 8.4, 1.6 Hz), 4.73 (1H, brd, *J* = 8.4 Hz), 4.62 (1H, brdd, *J* = 12.4, 8.4 Hz), 3.84 (1H, brd, *J* = 12.4 Hz), 1.42 (9H, brs), 1.33 (9H, s).

A solution of **S5** (35.3 mg, 0.079 mmol), palladium(II) trifluoroacetate (2.6 mg, 0.008 mmol), (±)-BINAP (5.0 mg, 0.008 mmol) and cesium carbonate (38.6 mg 0.12 mmol) in dry toluene (0.8 mL) was degassed by alternating vacuum evacuation/Ar backfill. The reaction mixture was then refluxed with stirring for 48 h. After cooling to room temperature, the mixture was filtered with the aid of EtOAc and the resulting filtrates were concentrated. Purification of the crude residue by column chromatography on CHROMATOREX COOH (Hex/EtOAc = 20:1 as eluent) furnished **10** (26.3 mg, 0.064 mmol, 82% yield, 92% ee) as a white solid. **10**: $[\alpha]_D^{25}$ = +120.9 (c = 1.5, CH_2Cl_2) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 7.2 Hz), 7.45 (1H, br), 7.31 (2H, t, *J* = 7.2 Hz), 7.25 (1H, t, *J* = 6.8 Hz), 6.96 (1H, td, *J* = 7.6, 1.6 Hz), 6.80 (1H, dd, *J* = 8.2, 1.4 Hz), 6.68 (1H, td, *J* = 7.6, 1.2 Hz), 5.03 (1H, brs), 4.68 (1H, brd, *J* = 13.0 Hz), 3.57 (1H, brd, *J* = 13.0 Hz), 1.47 (9H, s), 1.25 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 152.8, 139.8, 135.6, 128.5, 128.0, 126.3, 124.8, 124.3, 124.2, 117.2, 114.6, 83.3, 80.9, 64.1, 28.1, 28.0, one peak for aliphatic carbon was not found probably due to overlapping or broadening; IR 3395, 2976, 2930, 1703, 1607, 1503, 1368, 1254, 1153, 843, 745 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_4Na^+$ ([M+ Na]$^+$) 433.2098. Found 433.2090.; HPLC AD3, Hex/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 19.0 min (minor isomer), 23.6 min (major isomer).

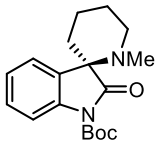
Procedure for catalytic asymmetric intramolecular amination:



11b **12b**

A solution of **2d·Br** (4.88 mg, 0.005 mmol), oxindole **11b** (32.0 mg, 0.10 mmol), and K_2CO_3 (13.8 mg, 0.10 mmol) in toluene (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. Then, the resulting mixture was cooled to 0 °C. After the introduction of trichloroacetonitrile (10 μL, 0.10 mmol) into the reaction flask, the stirring was kept for 24 h at the same temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the crude residue was purified by column chromatography on CHROMATOREX NH (Hex/EtOAc = 20:1 as eluent) to afford **12b** as a white solid (19.4 mg, 0.064 mmol, 64% yield, 97% ee). **12b**: $[\alpha]_D^{23}$ = +14.3 (c = 0.8, acetone) for 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8.0 Hz), 7.33-7.29 (2H, m), 7.18 (1H, td, *J* = 7.4, 1.2 Hz), 3.31-3.20 (2H, m), 2.31-2.07 (4H, m), 2.14 (3H, s), 1.64 (9H, s); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 177.5, 149.4, 140.2, 129.6, 129.1, 124.9, 123.9, 114.9, 84.3, 71.3, 54.1, 38.0, 35.3, 28.3, 22.3; IR 2976, 2843, 1728, 1609, 1466, 1346, 1292, 1146, 1094, 843, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{23}N_2O_3^+$ ($[M+H]^+$) 303.1703. Found 303.1703.; HPLC IF3, Hex/EtOH = 99:1, flow rate = 0.5 mL/min, column oven 15 °C, λ = 210 nm, 11.6 min (*R*), 13.2 min (*S*).

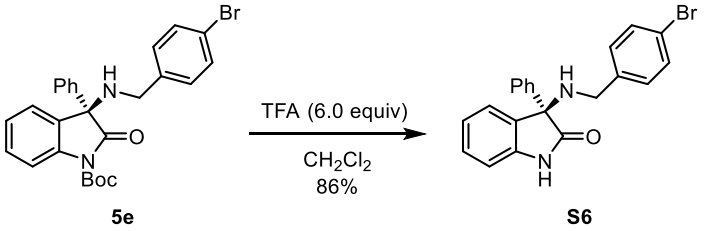


12c

12c: The reaction was carried out in toluene (0.03 M) at room temperature for 24 h. $[\alpha]_D^{26}$ = +49.2 (c = 0.9, acetone) for 88% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 8.0 Hz), 7.34 (1H, dd, *J* = 7.2, 0.8 Hz), 7.30 (1H, td, *J* = 8.0, 1.2 Hz), 7.18 (1H, dd, *J* = 8.0, 7.2 Hz), 3.32 (1H, td, *J* = 11.6, 3.6 Hz), 2.76 (1H, dt, *J* = 11.6, 3.6 Hz), 2.09-1.96 (1H, m), 2.03 (3H, s), 1.88-1.74 (3H, m), 1.69-1.59 (2H, m), 1.65 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 149.4, 139.2, 131.6, 128.8, 124.8, 123.6, 114.9, 84.3, 65.5, 50.2, 40.0, 35.7, 28.3, 25.8, 18.7; IR 2936, 2849, 2359, 1728, 1607, 1466, 1352, 1288, 1142, 1092, 845, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{25}N_2O_3^+$ ($[M+H]^+$) 317.1860. Found 317.1856.; HPLC IC3, Hex/IPA = 99:1, flow rate = 1.0 mL/min, column oven 15 °C, λ = 210 nm, 8.5 min (minor isomer), 9.5 min (major isomer).

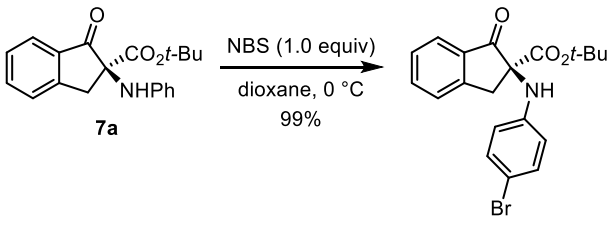
Determination of the absolute configuration of amination product:

The absolute configurations of **5e**, **7a**, and **12b** were unequivocally determined by X-ray crystallographic analysis after the derivatizations described as follows (see also VI Crystallographic Structure Determination).



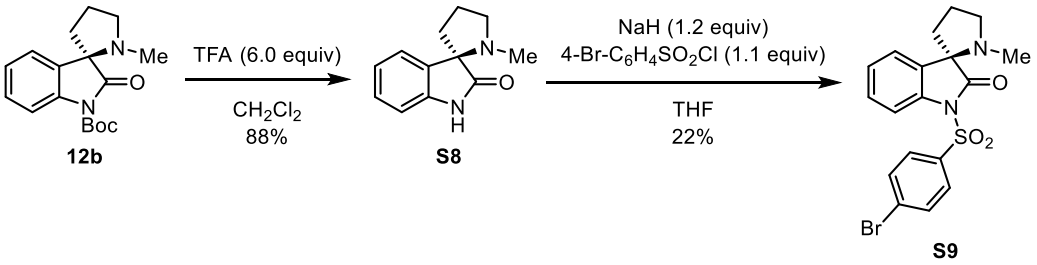
5e **S6**

To a solution of **5e** (32.0 mg, 0.065 mmol, 99% ee) in CH_2Cl_2 (0.7 mL) was added trifluoroacetic acid (TFA) (30 μL, 0.39 mmol), and the resulting solution was stirred for 17 h at room temperature. After cooling to 0 °C, the mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and the extractive workup was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the crude residue was purified by column chromatography on silica gel (Hex/EtOAc = 2:1 as eluent) to give **S6** (22.0 mg, 0.056 mmol, 86% yield). **S6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, br), 7.54 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 7.34-7.26 (5H, m), 7.23-7.19 (2H, m), 7.06 (1H, td, *J* = 7.2, 1.2 Hz), 6.92 (1H, d, *J* = 7.2 Hz), 3.62 (1H, d, *J* = 13.0 Hz), 3.42 (1H, d, *J* = 13.0 Hz), 2.46 (1H, br).



7a **S7**

To a solution of **7a** (23.6 mg, 0.073 mmol, 90% ee) in 1,4-dioxane (0.7 mL) was added *N*-bromosuccinimide (NBS) (13.0 mg, 0.073 mmol), and the resulting mixture was stirred for 5 min at 0 °C. The mixture was then diluted with water and the extractive workup was performed with EtOAc. The organic extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvents and purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 10:1 as eluent) furnished **S7** (29.4 mg, 0.073 mmol, 99% yield). **S7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 8.0 Hz), 7.69 (1H, td, *J* = 8.0, 1.2 Hz), 7.53 (1H, d, *J* = 8.0 Hz), 7.45 (1H, t, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 6.42 (2H, d, *J* = 8.4 Hz), 5.17 (1H, s), 3.96 (1H, d, *J* = 16.6 Hz), 3.38 (1H, d, *J* = 16.6 Hz), 1.24 (9H, s).



To a solution of **12b** (18.1 mg, 0.064 mmol, 97% ee) in CH_2Cl_2 (0.6 mL) was added trifluoroacetic acid (28 μL, 0.36 mmol) and the resulting solution was stirred for 17 h at room temperature. After cooling to 0 °C, the mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and the extractive workup was performed with EtOAc. After drying over Na_2SO_4 and subsequent filtration, the solvents was removed under vacuum. The crude residue was purified by column chromatography on silica gel (Hex/EtOAc = 2:1 as eluent) to afford **S8** (22.0 mg, 0.056 mmol, 88% yield). **S8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 7.2 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.04 (1H, t, J = 7.6 Hz), 6.85 (1H, d, J = 7.6 Hz), 3.34-3.28 (1H, m), 3.20-3.15 (1H, m), 2.35-2.10 (4H, m), 2.17 (3H, s).

To a solution of **S8** in THF (0.5 mL) was carefully added sodium hydride (2.2 mg, 0.055 mmol) at 0 °C. After 30 min of stirring, 4-bromobenzenesulfonylchloride (12.8 mg, 0.05 mmol) was added and the whole reaction mixture was stirred for 10 h at room temperature. The reaction was then quenched by the addition of water and the extractive workup was performed with EtOAc. The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the solvents followed by the purification of the crude residue by column chromatography on silica gel (Hex/EtOAc = 5:1 as eluent) gave **S9** (4.2 mg, 0.012 mmol, 22% yield). **S9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.4 Hz), 7.89 (1H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.36 (1H, td, J = 8.0, 2.0 Hz), 7.29 (1H, dd, J = 7.2, 1.2 Hz), 7.22 (1H, td, J = 7.2, 1.2 Hz), 3.18-3.07 (2H, m), 2.17-2.03 (4H, m), 1.84 (3H, s).

VI: Crystallographic structure determination

Recrystallization of S6, S7, and S9:

A single crystal of **S6** and **S9** were obtained from CH_2Cl_2/pentane solvent system at room temperature. Single crystals of **S7** was obtained from pentane at room temperature. The single crystals thus obtained were mounted on CryoLoop. Data of X-ray diffraction were collected at 123 K on a Rigaku FR-X with Pilatus diffractometer with fine-focus sealed tube Mo/Kα radiation (λ = 0.71075 Å). An absorption correction was made using Crystal Clear. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on F^2 by using SHELXL-2014.[33] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to nitrogen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions and isotropic thermal parameters refined. The crystallographic data were

summarized in Tables S1, S2 and S3. The three dimensional structures were shown in Figs. S1, S2, and S3.

Table S1. Crystal Data, Structure Refinement for **S6** (CCDC 1509736).

Empirical formula	$C_{21}H_{17}BrN_2O$	
Formula weight	393.27	
Temperature	293(2) K	
Wavelength	0.71069 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.280(5) Å	α = 90.000(5)°.
	b = 6.124(5) Å	β = 117.721(5)°.
	c = 13.194(5) Å	γ = 90.000(5)°.
Volume	878.3(9) $Å^3$	
Z	2	
Density (calculated)	1.487 Mg/m^3	
Absorption coefficient	2.351 mm^{-1}	
F(000)	400	
Crystal size	0.25 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.097 to 25.467°.	
Index ranges	–12<=h<=14, –5<=k<=7, –15<=l<=15	
Reflections collected	6204	
Independent reflections	2947 [R(int) = 0.0289]	
Completeness to theta = 25.240°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.762	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2947 / 1 / 234	
Goodness-of-fit on F^2	0.966	
Final R indices [I>2sigma(I)]	R_1 = 0.0269, wR_2 = 0.0613	
R indices (all data)	R_1 = 0.0292, wR_2 = 0.0616	
Absolute structure parameter	0.010(5)	
Extinction coefficient	0	
Largest diff. peak and hole	0.567 and –0.506 e.$Å^{-3}$	

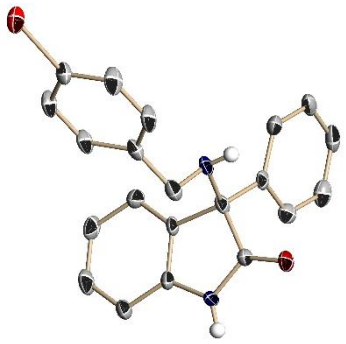


Figure S1. Molecular Structure of **S6**. Calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, bromine, grey = carbon.

Table S2. Crystal Data, Structure Refinement for **S7** (CCDC 1509662).

Empirical formula	$C_{20}H_{20}BrNO_3$	
Formula weight	402.28	
Temperature	123(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.6748(7) Å	α = 90°.
	b = 9.1072(10) Å	β = 90°.
	c = 30.371(4) Å	γ = 90°.
Volume	1846.2(4) $Å^3$	
Z	4	
Density (calculated)	1.447 Mg/m^3	
Absorption coefficient	2.245 mm^{-1}	
F(000)	824	
Crystal size	0.350 x 0.200 x 0.200 mm^3	
Theta range for data collection	3.009 to 25.498°.	
Index ranges	–8<=h<=6, –9<=k<=11, –36<=l<=36	
Reflections collected	11859	
Independent reflections	3344 [R(int) = 0.0327]	
Completeness to theta = 25.242°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.868	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3344 / 0 / 233	

Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R_1 = 0.0450, wR_2 = 0.1280
R indices (all data)	R_1 = 0.0514, wR_2 = 0.1303
Absolute structure parameter	0.021(4)
Extinction coefficient	0
Largest diff. peak and hole	1.360 and –0.693 e.Å^{-3}

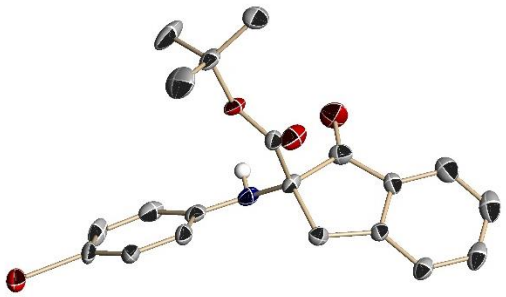


Figure S2. Molecular Structure of **S7**. Calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, bromine, grey = carbon.

Table S3. Crystal Data, Structure Refinement for **S9** (CCDC 1509683).

Empirical formula	$C_{18}H_{17}BrN_2O_3S$	
Formula weight	421.30	
Temperature	123(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.1772(13) Å	α = 90°.
	b = 10.2138(17) Å	β = 90°.
	c = 19.386(3) Å	γ = 90°.
Volume	1817.1(5) Å^3	
Z	4	
Density (calculated)	1.540 Mg/m^3	
Absorption coefficient	2.396 mm^{-1}	
F(000)	856	
Crystal size	0.400 x 0.300 x 0.300 mm^3	
Theta range for data collection	3.057 to 25.499°.	
Index ranges	–9<=h<=11, –12<=k<=12, –23<=l<=16	
Reflections collected	12678	
Independent reflections	3358 [R(int) = 0.0732]	

Completeness to theta = 25.242°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.830
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3358 / 0 / 227
Goodness-of-fit on F^2	0.858
Final R indices [I>2sigma(I)]	R_1 = 0.0287, wR_2 = 0.0596
R indices (all data)	R_1 = 0.0334, wR_2 = 0.0602
Absolute structure parameter	–0.001(8)
Extinction coefficient	0
Largest diff. peak and hole	0.285 and –0.308 e.Å^{-3}

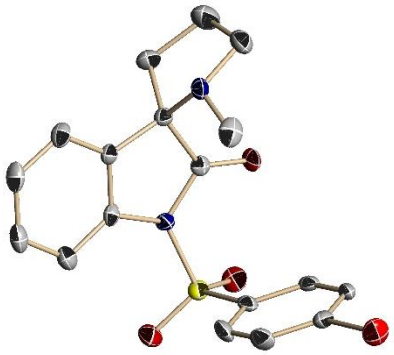


Figure S3. Molecular Structure of **S9**. Calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, bromine, yellow = sulfur, grey = carbon.

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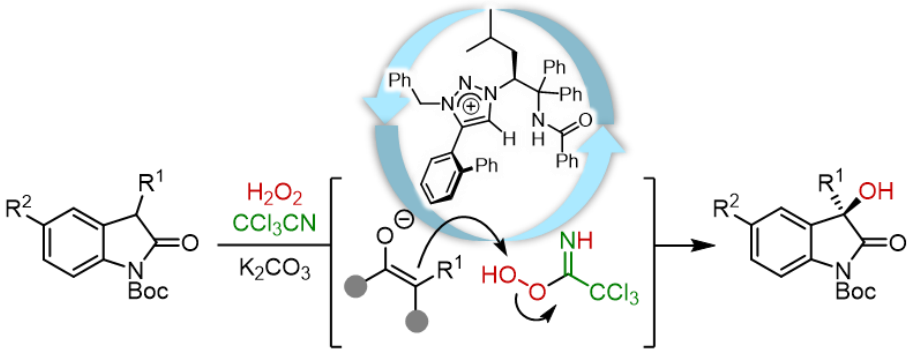
Chapter 4

In Situ Electrophilic Activation of Hydrogen Peroxide for Catalytic Asymmetric α-Hydroxylation of 3-Substituted Oxindoles

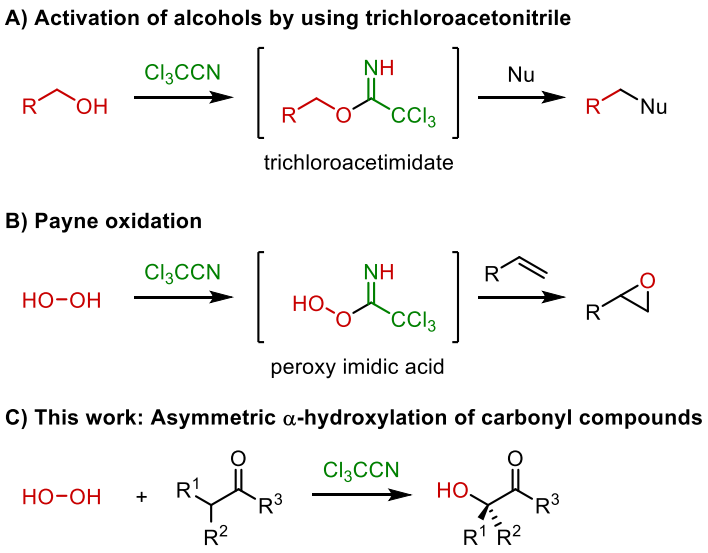


Abstract:

Peroxy trichloroacetimidic acid, *in situ* generated from aqueous hydrogen peroxide and trichloroacetonitrile, was found to act as a competent electrophilic oxygenating agent for the direct α-hydroxylation of oxindoles. The use of chiral 1,2,3-triazolium salt as a phase transfer catalyst enabled the rigorous stereocontrol of carbon–oxygen bond-forming reaction. The present study provides a new yet practical method for the straightforward access to optically active α-hydroxycarbonyl compounds.

1. Introduction

The conversion of hydroxyl group into better leaving group, such as acetoxy or sulfonyloxy, represents one of the most fundamental yet versatile activation processes for implementing subsequent bond-forming reactions. The facile generation of trichloroacetimidates from alcohols by the treatment with trichloroacetonitrile is a particularly unique example (Scheme 1A),[1,2] which has been classically utilized for glycosylation reactions.[3] The trichloroacetimidate is a reactive electrophile, yet compatible with Brønsted acid or hydrogen-bonding donor catalysis. The groundwork for this hydroxyl-group activation tactics was laid by Payne through the development of the epoxidation of alkenes by peroxy trichloroacetimidic acid generated *in situ* from hydrogen peroxide and trichloroacetonitrile under basic conditions (Scheme 1B).[4] In conjunction with our recent study on the establishment of a catalytic system for the direct asymmetric α-amination of carbonyl compounds based on the activation of hydroxylamines by trichloroacetonitrile as an electrophilic amine source,[5] the author became interested in the possibility of exploiting the reactivity of the peroxy imidic acid as an electrophilic oxygenating agent in achieving the direct installation of hydroxyl group onto the α-position of carbonyl compounds with hydrogen peroxide as a terminal oxidant (Scheme 1C).



Scheme 1 Transformations Based on the Activation of Hydroxyl Group with Trichloroacetonitrile.

The asymmetric hydroxylation of carbonyls is an efficient and straightforward method to access chiral tertiary α-hydroxycarbonyl compounds, which constitute structural components of many biologically active organic molecules and serve as versatile synthetic intermediates.[6] Although there has been a wide variety of successful examples that relied on the combined use of effective catalysts and appropriate oxygenating reagents, such as alkyl hydroperoxide,[7] dimethyldioxirane,[8] oxaziridine,[9] nitrosoarene,[10] and molecular oxygen,[11] reliable catalytic systems that can use abundant and safe-to-

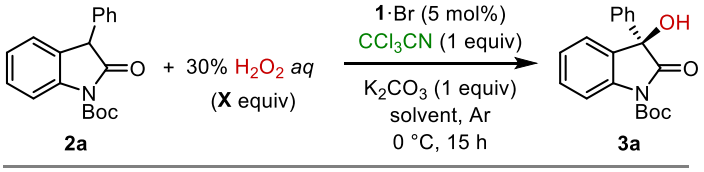
handle hydrogen peroxide as an oxidant are extremely scarce due to its low electrophilicity.[12] Here, the author communicates our solution to this problem through the development of a highly enantioselective direct α-hydroxylation of 3-substituted oxindoles under the catalysis of chiral 1,2,3-triazolium salts.

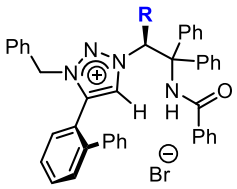
2. Result and Discussion

2.1. Optimization of the Reaction Conditions

As an initial attempt, the reaction was carried out by treating *N*-Boc-3-phenyloxindole (**2a**) with an excess amount of a 30% aqueous solution of hydrogen peroxide (20 equiv) in the presence of trichloroacetonitrile (1.0 equiv), potassium carbonate (1.0 equiv), and a catalytic quantity of *L*-alanine-derived chiral 1,2,3-triazolium bromide **1a**·Br (5 mol%) in toluene at 0 °C under argon atmosphere (Table 1, entry 1).[13] The carbon–oxygen bond formation proceeded smoothly, and the desired α-hydroxyoxindole **3a** was obtained with moderate enantioselectivity. It should be noted that no oxidation products were detected in the absence of trichloroacetonitrile and the substrate **2a** was recovered quantitatively (entry 2). This observation indicates the critical importance of the combination of hydrogen peroxide and trichloroacetonitrile in promoting the direct α-hydroxylation. For the improvement of stereoselectivity, the author evaluated the effect of the catalyst structure, specifically the aliphatic substituent (R) on the stereogenic center of amino acid origin, which led to the identification of L-leucine-derived triazolium salt **1c**·Br as an optimal candidate (entry 4). The subsequent screening of other solvents revealed the significant influence on the reactivity and selectivity profiles (entries 6-9). In particular, diethyl ether proved to be a solvent of choice, making it feasible to attain high reaction efficiency and enantioselectivity (entry 7). An additional insight the author gained from a control experiment was that the present hydroxylation could occur in the absence of the triazolium catalyst to give the racemic product (data not shown). The author assumed that this competitive background pathway could be suppressed by reducing the amount of hydrogen peroxide. Indeed, the use of 5 equivalents of hydrogen peroxide enabled higher enantiocontrol without notable rate retardation (entry 10). Finally, lowering the temperature to –10 °C with prolonged reaction time resulted in the formation of **3a** almost quantitatively with a satisfactory level of enantiomeric purity (entry 12).

Table 1. Optimization of reaction conditions[a]





1a·Br (**R** = Me)
1b·Br (**R** = CH_2Ph)
1c·Br (**R** = CH_2*i*-Pr)
1d·Br (**R** = *n*-Pr)

entry	**1**	solvent	H_2O_2 (**X** equiv)	yield (%)[b]	ee (%)[c]
1	**1a**	toluene	20	65	65
2[d]	**1a**	toluene	20	0	–
3	**1b**	toluene	20	77	79
4	**1c**	toluene	20	66	83
5	**1d**	toluene	20	82	79
6	**1c**	CH_2Cl_2	20	49	61
7	**1c**	Et_2O	20	80	90
8	**1c**	THF	20	10	24
9	**1c**	EtOAc	20	54	75
10	**1c**	Et_2O	5	83	92
11	**1c**	Et_2O	2	57	92
12[e]	**1c**	Et_2O	5	97	94

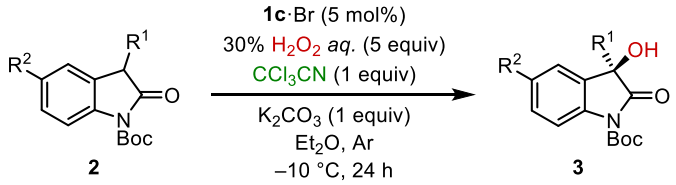
[a] Unless otherwise noted, reaction was conducted with **2a** (0.1 mmol), 30% aqueous solution of H_2O_2, CCl_3CN (1 equiv), K_2CO_3 (1 equiv), and **1·Br** (5 mol%) in solvent (1 mL) at 0 °C for 15 h under Ar. [b] Isolated yield. [c] Determined by HPLC with chiral column. [d] Without CCl_3CN. [e] Reaction was performed at –10 °C for 24 h.

2.2. Substrate Scope

The scope of the **1c**·Br-catalyzed asymmetric direct α-hydroxylation of 3-substituted oxindoles **2** was explored under the optimized conditions, and the representative results are summarized in Table 2. Generally, 5 mol% of **1c**·Br was sufficient for controlling the hydroxylation of a range of *N*-Boc oxindoles, giving rise to the corresponding chiral hydroxyoxindole **3** with uniformly high enantioselectivity. With respect to 3-aryl oxindoles, this protocol tolerated the incorporation of both electron-donating and electron-withdrawing substituents (entries 1-5). The reaction with 3-(1-naphthyl)oxindole showed slightly lower conversion (entry 6), whereas the product was isolated in excellent yield in the oxidation of **2** having 2-naphthyl substituent (entry 7). 3-Alkyl oxindoles also

appeared to be suitable nucleophiles, and similar degree of reactivity and selectivity was observed (entries 8-14). Moreover, this catalytic system well accommodated differently 5-substituted 3-pheyloxindoles (entries 15-17).

Table 2. Scope of substrate[a]



entry	R^1	R^2	**3**	yield (%)[b]	ee (%)[c]
1	4-Me-C_6H_5	H	**3b**	86	93
2	4-MeO-C_6H_5	H	**3c**	80	92
3	4-F-C_6H_5	H	**3d**	81	93
4	3-Me-C_6H_5	H	**3e**	89	90
5	3-MeO-C_6H_5	H	**3f**	90	93
6	1-Naph	H	**3g**	67	92
7	2-Naph	H	**3h**	93	90
8	Et	H	**3i**	58	94
9	*n*-Bu	H	**3j**	71	89
10	*c*-HexCH_2	H	**3k**	87	94
11	CH_2=$CHCH_2$	H	**3l**	96	95
12	$PhCH_2$	H	**3m**	97	97
13	4-MeO-$C_6H_4CH_2$	H	**3n**	96	94
14	4-F-$C_6H_4CH_2$	H	**3o**	89	98
15	Ph	Me	**3p**	90	94
16	Ph	MeO	**3q**	89	94
17	Ph	F	**3r**	71	90

[a] Reaction was conducted with **2** (0.1 mmol), 30% aqueous solution of H_2O_2 (5 equiv), CCl_3CN (1 equiv), K_2CO_3 (1 equiv), and **1c·Br** (5 mol%) in Et_2O (1 mL) at –10 °C for 24 h under Ar. [b] Isolated yield. [c] Determined by HPLC with chiral column.

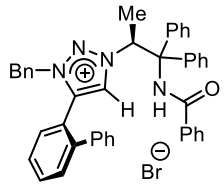
3. Conclusion

In conclusion, the author have developed a catalytic enantioselective α-hydroxylation of 3-substituted oxindoles with aqueous hydrogen peroxide. The judicious use of trichloroacetonitrile and chiral 1,2,3-triazolium salt for the electrophilic activation of hydrogen peroxide and the stereocontrol of carbon–oxygen bond formation, respectively, allows for the direct asymmetric transfer of hydroxyl group into the α-position of carbonyls. The author believe that this operationally simple yet powerful method will be further applied to the development of synthetically valuable asymmetric hydroxylation reactions.

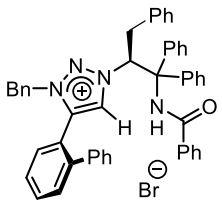
4. Experimental Section

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 tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept =septet, m = multiplet, and 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 as the internal standard ($CDCl_3$; 77.16 ppm). ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (–64.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on PSQ60AB (spherical, av. 55 μm; Fuji Silysia Chemical ltd.) and Silica gel 60 (Merck 1.09385.9929, 230-400 mesh). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALCEL OZ-3 (OZ3), CHIRALPAK AS-H (ASH) and CHIRALPAK ID-3 (ID3) with hexane (Hex), isopropyl alcohol (IPA) and ethanol (EtOH) as eluent. All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by passing through neutral alumina under nitrogen atmosphere. Ethyl Acetate (EtOAc) was purchased from Wako Pure Chemical Industries, Ltd. as “Dehydrated”. 1,2,3-Triazolium salts **1·X** were synthesized by following the literature methods.[13] Other simple chemicals were purchased and used as such.

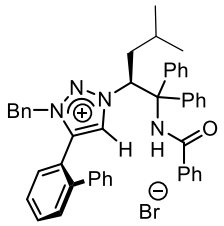
Characterization of 1,2,3-Triazolium Salt 1▪Br



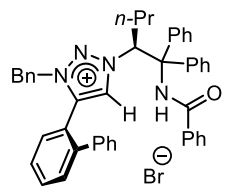
1a·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (1H, brs), 8.65 (1H, brs), 8.20 (2H, d, *J* = 6.9 Hz), 7.87-7.82 (3H, m), 7.64 (1H, t, *J* = 7.6 Hz), 7.45-7.29 (8H, m), 7.27-7.22 (2H, m), 7.20-7.14 (4H, m), 7.03-6.97 (4H, m), 6.91-6.84 (4H, m), 6.55 (2H, d, *J* = 7.8 Hz), 4.85 (2H, s), 1.63 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 142.9, 140.3, 139.9, 138.5, 135.3, 133.7, 132.9, 132.4, 132.0, 131.9, 131.1, 130.2, 129.9, 129.4, 129.2, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.2, 120.3, 69.4, 65.9, 55.2, 15.8, two peaks for aromatic carbons were not found probably due to overlapping; IR 3221, 2934, 1672, 1520, 1275, 1148, 746, 702 cm^{-1}; HRMS (ESI) Calcd for $C_{43}H_{37}N_4O^+$ ([M]$^+$) 625.2962. Found 625.2969.; $[\alpha]_D^{22}$ = –44.3 (c = 1.0, MeOH).



1b·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (1H, brs), 9.07 (1H, brs), 8.29 (2H, brd), 8.20-7.98 (3H, m), 7.61 (1H, t, *J* = 7.6 Hz), 7.47-7.43 (6H, m), 7.37 (1H, t, *J* = 7.3 Hz), 7.31 (2H, t, *J* = 7.4 Hz), 7.28 (2H, t, *J* = 7.8 Hz), 7.22 (2H, t, *J* = 7.6 Hz), 7.18-7.06 (7H, m), 7.06-6.96 (5H, m), 6.96-6.92 (2H, m), 6.42 (2H, d, *J* = 7.3 Hz), 4.76 (2H, brs), 3.55 (1H, brd, *J* = 14.6 Hz), 3.03 (1H, dd, *J* = 14.6, 11.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 142.4, 140.3, 139.9, 138.2, 135.4, 134.6, 133.5, 132.9, 132.4, 132.0, 131.8, 130.8, 130.3, 129.6, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.1, 127.1, 119.8, 70.4, 69.1, 55.1, 35.4, four peaks for aromatic carbons were not found probably due to overlapping; IR 3219, 3029, 2193, 1967, 1674, 1486, 1290 cm^{-1}; HRMS (ESI) Calcd for $C_{51}H_{45}N_4O^+$ ([M]$^+$) 701.3275. Found 701.3267.; $[\alpha]_D^{27}$ = –39.0 (c = 1.0, MeOH).



1c·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (1H, brs), 8.71 (1H, brs), 8.25 (2H, brs), 7.83 (2H, brs), 7.67 (2H, m), 7.52-7.36 (8H, m), 7.29-7.05 (12H, m), 6.89 (2H, brs), 6.64 (2H, d, *J* = 7.3 Hz), 5.04 (2H, brs), 1.86 (2H, brm), 1.07 (3H, d, *J* = 6.4 Hz), 0.91, (1H, m), 0.63 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 142.7, 140.4, 138.5, 133.5, 132.3, 132.1, 131.8, 130.8, 130.5, 129.7, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.1, 69.1, 68.7, 55.6, 38.4, 25.5, 23.2, 22.0, five peaks for aromatic carbons were not found probably due to overlapping; IR 3030, 2957, 1674, 1519, 1485, 1287, 1146 cm^{-1}; HRMS (ESI) Calcd for $C_{48}H_{39}N_4OF_6Cl_2^+$ ([M]$^+$) 667.3431. Found 667.3429.; $[\alpha]_D^{19}$ = +35.4 (c = 1.0, $CHCl_3$).

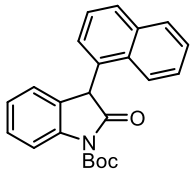


1d·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (1H, brs), 8.51 (1H, brs), 8.20 (2H, d, *J* = 6.2 Hz), 7.79 (2H, brs), 7.66 (2H, td, *J* = 7.7, 1.2 Hz), 7.51-7.35 (9H, m), 7.30-7.15 (9H, m), 7.07 (2H, t, *J* = 7.6 Hz), 6.85 (2H, d, *J* = 7.1 Hz), 6.64 (2H, d, *J* = 7.5 Hz), 5.07 (2H, brs), 2.13-2.07 (1H, m), 1.90-1.81 (1H, m), 1.33-1.25

(1H, m), 0.84-0.75 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 142.8, 140.6, 138.6, 133.7, 133.1, 132.4, 132.2, 131.9, 130.8, 130.6, 129.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.6, 128.4, 128.3, 128.3, 127.8, 127.7, 127.4, 120.3, 70.4, 69.1, 55.8, 31.9, 19.3, 13.7, three peaks for aromatic carbons were not found probably due to overlapping; IR 3235, 2932, 1674, 1485, 1285, 1146, 748, 704 cm^{-1}; HRMS (ESI) Calcd for $C_{45}H_{41}N_4O^+$ ([M]$^+$) 653.3275. Found 653.3270.; $[\alpha]_D^{22}$ = –27.7 (c = 1.0, MeOH).

Preparation of 3-Substituted Oxindole:

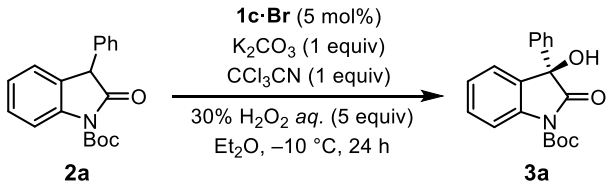
N-Boc oxindoles were synthesized by following the literature methods.[14] Substrates **2a-f** and **2h-2r** are known compounds, and their characterization date were in agreement with those reported in the literature. Unknown compound **2g** was characterized.



2g

2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, brs), 8.00 (1H, d, *J* = 8.7 Hz), 7.89 (1H, d, *J* = 8.2 Hz), 7.82 (1H, d, *J* = 8.2 Hz), 7.53 (2H, brm), 7.38 (2H, t, *J* = 8.0 Hz), 7.11 (3H, brm), 5.64 (1H, brs), 1.64 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 149.6, 140.6, 134.4, 129.0, 128.7, 128.2, 126.8, 126.1, 125.7, 125.5, 124.8, 124.0, 115.3, 84.5, 53.5, 28.2, four peaks for aromatic carbons were not found probably due to overlapping; IR 3049, 2982, 2253, 1768, 1607, 1479, 1288, 1145, 912, 773 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{21}NO_3Na^+$ ([M+Na]$^+$) 382.1414. Found 382.1414.

General Procedure for 1c·Br-Catalyzed Asymmetric α-Hydroxylation of Oxindole 2:

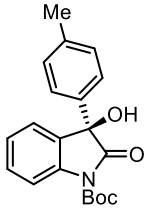


2a **3a**

A solution of **1c·Br** (3.76 mg, 0.005 mmol), oxindole **2a** (30.9 mg, 0.10 mmol) and K_2CO_3 (13.8 mg, 0.10 mmol) in Et_2O (1.0 mL) was degassed by alternating vacuum evacuation/Ar backfill. Then the resulting mixture was cooled to –10 °C. To this solution was added 30% H_2O_2 *aq.* (50 μL, 0.50 mmol) and CCl_3CN (10 μL, 0.10 mmol), then the mixture was stirred for 24 h. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and the extractive work-up was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the resulting crude residue was purified by column chromatography using CHROMATOREX DIOL MB100-40/75 (Hex/$CHCl_3$ = 3:1 as eluent) to afford **3a** (28.6 mg, 0.088 mmol, 88% yield) as a white solid. **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 8.2 Hz), 7.40 (1H, dt, *J* = 8.0, 1.2 Hz), 7.36-7.29 (6H, m), 7.20 (1H, t, *J* = 7.8 Hz), 3.42 (1H, s), 1.63 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 149.2, 139.9,

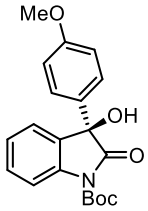
139.8, 130.3, 128.8, 128.7, 125.7, 125.4, 125.2, 115.6, 85.0, 77.8, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR 3456, 3001, 2978, 1788, 1609, 1479, 1342, 1285, 1146, 908, 719 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{19}NO_4Na^+$ ([M+Na]$^+$) 348.1206. Found 348.1206.; HPLC ID3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.8 min (major isomer), 17.5 min (minor isomer). $[\alpha]_D^{23}$ = +45.6 (c = 3.0, $CHCl_3$).

Characterization of Hydroxylation Products 3:



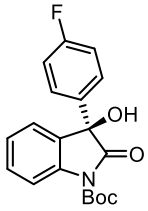
3b

3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.39 (1H, t, *J* = 8.1 Hz), 7.31 (1H, d, *J* = 7.6 Hz), 7.23 (2H, d, *J* = 8.4 Hz), 7.19 (1H, t, *J* = 7.7 Hz), 7.13 (2H, d, *J* = 8.4 Hz), 3.33 (1H, s), 2.31 (3H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 149.2, 139.8, 138.6, 137.0, 130.3, 130.2, 129.5, 125.6, 125.4, 125.2, 115.5, 84.9, 77.7, 28.2, 21.2; IR 3482, 2984, 2932, 1730, 1609, 1468, 1369, 1285, 1146, 999, 732 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_4Na^+$ ([M+Na]$^+$) 362.1363. Found 362.1364.; HPLC OD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.5 min (minor isomer), 7.2 min (major isomer). $[\alpha]_D^{24}$ = +37.6 (c = 2.6, $CHCl_3$).



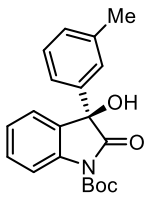
3c

3c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.40 (1H, dt, *J* = 8.1, 1.6 Hz), 7.33 (1H, dd, *J* = 7.6, 0.7 Hz), 7.28 (2H, d, *J* = 9.2 Hz), 7.21 (1H, dt, *J* = 7.7, 0.9 Hz), 6.85 (2H, d, *J* = 9.2 Hz), 3.78 (3H, s), 3.30 (1H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 159.9, 149.2, 139.7, 131.9, 130.3, 130.2, 127.2, 125.4, 125.2, 115.5, 114.2, 84.9, 55.4, 28.2, one peak for aliphatic carbon was not found probably due to overlapping; IR 3445, 2974, 2932, 1730, 1607, 1464, 1342, 1248, 1146, 999, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_5Na^+$ ([M+Na]$^+$) 378.1312. Found 378.1311.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 12.5 min (major isomer), 15.0 min (minor isomer). $[\alpha]_D^{24}$ = +22.5 (c = 2.2, $CHCl_3$).



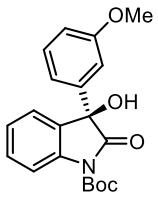
3d

3d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.41 (1H, dt, *J* = 7.8, 1.6 Hz), 7.35-7.28 (3H, m), 7.21 (1H, dt, *J* = 7.8, 0.9 Hz), 7.01 (2H, t, *J* = 8.9 Hz), 3.41 (1H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 163.0 (d, $J_{F\text{-}C}$ = 254.3 Hz), 149.1, 139.7, 135.6 (d, $J_{F\text{-}C}$ = 2.9 Hz), 130.5, 130.0, 127.8 (d, $J_{F\text{-}C}$ = 8.7 Hz), 125.5, 125.1, 115.7 (d, $J_{F\text{-}C}$ = 22.2 Hz), 115.6, 85.2, 77.3, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.1; IR 3443, 2980, 2972, 1768, 1605, 1504, 1369, 1285, 1111, 908, 771 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{18}NO_4FNa^+$ ([M+Na]$^+$) 366.1112. Found 366.1116.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.6 min (major isomer), 7.7 min (minor isomer). $[\alpha]_D^{24}$ = +20.5 (c = 2.1, $CHCl_3$).



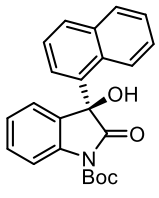
3e

3e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.4 Hz), 7.39 (1H, dt, *J* = 8.0, 1.5 Hz), 7.30 (1H, dd, *J* = 7.6, 0.9 Hz), 7.21 (1H, t, *J* = 7.3 Hz), 7.19-7.17 (2H, m), 7.12-7.10 (2H, m), 3.32 (1H, brs), 2.31 (3H, s), 1.63 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 149.2, 139.8, 138.6, 130.4, 130.3, 129.5, 128.7, 126.2, 125.4, 125.2, 122.7, 115.5, 85.0, 77.8, 28.2, 21.7, one peak for aromatic carbon was not found probably due to overlapping; IR 3444, 2972, 2932, 1730, 1605, 1479, 1337, 1248, 1142, 908, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_4Na^+$ ([M+Na]$^+$) 362.1363. Found 362.1364.; HPLC OD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.2 min (major isomer), 5.8 min (minor isomer). $[\alpha]_D^{24}$ = +42.3 (c = 2.6, $CHCl_3$).



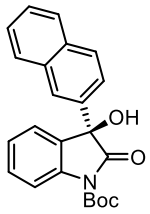
3f

3f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 8.4 Hz), 7.39 (1H, dt, *J* = 8.0, 1.6 Hz), 7.30 (1H, dd, *J* = 7.6, 1.1 Hz), 7.23 (1H, t, *J* = 8.0 Hz), 7.19 (1H, dt, *J* = 7.6, 1.1 Hz), 6.98 (1H, t, *J* = 2.1 Hz), 6.86-6.82 (2H, m), 3.78 (3H, s), 3.40 (1H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 159.9, 149.1, 141.5, 139.8, 130.3, 130.3, 129.8, 125.4, 125.1, 117.9, 115.6, 114.0, 111.7, 85.0, 77.8, 55.4, 28.2; IR 3462, 2980, 2938, 1730, 1599, 1454, 1393, 1285, 1144, 910, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_5Na^+$ ([M+Na]$^+$) 378.1312. Found 378.1311.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.7 min (minor isomer), 13.6 min (major isomer). $[\alpha]_D^{24}$ = +47.1 (c = 2.9, $CHCl_3$).



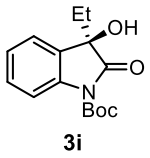
3g

3g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 8.2 Hz), 7.89 (1H, d, *J* = 7.3 Hz), 7.84 (2H, d, *J* = 8.0 Hz), 7.70 (1H, brd, *J* = 7.8 Hz), 7.48 (1H, t, *J* = 7.8 Hz), 7.41 (1H, dt, *J* = 6.9, 1.2 Hz), 7.40 (1H, d, *J* = 7.2 Hz), 7.35 (1H, dt, *J* = 8.3, 1.4 Hz), 7.17 (1H, dd, *J* = 7.6, 1.2 Hz), 7.08 (1H, dt, *J* = 7.6, 0.9 Hz), 3.32 (1H, s), 1.65 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 149.4, 139.8, 134.7, 134.5, 130.6, 130.5, 130.1, 130.1, 129.3, 126.7, 125.8, 125.4, 125.1, 125.0, 125.0, 124.3, 115.9, 85.1, 78.5, 28.2; IR 3514, 3009, 2916, 1788, 1607, 1454, 1369, 1250, 1145, 976, 734 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{21}NO_4Na^+$ ([M+Na]$^+$) 398.1363. Found 398.1354.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 10.5 min (minor isomer), 11.4 min (major isomer). $[\alpha]_D^{25}$ = +102.7 (c = 2.2, $CHCl_3$).



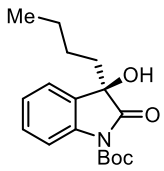
3h

3h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 8.4 Hz), 7.84-7.79 (3H, m), 7.78 (1H, s), 7.49-7.40 (4H, m), 7.33 (1H, dt, *J* = 7.8, 0.9 Hz), 7.20 (1H, dt, *J* = 7.8, 0.9 Hz), 3.45 (1H, br), 1.63 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 149.2, 139.9, 137.2, 133.3, 133.1, 130.5, 130.2, 128.9, 128.5, 127.7, 126.7, 126.6, 125.5, 125.3, 124.9, 123.3, 115.7, 85.1, 78.0, 28.2; IR 3453, 3022, 2980, 1730, 1607, 1479, 1337, 1248, 1146, 1009, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{21}NO_4Na^+$ ([M+Na]$^+$) 398.1363. Found 398.1359.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.9 min (major isomer), 11.1 min (minor isomer). $[\alpha]_D^{24}$ = +63.9 (c = 1.9, $CHCl_3$).



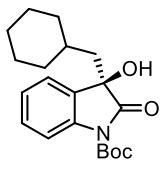
3i

3i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.2 Hz), 7.39 (1H, dt, *J* = 8.4, 0.7 Hz), 7.36 (1H, dd, *J* = 8.2, 1.4 Hz), 7.22 (1H, dt, *J* = 7.8, 1.4 Hz), 2.70 (1H, s), 2.00 (2H, q, *J* = 7.8 Hz), 1.64 (9H, s), 0.79 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 149.1, 139.7, 130.0, 128.8, 125.0, 124.0, 115.4, 84.8, 77.0, 32.7, 28.2, 7.7; IR 3489, 2976, 2931, 1788, 1611, 1454, 1346, 1287, 1144, 928, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{19}NO_4Na^+$ ([M+Na]$^+$) 300.1206. Found 300.1207.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.3 min (major isomer), 9.9 min (minor isomer). $[\alpha]_D^{25}$ = +42.1 (c = 1.2, $CHCl_3$).



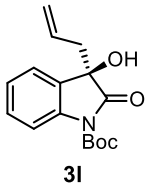
3j

3j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.5 Hz), 7.39 (1H, t, *J* = 8.2 Hz), 7.36 (1H, d, *J* = 8.2 Hz), 7.21 (1H, t, *J* = 7.8 Hz), 2.72 (1H, brs), 2.02-1.91 (2H, m), 1.64 (9H, s), 1.30-1.21 (2H, m), 1.19-1.12 (1H, m), 1.08-0.99 (1H, m), 0.82 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 149.1, 139.6, 130.0, 129.0, 125.0, 124.0, 115.4, 84.8, 76.5, 39.4, 28.2, 25.2, 22.8, 13.9; IR 3446, 2934, 2872, 1728, 1612, 1454, 1337, 1287, 1140, 978, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{23}NO_4Na^+$ ([M+Na]$^+$) 328.1519. Found 328.1518.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.0 min (major isomer), 8.4 min (minor isomer). $[\alpha]_D^{24}$ = +41.5 (c = 1.7, $CHCl_3$).



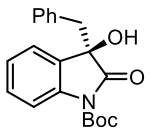
3k

3k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.4 Hz), 7.38 (1H, dd, *J* = 7.6, 0.9 Hz), 7.37 (1H, dt, *J* = 8.0, 1.6 Hz), 7.21 (1H, dt, *J* = 7.6, 0.9 Hz), 2.67 (1H, s), 1.92 (2H, d, *J* = 6.0 Hz), 1.64 (9H, s), 1.61-1.43 (5H, m), 1.21-1.04 (4H, m), 0.97-0.80 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 149.1, 139.6, 130.0, 129.1, 125.0, 124.3, 115.4, 84.7, 76.2, 46.6, 34.4, 34.2, 33.3, 28.2, 26.1; IR 3462, 2978, 2920, 1730, 1610, 1468, 1344, 1287, 1150, 1001, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{27}NO_4Na^+$ ([M+Na]$^+$) 368.1832. Found 368.1810.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.4 min (major isomer), 9.3 min (minor isomer). $[\alpha]_D^{25}$ = +45.5 (c = 2.5, $CHCl_3$).



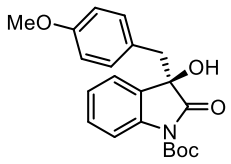
3l

3l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, J = 8.4 Hz), 7.40 (1H, dd, J = 7.6, 1.4 Hz), 7.36 (1H, dt, J = 8.0, 1.4 Hz), 7.21 (1H, t, J = 7.6 Hz), 5.72-5.61 (1H, m), 5.16 (1H, brs), 5.13 (1H, brd, J = 6.4 Hz), 2.82 (1H, s), 2.72 (1H, dd, J = 13.8, 6.4 Hz), 2.62 (1H, dd, J = 13.8, 8.5 Hz), 1.64 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 149.0, 139.4, 130.1, 130.0, 128.7, 125.0, 124.2, 121.3, 115.4, 84.8, 75.6, 43.9, 28.2; IR 3458, 2920, 2849, 1728, 1610, 1479, 1344, 1287, 1150, 984, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{19}NO_4Na^+$ ([M+Na]$^+$) 312.1206. Found 312.1207.; HPLC OZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.4 min (major isomer), 9.7 min (minor isomer). $[\alpha]_D^{24}$ = +32.6 (c = 0.9, $CHCl_3$).



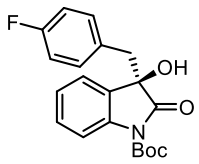
3m

3m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, J = 8.2 Hz), 7.28 (1H, dt, J = 8.2, 1.4 Hz), 7.19-7.10 (5H, m), 6.91 (2H, d, J = 6.2 Hz), 3.27 (1H, d, J = 12.8 Hz), 3.15 (1H, d, J = 12.8 Hz), 3.00 (1H, s), 1.57 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 148.6, 139.3, 133.4, 130.4, 130.0, 128.2, 128.0, 127.2, 124.7, 124.4, 115.1, 84.5, 46.1, 28.1, one peak for aliphatic carbon was not found probably due to overlapping; IR 3429, 2980, 2961, 1776, 1604, 1468, 1341, 1287, 1149, 912, 785 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_4Na^+$ ([M+Na]$^+$) 362.1363. Found 362.1367.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.2 min (major isomer), 9.3 min (minor isomer). $[\alpha]_D^{24}$ = +65.3 (c = 2.1, $CHCl_3$).



3n

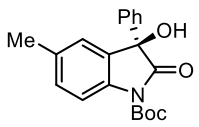
3n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.5 Hz), 7.29 (1H, dt, J = 8.5, 1.8 Hz), 7.19 (1H, dd, J = 7.6, 1.8 Hz), 7.15 (1H, t, J = 7.6 Hz), 6.84 (2H, d, J = 8.7 Hz), 6.67 (2H, d, J = 8.7 Hz), 3.75 (3H, s), 3.21 (1H, d, J = 13.6 Hz), 3.09 (1H, d, J = 13.6 Hz), 2.88 (1H, brs), 1.58 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 158.9, 148.7, 139.4, 131.5, 130.0, 128.3, 125.4, 124.7, 124.4, 115.2, 113.5, 84.6, 55.3, 45.3, 28.2, one peak for aliphatic carbon was not found probably due to overlapping; IR 3429, 2980, 2913, 1776, 1612, 1468, 1369, 1250, 1150, 912, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{23}NO_5Na^+$ ([M+Na]$^+$) 392.1468. Found 392.1455.; HPLC ASH, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 10.0 min (major isomer), 17.9 min (minor isomer). $[\alpha]_D^{24}$ = +56.9 (c = 2.0, $CHCl_3$).



3o

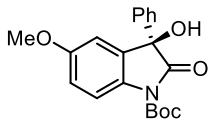
3o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 8.3 Hz), 7.29 (1H, dt, J = 8.3, 1.9 Hz), 7.19 (1H, dd, J = 7.6, 1.9 Hz), 7.15 (1H, dt, J = 7.6, 0.9 Hz), 6.89-6.78 (4H, m), 3.24 (1H, d, J = 13.4 Hz), 3.16 (1H, brs), 3.13 (1H, d, J = 13.4 Hz), 1.57 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 162.2 (d, $J_{F\text{-}C}$ = 251.4 Hz), 148.5, 139.3, 131.9 (d, $J_{F\text{-}C}$ = 7.7 Hz), 130.1, 129.2, 128.0, 124.8, 124.3, 115.1, 114.9 (d, $J_{F\text{-}C}$ = 22.2 Hz), 84.7, 45.2, 28.1, one peak for aliphatic carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.4; IR 3478, 2982, 2922, 1788, 1603, 1468, 1344,

1250, 1148, 837, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{20}NO_4FNa^+$ ($[M+Na]^+$) 380.1269. Found 380.1269.; HPLC ASH, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.8 min (major isomer), 23.3 min (minor isomer). $[\alpha]_D^{24}$ = +58.1 (c = 2.5, $CHCl_3$).



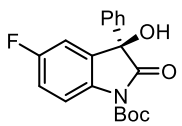
3p

3p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.2 Hz), 7.37-7.30 (5H, m), 7.18 (1H, dd, *J* = 8.2, 1.4 Hz), 7.10 (1H, d, *J* = 1.4 Hz), 3.37 (1H, s), 2.31 (3H, s), 1.62 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 149.2, 140.1, 137.4, 135.2, 130.8, 130.2, 128.8, 128.6, 125.6, 115.3, 84.8, 77.9, 28.2, 21.1, one peak for aromatic carbons was not found probably due to overlapping; IR 3469, 2980, 2930, 1726, 1599, 1485, 1332, 1277, 1105, 906, 731 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_4Na^+$ ($[M+Na]^+$) 362.1363. Found 362.1364.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.6 min (major isomer), 9.4 min (minor isomer). $[\alpha]_D^{24}$ = +25.5 (c = 2.6, $CHCl_3$).



3q

3q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 9.0 Hz), 7.36-7.30 (5H, m), 6.91 (1H, dd, *J* = 9.0, 2.8 Hz), 6.84 (1H, d, *J* = 2.8 Hz), 3.75 (3H, s), 3.53 (1H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 157.5, 149.2, 139.9, 133.0, 131.5, 128.8, 128.7, 125.6, 116.7, 115.8, 110.5, 84.8, 78.1, 55.8, 28.2; IR 3435, 2978, 2934, 1726, 1599, 1412, 1333, 1246, 1144, 1003, 772 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}NO_5Na^+$ ($[M+Na]^+$) 378.1312. Found 378.1311.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.1 min (major isomer), 13.5 min (minor isomer). $[\alpha]_D^{25}$ = –13.5 (c = 2.8, MeOH).

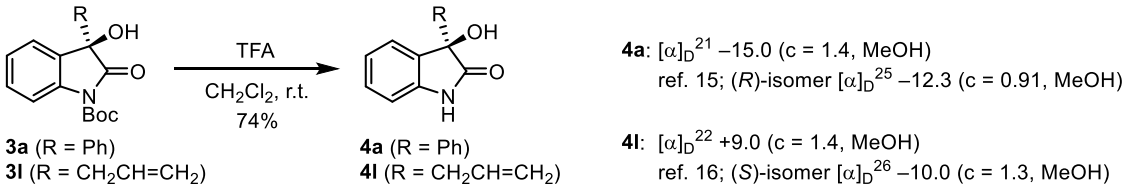


3r

3r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, dd, *J* = 9.0, J_{F-H} = 4.6 Hz), 7.36-7.32 (5H, m), 7.08 (1H, dt, *J* = 9.0, 2.7 Hz), 7.01 (1H, dd, *J* = 2.7, J_{F-H} = 7.3 Hz), 3.57 (1H, s), 1.61 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 160.4 (d, J_{F-C} = 248.7 Hz), 149.1, 139.4, 135.6 (d, J_{F-C} = 1.9 Hz), 132.1 (d, J_{F-C} = 8.7 Hz), 128.9, 125.5, 117.1 (d, J_{F-C} = 8.7 Hz), 116.9 (d, J_{F-C} = 24.2 Hz), 112.6 (d, J_{F-C} = 24.2 Hz), 85.3, 77.8, 28.2, one peak for aromatic carbon was not found probably due to overlapping; ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.3; IR 3464, 2984, 2934, 1726, 1611, 1479, 1342, 1261, 1144, 1009, 760 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{18}NO_4FNa^+$ ($[M+Na]^+$) 366.1112. Found 366.1114.; HPLC ID3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.0 min (major isomer), 6.9 min (minor isomer). $[\alpha]_D^{24}$ = +54.2 (c = 2.3, $CHCl_3$).

Determination of the absolute configuration of hydroxylation product:

The absolute configuration of the hydroxylation products **3a** and **3l** were established to be *R* by comparing their optical rotations with that of known enantiomers after removing the *N*-Boc group.[15,16] The absolute configuration of **3b**-**3k** and **3m**-**3r** were assumed by analogy.



To a solution of **3a** (27.7 mg, 0.085 mmol, 93% ee) in dichloromethane (1.0 mL) was added trifluoroacetic acid (TFA) (38 μL) and the resulting solution was stirred for 17 h at room temperature. The mixture was then diluted with a saturated aqueous solution of $NaHCO_3$ at 0 °C and the extractive workup was performed with EtOAc. After drying over Na_2SO_4, filtration, and removal of solvent, the resulting crude powder was washed with hexane to afford **4a** (14.2 mg, 0.063 mmol, 74% yield, 93%ee)

References and Notes

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List of Publications

Chapter 2

(1) Asymmetric Substitution at the Tetrasubstituted Chiral Carbon: Catalytic Ring-Opening Alkylation of Racemic 2,2-Disubstituted Aziridines with 3-Substituted Oxindoles
Ohmatsu, K.; Ando, Y.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 18706-18709.

Chapter 3

(2) A Modular Strategy for the Direct Catalytic Asymmetric α-Amination of Carbonyl Compounds
Ohmatsu, K.; Ando, Y.; Nakashima, T.; Ooi, T. *Chem* **2016**, *1*, 802-810.

Chapter 4

(3) *In Situ* Electrophilic Activation of Hydrogen Peroxide for Catalytic Asymmetric α-Hydroxylation of 3-Substituted Oxindoles
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