Catalytic Asymmetric Transformations

Based on Exploitation of Cyanide Ion and Cyano Group

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Contents

Chapter 1 General Introduction and Summary

1.1 Nitrile Compounds

Nitriles are compounds that have cyano group consisting of a carbon-nitrogen triple bond. These compounds are often found in useful materials such as polymers and pharmaceuticals.[1] Especially, growing attention has been paid in the drug development area due to the potential to play an important role as hydrogen bond acceptors in vivo. In addition, nitriles are useful synthetic intermediate because they can be readily converted into amino-, amide- and carbonyl groups (Figure 1). For a long time, numerous methods for the synthesis of nitriles have been developed.

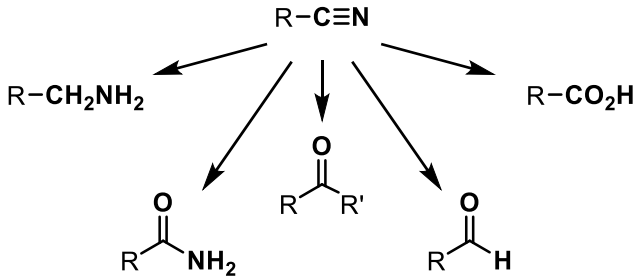


Figure 1. Cyano Compounds as Synthetic Intermediates.

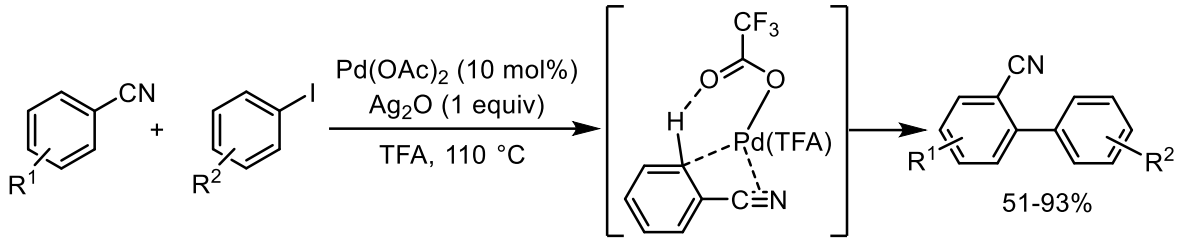
1.1.1 The Properties of Cyano group

Cyano group is a strong electron-withdrawing group, which can change the electronic properties of molecules by introducing it. Moreover, the lone pair on nitrogen can form the hydrogen bond with protic molecules as well as the coordination through the lone pair or π-orbital between carbon and nitrogen with metal ions.

In bioorganic systems, cyano group is known to act as a mimic of the carbonyl group by functioning as a hydrogen bond acceptor. Several crystal structures revealed the intermolecular hydrogen bonding network between the nitrile and the hydrogen-bond donor such as amino acids or water.[2]

On the other hand, cyano group has been used as a directing group for a regioselective C-H functionalization.[3] For example, Sun's group developed palladium catalyzed C−H bond activation of benzonitriles.[4] They proposed that this reaction proceeds via the cyclometalated intermediate with the coordination of a π-electron between carbon and

nitrogen to Pd(II) species, to give *ortho*-selective C−H functionalized products (Scheme 1).



Scheme 1. The Nitrile-Directed *ortho*-Selective C−H Functionalization

1.2 Catalytic Asymmetric Cyanation

Catalytic asymmetric cyanation with cyanide ion as nucleophile is one of the most effective methods to synthesize chiral nitriles, and one of the most useful C−C bond-forming reactions. It has proven to be applicable for a wide variety of electrophiles such as aldehydes, ketones, imines, electron-deficient olefins, epoxides, aziridines, affording the corresponding chiral nitriles.[5] Therefore, this type of reactions has been intensively studied.

1.2.1 Cyano Source for Asymmetric Cyanation

Focusing on the cyano sources, asymmetric cyanation reactions have mainly relied on the use of cyano-containing organic reagents, such as trimethylsilyl cyanide or hydrogen cyanide, because they have mild reactivity and well solubility toward a wide range of organic solvents. However, there are some demerits that trimethylsilyl cyanide is unstable and expensive for large scale use, hydrogen cyanide is hard to handle due to its toxicity and volatility.

On the other hand, alkali metal cyanide such as potassium cyanide is one of the most ideal cyano source because of its ease to handling and inexpensiveness. Metal cyanide is insoluble in most of the organic solvents, and thus is necessarily used under solid-solid or solid-liquid phase-transfer conditions.

1.2.2 Phase Transfer Catalyzed Asymmetric Cyanation

Asymmetric phase-transfer cyanation reaction with metal cyanide is more difficult than the asymmetric cyanation with trimethylsilyl cyanide. In the previous reports, metal cyanide has been successfully used only in asymmetric cyanide addition to aldehydes, aldimines, and activated olefins which are highly reactive and easy to control stereochemistry. This is because the cyanide ion possesses high hydrophilicity and it is difficult to control the asymmetric cyanide additions by chiral phase-transfer catalysts (PTC).

Herein below discusses about the problems in the asymmetric cyanation under phase-transfer condition by comparing the asymmetric Strecker reaction with asymmetric alkylation as a typical phase-transfer reaction.

(i) Asymmetric Nucleophilic Substitution of Alkyl Halide by PTC

Asymmetric substitution of alkyl halide under basic condition has been extensively studied as a classical PTC reaction.[6] Especially, asymmetric alkylation of Schiff-base is powerful method for the preparation of α-alkyl-α-amino acid derivatives.

The simplified extraction mechanism which was proposed by Starks[7] is shown in Figure 2. Firstly, deprotonation of Nu-H gives rise to the ion pair of metal/nucleophilic anion in the interface. Then, ion exchange between this ion pairs and chiral ammonium bromide generates chiral ionic intermediate [$Q^+ \cdot Nu^-$] and metal bromide. This chiral intermediate reacts with alkyl halide, affording the product and regenerating chiral ammonium bromide.

The key step in the PTC system is ion exchange between metal salt of nucleophile and ammonium bromide, which is promoted by the generation of hydrophilic metal bromide and lipophilic chiral ammonium inter mediate.

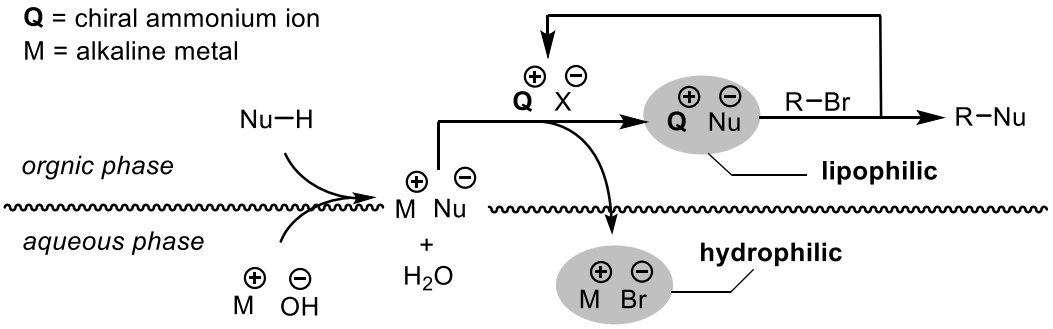


Figure 2. A Mechanism of Asymmetric Alkylation under Phase-Transfer Condition.

(ii) Asymmetric Strecker Reaction by PTC

The mechanism of asymmetric Strecker reaction catalyzed by PTC is shown in Figure 3. Ion exchange between potassium cyanide and ammonium bromide generates chiral ammonium cyanide, which attacks imine and subsequent protonation leading to the chiral Strecker product. In this reaction, there are three challenging points to obtain chiral cyanation product as follows.

(A) In the first ion exchange step, the equilibrium is shifted towards the ammonium bromide side in non-polar organic phase so chiral ammonium cyanide as the key intermediate is difficult to generate. This is due to high hydrophilicity and basicity of cyanide ion.

(B) The addition of chiral ammonium cyanide to imine gives rise to precursor/ammonium ion pairs, and then the protonation of this precursor leads to product and regenerate ammonium cyanide. However, precursor/ammonium ion pairs are highly lipophilic, which hinders regeneration of chiral ammonium cyanide.

(C) Cyanide ion with high nucleophilicity has potential to attack imine without forming the cyanide/chiral ammonium ion pairs, leading to the racemic Strecker product.

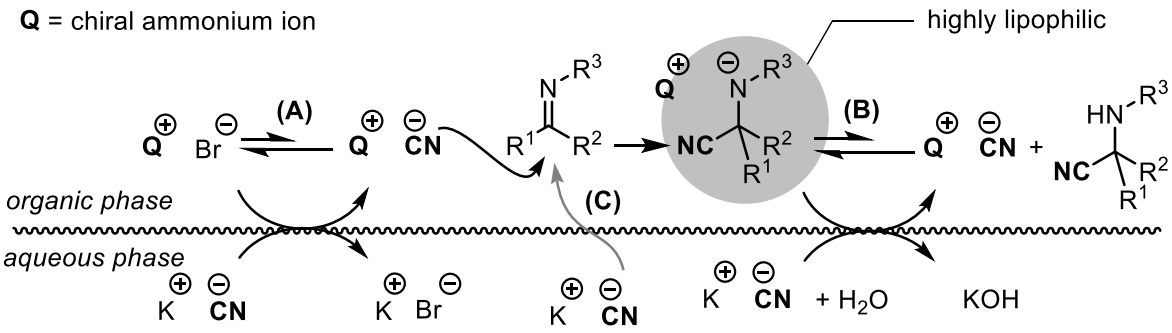


Figure 3. A Mechanism of Asymmetric Strecker Reaction under Phase-Transfer Condition.

From the above, it is supposed that cyanide ion's high hydrophilicity and nucleophilicity are making the asymmetric cyanation under phase-transfer condition difficult. To achieve a highly enantioselective cyanation with metal cyanide, the PTC which possesses the strong anion-binding ability is required.

1.2.3 Catalytic Asymmetric Strecker reaction

The asymmetric cyanation of imines namely asymmetric Strecker reaction is a standard method for producing chiral α-amino acid derivative.[8] There are two strategies to accomplish asymmetric Strecker reaction affording enantioenriched α-amino nitriles.

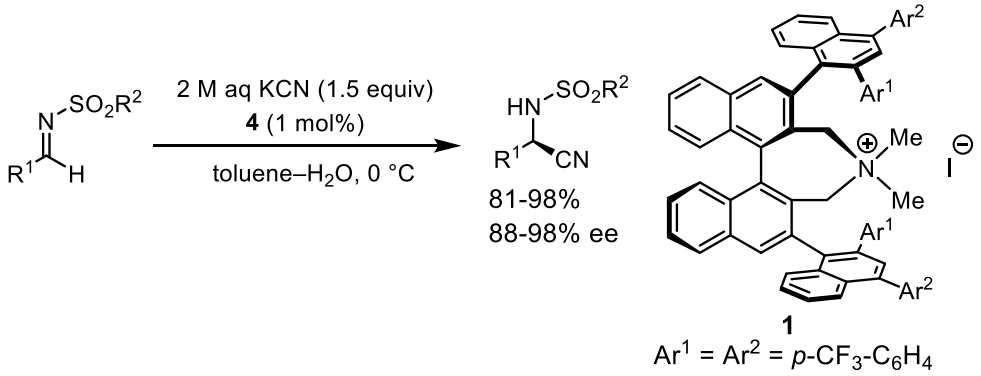
First, the nucleophilic cyanation of non-racemic imines which have the chiral auxiliary group. In this approach, there are serious problems that it needs to prepare the optically active imines and the substrates are limited.

Second is the catalytic asymmetric cyanation of prochiral imines, which has been attracted attention as the most powerful method because it is applicable to a wide variety of substrates, affording various chiral α-amino nitriles effectively.

(i) Aldimines

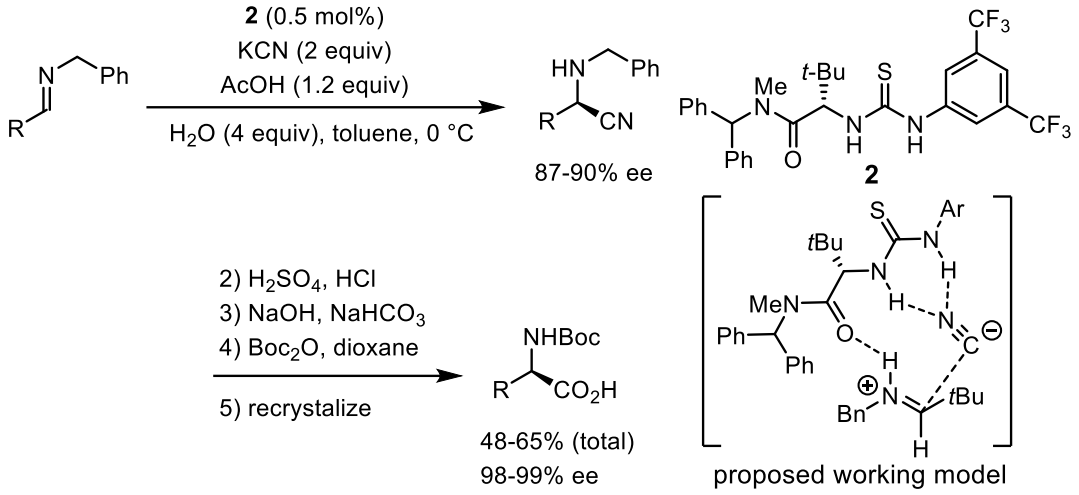
Lipton and co-workers reported the first catalytic enantioselective Strecker reaction of aldimines in 1996. In the presence of chiral organocatalyst derived from dipeptide, the asymmetric addition of hydrogen cyanide to aldimine proceeded in high yield and good enantioselectivity.[9] Since then, the enantioselective Strecker reaction has been studied intensively and many successful examples have been reported, but most of the methodologies depends on the use of organic cyanide such as trimethylsilyl cyanide, hydrogen cyanide.

In 2006, a pioneering work on the asymmetric Strecker reaction with potassium cyanide was reported by Maruoka and Ooi group (Scheme 2).[10] By using the aqueous potassium cyanide and 1 mol% of the chiral quaternary ammonium salt (Maruoka catalyst), the asymmetric cyanation of *N*-arylsulfonyl aldimine afforded α-amino nitriles in high yield with excellent enantiomeric excess.



Scheme 2. Asymmetric Strecker Reaction of Aldimines with Potassium Cyanide

Followed by Maruoka's report, the breakthrough for asymmetric Strecker reaction was made by Jacobsen and co-workers (Scheme 3). They found that potassium cyanide/AcOH mixture could be used as a cyano source in the coexistence of H_2O, and simple chiral thiourea could efficiently catalyze asymmetric cyanation with high enantioselectivity.[11] This method enables the large-scale synthesis of chiral α-amino acid. Furthermore, they carried out computational studies of this reaction, that indicate the thiourea catalyst promotes imine protonation, and then the cyanide ion interacted with the catalyst attacks iminium ion. This protocol is effective for various aryl and aliphatic aldimines.



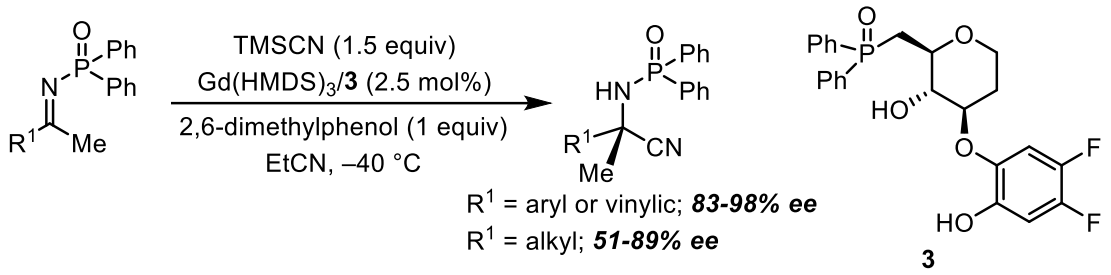
Scheme 3. Scalable Catalytic Asymmetric Strecker Synthesis

(ii) Ketoimines

Recently, the catalytic enantioselective Strecker reactions of ketoimines as a substrate have been reported by some groups. It allows for the access to the chiral tetrasubstituted α-amino acids which are useful in synthetic and biological chemistry. However, the asymmetric cyanation of ketoimines is more difficult than that of aldimines, because ketoimines are generally less reactive than aldimines due to the steric hindrance. Moreover, the dissimilarities of the two substituents are lesser, so controlling the stereochemistry is difficult.

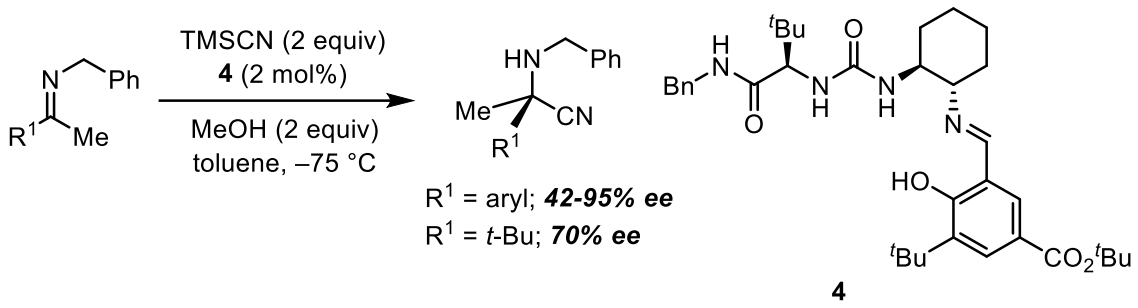
Shibasaki group developed chiral gadolinium complex for enantioselective Strecker reaction (Scheme 4).[12] They examined the reactions of several *N*-protected ketoimines and found that oxygen containing *N*-phosphinoyl or furfuryl -protected ketoimines are suitable substrate probably because of the oxophilicity of the lanthanide catalyst.

Subsequently, they further studied this reaction, it proved that protic additives such as phenol is effective for the reaction proceeds smoothly. Unfortunately, dialkyl ketoimine shows relatively low enantioselectivity.



Scheme 4. Asymmetric Strecker Reaction of *N*-Phosphinoyl Ketoimines with Chiral Gadolinium Catalyst

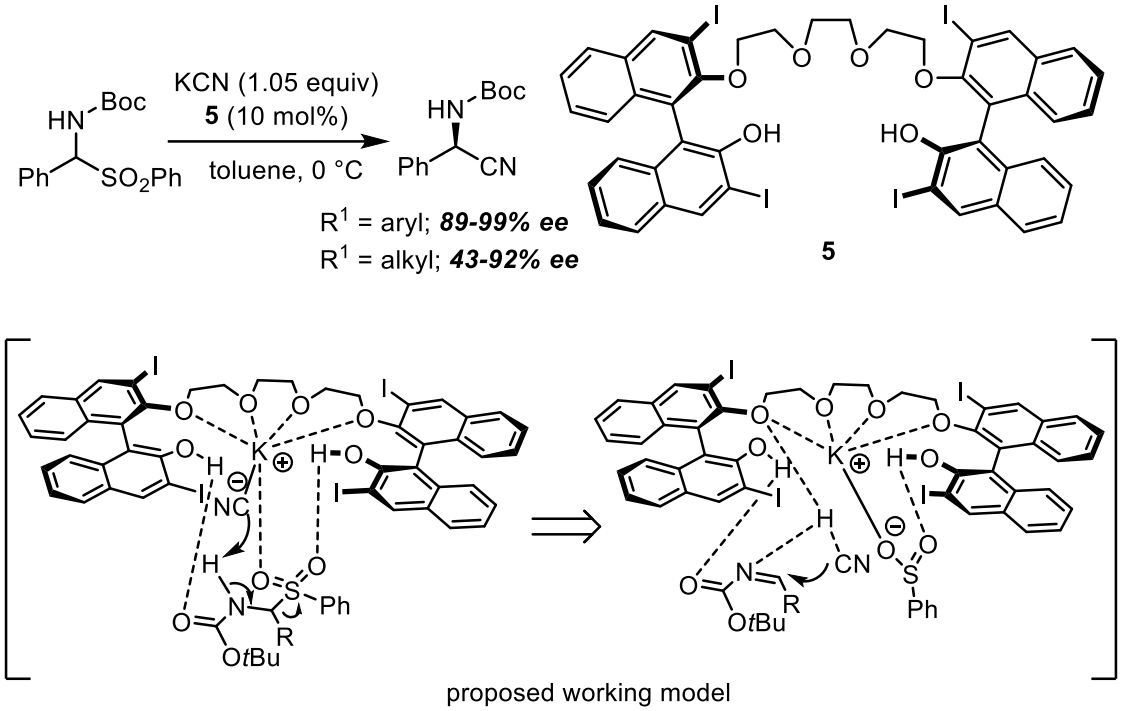
In 2010, organocatalyzed enantioselective Strecker reaction of ketoimines was reported by Jacobsen and co-workers (Scheme 5).[13] They used trimethylsilyl cyanide and methanol to generate hydrogen cyanide, and the enantioselective addition of hydrogen cyanide to *N*-benzyl ketoimines proceeds with good enantioselectivity under the simple chiral urea catalyst. However, this protocol is also not effective for dialkyl ketoimine.



Scheme 5. Asymmetric Organocatalyzed Strecker Reaction of *N*-Benzyl Ketoimines

Song group reported enantioselective Strecker reaction with potassium cyanide catalyzed by the BINOL-based bis(hydroxy) polyether which was designed for enantioselective nucleophilic substitution with potassium salts (Scheme 6).[14] They used α-amido sulfone substrate as an imine synthon and potassium cyanide, which were activated by catalyst to generate chiral cyanide and iminium pairs, and then asymmetric cyanation of iminium provide enantiomerically enriched α-aminonitrile. When using *in situ* generated benzaldimines, the corresponding α-aminonitrile was formed in high

enantioselectivity. Unfortunately, the reaction of primary alkyl imine afforded the α-aminonitrile with low enantioselectivity.



Scheme 6. Asymmetric Strecker Reaction of *In Situ* Generated *N*-Boc Aldimines with Chiral Organocatalyst

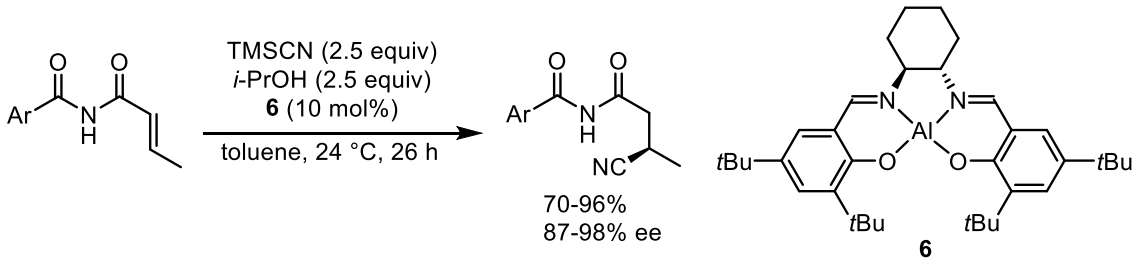
As mentioned in this section, there are several successful examples of catalytic enantioselective Strecker reaction. However, Strecker reaction of ketoimines has been less explored than that of aldimines and trimethylsilyl cyanide was used as a cyano source in many cases. Moreover, existing protocols are not effective for enantioselective cyanide addition to aliphatic ketoimines.

Based on these backgrounds, the author redesigned chiral 1,2,3-triazolium ion catalyst which have high anion binding ability[15] to enhance its characteristic and achieved highly enantioselective Strecker reaction of ketoimines with potassium cyanide. The detail is explained in Chapter 2.

1.2.4 Asymmetric Cyanation of Electron-Deficient Olefines

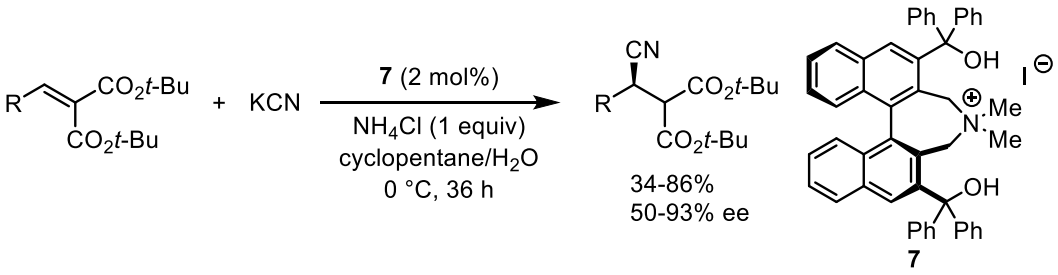
The asymmetric conjugate cyanation of electron-deficient olefins has been less explored than that of highly polarized and reactive substrates such as aldehydes, aldimines. The enantioselective conjugate addition of cyanide to α,β-unsaturated carbonyl compounds would provide access to useful intermediates that can be converted into chiral α-substituted-β-amino acids or chiral β-substituted-*γ*-aminobutyric acids.

Jacobsen's group reported asymmetric conjugate addition of cyanide to α,β-unsaturated imides catalyzed by chiral aluminum complex (Scheme 7).[16] They used trimethylsilyl cyanide and 2-propanol to generate hydrogen cyanide *in situ*, affording the cyanide adducts in high enantioselectivity. Moreover, they found that the reactivity largely depends on the steric characters of the substituent.



Scheme 7. An Enantioselective Conjugate Cyanide Addition to α,β-Unsaturated Imides with Chiral Aluminum Catalyst

In 2013, Maruoka group developed asymmetric conjugate addition of cyanide to alkylidene malonates with potassium cyanide in the presence of chiral PTC under cyclopentane-water two-phase conditions (Scheme 8).[17] This reaction was accelerated by the addition of Brønsted acids to promote the regeneration of ammonium cyanide from the anion intermediate/ammonium ion pairs.



Scheme 8. An Enantioselective Conjugate Cyanation of Alkylidenemalonates with Potassium Cyanide

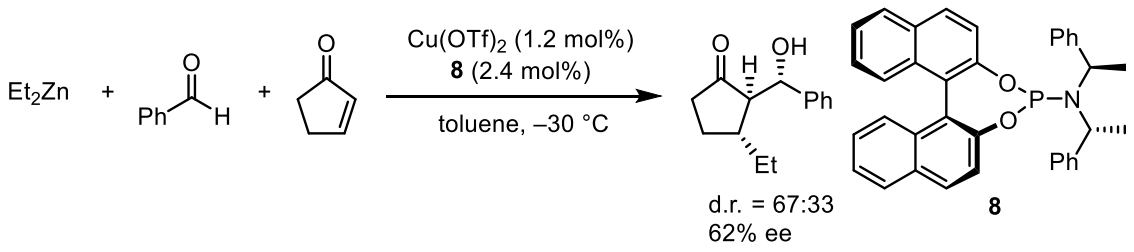
Although several successful examples of the enantioselective conjugate cyanation of electron-defficient olefins has been reported, it is limited to hydrocyanation of olefins. If the chiral α-cyano carbanion intermediate generated by the asymmetric conjugate cyanide addition of olefins could react with another electrophile in stereoselective manner, it could expand the synthetic utility of asymmetric conjugate cyanation of olefins. For example, when carbon electrophiles such as alkyl halide was used in this reaction, double C−C bond could be formed in single synthetic operation. This method, namely, asymmetric dicarbofunctionalization of olefines has the potential for rapid synthesis of chiral building block which have complex carbon skeleton.[18]

1.2.4.1 Asymmetric Dicarbofunctionalization of Olefines

Asymmetric dicarbofunctionalization of olefins suffers from fundamental problems. First is chemoselectivity, multicomponent reaction is a reaction that multiple nucleophilic or electrophilic substrates react in a single operation, so it is difficult to suppress the undesired bond-forming reaction. In the previous reports, the electrophilic substrate is limited to aldehyde, imine or electron-deficient olefin.

Second, when the acyclic olefin is used as the substrate, the control of the relative stereochemistry should become challenging, [19] because the chiral anion intermediate afforded by the first C−C bond formation causes a flexible conformational change due to free bond rotation. Therefore, the previous successful examples depend on the use of cyclic olefins or terminal olefins in many cases.

For example, Feringa group reported copper catalyzed asymmetric tandem 1,4-addition-aldol reaction of dialkylzinc to cyclopenten-3,5-dione monoacetals in the presence of aldehyde (Scheme 9).[20] They chose dialkylzinc which is less reactive toward aldehydes as the nucleophile, affording the 1,4-addition product with low diastereoselectivity and moderate enantioselectivity.



Scheme 9. An Asymmetric 1,4-Addition/Aldol Reaction of Cyclopentenone with Dialkylzinc and Aldehyde

Followed by the Feringa's report, they and other groups reported several asymmetric tandem reactions of organometallic reagents, aldehydes and olefins. However, olefinic substrate is limited to cyclohexanone or cyclopentenone, and this reaction require the copper catalyst in many cases.

On the other hand, the mechanistic studies of asymmetric Strecker reaction suggested that enantioselective retro-Strecker reaction occurred in the presence of chiral triazolium ion (Chapter 2). From this finding, it is supposed that there is the interaction between triazolium ion and cyano group of amide ion intermediate through hydrogen bond, and this interaction is crucial in discrimination of amide ion stereochemistry (Figure 4).

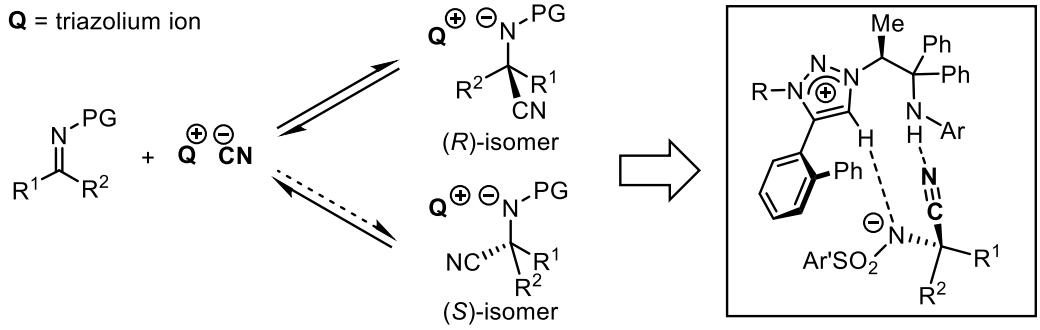


Figure 4. The Interaction Between Cyano Group and Chiral Triazolium Ion

Based on the above background, the author devised asymmetric cyanoalkylation of electron-deficient olefins with potassium cyanide and alkyl halide utilizing the cyano group as the directing group. The author envisioned that chiral ammonium ion could associate with the cyano group of α-cyano carbanion intermediate through hydrogen bond as with amide ion intermediate, and it leads to the restriction of the C−C bond rotation in the diastereoselective alkylation step (Figure 5). The detail is explained in chapter 3.

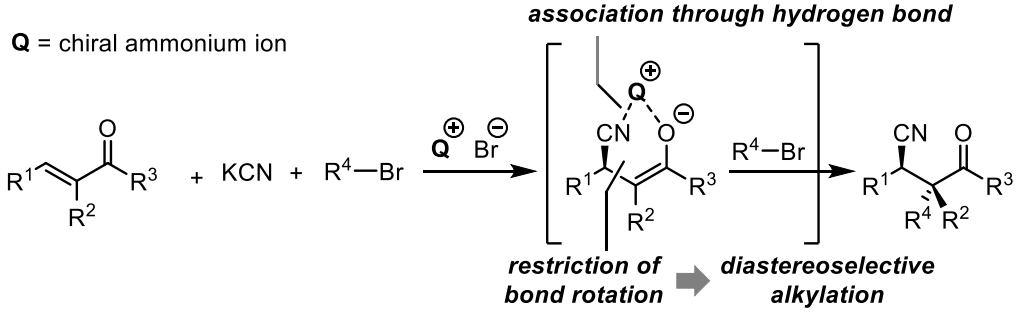


Figure 5. A Strategy for Asymmetric Cyanoalkylation of Electron-Deficient Olefins

1.3 Conclusion

In this doctoral thesis, the author describes the catalytic asymmetric cyanation reaction with potassium cyanide. The control of the highly hydrophilic and nucleophilic cyanide ion was succeeded by enhancing the anion-binding ability of the chiral 1,2,3-triazolium catalyst. And then, the highly enantioselective Strecker reaction of ketoimines with potassium cyanide has been achieved by using the redesigned catalyst. Furthermore, asymmetric cyanoalkylaton of electron-deficient olefins with potassium cyanide and alkyl halide have been developed. This powerful method enables rapid construction of chiral complex carbon skeleton under mild condition.

Reference and Notes

(1) (a)Segura, J. L.; Martin, N.; Hanack, M. *Eur. J. Org. Chem.* **1999**, 643. (b)Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.

(2) Turner, D. R. *Cryst. Eng. Comm*. **2012**, *14*, 6447.

(3) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front*., **2014**, *1*, 843.

(4) Li, W.; Xu, Z.; Sun, P.; Jiang, X.; Fang, M. *Org. Lett.* **2011**, *13*, 1286.

(5) Kuruno, N.; Ohkuma, T. *ACS Catal*. **2016**, *6*, 989.

(6) (a)Ooi, T.; Maruoka, K. *Chem*. *Rev*. **2003**, *103*, 3013. (b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 2.

(7) Starks, C. M. *J*. *Am*. *Chem*. *Soc*. **1971**, *93*, 195.

(8) Wang, J.; Liu, X.; Feng, X. *Chem*. *Rev*. **2011**, *111*, 6947.

(9) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J*. *Am*. *Chem*. *Soc*. **1996**, *118*, 4910.

(10) Ooi, T.; Uematsu, Y.; Maruoka, K. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 2548.

(11) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N.; *Nature* **2009**, *461*, 968.

(12) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.

(13) Vachal, P.; Jacobsen, E. N. *Org*. *Lett*. **2000**, *2*, 867.

(14) Yan, H.; Oh, J. S.; Lee, J. -W.; Song, C. E. *Nat*. *Commun*. **2012**, *3*, 1.

(15) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 1307.

(16) Sammis, G. M.; Jacobsen, E. N.; *J*. *Am*. *Chem*. *Soc*. **2003**, *125*, 4442.

(17) Liu, Y.; Shirakawa, S.; Maruoka, K. *Org*. *Lett*. **2013**, *15*, 1230.

(18) (a)Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem*. *Rev*. **2014**, *114*, 2390. (b)Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. *Chem*. *Rec*. **2018**, *18*, 1.

(19) Eppe, G.; Didier, D.; Marek, I. *Chem*. *Rev*. **2015**, *115*, 9175.

(20) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841.

Chapter 2.

Catalytic Asymmetric Strecker Reaction of Ketoimines with Potassium Cyanide

Abstract:

Catalytic asymmetric Strecker reactions of ketoimines with potassium cyanide is described. The highly enantioselective Strecker reaction of ketoimines using potassium cyanide as a cyanide source is the rare example, because potassium cyanide has poor solubility to organic solvents and it is difficult to control cyanide ion by a catalyst. This reaction has been achieved by using chiral 1,2,3-triazolium salt which has high anion-binding ability.

2.1 Introduction

Catalytic enantioselective Strecker reaction is the most useful synthesis method of chiral amino acids, many successful examples have been reported.[1] By applying ketoimines to this reaction, it leads to the synthesis of chiral tetrasubstituted α-amino acid which is important for synthetic chemistry and biochemistry. However, the existing methods are not effective for the enantioselective cyanation of aliphatic imines.[2] Moreover, the cyanation reagent which is difficult to handle such as cyanohydrin or silylcyanide is required for these methods.[3]

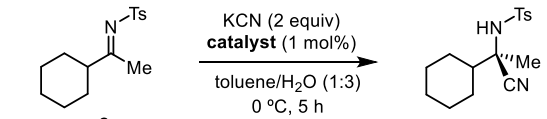
On the other hand, alkali metal cyanide including potassium cyanide is ideal reagent because it is inexpensive and easy to handle. These reagents are insoluble in the organic solvents so these are used under phase-transfer condition. In general, catalytic asymmetric phase-transfer reaction using metal cyanide as a cyano source is difficult due to high nucleophilicity and high hydrophilicity of cyanide ion.[4,6] To proceed highly enantioselective cyanide addition, the chiral ammonium cyanide as a key intermediate need to be generated in organic phase efficiently. However, ammonium cyanide is unstable in non-protic solvents because cyanide ion has high hydrophilicity. In addition, highly nucleophilic cyanide ion can react with imine before formation of cyanide/ammonium ion pairs and afford the racemic product. For these reasons, efficient extraction of the cyanide ion from aqueous phase to organic phase, and controlling the cyanide ion are important to achieve highly enantioselective Strecker reaction. Herein, the author describes the highly enantioselective Strecker reaction of ketoimines catalyzed by chiral 1,2,3-triazolium catalyst which possesses high anion-binding ability.[5]

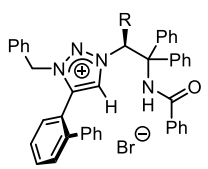
2.2 Result and Discussion

At the outset of the study, the author examined the effectiveness of chiral 1,2,3-triazolium catalyst in the asymmetric Strecker reaction of *N*-sulfonyl ketoimine with potassium cyanide in toluene/H_2O biphasic condition at 0 ℃ (Table 1). In the absence of the catalyst, the reaction proceeded slowly and afforded a trace amount of product **3a** (Entry 1), also TBAB gave only 8% of cyanation product (Entry 2). In contrast, the reaction proceeded smoothly and the product was obtained in moderate yield and enantiomeric excess in the presence of the L-alanine-derived chiral 1,2,3-triazolium bromide **1a** (Entry 3), the absolute configuration of major isomer was established to be (*R*) by X-ray crystal analysis. This result indicates that 1,2,3-triazolium ion possesses the

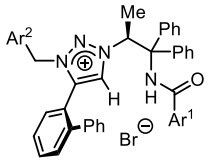
potential to extract cyanide ion from aqueous phase to organic phase efficiently. The author then optimized the structure of the chiral 1,2,3-triazolium catalyst. At first, the author evaluated the effect of the amino acid origin alkyl substituent (R), α-aminobutyric acid-derived catalyst **1b** (Entry 4), valine-derived catalyst **1c** (Entry 5), leucine derived catalyst **1d** showed lower enantioselectivity (Entry 6). This observation leads the author to further modification of the amide substituent **Ar[1]**. To introduce of the 3,5-disubstituted phenyl ring improved enantioselectivity (Entry 7), especially, when the catalyst having 3,5-bis(trifluormethyl)phenyl group **1f** showed high enantiomeric excess (Entry 8). As a result of further optimization, the catalyst which has 4-methoxybenzyl group on triazole N(3) (Ar^2) **1g** showed higher enantioselectivity but the yield of **3a** remained moderate as yet (Entry 9). The author then examined to extend reaction time to improve the yield, **3a** was obtained in higher yield but ee value decreased (Entry 10).

Table 1. Optimization of Reaction Condition[a]





1a (R = Me)
1b (R = Et)
1c (R = *i*-Pr)
1d (R = CH_2*i*-Pr)



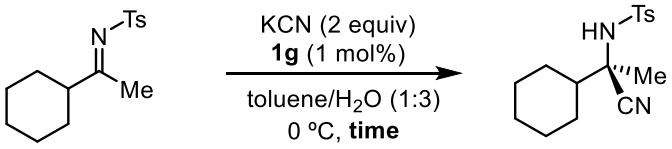
1e [Ar^1 = 3,5-$Me_2C_6H_3$, Ar^2 = Ph]
1f [Ar^1 = 3,5-$(CF_3)_2C_6H_3$, Ar^2 = Ph]
1g [Ar^1 = 3,5-$(CF_3)_2C_6H_3$, Ar^2 = 4-$MeOC_6H_4$]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	None	Trace	-
2[d]	TBAB	8	-
3	**1a**	44	44
4	**1b**	34	8
5	**1c**	49	10
6	**1d**	48	16
7	**1e**	58	72
8	**1f**	65	82
9	**1g**	58	88
10[e]	**1h**	72	78

[a] Reactions were carried out with **2a** (0.1 mmol), **1** (1 mol%), and KCN (2 equiv) in toluene/H_2O (1:3) at 0 °C for 5 h. [b] Isolated yield. [c] Determined by HPLC with chiral column. [d] With 10 mol% of TBAB. [e] Reaction was performed for 24 h.

On the basis of these results, the author carried out further control experiment to reveal the relationship between reaction time and enantioselectivity (Table 2). The reaction using **1g** for 1.5 h gave the product **3a** with higher enantiomeric excess (Entry 1). When reaction time was prolonged to 72 h, enantiomeric excess of **3a** decreased (Entry 4).

Table 2. Asymmetric Strecker Reaction for Different Reaction time[a]

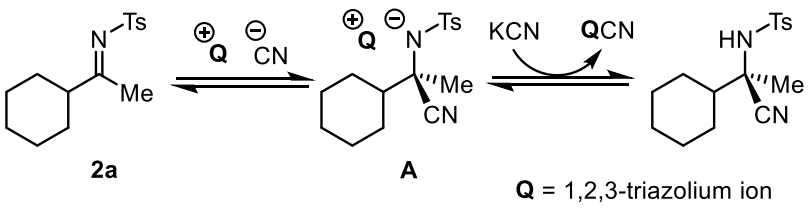


2a **3a**

Entry	Time (h)	Yield (%)	ee (%)
1	1.5	55	93
2	5	58	88
3	24	72	78
4	72	66	55

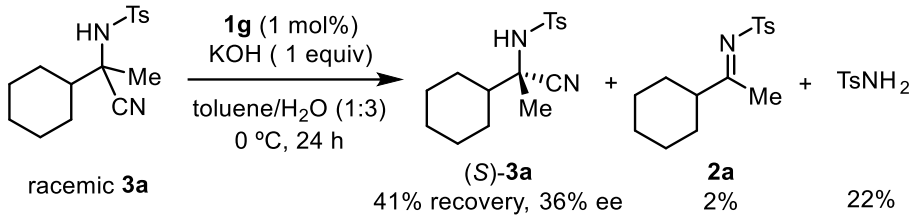
[a] Reactions were conducted with **2a** (0.1 mmol), **1g** (1 mol%), and KCN (2 equiv) in toluene/H_2O (1:3) at 0 °C. [b] Isolated yield. [c] Determined by HPLC with chiral column.

The author assumed that the fluctuation of the optical purity of the product was caused by retro-Strecker reaction. The enantioselective cyanation of **2a** gives cyanated amide ion/ammonium ion pairs **A**, subsequently, ion-exchange with potassium cyanide produces potassium amidate salt (Scheme 1). Finally, the protonation of this salt with H_2O affords the Strecker product (*R*)-**3a** and potassium hydroxide as a byproduct. Potassium hydroxide can deprotonate the sulfonamides and cause retro-Strecker reaction. A series of these processes is reversible so racemization proceeds and decrease the ee of **3a**.



Scheme 1. Possible Retro-Strecker Reaction

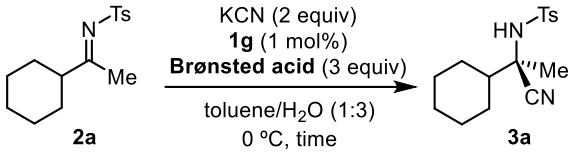
To support the assumption that retro-Strecker reaction involves reduction of ee, control experiment was conducted (scheme 2). Treatment of racemic Strecker product **3a** with KOH (1.0 equiv) in toluene/H_2O at 0 ℃ in the presence of 1,2,3-triazolium salt **1g**, 41% of (S)-**3a** was recovered with 36% ee and ketoimine **2a** and sulfonamide were obtained. This result suggests that major enantiomer of Strecker-product (*R*)-**3a** underwent enantioselective retro-Strecker reaction in the presence of chiral 1,2,3-triazolium salt, and this reaction caused decrease of ee.



Scheme 2. Retro-Strecker Reaction of Racemic Amino nitrile with Potassium hydroxide

The author presumed that the prevention of retro-Strecker reaction is effective to improve yield and enantioselectivity. Based on this presumption, the reaction using Brønsted acid as an additive to protonate the amide ion rapidly was conducted (Table 3).[6] When the catalyst **1g** was used, ketoimine underwent smooth cyanation with acetic acid and showed that decrease of ee of **3a** according to reaction time was suppressed, and gave product in excellent yield and high ee (Entries 1-4). When less acidic HFIP was used as an additive, yield of **2a** was improved but ee decreased slightly. While more acidic benzoic acid and TFA showed drastic decrease of yield of **2a** (Entries 6 and 7). Then, the author optimized reaction conditions again with acetic acid and found that enantioselectivity was improved by using solid potassium cyanide at -40 ℃ (Entry 8). Remarkably, the use of a lot more amount of acetic acid than that of potassium cyanide didn't affect the yield and enantioselectivity (entry 9), and the amount of acetic acid and potassium cyanide could be eventually reduced to 1.5 equiv (Entry 10).

Table 3. Asymmetric Strecker Reaction with Brønsted acid[a]



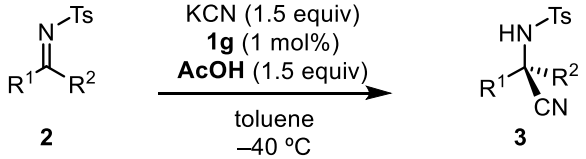
2a **3a**

Entry	Time	Brønsted acid	Yield (%)[b]	ee (%)[c]
1	1.5	AcOH	61	89
2	5	AcOH	83	90
3	24	AcOH	95	90
4	72	AcOH	94	89
5	24	HFIP	85	62
6	24	$PhCO_2H$	2	87
7	24	TFA	19	94
8[d]	24	AcOH	89	96
9[d, e]	24	AcOH	99	93
10[d, f]	24	AcOH	99	93

[a] Reactions were conducted with **2a** (0.1 mmol), **1g** (1 mol%), Brønsted acid (3 equiv), and KCN (2 equiv) in toluene/H_2O (1:3) at 0 °C. [b] Isolated yield. [c] Determined by HPLC with chiral column. [d] Reaction was performed in toluene at –40 °C. [e] With 2 equiv of AcOH. [f] With each 1.5 equiv of AcOH and KCN.

With the optimal condition, the author investigated substrate scope of asymmetric Strecker reaction (Table 4). The reaction of several alkyl ketoimine with potassium cyanide and acetic acid in the presence of 1 mol% of catalyst **1g** afforded Strecker product in high yields with good enantioselectivity. Notably, the ketoimine possessing two substituents with little difference in steric properties also furnished the corresponding product with high enantiomeric excess (Entry 6). While the reaction of the aryl ketoimine afforded the product **3h** in high yield and moderate enantioselectivity.

Table 4. Substrate Scope of Asymmetric Strecker Reaction of Ketoimines



2 **3**

Entry	**2** (R^1, R^2)	**3**	Yield (%)[b]	ee (%)[c]
1	**2a** (*c*-Hex, Me)	**3a**	99	93
2	**2b** (*c*-C_5H_9, Me)	**3b**	99	90
3[d]	**2c** (*i*-Pr, Me)	**3c**	92	80
4	**2d** (*t*-Bu, Me)	**3d**	92	90
5	**2e** (Adm, Me)	**3e**	99	96
6[d]	**2f** (Et, Me)	**3f**	91	83
7	**2g** (*c*-Hex, *n*-Bu)	**3g**	98	91
8	**2h** (Ph, Me)	**3h**	95	52

[a] Reaction were conducted with **2a** (0.1 mmol), **1g** (1 mol%), acetic acid (1.5 equiv), and KCN (1.5 equiv) in toluene at –40 °C. [b] Isolated yield. [c] Determined by HPLC with chiral column. [d] With 2 equiv of AcOH. Adm = 1-adamantyl.

2.3 Summary

In conclusion, a highly enantioselective Strecker reaction of ketoimines with potassium cyanide has been developed by using the chiral 1,2,3-triazolium catalyst. As a result of the tuning of the catalyst structure, efficient extraction of cyanide ion was achieved. Moreover, the examination of the effect of reaction time on enantioselectivity revealed that this reaction is competing enantioselective retro-Strecker reaction, and it decreased the enantiomeric excess of the Strecker product. The author found that the addition of the Brønsted acid could suppress the retro-Strecker reaction. In the presence of the chiral 1,2,3-triaazolium catalyst and acetic acid, the reaction of various alkyl kerimine proceeded with high levels of enantiocontrol.

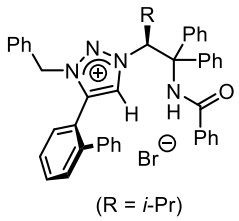
Experimental Section

General information:

^{1}H NMR spectra were recorded on a JEOL JNM-ECA600II (600 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, sext = sextet, m = multiplet, and br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a 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). The high-resolution mass spectra were measured on Thermo Fisher Scientific Exactive Plus (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 N (spherical, neutral, 40~50μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [φ 4.6 mm x 250 mm, DAICEL CHIRALPAK AY-3 (AY3), CHIRALPAK AS-3 (AS3), CHIRALCEL CZ-3 (OZ3), CHIRALPAK IB-3 (IB3)] with hexane (H) and isopropyl alcohol (IPA) as eluent.

Toluene was supplied from Kanto Chemical Co., Inc. as "Dehydrated" and further purified by both A2 alumina and Q5 reactant using a Glass Contour solvent dispensing system. 1,2,3-Triazolium salts **1** were synthesized by following the literature methods. Other simple chemicals were purchased and used as such.

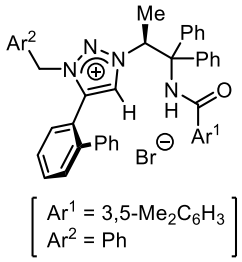
Characterization of 1,2,3-triazolium bromide 1:



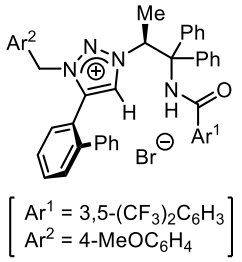
(R = *i*-Pr)

1c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (1H, br), 9.14 (1H, br), 8.41 (2H, d, J = 8.2 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.84 (1H, q, J = 6.9 Hz), 7.75-7.63 (3H, m), 7.55-7.47 (2H, m), 7.47-7.41 (3H, m), 7.38 (2H, t, J = 7.8 Hz), 7.30 (1H, d, J = 7.8 Hz), 7.25-7.17 (2H, m), 7.14-6.86 (8H, m), 6.71 (2H, d, J = 8.0 Hz), 4.99 (1H, d, J = 14.9 Hz), 4.91 (1H, d, J = 14.9 Hz), 1.65 (3H, d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 142.8, 140.7, 139.5, 138.3, 136.7, 134.7, 133.6, 133.3 (q, JC-F = 32.9 Hz), 132.8, 132.7, 132.1 (q, JC-F = 33.7 Hz), 131.9, 131.3, 129.4, 129.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.2, 128.0, 127.6, 127.2, 126.1 (q, JC-F = 3.9 Hz), 125.4 (q, JC-F = 3.9 Hz), 123.9 (q, JC-F = 276.7 Hz), 123.5 (q, JC-F = 276.5 Hz), 119.9, 69.6, 65.9, 54.5, 15.8; IR 3032, 1680, 1526, 1476, 1325, 1267, 1167, 1115, 1067, 758, 704 cm^{-}

[1]; HRMS (ESI) Calcd for $C_{45}H_{35}F_6N_4O^+$ ([M–Br]$^+$) 761.2710. Found 761.2699.; $[\alpha]_D^{22}$ = –39.6 (c = 1.0, MeOH).

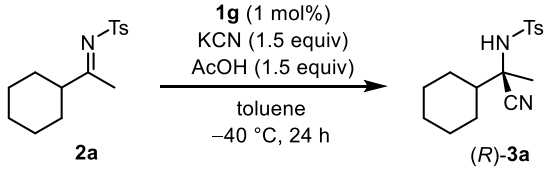


1e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (1H, br), 9.37 (1H, br), 8.45 (2H, d, J = 8.2 Hz), 8.30-7.89 (3H, m), 7.70 (2H, d, J = 8.2 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.51-7.41 (3H, m), 7.41-7.28 (5H, m), 7.28-7.09 (9H, m), 7.09-6.98 (4H, m), 6.98-6.81 (2H, m), 6.47 (2H, d, J = 7.3 Hz), 4.81 (2H, br), 3.59 (1H, brd, J = 14.2 Hz), 3.02 (1H, brdd, J = 14.2, 14.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 142.4, 141.0, 139.8, 138.2, 136.7, 135.5, 134.6, 134.1, 133.5 (q, JC-F = 32.9 Hz), 133.2, 132.8, 132.2, 131.9 (q, JC-F = 32.9 Hz), 131.2, 129.4, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.4, 126.0 (q, JC-F = 3.9 Hz), 125.6 (q, JC-F = 3.9 Hz), 123.9 (q, JC-F = 276.7 Hz), 123.5 (q, JC-F = 276.7 Hz), 119.6, 70.2, 69.5, 54.4, 35.5, four peaks for aromatic carbons were not found probably due to broadening or overlapping; IR 3030, 1682, 1531, 1497, 1323, 1294, 1163, 1130, 1067, 756, 706 cm^{-1}; HRMS (ESI) Calcd for $C_{51}H_{39}F_6N_4O^+$ ([M–Br]$^+$) 837.3023. Found 837.3016.; $[\alpha]_D^{21}$ = –35.5 (c = 1.1, MeOH).



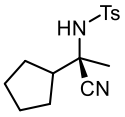
1g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, br), 8.63 (1H, br), 8.13 (2H, d, J = 8.2 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.70 (2H, d, J = 8.7 Hz), 7.67 (1H, t, J = 7.8 Hz), 7.50-7.42 (4H, m), 7.41 (2H, d, J = 8.2 Hz), 7.23 (1H, dd, J = 7.8, 7.3 Hz), 7.20-6.95 (10H, m), 6.91 (1H, br), 6.82 (2H, d, J = 7.3 Hz), 6.78 (2H, d, J = 8.2 Hz), 5.46 (1H, d, J = 14.7 Hz), 5.13 (1H, d, J = 14.7 Hz), 5.05 (1H, br), 4.19 (2H, br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 142.5, 141.4, 138.9, 138.5, 136.9, 136.4, 134.0, 133.7 (q, JC-F = 33.1 Hz), 132.9, 132.4, 132.3, 131.8 (q, JC-F = 32.9 Hz), 131.2, 130.1, 129.0, 128.9, 128.4, 128.2, 128.1, 128.1, 128.0, 125.9 (q, JC-F = 2.9 Hz), 125.8 (q, JC-F = 3.9 Hz), 123.8 (q, JC-F = 276.7 Hz), 123.7 (q, JC-F = 275.8 Hz), 120.3, 73.4, 68.2, 60.6, 55.0, four peaks for aromatic carbons were not found probably due to broadening or overlapping; IR 3223, 1682, 1526, 1489, 1323, 1296, 1169, 1130, 1067, 758, 704 cm^{-1}; HRMS (ESI) Calcd for $C_{45}H_{35}F_6N_4O_2^+$ ([M–Br]$^+$) 777.2659. Found 777.2651.; $[\alpha]_D^{21}$ = –25.7 (c = 1.1, MeOH).

General procedure for 1g-catalysed asymmetric Strecker reaction of ketoimines with potassium cyanide:

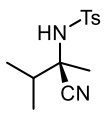


A solution of **1g** (0.87 mg, 0.001 mmol), *N*-tosyl ketoimine **2a** (27.9 mg, 0.10 mmol), and acetic acid (8.6 μL, 0.15 mmol) in wet toluene (1 mL) was cooled to –40 °C. To this solution was added potassium cyanide powder (9.8 mg, 0.15 mmol) under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (H/EtOAc = 4:1 as eluent) to afford **3a** (30.3 mg, 0.099 mmol, 99% yield, 93% ee) as a white solid. **3a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (2H, d, J = 7.8 Hz), 7.34 (2H, d, J = 7.8 Hz), 4.95 (1H, br), 2.44 (3H, s), 1.91-1.80 (4H, m), 1.70-1.65 (2H, m), 1.58 (3H, s), 1.26-1.03 (5H, m); ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.3, 137.7, 129.9, 127.6, 119.0, 57.2, 47.0, 27.4, 26.8, 26.0, 25.9, 22.8, 21.8, one peak for aliphatic carbon was not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{16}H_{22}N_2NaO_2S^+$ ([M+Na]$^+$) 329.1294. Found 329.1292.; HPLC AY3, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 24.3 min (*R*), 30.7 min (*S*); $[\alpha]_D^{21}$ = +27.6 (c = 1.1, acetone).

Characterization of Strecker products 3:

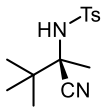


3b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.1 Hz), 5.03 (1H, br), 2.44 (3H, s), 2.24 (1H, quin, J = 9.0 Hz), 1.86-1.77 (2H, m), 1.75-1.66 (2H, m), 1.64 (3H, s), 1.63-1.52 (2H, m), 1.45-1.37 (2H, m); ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.4, 137.6, 129.9, 127.7, 118.7, 57.2, 49.9, 28.1, 25.6, 24.8, 21.8; HRMS (ESI) Calcd for $C_{15}H_{20}N_2NaO_2S^+$ ([M+Na]$^+$) 315.1138. Found 315.1137.; HPLC AS3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 19.0 min (major), 24.9 min (minor); $[\alpha]_D^{20}$ = +16.1 (c = 1.1, acetone).

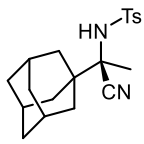


3c: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 4.8 (1H, br), 2.44 (3H, s), 2.08 (1H, sept, J = 7.2 Hz), 1.58 (3H, s), 1.07 (3H, d, J = 7.2 Hz), 1.04 (3H, d, J = 7.2 Hz), ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.4, 137.5, 129.9, 127.7, 118.9, 57.5, 37.6, 22.4, 21.8, 17.3, 16.8; HRMS (ESI) Calcd

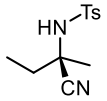
for $C_{13}H_{18}N_2NaO_2S^+$ ([M+Na]$^+$) 289.0981. Found 289.0979.; HPLC OZ3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 20.5 min (minor), 23.9 min (major); $[\alpha]_D^{22}$ = +13.2 (c = 1.6, acetone).



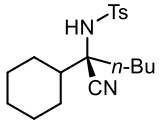
3d: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (2H, d, J = 7.8 Hz), 7.34 (2H, d, J = 7.8 Hz), 4.86 (1H, br), 2.44 (3H, s), 1.59 (3H, s), 1.07 (9H, s), ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.3, 137.5, 129.9, 127.8, 118.8, 60.5, 38.9, 24.8, 21.8, 20.5; HRMS (ESI) Calcd for $C_{14}H_{20}N_2NaO_2S^+$ ([M+Na]$^+$) 303.1138. Found 303.1137.; HPLC IB3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.4 min (minor), 10.1 min (major); $[\alpha]_D^{17}$ = +45.7 (c = 1.0, acetone).



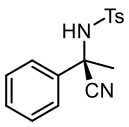
3e: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 4.80 (1H, br), 2.44 (3H, s), 2.09 (3H, br), 1.72 (3H, brd, J = 12.6 Hz), 1.66 (6H, br), 1.61 (3H, brd, J = 12.0 Hz), 1.56 (3H, s); ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.2, 137.7, 129.9, 127.7, 118.4, 60.8, 40.0, 36.4, 36.0, 28.2, 21.8, 19.3; HRMS (ESI) Calcd for $C_{20}H_{26}N_2NaO_2S^+$ ([M+Na]$^+$) 381.1607. Found 381.1608.; HPLC AS3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 20.7 min (major), 26.3 min (minor); $[\alpha]_D^{17}$ = +43.4 (c = 1.0, acetone).



3f: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 5.01 (1H, br), 2.44 (3H, s), 1.95-1.82 (2H, m), 1.62 (3H, s), 1.05 (3H, t, J = 7.2 Hz); ^{13}C NMR (600 MHz, $CDCl_3$) δ 144.4, 137.5, 129.9, 127.6, 119.2, 53.8, 34.5, 25.4, 21.8, 8.4; HRMS (ESI) Calcd for $C_{12}H_{16}N_2NaO_2S^+$ ([M+Na]$^+$) 275.0825. Found 275.0824.; HPLC OZ3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 26.5 min (minor), 39.2 min (major); $[\alpha]_D^{21}$ = +10.6 (c = 1.1, acetone).



3g: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 4.72 (1H, br), 2.44 (3H, s), 1.96-1.91 (1H, m), 1.82-1.78 (6H, m), 1.69-1.66 (1H, m), 1.34-1.08 (9H, m,), 0.86 (3H, t, J = 6.6 Hz);^{13}C NMR (600 MHz, $CDCl_3$) δ 144.1, 137.8, 129.8, 127.7, 118.0, 61.5, 44.1, 35.0, 27.2, 27.0, 26.1, 25.9, 25.6, 22.5, 21.7, 13.9, one peak for aliphatic carbon was not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{19}H_{28}N_2NaO_2S^+$ ([M+Na]$^+$) 371.1764. Found 371.1765.; HPLC IB3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.8 min (minor), 8.5 min (major); $[\alpha]_D^{22}$ = +10.5 (c = 1.2, acetone).



3h: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 7.8 Hz), 7.35-7.31 (3H, m), 7.25 (2H, d, J = 8.4 Hz), 5.13 (1H, br), 2.43 (3H, s), 1.95 (3H, s) ;^{13}C NMR (600 MHz, $CDCl_3$) δ 144.3, 137.5, 137.2, 129.8, 129.5, 129.1, 127.7, 125.7, 119.0, 56.8, 30.2, 21.8; HRMS (ESI) Calcd for $C_{19}H_{28}N_2NaO_2S^+$ ([M+Na]$^+$) 371.1764. Found 371.1765.; HPLC IB3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.5 min (major), 17.4 min (minor); $[\alpha]_D^{22}$ = +9.1 (c = 0.6, $CHCl_3$).

Crystallographic Structure Determination:

Absolute stereochemistry of the Strecker product **3a** was unequivocally determined by X-ray crystallographic analysis. Single crystal of **3a** (CCDC: 2096899) was obtained from CH_2Cl_2/hexane solvent system at room temperature. The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 123 K on a Rigaku XtaLAB P200 diffractometer with multi-layer mirror monochromated Mo-Kα radiation (λ = 0.71075 Å). The structure was solved by direct method and refined by a full-matrix least square method on F^2 for all reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms, except for a hydrogen on nitrogen atom, were placed using AFIX instruction The crystallographic data were summarized in the following Table.

formula	$C_{16}H_{22}N_2O_2S$
formula weight	306.41
T (K)	123(2)
λ (Å)	0.71075
cryst syst	monoclinic
space group	$P2_1$
a (Å)	6.3816(19)
b (Å)	10.134(3)
c (Å)	11.995(3)
α (°)	90
β (°)	93.384(5)
γ (°)	90
volume (Å^3)	774.4(4)
Z value	2
D_{calc} (g/cm^3)	1.314

μ (mm^{-1})	0.215
F000	328
cryst size (mm)	0.300 × 0.300 × 0.100
2θ range (deg)	3.198-27.491
Index ranges	-7<=h<=8 -13<=k<=10 -15<=l<=15
reflns collected	6159
indep refins/R_{int}	3116/0.0504
params	194
GOF on F^2	1.011
R_1, wR_2 [I>2σ(I)]	0.0338, 0.0829
R_1, wR_2 (all data)	0.0350, 0.0837
absolute structure parameter	0.01(5)
peak and hole (e. $Å^3$)	0.294, -0.271

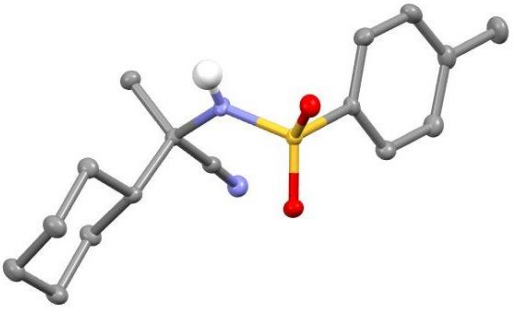


Figure S1. Molecular structure of **3a**. Calculated hydrogen atoms are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, grey = carbon.

Reference and Notes

(1) Reviews for asymmetric cyanation of ketones, imines, and α,β-unsaturated carbonyl compounds, see: (a) (a) Gregory, R. J. H. *Chem. Rev.* 1999, **99**, 3649-3682; (b) North, M. *Tetrahedron: Asymmetry* 2003, **14**, 147-176; (c) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* 2004, **43**, 2752-2778; (d) Chen, F.-X.; Feng, X. *Curr. Org. Synth.* 2006, **3**, 77-97; (e) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Coord. Chem. Rev.* 2008, **252**, 593-623; (f) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* 2008, **108**, 5146-5226; (g) Moberg, C.; Wingstrand, E. *Synlett* 2010, 355-367; (h) Wang, W.; Liu, X.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* 2010, 4751-4769 (i) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* 2011, **111**, 6947-6983 (j) Liu, Y.-L.; Zhou, J. *Synthesis* 2015, **47**, 1210-1226; (k) Kurono, N.; Ohkuma, T. *ACS Catal.* 2016, **6**, 989-1023.

(2) (a) Byrne, J. J.; Chavarot, M.; Chavant, P.-Y.; Vallée, Y. *Tetrahedron Lett.* 2000, **41**, 873-876; (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* 2000, **6**, 867-870; (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 5634. (d) Wang, J.; Hu, X.; Jiang, J.; Gou, S.; Huang, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* 2007, **46**, 8468-8470. (e) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc*. **2009**, *131*, 15118. (f) Liu, Y.-L.; Shi, T.-D.; Zhou, F.; Zhao, X.-L.; Wang, X.; Zhou, J. *Org. Lett.* 2011, **13**, 3826-3829.

(3) For examples of asymmetric Strecker reaction using cyanohydrin as a cyanide source, see: (a) Juliá, S.; Ginebreda, A. *Tetrahedron Lett.* 1979, **20**, 2171-2174; (b) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* 2002, **85**, 3301-3312; (c) Huang, W.; Song, Y.; Wang, J.; Cao, G.; Zheng, Z. *Tetrahedron* 2004, **60**, 10469-10477; (d) Brodbeck, D.; Álvarez-Barcia, S.; Meisner, J.; Broghammer, F.; Klepp, J.; Garnier, D.; Frey, W.; Kästner, J.; Peters, R. *Chem. Eur. J.* 2019, **25**, 1515-1524.

(4) For examples of asymmetric cyanation reaction using alkali metal cyanide, see: (a) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* 2006, **128**, 2548-2549; (b) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* 2009, **461**, 968-970; (c) Yan, H.; Oh, J. S.; Lee, J.-W.; Song, C. E. *Nature Commun.* 2012, **3**, 1212.

(5) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* 2011, **133**, 1307-1309

(6) Liu, Y.; Shirakawa, S.; Maruoka, K. *Org. Lett.* 2013, **15**, 1230-1233.

Chapter 3.

Catalytic Asymmetric Cyanoalkylation of Electron-Deficient Olefins with Potassium Cyanide and Alkyl Halides

Abstract:

Asymmetric cyanoalkylation of electron-deficient olefins with potassium cyanide and alkyl halides catalyzed by chiral 1,2,3-triazolium salt is described. The stereoselective dicarbofunctionalization of olefin proceeds through an enantioselective conjugate cyanation of olefins and subsequent diastereoselective alkylation of chiral triazolium enolate as a key intermediate.

3.1 Introduction

A stereoselective dicarbofunctionalization of olefins is a powerful approach for the rapid construction of a chiral complex molecular architecture.[1-3] This reaction has been attracting attention as a useful reaction in synthetic chemistry because it can introduce two carbon-carbon bonds in a single operation step using readily available olefins.[4-9] However, since the reaction involves multiple nucleophilic or electrophilic substrates, it is very difficult to prevent the bond formation between undesirable substrates. For the previous reports, some copper catalyzed asymmetric conjugate addition and sequent enolate trapping reactions have been achieved, but substrates are limited to electron-deficient olefins and aldehyde or imine. Furthermore, the reaction of acyclic olefins is difficult to control the stereochemical outcome of second C-C bond formation because the chiral intermediate produced by first C-C bond forming reaction can cause bond rotation so substrates have been limited to cyclic enones in the previous reports.[10-16]

Based on the asymmetric dicarbofunctionalization of olefins has these problems, the author devised asymmetric cyanoalkylation of electron-deficient olefins with potassium cyanide catalyzed by chiral 1,2,3-triazolium salt.[17] The author selected alkyl halide as an electrophile because it is typically less reactive than electron-deficient olefin so conjugate addition reaction can occur preferentially to the nucleophilic substitution reaction. Moreover, the author expected that chiral 1,2,3-triazolium ion would form hydrogen-bonding interaction with the enolate intermediate generated by conjugate cyanide addition of the olefin, which would suppress the bond rotation of the flexible enolate and allow the alkylation of enolate to proceed in a diastereoselective manner (Figure 1).[18]

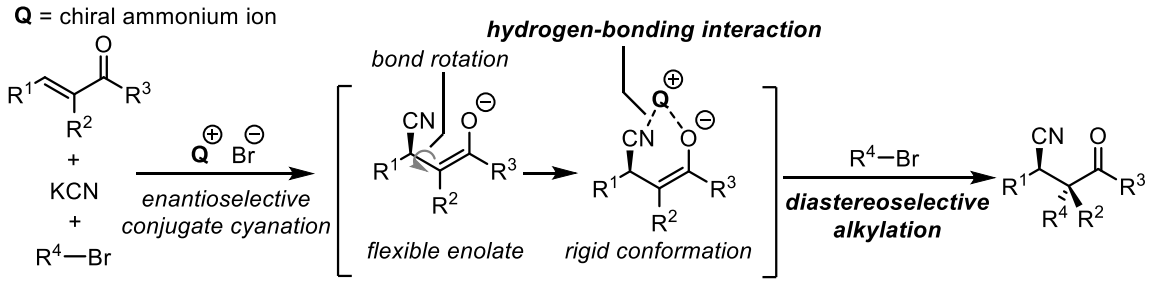
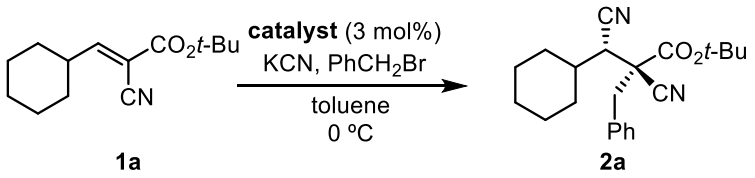


Figure 1. The Working Hypothesis of Asymmetric Cyanoalylation of Electron-Deficient Olefins

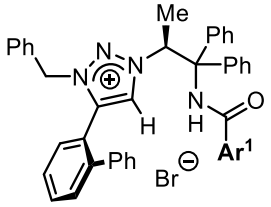
3.2 Result and Discussion

At the outset of the investigation, the author chose acyclic alkylidene cyanoester **1a** as a substrate and treated it with potassium cyanide and benzyl bromide in toluene at 0 ℃ as the model condition (Table 1). When TBAB was used as a catalyst, the reaction proceeded smoothly and product **2a** was obtained in high yield yet moderate diastereoselectivity (Entry 1). While the cinchona alkaloid-derived catalyst **3a** afforded trace amount of **2a**, and catalyst **3b** showed low yield and ee and moderate diastereoselectivity. On the other hand, L-alanine-derived chiral 1,2,3-triazolium catalyst **4a** gave the product **2a** quantitatively in high diastereoselectivity and moderate enantioselectivity (Entry 4). Remarkably, methyl substituted at triazole C(5) position catalyst **5a** gave **2a** quantitatively but diastereoselectivity decreased (Entry 5). These results suggest that hydrogen-bonding donor ability at triazole C(5) position is crucial for diastereoselective alkylation step. Based on these observations, the author optimized triazolium catalyst structure, and found that the introduction of 3,5-disubstituted phenyl group (Ar^1) on the amide group improved enantioselectivity (Entries 6-9). The author subsequently modified the catalyst structure, **4f** bearing 4-methoxy benzyl group at triazolium N(3) (CH_2Ar^2) showed good yield and keep high diastereoselectivity and good enantioselectivity (Entry 10). Finally, the author modified the aryl group on the carbon attached amide group (Ar^3), 4-chrolo phenyl substituted catalyst **4g** showed high enantioselectivity (Entry 11). The author then optimized reaction condition again with catalyst **4g**, enantioselectivity was successfully improved by lowering reaction temperature to -20 ℃ (Entry 12).

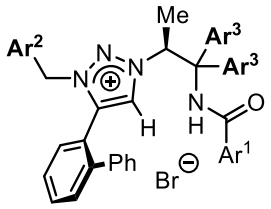
Table 1. Optimization of Reaction Condition[a]



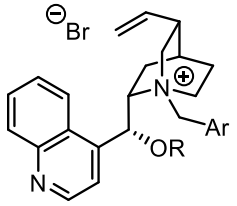
1a **2a**



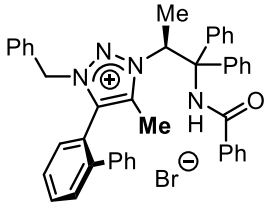
4a (Ar^1 = Ph)
4b (Ar^1 = 4-*t*-BuC_6H_4)
4c (Ar^1 = 3,5-*t*-$Bu_2C_6H_3$)
4d (Ar^1 = 3,5-$Ph_2C_6H_3$)
4e (Ar^1 = 3,5-(4-*t*-$BuC_6H_4)_2C_6H_3$)



(Ar^1 = 3,5-(4-*t*-$BuC_6H_4)_2C_6H_3$)
4f (Ar^2 = 4-$MeOC_6H_4$, Ar^3 = Ph)
4g (Ar^2 = 4-$MeOC_6H_4$, Ar^3 = 4-ClC_6H_4)



(Ar = 9-anthryl)
3a (R = H)
3b (R = $CH_2CH{=}CH_2$)



5a

Entry	catalyst	Yield (%)[b]	d.r.[c]	ee (%)[d]
1[e]	TBAB	98	6:1	-
2	**3a**	Trace	-	-
3	**3b**	12	5:1	-25
4	**4a**	99	18:1	36
5	**5a**	99	7:1	4
6	**4b**	99	18:1	37
7	**4c**	78	17:1	59
8	**4d**	99	>20:1	67
9	**4e**	69	>20:1	73
10	**4f**	86	>20:1	73
11	**4g**	61	>20:1	79
12[f]	**4g**	72	>20:1	95

[a] The reactions were conducted with 0.10 mmol of **1a**, 0.20 mmol of benzyl bromide, and 0.20 mmol of KCN in the presence of catalyst (3 mol%) in toluene (1.0 mL) at 0 °C for 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Enantiomeric ex-cess for major diastereomer. Determined by chiral HPLC analysis. [e] With TBAB (50 mol%). [f] Conducted with each 0.50 mmol of benzyl bromide and KCN at −20 °C.

Using the optimized reaction condition, the author explored the substrate scope of asymmetric cyanoalkylation of electron-deficient olefins (Figure 2). Initially, the reaction of a wide range of trisubstituted olefins with potassium cyanide and benzyl bromide in the presence of L-alanine-derived catalyst **4g** was conducted, alkylidene cyanoester gave products **2a**-**2d** with high enantiomeric excess and diastereomeric excess. Remarkably, this method is applicable to the oxindole-derived olefins **6**.[19] Using catalyst **4h**, the 3-alkylidene oxindole **6a**-**6b** and 3-arylidene oxindole **6c**-**6f** provided corresponding products **7** in excellent enantioselectivity and diastereoselectivity. Subsequently, the various alkyl halides were tested in reaction with the olefin **1a** and **6c**. The reaction of **1a** catalyzed by **4g** with alkyl halides having different electronic and steric properties substituents furnished the cyanoalkylation products **2e**-**2j** with high enantioselectivity and excellent diastereoselectivity. The oxindole-derived olefins also reacted with each alkyl halides in the presence of L-leucine-derived catalyst **4h** to give the products **7g**-**7j** with high selectivity, however propargyl bromide afforded **7k** with moderate diastereomeric ratio.

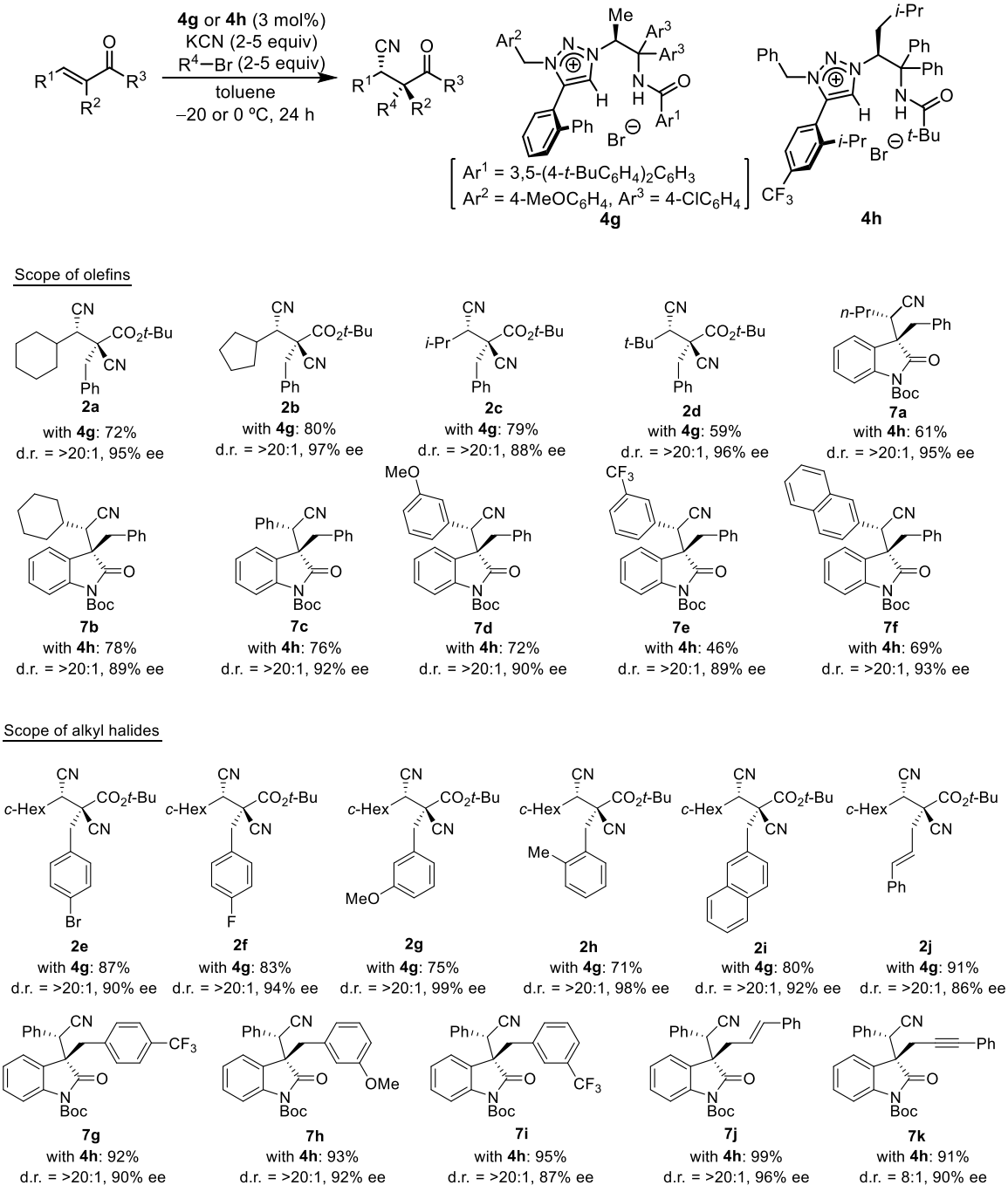
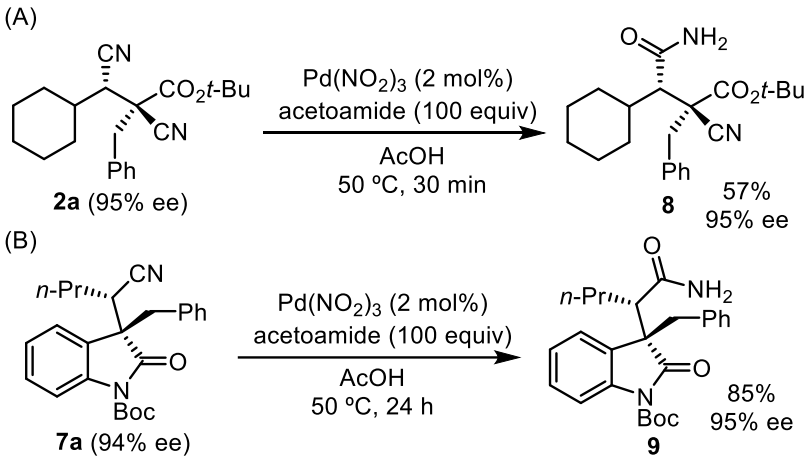


Figure 2. Substrate scope of Asymmetric Cyanoalkylation

The utility of the cyanoalkylation product was demonstrated by nitrile hydration catalyzed by palladium nitrate (Scheme 1).[20] The product **3a** was treated with 100 equiv of acetoamide in the presence of a catalytic amount of palladium nitrate in acetic acid at 50 °C, affording the hydration product **8** in 57% yield retaining enantiomeric excess

(Scheme 1A). The hydration of oxindole-derived product **7a** also gave corresponding hydration product **9** in 85% yield without loss of enantiomeric excess (Scheme 1B).



Scheme 1. Palladium Catalyzed Nitrile Hydration of the Cyanoalkylation product

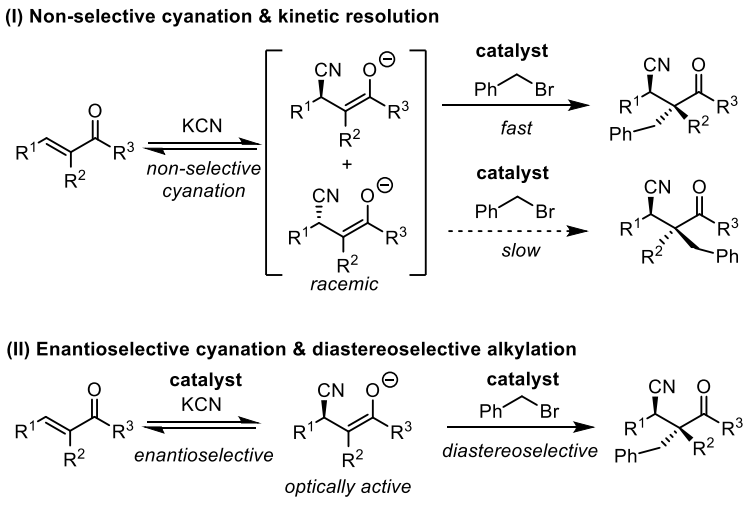
Then, the author investigated the mechanism of expression of stereoselectivity in this cyanoalkylation reaction. As below, there are two main scenarios that this reaction proceeds in a stereoselective manner.

(I) Non-selective cyanation & kinetic resolution (Scheme 2-I)

The first conjugate cyanation proceeds in a non-selective manner to generates racemic enolate, subsequent enolate alkylation proceeds with kinetic resolution.

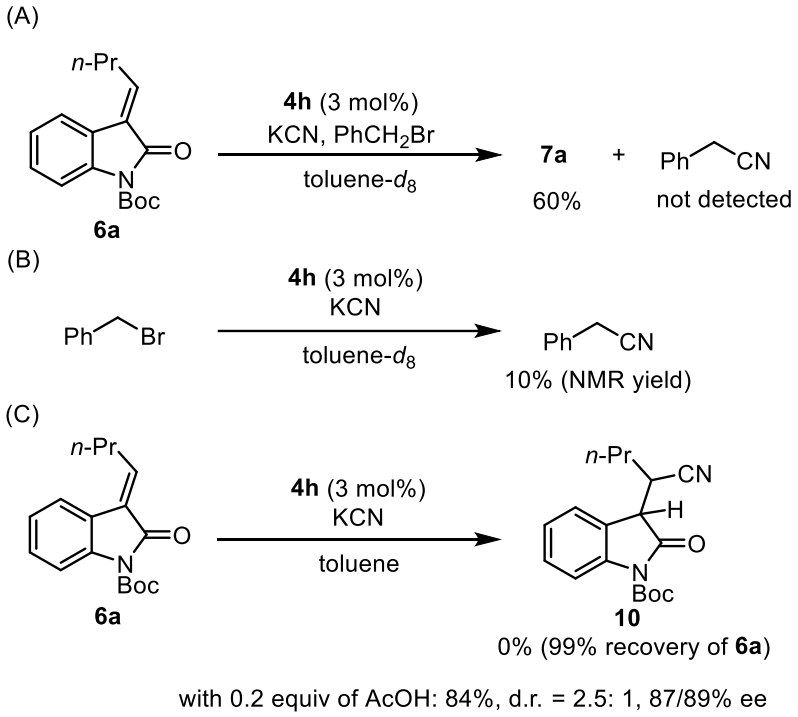
(II) Enantioselective cyanation & diastereoselective alkylation (Scheme 2-II)

The conjugate cyanation proceeds in enantioselective manner and affords the optically active enolate, which reacts with the alkyl halide in a diastereoselective fashion.



Scheme 2. Possible Scenarios for Cyanoalkylation Proceeds in Stereoselective manner

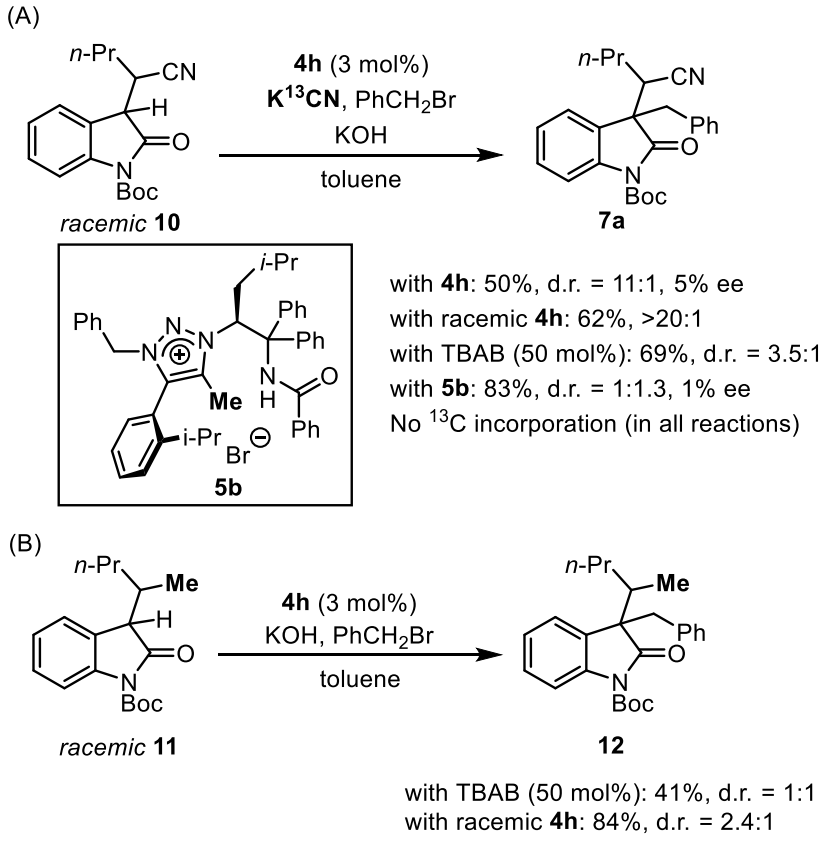
To gain an understanding of mechanism of asymmetric cyanoalkylation reaction, some control experiments were performed (Scheme 3). Initially, oxindole-derived olefin **6a** was subjected to standard condition in toluene-d_8, cyanoalkylation product **7a** was obtained yet benzyl cyanide was not detected (Scheme 3-A). Subsequently, benzyl bromide was subjected to potassium cyanide without the olefin, only 10% of benzyl cyanide was obtained (Scheme 3-B). These results suggest that conjugate cyanide addition to olefins is much faster than nucleophilic substitution of benzyl bromide. On the other hand, the reaction of olefin **6a** in the absence of benzyl bromide gave no cyanide adduct **10**, however in the presence of acetic acid, cyanoprotonation product **10** was obtained in 84% yield and low diastereoselectivity. Besides, enantiomeric excess of both diastereomer was high (Scheme 3-C). Low diastereoselectivity of cyanoprotonation product would be caused by rapid epimerization of C3 stereocenter of oxindole skeleton. Furthermore, this result suggests that conjugate cyanide addition proceeds in highly enantioselective manner, so non-selective cyanation is not the plausible scenario (Scheme2-I).



Scheme 3. Control Experiments of Asymmetric Cyanoalkylation

Considering the conjugate cyanide addition proceeds through in enantioselective manner, the possible mechanism that the cyanoalkylation proceeds under stereocontrol was enantioselective conjugate cyanation and subsequent diastereoselective alkylation

process (Scheme 2-II). Then, the author conducted several more control experiments to investigate further reaction mechanism and support the scenario (II) (Scheme 4). Firstly, when the racemic cyanoprotonation product **10** was treated with ^{13}C-labeled potassium cyanide, alkyl halide and potassium hydroxide in the presence of the catalyst **4h**, alkylation product was obtained in 11:1 diastereomeric ratio and major diastereomer was observed to be nearly racemic. Moreover, ^{13}C-labeled cyanoalkylation product **7a** was not observed (Scheme 4A). This result indicates that the reaction rate of alkylation of **10** is faster than that of retro-cyanide addition. The alkylation of racemic **10** proceeded with lower diastereoselectivity than cyanide addition-alkylation of the olefin **6a** stem from mismatch between (*S*)-**4h** and (*R*)-enolate produced by deprotonation of racemic **10**. Given this result, the author conducted the reaction of racemic **10** in the presence of racemic catalyst **4h**, the product was obtained in excellent diastereoselectivity. Furthermore, the reaction of racemic **10** with TBAB or triazolium C(5) methylated **5b** afforded the product in lower diastereomeric ratio. From these results, the chiral 1,2,3-triazolium ion would plays important role in the highly diastereoselective alkylation step. Finally, the author prepared the racemic **11** in which the cyano group of racemic **10** was replaced by a methyl group and treated it with potassium hydroxide and benzyl bromide in the presence of TBAB or catalyst **4h**, affording the alkylation product with low diastereoselectivity (Scheme 4B). These observations suggested that the hydrogen-bonding interaction of triazolium ion between the cyano group of enolate intermediate generated by conjugate cyanide addition leads to achieving the highly diastereoselective alkylation.



Scheme 4. Control Experiments of Diastereoselective Alkylation

3.3 Summary

In conclusion, the author has developed asymmetric cyanoalkylation of electron deficient olefins with potassium cyanide and alkyl halides catalyzed by chiral 1,2,3-triazolium salt. This protocol tolerates various alkylidene cyanoesters and oxindole-derived olefins, affording corresponding products in high enantio- and diastereoselectivity. The author conducted several control experiments, which suggested that the interaction between chiral 1,2,3-triazolium ion between the enolate intermediate played vital role in diastereoselective alkylation step.

Experimental Section

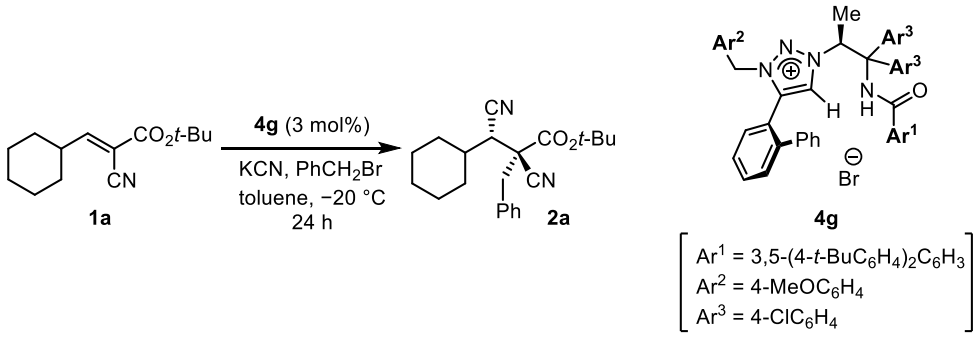
General information:

^{1}H NMR spectra were recorded on a JEOL JNM-ECA600II (600 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, sext = sextet, m = multiplet, and br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a 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). The high-resolution mass spectra were measured on Thermo Fisher Scientific Exactive Plus (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 N (spherical, neutral, 40~50μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALCEL OX-3 (OX3), CHIRALPAK AZ-3 (AZ3), CHIRALPAK IC-3 (IC3), CHIRALPAK IE-3 (IE3) , CHIRALPAK IF-3 (IF3) , CHIRALPAK IB N-3 (IBN3)] with hexane (Hex) and isopropyl alcohol (IPA) as eluent.

All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. Toluene 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 **4** and **5** were synthesized by following the literature methods. Potassium cyanide and potassium hydroxide were grounded by mortar and pestle. Other simple chemicals were purchased and used as such.

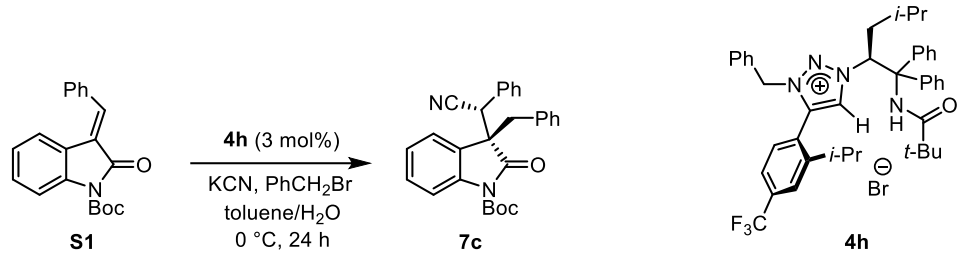
Representative Procedure for Asymmetric Cyanoalkylations:

1. Reaction of Alkylidene Cyanoesters



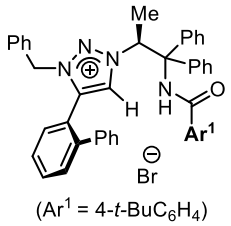
A solution of triazolium bromide **4g** (3.21 mg, 0.003 mmol), **1a** (23.5 mg, 0.10 mmol), and benzyl bromide (59.5 μL, 0.50 mmol) in toluene saturated with water (1.0 mL) was cooled to −20 °C, and potassium cyanide (32.5 mg, 0.50 mmol) was added under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 20:1 as eluent) to afford **2a** (25.5 mg, 0.072 mmol, 72% yield) as a colorless oil.

2. Reaction of Arylidene Oxindoles



A biphasic mixture of triazolium bromide **4h** (2.28 mg, 0.003 mmol), olefin **S1** (32.1 mg, 0.10 mmol), and benzyl bromide (23.8 μL, 0.20 mmol) in toluene (1.0 mL) and water (50 μL) was cooled to 0 °C, and potassium cyanide (13.0 mg, 0.20 mmol) was added under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 15:1 as eluent) to afford **7c** (33.7 mg, 0.076 mmol, 76% yield) as a colorless oil.

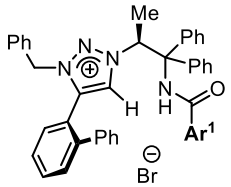
Characterization of Chiral 1,2,3-Triazolium Bromides 4 and 5:



(Ar^1 = 4-*t*-BuC_6H_4)

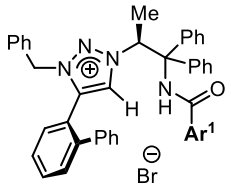
4b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (1H, br), 8.57 (1H, br), 8.18 (2H, d, J = 7.8 Hz), 7.91-7.86 (3H, m), 7.67 (1H, t, J = 7.8 Hz), 7.45-7.43 (4H, m), 7.38-7.25 (5H, m), 7.24-7.17 (4H, m), 7.05-6.99 (4H, m), 6.94-6.90 (4H, m), 6.58 (2H, d, J = 7.2 Hz), 4.89 (1H, d, J = 13.8 Hz), 4.86 (1H, d, J = 13.8 Hz), 1.65 (3H, d, J = 6.6 Hz), 1.28 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 155.4, 143.0, 140.3, 140.0, 138.5, 135.5, 133.0, 132.4, 132.0, 131.1, 130.9, 130.3, 129.9, 129.4, 129.2, 129.1, 129.0,

128.8(4), 128.7(9), 128.6, 128.5, 128.3, 128.2, 127.8, 127.2, 125.5, 120.4, 69.3, 66.0, 55.2, 35.1, 31.3, 15.8; HRMS (ESI) Calcd for $C_{47}H_{45}N_4O^+$ ([M−Br]$^+$) 681.3588, Found 681.3575.



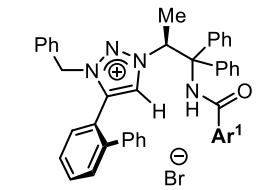
(Ar^1 = 3,5-*t*-Bu$_2$C$_6$H$_3$)

4c: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (1H, br), 8.79 (1H, br), 8.03 (1H, brq, J = 7.0 Hz), 7.96 (4H, br), 7.67 (1H, t, J = 7.8 Hz), 7.50-7.43 (3H, m), 7.39 (2H, t, J = 7.8 Hz), 7.32-7.14 (8H, m), 7.05-6.99 (6H, m), 6.88 (1H, br), 6.54 (2H, d, J = 7.8 Hz), 4.79 (1H, d, J = 15.0 Hz), 4.72 (1H, d, J = 15.0 Hz), 1.65 (3H, d, J = 7.0 Hz), 1.31 (18H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 151.1, 142.7, 140.2, 139.8, 138.6, 135.5, 133.5, 133.4, 132.5, 132.1, 131.1, 130.3, 129.9, 129.6, 129.2(4), 129.2(0), 128.9, 128.7, 128.6, 128.5, 128.2, 127.8, 127.5, 127.1, 126.3, 122.7, 120.4, 69.4, 65.8, 55.1, 35.3, 31.6, 15.7, one signal for aromatic carbon was not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{51}H_{53}N_4O^+$ ([M−Br]$^+$) 737.4214, Found 737.4200.



(Ar^1 = 3,5-Ph$_2$C$_6$H$_3$)

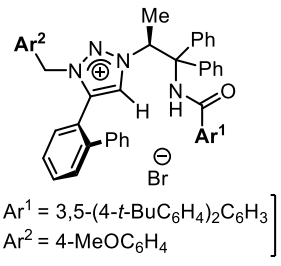
4d: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.33 (1H, br), 9.10 (1H, br), 8.25 (2H, s), 7.98-7.92 (4H, m), 7.81 (4H, d, J = 7.8 Hz), 7.62 (1H, t, J = 7.8 Hz), 7.41-7.38 (8H, m), 7.33-7.21 (7H, m), 7.18-6.98 (8H, m), 6.84 (2H, d, 7.2 Hz), 6.57 (2H, d, J = 7.2 Hz), 4.88 (1H, d, J = 14.4 Hz), 4.83 (1H, d, J = 14.4 Hz), 1.69 (3H, d, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.7, 142.8, 142.0, 140.5(2), 140,4(5), 139.8, 138.5, 135.5, 135.2, 132.9, 132.4, 131.9, 131.2, 130.2, ,129.9, 129.5, 129.4, 129.2, 129.0, 128.9(2), 128.(8), 128.8, 128.7, 128.5(4), 128.4(6), 128.3, 127.8, 127.7, 127.6, 127.3, 126.0, 120.3, 69.5, 65.9, 55.2, 16.0, one signal for aromatic carbon was not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{55}H_{45}N_4O^+$ ([M−Br]$^+$) 777.3588, Found 777.3554.



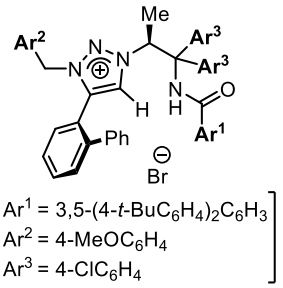
(Ar^1 = 3,5-(4-*t*-BuC$_6$H$_4$)$_2$C$_6$H$_3$)

4e: ^{1}H NMR (600 MHz, $CDCl_3$ at 60 °C) δ 9.93 (1H, br), 8.45 (1H, br), 8.12 (2H, s), 7.91 (1H, s), 7.82 (2H, br), 7.68-7.67 (4H, m), 7.59 (1H, t, J = 7.8 Hz), 7.42-7.32 (9H, m), 7.28-7.19 (4H, m), 7.15-7.01 (9H, m), 6.87 (2H, d, J = 7.8 Hz), 6.57 (2H, d, J = 7.2 Hz), 4.84 (1H, brd, J = 14.4 Hz), 4.81 (1H, d, J = 14.4 Hz), 1.67 (3H, br), 1.33 (18H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 150.7, 142.7, 141.9, 140.5, 139.8, 138.5, 137.5, 135.9, 135.3, 132.9, 132.5, 131.1, 130.3, 129.9, 129.6, 129.3, 129.1, 129.0, 128.9, 128.7, 128.5, 128.4, 127.9, 127.7, 127.5, 127.1, 126.0, 120.4, 69.4, 65.6, 55.6, 34.7, 31.5, 16.8, four signals for aromatic carbons

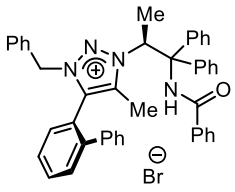
were not found probably due to the overlapping and broadening; HRMS (ESI) Calcd for $C_{63}H_{61}N_4O^+$ ([M−Br]$^+$) 889.4840, Found 889.4815.



4f: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.20 (1H, br), 8.87 (1H, br), 8.18 (2H, s), 7.93 (1H, s), 7.89 (2H, br), 7.74 (4H, d, J = 8.4 Hz), 7.62 (1H, t, J = 7.2 Hz), 7.44-7.32 (9H, m), 7.28-7.19 (4H, m), 7.15-7.01 (6H, m), 6.88-6.85 (2H, m), 6.64 (2H, d, J = 7.8 Hz), 6.50 (2H, d, J = 7.8 Hz), 4.85 (1H, brd, J = 13.8 Hz), 4.78 (1H, d, J = 13.8 Hz), 3.71 (3H, s), 1.69 (3H, br), 1.33 (18H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 160.7, 150.7, 142.7, 141.8, 140.4, 139.9, 138.5, 137.5, 135.8, 135.1, 132.8, 132.4, 132.3, 131.1, 130.6, 129.4, 129.1, 128.8, 128.5(3), 128.5(0), 128.3, 127.8, 127.6, 127.4, 127.3, 127.1, 126.1, 125.9, 125.4, 122.1, 120.5, 114.5, 69.5, 65.8, 55.5, 55.1, 34.7, 31.5, 16.2; HRMS (ESI) Calcd for $C_{64}H_{63}N_4O_2^+$ ([M−Br]$^+$) 919.4946, Found 919.4955.

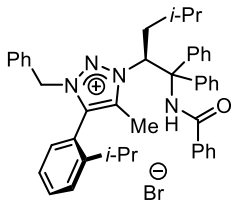


4g: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.54 (1H, br), 9.38 (1H, br), 8.26 (2H, s), 8.08 (1H, br), 7.94-7.62 (3H, m), 7.77 (4H, d, J = 8.4 Hz), 7.64 (1H, t, J = 7.2 Hz), 7.43 (4H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.31 (1H, br), 7.10-7.02 (3H, m), 7.00-6.96 (2H, m), 6.82 (2H, br), 6.74 (2H, br), 6.73 (2H, d, J = 7.8 Hz), 6.48 (2H, d, J = 7.8 Hz), 4.90 (1H, brd, J = 14.4 Hz), 4.83 (1H, d, J = 14.4 Hz), 3.75 (3H, s), 1.62 (3H, br), 1.33 (18H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 160.8, 150.6, 142.9, 141.6, 140.2, 138.4, 138.0, 137.4, 134.5, 133.8, 133.5, 133.4, 132.9, 132.3, 131.5, 131.1, 130.9, 130.1, 129.1, 128.8, 128.5, 128.4, 128.3, 127.5, 127.2, 125.8, 125.6, 121.5, 120.4, 114.5, 68.6, 65.2, 55.5, 55.4, 34.6, 31.4, 15.7, two peaks for aromatic carbons were not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{64}H_{61}Cl_2N_4O_2^+$ ([M−Br]$^+$) 987.4166, Found 987.4180.



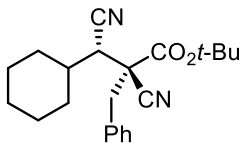
5a: ^{1}H NMR (600 MHz, $CDCl_3$) mixture of diastereomers: δ 8.35 (1H, brd, J = 7.2 Hz), 8.07 (1H, br), 8.01 (1H, d, J = 7.2 Hz), 7.81 (2H, s), 7.71-7.56 (8H, m), 7.54-7.44 (9H, m), 7.39 (1H, t, J = 7.2 Hz), 7.34-7.19 (18H, m), 7.18-7.12 (6H, m), 7.09 (2H, t, J = 7.2 Hz), 7.03 (1H, t, J = 7.2 Hz), 6.90 (2H, t, J = 7.8 Hz), 6.78-6.76 (6H, m), 6.63 (2H, d, J = 7.2 Hz), 6.60 (1H, q, J = 7.2 Hz), 6.21 (1H, q, J = 7.2 Hz), 5.69 (1H, d, J = 14.7 Hz), 5.59 (1H, d, J = 14.7 Hz), 5.34 (1H, d, J = 14.4 Hz), 5.19 (1H, d, J = 14.4

Hz), 2.17 (3H, s), 1.92 (3H, d, J = 7.2 Hz), 1.85 (3H, d, J = 7.2 Hz), 1.63 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) mixture of diastereomers: δ 167.4, 167.3, 142,6, 142.3, 141.7, 141,6, 141.0, 140.8, 139.4, 139.2, 138.8, 138.7, 138.6, 138.5, 134.2, 133.9, 132.5(3), 132.5(1), 132.4, 132.3, 132.2, 131.0, 130.7, 130.6, 129.8, 129.6, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8(0), 128.7(5), 128.5(4), 128.4(9), 128.3, 128.3, 128.2, 128.1(2), 128.0(8), 128.0, 127.9, 127.7, 127.2, 120.6, 120.4, 68.6, 38.3, 64.1, 64.0, 57.2, 56.1, 20.0, 19.8, 10.0, 8.8; HRMS (ESI) Calcd for $C_{44}H_{39}N_4O^+$ ([M−Br]$^+$) 639.3118, Found 639.3125.

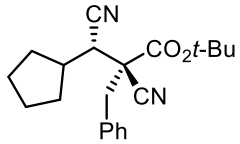


5b: ^{1}H NMR (600 MHz, $CDCl_3$) mixture of diastereomers: δ 8.22 (1H, brd, J = 7.8 Hz), 8.15 (1H, br), 8.10 (1H, br), 8.04 (1H, d, J = 7.8 Hz), 7.85 (2H, d, J = 7.8 Hz), 7.75 (1H, br), 7.64 (1H, s), 7.59-7.32 (25H, m), 7.30-7.23 (10H, m), 7.20 (1H, t, J = 7.8 Hz), 7.13-7.09 (4H, m), 6.90 (2H, d, J = 7.8 Hz), 6.25 (1H, br), 6.15 (1H, br), 6.09 (1H, d, J = 15.6 Hz), 5.98 (2H, br), 5.64 (1H, d, J = 15.6 Hz), 2.42-2.37 (1H, m), 2.19 (3H, s), 2.10-1.98 (3H, m), 1.94-1.85 (3H, m), 1.82 (3H, s), 1.63-1.56 (1H, m), 1.13 (1H, d, J = 6.0 Hz), 1.10 (1H, d, J = 6.0 Hz), 1.05 (1H, d, J = 6.0 Hz), 0.88 (1H, d, J = 6.0 Hz), 0.79 (1H, d, J = 6.0 Hz), 0.72 (1H, d, J = 6.0 Hz), 0.67 (1H, d, J = 6.6 Hz), 0.61 (1H, d, J = 6.6 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) mixture of diastereomers: δ 168.0, 166.6, 149.3, 148.3, 142.6, 140.7, 140.5, 139.4, 138.9 133.4, 133.1, 132.8, 132.7, 132.6, 132.5, 132.3, 131.6, 129.7, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0(1), 128.9(8), 128.8, 128.6(2), 128.5(7), 128.5, 128.4, 128.3, 128.2, 128.0, 127.9(3), 127.8(9), 127.7, 127.5, 127.3, 126.7, 126.2, 119.8, 119.6, 68.1(4), 68.0(6), 66.8, 57.4, 57.0, 43.2, 30.9, 30.6, 26.5, 25.4, 24.2, 24.1(3), 24.0(6), 23.9, 23.1, 23.0, 21.9, 21.7; HRMS (ESI) Calcd for $C_{44}H_{47}N_4O^+$ ([M−Br]$^+$) 647.3744, Found 647.3769.

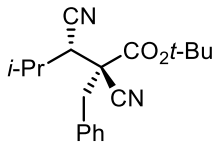
Characterization of Cyanoalkylated Products 2 and 7:



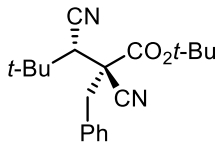
2a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.31 (5H, m), 3.50 (1H, d, J = 13.8 Hz), 3.15 (1H, d, J = 13.8 Hz), 3.11 (1H, d, J = 5.4 Hz), 2.33-2.27 (1H, m), 1.89-1.84 (1H, m), 1.81-1.75 (1H, m), 1.74-1.64 (3H, m), 1.39-1.16 (5H m), 1.27 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 132.7, 130.5, 128.7, 128.4, 117.0, 116.8, 86.0, 52.0, 46.0, 44.3, 38.8, 32.3, 29.9, 27.6, 26.2, 25.8, 25.6; HRMS (ESI) Calcd for $C_{22}H_{28}N_2O_2Na^+$ ([M+Na]$^+$) 375.2048, Found 375.2051; HPLC IC3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 13.5 min (minor), 18.9 min (major).



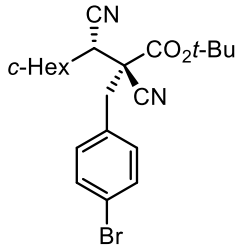
2b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.31 (5H, m), 3.52 (1H, d, J = 13.8 Hz), 3.33 (1H, d, J = 5.4 Hz), 3.15 (1H, d, J = 13.8 Hz), 2.19-2.13 (2H, m), 1.89-1.83 (1H, m), 1.82-1.66 (3H, m), 1.65-1.55 (2H, m), 1.38-1.33 (1H, m), 1.26 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 132.8, 130.4, 128.7, 128.4, 117.1, 116.7, 86.0, 53.1, 44.3, 44.1, 40.7, 32.0, 30.2, 27.6, 25.0, 24.8; HRMS (ESI) Calcd for $C_{21}H_{26}N_2O_2Na^+$ ([M+Na]$^+$) 361.1892, Found 361.1888; HPLC IC3, Hex/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 29.7 min (minor), 37.5 min (major).



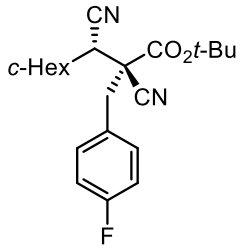
2c: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.32 (5H, m), 3.51 (1H, d, J = 13.2 Hz), 3.17-3.15 (2H, m), 2.09-2.04 (1H, m), 1.33 (3H, d J = 6.6 Hz), 1.27 (9H, s), 1.12 (3H, d J = 6.6 Hz), 1.65-1.55 (2H, m), 1.38-1.33 (1H, m), 1.26 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 132.7, 130.5, 128.7, 128.4, 116.7, 116.6, 86.1, 52.3, 46.5, 44.4, 29.7, 27.6, 22.4, 19.4; HRMS (ESI) Calcd for $C_{19}H_{24}N_2O_2Na^+$ ([M+Na]$^+$) 335.1735, Found 335.1736; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 11.1 min (major), 12.2 min (minor).



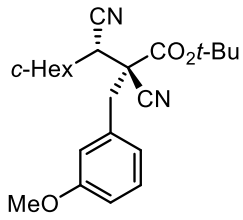
2d: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.31 (5H, m), 3.66 (1H, d, J = 13.2 Hz), 3.37 (1H, s), 3.04 (1H, d, J = 13.2 Hz), 1.26 (9H, s), 1.14 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 132.5, 130.8, 128.7, 128.4, 117.5(0), 117.4(6), 86.0, 49.9, 49.2, 46.2, 35.4, 28.6, 27.4; HRMS (ESI) Calcd for $C_{20}H_{26}N_2O_2Na^+$ ([M+Na]$^+$) 349.1892, Found 349.1900; HPLC IC3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 10.0 min (minor), 11.2 min (major).



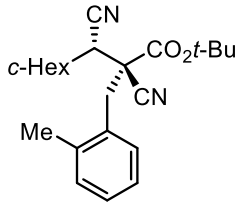
2e: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 8.7 Hz), 7.02 (2H, d, J = 8.7 Hz), 3.42 (1H, d, J = 12.9 Hz), 3.13 (1H, d, J = 12.9 Hz), 3.09 (1H, d, J = 5.4 Hz), 2.32-2.26 (1H, m), 1.90-1.85 (1H, m), 1.80-1.77 (1H, m), 1.72-1.63 (3H, m), 1.43-1.16 (5H, m), 1.32 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 132.1, 131.9, 131.8, 122.7, 116.8, 116.6, 86.4, 51.9, 46.1, 43.6, 38.8, 32.4, 29.8, 27.7, 26.2, 25.8, 25.5; HRMS (ESI) Calcd for $C_{22}H_{27}BrN_2O_2Na^+$ ([M+Na]$^+$) 453.1154, Found 453.1166; HPLC AZ3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 254 nm, 18.6 min (major), 21.8 min (minor).



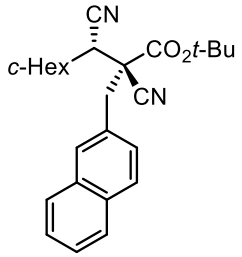
2f: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.28 (2H, m), 7.05-7.01 (2H, m), 3.45 (1H, d, J = 13.2 Hz), 3.14 (1H, d, J = 13.2 Hz), 3.09 (1H, d, J = 4.8 Hz), 2.32-2.27 (1H, m), 1.90-1.85 (1H, m), 1.81-1.77 (1H, m), 1.72-1.63 (3H, m), 1.43-1.15 (5H, m), 1.31 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 162.9 (d, J_{C-F} = 248.7 Hz), 132.1 (d, J_{C-F} = 8.8 Hz), 128.5 (d, J_{C-F} = 2.9 Hz), 116.8, 116.7, 115.7 (d, J_{C-F} = 20.2 Hz), 86.2, 52.1, 46.0, 43.4, 38.8, 32.3, 29.8, 27.7, 26.2, 25.8, 25.5; HRMS (ESI) Calcd for $C_{22}H_{27}FN_2O_2Na^+$ ([M+H]$^+$) 393.1954, Found 393.1956; HPLC IF3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 254 nm, 13.3 min (major), 15.0 min (minor).



2g: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.21 (1H, m), 6.90-6.85 (3H, m), 3.80 (3H, s), 3.47 (1H, d, J = 12.9 Hz), 3.13 (1H, d, J = 12.9 Hz), 3.11 (1H, d, J = 5.4 Hz), 2.32-2.26 (1H, m), 1.90-1.65 (5H, m), 1.41-1.16 (5H, m), 1.30 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 159.7, 134.1, 129.7, 122.7, 117.0, 116.9, 115.8, 114.1, 86.0, 55.4, 52.0, 46.0, 44.3, 38.8, 32.3, 29.9, 27.6, 26.2, 25.8, 25.4; HRMS (ESI) Calcd for $C_{23}H_{30}N_2O_3Na^+$ ([M+Na]$^+$) 405.2154, Found 405.2161; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 18.4 min (minor), 35.1 min (major).

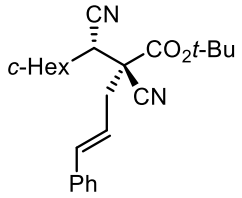


2h: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (1H, d, J = 7.8 Hz), 7.22-7.14 (3H, m), 3.58 (1H, d, J = 13.8 Hz), 3.25 (1H, d, J = 13.8 Hz), 3.16 (1H, d, J = 5.4 Hz), 2.40 (3H, s), 2.32-2.28 (1H, m), 1.89-1.84 (1H, m), 1.80-1.65 (4H, m), 1.40-1.16 (5H, m), 1.29 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 137.7, 131.6, 131.2, 130.4, 128.3, 126.2, 117.2, 117.0, 86.0, 51.4, 46.5, 40.2, 38.8, 32.3, 29.9, 27.5, 26.2, 25.8, 25.6, 20.0; HRMS (ESI) Calcd for $C_{23}H_{30}N_2O_2Na^+$ ([M+Na]$^+$) 389.2205, Found 389.2201; HPLC IBN3, Hex/IPA = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 6.6 min (minor), 9.5 min (major).

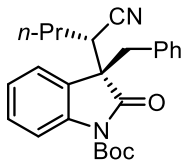


2i: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85-7.78 (3H, m), 7.74 (1H, brs), 7.51-7.45 (3H, m), 3.65 (1H, d, J = 13.2 Hz), 3.35 (1H, d, J = 13.2 Hz), 3.17 (1H, d, J = 5.4 Hz), 2.33-2.28 (1H, m), 1.89-1.85 (1H, m), 1.81-1.66 (4H, m), 1.40-1.16 (5H, m), 1.20 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2, 133.3, 133.1, 130.3, 129.7, 128.5, 128.0, 127.9, 127.8, 126.5, 126.4, 117.0, 116.8, 86.1, 52.2, 46.1, 44.4, 38.8, 32.4, 29.8, 27.6, 26.2, 25.8, 25.6; HRMS (ESI) Calcd for $C_{26}H_{30}N_2O_2Na^+$ ([M+Na]$^+$)

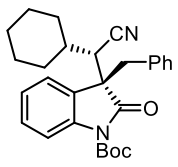
425.2205, Found 425.2207; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 19.0 min (minor), 19.8 min (major).



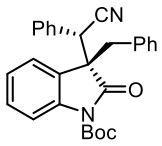
2j: The reaction was conducted at −40 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (2H, d, J = 6.9 Hz), 7.33 (2H, t, J = 6.9 Hz), 7.28-7.25 (1H, m), 6.57 (1H, d, J = 15.6 Hz), 6.15 (1H, ddd, J = 15.6, 9.6, 5.4 Hz), 3.13 (1H, dd, J = 13.8, 5.4 Hz), 3.06 (1H, d, J = 6.0 Hz), 2.82 (1H, dd, J = 13.8, 9.6 Hz), 2.30-2.26 (1H, m), 1.89-1.84 (1H, m), 1.82-1.66 (4H, m), 1.44 (9H, s), 1.40-1.13 (5H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.3, 136.7, 136.2, 128.8, 128.3, 126.6, 120.0, 116.9, 116.7, 86.1, 50.6, 44.7, 42.3, 39.0, 32.2, 30.1, 27.9, 26.2, 25.8, 25.6; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_2Na^+$ ($[M+H]^+$) 401.2205, Found 401.2209; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 13.4 min (major), 15.9 min (minor).



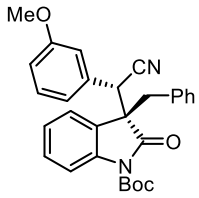
7a: The reaction was conducted in wet toluene at −40 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 7.8 Hz), 7.54-7.52 (1H, m), 7.29-7.25 (2H, m), 7.07 (1H, t, J = 7.8 Hz), 7.00 (2H, t, J = 7.8 Hz), 6.75 (2H, d, J = 7.8 Hz), 3.46 (1H, d, J = 12.3 Hz), 3.32 (1H, dd, J = 9.6, 5.4 Hz), 3.27 (1H, d, J = 12.3 Hz), 1.65-1.55 (1H, m), 1.53 (9H, s), 1.42-1.36 (1H, m), 1.15-1.11 (2H, m), 0.85 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5, 148.2, 140.0, 133.5, 129.8, 129.4, 127.9, 127.2, 126.3, 125.0, 123.8, 120.1, 115.1, 84.7, 55.7, 44.9, 38.8, 30.5, 28.1, 20.9, 13.4; HRMS (ESI) Calcd for $C_{25}H_{28}N_2O_3Na^+$ ($[M+Na]^+$) 427.1992, Found 427.1996; HPLC IE3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.1 min (minor), 6.6 min (major).



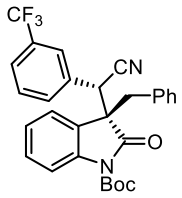
7b: The reaction was conducted in wet toluene at −40 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81-7.79 (1H, m), 7.49 (1H, d, J = 7.8 Hz), 7.27-7.22 (2H, m), 7.06 (1H, t, J = 7.8 Hz), 7.07-6.97 (2H, m), 6.70-6.68 (2H, m), 3.47 (1H, d, J = 12.9 Hz), 3.28 (1H, d, J = 4.8 Hz), 3.22 (1H, d, J = 12.9 Hz), 1.65-1.61 (1H, m), 1.52 (9H, s), 1.52-1.44 (3H, m), 1.39-1.33 (1H, m), 1.22-1.16 (2H, m), 1.08-0.88 (4H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5, 148.3, 139.7, 133.2, 129.9, 129.3, 129.1, 127.8, 127.2, 127.0, 124.8, 124.3, 119.4, 115.1, 84.5, 54.9, 46.5, 45.2, 37.9, 32.9, 30.4, 28.1, 26.1, 25.8, 25.6; HRMS (ESI) Calcd for $C_{28}H_{32}N_2O_3Na^+$ ($[M+Na]^+$) 467.2305, Found 467.2304; HPLC IE3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 12.2 min (minor), 16.7 min (major).



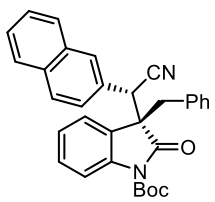
7c: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 7.8 Hz), 7.28-7.12 (4H, m), 7.10-7.02 (5H, m), 6.95-6.94 (2H, m), 6.89-6.88 (2H, m), 6.95-6.93 (3H, m), 6.62-6.58 (1H, m), 6.50 (1H, d, J = 7.8 Hz), 6.40-6.38 (1H, m), 4.51 (1H, s), 3.64 (1H, d, J = 13.2 Hz), 3.53 (1H, d, J = 13.2 Hz), 1.43 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 147.9, 140.1, 134.0, 130.2, 129.5, 129.0, 128.8, 128.4, 128.1, 127.2, 125.3, 124.5(3), 124.4(8), 118.9, 115.0, 84.3, 58.1, 45.1, 42.9, 28.0; HRMS (ESI) Calcd for $C_{28}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 461.1836, Found 461.1835; HPLC OX3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 8.2 min (minor), 9.0 min (major).



7d: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 7.8 Hz), 7.31-7.26 (2H, m), 7.21-7.18 (1H, m), 7.07-6.98 (4H, m), 6.91-6.89 (2H, m), 6.70-6.68 (1H, m), 6.56 (1H, d, J = 7.8 Hz), 6.41-6.40 (1H, m), 4.48 (1H, s), 3.63 (1H, d, J = 13.2 Hz), 3.54 (3H, s), 3.52 (1H, d, J = 13.2 Hz), 1.44 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 159.3, 147.9, 140.3, 134.0, 131.4, 130.2, 129.5, 129.4, 128.1, 127.2, 125.4, 124.5, 124.4, 121.4, 118.8, 115.6, 115.0, 113.4, 84.4, 58.0, 55.2, 45.1, 42.8, 28.0; HRMS (ESI) Calcd for $C_{29}H_{28}N_2O_4Na^+$ ([M+Na]$^+$) 491.1941, Found 491.1942; HPLC IC3, Hex/IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 11.3 min (minor), 17.9 min (major).

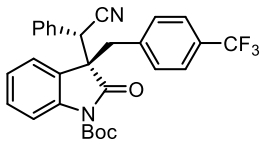


7e: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 7.8 Hz), 7.44-7.42 (1H, m), 7.32-7.26 (2H, m), 7.25-7.14 (4H, m), 7.09-7.02 (3H, m), 6.91-6.89 (2H, m), 4.56 (1H, s), 3.65 (1H, d, J = 13.5 Hz), 3.54 (1H, d, J = 13.5 Hz), 1.43 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 147.8, 140.0, 133.7, 132.4, 131.4, 130.9 (q, J_{C-F} = 33.2 Hz), 130.2, 129.9, 129.0, 128.2, 127.3, 125.8 (q, J_{C-F} = 2.9 Hz), 125.7 (q, J_{C-F} = 3.0 Hz), 124.7, 124.6, 124.4, 123.5 (q, J_{C-F} = 273.3 Hz), 118.2, 84.7, 58.0, 44.8, 42.7, 27.9; HRMS (ESI) Calcd for $C_{29}H_{25}F_3N_2O_3Na^+$ ([M+Na]$^+$) 529.1709, Found 529.1707; HPLC IC3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.6 min (minor), 11.5 min (major).

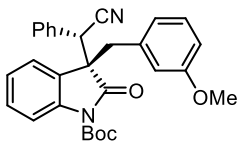


7f: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (1H, d, J = 7.8 Hz), 7.69 (1H, brd, J = 6.6 Hz), 7.64 (1H, d, J = 8.4 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.47 (1H, s), 7.42-7.40 (2H, m), 7.32-7.29 (1H, m), 7.18-7.17 (2H, m), 7.07-7.03 (3H, m), 6.98 (1H, d, J = 9.0 Hz), 6.92(1H, d, J = 7.8 Hz), 6.50 (1H, d, J = 7.8 Hz), 4.68 (1H, s), 3.69 (1H, d, J = 12.9 Hz), 3.59 (1H, d, J = 12.9 Hz), 1.26 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 147.7, 140.1, 134.0,

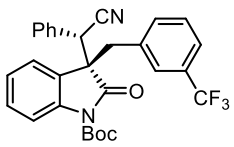
133.0, 132.8, 130.2, 129.6, 129.0, 128.3, 128.2, 128.1, 127.6, 127.2, 126.9, 126.5, 125.8, 125.2, 124.6, 124.5, 118.9, 115.0, 84.2, 58.2, 45.2, 42.9, 27.8, one peak for aromatic carbon was not found probably due to overlapping; HRMS (ESI) Calcd for $C_{32}H_{28}N_2O_3Na^+$ ([M+Na]$^+$) 511.1992, Found 511.1998; HPLC IC3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.9 min (minor), 9.8 min (major).



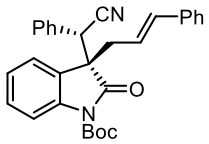
7g: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (1H, d, J = 7.8 Hz), 7.31-7.26 (3H, m), 7.24-7.21 (1H, m), 7.16 (1H, t, J = 7.8 Hz), 7.10-7.07 (2H, m), 7.01 (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 7.8 Hz), 4.52 (1H, s), 3.69 (1H, d, J = 12.9 Hz), 3.67 (1H, d, J = 12.9 Hz), 1.43 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.2, 147.6, 138.1, 130.5, 129.9(1), 129.8(6), 129.5 (q, $J_{C–F}$ = 33.4 Hz), 129.0, 128.5, 125.0 (q, $J_{C–F}$ = 4.2 Hz), 124.7(1), 124.6(8), 124.4, 124.1 (q, $J_{C–F}$ = 271.8 Hz), 118.7, 115.1, 84.7, 57.8, 45.1, 42.4, 27.9; HRMS (ESI) Calcd for $C_{29}H_{25}F_3N_2O_3Na^+$ ([M+Na]$^+$) 529.1709, Found 529.1708; HPLC OD3, Hex/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.9 min (minor), 27.7 min (major).



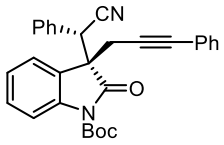
7h: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 7.8 Hz), 7.31-7.26 (2H, m), 7.21-7.18 (1H, m), 7.17-7.14 (1H, m), 7.08 (2H, t, J = 7.8 Hz), 6.95-6.93 (3H, m), 6.62-6.58 (1H, m), 6.50 (1H, d, J = 7.8 Hz), 6.40-6.38 (1H, m), 4.51 (1H, s), 3.61 (1H, d, J = 13.2 Hz), 3.57 (3H, s), 3.50 (1H, d, J = 13.2 Hz), 1.44 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 159.2, 147.9, 140.2, 135.4, 130.2, 129.5, 129.1, 129.0, 128.8, 128.4, 125.4, 124.5, 124.4, 118.9, 115.0, 114.8, 113.6, 84.3, 58.0, 55.1, 45.0, 43.0, 28.0; HRMS (ESI) Calcd for $C_{29}H_{28}N_2O_4Na^+$ ([M+Na]$^+$) 491.1941, Found 491.1940; HPLC OD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 13.3 min (minor), 16.1 min (major).



7i: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (1H, d, J = 7.2 Hz), 7.33-7.26 (3H, m), 7.22-7.19 (1H, m), 7.18-7.15 (2H, m), 7.10-7.07 (4H, m), 6.96 (2H, d, J = 7.2 Hz), 4.53 (1H, s), 3.69 (1H, d, J = 13.2 Hz), 3.56 (1H, d, J = 13.2 Hz), 1.43 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 147.7, 140.0, 135.0, 133.5, 130.4 (q, $J_{C–F}$ = 33.2 Hz), 130.0, 129.9, 129.0, 128.9, 128.6, 128.5, 126.8 (q, $J_{C–F}$ = 4.4 Hz), 124.7, 124.4, 124.1 (q, $J_{C–F}$ = 4.4 Hz), 123.9 (q, $J_{C–F}$ = 271.8 Hz), 118.7, 115.0, 84.6, 58.0, 44.9, 42.6, 27.9; HRMS (ESI) Calcd for $C_{29}H_{25}F_3N_2O_3Na^+$ ([M+Na]$^+$) 529.1709, Found 529.1708; HPLC IC3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.4 min (major), 11.9 min (minor).



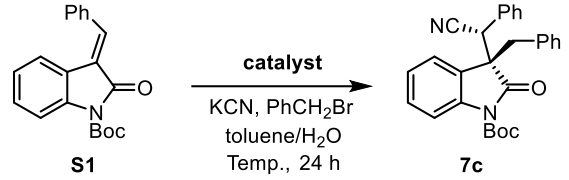
7j: The reaction was conducted in wet toluene at −40 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85-7.82 (1H, m), 7.48-7.43 (1H, m), 7.31-7.27 (2H, m), 7.25-7.15 (6H, m), 7.08 (2H, t, J = 8.4 Hz), 6.89 (2H, d, J = 8.4 Hz), 6.52 (1H, d, J = 15.6 Hz), 5.89 (1H, ddd, J = 15.6, 8.4, 6.6 Hz), 4.40 (1H, s), 3.17 (1H, dd, J = 13.8, 6.6 Hz), 3.13 (1H, dd, J = 13.8, 8.4 Hz), 1.46 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 148.1, 140.0, 136.8, 135.5, 130.0, 129.7, 128.8, 128.5, 128.4, 127.7, 126.5, 125.8, 124.9, 124.1, 121.7, 118.5, 115.1, 84.5, 56.3, 44.9, 39.9, 28.0; HRMS (ESI) Calcd for $C_{30}H_{28}N_2O_3Na^+$ ($[M+Na]^+$) 487.1992, Found 487.1994; HPLC OX3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 13.8 min (major), 15.5 min (minor).

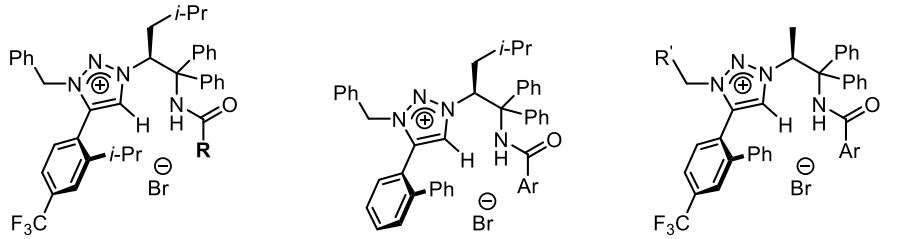


7k: for major diastereomer ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86-7.83 (1H, m), 7.56 (1H, d, J = 8.4 Hz), 7.33-7.28 (2H, m), 7.25-7.08 (8H, m), 6.95 (2H, d, J = 7.8 Hz), 4.48 (1H, s), 3.37 (1H, d, J = 16.2 Hz), 3.29 (1H, d, J = 16.2 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.0, 148.2, 140.4, 131.7, 129.9, 129.0, 128.9, 128.5, 128.2, 128.1, 125.5, 124.9, 124.2, 122.8, 118.3, 115.0, 84.6, 84.3, 82.7, 55.4, 44.1, 28.0, 27.9; (ESI) Calcd for $C_{30}H_{26}N_2O_3Na^+$ ($[M+Na]^+$) 485.1836, Found 485.1839; HPLC IC3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 18.5 min (minor), 21.1 min (major).

Additional Data for Optimization of Reaction Conditions:

Effect of Catalyst Structure and Reaction Conditions on The Asymmetric Cyanoalkylation of Arylidene Oxindole S1





4h (**R** = *t*-Bu)
S2 (**R** = 3,5-$(CF_3)_2C_6H_3$)
S3 (**R** = 3,5-$Et_2C_6H_3$)
S4 (**R** = $CHPh_2$)

S5 (Ar = 4-*t*-BuC_6H_4)

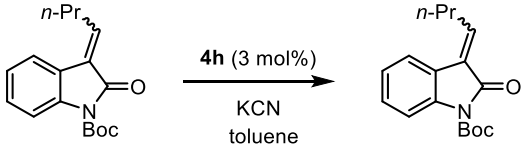
S6 (R' = 4-$CF_3C_6H_4$)
(Ar = 3,5-$(CF_3)_2C_6H_3$)

Entry	catalyst	Temp. (°C)	Yield (%)[a]	d.r.[b]	ee (%)[c]
1	**4h** (1mol%)	r.t.	64	>20:1	78
2	**4h** (1mol%)	0	36	>20:1	90
3	**4h** (3mol%)	0	76	>20:1	92
4	**S2** (1mol%)	r.t.	55	>20:1	74
5	**S3** (1mol%)	r.t.	59	>20:1	75
6	**S4** (1mol%)	r.t.	17	>20:1	68
7	**S5** (1mol%)	r.t.	trace	-	-
8	**S6** (1mol%)	r.t.	trace	-	-

The reactions were conducted with **S1** (0.10 mmol), benzyl bromide (0.20 mmol), and KCN (0.20 mmol) in the presence of catalyst in toluene (1.0 mL) and H_2O (50 μL) for 24 h. [a] Isolated yield. [b] Determined by ^1H NMR analysis of crude reaction mixture. [c] Enantiomeric excess of major diastereomer, determined by chiral HPLC analysis.

Details for Control Experiments:

1. Reactions of Alkylidene Oxindole 6a with KCN in The Absence of Benzyl Bromide



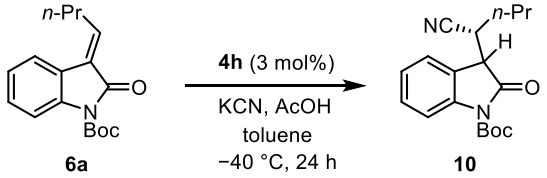
From (*E*)-**6a**: 99% recovery of (*E*)-**6a**
From (*Z*)-**6a**: 99% of **6a**, *E*/*Z* = 1.8:1
From (*Z*)-**6a** without KCN: 99% recovery of (*Z*)-**6a**

The reaction of (*E*)-**6a** with KCN in the absence of benzyl bromide in toluene saturated with water at −40°C resulted in the quantitative recovery of (*E*)-**6a**. On the other hand, (*Z*)-**6a** underwent isomerization into (*E*)-**6a** under identical reaction conditions, leading to the formation of a mixture of geometrical isomers in the *E*/*Z* ratio of 1.8:1.

This isomerization would be ascribable to the reversible conjugate addition of cyanide ion as we confirmed the quantitative recovery of (*Z*)-**6a** in the absence of benzyl bromide and KCN under otherwise similar conditions.

(*E*)-**6a** and (*Z*)-**6a** were synthesized by following the literature procedure. The resulting geometrical isomers were separable via column chromatography on silica gel (Hex/Et_2O = 15:1 as eluent). (*E*)-**6a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (1H, d, 7.8 Hz), 7.60 (1H, d, *J* = 7.8 Hz), 7.32 (1H, t, *J* = 7.8 Hz), 7.17 (1H, t, *J* = 7.8 Hz), 7.10 (1H, t, *J* = 7.8 Hz), 2.66 (2H, q, *J* = 7.8 Hz), 1.69 (2H, sext, *J* = 7.8 Hz), 1.65 (9H, s), 1.04 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2, 149.6, 143.8, 139.5, 129.1, 126.7, 124.1, 123.3, 122.8, 114.2, 84.2, 31.5, 28.3, 22.1, 14.1; HRMS (ESI) Calcd for $C_{17}H_{21}NO_3Na^+$ ([M+Na]$^+$) 310.1419, Found 310.1417. (*Z*)-**6a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (1H, d, 7.8 Hz), 7.43 (1H, d, *J* = 7.8 Hz), 7.29 (1H, t, *J* = 7.8 Hz), 7.13 (1H, t, *J* = 7.8 Hz), 6.93 (1H, t, *J* = 7.8 Hz), 2.98 (2H, q, *J* = 7.8 Hz), 1.66 (9H, s), 1.61 (2H, sext, *J* = 7.8 Hz), 1.02 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.5, 149.7, 146.9, 144.5, 138.1, 128.9, 126.1, 124.0, 123.4, 118.7, 115.2, 85.3, 30.2, 28.3, 27.6, 14.1; HRMS (ESI) Calcd for $C_{17}H_{21}NO_3Na^+$ ([M+Na]$^+$) 310.1419, Found 310.1412.

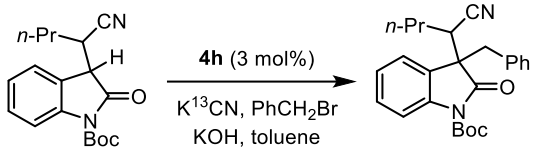
2. Procedure for Asymmetric Cyanoprotonation of Alkylidene Oxindole 6a



A solution of triazolium bromide **4h** (2.29 mg, 0.003 mmol), **6a** (28.7 mg, 0.10 mmol), and acetic acid (11.4 μL, 0.20 mmol) in toluene saturated with water (1.0 mL) was cooled to −40 °C, and potassium cyanide (13.0 mg, 0.20 mmol) was added under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 20:1 as eluent) to afford **10** (26.4 mg, 0.084 mmol, 84% yield) as a colorless oil. **10**: ^{1}H NMR (600 MHz, $CDCl_3$) for major diastereomer: δ 7.86 (1H, d, *J* = 7.8 Hz), 7.65 (1H, d, *J* = 7.8 Hz), 7.39 (1H, t, *J* = 7.8 Hz), 7.24 (1H, t, *J* = 7.8 Hz), 3.94 (1H, br), 3.42-3.40 (1H, m), 1.65 (9H, s), 1.63-1.51 (1H, m), 1.43-1.32 (2H, m), 1.25-1.18 (1H, m), 0.88 (3H, t, *J* = 7.2 Hz), for minor diastereomer: 7.89 (1H, d, *J* = 7.8 Hz), 7.40-7.36 (2H, m), 7.22-7.19 (1H, m), 3.69 (1H, br), 3.29-3.27 (1H, m), 1.65 (9H, s), 1.63-1.51 (1H, m), 1.43-1.32 (2H, m), 1.25-1.18 (1H,

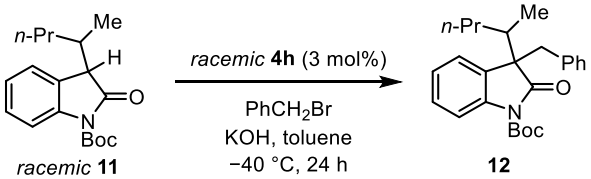
m), 1.00 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) for major diastereomer: δ 172.6, 148.8, 140.6, 129.5, 125.1, 124.4, 123.2, 120.5, 115.5, 85.2, 47.2, 32.4, 29.5, 28.2, 20.8, 13.4, for minor diastereomer: 172.8, 148.9, 140.7, 129.7, 124.8, 124.4, 123.6, 118.9, 115.6, 85.1, 47.1, 34.1, 32.0, 13.5, two peaks for aliphatic carbons were not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{18}H_{22}N_2O_3Na^+$ ($[M+Na]^+$) 337.1528, Found 337.1532; HPLC AD3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 5.1 min (major of major diastereomer), 6.1 min (minor of major diastereomer), 8.0 min (minor of minor diastereomer), 8.6 min (major of minor diastereomer).

3. Representative Procedure for Catalytic Alkylation of 10



A solution of triazolium bromide **4h** (2.28 mg, 0.003 mmol), racemic **10** (23.5 mg, 0.10 mmol), benzyl bromide (23.8 μL, 0.20 mmol), and potassium cyanide-^{13}C (13.2 mg, 0.20 mmol) in toluene saturated with water (1.0 mL) was cooled to −40 °C, and potassium hydroxide (11.2 mg, 0.20 mmol) was added under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 15:1 as eluent) to afford **7a** (20.3 mg, 0.050 mmol, 50% yield) as a colorless oil.

4. Representative Procedure for Catalytic Alkylation of 11



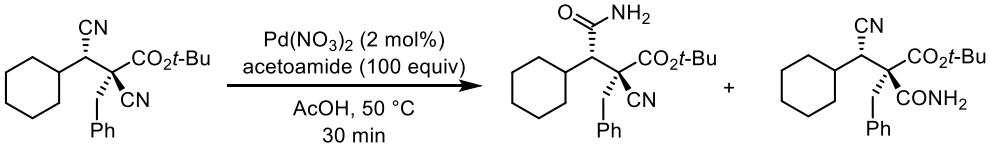
A solution of racemic triazolium bromide **4h** (2.28 mg, 0.003 mmol), racemic **11** (30.3 mg, 0.10 mmol), and benzyl bromide (23.8 μL, 0.20 mmol) in toluene saturated with water (1.0 mL) was cooled to −40 °C, and potassium hydroxide (11.2 mg, 0.20 mmol) was added under ambient atmosphere. After stirring for 24 h at the same temperature, the reaction mixture was diluted with water and the extractive work-up was performed with EtOAc three times. The combined organic layers were washed with brine and

dried over anhydrous Na_2SO_4. After filtration and removal of solvents via evaporation, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 15:1 as eluent) to afford **12** (30.1 mg, 0.084 mmol, 84% yield) as a colorless oil.

11: ^{1}H NMR (600 MHz, $CDCl_3$) mixture of diastereomers: δ 7.83-7.80 (2H, m), 7.31-7.23 (4H, m), 7.16-7.11 (2H, m), 3.55-3.53 (2H, m), 2.40-2.28 (2H, m), 1.50-1.26 (8H m), 0.96-0.86 (9H, m), 0.79 (3H, d, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) mixture of diastereomers: δ 176.4, 175.6, 149.5, 149.4, 140.8, 140.6, 128.1, 128.0, 127.6, 126.5, 124.4, 124.2, 124.1, 123.9, 114.9(4), 114.9(0), 84.3(3), 84.2(9), 51.0, 50.8, 36.7, 36.4, 36.3, 35.2, 29.9, 28.3, 20.8, 16.6, 15.7, 14.2(2), 14.1(9); HRMS (ESI) Calcd for $C_{18}H_{25}NO_3Na^+$ ([M+Na]$^+$) 326.1732, Found 326.1730.

12: ^{1}H NMR (600 MHz, $CDCl_3$) for major diastereomer: δ 7.53 (1H, d, J = 7.8 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.21-7.15 (2H, m), 7.02-6.96 (3H, m), 6.73 (2H, d, J = 6.6 Hz), 3.21 (1H, d, J = 12.6 Hz), 3.14 (1H, d, J = 12.6 Hz), 2.27-2.20 (1H, m), 1.51 (9H, s), 1.43-1.35 (1H, m), 1.28-1.16 (2H, m), 1.12 (3H, d, J = 6.6 Hz), 1.01-0.92 (1H, m), 0.83 (3H, t, J = 7.2 Hz), for minor diastereomer: 7.83-7.80 (2H, m), 7.31-7.23 (4H, m), 7.16-7.11 (2H, m), 3.55-3.52 (2H, m), 2.40-2.28 (2H, m), 1.50-1.26 (8H m), 0.96-0.86 (9H, m), 0.79 (3H, d, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) for major diastereomer: δ 178.4, 148.9, 140.2, 135.7, 129.9, 127.9, 127.6, 126.5, 124.0, 123.9, 114.7, 83.8, 58.9, 43.2, 40.7, 34.3, 28.1, 20.9, 14.2(2), 14.1(5), detectable peaks for minor diastereomer: 178.3, 148.9, 140.3, 135.8, 129.9, 123.9, 114.6, 58.7, 42.9, 40.8, 33.3, 21.1, 14.7, 14.3; HRMS (ESI) Calcd for $C_{25}H_{31}NO_3Na^+$ ([M+Na]$^+$) 416.2202, Found 416.2211.

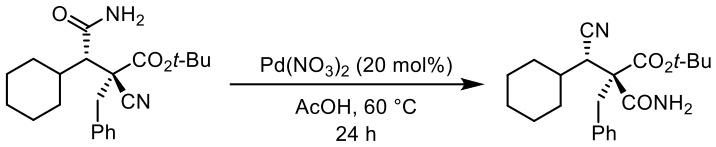
Transfer Hydration of Cyanoalkylated Products:



2a (95% ee) **8** (95% ee) **S7** (95% ee)

To a solution of **2a** (17.6 mg, 0.05 mmol) and palladium nitrate (0.2 mg, 1×10^{-3} mmol) in acetic acid (0.5 mL) was added acetoamide (254 μL, 5.0 mmol) at room temperature under Ar. The resulting mixture was heated with stirring for 30 min, and then diluted with water. The extractive work-up was performed with EtOAc three times, and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After filtration and evaporation to remove the volatiles, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 15:1 as eluent) to afford **8** (10.6 mg, 0.0285 mmol, 57% yield) and **S7** (1.3 mg, 3.5×10^{-3} mmol).

The isomer **S7**, with the more hindered cyano group hydrated selectively, would be formed through intramolecular transfer hydration of **8** as we confirmed that the reaction of isolated **8** without the use of acetoamide as an external hydration reagent gave rise to **S7** in moderate yield.



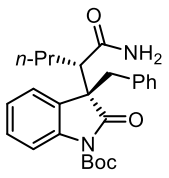
8 (95% ee) **S7** (95% ee)

8: 69% recovery, **S7**: 30%

A mixture of **8** (10.6 mg, 0.0285 mmol) and palladium nitrate (1.1 mg, 5.7×10^{-3} mmol) in acetic acid (0.2 mL) was heated with stirring for 24 h under Ar, and then diluted with water. The extractive work-up was performed with EtOAc three times, and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After filtration and evaporation to remove the volatiles, the resulting crude residue was purified by column chromatography (Hex/EtOAc = 15:1 as eluent) to afford **S7** (3.2 mg, 8.6×10^{-3} mmol, 30% yield).

8: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.28 (5H, m), 5.81 (2H, br), 3.34 (1H, d, J = 13.8 Hz), 2.98 (1H, d, J = 13.8 Hz), 2.76 (1H, d, J = 9.6 Hz), 1.99-1.89 (2H, m), 1.84-1.58 (4H, m), 1.38-1.26 (2H, m), 1.20-1.08 (2H, m), 1.14 (9H, s), 1.00-0.94 (1H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.6, 166.8, 133.7, 130.6, 128.5, 128.0, 118.3, 84.9, 58.5, 51.4, 42.6, 39.3, 31.3, 31.0, 37.4, 26.2, 26.1, 26.0; (ESI) Calcd for $C_{22}H_{30}N_2O_3Na^+$ ([M+Na]$^+$) 393.2149, Found 393.2140; HPLC AZ3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 16.5 min (major), 21.6 min (minor).

S7: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (1H, br), 7.27-7.24 (3H, m), 7.21-7.18 (2H, m), 5.68 (1H, br), 3.81 (1H, d, J = 13.2 Hz), 3.21 (1H, d, J = 3.0 Hz), 3.10 (1H, d, J = 13.2 Hz), 2.03-1.99 (1H, m), 1.80-1.75 (2H, m), 1.67-1.52 (3H, m), 1.45 (9H, s), 1.37-1.13 (5H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 170.6, 135.0, 130.0, 128.4, 127.6, 118.4, 84.7, 58.9, 45.7, 44.0, 38.3, 33.5, 30.4, 28.0, 26.6, 26.1, 26.0; (ESI) Calcd for $C_{22}H_{30}N_2O_3Na^+$ ([M+Na]$^+$) 393.2149, Found 393.2137; HPLC AZ3, Hex/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 15.2 min (major), 17.7 min (minor).

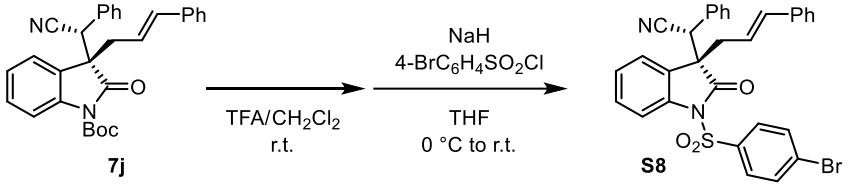


9: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99-7.97 (1H, m), 7.42-7.40 (1H, m), 7.20-7.18 (2H, m), 7.02 (1H, t, J = 7.8 Hz), 6.94 (2H, t, J = 7.8 Hz), 6.64 (2H, d, J = 7.8 Hz), 6.22 (1H, br), 5.85 (1H, br), 3.23 (1H, d, J = 12.3 Hz), 3.15 (1H, d, J = 12.3 Hz), 3.08-3.04 (1H, m), 2.03-1.99 (1H, m), 1.70-1.55 (1H, m), 1.52 (9H, s), 1.45-1.30 (1H, m), 128-1.18 (1H, m) 1.15-0.98 (1H, m), 0.78 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.4, 175.1, 148.4, 139.9, 134.5, 129.8,

128.4, 127.8, 127.6, 126.8, 126.7, 124.4, 114.4, 84.2, 57.0, 55.6, 44.0, 31.6, 28.1, 21.2, 14.0; (ESI) Calcd for $C_{25}H_{30}N_2O_4Na^+$ ([M+Na]$^+$) 445.2098, Found 445.2091; HPLC IC3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 9.2 min (major), 19.3 min (minor).

Crystallographic Structure Determination:

Absolute stereochemistries of the cyanoalkylation products **2e** and **7j**-derived compound **S8** having *N*-sulfonyl oxindole framework were unequivocally determined by X-ray crystallographic analyses. **S8** was synthesized through the following procedure.



To a solution of **7j** (23.2 mg, 0.05 mmol, 96% ee) in CH_2Cl_2 (0.5 mL) was added trifluoroacetic acid (100 μL) under Ar, 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 were removed under vacuum. The crude residue was used for the next step without purification. To a solution of this crude compound 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-bromobenzenesulfonyl chloride (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 **S8** (16.0 mg, 0.027 mmol, 54% yield for 2 steps). **S8**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89-7.87 (1H, m), 7.63-7.59 (3H, m), 7.37-7.32 (4H, m), 7.26-7.20 (3H, m), 7.14 (1H, t, J = 7.2 Hz), 7.01 (2H, d, J = 6.6 Hz), 6.96 (2H, t, J = 7.8 Hz), 6.77 (2H, d, J = 8.4 Hz), 6.33 (1H, d, J = 15.6 Hz), 5.60 (1H, ddd, J = 15.6, 9.0, 6.6 Hz), 4.35 (1H, s), 3.14 (1H, dd, J = 13.8, 6.6 Hz), 3.01 (1H, dd, J = 13.8, 9.0 Hz).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.3, 139.1, 136.6, 136.3, 135.9, 132.5, 130.3, 129.9, 129.4, 129.2, 129.0, 128.7, 128.6, 128.0, 126.4, 126.0, 125.5, 124.7, 120.6, 118.3, 113.4, 56.2, 44.1, 40.5, one peak for aromatic carbon was not found probably due to the overlapping; HRMS (ESI) Calcd for $C_{31}H_{23}BrN_2O_3SNa^+$ ([M+Na]$^+$) 605.0510, Found 605.0522.

Single crystals of **2e**, **S8**, racemic **8**, and racemic **S7** were obtained from CH_2Cl_2/hexane solvent system 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 XtaLAB P200 diffractometer with multi-layer mirror monochromated Mo-Kα radiation (λ = 0.71075 Å). The structure was solved by direct method and refined by a full-matrix least square method on F^2 for all reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed using AFIX instruction The crystallographic data were summarized in **Tables S1-S4.**

Table S1. Crystal data, structure refinement for **2e**.

formula	**$C_{22}H_{27}BrN_2O_2$**
formula weight	431.36
T (K)	123(2)
λ (Å)	0.71075
cryst syst	monoclinic
space group	$P2_1$
a (Å)	6.5022(9)
b (Å)	18.336(3)
c (Å)	18.537(3)
α (°)	90
β (°)	99.943(2)
γ (°)	90
volume (Å^3)	2176.9(6)
Z value	4
D_{calc} (g/cm^3)	1.316
μ (mm^{-1})	1.906
F000	896
cryst size (mm)	0.300 × 0.020 × 0.020
2θ range (deg)	3.149-27.498
Index ranges	-8<=h<=8 -23<=k<=23 -24<=l<=24
reflns collected	34748
indep refins/R_{int}	9963/0.0398
params	487

GOF on F^2	0.945
R_1, wR_2 [I>2σ(I)]	0.0315, 0.0513
R_1, wR_2 (all data)	0.0485, 0.0545
absolute structure parameter	0.006(3)
peak and hole (e. Å^3)	0.500, -0.640

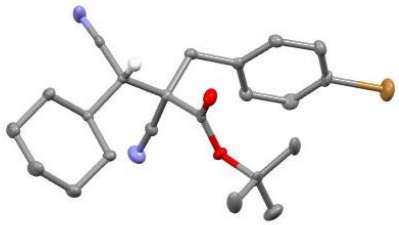


Figure S1. Molecular structure of **2e**. Calculated hydrogen atoms, except for a hydrogen on tertiary stereocenter, are omitted for clarity. Blue = nitrogen, red = oxygen, brown = bromine, grey = carbon.

Table S2. Crystal data, structure refinement for **S8**.

formula	**$C_{31}H_{23}BrN_2O_3S$**
formula weight	583.48
T (K)	123(2)
λ (Å)	0.71075
cryst syst	orthorhombic
space group	$P2_12_12_1$
a (Å)	10.1020(19)
b (Å)	11.475(2)
c (Å)	23.008(4)
α (°)	90
β (°)	90
γ (°)	90
volume (Å^3)	2667.1(8)
Z value	4
D_{calc} (g/cm^3)	1.453
μ (mm^{-1})	1.656
F000	1192
cryst size (mm)	0.200 × 0.200 × 0.050
2θ range (deg)	3.195-27.496
	-13<=h<=13

Index ranges	-14<=k<=14
	-29<=l<=29
reflns collected	42526
indep refins/R_{int}	6105/0.0489
params	343
GOF on F^2	0.981
R_1, wR_2 [I>2σ(I)]	0.0211, 0.0444
R_1, wR_2 (all data)	0.0268, 0.0454
absolute structure parameter	0.002(2)
peak and hole (e. Å^3)	0.222, -0.351

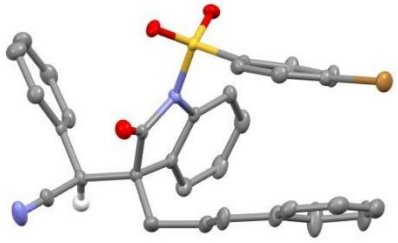


Figure S2. Molecular structure of **S8**. Calculated hydrogen atoms, except for a hydrogen on tertiary stereocenter, are omitted for clarity. Blue = nitrogen, red = oxygen, yellow = sulfur, brown = bromine, grey = carbon.

Table S3. Crystal data, structure refinement for racemic **8**.

formula	**$C_{22}H_{30}N_2O_3$**
formula weight	370.48
T (K)	123(2)
λ (Å)	0.71075
cryst syst	monoclinic
space group	$P2_1/c$
a (Å)	8.875(3)
b (Å)	27.834(8)
c (Å)	9.556(3)
α (°)	90
β (°)	116.168(6)
γ (°)	90
volume (Å^3)	2118.6(12)
Z value	4
D_{calc} (g/cm^3)	1.161

μ (mm^{-1})	0.077
F000	800
cryst size (mm)	0.300 × 0.020 × 0.020
2θ range (deg)	3.235-27.500
Index ranges	-11<=h<=11 -36<=k<=36 -11<=l<=11
reflns collected	21361
indep refins/R_{int}	4517/0.1246
params	249
GOF on F^2	0.971
R_1, wR_2 [I>2σ(I)]	0.0723, 0.1615
R_1, wR_2 (all data)	0.1630, 0.2009
peak and hole (e. $Å^3$)	0.436, -0.353

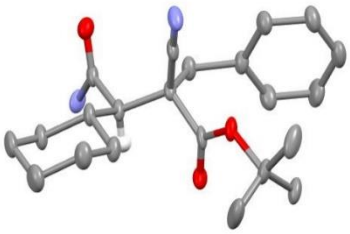


Figure S3. Molecular structure of racemic **8**. Calculated hydrogen atoms, except for a hydrogen on tertiary stereocenter, are omitted for clarity. Blue = nitrogen, red = oxygen, grey = carbon.

Table S4. Crystal data, structure refinement for racemic **S7**.

Formula	**$C_{22}H_{30}N_2O_3$**
formula weight	370.48
T (K)	123(2)
λ (Å)	0.71075
cryst syst	monoclinic
space group	$P2_1/a$
a (Å)	24.967(5)
b (Å)	9.4430(18)
c (Å)	27.584(6)
α (°)	90
β (°)	95.971(4)

γ (°)	90
volume (Å^3)	6468(2)
Z value	12
D_{calc} (g/cm^3)	1.141
μ (mm^{-1})	0.076
F000	2400
cryst size (mm)	0.300 × 0.200 × 0.040
2θ range (deg)	3.007-27.500
Index ranges	-32<=h<=32 -12<=k<=12 -35<=l<=35
reflns collected	98886
indep refins/R_{int}	14855/0.0978
params	730
GOF on F^2	1.161
R_1, wR_2 [I>2σ(I)]	0.0735, 0.1639
R_1, wR_2 (all data)	0.1059, 0.1907
peak and hole (e. Å^3)	0.627, -0.309

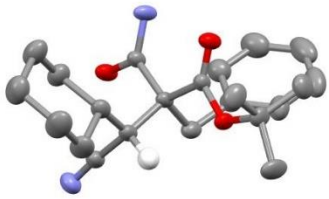


Figure S4. Molecular structure of racemic **S7**. Calculated hydrogen atoms, except for a hydrogen on tertiary stereocenter, are omitted for clarity. Blue = nitrogen, red = oxygen, grey = carbon.

Reference and notes

(1) Natural Product Synthesis Using Multicomponent Reaction Strategies: Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486

(2) Catalytic C−C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis: Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390−2431.

(3) Stereocontrolled Formation of Several Carbon−Carbon Bonds in Acyclic Systems : Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175−9206.

(4) Catalytic Asymmetric Tandem Transformations Triggered by Conjugate Additions: Guo, H.-C.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366.

(5) Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions: Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.

(6) Recent advances in enantioselective copper-catalyzed 1,4-addition: Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075.

(7) Asymmetric Transition-Metal Catalysis in the Formation and Functionalization of Metal Enolates: Vargová, D.; Némethová, I.; Plevová, K.; Šebesta, R. € *ACS Catal.* **2019**, *9*, 3104−3143.

(8) Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins: Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. *Chem. Rec.* **2018**, *18*, 1314–1340.

(9) Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling: Derosa, J.; Tran, V. T.; van der Puyl, V. A.; Engle, K. M. *Aldrichimica Acta* **2018**, *51*, 21–32.

(10) Tissot, M.; Poggiali, D.; Hénon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. *Chem. Eur. J.* **2012**, *18*, 8731–8747.

(11) Germain, N.; Guénée, L.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2014**, *16*, 118−121.

(12) Germain, N.; Schlaefli, D.; Chellat, M.; Rosset, S.; Alexakis, A. *Org. Lett.* **2014**, *16*, 2006−2009.

(13) Chang, S.-Q.; Zou, X.; Gong, Y.; He, X.-W.; Liu, X.-L.; Zhou, Y. *Chem. Commun.* **2019**, *55*, 14003−14006.

(14) Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 2728–2731.

(15) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472–9473.

(16) Lee, S.; Kim, S. *Org. Lett.* **2008**, *10*, 4255–4258.

(17) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307–1309.

(18) Ping, Y.; Wang, L.; Ding, Q.; Peng, Y. *Adv.Synth. Catal.* **2017**, *359*, 3274–3291.
(19) For details, see the Supporting Information.
(20) Kanda, T.; Naraoka, A.; Naka, H. *J. Am. Chem. Soc.* **2019**, *141*, 825−830.

List of Publications

1. Catalytic Asymmetric Strecker Reaction of Ketoimines with Potassium Cyanide
   Ohmatsu, K.; Morita, Y.;Kiyokawa, M.; Hoshino, K.; Ooi, T. *Chem. Commun.* **2021**, *XX*, XX.

2. Catalytic Asymmetric Cyanoalkylation of Electron-Deficient Olefins with Potassium Cyanide and Alkyl Halides
   Ohmatsu, K.; Morita, Y.;Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2021**, *143*, 11218.

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