Development of Enantioselective Cyano-Alkoxycarbonylation Induced by Brønsted Acid–Lewis Base Cooperative Catalysts

Yoshihiro Ogura

Graduate School of Engineering, Nagoya University

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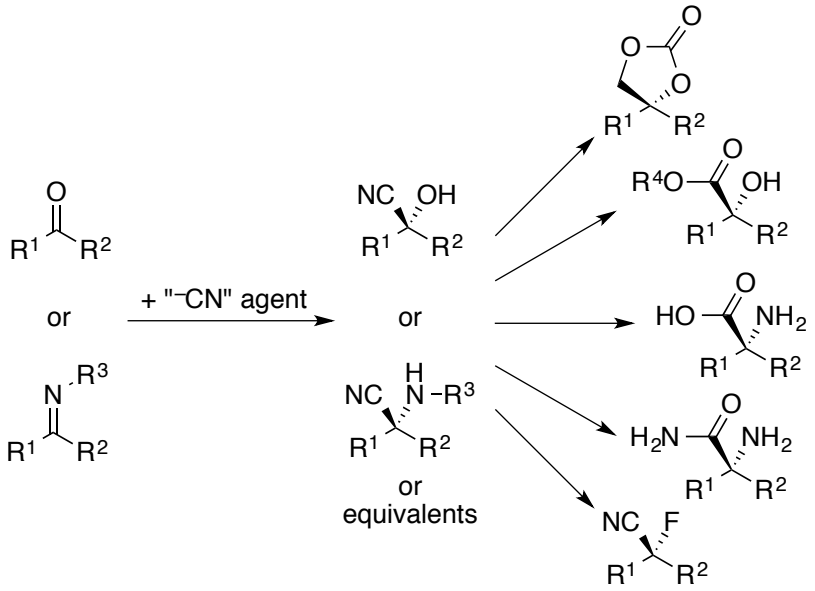
Chapter 1

Introduction and General Summary

1-1. Introduction

The addition of cyanide to carbonyl or imino compounds is one of the most powerful methods for achieving C–C bond formation and for introducing carbonyl- or nitrogen-containing moieties in synthetic organic chemistry. The Strecker reaction, especially, is widely used for the synthesis of amino acids and their derivatives.[1] The reaction products, α-cyanohydrins, α-aminonitriles and their equivalents, are useful for the synthesis of valuable intermediates of drugs, agricultural chemicals, bioactive compounds and other useful compounds.[1,2] Cyano, amino, and hydroxy groups can be easily transformed to other functional groups such as carboxyl, hydroxy, halogen and aminomethyl groups (Scheme 1.1).

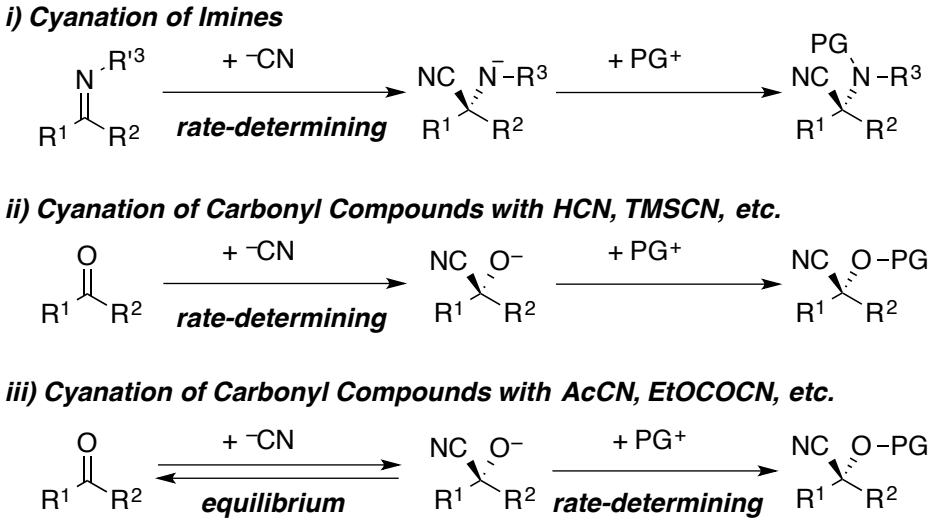
Scheme 1.1 Cyanide Addition Reactions to Carbonyl or Imino Compounds



Although α-cyanohydrin and α-aminonitrile show similar synthetic utility, the mechanism of cyanide addition and the stability of these compounds are different. In the case of cyanide addition to imino compounds under basic conditions, the rate-determining step is the first step due to the highly nucleophilic or basic aza anion intermediate (Scheme 1.2 i).[3] In contrast, cyanide addition to carbonyl compounds can be categorized into two patterns. The first includes a rate-determining cyanation step and rapid *O*-protection of the oxyanion intermediate (Scheme 1.2 ii).[4] The second pattern includes a fast cyanation step and a slow and rate-determining *O*-protection of the oxyanion intermediate (Scheme 1.2 iii). The rate of the *O*-protection of the generated oxyanion species depends on the reactivity of the protecting group, and the fast

equilibrium of the cyanation step causes racemization of the enantio-enriched intermediate. A protecting group such as a proton[5] or trimethyl silyl group[4] prevents racemization by the reverse reaction of the oxyanion intermediate due to its high reactivity. Therefore, hydrogen cyanide or trimethylsilyl cyanide is commonly used as a cyanating agent for highly enantioselective cyanohydrin synthesis.

Scheme 1.2 Categorization and Details of Cyanide Addition Reactions to Carbonyl or Imino Compounds under Basic Conditions



In sharp contrast to the progress with the Strecker reaction over the past few decades, there are still some challenges regarding the development of cyanohydrin synthesis because of the differences in reactivity and stability of the anionic intermediates and the product itself.

1-2. Cyano-Alkoxycarbonylation of Carbonyl Compounds

Trimethylsilyl cyanide and hydrogen cyanide are widely used cyanating agents in synthetic organic chemistry.[4,5] However, due to their high toxicity, difficulty of handling, and instability, alternatives to these cyanating agents are needed for the development of safe and easy-to-handle protocols. To address these problems, cyanoformates are attractive as safe, stable, and user-friendly cyanating agents (Figure 1.1). Cyanoformates, especially methyl cyanoformate (Mander's reagent), have been used as acylating agents for a long time (Scheme 1.3 i).[6] After three years from the first report[7a] of Mander's reagent, in 1986 Hünig and co-workers reported the

first example of cyanoethoxy-carbonylation using ethyl cyanoformate as a cyanating agent for aldehydes (Scheme 1.3 ii).[7]

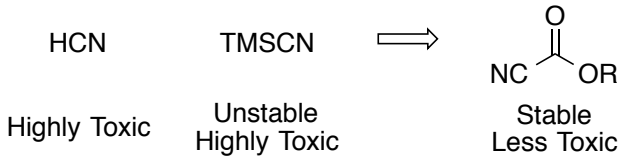
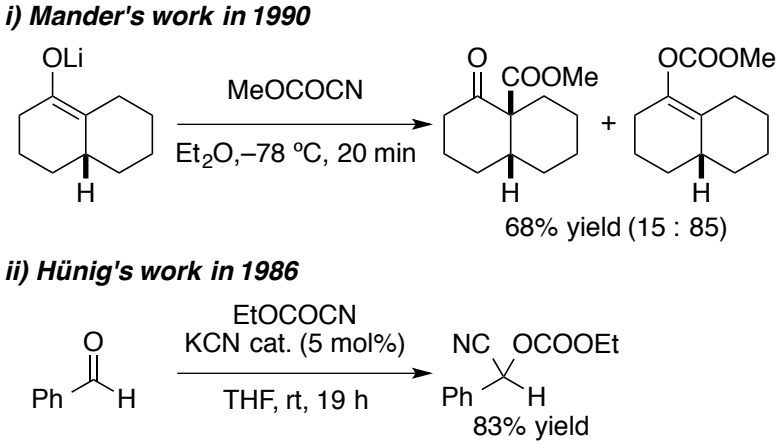


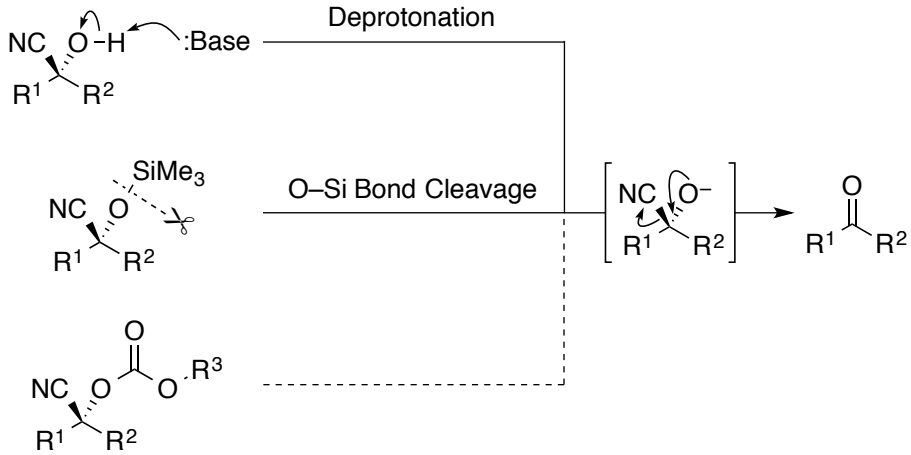
Figure 1.1 Toxicity and stability of cyanating agents.

Scheme 1.3 Utility of Cyanoformates



In addition, the reaction products with cyanoformate are more stable than those obtained with hydrogen cyanide or trimethylsilyl cyanide (Scheme 1.4). The cyanation products of carbonyl compounds, cyanohydrins, readily decompose under basic conditions with the generation of hydrogen cyanide or its salts.[8] Cyanohydrin trimethylsilyl ethers also readily decompose by O–Si bond cleavage under acidic or basic conditions. Due to this nature, cyanohydrin silyl ethers were used as a protecting group of carbonyl moiety or an acyl anion equivalent.[9] On the other hand, cyano-alkoxycarbonylation products are more stable due to the stability of the carbonate moiety.

Scheme 1.4 Decomposition of Cyanohydrins and *O*-Protected Cyanohydrins



1-3. Catalytic Enantioselective Cyano-Alkoxycarbonylation

Due to the advantages of cyanoformates in comparison with other cyanating agents, numerous successful examples of the catalytic cyano-alkoxycarbonylation of aldehydes and simple ketones have been reported. Since the first successful example reported by North and co-workers in 2003, chiral Lewis acid catalysis using Ti-complexes has been reported by many groups (Figure 1.2).[10,11]

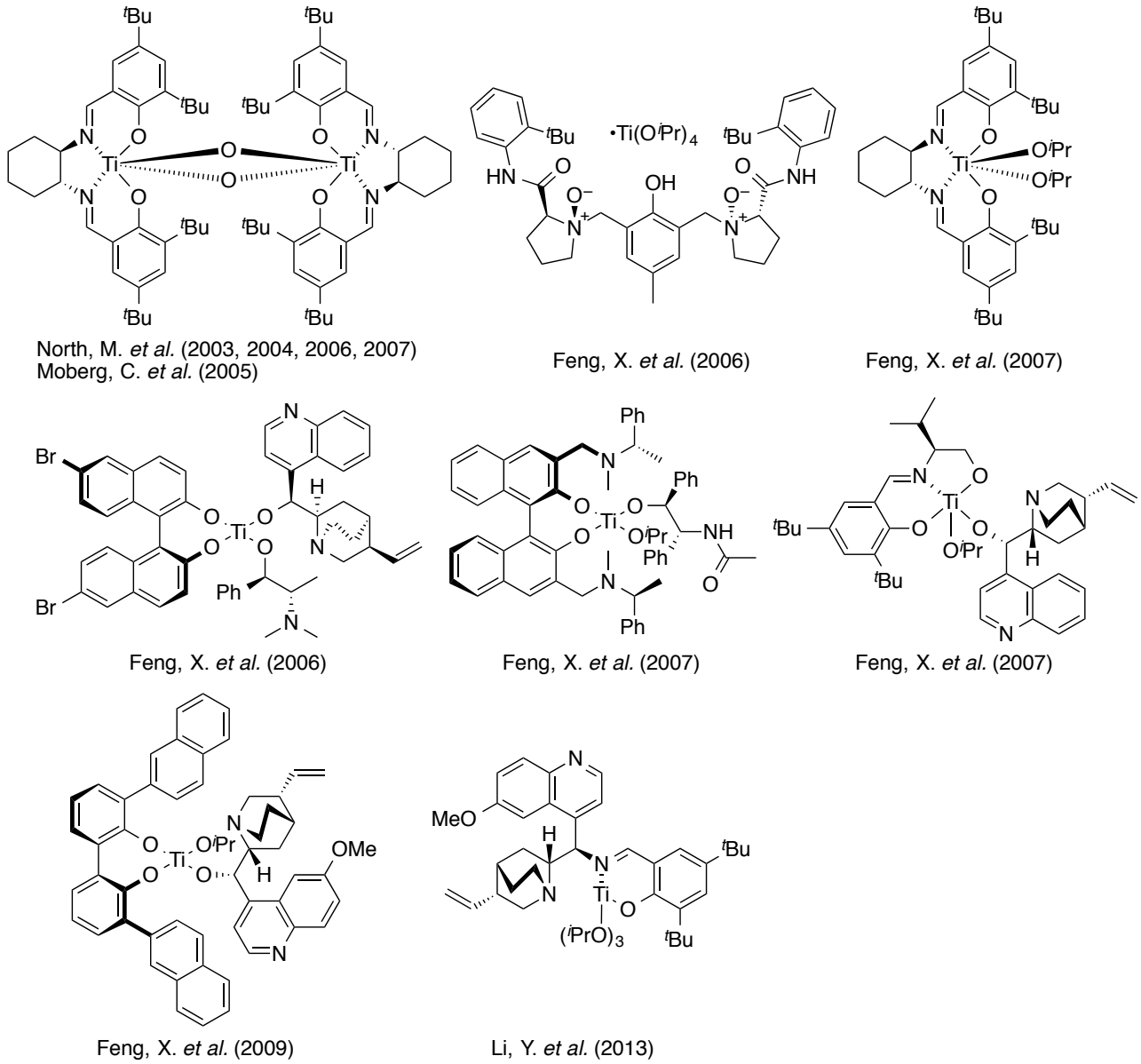


Figure 1.2 Chiral Ti-complex catalysts for the cyano-alkoxycarbonylation of aldehydes.

Other transition metal-catalyzed cyano-alkoxycarbonylations of aldehydes using V-, Li–Y- or Al-complexes have also been reported (Figure 1.3 i, ii, and iii).[11,12,13,14] Despite these many examples, this transition metal catalysis is still limited to highly reactive benzaldehyde or α,β-unsaturated aldehydes. In addition, this transition metal catalysis would be preferable to avoid the use of highly toxic and/or rare heavy metals from the perspective of element strategy and the development of environment-friendly methods.[15]

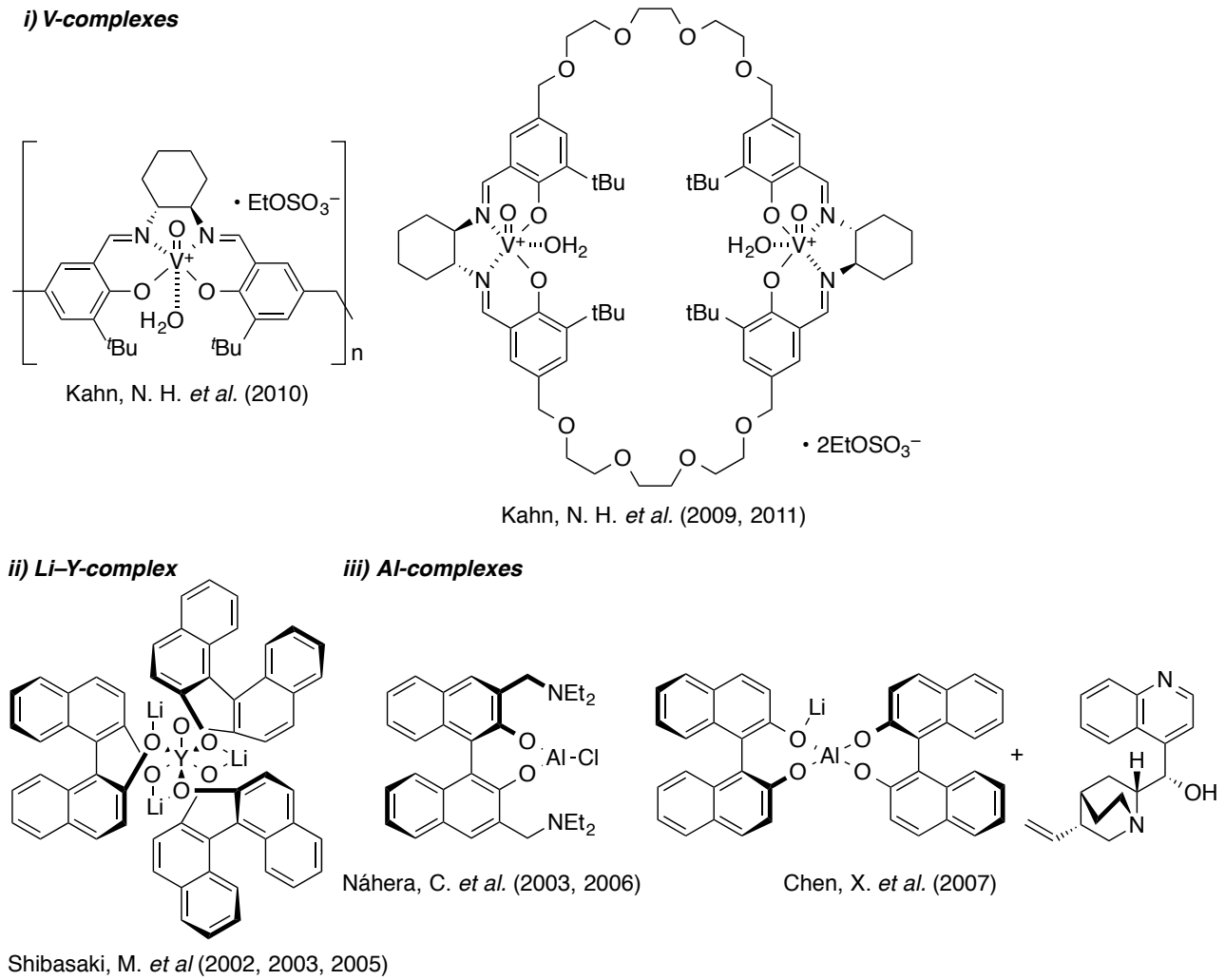
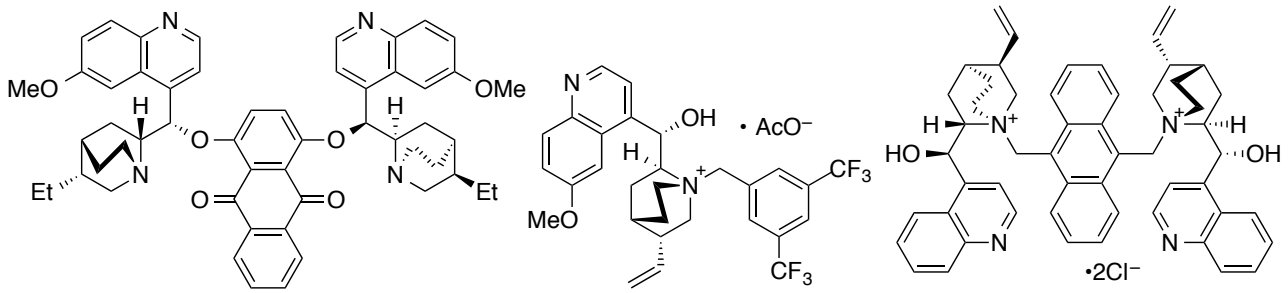


Figure 1.3 Chiral V-, Y-Li-, and Al-complex catalysts for the cyano-alkoxycarbonylation of aldehydes.

In contrast to transition metal catalysis, there are few organocatalysts for the cyano-alkoxycarbonylation of aldehydes or simple ketones. Since Deng and co-workers' pioneering work in 2001,[16f] there have been only three successful examples using modified cinchona alkaloid derivatives (Figure 1.4).[16] Deng's report is the first and only example of the highly enantioselective cyano-alkoxycarbonylation of ketones.



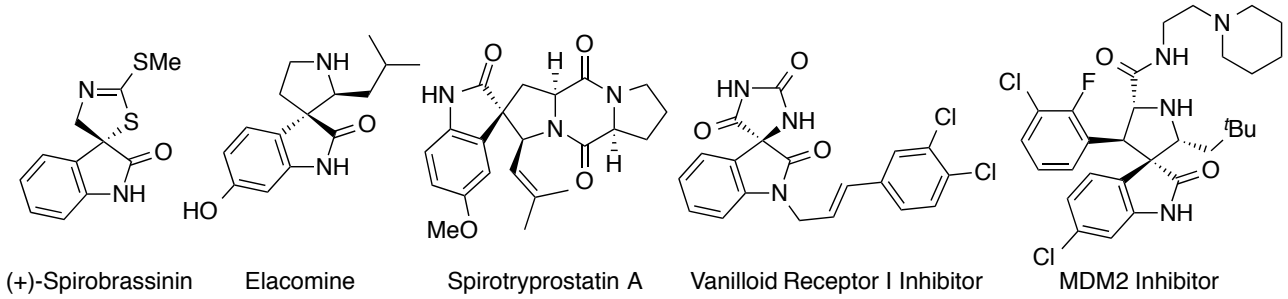
Deng, L. *et al.* (2001, 2006) **For Ketone** | Feng, X. *et al.* (2007) **For Aldehyde** | Chinchilla, R. *et al.* (2008, 2009) **For Aldehyde**

Figure 1.4 Chiral organocatalysts for the cyano-alkoxycarbonylation of aldehydes or ketones.

To extend the substrate scope of cyano-alkoxycarbonylation to structurally complex substrates and for the development of user-friendly methods, alternative catalysts are needed.

1-4. Enantioselective Transformation of Isatin Derivatives and α-Ketoesters

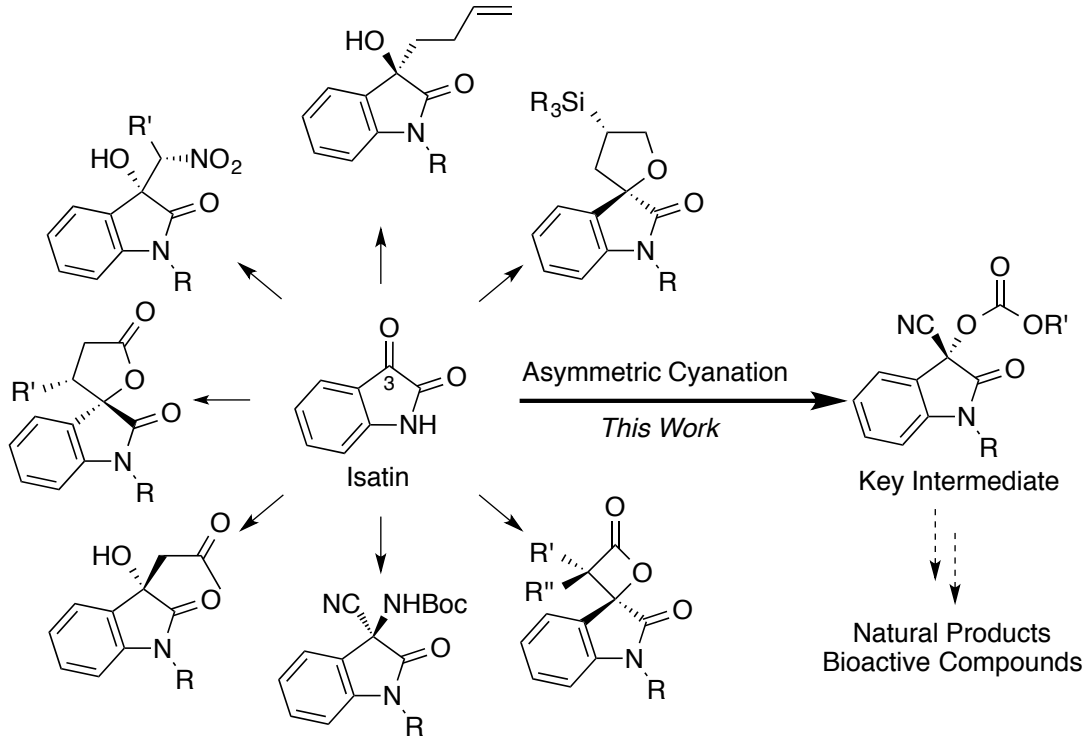
An oxindole bearing a chiral center at the C-3 position is an important core structure found in many natural products and useful bioactive compounds.[17] Spiro-fused oxindole alkaloids, such as (+)-spirobrassinin,[18] elacomine,[19] spirotryprostatin A,[20] a synthetic vanilloid receptor I inhibitor[21] and an MDM2 inhibitor[22] have received considerable attention because of their unique bioactivities (Figure 1.5). With regard to the synthesis of these useful compounds, numerous enantioselective transformations of the C3 carbonyl moiety of isatins have been reported by many groups.[17] Although various asymmetric reactions of isatins have been developed, direct asymmetric cyanation of the C-3 carbonyl has not yet been reported (Scheme 1.5). Isatin is a natural oxindole derivative found in various plants and in human blood, and its derivatives have characteristic bioactivities.[17,23] This synthetic issue led to the hypothesis that the asymmetric cyanation of isatins using a safe cyanating agent, especially ethyl cyanoformate, might be a powerful tool for the synthesis of these bioactive oxindole alkaloids.



(+)-Spirobrassinin | Elacomine | Spirotryprostatin A | Vanilloid Receptor I Inhibitor | MDM2 Inhibitor

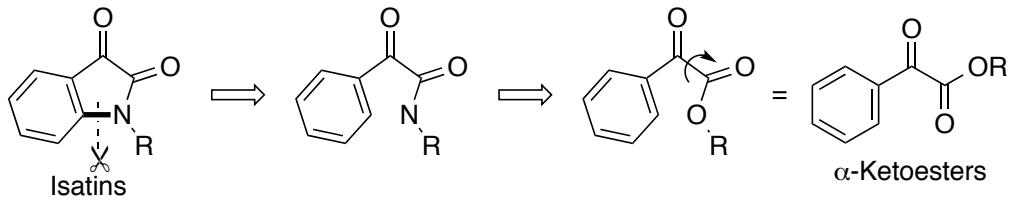
Figure 1.5 Spiro-oxindole alkaloids: natural products and synthetic compounds.

Scheme 1.5 Enantioselective Transformation of Isatins and Useful Compounds



In addition, the structural similarity between isatins and α-ketoesters might be a key strategy for the enantioselective cyano-ethoxycarbonylation of α-ketoesters. The similarity of these compounds is shown in Scheme 1.6. A method that includes breaking the C–N bond of isatins, replacing this nitrogen atom with oxygen, and rotating the C–C bond between two carbonyl groups gives α-ketoesters.

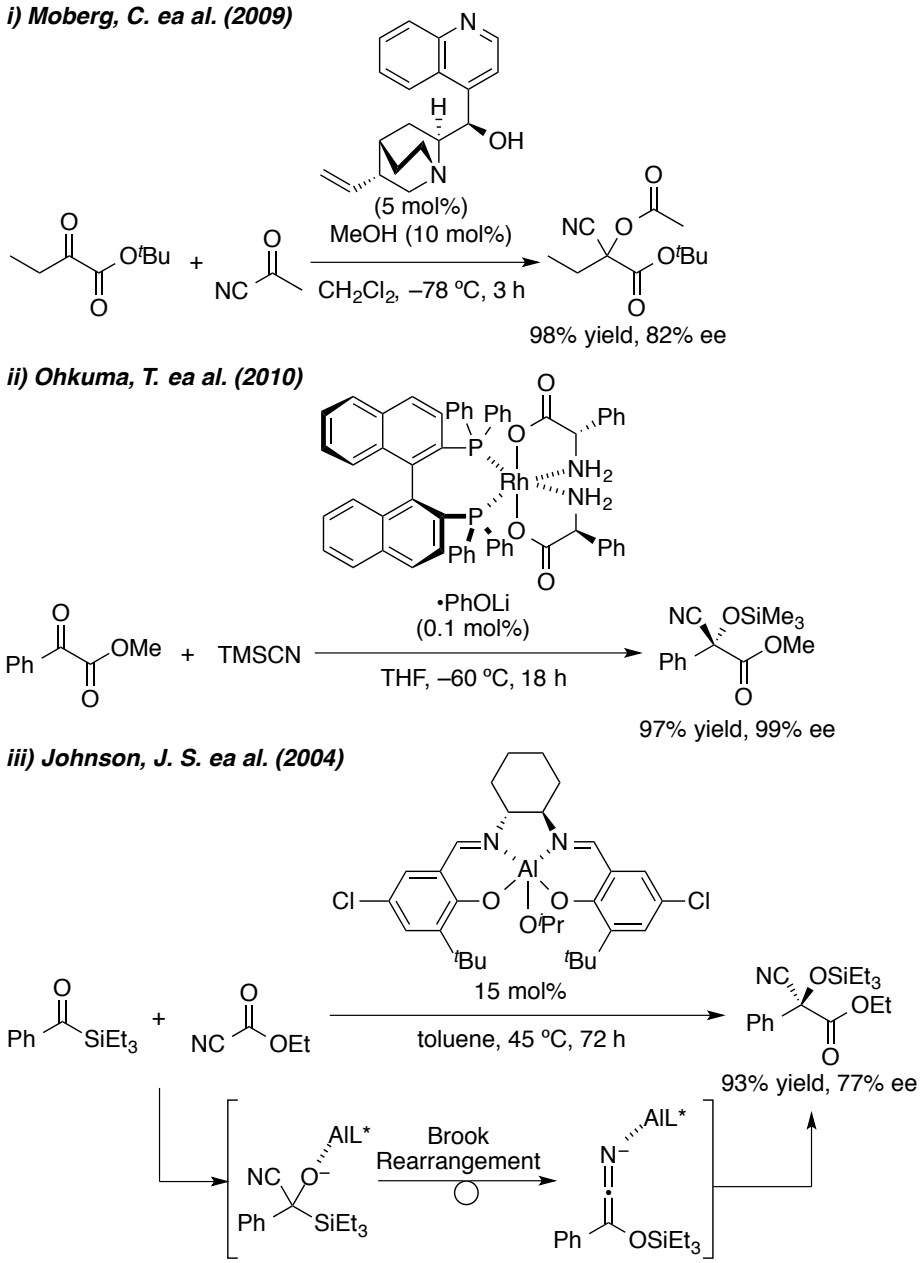
Scheme 1.6 Structural Similarity between Isatins and α-Ketoesters



α-Ketoesters are more reactive than simple ketones because of the electron-withdrawing nature of the ester moiety. Therefore, α-ketoesters can be used as a surrogate for aldehydes. There are many successful examples of the enantioselective addition of some nucleophiles, like organometallic reagents, silyl enol ethers, and electron-rich aromatics, etc.[24-28] In contrast, there are only three successful examples of the enantioselective cyanation of α-ketoesters. In 2009,

Moberg and co-workers reported the first enantioselective cyano-acetylation of α-ketoesters (Scheme 1.7 i).[29b] Ohkuma and co-workers reported the first example of the transition metal-catalyzed cyanation of α-ketoesters in 2010 (Scheme 1.7 ii).[29a] In 2004, Johnson and co-workers reported the tandem cyanation/Brook rearrangement/*C*-acylation reaction of acylsilanes as an alternative method for synthesis of the cyanide adduct of α-ketoesters (Scheme 1.7 iii).[29c-d] Despite the moderate to high enantioselectivity in these three examples, the substrate scope was still limited and a low reaction temperature was required for good enantioselectivity.

Scheme 1.7 Enantioselective Cyanation of α-Ketoesters and Alternative Methods



1-5. Design of Brønsted Acid–Lewis Base Cooperative Organocatalysts for the Cyano-Alkoxycarbonylation of Isatins and α-Ketoesters

Various achiral Lewis base catalysts have been reported for the activation of cyanoformates as an acyl onium salt (Figure 1.6 i, ii). Some N-,[30] NHC-,[31a-b] O⁻-,[31c] Br⁻-,[31d] P-,[31e] and π-nuclephilic catalysts[31f] have been shown to exhibit catalytic activity for cyano-alkoxycarbonylation.

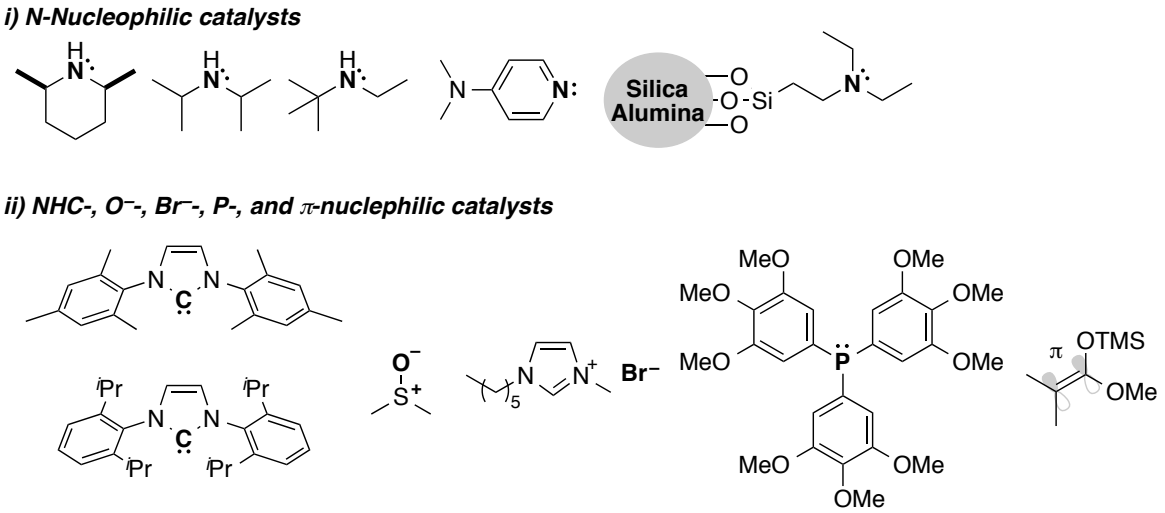
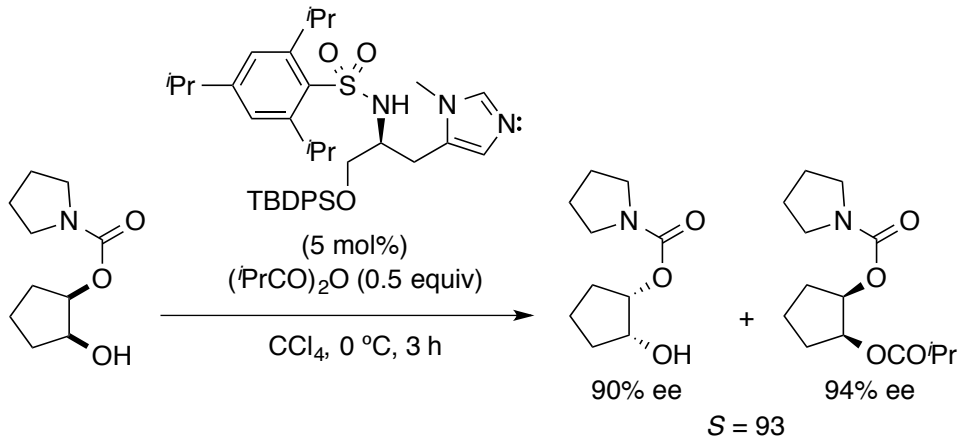


Figure 1.6 Lewis base catalysts for cyano-alkoxycarbonylation.

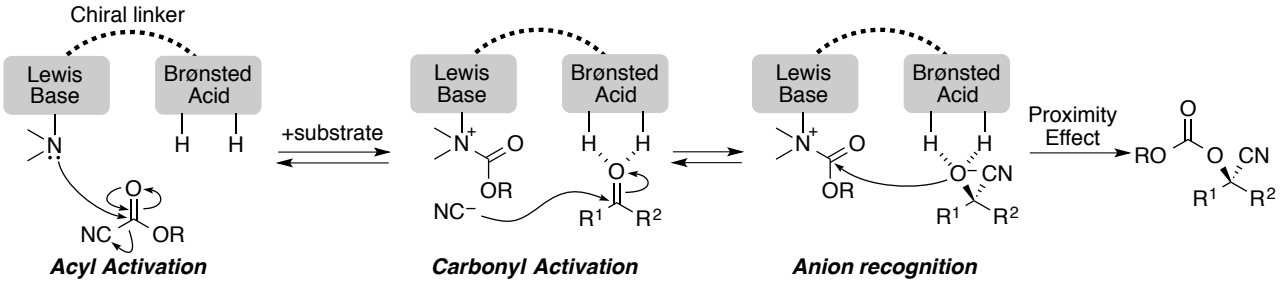
According to these reports, a highly nucleophilic Lewis base amine is necessary for smooth acyl activation and the generation of cyanoformates. Since 2004, our group reported an L-histidine-derived Brønsted acid–Lewis base cooperative catalyst for the kinetic resolution of racemic or *meso*-alcohols and racemic carboxylic acids *via* acyl activation and the chiral recognition of substrates (Scheme 1.8).[32, 33]

Scheme 1.8 Brønsted Acid–Lewis Base Cooperative Catalyst for Acyl Activation[32f]



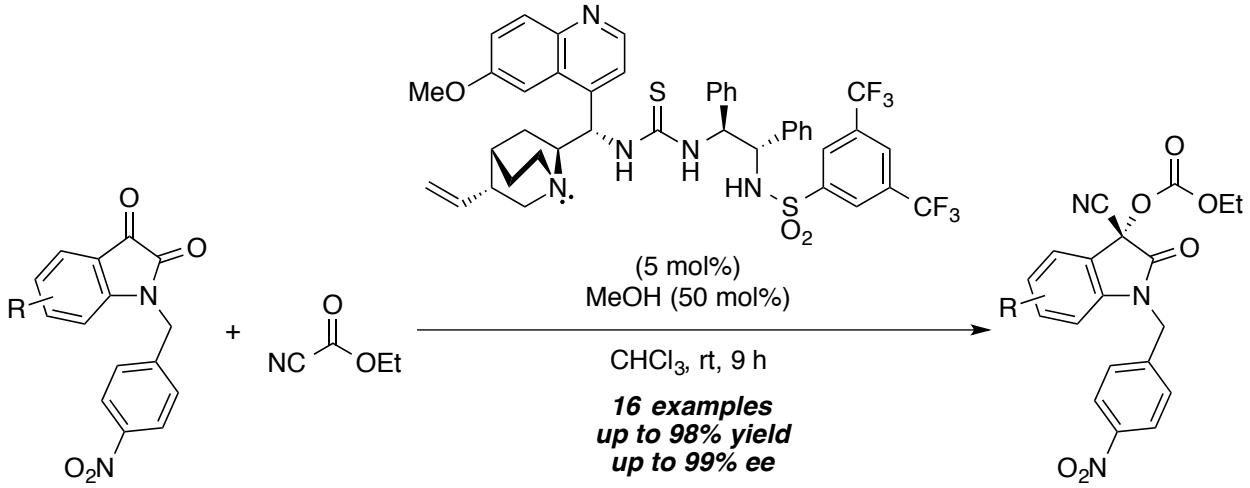
Based on these reports and Deng's pioneering work[16e-f], we planned to design the catalyst. The three essential components of the catalyst were a highly nucleophilic Lewis base moiety as an activation site of cyanoformate, a Brønsted acid site to recognize the substrate or oxyanion intermediate, and a chiral linker (Scheme 1.9). According to this strategy, various catalysts were examined with respect to their ability to catalyze enantioselective cyano-alkoxycarbonylation.

Scheme 1.9 Design Concept of Brønsted Acid–Lewis Base Cooperative Catalyst



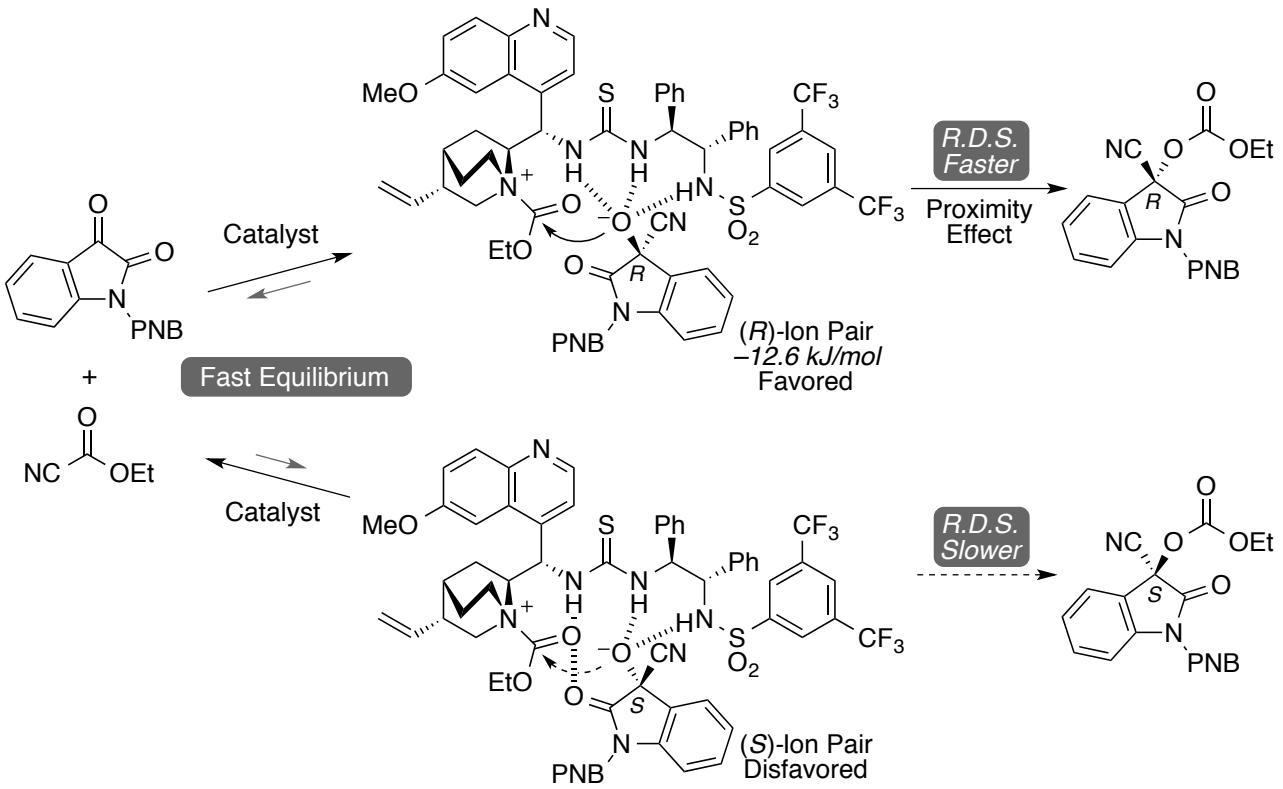
Chapter 2 describes the enantioselective cyano-ethoxycarbonylation of isatins promoted by a cinchona alkaloid-derived acid–base cooperative catalyst.[34] The catalyst bearing a highly nucleophilic quinuclidine moiety, a thiourea group, and a sulfonamide group successfully promoted this reaction. The use of an electron-deficient *p*-(nitro)benzyl (PNB) group as a protecting group for the amide moiety of isatins successfully improved the enantioselectivity. The addition of methanol might dissociate the oligomeric catalyst into a highly active monomeric catalyst and increase the catalytic activity. Optimization of the reaction conditions and catalysts gave the desired product in high yield with high enantioselectivity (Scheme 1.10).

Scheme 1.10 Enantioselective Cyano-Ethoxycarbonylation of Isatins



Kinetic studies suggested that the second carbonylation step was rate-determining and the first cyanation step was in fast equilibrium. The high enantioselectivity might be induced by the dynamic kinetic resolution of oxyanion intermediates (Scheme 1.11). According to ~~the~~ kinetic studies, this catalyst recognized the chirality of anionic intermediate and stabilized only the (*R*)-oxyanion selectively. DFT calculations also suggested that the (*R*)-oxyanion pair was more stable than the (*S*)-oxyanion pair by 12.6 kJ/mol, and the electron-withdrawing *p*-(nitro)benzyl protecting group might stabilize the ion-pair intermediate through a reverse-directional dipole moment between the catalyst and oxyanion intermediate.

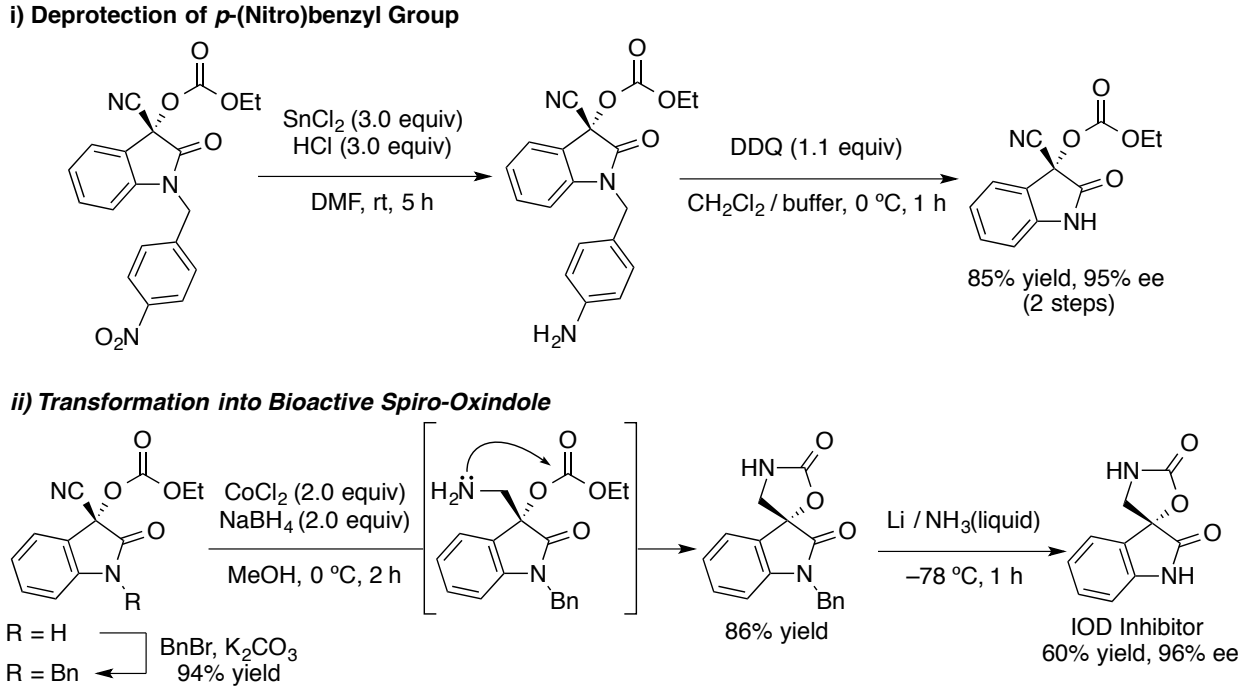
Scheme 1.11 Proposed Mechanism for the Cyano-Ethoxycarbonylation of Isatins Based on Kinetic Studies and DFT Calculations



To derive the cyano-ethoxycarbonylation products of isatins as valuable bioactive compounds, deprotection of the *p*-(nitro)benzyl group and subsequent transformations were tried (Scheme 1.12). First, the nitro group of the cyano-ethoxycarbonylation product was selectively reduced to an electron-donating amino group. Next, oxidative cleavage using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave selective deprotection at the benzylic position. This novel method for removing the *p*-(nitro)benzyl group gave the desired products in good yield without any loss of ee. After re-protection by a benzyl group, sequential

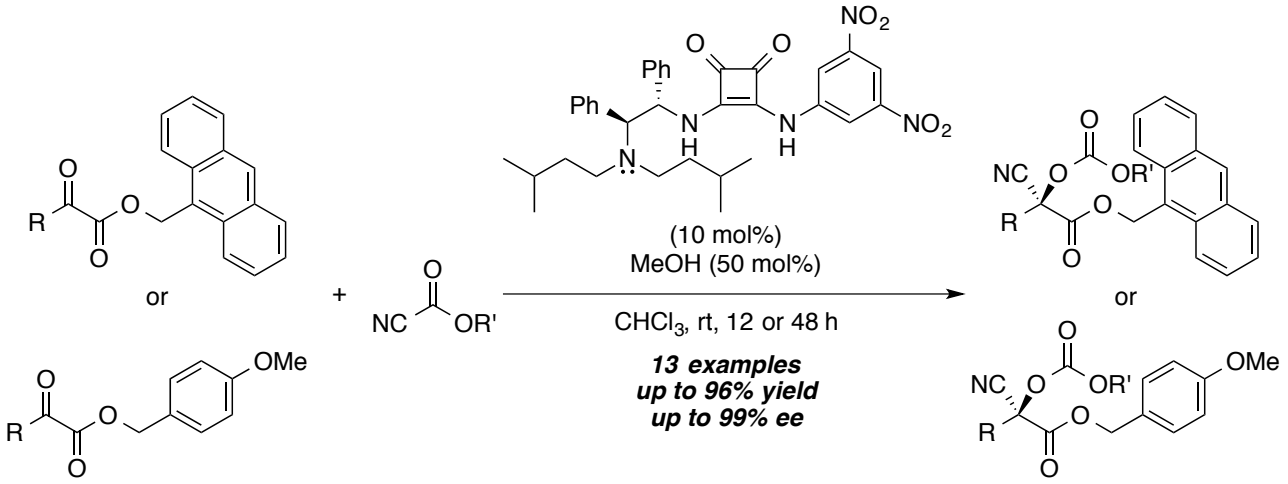
nitrile-selective reduction using cobalt borohydride prepared *in situ* generated primarily amine, and rapid intramolecular cyclization gave the spiro-urethane core.[35] The benzyl protecting group was removed under Birch conditions to give a bioactive chiral spiro-oxindole as a known IDO inhibitor.[36]

Scheme 1.12 Deprotection of a *p*-(Nitro)benzyl Group and Transformation of the Isatin Product into a Bioactive Spiro-Oxindole



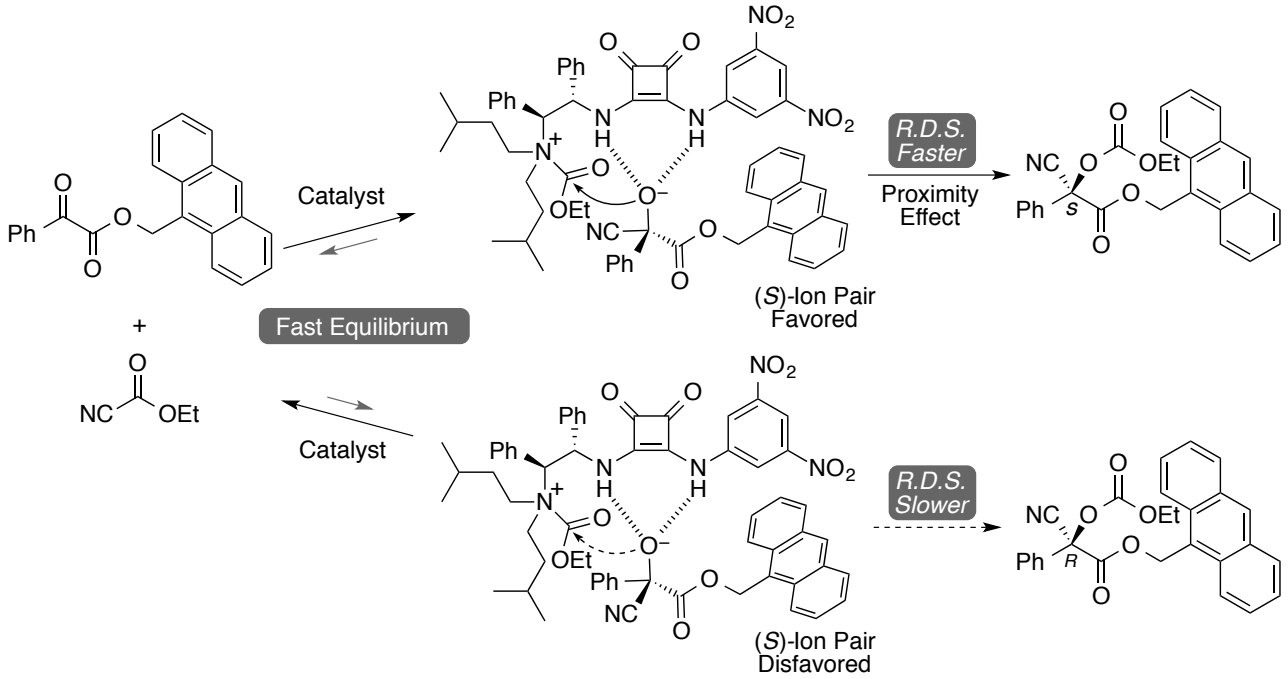
Chapter 3 describes the enantioselective cyano-alkoxycarbonylation of α-ketoesters using acid–base cooperative catalysts (Scheme 1.13).[37] The catalyst structure was modified from cinchona alkaloid-derived β-amino thiourea into β-amino squaramide bearing a 1,2-diphenylethylene-1,2-diamine backbone. The use of a benzyl-type ester like bulky 9-anthracenylmethyl ester or *p*-(methoxy)benzyl ester was necessary to improve the enantioselectivity. Optimization of the reaction conditions and catalysts gave the desired products in high yield with high enantioselectivity.

Scheme 1.13 Enantioselective Cyano-Alkoxycarbonylation of α-Ketoesters



The results of a kinetic study suggested that the second carbonylation step was also rate-determining and the first cyanation step was in fast equilibrium, as in the case of isatin. The high enantioselectivity might be induced by dynamic kinetic resolution of the oxyanion intermediate (Scheme 1.14).

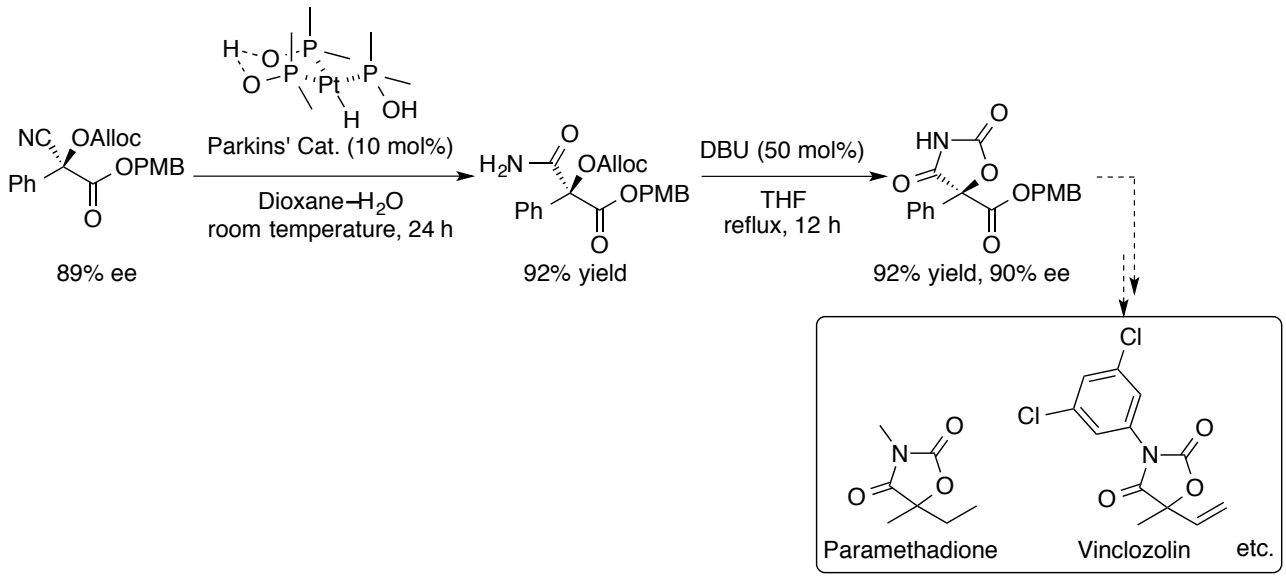
Scheme 1.14 Proposed Mechanism of the Cyano-Alkoxycarbonylation of α-Ketoesters Based on Kinetic Studies



A nitrile-selective transformation was tried to derive cyano-ethoxycarbonylation products (Scheme 1.15). The protective group of cyanohydrin carbonates could be easily changed by the

choice of cyanating agent. For the subsequent transformation, an allyloxycarbonyl (Alloc) group was installed in high yield with high ee value. The highly nitrile-selective hydrolysis of cyanohydrin allyloxycarbonates catalyzed by Parkins' catalyst gave primarily amide intermediates.[38] DBU-catalyzed intramolecular cyclization then gave chiral oxazolidinedione cores. The core analogues of the chiral oxazolidinedione are found in the anticonvulsant paramethadione,[39] the fungicide vinclozolin,[40] which has antiandrogenic properties, etc.

Scheme 1.15 Transformation of α-Ketoester Product into a Bioactive Oxazolidinedione Core

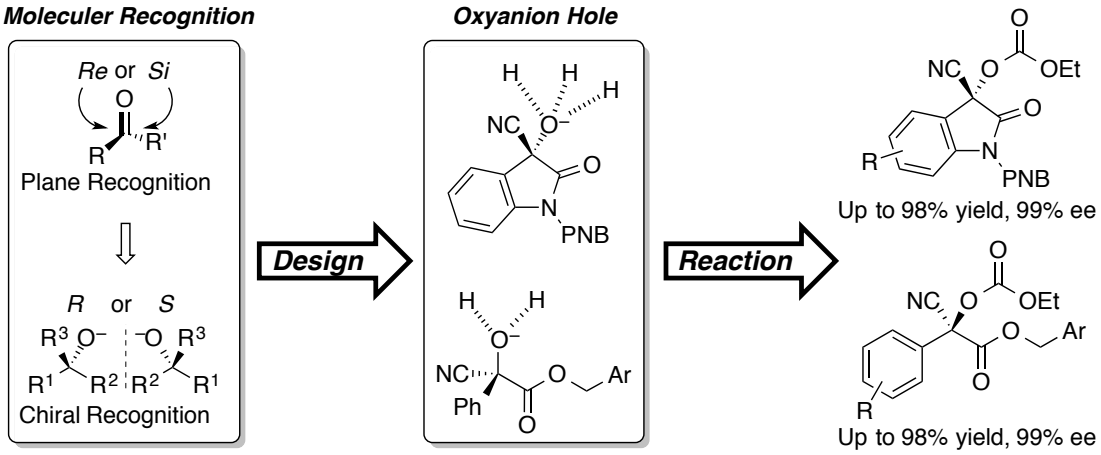


1-6. Summary

In summary, we have developed an enantioselective cyano-alkoxycarbonylation of isatins and α-ketoesters promoted by a Brønsted acid–Lewis base cooperative organocatalyst.[34,37] We investigated the catalytic mechanism of cyano-alkoxycarbonylation and revealed that the Brønsted acid site plays a key role as an "oxyanion hole" mimic.[41,42] The enantioselectivity in this reaction did not originate in two-dimensional chiral recognition, but rather in three-dimensional chiral recognition (Scheme 1.16). This design of a chiral oxyanion hole enabled the enantioselective cyano-ethoxycarbonylation of isatins and α-ketoesters. This catalytic reaction can be carried out at room temperature, and is both user-friendly and suitable for large-scale application. In addition, anew method for deprotection of a *p*-(nitro)benzyl (PNB) group and highly nitrile-selective hydrolysis may enable the realization of novel routes to bioactive compounds or useful building blocks. Although the details of the reaction mechanism and the transition state model for chiral

recognition require further investigation,[43] we anticipate that these findings will lead to new concepts for the further design of multiple hydrogen bond donor catalysis by molecular recognition and the catalytic enantioselective cyanation of carbonyl compounds.

Scheme 1.16 Summary



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43. We could not exclude the possibility that asymmetric induction arose solely from the first cyanation step.

Chapter 2

Enantioselective Cyano-Ethoxycarbonylation of Isatins Induced by Brønsted Acid–Lewis Base Cooperative Catalysts

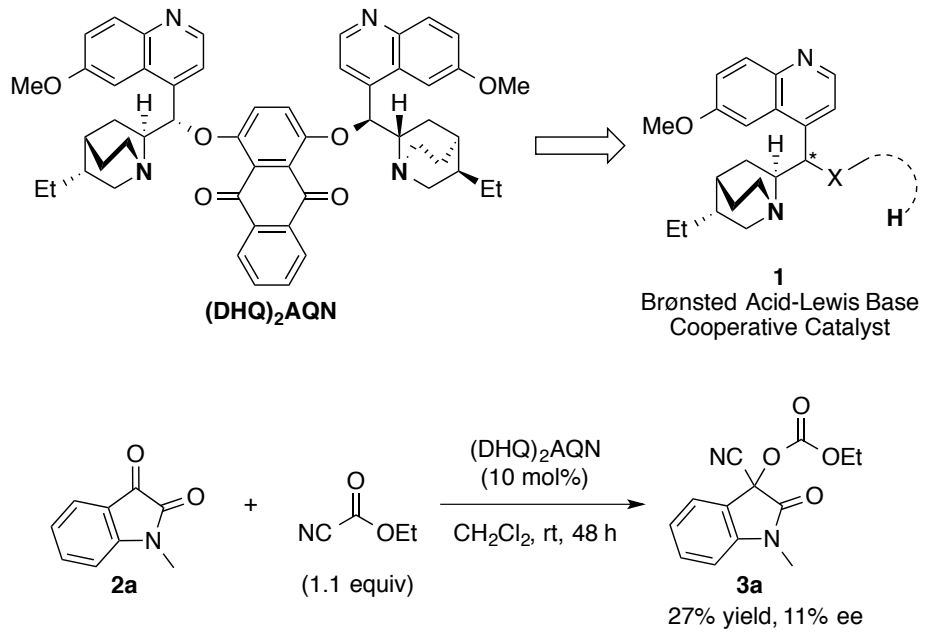
Abstract: The first enantioselective cyano-ethoxycarbonylation of isatins has been developed using Brønsted acid–Lewis base cooperative catalyst. The flexible Brønsted acidic cavity of the catalyst acts as an oxyanion hole mimic at the key intermediate of the reaction. Interestingly, the use of *p*-nitrobenzyl (PNB) protecting group successfully improved the enantioselectivity, and the addition of methanol increased the catalytic activity.

2-1. Introduction

Oxindole is an important core structure found in many natural and synthetic bioactive compounds.[1] For the chemical synthesis of these useful bioactive compounds, much attention has been devoted to the development of the stereoselective carbon–carbon bond-forming reactions on the *C*3-carbonyl carbon atom of isatins, and many enantioselective methods have been reported.[2] However, the enantioselective cyanation of isatins has not yet been reported. Enantioselective cyanation affords the corresponding cyanohydrin or its equivalent, which would be a useful chiral building block for the synthesis of these bioactive compounds.

The asymmetric cyanation of carbonyl compounds is an important reaction for the construction of chiral tetrasubstituted carbon stereocenters.[3] Representative cyanation methods include hydrocyanation with hydrogen cyanide, and silylcyanation with a silyl cyanide.[4] Although many chiral catalysts have been developed for asymmetric hydrocyanation and silylcyanation, these methods require a highly toxic cyanation reagent, and the corresponding cyanation products are rather unstable. In contrast, cyano-alkoxycarbonylation with a less toxic acylcyanide or alkyl cyanoformate[5] is also useful for the cyanation of carbonyl compounds, and the products are rather stable.

Scheme 2.1 Organocatalytic Enantioselective Cyano-Ethoxycarbonylation of Isatins



In 2001, Deng and co-workers reported the first enantioselective cyano-ethoxycarbonylation with $(DHQ)_2AQN$ as a chiral nucleophilic-base catalyst.[6,7] Although this pioneering method is highly efficient for the reaction of ketones, $(DHQ)_2AQN$ gave poor results in the reaction of *N*-methylisatin **2a** in our study, probably because *N*-methylisatin was much less reactive than ketones (Scheme 2.1).

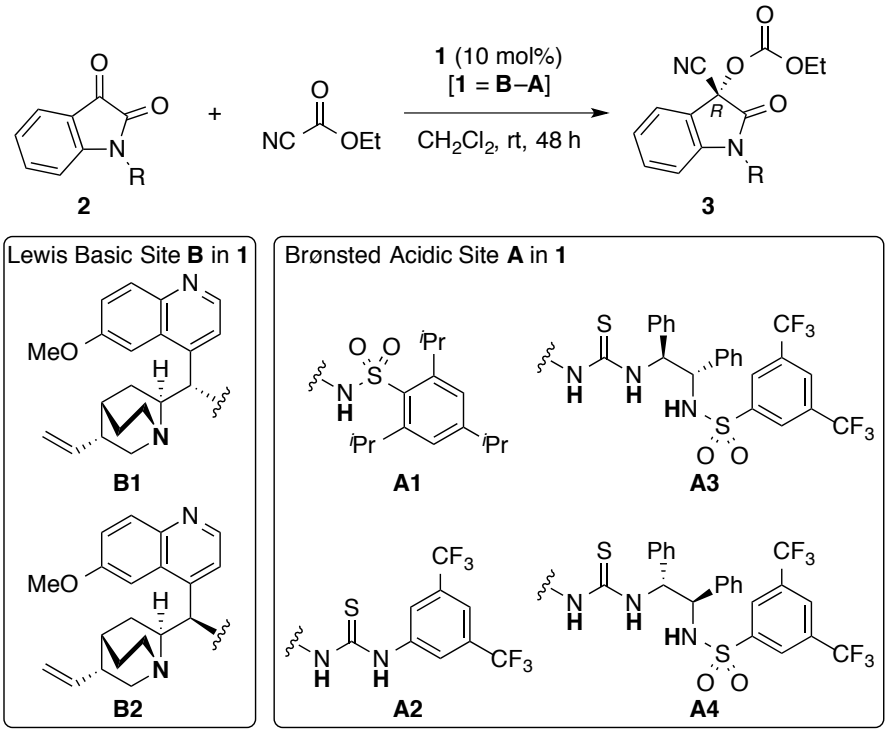
We envisioned that acid–base cooperative catalysts **1**,[8] which have a Lewis basic site and a Brønsted acidic site, may be able to promote the enantioselective cyano-ethoxycarbonylation of isatins. The Lewis basic site would activate the cyano-ethoxycarbonylation reagent, and the Brønsted acidic site would simultaneously activate the carbonyl group of isatins through hydrogen bonding to promote the reaction. We report herein the enantioselective cyano-ethoxycarbonylation of isatins with acid–base cooperative organocatalysts.

2-2. Result and Discussion

On the basis of the findings of the Deng research group and our preliminary experiments,, we chose the chiral quinuclidine **B1** derived from cinchonidine as the Lewis basic site (**B**) in the acid–base cooperative catalyst **1** (**B**—**A**), and optimized the Brønsted acidic site (**A**) (Table 2.1). The reaction of *N*-methylisatin (R = Me) was conducted with ethyl cyanoformate (1.1 equiv) in CH_2Cl_2 in the presence of **1** (10 mol%) at ambient temperature. Catalyst **1a** bearing sulfonamide **A1** as the Brønsted acidic site did not give any products, whereas the use of thiourea **A2** gave the product in moderate yield with moderate enantioselectivity (Table 2.1, entries 1 and 2). Upon further investigation of the Brønsted acidic site in the catalyst **1**, we found that the introduction of a third Brønsted acid (**A3**)[9,10] successfully improved both the yield and enantioselectivity to 73% and 65% ee (entry 3). In contrast, the use of diastereomeric chiral Lewis base **B2** and/or enantiomeric chiral Brønsted acid **A4** decreased both the yields and enantioselectivity (entries 4–6). Therefore, we concluded that catalyst **1c** with the Lewis basic site **B1** and Brønsted acidic site **A3**, was the optimized catalyst.

With this optimized catalyst in hand, we turned our focus to the protecting group of the amide group of isatin. We found that the use of a benzyl group improved the enantioselectivity (entry 7). Interestingly, the use of a benzyl group substituted with an electron-donating methoxy group led to a decrease in enantioselectivity (entry 8), whereas the introduction of an electron-withdrawing *p*-nitrobenzyl (PNB) substituent led to an increase in enantioselectivity, and the product was obtained with 82% ee (entry 9). During further optimization of the reaction conditions, we found

Table 2.1 Catalytic Activity of **1** [B–A].[a]



Entry	Catalyst **1** [B–A]	**2** (R)	**3**, Yield [%][b]	Ee [%]
1	**1a** = **B1–A1**	**2a** (Me)	**3a**, 0	–
2	**1b** = **B1–A2**	**2a** (Me)	**3a**, 34	33
3	**1c** = **B1–A3**	**2a** (Me)	**3a**, 73	65
4	**1d** = **B1–A4**	**2a** (Me)	**3a**, 30	20
5	**1e** = **B2–A3**	**2a** (Me)	**3a**, 22	–18
6	**1f** = **B2–A4**	**2a** (Me)	**3a**, 42	–55
7	**1c** = **B1–A3**	**2b** (Bn)	**3b**, 71	72
8	**1c** = **B1–A3**	**2c** (*p*-(MeO)$C_6H_4CH_2$)	**3c**, 41	61
9	**1c** = **B1–A3**	**2d** (*p*-(NO_2)$C_6H_4CH_2$)	**3d**, 59	82
10[c]	**1c** = **B1–A3**	**2d** (*p*-(NO_2)$C_6H_4CH_2$)	**3d**, 87	95
11[c,d]	**1c** = **B1–A3**	**2d** (*p*-(NO_2)$C_6H_4CH_2$)	**3d**, 98	95
12[c,d,e]	**1c** = **B1–A3**	**2d** (*p*-(NO_2)$C_6H_4CH_2$)	**3d**, 94	95

[a] The reaction of *N*-protected isatin **2** (0.50 mmol) was conducted with EtOCOCN (1.1 equiv) in the presence of **1** (10 mol%) in CH_2Cl_2 at ambient temperature for 48 h. [b] Isolated yield. [c] The reaction was conducted with EtOCOCN (2.2 equiv) in the presence of **1c** (5 mol%) in $CHCl_3$ for 6 h. [d] The reaction was conducted with MeOH (50 mol%). [e] 5 mmol scale. The reaction was conducted in the presence of **1c** (5 mol%) for 24 h.

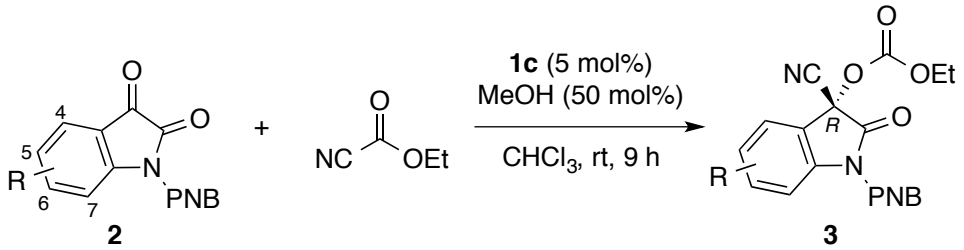
that the use of chloroform as the solvent and 2.2 equivalents of ethyl cyanoformate improved both the reactivity and the enantioselectivity (87% yield, 95% ee, entry 10). Furthermore, the addition of MeOH (50 mol%) improved the reactivity remarkably: the reaction reached completion in only 2 h under the optimized conditions (entry 11). The results of ^{1}H NMR spectroscopic analysis suggested that catalyst **1c** largely existed as a less active oligomeric species in $CHCl_3$. The addition of MeOH might dissociate oligomeric **1c** to become an active monomer[11] and thus promote the reaction.

The protocol of the present reaction was very simple: the substrate, reagent and catalyst were stirred together at ambient temperature in simple glassware. Thus, this reaction could be easily applied to a large-scale synthesis without any difficulties. When the reaction of *N*-PNB-protected isatin (1.4 g, 5 mmol) was conducted in the presence of **1c** (5 mol%) under the optimized reaction conditions, 1.8 g of the product was obtained (94% yield, entry 12).[12]

Under the optimized reaction conditions, isatin derivatives **2** bearing a variety of substituents were converted to the corresponding products in high yields with excellent enantioselectivity (Table 2.2). For example, isatin derivatives with electron-donating methyl, methoxy and trifluoromethoxy groups and electron-withdrawing nitro, fluoro, chloro, bromo and iodo groups at the 5-positions were converted to the corresponding products in up to 98% yield with 88-98% ee (Table 2.2, entries 1–10). Furthermore, the reactions of isatins bearing a bromine substituent proceeded with excellent enantioselectivities regardless of the position of the bromine substituent (entries 10–13). The absolute configuration of the 5-brominated product **3n** was determined to be *R* by X-ray single-crystal analysis.[13,14]

A proposed mechanism for the enantioselective cyano-ethoxycarbonylation of isatins is shown in Scheme 2.2. The cyano-ethoxycarbonylation is a two-step reaction: the first step is a reversible cyanation of the carbonyl group, and the second step is the irreversible acylation of the cyanohydrin alkoxide intermediate. Kinetic studies on the present **1c**-catalyzed cyano-ethoxycarbonylation of isatins showed that the initial reaction rate did not depend on the concentration of the substrate or EtOCOCN.[14] Furthermore, the ee value of the product was completely independent of the conversion of the reaction.[14,15] These results suggested that the first cyanation step was a rapid equilibrium and the second acylation step was rate-determining.

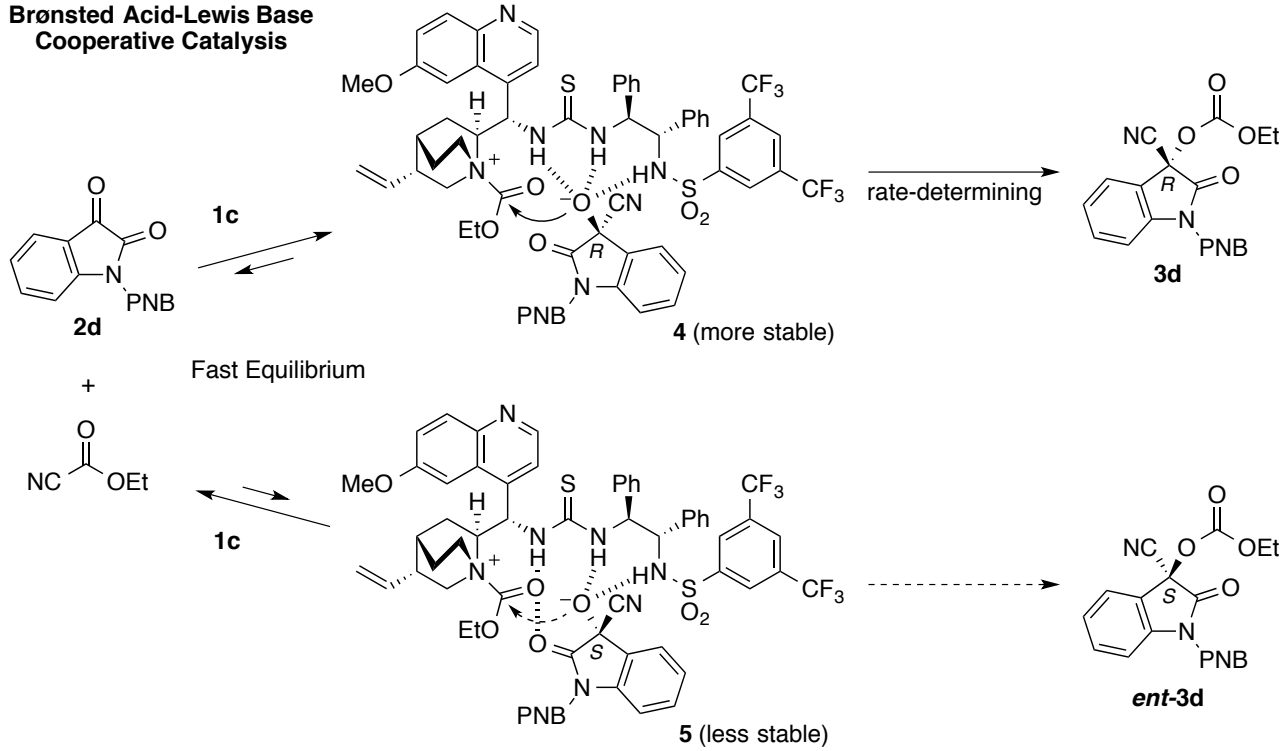
Table 2.2 Exploration of the Generality of Cyano-Ethoxycarbonylation Catalyzed by **1c**.[a]



Entry	**2** (R)	**3**, Yield [%][b]	Ee [%]
1	**2e** (5-Me)	**3e**, 96	95
2	**2f** (5,7-Me_2)	**3f**, 70	94
3	**2g** (5-MeO)	**3g**, 88	95
4	**2h** (5,6-$(MeO)_2$)	**3h**, 61	88
5	**2i** (5-CF_3O)	**3i**, 97	96
6	**2j** (5-NO_2)	**3j**, 85	98
7	**2k** (5-F)	**3k**, 96	96
8	**2l** (5-Cl)	**3l**, 97	97
9	**2m** (5-I)	**3m**, 94	97
10	**2n** (5-Br)	**3n**, 98	96
11	**2o** (4-Br)	**3o**, 96	99
12	**2p** (6-Br)	**3p**, 91	95
13	**2q** (7-Br)	**3q**, 87	94
14	**2r** (5,7-Br_2)	**3r**, 67	96
15	**2s** (7-CF_3)	**3s**, 94	95

[a] The reaction of an *N*-PNB-isatin **2** (0.5 mmol) was conducted with ethyl cyanoformate (2.0 equiv) in $CHCl_3$ (2.5 mL) in the presence of **1c** (5 mol%) and MeOH (50 mol%) at ambient temperature for 9 h. [b] Isolated yield.

Scheme 2.2 Proposed Mechanism for the **1c**-Catalyzed Cyano-Ethoxycarbonylation of Isatins



Deng and co-workers reported that asymmetric induction in the Lewis base catalyzed cyano-ethoxycarbonylation of ketones from kinetic resolution of the cyanohydrin alkoxy anion intermediates through asymmetric acylation, since the ee value of the cyanohydrin intermediates was much lower than those of the cyano-ethyoxycarbonylation products.[6] In contrast, in the present **1c**-catalyzed cyano-ethoxycarbonylation of isatins, a theoretical calculation showed that ion pair **4** of the (*R*)-alkoxy anion (Figure 2.1) was 12.6 kJ/mol more stable than ion pair **5** of the (*S*)-alkoxy anion.[14,16] In ion pair **4**, three acidic protons of **1c** act as an "oxyanion hole,"[17,18] and stabilize the oxyanion through three hydrogen bonding interactions. These results implied that asymmetric induction would arise not only from the kinetic resolution of the cyanohydrin alkoxy anion intermediates in the second step, but also from the cyanation of isatins in the first step.[19] It is conceivable that when a Lewis base such as $(DHQ)_2AQN$ is used as a catalyst for the cyano-ethoxycarbonylation of isatins, the first-step equilibrium greatly favors the starting materials in contrast to the **1c**-catalyzed reaction, and that the $(DHQ)_2AQN$-catalyzed cyano-ethoxycarbonylation of isatins showed poor reactivity for this reason (Scheme 2.1).

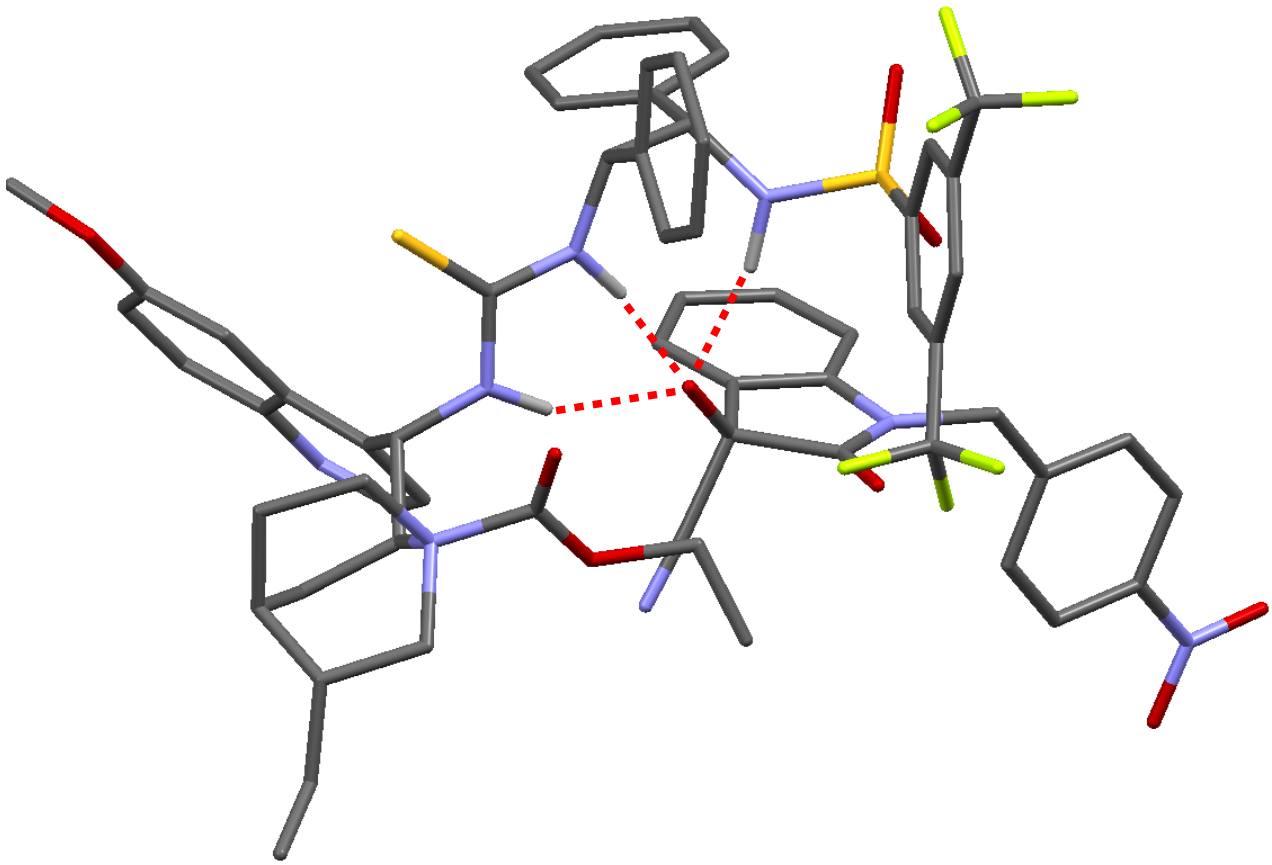
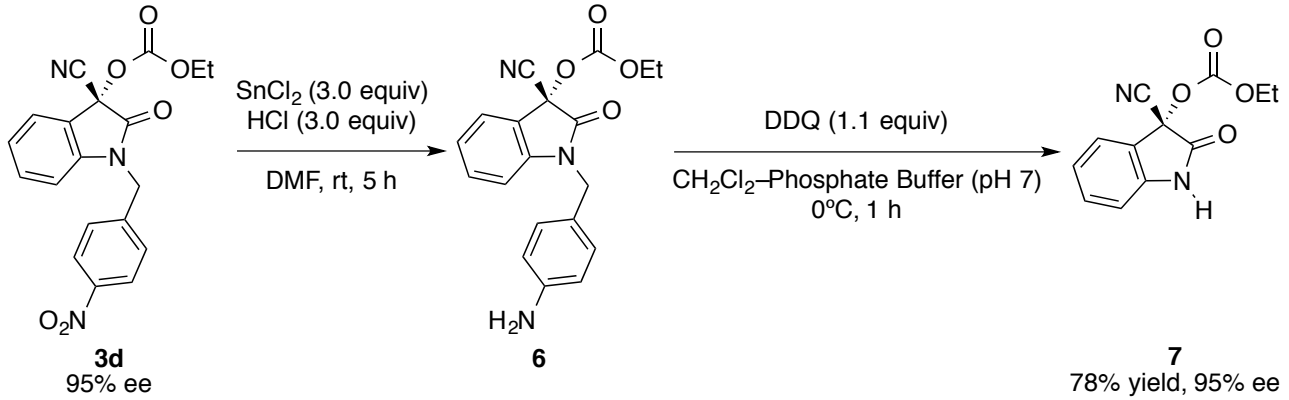


Figure 2.1 Optimized geometry (B3LYP/6-31G(d)) of ion pair **4**.[21,22] Hydrogen atoms, except for those in the thiourea and sulfonamide groups, are omitted for clarity.

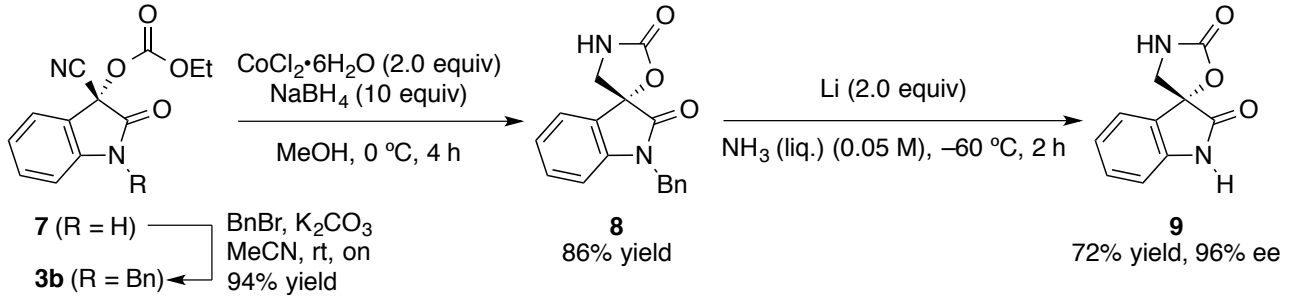
We next investigated the removal of the PNB group in the products. Since the carbonate moiety is rather unstable under strongly acidic and basic conditions, deprotection should be conducted under weakly acidic or basic conditions. Therefore, we attempted deprotection by DDQ oxidation, which is generally conducted under nearly neutral mild conditions. Since the electron-deficient benzyl group is less reactive toward oxidation with DDQ, we had to convert the electron-withdrawing nitro group of **3d** into an electron-donating group to make the benzyl group electron-rich. We first selectively reduced the PNB nitro group with tin(II) chloride to an electron-donating amino group **6** (Scheme 2.3). Subsequent DDQ oxidation of the electron-rich *p*-aminobenzyl group successfully gave the deprotected compound **7** in 78% yield.

Scheme 2.3 Removal of *p*-Nitrobenzyl (PNB) Protection



The spiro-fused compound **9** was obtained by the selective reduction of the cyano group of **3b**, which was obtained from **7** by benzylation of the amide group (Scheme 2.4). Reduction of the cyano group with cobalt(II) chloride and sodium borohydride[20] gave the corresponding primary amine, which underwent simultaneously cyclized with the carbonate moiety to give cyclic carbamate **8** without any loss of optical purity. Remobal of the benzyl group under Birch conditions gave **9** in 52% yield. Compound **9** is a promising chiral building block for the synthesis of various bioactive oxindoles.

Scheme 2.4 Synthesis of Spiro-Fused Compound **9**



2-3. Conclusion

In conclusion, we have developed the first enantioselective cyano-ethoxycarbonylation of isatins by using Brønsted acid–Lewis base cooperative catalyst **1c**. The Lewis basic site of **1c** caused nucleophilic activation of ethyl cyanoformate, and the Brønsted acidic, deep, and flexible cavity simultaneously stabilized and selectively recognized the (*R*)-alkoxy anion intermediate to promote asymmetric acylation. Furthermore, the use of a *p*-nitrobenzyl protecting group

successfully improved the enantioselectivity. The protocol was very simple, all the reagents could be used without purification, and the reaction could be easily applied to a large-scale synthesis without any difficulties.

2-4. References and Notes

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11. Since a linear relationship was observed between the optical purity of **3c** and the enantiomeric excess of the product, monomeric **3c** should be the active catalytic species. See the experimental section. See also: (a) Oh, J.; Lee, J.; Ryu, T.; Lee, J. H.; Song, C. *Org. Biomol. Chem.* **2012**, *10*, 1052. (b) Jang, H.; Rho, H.; Oh, J.; Nam, E.; Park, S.; Bae, H.; Song, C. *Org. Biomol. Chem.* **2010**, *8*, 3918. (c) Kaminsky, W.; Responte, D.; Daranciang, D.; Gallegos, J. B.; Tran, B.; Pham, T. *Molecules*, **2010**, *15*, 554. (d) Rho, H.; Oh, S.; Lee, J.; Lee, J.; Chin, J.; Song, C. *Chem. Commun.* **2008**, 1208. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*,1520.

12. The catalyst was recovered in 98% yield after flash column chromatography.

13. CCDC-925315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

14. See the experimental section for details.

15. Deng and Tian also observed that the enantiomeric excess of the product only slightly depended on the conversion in the Lewis base-catalyzed cyano-ethyoxycarbonylation of ketones.[6]

16. The present cyano-ethoxycarbonylation of isatins did not give any cyanohydrin intermediates, which suggested that the cyanohydrin alkoxy anion intermediates of isatins were highly unstable.

17. For oxyanion holes in enzyme-catalyzed processes, see: (a) Whiting, A. K.; Peticolas, W. L. *Biochemistry* **1994**, *33*, 552. (b) Zhang, Y.; Kua, J.; McCammon, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 10572. (c) Sigala, P. A.; Kraut, D. A.; Caaveiro, J. M. M.; Pybus, B.; Ruben, E. A.; Ringe, D.; Petsko, G. A.; Herschlag, D. *J. Am. Chem. Soc.* **2008**, *130*, 13696. (d) Childs, W.; Boxer, S. G. *Biochemistry* **2010**, *49*, 2725.

18. For oxyanion hole mimics in chemical processes, see: a) Kondo, S.; Harada, T.; Tanaka, R.; Unno, M. *Org. Lett.* **2006**, *8*, 4621. (b) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. (c) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678. (d) Muñiz, F. M.; Alcázar, V.; Sanz, F.; Simón, L.; Fuentes de Arriba Á. L.; Raposo, C.; Morán, J. R. *Eur. J. Org. Chem.* **2010**, 6179. (e) Jiménez, M. B.; Alcázar, V.; Peláez, R.; Sanz, F.; Fuentes de Arriba, Á. L.; Caballero, M. C. *Org. Biomol. Chem.* **2012**, *10*, 1181. (f) Beletskiy, E. V.; Schmidt, J.; Wang, X.; Kass, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 18534.

19. We could not exclude the possibility that asymmetric induction arose solely from the first cyanation step.

20. For selected reports on nitrile group-selective reduction with $CoCl_2$ and $NaBH_4$, see: (a) Könekamp, T.; Ruiz, A.; Duwenhorst, J.; Schmidt, W.; Borrmann, T.; Stohrer, W.; Montforts, F. *Chem. Eur. J.* **2007**, *13*, 6595. (b) Ducatel, H.; Nhien, A. N. V.; Postel, D. *Tetrahedron: Asymmetry* **2008**, *19*, 67.

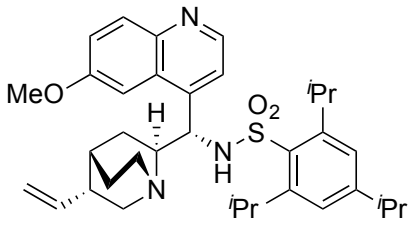
21. (a) Frisch M. J. *et al. GAUSSIAN03, Revision E01*, Gaussian, Inc., Wallingford, CT, 2004. (b) Frisch M. J. *et al. GAUSSIAN09, Revision C 01*, Gaussian, Inc., Wallingford, CT, 2009.

22. All optimized structures of complexes and calculation data are described in the experimental section.

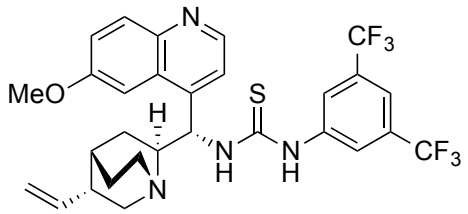
2-5. Experimental Section

General Methods. IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (DMSO-d_6: 2.50 ppm, CD_3OD: 3.31 ppm) or Me_4Si resonance (0.00 ppm; $CDCl_3$) as the internal standard. Data were recorded as follows: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$: 77.16 ppm, DMSO-d_6: 39.52 ppm, CD_3OD: 49.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALPACK IA-H (4.6 mm × 25 cm), IA-3 (4.6 mm × 25 cm) or ID-3 (4.6 mm × 25 cm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Facility, Nagoya University. Dry dichloromethane was purchased from Kanto as the "anhydrous" and stored under nitrogen. Dry chloroform was distilled fractionally from P_2O_5 and stored over 4A molecular sieves and Ag foil. Other materials were obtained from commercial supplies and used without further purification.

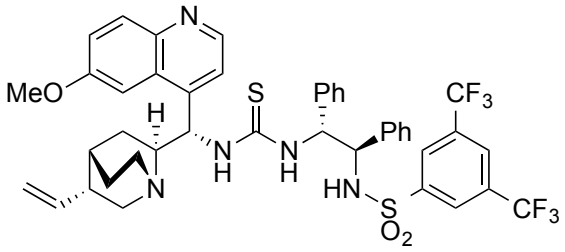
Synthesis of Lewis Base–Brønsted Acid Cooperative Catalysts 1.



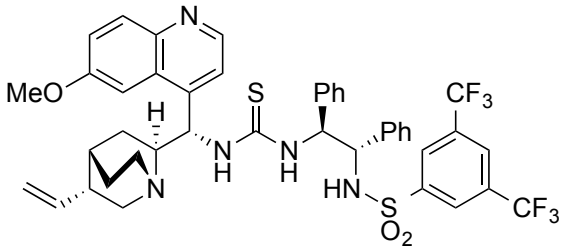
2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (1a)[1]



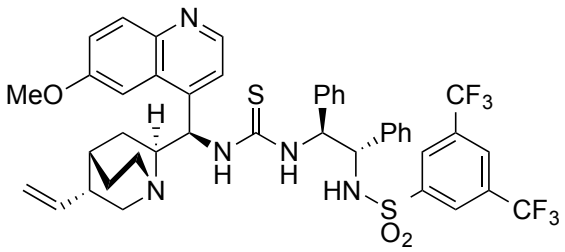
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (1b)[2]



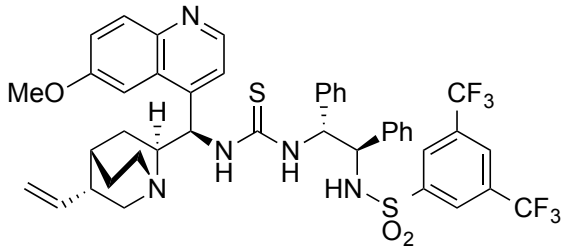
***N*-((1*R*,2*R*)-2-(3-((*S*)-(6-Methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoro methyl)benzenesulfonamide (1c)**[3]



***N*-((1*S*,2*S*)-2-(3-((*S*)-(6-Methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoro methyl)benzenesulfonamide (1d)**[3]



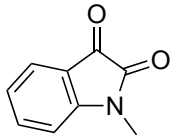
***N*-((1*S*,2*S*)-2-(3-((*R*)-(6-Methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoro methyl)benzenesulfonamide (1e):** A solution of (1*S*,2*S*,5*R*)-2-((*R*)-isothiocyanato-(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (365 mg, 1.0 mmol) and *N*-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-3,5-bis(trifluoro- methyl)benzenesulfonamide (541 mg, 1.0 mmol) in THF (5.0 mL) was stilled for 3 h under reflux condition. After the completion of the reaction, the mixture was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (diethyl ether only) to give **1e** (672 mg, 74% yield). Colorless solid; $[\alpha]^{23}_{D}$ 109.2 (*c* 1.0, $CHCl_3$); IR (KBr) 1624, 1509, 1361, 1281, 1162, 1141 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.91 (s, 1H), 7.86 (d, *J* = 5.7 Hz, 1H), 7.84 (s, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.33 (dd, *J* = 2.8, 9.3 Hz, 1H), 7.30–6.95 (m, 3H), 6.94–6.77 (m, 5H), 6.74 (s, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 6.11 (d, *J* = 8.2 Hz, 1H), 5.91 (ddd, *J* = 6.2, 10.8, 17.4 Hz, 1H), 5.60 (d, *J* = 8.2 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.10 (d, *J* = 10.8 Hz, 1H), 4.77 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H), 3.36 (brs, 1H), 3.33–3.21 (m, 2H), 3.09–2.92 (m, 3H), 2.38–2.27 (m, 1H), 1.64–1.44 (m, 3H), 1.23–1.11 (m, 1H), 1.05–0.91 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 207.0, 184.6, 159.5, 148.1, 145.9, 144.9, 141.6, 139.7, 138.0, 133.0 (q, $J_{C\text{-}F}$ = 34.3 Hz, 2C), 131.0, 130.0, 129.13 (2C), 129.08 (2C), 129.04 (2C), 129.01 (2C), 128.6, 128.5, 128.4 (2C), 126.3, 123.91 (q, $J_{C\text{-}F}$ = 272.8 Hz, 2C), 123.87, 120.9, 115.3, 103.8, 66.8, 64.3, 63.6, 62.0, 56.5, 56.0, 50.3, 40.1, 28.8, 27.3, 26.5; HRMS (FAB+) calcd for $C_{43}H_{42}F_6N_5O_3S_2$ $[M+H]^+$ 854.2628, found 854.2632.



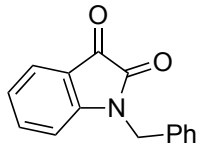
***N*-((1*R*,2*R*)-2-(3-((*R*)-(6-Methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoro methyl)benzenesulfonamide (1f):** **1f** was prepared from (1*S*,2*S*,5*R*)-2-((*R*)-isothiocyanato(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (365 mg, 1.0 mmol) and *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (541 mg, 1.0 mmol) according to

the same manner as **1f**. 69% yield. Colorless solid; $[\alpha]^{23}_{D}$ 157.8 (*c* 1.0, $CHCl_3$); IR (KBr) 1624, 1509, 1361, 1280, 1162, 1141 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.67 (br s, 1H), 7.96 (br s, 1H), 7.94 (d, *J* = 10.0 Hz, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.58 (br s, 1H), 7.43 (dd, *J* = 1.8, 9.2 Hz, 1H), 7.12–7.00 (m, 3H), 7.00–6.89 (m, 2H), 6.83 (dd, *J* = 7.1, 7.3 Hz, 1H), 6.73 (dd, *J* = 7.1, 7.3 Hz, 2H), 6.62 (d, *J* = 7.3 Hz, 2H), 6.15 (br s, 1H), 5.93 (ddd, *J* = 6.2, 10.8, 17.2 Hz, 1H), 5.62 (br s, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.75 (d, *J* = 8.7 Hz, 1H), 4.03 (s, 3H), 3.33–3.19 (m, 2H), 3.17–2.90 (m, 3H), 2.38–2.28 (m, 1H), 1.64–1.15 (m, 3H), 1.30–1.19 (m, 1H), 1.00–0.90 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 211.6, 184.0, 159.5, 148.4, 145.7, 144.9, 141.5, 139.4, 137.8, 131.1, 132.9 (q, $J_{C\text{-}F}$ = 33.6 Hz, 2C), 130.2, 129.1 (2C), 128.9 (4C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 126.3, 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz, 2C), 123.8, 120.8, 115.4, 103.9, 70.2, 64.0, 63.3, 61.7, 56.5, 55.6, 50.0, 40.0, 28.7, 27.1, 26.2; HRMS (FAB+) calcd for $C_{43}H_{42}F_6N_5O_3S_2$ $[M+H]^+$ 854.2628, found 854.2632.

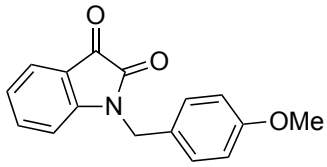
Preparation of Isatin Derivatives.



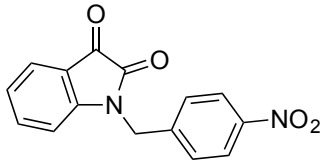
1-Methylindoline-2,3-dione:[4] To a solution of isatin (736 mg, 5 mmol) in DMF (25 mL) was added NaH (60% dispersion in mineral oil, 132.0 mg, 5.5 mmol) at 0 ºC, and the mixture was stirred for 5 minutes. To the reaction mixture was added methyl iodide (343 μL, 5.5 mmol), and the mixture was wormed to ambient temperature, and then stirred for 3 h. After the completion of the reaction, water (1 mL) was added to the reaction mixture dropwise, and the solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel to give 1-methylindoline-2,3-dione (645 mg, 80% yield) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, J = 6.9, 7.8 Hz, 2H), 7.61 (d, J = 7.3 Hz, 1H), 7.14 (dd, J = 6.9, 7.3 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 158.4, 151.6, 138.6, 125.4, 124.0, 117.6, 110.1, 26.4.



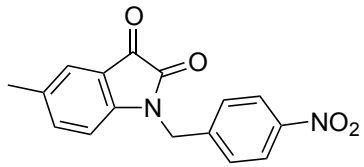
1-Benzylindoline-2,3-dione:[5] 1-Benzylindoline-2,3-dione was prepared from isatin and benzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 80% yield; orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 2H), 7.38–7.28 (m, 5H), 6.78 (d, J = 7.8 Hz, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 158.4, 150.8, 138.5, 134.6, 129.2 (2C), 128.3, 127.6 (2C), 125.6, 124.0, 117.8, 111.1, 44.2.



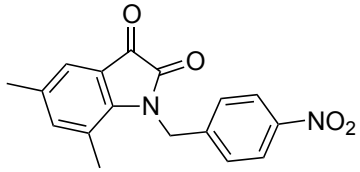
1-(4-Methoxybenzyl)indoline-2,3-dione:[6] 1-(4-Methoxybenzyl)-indoline-2,3-dione was prepared from isatin and 4-methoxybenzyl chloride according to the same manner as 1-methylindoline-2,3-dione. 46% yield; orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 1.4, 6.9 Hz, 1H), 7.48 (ddd, J = 1.4, 7.8, 7.8 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.08 (dd, J = 6.9, 7.8 Hz, 1H), 6.87 (d, J = 9.2 Hz, 2H), 4.87 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 159.6, 158.3, 150.9, 138.4, 129.0 (2C), 126.6, 125.5, 123.9, 117.8, 114.5 (2C), 111.1, 55.4, 43.7.



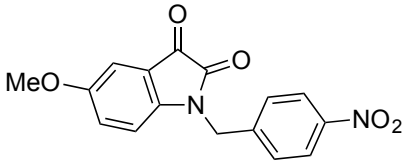
1-(4-Nitrobenzyl)indoline-2,3-dione:[7] 1-(4-Nitrobenzyl)indoline-2,3-dione was prepared from isatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 83% yield; orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.56–7.49 (m, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.61 (dd, *J* = 7.3, 8.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 158.4, 150.1, 147.9, 142.0, 138.6, 128.3 (2C), 126.0, 124.53, 124.45 (2C), 117.9, 110.6, 43.5.



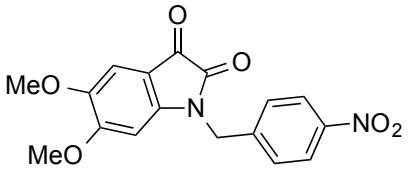
5-Methyl-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Metnyl-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-methylisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 73% yield; orange solid; IR (KBr) 1722, 1621, 1598, 1544, 1523, 1491, 1343 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.42 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.04 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.0, 158.7, 147.8, 147.0, 143.7, 138.1, 132.9, 128.5 (2C), 124.8, 123.7 (2C), 117.9, 110.8, 42.4, 20.1; HRMS (FAB+) calcd for $C_{16}H_{12}N_2O_4$ $[M+H]^+$ 297.0870, found 297.0865.



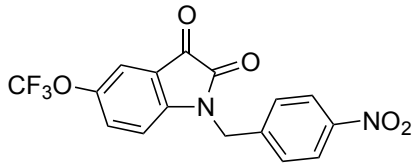
5,7-Dimethyl-1-(4-nitrobenzyl)indoline-2,3-dione: 5,7-Dimethyl-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5,7-dimethylisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 72% yield; orange solid; IR (KBr) 1728, 1622, 1604, 1517, 1491, 1343, 1168 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.30 (s, 1H), 7.19 (s, 1H), 5.23 (s, 1H), 2.23 (s, 1H), 2.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.3, 159.8, 146.8, 145.6, 145.5, 142.0, 133.0, 127.2 (2C), 124.0 (2C), 122.9, 121.2, 119.1, 44.3, 19.8, 17.6; HRMS (FAB+) calcd for $C_{17}H_{14}N_2O_4$ $[M+H]^+$ 311.1027, found 311.1046.



5-Methoxy-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Methoxy-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-methoxyisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 34% yield; orange solid; IR (KBr) 1744, 1729, 1599, 1514, 1492,1437, 1344, 1242, 1177 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.22–7.12 (m, 3H), 6.86 (d, J = 8.3 Hz, 1H), 5.04 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.5, 159.1, 156.4, 147.5, 144.21, 144.15, 129.0 (2C), 124.2 (2C), 124.0, 119.0, 112.4, 109.9, 56.4, 42.9; HRMS (FAB+) calcd for $C_{16}H_{12}N_2O_5$ $[M+H]^+$ 313.0819, found 313.0824.

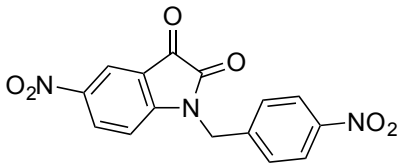


5,6-Dimethoxy-1-(4-nitrobenzyl)indoline-2,3-dione: 5,6-Dimethoxy-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5,6-dimethoxyisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 23% yield; orange solid; IR (KBr) 1748, 1715, 1611, 1520, 1482, 1385, 1346, 1243, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 6.12 (s, 1H), 5.01 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 159.6, 158.6, 148.0, 147.9, 146.3, 142.5, 128.0 (2C), 124.4 (2C), 109.3, 107.8, 94.8, 56.8, 56.6, 43.3; HRMS (FAB+) calcd for $C_{17}H_{14}N_2O_6$ $[M+H]^+$ 343.0925, found 343.0942.

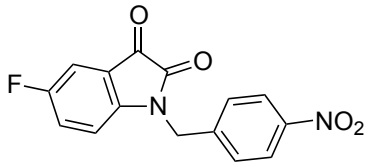


1-(4-Nitrobenzyl)-5-(trifluoromethoxy)indoline-2,3-dione: 1-(4-nitrobenzyl)-5-(trifluoromethoxy)indoline-2,3-dione was prepared from 5-(trifluoromethoxy)isatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 43% yield; orange solid; IR (KBr) 1735, 1619, 1524, 1488, 1353, 1255, 1214, 1173, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 2H), 7.57–7.49 (m, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.06 (s, 2H); ^{13}C

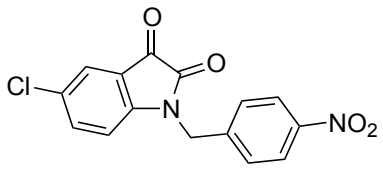
NMR (100 MHz, $CDCl_3$) δ 181.6, 158.0, 148.4, 148.1, 145.8, 141.4, 131.3, 128.3 (2C), 124.6 (2C), 120.4 (q, $J_{C\text{-}F}$ = 258 Hz), 119.0, 118.4, 118.8, 43.7; HRMS (FAB+) calcd for $C_{16}H_9N_2O_5$ $[M+H]^+$ 367.0537, found 367.0523.



5-Nitro-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Nitro-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-nitroisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 63% yield; orange solid; IR (KBr) 1750, 1615, 1520, 1336 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (dd, J = 2.3, 8.7 Hz, 1H), 8.29 (d, J = 2.3 Hz, 1H), 8.21 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.7 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.5, 159.2, 154.2, 147.1, 143.2, 143.0, 132.7, 128.5 (2C), 123.7 (2C), 119.1, 118.6, 111.2, 42.8; HRMS (FAB+) calcd for $C_{15}H_9N_3O_6$ $[M+H]^+$ 328.0564, found 328.0590.

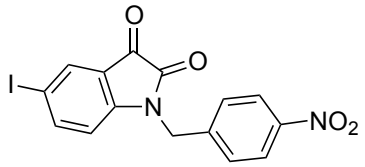


5-Fluoro-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Fluoro-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-fluoroisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 38% yield; orange solid; IR (KBr) 1758, 1732, 1622, 1608, 1521, 1486, 1346, 1267, 1172 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.52 (dd, J_H = 2.3 Hz, $J_{H\text{-}F}$ = 6.4 Hz, 1H), 7.45 (ddd, J_H = 2.3, 8.3 Hz, $J_{H\text{-}F}$ = 10.1 Hz, 1H), 6.94 (dd, J_H = 8.3 Hz, $J_{H\text{-}F}$ = 3.6 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.1, 158.64, 158.63 (d, $J_{C\text{-}F}$ = 240 Hz), 147.0, 146.1, 143.5, 128.5 (2C), 123.72 (d, $J_{C\text{-}F}$ = 23.8 Hz), 123.71 (2C), 119.0 (d, $J_{C\text{-}F}$ = 6.7 Hz), 112.2 (d, $J_{C\text{-}F}$ = 6.7 Hz), 111.6 (d, $J_{C\text{-}F}$ = 23.8 Hz), 42.5; HRMS (FAB+) calcd for $C_{15}H_9FN_2O_6$ $[M+H]^+$ 301.0619, found 301.0630.

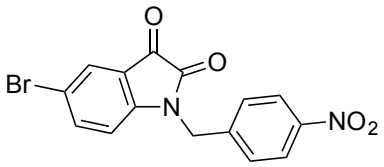


5-Chloro-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Chloro-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 4-chloroisatin and 4-nitrobenzyl

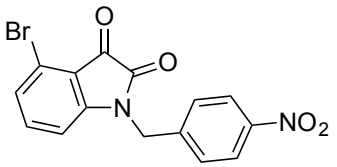
bromide according to the same manner as 1-methylindoline-2,3-dione. 53% yield; orange solid; IR (KBr) 1739, 1607, 1521, 1474, 1446, 1334, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.45 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 157.8, 148.3, 148.0, 141.5, 138.0, 130.5, 128.3 (2C), 125.9, 124.6 (2C), 118.7, 111.9, 43.7; HRMS (FAB+) calcd for $C_{15}H_9ClN_2O_4$ $[M+H]^+$ 317.0324, found 317.0340.



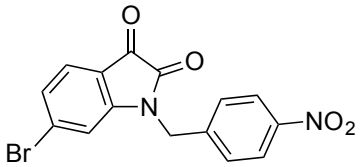
5-Iodo-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Iodo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-iodoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 24% yield; orange solid; IR (KBr) 1732, 1601, 1519, 1469, 1430, 1348, 1324, 1174, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.92 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 157.3, 149.3, 148.0, 146.7, 141.5, 134.4, 128.3 (2C), 124.6 (2C), 119.3, 112.7, 87.0, 43.6; HRMS (FAB+) calcd for $C_{15}H_9IN_2O_4$ $[M+H]^+$ 408.9680, found 408.9692.



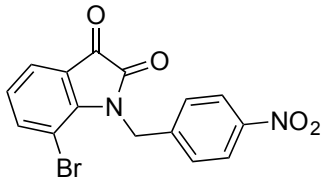
5-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione: 5-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5-bromoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 83% yield; orange solid; IR (KBr) 1737, 1604, 1520, 1472, 1438, 1352, 1261, 1127 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.77–7.70 (m, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5, 158.2, 148.8, 147.0, 143.4, 139.5, 128.5 (2C), 126.8, 123.7 (2C), 119.9, 115.2, 113.0, 42.5; HRMS (FAB+) calcd for $C_{15}H_9BrN_2O_4$ $[M+H]^+$ 360.9819, found 360.9858.



4-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione: 4-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 4-bromoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 38% yield; orange solid; IR (KBr) 1739, 1599, 1523, 1446, 1346, 1326, 1233 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.44 (t, J = 8.2 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.1, 157.9, 151.7, 147.0, 143.4, 138.3, 128.5 (2C), 127.5, 123.7 (2C), 119.4, 116.7, 110.0, 42.5; HRMS (FAB+) calcd for $C_{15}H_9BrN_2O_4$ $[M+H]^+$ 360.9819, found 360.9801.

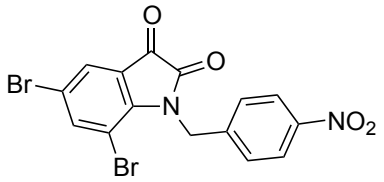


6-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione: 6-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 6-bromoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 43% yield; orange solid; IR (KBr) 1738, 1606, 1509, 1431, 1343, 1102 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.33 (dd, J = 1.4, 6.9 Hz, 1H), 7.30 (d, J = 1.4 Hz, 1H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.6, 158.6, 151.0, 147.0, 143.4, 131.3, 128.5 (2C), 126.3, 126.0, 123.7 (2C), 117.3, 113.9, 42.5; HRMS (FAB+) calcd for $C_{15}H_9BrN_2O_4$ $[M+H]^+$ 360.9819, found 360.9831.

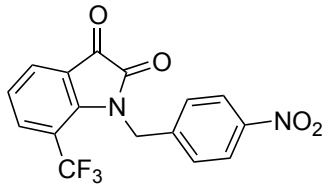


7-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione: 7-Bromo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 7-bromoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 62% yield; orange solid; IR (KBr) 1747, 1605, 1514, 1469, 1443, 1341, 1160, 1121 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.7 Hz, 2H), 7.75 (dd, J = 1.4, 8.2 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.65 (dd, J = 1.4, 7.3 Hz, 1H), 7.09 (dd, J = 7.3, 8.7 Hz, 1H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.6, 159.6, 146.7, 145.6, 142.6, 127.5 (2C), 125.2, 124.0, 123.61, 123.60 (2C), 121.8, 103.0, 44.1; HRMS

(FAB+) calcd for $C_{15}H_9BrN_2O_4$ $[M+H]^+$ 360.9819, found 360.9858.



5,7-Dibromo-1-(4-nitrobenzyl)indoline-2,3-dione: 5,7-Dibromo-1-(4-nitrobenzyl)indoline-2,3-dione was prepared from 5,7-dibromoisatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 42% yield; orange solid; IR (KBr) 1745, 1602, 1511, 1450, 1341, 1320, 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.2 Hz, 2H), 8.00 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.3, 159.3, 146.7, 145.9, 145.4, 143.1, 127.5 (2C), 126.3, 123.6 (2C), 123.0, 115.8, 104.1, 44.2; HRMS (FAB+) calcd for $C_{15}H_8Br_2N_2O_4$ $[M+H]^+$ 440.8903, found 440.8929.

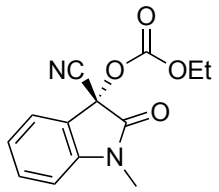


1-(4-Nitrobenzyl)-7-(trifluoromethyl)indoline-2,3-dione: 1-(4-nitrobenzyl)-7-(trifluoromethyl)indoline-2,3-dione was prepared from 7-(trifluoromethyl)isatin and 4-nitrobenzyl bromide according to the same manner as 1-methylindoline-2,3-dione. 52% yield; orange solid; IR (KBr) 1745, 1596, 1526, 1447, 1352, 1181, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.32 (dd, J = 8.7, 8.9 Hz, 1H), 5.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 159.3, 148.1, 147.5, 142.7, 136.1 (q, $J_{C\text{-}F}$ = 5.7 Hz), 129.4, 126.7 (2C), 124.3, 124.1 (2C), 122.6 (q, $J_{C\text{-}F}$ = 202 Hz), 120.3, 114.9 (q, $J_{C\text{-}F}$ = 33.4 Hz), 46.1 (q, $J_{C\text{-}F}$ = 4.8 Hz); HRMS (FAB+) calcd for $C_{16}H_9F_3N_2O_4$ $[M+H]^+$ 351.0587, found 351.0597.

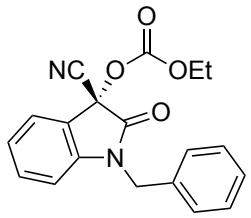
General Procedure for the Asymmetric Cyano-Ethoxycarbonylation of Isatins using Bønsted Acid-Lewis Base Cooperative Catalyst 1.

To a solution of an isatin derivative (0.50 mmol) and **1** (0.050 mmol, 10 mol%) in chloroform (2.5 mL) was added ethyl cyanoformate (108.6 μL, 1.1 mmol, 2.2 equiv) at ambient temperature, and the mixture was stirred for 6–9 h. To the reaction mixture was added brine (2 mL), and the aqueous layer was extracted with chloroform. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography on silica gel to give a cyano-ethoxycarbonylation product.

The corresponding physical and spectroscopic data for the products are as follows.

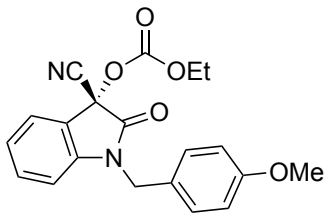


(*R*)-3-Cyano-1-methyl-2-oxoindolin-3-yl ethyl carbonate: Pale yellow oil; $[\alpha]^{23}_{D}$ 67.6 (*c* 1.0, $CHCl_3$) for 65% ee; IR (KBr) 1748, 1613, 1486, 1469, 1370, 1261, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.19 (dd, *J* = 7.8 Hz, 1H), 4.26–4.13 (m, 2H), 3.28 (s, 3H), 1.29 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.7, 144.3, 133.0, 125.9, 124.3, 121.6, 113.1, 109.7, 71.2, 66.1, 27.3, 14.1; HRMS (FAB+) calcd for $C_{13}H_{13}N_2O_4$ $[M+H]^+$ 261.0870, found 261.0867. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 9.8 (minor enantiomer), 11.5 (major enantiomer) min.

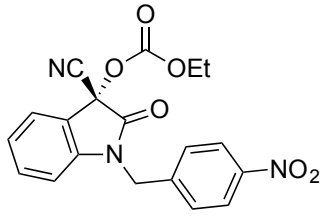


(*R*)-1-Benzyl-3-cyano-2-oxoindolin-3-yl ethyl carbonate (3): Colorless oil; $[\alpha]^{23}_{D}$ 23.4 (*c* 1.0, $CHCl_3$) for 70% ee; IR (KBr) 1748, 1613, 1469, 1371, 1262, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.40–7.28 (m, 6H), 7.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.91 (d, *J* = 15.6 Hz, 1H), 4.30–4.16 (m, 2H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 151.7, 143.4, 134.2, 132.8, 129.2 (2C), 128.2, 127.4 (2C), 125.8, 124.3, 121.7, 113.1, 110.8, 71.4, 66.2, 45.0, 14.1; HRMS (FAB+) calcd for $C_{19}H_{16}N_2O_4$ $[M+H]^+$ 337.1183, found 337.1168. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R=

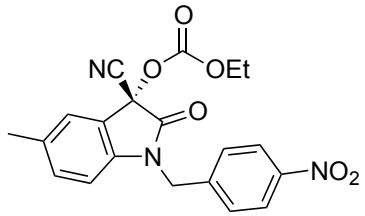
11.9 (minor enantiomer), 12.6 (major enantiomer) min.



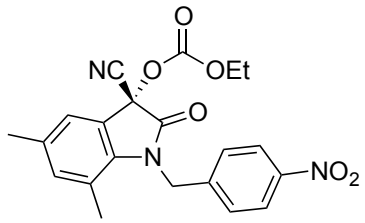
(*R*)-3-Cyano-1-(4-methoxybenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow oil; $[\alpha]^{24}_{D}$ 34.8 (*c* 1.0, $CHCl_3$) for 61% ee; IR (KBr) 1746, 1606, 1516, 1258, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz,1 H), 7.35 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.13 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.22 (m, 2H), 4.29–4.15 (m, 2H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.4, 151.6, 143.3, 132.7, 128.8 (2C), 126.1, 125.7, 124.2, 121.6, 114.4 (2C), 113.1, 110.8, 71.4, 66.1, 55.3, 44.4, 14.1; HRMS (FAB+) calcd for $C_{20}H_{16}N_2O_5$ $[M+H]^+$ 367.1289, found 367.1281. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 12.6 (minor enantiomer), 16.7 (major) min.



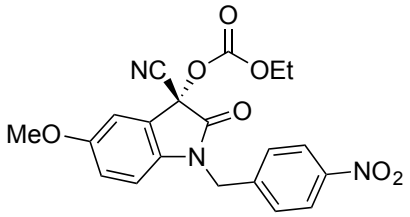
(*R*)-3-Cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{25}_{D}$ 0.4 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1766, 1745, 1614, 1524, 1368, 1343, 1265, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.65 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.34 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1H), 7.20 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.28 (d, *J* = 16.5 Hz, 1H), 4.87 (d, *J* = 16.5 Hz, 1H), 4.30–4.16 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.5, 147.8, 142.6, 141.6, 132.9, 128.2 (2C), 125.7, 124.8, 124.3 (2C), 121.5, 112.5, 110.3, 71.3, 66.4, 44.2, 14.1; HRMS (FAB+) calcd for $C_{19}H_{15}N_3O_6$ $[M+H]^+$ 382.1034, found 382.1013. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 22.5 (minor enantiomer), 32.6 (major enantiomer) min.



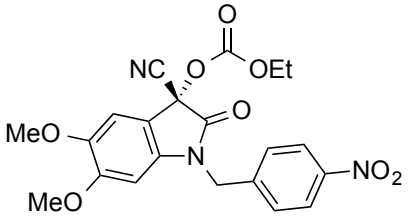
(*R*)-3-Cyano-5-methyl-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{24}_{D}$ –6.3 (*c* 1.0, $CHCl_3$) for 95% ee; IR (KBr) 1748, 1523, 1498, 1342, 1264, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 5.26 (d, *J* = 16.5 Hz, 1H), 4.84 (d, *J* = 16.5 Hz, 1H), 4.31–4.16 (m, 2H), 2.35 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.6, 147.8, 141.8, 140.2, 134.9, 133.2, 128.2 (2C), 126.3, 124.3 (2C), 121.5, 113.0, 110.1, 71.5, 66.3, 44.3, 21.1, 14.1; HRMS (FAB+) calcd for $C_{20}H_{17}N_3O_6$ $[M+H]^+$ 396.1190, found 396.1207. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 19.0 (minor enantiomer), 28.4 (major enantiomer) min.



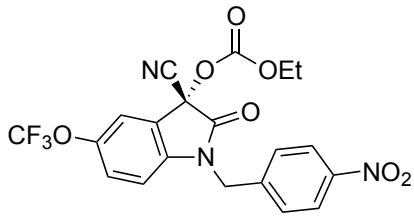
(*R*)-3-Cyano-5,7-dimethyl-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{24}_{D}$ 14.1 (*c* 1.0, $CHCl_3$) for 94% ee; IR (KBr) 1744, 1604, 1523, 1483, 1343, 1264, 1159, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.30 (s, 1H), 6.96 (s, 1H), 5.43 (d, *J* = 17.8 Hz, 1H), 5.14 (d, *J* = 17.8 Hz, 1H), 4.31–4.16 (m, 2H), 2.32 (s, 3H), 2.16 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.4, 147.6, 144.0, 138.1, 137.2, 134.8, 126.9 (2C), 124.4 (2C), 123.8, 122.3, 120.8, 113.2, 71.4, 66.3, 45.9, 20.8, 18.5, 14.1; HRMS (FAB+) calcd for $C_{21}H_{19}N_3O_6$ $[M+H]^+$ 410.1347, found 410.1331. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 14.0 (minor enantiomer), 28.3 (major enantiomer) min.



(*R*)-3-Cyano-5-methoxy-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{24}_{D}$ –1.2 (*c* 1.0, $CHCl_3$) for 95% ee; IR (KBr) 1746, 1524, 1497, 1343, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 2.3 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 5.25 (d, *J* = 16.5 Hz, 1H), 4.84 (d, *J* = 16.5 Hz, 1H), 4.31–4.17 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.3, 151.5, 147.9, 141.7, 135.6, 128.2 (2C), 124.4 (2C), 122.5, 117.6, 112.9, 112.2, 111.1, 71.7, 66.4, 56.1, 44.3, 14.1; HRMS (FAB+) calcd for $C_{20}H_{17}N_3O_7$ $[M+H]^+$ 412.1139, found 412.1142. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 27.4 (minor enantiomer), 38.3 (major enantiomer) min.

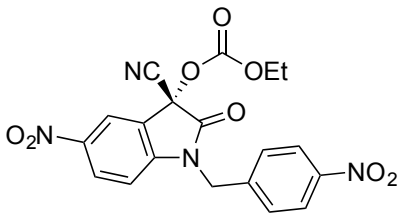


(*R*)-3-Cyano-5,6-dimethoxy-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Peal yellow solid; $[\alpha]^{24}_{D}$ –13.9 (*c* 1.0, $CHCl_3$) for 88% ee; IR (KBr) 1720, 1603, 1522, 1346, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.19 (s, 1H), 6.20 (s, 1H), 5.25 (d, *J* = 16.5 Hz, 1H), 4.85 (d, *J* = 16.5 Hz, 1H), 4.31–4.18 (m, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 153.2, 151.6, 147.9, 146.6, 141.9, 137.2, 128.1 (2C), 124.4 (2C), 113.1, 111.5, 109.4, 95.4, 71.8, 66.3, 56.8, 56.4, 44.2, 14.1; HRMS (FAB+) calcd for $C_{21}H_{19}N_3O_8$ $[M+H]^+$ 442.1245, found 442.1271. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 29.7 (minor enantiomer), 44.4 (major enantiomer) min.

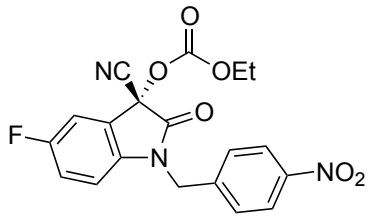


(*R*)-3-Cyano-1-(4-nitrobenzyl)-2-oxo-5-(trifluoromethoxy)indolin-3-yl ethyl carbonate: Pale

yellow solid; $[\alpha]^{23}_{D}$ 4.5 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1758, 1525, 1496, 1345, 1264, 1218, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 1.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.25 (dd, *J* = 1.4, 8.7 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 5.29 (d, *J* = 16.5 Hz, 1H), 4.86 (d, *J* = 16.5 Hz, 1H), 4.33–4.19 (m, 2H), 1.34 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.6, 148.0, 145.9, 141.2, 141.0, 128.3 (2X), 125.9, 124.5 (2C), 122.8, 120.4 ($J_{C\text{-}F}$ = 260 Hz), 112.3, 111.2, 70.9, 66.7, 44.5, 14.1; HRMS (FAB+) calcd for $C_{20}H_{14}F_3N_3O_7$ $[M+H]^+$ 466.0857, found 466.0834. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 15.9 (minor enantiomer), 23.2 (major enantiomer) min.

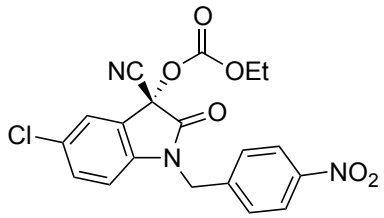


(*R*)-3-Cyano-5-nitro-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{25}_{D}$ 8.6 (*c* 1.0, $CHCl_3$) for 97% ee; IR (KBr) 1762, 1619, 1524, 1341, 1261, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.3 Hz, 1H), 8.33 (dd, *J* = 2.3, 8.7 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 16.5 Hz, 1H), 4.92 (d, *J* = 16.5 Hz, 1H), 4.33–4.18 (m, 2H), 1.35 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.4, 147.9, 147.8, 144.5, 140.9, 129.3, 128.2 (2C), 124.4 (2C), 122.2, 121.5, 111.8, 110.5, 70.2, 67.0, 44.6, 14.0; HRMS (FAB+) calcd for $C_{19}H_{14}N_4O_8$ $[M+H]^+$ 427.0885, found 427.0891. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 34.1 (minor enantiomer), 48.4 (major enantiomer) min.

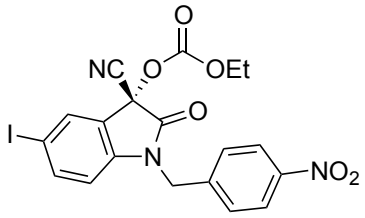


(*R*)-3-Cyano-5-fluoro-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Peal yellow solid; $[\alpha]^{23}_{D}$ –9.2 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1753, 1524, 1494, 1343, 1269, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.41 (dd, J_H = 2.3 Hz, $J_{H\text{-}F}$ = 4.6 Hz, 1H), 7.09 (ddd, J_H = 2.3, 5.0 Hz, $J_{H\text{-}F}$ = 5.8 Hz, 1H), 6.61 (dd, J_H = 5.0 Hz, $J_{H\text{-}F}$ = 3.7 Hz, 1H), 5.72 (d, *J* = 17.0 Hz, 1H), 4.85 (d, *J* = 17.0 Hz, 1H), 4.32–4.19

(m, 2H), 1.34 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.7 (d, J_{C-F} = 247 Hz), 151.5, 147.9, 141.3, 138.6, 128.2 (2C), 124.4 (2C), 122.7 (d, J_{C-F} = 8.6 Hz), 119.5 (d, J_{C-F} = 23.9 Hz), 114.0 (d, J_{C-F} = 25.9 Hz), 112.4, 111.4 (d, J_{C-F} = 7.7 Hz), 71.1, 66.6, 44.4, 14.1; HRMS (FAB+) calcd for $C_{19}H_{14}FN_3O_6$ $[M+H]^+$ 400.0940, found 400.0958. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 20.4 (minor enantiomer), 28.3 (major enantiomer) min.

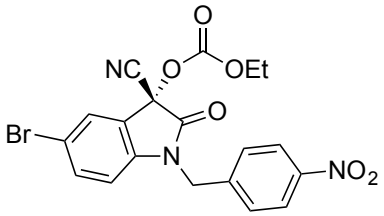


(*R*)-5-Chloro-3-cyano-methyl-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{23}_D$ 1.0 (*c* 1.0, $CHCl_3$) for 97% ee; IR (KBr) 1755, 1616, 1524, 1486, 1344, 1264, 1178 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.35 (dd, J = 2.3, 8.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 5.23 (d, J = 16.5 Hz, 1H), 4.85 (d, J = 16.5 Hz, 1H), 4.32–4.18 (m, 2H), 1.35 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.5, 147.9, 141.12, 141.10, 132.9, 130.3, 128.2 (2C), 126.1, 124.4 (2C), 122.9, 112.4, 111.5, 70.9, 66.7, 44.4, 14.1; HRMS (FAB+) calcd for $C_{19}H_{14}ClN_3O_7$ $[M+H]^+$ 416.0644, found 416.0658. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 20.3 (minor enantiomer), 28.8 (major enantiomer) min.

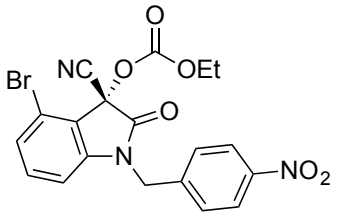


(*R*)-3-Cyano-5-iodo-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{24}_D$ 9.0 (*c* 1.0, $CHCl_3$) for 97% ee; IR (KBr) 1753, 1604, 1523, 1479, 1346, 1263, 1178 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 1.8, 8.2 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 6.44 (d, J = 8.2 Hz, 1H), 5.27 (d, J = 16.5 Hz, 1H), 4.83 (d, J = 16.5 Hz, 1H), 4.32–4.18 (m, 2H), 1.35 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 151.5, 148.0, 142.3, 141.6, 141.1, 134.3, 128.2 (2C), 124.4 (2C), 123.5, 112.4, 112.2, 86.9, 70.6, 66.7, 44.3, 14.1; HRMS (FAB+) calcd for $C_{19}H_{14}IN_3O_6$ $[M+H]^+$ 5008.0000, found 508.0014. The ee was determined by HPLC analysis (Daicel

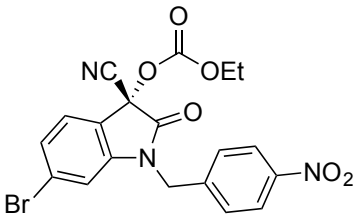
Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 24.6 (minor enantiomer), 35.1 (major enantiomer) min.



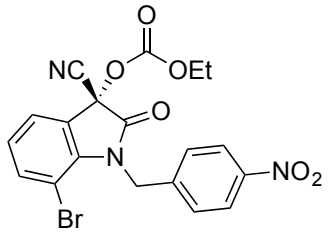
(*R*)-5-Bromo-3-cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{23}_{D}$ 6.6 (*c* 1.0, $CHCl_3$) for 98% ee; IR (KBr) 1769, 1741, 1610, 1526, 1485, 1339, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.50 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.28 (d, *J* = 16.5 Hz, 1H), 4.85 (d, *J* = 16.5 Hz, 1H), 4.32–4.19 (m, 2H), 1.35 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 151.5, 148.0, 141.6, 141.1, 135.8, 128.8, 128.2 (2C), 124.5 (2C), 123.3, 117.4, 112.4, 111.8, 70.8, 66.7, 44.4, 14.1; HRMS (FAB+) calcd for $C_{19}H_{14}BrN_3O_6$ $[M+H]^+$ 460.0139, found 460.0127. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 22.7 (minor enantiomer), 32.9 (major enantiomer) min.



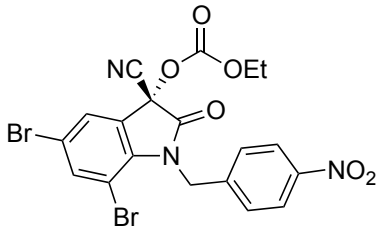
(*R*)-4-Bromo-3-cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{23}_{D}$ 0.4 (*c* 1.0, $CHCl_3$) for 99% ee; IR (KBr) 1605, 1523, 1457, 1343, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 7.3, 8.3 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.31 (d, *J* = 16.5 Hz, 1H), 4.84 (d, *J* = 16.5 Hz, 1H), 4.31–4.16 (m, 2H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.3, 148.0, 144.3, 141.2, 133.9, 128.4, 128.2 (2C), 124.4 (2C), 120.5, 120.3, 111.3, 109.2, 72.1, 66.6, 44.5, 14.2; HRMS (FAB+) calcd for $C_{19}H_{14}BrN_3O_6$ $[M+H]^+$ 460.0139, found 460.0090. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 23.3 (minor enantiomer), 37.6 (major enantiomer) min.



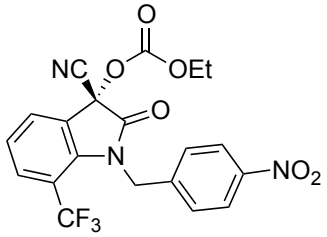
(*R*)-6-Bromo-3-cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Colorless solid; $[\alpha]^{23}_{D}$ 31.6 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1753, 1607, 1523, 1345, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.34 (dd, *J* = 1.4, 8.3 Hz, 1H), 6.83 (d, *J* = 1.4 Hz, 1H), 5.25 (d, *J* = 16.5 Hz, 1H), 4.84 (d, *J* = 16.5 Hz, 1H), 4.30–4.17 (m, 2H), 1.33 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.4, 147.8, 143.8, 141.0, 128.1 (2C), 127.7, 127.0, 126.9, 124.4 (2C), 120.3, 113.8, 112.4, 70.8, 66.5, 44.3, 14.0; HRMS (FAB+) calcd for $C_{19}H_{14}BrN_3O_6$ $[M+H]^+$ 460.0139, found 460.0168. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 20.4 (minor enantiomer), 29.8 (major enantiomer) min.



(*R*)-7-Bromo-3-cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate (2n): Colorless solid; $[\alpha]^{23}_{D}$ 0.6 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1752, 1523, 1449, 1343, 1263, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.61 (dd, *J* = 0.9, 7.3 Hz, 1H), 7.57 (dd, *J* = 0.9, 8.2 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.11 (dd, *J* = 7.3, 8.2 Hz, 1H), 5.53 (d, *J* = 17.0 Hz, 1H), 5.48 (d, *J* = 17.0 Hz, 1H), 4.30–4.16 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.4, 147.5, 143.7, 140.3, 138.7, 127.3 (2C), 126.0, 124.62, 124.57, 124.2 (2C), 112.4, 103.6, 70.7, 66.7, 45.7, 14.1; HRMS (FAB+) calcd for $C_{19}H_{14}BrN_3O_6$ $[M+H]^+$ 460.0139, found 460.0126. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 14.3 (minor enantiomer), 24.2 (major enantiomer) min.



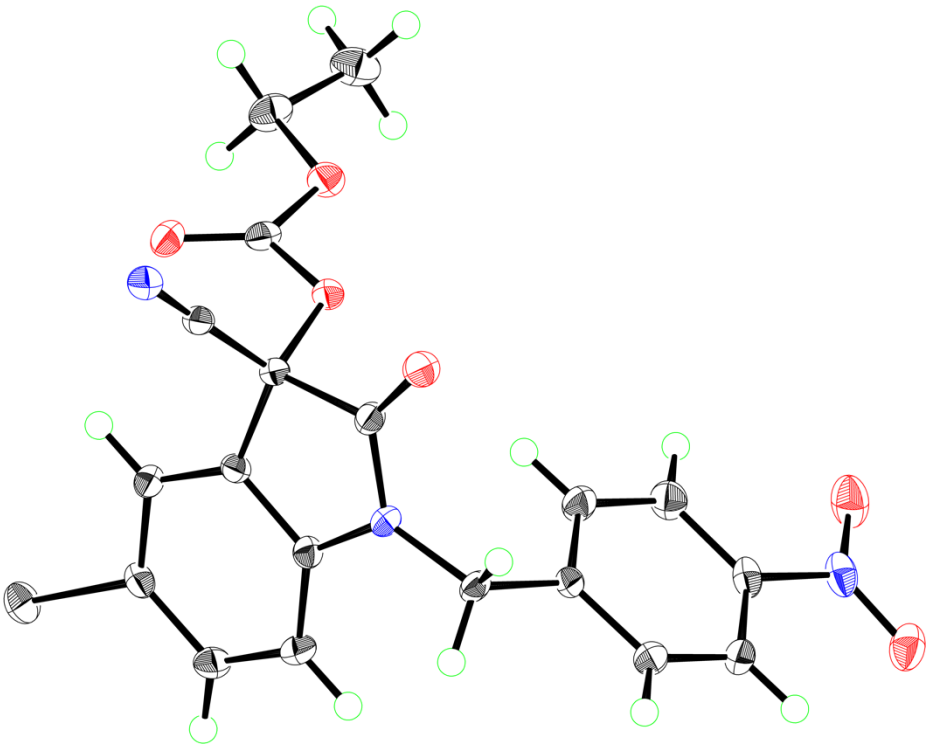
(*R*)-5,7-Dibromo-3-Cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{23}_{D}$ 5.0 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 1756, 1523, 1455, 1346, 1264, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.48 (s, 1H), 7.46 (s, 1H), 5.51 (d, *J* = 17.4 Hz, 1H), 5.45 (d, *J* = 17.4 Hz, 1H), 4.33–4.19 (m, 2H), 1.35 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.3, 147.6, 143.4, 140.5, 139.5, 127.6, 127.2 (2C), 125.8, 124.2 (2C), 117.7, 111.9, 104.2, 70.3, 66.9, 45.7, 14.1; HRMS (FAB+) calcd for $C_{19}H_{13}Br_2N_3O_6$ $[M+H]^+$ 539.9224, found 539.9241. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 12.6 (minor enantiomer), 21.9 (major enantiomer) min.



(*R*)-3-Cyano-1-(4-nitrobenzyl)-2-oxo-7-(trifluoromethyl)indolin-3-yl ethyl carbonate: Pale yellow solid; $[\alpha]^{24}_{D}$ 10.0 (*c* 1.0, $CHCl_3$) for 86% ee; IR (KBr) 1758, 1601, 1524, 1454, 1345, 1266, 1168, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.37 (dd, *J* = 7.8, 8.2 Hz, 1H), 5.36 (d, *J* = 17.9 Hz, 1H), 5.24 (d, *J* = 17.9 Hz, 1H), 4.30–4.16 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 151.4, 147.4, 142.5, 141.1, 130.9 (q, J_{C-F} = 5.8 Hz), 129.1 (2C), 126.7, 124.5, 124.4, 124.0 (2C), 122.6 (q, J_{C-F} = 273 Hz), 114.4 (q, J_{C-F} = 33.5 Hz), 112.2, 69.6, 66.8, 46.9 (q, J_{C-F} = 4.8 Hz), 14.0; HRMS (FAB+) calcd for $C_{20}H_{14}F_3N_3O_6$ $[M+H]^+$ 450.0908, found 450.0906. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 11.2 (minor enantiomer), 17.2 (major enantiomer) min.

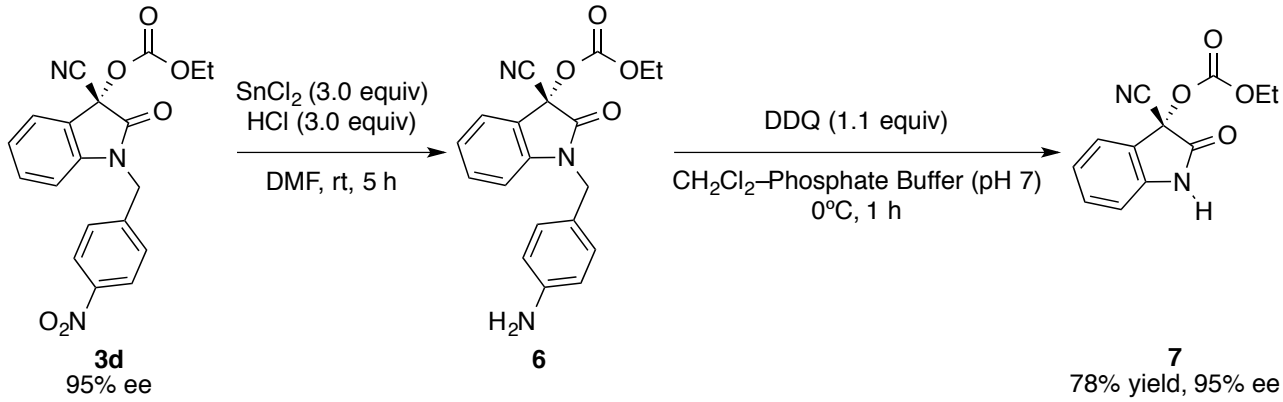
Crystal Data for (*R*)-5-Bromo-3-cyano-1-(4-nitrobenzyl)-2-oxoindolin-3-yl Ethyl Carbonate.

Bruker SMART APEX diffractometer with CCD detector (graphite monochromator, MoKa radiation, $l = 0.71073$ Å). The structure was solved by direct methods and expanded using Fourier techniques. Formula $C_{19}H_{14}BrN_3O_6$, colorless, crystal dimensions 0.40 × 0.40 × 0.30 mm^3, monoclinic, space group *C2(#5)*, a = 26.033(3) Å, b = 8.1523 (9) Å, c = 8.9677 (10) Å, β = 93.684(2)°, V = 1899.3(4) $Å^3$, Z = 4, and D_{calc} = 1.610 g cm^{-3}, F(000) = 928, μ = 2.207 mm^{-1}, T = 123(2) K. 4072 reflections collected, 3954 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 28.25°), and 263 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0198 and *wR2* = 0.0476, GOF = 0.916. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk]. Supplementary publication no. CCDC-925315.



Transformation of the Cyano-Ethoxycarbonylation Product.

Deprotection of *p*-Nitrobenzyl Group

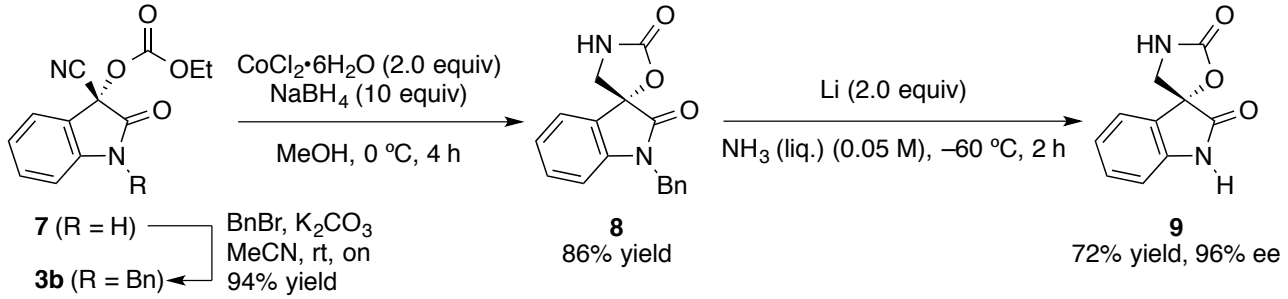


To the solution of **3d** (381 mg, 1.0 mmol) in DMF (10 mL) was added a 4.0 M solution of HCl in dioxane (0.75 mL) and $SnCl_2$ (569 mg, 3.0 mmol). The mixture was stirred at ambient temperature for 5 h. After the completion of the reaction, the mixture was diluted with water and ethyl acetate. Saturated aqueous $NaHCO_3$ was added to the reaction mixture to neutralize. The resultant mixture was passed through a Celite® pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:1) to give **6** (337 mg) as colorless solid. IR (KBr) 3438, 3390, 1760, 1739, 1629, 1613, 1520, 1371, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 0.9, 7.8 Hz, 1H), 7.34 (ddd, J = 0.9, 7.8, 7.8 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.12 (dd, J = 7.8, 7.8 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 8.2 Hz, 2H), 4.88 (d, J = 15.1 Hz, 1H), 4.79 (d, J = 15.1 Hz, 1H), 4.28–4.15 (m, 2H), 3.68 (br, 2H), 1.29 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.7, 146.4, 143.6, 132.7, 128.9 (2C), 125.8, 124.2, 123.8, 121.7, 115.5 (2C), 113.2, 110.9, 71.4, 66.1, 44.8, 14.2; HRMS (FAB+) calcd for $C_{19}H_{17}N_3O_4$ $[M+H]^+$ 352.1292, found 352.1282.

To the solution of **6** (337 mg) in CH_2Cl_2 (9 ml) and 0.05 M aqueous phosphate buffer (pH 6.9, 1.0 mL) was added DDQ (241 mg, 1.05 mmol) at 0 ºC, and the mixture was stirred for 1 h. To the reaction mixture 0.5 M aqueous Na_2SO_3 was added. The resultant biphasic mixture was through a Celite® pad. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1) to give **7** (201 mg, 89% yield) as pale yellow oil. $[\alpha]^{24}_D$ 44.7 (*c* 1.0, $CHCl_3$) for 95% ee; IR (neat) 3303, 1763, 1621, 1474, 1261, 1194, 1116, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (br, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.8, 7.8 Hz, 1H), 7.17 (dd, J = 7.8, 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 4.29–4.17 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 167.6, 151.8, 141.4, 133.1, 126.3, 124.4, 122.0, 112.9, 111.7, 71.5, 66.3, 14.1; HRMS (FAB+) calcd for $C_{12}H_{11}N_2O_4$ $[M+H]^+$ 247.0713, found 247.0694. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 23.2 (minor enantiomer), 31.3 (major enantiomer) min.

Synthesis of Spiro-Fused Compound **9**



To a solution of **7** (201 mg, 0.82 mmol) and K_2CO_3 (68 mg, 0.49 mmol) in MeCN (8.2 mL) was added benzylbromide (108 μL, 0.90 mmol), and the mixture was stirred under reflux condition for 2 h. To the reaction mixture was added saturated aqueous $NaHCO_3$. The organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 5:1) to give **3b** (260 mg, 94% yield) as pale yellow oil.

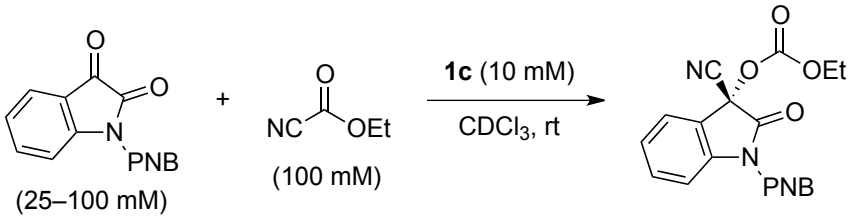
To a solution of **3b** (260 mg, 0.77 mmol) and $CoCl_2$ (200 mg, 1.54 mmol) in MeOH (15.4 mL) was added $NaBH_4$ (58 mg, 1.54 mmol) at 0 ºC, and the mixture was stirred for 4 h. To the reaction mixture was added saturated aqueous $NaHCO_3$ to quench. The biphesic mixture was deluted with ethyl acetate and through the Cerite® pad. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by short path column chromatography on silica gel (hexane–EtOAc = 2:1) to give **8** (195mg, 86% yield) as pale yellow solid. IR (neat) 1669, 1469, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48–8.33 (m, 1H), 7.65–7.58 (m, 1H), 7.32–7.18 (m, 6H), 7.04–6.94 (m, 2H), 6.77 (d, J = 7.8 Hz, 1H), 5.29 (br s, 1H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 143.2, 137.6, 137.1, 128.8 (2C), 127.3 (2C), 124.1, 123.8, 121.1, 115.6, 115.4, 108.7, 97.9, 86.1, 43.1; HRMS (FAB+) calcd for $C_{17}H_{15}N_2O_3$ $[M+H]^+$ 295.1077, found 295.1081.

To a solution of **8** (195 mg, 0.66 mmol) in liquid ammonia (ca. 13 mL) was added Li (13.9 mg, 2.0 mmol) at –78ºC, and the mixture was stirred at –60 ºC for 2 h. Saturated aqueous $NaHCO_3$ was added to the reaction mixture to quench. After the mixture was warmed to ambient

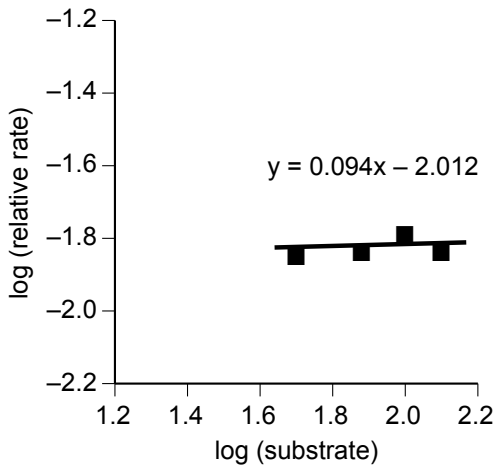
temperature, the residue was diluted with chloroform. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc–MeOH = 10:10:1 → 8:8:1) to give **9** (97.4 mg, 72% yield) as pale yellow solid. $[\alpha]^{25}_{D}$ 116.7 (*c* 1.0, $CHCl_3$) for 96% ee; IR (KBr) 3311, 1673, 1619, 1554, 1469, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (br, 1H), 7.58 (dd, *J* = 10.8, 11.5 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 7.8 Hz, 1H), 6.98 (dd, *J* = 7.6, 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.28 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 143.6, 125.0, 124.0, 121.2, 115.8, 109.4, 77.4, 59.9; HRMS (FAB+) calcd for $C_{10}H_9N_2O_3$ $[M+H]^+$ 205.0608, found 205.0608. The ee was determined by HPLC analysis (Daicel Chiralpack IA column, hexane–*i*-PrOH = 2:1, flow rate = 1.0 mL/min) t_R= 6.8 (minor enantiomer), 11.1 (major enantiomer) min.

Mechanistic Studies.

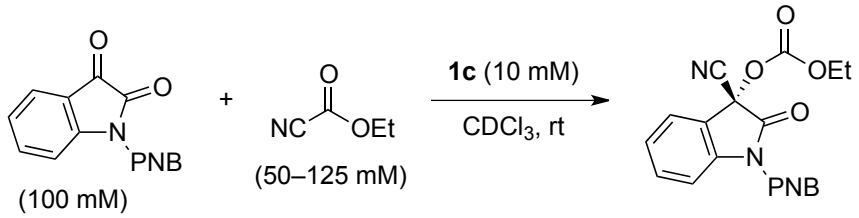
Initial rate kinetics for *N*-(*p*-nitrobenzyl)-protected isatin



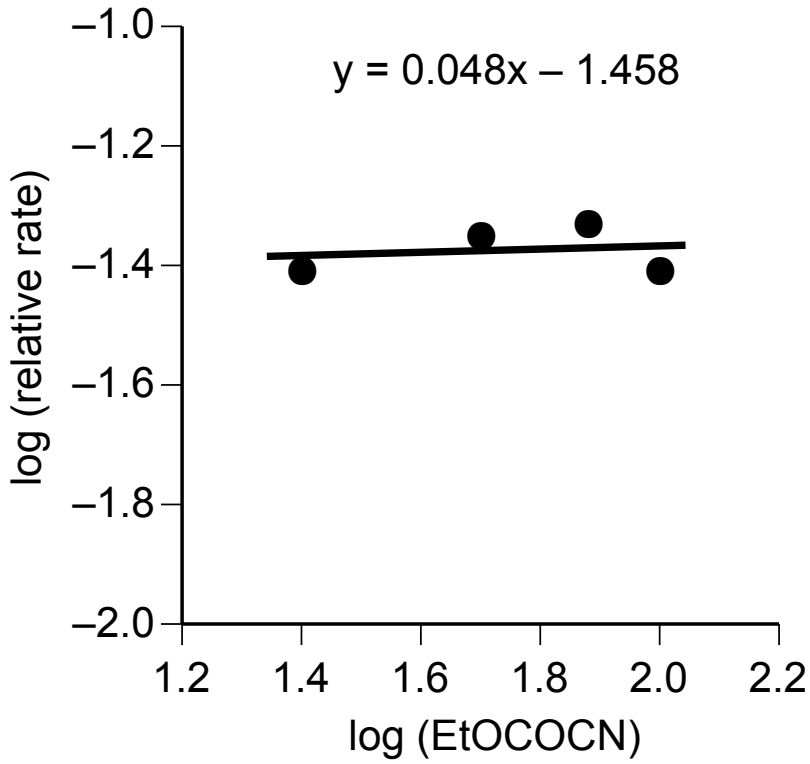
substrate [mM]	log (substrate)	relative rate [mM/min]	log (relative rate)
25	1.40	0.0386	–1.41
50	1.70	0.0451	–1.35
75	1.88	0.0469	–1.33
100	2.00	0.0393	–1.41



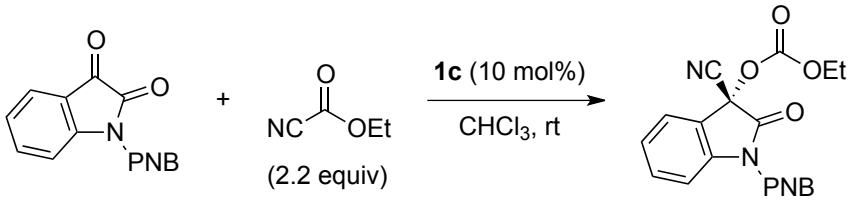
Initial rate kinetics for ethyl cyanoformate



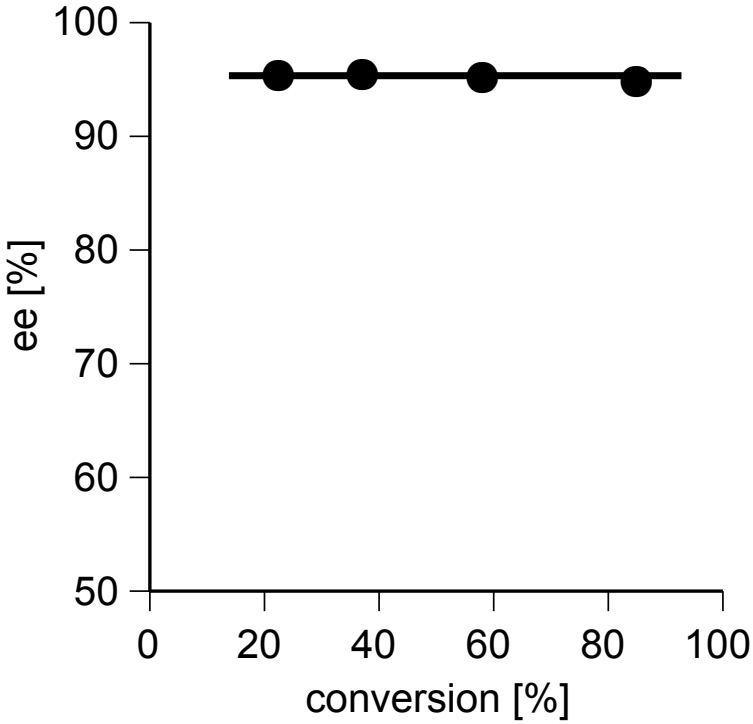
EtOCOCN [mM]	log (EtOCOCN)	relative rate [mM/min]	log (relative rate)
50	1.70	0.0140	–1.85
75	1.88	0.0143	–1.84
100	2.00	0.0163	–1.79
125	2.10	0.0146	–1.84



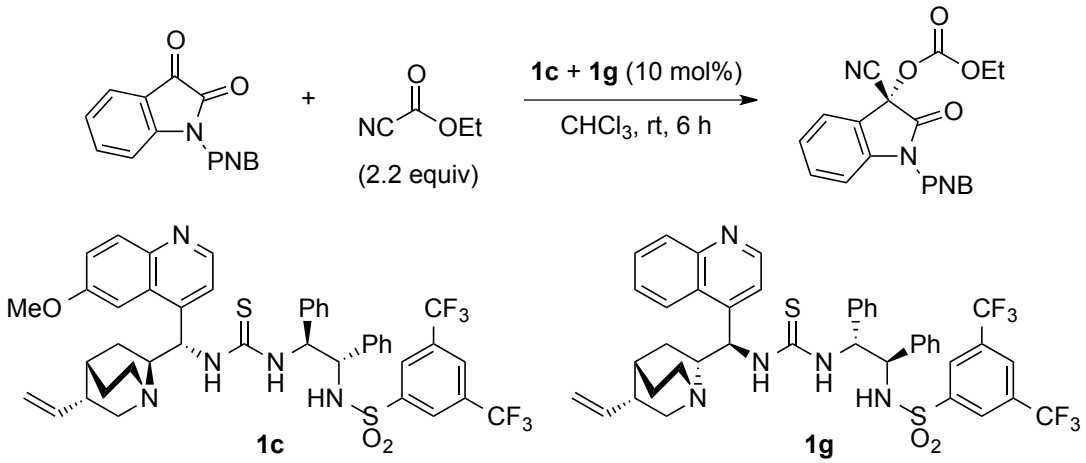
Conversion versus enantioselectivity



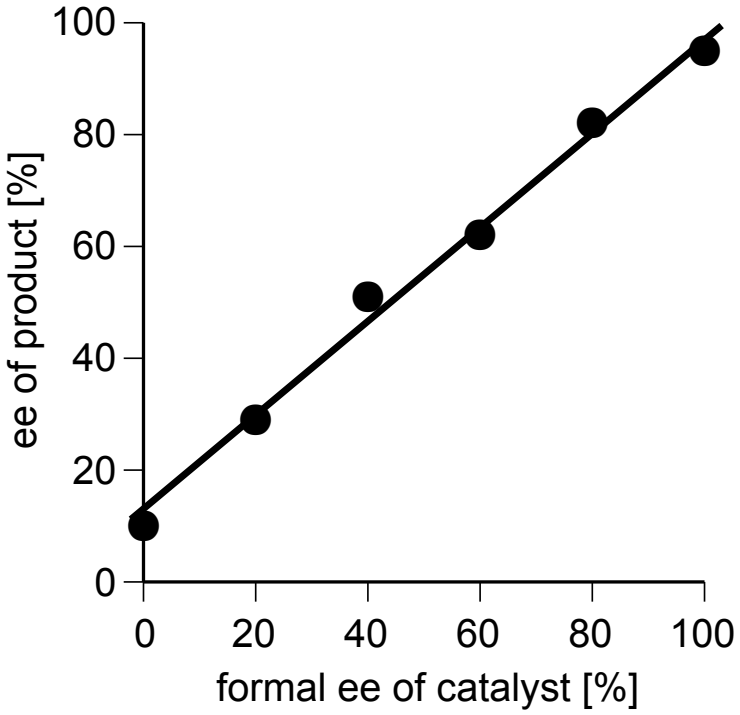
time [h]	1	2	4	6
conversion [%]	22.4	37.1	58.0	84.9
ee [%]	95.3	95.4	95.1	94.8



Correlation between the optical purity of **3c** and the enantiomeric excess of the product



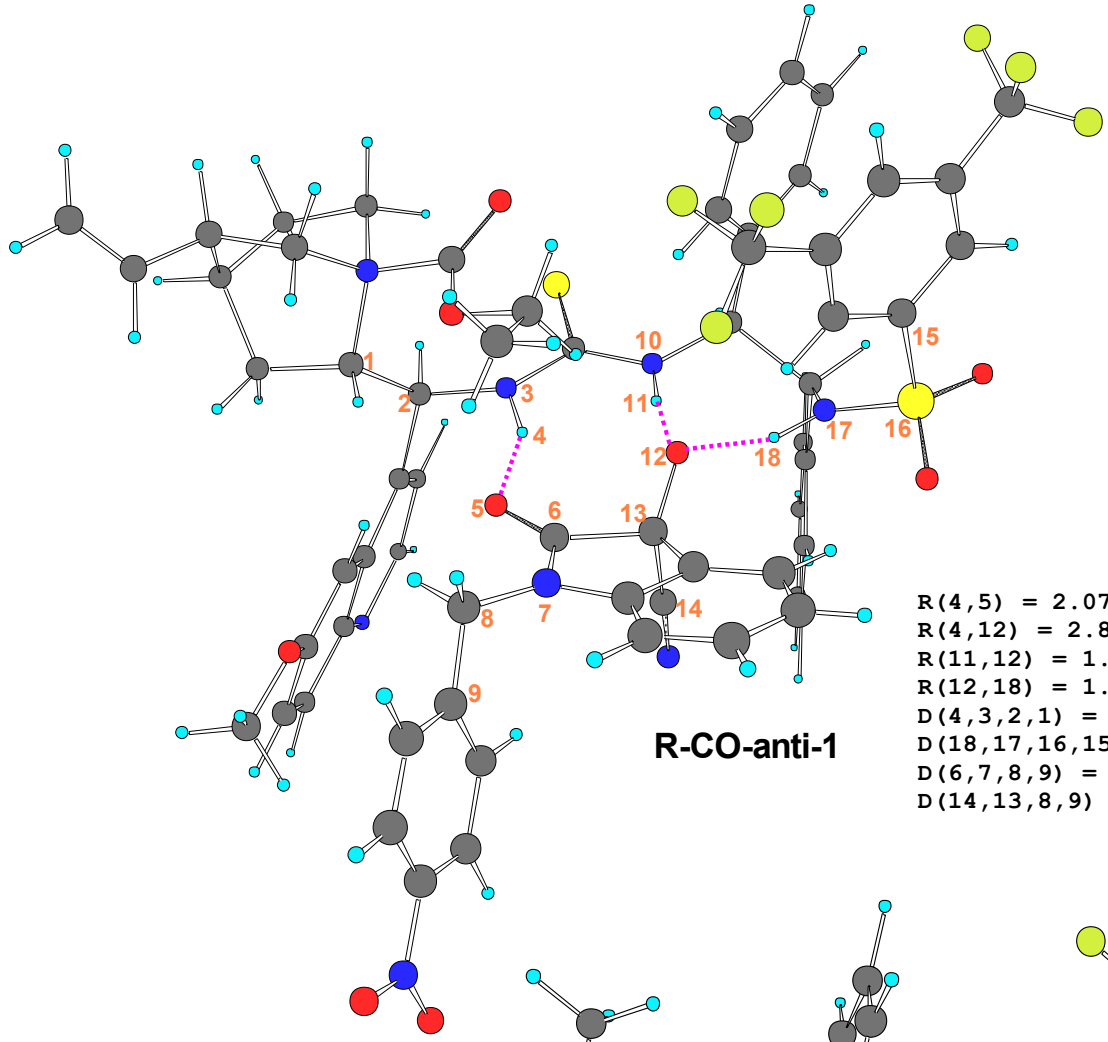
1c : **1g**	formal ee of catalyst [%]	conv. [%] of product	ee [%] of product
100 : 0	100	87	95
90 : 10	80	89	82
80 : 20	60	84	62
70 : 30	40	78	51
60 : 40	20	71	29
50 : 50	0	68	10



Computational Methods

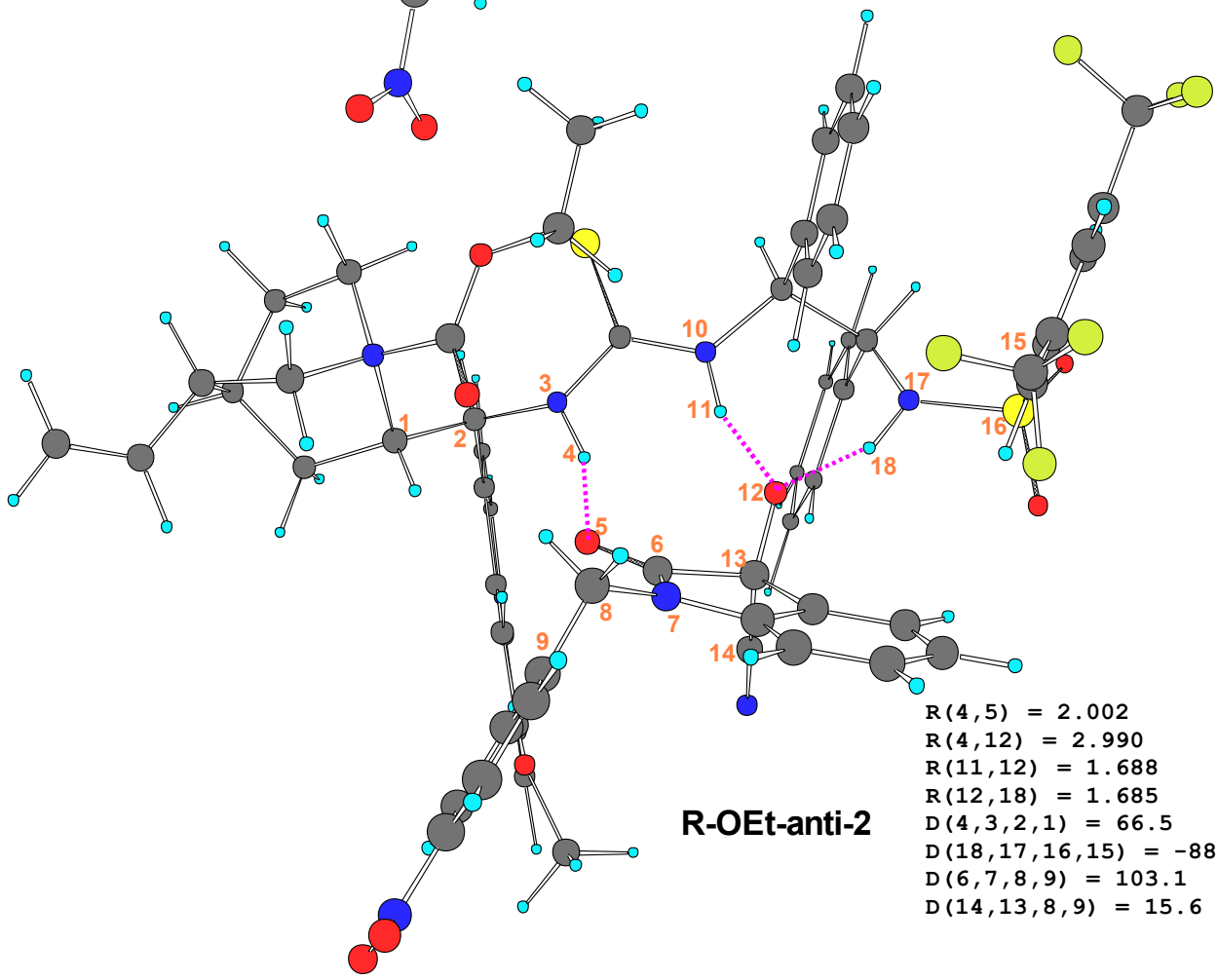
The quantum chemical calculations were performed using the Gaussian03[8] and Gaussian09[9] suites of programs. All structures were fully optimized using density functional theory (DFT) methods employing three nonlocal functionals (B3LYP).[10] The standard 6-31G(d) basis set was used for geometry optimizations of the stable structures. Single-point energy calculations at the same level with the default polarizable continuum model (PCM),[11] specifying $CHCl_3$ (ε = 4.7113) as the solvent.

All calculations with the PCM model were performed using the Gaussian09 package, while those *in vacuo* were made with Gaussian03 version. In all calculations, the default parameters defined in the Gaussian09 package for the PCM description of the solvents were used.



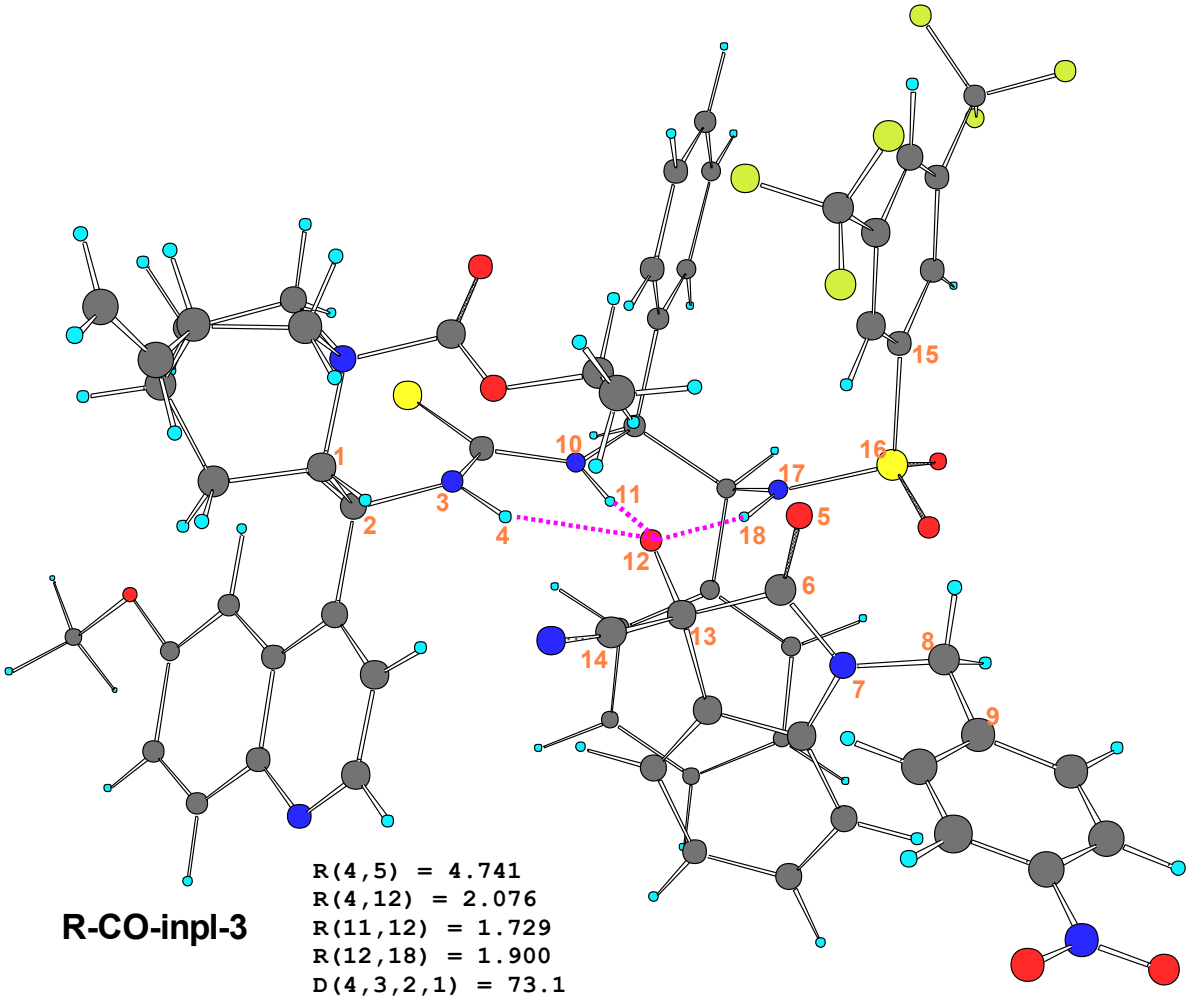
R-CO-anti-1

R(4,5) = 2.072
R(4,12) = 2.884
R(11,12) = 1.799
R(12,18) = 1.748
D(4,3,2,1) = 71.0
D(18,17,16,15) = -72.0
D(6,7,8,9) = 117.5
D(14,13,8,9) = 29.5



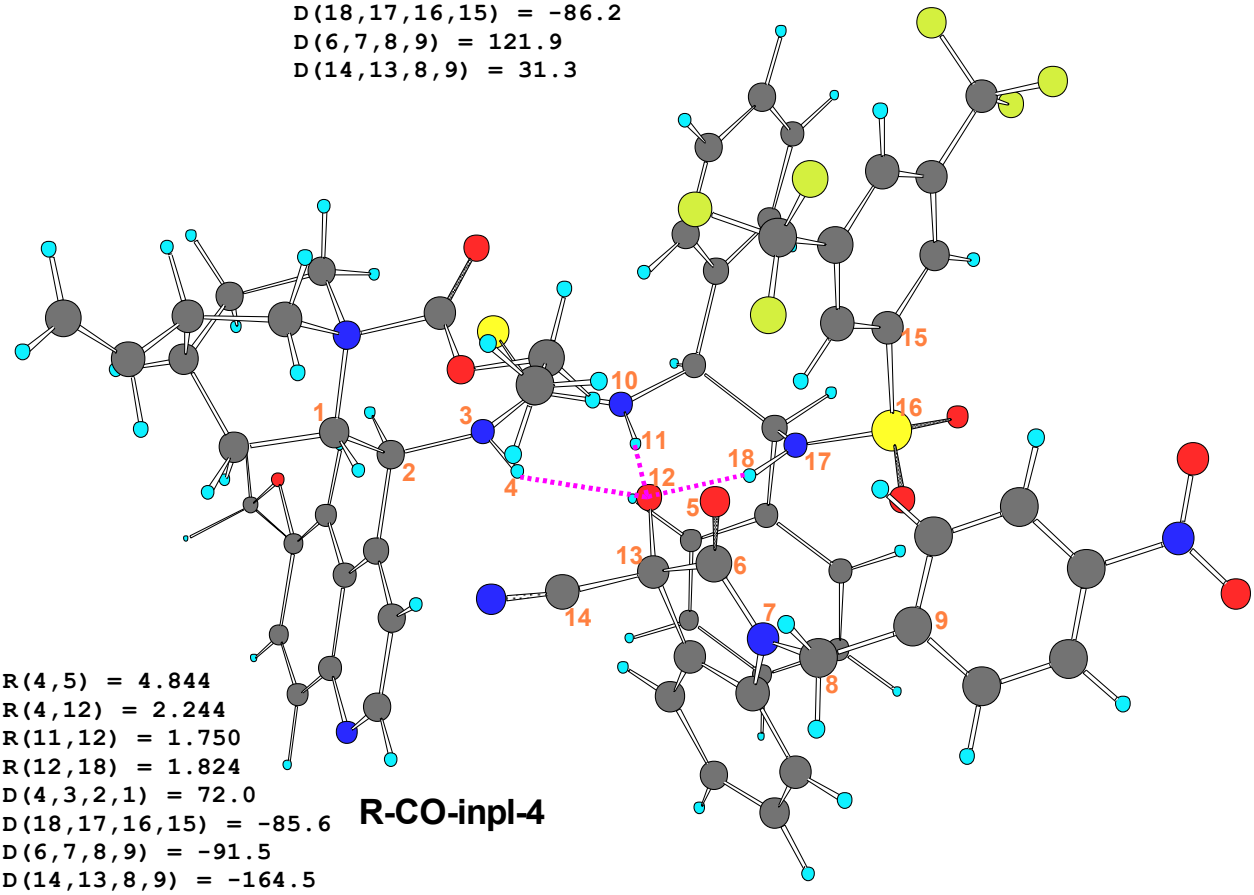
R-OEt-anti-2

R(4,5) = 2.002
R(4,12) = 2.990
R(11,12) = 1.688
R(12,18) = 1.685
D(4,3,2,1) = 66.5
D(18,17,16,15) = -88.1
D(6,7,8,9) = 103.1
D(14,13,8,9) = 15.6



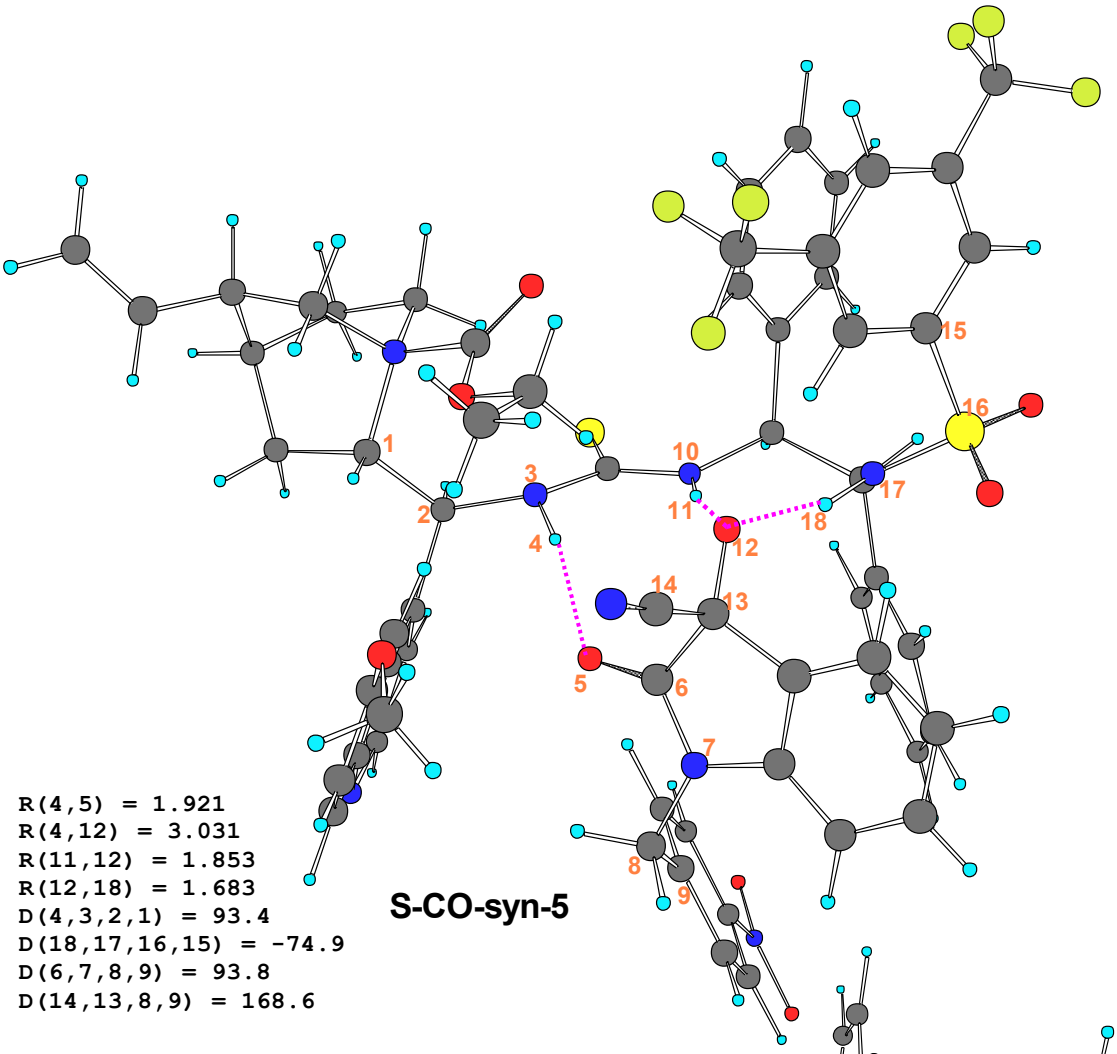
R-CO-inpl-3

```
R(4,5) = 4.741
R(4,12) = 2.076
R(11,12) = 1.729
R(12,18) = 1.900
D(4,3,2,1) = 73.1
D(18,17,16,15) = -86.2
D(6,7,8,9) = 121.9
D(14,13,8,9) = 31.3
```



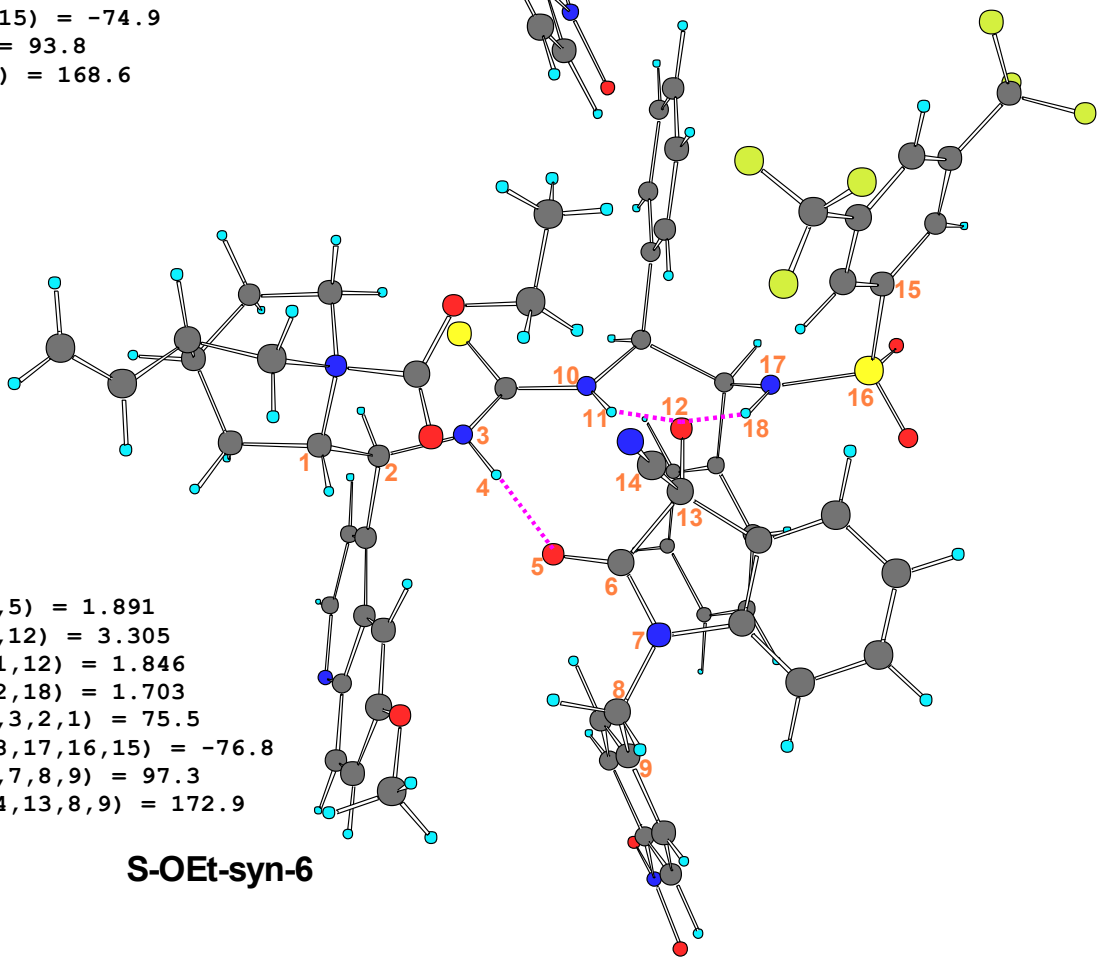

```
R(4,5) = 4.844
R(4,12) = 2.244
R(11,12) = 1.750
R(12,18) = 1.824
D(4,3,2,1) = 72.0
D(18,17,16,15) = -85.6
D(6,7,8,9) = -91.5
D(14,13,8,9) = -164.5
```

R-CO-inpl-4



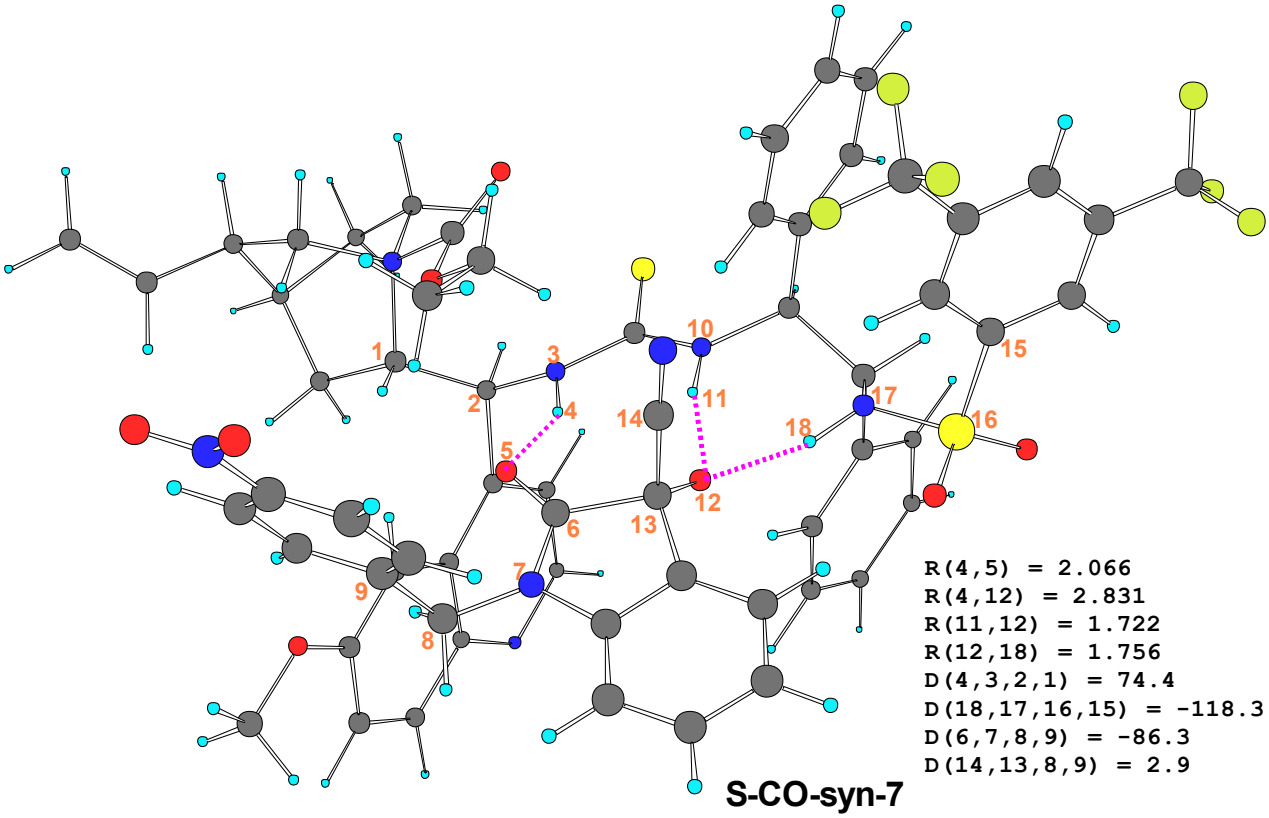
R(4,5) = 1.921
R(4,12) = 3.031
R(11,12) = 1.853
R(12,18) = 1.683
D(4,3,2,1) = 93.4
D(18,17,16,15) = -74.9
D(6,7,8,9) = 93.8
D(14,13,8,9) = 168.6

S-CO-syn-5



R(4,5) = 1.891
R(4,12) = 3.305
R(11,12) = 1.846
R(12,18) = 1.703
D(4,3,2,1) = 75.5
D(18,17,16,15) = -76.8
D(6,7,8,9) = 97.3
D(14,13,8,9) = 172.9

S-OEt-syn-6


1
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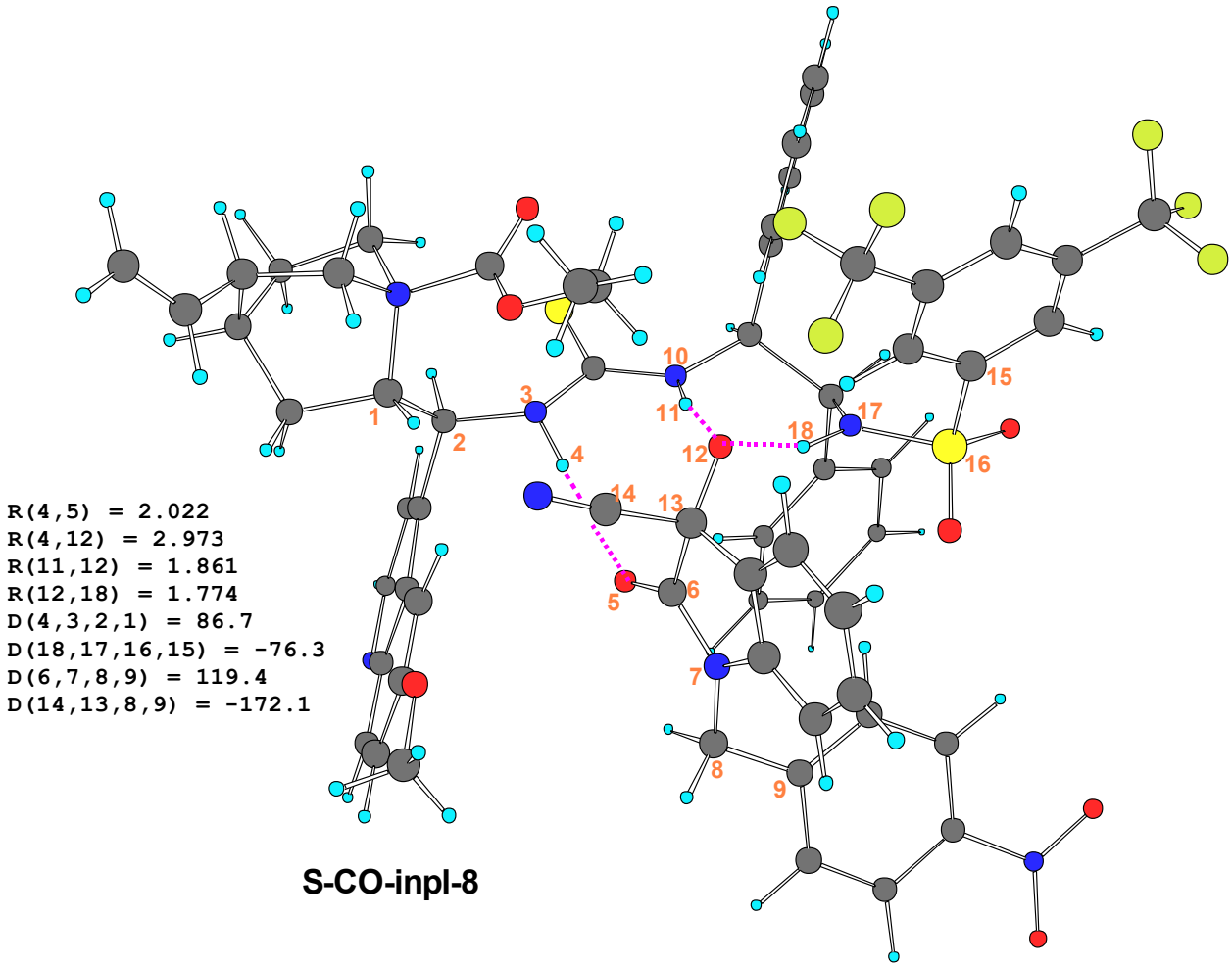
9
10
11
12
13
14
15
16
17
18
R(4,5) = 2.066
R(4,12) = 2.831
R(11,12) = 1.722
R(12,18) = 1.756
D(4,3,2,1) = 74.4
D(18,17,16,15) = -118.3
D(6,7,8,9) = -86.3
D(14,13,8,9) = 2.9
S-CO-syn-7


1
2
3
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9
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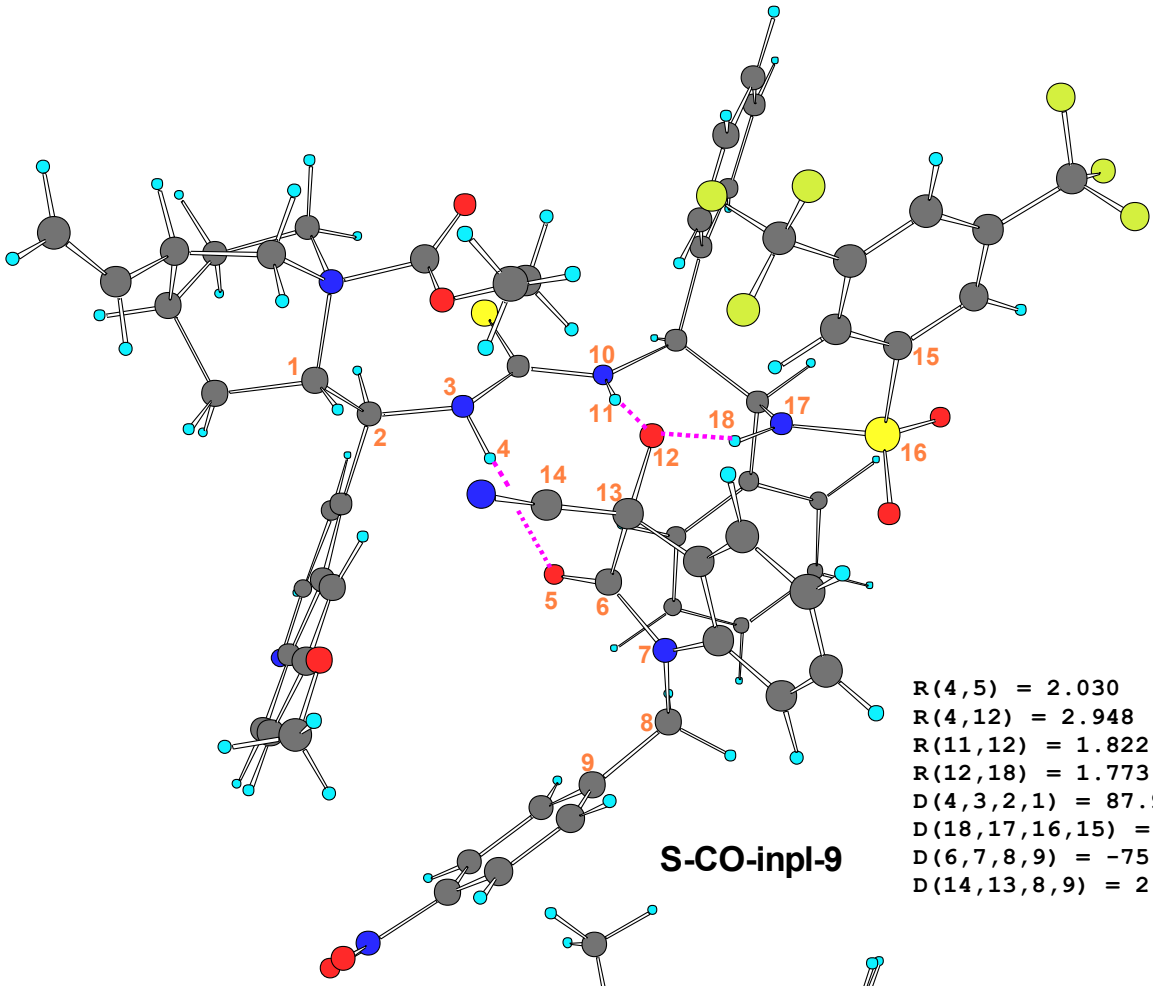
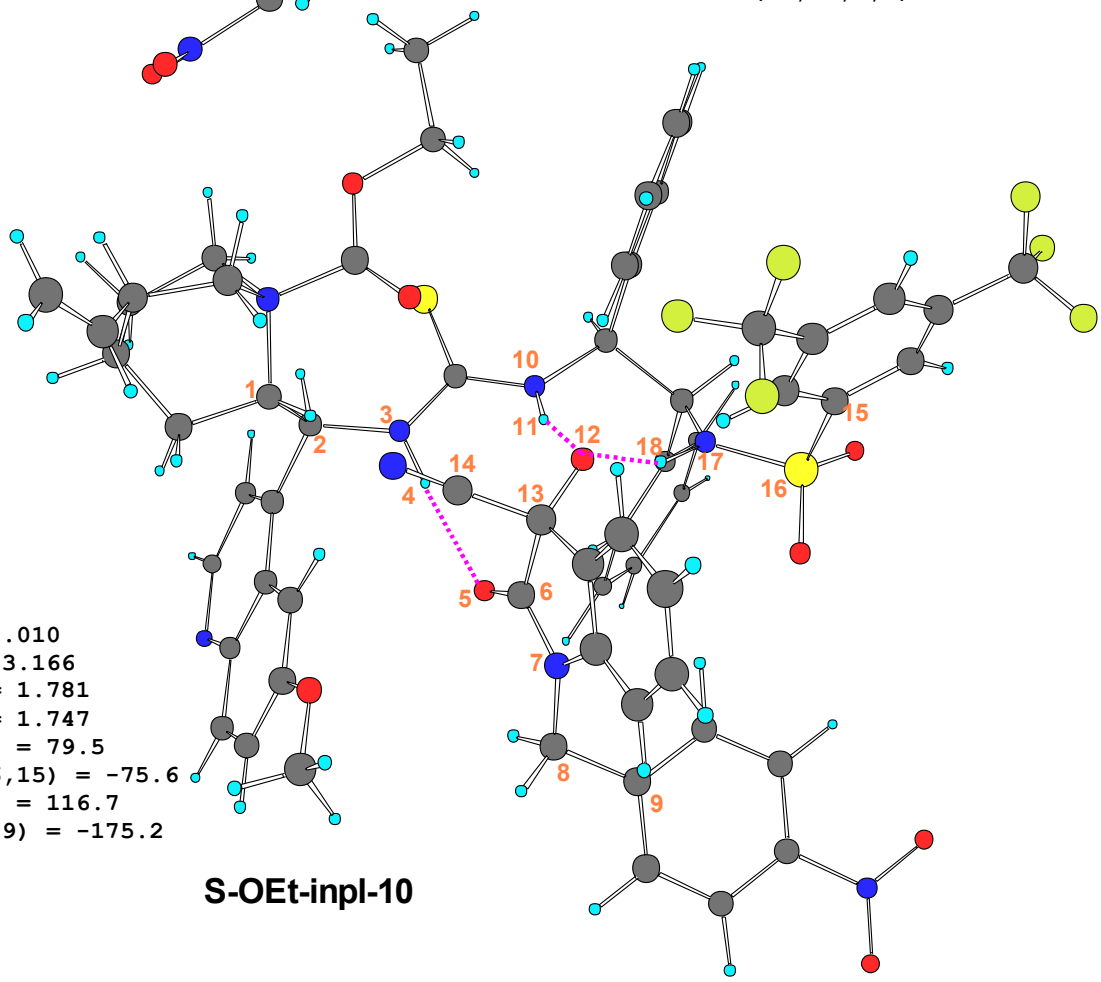
11
12
13
14
15
16
17
18
R(4,5) = 2.022
R(4,12) = 2.973
R(11,12) = 1.861
R(12,18) = 1.774
D(4,3,2,1) = 86.7
D(18,17,16,15) = -76.3
D(6,7,8,9) = 119.4
D(14,13,8,9) = -172.1
S-CO-inpl-8



R(4,5) = 2.030
R(4,12) = 2.948
R(11,12) = 1.822
R(12,18) = 1.773
D(4,3,2,1) = 87.9
D(18,17,16,15) = -73.4
D(6,7,8,9) = -75.8
D(14,13,8,9) = 2.1

S-CO-inpl-9



R(4,5) = 2.010
R(4,12) = 3.166
R(11,12) = 1.781
R(12,18) = 1.747
D(4,3,2,1) = 79.5
D(18,17,16,15) = -75.6
D(6,7,8,9) = 116.7
D(14,13,8,9) = -175.2

S-OEt-inpl-10

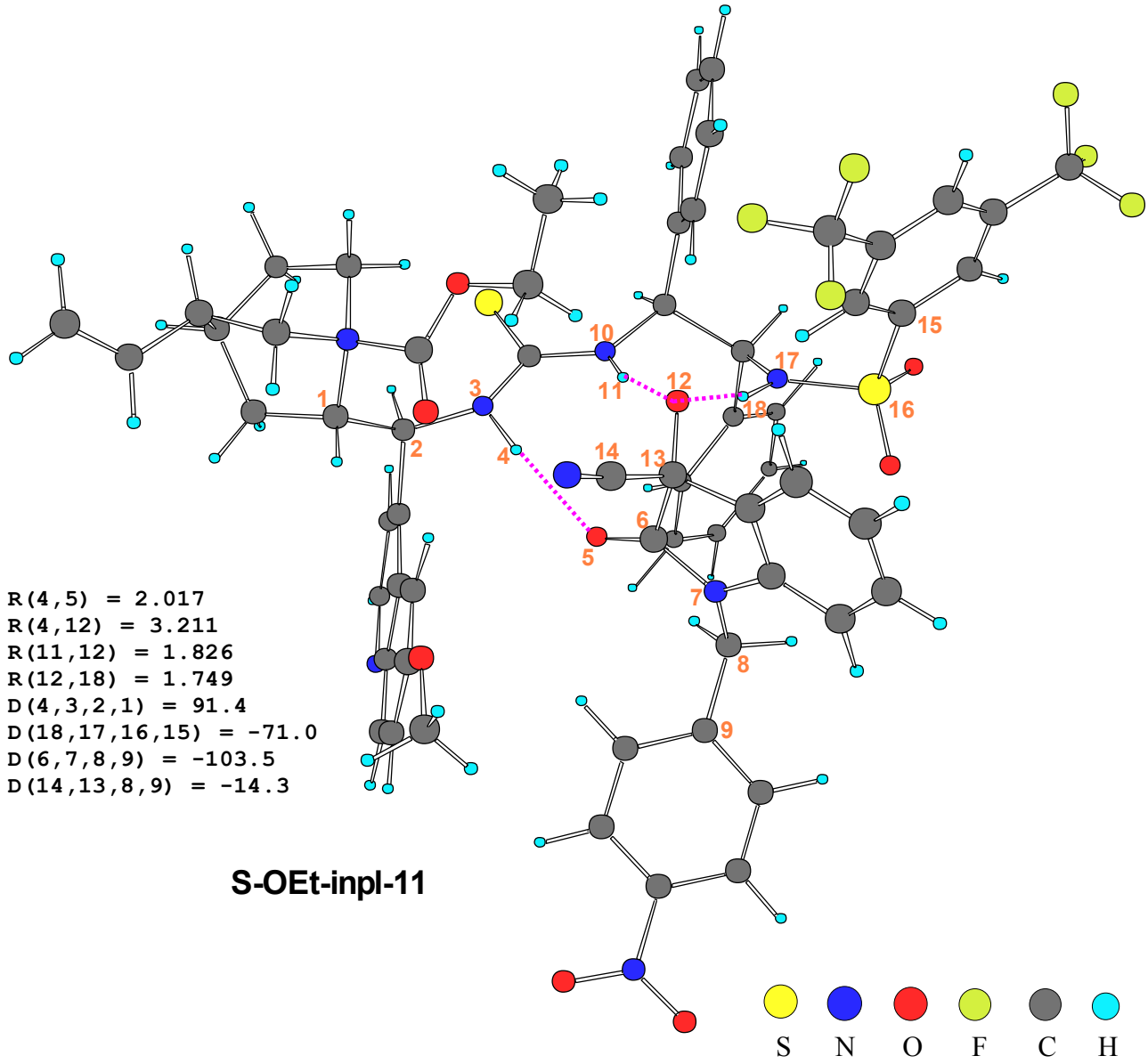
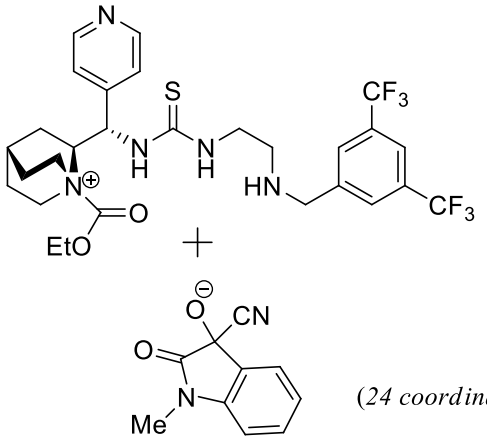


Figure S1. B3LYP optimized structures of the ion pairs of akoxy aion intermediate.

Table S1. Relative electron energies of the optimized structures of the ion pairs in kcal mol^{-1}. Relative to **R-CO-anti-1**.

	in vacuo	in $CHCl_3$ (SCRF=PCM)
	B3LYP/6-31G(d)	PCM-B3LYP/6-31G(d) //B3LYP/6-31G(d)
R-CO-anti-1	0.00	0.00
R-OEt-anti-2	-1.43	-1.04
R-CO-inpl-3	-7.03	-4.13
R-CO-inpl-4	-3.56	-1.23
S-CO-syn-5	-0.05	1.94
S-OEt-syn-6	0.94	1.36
S-CO-syn-7	1.29	0.93
S-CO-inpl-8	-2.49	-1.13
S-CO-inpl-9	-1.46	0.41
S-OEt-inpl-10	0.29	1.71
S-OEt-inpl-11	0.04	1.38

Optimization calculations of simpler molecure ion-pairs were carried out for the purpose of confirmation of the desirable coordination style.



(*24 coordination styles*)

R-CO-anti-1

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57758435 A.U. after 6 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61231031 A.U. after 17 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.016227	4.125009	1.749056
2	6	0	-0.575542	2.551246	1.260791
3	7	0	0.608345	2.288999	0.579486
4	7	0	-1.353176	1.474339	1.450989
5	6	0	1.690597	3.266077	0.518110
6	6	0	2.216025	3.426276	-0.929428
7	6	0	-2.697427	1.549192	2.030475
8	6	0	2.782267	3.091653	1.596769
9	6	0	-3.018367	0.279346	2.883003
10	6	0	-3.796285	1.826884	1.007751
11	6	0	-2.204505	0.230006	4.180676
12	7	0	-2.912574	-0.936761	2.080365
13	16	0	-4.089096	-2.071408	1.967813
14	8	0	-5.150618	-1.749789	2.926162
15	6	0	3.987789	2.309984	1.509673
16	6	0	-4.796420	-1.879769	0.313166
17	6	0	2.571091	3.801979	2.764223
18	6	0	3.354300	4.477286	-1.052020
19	8	0	-3.445861	-3.391576	1.952627
20	7	0	1.077014	3.869395	-1.897169
21	6	0	4.903911	2.405374	2.618105
22	6	0	3.517853	3.773018	3.814563
23	6	0	4.358006	1.486590	0.419278
24	6	0	1.708025	4.059360	-3.282260
25	6	0	0.449928	5.193934	-1.473494
26	6	0	2.882853	5.712585	-1.838340
27	6	0	2.588794	5.332874	-3.311837
28	6	0	6.141585	1.718627	2.552945
29	7	0	4.659563	3.125525	3.749790
30	6	0	1.571856	6.215993	-1.209272
31	6	0	3.816382	5.110875	-4.157463
32	6	0	5.576516	0.829262	0.388391
33	6	0	4.103519	5.802245	-5.260531
34	8	0	5.818035	0.069121	-0.724729
35	6	0	6.489807	0.954155	1.463926
36	6	0	7.077930	-0.582137	-0.838425
37	6	0	-6.169943	-1.709112	0.179107
38	6	0	-3.956994	-1.934848	-0.801206
39	6	0	-6.719221	-1.603452	-1.102028
40	6	0	-4.996200	2.398156	1.453809
41	6	0	-4.523169	-1.828521	-2.070605
42	6	0	-8.192526	-1.338501	-1.271510
43	6	0	-5.902776	-1.671480	-2.228134
44	6	0	-3.638646	-1.779504	-3.283874
45	9	0	-3.319928	-0.491877	-3.612787
46	9	0	-4.229079	-2.312717	-4.372107
47	9	0	-2.465786	-2.422411	-3.094911
48	9	0	-8.916182	-1.836931	-0.249845
49	9	0	-8.667314	-1.880960	-2.415614
50	9	0	-8.450030	-0.010496	-1.332203

51	6	0	-1.333883	-0.818994	4.479740
52	6	0	-3.673912	1.504167	-0.345080
53	6	0	-6.052819	2.625649	0.573743
54	6	0	-4.726689	1.738153	-1.232703
55	6	0	-5.922660	2.291395	-0.776354
56	6	0	-2.358392	1.261877	5.119379
57	6	0	-0.609758	-0.826844	5.674663
58	6	0	-1.645756	1.251928	6.316395
59	6	0	-0.761150	0.207224	6.596152
60	6	0	-0.030766	2.821029	-2.066312
61	8	0	0.518070	1.697024	-2.454867
62	8	0	-1.180903	3.140770	-1.982768
63	6	0	-0.393456	0.556942	-2.710401
64	6	0	0.268058	-0.325599	-3.745411
65	1	0	0.877365	1.309728	0.442793
66	1	0	-1.023285	0.561091	1.080169
67	1	0	1.204830	4.206298	0.789827
68	1	0	2.511547	2.464361	-1.340414
69	1	0	-2.678095	2.392866	2.722965
70	1	0	-4.072470	0.370373	3.161144
71	1	0	-2.053390	-1.138745	1.524620
72	1	0	1.667021	4.391037	2.883740
73	1	0	4.233679	4.020106	-1.514801
74	1	0	3.660052	4.784560	-0.048885
75	1	0	3.321840	4.332988	4.727904
76	1	0	3.673018	1.275777	-0.387833
77	1	0	2.280710	3.153610	-3.483739
78	1	0	0.886263	4.113628	-4.000269
79	1	0	-0.200291	5.485118	-2.299319
80	1	0	-0.180535	5.002437	-0.602602
81	1	0	3.650150	6.491362	-1.803022
82	1	0	2.013277	6.150150	-3.763232
83	1	0	6.806130	1.818430	3.404981
84	1	0	1.282727	7.182805	-1.634207
85	1	0	1.703360	6.366063	-0.132337
86	1	0	4.500121	4.328602	-3.825130
87	1	0	5.007691	5.613250	-5.831858
88	1	0	3.448825	6.587218	-5.633753
89	1	0	7.444807	0.442199	1.448058
90	1	0	7.056405	-1.106660	-1.794731
91	1	0	7.229515	-1.312470	-0.034940
92	1	0	7.904402	0.139999	-0.837820
93	1	0	-6.793513	-1.659007	1.064356
94	1	0	-2.880371	-2.023294	-0.679368
95	1	0	-5.103455	2.671464	2.501751
96	1	0	-6.335675	-1.600163	-3.219409
97	1	0	-1.220729	-1.641912	3.784996
98	1	0	-2.749990	1.069762	-0.709214
99	1	0	-6.975670	3.066931	0.940994
100	1	0	-4.610336	1.469260	-2.278805
101	1	0	-6.747999	2.457665	-1.463008
102	1	0	-3.047996	2.080099	4.921993
103	1	0	0.076481	-1.645177	5.871982
104	1	0	-1.783741	2.059043	7.031476
105	1	0	-0.199871	0.200103	7.526918
106	1	0	-1.342925	0.964595	-3.056479
107	1	0	-0.533328	0.052796	-1.749272
108	1	0	-0.365454	-1.203207	-3.902896
109	1	0	1.249989	-0.661509	-3.400992
110	1	0	0.385372	0.193743	-4.702453
111	6	0	0.208138	-3.317925	-0.062376

112	6	0	1.292267	-3.603254	-0.899994
113	6	0	0.320986	-1.869610	0.442235
114	6	0	-0.739756	-4.292145	0.208894
115	6	0	1.463565	-4.849030	-1.488678
116	7	0	2.104116	-2.445786	-1.052611
117	8	0	-0.761670	-1.061941	0.349530
118	6	0	-0.590123	-5.555017	-0.384548
119	6	0	0.496482	-5.827392	-1.215998
120	6	0	3.324636	-2.376967	-1.834900
121	6	0	1.546353	-1.369212	-0.412832
122	6	0	4.452745	-3.234103	-1.283470
123	8	0	1.924425	-0.205216	-0.506062
124	6	0	4.660890	-3.358626	0.097699
125	6	0	5.328536	-3.879365	-2.167226
126	6	0	5.726304	-4.107873	0.589083
127	6	0	6.402683	-4.627783	-1.693082
128	6	0	6.586363	-4.728870	-0.316148
129	7	0	7.720543	-5.514953	0.194598
130	8	0	8.458608	-6.054453	-0.630341
131	8	0	7.867141	-5.580829	1.414112
132	6	0	0.915790	-1.952789	1.829288
133	7	0	1.402349	-2.004334	2.884375
134	1	0	-1.579509	-4.084106	0.865908
135	1	0	2.311832	-5.069196	-2.128705
136	1	0	-1.326161	-6.328721	-0.186771
137	1	0	0.602750	-6.812672	-1.661564
138	1	0	3.630398	-1.325058	-1.827314
139	1	0	3.116794	-2.661340	-2.874726
140	1	0	3.982252	-2.877780	0.795655
141	1	0	5.167633	-3.800036	-3.239730
142	1	0	5.896468	-4.218145	1.653104
143	1	0	7.085913	-5.134965	-2.363068

R-OEt-anti-2

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57985991 A.U. after 7 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61396529 A.U. after 17 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.057364	-4.337944	-1.098921
2	6	0	-0.211224	-2.758161	-0.465291
3	7	0	-1.437013	-2.098555	-0.443849
4	7	0	0.807597	-2.019028	-0.012186
5	6	0	-2.691071	-2.842252	-0.371137
6	6	0	-3.778756	-2.161794	-1.240634
7	6	0	2.209424	-2.442602	-0.021492
8	6	0	-3.140328	-3.197678	1.055143
9	6	0	2.892556	-2.215545	1.375157
10	6	0	2.996482	-1.812278	-1.163706
11	6	0	2.149219	-2.960268	2.481809
12	7	0	3.091901	-0.793843	1.653185
13	16	0	4.446293	-0.180783	2.340285
14	8	0	5.281343	-1.289569	2.814351

15	6	0	-3.656101	-2.279380	2.030764
16	6	0	5.376186	0.596268	0.992142
17	6	0	-3.003662	-4.521069	1.428733
18	6	0	-5.179314	-2.820132	-1.121863
19	8	0	4.041087	0.928243	3.211890
20	7	0	-3.380900	-2.204369	-2.755413
21	6	0	-4.010410	-2.828027	3.313967
22	6	0	-3.381839	-4.948091	2.723784
23	6	0	-3.816448	-0.889048	1.828035
24	6	0	-4.542666	-1.592947	-3.550771
25	6	0	-3.172439	-3.637365	-3.234928
26	6	0	-5.553389	-3.560600	-2.416715
27	6	0	-5.759277	-2.548377	-3.570652
28	6	0	-4.511558	-1.961095	4.316350
29	7	0	-3.879088	-4.146206	3.638771
30	6	0	-4.386507	-4.487316	-2.804287
31	6	0	-7.047646	-1.769236	-3.497980
32	6	0	-4.284365	-0.067219	2.839884
33	6	0	-7.990811	-1.790260	-4.439793
34	8	0	-4.380413	1.262937	2.548589
35	6	0	-4.646965	-0.610971	4.097563
36	6	0	-4.448593	2.185966	3.637071
37	6	0	6.445643	-0.084674	0.414765
38	6	0	5.003738	1.862789	0.544739
39	6	0	7.144591	0.512742	-0.635616
40	6	0	3.912591	-2.595583	-1.877349
41	6	0	5.712446	2.448237	-0.505147
42	6	0	8.258889	-0.230972	-1.324241
43	6	0	6.783826	1.778543	-1.097362
44	6	0	5.270343	3.779447	-1.051755
45	9	0	4.322355	3.627089	-2.013414
46	9	0	6.291807	4.456671	-1.620075
47	9	0	4.735516	4.568001	-0.098329
48	9	0	8.811461	-1.167666	-0.528474
49	9	0	9.244390	0.604720	-1.722529
50	9	0	7.815182	-0.865222	-2.437058
51	6	0	1.126732	-2.354247	3.221221
52	6	0	2.858557	-0.456472	-1.500009
53	6	0	4.684663	-2.042421	-2.900888
54	6	0	3.626461	0.095797	-2.527992
55	6	0	4.542823	-0.693176	-3.229410
56	6	0	2.472909	-4.296259	2.745009
57	6	0	0.439718	-3.073543	4.199685
58	6	0	1.788214	-5.017182	3.723856
59	6	0	0.766925	-4.406789	4.453544
60	6	0	-2.191449	-1.275939	-3.023585
61	8	0	-1.218683	-1.945416	-3.578512
62	8	0	-2.317778	-0.098737	-2.833071
63	6	0	0.024219	-1.196871	-3.858810
64	6	0	0.984490	-2.161383	-4.514487
65	1	0	-1.444912	-1.160198	-0.031144
66	1	0	0.612585	-1.067141	0.377882
67	1	0	-2.455828	-3.807024	-0.823273
68	1	0	-3.818144	-1.092361	-1.034673
69	1	0	2.195128	-3.524597	-0.169619
70	1	0	3.887590	-2.660675	1.282023
71	1	0	2.278935	-0.140946	1.596647
72	1	0	-2.581439	-5.243891	0.736987
73	1	0	-5.927625	-2.062857	-0.870266
74	1	0	-5.164497	-3.528086	-0.290341
75	1	0	-3.266716	-5.995856	2.998342

76	1	0	-3.491780	-0.404199	0.917555
77	1	0	-4.763320	-0.638885	-3.071589
78	1	0	-4.165806	-1.387674	-4.555407
79	1	0	-3.075282	-3.571020	-4.320032
80	1	0	-2.223165	-3.994461	-2.831754
81	1	0	-6.467965	-4.140709	-2.264179
82	1	0	-5.757348	-3.106173	-4.515260
83	1	0	-4.770054	-2.405018	5.272272
84	1	0	-4.671830	-5.145821	-3.631288
85	1	0	-4.120108	-5.131284	-1.959568
86	1	0	-7.195268	-1.156010	-2.608258
87	1	0	-8.909232	-1.219575	-4.338437
88	1	0	-7.883703	-2.381303	-5.347172
89	1	0	-5.013870	0.030323	4.890173
90	1	0	-4.340724	3.175929	3.190340
91	1	0	-3.629997	2.013244	4.342863
92	1	0	-5.416397	2.130976	4.151290
93	1	0	6.732979	-1.056816	0.797798
94	1	0	4.179139	2.387490	1.014352
95	1	0	4.022202	-3.649139	-1.629268
96	1	0	7.340369	2.243805	-1.902822
97	1	0	0.867782	-1.316522	3.038740
98	1	0	2.168674	0.168386	-0.937142
99	1	0	5.397629	-2.663065	-3.436870
100	1	0	3.534959	1.154875	-2.754577
101	1	0	5.153250	-0.256557	-4.015425
102	1	0	3.274327	-4.775393	2.185770
103	1	0	-0.350838	-2.585276	4.763010
104	1	0	2.059476	-6.051234	3.921125
105	1	0	0.233824	-4.963797	5.219710
106	1	0	0.394799	-0.828096	-2.901381
107	1	0	-0.245391	-0.348689	-4.493945
108	1	0	1.938103	-1.649569	-4.676682
109	1	0	0.603012	-2.512075	-5.479104
110	1	0	1.165553	-3.018763	-3.861016
111	6	0	0.603248	2.892331	1.421800
112	6	0	-0.085335	3.705608	0.514999
113	6	0	0.000856	1.482212	1.402793
114	6	0	1.678574	3.394651	2.138018
115	6	0	0.265861	5.033021	0.305426
116	7	0	-1.114371	2.959536	-0.117441
117	8	0	0.825287	0.481997	1.014182
118	6	0	2.058306	4.729645	1.929885
119	6	0	1.357400	5.533671	1.029404
120	6	0	-1.909344	3.405470	-1.253294
121	6	0	-1.141005	1.670333	0.341264
122	6	0	-3.146067	4.202518	-0.876456
123	8	0	-1.887984	0.791223	-0.080721
124	6	0	-4.077299	3.675805	0.032811
125	6	0	-3.394624	5.448001	-1.465419
126	6	0	-5.235240	4.380474	0.344641
127	6	0	-4.549557	6.166822	-1.163464
128	6	0	-5.455381	5.618309	-0.260119
129	7	0	-6.682185	6.363239	0.061372
130	8	0	-6.851831	7.451842	-0.487786
131	8	0	-7.468934	5.852380	0.858704
132	6	0	-0.662773	1.226522	2.729666
133	7	0	-1.155569	0.995935	3.757231
134	1	0	2.221374	2.761214	2.835183
135	1	0	-0.280666	5.668335	-0.384572
136	1	0	2.901406	5.140811	2.476906

137	1	0	1.658028	6.567361	0.883037
138	1	0	-2.204589	2.495922	-1.787491
139	1	0	-1.266748	3.993541	-1.917620
140	1	0	-3.901631	2.710412	0.498778
141	1	0	-2.679146	5.863431	-2.170743
142	1	0	-5.968012	3.985424	1.037436
143	1	0	-4.754413	7.132648	-1.608546

R-CO-inpl-3

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.58879496 A.U. after 6 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61890065 A.U. after 15 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-3.975268	1.640687	-1.396623
2	6	0	-2.616792	0.786610	-0.856302
3	7	0	-2.644658	-0.133222	0.188723
4	7	0	-1.380098	0.931492	-1.357035
5	6	0	-3.861612	-0.825389	0.587181
6	6	0	-4.001966	-0.874618	2.129718
7	6	0	-0.939110	1.927599	-2.325441
8	6	0	-3.964528	-2.251664	0.029191
9	6	0	0.373499	1.413813	-2.989223
10	6	0	-0.763733	3.324993	-1.732986
11	6	0	0.181186	0.245625	-3.969211
12	7	0	1.385409	1.104630	-1.961740
13	16	0	2.928058	1.670356	-1.957922
14	8	0	3.200997	2.274624	-3.267965
15	6	0	-4.957992	-2.618893	-0.941766
16	6	0	2.995500	3.014777	-0.752967
17	6	0	-3.097025	-3.229996	0.468291
18	6	0	-5.375202	-1.448078	2.581894
19	8	0	3.779455	0.607826	-1.408398
20	7	0	-3.848067	0.525321	2.776177
21	6	0	-4.983500	-3.997849	-1.354129
22	6	0	-3.199917	-4.552428	-0.029760
23	6	0	-5.905077	-1.728941	-1.502805
24	6	0	-4.071909	0.365478	4.285015
25	6	0	-4.880516	1.503921	2.231657
26	6	0	-6.223388	-0.359923	3.262901
27	6	0	-5.562900	0.082378	4.593282
28	6	0	-5.964214	-4.416078	-2.286993
29	7	0	-4.108936	-4.940173	-0.897656
30	6	0	-6.281171	0.865804	2.334073
31	6	0	-5.693486	-0.912353	5.718132
32	6	0	-6.850798	-2.173195	-2.413386
33	6	0	-6.302477	-0.659625	6.876726
34	8	0	-7.713771	-1.228856	-2.883426
35	6	0	-6.884856	-3.535555	-2.807094
36	6	0	-8.655457	-1.594541	-3.881682
37	6	0	3.118524	4.323203	-1.212226
38	6	0	2.923356	2.721298	0.609630
39	6	0	3.162730	5.364753	-0.284865

40	6	0	-0.741022	4.428389	-2.596446
41	6	0	2.956360	3.778321	1.520475
42	6	0	3.315758	6.791274	-0.745162
43	6	0	3.081326	5.097432	1.080397
44	6	0	2.758056	3.518313	2.989278
45	9	0	3.455531	4.383965	3.754608
46	9	0	3.114849	2.270208	3.346079
47	9	0	1.447438	3.668647	3.335645
48	9	0	3.029402	6.936065	-2.053310
49	9	0	4.576611	7.241513	-0.555242
50	9	0	2.499297	7.620519	-0.052292
51	6	0	-1.048689	-0.388259	-4.184483
52	6	0	-0.612192	3.542187	-0.361703
53	6	0	-0.559259	5.719284	-2.100854
54	6	0	-0.442523	4.834086	0.139253
55	6	0	-0.410226	5.926963	-0.727419
56	6	0	1.288632	-0.170518	-4.724737
57	6	0	-1.166568	-1.414994	-5.126574
58	6	0	1.170969	-1.192790	-5.663129
59	6	0	-0.059672	-1.821860	-5.868092
60	6	0	-2.439349	1.127760	2.623750
61	8	0	-1.572309	0.250035	3.046406
62	8	0	-2.313880	2.277290	2.309218
63	6	0	-0.132796	0.651608	3.065038
64	6	0	0.521953	-0.049554	4.232107
65	1	0	-1.750406	-0.622690	0.329332
66	1	0	-0.678983	0.274777	-0.985942
67	1	0	-4.675751	-0.226199	0.181380
68	1	0	-3.174820	-1.443980	2.554070
69	1	0	-1.699542	1.999154	-3.110208
70	1	0	0.780644	2.251605	-3.561423
71	1	0	1.187878	0.382353	-1.246025
72	1	0	-2.318864	-3.020629	1.195593
73	1	0	-5.224315	-2.303474	3.247002
74	1	0	-5.909534	-1.827094	1.706602
75	1	0	-2.500906	-5.308851	0.323464
76	1	0	-5.885230	-0.666347	-1.288514
77	1	0	-3.419422	-0.448330	4.603654
78	1	0	-3.723947	1.288867	4.754037
79	1	0	-4.779825	2.404623	2.837616
80	1	0	-4.594741	1.754538	1.207834
81	1	0	-7.230112	-0.740300	3.458957
82	1	0	-6.042152	1.015858	4.912307
83	1	0	-5.959790	-5.461852	-2.577223
84	1	0	-6.987575	1.608805	2.718588
85	1	0	-6.637099	0.571730	1.340953
86	1	0	-5.252311	-1.895700	5.550696
87	1	0	-6.380033	-1.412938	7.655222
88	1	0	-6.749041	0.309123	7.091755
89	1	0	-7.623178	-3.887205	-3.518454
90	1	0	-9.196711	-0.679084	-4.126426
91	1	0	-9.366595	-2.346211	-3.514341
92	1	0	-8.160781	-1.973892	-4.784943
93	1	0	3.173330	4.518089	-2.276135
94	1	0	2.847057	1.694414	0.956798
95	1	0	-0.875607	4.277960	-3.666106
96	1	0	3.105113	5.910219	1.797990
97	1	0	-1.930193	-0.093707	-3.625493
98	1	0	-0.641668	2.701760	0.321745
99	1	0	-0.542562	6.562991	-2.785693
100	1	0	-0.325379	4.976434	1.210217

101	1	0	-0.262156	6.930956	-0.339774
102	1	0	2.246123	0.321346	-4.580974
103	1	0	-2.131625	-1.892267	-5.276545
104	1	0	2.041677	-1.494872	-6.239286
105	1	0	-0.153399	-2.617762	-6.602506
106	1	0	-0.103175	1.737652	3.152976
107	1	0	0.261728	0.332756	2.096324
108	1	0	1.588505	0.191237	4.205640
109	1	0	0.415903	-1.134136	4.147960
110	1	0	0.108518	0.285687	5.189835
111	6	0	1.360493	-2.690133	-0.822647
112	6	0	2.746764	-2.868914	-0.908169
113	6	0	1.040109	-1.760838	0.349706
114	6	0	0.518109	-3.286591	-1.746290
115	6	0	3.320406	-3.652507	-1.902185
116	7	0	3.399132	-2.144224	0.116402
117	8	0	0.313304	-0.635484	0.099268
118	6	0	1.077251	-4.076304	-2.760217
119	6	0	2.459666	-4.255341	-2.829389
120	6	0	4.830021	-1.896554	0.173215
121	6	0	2.498771	-1.416781	0.860901
122	6	0	5.654177	-3.101112	0.588458
123	8	0	2.777509	-0.610978	1.734373
124	6	0	5.180172	-4.018728	1.536486
125	6	0	6.935273	-3.283011	0.048603
126	6	0	5.963478	-5.095020	1.940572
127	6	0	7.735496	-4.350921	0.444309
128	6	0	7.234376	-5.245512	1.387546
129	7	0	8.067274	-6.381104	1.807693
130	8	0	9.184289	-6.491203	1.300929
131	8	0	7.600398	-7.156479	2.642513
132	6	0	0.390133	-2.557298	1.446509
133	7	0	-0.188933	-3.096156	2.300718
134	1	0	-0.555839	-3.132364	-1.691379
135	1	0	4.393826	-3.796754	-1.964000
136	1	0	0.432397	-4.543061	-3.498306
137	1	0	2.883587	-4.870344	-3.618544
138	1	0	4.955743	-1.085704	0.899075
139	1	0	5.163170	-1.512060	-0.796905
140	1	0	4.186674	-3.891738	1.955240
141	1	0	7.311019	-2.580278	-0.690748
142	1	0	5.610017	-5.813227	2.670066
143	1	0	8.726055	-4.504163	0.034221

R-CO-inpl-4

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.58326202 A.U. after 11 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61427628 A.U. after 15 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-3.355180	-1.256235	2.542455
2	6	0	-2.379012	-0.554449	1.351135
3	7	0	-2.795580	-0.346487	0.037985

4	7	0	-1.110676	-0.162871	1.540208
5	6	0	-4.201575	-0.248489	-0.330122
6	6	0	-4.473494	-1.017714	-1.645982
7	6	0	-0.321875	-0.324639	2.756301
8	6	0	-4.707906	1.194961	-0.461891
9	6	0	0.756311	0.799586	2.793440
10	6	0	0.300861	-1.712243	2.902934
11	6	0	0.210058	2.206438	3.083825
12	7	0	1.561259	0.782998	1.563140
13	16	0	3.199432	0.711354	1.503200
14	8	0	3.723808	0.959740	2.852266
15	6	0	-5.685391	1.741713	0.438926
16	6	0	3.643857	-0.991632	1.090817
17	6	0	-4.240889	2.004208	-1.476434
18	6	0	-5.981701	-1.056019	-2.021481
19	8	0	3.616758	1.509846	0.345424
20	7	0	-3.979305	-2.487820	-1.565921
21	6	0	-6.118295	3.091234	0.186354
22	6	0	-4.723499	3.329267	-1.612868
23	6	0	-6.250548	1.047175	1.535197
24	6	0	-4.357931	-3.172830	-2.884749
25	6	0	-4.649066	-3.234337	-0.419332
26	6	0	-6.539694	-2.484331	-1.901647
27	6	0	-5.886873	-3.406128	-2.962794
28	6	0	-7.101360	3.665435	1.029559
29	7	0	-5.633662	3.863546	-0.828300
30	6	0	-6.175429	-3.034105	-0.510783
31	6	0	-6.385321	-3.193569	-4.369352
32	6	0	-7.211255	1.640001	2.339131
33	6	0	-6.979452	-4.133552	-5.104548
34	8	0	-7.686056	0.874078	3.361645
35	6	0	-7.646652	2.964984	2.080875
36	6	0	-8.603676	1.448143	4.281103
37	6	0	4.242236	-1.795284	2.057592
38	6	0	3.398405	-1.463621	-0.198628
39	6	0	4.599340	-3.102320	1.724034
40	6	0	0.796736	-2.102105	4.154676
41	6	0	3.767399	-2.771896	-0.515625
42	6	0	5.254688	-4.002625	2.739094
43	6	0	4.369757	-3.592891	0.439119
44	6	0	3.448793	-3.329625	-1.876446
45	9	0	4.332501	-4.276913	-2.254909
46	9	0	3.433918	-2.375667	-2.829327
47	9	0	2.220891	-3.919195	-1.892421
48	9	0	5.163138	-3.512129	3.989759
49	9	0	6.566263	-4.185558	2.468927
50	9	0	4.684910	-5.232637	2.739592
51	6	0	-1.153384	2.500006	3.209921
52	6	0	0.396461	-2.607075	1.835210
53	6	0	1.388170	-3.352407	4.330921
54	6	0	0.979380	-3.863723	2.010618
55	6	0	1.481469	-4.240329	3.256382
56	6	0	1.136989	3.244148	3.270204
57	6	0	-1.579081	3.800089	3.502161
58	6	0	0.713300	4.537894	3.563850
59	6	0	-0.649930	4.823280	3.678031
60	6	0	-2.450721	-2.629016	-1.438736
61	8	0	-1.896145	-1.963625	-2.413142
62	8	0	-1.987451	-3.384041	-0.631578
63	6	0	-0.408735	-2.030741	-2.536413
64	6	0	-0.069219	-1.987785	-4.007776

65	1	0	-2.127296	0.184581	-0.529141
66	1	0	-0.659648	0.287632	0.731989
67	1	0	-4.740548	-0.736241	0.480794
68	1	0	-3.874970	-0.587588	-2.450159
69	1	0	-0.990905	-0.175330	3.609698
70	1	0	1.445880	0.545603	3.602961
71	1	0	1.115193	0.947072	0.639116
72	1	0	-3.501673	1.656549	-2.191301
73	1	0	-6.125599	-0.661916	-3.031784
74	1	0	-6.534153	-0.393656	-1.349912
75	1	0	-4.337581	3.955057	-2.416118
76	1	0	-5.907433	0.059498	1.821334
77	1	0	-3.994696	-2.520865	-3.679880
78	1	0	-3.797795	-4.109982	-2.925777
79	1	0	-4.351378	-4.276910	-0.534561
80	1	0	-4.217359	-2.866680	0.513679
81	1	0	-7.624992	-2.473797	-2.037815
82	1	0	-6.100943	-4.444963	-2.683588
83	1	0	-7.407640	4.683841	0.812862
84	1	0	-6.674399	-3.991683	-0.329488
85	1	0	-6.515994	-2.344094	0.268404
86	1	0	-6.237104	-2.199253	-4.792406
87	1	0	-7.330553	-3.931073	-6.112165
88	1	0	-7.140257	-5.141550	-4.727434
89	1	0	-8.397683	3.432409	2.707236
90	1	0	-8.801823	0.673220	5.023483
91	1	0	-9.546404	1.729045	3.793204
92	1	0	-8.177995	2.327252	4.781573
93	1	0	4.421976	-1.400498	3.050010
94	1	0	2.927362	-0.828836	-0.942997
95	1	0	0.712482	-1.425005	5.002761
96	1	0	4.652820	-4.608266	0.184225
97	1	0	-1.902435	1.725594	3.086425
98	1	0	0.001215	-2.328664	0.865252
99	1	0	1.769392	-3.635946	5.308355
100	1	0	1.044031	-4.543362	1.164952
101	1	0	1.950157	-5.211110	3.389032
102	1	0	2.198806	3.029863	3.190560
103	1	0	-2.642781	4.004569	3.593413
104	1	0	1.450161	5.323802	3.707638
105	1	0	-0.981857	5.832433	3.908566
106	1	0	-0.088437	-2.954378	-2.055096
107	1	0	-0.037473	-1.162909	-1.984136
108	1	0	1.020509	-1.974900	-4.096394
109	1	0	-0.458012	-1.078107	-4.472285
110	1	0	-0.458168	-2.864647	-4.537429
111	6	0	0.406997	3.136298	-1.407940
112	6	0	1.553551	3.663098	-2.019105
113	6	0	0.260889	1.658584	-1.784697
114	6	0	-0.387594	3.930701	-0.599879
115	6	0	1.911991	4.995336	-1.857413
116	7	0	2.217563	2.654089	-2.754504
117	8	0	0.027509	0.744806	-0.811335
118	6	0	-0.036042	5.275761	-0.417077
119	6	0	1.094223	5.796353	-1.047631
120	6	0	3.407711	2.826343	-3.586360
121	6	0	1.609045	1.433921	-2.589251
122	6	0	4.735836	2.689337	-2.862243
123	8	0	2.027159	0.366906	-3.012862
124	6	0	5.518625	3.815741	-2.581742
125	6	0	5.208782	1.419677	-2.499263

126	6	0	6.749356	3.692363	-1.942571
127	6	0	6.435302	1.277570	-1.860473
128	6	0	7.188667	2.418938	-1.591163
129	7	0	8.492345	2.274398	-0.926345
130	8	0	8.868239	1.137096	-0.641989
131	8	0	9.136086	3.299098	-0.697345
132	6	0	-0.810272	1.546469	-2.844663
133	7	0	-1.677452	1.355876	-3.598099
134	1	0	-1.259461	3.512722	-0.104820
135	1	0	2.802298	5.408342	-2.319668
136	1	0	-0.640419	5.908595	0.225268
137	1	0	1.360515	6.839551	-0.900756
138	1	0	3.336372	3.807088	-4.067234
139	1	0	3.338236	2.062690	-4.366854
140	1	0	5.170563	4.803253	-2.873658
141	1	0	4.605441	0.544280	-2.717519
142	1	0	7.366743	4.553334	-1.718816
143	1	0	6.816525	0.306553	-1.570472

S-CO-syn-5

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57766899 A.U. after 7 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.60921719 A.U. after 16 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.690781	1.079780	-3.576816
2	6	0	-0.513248	0.780928	-1.909497
3	7	0	-1.065717	1.615570	-0.927609
4	7	0	0.195301	-0.250373	-1.417601
5	6	0	-2.058009	2.633638	-1.282137
6	6	0	-1.693570	4.074970	-0.814523
7	6	0	1.067985	-1.080492	-2.261910
8	6	0	-3.490839	2.308853	-0.843818
9	6	0	1.280201	-2.510858	-1.673488
10	6	0	2.414445	-0.421125	-2.557577
11	6	0	0.040894	-3.417646	-1.730476
12	7	0	1.878226	-2.448029	-0.345102
13	16	0	3.242605	-3.246511	0.090914
14	8	0	3.725203	-4.022108	-1.057661
15	6	0	-3.966040	2.369574	0.511210
16	6	0	4.462292	-1.952532	0.411858
17	6	0	-4.397495	1.962870	-1.825967
18	6	0	-2.558934	5.148267	-1.534990
19	8	0	3.021116	-3.883525	1.395548
20	7	0	-0.210972	4.439589	-1.038734
21	6	0	-5.362265	2.100995	0.724941
22	6	0	-5.751553	1.708624	-1.497444
23	6	0	-3.158224	2.633409	1.641950
24	6	0	-0.013003	5.874732	-0.532059
25	6	0	0.179418	4.394406	-2.511691
26	6	0	-1.680188	6.085494	-2.378938
27	6	0	-0.717099	6.890571	-1.468413
28	6	0	-5.875826	2.138797	2.047124

29	7	0	-6.233905	1.786420	-0.276377
30	6	0	-0.828541	5.225399	-3.327714
31	6	0	-1.380276	7.982422	-0.667965
32	6	0	-3.684905	2.647985	2.921613
33	6	0	-1.078113	9.276836	-0.769690
34	8	0	-2.800959	2.904121	3.924958
35	6	0	-5.067400	2.406584	3.128752
36	6	0	-3.162252	2.580952	5.264340
37	6	0	5.709886	-2.040521	-0.192796
38	6	0	4.146492	-0.911426	1.289220
39	6	0	6.674069	-1.068215	0.093168
40	6	0	3.009282	0.489311	-1.682316
41	6	0	5.118280	0.049198	1.558236
42	6	0	8.003365	-1.105552	-0.614459
43	6	0	6.385923	-0.028246	0.971382
44	6	0	4.798849	1.242544	2.414166
45	9	0	4.613801	2.355885	1.646487
46	9	0	5.797858	1.536614	3.271653
47	9	0	3.670770	1.078561	3.136597
48	9	0	8.408419	-2.368629	-0.855517
49	9	0	8.970806	-0.493245	0.104166
50	9	0	7.943020	-0.473844	-1.810663
51	6	0	-0.719456	-3.512289	-2.906940
52	6	0	3.100907	-0.772308	-3.727743
53	6	0	4.261259	1.039167	-1.964448
54	6	0	4.357963	-0.237326	-4.006859
55	6	0	4.945671	0.670802	-3.122474
56	6	0	-0.283675	-4.260798	-0.661800
57	6	0	-1.767191	-4.426675	-3.012179
58	6	0	-1.333928	-5.176182	-0.765027
59	6	0	-2.076321	-5.267385	-1.940554
60	6	0	0.762228	3.578090	-0.226441
61	8	0	0.332924	3.495381	1.007086
62	8	0	1.799197	3.233796	-0.715649
63	6	0	1.207588	2.767138	1.972415
64	6	0	0.909653	3.316551	3.347482
65	1	0	-1.246268	1.127651	-0.041734
66	1	0	0.256214	-0.372447	-0.387030
67	1	0	-2.062830	2.643428	-2.375552
68	1	0	-1.809664	4.165241	0.260471
69	1	0	0.549701	-1.194969	-3.214878
70	1	0	2.034295	-2.970741	-2.320616
71	1	0	1.353609	-1.981396	0.434323
72	1	0	-4.077116	1.882477	-2.860904
73	1	0	-3.144040	5.709065	-0.799895
74	1	0	-3.281729	4.647719	-2.185447
75	1	0	-6.454540	1.442602	-2.285785
76	1	0	-2.084744	2.739117	1.562022
77	1	0	-0.413902	5.897418	0.482283
78	1	0	1.065503	6.041533	-0.481992
79	1	0	1.195771	4.784690	-2.559038
80	1	0	0.200842	3.347796	-2.819158
81	1	0	-2.310013	6.776278	-2.947180
82	1	0	0.038662	7.357108	-2.111569
83	1	0	-6.935241	1.938806	2.172883
84	1	0	-0.285562	5.856488	-4.038825
85	1	0	-1.468561	4.556729	-3.913160
86	1	0	-2.154819	7.669727	0.033830
87	1	0	-1.592017	10.029540	-0.178970
88	1	0	-0.307695	9.635527	-1.449235
89	1	0	-5.486314	2.425002	4.128702

90	1	0	-2.244263	2.667475	5.845865
91	1	0	-3.534114	1.552612	5.337518
92	1	0	-3.916043	3.276029	5.656486
93	1	0	5.917520	-2.853635	-0.879120
94	1	0	3.152540	-0.834846	1.723605
95	1	0	2.491045	0.781009	-0.777012
96	1	0	7.138132	0.719365	1.197063
97	1	0	-0.490168	-2.884093	-3.763458
98	1	0	2.647121	-1.469991	-4.428991
99	1	0	4.698823	1.745117	-1.263779
100	1	0	4.876044	-0.525771	-4.917751
101	1	0	5.929067	1.081790	-3.333314
102	1	0	0.303991	-4.222180	0.248348
103	1	0	-2.341758	-4.484455	-3.933091
104	1	0	-1.559293	-5.822420	0.078979
105	1	0	-2.885317	-5.987904	-2.025604
106	1	0	2.236868	2.935862	1.658575
107	1	0	0.961424	1.707171	1.864045
108	1	0	1.512702	2.761025	4.071416
109	1	0	-0.140265	3.177665	3.616365
110	1	0	1.171619	4.378534	3.413296
111	6	0	-0.426877	-2.612459	2.814732
112	6	0	-1.750754	-3.070343	2.753659
113	6	0	-0.358377	-1.171371	2.273334
114	6	0	0.565356	-3.420581	3.342920
115	6	0	-2.114667	-4.328561	3.213440
116	7	0	-2.575251	-2.084661	2.154540
117	8	0	0.596050	-0.813377	1.380771
118	6	0	0.220568	-4.700011	3.804142
119	6	0	-1.101438	-5.140527	3.745011
120	6	0	-4.027576	-2.147115	2.005016
121	6	0	-1.830628	-1.016753	1.738417
122	6	0	-4.530490	-2.840794	0.751337
123	8	0	-2.250912	-0.091392	1.051583
124	6	0	-4.261991	-2.292785	-0.512062
125	6	0	-5.312567	-3.998572	0.843046
126	6	0	-4.758362	-2.892931	-1.663129
127	6	0	-5.822118	-4.610523	-0.299784
128	6	0	-5.533544	-4.045348	-1.538929
129	7	0	-6.053663	-4.689650	-2.753422
130	8	0	-6.751165	-5.695343	-2.615932
131	8	0	-5.759709	-4.188672	-3.839450
132	6	0	-0.328935	-0.275581	3.491728
133	7	0	-0.284424	0.438209	4.409421
134	1	0	1.595427	-3.084314	3.371287
135	1	0	-3.137106	-4.687147	3.150187
136	1	0	0.991985	-5.352438	4.201423
137	1	0	-1.355985	-6.133539	4.105357
138	1	0	-4.375973	-1.109303	2.007159
139	1	0	-4.431023	-2.637630	2.896603
140	1	0	-3.662624	-1.391280	-0.586700
141	1	0	-5.535618	-4.424911	1.817988
142	1	0	-4.553297	-2.488806	-2.646039
143	1	0	-6.428767	-5.506000	-0.246583

S-OEt-syn-6

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57608445 A.U. after 12 cycles

Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61014891 A.U. after 16 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.868288	2.288412	-3.323132
2	6	0	-0.767255	1.463236	-1.828295
3	7	0	-1.722259	1.634720	-0.824603
4	7	0	0.250170	0.643118	-1.519864
5	6	0	-3.015845	2.238367	-1.154085
6	6	0	-3.500950	3.312730	-0.144309
7	6	0	1.341002	0.369078	-2.470590
8	6	0	-4.144238	1.254909	-1.505739
9	6	0	1.861800	-1.098844	-2.363212
10	6	0	2.471611	1.388797	-2.415829
11	6	0	0.779528	-2.139888	-2.687399
12	7	0	2.532154	-1.328300	-1.088872
13	16	0	3.902176	-2.225112	-0.944897
14	8	0	4.373907	-2.580945	-2.288478
15	6	0	-4.949781	0.517148	-0.569135
16	6	0	5.118111	-1.087659	-0.239570
17	6	0	-4.440833	1.118653	-2.848740
18	6	0	-4.619925	4.202696	-0.753009
19	8	0	3.703544	-3.250876	0.086669
20	7	0	-2.352348	4.243980	0.298332
21	6	0	-6.054012	-0.230665	-1.115084
22	6	0	-5.521865	0.310217	-3.273498
23	6	0	-4.746008	0.477503	0.832079
24	6	0	-2.951506	5.316751	1.217214
25	6	0	-1.697038	4.935715	-0.890564
26	6	0	-4.116461	5.642134	-0.959773
27	6	0	-3.824366	6.308278	0.409499
28	6	0	-6.922160	-0.921763	-0.234544
29	7	0	-6.324516	-0.324705	-2.448830
30	6	0	-2.796449	5.596284	-1.750025
31	6	0	-5.052458	6.698716	1.191356
32	6	0	-5.607960	-0.223469	1.660679
33	6	0	-5.347022	7.947922	1.551688
34	8	0	-5.292775	-0.214715	2.991576
35	6	0	-6.721289	-0.917753	1.126228
36	6	0	-6.170932	-0.855444	3.907332
37	6	0	6.398159	-1.054579	-0.781510
38	6	0	4.781142	-0.316258	0.873740
39	6	0	7.367848	-0.241528	-0.185804
40	6	0	3.022676	1.831621	-1.208007
41	6	0	5.759040	0.487922	1.455770
42	6	0	8.775277	-0.237638	-0.725316
43	6	0	7.055416	0.525624	0.934083
44	6	0	5.409476	1.379090	2.616657
45	9	0	5.180891	2.660976	2.205550
46	9	0	6.411199	1.445633	3.518186
47	9	0	4.298451	0.973265	3.257739
48	9	0	9.533750	-1.191860	-0.140250
49	9	0	9.390350	0.945599	-0.502175
50	9	0	8.801583	-0.468519	-2.053561
51	6	0	0.074019	-2.063618	-3.898370
52	6	0	3.003246	1.875512	-3.616183
53	6	0	4.087530	2.735640	-1.203340

54	6	0	4.066249	2.779113	-3.615294
55	6	0	4.612173	3.212230	-2.406392
56	6	0	0.521397	-3.217517	-1.834181
57	6	0	-0.870828	-3.030114	-4.239826
58	6	0	-0.420628	-4.190051	-2.178768
59	6	0	-1.124709	-4.100955	-3.379228
60	6	0	-1.387897	3.463752	1.200031
61	8	0	-0.167280	3.863298	0.981666
62	8	0	-1.842719	2.735387	2.037134
63	6	0	0.894037	3.247933	1.826887
64	6	0	2.099330	4.154045	1.747844
65	1	0	-1.702214	0.944659	-0.063873
66	1	0	0.358655	0.284423	-0.549368
67	1	0	-2.810743	2.764743	-2.088972
68	1	0	-3.828085	2.862120	0.788384
69	1	0	0.888399	0.454334	-3.458659
70	1	0	2.635563	-1.178895	-3.134098
71	1	0	2.001820	-1.162842	-0.202446
72	1	0	-3.840420	1.635817	-3.590806
73	1	0	-5.506245	4.184677	-0.111460
74	1	0	-4.927230	3.780961	-1.713901
75	1	0	-5.734482	0.212845	-4.337311
76	1	0	-3.876027	0.923022	1.296528
77	1	0	-3.521587	4.776337	1.974790
78	1	0	-2.110883	5.812879	1.707928
79	1	0	-0.999314	5.658401	-0.468005
80	1	0	-1.128940	4.190439	-1.448165
81	1	0	-4.866344	6.226392	-1.500994
82	1	0	-3.241767	7.218347	0.222276
83	1	0	-7.749069	-1.465432	-0.679833
84	1	0	-2.478912	6.607280	-2.025335
85	1	0	-2.924180	5.034257	-2.681033
86	1	0	-5.729934	5.890090	1.469117
87	1	0	-6.251153	8.182382	2.105896
88	1	0	-4.697904	8.785641	1.304936
89	1	0	-7.400065	-1.461687	1.772829
90	1	0	-5.737395	-0.692197	4.895406
91	1	0	-6.241105	-1.934166	3.716748
92	1	0	-7.176551	-0.416936	3.876053
93	1	0	6.625628	-1.646988	-1.660596
94	1	0	3.765719	-0.320138	1.260024
95	1	0	2.625447	1.452013	-0.271814
96	1	0	7.810556	1.153608	1.393218
97	1	0	0.266341	-1.249618	-4.592982
98	1	0	2.573043	1.551603	-4.561005
99	1	0	4.520829	3.046783	-0.257201
100	1	0	4.462655	3.147126	-4.558061
101	1	0	5.442976	3.913142	-2.400949
102	1	0	1.078991	-3.315687	-0.908966
103	1	0	-1.403252	-2.950981	-5.184184
104	1	0	-0.596075	-5.023673	-1.504332
105	1	0	-1.860298	-4.856831	-3.641866
106	1	0	1.069094	2.251357	1.415007
107	1	0	0.494155	3.142253	2.835027
108	1	0	2.915613	3.695527	2.313607
109	1	0	1.889303	5.138166	2.180178
110	1	0	2.433187	4.279053	0.713776
111	6	0	0.994017	-2.170475	2.663209
112	6	0	-0.134378	-2.967360	2.893316
113	6	0	0.551377	-0.808658	2.095513
114	6	0	2.252821	-2.641289	2.995265

115	6	0	-0.038941	-4.238706	3.442468
116	7	0	-1.302940	-2.282004	2.474273
117	8	0	1.167902	-0.297495	1.004023
118	6	0	2.374482	-3.925432	3.544731
119	6	0	1.242065	-4.708179	3.766335
120	6	0	-2.672310	-2.757638	2.643119
121	6	0	-0.988436	-1.083861	1.894846
122	6	0	-3.155480	-3.718430	1.570945
123	8	0	-1.784371	-0.364208	1.298636
124	6	0	-3.213778	-3.305568	0.231802
125	6	0	-3.580718	-5.010035	1.907635
126	6	0	-3.676772	-4.167591	-0.756229
127	6	0	-4.050759	-5.886064	0.932021
128	6	0	-4.085796	-5.449441	-0.390079
129	7	0	-4.561837	-6.372130	-1.431696
130	8	0	-4.994953	-7.467181	-1.072570
131	8	0	-4.498556	-5.997037	-2.603112
132	6	0	0.622277	0.156930	3.256558
133	7	0	0.728991	0.937862	4.111932
134	1	0	3.132199	-2.027260	2.833628
135	1	0	-0.913889	-4.860499	3.602427
136	1	0	3.357826	-4.313672	3.791179
137	1	0	1.348308	-5.703316	4.189227
138	1	0	-3.304336	-1.864277	2.655712
139	1	0	-2.739780	-3.228510	3.629740
140	1	0	-2.893486	-2.303228	-0.032587
141	1	0	-3.544064	-5.338235	2.943590
142	1	0	-3.717865	-3.864908	-1.794330
143	1	0	-4.378389	-6.889446	1.174366

S-CO-syn-7

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57553330 A.U. after 8 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61082734 A.U. after 16 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	0.057328	-4.040291	-1.613828
2	6	0	-0.110895	-2.554437	-0.790251
3	7	0	-1.353597	-1.944991	-0.613731
4	7	0	0.915504	-1.852143	-0.299340
5	6	0	-2.581156	-2.734901	-0.623825
6	6	0	-3.687809	-2.057348	-1.466282
7	6	0	2.316597	-2.239558	-0.475660
8	6	0	-3.007398	-3.232199	0.775513
9	6	0	3.130512	-2.067046	0.850320
10	6	0	2.977564	-1.546149	-1.660647
11	6	0	2.620952	-2.996777	1.950265
12	7	0	3.222341	-0.649792	1.225203
13	16	0	4.561853	-0.080080	2.005620
14	8	0	5.321548	-1.174933	2.619070
15	6	0	-3.911241	-2.606115	1.704351
16	6	0	5.616967	0.566384	0.687489
17	6	0	-2.442659	-4.435809	1.156727

18	6	0	-5.013969	-2.868585	-1.494043
19	8	0	4.127457	1.083031	2.790761
20	7	0	-3.238439	-1.869792	-2.947135
21	6	0	-4.214046	-3.340667	2.906775
22	6	0	-2.761187	-5.029579	2.399429
23	6	0	-4.550051	-1.353423	1.521341
24	6	0	-4.419497	-1.249313	-3.704015
25	6	0	-2.888801	-3.195906	-3.613804
26	6	0	-5.286960	-3.437781	-2.896803
27	6	0	-5.550840	-2.287842	-3.901697
28	6	0	-5.171184	-2.822351	3.813729
29	7	0	-3.635111	-4.528346	3.243426
30	6	0	-4.033103	-4.197272	-3.364725
31	6	0	-6.902290	-1.635091	-3.764239
32	6	0	-5.489121	-0.884498	2.424927
33	6	0	-7.816063	-1.588378	-4.733735
34	8	0	-6.056081	0.331252	2.130394
35	6	0	-5.815033	-1.629636	3.583607
36	6	0	-7.030217	0.862269	3.022088
37	6	0	6.904336	0.060898	0.548933
38	6	0	5.145065	1.589255	-0.138695
39	6	0	7.738762	0.585585	-0.444277
40	6	0	3.946388	-2.237209	-2.398592
41	6	0	5.983930	2.094796	-1.127365
42	6	0	9.152229	0.079558	-0.569613
43	6	0	7.282217	1.597883	-1.282857
44	6	0	5.517209	3.183394	-2.058686
45	9	0	5.686061	2.822467	-3.354959
46	9	0	6.227729	4.321441	-1.882216
47	9	0	4.217040	3.484697	-1.889177
48	9	0	9.987513	0.723230	0.276843
49	9	0	9.640203	0.257820	-1.817156
50	9	0	9.237156	-1.236737	-0.281975
51	6	0	1.577208	-2.639010	2.814380
52	6	0	2.672475	-0.228973	-2.020121
53	6	0	4.606302	-1.623221	-3.464114
54	6	0	3.326921	0.386773	-3.087631
55	6	0	4.300216	-0.306030	-3.809996
56	6	0	3.191332	-4.270084	2.069721
57	6	0	1.119174	-3.545737	3.772510
58	6	0	2.732289	-5.175361	3.026147
59	6	0	1.691123	-4.814261	3.882295
60	6	0	-2.061721	-0.896638	-3.113813
61	8	0	-2.401207	0.249476	-2.577350
62	8	0	-1.113608	-1.198673	-3.776445
63	6	0	-1.407371	1.341963	-2.670871
64	6	0	-2.141197	2.644124	-2.452151
65	1	0	-1.371406	-1.100356	-0.032648
66	1	0	0.713060	-1.010402	0.286818
67	1	0	-2.297136	-3.649639	-1.150205
68	1	0	-3.845676	-1.031375	-1.141539
69	1	0	2.311199	-3.313648	-0.675436
70	1	0	4.143730	-2.389030	0.591513
71	1	0	2.334954	-0.170665	1.496547
72	1	0	-1.739813	-4.936053	0.497562
73	1	0	-5.842221	-2.241442	-1.152085
74	1	0	-4.939006	-3.693414	-0.781225
75	1	0	-2.287732	-5.968707	2.681206
76	1	0	-4.283843	-0.699003	0.703069
77	1	0	-4.742185	-0.390146	-3.115513
78	1	0	-4.027944	-0.884039	-4.656312

79	1	0	-2.754753	-2.963287	-4.671015
80	1	0	-1.924440	-3.522956	-3.217245
81	1	0	-6.151838	-4.106795	-2.864170
82	1	0	-5.478977	-2.701352	-4.914980
83	1	0	-5.376609	-3.410103	4.702458
84	1	0	-4.234873	-4.748779	-4.288823
85	1	0	-3.734962	-4.933764	-2.610746
86	1	0	-7.124137	-1.176950	-2.799434
87	1	0	-8.781593	-1.114052	-4.584229
88	1	0	-7.636122	-2.024618	-5.714198
89	1	0	-6.547731	-1.266228	4.294421
90	1	0	-7.331265	1.821177	2.596777
91	1	0	-6.614749	1.026524	4.024019
92	1	0	-7.907078	0.207267	3.094913
93	1	0	7.240403	-0.734063	1.204801
94	1	0	4.136650	1.970390	-0.025784
95	1	0	4.181212	-3.268281	-2.141801
96	1	0	7.924825	1.990875	-2.062946
97	1	0	1.120148	-1.655702	2.741571
98	1	0	1.930427	0.328688	-1.459589
99	1	0	5.354328	-2.176717	-4.026118
100	1	0	3.090424	1.417268	-3.335697
101	1	0	4.817452	0.179599	-4.633075
102	1	0	4.011824	-4.553555	1.413313
103	1	0	0.310925	-3.255057	4.439105
104	1	0	3.195056	-6.155566	3.108424
105	1	0	1.333950	-5.513131	4.634628
106	1	0	-0.934493	1.271346	-3.652221
107	1	0	-0.666095	1.152709	-1.896479
108	1	0	-1.404620	3.453227	-2.426226
109	1	0	-2.669226	2.630493	-1.495442
110	1	0	-2.855856	2.846245	-3.256895
111	6	0	0.228567	2.291563	2.774259
112	6	0	-1.025508	2.819059	3.103406
113	6	0	0.099856	1.410382	1.520138
114	6	0	1.339137	2.598851	3.543498
115	6	0	-1.202840	3.680258	4.178984
116	7	0	-2.011713	2.313142	2.213986
117	8	0	0.612778	0.168209	1.538822
118	6	0	1.177359	3.455438	4.643363
119	6	0	-0.072593	3.992629	4.949043
120	6	0	-3.443881	2.554002	2.303455
121	6	0	-1.468040	1.429393	1.322719
122	6	0	-3.950421	3.613001	1.337205
123	8	0	-2.105533	0.750501	0.519209
124	6	0	-3.289374	4.841567	1.188550
125	6	0	-5.111147	3.367845	0.590065
126	6	0	-3.778107	5.811664	0.318644
127	6	0	-5.615547	4.329237	-0.282147
128	6	0	-4.939323	5.540556	-0.404060
129	7	0	-5.462858	6.558028	-1.328286
130	8	0	-6.478087	6.280272	-1.968302
131	8	0	-4.856315	7.625226	-1.408057
132	6	0	0.628876	2.217067	0.349413
133	7	0	1.063799	2.737728	-0.597201
134	1	0	2.310320	2.175311	3.306886
135	1	0	-2.172927	4.099359	4.429767
136	1	0	2.036798	3.701882	5.259801
137	1	0	-0.181934	4.660769	5.798952
138	1	0	-3.669407	2.843937	3.335811
139	1	0	-3.957599	1.610565	2.113005

140	1	0	-2.381442	5.039700	1.750383
141	1	0	-5.613141	2.409437	0.687790
142	1	0	-3.278919	6.764506	0.192200
143	1	0	-6.509085	4.156315	-0.869274

S-CO-inpl-8

Method: B3LYP/6-31+G(d)
SCF Done: E(RB3LYP) = -4906.58155457 A.U. after 8 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61411300 A.U. after 14 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-2.368158	-1.069745	3.702327
2	6	0	-1.775889	-0.662059	2.166115
3	7	0	-2.595884	-0.334755	1.086968
4	7	0	-0.473247	-0.648137	1.829585
5	6	0	-4.034133	-0.152710	1.240208
6	6	0	-4.798137	-0.983689	0.172462
7	6	0	0.619518	-0.982739	2.743616
8	6	0	-4.461839	1.319447	1.352209
9	6	0	1.862164	-0.061564	2.510239
10	6	0	0.989608	-2.462655	2.722150
11	6	0	1.682276	1.339045	3.092647
12	7	0	2.260877	-0.077438	1.094585
13	16	0	3.818986	0.091033	0.604216
14	8	0	4.673548	0.228969	1.788562
15	6	0	-4.603340	2.251166	0.266366
16	6	0	4.234699	-1.497763	-0.156595
17	6	0	-4.720735	1.780802	2.628384
18	6	0	-6.328240	-0.712194	0.129701
19	8	0	3.864432	1.078225	-0.483991
20	7	0	-4.616660	-2.516073	0.421182
21	6	0	-5.055251	3.576120	0.604864
22	6	0	-5.128654	3.118471	2.845195
23	6	0	-4.345342	1.963198	-1.094153
24	6	0	-5.448594	-3.248034	-0.639846
25	6	0	-5.129502	-2.929580	1.795709
26	6	0	-7.122230	-1.926069	0.640018
27	6	0	-6.960468	-3.119869	-0.333727
28	6	0	-5.251523	4.522487	-0.430785
29	7	0	-5.310430	3.991138	1.879331
30	6	0	-6.539649	-2.343191	2.002206
31	6	0	-7.750754	-2.995913	-1.611028
32	6	0	-4.543252	2.914895	-2.083184
33	6	0	-8.683653	-3.863673	-2.003319
34	8	0	-4.258871	2.518689	-3.355125
35	6	0	-5.011176	4.210687	-1.748938
36	6	0	-4.398116	3.452088	-4.415142
37	6	0	5.450913	-2.092298	0.169971
38	6	0	3.353775	-2.090043	-1.060706
39	6	0	5.794864	-3.306970	-0.426447
40	6	0	1.221915	-3.119247	3.936936
41	6	0	3.705440	-3.316893	-1.629133
42	6	0	7.135148	-3.932839	-0.136981

43	6	0	4.922666	-3.926532	-1.321218
44	6	0	2.718303	-4.011911	-2.525946
45	9	0	1.623238	-4.430065	-1.827669
46	9	0	3.237448	-5.099842	-3.125774
47	9	0	2.246393	-3.200360	-3.501478
48	9	0	8.077189	-3.503885	-1.006938
49	9	0	7.088461	-5.279976	-0.240892
50	9	0	7.571689	-3.631832	1.102527
51	6	0	0.737025	2.249674	2.600406
52	6	0	1.140424	-3.181916	1.530561
53	6	0	1.604793	-4.460586	3.964494
54	6	0	1.522153	-4.524372	1.554882
55	6	0	1.757146	-5.167683	2.771203
56	6	0	2.484303	1.722754	4.174750
57	6	0	0.595619	3.507381	3.187775
58	6	0	2.344923	2.981530	4.761196
59	6	0	1.396216	3.878119	4.270054
60	6	0	-3.166102	-3.013889	0.258508
61	8	0	-2.785997	-2.774319	-0.966568
62	8	0	-2.643117	-3.627241	1.142701
63	6	0	-1.443961	-3.260928	-1.380715
64	6	0	-1.565202	-3.780966	-2.796411
65	1	0	-2.148417	0.299937	0.417262
66	1	0	-0.254097	-0.544870	0.822559
67	1	0	-4.259829	-0.574745	2.221708
68	1	0	-4.342532	-0.847533	-0.807342
69	1	0	0.258434	-0.747911	3.747244
70	1	0	2.677579	-0.533194	3.064218
71	1	0	1.569616	-0.015469	0.319699
72	1	0	-4.594113	1.119997	3.480569
73	1	0	-6.626946	-0.440401	-0.886930
74	1	0	-6.552089	0.152534	0.758449
75	1	0	-5.321849	3.462430	3.860518
76	1	0	-3.936061	1.014193	-1.415078
77	1	0	-5.177398	-2.804487	-1.598041
78	1	0	-5.119205	-4.289661	-0.640196
79	1	0	-5.126948	-4.020609	1.790595
80	1	0	-4.399797	-2.603391	2.538182
81	1	0	-8.180347	-1.666391	0.737649
82	1	0	-7.297239	-4.027147	0.182876
83	1	0	-5.598445	5.508967	-0.140140
84	1	0	-7.172231	-3.095958	2.484088
85	1	0	-6.500677	-1.479265	2.674161
86	1	0	-7.525685	-2.133271	-2.239282
87	1	0	-9.234423	-3.727529	-2.929453
88	1	0	-8.935429	-4.742690	-1.413231
89	1	0	-5.172774	4.957053	-2.518106
90	1	0	-4.095352	2.919341	-5.318026
91	1	0	-3.747104	4.325133	-4.275884
92	1	0	-5.436835	3.790598	-4.526115
93	1	0	6.105211	-1.617190	0.892130
94	1	0	2.397807	-1.619999	-1.288568
95	1	0	1.091015	-2.577144	4.870603
96	1	0	5.183505	-4.880208	-1.763471
97	1	0	0.104218	1.985455	1.760343
98	1	0	0.960979	-2.692558	0.579254
99	1	0	1.775737	-4.953232	4.918195
100	1	0	1.642695	-5.061543	0.618692
101	1	0	2.054294	-6.213119	2.788789
102	1	0	3.237930	1.035126	4.550672
103	1	0	-0.146018	4.199287	2.796571

104	1	0	2.982718	3.261461	5.595551
105	1	0	1.284931	4.860080	4.722600
106	1	0	-1.142443	-4.027285	-0.665565
107	1	0	-0.782087	-2.394917	-1.297476
108	1	0	-0.568167	-4.076324	-3.136684
109	1	0	-1.944754	-3.001741	-3.462043
110	1	0	-2.221055	-4.656936	-2.850396
111	6	0	0.946918	0.893878	-2.924355
112	6	0	1.096310	2.283832	-2.852556
113	6	0	-0.038358	0.432979	-1.844685
114	6	0	1.641561	0.167136	-3.876941
115	6	0	1.924163	2.979584	-3.723735
116	7	0	0.302472	2.803945	-1.797705
117	8	0	0.390134	-0.474808	-0.922520
118	6	0	2.488856	0.848255	-4.762204
119	6	0	2.621328	2.235072	-4.685005
120	6	0	0.183563	4.205322	-1.431777
121	6	0	-0.411024	1.809971	-1.185754
122	6	0	1.462308	4.860173	-0.934079
123	8	0	-1.189245	1.951585	-0.246784
124	6	0	1.569043	6.257377	-1.011405
125	6	0	2.513084	4.122360	-0.377841
126	6	0	2.696245	6.914992	-0.532990
127	6	0	3.654945	4.765710	0.096482
128	6	0	3.728078	6.153826	0.015693
129	7	0	4.928384	6.843036	0.512427
130	8	0	5.830787	6.155272	0.987022
131	8	0	4.960134	8.072233	0.424030
132	6	0	-1.304196	-0.027373	-2.522088
133	7	0	-2.298885	-0.421091	-2.980053
134	1	0	1.536507	-0.911644	-3.929870
135	1	0	2.047065	4.055316	-3.657597
136	1	0	3.046615	0.292713	-5.510406
137	1	0	3.282583	2.752739	-5.374220
138	1	0	-0.586301	4.237122	-0.652781
139	1	0	-0.202560	4.765817	-2.293567
140	1	0	0.760376	6.837874	-1.449732
141	1	0	2.470039	3.040533	-0.325196
142	1	0	2.793897	7.992228	-0.583532
143	1	0	4.475776	4.199143	0.518382

S-CO-inpl-9

Method: B3LYP/6-31+G(d)
SCF Done: E(RB+HF-LYP) = -4906.57991836 A.U. after 10 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61165142 A.U. after 16 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	0.503295	2.507738	3.517126
2	6	0	0.380916	1.576956	2.102962
3	7	0	1.339963	1.582048	1.089125
4	7	0	-0.656691	0.770787	1.816672
5	6	0	2.621810	2.259013	1.252601
6	6	0	2.911283	3.194940	0.047687

7	6	0	-1.810203	0.571550	2.696415
8	6	0	3.785251	1.326022	1.632267
9	6	0	-2.323429	-0.904458	2.658108
10	6	0	-2.942310	1.562065	2.436467
11	6	0	-1.461092	-1.891935	3.450505
12	7	0	-2.583988	-1.331094	1.275667
13	16	0	-3.833718	-2.307491	0.846879
14	8	0	-4.605280	-2.631723	2.054136
15	6	0	4.589313	0.544394	0.731429
16	6	0	-4.894621	-1.261788	-0.181908
17	6	0	4.093724	1.270712	2.978628
18	6	0	4.307071	3.877716	0.114005
19	8	0	-3.333534	-3.361147	-0.041352
20	7	0	1.852264	4.337513	-0.047407
21	6	0	5.711834	-0.151399	1.309792
22	6	0	5.181395	0.493851	3.440445
23	6	0	4.382511	0.427954	-0.664260
24	6	0	2.260815	5.237583	-1.221505
25	6	0	1.821626	5.186902	1.217350
26	6	0	4.175806	5.390093	0.357413
27	6	0	3.512097	6.074945	-0.863030
28	6	0	6.599070	-0.856723	0.459170
29	7	0	5.986751	-0.175672	2.645619
30	6	0	3.261029	5.605387	1.576225
31	6	0	4.412847	6.222676	-2.062464
32	6	0	5.266175	-0.279837	-1.467303
33	6	0	4.732874	7.389796	-2.621529
34	8	0	4.968686	-0.321515	-2.793178
35	6	0	6.402439	-0.912560	-0.900629
36	6	0	5.823802	-1.049703	-3.666543
37	6	0	-6.268993	-1.279626	0.037748
38	6	0	-4.329437	-0.483601	-1.192285
39	6	0	-7.097699	-0.504786	-0.777424
40	6	0	-3.680893	2.043495	3.524815
41	6	0	-5.172201	0.297930	-1.984920
42	6	0	-8.592439	-0.561000	-0.594418
43	6	0	-6.554402	0.288932	-1.786860
44	6	0	-4.565311	1.224424	-3.001531
45	9	0	-4.009425	2.320293	-2.408488
46	9	0	-5.467868	1.680726	-3.891100
47	9	0	-3.565818	0.637562	-3.703402
48	9	0	-9.144192	-1.551303	-1.332166
49	9	0	-9.186016	0.591892	-0.977272
50	9	0	-8.930984	-0.788922	0.690817
51	6	0	-0.066497	-1.973597	3.325640
52	6	0	-3.297800	1.975312	1.148244
53	6	0	-4.755729	2.911185	3.332672
54	6	0	-4.372603	2.844569	0.952309
55	6	0	-5.105981	3.313692	2.042700
56	6	0	-2.102871	-2.755724	4.348987
57	6	0	0.661328	-2.886226	4.092590
58	6	0	-1.376195	-3.673193	5.109416
59	6	0	0.011675	-3.739052	4.987238
60	6	0	0.425075	3.847253	-0.357680
61	8	0	0.445081	3.219237	-1.502563
62	8	0	-0.486848	4.184432	0.340215
63	6	0	-0.862305	2.784314	-2.063075
64	6	0	-0.779878	2.924249	-3.566995
65	6	0	-0.698385	-2.266192	-2.275436
66	6	0	-0.224648	-3.467606	-1.733342
67	6	0	-0.127686	-1.092925	-1.475643

68	6	0	-1.583880	-2.281831	-3.339976
69	6	0	-0.609516	-4.700233	-2.243828
70	7	0	0.654958	-3.194971	-0.654701
71	8	0	-1.026449	-0.319185	-0.793828
72	6	0	-1.990033	-3.516396	-3.865807
73	6	0	-1.505467	-4.705568	-3.321751
74	6	0	1.306730	-4.172442	0.210040
75	6	0	0.816173	-1.848896	-0.477368
76	6	0	2.785231	-4.324311	-0.100306
77	8	0	1.523891	-1.317139	0.372347
78	6	0	3.220346	-4.528128	-1.418577
79	6	0	3.733116	-4.230263	0.924835
80	6	0	4.575848	-4.593961	-1.716467
81	6	0	5.095121	-4.307889	0.648332
82	6	0	5.496151	-4.468165	-0.675661
83	7	0	6.926984	-4.446816	-0.991905
84	8	0	7.727152	-4.473426	-0.057496
85	8	0	7.251295	-4.380538	-2.182028
86	6	0	0.765325	-0.260043	-2.349125
87	7	0	1.448526	0.444191	-2.974028
88	1	0	1.381097	0.698394	0.570257
89	1	0	-0.696222	0.382555	0.854898
90	1	0	2.485800	2.889450	2.133896
91	1	0	2.771525	2.663196	-0.891413
92	1	0	-1.450879	0.740960	3.714273
93	1	0	-3.296981	-0.879598	3.153187
94	1	0	-1.913016	-1.137558	0.505236
95	1	0	3.495286	1.825810	3.694860
96	1	0	4.864989	3.668418	-0.803244
97	1	0	4.880141	3.433018	0.930716
98	1	0	5.399443	0.455054	4.507094
99	1	0	3.505473	0.834115	-1.152780
100	1	0	2.433153	4.572964	-2.068205
101	1	0	1.399398	5.868727	-1.452214
102	1	0	1.182902	6.039012	0.980808
103	1	0	1.323279	4.608277	1.996886
104	1	0	5.162974	5.825960	0.536721
105	1	0	3.193243	7.079018	-0.557184
106	1	0	7.441456	-1.359575	0.923427
107	1	0	3.261682	6.656551	1.882990
108	1	0	3.626547	5.022894	2.428794
109	1	0	4.816049	5.300909	-2.483472
110	1	0	5.394815	7.446920	-3.480703
111	1	0	4.348442	8.334004	-2.240911
112	1	0	7.102105	-1.456960	-1.524253
113	1	0	5.358121	-0.986033	-4.651290
114	1	0	5.911151	-2.101797	-3.369851
115	1	0	6.826951	-0.605467	-3.710417
116	1	0	-6.677363	-1.877674	0.844611
117	1	0	-3.249338	-0.459588	-1.332673
118	1	0	-3.404195	1.743573	4.533277
119	1	0	-7.199698	0.902550	-2.403760
120	1	0	0.460523	-1.330829	2.631067
121	1	0	-2.732102	1.620881	0.293301
122	1	0	-5.313199	3.278202	4.190574
123	1	0	-4.636644	3.146506	-0.057010
124	1	0	-5.942277	3.990924	1.889410
125	1	0	-3.185100	-2.720256	4.437633
126	1	0	1.744624	-2.916750	3.998262
127	1	0	-1.896798	-4.333487	5.798202
128	1	0	0.582155	-4.445850	5.584482

129	1	0	-1.629893	3.417968	-1.617620
130	1	0	-0.997882	1.751409	-1.731327
131	1	0	-1.711623	2.542572	-3.995293
132	1	0	0.050536	2.335889	-3.964442
133	1	0	-0.664731	3.971124	-3.868900
134	1	0	-1.966330	-1.352237	-3.750737
135	1	0	-0.247514	-5.634753	-1.826544
136	1	0	-2.686950	-3.546777	-4.698104
137	1	0	-1.827919	-5.657916	-3.733099
138	1	0	0.778535	-5.123777	0.094642
139	1	0	1.170082	-3.850078	1.246027
140	1	0	2.493766	-4.607297	-2.222075
141	1	0	3.404387	-4.062624	1.946279
142	1	0	4.928326	-4.730362	-2.731281
143	1	0	5.840033	-4.207716	1.427741

S-OEt-inpl-10

Method: B3LYP/6-31+G(d)
SCF Done: E(RB3LYP) = -4906.57711533 A.U. after 6 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.60957836 A.U. after 16 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	2.671866	-1.982969	-3.096852
2	6	0	1.963062	-0.977171	-1.902876
3	7	0	2.709204	-0.155676	-1.101876
4	7	0	0.647308	-0.932775	-1.636202
5	6	0	4.159523	-0.186700	-1.039629
6	6	0	4.662465	-0.823027	0.307059
7	6	0	-0.382369	-1.623287	-2.406568
8	6	0	4.758082	1.175478	-1.407386
9	6	0	-1.615529	-0.686191	-2.636692
10	6	0	-0.775934	-2.976017	-1.817032
11	6	0	-1.275609	0.466252	-3.577929
12	7	0	-2.183758	-0.256915	-1.354559
13	16	0	-3.780952	0.045770	-1.143935
14	8	0	-4.458244	-0.088469	-2.437415
15	6	0	4.699235	2.352357	-0.586029
16	6	0	-4.392323	-1.293852	-0.092391
17	6	0	5.350361	1.291346	-2.648385
18	6	0	6.041163	-0.325570	0.832600
19	8	0	-3.917457	1.264035	-0.332470
20	7	0	4.775491	-2.389316	0.210568
21	6	0	5.286428	3.551713	-1.119721
22	6	0	5.886829	2.530285	-3.078079
23	6	0	4.124848	2.398123	0.703551
24	6	0	5.256711	-2.882452	1.587945
25	6	0	5.790866	-2.820853	-0.840327
26	6	0	7.104225	-1.432092	0.782788
27	6	0	6.754281	-2.554571	1.791267
28	6	0	5.266539	4.730888	-0.335445
29	7	0	5.870948	3.625203	-2.351149
30	6	0	7.094820	-2.026022	-0.636914
31	6	0	7.027777	-2.203761	3.231364

32	6	0	4.111207	3.571724	1.440118
33	6	0	7.870900	-2.872567	4.018052
34	8	0	3.505891	3.501432	2.660089
35	6	0	4.696417	4.752527	0.917456
36	6	0	3.500757	4.651887	3.491806
37	6	0	-5.553330	-1.961533	-0.472063
38	6	0	-3.725125	-1.607764	1.091658
39	6	0	-6.062674	-2.962777	0.357928
40	6	0	-1.059617	-4.032478	-2.693955
41	6	0	-4.246173	-2.615221	1.906158
42	6	0	-7.346625	-3.658905	-0.012738
43	6	0	-5.413892	-3.291023	1.547560
44	6	0	-3.546426	-2.953622	3.195892
45	9	0	-2.201444	-3.032180	3.031466
46	9	0	-3.956420	-4.134091	3.706049
47	9	0	-3.760687	-2.014349	4.147047
48	9	0	-8.426142	-2.982245	0.439448
49	9	0	-7.411660	-4.901969	0.515363
50	9	0	-7.483848	-3.775206	-1.349899
51	6	0	-0.619468	1.622121	-3.136968
52	6	0	-0.880257	-3.197244	-0.436125
53	6	0	-1.442336	-5.284894	-2.210235
54	6	0	-1.267537	-4.449909	0.047256
55	6	0	-1.548112	-5.496882	-0.833820
56	6	0	-1.600271	0.351835	-4.934635
57	6	0	-0.292255	2.635600	-4.038200
58	6	0	-1.274080	1.364391	-5.837412
59	6	0	-0.616516	2.510815	-5.390449
60	6	0	3.411767	-3.075962	0.047414
61	8	0	3.583545	-4.216558	-0.579106
62	8	0	2.443826	-2.625713	0.581089
63	6	0	2.351761	-4.985478	-0.858147
64	6	0	2.776934	-6.293616	-1.484806
65	1	0	2.208128	0.582646	-0.599283
66	1	0	0.360434	-0.560625	-0.705674
67	1	0	4.446111	-0.848573	-1.859185
68	1	0	3.891184	-0.687462	1.065251
69	1	0	0.042107	-1.803476	-3.396640
70	1	0	-2.370241	-1.303996	-3.131942
71	1	0	-1.586059	-0.033616	-0.532960
72	1	0	5.387473	0.438008	-3.319974
73	1	0	5.919635	0.061088	1.848575
74	1	0	6.380557	0.511804	0.222502
75	1	0	6.346678	2.602466	-4.062999
76	1	0	3.646954	1.533305	1.147530
77	1	0	4.611503	-2.388014	2.317620
78	1	0	5.067059	-3.957225	1.622689
79	1	0	5.935224	-3.890136	-0.690818
80	1	0	5.328361	-2.683698	-1.818325
81	1	0	8.088646	-1.016514	1.016837
82	1	0	7.351450	-3.440342	1.540498
83	1	0	5.718198	5.620348	-0.762889
84	1	0	7.947688	-2.694887	-0.793480
85	1	0	7.174458	-1.219873	-1.374141
86	1	0	6.486645	-1.346233	3.632153
87	1	0	8.043099	-2.576834	5.048797
88	1	0	8.423228	-3.740452	3.662993
89	1	0	4.694924	5.671951	1.491705
90	1	0	2.984685	4.353141	4.405719
91	1	0	2.959784	5.487392	3.027955
92	1	0	4.519346	4.977178	3.740860

93	1	0	-6.037046	-1.706534	-1.408226
94	1	0	-2.798534	-1.101709	1.353611
95	1	0	-0.971353	-3.874859	-3.766917
96	1	0	-5.804221	-4.078428	2.180582
97	1	0	-0.361746	1.737363	-2.089260
98	1	0	-0.654484	-2.396754	0.263158
99	1	0	-1.657449	-6.090847	-2.907464
100	1	0	-1.360627	-4.597001	1.119733
101	1	0	-1.853039	-6.468247	-0.452120
102	1	0	-2.127540	-0.532653	-5.286295
103	1	0	0.217843	3.526010	-3.679856
104	1	0	-1.543739	1.261308	-6.885342
105	1	0	-0.364868	3.304560	-6.089079
106	1	0	1.751604	-4.371363	-1.530974
107	1	0	1.820618	-5.112057	0.086975
108	1	0	1.878457	-6.877068	-1.710176
109	1	0	3.409174	-6.880460	-0.810150
110	1	0	3.316782	-6.122569	-2.421054
111	6	0	-0.909586	1.133430	2.827674
112	6	0	-1.085120	2.517634	2.715046
113	6	0	0.016235	0.645901	1.710058
114	6	0	-1.563729	0.423478	3.820178
115	6	0	-1.903135	3.225066	3.586518
116	7	0	-0.333221	3.013209	1.619487
117	8	0	-0.500295	-0.237710	0.820108
118	6	0	-2.400058	1.116659	4.707104
119	6	0	-2.560134	2.497969	4.589734
120	6	0	-0.273944	4.397509	1.183366
121	6	0	0.370230	2.008201	1.010851
122	6	0	-1.588032	4.969234	0.675999
123	8	0	1.099323	2.135565	0.030739
124	6	0	-2.559327	4.162582	0.072155
125	6	0	-1.813635	6.349458	0.785632
126	6	0	-3.739464	4.719131	-0.416562
127	6	0	-2.981194	6.923027	0.294362
128	6	0	-3.931286	6.093917	-0.301039
129	7	0	-5.173511	6.694579	-0.810437
130	8	0	-5.311203	7.913716	-0.688912
131	8	0	-6.002410	5.947954	-1.327597
132	6	0	1.301626	0.141469	2.320888
133	7	0	2.311734	-0.266320	2.729968
134	1	0	-1.437270	-0.651441	3.900383
135	1	0	-2.051395	4.295384	3.488430
136	1	0	-2.931215	0.572062	5.481886
137	1	0	-3.213847	3.025239	5.279036
138	1	0	0.480125	4.417874	0.388498
139	1	0	0.102056	5.016465	2.008719
140	1	0	-2.425716	3.089954	-0.010414
141	1	0	-1.068128	6.983489	1.260316
142	1	0	-4.495983	4.092793	-0.872693
143	1	0	-3.171350	7.986338	0.370527

S-OEt-inpl-11

Method: B3LYP/6-31+G(d)
SCF Done: E(RB3LYP) = -4906.57751403 A.U. after 7 cycles
Method: B3LYP/6-31G(d) SCRF=(Solvent=Chloroform)
SCF Done: E(RB3LYP) = -4906.61011647 A.U. after 14 cycles

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.981507	-3.276064	2.936855
2	6	0	-0.812040	-2.148549	1.668616
3	7	0	-1.837732	-1.879491	0.751310
4	7	0	0.320217	-1.466502	1.435036
5	6	0	-3.203179	-2.322476	1.051964
6	6	0	-3.895822	-3.142508	-0.076318
7	6	0	1.502564	-1.556456	2.303199
8	6	0	-4.139854	-1.215578	1.546281
9	6	0	2.104475	-0.154141	2.634610
10	6	0	2.553824	-2.538100	1.797631
11	6	0	1.238924	0.644417	3.612051
12	7	0	2.456125	0.575829	1.411182
13	16	0	3.701558	1.644893	1.352085
14	8	0	4.322478	1.701553	2.681558
15	6	0	-4.734685	-0.202442	0.715888
16	6	0	4.920185	0.883596	0.248151
17	6	0	-4.470476	-1.223974	2.887040
18	6	0	-5.066200	-4.001302	0.475399
19	8	0	3.253866	2.866053	0.673995
20	7	0	-2.923692	-4.087036	-0.816825
21	6	0	-5.695352	0.665747	1.346082
22	6	0	-5.391998	-0.283940	3.407740
23	6	0	-4.453285	-0.004465	-0.657475
24	6	0	-3.741033	-4.851498	-1.866425
25	6	0	-2.278939	-5.101648	0.115654
26	6	0	-4.760049	-5.500595	0.315581
27	6	0	-4.686846	-5.874927	-1.187900
28	6	0	-6.366100	1.635724	0.560008
29	7	0	-6.007719	0.616016	2.673255
30	6	0	-3.384774	-5.792352	0.941018
31	6	0	-6.020404	-5.915536	-1.889246
32	6	0	-5.124977	0.958393	-1.397510
33	6	0	-6.531464	-7.002814	-2.466923
34	8	0	-4.779311	1.044291	-2.708970
35	6	0	-6.107336	1.779155	-0.784383
36	6	0	-5.346041	2.071397	-3.511549
37	6	0	6.262556	0.925668	0.618539
38	6	0	4.519088	0.306651	-0.955976
39	6	0	7.222205	0.385274	-0.239061
40	6	0	3.127321	-3.429692	2.713815
41	6	0	5.491942	-0.243223	-1.795058
42	6	0	8.683620	0.476393	0.117018
43	6	0	6.841991	-0.202322	-1.446123
44	6	0	5.057114	-0.892526	-3.081729
45	9	0	4.087406	-1.822056	-2.864604
46	9	0	6.071152	-1.516618	-3.712997
47	9	0	4.535552	0.002456	-3.952596
48	9	0	9.240023	1.610208	-0.366732
49	9	0	9.387904	-0.556730	-0.397656
50	9	0	8.875695	0.478387	1.452028
51	6	0	-0.071465	1.048180	3.316515
52	6	0	2.997866	-2.559706	0.469315
53	6	0	4.128898	-4.317814	2.320690
54	6	0	4.002057	-3.447640	0.074982
55	6	0	4.570811	-4.327832	0.997320
56	6	0	1.771823	0.970595	4.865237

57	6	0	-0.828170	1.745551	4.259262
58	6	0	1.018246	1.673649	5.806878
59	6	0	-0.287659	2.060681	5.507836
60	6	0	-1.945868	-3.237157	-1.635288
61	8	0	-0.758839	-3.776011	-1.628435
62	8	0	-2.385355	-2.314131	-2.260841
63	6	0	0.278842	-3.076321	-2.440059
64	6	0	1.400268	-4.062229	-2.669571
65	1	0	-1.754447	-0.952571	0.316142
66	1	0	0.409973	-0.921101	0.552393
67	1	0	-3.074754	-3.002692	1.897116
68	1	0	-4.245440	-2.485537	-0.867235
69	1	0	1.135990	-1.939179	3.256807
70	1	0	3.042198	-0.369949	3.154081
71	1	0	1.884943	0.498709	0.540781
72	1	0	-4.023991	-1.956133	3.553705
73	1	0	-5.998383	-3.735155	-0.032176
74	1	0	-5.214343	-3.767527	1.533640
75	1	0	-5.636666	-0.302115	4.469020
76	1	0	-3.677528	-0.555982	-1.174334
77	1	0	-4.280982	-4.093812	-2.436462
78	1	0	-3.020618	-5.334062	-2.531277
79	1	0	-1.735105	-5.793422	-0.528081
80	1	0	-1.563139	-4.579268	0.749696
81	1	0	-5.537028	-6.095423	0.804634
82	1	0	-4.237460	-6.872620	-1.262224
83	1	0	-7.095051	2.263850	1.061982
84	1	0	-3.194554	-6.870272	0.967968
85	1	0	-3.347266	-5.431511	1.974257
86	1	0	-6.585466	-4.982987	-1.913243
87	1	0	-7.503000	-6.986516	-2.952087
88	1	0	-6.000108	-7.952392	-2.475609
89	1	0	-6.647943	2.520482	-1.361897
90	1	0	-4.884587	1.962750	-4.493985
91	1	0	-5.116637	3.067831	-3.113176
92	1	0	-6.433936	1.959001	-3.606955
93	1	0	6.543768	1.359225	1.571556
94	1	0	3.465165	0.254721	-1.220910
95	1	0	2.779689	-3.432470	3.744229
96	1	0	7.588646	-0.638779	-2.098152
97	1	0	-0.511154	0.819427	2.352428
98	1	0	2.565226	-1.879950	-0.258266
99	1	0	4.558370	-5.003059	3.046940
100	1	0	4.346438	-3.436916	-0.954585
101	1	0	5.353107	-5.015576	0.686565
102	1	0	2.795187	0.688071	5.097759
103	1	0	-1.847696	2.037031	4.017896
104	1	0	1.455279	1.920953	6.770860
105	1	0	-0.879258	2.605480	6.239108
106	1	0	0.583916	-2.198365	-1.863498
107	1	0	-0.202751	-2.741236	-3.359707
108	1	0	2.194132	-3.554932	-3.227363
109	1	0	1.065053	-4.926087	-3.253346
110	1	0	1.823748	-4.408122	-1.722509
111	6	0	1.167271	2.137283	-2.070067
112	6	0	0.751102	3.274156	-1.372472
113	6	0	0.371496	0.923667	-1.578124
114	6	0	2.159287	2.231979	-3.032402
115	6	0	1.306881	4.523515	-1.609248
116	7	0	-0.275510	2.930387	-0.455737
117	8	0	1.073129	-0.049276	-0.908895

118	6	0	2.744722	3.481724	-3.277331
119	6	0	2.320262	4.608720	-2.572563
120	6	0	-0.725240	3.786430	0.639346
121	6	0	-0.614705	1.610450	-0.569144
122	6	0	-1.843408	4.739270	0.261048
123	8	0	-1.465284	1.032960	0.108775
124	6	0	-1.670957	6.125824	0.348384
125	6	0	-3.084057	4.228317	-0.150422
126	6	0	-2.707209	6.998945	0.022288
127	6	0	-4.128678	5.084269	-0.477339
128	6	0	-3.923056	6.461330	-0.390725
129	7	0	-5.025028	7.368892	-0.741299
130	8	0	-6.082897	6.864844	-1.121963
131	8	0	-4.827638	8.579213	-0.636782
132	6	0	-0.379171	0.380777	-2.753024
133	7	0	-0.882388	-0.059075	-3.704110
134	1	0	2.481129	1.353061	-3.581957
135	1	0	0.975691	5.407445	-1.074997
136	1	0	3.530429	3.572595	-4.021632
137	1	0	2.778306	5.573464	-2.771961
138	1	0	0.145863	4.332099	1.014569
139	1	0	-1.062870	3.116440	1.434888
140	1	0	-0.718339	6.530847	0.680031
141	1	0	-3.229720	3.153203	-0.200435
142	1	0	-2.588156	8.073734	0.081756
143	1	0	-5.096263	4.706322	-0.781571

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Chapter 3

Enantioselective Cyano-Ethoxycarbonylation of α-Ketoesters Induced by Brønsted Acid–Lewis Base Cooperative Catalysts

Abstract: The highly enantioselective cyano-alkoxycarbonylation of α-oxoesters with alkyl cyanoformates is promoted by a new chiral Brønsted acid–Lewis base cooperative organocatalyst. The present catalysis can be performed at room temperature under nitrogen or air.

3-1. Introduction

Optically active cyanohydrins serve as highly versatile synthetic building blocks in biologically active compounds. However, cyanohydrins are not very stable and readily decompose under basic conditions. In particular, it is difficult to develop the catalytic enantioselective addition of cyanides to ketones due to the rapid reversibility of the reaction. Thus, procedures that allow for direct access to *O*-protected enantioenriched cyanohydrins are needed to avoid the reversibility of the cyanide addition and a decrease in enantioselectivity.[1]

Enantioselective cyano-alkoxycarbonylation is one of the most powerful methods for preparing *O*-protected non-racemic cyanohydrins because alkyl cyanoformate is an easy-to-handle and user-friendly cyanide source.[2-8] There have been numerous successful examples of the catalytic cyano-alkoxycarbonylation reaction of aldehydes since the report by Shibasaki and co-workers in 2002.[2,3] In sharp contrast, there are a few examples of the use of ketones.[4,5,7] The first success with unconjugated ketones was achieved by Deng and co-workers in 2001.[4] They used modified cinchona alkaloids as chiral Lewis base catalysts. In 2014, we developed the enantioselective cyano-alkoxycarbonylation of isatins catalyzed by chiral β-aminothiourea **1** as an acid–base cooperative catalyst (Figure 3.1 and Scheme 3.1).[5]

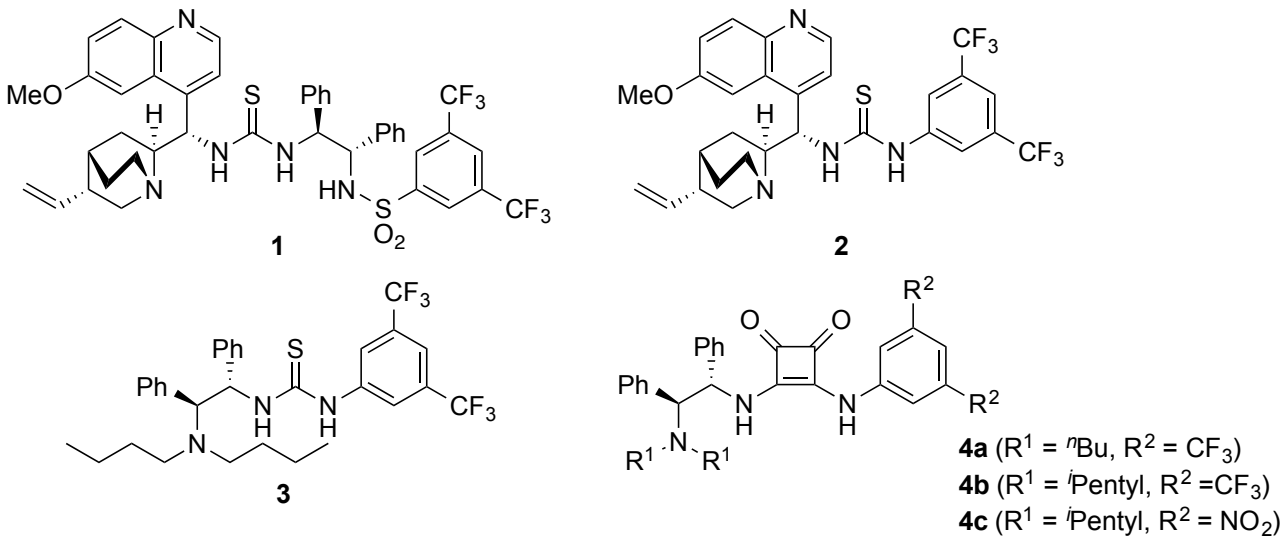
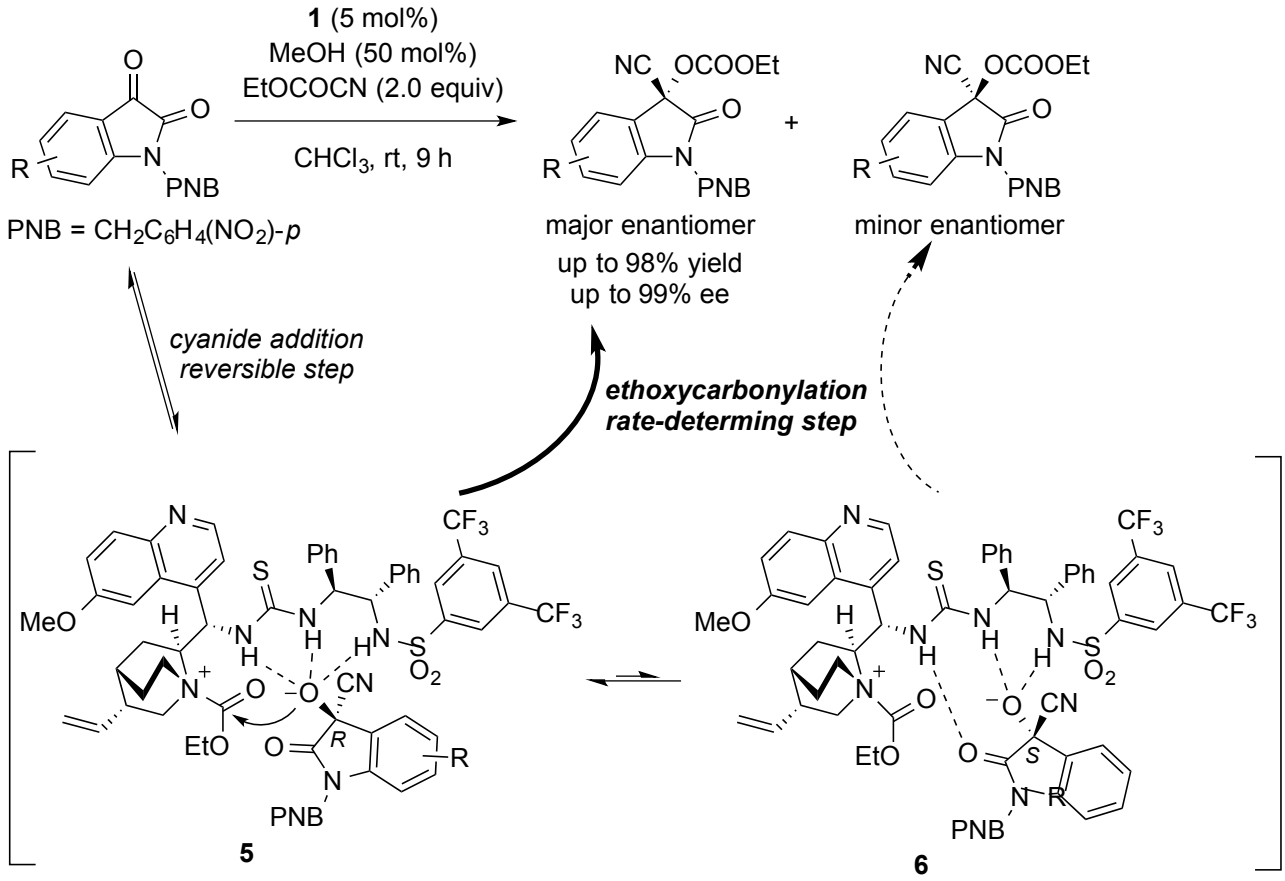


Figure 3.1 Brønsted acid–Lewis base cooperative organocatalysts.

Scheme 3.1 Enantioselective Cyano-Ethoxycarbonylation of Isatins



As shown in Scheme 3.1, catalyst **1** initially activates ethyl cyanoformate as an ammonium oxyanion intermediate, which reacts with *N*-protected isatins to generate a diastereomeric mixture of **5** and **6**. The first step is in equilibrium. The subsequent alkoxycarbonylation is the rate-determining step, and the final product is obtained with high enantioselectivity through dynamic kinetic resolution of deprotonated cyanohydrin. Mechanistic studies by Deng and co-workers.[4] also support this proposed mechanism.

Tertiary cyanohydrin derivatives derived from α-ketoesters are very valuable as optically active compounds with a multi-functionalized carbon center. To the best of our knowledge, three successful examples have been reported. In 2004, Johnson and co-workers reported tandem enantioselective cyanation/Brook rearrangement/*C*-acylation reactions of benzoylsilanes catalyzed by a chiral (salen)aluminum complex to give α-aryl-α-cyano-α-silyloxyacetates.[6] The enantioselectivity was good to moderate, and aliphatic acylsilanes were unreactive. In 2009, Moberg and co-workers reported the first enantioselective cyano-acetylation of α-ketoesters catalysed by cinchonidine.[7] The substrate was limited to alkyl 2-oxo-2-phenylacetates, and the reaction temperature had to be lowered to –40 or –78 °C to induce higher enantioselectivity. In

2010, Ohkuma and co-workers reported the highly catalytic enantioselective cyanosilylation of α-ketoesters by using a [Ru(phgly)$_2$(binap)]–PhOLi system.[8] The substrate scope was extended to aryl-, heteroaryl-, alkenyl, and alkylacetates. However, the reaction temperature had to be lowered to –50 or –60 °C. Thus, more efficient methods are needed for the enantioselective synthesis of *O*-protected cyanohydrins derived from α-ketoesters.[9] Here we report the highly enantioselective cyano-alkoxycarbonylation of α-ketoesters with alkyl cyanoformates catalyzed by a new chiral Brønsted acid–Lewis base cooperative catalyst **4** at room temperature.

3-2. Result and Discussion

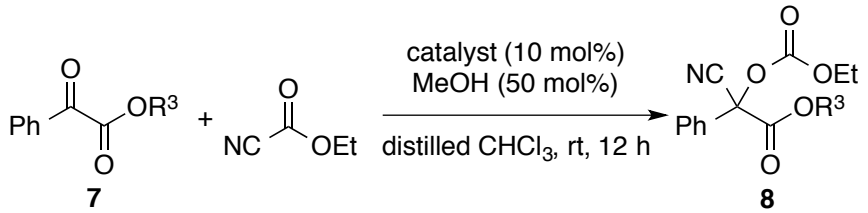
First, **1** was examined as a catalyst for the enantioselective cyano-ethoxycarbonylation of methyl 2-oxo-2-phenylacetate (**7a**) with ethyl cyanoformate in distilled chloroform,[10] based on our previous results (Table 3.1).[5]

The addition of 50 mol% of methanol was slightly effective for improving the catalytic activity. The desired product **8a** was obtained in quantitative yield with 67% ee. Structurally simpler catalyst **2** gave the same results as with **1** (Table 3.1, entry 2). Catalyst **3** gave higher enantioselectivity than **1** and **2** (entry 3). Interestingly, β-aminosquaramide **4**[11] was superior to β-aminothiourea **3** with respect to enantioselectivity (entry 4). Allyl cyanoformate could also be used in place of ethoxycarbonylcyanide (entry 7).

Next, the effect of an alkoxy moiety (R^3) of **7** was explored (entries 6, 8–11, 13–14). When 9-anthrathenylmethyl ester **7g** was used as a substrate, the highest enantioselectivity (97% ee) was observed (entry 14). *p*-Methoxybenzyl (PMB) ester **7e** could also be used (entry 11).

To investigate the substrate scope, several 9-anthrathenylmethyl 2-oxoacetates (**10**) and 4-methoxybenzyl 2-oxoacetates (**12**) were examined in the cyano-ethoxycarbonylation under the optimized conditions (Table 3.2). A series of 2-aromatic, α,β-unsaturated, and aliphatic group-substituted 2-oxoacetates were converted into the desired products with good to high enantioselectivity.[12]

Table 3.1 Screening of Catalysts and the Reaction Conditions[a]



Entry	**7** (R^3)	**catalyst**	**8**, Yield [%][b,c]	Ee [%]
1[e]	**7a** (Me)	**1**	**8a**, >99 [99]	67 [61]
2	**7a** (Me)	**2**	**8a**, [83]	[61]
3	**7a** (Me)	**3**	**8a**, >99 [93]	67 [67]
4	**7a** (Me)	**4a**	**8a**, [92]	[77]
5	**7a** (Me)	**4b**	**8a**, [90]	[79]
6	**7a** (Me)	**4c**	**8a**, 98 [93]	79 [79]
7[f,h]	**7a** (Me)	**4c**	**9a**, 91	81
8[g]	**7b** (Et)	**4c**	**8b**, 88	79
9[g]	**7c** (^{i}Pr)	**4c**	**8c**, 89	71
10[g]	**7d** (Bn)	**4c**	**8d**, 95	82
11[g]	**7e** (p-(MeO)$C_6H_4CH_2$)	**4c**	**8e**, 81	89
12[f,g,h]	**7e** (p-(MeO)$C_6H_4CH_2$)	**4c**	**9b**, 98	89
13[g]	**7f** (p-(NO_2)$C_6H_4CH_2$)	**4c**	**8f**, 72	84
14[g]	**7g** (9-(anthracenyl)CH_2)	**4c**	**8g**, 98	97

[a] Unless otherwise noted, the reaction of **7** (0.2 mmol) with ethyl cyanoformate (2.0 equiv) was carried out in the presence of methanol (50 mol %) and catalyst (10 mol %) in distilled chloroform (0.2 mL) at room temperature for 12 h. [b] Isolated yield. [c] Results without methanol are shown in brackets. [d] Determined by chiral HPLC. [e] Reaction time was 6 h. [f] Reaction was carried out using allyl cyanoformate for 24 h. [g] Distilled chloroform (0.4 mL) was used.

[h]

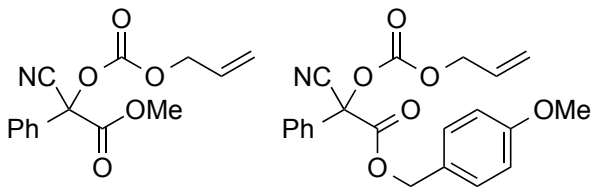
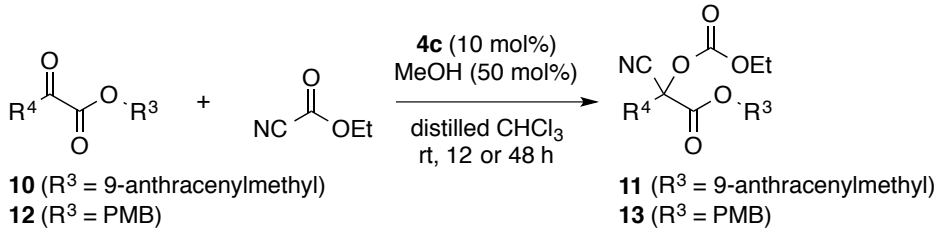


Table 3.2 Substrate Scope[a]

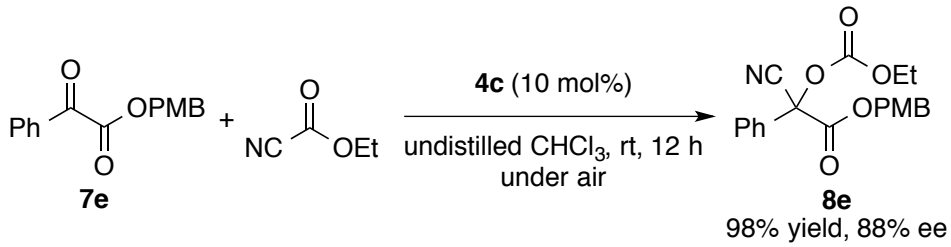


Entry	**ketoester** (R^4)	**product**, Yield [%][b]	Ee [%][c]
1	**10a** (*p*-MeC_6H_6)	**11a**, 96	97
2	**10b** (*p*-ClC_6H_6)	**11b**, 76	97
3	**10c** (*p*-BrC_6H_6)	**11c**, 89	98
4	**10d** (*p*-(MeO)C_6H_6)	**11d**, 80	98
5	**10e** (3,4-(CH_2O_2)-MeC_6H_6)	**11e**, 88	98
6[d]	**10f** ((*E*)-PhCH=CH)	**11f**, 66	97
7[d]	**10g** ((*E*)-*p*-BrC_6H_6CH=CH)	**11g**, 74	99
8[d]	**10h** ((*E*)-*m*-BrC_6H_6CH=CH)	**11h**, 87	97
9[d]	**10i** ((*E*)-*p*-$CF_3C_6H_6$CH=CH)	**11i**, 87	97
10	**12a** (*i*-Bu)	**13a**, 93	73
11	**12b** ($PhCH_2CH_2$)	**13b**, 90	80

[a] Unless otherwise noted, the reaction of **10** or **12** (0.2 mmol) with ethyl cyanoformate (2.0 equiv) was carried out in the presence of methanol (50 mol %) and catalyst (10 mol %) in distilled chloroform (0.4 mL) at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction was carried out in chloroform (0.6 mL) at room temperature for 48 h.

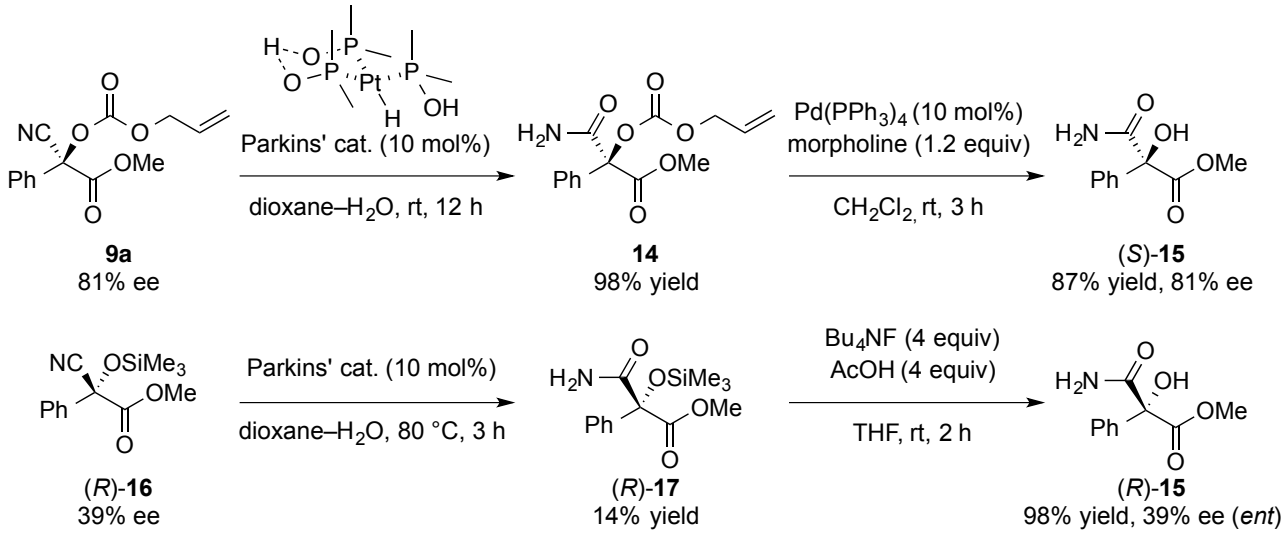
The present organocatalysis smoothly proceeded in commercially available chloroform[10] even under air (Scheme 3.2). The addition of methanol was not required because 0.5–1.0 % ethanol was included as stabilizer in commercially available chloroform.

Scheme 3.2 Reaction using commercially available chloroform under air conditions



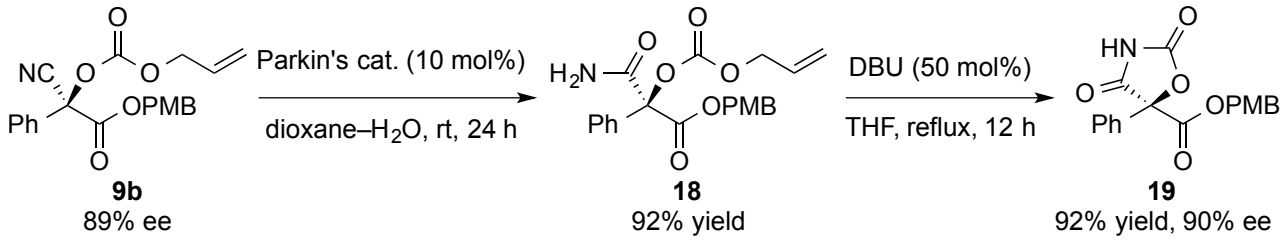
The absolute configuration of product **9a** was determined by transformation to known compound **15** and comparison of their specific rotations, as shown in Scheme 3.3. It was quite difficult to obtain cyano-alkoxycarbonated products chemoselectively. Fortunately, we found that the chemoselective hydrolysis of **9a** promoted by Parkins' catalyst[13] and subsequent deprotection of the alloc group gave **15** in high yield. The authentic sample of (*R*)-**15** was synthesized from (*R*)-**16**, which was prepared by a known method.[8,14] Thus, the absolute configuration of **9a** was determined to be (*S*). Notably, chemoselective hydrolysis of (*R*)-**16** gave (*R*)-**17** in low yield because of the instability of the silyloxy moiety of **16**.

Scheme 3.3 Determination of Absolute Configuration of **9a**



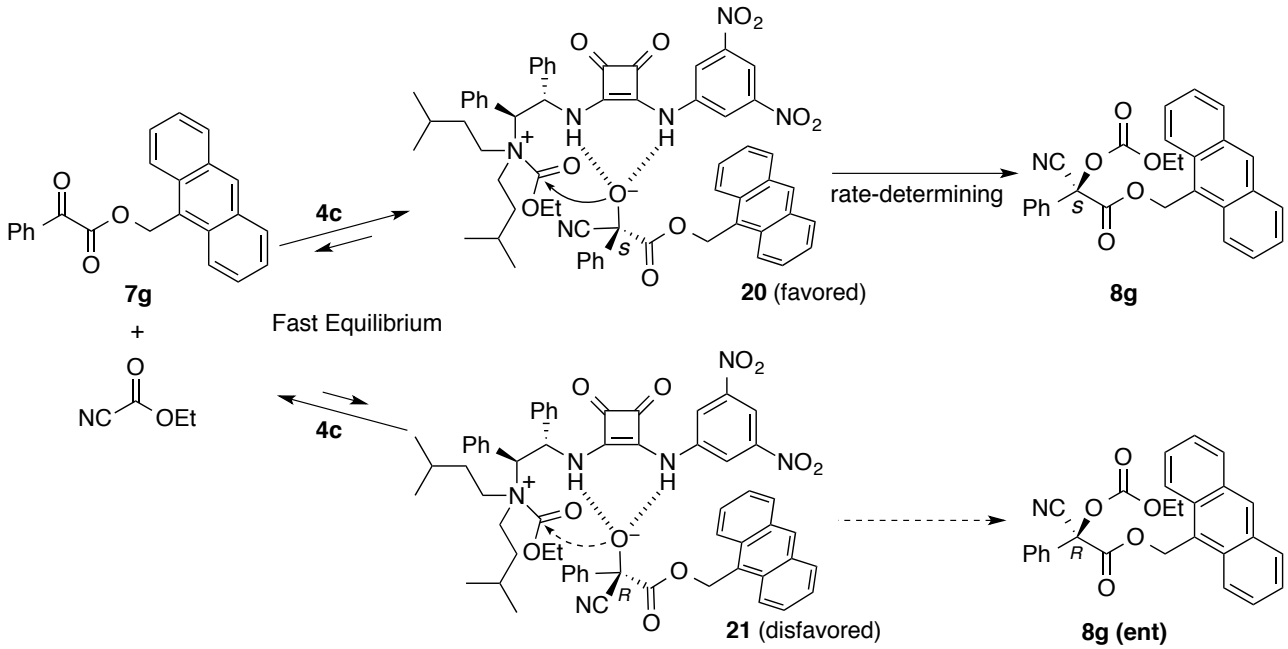
To demonstrate the synthetic utility of cyano-alkoxycarbonated products, we converted primary amide **18** derived from **9b** to 4-methoxybenzyl (*S*)-2,4-dioxo-5-phenyloxazolidine-5-carboxylate (**19**) in high yield in two steps (Scheme 3.4). The skeletons analogous to **19** are included in vinclozoline as a fungicide with antiandrogenic properties, paramethadione as anticonvulsant, etc.

Scheme 3.4 Chemoselective Transformation from **9b** to**19**



Finally, a diastereomeric ion pair, **20** and **21**, of a cyanohydrinated oxyanion of **7** and a quaternary ammonium cation via catalyst **4c** were speculated to exist as shown in Scheme 3.5. The squaramide moiety of **4c** acts as an "oxyanion hole" and contributes to recognition of the enantiomeric oxyanion through multiple hydrogen-bonding interactions.[5,15,16] Enantioselective ethoxycarbonylation may occur through the more-favored ion pair intermediate **20** to give (*S*)-adduct **8** because of the serious steric hindrance between the α-phenyl group of (*R*)-cyanohydrinated oxyanion and the quaternary ammonium moiety in **21**. Moreover, it is expected that π–π attractive interaction between a 3,5-nitrophenyl moiety and a 9-anthrathenylmethyl group (R^3) contribute to the stability of **20** and the transition from **20** to (*S*)-**8**. Further mechanistic study is in progress.[17-19]

Scheme 3.5 Proposed Mechanism for the **4c**-Catalyzed Cyano-alkoxycarbonylation of α-ketoesters



3-3. Conclusion

In conclusion, we have developed a highly enantioselective cyano-alkoxycarbonylation of α-ketoesters with alkyl cyanoformates catalyzed by a new chiral Brønsted acid–Lewis base cooperative organocatalyst. The present catalysis at room temperature is of great advantage for large-scale application.

3-4. References and Notes

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10. Commercially available chloroform includes 0.5–1.0% ethanol as stabilizer. Chloroform was distilled in the presence of P_2O_5 to remove ethanol and water before its use as solvent for the cyano-alkoxycarbonylation.

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12. The cyano-alkoxycarbonylation of aliphatic-group-substituted 2- oxoacetates 12a and 12b gave moderate enantioselectivities (entries 10 and 11, Table 3.2). In contrast, these 9-anthrathenylmethyl esters were not used as substrates because of their instability, although 9-anthrathenylmethyl esters are expected to be more suitable than PMB esters for inducing higher enantioselectivity. See also ref 19.

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17. Although the present kinetic studies (see the Experimental Section) and the previous reports support our proposed mechanism,[4,5] we cannot exclude the possibility that asymmetric induction arises solely from the first cyanation step.

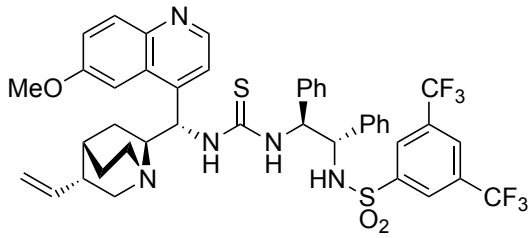
18. Cyanohydrins were not observed during the present cyano- alkoxycarbonylation. This suggests that the cyanohydrinated oxyanion intermediates were highly unstable.

19. The enantioselectivity in the reaction of aliphatic-group-substituted 2-oxoacetates 12a and 12b (entries 10 and 11, Table 3.2) was slightly lower than that of 2-oxo-2-phenylacetate 7e (entry 11, Table 1). In the reaction of aliphatic substrates, the equilibrium between diastereomeric intermediates 20 and 21 might not be high enough for high enantioselectivity to be induced in the next step.

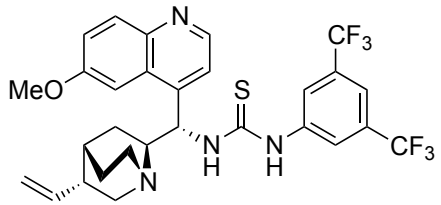
3-5. Experimental Section

General Methods. IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (CD_3OD: 3.31 ppm) or Me_4Si resonance (0.00 ppm; $CDCl_3$) as the internal standard. Data were recorded as follows: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; sept = septet; m = multiplet, br = broad), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$: 77.16 ppm, CD_3OD: 49.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel Chiralcel OJ-H (4.6 mm × 25 cm), Daicel Chiralpack IA-H (4.6 mm × 25 cm), Daicel Chiralpack IA-3 (4.6 mm × 25 cm) or Daicel Chiralpack IC-3 (4.6 mm × 25 cm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Facility, Nagoya University. Dry dichloromethane and tetrahydrofurane were purchased from Kanto as the "anhydrous" and stored under nitrogen. Dry chloroform was dried fractionally from P_2O_5 and stored over 4A molecular sieves and Ag foil. Other materials were obtained from commercial supplies and used without further purification.

Synthesis of Brønsted Acid–Lewis Base Cooperative Catalysts 1, 2, 3, 4a, 4b, and 4c

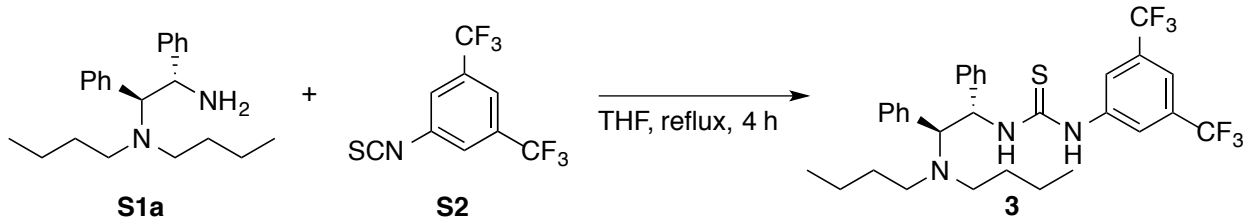


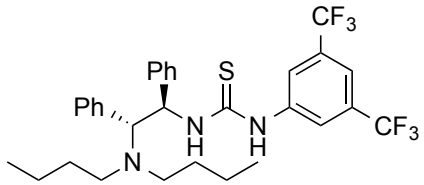
***N*-((1*S*,2*S*)-2-(3-((*S*)-(6-Methoxyquinolin-4-yl)-((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoro methyl)benzenesulfonamide (1):**[1]



1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (2):[2]

Synthesis of **3**

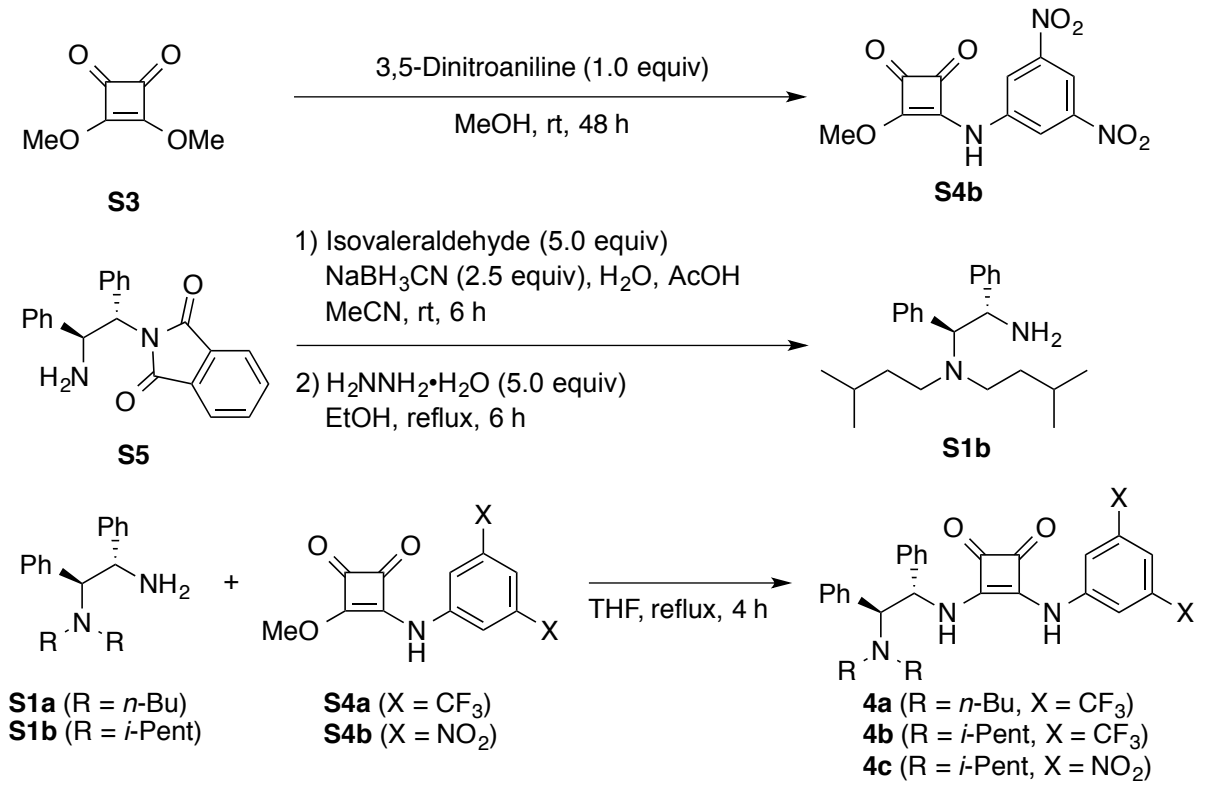


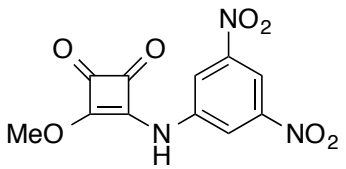


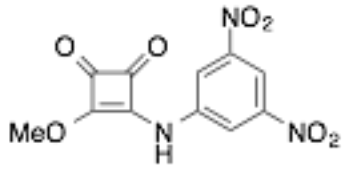
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(dibutylamino)-1,2-diphenylethyl)thiourea (3): A solution of **S1a**[3] (162 mg, 0.5 mmol) and **S2** (92.2 μL, 0.5 mmol, 1.0 equiv) in THF (2.5 mL) was stirred for 3 hours under reflux condition. After the completion of the reaction, the mixture was concentrated in *vacuo.* The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:1) to give **3** (241 mg, 81% yield). Colorless solid; $[\alpha]^{24}_{D}$ –157.7 (*c* 1.0, $CHCl_3$); IR (KBr) 3172, 2961, 2931, 1493, 1382, 1277, 1180, 1139, 889, 700, 682 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 2H), 7.63 (s, 1H), 7.23–7.09 (m, 7H), 7.09–6.96 (m, 3H), 5.80 (d, 11.2 Hz, 1H), 4.90 (br, 1H), 4.07 (d, 11.2 Hz, 1H), 2.72–2.61 (m, 2H), 2.17–2.07 (m, 2H),

1.60–1.49 (m, 2H), 1.49–1.33 (m, 2H), 1.33–1.20 (m, 2H), 0.90 (t, 7.3 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 182.4, 142.9, 142.2, 135.8, 132.8 (q, J_{C-F} = 33.5 Hz, 2C), 130.8 (2C), 129.2 (2 C), 128.9 (2C), 128.8 (2C), 128.6, 127.9, 124.6 (q, J_{C-F} = 273 Hz, 2C), 123.7 (2C), 117.9, 70.8, 59.8, 50.5 (2C), 31.8 (2C), 21.6 (2C), 14.5 (2C), HRMS (ESI+) calcd for $C_{31}H_{36}F_6N_3S$ $[M+H]^+$ 596.2529, found 596.2530.

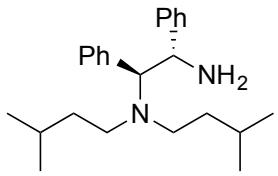
Synthesis of **4a ~ 4c**



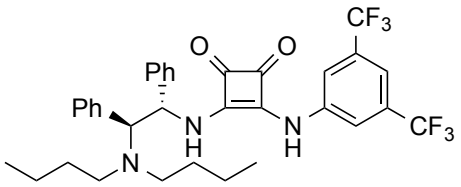




3-((3,5-Dinitorophenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (S4b): A solution of **S3** (284 mg, 2.0 mmol) and 3,5-dinitroaniline (366 mg, 2.0 mmol, 1.0 equiv) in MeOH (2.0 mL) was stirred vigorously for 48 h at ambient temperature. After the stirring, the solid precipitation was filtered to give 3-((3,5-dinitorophenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**S4b**) (463 mg, 79% yield) as yellow solid. It was used for next step without farther purification.

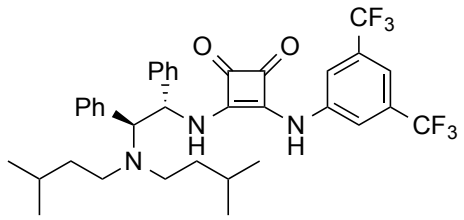


(1*S*,2*S*)-*N*^{1}, *N*^{1}-Diisopentyl-1,2-diphenylethane-1,2-diamine (S1b): To a solution of **S5**[4] (684.8 mg, 2.0 mmol) in THF (10 mL) were added H_2O (600 μL) and isovaleraldehyde (1.08 mL, 10.0 mmol) and stirred the mixture for 15 minutes at ambient temperature. After the stirring, $NaBH_3CN$ (377.0 mg, 6.0 mmol) was added to a reaction mixture and stirred for 15 minutes at ambient temperature. To the resultant mixture AcOH (600 μL) was added and stirred for 3 hours at ambient temperature. After the stirring, to a reaction mixture saturated aqueous $NaHCO_3$ (10.0 mL) was added to basify and extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine and dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The residue was dissolved in EtOH (4.0 mL) and stirred with hydrazin monohydrate (243 μL, 5.0 mmol) for 6 hours under reflux condition. After the stirring, the reaction mixture was filtered and concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (EtOAc–MeOH = 10:1 → 5:1) to give **S1b** (684.8 mg, 97% yield). Clear oil; $[\alpha]^{25}_D$ 31.5 (*c* 1.0, $CHCl_3$); IR (neat) 3028, 2954, 2926, 2868, 1468, 1453, 757, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 7.3 Hz, 2H), 7.17–7.07 (m, 5H), 7.06–6.98 (m, 3H), 4.43 (d, 10.6 Hz, 1H), 3.80 (d, 10.6 Hz, 1H), 2.74–2.64 (m, 2H), 2.12–2.00 (m, 4H), 1.67 (sept, 6.4 Hz, 2H), 1.49–1.42 (m, 4H), 0.95 (d, 6.4 Hz, 6H), 0.93 (d, 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 135.9, 129.8 (2C), 128.2 (2C), 128.1 (2C), 127.5 (2C), 126.9, 126.8, 70.7, 55.9, 48.4 (2C), 38.2 (2C), 26.5 (2C), 23.4 (2C), 22.6 (2C); HRMS (ESI+) calcd for $C_{24}H_{36}N_2Na$ $[M+Na]^+$ 353.2951, found 353.2952.

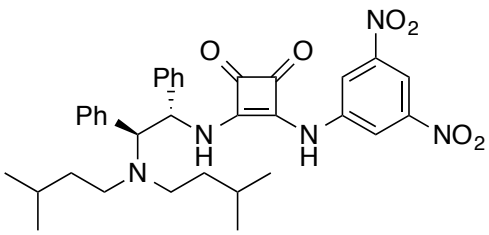


3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*R*,2*R*)-2-(dibutylamino)-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (4a): A solution of **S1a**[3] (45.4 mg, 0.14 mmol) and **S4a**[5] (47.5 mg, 0.14 mmol, 1.0 equiv) in THF (0.7 mL) was stirred for 4 hours under reflux condition. After the completion of the reaction, the mixture was concentrated in *vacuo.* The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:1) to give **4a** (58.4 mg, 66% yield). Colorless solid; $[\alpha]^{25}_D$ 52.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3206, 2958, 2860, 1799, 1665, 1577, 1456, 1376, 1280, 1177, 1139, 884, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (br, 2H), 7.45 (s, 1H),

7.29–7.23 (m, 2H), 7.23–7.09 (m, 7H), 7.09–7.03 (m, 1H), 5.87 (d, 11.0 Hz, 1H), 4.18 (d, 11.0 Hz, 1H), 2.77–2.67 (m, 2H), 2.18–2.09 (m, 2H), 1.57–1.31 (m, 5H), 1.31–1.18 (m, 3H), 0.89 (t, 7.3, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 184.8, 184.4, 172.1, 167.4, 146.3, 142.2, 136.3, 133.4 (q, J_{C-F} = 33.4 Hz, 2C), 130.8 (2C), 129.4 (2C), 128.9 (2C), 128.8 (2C), 128.4, 128.3, 124.9 (q, J_{C-F} = 271 Hz, 2C), 120.9, 115.5, 70.6, 60.0, 50.9 (2C), 31.9 (2C), 21.7 (2C), 14.6 (2C); HRMS (ESI+) calcd for $C_{34}H_{36}F_6N_3O_2$ $[M+H]^+$ 632.2706, found 632.2714.



3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*R*,2*R*)-2-(diisopentylamino)-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (4b): 4b was prepared from **S1b** (272 mg, 0.77 mmol) and 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (261 mg, 0.77 mmol, 1.0 equiv) according to the same manner as **4a**. 88% yield (418 mg); colorless solid; $[\alpha]^{25}_D$ 14.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3209, 2957, 2870, 1797, 1664, 1578, 1455, 1377, 1280, 1178, 1139, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (br, 2H), 7.58 (s, 1H), 7.28–7.08 (m, 10H), 5.86 (d, 11.0 Hz, 1H), 4.16 (d, 11.0 Hz, 1H), 2.82–2.71 (m, 2H), 2.24–2.12 (m, 2H), 1.62–1.50 (m, 2H), 1.50–1.38 (m, 2H), 1.38–1.25 (m, 2H), 0.90 (d, 6.4 Hz, 6H), 0.86 (d, 6.9 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 189.6, 188.4, 170.9, 167.8, 142.5, 141.6, 135.9, 134.0 (q, J_{C-F} = 33.4 Hz, 2C), 130.8 (2C), 129.6 (2C), 129.0 (2C), 128.9, 128.8 (2C), 128.6, 124.6 (q, J_{C-F} = 272 Hz, 2C), 119.3 (2C), 116.7, 70.7, 60.3, 49.6 (2C), 38.8 (2C), 27.9 (2C), 23.6 (2C), 23.0 (2C); HRMS (ESI+) calcd for $C_{36}H_{40}F_6N_3O_2$ $[M+H]^+$ 660.3019, found 660.3018.

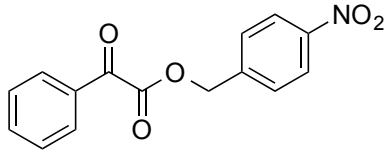


3-((3,5-Binitrophenyl)amino)-4-(((1*R*,2*R*)-2-(diisopentylamino)-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (4c): 4c was prepared from **S1b** (70.5 mg, 0.2 mmol) and **S4b** (58.6 mg, 0.2 mmol, 1.0 equiv) according to the same manner as **4a**. 79% yield (97.1 mg); yellow solid; $[\alpha]^{24}_D$ 22.2 (*c* 1.0, $CHCl_3$); IR (KBr) 2954, 2869, 1796, 1666, 1579, 1548, 1442, 1344, 1079, 731, 700

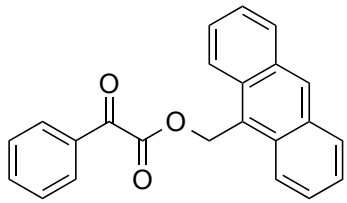
cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (br, 2H), 8.59 (s, 1H), 7.28–7.09 (m, 12H), 5.88 (d, 11.4 Hz, 1H), 4.22 (d, 11.4 Hz, 1H), 2.83–2.72 (m, 2H), 2.23–2.12 (m, 2H), 1.63–1.52 (m, 2H), 1.52–1.40 (m, 2H), 1.38–1.26 (m, 2H), 0.91 (d, 6.9 Hz, 6H), 0.87 (d, 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 186.1, 182.2, 171.1, 163.5, 150.8 (2C), 143.1, 141.6, 135.9, 130.8 (2C), 30.7, 129.6 (2C), 129.0 (2C), 128.9 (2C), 128.6, 118.8 (2C), 112.6, 70.6, 60.3, 49.4 (2C),, 38.8 (2C), 27.9 (2C), 23.6 (2C), 23.0 (2C); HRMS (ESI+) calcd for $C_{34}H_{40}N_5O_6$ $[M+H]^+$ 614.2973, found 614.2977.

Preparation of α-Ketoesters.

Methyl benzoylformate (**7a**), and ethyl benzoylformate (**7b**) were obtained from commercial supplies and used without further purification. Isopropyl benzoylformate[6] (**7c**), benzyl benzoylformate[6] (**7d**), 4-methoxybenzyl benzoylformate[7] (**7e**) were synthesized as reported procedures.

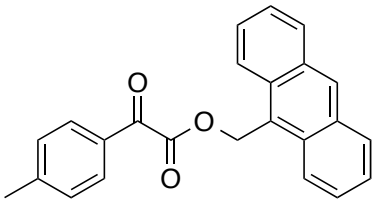


4-Nitrobenzyl benzoylformate (7f): To a solution of benzoformic acid (751 mg, 5.0 mmol), and DMF (1 drop) in CH_2Cl_2 (10 mL) was added oxalyl chloride (643 μL, 7.5 mmol, 1.5 equiv) at 0 ºC, and stirred for 3 h at ambient temperature. The mixture was concentrated in *vacuo*. To a solution of resultant residue in CH_2Cl_2 (25 mL) were added Et_3N (1.05 mL, 7.5 mmol, 1.5 equiv) and (4-nitrophenyl)methanol (766 mg, 5.0 mmol, 1.0 equiv) at 0 ºC, and stirred for 13 h at ambient temperature. After the stirring, saturated aqueous $NaHCO_3$ (25 mL) was added to quench. The organic layer was separated, washed with brine, and dried with Na_2SO_4. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 4:1) to give **7f** (685 mg, 48% yield).; Pale yellow solid; IR (KBr) 1725, 1686, 1527, 1351, 1196, 1173, 989, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 8.7 Hz, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.53 (, J = 7.8, 8.7 Hz, 2H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 163.2, 148.1, 141.7, 135.4, 132.3, 130.2 (2C), 129.2 (2C), 128.8 (2C), 124.1 (2C), 66.1; HRMS (ESI+) calcd for $C_{15}H_{11}NNaO_5$ $[M+Na]^+$ 308.0529, found 308.0532.

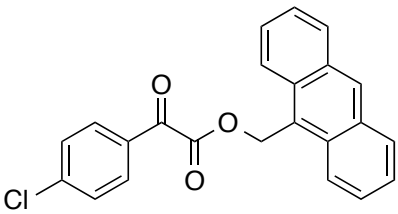


Anthracene-9-ylmethyl benzoformate (7g):[8] The mixture of benzoylformic acid (751 mg, 5.0 mmol), 9-(bromomethyl)anthracene (1.28 g, 4.75mmol, 0.95 equiv), and K_2CO_3 (829 mg, 6.0 mmol, 1.2 equiv) in DMF (25 mL) was stirred for 3 h at 60 ºC. After the stirring, the mixture was concentrated in *vacuo*. The residue was dissolved in toluene (50 mL) and H_2O (50 mL). The organic layer was separated and washed with brine, dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was recrystallized from toluene/hexane to give **7g** (746 mg, 46% yield).; yellow solid; IR (KBr) 1732,

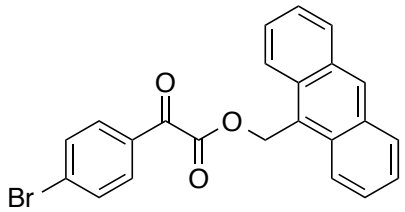
1682, 1594, 1280, 1202, 1175, 984, 915, 883, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.42 (d, *J* = 9.2 Hz, 2H), 8.06 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.62 (dd, *J* = 7.8, 8.7 Hz, 2H), 7.57 (t, *J* = 7.8, 8.7 Hz, 2H), 7.52 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.39 (dd, *J* = 7.8, 9.2 Hz, 2H), 6.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 164.2, 135.0, 132.5, 131.5, 131.3 (2C), 130.1 (2C), 130.0 (2C), 129.4 (2C), 129.0 (2C), 127.2 (2C), 125.4 (2C), 124.7 (2C), 123.8 (2C), 60.6; HRMS (ESI+) calcd for $C_{33}H_{16}NaO_3$ $[M+Na]^+$ 363.0992, found 363.0998.



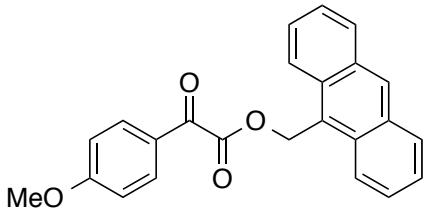
Anthracene-9-ylmethyl 2-oxo-2-(4-methylphenyl)acetate (10a): 10a was prepared from 2-oxo-2-(4-methylphenyl)acetic acid (328 mg, 2.0 mmol) and 9-(bromomethyl)anthracene (515 mg, 1.9 mmol, 0.95 equiv) according to the same manner as **7g**. 69% yield (464 mg); yellow solid; IR (KBr) 1736, 1678, 1604, 1285, 1227, 1202, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.42 (d, *J* = 8.7 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.61 (dd, *J* = 7.8, 8.7 Hz, 2H), 7.51 (dd, *J* = 7.8, 8.7Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.47 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 164.5, 146.3, 131.5, 131.3, 130.2 (2C), 130.0 (2C), 130.0 (2C), 129.7 (2C), 129.3 (2C), 127.1 (2C), 125.3 (2C), 124.8, 123.8 (2C), 60.5, 22.0; HRMS (ESI+) calcd for $C_{24}H_{18}NaO_3$ $[M+Na]^+$ 377.1148, found 377.1164.



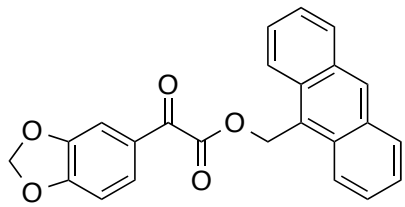
Anthracene-9-ylmethyl 2-oxo-2-(4-chlorophenyl)acetate (10b):[8] **10b** was prepared from 2-(4-chlorophenyl)-2-oxoacetic acid (369 mg, 2.0 mmol) and 9-(bromomethyl)anthracene according (515 mg, 1.9 mmol, 0.95 equiv) to the same manner as **7g**. 77% yield (550 mg); yellow solid; IR (KBr) 1724, 1686, 1585, 1203, 1174, 984, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 2H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 6.9 Hz, 2H), 7.63 (dd, *J* = 6.9, 9.2 Hz, 2H), 7.52 (dd, *J* = 6.9, 8.2 Hz, 2H), 7.36 (d, *J* = 6.9 Hz, 2H), 6.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 163.9, 141.7, 131.5 (2C), 131.5, 131.3 (2C), 130.9, 130.2 (2C), 129.4 (2C), 129.3 (2C), 127.2 (2C), 125.4 (2C), 124.6, 123.7 (2C), 60.8; HRMS (ESI+) calcd for $C_{23}H_{15}ClNaO_3$ $[M+Na]^+$ 397.0602, found 397.0594.



Anthracene-9-ylmethyl 2-oxo-2-(4-bromophenyl)acetate (10c): 10c was prepared from 2-(4-bromophenyl)-2-oxoacetic acid (458 mg, 2.0 mmol) and 9-(bromomethyl)anthracene (515 mg, 1.9 mmol, 0.95 equiv) according to the same manner as **7g**. 79% yield (630 mg); yellow solid; IR (KBr) 1721, 1687, 1585, 1205, 1175, 988, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.40 (d, *J* = 9.2 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 12.0 Hz, 2H), 7.62 (dd, *J* = 6.9, 8.2Hz, 2H), 7.58–7.49 (m, 4H), 6.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 163.6, 132.4 (2C), 132.3 (2C), 131.5, 131.4 (2C), 131.3 (2C), 130.6, 130.2, 129.4 (2C), 127.3 (2C), 125.4 (2C), 124.6, 123.7 (2C), 60.8; HRMS (ESI+) calcd for $C_{23}H_{15}BrNaO_3$ $[M+Na]^+$ 441.0097, found 441.0103.

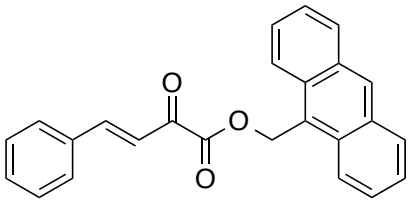


Anthracene-9-ylmethyl 2-oxo-2-(4-methoxyphenyl)acetate (10d): 10d was prepared from 2-(4-methoxyphenyl)-2-oxoacetic acid (360 mg, 2.0 mmol) and 9-(bromomethyl)anthracene (515 mg, 1.9 mmol, 0.95 equiv) according to the same manner as **7g**. 71% yield (499 mg); yellow solid; IR (KBr) 1731, 1669, 1597, 1509, 1271, 1202, 1167, 982 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.43 (d, *J* = 8.7 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.62 (dd, *J* = 6.9, 8.2 Hz, 2H), 7.51 (dd, *J* = 6.9, 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.47 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 165.0, 164.6, 132.6 (2C), 131.5 (2C), 131.3, 130.0 (2C), 129.3 (2C), 127.1 (2C), 125.5 (2C), 125.3 (2C), 124.9, 123.8 (2C), 114.3 (2C), 60.5, 55.7; HRMS (ESI+) calcd for $C_{24}H_{18}NaO_4$ $[M+Na]^+$ 393.1097, found 393.1104.

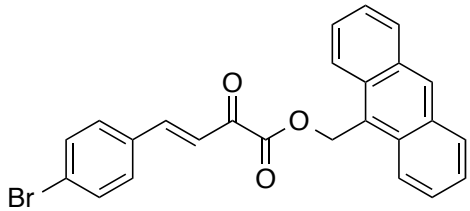


Anthracene-9-ylmethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoacetate (10e): 10e was prepared from

2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoacetic acid (388 mg, 2.0 mmol) and 9-(bromomethyl)anthracene (515 mg, 1.9 mmol, 0.95 equiv) according to the same manner as **7g**. 60% yield (462 mg); yellow solid; IR (KBr) 1716, 1674, 1489, 1272, 1246, 1179, 1097, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.41 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 2H), 7.62 (dd, *J* = 6.4, 7.8 Hz, 2H), 7.51 (dd, *J* = 6.4, 7.2 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.38 (s, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.46 (s, 2H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 164.4, 153.6, 148.5, 131.4, 131.3, 130.0, 129.3 (2C), 128.0, 127.2, 127.1 (2C), 125.3 (2C), 124.8, 123.7 (2C), 108.6, 108.3 (2C), 102.3 (2C), 60.6; HRMS (ESI+) calcd for $C_{20}H_{16}NO_6$ $[M+Na]^+$ 407.0890, found 407.0892.

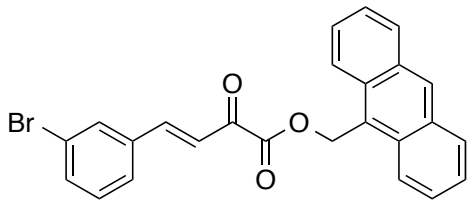


Anthracene-9-ylmethyl (*E*)-2-oxo-4-phenylbut-3-enoate (10f): 10f was prepared from (*E*)-2-oxo-4-phenylbut-3-enoic acid (555 mg, 3.15 mmol) and 9-(bromomethyl)anthracene (813 mg, 3.00 mmol, 0.95 equiv) according to the same manner as **7g**. 52% yield (570 mg); yellow solid; IR (KBr) 1730, 1690, 1610, 1263, 1085, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 2H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.62 (dd, *J* = 6.7, 8.2 Hz, 2H), 7.52 (dd, *J* = 6.7, 9.2 Hz, 2H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.43–7.32 (m, 3H), 7.23 (d, *J* = 16.0 Hz, 1H), 6.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 162.5, 148.8, 134.0, 131.7, 131.7, 131.5, 131.3, 130.0, 129.3 (2C), 129.1 (2C), 129.1 (2C), 127.2 (2C), 125.3 (2C), 124.9, 123.8 (2C), 120.9 (2C), 60.9; HRMS (ESI+) calcd for $C_{25}H_{18}NaO_3$ $[M+Na]^+$ 389.1148, found 389.1148.

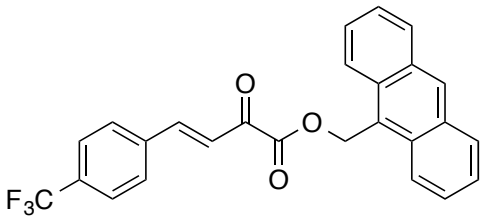


Anthracene-9-ylmethyl (*E*)-4-(4-bromophenyl)-2-oxobut-3-enoate (10g): 10g was prepared from (*E*)-4-(4-bromophenyl)-2-oxobut-3-enoic acid (803 mg, 3.15 mmol) and 9-(bromomethyl)anthracene (813 mg, 3.00 mmol, 0.95 equiv) according to the same manner as **7g**. 63% yield (846 mg); yellow solid; IR (KBr) 1729, 1693, 1608, 1585, 1256, 1083, 1069, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.41 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 15.6 Hz, 1H), 7.62 (dd, *J* = 7.8, 8.2 Hz, 2H), 7.53 (dd, *J* = 7.8,

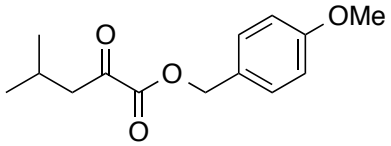
8.7 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 15.6 Hz, 1H), 6.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 162.4, 147.2, 132.9, 132.4 (2C), 131.5, 131.3, 130.3 (2C), 130.0 (2C), 129.4 (2C), 127.2 (2C), 126.2, 125.4 (2C), 124.9, 123.9 (2C), 121.3 (2C), 61.0; HRMS (ESI+) calcd for $C_{25}H_{17}BrNaO_3$ $[M+Na]^+$ 467.0253, found 467.0253.



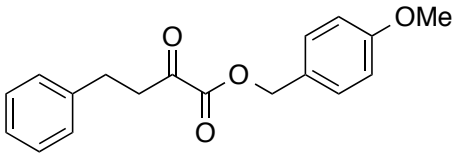
Anthracene-9-ylmethyl (*E*)-4-(3-bromophenyl) -2-oxobut-3-enoate (10h): 10h was prepared from (*E*)-4-(3-bromophenyl)-2-oxobut-3-enoic acid (803 mg, 3.15 mmol) and 9-(bromomethyl)anthracene (813 mg, 3.00 mmol, 0.95 equiv) according to the same manner as **7g**. 63% yield (840 mg); yellow solid; IR (KBr) 1719, 1698, 1611, 1274, 1086, 1068, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.41 (d, J = 9.2 Hz, 2H), 8.06 (d, J = 8.2 Hz, 2H), 7.62 (dd, J = 7.8. 8.2 Hz, 2H), 7.57 (d, J = 16.0 Hz, 1H), 7.55–7.49 (m, 4H), 7.36 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 7.8 Hz, 1H), 7.19 (d, J = 16.0 Hz, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 162.3, 146.8, 136.0, 134.3, 131.6 (2C), 131.5, 131.3, 130.6 (2C), 130.1, 129.4 (2C), 127.5, 127.2 (2C), 125.4 (2C), 124.8, 123.8 (2C), 123.2, 122.1, 61.0; HRMS (ESI+) calcd for $C_{25}H_{17}BrNaO_3$ $[M+Na]^+$ 467.0253, found 467.0251.



Anthracene-9-ylmethyl (*E*)-2-oxo-4-(4-(trifluoromethyl)phenyl)but-3-enoate (10i): 10i was prepared from (*E*)-2-oxo4-(4-(trifluoromethyl)phenyl)but-3-enoic acid (769 mg, 3.15 mmol) and 9-(bromomethyl)anthracene (813 mg, 3.00 mmol, 0.95 equiv) according to the same manner as **7g**. 28% yield (370 mg); yellow solid; IR (KBr) 1729, 1697, 1615, 1326, 1256, 1120, 1066, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, H), 8.41 (d, J = 9.2 Hz, 2H), 8.07 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 16.0 Hz, 1H), 7.65–7.60 (m, 4H), 7.57–7.50 (m, 4H), 7.29 (d, J = 16.0 Hz, 1H), 6.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 162.1, 146.5, 137.2, 132.9 (q, J_{C-F} = 32.4 Hz), 131.5, 131.4, 130.1 (2C), 129.4 (2C), 129.1 (2C), 127.2 (2C), 126.1 (q, J_{C-F} = 3.8 Hz, 2C), 125.4 (2C), 124.7, 124.0, 123.8 (2C), 123.8 (q, J_{C-F} = 272 Hz), 123.0 (2C), 61.1; HRMS (ESI+) calcd for $C_{26}H_{17}F_3NaO_3$ $[M+Na]^+$ 457.1022, found 457.1023.



4-Methoxybenzyl 4-methyl-2-oxopentanoate (12a): The mixture of DL-leucic acid (661 mg, 5.0 mmol), 1-(bromomethyl)-4-methoxybenzene (729 μL, 5.0 mmol, 1.0 equiv), and Cs_2CO_3 (1.63 g, 1.0 equiv) in DMF (10 mL) was stirred for 12 h at ambient temperature. After the stirring, the mixture was concentrated in *vacuo*. The residue was dissolved in toluene (50 mL) and H_2O (50 mL). The organic layer was separated and washed with brine, dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 4:1 → 2:1) to give 4-methoxybenzyl 2-hydroxy-4-methylpentanoate (478 mg, 38% yield). To a solution of 4-methoxybenzyl 2-hydroxy-4-methylpentanoate (478 mg, 1.9 mmol) in CH_2Cl_2 (9.5 mL) was added Dess-Martin periodinate (976 mg, 2.3 mmol, 1.2 equiv.), and stirred for 12 h at ambient temperature. After the stirring, to the reaction mixture were added saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL), and stirred vigorously. The organic layer was separated, and aqueous layer was washed with CH_2Cl_2 (20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 10:1) to give **12a** (395 mg, 83% yield).; colorless oil; IR (KBr) 2960, 1727, 1614, 1517, 1304, 1250, 1177, 1137, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.21 (s, 2H), 3.82 (s, 3H), 2.70 (d, J = 6.9 Hz, 2H), 2.17 (t, sept, J = 6.9, 6.9 Hz, 1H), 0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 161.2, 160.1, 130.7 (2C), 126.7, 114.1 (2C), 67.8, 55.3, 48.0, 24.1, 22.5 (2C); HRMS (ESI+) calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$ 273.1097, found 273.1098.



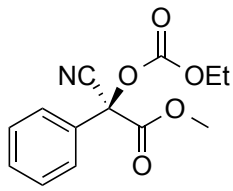
4-Methoxybenzyl 2-oxo-4-phenylbutanoate (12b): 12b was prepared from 2-hydroxy-4-phenylbutanoic acid (901 mg, 5.0 mmol) and 1-(bromomethyl)-4-methoxybenzene (729 μL, 5.0 mmol, 1.0 equiv) according to the same manner as **12a**. 40% yield (737 mg, 2 steps); colorless oil; IR (KBr) 3029, 2957, 2837, 1730, 1613, 1515, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 2H), 7.31–7.15 (m, 5H), 6.89 (d, J = 8.7 Hz, 2H), 5.21 (s, 2H), 3.81 (s, 3H), 3.16 (t, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 193.4, 160.7, 160.1, 140.1, 130.8 (2C), 128.6 (2C), 128.4 (2C), 126.6, 126.4, 114.1 (2C), 68.0, 55.4, 41.1, 29.0; HRMS (ESI+) calcd for $C_{18}H_{18}NaO_4$ $[M+Na]^+$ 321.1097, found 321.1097.

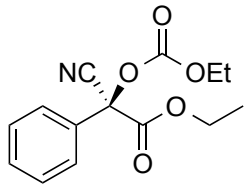
General Procedure for the Asymmetric Cyano-Alkoxycarbonylation of α-Ketoesters using Brønsted Acid-Lewis Base Cooperative Catalyst.

To a solution of an α-ketoester (0.20 mmol), **4c** (12.3 mg, 0.020 mmol, 10 mol%), and methanol (4.0 μL, 0.1 mmol, 50 mol%) in chloroform (0.4 or 0.6 mL) was added ethyl cyanoformate (39.5 μL, 0.4 mmol, 2.0 equiv) or allyl cyanoformate[9] (44.4 mg, 0.4 mmol, 2.0 equiv) at ambient temperature, and the mixture was stirred for 12–48 h. To the reaction mixture was added brine (2 mL), and the aqueous layer was extracted with chloroform. The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 10:1 → 5:1) to give a cyano-alkoxycarbonylation product.

The corresponding physical and spectroscopic data for the products are as follows.

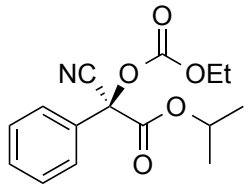


Methyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8a): 90% yield (47.4 mg); Clear oil; $[\alpha]^{25}_{D}$ –6.8 (*c* 1.0, $CHCl_3$) for 78% ee; IR (neat) 1760, 1453, 1372, 1253, 1203, 1035, 1004, 775, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 1.8, 7.5 Hz, 2H), 7.52–7.44 (m, 3H), 4.36 (q, *J* = 6.8 Hz, 2H), 3.86 (s, 3H), 1.39 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 153.0, 131.0, 130.7, 129.3 (2C), 126.2 (2C), 114.9, 76.5, 66.3, 54.7, 14.2; HRMS (ESI+) calcd for $C_{13}H_{13}NNaO_5$ $[M+Na]^+$ 286.0686, found 286.0689. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 9.1 (minor enantiomer), 10.0 (major) min.

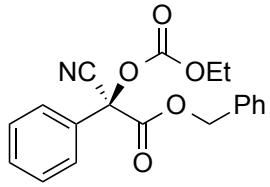


Ethyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8b): 88% yield (49.0 mg); Clear oil; $[\alpha]^{25}_{D}$ –6.9 (*c* 1.0, $CHCl_3$) for 79% ee; IR (neat) 1761, 1371, 1273, 1202, 1034, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H), 7.50–7.43 (m, 3H), 4.36 (q, *J* = 6.8 Hz, 2H), 4.35–4.25 (m, 2H), 1.39 (t, *J* = 6.8 Hz, 3H), 1.28 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 153.1, 130.9, 129.3 (2C), 126.2 (2C), 115.0, 76.6, 66.2, 64.3, 14.2, 13.9; HRMS (ESI+) calcd for $C_{14}H_{15}NNaO_5$ $[M+Na]^+$ 300.0842, found 300.0842. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate =

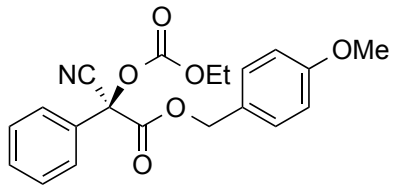
1.0 mL/min) t_R= 8.1 (minor enantiomer), 9.4 (major) min.



Isopropyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8c): 89% yield (51.7 mg); Clear oil; $[\alpha]^{25}_D$ –4.8 (*c* 1.0, $CHCl_3$) for 71% ee; IR (neat) 1764, 1373, 1278, 1203, 1102, 1030, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.70 (m, 2H), 7.49–7.43 (m, 3H), 5.09 (qq, *J* = 6.4, 6.4 Hz, 1H), 4.36 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 153.0, 131.0, 130.8, 129.2 (2C), 126.1 (2C), 115.1, 76.7, 72.8, 66.1, 21.4, 21.2, 14.2; HRMS (ESI+) calcd for $C_{15}H_{17}NNaO_5$ $[M+Na]^+$ 314.0999, found 314.1002. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 6.9 (minor enantiomer), 7.7 (major) min.

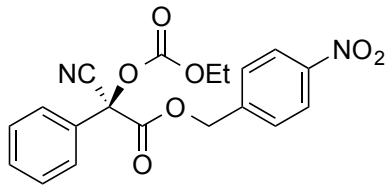


Benzyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8d): 95% yield (64.5 mg); Clear oil; $[\alpha]^{25}_D$ –14.2 (*c* 1.0, $CHCl_3$) for 82% ee; IR (neat) 1768, 1454, 1372, 1274, 1200, 1029, 1004, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.50–7.38 (m, 3H), 7.35–7.29 (m, 3H), 7.25–7.21 (m, 2H), 5.28 (d, *J* = 12.4 Hz, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 4.33 (q, *J* = 7.3 Hz, 2H), 1.36 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 153.0, 134.0, 130.9, 130.6, 129.3 (2C), 128.8, 128.7 (2C), 128.1 (2C), 126.2 (2C), 114.9, 76.6, 69.4, 66.2, 14.2; HRMS (ESI+) calcd for $C_{19}H_{17}NNaO_5$ $[M+Na]^+$ 362.0999, found 362.0997. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 13.6 (minor enantiomer), 16.5 (major) min.

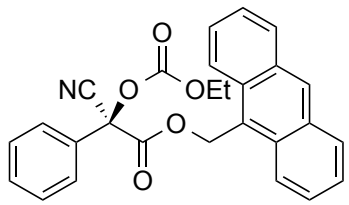


4-Methoxybenzyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8e): 81% yield (59.8 mg); Clear oil;

$[\alpha]^{24}_{D}$ –7.8 (*c* 1.0, $CHCl_3$) for 89% ee; IR (neat) 1750, 1517, 1247, 1176, 1029, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 1.8, 6.2 Hz, 2H), 7.49–7.38 (m, 3H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.23 (d, *J* = 11.9 Hz, 1H), 5.16 (d, *J* = 11.9 Hz, 1H), 4.32 (q, *J* = 7.3 Hz, 2H), 3.80 (s, 3H), 1.36 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.1, 152.9, 130.8, 130.7, 130.2 (2C), 129.2 (2C), 126.2 (2C), 126.1, 114.9, 114.0 (2C), 76.6, 69.5, 66.2, 55.4, 14.2; HRMS (ESI+) calcd for $C_{20}H_{19}NNaO_6$ $[M+]^+$ 392.1105, found 392.1108. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 19:1, flow rate = 1.0 mL/min) t_R= 16.3 (minor enantiomer), 20.6 (major) min.

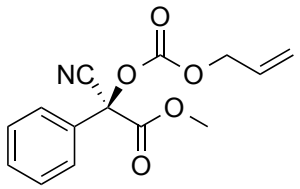


4-Nitrobenzyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8f): 72% yield (55.2 mg); Clear oil; $[\alpha]^{24}_{D}$ –17.0 (*c* 1.0, $CHCl_3$) for 84% ee; IR (neat) 1764, 1524, 1349, 1274, 1200, 1033, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.72 (dd, *J* = 1.8, 8.2 Hz, 2H), 7.54–7.43 (m, 3H), 7.39 (d, *J* = 8.7 Hz, 2H), 5.40 (d, *J* = 13.3 Hz, 1H), 5.31 (d, *J* = 13.3 Hz, 1H), 4.35 (q, *J* = 7.4 Hz, 2H), 1.38 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 153.1, 148.1, 141.2, 131.2, 130.2, 129.4 (2C), 28.2 (2C), 126.2 (2C), 124.0 (2C), 114.6, 76.5, 67.6, 66.4, 14.2; HRMS (ESI+) calcd for $C_{19}H_{16}N_2NaO_7$ $[M+Na]^+$ 407.0850, found 407.0850. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 18.4 (minor enantiomer), 25.2 (major) min.

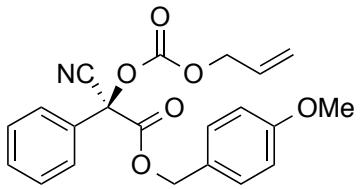


Anthracene-9-ylmethyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-phenylacetate (8g): 98% yield (86.3 mg); Pale yellow oil; $[\alpha]^{25}_{D}$ –8.0 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1760, 1272, 1200, 1025, 1003, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.53–7.45 (m, 4H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.30–7.23 (m, 2H), 6.37 (d, *J* = 12.4 Hz, 1H), 6.15 (d, *J* = 12.4 Hz, 1H), 4.24–4.08 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 153.0, 131.3 (2C), 131.2, 130.7, 130.5, 130.1 (2C), 129.2 (2C), 129.1 (2C), 127.0 (2C),

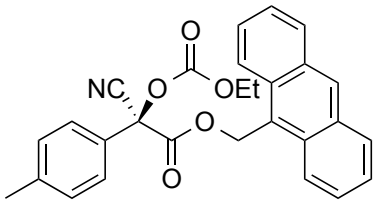
126.1 (2C), 125.3 (2C), 123.9, 123.6 (2C), 114.8, 77.4, 66.1, 62.9, 14.0; (ESI+) calcd for $C_{27}H_{21}NNaO_5$ $[M+Na]^+$ 462.1312, found 462.1313. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 20.6 (minor enantiomer), 23.7 (major) min.



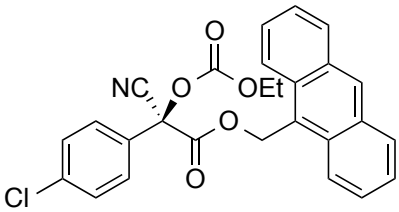
Methyl (*S*)-2-(((allyloxy)carbonyl)oxy)-2-cyano-2-phenylacetate (9a): 91% yield (50.0 mg); Clear oil; $[\alpha]^{27}_D$ –49.7 (*c* 1.0, $CHCl_3$) for 81% ee; IR (neat) 1764, 1453, 1368, 1249, 1202, 1131, 1065, 1038, 972, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71 (m, 2H), 7.52–7.43 (m, 3H), 5.97 (ddt, *J* = 6.0, 11.0, 16.9 Hz, 1H), 5.44 (d, *J* = 16.9 Hz, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 152.9, 131.0, 130.7, 130.5, 129.4 (2C) 126.3 (2C), 120.4, 114.9, 77.4, 70.4, 54.8; HRMS (ESI+) calcd for $C_{14}H_{13}NNaO_5$ $[M+Na]^+$ 298.0686, found 298.0686. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 10.1 (minor enantiomer), 10.4 (major) min.



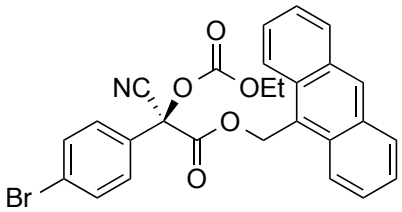
4-Methoxybenzyl (*S*)-2-(((allyloxy)carbonyl)oxy)-2-cyano-2-phenylacetate (9b): 98% yield (74.8 mg); Clear oil; $[\alpha]^{25}_D$ –9.0 (*c* 1.0, $CHCl_3$) for 89% ee; IR (neat) 1759, 1612, 1515, 1247, 1195, 1173 1128, 1029, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.48–7.38 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.83 (d, 8.7, *J* = 8.7 Hz, 2H), 5.93 (ddt, *J* = 6.0, 10.6, 17.0 Hz, 1H), 5.42 (d, *J* = 17.0 Hz, 1H), 5.33 (d, *J* = 10.6 Hz, 1H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.16 (d, *J* = 11.9 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 160.1, 152.9, 130.9, 130.6, 130.5, 130.2 (2C), 129.2 (2C), 126.2 (2C), 126.1, 120.3, 114.9, 114.1 (2C), 77.4, 70.3, 69.6, 55.4; HRMS (ESI+) calcd for $C_{21}H_{19}NNaO_6$ $[M+Na]^+$ 404.1105, found 404.1105. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 20.2 (minor enantiomer), 24.4 (major) min.



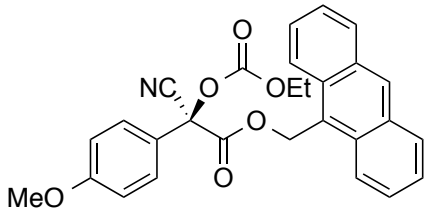
Anthracene-9-ylmethyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-(4-methypherapyl)acetate (11a): 96% yield (87.1 mg); Pale yellow oil; $[\alpha]^{25}_{D}$ –9.4 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1759, 1508, 1272, 1202, 1187, 1025, 1000, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.17–8.10 (m, 2H), 8.05–7.99 (m, 2H), 7.53–7.45 (m, 4H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.36 (d, *J* = 12.4 Hz, 1H), 6.13 (d, *J* = 12.4 Hz, 1H), 4.24–4.07 (m, 2H), 2.31 (s, 3H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 153.0, 141.0, 131.3, 131.2, 130.0, 129.7 (2C), 129.1 (2C), 127.5, 127.0 (2C), 126.0 (2C), 126.0 (2C), 125.2 (2C), 124.0, 123.6 (2C), 114.9, 76.9, 66.0, 62.5, 21.3, 14.0; HRMS (ESI+) calcd for $C_{28}H_{23}NNaO_5$ $[M+Na]^+$ 476.1468, found 476.1466. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 23.1 (minor enantiomer), 24.1 (major) min.



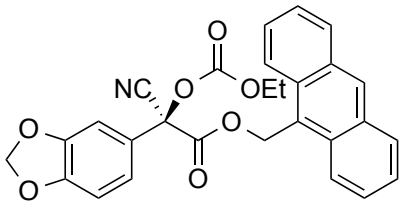
Anthracene-9-ylmethyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-(4-chlorophenyl)pacetate (11b): 76% yield (72.3 mg); Pale yellow oil; $[\alpha]^{25}_{D}$ –10.2 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1760, 1371, 1270, 1200, 1094, 1025, 1002, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.13–8.08 (m, 2H), 8.05–8.00 (m, 2H), 7.54–7.47 (m, 4H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 12.4 Hz, 1H), 6.14 (d, *J* = 12.4 Hz, 1H), 4.25–4.12 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 152.8, 137.0, 131.3 (2C), 131.2 (2C), 130.2 (2C), 129.7, 129.3, 129.2 (2C), 127.4 (2C),127.1 (2C), 125.3 (2C), 123.8, 123.4 (2C), 114.5, 76.3, 66.3, 62.8, 14.0; HRMS (ESI+) calcd for $C_{27}H_{20}ClNNaO_5$ $[M+Na]^+$ 496.0922, found 496.0931. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 20.6 (minor enantiomer), 22.4 (major) min.



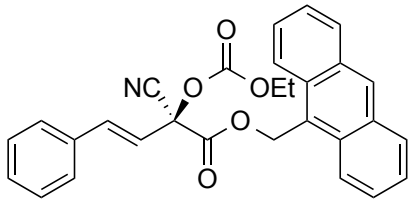
Anthracene-9-ylmethyl (*S*)-2-(4-bromolphenyl)-)2-cyano-2-((ethoxycarbonyl)oxy)acetate (11c): 89% yield (92.3 mg); Pale yellow oil; $[\alpha]^{27}_{D}$ –10.8 (*c* 1.0, $CHCl_3$) for 98% ee; IR (neat) 1760, 1269, 1199, 1074, 1025, 1002, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.13–8.08 (m, 2H), 8.06–8.01 (m, 2H), 7.54–7.47 (m, 4H), 7.36–7.27 (m, 4H), 6.40 (d, *J* = 12.4 Hz, 1H), 6.14 (d, *J* = 12.4 Hz, 1H), 4.25–4.13 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 152.8, 132.2 (2C), 131.3 (2C), 131.1 (2C), 130.2 (2C), 129.5, 129.3 (2C), 127.6 (2C), 127.1 (2C), 125.3 (2C), 125.3 (2C), 123.7, 123.4, 114.4, 76.3, 66.3, 62.8, 14.0; HRMS (ESI+) calcd for $C_{27}H_{20}BrNNaO_5$ $[M+Na]^+$ 540.0417, found 540.0419. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 21.8 (minor enantiomer), 23.8 (major) min.



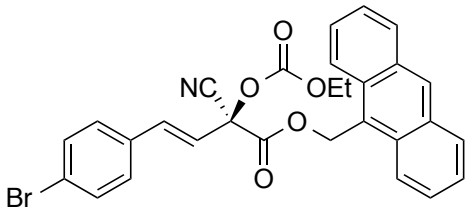
Anthracene-9-ylmethyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-2-(4-methoxyphenyl)acetate (11d): 80% yield (75.0 mg); Pale yellow oil; $[\alpha]^{25}_{D}$ –13.8 (*c* 1.0, $CHCl_3$) for 98% ee; IR (neat) 1759, 1509, 1260, 1181, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.54–7.45 (m, 4H), 7.44 (d, *J* = 9.2 Hz, 2H), 6.72 (d, *J* = 9.2 Hz, 2H), 6.37 (d, *J* = 12.4 Hz, 1H), 6.14 (d, *J* = 12.4 Hz, 1H), 4.25–4.09 (m, 2H), 3.77 (s, 3H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 161.3, 153.1, 131.3, 131.2, 130.0, 129.2 (2C), 127.7 (2C), 127.0 (2C), 125.3 (2C), 124.0, 123.6 (2C), 123.6 (2C), 122.2, 114.9, 114.3 (2C), 76.8, 66.0, 62.5, 55.5, 14.0; HRMS (ESI+) calcd for $C_{28}H_{23}NNaO_6$ $[M+Na]^+$ 492.1418, found 492.1419. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 37.0 (minor enantiomer), 41.7 (major) min.



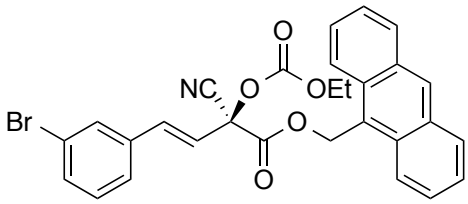
Anthracene-9-ylmethyl (*S*)-2-(benzo[*d*][1,3]dioxol-5-yl)-2-cyano-2-((ethoxycarbonyl)oxy)acetate (11e): 88% yield (85.1 mg); Pale yellow oil; $[\alpha]^{26}_{D}$ –12.1 (*c* 1.0, $CHCl_3$) for 98% ee; IR (neat) 1759, 1504, 1490, 1249, 1038, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.56–7.46 (m, 4H), 7.03 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 12.4 Hz, 1H), 6.15 (d, *J* = 12.4 Hz, 1H), 5.95 (s, 2H), 4.24–4.08 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 152.9, 149.7, 148.3, 131.4, 130.3 (2C), 130.1 (2C), 129.2 (2C), 127.1 (2C), 125.3 (2C), 124.0, 123.9, 123.6 (2C), 120.7 (2C), 108.4, 106.6, 101.9, 77.4, 66.1, 62.6, 14.1; HRMS (ESI+) calcd for $C_{28}H_{21}NNaO_7$ $[M+Na]^+$ 506.1210, found 506.1212. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 38.8 (minor enantiomer), 42.3 (major) min.



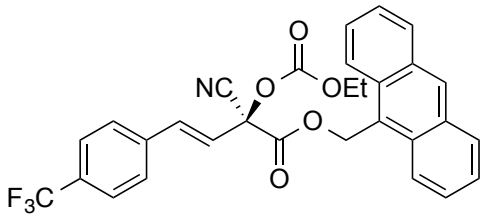
Anthracene-9-ylmethyl (*S*,*E*)-2-cyano-2-((ethoxycarbonyl)oxy)-4-phenylbut-3-enoate (11f): 66% yield (61.6 mg); Pale yellow oil; $[\alpha]^{26}_{D}$ –11.6 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1759, 1371, 1267, 1018, 967, 891, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.28 (d, *J* = 8.7 Hz, 2H), 8.24 (d, *J* = 8.2 Hz, 2H), 7.57–7.44 (m, 4H), 7.33–7.26 (m, 3H), 7.15 (dd, *J* = 1.8, 7.2 Hz, 2H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.47 (d, *J* = 12.4 Hz, 1H), 6.24 (d, *J* = 12.4 Hz, 1H), 6.04 (d, *J* = 16.0 Hz, 1H), 4.23–4.08 (m, 3H), 1.20 (t, *J* = 7.3 Hz, 3H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 152.8, 137.7, 133.9, 131.3 (2C), 131.2, 130.1, 129.7, 129.2 (2C), 128.8 (2C), 127.4 (2C), 127.1 (2C), 125.3 (2C), 124.0, 123.6 (2C), 118.0 (2C), 114.0, 75.9, 66.1, 62.6, 14.0; HRMS (ESI+) calcd for $C_{29}H_{23}NNaO_5$ $[M+Na]^+$ 488.1468, found 488.1466. The ee was determined by HPLC analysis (Daicel Chiralpack IC3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 27.5 (minor enantiomer), 35.7 (major) min.



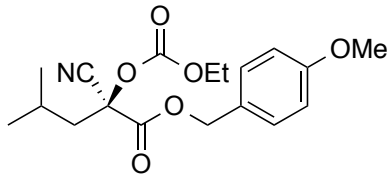
Anthracene-9-ylmethyl (*S*,*E*)-4-(4-bromophenyl)-2-cyano-2-((ethoxycarbonyl)oxy)but-3-enoate (11g): 74% yield (81.0 mg); Pale yellow oil; $[\alpha]^{25}_{D}$ –12.9 (*c* 1.0, $CHCl_3$) for 99% ee; IR (neat) 1759, 1263., 1071, 1011, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.28 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 7.8, 8.2 Hz, 2H), 7.48 (dd, *J* = 7.8, 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.49 (d, *J* = 12.4 Hz, 1H), 6.23 (d, *J* = 12.4 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 4.25–4.10 (m, 2H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 152.7, 136.4, 132.8, 132.0 (2C), 131.4, 131.2, 130.2, 129.3 (2C), 128.8 (2C), 127.2 (2C), 125.3 (2C), 125.3 (2C), 124.1, 123.9, 123.6 (2C), 118.7, 113.9, 75.6, 66.2, 62.7, 14.1; HRMS (ESI+) calcd for $C_{29}H_{22}BrNNaO_5$ $[M+Na]^+$ 566.0574, found 566.0572. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 19:1, flow rate = 1.0 mL/min) t_R= 37.2 (minor enantiomer), 40.0 (major) min.



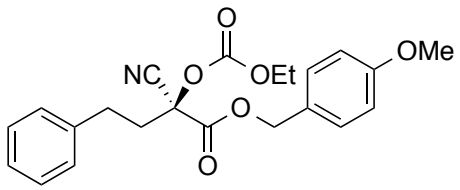
Anthracene-9-ylmethyl (*S*,*E*)-4-(3-bromophenyl)-2-cyano-2-((ethoxycarbonyl)oxy)but-3-enoate (11h): 87% yield (94.7 mg); Pale yellow oil; $[\alpha]^{27}_{D}$ –11.8 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1760, 1371, 1271, 1019, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.55 (dd, *J* = 7.6, 8.7 Hz, 2H), 7.48 (dd, *J* = 7.6, 8.7 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.51 (d *J* = 12.4 Hz, 1H), 6.23 (d, *J* = 12.4 Hz, 1H), 5.98 (d, *J* = 16.0 Hz, 1H), 4.26–4.10 (m, 2H), 1.23 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 152.7, 136.1, 135.9, 132.5 (2C), 131.4, 131.2, 130.3, 130.2, 130.1 (2C), 129.3 (2C), 127.2 (2C), 126.0, 125.3 (2C), 124.0, 123.6 (2C), 122.9, 119.5, 113.9, 75.5, 66.2, 62.8, 14.1; HRMS (ESI+) calcd for $C_{29}H_{22}BrNNaO_5$ $[M+Na]^+$566.0574, found 566.0565. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 27.1 (minor enantiomer), 40.3 (major) min.



Anthracene-9-ylmethyl (*S*,*E*)-2-cyano-2-((ethoxycarbonyl)oxy)-4-(4-(trifluoromethyl)phenyl)but-3-enoate (11i): 75% yield (80.3 mg); Pale yellow oil; $[\alpha]^{26}_{D}$ –12.8 (*c* 1.0, $CHCl_3$) for 97% ee; IR (neat) 1761, 1325, 1267, 1160, 1126, 1067, 1017, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.57–7.44 (m, 6H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 12.4 Hz, 1H), 6.24 (d, *J* = 12.4 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 4.27–4.12 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 152.7, 137.2, 136.0, 131.4, 131.4 (q, J_{C-F} = 32.4 Hz), 131.2, 130.3 (2C), 129.3 (2C), 127.6 (2C), 127.2 (2C), 125.8 (q, J_{C-F} = 3.8 Hz, 2C), 125.3 (2C), 124.0, 123.9 (q, J_{C-F} = 271 Hz), 123.6 (2C), 120.7 (2C), 113.8, 75.4, 66.3, 62.8, 14.1; HRMS (ESI+) calcd for $C_{30}H_{22}F_3NNaO_5$ $[M+Na]^+$ 556.1342, found 556.1340. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 19.2 (minor enantiomer), 28.3 (major) min.

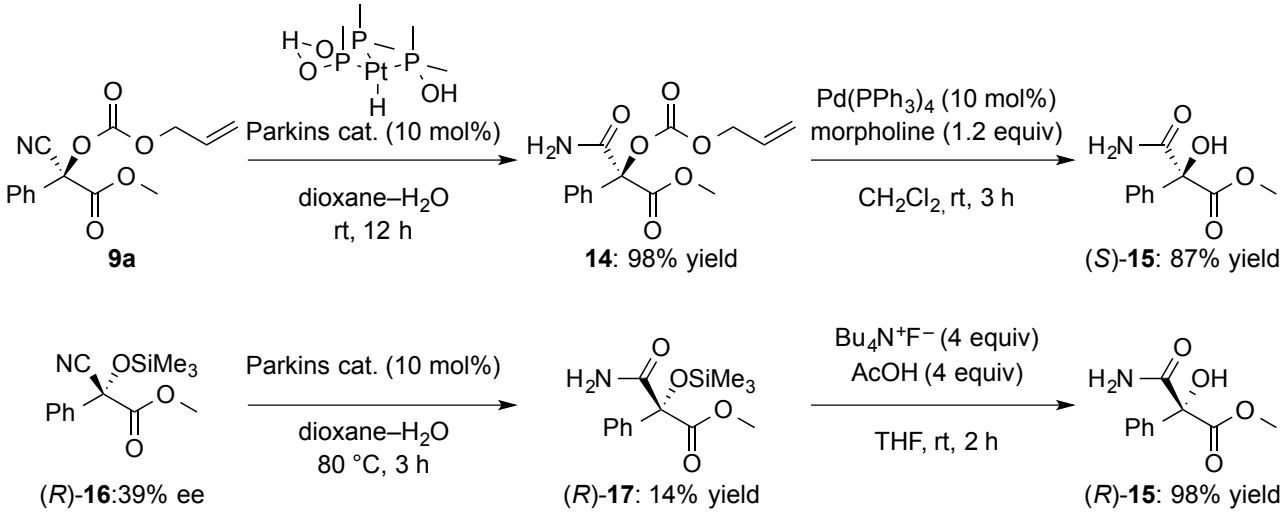


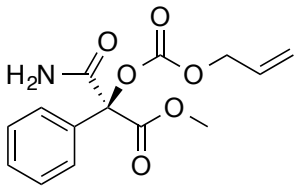
4-Methoxybenzyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-4-methylpentanoate (13a): 93% yield (65.2 mg); Clear oil; $[\alpha]^{27}_{D}$ –3.3 (*c* 1.0, $CHCl_3$) for 73% ee; IR (neat) 2964, 1760, 1613, 1517, 1467, 1372, 1259, 1176, 1137, 1116, 1019, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.29 (d, *J* = 11.9 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 2.00–1.89 (m, 3H), 1.32 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 160.2, 153.0, 130.6 (2C), 126.2, 115.3, 114.1 (2C), 75.1, 69.1, 65.9, 55.4, 44.8, 24.9, 23.4, 23.2, 14.1; HRMS (ESI+) calcd for $C_{18}H_{23}NNaO_6$ $[M+Na]^+$ 372.1418, found 372.1417. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 10.6 (minor enantiomer), 12.9 (major) min.



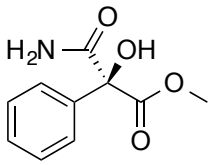
4-Methoxybenzyl (*S*)-2-cyano-2-((ethoxycarbonyl)oxy)-4-methylpentanoate (13b): 90% yield (71.5 mg); Clear oil; $[\alpha]^{26}_{D}$ –5.6 (*c* 1.0, $CHCl_3$) for 80% ee; IR (neat) 1760, 1613, 1517, 1456, 1372, 1272, 1176, 1119, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.30 (d, *J* = 11.9 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 3.81 (s, 3H), 2.79 (dd, *J* = 7.6, 10.0 Hz, 2H), 2.40–2.26 (m, 2H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.3, 152.9, 138.9, 130.7 (2C), 128.8 (2C), 128.5 (2C), 126.8, 126.2, 114.9, 114.2 (2C), 74.9, 69.3, 66.1, 66.1, 55.4, 38.7, 29.8, 14.2; HRMS (ESI+) calcd for $C_{22}H_{23}NNaO_6$ $[M+Na]^+$ 420.1418, found 420.1408. The ee was determined by HPLC analysis (Daicel Chiralpack IA-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 10.9 (minor enantiomer), 13.7 (major) min.

Determination of Absolute Configuration



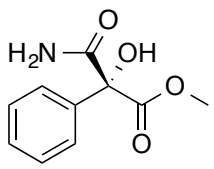


Methyl (*S*)-2-cyano-2-(((allyloxy)carbonyl)oxy)-3-amino-3-oxo-2-propanate (14): To a solution of **9a** (88.0 mg, 0.30 mmol) in dioxane (1.2 mL) and H_2O (0.3 mL) was added Parkins catalyst[10] (6.4 mg, 0.015 mmol, 5 mol%) at ambient temperature, and the mixture was stirred for 12 h. After the stirring, the mixture was filtered to remove Parkins catalyst. The residue was diluted by ethyl acetate and washed with brine, and dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 4:1 → 2:1) to give **14** (86.4 mg, 98% yield). Colorless solid; $[\alpha]^{26}_{D}$ 35.1 (*c* 1.0, $CHCl_3$) for 89% ee; IR (KBr) 3420, 3200, 1753, 1733, 1704, 1370, 1305, 1195, 1041, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11(br, 1H), 7.67–7.61 (m, 2H), 7.43–7.36 (m, 3H), 5.97 (ddt, 6.0, 10.5, 17.0 Hz, 1H), 5.82 (br, 1H), 5.42 (d, 17.0 Hz, 1H), 5.31 (d, 10.5 Hz, 1H), 4.75–4.70 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 167.6, 154.1, 133.4, 131.0, 129.6, 129.0 (2C), 125.5 (2C), 119.3, 83.4, 69.5, 53.8; HRMS (ESI+) calcd for $C_{14}H_{15}NNaO_6$ $[M+Na]^+$ 316.0792, found 316.0792.



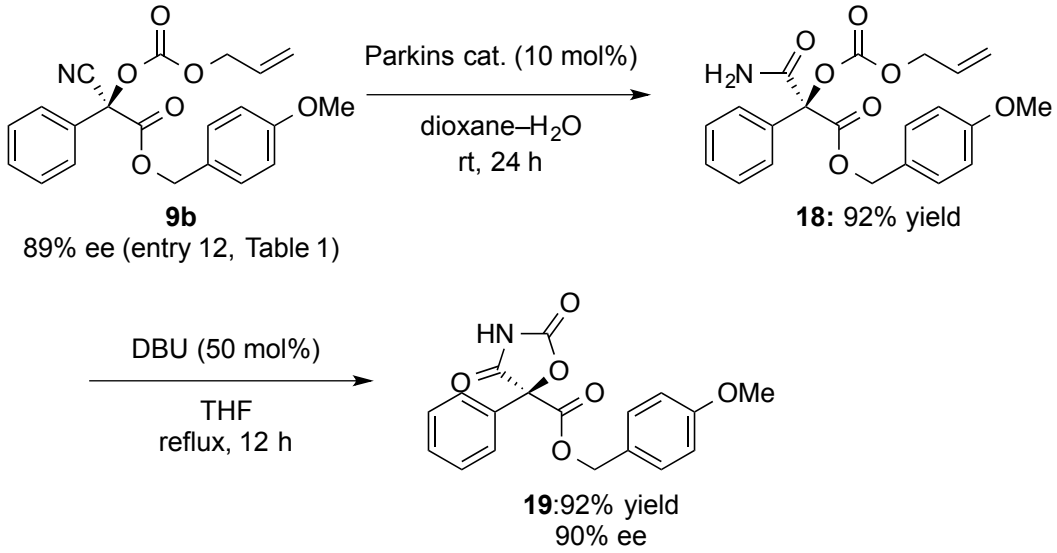
Methyl (*S*)-3-amino-2-hydroxy-3-oxo-2-propanoate ((*S*)-15): To a solution

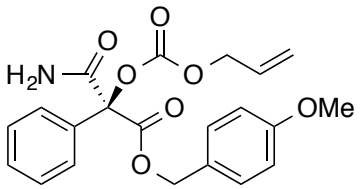
of **14** (86.4 mg, 0.29 mmol) in THF (1.47 mL) were added morpholine (30.5 μL, 0.35 mmol, 1.2 equiv) and tetrakis(triphenylphosphine)palladium(0) (40.4 mg, 0.035 mmol, 10 mol%) at ambient temperature, and the mixture was stirred for 3 h. After the stirring, the mixture was concentrated in *vacuo.* The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:1) to give **(*S*)-15** (52.8 mg, 87% yield). Colorless solid; $[\alpha]^{26}_{D}$ –23.1 (*c* 1.0, $CHCl_3$) for 90% ee (*S*); IR (KBr) 3474, 3336, 3247, 1727, 1683, 1434, 1281, 1178, 1128, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.63 (m, 2H), 7.50–7.33 (m, 3H), 6.99 (br, 1H), 5.96 (br, s), 4.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.4, 137.5, 128.9, 128.6 (2C), 126.1 (2C), 80.0, 54.2; HRMS (ESI+) calcd for $C_{10}H_{11}NNaO_4$ $[M+Na]^+$ 232.0580, found 232.0578. The ee was determined by HPLC analysis (Daicel Chiralpack IA3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 21.0 (major enantiomer), 23.9 (minor) min.



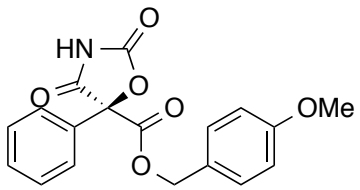
Methyl (*R*)- 3-amino-2-hydroxy-3-oxo-2-propanoate ((*R*)-15): To a solution of **16**[11] (88.0 mg, 0.30 mmol) in dioxane/H_2O (1.20 mL/0.30 mL, 4/1 v/v) was added Parkins catalyst[10] (6.4 mg, 0.015 mmol, 5 mol%) at ambient temperature, and the mixture was stirred for 3 h at 80 ºC. After the stirring, the mixture was filtered to remove Parkins catalyst. The residue was diluted by ethyl acetate and washed with brine, and dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 5:1 → 3:1) to give **17** (11.8 mg, 14% yield). To a solution acetic acid (9.7 μL, 0.17 mmol) in THF (250 μL) was added 1.0 M THF solution of TBAF (170 μL, 0.17 mmol). The mixture was added to a solution **17** (11.8 mg, 0.04 mmol) in THF (400 μL) at 0 ºC, and stirred for 2 h at ambient temperature. After the stirring, saturated aqueous $NaHCO_3$ (1.0 mL) was added to quench. The organic layer was separated, washed with brine, and dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:1) to give **(*R*)-15** (8.2 mg, 98% yield).; $[\alpha]^{26}_{D}$ 9.1 (*c* 1.0, $CHCl_3$) for 39% ee (*R*); The ee was determined by HPLC analysis (Daicel Chiralpack IA3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 20.7 (minor enantiomer), 22.4 (major) min.

Transformation of Cyano-allyloxycarbonylation Product





4-Methoxybenzyl (*S*)-2-(((allyloxy)carbonyl)oxy)-3-amino-3-oxo-2-propanate (18): **18** was prepared from **9b** (370 mg, 0.97 mmol) and Parkins catalyst[10] according to the same manner as **14a**. 92% yield (356 mg); Clear oil; $[\alpha]^{27}_{D}$ –3.0 (*c* 1.0, $CHCl_3$); IR (neat) 3446, 3357, 1752, 1704, 1516, 1300, 1282, 1249, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (br, 1H), 7.63–7.56 (m, 2H), 7.40–7.32 (m, 3H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.85 (ddt, *J* = 6.0, 11.9, 17.4 Hz, 1H), 5.63 (br, 1H), 5.34 (d, *J* = 17.4 Hz, 1H), 5.24 (d, *J* = 11.5 Hz, 2H), 5.10 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.7, 160.0, 153.9, 133.4, 131.0, 130.3 (2C), 129.5, 128.8 (2C), 126.4, 125.5 (2C), 119.3, 113.9 (2C), 83.4, 69.4, 68.5, 55.3; HRMS (ESI+) calcd for $C_{21}H_{21}NNaO_7$ $[M+Na]^+$ 422.1210, found 422.1196.

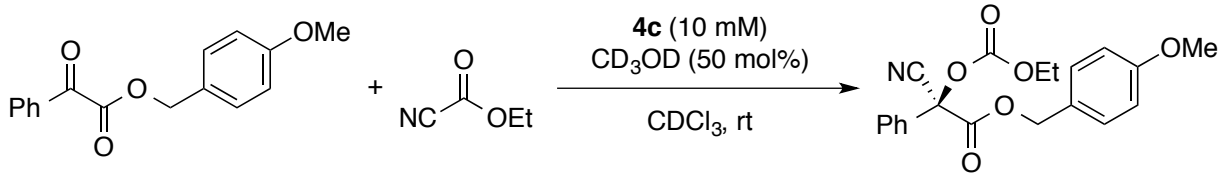


4-Methoxybenzyl (*S*)-2,4-dioxo-5-phenyloxazolidine-5-carboxylate (19): The mixture of **18** (79.9 mg, 0.2 mmol) and DBU (14.9 μL, 0.1 mmol, 50 mol%) in THF (1.0 mL) was stirred for 12 h under reflux

condition. After the stirring, 0.1 M aqueous HCl (2.0 mL) was added to quench. The resultant mixture was extracted with ethyl acetate (3.0 mL x 2). The combined organic layer was washed with water and brine, and dried with Na_2SO_4. After the filtration, the residue was concentrated in *vacuo*. The resultant residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:1 → 1:2) to give **19** (62.8 mg, 92% yield). Clear oil; $[\alpha]^{27}_{D}$ 2.9 (*c* 1.0, $CHCl_3$) for 90% ee; IR (neat) 3579, 1834, 1766, 1516, 1348, 1248, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.45–7.37 (m, 3H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.19 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 163.6, 160.1, 152.8, 130.8, 130.3 (2C), 130.1, 128.8 (2C), 126.3, 125.6 (2C), 114.2 (2C), 87.2, 69.3, 55.4; HRMS (ESI+) calcd for $C_{18}H_{15}NNaO_6$ $[M+Na]^+$ 364.0792, found 364.0797. The ee was determined by HPLC analysis (Daicel Chiralpack IA-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R= 38.1 (minor enantiomer), 43.2 (major) min.

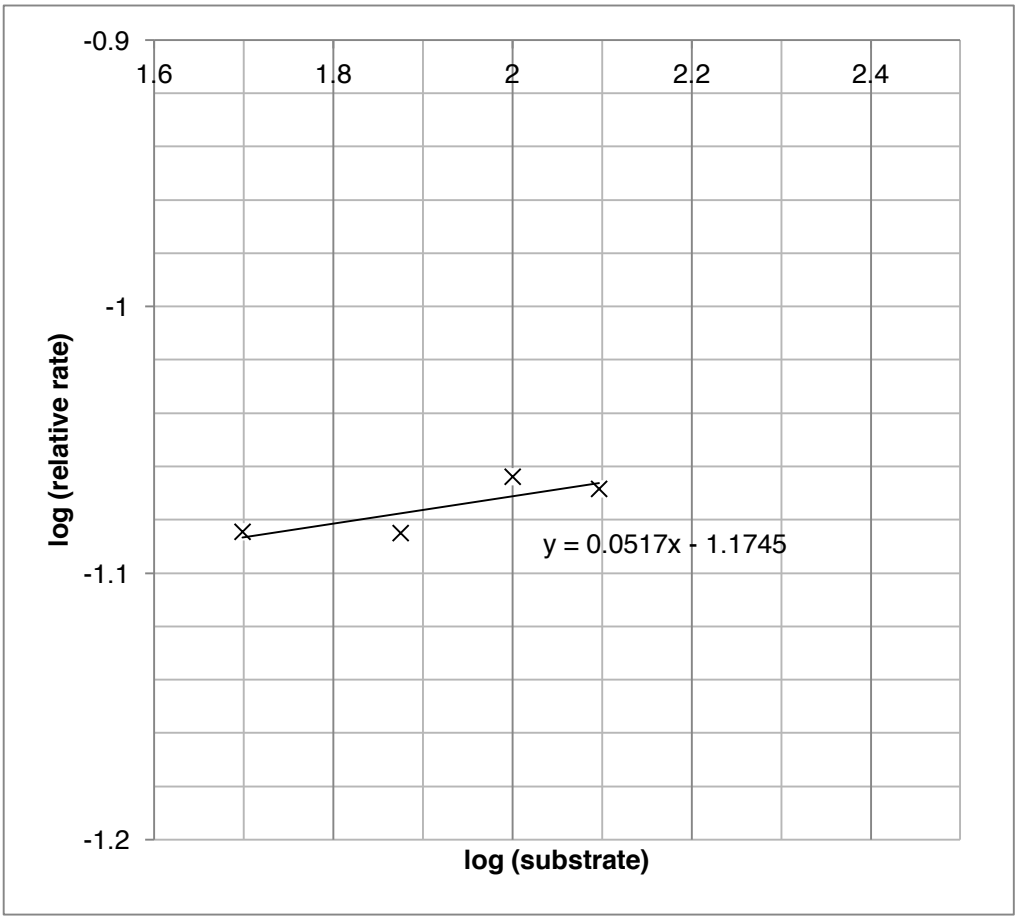
Mechanistic Studies.

Initiral rate kinetics for α-Ketoester

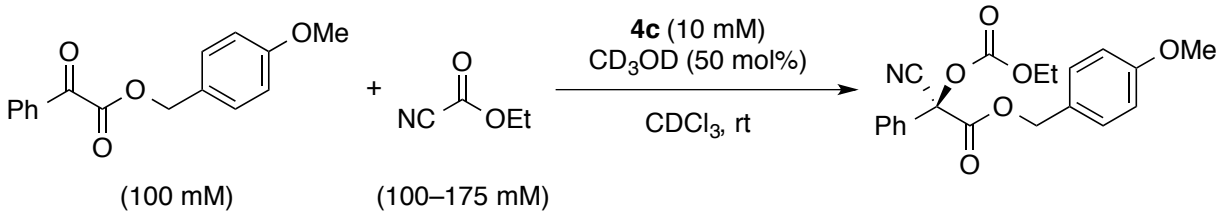


(50–125 mM) (150 mM)

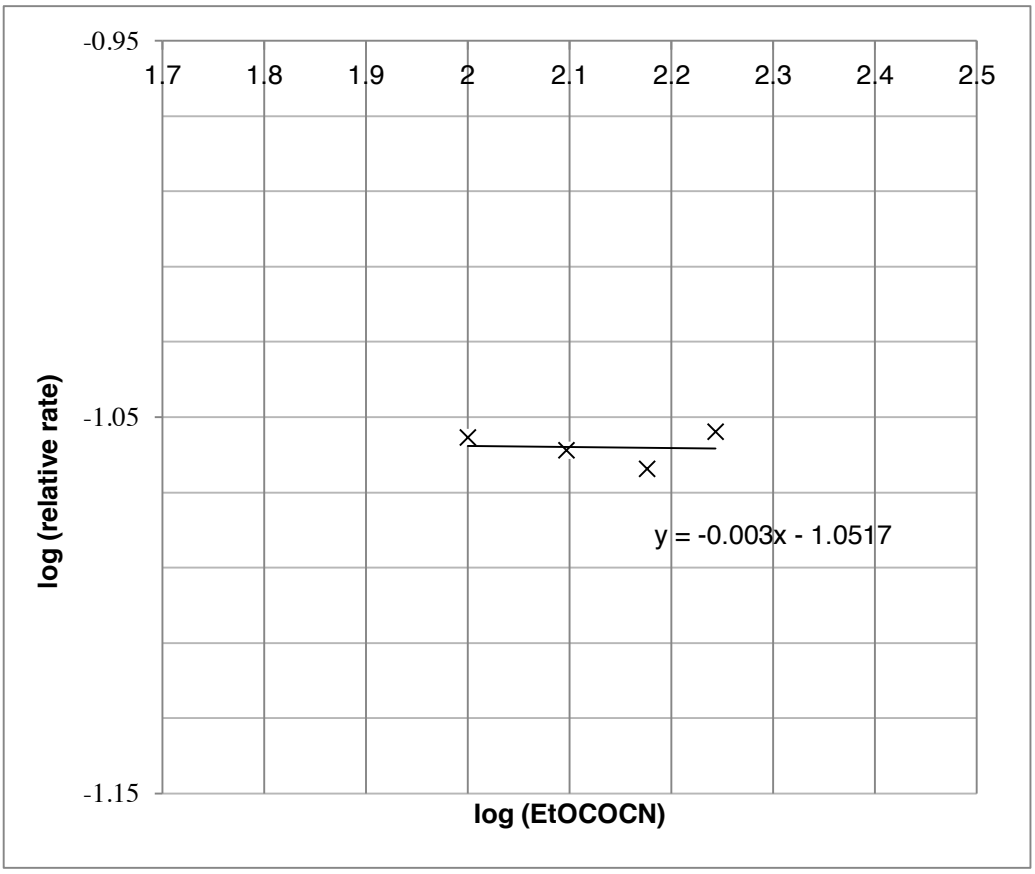
substrate [mM]	log (substrate)	relative rate [mM/min]	log (relative rate)
50	1.70	0.0823	–1.08
75	1.88	0.0823	–1.08
100	2.00	0.0463	–1.06
125	2.10	0.0354	–1.07



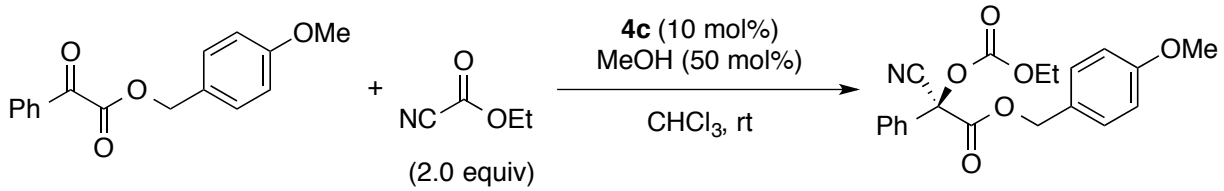
Initial rate kinetics for ethyl cyanoformate



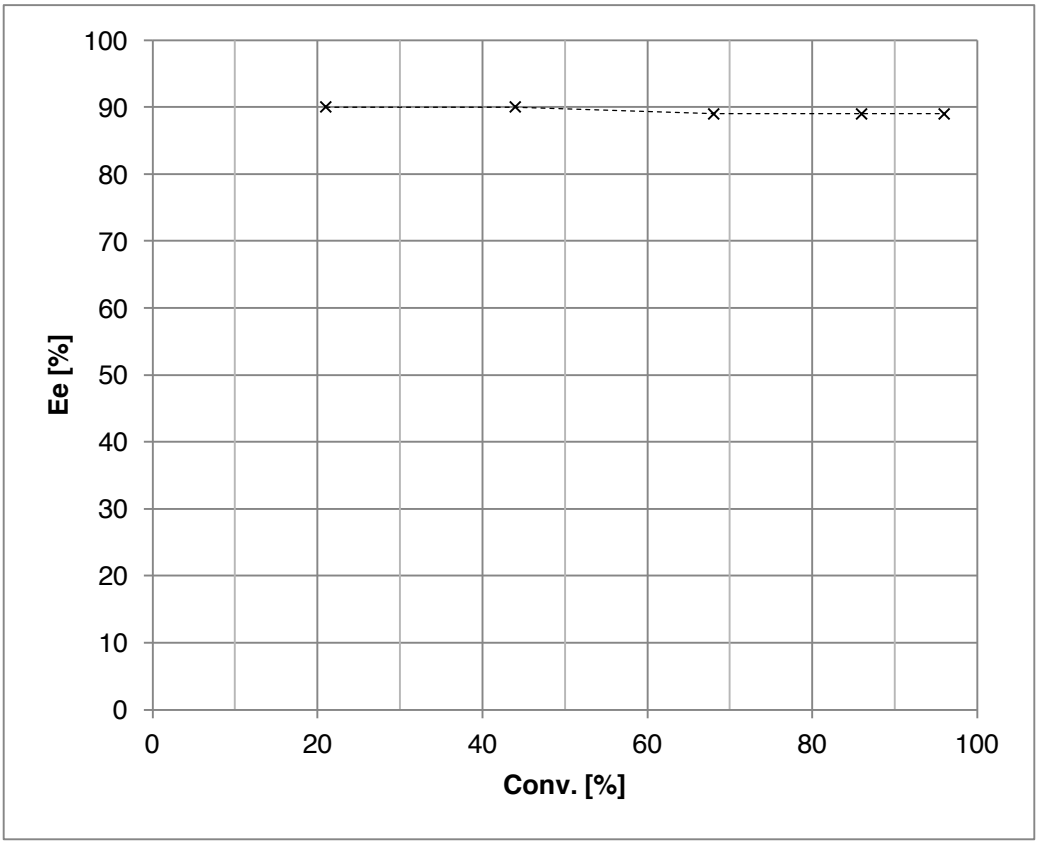
EtOCOCN [mM]	log (substrate)	relative rate [mM/min]	log (relative rate)
100	2.00	0.0880	–1.06
125	2.10	0.0873	–1.06
150	2.18	0.0863	–1.06
175	2.24	0.0883	–1.05



Conversion versus enantioselectivity



time [h]	1	3	6	9	12
conversion [%]	21	44	68	86	96
ee [%]	90	90	89	89	89



References and Notes for Experimental Section

1. Recent report of the synthetic method of **1**; (a) Ogura, Y.; Akakura, M.; Sakakura, A.; Ishihara, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8299. (b) Zhao, M.; Dai, T.; Liu, R.; Wei, D.; Zhou, H.; Ji, F.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 7970. (c) Li, W.; Wu, W.; Yu, F.; Huang, H.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2011**, *9*, 2505.
2. Recent report of the synthetic method of **2**; (a) Bae, H. Y.; Song, C. *ACS Catal.* **2015**, *5*, 3613. (b) Yoneda, N.; Hotta, A.: Asano, K.; Matsubara, S. *Org. Lett.* **2014**, *16*, 6264. (c) Fukata, Y.; Miyajo, R.; Okamura, T.; Asano, K.; Matsubara, S. *Synthesis*, **2013**, *45*, 1627. (d) Jin, Z.; Xu, J.; Yang, S.; Song, B.; Chi, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 12354. (e) Fukase, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2013**, *135*, 12160.
3. Synthetic method of **S1a**; Li, J.; Fu, N.; Zhang, L.; Zhou, P.; Luo, S.; Cheng, J. *Eur. J. Org. Chem.* **2010**, 6840.
4. Synthetic method of **S5**; Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2012**, *48*, 5040.
5. Recent report of the synthetic method of **S4a**; (a) Edwards, S. J.; Valkenier, H.; Busschaert, N.; Gale, P. A.; Davis, A. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 4592. (b) Ghosh, D.; Gupta, N.; Abdi, S. H. R.; Nandi, S.; Khan, N. H.; Kureshy, R. I.; Bajaj, H. C. *Eur. J. Org. Chem.* **2015**, 2801.
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7. Synthetic method of 4-methoxybenzyl benzoylformate **(7e)**; Sagar, A.; Vidyacharan, S.; Shinde, D. S. *RSC Adv.* **2014**, *4*, 37047.
8. Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett*. **2013**, *15*, 220.
9. Synthetic method of allyl cyanoformate; Donnelly, D. M. X.; Finet, J. P.; Rattigan, B. A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1729.
10. Synthetic method of Parkins' catalyst; (a) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A Chem.* **2000**, *160*, 249. (b)Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.
11. **16** was synthesized as reported procedure.; Kurono, N.; Uemura, M.; Ohkuma, *Eur. J. Org. Chem.* **2010**, 1455.; $[\alpha]^{22}_{D}$ 10.1 (*c* 1.1, $CHCl_3$) for 39% ee (*R*) (lit. $[\alpha]^{24}_{D}$ 24.0 (*c* 1.1, $CHCl_3$) for 99% ee (*R*)); The ee was determined by HPLC analysis (Daicel Chiralpack OJ-H column, hexane–*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min) t_R= 13.2 (major enantiomer), 14.1 (minor)

min.

Research Achievement

A. Publication List

Chapter 2

1. "Enantioselective Cyano-ethoxycarbonylation of Isatins Promoted by a Lewis Base-Brønsted Acid Cooperative Catalyst"
   Yoshihiro Ogura, Matsujiro Akakura, Akira Sakakura, Kazuaki Ishihara
   Angew. Chem. Int. Ed. **2013**, *52*, 8299–8303.

Chapter 3

2. "Enantioselective Cyano-Alkoxycarbonylation of α-Oxoesters Promoted by Brønsted Acid–Lewis Base Cooperative Catalysts"
   Kazuaki Ishihara, Yoshihiro Ogura
   Org. Lett. **2015**, *17*, 6070–6073.

Following publication is not included in this thesis.

3. "Enantioselective Bromocyclization of 2-Geranyl Phenols Induced by Phosphite-Urea Bifunctional Catalysts"
   Kazuaki Ishihara, Yasuhiro Sawamura, Hidefumi Nakatsuji, Yoshihiro Ogura
   Chem. Commun. Accepted.
4. "Transesterification Reaction Promoted by Highly Active Tetraalkylammonium Methylcarbonate"
   Manabu Hatano, Yurika Yoshida, Yuji Tabata, Yoshihiro Ogura, Kenji Yamashita, Kazuaki Ishihara
   Manuscript in preparation.
5. "Tandem Isomerization/Enantioselective Cycloaddition Reaction of 3-Butynoyl-1H-pyrazole Promoted by Chiral π-Cu(II) Catalysts"
   Kazuaki Ishihara, Yoshihiro Ogura, Masahiro Hori
   Manuscript in preparation.
6. "Enantioselective α-Halogenantion Reaction of Acyl-1*H*-pyrazoles Promoted by Chiral π-Cu(II) Catalyst"
   Kazuaki Ishihara, Yanzhao Wang, Yoshihiro Ogura
   Manuscript in preparation.

B. International Conferences

Oral Presentations

1. ◯Yoshihiro Ogura, Matsujiro Akakura, Kazuaki Ishihara
   "Enantioselective Cyano-ethoxycarbonylation of Isatins and a-Ketoesters Promoted by **Lewis Base-Brønsted Acid Cooperative Organocatalyst"**
   SJTU-NU Inter-University Research Seminar for Ph. D. Course Students of Bio-Related Chemistry, OL9, Shanghigh Jiaotong University, Shanghai, China, March, 2014

Poster Presentations

1. ◯Yoshihiro Ogura, Matsujiro Akakura, Akira Sakakura, Kazuaki Ishihara
   "Development of Highly Enantioselective Cyano-Ethoxycarbonylation of Isatin Derivatives"
   Nagoya Symposium 2013, P-30, Nagoya University, Nagoya, Japan, May, 2013
2. ◯Yoshihiro Ogura, Matsujiro Akakura, Akira Sakakura, Kazuaki Ishihara,
   "Catalytic Asymmetric Cyano-ethoxycarbonylation of Isatins Promoted by Oxyanion Hole Mimetic Lewis Base-Brønsted Acid Cooperative Organocatalyst"
   ACP The 3rd Junior Conference on Cutting-Edge Organic Chemistry in Asia, P-25, Seimei no Mori Resort Hotel, Chiba, Japan, November, 2013

C. Domestic Conferences

Oral Presentations

1. ◯小倉 義浩・坂倉 彰・石原 一彰
   「エナンチオ選択的シアノカルボニル化反応に有効な酸・塩基複合型不斉有機触媒の精密設計」
   日本化学会第 92 春季年会, 3K3-37, 慶応大学, 神奈川, 2012 年 3 月
2. ◯小倉 義浩・坂倉 彰・石原 一彰
   「エナンチオ選択的シアノカルボニル化反応に有効な酸・塩基複合型不斉有機触媒の精密設計」
   名古屋大学–理化学研究所有機化学系研究交流会, 3, 理化学研究所, 埼玉, 2012 年 3 月
3. ◯小倉 義浩・坂倉 彰・石原 一彰
   「イサチン類の高エナンチオ選択的シアノエトキシカルボニル化反応の開発」
   日本化学会第 93 春季年会, 3E5-06, 立命館大学, 滋賀, 2013 年 3 月
4. ◯小倉 義浩・石原 一彰

「ブレンステッド酸ールイス塩基協奏型キラル有機触媒を用いるα−ケトエステル類のエナンチオ選択的シアノエトキシカルボニル化反応」

日本化学会第 94 春季年会, 2B6-44, 名古屋大学, 愛知, 2014 年 3 月

5. ○小倉 義浩・石原 一彰

「オキシアニオンホール触媒を用いるα−ケトエステル類の不斉シアノエトキシカルボニル化反応とオキサゾリジノン類への誘導」

日本化学会第 95 春季年会, 2E3-17, 日本大学, 千葉, 2015 年 3 月

6. ○吉田 有梨花・小倉 義浩・神谷 渉・波多野 学・石原 一彰

「金属元素を含まないメチル炭酸テトラアルキルアンモニウム触媒を用いるエステル交換反応」

日本化学会第 95 春季年会, 2E3-56, 日本大学, 千葉, 2015 年 3 月

7. ○Yoshihiro Ogura

"Asymmetric Cyanation of Isatins and α-Ketoesters *via* Recognition of Anion Chiraltiy"

第一回野依フォーラム若手育成塾, 005, 名古屋大学、愛知、2015 年 7 月

8. ○小倉 義浩・石原 一彰

"Tandem Isomerization/Enantioselective Cycloaddition Reaction of 3-Butynoyl-1*H*-pyrazole Promoted by Chiral π-Cu(II) Catalysts"

日本化学会第 96 春季年会, 4H1-17, 同志社大学, 京都, 2016 年 3 月

9. ○王 彦兆・小倉 義浩・石原 一彰

"Enantioselective α-Halogenation Reaction of Acyl-1H-pyrazoles Promoted by Chiral π-Cu(II) Catalysts"

日本化学会第 96 春季年会, 4H1-19, 同志社大学, 京都, 2016 年 3 月

10. ○吉田 有梨花・小倉 義浩・波多野 学・石原 一彰

「メチル炭酸トリオクチルメチルアンモニウム触媒を用いるキレート性基質のエステル交換反応」

日本化学会第 96 春季年会, 4H1-39, 同志社大学, 京都, 2016 年 3 月

Poster Presentations

1. ○小倉 義浩・坂倉 彰・石原 一彰

「シアノカルボニル化反応に有効な酸・塩基複合型不斉触媒の設計」

第 47 回有機反応若手の会, P56, 湯郷グランドホテル, 岡山, 2013 年 3 月

2. ○小倉 義浩・坂倉 彰・石原 一彰

「酸・塩基複合型不斉有機触媒を用いたα−ケトアミド類に対する不斉シアノカルボニル化反応」

第 43 回中部化学関係学協会支部連合秋季大会, 1P28, 名古屋工業大学, 愛知, 2012 年 11 月

3. ○小倉 義浩・坂倉 彰・石原 一彰

"Development of Highly Enantioselective Cyano-ethoxycarbonylation of Isatin Derivatives"

IGER Annual Meeting 2012, G-20, 名古屋大学, 愛知, 2013 年 1 月

4. ○小倉 義浩・赤倉 松次郎・坂倉 彰・石原 一彰

「生物活性オキシインドールの合成を目指した不斉シアノエトキシカルボニル化反応の開発」

第 48 回天然物化学談話会, B16, アヤハレークサイドホテル, 滋賀, 2013 年 7 月

5. ○小倉 義浩・赤倉 松次郎・坂倉 彰・石原 一彰

「生物活性オキシインドールの合成を目指した触媒的不斉シアノエトキシカルボニル化反応の開発」

八大学工学研究科拠点博士課程学生交流セミナー, P-03, 名古屋大学, 愛知, 2013 年 11 月

6. ○小倉 義浩・石原 一彰

"Highly Enantioselective Cyano-ethoxycarbonylation of Isatins and α-Ketoesters Promoted by a Brønsted Acid-Lewis Base Cooperative Chiral Organocatalyst and Investigation of Its Catalytic Mechanism"

IGER Annual Meeting 2013, G-8, 名古屋大学, 愛知, 2014 年 1 月

7. ○小倉 義浩・石原 一彰

「オキシアニオンホール触媒を用いるイサチン類及びα-ケトエステル類の不斉シアノエトキシカルボニル化反応」

4th CSJ 化学フェスタ 2014, P1-041, タワーホール船堀, 東京, 2014 年 10 月

Highlighted in *化学と工業 (Kagaku to Kogyo (Tokyo, Japan))* **2015**, *68(1)*, 37.

8. ○小倉 義浩・石原 一彰

"Enantioselective Cyanoethoxycarbonylation of Isatins and α-Ketoesters Using Oxyanion Hole Catalyst"

IGER Annual Meeting 2014, G-20, 名古屋大学, 愛知, 2014 年 12 月

9. ◯吉田 有梨花・小倉 義浩・神谷 渉・波多野 学・石原 一彰
「金属元素を含まないメチル炭酸テトラアルキルアンモニウム触媒を用いるエステル交換反応」
日本化学会第 95 春季年会, 1PC-032, 日本大学, 千葉, 2015 年 3 月

10. ◯小倉 義浩・石原 一彰
「アニオン認識を鍵とする不斉シアノエトキシカルボニル化反応の開発」
第 32 回有機合成化学セミナー, P-04, ニューウェルシティ湯河原, 静岡, 2015 年 9 月
Highlighted in *有機合成化学協会誌 (J. Synth. Org. Chem. (Tokyo, Japan))* **2015**, *73(12)*, 1266.

11. ◯小倉 義浩・石原 一彰
"Tandem Isomerization/Enantioselective Cycloaddition Reaction of 3-Butynoyl-1*H*-pyrazole Promoted by Chiral π-Cu(II) Catalysts"
IGER Annual Meeting 2015, G-25, 名古屋大学, 愛知, 2016 年 1 月

12. ◯吉田 有梨花・多畑 勇志・小倉 義浩・山下 賢二・波多野 学・石原 一彰
「高活性第四級アンモニウム塩触媒を用いるエステル交換反応」
日本化学会第 96 春季年会, 1PC-036, 同志社大学, 京都, 2016 年 3 月

D. Awards

1. 優秀賞（第 43 回中部化学関係学協会支部連合秋季大会）
2. Award of The Best Poster Presentation （ACP The 3rd Junior Conference on Cutting-Edge Organic Chemistry in Asia）
3. 最優秀ポスター発表賞（4th CSJ 化学フェスタ 2014）
Highlighted in *化学と工業 (Kagaku to Kogyo (Tokyo, Japan))* **2015**, *68(1)*, 37.
4. Poster Award（IGER Annual Meeting 2014）
5. 優秀ポスター賞（第 32 回有機合成化学セミナー）
Highlighted in *有機合成化学協会誌 (J. Synth. Org. Chem. (Tokyo, Japan))* **2015**, *73(12)*, 1266.

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