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Chiral *N,N′*-Dioxide Organocatalyzed Asymmetric Electrophilic *α*-Cyanation of *β*-Keto Esters and *β*-Keto Amides

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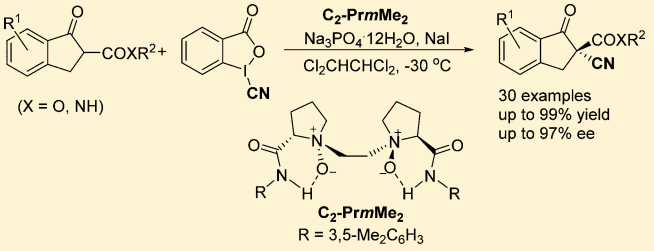
Supporting Information

ABSTRACT: An enantioselective electrophilic *α*-cyanation of 1-indanone-derived *β*-keto esters and *β*-keto amides using a hypervalent iodine as the cyanide-transfer reagent was realized. A chiral *N,N′*-dioxide was used as the efficient bifunctional organocatalyst in the presence of inorganic base, which gave the corresponding *α*-cyano dicarbonyl compounds in yields of 50−99% with good enantioselectivities (87−97% ee).

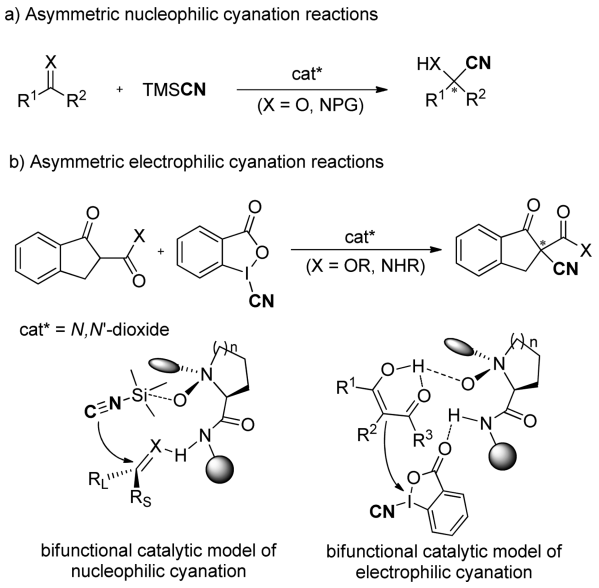


INTRODUCTION

The enantioselective introduction of a cyano group into molecules is vital to research in organic chemistry.[1] There are several successful examples of asymmetric nucleophilic addition of cyano reagents to electrophiles including C═O, C═N, and C═C bonds (Scheme 1, eq a).[2] Nonetheless, as an alternative method, catalytic enantioselective electrophilic cyanation reaction is less explored. Until very recently, asymmetric electrophilic *α*-cyanations of *β*-keto esters[3] were reported by Waser[4a] and Zheng,[4b] respectively (Scheme 1, eq b). The use of cinchona alkaloids allows the enantioselective *α*-cyanation reaction of 1-indanone derived *β*-keto esters in 20−52% ee.[4a] And in the presence of cinchona alkaloid-based chiral quaternary ammonium salt and using *tert*-butyl substituted cyano benziodoxole as the cyanide transfer reagent, up to 93% ee was obtained for the reaction, but organic base was found crucial to both the yield and the enantioselectivity.[4b] In addition, previous synthesis of racemic *α*-cyanation products reported by the Chen group could be performed without additional catalyst in DMF.[4c] We propose that a proper chiral Brønsted base would enable the formation of enol or enolate intermediate from the *β*-keto ester, which undergoes electrophilic addition of hypervalent iodine reagent[5] and cyano group rearrangement, generating the *α*-cyanation *β*-keto ester product[6] in an enantioselective manner.

Acting as a bifunctional organocatalyst, chiral *N,N′*-dioxides[7] has been proven useful for the asymmetric cyanosilylation of carbonyl compounds and imines.[7b] In these cases, *O*-amine units of the catalysts act as Lewis base for activation of silicon-based cyanide and the amide units act as hydrogen-bond donor to activate the electrophiles (Scheme 1, lower-left model). We envision that chiral *N,N′*-dioxides could also work as an efficient bifunctional catalyst for the asymmetric electrophilic cyanation reaction of the *β*-keto esters, in view of the fact that the asymmetric *α*-functionalization reaction of *β*-keto esters has been realized by such chiral catalyst.[8] *N,N′*-dioxides could act as Brønsted base catalysts to activate the enol of *β*-keto carbonyl compounds, and the amide-NH as a hydrogen-bond donor to bind the cyano benziodoxole (Scheme 1, lower-right model). Herein, we expand chiral *N,N′*-dioxides in asymmetric electrophilic cyanation of both *β*-keto esters and *β*-keto amides. Unlike earlier study,[4b] an inorganic base $Na_3PO_4·12H_2O$ instead of DMAP, and an unsubstituted cyano benziodoxole as the cyanide reagent[9] are involved. Excellent enantioselectiv-

Scheme 1. Asymmetric Nucleophilic and Electrophilic Cyanations and the Possible Bifunctional Catalytic Models of chiral *N,N′*-Dioxides Catalysts



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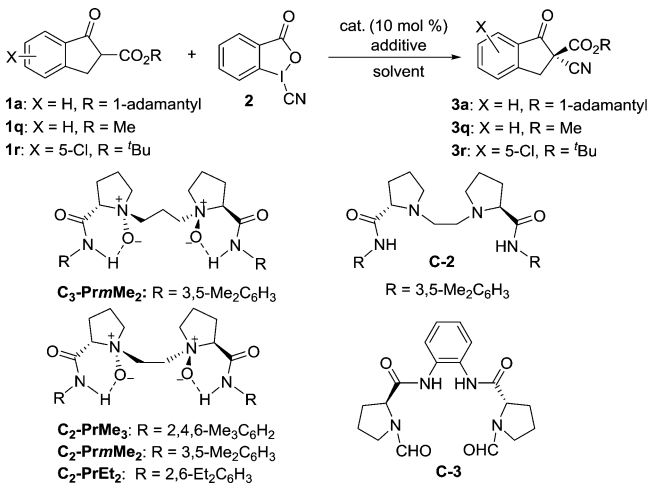
ities (87−97% ee) are achieved for 1-indanone-derived β-keto esters and β-keto amides regardless of the nature of the substituents.

RESULTS AND DISCUSSION

Initially, we chose the asymmetric cyanation of 1-indanone-derived β-keto ester **1a** and cyano benziodoxole **2** as the model reaction to optimize the chiral catalysts (Table 1). Chiral *N*,*N*′-dioxides with variable amide substituents and amino acid backbone are investigated in CH_2Cl_2 at 35 °C. Assessment of the amino acid backbone of *N*,*N*′-dioxides shows that L-proline-derived ones give better outcomes in terms of enantioselectivity than other amino acid derived ones (see SI for details). Aniline subunits of the catalysts with substituents at *meta*-positions are superior in enantioselectivity than substituents at *ortho*-positions (entry 1 vs entries 2 and 3). *N*,*N*′-dioxide **C_2-Pr*m*Me_2** bearing a two carbon linkage shows better enantiocontrol than 3C-linked **C_3-Pr*m*Me_2** (35% yield and 56% ee; entry 1 vs entry 4). Next, a series of solvents are screened when **C_2-Pr*m*Me_2** is employed as the catalyst of the reaction. It is found that the yield and the enantioselectivity improved to 50% and 66% ee, respectively, when TCE is used as the reaction solvent (entries 5−7). The reactions in THF and EtOAc led to a significant improvement in the yields (up to 80%) but afforded the products in sharply decreased enantiomeric excess (entries 6 and 7). It is possible that oxygen-containing solvent might interfere with the hydrogen-bond network between the catalyst and the reactants. Thus, TCE is chosen as the best solvent to investigate the effect of reaction temperature. The enantioselectivity increases to 91% ee upon decreasing the reaction temperature to −30 °C and increasing the catalyst loading, but the yield is extremely low (23% yield; entries 8 and 9). To improve the reactivity, basic additives, such as K_2CO_3, and DMAP, are included in the reaction, and almost in all cases the yields increase a lot but the enantioselectivities reduce a little (entries 10 and 11). These bases brought more or less background reaction (64% and 88% yield, respectively; entries 12 and 13), which made the enantioselectivity slightly lower. While $Na_3PO_4{\cdot}12H_2O$ is used as an additive, high yield (85%) and 90% ee are obtained (entry 14). Moreover, increasing the amount of $Na_3PO_4{\cdot}12H_2O$ and adding NaI yields a further increased outcome (99% yield and 93% ee; entry 15). In addition, replacing the chiral *N*,*N*′-dioxide catalyst with the bisaminoamide **C-2**, the precursor of **C_2-Pr*m*Me_2**, affords the desired product **3a** in 69% yield as a racemate (entry 16). It indicates that the *N*-oxide units of the catalyst are crucial for the enantiocontrol. Racemic cyanation reaction performs well in DMF,[4c] which might act as both a Brønsted base catalyst and reaction solvent. Therefore, a chiral bisformamide **C-3**, which included a formamide structure similar to DMF, was tested in the presence of additives. Although a moderate yield of 55% was given, the enantioselectivity was poor (entry 17). Moreover, it is found that the steric hindrance of the ester unit on the substrate **1** greatly affects the enantioselectivity. Bulky protecting groups, such as 1-adamantoyl and *tert*-butyl protection groups are important to afford higher enantioselectivity, and methyl-substituted one gives sharply decreased enantioselectivity (entries 18 and 19). Therefore, chiral *N*,*N*′-dioxide **C_2-Pr*m*Me_2** and $Na_3PO_4{\cdot}12H_2O$/NaI are used as the optimal catalysts for the reaction of various 1-adamantyl substituted β-keto carbonyl compounds.

In the effort to explore the scope of the cyanation reaction, the standard conditions identified in Table 1, entry 15 are tested with a range of substituted 1-indanone-derived β-keto esters. As show in Table 2, a wide range of β-keto esters **1a−1l** bearing different substituents at variable positions participated in the asymmetric cyanation reactions with cyano benziodoxole **2** well, affording the corresponding cyano-substituted β-keto esters **3a−3l** in excellent yields (66−99%) and enantioselectivities (88−95% ee). It is obvious that the electronic nature and position of the substituents on the indanone unit have a slight effect on the enantioselectivity but a significant effect on the yield. This trend is different from chiral quaternary ammonium salt/DMAP system in which electron-donating groups give obviously higher enantioselectivity than electron-withdrawing ones.[4b] In the current system, comparatively, electron-donating

Table 1. Optimization of the Reaction Conditions[a]



entry	1	cat.	additive	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	**C_2-Pr*m*Me_2**		CH_2Cl_2	35	56
2	**1a**	**C_2-PrMe_3**		CH_2Cl_2	40	20
3	**1a**	**C_2-PrEt_2**		CH_2Cl_2	48	28
4	**1a**	**C_3-Pr*m*Me_2**		CH_2Cl_2	27	25
5	**1a**	**C_2-Pr*m*Me_2**		TCE	50	66
6	**1a**	**C_2-Pr*m*Me_2**		THF	80	32
7	**1a**	**C_2-Pr*m*Me_2**		EtOAc	74	37
8[d]	**1a**	**C_2-Pr*m*Me_2**		TCE	38	80
9[e]	**1a**	**C_2-Pr*m*Me_2**		TCE	23	91
10[e]	**1a**	**C_2-Pr*m*Me_2**	K_2CO_3	TCE	85	79
11[e]	**1a**	**C_2-Pr*m*Me_2**	DMAP	TCE	88	80
12[f]	**1a**		K_2CO_3	TCE	64	0
13[f]	**1a**		DMAP	TCE	88	0
14[e]	**1a**	**C_2-Pr*m*Me_2**	[Na_3PO_4]	TCE	85	90
15[g]	**1a**	**C_2-Pr*m*Me_2**	[Na_3PO_4]	TCE	99	93
16[g]	**1a**	**C-2**	[Na_3PO_4]	TCE	69	0
17[g]	**1a**	**C-3**	[Na_3PO_4]	TCE	55	9
18[g]	**1q**	**C_2-Pr*m*Me_2**	[Na_3PO_4]	TCE	62	65
19[g]	**1r**	**C_2-Pr*m*Me_2**	[Na_3PO_4]	TCE	82	89

[a]Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2** (1.2 equiv), catalyst (10 mol%) in solvent (1.0 mL) at 35 °C (entries 1−7 and entries 12 and 13, 24 h; entries 8−11 and entries 14−19, 96 h). [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]At 0 °C. [e]Catalyst (20 mol%) and additive (1.5 equiv) at −30 °C. [f]Without catalyst. [g]Catalyst (20 mol%), NaI (15 mol%), and $Na_3PO_4{\cdot}12H_2O$ (2.0 equiv) at −30 °C. TCE = $CHCl_2CHCl_2$. [Na_3PO_4] = $Na_3PO_4{\cdot}12H_2O$.

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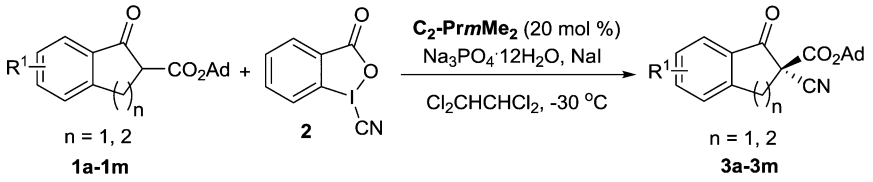
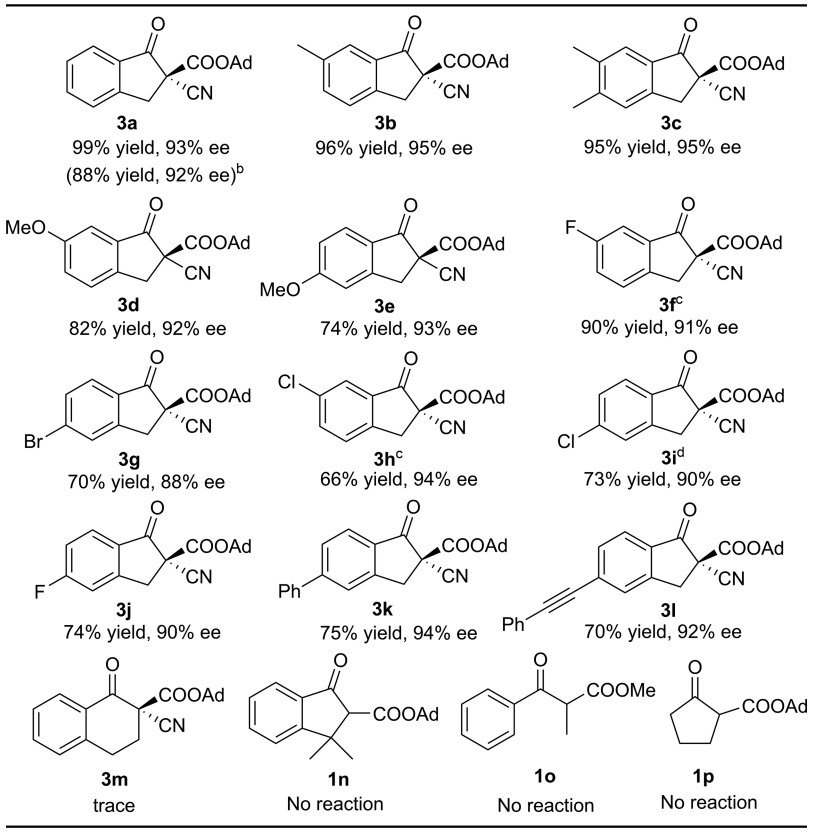
Table 2. Substrate Scope for β-Keto Esters[a]





[a]Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2** (1.2 equiv), **C$_2$-PrmMe$_2$** (20 mol%), and $Na_3PO_4·12H_2O$ (2.0 equiv), NaI (15 mol %) in TCE (1.0 mL) at −30 °C for 96 h. Isolated yield, and ee values were determined by HPLC analysis on a chiral stationary phase. [b]The reaction was carried out with **1a** (3.0 mmol) and $Na_3PO_4·12H_2O$ (3.0 equiv) in TCE (30 mL) instead. [c]NaI (20 mol%). [d]$Na_3PO_4·12H_2O$ (1.5 equiv). Ad = 1-adamantyl. TCE = $CHCl_2CHCl_2$.

substituted substrates give higher yields than the electron-withdrawing substituted ones. Substituents at C6-position afford slightly higher enantioselectivities than these at C5-position. Phenyl and alkynyl substituents are also tolerable, and the desired cyanation products **3k** and **3l** could be obtained in 75% and 70% yield, as well as 94% and 92% ee, respectively. We also attempted α-cyanation reaction of the dihydronaphthalen-1(2H)-one derived β-keto ester **1m**, only trace amount of the product **3m** was observed. Unfortunately, other substrates with varied skeleton, such as 3,3′-dimethyl substituted one **1n**, acyclic substrate **1o**, and 2-oxocyclopentanecarboxylate **1p**, do not react in the standard condition. In addition, the reaction between β-keto ester **1a** and **2** at a gram-scale performed well, giving the cyanation product **3a** in 88% yield and 92% ee. The absolute configuration of the product **3a** was determined to be *R* according to specific optical rotation of the known compound.[4b]

Subsequently, we examine the scope of β-keto amides in this α-cyanation reaction with the identified reaction conditions (Table 3). It is clear that a range of 1-indanone-derived β-keto amides **4** can be successfully employed in this electrophilic cyanation reaction without loss of enantioselectivities (87−97% ee). Similar to the situation of β-keto esters, both the electronic nature and position of the substituents on the indanone unit of β-keto amides have a slight effect on the enantioselectivity but a remarkable influence on the yield. Up to 92% yield and 97% ee are achieved when 6-chloro-substituted β-keto amide **4f** is used. However, 5,6-dimethyl substituted β-keto amide **4c** gives the lowest yield (50%) with 92% ee. These two examples are just to make up for the corresponding substituted β-keto esters **1c** and **1h**. Again, phenyl and alkynyl substituted β-keto amide **4k** and **4l** react efficiently, affording 69% and 76% yields, as well as 95% and 94% ee, respectively. 4-Substituted β-keto amides **4n−4q** are also readily employed to create the corresponding products. β-Keto amide **4m** incorporating a naphthyl group is applied to the reaction, giving 78% yield with 97% ee. Finally, *tert*-butyl substituted amide **4r** is tolerated in the process, and a slightly reduced yield and enantioselectivity are obtained.

We have suggested that chiral *N*,*N*′-dioxides may act as a bifunctional catalyst. We determined that no reaction occurred if additional 2-iodobenzoic acid (0.5 equiv) was added in the presence of 20 mol% of **C$_2$-PrmMe$_2$** without $Na_3PO_4·12H_2O$. It indicated that 2-iodobenzoic acid caused the deactivation of the chiral catalyst, which might occur through the hydrogen

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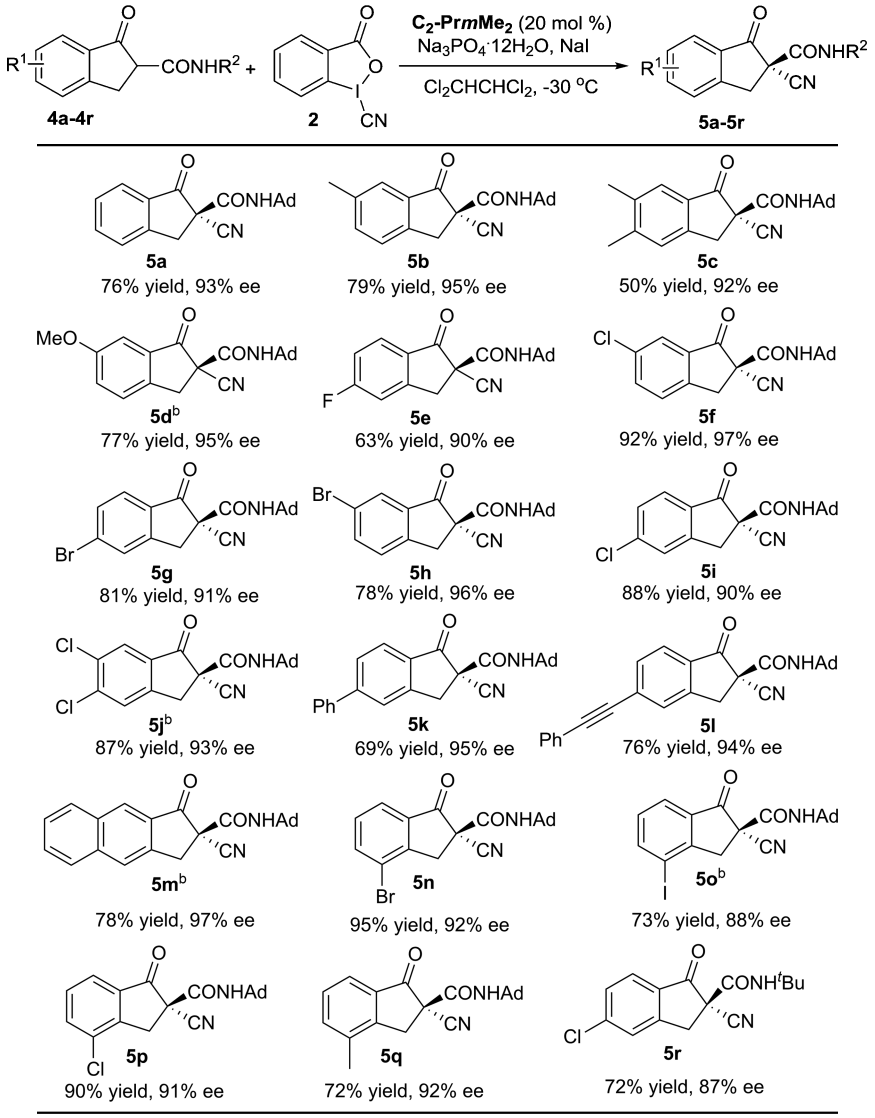
Table 3. Substrate Scope for β-Keto Amides[a]



[a]Unless otherwise noted, the reactions were performed with **4** (0.1 mmol), **2** (1.2 equiv), **C$_2$-PrmMe$_2$** (20 mol%), NaI (15 mol%), and $Na_3PO_4\cdot 12H_2O$ (2.0 equiv) in TCE (1.0 mL) at −30 °C for 96 h. Isolated yield, and ee values were determined by HPLC analysis on a chiral stationary phase. [b]$Na_3PO_4\cdot 12H_2O$ (3.0 equiv). Ad = 1-adamantyl. TCE = $CHCl_2CHCl_2$

bonding between the carboxylic acid and *N*-oxide unit of the catalyst. The inorganic base additive should benefit the recovery of the chiral catalyst by neutralizing 2-iodobenzoic acid generated from the cyanation of cyano benziodoxole **2**. Therefore, the yield of the reaction was greatly improved without the loss of the enantioselectivity after $Na_3PO_4\cdot 12H_2O$ was added. These experiment results support our hypothesis that the reaction goes through an enol intermediate of the β-keto esters or amides rather than an enolate assisted by an inorganic base. *N*-oxide units of the catalyst will activate the enol intermediate as a H-bond acceptor, on the other hand, the amide units will act as a H-bond donor to activate the cyano benziodoxole **2**. Such a bifunctional catalytic model makes the two reactants closer together with proper orientation, thus a high enantioselective cyanation occurs smoothly (Scheme 1).

SUMMARY

In summary, asymmetric electrophilic organocatalyzed α-cyanation reactions of 1-indanone-derived β-keto esters and β-keto amides have been realized with good to high yields and excellent enantioselectivities. An easily accessible and efficient chiral *N*,*N*′-dioxide catalyst exhibits its unique advantages in this asymmetric electrophilic cyanation reaction via a bifunctional catalytic model. In addition, developing asymmetric electrophilic cyanation reactions of simple carbonyl compounds is still a challenge. Further studies, regarding the catalytic performance of chiral *N*,*N*′-dioxide organocatalysts and ligands in other catalytic asymmetric transformations, are underway in our group.

EXPERIMENTAL SECTION

General Remarks. Reactions were carried out using commercial available reagents in oven-dried apparatus. $CHCl_2CHCl_2$ was dried over powdered CaH_2 and distilled under nitrogen. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at

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100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. The preparation of β-keto esters, β-keto amides and cyano benziodoxole followed the literature.[4b] Enantiomeric excesses were determined by chiral HPLC analysis on Daicel Chiralcel IA/IE in comparison with the authentic racemates. Optical rotations were reported as follows: $[\alpha]^{T}_{\lambda}$ = (c: g/100 mL, in CH_2Cl_2, D: 589 nm). HRMS was recorded on a commercial apparatus (ESI Source, TOF), and **3a**, **3b**, **3d**, **3e**, **3g**−**3j**, **3l**, and **3q** compounds had been reported.[4b] Cyano benziodoxole **2** was prepared according to the methods of the literature.[4b]

Typical Procedure for the Synthesis of β-Keto Esters and β-Keto Amides. To a stirred suspension of NaH (20 mmol, 60% in mineral oil) in dimethyl carbonate (5 mL) was added dropwise a solution of indanone (10.0 mmol) in dimethyl carbonate (15 mL). The mixture was refluxed at 80 °C for 1 h. After cooling to room temperature, HCl (2 mol/L, 20 mL) aqueous solution was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product thus obtained was subjected to column chromatography.

To a flask equipped with reflux condenser was added β-keto methyl ester (3.0 mmol), the corresponding alcohol or amine (6.0 mmol), the transesterification catalyst ZnO (20 mol%), toluene (10 mL), and 4 Å MS (1.0 g). The mixture was refluxed under N_2 until complete conversion was observed by TLC, then concentrated under reduced pressure, and the crude residue was purified by column chromatography. Then the pure β-keto ester or β-keto amide was obtained after recrystallization.

General Procedure for Asymmetric Electrophilic α-Cyanation Reaction. Chiral catalyst **C_2-Pr*m*Me_2** (20 mol%), NaI (15 mol %), β-keto esters or β-keto amides (0.1 mmol), cyano benziodoxole **2** (1.2 equiv), and $Na_3PO_4{\cdot}12H_2O$ (2.0 equiv) were stirred in 1,1,2,2-tetrachloroethane (1.0 mL) at −30 °C under N_2 atmosphere for 96 h. The reaction mixtures were purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:10) to afford the desired products.

*(R)-1-Adamantyl-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3a**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 90−92 °C); 33.2 mg, 99% yield, 93% ee; $[\alpha]^{26.4}_{D}$ = −27.0 (c 0.48, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 16.03 min, *t* (minor) = 22.32 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.74−7.70 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 3.89 (d, *J* = 17.2 Hz, 1H), 3.65 (d, *J* = 17.2 Hz, 1H), 2.18 (s, 3H), 2.12 (d, *J* = 3.0 Hz, 6H), 1.65 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 162.3, 151.6, 136.7, 132.3, 128.8, 126.4, 126.1, 116.1, 85.8, 55.3, 40.8, 37.5, 35.8, 30.9.

*(−)-1-Adamantyl-2-cyano-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3b**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 102−104 °C); 33.5 mg, 96% yield, 95% ee; $[\alpha]^{26.1}_{D}$ = −25.5 (c 0.65, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 17.02 min, *t* (minor) = 22.49 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 3.82 (d, *J* = 17.1 Hz, 1H), 3.58 (d, *J* = 17.1 Hz, 1H), 2.42 (s, 3H), 2.17 (s, 3H), 2.11 (d, *J* = 2.6 Hz, 6H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 162.4, 149.1, 139.0, 138.0, 132.5, 126.0, 125.9, 116.2, 85.7, 55.6, 40.8, 37.2, 35.8, 30.9, 21.0.

*(−)-1-Adamantyl-2-cyano-5,6-dimethyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3c**).* Purified by flash chromatography (petroleum ether: EtOAc = 12:1) to afford a colorless oil; 34.4 mg, 95% yield, 95% ee; $[\alpha]^{26.5}_{D}$ = −28.8 (c 0.33, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 26.05 min, *t* (minor) = 34.77 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.29 (s, 1H), 3.78 (d, *J* = 17.0 Hz, 1H), 3.54 (d, *J* = 17.0 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H), 2.12 (d, *J* = 2.8 Hz, 6H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 162.7, 149.9, 147.7, 138.0, 130.4, 127.0, 126.2, 116.4, 85.6, 55.6, 40.8, 37.1, 35.8, 30.9, 21.0, 19.8; HRMS (ESI-TOF): Calcd for $C_{23}H_{25}NO_3Na^+$ $[M+Na]^+$ 386.1727, Found 386.1731.

*(−)-1-Adamantyl-2-cyano-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3d**).* Purified by flash chromatography (petroleum ether: EtOAc = 6:1) to afford a colorless oil; 30.3 mg, 83% yield, 92% ee; $[\alpha]^{25.9}_{D}$ = −21.5 (c 0.54, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 17.55 min, *t* (minor) = 24.76 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 3.78 (d, *J* = 16.9 Hz, 1H), 3.57 (d, *J* = 16.9 Hz, 1H), 2.18 (s, 3H), 2.12 (d, *J* = 2.9 Hz, 6H), 1.64 (t, *J* = 2.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 162.4, 160.3, 144.6, 133.6, 127.0, 126.4, 116.1, 106.7, 85.8, 56.0, 55.7, 40.8, 36.9, 35.8, 30.9.

*(−)-1-Adamantyl-2-cyano-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3e**).* Purified by flash chromatography (petroleum ether: EtOAc = 6:1) to afford a colorless oil; 27.0 mg, 74% yield, 93% ee; $[\alpha]^{25.9}_{D}$ = −62.4 (c 0.49, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 25.44 min, *t* (minor) = 33.77 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 3.92 (s, 3H), 3.81 (d, *J* = 17.2 Hz, 1H), 3.56 (d, *J* = 17.2 Hz, 1H), 2.18 (s, 3H), 2.13 (d, *J* = 2.8 Hz, 6H), 1.64 (t, *J* = 2.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 166.8, 162.7, 154.9, 127.8, 125.2, 117.0, 116.4, 109.4, 85.6, 55.9, 55.6, 40.8, 37.4, 35.8, 30.9.

*(−)-1-Adamantyl-2-cyano-6-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3f**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 80−82 °C); 31.7 mg, 90% yield, 91% ee; $[\alpha]^{26.2}_{D}$ = −13.0 (c 1.00, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 11.87 min, *t* (minor) = 16.12 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.53−7.41 (m, 2H), 3.84 (d, *J* = 17.0 Hz, 1H), 3.61 (d, *J* = 17.0 Hz, 1H), 2.19 (s, 3H), 2.11 (d, *J* = 2.9 Hz, 6H), 1.64 (t, *J* = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4 (d, *J* = 3.4 Hz), 162.8 (d, *J* = 249 Hz), 161.9, 147.1 (d, *J* = 2.1 Hz), 134.2 (d, *J* = 8.1 Hz), 127.9 (d, *J* = 8.1 Hz), 124.6 (d, *J* = 23.7 Hz), 115.8, 111.94 (d, *J* = 22.6 Hz), 86.2, 56.0, 40.8, 37.0, 35.8, 30.9; HRMS (ESI-TOF): Calcd for $C_{21}H_{20}FNO_3Na^+$ $[M+Na]^+$ 376.1321, Found 376.1319.

*(−)-1-Adamantyl-5-bromo-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3g**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 115−117 °C); 28.9 mg, 70% yield, 88% ee; $[\alpha]^{26.4}_{D}$ = −37.9 (c 0.53, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 15.70 min, *t* (minor) = 18.62 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 3.86 (d, *J* = 17.4 Hz, 1H), 3.61 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 2.11 (s, 6H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 161.9, 153.0, 132.6, 132.5, 131.2, 129.7, 127.1, 115.7, 86.2, 55.3, 40.8, 37.0, 35.8, 30.9.

*(−)-1-Adamantyl-6-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3h**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 88−90 °C); 24.4 mg, 66% yield, 94% ee; $[\alpha]^{26.4}_{D}$ = −12.1 (c 0.42, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 12.94 min, *t* (minor) = 19.08 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 1.9 Hz, 1H), 7.67 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.49−7.47 (m, 1H), 3.84 (d, *J* = 17.3 Hz, 1H), 3.60 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 2.11 (d, *J* = 3.0 Hz, 6H), 1.64 (t, *J* = 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 161.8, 149.7, 136.8, 135.3, 133.9, 127.5, 125.7, 115.6, 86.2, 55.7, 40.8, 37.1, 35.8, 30.9; HRMS (ESI-TOF): Calcd for $C_{21}H_{20}{}^{34.9689}ClNO_3Na^+$ $[M+Na]^+$ 392.1024, Found 392.1028; Calcd for $C_{21}H_{20}{}^{36.9659}ClNO_3Na^+$ $[M+Na]^+$ 394.0994, Found 394.1006.

*(−)-1-Adamantyl-5-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3i**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 126−128 °C);

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27.0 mg, 73% yield, 90% ee; $[\alpha]^{26.1}_D$ = −47.6 (c 0.42, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 14.79 min, *t* (minor) = 18.47 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 3.85 (d, *J* = 17.4 Hz, 1H), 3.61 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 2.11 (d, *J* = 2.4 Hz, 6H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 161.9, 153.0, 143.6, 130.8, 129.7, 127.1, 126.7, 115.7, 86.2, 55.4, 40.8, 37.1, 35.8, 30.9.

(−)-1-Adamantyl-2-cyano-5-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate ***(3j)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow soid (120−122 °C); 26.1 mg, 74% yield, 90% ee; $[\alpha]^{26.3}_D$ = −77.8 (c 0.50, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 13.15 min, *t* (minor) = 17.54 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.3, 5.2 Hz, 1H), 7.21−7.16 (m, 2H), 3.87 (d, *J* = 17.4 Hz, 1H), 3.62 (d, *J* = 17.5 Hz, 1H), 2.19 (s, 3H), 2.12 (d, *J* = 3.0 Hz, 6H), 1.64 (t, *J* = 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 168.1(d, *J* = 259.2 Hz), 162.0, 154.7 (d, *J* = 10.7 Hz), 128.7 (d, *J* = 1.8 Hz), 128.6 (d, *J* = 10.9 Hz), 117.40 (d, *J* = 23.8 Hz), 115.8, 113.3 (d, *J* = 23.0 Hz), 86.1, 55.5, 40.8, 37.2, 35.8, 30.9.

(−)-1-Adamantyl--2-cyano-5-phenyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate ***(3k)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 110−112 °C); 30.8 mg, 75% yield, 94% ee; $[\alpha]^{27.0}_D$ = −64.5 (c 0.22, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 22.02 min, *t* (minor) = 26.12 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.51−7.43 (m, 3H), 3.93 (d, *J* = 17.2 Hz, 1H), 3.68 (d, *J* = 17.2 Hz, 1H), 2.19 (s, 3H), 2.14 (s, 6H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 162.4, 152.3, 149.9, 139.3, 131.1,129.1, 129.0, 128.1, 127.5, 126.4, 124.7, 116.1, 85.8, 55.6, 40.8, 37.5, 35.9, 30.9; HRMS (ESI-TOF): Calcd for $C_{27}H_{25}NO_3Na^+$ $[M+Na]^+$ 434.1734, Found 434.1727.

(−)-1-Adamantayl-2-cyano-5-phenylethynyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate ***(3l)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow oil; 30.5 mg, 70% yield, 92% ee; $[\alpha]^{26.1}_D$ = −60.9 (c 0.22, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IA column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 13.32 min, *t* (minor) = 15.86 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.66−7.55 (m, 3H), 7.40 (s, 3H), 3.87 (d, *J* = 17.2 Hz, 1H), 3.63 (d, *J* = 17.2 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 6H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 162.2, 151.4,132.1, 132.0, 131.9, 131.5, 129.3, 129.0, 128.5, 125.9, 122.1, 115.9, 94.9, 88.2, 85.9, 55.4, 40.8, 37.2, 35.8, 30.9.

(−)-Methyl-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate ***(3q)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a colorless oil ; 13.3 mg, 62% yield, 65% ee; $[\alpha]^{26.4}_D$ = −31.7 (c 0.23, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 20.23 min, *t* (minor) = 23.47 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 3.96 (d, *J* = 17.3 Hz, 1H), 3.89 (s, 3H), 3.71 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 164.6, 151.5, 137.0, 132.0, 129.0, 126.5, 126.4, 115.7, 54.7, 54.2, 37.5.

(−)-tert-Butyl-5-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxylate ***(3r)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 74−76 °C); 23.8 mg, 82% yield, 89% ee; $[\alpha]^{26.1}_D$ = −30.1 (c 0.77, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 9.68 min, *t* (minor) = 12.17 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 0.9 Hz, 1H), 7.47−7.44 (m, 1H), 3.86 (d, *J* = 17.4 Hz, 1H), 3.62 (d, *J* = 17.4 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 162.4, 153.0, 143.7, 130.7, 129.7, 127.1, 126.7, 115.7, 86.2, 55.2, 37.0, 27.6; HRMS (ESI-TOF): Calcd for $C_{15}H_{14}{}^{34.9689}ClNO_3Na^+$ $[M+Na]^+$ 314.0554, Found 314.0558; Calcd for $C_{15}H_{14}{}^{36.9659}ClNO_3Na^+$ $[M+Na]^+$ 316.0525, Found 316.0533.

(−)-N-1-Adamantyl-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide ***(5a)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow oil; 25.4 mg, 76% yield, 93% ee; $[\alpha]^{26.4}_D$ = −43.1 (c 0.59, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 11.43 min, *t* (minor) = 22.39 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.78−7.63 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 6.39 (s, 1H), 4.19 (d, *J* = 17.2 Hz, 1H), 3.51 (d, *J* = 17.2 Hz, 1H), 2.09 (s, 3H), 2.01 (d, *J* = 2.6 Hz, 6H),1.66 (d, *J* = 3.2, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.9, 152.8, 137.0, 132.0, 128.6, 126.5, 125.9, 117.6, 54.3, 53.6, 40.9, 36.1, 35.4, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{22}N_2O_2Na^+$ $[M+Na]^+$ 357.1573, Found 357.1577.

(−)-N-1-Adamantyl-2-cyano-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide ***(5b)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 150−152 °C); 27.5 mg, 79% yield, 95% ee; $[\alpha]^{27.4}_D$ = −84.6 (c 0.30, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 12.57 min, *t* (minor) = 24.52 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 6.38 (s, 1H), 4.12 (d, *J* = 17.2 Hz, 1H), 3.44 (d, *J* = 17.2 Hz, 1H), 2.41 (s, 3H), 2.08 (s, 3H), 2.00 (d, *J* = 2.6 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 159.0, 150.3, 138.8, 138.4, 132.2, 126.1, 125.7, 117.7, 54.6, 53.5, 40.9, 36.1, 35.1, 29.3, 21.0; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}N_2O_2Na^+$ $[M+Na]^+$ 371.1730, Found 371.1737.

(−)-N-1-Adamantyl--2-cyano-5,6-dimethyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide ***(5c)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a colorless oil; 18.1 mg, 50% yield, 92% ee; $[\alpha]^{26.4}_D$ = −47.8 (c 0.32, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 17.55 min, *t* (minor) = 34.55 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.29 (s, 1H), 6.40 (s, 1H), 4.08 (d, *J* = 17.2 Hz, 1H), 3.40 (d, *J* = 17.2 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 2.08 (s, 3H), 2.00 (s, 6H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 159.2, 151.0, 148.1, 137.9, 130.1, 127.1, 126.0, 117.9, 54.5, 53.5, 40.9, 36.1, 35.0, 29.3, 21.0, 19.7; HRMS (ESI-TOF): Calcd for $C_{23}H_{26}N_2O_2Na^+$ $[M+Na]^+$ 385.1886, Found 385.1895.

(−)-N-1-Adamantyl-2-cyano-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxamide ***(5d)***. Purified by flash chromatography (petroleum ether: EtOAc = 8:1) to afford a light yellow oil; 28.0 mg, 77% yield, 95% ee; $[\alpha]^{26.3}_D$ = −34.0 (c 0.40, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 17.45 min, *t* (minor) = 41.48 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.38 (s, 1H), 4.09 (d, *J* = 17.1 Hz, 1H), 3.84 (s, 3H), 3.43 (d, *J* = 17.1 Hz, 1H), 2.09 (s, 3H), 2.01 (d, *J* = 2.2 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 160.2, 159.0, 145.9, 133.2, 127.1, 126.7, 117.6, 106.5, 55.7, 55.0, 53.6, 40.9, 36.1, 34.8, 29.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}N_2O_3Na^+$ $[M+Na]^+$ 387.1679, Found 387.1684.

(−)-N-1-Adamantyl-2-cyano-5-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxamide ***(5e)***. Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 122−124 °C); 22.2 mg, 63% yield, 90% ee; $[\alpha]^{25.8}_D$ = −48.3 (c 0.53, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 9.11 min, *t* (minor) = 14.43 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.21−7.14 (m,2H), 6.36 (s, 1H), 4.18 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 17.6 Hz, 1H), 2.10 (s, 3H), 2.01 (d, *J* = 2.6 Hz, 6H), 1.67 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 168.4 (d, *J* = 259.6 Hz), 158.7, 155.8 (d, *J* = 10.9 Hz), 128.5 (d, *J* = 10.8 Hz),128.4, 117.3 (d, *J* = 23.9 Hz), 117.2, 113.4 (d, *J* = 23.0 Hz), 54.6, 53.7, 40.9, 36.1, 35.2, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{21}FN_2O_2Na^+$ $[M+Na]^+$ 375.1479, Found 375.1482.

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*(−)-N-1-Adamantyl-6-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5f**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 148−150 °C); 33.9 mg, 92% yield, 97% ee; $[\alpha]^{26.5}_{D}$ = −83.3 (c 0.45, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 10.37 min, *t* (minor) = 27.88 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 6.30 (s, 1H), 4.14 (d, *J* = 17.4 Hz, 1H), 3.46 (d, *J* = 17.4 Hz, 1H), 2.09 (s, 3H), 1.99 (d, *J* = 2.4 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 158.5, 150.8, 137.0, 135.1, 133.5, 127.6, 125.5, 117.1, 54.9, 53.7, 40.9, 36.0, 35.1, 29.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}{}^{34.9689}ClN_2O_3Na^+$ $[M+Na+CH_3OH]^+$ 423.1446, Found 423.1449; Calcd for $C_{22}H_{25}{}^{36.9659}ClN_2O_3Na^+$ $[M+Na+CH_3OH]^+$ 425.1416, Found 425.1416.

*(−)-N-1-Adamantyl-5-bromo-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5g**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 168−170 °C); 33.4 mg, 81% yield, 91% ee; $[\alpha]^{26.8}_{D}$ = −68.2 (c 0.41, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 10.86 min, *t* (minor) = 16.26 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.61−7.56 (m, 1H), 6.32 (s, 1H), 4.16 (d, *J* = 17.5 Hz, 1H), 3.48 (d, *J* = 17.5 Hz, 1H), 2.09 (s, 3H), 2.00 (d, *J* = 2.6 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 158.6, 154.1, 132.9, 132.4, 130.9, 129.9, 126.9, 117.1, 54.5, 53.7, 40.9, 36.0, 35.0, 29.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}{}^{78.9183}BrN_2O_3H^+$ $[M+H+CH_3OH]^+$ 445.1127, Found 445.1124; Calcd for $C_{22}H_{25}{}^{80.9163}BrN_2O_3H^+$ $[M+H+CH_3OH]^+$ 447.1106, Found 447.1109.

*(−)-N-1-Adamantyl-6-bromo-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5h**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 124−126 °C); 32.2 mg, 78% yield, 96% ee; $[\alpha]^{25.9}_{D}$ = −29.0 (c 0.63, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 13.16 min, *t* (minor) = 37.83 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 6.30 (s, 1H), 4.12 (d, *J* = 17.5 Hz, 1H), 3.43 (d, *J* = 17.5 Hz, 1H), 2.09 (s, 3H), 1.99 (d, *J* = 2.6 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 158.5, 151.3, 139.7, 133.8, 128.6, 127.9, 122.8, 117.1, 54.8, 53.8, 40.9, 36.0, 35.2, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{21}{}^{78.9183}BrN_2O_2Na^+$ $[M+Na]^+$ 435.0679, Found 435.0684; Calcd for $C_{21}H_{21}{}^{80.9163}BrN_2O_2Na^+$ $[M+Na]^+$ 437.0658, Found 437.0661.

*(−)-N-1-Adamantyl-5-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5i**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 168−170 °C); 32.4 mg, 88% yield, 90% ee; $[\alpha]^{26.4}_{D}$ = −76.1 (c 0.38, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 9.71 min, *t* (minor) = 14.76 min; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.32 (s, 1H), 4.16 (d, *J* = 17.5 Hz, 1H), 3.47 (d, *J* = 17.5 Hz, 1H), 2.09 (s, 3H), 2.00 (d, *J* = 2.5 Hz, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 158.6, 154.1, 144.0, 130.5, 129.6, 126.8, 126.9, 117.2, 54.5, 53.7, 40.9, 36.0, 35.1, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{21}{}^{34.9689}ClN_2O_2Na^+$ $[M+Na]^+$ 391.1184, Found 391.1187; Calcd for $C_{21}H_{21}{}^{36.9659}ClN_2O_2Na^+$ $[M+Na]^+$ 393.1154, Found 393.1186.

*(−)-N-1-Adamantyl-5,6-dichloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5j**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow solid (mp 182−184 °C); 35.1 mg, 87% yield, 93% ee; $[\alpha]^{27.0}_{D}$ = −48.7 (c 0.46, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 9.36 min, *t* (minor) = 16.90 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.67 (s, 1H), 6.27 (s, 1H), 4.13 (d, *J* = 17.5 Hz, 1H), 3.45 (d, *J* = 17.5 Hz, 1H), 2.10 (s, 3H), 1.99 (s, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 158.3, 151.2, 142.0, 134.0, 131.5, 128.3, 127.0, 116.8, 54.9, 53.8, 40.9, 36.0, 34.8, 29.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}{}^{34.9689}Cl_2N_2O_3Na^+$ $[M+Na+CH_3OH]^+$ 457.1056, Found 457.1058; Calcd for $C_{22}H_{24}{}^{36.9659}Cl_2N_2O_3Na^+$ $[M+Na+CH_3OH]^+$ 459.1027, Found 459.1034.

*(−)-N-1-Adamantyl-2-cyano-5-phenyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5k**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow oil; 28.3 mg, 69% yield, 95% ee; $[\alpha]^{26.5}_{D}$ = −69.4 (c 0.68, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 15.84 min, *t* (minor) = 23.18 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.51−7.42 (m, 3H), 6.42 (s, 1H), 4.24 (d, *J* = 17.3 Hz, 1H), 3.54 (d, *J* = 17.3 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 159.1, 153.4, 150.3, 139.3, 130.8, 129.1, 129.0, 128.0, 127.5, 126.2, 124.8, 117.6, 54.6, 53.6, 41.0, 36.1, 35.5, 29.3; HRMS (ESI-TOF): Calcd for $C_{27}H_{26}N_2O_2Na^+$ $[M+Na]^+$ 433.1886, Found 433.1894.

*(−)-N-1-Adamantayl-2-cyano-5-phenylethynyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5l**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a colorless oil; 33.1 mg, 76% yield, 94% ee; $[\alpha]^{26.7}_{D}$ = −28.5 (c 0.35, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 16.97 min, *t* (minor) = 20.59 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.58−7.56 (m 3H), 7.40−7.38 (m, 3H), 6.38 (s, 1H), 4.19 (d, *J* = 17.4 Hz, 1H), 3.49 (d, *J* = 17.4 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 158.8, 152.5, 132.4, 131.9, 131.8, 131.1, 129.3, 129.2, 128.5, 125.7, 122.1, 117.4, 95.0, 88.3, 54.4, 53.6, 40.9, 36.1, 35.1, 29.3; HRMS (ESI-TOF): Calcd for $C_{29}H_{27}N_2O_2^+$ $[M+H]^+$ 435.2067, Found 435.2065.

*(−)-N-1-Adamantyl-2-cyano-1-oxo-2,3-dihydro-1H-cyclopenta-[b]naphthalene-2-carboxamide (**5m**).* Purified by flash chromatography (petroleum ether: EtOAc = 8:1) to afford a white solid (mp 178−180 °C); 30.0 mg, 78% yield, 97% ee; $[\alpha]^{26.8}_{D}$ = −38.1 (c 0.52, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 18.14 min, *t* (minor) = 35.54 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.92 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 6.42 (s, 1H), 4.35 (d, *J* = 17.1 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 2.09 (s, 3H), 2.02 (s, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 159.1, 144.0, 138.1, 132.5, 130.5, 130.1, 129.5, 128.0, 127.8, 126.9, 124.9, 117.7, 55.2, 53.6, 40.1, 40.9, 36.1, 35.0, 29.3; HRMS (ESI-TOF): Calcd for $C_{25}H_{24}N_2O_2Na^+$ $[M+Na]^+$ 407.1730, Found 407.1731.

*(−)-N-1-Adamantyl-4-bromo-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5n**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a colorless oil; 39.2 mg, 95% yield, 92% ee; $[\alpha]^{26.4}_{D}$ = −54.2 (c 0.66, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane =10/90, 1.0 mL/min, λ = 254 nm), *t* (major) = 20.42 min, *t* (minor) = 18.64 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 6.32 (s, 1H), 4.13 (d, *J* = 17.9 Hz, 1H), 3.44 (d, *J* = 17.8 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 158.6, 152.4, 139.7, 134.0, 130.3, 124.7, 121.8, 117.1, 54.4, 53.8, 40.9, 36.6, 36.1, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{21}{}^{78.9183}BrN_2O_2Na^+$ $[M+Na]^+$ 435.0679, Found 435.0684; Calcd for $C_{21}H_{21}{}^{80.9163}BrN_2O_2Na^+$ $[M+Na]^+$ 437.0658, Found 437.0666.

*(−)-N-1-Adamantyl-2-cyano-4-iodo-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5o**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow oil; 33.6 mg, 73% yield, 88% ee; $[\alpha]^{25.8}_{D}$ = −39.3 (c 0.57, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 11.68 min, *t* (minor) = 12.80 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.33 (s, 1H), 4.02 (d, *J* = 17.7 Hz, 1H), 3.35 (d, *J* = 17.7 Hz, 1H), 2.10 (s, 3H),

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2.01 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 158.6, 156.4, 145.9, 133.6, 130.3, 125.4, 117.1, 95.5, 54.6, 53.8, 40.9, 40.4, 36.1, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{22}IN_2O_2^+$ $[M+H]^+$ 461.0720, Found 461.0725.

*(−)-N-1-Adamantyl-4-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5p**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a light yellow oil; 33.2 mg, 90% yield, 91% ee; $[\alpha]^{26.4}_D$ = −51.0 (c 0.57, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 13.47 min, *t* (minor) = 11.84 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 6.33 (s, 1H), 4.18 (d, *J* = 17.9 Hz, 1H), 3.48 (d, *J* = 17.9 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 158.6, 150.3, 136.6, 133.9, 132.8, 130.1, 124.1, 117.1, 54.3, 53.8, 40.9, 36.0, 34.6, 29.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{21}{}^{34.9689}ClN_2O_2Na^+$ $[M+Na]^+$ 391.1184, Found 391.1190; Calcd for $C_{21}H_{21}{}^{36.9659}ClN_2O_2Na^+$ $[M+Na]^+$ 393.1154, Found 393.1169.

*(−)-N-1-Adamantyl-2-cyano-4-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5q**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 146−148 °C); 25.0 mg, 72% yield, 92% ee; $[\alpha]^{27.1}_D$ = −61.0 (c 0.46, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 11.75 min, *t* (minor) = 13.71 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.10 (d, *J* = 17.4 Hz, 1H), 3.37 (d, *J* = 17.4 Hz, 1H), 2.39 (s, 3H), 2.09 (s, 3H), 2.01 (s, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 159.0, 151.7, 137.5, 136.1, 131.8, 128.8, 123.3, 117.7, 54.2, 53.6, 40.9, 36.1, 34.4, 29.3, 17.7; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}N_2O_2Na^+$ $[M+Na]^+$ 371.1730, Found 371.1737.

*(−)-N-tert-Butyl-5-chloro-2-cyano-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (**5r**).* Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (mp 68−70 °C); 20.9 mg, 72% yield, 87% ee; $[\alpha]^{26.5}_D$ = −59.1 (c 0.67, CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, λ= 254 nm), *t* (major) = 6.54 min, *t* (minor) = 8.16 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.48 (s, 1H), 4.18 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 17.6 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 159.0, 154.1, 144.0, 130.4, 129.6, 126.9, 126.8, 117.1, 54.4, 53.1, 35.1, 28.2; HRMS (ESI-TOF): Calcd for $C_{15}H_{15}{}^{34.9689}ClN_2O_2Na^+$ $[M + Na]^+$ 313.0714, Found 313.0719; Calcd for $C_{15}H_{15}{}^{36.9659}ClN_2O_2Na^+$ $[M+Na]^+$ 315.0685, Found 315.0697.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02726.

Optimization detail, ^{1}H and ^{13}C NMR spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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