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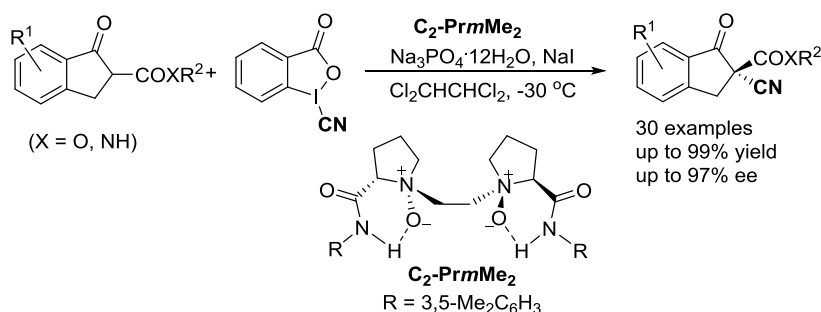
Chiral *N,N'*-Dioxide Organocatalyzed Asymmetric Electrophilic α -Cyanation of β -Keto Esters and β -Keto Amides

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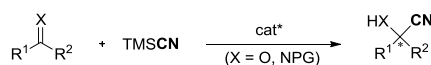
Abstract: An enantioselective electrophilic α -cyanation of 1-indanone-derived β -keto esters and β -keto amides using a hypervalent iodine as the cyanide-transfer reagent was realized. A chiral *N,N'*-dioxide was used as the efficient bifunctional organocatalyst in the presence of inorganic base, which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

INTRODUCTION

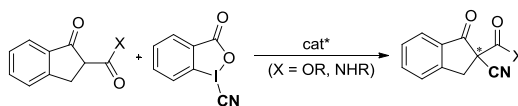
The enantioselective introduction of a cyano group into molecules is vital to research in organic chemistry.¹ There are several successful examples of asymmetric nucleophilic addition of cyano reagents to electrophiles including C=O, C=N and C=C bonds (Scheme 1, eq. a).² Nonetheless, as an alternative method, catalytic enantioselective electrophilic cyanation reaction is less explored. Until very recently, asymmetric electrophilic α -cyanations of β -keto esters³ 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 reagent⁵ and cyano group rearrangement, generating the α -cyanation β -keto ester product⁶ in an enantioselective manner.

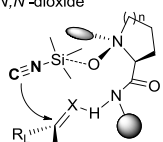
a) Asymmetric nucleophilic cyanation reactions



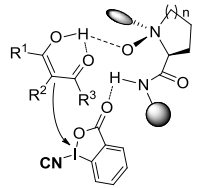
b) Asymmetric electrophilic cyanation reactions



cat* = *N,N'*-dioxide



bifunctional catalytic model of nucleophilic cyanation



bifunctional catalytic model of electrophilic cyanation

Scheme 1. Asymmetric nucleophilic and electrophilic cyanations and the possible bifunctional catalytic models of chiral *N,N'*-dioxides catalysts

Acting as a bifunctional organocatalyst, chiral *N,N'*-dioxides⁷ 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 $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ instead of DMAP, and an unsubstituted cyano benziodoxole as the cyanide reagent⁹ are involved. Excellent enantioselectivities (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

Table 1. Optimization of the Reaction Conditions^[a]

1a: X = H, R = 1-adamantyl
1q: X = H, R = Me
1r: X = 5-Cl, R = *t*Bu

3a: X = H, R = 1-adamantyl
3q: X = H, R = Me
3r: X = 5-Cl, R = *t*Bu

C₃-PrmMe₂: R = 3,5-Me₂C₆H₃

C-2
R = 3,5-Me₂C₆H₃

C₂-PrMe₃: R = 2,4,6-Me₃C₆H₂

C₂-PrmMe₂: R = 3,5-Me₂C₆H₃

C₂-PrEt₂: R = 2,6-Et₂C₆H₃

C-3

entry	1	cat.	additive	solvent	yield (%) ^[b]	ee (%) ^[c]
1	1a	C₂-PrmMe₂	—	CH ₂ Cl ₂	35	56
2	1a	C₂-PrMe₃	—	CH ₂ Cl ₂	40	20
3	1a	C₂-PrEt₂	—	CH ₂ Cl ₂	48	28
4	1a	C₃-PrmMe₂	—	CH ₂ Cl ₂	27	25
5	1a	C₂-PrmMe₂	—	TCE	50	66
6	1a	C₂-PrmMe₂	—	THF	80	32
7	1a	C₂-PrmMe₂	—	EtOAc	74	37

8 ^[d]	1a	C₂-PrmMe₂	—	TCE	38	80
9 ^[e]	1a	C₂-PrmMe₂	—	TCE	23	91
10 ^[e]	1a	C₂-PrmMe₂	K ₂ CO ₃	TCE	85	79
11 ^[e]	1a	C₂-PrmMe₂	DMAP	TCE	88	80
12 ^[f]	1a	—	K ₂ CO ₃	TCE	64	0
13 ^[f]	1a	—	DMAP	TCE	88	0
14 ^[e]	1a	C₂-PrmMe₂	[Na ₃ PO ₄]	TCE	85	90
15 ^[g]	1a	C₂-PrmMe₂	[Na ₃ PO ₄]	TCE	99	93
16 ^[g]	1a	C-2	[Na ₃ PO ₄]	TCE	69	0
17 ^[g]	1a	C-3	[Na ₃ PO ₄]	TCE	55	9
18 ^[g]	1q	C₂-PrmMe₂	[Na ₃ PO ₄]	TCE	62	65
19 ^[g]	1r	C₂-PrmMe₂	[Na ₃ PO 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, 13, 24 h; entries 8–11 and entries 14–19, 96 h).

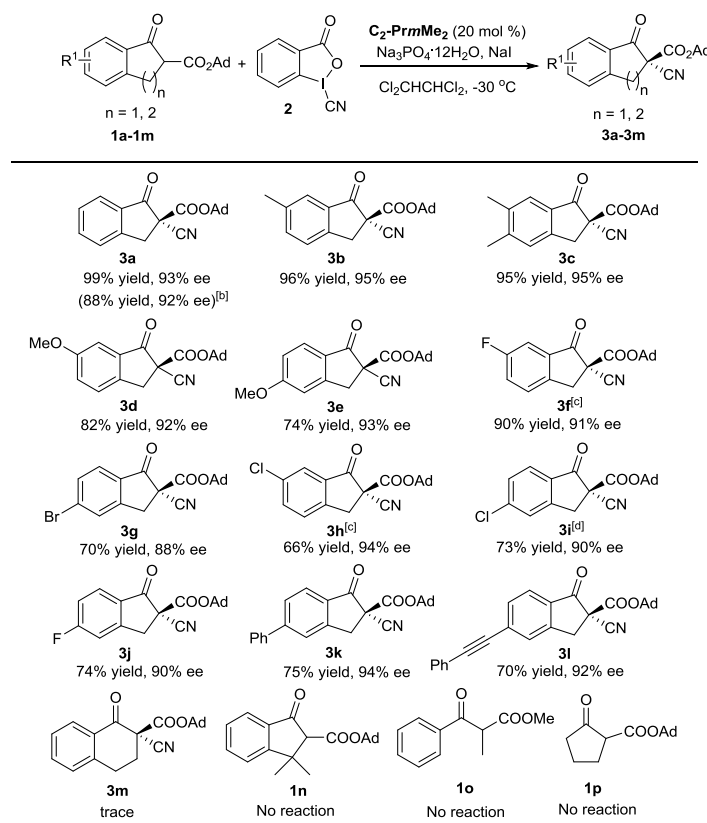
[b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At 0 °C. [e] Catalyst (20 mol %) and additive (1.5 equiv) at –30 °C. [f] Without catalyst. [g] Catalyst (20 mol %), NaI (15 mol %) and Na₃PO₄·12H₂O (2.0 equiv) at –30 °C. TCE = CHCl₂CHCl₂. [Na₃PO₄] = Na₃PO₄·12H₂O.

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 CH₂Cl₂ 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 **C₂-PrmMe₂** bearing a two carbon linkage shows better enantiocontrol than 3C-linked **C₃-PrmMe₂** (35% yield and 56% ee; entry 1 vs entry 4). Next, a series of solvents are screened when **C₂-PrmMe₂** 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 $-30\text{ }^{\circ}\text{C}$ 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 enantioselectivity 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 $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ is used as an additive, high yield (85%) and 90% ee are obtained (entry 14). Moreover, increasing the amount of $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ 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 **C₂-PrmMe₂**, 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 **C₂-PrmMe₂** and Na₃PO₄·12H₂O/NaI are used as the optimal catalysts for the reaction of various 1-adamantyl substituted β -keto carbonyl compounds.

Table 2. Substrate scope for β -keto esters^[a]

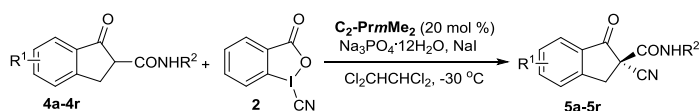


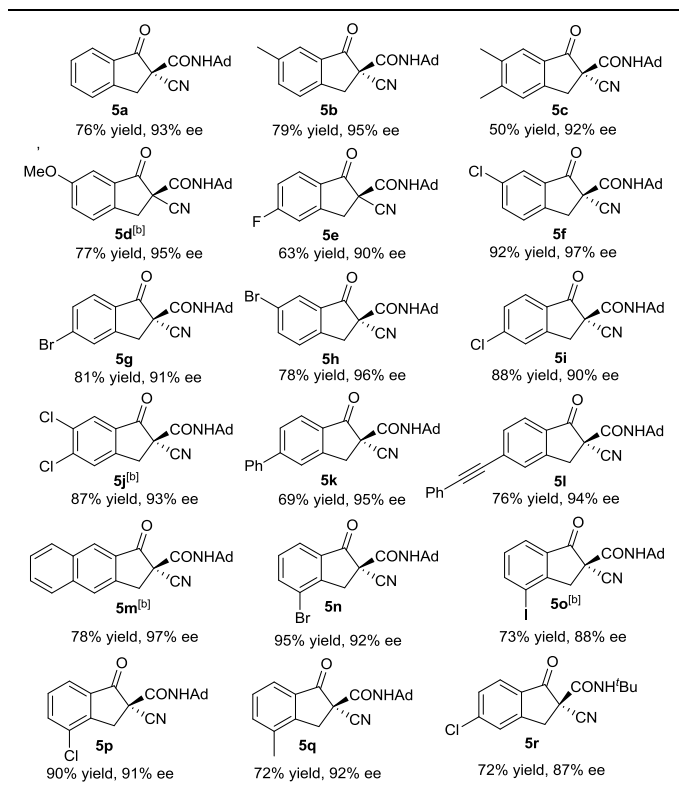
[a] Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2** (1.2 equiv), **C₂-PrmMe₂** (20 mol %) and Na₃PO₄·12H₂O (2.0 equiv), NaI (15 mol %) in TCE (1.0 mL) at -30 °C for 96 h. Isolated yield, and ee values were determined by HPLC analysis on a chiral stationary phase. [b] The reaction was carried out with **1a** (3.0 mmol) and Na₃PO₄·12H₂O (3.0 equiv) in TCE (30 mL) instead. [c] NaI (20 mol %). [d] Na₃PO₄·12H₂O (1.5 equiv). Ad = 1-adamantyl. TCE = CHCl₂CHCl₂.

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 positons 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 gave obviously higher enantioselectivity than electron-withdrawing ones.^{4b} In the current system, comparatively, electron-donating 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 attempts α -cyanation reaction of the dihydronaphthalen-1(2H)-one derived β -keto ester **1m**, only trace amount of the product **3m** is 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}

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), $C_2\text{-PrmMe}_2$ (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 = $CHCl_2CHCl_2$.

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** gave 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 determine that no reaction occurred if additional 2-iodobenzoic acid (0.5 equiv) was added in the presence of 20 mol % of **C₂-PrmMe₂** without Na₃PO₄·12H₂O. It indicates that 2-iodobenzoic acid caused the deactivation of the chiral catalyst, which might occur through the hydrogen 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 Na₃PO₄·12H₂O 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. $\text{CHCl}_2\text{CHCl}_2$ was dried over powdered CaH_2 and distilled under nitrogen. ^1H 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 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: $[\alpha]_\lambda^T = (c: \text{g}/100 \text{ mL, in } \text{CH}_2\text{Cl}_2, \text{D: } 589 \text{ nm})$. 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 CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried (Na₂SO₄) 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 N₂ 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 **C₂-PrmMe₂** (20 mol %), NaI (15 mol %), β-keto esters or β-keto amides (0.1 mmol), cyano beniodoxole **2** (1.2 equiv) and Na₃PO₄·12H₂O (2.0 equiv) were stirred in 1,1,2,2-tetrachloroethane (1.0 mL) at –30 °C under N₂ 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 (m.p. 90 – 92 °C); 33.2 mg, 99% yield, 93% ee; [α]_D^{26.4} = –27.0 (c 0.48, CH₂Cl₂); the ee was determined by HPLC analysis using a chiral IE column (iPrOH/hexane = 20/80, 1.0 mL/min, λ = 254 nm), *t* (major) = 16.03 min, *t* (minor) = 22.32 min; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (m.p. 102 – 104 °C); 33.5 mg, 96% yield, 95% ee; $[\alpha]^{26.1}_D = -25.5$ (c 0.65, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₂₅NO₃Na⁺ [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, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; $[\alpha]^{25.9}_{\text{D}} = -62.4$ (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, $\lambda = 254$ nm), t (major) = 25.44 min, t (minor) = 33.77 min; ^1H 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 (m.p. 80 – 82 °C); 31.7 mg, 90% yield, 91% ee; $[\alpha]^{26.2}_{\text{D}} = -13.0$ (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, $\lambda = 254$ nm), t (major) = 11.87 min, t (minor) = 16.12 min; ^1H 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 $\text{C}_{21}\text{H}_{20}\text{FNO}_3\text{Na}^+ [\text{M}+\text{Na}]^+$ 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 (m.p. 115 – 117 °C); 28.9 mg, 70% yield, 88% ee; $[\alpha]^{26.4}_{\text{D}} = -37.9$ (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, $\lambda = 254$ nm), t (major) = 15.70 min, t (minor) = 18.62 min; ^1H 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 (m.p. 88 – 90 °C); 24.4 mg, 66% yield, 94% ee; $[\alpha]^{26.4}_D = -12.1$ (c 0.42, CH₂Cl₂); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, $\lambda = 254$ nm), *t* (major) = 12.94 min, *t* (minor) = 19.08 min; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₀^{34.9689}CINO₃Na⁺ [M+Na]⁺ 392.1024, Found 392.1028; Calcd for C₂₁H₂₀^{36.9659}CINO₃Na⁺ [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 (m.p. 126 – 128 °C); 27.0 mg, 73% yield, 90% ee; $[\alpha]^{26.1}_D = -47.6$ (c 0.42, CH₂Cl₂); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, $\lambda = 254$ nm), *t* (major) = 14.79 min, *t* (minor) = 18.47 min; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 solid (120 – 122 °C); 26.1 mg, 74% yield, 90% ee; $[\alpha]^{26.3}_D = -77.8$ (c 0.50, CH₂Cl₂); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, $\lambda = 254$ nm), *t* (major) = 13.15 min, *t* (minor) = 17.54 min; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (m.p. 110 – 112 °C); 30.8 mg, 75% yield, 94% ee; $[\alpha]^{27.0}_D = -64.5$ (c 0.22,

CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₇H₂₅NO₃Na⁺ [M+Na]⁺ 434.1734, Found 434.1727.

(–)-1-adamantyl-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; [α]^{26.1}_D = –60.9 (c

0.22, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR

(100 MHz, CDCl₃) 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; [α]^{26.4}_D = –31.7 (c 0.23, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (m.p. 74 – 76 °C); 23.8 mg, 82% yield, 89% ee; [α]^{26.1}_D = –30.1 (c 0.77,

CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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 $\text{C}_{15}\text{H}_{14}^{34,9689}\text{ClNO}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 314.0554, Found 314.0558; Calcd for $\text{C}_{15}\text{H}_{14}^{36,9659}\text{ClNO}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 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; $[\alpha]_D^{26.4} = -43.1$ (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, $\lambda = 254$ nm), t (major) = 11.43 min, t (minor) = 22.39 min; ^1H 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 $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 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 (m.p. 150 – 152 °C); 27.5 mg, 79% yield, 95% ee; $[\alpha]_D^{27.4} = -84.6$ (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, $\lambda = 254$ nm), t (major) = 12.57 min, t (minor) = 24.52 min; ^1H 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 $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 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; $[\alpha]_D^{26.4} = -47.8$ (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, $\lambda = 254$ nm), t (major) = 17.55 min, t (minor) = 34.55 min; ^1H 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,

CDCl₃) 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 C₂₃H₂₆N₂O₂Na⁺ [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; [α]_D^{26.3} = -34.0 (c 0.40, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₂₄N₂O₃Na⁺ [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 (m.p. 122 – 124 °C); 22.2 mg, 63% yield, 90% ee; [α]_D^{25.8} = -48.3 (c 0.53, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₁FN₂O₂Na⁺ [M+Na]⁺ 375.1479, Found 375.1482.

(-)-***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 (m.p. 148 – 150 °C); 33.9 mg, 92% yield, 97% ee; [α]_D^{26.5} = -83.3 (c 0.45, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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 $\text{C}_{22}\text{H}_{25}^{34.9689}\text{CIN}_2\text{O}_3\text{Na}^+ [\text{M}+\text{Na}+\text{CH}_3\text{OH}]^+$ 423.1446, Found 423.1449; Calcd for $\text{C}_{22}\text{H}_{25}^{36.9659}\text{CIN}_2\text{O}_3\text{Na}^+ [\text{M}+\text{Na}+\text{CH}_3\text{OH}]^+$ 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 (m.p. 168 – 170 °C); 33.4 mg, 81% yield, 91% ee; $[\alpha]_D^{26.8} = -68.2$ (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, $\lambda = 254$ nm), t (major) = 10.86 min, t (minor) = 16.26 min; ^1H 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 $\text{C}_{22}\text{H}_{25}^{78.9183}\text{BrN}_2\text{O}_3\text{H}^+ [\text{M}+\text{H}+\text{CH}_3\text{OH}]^+$ 445.1127, Found 445.1124; Calcd for $\text{C}_{22}\text{H}_{25}^{80.9163}\text{BrN}_2\text{O}_3\text{H}^+ [\text{M}+\text{H}+\text{CH}_3\text{OH}]^+$ 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 (m.p. 124 – 126 °C); 32.2 mg, 78% yield, 96% ee; $[\alpha]_D^{25.9} = -29.0$ (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, $\lambda = 254$ nm), t (major) = 13.16 min, t (minor) = 37.83 min; ^1H 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 $\text{C}_{21}\text{H}_{21}^{78.9183}\text{BrN}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 435.0679, Found 435.0684; Calcd for $\text{C}_{21}\text{H}_{21}^{80.9163}\text{BrN}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 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 (m.p. 168 – 170 °C); 32.4 mg, 88% yield, 90% ee; $[\alpha]_D^{26.4} = -76.1$ (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, $\lambda = 254$ nm), t

(major) = 9.71 min, t (minor) = 14.76 min; ^1H NMR (400 MHz, CDCl_3) ^1H 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 $\text{C}_{21}\text{H}_{21}^{34.9689}\text{ClN}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 391.1184, Found 391.1187; Calcd for $\text{C}_{21}\text{H}_{21}^{36.9659}\text{ClN}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 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 (m.p. 182 – 184 °C); 35.1 mg, 87% yield, 93% ee; $[\alpha]^{27.0}_{\text{D}} = -48.7$ (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; ^1H 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 $\text{C}_{22}\text{H}_{24}^{34.9689}\text{Cl}_2\text{N}_2\text{O}_3\text{Na}^+ [\text{M}+\text{Na}+\text{CH}_3\text{OH}]^+$ 457.1056, Found 457.1058; Calcd for $\text{C}_{22}\text{H}_{24}^{36.9659}\text{Cl}_2\text{N}_2\text{O}_3\text{Na}^+ [\text{M}+\text{Na}+\text{CH}_3\text{OH}]^+$ 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; $[\alpha]^{26.5}_{\text{D}} = -69.4$ (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; ^1H 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 $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 433.1886, Found 433.1894.

(-)-*N*-1-adamantyl-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; $[\alpha]_{\text{D}}^{26.7} = -28.5$ (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, $\lambda = 254$ nm), t (major) = 16.97 min, t (minor) = 20.59 min; ^1H 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 $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 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 (m.p. 178 – 180 °C); 30.0 mg, 78% yield, 97% ee; $[\alpha]_{\text{D}}^{26.8} = -38.1$ (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, $\lambda = 254$ nm), t (major) = 18.14 min, t (minor) = 35.54 min; ^1H 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 $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 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; $[\alpha]_{\text{D}}^{26.4} = -54.2$ (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, $\lambda = 254$ nm), t (major) = 20.42 min, t (minor) = 18.64 min; ^1H 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 $\text{C}_{21}\text{H}_{21}^{78,9183}\text{BrN}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 435.0679, Found 435.0684; Calcd for $\text{C}_{21}\text{H}_{21}^{80,9163}\text{BrN}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 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; $[\alpha]_{\text{D}}^{25.8} = -39.3$ (c 0.57, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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), 2.01 (s, 6H), 1.68 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₂IN₂O₂⁺ [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; $[\alpha]_{\text{D}}^{26.4} = -51.0$ (c 0.57, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₁^{34.9689}CIN₂O₂Na⁺ [M+Na]⁺ 391.1184, Found 391.1190; Calcd for C₂₁H₂₁^{36.9659}CIN₂O₂Na⁺ [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 (m.p. 146 – 148 °C); 25.0 mg, 72% yield, 92% ee; $[\alpha]_{\text{D}}^{27.1} = -61.0$ (c 0.46, CH₂Cl₂); 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₂₄N₂O₂Na⁺ [M+Na]⁺ 371.1730, Found 371.1737.

(-)-*N*-tert-butyl-5-chloro-2-cyano-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (**5r**): Purified by flash chromatography (petroleum ether: EtOAc = 10:1) to afford a white solid (m.p. 68 – 70 °C); 20.9 mg, 72% yield, 87% ee; $[\alpha]_{\text{D}}^{26.5} = -59.1$ (c 0.67, CH₂Cl₂); the ee was determined by HPLC analysis using a chiral IE column (*i*PrOH/hexane = 20/80, 1.0 mL/min, $\lambda = 254$ nm), *t* (major) = 6.54 min, *t* (minor) = 8.16 min; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₁₅^{34.9689}CIN₂O₂Na⁺ [M+Na]⁺ 313.0714, Found 313.0719; Calcd for C₁₅H₁₅^{36.9659}CIN₂O₂Na⁺ [M+Na]⁺ 315.0685, Found 315.0697.

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Supporting Information

Optimization detail, ¹H and ¹³C NMR spectra, and HPLC data are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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