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Asymmetric Conjugate Addition of α-Cyanoketones to Benzoyl Acrylonitrile Derivatives Using a Diaminomethylenemalononitrile Organocatalyst

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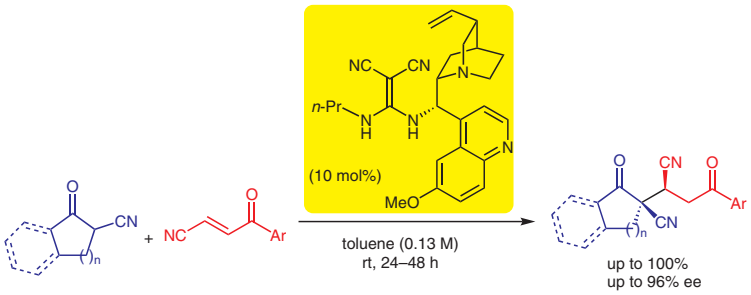

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Abstract A diaminomethylenemalononitrile (DMM) organocatalyst was used to efficiently promote asymmetric conjugate addition of various α-cyanoketones to benzoyl acrylonitrile derivatives. The corresponding 1,5-dicarbonyl compounds containing vicinal tertiary and quaternary stereogenic centers are versatile synthetic intermediates and were obtained in good yields and with excellent enantioselectivities (up to 96% ee). The present study describes the first successful examples of asymmetric conjugate addition reactions of α-cyanoketones with benzoyl acrylonitriles. In addition, the DMM organocatalyst can be recovered and reused up to five times without significant loss of either catalytic activity or enantioselectivity.

Key words α-cyanoketone, benzoyl acrylonitrile, organocatalyst, asymmetric conjugate addition, vicinal tertiary and quaternary stereogenic centers

Stereoselective synthesis of highly functionalized quaternary stereogenic centers is typically challenging due to steric hindrance, and their construction involves highly reactive reagents and harsh reaction conditions.[1] Moreover, although vicinal tertiary and quaternary stereogenic centers are ubiquitous in natural products and bioactive compounds, the stereoselective construction of these motifs is even more difficult.[2] Asymmetric conjugate addition of a Michael donor bearing an active methine moiety to an electron-deficient disubstituted alkene is one of the approaches utilized for the synthesis of vicinal tertiary and quaternary stereogenic centers. As α-alkylated α-cyanoketones are good Michael donors and contain active methine groups, several studies involving asymmetric conjugate additions to electron-deficient alkenes, employing organocatalysts with environmentally benign properties, have recently been reported.[3,4] However, although the reaction between α-cyanoketones and aromatic vinyl ketones is challenging, pioneering work using a chiral yttrium catalyst was reported by Shibasaki et al.[4] Furthermore, we have previously described valuable asymmetric transformations, such as Michael addition, aldol, and Pudovik reactions employing organocatalysts bearing a diaminomethylenemalononitrile (DMM) motif as the hydrogen-bond donor.[5] In addition, we have recently reported an asymmetric conjugate addition of α-cyanoketones to aromatic vinyl ketones using the aforementioned DMM organocatalyst.[6] Benzoyl acrylonitriles are good Michael acceptors, allowing access to vicinal tertiary and quaternary stereogenic centers. In addition, the nitrile moiety is a versatile functional group because it can be readily converted into a range of other functional groups. Nevertheless, only one report on the asymmetric conjugate addition using benzoyl acrylonitriles as Michael acceptors currently exists, despite the value of chiral addition products as synthetic intermediates.[7] Furthermore, to our knowledge, asymmetric conjugate additions of α-cyanoketones to benzoyl acrylonitrile derivatives have not yet been reported. In the present study, we describe a highly efficient synthesis of chiral 1,5-dicarbonyl compounds containing vicinal tertiary and quaternary stereogenic centers. The conducted reactions involved asymmetric conjugate addition of α-cyanoketones to benzoyl acrylonitriles using DMM organocatalysts.

Thiourea and squaramide scaffolds are popular motifs that are often utilized as hydrogen-bond donors.[8,9] Thus, in the first instance, thiourea and squaramide organocatalysts **1** and **2**, bearing a chiral cinchona moiety (Figure 1), were examined as catalysts for the conjugate addition of 2-oxocyclopentane-1-carbonitrile (**7a**) to (*E*)-4-oxo-4-phenylbut-2-enenitrile (**8a**) at room temperature in toluene (Table 1). Compounds **1** and **2** proved to be poor catalysts, affording the products in low stereoselectivities (entries 1 and 2). Pleasingly, when DMM organocatalyst **3** was used, higher enantioselectivity was obtained (entry 3). Therefore, it was

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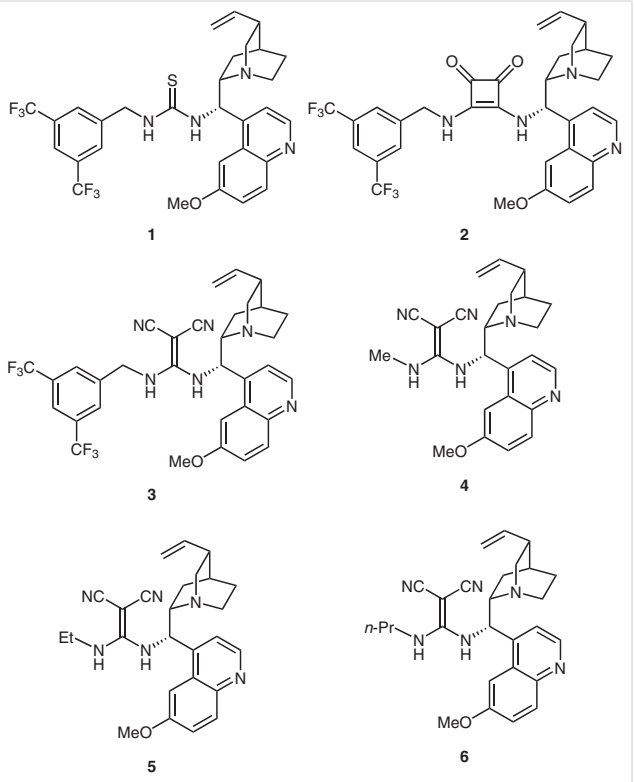
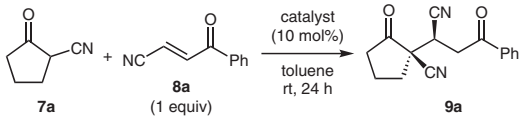


Figure 1 Structure of organocatalysts

found that in comparison to the thiourea and squaramide motifs, the DMM skeleton was preferable for the asymmetric conjugate addition of **7a** to **8a**. Moreover, organocatalyst **4**, which bears a methyl functionality instead of the 3,5-bis(trifluoromethyl)benzylamine group, provided lower stereoselectivity (entry 4). Organocatalysts **5** and **6**, containing alkyl groups of varying lengths, including ethyl and *n*-propyl chains, afforded the corresponding adduct **9a** with high enantioselectivities (entries 5 and 6). Overall, considering both the yield and stereoselectivity, organocatalyst **6**, bearing the *n*-propyl group, was the most effective.

Subsequently, the optimal reaction medium for the asymmetric conjugate addition of **7a** to **8a** using organocatalyst **6** was investigated (Table 2). We examined a variety of organic solvents for the transformation, including toluene, xylene, hexane, CH_2Cl_2, EtOAc, and MeOH (entries 1–6). It was determined that toluene was the most suitable reaction medium (entry 1). To further improve the stereoselectivity, we then examined the reaction concentration (0.50–0.06 M) (entries 7–10). It is noteworthy that when the reaction was carried out at a concentration of 0.13 M, higher enantioselectivity and diastereoselectivity were obtained (entry 9). In addition, the reactions performed at lower temperatures (0, –20, and –40 °C) resulted in improvements in the stereoselectivity; however, in this case, the achieved yields were lower and the reaction times were

Table 1 Catalyst Screening



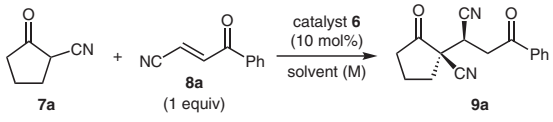
Entry	Catalyst	Yield (%)[a]	*syn*/*anti*[b]	ee (%)[c]
1	**1**	99	44:56	21
2	**2**	76	49:51	40
3	**3**	96	44:56	63
4	**4**	90	44:56	56
5	**5**	87	59:41	86
6	**6**	95	56:44	83

[a] Yield of both diastereomers.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.

longer (entries 11–13). Based on the obtained results, taking into account both yield and enantioselectivity, we determined that the reaction conditions summarized in entry 9 were optimal.

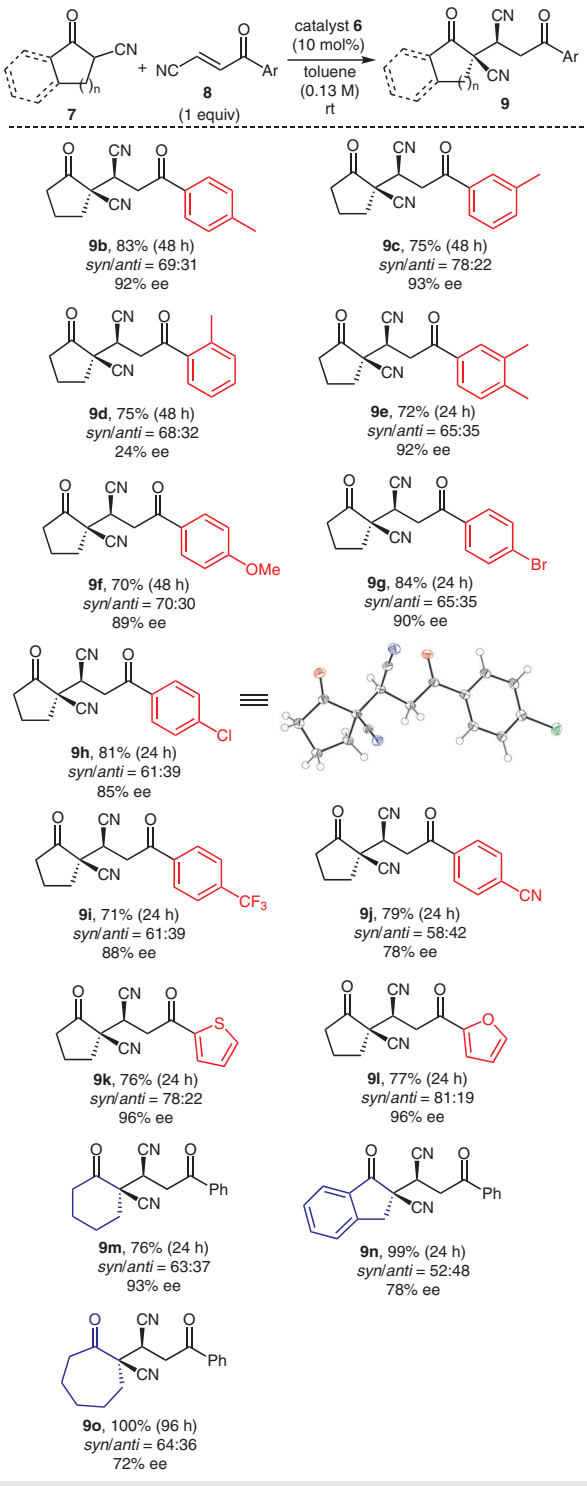
With the optimized reaction conditions in hand, we examined the scope and limitations of the asymmetric conjugate additions of α-cyanoketones to benzoyl acrylonitrile derivatives **8** (Scheme 1). The reactions of 2-oxocyclopen-

Table 2 Optimization of Reaction Conditions Using Organocatalyst **6**



Entry	Solvent (M)	Temp (°C)	Time (h)	Yield (%)[a]	*syn*/*anti*[b]	ee (%)[c]
1	toluene (1.0)	rt	24	95	56:44	83
2	xylene (1.0)	rt	24	87	60:40	83
3	hexane (1.0)	rt	24	83	45:55	34
4	CH_2Cl_2 (1.0)	rt	24	98	60:40	81
5	EtOAc (1.0)	rt	24	88	50:50	65
6	MeOH (1.0)	rt	24	97	43:57	–4
7	toluene (0.50)	rt	24	91	64:36	87
8	toluene (0.25)	rt	24	92	69:31	90
9	toluene (0.13)	rt	24	83	71:29	93[d]
10	toluene (0.06)	rt	48	72	69:31	90
11	toluene (0.13)	0	72	71	75:25	96
11	toluene (0.13)	–20	96	74	79:21	97
12	toluene (0.13)	–40	84	41	79:21	96

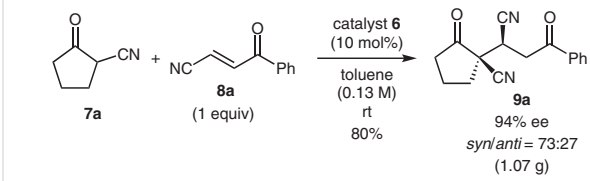
[a] Yield of both diastereomers.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] 46% ee for the *anti* isomer.



Scheme 1 Asymmetric conjugate additions using organocatalyst **6**. Yields are given for both diastereomers. Diastereomeric ratio was determined by ^{1}H NMR analysis; enantiomeric excess was determined by chiral HPLC analysis.

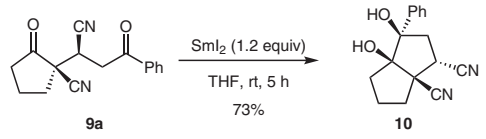
tane-1-carbonitrile (**7a**) with benzoyl acrylonitrile derivatives **8b** and **8c**, containing a methyl moiety at the *para*- and *meta*-positions on the benzene ring, afforded the corresponding addition products **9b** and **9c** with high enantioselectivities. Moreover, the benzoyl acrylonitrile derivative **8d**, bearing a methyl functionality at the *ortho*-position, reacted with **7a** to provide adduct **9d** in low enantioselectivity due to steric hindrance. On the other hand, the addition of **7a** to substrate **8e**, containing two methyl groups, proceeded with high enantioselectivity and afforded product **9e**. Benzoyl acrylonitrile derivatives **8f**, possessing methoxy groups as representative electron-donating moieties, provided the expected products also with high stereoselectivity. Pleasingly, substrates **8g–j**, which contain electron-withdrawing groups, such as chloro, bromo, trifluoromethyl, and cyano functionalities at the *para*-position, reacted with **7a** to obtain addition products **9g–j** in good to high yields with high enantioselectivities. Furthermore, conjugate addition to **8k–l**, bearing thiophene and furan rings, smoothly provided adducts **9k–l** with excellent enantioselectivities. We subsequently examined other types of α-cyanoketones for the transformation. The reaction between 2-oxocyclohexane-1-carbonitrile (**7b**) and **8a** resulted in the formation of adduct **9m** in high yield and excellent enantioselectivity. In addition, 1-oxo-2,3-dihydro-1*H*-indene-2-carbonitrile (**7c**) reacted with **8a**, providing adduct **9n** in high yield; however, in this case, the stereoselectivity decreased. 2-Oxocycloheptane-1-carbonitrile (**7d**) also smoothly coupled with **8a** to afford adduct **9o** in moderate stereoselectivity. The absolute configuration of the addition product **9h** was determined by X-ray crystallographic analysis. The stereochemistry of the remaining products with the general structure **9** were tentatively assigned by analogy.

To demonstrate the usefulness of the asymmetric conjugate addition reactions utilizing organocatalyst **6**, we carried out the synthesis of adduct **9a** on gram scale and obtained the desired product in a high yield and excellent enantioselectivity (Scheme 2). According to the previous report,[4] the treatment of **9a** with SmI_2 in tetrahydrofuran (THF) resulted in the formation of the cyclized product **10** in 73% yield (Scheme 3). Furthermore, we aimed to determine whether organocatalyst **6** could be recycled and reused. Based on the conducted evaluation, we established that the catalyst is stable and can be easily recovered (89–100%) from the reaction mixture using flash silica gel chro-



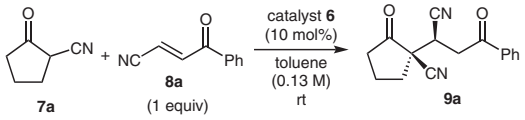
Scheme 2 Gram-scale synthesis of **9a** using organocatalyst **6**

matography. Notably, the recovered catalyst **6** can be repeatedly reused without any loss in the catalytic activity and with the same level of enantioselectivity for five cycles (Table 3). Therefore, we demonstrated that the degradation of catalyst **6** does not occur in the reaction system.



Scheme 3 Transformation of the conjugate addition products

Table 3 Recycling and Reuse of Organocatalyst **6**



Entry	Time (h)	Yield (%)[a]	*syn*/*anti*[b]	ee (%)[c]	Cat. recovery (%)
initial	24	80	73:27	94	100
first reuse	24	76	78:22	92	99
second reuse	24	79	76:24	93	93
third reuse	48	81	78:22	92	89
fourth reuse	48	77	78:22	92	97
fifth reuse	48	82	77:23	91	97

[a] Yield of both diastereomers.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.

We did not attempt to elucidate the reaction mechanism experimentally; however, it was inferred that the conjugate addition of α-cyanoketones to benzoyl acrylonitrile using organocatalyst **6** would proceed via a plausible transition state, as shown in Figure 2, based on the stereochemistry of the adduct **9**. The tertiary amine functionality of the quinuclidine group in organocatalyst **6** removes a proton from α-cyanoketones to afford a reactive enol intermediate. Subsequently, the hydrogen atoms of the DMM motif interact with the carbonyl oxygen atom in benzoyl acrylonitrile **8**, directing the approach of the enol to enone (*Re*-face attack). Finally, it is suspected that these interactions result in the formation of addition products **9** with excellent enantioselectivities.

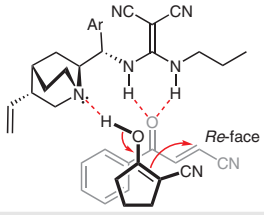


Figure 2 Plausible transition-state models

In conclusion, in the current study, we successfully demonstrated that the DMM organocatalyst **6** efficiently promoted the asymmetric conjugate addition of α-cyanoketones to benzoyl acrylonitrile derivatives **8** to afford the enantiomerically enriched 1,5-dicarbonyl compounds **9**. The products **9** possess vicinal tertiary and quaternary stereogenic centers and were obtained in high yields with high to excellent enantioselectivities. The present work is the first example of efficient asymmetric conjugate additions of α-cyanoketones to benzoyl acrylonitrile derivatives. The synthesized chiral addition products are highly desirable as versatile synthetic intermediates. Further applications of the DMM catalysts to other types of asymmetric reactions as well as the development of novel DMM organocatalysts are being investigated in our laboratory.

NMR spectra were recorded with a Bruker Avance III Nanobay 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). The chemical shifts are expressed in ppm downfield from tetramethylsilane (δ = 0.00 ppm) as an internal standard and $CDCl_3$ (δ = 77.16 ppm). Mass spectra were recorded with an electrospray ionization-time of flight (ESI-TOF) mass spectrometer (Xevo G2-XS QTof). Specific rotations were measured with a Jasco P-2200. Melting points were obtained with a Yanaco MP-J3. For thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Flash column chromatography was performed on neutral silica gel (Kanto Silica gel 60N, 40–50 μm).

Preparation of Organocatalysts

Organocatalysts **1**–**6** were prepared according to a reported procedure.[6]

Preparation of β-Cyanoenones

(*E*)-4-Oxo-4-phenylbut-2-enenitrile (**8a**) was prepared according to a reported procedure.[10]

Preparation of β-Cyanoenones 8b–m; General Procedure[10,11]

To a 100 mL two-neck round-bottom flask, SeO_2 (2.00 g, 18.0 mmol), H_2O (0.31 g, 17.0 mmol) and 1,4-dioxane (10.0 mL) were added and the flask was fitted with a condenser. The mixture was heated to reflux with stirring until the solid dissolved. Then, substituted aryl ketone (10.0 mmol) was added into the solution and the reaction mixture was allowed to reflux. After the reaction was completed, the reaction mixture was cooled to r.t. and filtered through a Celite pad, which was then washed several times with diethyl ether. The combined filtrate was evaporated on a rotary evaporator to afford the crude product, which was used in the next step without further purification. A solution of aryllglyoxal monohydrate (10.0 mmol) in benzene (40 mL) was heated under reflux with azeotropic removal of water (Dean–Stark). Thereafter, cyanomethylidenetriphenylphosphorane (3.80 g, 12.6 mmol) and benzoic acid (211 mg, 1.73 mmol) were added and the mixture was stirred for 10 h under an argon atmosphere at 80 °C. The cooled mixture was concentrated in vacuo and the residue was subjected to column chromatography on silica gel (hexane/EtOAc, 2:1) and recrystallization to give **8** as yellow crystals.

Asymmetric Conjugate Addition; Typical Procedure

To a solution of β-cyanoenone (**8a**, 31.4 mg, 0.200 mmol) and organocatalyst **6** (9.1 mg, 0.020 mmol) in toluene (1.6 mL) was added α-cyanoketone (**7a**, 20.0 μL, 0.200 mmol) at r.t. After stirring at r.t. for the indicated time, the reaction mixture was purified by flash column chromatography on silica gel with a 10:1 to 6:1 mixture of hexane and acetone to afford **9a**.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-phenylpropyl)-2-oxocyclopentane-1-carbonitrile (9a)

Yield: 44.4 mg (83%); white solid; mp 116–117 °C; *syn*/*anti* = 71:29; $[\alpha]_D^{26}$ = −2.6 (c 1.00, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ =254 nm): t_R = 31.7 (minor), 35.9 (major) min; 93% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.24 (m, 1 H), 2.26–2.30 (m, 1 H), 2.34–2.43 (m, 1 H), 2.47–2.56 (m, 1 H), 2.67–2.73 (m, 2 H), 3.58 (dd, *J* = 18.1, 3.5 Hz, 1 H), 3.80 (dd, *J* = 9.9, 3.4 Hz, 1 H), 4.02 (dd, *J* = 18.1, 9.9 Hz, 1 H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.64 (t, *J* = 7.3 Hz, 1 H), 8.00 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 31.2, 34.6, 37.4, 38.0, 49.2, 115.9, 117.6, 128.4, 129.1, 134.4, 135.3, 194.3, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_2Na$: 289.0947; found: 289.0956.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-(*p*-tolyl)propyl)-2-oxocyclopentane-1-carbonitrile (9b)

Yield: 46.5 mg (83%); brown solid; mp 117–118 °C; *syn*/*anti* = 69:31; $[\alpha]_D^{23}$ = +3.7 (c 0.35, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ =254 nm): t_R = 32.9 (minor), 35.5 (major) min; 92% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.25 (m, 1 H), 2.26–2.35 (m, 1 H), 2.36–2.42 (m, 1 H), 2.44 (s, 3 H), 2.47–2.57 (m, 1 H), 2.66–2.74 (m, 2 H), 3.56 (dd, *J* = 18.0, 3.7 Hz, 1 H), 3.80 (dd, *J* = 9.8, 3.7 Hz, 1 H), 3.99 (dd, *J* = 18.0, 9.8 Hz, 1 H), 7.30–7.32 (m, 2 H), 7.88–7.91 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 21.8, 31.2, 34.7, 37.4, 37.9, 49.3, 116.0, 117.6, 128.5, 129.7, 133.0, 145.5, 193.8, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1102.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-(*m*-tolyl)propyl)-2-oxocyclopentane-1-carbonitrile (9c)

Yield: 41.9 mg (75%); white solid; mp 92–93 °C; *syn*/*anti* = 78:22; $[\alpha]_D^{24}$ = +0.5 (c 1.00, CH_2Cl_2); HPLC (ChiralPak IG; hexane/*i*-PrOH, 80:20; 1.0 mL/min; λ =254 nm): t_R = 26.7 (minor), 35.3 (major) min; 93% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.25 (m, 1 H), 2.27–2.33 (m, 1 H), 2.34–2.42 (m, 1 H), 2.44 (s, 3 H), 2.47–2.57 (m, 1 H), 2.67–2.75 (m, 2 H), 3.57 (dd, *J* = 18.1, 3.6 Hz, 1 H), 3.80 (dd, *J* = 9.8, 3.6 Hz, 1 H), 4.01 (dd, *J* = 18.1, 9.8 Hz, 1 H), 7.38–7.42 (m, 1 H), 7.44–7.46 (m, 1 H), 7.79–7.80 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 21.4, 31.2, 34.6, 37.3, 38.1, 49.3, 116.0, 117.6, 125.6, 128.9, 128.9, 135.1, 135.4, 139.0, 194.4, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1112.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-(*o*-tolyl)propyl)-2-oxocyclopentane-1-carbonitrile (9d)

Yield: 42.3 mg (75%); white solid; mp 138–139 °C; *syn*/*anti* = 68:32; $[\alpha]_D^{24}$ = −1.5 (c 0.45, CH_2Cl_2); HPLC (ChiralPak IG; hexane/*i*-PrOH, 80:20; 1.0 mL/min; λ =254 nm): t_R = 21.9 (minor), 30.4 (major) min; 24% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.24 (m, 1 H), 2.25–2.31 (m, 1 H), 2.33–2.42 (m, 1 H), 2.46–2.53 (m, 1 H), 2.56 (s, 3 H), 2.65–2.73 (m, 2 H), 3.58 (dd, *J* = 18.1, 3.5 Hz, 1 H), 3.80 (dd, *J* = 9.9, 3.4 Hz, 1 H), 4.02 (dd, *J* = 18.1, 9.9 Hz, 1 H), 7.29–7.35 (m, 2 H), 7.43–7.47 (m, 1 H), 7.73–7.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 21.8, 31.4, 34.7, 37.4, 40.2, 49.2, 116.0, 117.7, 126.2, 129.2, 132.6, 132.8, 135.5, 139.7, 197.1, 206.0.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1110.

(*S*)-1-((*S*)-1-Cyano-3-(3,4-dimethylphenyl)-3-oxopropyl)-2-oxocyclopentane-1-carbonitrile (9e)

Yield: 42.4 mg (72%); yellow solid; mp 132–133 °C; *syn*/*anti* = 65:35; $[\alpha]_D^{24}$ = +3.1 (c 0.90, CH_2Cl_2); HPLC (ChiralPak IG; hexane/*i*-PrOH, 80:20; 1.0 mL/min; λ =254 nm): t_R = 36.7 (minor), 39.6 (major) min; 92% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.24 (m, 1 H), 2.26–2.32 (m, 1 H), 2.34 (s, 6 H), 2.36–2.42 (m, 1 H), 2.47–2.57 (m, 1 H), 2.67–2.74 (m, 2 H), 3.54 (dd, *J* = 18.0, 3.7 Hz, 1 H), 3.80 (dd, *J* = 9.7, 3.7 Hz, 1 H), 3.97 (dd, *J* = 18.0, 9.7 Hz, 1 H), 7.26 (d, *J* = 7.6 Hz, 1 H), 7.73 (dd, *J* = 7.8, 2.0 Hz, 1 H), 7.76 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.9, 20.3, 31.2, 34.6, 37.4, 38.0, 49.3, 116.0, 117.7, 126.1, 129.5, 130.3, 133.4, 137.5, 144.2, 194.0, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}N_2O_2Na$: 317.1260; found: 317.1259.

(*S*)-1-((*S*)-1-Cyano-3-(4-methoxyphenyl)-3-oxopropyl)-2-oxocyclopentane-1-carbonitrile (9f)

Yield: 41.5 mg (70%); white solid; mp 128–129 °C; *syn*/*anti* = 70:30; $[\alpha]_D^{23}$ = +9.6 (c 1.00, CH_2Cl_2); HPLC (ChiralPak IC; hexane/*i*-PrOH, 70:30; 1.0 mL/min; λ =270 nm): t_R = 47.0 (major), 71.2 (minor) min; 89% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.24 (m, 1 H), 2.26–2.34 (m, 1 H), 2.35–2.43 (m, 1 H), 2.46–2.56 (m, 1 H), 2.65–2.73 (m, 2 H), 3.52 (dd, *J* = 17.8, 3.7 Hz, 1 H), 3.80 (dd, *J* = 9.7, 3.7 Hz, 1 H), 3.89 (s, 3 H), 3.95 (dd, *J* = 17.8, 9.7 Hz, 1 H), 6.96–6.99 (m, 2 H), 7.96–7.99 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 31.2, 34.6, 37.3, 37.7, 49.3, 55.7, 114.2, 116.0, 117.7, 128.5, 130.8, 164.5, 192.6, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_3Na$: 319.1053; found: 319.1062.

(*S*)-1-((*S*)-3-(4-Bromophenyl)-1-cyano-3-oxopropyl)-2-oxocyclopentane-1-carbonitrile (9g)

Yield: 57.8 mg (84%); brown solid; mp 177–179 °C; *syn*/*anti* = 65:35; $[\alpha]_D^{25}$ = +4.8 (c 1.0, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ =254 nm): t_R = 48.5 (minor), 58.0 (major) min; 90% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.25 (m, 1 H), 2.27–2.33 (m, 1 H), 2.33–2.45 (m, 1 H), 2.47–2.57 (m, 1 H), 2.68–2.74 (m, 2 H), 3.56 (dd, *J* = 18.1, 3.6 Hz, 1 H), 3.78 (dd, *J* = 9.8, 3.5 Hz, 1 H), 4.00 (dd, *J* = 18.1, 9.9 Hz, 1 H), 7.67 (d, *J* = 8.4, 7.6 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 31.2, 34.7, 37.4, 38.0, 49.1, 115.9, 117.4, 129.8, 129.9, 132.5, 134.1, 193.4, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}N_2O_2BrNa$: 367.0053; found: 367.0051.

(*S*)-1-((*S*)-3-(4-Chlorophenyl)-1-cyano-3-oxopropyl)-2-oxocyclopentane-1-carbonitrile (9h)

Yield: 48.8 mg (81%); brown solid; mp 167–169 °C; *syn*/*anti* = 61:39; $[\alpha]_D^{25}$ = +3.5 (c 0.75, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ =254 nm): t_R = 39.7 (minor), 50.1 (major) min; 85% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.25 (m, 1 H), 2.27–2.31 (m, 1 H), 2.34–2.44 (m, 1 H), 2.47–2.57 (m, 1 H), 2.68–2.74 (m, 2 H), 3.56 (dd, *J* = 18.1, 3.6 Hz, 1 H), 3.79 (dd, *J* = 9.8, 3.5 Hz, 1 H), 4.01 (dd, *J* = 18.1, 9.9 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 31.2, 34.7, 37.4, 38.0, 49.1, 115.9, 117.4, 129.4, 129.8, 133.6, 141.0, 193.2, 206.2.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}N_2O_2ClNa$: 323.0558; found: 323.0563.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-(4-(trifluoromethyl)phenyl)propyl)-2-oxocyclopentane-1-carbonitrile (9i)

Yield: 47.4 mg (71%); white solid; mp 167–169 °C; *syn*/*anti* = 61:39; $[\alpha]_D^{24}$ = −2.0 (c 0.75, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ =230 nm): t_R = 38.7 (minor), 50.0 (major) min; 88% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.26 (m, 1 H), 2.28–2.37 (m, 1 H), 2.38–2.48 (m, 1 H), 2.50–2.58 (m, 1 H), 2.68–2.76 (m, 2 H), 3.64 (dd, *J* = 18.3, 3.7 Hz, 1 H), 3.80 (dd, *J* = 9.8, 3.6 Hz, 1 H), 4.08 (dd, *J* = 18.3, 9.8 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 8.12 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 31.2, 34.7, 37.4, 38.3, 49.1, 115.8, 117.3, 123.5 (q, $^1J_{C-F}$ = 273.4 Hz), 126.2 (q, $^3J_{C-F}$ = 3.7 Hz), 135.7 (q, $^2J_{C-F}$ = 32.0 Hz), 138.0, 193.6, 206.1.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}N_2O_2F_3Na$: 357.0821; found: 357.0821.

4-((*S*)-3-Cyano-3-((*S*)-1-cyano-2-oxocyclopentyl)propanoyl)benzonitrile (9j)

Yield: 46.2 mg (79%); white solid; mp 138–140 °C; *syn*/*anti* = 58:42; $[\alpha]_D^{25}$ = +3.2 (c 0.75, CH_2Cl_2); HPLC (ChiralPak IG; hexane/*i*-PrOH, 70:30; 1.0 mL/min; λ = 254 nm): t_R = 23.8 (minor), 32.6 (major) min; 78% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.26 (m, 1 H), 2.26–2.37 (m, 1 H), 2.39–2.46 (m, 1 H), 2.48–2.58 (m, 1 H), 2.68–2.76 (m, 2 H), 3.63 (dd, *J* = 18.4, 3.6 Hz, 1 H), 3.79 (dd, *J* = 9.9, 3.6 Hz, 1 H), 4.08 (dd, *J* = 18.4, 9.9 Hz, 1 H), 7.82–7.85 (m, 2 H), 8.09–8.12 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 31.1, 34.6, 37.3, 38.2, 48.9, 115.7, 117.0, 117.6, 128.7, 132.8, 138.1, 193.2, 206.0.

HRMS (ESI$^-$-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{12}N_3O_2$: 290.0935; found: 290.0930.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-(thiophen-2-yl)propyl)-2-oxocyclopentane-1-carbonitrile (9k)

Yield: 41.3 mg (76%); white solid; mp 166–168 °C; *syn*/*anti* = 78:22; $[\alpha]_D^{25}$ = +7.6 (c 1.00, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ = 254 nm): t_R = 55.6 (minor), 60.7 (major) min; 96% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.25 (m, 1 H), 2.26–2.32 (m, 1 H), 2.34–2.42 (m, 1 H), 2.47–2.56 (m, 1 H), 2.66–2.74 (m, 2 H), 3.53 (dd, *J* = 17.7, 3.8 Hz, 1 H), 3.79 (dd, *J* = 9.7, 3.8 Hz, 1 H), 3.96 (dd, *J* = 17.6, 9.7 Hz, 1 H), 7.20 (dd, *J* = 4.8, 3.9 Hz, 1 H), 7.75 (dd, *J* = 4.9, 0.9 Hz, 1 H), 7.84 (dd, *J* = 3.8, 0.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 31.0, 34.6, 37.3, 38.4, 49.2, 115.8, 117.3, 128.6, 133.3, 135.4, 142.2, 186.9, 206.0.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{12}N_2O_2SNa$: 295.0512; found: 295.0519.

(*S*)-1-((*S*)-1-Cyano-3-(furan-2-yl)-3-oxopropyl)-2-oxocyclopentane-1-carbonitrile (9l)

Yield: 39.7 mg (77%); white solid; mp 121–123 °C; *syn*/*anti* = 81:19; $[\alpha]_D^{25}$ = +20.0 (c 1.00, CH_2Cl_2); HPLC (ChiralPak IC; hexane/*i*-PrOH, 70:30; 1.0 mL/min; λ = 254 nm): t_R = 41.2 (major), 95.6 (minor) min; 96% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.24 (m, 1 H), 2.24–2.31 (m, 1 H), 2.31–2.39 (m, 1 H), 2.45–2.55 (m, 1 H), 2.64–2.74 (m, 2 H), 3.42 (dd, *J* = 17.7, 3.5 Hz, 1 H), 3.77 (dd, *J* = 9.9, 3.5 Hz, 1 H), 3.87 (dd, *J* = 17.7, 9.9 Hz, 1 H), 6.61 (dd, *J* = 3.6, 1.7 Hz, 1 H), 7.34 (dd, *J* = 3.6, 0.7 Hz, 1 H), 7.66 (dd, *J* = 1.7, 0.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 30.4, 34.3, 37.2, 37.6, 49.3, 113.0, 115.8, 117.3, 118.7, 147.5, 151.5, 183.0, 205.9.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{12}N_2O_3Na$: 279.0740; found: 279.0742.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-phenylpropyl)-2-oxocyclohexane-1-carbonitrile (9m)

Yield: 42.4 mg (76%); yellow oil; *syn*/*anti* = 63:37; $[\alpha]_D^{24}$ = +88.2 (c 0.50, CH_2Cl_2); HPLC (ChiralPak IG; hexane/*i*-PrOH, 70:30; 1.0 mL/min; λ = 254 nm): t_R = 20.7 (minor), 47.7 (major) min; 93% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74–1.86 (m, 1 H), 2.02–2.10 (m, 1 H), 2.11–2.19 (m, 2 H), 2.22–2.28 (m, 1 H), 2.38–2.50 (m, 1 H), 2.59–2.64 (m, 1 H), 2.86–2.95 (m, 1 H), 3.37 (dd, *J* = 18.0, 3.6 Hz, 1 H), 3.75 (dd, *J* = 9.2, 3.5 Hz, 1 H), 3.94 (dd, *J* = 18.0, 9.2 Hz, 1 H), 7.48–7.52 (m, 2 H), 7.61–7.65 (m, 1 H), 7.96–7.99 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 27.6, 31.1, 37.8, 38.2, 39.5, 53.1, 117.0, 117.8, 128.3, 129.0, 134.3, 135.5, 194.2, 199.7.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1106.

(*S*)-2-((*S*)-1-Cyano-3-oxo-3-phenylpropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carbonitrile (9n)

Yield: 62.2 mg (99%); white solid; mp 151–153 °C; *syn*/*anti* = 52:48; $[\alpha]_D^{24}$ = −1.2 (c 1.00, CH_2Cl_2).

HPLC (ChiralPak IG; hexane/*i*-PrOH, 80:20; 1.0 mL/min; λ = 254 nm): t_R = 48.5 (minor), 65.8 (major) min; 78% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (d, *J* = 17.8 Hz, 1 H), 3.67 (dd, *J* = 17.8, 3.0 Hz, 1 H), 3.92 (d, *J* = 17.7 Hz, 1 H), 3.97 (dd, *J* = 17.8, 10.3 Hz, 1 H), 4.07 (dd, *J* = 10.3, 3.0 Hz, 1 H), 7.50–7.54 (m, 2 H), 7.54–7.59 (m, 2 H), 7.62–7.66 (m, 1 H), 7.77–7.91 (m, 1 H), 7.89–7.91 (m, 1 H), 7.99–8.01 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0, 37.6, 38.4, 47.6, 116.8, 117.1, 126.1, 126.7, 128.4, 129.0, 129.5, 133.3, 134.3, 135.4, 137.6, 150.4, 194.2, 194.5.

HRMS (ESI$^+$-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{14}N_2O_2Na$: 337.0947; found: 337.0948.

(*S*)-1-((*S*)-1-Cyano-3-oxo-3-phenylpropyl)-2-oxocycloheptane-1-carbonitrile (9o)

Yield: 61.4 mg (quant.); white solid; mp 154–156 °C; *syn*/*anti* = 64:36; $[\alpha]_D^{29}$ = –10.6 (c 0.50, CH_2Cl_2); HPLC (ChiralPak IB; hexane/*i*-PrOH, 90:10; 1.0 mL/min; λ = 254 nm): t_R = 29.4 (minor), 32.8 (major) min; 72% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.44 (m, 1 H), 1.79–1.88 (m, 2 H), 1.98–2.10 (m, 4 H), 2.22–2.28 (m, 1 H), 2.79–2.96 (m, 2 H), 3.45 (dd, *J* = 18.1, 3.4 Hz, 1 H), 3.66 (dd, *J* = 18.1, 9.5 Hz, 1 H), 3.83 (dd, *J* = 9.5, 3.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.63 (t, *J* = 7.3 Hz, 1 H), 7.96 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 26.2, 28.2, 35.0, 38.3, 42.2, 55.6, 117.6, 117.7, 128.4, 129.1, 134.4, 135.4, 194.0, 202.6.

HRMS (ESI$^+$-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_2$: 295.1447; found: 295.1439.

Procedure for the Gram-Scale Experiment

To a solution of β-cyanoenone **8a** (785.9 mg, 5.0 mmol) and organocatalyst **6** (228.3 mg, 0.5 mmol) in toluene (40 mL) was added α-cyanoketone **7a** (501. μL, 5.0 mmol) at r.t. After stirring at r.t. the for indicated time, the reaction mixture was purified by flash column chromatography on silica gel with a 10:1 to 6:1 mixture of hexane and acetone to afford **9a** (1.07 g, 80% yield, *syn*/*anti* = 73:27, 94% ee).

Transformation of the Conjugate Addition Products

To a solution of (*S*)-1-((*S*)-1-cyano-3-oxo-3-phenylpropyl)-2-oxocyclopentane-1-carbonitrile (**9a**; 93% ee, 79.9 mg, 0.3 mmol) in THF (4 mL) was added SmI_2 (12 mL, 1.2 mmol; 0.1 M in THF) at r.t. After stirring at r.t. for 5 h, the mixture was diluted with Et_2O and the reaction was quenched with sat. $NaHCO_3$ aq., then the resulting biphasic mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with a 3:1 mixture of hexane and EtOAc to afford **10**.

(1*S*,3*R*,3a*R*,6a*S*)-3,3a-Dihydroxy-3-phenylhexahydropentalene-1,6a(1*H*)-dicarbonitrile (10)

Yield: 58.8 mg (73%); white solid; mp 120–122 °C; $[\alpha]_D^{24}$ = +44.7 (c 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.35 (m, 1 H), 1.57–1.63 (m, 1 H), 1.71–1.79 (m, 1 H), 1.91–2.02 (m, 1 H), 2.10–2.17 (m, 1 H), 2.50–2.54 (m, 1 H), 2.55–2.57 (m, 1 H), 2.58–2.60 (m, 1 H), 2.69 (d, *J* = 9.9 Hz, 1 H), 3.84–3.87 (m, 1 H), 3.89 (s, 1 H), 7.39–7.42 (m, 3 H), 7.48–7.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 34.3, 38.0, 38.1, 38.4, 53.1, 81.1, 94.3, 118.1, 120.6, 126.1, 128.8, 129.1, 139.2.

HRMS (ESI$^-$-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{15}N_2O_2$: 267.1139; found: 267.1129.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707285.

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