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Note

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Synthesis of Chiral Homoallylic Nitriles by Iridium-Catalyzed Allylation of Cyanoacetates

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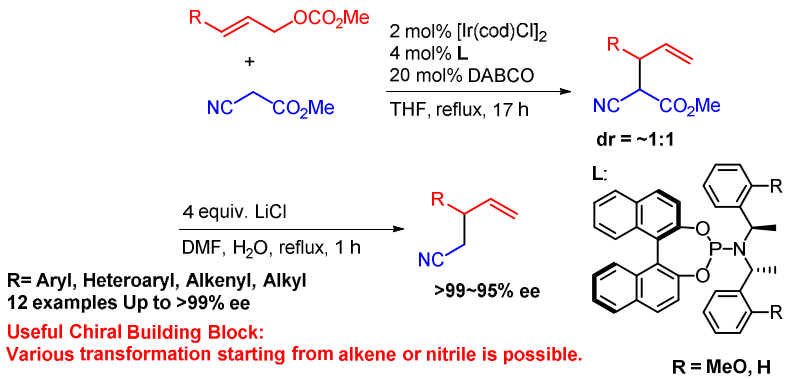
Supporting Information Placeholder



ABSTRACT: A synthesis of chiral homoallylic nitriles by the iridium-catalyzed allylation of cyanoacetates followed by Krapcho demethoxycarbonylation has been developed. A wide range of homoallylic nitriles were obtained with high enantioselectivity (>95~99%ee). These compounds are useful chiral building blocks because further synthetic elaboration starting from a nitrile or terminal alkene is possible.

Nitriles are versatile synthetic intermediates for the synthesis of pharmaceuticals and other biologically active compounds because nitriles can be easily converted to other functional groups such as carboxylic acids, aldehydes, ketones and amines.[1] Nitrile is also found in numerous natural products and medicinal compounds.[2] Due to their significance in organic synthesis, much attention has been devoted to the enantioselective synthesis of nitriles. Nucleophilic cyanation of aldehydes and ketones,[3] conjugate cyanation of α,β-unsaturated carbonyl compounds,[4] hydrogenation of α,β-unsaturated nitriles[5] and hydrocyanation of alkenes[6] have all been reported as efficient methods for the synthesis of chiral nitriles.

Branch-selective allylic substitution catalyzed by an iridium complex was first reported by us in 1997.[7] Iridium-catalyzed allylic substitution has been extensively studied and recognized as one of the most reliable methods for enantioselective carbon-carbon or carbon-heteroatom bond-formation.[8] These products are useful chiral building blocks because further synthetic elaboration starting from a terminal alkene such as oxidation to a carbonyl compound, hydroboration followed by Suzuki-Miyaura cross-coupling or ring-closing metathesis is possible. The synthesis of natural products and medicinally useful compounds via iridium-catalyzed allylation as a key step has been reported.[9] As mentioned above, methods for the synthesis of chiral nitriles are needed. To the best of our knowledge, only three examples of the synthesis of chiral homoallylic nitriles using transition metal-catalyzed allylic substitution has been reported.[10] We report here the synthesis of chiral homoallylic nitriles using iridium-catalyzed allylation of cyanoacetates followed by demethoxycarbonylation.

The reaction of carbonate **1a** with methyl cyanoacetate (**2**) in the presence of 2 mol% $[Ir(cod)Cl]_2$, 4 mol% **L** and 20 mol% base under refluxing THF gave **3a** as a diastereomeric mixture. Krapcho demethoxycarbonylation of **3a** in the presence of 4 equiv. of LiCl in refluxing DMF gave homoallylic nitrile **4a** with high enantioselectivity. Hartwig studied the mechanism of iridium-catalyzed allylation[11] and found that iridacycle generated from $[Ir(cod)Cl]_2$ and phosphoramidite **L** is the active catalyst.[12] Based on their mechanistic study, it is believed that an iridacycle catalyst is generated in situ prior to the reaction. It is well known that alkoxide anion generated by the oxidative addition of allylic carbonate to a transition metal complex acts as a base to deprotonate a pro-nucleophile.[13] However, a catalytic amount of base besides alkoxide anion derived from an allylic carbonate is needed to generate an iridacycle catalyst. We screened the effect of bases and optimized the reaction conditions. The results are summarized in

Table 1. No product was obtained in the absence of base (entry 1). The reaction using 10 mol% DABCO gave **3a** in 78% yield as a 53:47 mixture of diastereomers (entry 2). Krapcho demethoxycarbonylation of **3a** gave **4a** with 94% ee. An increase in the amount of DABCO to 30 or 40 mol% decreased the yield of **3a**, but the ee of **4a** remained the same (entries 4 and 5). The reaction at 40 °C considerably decreased the yield of **3a** (entry 6). TBD and DBU were effective for the reaction (entries 7 and 8). Inorganic bases were also as effective as DBU (entries 10-12). We screened the effect of solvent using DABCO as a base (entries 13-16). Benzene gave a comparable result to THF (entry 13). MeCN, DCE and MeOH were less effective than THF. Based on a consideration of the yield of **3a** and ee of **4a**, the use of DABCO in refluxing THF represented the optimal conditions. The diastereomeric ratio was nearly 1:1 regardless of the reaction conditions.

With the optimal reaction conditions in hand (Table 1 entry 3), we examined the scope of the iridium-catalyzed allylation of **2** with **1**. The results are summarized in Scheme 1. These reactions were performed using **L1** and **L2**. The substituent on the aromatic ring affected the yield of **3**. Substrates with an electron-donating substituent on the aromatic ring (**3b**, **3c** and **3d**) gave products in higher yields than those with electron-withdrawing substituent on the aromatic ring (**3e** and **3f**). Both 1-naphthyl substrate (**1g**) and 2-naphthyl substrate (**1h**) smoothly reacted with **2** with the use of **L1**. In contrast, the reactions of **1g** and **1h** using **L2**, a more bulky phosphoramidite, showed decreased yield. Thiophene and furan rings were tolerated under the reaction conditions. The reaction of thiophene substrate (**1i**) gave the product in a higher yield than that of furan substrate (**1j**). Dienyl substrate **1k** reacted with **2** to give **3k**. The reaction of alkyl-substituted substrate (**1l**) was examined. Ester **1l** reacted with **2** similarly. The yield of **3l** was comparable to that of **3a**, but the reaction of **1l** was less branched product-selective than those of **1a**-**1k**. Products **3a**-**3l** were obtained as diastereomeric mixtures. The diastereomeric ratios were nearly 1:1, except in the case of **3h**. We did not observe a large difference in the diastereomeric ratio between **L1** and **L2**.

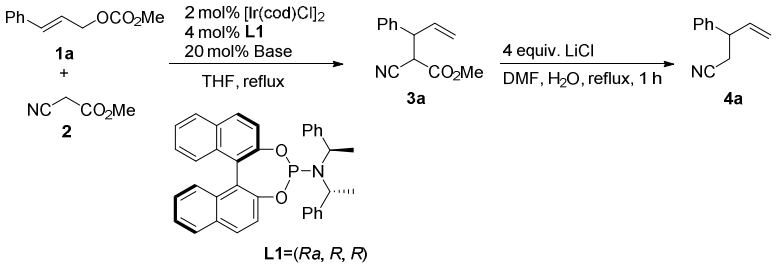


Table 1. Optimization of the Reaction Conditions.[a]

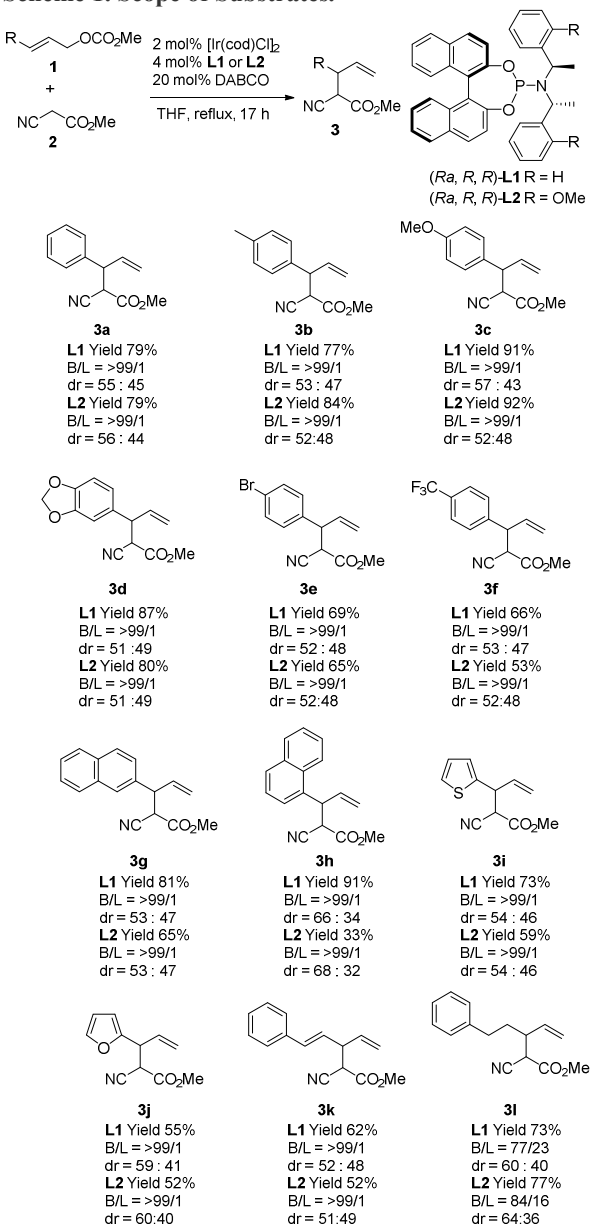
Entry	Base (mol%)	Solvent Temp.	Time (h)	Yield of **3a** (%)[b]	Dr[c]	Yield of **4a** (%)[d]	Ee (%)[e]
1	none	THF reflux	24 h	-	-	-	-
2	DABCO (10)	THF reflux	18 h	78	53:47	90	94
3	DABCO (20)	THF reflux	18 h	79	55:45	88	93
4	DABCO (30)	THF reflux	17 h	70	53:47	87	94
5	DABCO (40)	THF reflux	17 h	66	54:46	88	94
6	DABCO (20)	THF 40 °C	24 h	13	59:41	-	-
7	TBD (20)	THF reflux	15 h	68	53:47	87	92
8	DBU (20)	THF reflux	15 h	74	54:46	89	94
9	BSA (20)	THF reflux	24 h	12	56:44	-	-
10	Cs_2CO_3 (20)	THF reflux	15 h	69	58:42	80	89
11	CsF (20)	THF reflux	16 h	74	56:44	86	93
12	K_2CO_3 (20)	THF reflux	15 h	75	56:44	80	94
13	DABCO (20)	benzene reflux	15 h	73	53:47	85	93
14	DABCO (20)	MeCN reflux	15 h	64	55:45	86	85
15	DABCO (20)	DCE reflux	24 h	19	60:40	-	-

16	DABCO (20)	MeOH reflux	16 h	75	56:44	85	50	

[a]A mixture of **1a** (0.5 mmol), **2** (1 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), **L1** (0.02 mmol), base (0.05~0.2 mmol) and solvent (4 mL) was stirred under Ar. [b]Based on **1a**. [c]Determined by ^{1}H-NMR. [d]Based on **3a**. [e]Determined by HPLC.

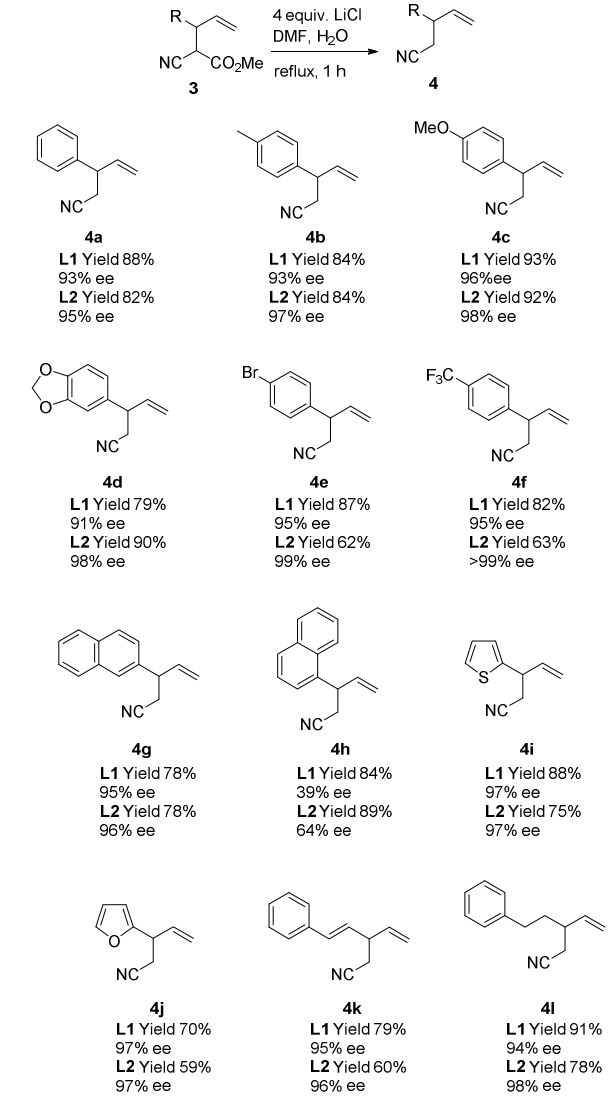
Krapcho demethoxycarbonylation of **3** in the presence of LiCl and H_2O in refluxing DMF for 1 h gave enantio-enriched homoallylic nitrile **4** (Scheme 2). Ligand **L2** gave the product in the same or better enantioselectivity than ligand **L1**.[14] In the case of allylation using **L2**, aromatic nitriles **4a-4f** were obtained with 95~99% ee. 1-Naphthyl nitrile **4h** was obtained less enantio-enriched than 2-naphthyl nitrile **4g**.[7e, 15] Heteroaromatic and dienyl nitriles **4i-4k** were obtained with 96~97% ee. Alkyl-substituted nitrile **4l** was obtained in 98% ee using **L2**.

Scheme 1. Scope of Substrates.



The absolute configuration of **4a** was determined as follows (Scheme 3). (*S*)-**5** was prepared as described in the literature ($[\alpha]_D$ = -32.4 (*c* = 1.34, $CHCl_3$, 95% ee)).[16] The absolute configuration was determined by comparison of its specific rotation with the reported value for (*R*)-**5** ($[\alpha]_D$ = +31.3 (*c* = 0.97, $CHCl_3$, 88% ee)).[17] Krapcho demethoxycarbonylation of (***S***)-**5** gave (***R***)-**6** with 95% ee ($[\alpha]_D$ = +10.4). Compound **4a** led to **6** (85% ee) by hydrolysis followed by esterification with MeOH. The specific rotation of **6** derived from **4a** was $[\alpha]_D$=+7.4, indicating that the absolute configuration of **6** was ***R***. Thus, the absolute configuration of **4a** was determined to be ***R***, because **4a** gave (***R***)-**6**.

Scheme 2. Synthesis of Chiral Nitriles by Krapcho-Demethoxycarbonylation of 3.



Based on the absolute configuration of **4a** obtained by using (***Ra, R, R***)-**L1**, the transition state for the nucleophilic attack of a π-allyl iridium intermediate is shown in Figure 1. The transition state shown in Figure 1 is consistent with the structure of isolated π-allyl iridium complex with (***Ra***, ***R***, ***R***)-**L1** reported by Hartwig *et al*.[11c,d]

Scheme 3. Determination of Absolute Configuration of 4a.

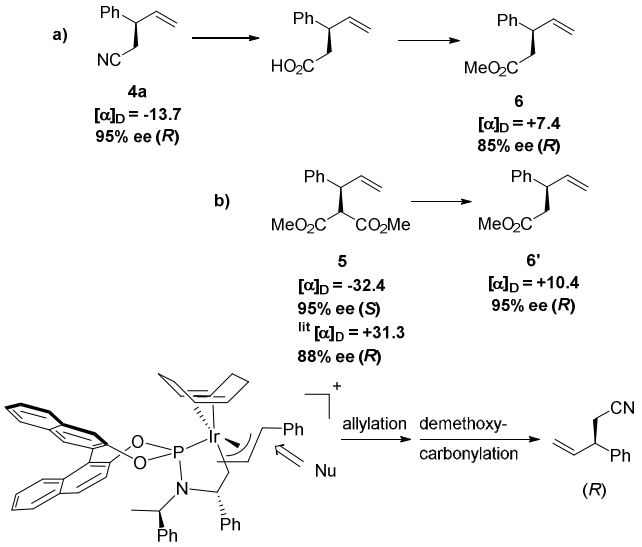
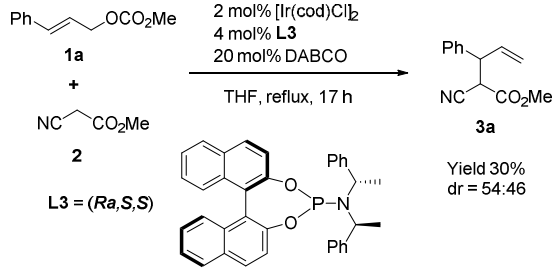


Figure 1. Transition state of the nucleophile attack to π-allyl iridium intermediate.

Scheme 4. The reaction of 1a with 2 using L3.



The reaction of **1a** with **2** using **L3**, a diastereomer of **L1**, was performed under the same optimized reaction conditions described above (Scheme 4). Product **3a** was obtained in only 30% yield with almost the same diastereomeric ratio given by **L1**. A large match-mismatch effect between **L1** and **L3** was observed.

In summary, we have developed a method for the synthesis of chiral homoallylic nitriles by the iridium-catalyzed allylation of cyanoacetates. A wide range of homoallylic nitriles were obtained with high enantioselectivity. Further application of these chiral building blocks to the synthesis of medicinally useful compounds is underway in our laboratory.

EXPERIMENTAL SECTION

General Information. The ^{1}H and ^{13}CNMR spectra were measured on a 500MHz spectrometers using TMS as an internal standard. Samples were dissolved in $CDCl_3$. HPLC analyses were performed on with commercially available chiral columns. The products were purified by column chromatography on 63-210 mesh silica gel. High-resolution mass spectra were obtained by using a double-focusing analyzer. Infrared spectra were recorded with a FT-IR spectrometer. Optical rotations were measured on a polarimeter. All solvents were dried and distilled before use by the usual procedures. $[Ir(cod)Cl]_2$ was prepared as described in the literature.[18] Esters **1a**, **1b** and **1i** were prepared according to the literature.[7d] Esters **1c**, **1d**, **1e**, **1f**, **1h** and **1j** were prepared according to the literature.[19] Ester **1k** was prepared according to the literature.[20] Ester **1l** was prepared according to the literature.[21] Ester **1g** was prepared according to the literature.[22] Ester **1l** was prepared by the reaction of (*E*)-5-phenyl-2-penten-1-ol[23] with methyl chloroformate. **L1** was prepared according to the literature.[24] **L2** was purchased.

General procedure for the reaction of 1 with 2. A flask was charged with $[Ir(cod)Cl]_2$ (6.9 mg, 0.01 mmol), **L1** (11.3 mg, 0.02 mmol), and DABCO (11.1mg, 0.01 mmol), and then evacuated and filled with argon. To the flask was added THF (1 mL). The mixture was stirred under argon for 2 h. To the flask were added allyl carbonate **1a** (96.9 mg, 0.50 mmol) and THF (3 mL). Cyanoacetate **2** (100.0 mg, 1.0 mmol) was then added to the mixture. The mixture was stirred under reflux for 18 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated in vacuo. Column chromatography of the residue gave **3a** (*n*-hexane/AcOEt = 9/1, 86.0 mg, 0.40 mmol, 80% yield).

Methyl 2-cyano-3-phenylpent-4-enoate (3a) (mixture of diastereomers) Pale yellow oil, Yield 80%, 86.0 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.72 (s, 3H), 3.82 (d, *J* = 6.3 Hz, 1H), 3.89 (d, *J* = 7.4 Hz, 1H), 4.08-4.03 (m, 2H), 5.33-5.24 (m, 4H), 6.21-6.07 (m, 2H), 7.37-7.25 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.8, 44.3, 49.5, 53.3, 53.4, 115.1, 115.2, 118.2, 119.4, 127.6, 127.9, 128.1, 128.9, 129.0, 134.5, 135.8, 137.6, 138.3, 165.3; IR (neat, cm^{-1}) 3029, 2952, 2247, 1745, 1436, 1251; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{13}H_{13}NO_2$ 215.0946; found 215.0944

Methyl 2-cyano-3-(4-methylphenyl)pent-4-enoate (3b) (mixture of diastereomers) Pale yellow oil, Yield 77%, 88.6 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 6H), 3.715 (s, 3H), 3.724 (s, 3H), 3.79 (d, *J* = 6.9 Hz, 1H), 3.86 (d, *J* = 7.4 Hz, 1H), 3.99-4.05 (m, 2H), 5.22-5.31 (m, 4H), 6.05-6.19 (m, 2H), 7.16 (d, *J* = 8.6 Hz, 4H), 7.18 (d, *J* = 8.6 Hz, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.01, 21.05, 43.9, 44.4, 49.3, 53.32, 53.37, 115.2, 115.3, 117.9, 119.1, 127.4, 127.8, 129.59, 129.63, 134.6, 134.7, 135.3, 136.1, 137.7, 137.8, 165.39, 165.42; IR (neat, cm^{-1}) 2952, 2250, 1749, 1516, 1436, 1247, 1018; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{14}H_{15}NO_2$ 229.1103; found 229.1104.

Methyl 2-cyano-3-(4-methoxyphenyl)pent-4-enoate(3c) (mixture of diastereomers) Colorless oil, Yield 91%, 111.2 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.73 (s, 3H), 3.78 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 6H), 3.85 (d, *J* = 6.9 Hz, 1H), 4.02 (q, *J* = 6.9 Hz, 2H), 5.22-5.31 (m, 4H), 6.05-6.19 (m, 2H), 6.88 (d, *J* = 9.2 Hz, 4H), 7.23-7.21 (m, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 44.1, 44.5, 48.8, 48.9, 53.34, 53.38, 55.20, 55.24, 114.27, 114.32, 115.2, 115.3, 117.8, 119.0, 128.7, 129.1, 129.5, 130.3, 134.8, 136.1, 159.2, 159.3, 165.41, 165.45; IR (neat, cm^{-1}) 3002, 2955, 2249, 1751, 1612, 1517, 1184; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{14}H_{15}NO_3$ 245.1052; found 245.1051.

Methyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanopent-4-enoate (3d) (mixture of diastereomers) Pale yellow oil, Yield 87%, 119.0 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.732 (s, 3H), 3.738 (s, 3H), 3.77 (d, *J* = 6.3 Hz, 1H), 3.85 (d, *J* = 7.4 Hz, 1H), 3.98 (q, *J* = 7.4 7Hz, 2H), 5.22-5.32 (m, 4H), 5.95 (s, 4H), 6.01-6.15 (m, 2H), 6.74-6.80 (m, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 15.2, 44.0, 44.5, 49.17, 49.24, 53.41, 53.45, 65.8, 101.22, 101.24, 107.9, 108.2, 108.54, 108.58, 115.1, 115.2, 117.9, 119.2, 121.0, 121.5, 131.2, 132.0, 134.6, 135.9, 147.3, 147.4, 148.03, 148.08, 165.29, 165.34; IR (neat, cm^{-1}) 3083, 2952, 2247, 1752, 1505, 1439, 1105; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{14}H_{13}NO_4$ 259.0845; found 259.0846.

Methyl 3-(4-bromophenyl)-2-cyanopent-4-enoate (3e) (mixture of diastereomers) Pale yellow oil, Yield 69%, 101.9

mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.74 (s, 3H), 3.79 (d, *J* = 6.3 Hz, 1H), 3.88 (d, *J* = 6.9 Hz, 1H), 4.02-4.06 (m, 2H), 5.24-5.35 (m, 4H), 6.03-6.16 (m, 2H), 7.18-7.21 (m, 4H), 7.48-7.50 (m, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.5, 44.1, 48.7, 48.9, 53.50, 53.55, 114.88, 114.92, 118.6, 119.9, 122.0, 122.2, 129.3, 129.8, 132.06, 132.12, 134.0, 135.3, 136.6, 137.4, 165.07, 165.10; IR (neat, cm^{-1}) 2956, 2243, 1744, 1487, 1433, 1072; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{13}H_{12}{}^{79}BrNO_2$ 293.0051; found 293.0047.

Methyl 2-cyano-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (3f) (mixture of diastereomers) Yellow oil, Yield 66%, 94.5 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.75 (s, 3H), 3.84 (d, *J* = 5.7 Hz, 1H), 3.93 (d, *J* = 7.4 Hz, 1H), 4.14 (q, *J* = 6.5 Hz, 2H), 775.27-5.39 (m, 4H), 6.06-6.20 (m, 2H), 7.44-7.46 (m, 4H), 7.63 (d, *J* = 8.0 Hz, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.3, 43.9, 48.9, 49.1, 53.48, 53.54, 114.8, 119.0, 120.2, 123.82 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 123.85 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 125.82 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 125.88 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 128.1, 128.5, 130.19 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 130.30 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 133.6, 135.0, 141.6, 142.4, 164.9; IR (neat, cm^{-1}) 2959, 2251, 1753, 1618, 1437, 1325, 1125, 1069, 1018; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{14}H_{12}F_3NO_2$ 283.0820; found 283.0819.

Methyl 2-cyano-3-(naphthalen-2-yl)pent-4-enoate (3g) (mixture of diastereomers) Yellow oil, Yield 81%, 106.7 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.69 (s, 3H), 3.93 (d, *J* = 6.3 Hz, 1H), 3.98 (d, *J* = 7.5 Hz, 1H), 4.21-4.25 (m, 2H), 5.27-5.37 (m, 4H), 6.14-6.30 (m, 2H), 7.39-7.48 (m, 6H), 77.76-7.84 (m, 8H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.7, 44.2, 49.6, 53.35, 53.4, 115.1, 115.2, 118.4, 119.6, 125.2, 125.5, 126.26, 126.28, 126.34, 126.4, 126.6, 127.2, 127.6, 127.87, 127.93, 128.7, 128.8, 132.8, 132.9, 133.3, 134.5, 135.0, 135.7, 135.8, 165.3; IR (neat, cm^{-1}) 3049, 2954, 2250, 1749, 1603, 1437, 1260; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{17}H_{15}NO_2$ 265.1103; found 265.1102.

Methyl 2-cyano-3-(naphthalen-1-yl)pent-4-enoate (3h) (mixture of diastereomers) Pale yellow oil, Yield 91%, 119.9 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.80 (s, 3H), 4.04 (d, *J* = 5.1 Hz, 1H), 4.13 (d, *J* = 8.0 Hz, 1H), 4.92-5.00 (m, 2H), 5.27-5.30 (m, 2H), 5.37-5.41 (m, 2H), 6.11-6.18 (m, 1H), 6.35-6.42 (m, 1H), 7.49-7.60 (m, 8H), 7.81-7.91 (m, 4H), 8.06 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.0, 43.9, 44.1, 44.2, 53.4, 53.6, 114.97, 115.3, 118.6, 119.8, 121.7, 122.5, 125.0, 125.36, 125.39, 125.47, 125.86, 125.91, 126.5, 126.9, 128.7, 129.2, 129.5, 130.3, 131.1, 133.6, 133.99, 134.08, 134.1, 136.0, 165.5, 165.6; IR (neat, cm^{-1}) 3052, 2955, 2250, 1749, 1511, 1268; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{17}H_{15}NO_2$ 265.1103; found 265.1104.

Methyl 2-cyano-3-(thiophen-2-yl)pent-4-enoate (3i) (mixture of diastereomers) Pale yellow oil, Yield 73%, 81.2 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.79 (s, 3H), (d, *J* = 10.3 Hz, 6H), 3.87 (d, *J* = 6.3 Hz, 1H), 3.90 (d, *J* = 5.7 Hz, 1H), 4.34-4.40 (m, 2H), 5.30-5.36 (m, 4H), 6.07-6.17 (m, 2H), 6.98-7.06 (m, 4H), 7.25-7.26 (m. 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 44.80, 44.85, 45.0, 45.1, 53.6, 114.76, 114.83, 118.6, 119.9, 125.1, 125.3, 125.4, 126.0, 127.1, 127.20, 134.1, 135.5, 139.7, 141.0, 164.9, 165.0; IR (neat, cm^{-1}) 3006, 2956, 2251, 1752, 1436, 1254; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{11}H_{11}NO_2S$ 221.0510; found 221.0511.

Methyl 2-cyano-3-(furan-2-yl)pent-4-enoate (3j) (mixture of diastereomers) Pale yellow oil, Yield 55%, 56.3 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.80 (s, 3H), 3.88 (d, *J* = 6.3 Hz, 1H), 4.06 (d, *J* = 5.1 Hz, 1H), 4.16-4.21 (m, 2H), 5.31-5.38 (m, 4H), 5.99-6.09 (m. 2H), 6.24 (d, *J* = 3.5 Hz, 1H), 6.28 (d, *J* = 3.5 Hz, 1H), 6.33-6.34 (m, 7.39 (m, 2H), 7.39 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 42.3, 42.4, 43.6, 43.7, 53.5, 107.7, 107.9, 110.49, 110.56, 114.6, 114.7, 119.7, 120.9, 131.7, 133.0, 142.5, 142.6, 150.6, 151.0, 165.0; IR (neat, cm^{-1}) 3085, 2958, 2254, 1752, 1436; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{11}H_{11}NO_3$ 205.0739; found 205.0741.

Methyl (*E*)-2-cyano-5-phenyl-3-vinylpent-4-enoate (3k) (mixture of diastereomers) Yellow oil, Yield 62%, 75.1 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.64-3.70 (m, 4H), 3.79 (s, 3H), 3.80 (s, 3H), 5.28-5.33 (m, 4H), 5.89-5.98 (m, 2H), 6.15-6.22 (m, 2H), 6.55 (d, *J* = 6.9 Hz, 2H), 6.58 (d, *J* = 6.9 Hz, 2H),7.24-7.39 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 43.27, 43.38, 47.36, 47.55, 53.4, 114.9, 118.6, 119.4, 124.7, 125.8, 126.48, 126.54, 128.07, 128.09, 128.57, 128.61, 133.6, 134.0, 134.3, 135.2, 136.08, 136.14, 165.3; IR (neat, cm^{-1}) 3028, 2955, 2250, 1747, 1435, 1253; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{15}H_{15}NO_2$ 241.1103; found 241.1105.

Methyl 2-cyano-3-phenethylpent-4-enoate (3l) (mixture of diastereomers) Pale yellow oil, Yield 73%, 89.2 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.82-1.94 (m, 4H), 2.50-2.62 (m, 2H), 2.67-2.80 (m, 4H), 3.50 (d, *J* = 6.3 Hz, 1H), 3.58 (d, *J* = 4.6 Hz, 1H), 3.76 (s, 6H), 5.19-5.30 (m, 4H), 5.68-5.79 (m, 2H), 7.15-7.22 (m, 6H), 7.27-7.3 (m, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 32.77, 32.85, 33.0, 34.2, 43.24, 43.26, 43.87, 43.98, 53.27, 53.33, 114.9, 115.2, 119.6, 120.0, 126.1, 128.3, 128.46, 128.53, 135.2, 136.1, 140.7, 140.8, 165.6, 165.7; IR (neat, cm^{-1}) 3023, 2925, 2250, 1749, 1453, 1259; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{15}H_{17}NO_2$ 243.1259; found 243.1257.

General procedure for Krapcho-Demethoxycarbonylation of 3. A flask was charged with LiCl (58.5 mg, 1.38 mmol), **3a** (85.9 mg, 0.40 mmol), DMF (3 mL) and H_2O (25μL). The flask was flushed with argon. The mixture was stirred under reflux for 1 h. After the reaction was complete, a saturated aqueous solution of NH_4Cl (5 mL) was added. The aqueous layer was extracted three times with ether (5 mL). The combined organic layer was dried with $MgSO_4$. The solvent was evaporated in vacuo. Column chromatography of the residue gave **4a** (*n*-hexane/AcOEt = 9/1, 55.2 mg, 0.35 mmol, 88% yield).

3-Phenylpent-4-enenitrile (4a) Colorless oil, Yield 88%, 55.2 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.75 (dd, *J* = 16.6, 7.4 Hz, 1H), 3.70 (q, *J* = 7.3 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.3 Hz, 1H), 6.03 (ddd, *J* = 17.1, 10.3, 6.6 Hz, 1H), 7.23-7.30 (m, 3H), 7.34-7.37 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.9, 45.4, 116.8, 118.2, 127.3, 127.5, 128.9, 137.8, 140.3; IR (neat, cm^{-1}) 3029, 2983, 2353, 2246, 1736, 1491, 1122; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{11}H_{11}N$ 157.0891; found 157.0887. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 22.39 min (major) and 26.20 min (minor)). $[\alpha]_D^{25}$ -13.69 (c = 1.28, $CHCl_3$, 95% ee).

3-(4-Methylphenyl)pent-4-enenitrile (4b) Colorless oil, Yield 84%, 55.3 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 73H), 2.68 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 7.5 Hz, 1H), 3.66 (q, *J* = 7.3 Hz, 1H), 5.19 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 6.01 (ddd, *J* = 17.1, 10.3, 6.9 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.0, 24.0, 45.1, 116.6, 118.3,

127.1, 129.6, 137.2, 137.3, 138.0; IR (neat, cm^{-1}) 3023, 2984, 2247, 1638, 1513, 1416, 1110; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{12}H_{13}N$ 171.1048; found 171.1048. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent n-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 230 nm, retention time 20.20 min (major) and 23.09 min (minor)). $[\alpha]_D^{25}$ -9.22 (c = 1.00, $CHCl_3$, 93% ee).

3-(4-Methoxyphenyl)pent-4-enenitrile (4c) Colorless oil, Yield 93%, 78.6 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 7.1 Hz, 1H), 3.66 (q, *J* = 6.9 Hz, 1H), 3.79 (s, 3H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 6.01 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 24.1, 44.6, 55.2, 114.3, 116.4, 118.3, 128.3, 132.3, 138.1, 158.9; IR (neat, cm^{-1}) 3002, 2960, 2243, 1639, 1610, 1509, 1247, 1179; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{12}H_{13}NO$ 187.0997; found 187.0999. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 230 nm, retention time 26.83 min (major) and 30.79 min (minor)). $[\alpha]_D^{25}$ -13.46 (c = 0.91, $CHCl_3$, 96% ee).

3-(Benzo[d][1,3]dioxol-5-yl)pent-4-enenitrile (4d) Pale yellow oil, Yield 78%, 68.9 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.66 7(dd, *J* = 16.4, 7.7 Hz, 1H), 2.70 (dd, *J* = 16.4, 7.5 Hz, 1H), 3.62 (q, *J* = 6.9 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 9.1 Hz, 1H), 5.94 (s, 2H), 5.98 (ddd, *J* = 17.2, 9.1, 6.9 Hz, 1H), 6.68 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 24.0, 45.1, 101.1, 107.6, 108.5, 116.6, 118.1, 120.5, 134.1, 137.8, 146.9, 148.0; IR (neat, cm^{-1}) 3082, 2984, 2247, 1637, 1442, 1248, 1037: HRMS (EI^+) m/z $[M]^+$ calcd for $C_{12}H_{11}NO_2$ 201.0790; found 201.0791. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent n-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 230 nm, retention time 34.77 min (major) and 44.78 min (minor)). $[\alpha]_D^{25}$ -0.74 (c = 0.97, $CHCl_3$, 93% ee).

3-(4-Bromophenyl)pent-4-enenitrile (4e) Colorless oil, Yield 87%, 72.9 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.68 (dd, *J* = 16.6, 6.8 Hz, 1H), 2.74 (dd, *J* = 16.6, 6.9 Hz, 1H), 3.67 (q, *J* = 6.9 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 5.99 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.8, 44.8, 117.3, 117.8, 121.5, 129.1, 132.1, 137.2, 139.2; IR (neat, cm^{-1}) 3082, 2980, 2248, 1640, 1487, 1074, 928; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{11}H_{10}{}^{79}BrN$ 234.9997; found 235.0003. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent n-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 230 nm, retention time 27.90 min (major) and 32.90 min (minor)). $[\alpha]_D^{25}$ -14.50 (c = 0.95, $CHCl_3$, 92% ee).

3-(4-(Trifluoromethyl)phenyl)pent-4-enenitrile (4f) Pale yellow, oil, Yield 82%, 68.4 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 16.6, 7.4 Hz, 1H), 2.78 (dd, *J* = 16.6, 7.4 Hz, 1H), 3.78 (q, *J* = 6.9 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 1H), 6.02 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.6, 45.1, 117.61, 117.67, 123.9 (q, $^1J_{C\text{-}F}$ = 271.1 Hz), 125.9 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 127.8, 129.9 (q, $^2J_{C\text{-}F}$ = 33.6 Hz), 136.8, 144.2; IR (neat, cm^{-1}) 3085, 2988, 2249, 1618, 1419, 1327, 1166; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{12}H_{10}F_3N$ 225.0765; found 225.0762. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 210 nm, retention time 20.33 min (major) and 22.47 min (minor)). $[\alpha]_D^{25}$ -14.98 (c = 1.1, $CHCl_3$, 95% ee).

3-(Naphthalen-2-yl)pent-4-enenitrile (4g) Yellow oil, Yield 78%, 63.8 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.79 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.83 (dd, *J* = 16.6, 7.5 Hz, 1H), 3.86 (q, *J* = 6.8 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 6.10 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 7.32-7.34 (m, 1H), 7.45-7.50 (m, 2H), 7.68 (s, 1H), 7.80-7.84 (m, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.8, 45.5, 117.1, 118.2, 125.2, 126.07, 126.08, 126.4, 127.6, 127.8, 128.8, 132.7, 133.4, 137.6, 137.7; IR (neat, cm^{-1}) 3054, 2926, 2247, 1636, 1600, 1416, 1270, 1123; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{15}H_{13}N$ 207.1048; found 207.1049. The ee value was determined by HPLC analysis with a Chiracel OJ-H column (eluent *n*-hexane/2-propanol = 90/10, flow rate: 1.0 mL/min, column temperature 35°C, 210 nm, retention time 26.57 min (minor) and 28.15 min (major)). $[\alpha]_D^{25}$ -21.54 (c = 1.19, $CHCl_3$, 95% ee).

3-(Naphthalen-1-yl)pent-4-enenitrile (4h) Yellow oil, Yield 84%, 78.9 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.85 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.90 (dd, *J* = 17.2, 6.3 Hz, 1H), 4.54 (q, *J* = 6.9 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.3 Hz, 1H), 6.15 (ddd, *J* = 17.2, 10.3, 6.3 Hz, 1H), 7.38 (d, *J* = 6.9 Hz, 1H), 7.44-7.57 (m, 3H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 7.4 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.1, 40.3, 117.3, 118.3, 122.4, 124.2, 125.4, 125.8, 126.5, 128.2, 129.2, 130.8, 134.0, 136.1, 137.4; IR (neat, cm^{-1}) 3050, 2982, 2248, 1638, 1597, 1510, 1396, 994; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{15}H_{13}N$ 207.1048; found 207.1050. The ee value was determined by HPLC analysis with a Chiracel OJ-H column (eluent *n*-hexane/2-propanol = 90/10, flow rate: 1.0 mL/min, column temperature 35°C, 200 nm, retention time 17.18 min (minor) and 26.57 min (major)). $[\alpha]_D^{25}$ 1.19 (c = 1.14, $CHCl_3$, 34% ee).

3-(Thiophen-2-yl)pent-4-enenitrile (4i) Yellow oil, Yield 88%, 49.3 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 16.6, 7.4 Hz, 1H), 2.80 (dd, *J* = 16.6, 6.9 Hz, 1H), 3.98 (q, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 16.0 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 6.02 (ddd, *J* = 16.0, 10.3, 6.8 Hz, 1H), 6.94 (d, *J* = 3.4 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.23 (dd, *J* = 5.2, 1.4 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 25.0, 41.0, 117.59, 117.68, 124.6, 127.1, 137.2, 143.4; IR (neat, cm^{-1}) 3083, 2983, 2248. 1711, 1418, 1361, 1222, 930; HRMS (EI^+) m/z $[M]^+$ calcd for C_9H_9NS 163.0456; found 163.0460. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 99.5/0.5, flow rate: 1.0 mL/min, column temperature 35°C, 220 nm, retention time 28.83 min (minor) and 30.12 min (major)). $[\alpha]_D^{25}$ -48.89 (c = 0.91, $CHCl_3$, 97% ee).

3-(Furan-2-yl)pent-4-enenitrile (4j) Yellow oil, Yield 70%, 27.6 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.81 (dd, *J* = 16.6, 6.3 Hz, 1H), 3.79 (q, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 16.0 Hz, 1H), 5.30 (d, *J* = 9.7 Hz, 1H), 5.98 (ddd, *J* = 16.0, 10.3, 7.5 Hz, 1H), 6.17 (d, *J* = 2.9 Hz, 1H), 6.32-6.34 (m, 1H), 7.37 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 22.1, 39.6, 106.5, 110.4, 117.7, 118.4, 134.8, 142.2, 152.9: IR (neat, cm^{-1}) 3087, 2931, 2248, 1640, 1504, 1420, 1147, 1011; HRMS (EI^+) m/z $[M]^+$ calcd for C_9H_9NO 147.0684;

found 147.0688. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent n-hexane/2-propanol = 99.9/0.1, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 46.55 min (major) and 51.00 min (minor)). $[\alpha]_D^{25}$ -58.66 (c = 1.00, $CHCl_3$, 95% ee).

(*E*)-5-Phenyl-3-vinylpent-4-enenitrile (4k) Yellow oil, Yield 79%, 44.8 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.55 (d, *J* = 6.9 Hz, 2H), 3.28 (q, *J* = 6.8 Hz, 1H), 5.23 (d, *J* = 16.7 Hz, 1H), 5.24 (d, *J* = 11.5 Hz, 1H), 5.87 (ddd, *J* = 16.7, 11.5, 6.8 Hz), 6.13 (dd, *J* = 16.0, 7.5 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 7.22-7.26 (m, 2H), 7.29-7.34 (m, 2H), 7.36-7.41 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.2, 42.9, 117.2, 118.0, 126.4, 127.8, 128.1, 128.6, 132.3, 136.4, 137.0; IR (neat, cm^{-1}) 3027, 2980, 2247, 1716, 1638, 1494, 1419, 1262, 1072; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{13}H_{13}N$ 183.1048; found 183.1045. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 28.34 min (major) and 43.34 min (minor)). $[\alpha]_D^{25}$ -51.18 (c = 0.72, $CHCl_3$, 95% ee).

3-Phenethylpent-4-enenitrile (4l) Yellow oil, Yield 91%, 61.5 mg, ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.71-1.80 (m, 1H), 1.81-1.88 (m, 1H), 2.24-2.43 (m, 3H), 2.51-2.60 (m, 1H), 2.65-2.71 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 7.15-7.20 (m, 3H), 7.27-7.33 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 23.2, 32.9, 35.3, 39.5, 117.6, 118.2, 125.9, 128.3, 128.4, 138.4, 141.1; IR (neat, cm^{-1}) 3027, 2925, 2245, 1496, 1421, 1029; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{13}H_{15}N$ 185.1204; found 185.1203. The ee value was determined by HPLC analysis with a Chiracel OD-H column (eluent *n*-hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 23.09 min (major) and 25.89 min (minor)). $[\alpha]_D^{25}$ 11.60 (c = 1.00, $CHCl_3$, 95% ee).

Determination of Absolute Configuration of 4a. *Preparation of (R)-**6'**.* (*S*)-**5** was prepared as described in the literature ($[\alpha]_D$ = -32.4 (c = 1.34, $CHCl_3$, 95% ee).[16] The absolute configuration was determined by comparison of its specific rotation with the reported value for (*R*)-**5** ($[\alpha]_D$ = +31.3 (c = 0.97, $CHCl_3$, 88% ee)).[17] A flask was charged with LiCl (135.0 mg, 3.18 mmol), (*S*)-**5** (198.1 mg, 0.80 mmol), DMF (4 mL) and H_2O (30μL). The flask was flushed with argon. The mixture was stirred under reflux for 1 h. After the reaction was complete, a saturated aqueous solution of NH_4Cl (5 mL) was added. The aqueous layer was extracted three times with ether (5 mL). The combined organic layer was dried with $MgSO_4$. The solvent was evaporated in vacuo. Column chromatography of the residue gave (*R*)-**6'** (*n*-hexane/AcOEt = 95/5, 124.1 mg, 0.65 mmol, 81% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 15.4, 7.4 Hz, 1H), 2.77 (dd, *J* = 15.4, 8.0 Hz, 1H), 3.62 (s, 3H), 3.87 (q, *J* = 7.4 Hz, 1H), 5.071 (d, *J* = 16.6 Hz, 1H), 5.076 (d, *J* = 11.4 Hz, 1H), 5.98 (ddd, *J* = 16.6, 11.4, 7.4 Hz, 1H), 7.20-7.22 (m, 3H), 7.29-7.32 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 40.0, 45.5, 51.6, 114.8, 126.7, 127.5, 128.6, 140.2, 142.4, 172.3. The ee value was determined by HPLC analysis with a Chiracel OB column (eluent *n*-hexane/2-propanol = 99/1, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 12.81 min (minor) and 14.09 min (major)). $[\alpha]_D^{25}$ = 10.44 (c = 1.19, $CHCl_3$, 95% ee).

*Preparation of **6** from **4a**.* A mixture of **4a** (99.5 mg, 0.63 mmol, 95%ee, $[\alpha]_D$ = -13.7, c=1.28), 1M NaOH (4 mL), and dioxane (2 mL) was stirred at 100°C for 20 h. After the reaction was complete, the mixture was acidified by conc. HCl to pH=1. The aqueous layer was extracted three times with ether (5 mL). The combined organic layer was dried with $MgSO_4$. The solvent was evaporated in vacuo. The residue was subjected to esterification with MeOH without further purification. A mixture of the residue, MeOH (3 mL) and 2 drops of conc. HCl was stirred in refluxing MeOH for 1 h. The mixture was evaporated in vacuo. Column chromatography of the residue gave **6** (*n*-hexane/AcOEt = 95/5, 17.7 mg, 0.09 mmol, 14 % yield). The ee value was determined by HPLC analysis with a Chiracel OB column (eluent *n*-hexane/2-propanol = 99/1, flow rate: 0.5 mL/min, column temperature 35°C, 220 nm, retention time 12.70 min (minor) and 13.99 min (major)). $[\alpha]_D^{25}$ = 7.38 (c = 0.89, $CHCl_3$, 85% ee). The absolute configuration of **6** obtained here was determined to be R by comparison of its specific rotation to that of (*R*)-**6**. The absolute configuration of **4a** used here was determined to be R because **4a** led to (*R*)-**6**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra and HPLC charts for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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