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Lewis Base-Promoted Rearrangement of Allylic Cyanohydrins: Construction of Functionalized Nitriles Bearing 1,3-Diketone Moieties

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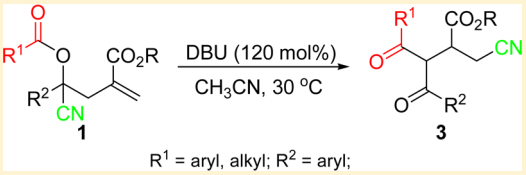
Supporting Information

ABSTRACT: A novel Lewis base-promoted rearrangement of allylic cyanohydrins has been developed, in which the cyano group was rearranged, directly coupled with the generation of new functional groups. This protocol provides a unique and facile way to prepare highly functionalized nitriles bearing 1,3-diketone moieties under mild reaction conditions. Furthermore, the synthetic transformations of the functionalized products have also been demonstrated.



INTRODUCTION

As one of most fundamental chemicals, nitriles are found widely in a number of pharmaceutical drugs, agrochemicals, and optoelectronic materials as well as synthetic intermediates for carboxylic acids, esters, amides, and amines.[1] Myriads of synthetic methods have been developed to arrive at nitriles with structural diversities.[1c] The formation of structurally diverse nitriles by functional group interconversion and nucleophilic and electrophilic cyanation reactions constitute an important task in organic synthesis.[1,2] However, the construction of functionalized nitriles via a Lewis base-promoted rearrangement of simple and readily available nitriles in which the cyano group was rearranged, directly coupled with the generation of new functional groups, has received less attention,[3] despite the fact that carbon skeleton rearrangement has proven to be a powerful and efficient strategy in organic synthesis to construct a variety of organic compounds.[2,4]

Cyanohydrins are important synthetic building blocks due to their diverse chemical transformations and ready availability from aldehydes and ketones.[5] Although a series of derivatized α-cyanohydrins have been reported to undergo displacement by a variety of nucleophiles to prepare corresponding nitriles,[5e,6] to our best knowledge, the employment of cyanohydrins in a Lewis base-promoted rearrangement process to build functionalized nitriles remains unexplored.

β-Diketone moieties are widely represented in natural products, pharmaceuticals, other biologically relevant compounds, and synthetic intermediates.[7] Recently, we have demonstrated an organocatalytic tandem process to furnish highly functionalized cyanohydrins and employed them in a unique Lewis base-mediated nucleophilic intramolecular acylcyanation reaction to prepare functionalized nitriles with 1,4-diketone units (Scheme 1, path A, TABCN = tetrabutylammonium cyanide).[8a,b] As part of an ongoing program aimed at developing efficient metal-free processes to construct diverse carbon frameworks incorporating the cyano functional group,[8] herein we report a novel protocol to access densely functionalized nitriles bearing 1,3-diketone moieties via a Lewis base-promoted rearrangement of allylic cyanohydrin wherein the cyano group was reassembled, accompanied by the creation of a 1,3-diketone moiety (Scheme 1 path B) under mild reaction conditions.

RESULTS AND DISCUSSION

Our initial investigation was examined with benzoyl cyanohydrin **1a**, which is prepared from commercial available aldehyde, cyanide source, and Morita–Baylis–Hillman (MBH) adduct,[8a] and did not undergo a Lewis base-catalyzed intramolecular acylcyanation reaction to provide acyclic ketone **2a** under the previous reaction conditions.[8b] Interestingly, treatment of *O*-benzoyl-substituted cyanohydrin **1a** with DBU (60 mol %) provided functionalized nitrile **3a** possessing a 1,3-diketone moiety, albeit in low yield (Table 1, entry 1). The structure of compound **3a** was unambiguously supported by NMR spectroscopic and X-ray structure analysis. Encouraged by this, further increase in the amount of DBU gave the desired product **3a** in improved yield (Table 1, entries 2 and 3). Screening of the solvents indicated that CH_3CN was the best solvent.[9] Considering the potential role which Lewis bases may play, a spectrum of Lewis bases has been evaluated with regard to the nucleophilicity and basicity.[10] Less basic Lewis bases such as DABCO and DMAP compared to DBU did not furnish any desired product (Table 1, entries 4 and 5), while tertiary amine DBN which has a basicity similar to that of DBU gave the desired product **3a** along with **4a** in low yield (Table 1, entry 6). The more basic tertiary amine TBD did not give any desired product **3a** (Table 1, entry 7).[11] These results indicated that both nucleophilicity and basicity were essential to this rearrangement. This hypothesis was confirmed further by the results in which the treatment of **1a** with PBu_3, PPh_3, or *t*BuOK

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Scheme 1. Synthetic Strategy

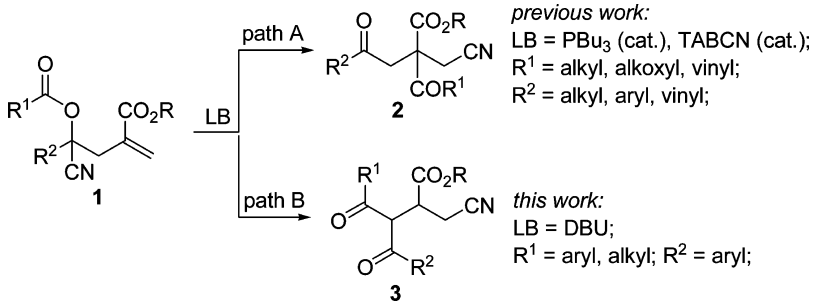
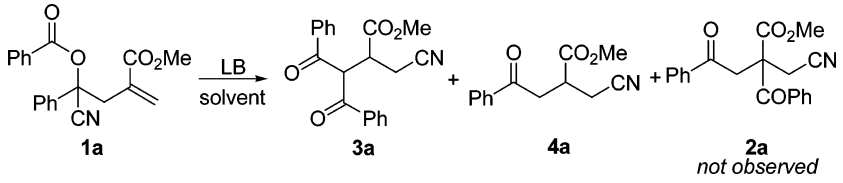


Table 1. Reaction Conditions Screening[a]



entry	LB (equiv)	T (°C)	t (h)	yield (%)[b]
1	DBU (0.6)	30	48	33 (**3a**)
2	DBU (1.2)	30	43	67 (**3a**)
3	DBU (2.0)	30	12	65 (**3a**)
4	DABCO (1.2)	30/80	14/14	–[c]
5	DMAP (1.2)	30/80	14/14	–[c]
6	DBN (1.2)	30	24	49 (**3a**)/21(**4a**)
7	TBD (1.2)	30	24	13 (**4a**)
8	PBu_3 (1.2)	30	3	42 (**4a**)
9	PPh_3 (1.2)	30/80	14/14	–[c]
10	*t*BuOK (1.2)	30	41	24 (**4a**)
11	DBU (1.2)	60	17	19 (**3a**)/9(**4a**)
12[d]	DBU (1.2)	30	45	54 (**3a**)

[a]Reactions were performed with **1a** (0.2 mmol) and Lewis base in CH_3CN (c = 0.1 M). [b]Isolated yield. [c]No desired product was detected. [d]4 Å molecular sieves were added. LB = Lewis base; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-(dimethylamino)pyridine; TBD = 1,5,7-triazabicyclo(4.4.0)dec-5-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

did not give any desired product, respectively (Table 1, entries 8–10). The attempt to accelerate this transformation at elevated temperature was unsuccessful, and the desired product **3a** was obtained in low yield (Table 1, entry 11). In addition, the reaction was performed with 4 Å molecular sieves, and no obvious improvement was observed (Table 1, entry 12).

With the optimized reaction conditions in hand, the scope of the rearrangement reaction was explored. The results are summarized in Table 2. Cyanohydrins with different O-aromatic acyl protecting groups were evaluated first. The electronic properties of the aromatic system of acyl substituents (R^1) seemed to have considerable effects on the conversion in this reaction. Cyanohydrin **1b** possessing a para-electron-withdrawing group such as Cl underwent the expected rearrangement to furnish product **3b** with 1/1 diastereoselectivity in a yield similar to that of its electron neutral analogue **1a** (Table 2, entries 1 and 2). The reaction of *p*-nitrophenyl-substituted cyanohydrin **1c** proceeded faster but provided the desired product **3c** in relatively low yield as a diastereoisomeric mixture along with a similar production of byproduct **4c** (Table 2, entry 3). The employment of cyanohydrin **1d** bearing a para-electron-donating group as the R^1 group delivered the desired product **4d** in low yield (Table 2, entry 4). Next, O-acylated cyanohydrins with the substituents (R^2) located at the α-position to the cyano group were investigated. The reactions of cyanohydrins **1e** and **1f** having a para-substituted delectron-withdrawing group were completed within a short reaction time and provided the desired products in high yields (Table 2, entries 5 and 6), while the rearrangement of substrate **1g** having an ortho-substituted electron-withdrawing group proceeded rather sluggishly and gave product **3g** in low yield (Table 2, entry 7). 2,4-Disubstituted cyanohydrin **1h** provided the desired product **3h** in moderate yield (Table 2, entry 8). O-Acylated cyanohydrins with electron-withdrawing groups at both R^1 and R^2 also were employed and furnished the desired products with 1,3-diketone moieties in moderate yield (Table 2, entries 9 and 10). Notably, *O*-cinnamoyl-substituted cyanohydrin **1k** was also a suitable substrate and provided the desired α,β-unsaturated ketone **3k** in good yield (Table 2, entry 11). In addition, ethyl ester analogue **1l** was employed, and the reaction gave rise to desired product **3l** in low yield (Table 2, entry 12).

Encouraged by the above success, the rearrangement reactions of various O-aliphatic acyl-protected cyanohydrins **1** were examined, and the results are illustrated in Table 3. Treatment of *O*-acetyl-protected cyanohydrin **1m** with DBU furnished 1,3-diketone derivative **3m** in good yield (Table 2, entry 1). When *O*-cyclohexylol-protected cyanohydrin **1n** was employed, the rearrangement reaction furnished the desired product **3n** in 54% yield (Table 2, entry 2). However,

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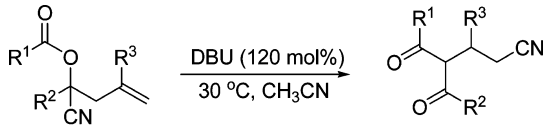
Table 2. Scope of the Rearrangement of O-Aromatic Acylated Cyanohydrins[a]

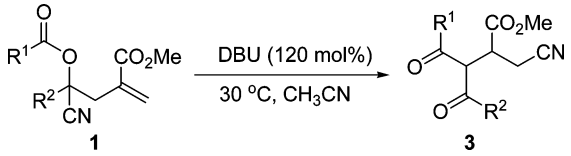


1a-1k: $R^3 = CO_2Me$; **1l**: $R^3 = CO_2Et$;

entry	R^1	R^2	1	t (h)	yield (%)[b]	dr[c]
1	C_6H_5	C_6H_5	**1a**	43	67 (**3a**)	–
2	4-ClC_6H_4	C_6H_5	**1b**	24	65 (**3b**)	1:1
3	4- $NO_2C_6H_4$	C_6H_5	**1c**	1	32 (**3c**)/ 33(**4a**)	1.1:1
4	4-$MeOC_6H_4$	C_6H_5	**1d**	53	31 (**3d**)	1:1
5	C_6H_5	4-ClC_6H_4	**1e**	6	83 (**3b**)	1:1
6	C_6H_5	4-BrC_6H_4	**1f**	7	77 (**3f**)	1.2:1
7	C_6H_5	2-BrC_6H_4	**1g**	48	38 (**3g**)	1.1:1
8	C_6H_5	2,4-$Cl_2C_6H_3$	**1h**	16	60 (**3h**)	1.1:1
9	4-BrC_6H_4	4-BrC_6H_4	**1i**	6	56 (**3i**)	–
10	4-ClC_6H_4	4-ClC_6H_4	**1j**	3	53 (**3j**)	–
11	PhCH=CH(*E*)	4-ClC_6H_4	**1k**	1	72 (**3k**)	1.4:1
12	C_6H_5	C_6H_5	**1l**	24	38 (**3l**)	–

[a]Reactions were performed with **1** (0.2 mmol) and DBU (120 mol %) in CH_3CN (c = 0.1 M). [b]Isolated yield. [c]Determined by ^1H NMR analysis of crude product.

Table 3. Rearrangement of O-Aliphatic Acylated Cyanohydrins[a]

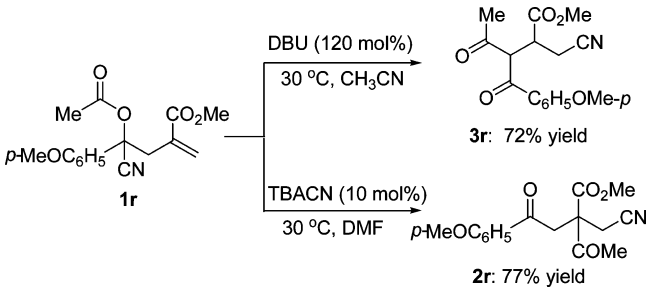


entry	R^1	R^2	1	t (h)	yield (%)[b]	dr[c]
1	Me	4-ClC_6H_4	**1m**	1.5	78 (**3m**)	1.1:1
2	cyclohexyl	4-ClC_6H_4	**1n**	4	54 (**3n**)	1:1
3	EtO	4-ClC_6H_4	**1o**	5	–[d]	–
4	Me	C_6H_5	**1p**	2	77 (**3p**)	1:1
5	Me	4-BrC_6H_4	**1q**	2	63 (**3q**)	1.2:1
6	Me	4-$MeOC_6H_4$	**1r**	6	72 (**3r**)	1.1:1
7	Me	2-naphthyl	**1s**	3.5	69 (**3s**)	1:1
8	Me	$Ph(CH_2)_2$	**1t**	6	20 (**3t**)	1:1

[a]Reactions were performed with **1** (0.2 mmol) and DBU (120 mol %) in CH_3CN (c = 0.1 M). [b]Isolated yield. [c]Determined by ^1H NMR analysis of crude product. [d]No desired product was detected.

performing the rearrangement reaction with cyanohydrin carbonate **1o** did not provide any desired product under optimal reaction conditions (Table 2, entry 3). Next, the rearrangement reaction of a spectrum of *O*-acetyl-protected cyanohydrins with a variety of aromatic substituents was also surveyed. The reaction proceeded well regardless of whether the aromatic group has an electron-neutral (**1p**), electron-withdrawing (**1q**), or electron-donating (**1r**) group (Table 2, entries 4–6). *β*-Naphthyl-substituted cyanohydrin **1s** can also be employed as a good substrate and provided the desired product in comparably good yield (Table 2, entry 7). The reaction of alkyl-substituted (R^2) cyanohydrin **1t** was examined, and the rearrangement reaction furnished the desired product **3t** in 20% yield. In addition, considering our previous work in which O-aliphatic acylated cyanohydrins could undergo an intramolecular acylcyanation reaction to provide functionalized nitriles **2** bearing 1,4-diketone moieties in the presence of a catalytic amount of phosphine or TBACN (Scheme 1, path A),[8b] we became interested in developing a diversity-oriented synthetic process to construct functionalized nitriles incorporating 1,3-diketone or 1,4-diketone moieties from the same available starting material by utilizing different promoters. To our delight, treatment of *O*-acetyl-protected cyanohydrin **1r** with TBACN (10 mol %) furnished 1,4-diketone derivative **2r** in good yield (Scheme 2), while 1,3-diketone derivate **2m** was obtained readily in moderate yield in the presence of DBU (Table 3, entry 6).[12,13]

Scheme 2. Controllable Protocol To Prepare Functionalized Nitriles



On the basis of the obtained experimental results, two possible reaction pathways were proposed to rationalize the formation of the rearrangement product **3** (Scheme 3). We envisage that a Lewis base promoter might undergo 1,2-addition to the carbonyl group of the *O*-acyl group of cyanohydrin **1** to form ketone **5** and intermediate **B**, which subsequently could undergo a series of transformations to provide the desired product **3** (Scheme 3, path A). Alternatively, a base-promoted *α*-proton abstraction and followed an elimination of cyanide from cyanohydrin **1** may result in conjugated diene **6**,[14] which could go through a possible 1,4-conjugate addition of cyanide to the activated terminal alkene moiety of conjugated diene **6** to provide O-acylated ketone **7**. Finally, ketone **7** may undergo a [1,3]-sigmatropic rearrangement in the presence of Lewis base to furnish the desired product **3**.[15]

To gain some preliminary mechanistic understanding of this rearrangement, control experiments were conducted. The reaction pathway A may be ruled out first due to the fact that treatment of neither ketone **5** nor **4a** with benzoyl cyanide and DBU could afford the product **3**, respectively (Scheme 4, eqs 1 and 2). Subsequently, the crossover experiment was carried out (Scheme 5), in which the mixture of O-acylated cyanohydrins (**1a** and **1i**) was employed, and no crossover rearranged product **3b** was obtained. These results indicated that the transfers of acyl groups of cyanohydrins **1** may proceed in an intramolecular fashion and were consistent with the pathway B outlined in Scheme 3.[16]

Finally, the synthetic utilities of Lewis base-promoted rearrangement products are illustrated in Scheme 6. Pyrazoles are synthetic targets of considerable importance in both the pharmaceutical and agrochemical industries.[17] The condensation of nitrile **3a** bearing a 1,3-diketone moiety and phenylhydrazine **8** provided a facile protocol to access the densely

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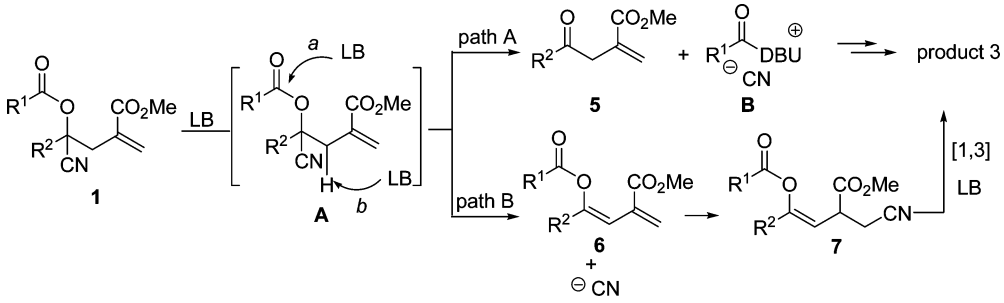
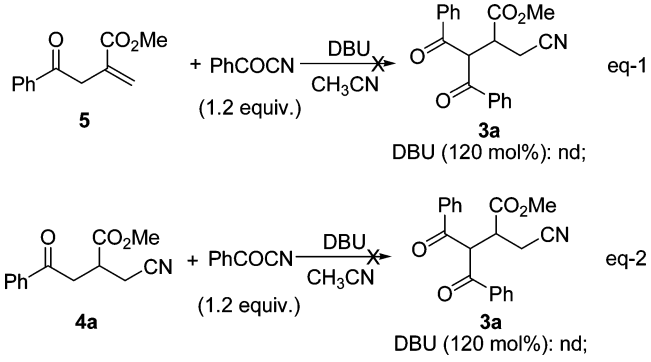
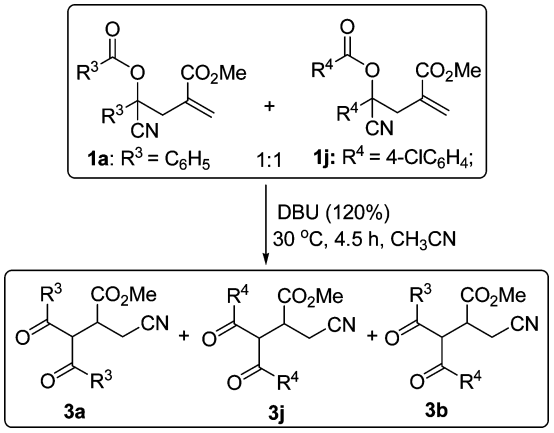
Scheme 3. Proposed Reaction Pathway



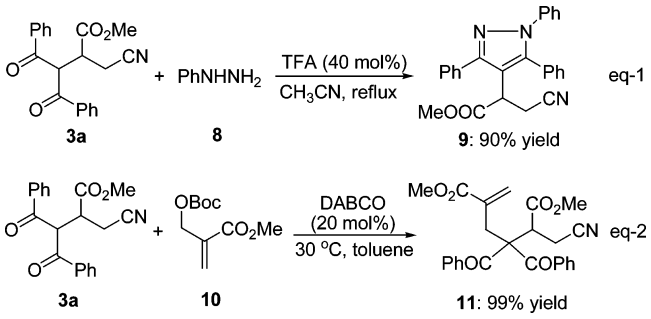
Scheme 4. Control Experiments



Scheme 5. Crossover Experiments



Scheme 6. Synthetic Applications



functionalized pyrazole **9** in good yield (Scheme 6, eq 1). In addition, nitrile **3a** could also serve as a suitable nucleophile and underwent a Lewis base (DABCO)-catalyzed allylic alkylation with MBH adduct **10** to offer the allylic-substituted nitrile **11** incorporating a quaternary carbon center in almost quantitative yield (Scheme 6, eq 2).

CONCLUSION

We have developed a novel Lewis base-mediated rearrangement of allylic cyanohydrins, which provided a useful synthetic protocol for the preparation of densely functionalized nitriles incorporating 1,3-diketone moieties under mild reaction conditions. Furthermore, the diverse synthetic process has been demonstrated to construct functionalized nitriles incorporating 1,3-diketone or 1,4-diketone moieties from the same available starting material by utilizing the different promoters. On the basis of these, a possible mechanism has been proposed. In addition, the synthetic transformations of the functionalized products have also been demonstrated, which will find potential utility in organic synthesis.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Allylic-Substituted Cyanohydrins 1. Allylic-substituted cyanohydrins **1** were prepared according to a published procedure.[8a] To a dried 25 mL round-bottom flask under a N_2 atmosphere were added DABCO (20 mol %), cyanohydrin (1 mmol), MBH carbonate (1.5 equiv), and toluene (5 mL). Upon completion, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum ether (60−90 °C)) to provide the following compounds.

1-Cyano-3-(methoxycarbonyl)-1-phenylbut-3-en-1-yl 4-Chlorobenzoate (Table 2, 1b). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (351 mg, 95% yield) as a white solid (mp: 85−87 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.94 (m, 2H), 7.57−7.53 (m, 2H), 7.47−7.37 (m, 5H), 6.46 (d, J = 0.7 Hz, 1H), 5.91 (d, J = 0.8 Hz, 1H), 3.67 (s, 3H), 3.55 (dd, J = 13.9, 0.6 Hz, 1H), 3.15 (dd, J = 13.9, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 163.2, 140.8, 136.3, 133.1, 131.8, 131.5, 129.6, 129.2, 129.1, 127.3, 125.0, 116.8, 77.7, 52.3, 43.4. HRMS (ESI): calcd for $C_{20}H_{16}ClNO_4Na$ ([M + Na]$^+$): 392.0660, found: 392.0660.

1-Cyano-3-(methoxycarbonyl)-1-phenylbut-3-en-1-yl 4-Nitrobenzoate (Table 2, 1c). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (342 mg, 90% yield) as a white solid (mp: 98−100 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35−8.30 (m, 2H), 8.24−8.19 (m, 2H), 7.59−7.55 (m, 2H), 7.47−7.39 (m, 3H), 6.49 (d, J = 0.6 Hz, 1H), 5.93 (d, J = 0.7 Hz, 1H), 3.69 (s, 3H), 3.61 (dd, J = 14.0, 0.4 Hz, 1H), 3.16 (dd, J = 14.0, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 162.2, 151.2, 135.9, 134.1, 132.9, 132.1, 131.2, 129.8, 129.2, 125.0, 123.9, 116.4, 78.5, 52.4, 43.3. HRMS (ESI): calcd for $C_{20}H_{16}N_2O_6Na$ ([M + Na]$^+$): 403.0901, found: 403.0907.

1-Cyano-3-(methoxycarbonyl)-1-phenylbut-3-en-1-yl 4-Methoxybenzoate (Table 2, 1d). The residue was purified by column

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chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (296 mg, 81% yield) as a white solid (mp: 85−86 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.96 (m, 2H), 7.57−7.52 (m, 2H), 7.43−7.35 (m, 3H), 6.97−6.92 (m, 2H), 6.45 (d, J = 0.8 Hz, 1H), 5.90 (d, J = 0.8 Hz, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 3.53 (dd, J = 13.9, 0.7 Hz, 1H), 3.17 (dd, J = 13.9, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 164.3, 163.6, 136.7, 133.3, 132.2, 131.5, 129.3, 128.9, 124.9, 121.1, 117.1, 114.0, 77.1, 55.6, 52.2, 43.5. HRMS (ESI): calcd for $C_{21}H_{19}NO_5Na$ ([M + Na]$^+$): 388.1155, found: 388.1150.

1-(4-Chlorophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl Benzoate (Table 2, 1e). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (266 mg, 72% yield) as a white solid (mp: 79−81 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−8.00 (m, 2H), 7.66−7.60 (m, 1H), 7.53−7.45 (m, 4H), 7.40−7.35 (m, 2H), 6.47 (d, J = 0.7 Hz, 1H), 5.93 (d, J = 0.7 Hz, 1H), 3.67 (s, 3H), 3.52 (dd, J = 13.9, 0.6 Hz, 1H), 3.18 (dd, J = 13.9, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 163.8, 135.4, 135.1, 134.2, 132.8, 131.9, 130.0, 129.2, 128.8, 128.4, 126.5, 116.6, 76.8, 52.3, 43.2. HRMS (ESI): calcd for $C_{20}H_{16}ClNO_4Na$ ([M + Na]$^+$): 392.0660, found: 392.0658.

1-(4-Bromophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl Benzoate (Table 2, 1f). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 15/1) to afford the title compound (360 mg, 87% yield) as a white solid (mp: 89−91 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dt, J = 8.5, 1.8 Hz, 2H), 7.66−7.60 (m, 1H), 7.56−7.41 (m, 6H), 6.47 (d, J = 0.6 Hz, 1H), 5.92 (d, J = 0.6 Hz, 1H), 3.67 (s, 3H), 3.51 (d, J = 13.9 Hz, 1H), 3.18 (dd, J = 13.9, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 163.9, 135.6, 134.3, 132.9, 132.2, 131.9, 130.1, 128.8, 128.5, 126.8, 123.7, 116.6, 76.9, 52.4, 43.2. HRMS (ESI): calcd for $C_{20}H_{16}BrNO_4Na$ ([M + Na]$^+$): 436.0155, found: 436.0146.

1-(2-Bromophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl Benzoate (Table 2, 1g). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (207 mg, 50% yield) as a white solid (mp: 81−83 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−8.06 (m, 2H), 7.77 (dd, J = 8.0, 1.6 Hz, 1H), 7.63−7.60 (m, 2H), 7.50−7.45 (m, 2H), 7.38 (td, J = 7.7, 1.4 Hz, 1H), 7.26−7.20 (m, 1H), 6.48 (d, J = 0.8 Hz, 1H), 5.95 (d, J = 0.8 Hz, 1H), 3.83 (dd, J = 13.9, 0.7 Hz, 1H), 3.66 (s, 3H), 3.49 (dd, J = 13.9, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 163.8, 135.9, 134.1, 133.4, 133.1, 132.2, 130.8, 130.4, 129.7, 128.7, 128.4, 127.8, 119.2, 116.2, 78.6, 52.2, 39.4. HRMS (ESI): calcd for $C_{20}H_{16}BrNO_4Na$ ([M + Na]$^+$): 436.0155, found: 436.0157.

1-Cyano-1-(2,4-dichlorophenyl)-3-(methoxycarbonyl)but-3-en-1-yl Benzoate (Table 2, 1h). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (271 mg, 67% yield) as a white solid (mp: 119−120 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−8.03 (m, 2H), 7.67−7.60 (m, 2H), 7.51−7.45 (m, 2H), 7.42 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.6, 2.2 Hz, 1H), 6.48 (d, J = 0.8 Hz, 1H), 5.96 (d, J = 0.8 Hz, 1H), 3.76 (dd, J = 13.9, 0.8 Hz, 1H), 3.67 (s, 3H), 3.46 (dd, J = 13.9, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 163.9, 136.1, 134.3, 132.9, 132.4, 132.0, 131.9, 130.9, 130.3, 130.2, 128.8, 128.2, 127.5, 116.0, 77.4, 52.3, 39.2. HRMS (ESI): calcd for $C_{20}H_{15}Cl_2NO_4Na$ ([M + Na]$^+$): 426.0270, found: 426.0269.

1-(4-Bromophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl 4-Bromobenzoate (Table 2, 1i). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 15/1) to afford the title compound (483 mg, 98% yield) as a white solid (mp: 134−135 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.85 (m, 2H), 7.64−7.61 (m, 2H), 7.56−7.52 (m, 2H), 7.44−7.40 (m, 2H), 6.47 (d, J = 0.5 Hz, 1H), 5.92 (d, J = 0.6 Hz, 1H), 3.68 (s, 3H), 3.51 (d, J = 13.9 Hz, 1H), 3.14 (d, J = 14.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 163.2, 135.3, 132.7, 132.2, 132.1, 132.0, 131.4, 129.6, 127.3, 126.7, 123.7, 116.3, 77.1, 52.3, 43.0. HRMS (ESI): calcd for $C_{20}H_{15}Br_2NO_4Na$ ([M + Na]$^+$): 513.9260, found: 513.9259.

1-(4-Chlorophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl 4-Chlorobenzoate (Table 2, 1j). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (344 mg, 85% yield) as a white solid (mp: 110−111 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97−7.93 (m, 2H), 7.52−7.43 (m, 4H), 7.40−7.36 (m, 2H), 6.47 (d, J = 0.7 Hz, 1H), 5.93 (d, J = 0.7 Hz, 1H), 3.68 (s, 3H), 3.52 (dd, J = 13.9, 0.7 Hz, 1H), 3.14 (dd, J = 14.0, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 163.1, 140.9, 135.7, 134.9, 132.8, 132.0, 131.4, 129.3, 129.2, 127.0, 126.5, 116.4, 77.2, 52.4, 43.2. HRMS (ESI): calcd for $C_{20}H_{15}Cl_2NO_4Na$ ([M + Na]$^+$): 426.0270, found: 426.0271.

(*E*)-Methyl 4-(4-Chlorophenyl)-4-(cinnamoyloxy)-4-cyano-2-methylenebutanoate (Table 2, 1k). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (388 mg, 98% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 16.0 Hz, 1H), 7.54 (dt, J = 5.4, 2.2 Hz, 2H), 7.49−7.35 (m, 7H), 6.45 (d, J = 0.8 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 5.87 (d, J = 0.7 Hz, 1H), 3.65 (s, 3H), 3.40 (dd, J = 13.8, 0.7 Hz, 1H), 3.18 (dd, J = 13.9, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 164.0, 147.8, 135.4, 135.0, 133.8, 132.8, 131.9, 131.2, 129.2, 129.1, 128.5, 126.6, 116.6, 115.9, 76.3, 52.3, 43.0. HRMS (ESI): calcd for $C_{22}H_{18}ClNO_4Na$ ([M + Na]$^+$): 418.0817, found: 418.0813.

1-Cyano-3-(ethoxycarbonyl)-1-phenylbut-3-en-1-yl Benzoate (Table 2, 1l). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 15/1) to afford the title compound (241 mg, 69% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−8.02 (m, 2H), 7.65−7.59 (m, 1H), 7.58−7.54 (m, 2H), 7.50−7.44 (m, 2H), 7.43−7.35 (m, 3H), 6.46 (d, J = 0.8 Hz, 1H), 5.91 (d, J = 0.6 Hz, 1H), 4.18−4.03 (m, 2H), 3.55 (dd, J = 13.9, 0.5 Hz, 1H), 3.19 (dd, J = 13.9, 0.7 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.9, 136.5, 134.1, 133.4, 131.4, 130.0, 129.4, 129.0, 128.8, 128.7, 125.0, 117.0, 77.4, 61.3, 43.2, 14.2. HRMS (ESI): calcd for $C_{21}H_{19}NO_4Na$ ([M + Na]$^+$): 372.1206, found: 372.1198.

Methyl 4-Acetoxy-4-(4-chlorophenyl)-4-cyano-2-methylenebutanoate (Table 3, 1m). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (255 mg, 83% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.35 (m, 4H), 6.40 (d, J = 0.8 Hz, 1H), 5.78 (d, J = 0.8 Hz, 1H), 3.62 (s, 3H), 3.28 (dd, J = 13.8, 0.8 Hz, 1H), 3.15 (dd, J = 13.9, 0.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 166.5, 135.4, 134.7, 132.6, 131.8, 129.0, 126.6, 116.5, 76.0, 52.2, 42.6, 20.9. HRMS (ESI): calcd for $C_{15}H_{14}ClNO_4Na$ ([M + Na]$^+$): 330.0504, found: 330.0504.

1-(4-Chlorophenyl)-1-cyano-3-(methoxycarbonyl)but-3-en-1-yl Cyclohexanecarboxylate (Table 3, 1n). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (334 mg, 89% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.34 (m, 4H), 6.41 (d, J = 0.8 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 3.64 (s, 3H), 3.31 (dd, J = 13.9, 0.8 Hz, 1H), 3.09 (dd, J = 13.9, 0.8 Hz, 1H), 2.35 (tt, J = 11.0, 3.7 Hz, 1H), 1.94−1.89 (m, 2H), 1.80−1.72 (m, 2H), 1.68−1.61 (m, 1H), 1.50−1.19 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 166.7, 135.4, 135.1, 132.9, 131.6, 129.1, 126.5, 116.7, 75.8, 52.3, 43.0, 42.9, 28.7, 28.5, 25.6, 25.4, 25.2. HRMS (ESI): calcd for $C_{20}H_{22}ClNO_4Na$ ([M + Na]$^+$): 398.1130, found: 398.1164.

Methyl 4-Acetoxy-4-(4-bromophenyl)-4-cyano-2-methylenebutanoate (Table 3, 1q). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (276 mg, 79% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.36−7.33 (m, 2H), 6.40 (s, 1H), 5.79 (s, 1H), 3.62 (s, 3H), 3.28 (d, J = 13.9 Hz, 1H), 3.15 (d, J = 13.9 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 166.5, 135.2, 132.6, 132.0, 131.8, 126.8, 123.5, 116.44, 76.1, 52.2, 42.6, 20.9. HRMS (ESI): calcd for $C_{15}H_{14}BrNO_4Na$ ([M + Na]$^+$): 373.9998, found: 373.9999.

Methyl 4-Acetoxy-4-cyano-4-(4-methoxyphenyl)-2-methylenebutanoate (Table 3, 1r). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (239 mg, 79% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.38 (m, 2H), 6.91−6.88 (m, 2H), 6.37 (d, J = 0.7 Hz, 1H), 5.75 (d, J = 0.4 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.31 (d, J = 14.0 Hz, 1H), 3.14 (d, J = 13.9 Hz, 1H), 2.11 (s, 3H). ^{13}C

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NMR (125 MHz, $CDCl_3$) δ 168.1, 166.8, 160.2, 133.1, 131.4, 128.0, 126.6, 117.0, 114.1, 76.4, 55.4, 52.2, 42.7, 21.1. HRMS (ESI): calcd for $C_{16}H_{17}NO_5Na$ ($[M + Na]^+$): 326.0999, found: 326.0997.

Methyl 4-Acetoxy-4-cyano-2-methylene-4-(naphthalen-2-yl)butanoate (Table 3, 1s). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 10/1) to afford the title compound (291 mg, 90% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 1.9 Hz, 1H), 7.89−7.81 (m, 3H), 7.56−7.49 (m, 3H), 6.38 (d, J = 0.9 Hz, 1H), 5.78 (d, J = 0.8 Hz, 1H), 3.48 (s, 3H), 3.41 (dd, J = 13.9, 0.8 Hz, 1H), 3.23 (dd, J = 13.9, 0.8 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 166.7, 133.4, 133.3, 132.9, 132.7, 131.5, 129.1, 128.5, 127.7, 127.2, 127.0, 125.2, 121.7, 116.9, 76.9, 52.1, 42.8, 21.1. HRMS (ESI): calcd for $C_{19}H_{17}NO_4Na$ ($[M + Na]^+$): 346.1044, found: 346.1042.

General Procedure for the Synthesis of Compounds 3. All reactions were carried out under a nitrogen atmosphere. To a dried 25 mL reaction tube were added **1** (0.2 mmoL) and CH_3CN (1.5 mL). After stirring for 5 min, DBU (120 mol %) and CH_3CN (0.5 mL) were added. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into EtOAc (15 mL) and washed with saturated NH_4Cl (15 mL), and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extract was washed with saturated brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum ether) to provide the product **3**.

Methyl 3-Benzoyl-2-(cyanomethyl)-4-oxo-4-phenylbutanoate (Table 2, 3a). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (45 mg, 67% yield) as a colorless solid (mp: 86−88 °C).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.94 (m, 4H), 7.62−7.57 (m, 2H), 7.50−7.42 (m, 4H), 5.99 (d, J = 8.0 Hz, 1H), 3.85 (dt, J = 8.0, 5.7 Hz, 1H), 3.68 (s, 3H), 2.88−2.85 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 193.8, 171.1, 135.8, 135.7, 134.4, 134.2, 129.2, 129.1, 128.9 (brs), 117.6, 56.2, 53.0, 42.1, 17.8. HRMS (ESI): calcd for $C_{20}H_{18}NO_4$ ($[M + H]^+$): 336.1230, found 336.1230.

Methyl 3-Benzoyl-4-(4-chlorophenyl)-2-(cyanomethyl)-4-oxobutanoate (Table 2, 3b). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (62 mg, 83% yield, **3b**/**3b**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.87 (m, 8H), 7.64−7.58 (m, 2H), 7.52−7.40 (m, 8H), 5.94 (d, J = 8.1 Hz, 1H), 5.93 (d, J = 8.4 Hz, 1H), 3.93−3.79 (m, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.94−2.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 193.5, 192.6, 192.5, 171.1, 171.0, 141.1, 140.8, 135.7, 135.5, 134.6, 134.4, 134.1, 134.0, 130.2, 129.6, 129.5, 129.3, 129.3, 128.9, 128.9, 117.5, 117.4, 56.1 (brs), 53.1, 42.2, 42.1, 18.0, 17.8. HRMS (ESI): calcd for $C_{20}H_{17}ClNO_4$ ($[M + H]^+$): 370.0841, found 370.0838.

Methyl 3-Benzoyl-2-(cyanomethyl)-4-(4-nitrophenyl)-4-oxobutanoate (Table 2, 3c). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (24 mg, 32% yield, **3c**/**3c**′ (dr) = 1.1/1) as an unseparated white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29−8.25 (m, 4H), 8.11−8.04 (m, 4H), 7.97 (ddd, J = 7.2, 4.8, 1.2 Hz, 4H), 7.68−7.61 (m, 2H), 7.50 (dt, J = 15.8, 8.0 Hz, 4H), 6.02 (d, J = 7.53 Hz, 1H of **3c**′), 6.00 (d, J = 8.78 Hz, 1H of **3c**), 3.99 (ddd, J = 8.7, 6.0, 4.9 Hz, 1H of **3c**′), 3.84−3.78 (m, 1H of **3c**),3.73 (s, 3H of **3c**), 3.69 (s, 3H of **3c**′), 2.94 (ddd, J = 22.2, 17.5, 5.7 Hz, 2H of **3c**′), 2.86 (ddd, J = 23.5, 17.4, 5.4 Hz, 2H of **3c**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 193.0, 192.9, 192.5, 171.0, 170.7, 150.8, 150.6, 140.7, 140.3, 135.6, 135.3, 134.9, 134.8, 129.8, 129.8, 129.5 (brs), 129.0, 128.9, 124.3, 124.2, 117.5, 117.1, 56.8, 53.3, 53.2, 42.4, 41.9, 18.1, 17.6. HRMS (EI): calcd for $C_{20}H_{17}N_2O_6$ ($[M + H]^+$): 381.1081, found 381.1075. Compound **4a**: 15 mg, 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.96 (m, 2H), 7.64−7.58 (m, 1H), 7.52−7.47 (m, 2H), 3.77 (s, 3H), 3.64 (dd, J = 17.7, 5.0 Hz, 1H), 3.46−3.42 (m, 2H), 2.88 (d, J = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 172.2, 136.0, 133.9, 128.9, 128.2, 117.7, 52.9, 38.6, 36.8, 19.2. HRMS (ESI): calcd for $C_{13}H_{14}NO_3$ ($[M + H]^+$): 232.0968, found 232.0969.

Methyl 3-Benzoyl-2-(cyanomethyl)-4-(4-methoxyphenyl)-4-oxobutanoate (Table 2, 3d). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (23 mg, 33% yield, **3d**/**3d**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.93 (m, 8H), 7.61−7.54 (m, 2H), 7.47−7.42 (m, 4H), 6.95−6.91(m, 4H), 5.92 (d, J = 8.5 Hz, 1H), 5.91 (d, J = 7.9 Hz, 1H), 3.91−3.84 (m, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.82−3.76 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 2.96−2.71 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 193.8, 192.1, 191.8, 171.4, 171.2, 164.8, 164.5, 135.8, 134.3, 134.0, 131.5, 131.4, 129.2, 129.1, 128.8, 128.8, 128.6, 128.4, 117.8, 117.5, 114.5, 114.4, 55.9, 55.8, 55.7, 55.7, 53.0, 42.3, 42.1, 17.9, 17.7. HRMS (ESI): calcd for $C_{21}H_{20}NO_5$ ($[M + H]^+$): 366.1366, found 366.1366.

Methyl 3-Benzoyl-4-(4-bromophenyl)-2-(cyanomethyl)-4-oxobutanoate (Table 2, 3f). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (64 mg, 77% yield, **3f**/**3f**′ (dr) = 1.2/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.94 (m, 4H), 7.85−7.79 (m, 4H), 7.65−7.57 (m, 6H), 7.48 (td, J = 7.6, 4.2 Hz, 4H), 5.94 (d, J = 8.0 Hz, 1H of **3f**′), 5.93 (d, J = 8.4 Hz, 1H of **3f**), 3.92−3.80 (m, 2H), 3.69 (s, 3H of **3f**), 3.68 (s, 3H of **3f**′), 2.94−2.75 (m, 2H of **3f**, 2H of **3f**′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 193.5, 192.9, 192.7, 171.1, 171.0, 135.7, 135.57, 134.6, 134.5, 134.5, 134.4, 132.6, 132.5, 130.3, 130.3, 129.9, 129.5, 129.3, 129.3, 128.9, 128.9, 117.5, 117.4, 56.1 (brs), 53.1, 42.2, 42.1, 18.0, 17.8. HRMS (ESI): calcd for $C_{20}H_{17}BrNO_4$ ($[M + H]^+$): 414.0335, found 414.0339.

Methyl 3-Benzoyl-4-(2-bromophenyl)-2-(cyanomethyl)-4-oxobutanoate (Table 2, 3g). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (31 mg, 38% yield, **3g**/**3g**′ (dr) = 1.2/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.83 (m, 4H), 7.72 (dd, J = 7.7, 1.7 Hz, 1H), 7.54−7.48 (m, 4H), 7.44 (dd, J = 8.0, 1.1 Hz, 1H), 7.40−7.30 (m, 5H), 7.28−7.18 (m, 3H), 6.09 (d, J = 8.4 Hz, 1H of **3g**), 6.04 (d, J = 8.9 Hz, 1H of **3g**′), 3.97 (ddd, J = 8.9, 6.5, 4.4 Hz, 1H of **3g**′), 3.91−3.84 (m, 1H of **3g**), 3.79 (s, 3H of **3g**′), 3.68 (s, 3H of **3g**), 3.08 (dd, J = 17.4, 6.2 Hz, 1H of **3g**), 3.00−2.90 (m, 2H of **3g**′), 2.76 (dd, J = 17.5, 6.5 Hz, 1H of **3g**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 195.2, 193.8, 193.1, 171.4, 171.0, 139.8, 139.7, 136.1, 134.5, 134.1, 133.9, 133.7, 132.5, 129.7, 129.6, 129.1, 128.9, 128.8, 127.7, 127.6, 119.3, 118.6, 117.6, 117.1, 60.6, 60.1, 53.1, 53.1, 41.4, 41.2, 18.2, 18.1. HRMS (ESI): calcd for $C_{20}H_{17}BrNO_4$ ($[M + H]^+$): 414.0335, found 414.0334.

Methyl 3-Benzoyl-2-(cyanomethyl)-4-(2,4-dichlorophenyl)-4-oxobutanoate (Table 2, 3h). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (48 mg, 60% yield, **3h**/**3h**′ (dr) = 1.1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.84 (m, 4H), 7.71−7.68 (m, 1H), 7.61−7.55 (m, 2H), 7.46−7.38 (m, 5H), 7.435−7.28 (m, 3H),7.23 (dd, J = 8.3, 2.0 Hz, 1H), 6.06 (d, J = 7.6 Hz, 1H of **3h**), 6.01 (d, J = 8.5 Hz, 1H of **3h**′), 3.94 (ddd, J = 8.5, 6.3, 4.8 Hz, 1H of **3h**′), 3.79−3.67 (m, 1H of **3h**), 3.78 (s, 3H of **3h**′) 3.70 (s, 3H of **3h**), 3.07 (dd, J = 17.4, 6.3 Hz, 1H of **3h**), 2.92 (dd, J = 12.6, 5.0 Hz, 1H of **3h**′), 2.86 (dd, J = 12.6, 5.1 Hz, 1H of **3h**′), 2.75 (dd, J = 17.5, 6.3 Hz, 1H of **3h**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 193.9, 193.8, 193.2, 171.2, 170.8, 138.4, 138.3, 136.0, 135.9, 135.9, 135.9, 134.6, 134.3, 132.3, 131.6, 131.1, 130.9, 130.6, 130.4, 129.1, 129.1, 128.9, 128.8, 127.8, 127.6, 117.5, 117.1, 60.5, 60.1, 53.2, 53.1, 41.4, 41.4, 18.1, 17.9. HRMS (ESI): calcd for $C_{20}H_{16}Cl_2NO_4$ ($[M + H]^+$): 404.0451, found 404.0451.

Methyl 3-(4-Bromobenzoyl)-4-(4-bromophenyl)-2-(cyanomethyl)-4-oxobutanoate (Table 2, 3i). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (55 mg, 56% yield) as a white solid (mp:134−136 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.78 (m, 4H), 7.64−7.59 (m, 4H), 5.86 (d, J = 8.4 Hz, 1H), 3.90−3.83 (m, 1H), 3.70 (s, 3H), 2.90 (dd, J = 17.4, 4.8 Hz, 1H), 2.80 (dd, J = 17.4,

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6.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 170.9, 134.4, 134.3, 132.7, 132.6, 130.3, 130.2, 129.8, 117.3, 56.0, 53.2, 42.1, 17.9. HRMS (ESI): calcd for $C_{20}H_{16}Br_2NO_4$ ($[M + H]^+$): 491.9441, found 491.9442.

Methyl 3-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-2-(cyanomethyl)-4-oxobutanoate (Table 2, 3j). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1) to afford the title compound (43 mg, 53% yield) as a white solid (mp:110−111 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.87 (m, 4H), 7.47−7.42 (m, 4H), 5.89 (d, J = 8.4 Hz, 1H), 3.87 (ddd, J = 8.2, 6.3, 4.8 Hz, 1H), 3.70 (s, 3H), 2.91 (dd, J = 17.4, 4.7 Hz, 1H), 2.81 (dd, J = 17.5, 6.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 192.3, 171.0, 141.3, 141.0, 134.1, 134.0, 130.3, 130.2, 129.7, 129.6, 117.3, 56.2, 53.2, 42.2, 17.9. HRMS (ESI): calcd for $C_{20}H_{16}Cl_2NO_4$ ($[M + H]^+$): 404.0451, found 404.0443.

***(E)*-Methyl 3-(4-Chlorobenzoyl)-2-(cyanomethyl)-4-oxo-6-phenylhex-5-enoate (Table 2, 3k).** The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (57 mg, 72% yield, **3k**/**3k**′ (dr) = 1.4/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.98 (m, 4H), 7.73 (d, J = 15.8 Hz, 1H of **3k**), 7.67 (d, J = 15.8 Hz, 1H of **3k**′), 7.53−7.46 (m, 8H), 7.45−7.33 (m, 6H), 6.83 (d, J = 15.8 Hz, 1H of **3k**′), 6.82 (d, J = 15.8 Hz, 1H of **3k**), 5.35 (d, J = 9.0 Hz, 1H of **3k**′), 5.30 (d, J = 9.6 Hz, 1H of **3k**), 3.91−3.80 (m, 2H), 3.75 (s, 3H of **3k**′), 3.73 (s, 3H of **3k**), 2.97−2.72 (m, 2H of **3k**, 2H of **3k**′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 192.7, 191.5, 191.3, 171.2, 171.1, 146.9, 145.9, 141.2, 140.8, 134.5, 134.5, 133.7, 133.5, 131.8, 131.5, 130.4, 130.3, 129.6, 129.4, 129.2, 129.1, 129.0, 128.9, 123.3, 122.8, 117.2, 116.9, 60.4, 60.3, 53.1, 53.1, 41.5, 18.1, 17.9. HRMS (ESI): calcd for $C_{22}H_{19}ClNO_4$ ($[M + H]^+$): 396.0997, found 396.0987.

Ethyl 3-Benzoyl-2-(cyanomethyl)-4-oxo-4-phenylbutanoate (Table 2, 3l). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (27 mg, 38% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (t, J = 8.2 Hz, 4H), 7.60−7.57 (m, 2H), 7.48−7.44 (m, 4H), 6.00 (d, J = 8.1 Hz, 1H), 4.19−4.07 (m, 2H), 3.86−3.82 (m, 1H), 2.91−2.81 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 193.8, 170.7, 135.9, 135.8, 134.4, 134.2, 129.2, 129.1, 128.9, 117.6, 62.4, 56.1, 42.2, 17.9, 13.9. HRMS (ESI): calcd for $C_{21}H_{20}NO_4$ ($[M + H]^+$): 350.1387, found 350.1387.

Methyl 3-(4-Chlorobenzoyl)-2-(cyanomethyl)-4-oxopentanoate (Table 3, 3m). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (47 mg, 78% yield, **3m**/**3m**′ (dr) = 1.1/1) as an unseparated colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.98 (m, 4H), 7.55−7.51 (m, 4H), 5.19 (d, J = 9.5 Hz, 1H of **3m**′), 5.11 (d, J = 8.9 Hz, 1H of **3m**), 3.82−3.72 (m, 2H), 3.77 (s, 3H of **3m**′), 3.69 (s, 3H **3m**), 2.95−2.80 (m, 2H of **3m**, 1H of **3m**′), 2.62 (dd, J = 17.4, 6.4 Hz, 1H of **3m**′), 2.23 (s, 3H of **3m**′), 2.17 (s, 3H of **3m**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 199.5, 193.2, 192.6, 171.2, 170.9, 141.7, 141.2, 134.4, 134.4, 130.6, 130.4, 129.8, 129.7, 117.1, 116.9, 61.7, 61.4, 53.2, 41.4, 41.4, 30.3, 30.1, 18.0. HRMS (ESI): calcd for $C_{15}H_{15}ClNO_4$ ($[M + H]^+$): 308.0684, found 308.0669.

Methyl 3-(4-Chlorobenzoyl)-2-(cyanomethyl)-4-cyclohexyl-4-oxobutanoate (Table 3, 3n). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (40 mg, 54% yield, **3n**/**3n**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−7.97 (m, 4H), 7.55−7.52 (m, 4H), 5.32 (d, J = 8.7 Hz, 1H), 5.31 (d, J = 9.1 Hz, 1H), 3.77−3.69 (m, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 2.85 (d, J = 5.3 Hz, 2H), 2.77 (dd, J = 17.5, 5.0 Hz, 1H), 2.58 (dd, J = 17.5, 6.3 Hz, 1H), 2.44−2.28 (m, 2H), 2.00−1.91 (m, 2H), 1.80−1.53 (m, 8H), 1.43−0.98 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 205.2, 193.3, 193.1, 171.1, 171.0, 141.4, 140.9, 134.7, 134.7, 130.4, 130.3, 129.7, 129.6, 117.2, 117.1, 59.2, 59.1, 53.1, 53.0, 51.2, 50.9, 41.5, 41.3, 29.3, 29.2, 28.0, 25.7, 25.7, 25.6, 25.5, 25.1, 25.0, 18.0, 17.9. HRMS (ESI): calcd for $C_{20}H_{23}ClNO_4$ ($[M + H]^+$): 376.1310, found 376.1311.

Methyl 3-Benzoyl-2-(cyanomethyl)-4-oxopentanoate (Table 3, 3p). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (42 mg, 77% yield, **3p**/**3p**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−8.02 (m, 4H), 7.70−7.63 (m, 2H), 7.58−7.52 (m, 4H), 5.25 (d, J = 9.5 Hz, 1H), 5.17 (d, J = 8.6 Hz, 1H), 3.83−3.69 (m, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.92 (dd, J = 17.4, 6.4 Hz, 1H), 2.82 (dd, J = 16.0, 4.7 Hz, 2H), 2.82 (dd, J = 17.6, 4.7 Hz, 2H), 2.62 (dd, J = 17.4, 6.5 Hz, 1H), 2.22 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 199.9, 194.4, 193.8, 171.3, 171.0, 136.1, 136.0, 134.8, 134.5, 129.4, 129.3, 129.1, 129.0, 117.2, 116.9, 61.6, 61.3, 53.1, 53.0, 41.4, 41.3, 30.3, 30.1, 18.0, 17.8. HRMS (ESI): calcd for $C_{15}H_{16}NO_4$ ($[M + H]^+$): 274.1074, found 274.1074.

Methyl 3-(4-Bromobenzoyl)-2-(cyanomethyl)-4-oxopentanoate (Table 3, 3q). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (44 mg, 63% yield, **3q**/**3q**′ (dr) = 1.2/1) as an unseparated yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.91 (m, 4H), 7.72−7.69 (m, 4H), 5.20 (d, J = 9.5 Hz, 1H of **3q**′), 5.11 (d, J = 8.9 Hz, 1H of **3q**), 3.77 (s, 3H of **3q**′), 3.82−3.72 (m, 2H of **3q**′), 3.69 (s, 3H of **3q**), 2.94−2.83 (m, 3H of **3q**), 2.63 (dd, J = 17.4, 6.4 Hz, 1H of **3q**′), 2.23 (s, 3H of **3q**′), 2.18 (s, 3H of **3q**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 199.5, 193.4, 192.9, 171.2, 171.0, 134.8, 132.8, 132.7, 130.6, 130.4, 123.0, 117.1, 116.9, 61.7, 61.3, 53.2, 41.4, 41.3, 30.3, 30.1, 29.8, 18.0. HRMS (ESI): calcd for $C_{15}H_{15}BrNO_4$ ($[M + H]^+$): 352.0179, found 352.0179.

Methyl 2-(Cyanomethyl)-3-(4-methoxybenzoyl)-4-oxopentanoate (Table 3, 3r). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (44 mg, 72% yield, **3r**/**3r**′ (dr) = 1.1/1) as an unseparated light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 25.5, 8.9 Hz, 4H), 7.02 (dd, J = 8.9, 2.7 Hz, 4H), 5.20 (d, J = 9.8 Hz, 1H of **3r**), 5.11 (d, J = 8.4 Hz, 1H of **3r**′), 3.91 (s, 6H, 3H of **3r**, 3H of **3r**′), 3.82−3.77 (m, 2H of **3r**′), 3.77 (s, 3H of **3r**), 3.68 (s, 3H of **3r**′), 2.93 (dd, J = 17.4, 6.7 Hz, 1H of **3r**′), 2.84−2.79 (m, 2H of **3r**), 2.58 (dd, J = 17.3, 6.5 Hz, 1H of **3r**), 2.22 (s, 3H of **3r**), 2.17 (s, 3H of **3r**′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 200.1, 192.6, 191.7, 171.5, 171.1, 165.0, 164.7, 131.8, 131.5, 129.1, 128.8, 117.4, 117.0, 114.6, 114.5, 61.2, 61.0, 55.8, 55.8, 53.1, 53.0, 41.4, 41.3, 30.1, 29.8, 18.0, 17.8. HRMS (ESI): calcd for $C_{16}H_{18}NO_5$ ($[M + H]^+$): 274.1074, found 274.1074.

Methyl 3-(2-Naphthoyl)-2-(cyanomethyl)-4-oxopentanoate (Table 3, 3s). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (45 mg, 69% yield, **3s**/**3s**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (dd, J = 19.8, 1.3 Hz, 2H), 8.08−8.04 (m, 4H), 7.97 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.70−7.58 (m, 4H), 5.41 (d, J = 9.5 Hz, 1H), 5.34 (d, J = 8.7 Hz, 1H), 3.90−3.75 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.01−2.82 (m, 3H), 2.65 (dd, J = 17.4, 6.5 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 200.0, 194.2, 193.6, 171.4, 171.1, 136.2, 136.1, 133.4, 133.3, 132.5, 132.5, 131.7, 131.2, 130.1, 130.0, 129.7, 129.5, 129.4, 129.3, 127.9, 127.5, 127.4, 124.0, 123.9, 117.3, 117.0, 61.6, 61.4, 53.1, 53.0, 41.5, 41.4, 30.3, 30.0, 18.0, 17.9. HRMS (ESI): calcd for $C_{19}H_{18}NO_4$ ($[M + H]^+$): 324.1230, found 324.1230.

Methyl 3-Acetyl-2-(cyanomethyl)-4-oxo-6-phenylhexanoate (Table 3, 3t). The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (12 mg, 20% yield, **3t**/**3t**′ (dr) = 1/1) as an unseparated yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.30 (m, 4H), 7.22−7.17 (m, 6H), 4.29 (d, J = 9.1 Hz, 2H), 3.72 (s, 3H), 3.72 (s, 3H), 3.57−3.52 (m, 2H), 3.09−3.03 (m, 2H), 3.01−2.90 (m, 6H), 2.73−2.71 (m, 2H), 2.67 (dd, J = 17.4, 4.8 Hz, 1H), 2.50 (dd, J = 17.4, 6.4 Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 202.4, 200.7, 200.6, 171.0, 170.9, 140.4, 140.1, 128.8, 128.7, 128.5, 126.7, 126.5, 116.9, 66.9, 66.8, 53.2, 45.6, 45.4, 40.9, 30.6, 29.5, 17.9, 17.7. HRMS (EI): calcd for $C_{17}H_{20}NO_4$ ($[M + H]^+$): 302.1387, found: 302.1380.

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Methyl 2-Acetyl-2-(cyanomethyl)-4-(4-methoxyphenyl)-4-oxobutanoate (Scheme 2, 2r). To a dried 25 mL reaction tube were added **1r** (0.2 mmol) and DMF (2 mL) under a N_2 atmosphere. After stirring for 5 min, TBACN (10 mol %) was added.[8b] The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into EtOAc (10 mL) and washed with saturated brine (2 × 5 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extract was washed with saturated brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum ether) to provide the desired product **2r**.

The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (47 mg, 77% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98−7.94 (m, 2H), 6.97−6.95 (m, 2H), 3.95−3.86 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.35 (d, J = 17.3 Hz, 1H), 3.19 (d, J = 17.3 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 194.6, 169.2, 164.5, 130.8, 128.8, 117.2, 114.2, 59.4, 55.7, 53.8, 41.4, 26.1, 21.7. HRMS (ESI): calcd for $C_{16}H_{18}NO_5$ ($[M + H]^+$): 304.1179, found 304.1179.

Methyl 3-Cyano-2-(1,3,5-triphenyl-1*H*-pyrazol-4-yl)-propanoate (Scheme 6, 9). To a dried 25 mL reaction tube was added **3a** (0.2 mmol) in CH_3CN (2 mL) under a N_2 atmosphere. Then TFA (40 mol %) and phenylhydrazine (2.2 equiv) were added. The mixture was heated to reflux. The reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum ether) to provide the desired product **9**.

The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (73 mg, 90% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.57 (m, 2H), 7.51−7.37 (m, 6H), 7.32−7.20 (m, 7H), 4.06 (dd, J = 9.2, 6.8 Hz, 1H), 3.73 (s, 3H), 2.77 (dd, J = 16.9, 6.8 Hz, 1H), 2.45 (dd, J = 17.0, 9.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 151.6, 142.6, 139.5, 132.8, 130.4, 129.6, 129.5, 129.0, 128.8, 128.79, 128.7, 127.4, 124.8, 117.9, 114.1, 52.9, 38.0, 19.8. HRMS (ESI): calcd for $C_{26}H_{22}N_3O_2$ ($[M + H]^+$): 408.1707, found 408.1707.

Dimethyl 3,3-Dibenzoyl-2-(cyanomethyl)-5-methylenehexanedioate (Scheme 6, 11). To a dried 25 mL reaction tube were added **3a** (0.2 mmol), DABCO (20 mol %), and CH_3CN (2 mL) under a N_2 atmosphere. After stirring for 5 min, MBH carbonate **10** (1.5 equiv) was added. The reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, EtOAc/petroleum ether) to provide the desired product **11**.

The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc: 8/1 to 5/1 gradient) to afford the title compound (86 mg, 99% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.76 (m, 2H), 7.64−7.60 (m, 2H), 7.50−7.43 (m, 2H), 7.36−7.28 (m, 4H), 6.29 (d, J = 1.1 Hz, 1H), 5.79 (d, J = 1.0 Hz, 1H), 3.82 (dd, J = 11.4, 3.0 Hz, 1H), 3.73 (s, 3H), 3.48 (d, J = 0.7 Hz, 2H), 3.40 (s, 3H), 2.96 (dd, J = 16.4, 3.0 Hz, 1H), 2.60 (dd, J = 16.4, 11.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 195.8, 171.3, 167.2, 137.1, 136.3, 135.2, 133.6, 133.4, 131.4, 129.8, 129.5, 128.8, 128.7, 117.8, 68.2, 52.7, 51.9, 46.9, 34.5, 18.2. HRMS (ESI): calcd for $C_{25}H_{24}NO_6$ ($[M + H]^+$): 434.1598, found 434.1599.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of products **1b−n**, **1q−s**, **3a−d**, **3f−n**, **3p−s**, **4a**, **2r**, **9**, and **11** as well as the X-ray structure of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) For details, see the Supporting Information. 1,3-Diketones bearing an α-hydrogen are prone to tautomerize, which may result in low diastereoselectivities for these transformations. See: Bartlett, S. L.; Beaudry, C. M. *J. Org. Chem.* **2011**, *76*, 9852−9855.

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(11) Inorganic bases such as Na_2CO_3, $NaHCO_3$, and K_2CO_3 were examined and did not give the desired product.

(12) *O*-Aryl acyl-protected cyanohydrin did not provide the corresponding 1,4-diketone compound **2** in the presence of TBACN.

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(15) The reaction of **1a** with a catalytic amount of DBU (50 mol%) and TBACN (20 mol%) in CH_3CN was carried out. This reaction proceeded faster than that with DBU (120 mol%) (7 h vs 43 h) and provided the desired product **3a** in 45% yield along with some unidentified substrates, while treatment of **1a** with TBACN (20 mol%) gave the desired product **3a** in 15% yield in 18 h. These results were in accordance with the hypothesis outlined in Scheme 3 (path B) that the elimination step from **1** to **6** may be fast (DBU is well-known to perform β-elimination reactions efficiently) and that the conversion of **6** to **7** could be the rate-determining step. Thus, an excess of a cyanide source could accelerate the step from **6** to **7**.

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