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Cobalt-Catalyzed Reductive Carboxylation of α,β-Unsaturated Compounds with Carbon Dioxide

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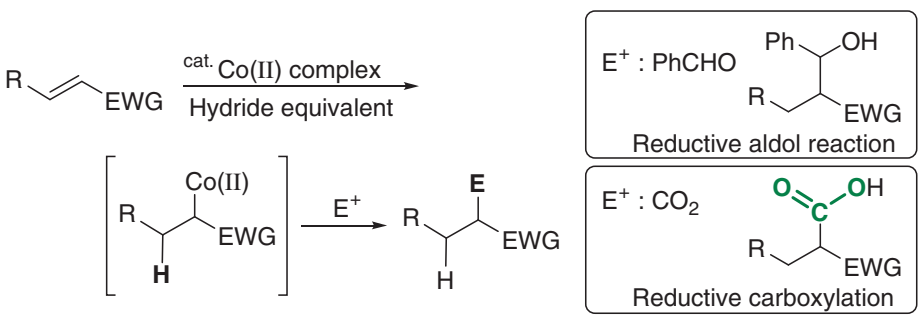
The gaseous carbon dioxide incorporation reaction with α,β-unsaturated compounds was examined in the presence of a catalytic amount of bis(acetylacetonato)cobalt(II) and using diethylzinc as a reductant. After screening with various electron-withdrawing groups, both α,β-unsaturated nitriles and carboxamides were found to efficiently capture carbon dioxide to provide the corresponding carboxylates or malonates in good to excellent yields under mild conditions.

Carbon–carbon bond formation is one of the most important subjects in organic synthetic chemistry. In 1973, Mukaiyama reported the Lewis acid catalyzed crossed aldol reaction[1] using silyl enol ether as a metal enolate analogue, which has been employed as a standard method in organic synthesis as it does not require the use of strong bases. Much effort has been exploited for the reaction to improve the catalytic efficiency and stereoselectivity by screening metal elements.[2] Also, improvement of the enantioselectivity has been achieved by optimizing the ligand design.[3]

Employing conjugate addition to provide the metal enolate equivalent makes it possible to exclude base species from the reaction by using a catalytic amount of metal catalysts and a stoichiometric amount of reducing agent for α,β-unsaturated carbonyl compounds. Isayama and Mukaiyama reported the reductive aldol reaction for α,β-unsaturated nitriles catalyzed by bis(acetylacetonato)cobalt(II) with phenylsilane in 1989.[4] They proposed the reaction mechanism as follows (Scheme 1): the phenylsilane reducing agent would promote the cobalt catalyst to a cobalt–hydride equivalent, which would add α,β-unsaturated compounds by 1,4-addition to form the cobalt enolate equivalent. It would capture electrophiles to afford the corresponding aldol adducts with exclusive regioselectivity at the α-position of the electron-withdrawing group.

During the course of our continuing studies on cobalt(II) complex catalysts with the combined use of reducing agents, a number of synthetic reactions were reported; in the presence of 2-propanol with molecular oxygen, the oxidation–reduction–hydration of alkenes was proposed.[5] With use of sodium borohydride,[6] the catalytic enantioselective reduction of various carbonyl compounds into optically active secondary alcohols[7] or amines[8] was proposed. Under similar conditions, the enantioselective 1,4-reduction of α,β-unsaturated carboxamides was reported.[9]

In order to construct frameworks for various complicated organic compounds, small molecules with effective functional groups, which are commonly obtained from the petrochemical industry have usually been employed. On the other hand, currently, renewable carbon resources, such as bio-ethanol or carbon dioxide, have attracted much attention for organic syntheses,[10] from the viewpoint of sustainability with respect to the limitations of petroleum resources. Also, from our research group, the reaction of carbon dioxide with epoxides catalyzed by cobalt(II) complexes[11a] and the reactions propargyl alcohols and amines catalyzed by silver(I) salts[11b,11c,11f–11j] have been reported. In these reactions, an oxygen or nitrogen nucleophile attacked carbon dioxide to afford cyclic carbonates or oxazolidinones as products. Whereas these products tend to release carbon dioxide by hydrolysis, the corresponding carboxylates produced by the carbon–carbon bond-forming reaction with carbon dioxide should be stable enough to be employed as further synthetic intermediates for carbon–carbon frameworks. Among an array of methods for the carbon–carbon bond-forming reaction with carbon dioxide,[10,12] our group has



Scheme 1. Cobalt-catalyzed C–C bond formations via enolate equivalents.

proposed the reactions of enolates with carbon dioxide. In the presence of a silver(I) catalyst, various ketones containing an alkyne group at the appropriate position afforded the corresponding γ-lactone derivatives[11d] or dihydroisobenzofuran derivatives[11e] in good to high yields under mild conditions.

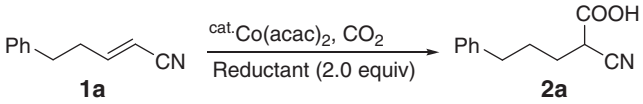
As another way to form new carbon–carbon bonds with carbon dioxide, carbon nucleophiles generated from various olefins in the presence of transition metals with appropriate reducing agents were reported. From styrene derivatives, the combined use of a nickel catalyst and diethylzinc,[13] or an iron catalyst and Grignard reagent[14] are examined to afford the corresponding carboxylates effectively. The nickel catalyst combined with diethylzinc also activated alkyne to trap carbon dioxide regioselectively.[15] Under the conditions using the palladium pincer complex and triethylaluminum, allenes reacted with carbon dioxide to give the carboxylate product regioselectively in high yield.[16] In these studies on hydrocarboxylation of olefins, metal–hydride species generated from the catalyst and reducing agent, which is the common key intermediate, produced the carbon nucleophiles from the substrates to attack carbon dioxide. However, as for α,β-unsaturated compounds of electron-deficient olefins, only a study on a photoreaction system using aluminum catalyst and diethylzinc was reported[12a] to obtain the alkylcarboxylate products regioselectively, but the substrate scope was not wide enough.

Based on these prior studies of the reductive aldol reaction and carbon dioxide incorporative reaction, we examined the reductive carboxylation reaction of α,β-unsaturated compounds with carbon dioxide in the presence of cobalt(II) catalysts and reducing agents.

Results and Discussion

Cobalt-Catalyzed Reductive Carboxylation of α,β-Unsaturated Nitriles with Carbon Dioxide. According to an earlier study of the reductive aldol reaction,[4] 5-phenylpent-2-enenitrile (**1a**) was subjected to the reported conditions then reacted with benzaldehyde to afford the corresponding aldol adduct in 88% yield. Under the same reaction conditions with gaseous carbon dioxide as an electrophile instead of aldehydes, the desired product **2a** was not obtained at all while the corresponding saturated product was produced (Table 1, Entry 1). Since it was assumed that the obtained saturated product was derived from the 1,4-reduction of the starting α,β-unsaturated nitrile, we presumed that the corresponding enolate equivalent should be properly generated, but could not capture carbon dioxide. When a stoichiometric amount of the cobalt complex was actually employed to cover the low reactivity of the intermediate, the desired product **2a** was obtained in 10% yield (Entry 2). Thus we confirmed that the desired reductive carboxylation actually proceeds in the presence of the cobalt complex and a reducing agent. Various reducing agents were then examined to improve the product yield. Triethylborane, diethylaluminum chloride, and diethylzinc were employed as reducing agents (Entries 3, 4, and 5).[17] Based on this examination, it was found that diethylzinc is the most suitable reducing agent to capture carbon dioxide in the reaction. Triethylborane showed a reactivity similar to that of phenylsilane. Diethylaluminum chloride showed a better yield than those of the silane and borane, and above all, diethylzinc gave the best yield. By using diethylzinc and

Table 1. Examination of Various Reductants for Reductive Carboxylation



Entry[a)]	Reductant	Amount of Co(II) complex/mol %	CO_2 pressure /MPa	Yield /%
1[b)]	$PhSiH_3$	5	1.0	0
2[b)]	$PhSiH_3$	100	1.0	10
3	Et_3B	100	1.0	10
4	Et_2AlCl	100	1.0	26
5	Et_2Zn	100	1.3	62
6	Et_2Zn	5	1.0	87[c)]
7	Et_2Zn	5	0.1	>99[c)]

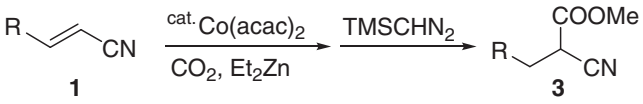
a) Reactions were carried out on a 0.25 mmol scale with 1.5 mL of THF at 20 °C. b) Reaction was carried out in 1.5 mL of 1,2-dichloroethane at 70 °C. c) Yield after methylation with TMS diazomethane.

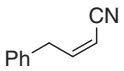
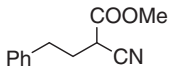
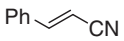
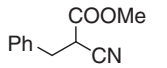
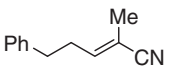
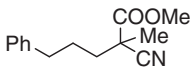
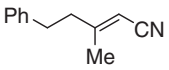
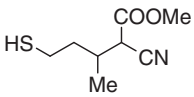
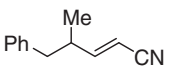
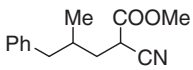
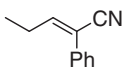
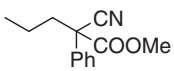
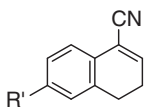
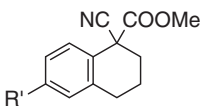
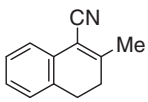
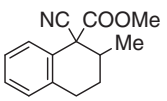
the 5 mol % of cobalt(II) complex, the desired product **2a** was obtained in 87% with some dicarboxylate detected as a side product. The side product seems to be generated by hydrolysis of desired cyanocarboxylate in the reaction system. Eventually the desired cyanocarboxylate was isolated in quantitative yield under very mild conditions at ambient temperature under atmospheric pressure of carbon dioxide probably because the amount of water in the reaction solution decreased by heating the reactor vessel before use (Entry 7).[18]

The optimized conditions were successfully applied to various α,β-unsaturated nitriles to afford the carboxylation products (Table 2). New carbon–carbon bond formations with carbon dioxide were exclusively observed at the α-position for all the substrates in Table 2. 5-Phenylpent-2-enenitrile (**1a**) and its derivatives with general substituents, such as alkyls, ethers, esters, and halogens showed good reactivity to produce the corresponding carboxylates **3a**–**3f** after methyl esterification in good-to-excellent yields (Entries 1–6). Carboxylic acids were obtained as products of the reaction. Methyl esterification was performed in order to make analysis easy as well as to confirm if the product was correctly formed. The substrates with a naphthyl group, benzyl group and shortened alkyl chain **1g**–**1i** also gave the products in high yields (Entries 7–9). From cinnamonitrile, the corresponding product **3j** was obtained in 81% yield (Entry 10). The β-methyl-substituted derivative was found not to be a suitable substrate for this reaction (Entry 12), in accordance with the 1,4-addition manner,[17b,19] while the α-methyl-substituted (Entry 11) and γ-methyl-substituted (Entry 13) α,β-unsaturated nitriles reacted with carbon dioxide to afford the desired carboxylates in moderate-to-good yields. The α-phenyl-substituted α,β-unsaturated nitrile could react with carbon dioxide to give the carboxylated product in good yield (Entry 14). The dihydronaphthalenes with a nitrile at the α-position **1o** and **1p** reacted with carbon dioxide to afford the products in good-to-high yield (Entries 15 and 16), while no reaction proceeded for the corresponding β-methyl-substituted nitrile **1q** (Entry 17).

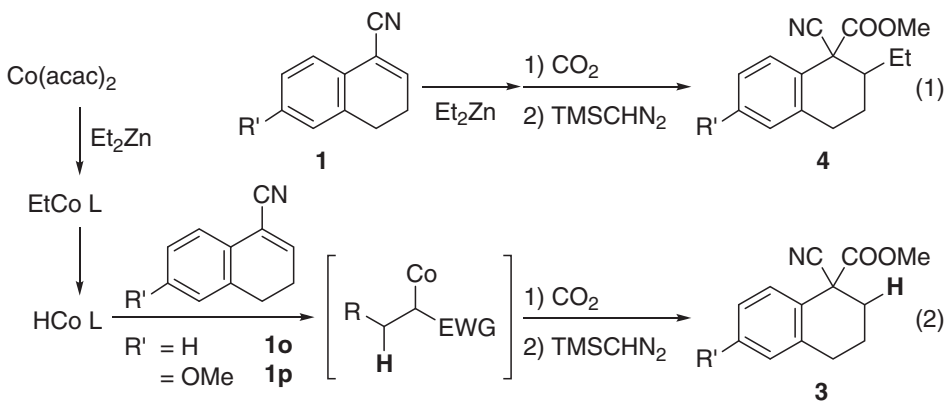
Based on the GC-MS analysis of the obtained products, a small amount of the corresponding β-ethyl-substituted carbox-

Table 2. Various α,β-Unsaturated Nitriles for Reductive Carboxylation



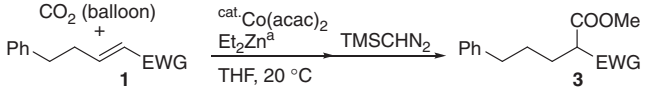
Entry[a]	Substrate	Product		Yield/%[d]
1		Ar = Ph	**3a**	>99
2	Ar, CN	= 4-Me-Ph	**3b**	77
3		= 4-CO_2Et-Ph	**3c**	85[e]
4		= 4-Br-Ph	**3d**	>99
5		= 4-Cl-Ph	**3e**	>99
6		= 4-OMe-Ph	**3f**	98
7		= OBn	**3g**	72
8		= 1-Naph	**3h**	>99
9			**3i**	78
10[b]			**3j**	81
11[b]			**3k**	38
12[b]			**3l**	9[f]
13[b]			**3m**	67
14[b]			**3n**	66
15[b]			R′ = H	**3o**	91
16[c]			R′ = OMe	**3p**	56
17[b]			**3q**	0

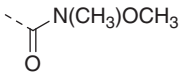
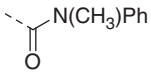
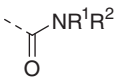
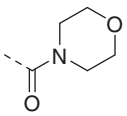
a) Reactions were carried out on a 0.25 mmol scale with 1.5 mL of THF at 20 °C under atmospheric pressure of CO_2 with 2 equiv of Et_2Zn (ca. 1.0 M in *n*-hexane) in the presence of 5 mol % of $Co(acac)_2$. b) 10 mol % of $Co(acac)_2$ and 4 equiv of Et_2Zn were employed. c) 15 mol % of $Co(acac)_2$ and 8 equiv of Et_2Zn were employed. d) Isolated yield. e) 1.0 MPa of CO_2. f) Diastereomer ratio = 60:40.



Scheme 2. Cobalt–hydride 1,4-addition mechanism.

Table 3. Scope of the Electron-Withdrawing Group



Entry	EWG		Conditions	Product	Yield/%
1			A	**3a**	>99
2			A	**3r**	20
3			B		35
4			B	**3s**	complex
5			A	**3t**	21
6			B		>99
7		$R^1 = Me$, $R^2 = Bn$	B	**3u**	64
8		$R^1 = Et$, $R^2 = Et$	B	**3v**	62
9		$R^1 = {}^i Pr$, $R^2 = {}^i Pr$	B	**3w**	13
10		$R^1 = Ph$, $R^2 = Ph$	B	**3x**	9
11			B	**3y**	82

a) Condition A involves 5 mol % of bis(acetylacetonato)cobalt(II) and 2 equiv of diethylzinc. Condition B involves 10 mol % of bis(acetylacetonato)cobalt(II) and 4 equiv of diethylzinc.

ylate was detected under some conditions. From the α,β-unsaturated nitrile **1p**, the ethyl-substituted carboxylate **4p** was isolated in 12% yield. Then, we tried to perform the reaction without the cobalt complex to find that the ethyl-substituted carboxylate was detected in the GC-MS analysis whereas the desired β-hydrogenated product was not detected (Scheme 2, eq 1). This observation provided clear evidence that the presence of the cobalt catalyst is crucial in order to generate the desired metal enolate intermediate which is hydrated at the β-position, via interposition of the generated cobalt–hydride (eq 2). As one example, in regard to the bis(acetylacetonato)-nickel(II) complex, the generation of nickel–hydride species was reported as the result of the transmetalation between the complex and alkylaluminum which would generate alkyl nickel species followed by β-elimination.[13–16,20] With respect to the present reaction, the cobalt–hydride species generated by the same process would add the α,β-unsaturated nitrile in the 1,4-addition manner to afford the resulting metal enolate equivalent.

Cobalt-Catalyzed Reductive Carboxylation of α,β-Unsaturated Carboxamides with Carbon Dioxide. As long as the cobalt–hydride equivalent could attack the substrates via the 1,4-addition sequence, not only nitriles, but also other α,β-unsaturated compounds with electron-withdrawing groups, such as ketones, esters, and amides could be employed in these carboxylation reactions. The derived malonate derivatives from these substrates would be widely applied as useful building blocks in organic syntheses, especially for natural compounds.[21] For widening the application of the reaction, several substrates with other electron-withdrawing groups were examined (Table 3). When the standard conditions involving 5 mol % of bis(acetylacetonato)cobalt(II) with 2 equivalents of diethylzinc (Conditions A) was employed for the α,β-unsaturated nitrile **1a**, the corresponding carboxylated product **3a** was obtained in quantitative yield after methylation (Entry 1). The ethyl α,β-unsaturated carboxylate **1r** was subjected to these conditions to afford the corresponding product **3r** in only 20% yield (Entry 2). When 10 mol % of the cobalt complex with 4 equivalents of zinc reagent (Conditions B) was reacted with the carboxylate **1r**, only 35% of the product was obtained (Entry 3). At the end of the reaction, the substrate **1r** was almost consumed as determined by TLC analysis. The side product was confirmed as the corresponding saturated ester. To the Weinreb amide[22] **1s**, the present carboxylation reaction could not be applied (Entry 4). For *N*-methylanilide, the corresponding carboxylated product **3t** was obtained in only 21% yield under conditions A (Entry 5), while conditions B afforded the carboxylated product in quantitative yield (Entry 6). Several carboxamides were examined under conditions B to afford the products **3u**–**3x** in moderate yields (Entries 7–10). Conditions B were also effective for the morpholine amide **1y** to give the product **3y** in 82% yield (Entry 11).

After the electron-withdrawing group screening, we next examined a variety of carboxylic substituents in the substrates. As shown in Tables 4 and 5, substrates with both aliphatic and aromatic carboxylic substituents could be used for the reaction (Entries 1, 3, and 7). The methoxy, methyl, chloro, and trifuluoromethyl group substituents well tolerated the reaction conditions to give good-to-excellent product yields (Entries 2, 3, 5, and 6). Based on a comparison between Tables 4 and 5, the yields of the anilides tended to be higher than those of the corresponding morpholides overall, except for the substrates with methyl and chloro substituents on the aromatic ring (Entries 3 and 5) and the substrate with long alkyl chain (Entry 8). As for the substrate with *N*-methyl anilide, a long alkyl chain with the substrate tends to decrease the yield

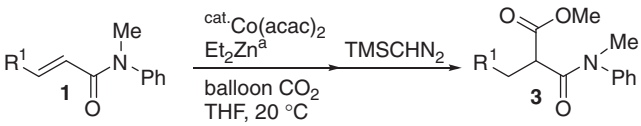
probably due to steric hindrance during the 1,4-addition step of the cobalt–hydride (Table 4, Entry 8).

The substrates with some substitutions close to the reactive olefin site were screened to examine the limitation of the reaction (Table 6). The substitution on both the α-position and β-positions would almost entirely prevent the reaction to proceed (Entries 2, 3, 6, and 7). The products were obtained in only low-to-moderate yields from the phenyl substituted derivatives at the α-position (Entries 4 and 5). In common with the conjugated addition reaction with nitriles, the methyl substitution at the β-position prohibited the cobalt–hydride addition to itself (Entries 10 and 11). The methyl substitution at the α-position would reduce the accessibility from the metal enolate equivalent to carbon dioxide, which eventually decreased the product yields (Entries 8 and 9). The methyl substitution at the γ-position would not disturb the reaction compared with the substitution at the α-position (Entries 12 and 13).

It is worth noting that geometric isomerization was observed when we employed the substrate **1ba** with a phenyl substituent at the α-position of the carboxamide (Scheme 3). This result may be explained as follows; during the reaction, the cobalt–hydride intermediate could attack the substrate to form the cobalt enolate equivalent but it could not trap carbon dioxide due to its bulkiness around the reactive α-position. Also the cobalt–hydride was kicked out via β-hydride elimination from the enolate equivalent because of repulsion between the phenyl group and amine group with isomerization of geometry.

We also tried to use the carboxamide conjugated with a triple bond **1bb** for the reaction. Actually, it was consumed in the system like the α,β-unsaturated compound, but the product **5bb** was obtained in fully-saturated state (Scheme 4). Presumably, once the product **2bb** including the conjugated double bond was generated by the first reaction, it could be attacked again by another cobalt–hydride intermediate for it still contained a reactive site to give the fully-saturated product.

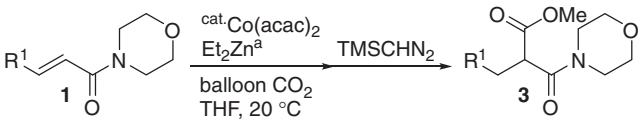
Table 4. Scope of the *N*-Methylanilide Derivatives



Entry	R^1	Product	Yield/%
1	$PhCH_2CH_2$	**3t**	>99
2	4-MeOPh	**3z**	77
3	4-MePh	**3aa**	65
4	Ph	**3ab**	88
5	4-ClPh	**3ac**	67
6	4-CF_3Ph	**3ad**	98
7	Me	**3ae**	80
8	C_5H_{11}	**3af**	20

a) 10 mol % of bis(acetylacetonato)cobalt(II) and 4 equiv of diethylzinc were used (condition B).

Table 5. Scope of the Morpholine Amide Derivatives



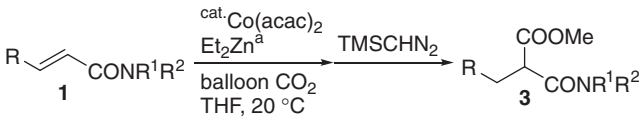
Entry	R^1	Product	Yield/%
1	$PhCH_2CH_2$	**3y**	92
2	4-MeOPh	**3ag**	70
3	4-MePh	**3ah**	90
4	Ph	**3ai**	68
5	4-ClPh	**3aj**	75
6	4-CF_3Ph	**3ak**	63
7	Me	**3al**	44
8	C_5H_{11}	**3am**	53

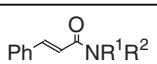
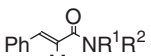
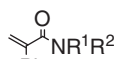
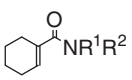
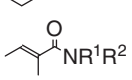
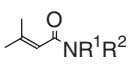
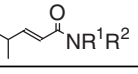
a) 10 mol % of bis(acetylacetonato)cobalt(II) and 4 equiv of diethylzinc were used (condition B).

Conclusion

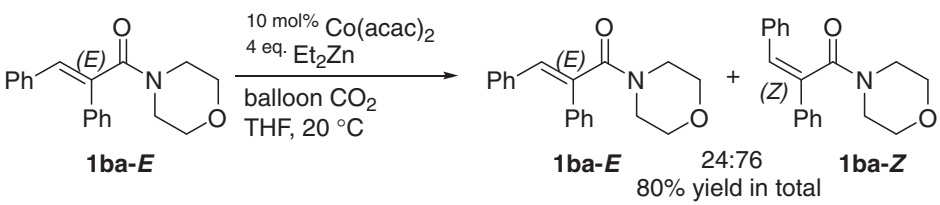
We studied the reductive carboxylation of α,β-unsaturated nitriles and carboxamides with gaseous carbon dioxide. A

Table 6. Limitation of Substrates

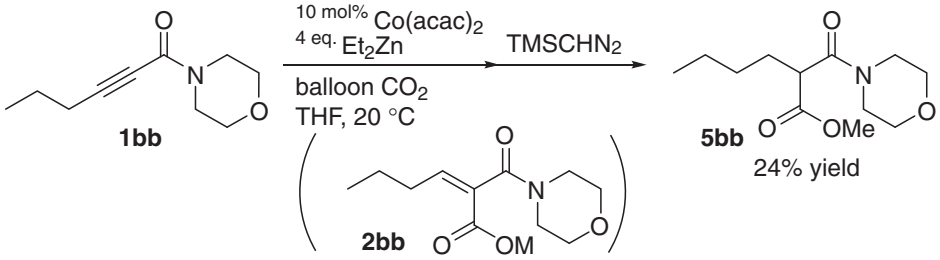


Entry	Substrate	R^1	R^2	Product	Yield/%
1		Me	Bn	**3an**	78
2		Me	Ph	**3ao**	trace
3		morpholine		**3ap**	trace
4		Me	Ph	**3aq**	37
5		morpholine		**3ar**	40
6		Me	Ph	**3as**	trace
7		morpholine		**3at**	trace
8		Me	Ph	**3au**	17
9		morpholine		**3av**	10
10		Me	Ph	**3aw**	12
11		morpholine		**3ax**	15
12		Me	Ph	**3ay**	94
13		morpholine		**3az**	50

a) 10 mol % of bis(acetylacetonato)cobalt(II) and 4 equiv of diethylzinc were used (condition B).



Scheme 3. Stereochemical isomerization of the substrate with α-phenyl substitution.



Scheme 4. Employing the substrate with a triple bond.

catalytic amount of the cobalt complex and the combined use of diethylzinc as the reducing agent realized the smooth reaction process to give the desired product in moderate to excellent yields at room temperature under atmospheric pressure of carbon dioxide.

Experimental

General. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL model AL-400, alpha-400, or ECX-400 spectrometer using $CDCl_3$ as the solvent. The IR spectra were measured on a Thermo Electron Corporation model NICOLET 6700 FT-IR spectrometer. The melting points were measured with a Stanford Research Systems MPA100 or SHIMADZU DSC-60. The ESI high resolution mass spectra were obtained using a Waters LCT Premier XE mass spectrometer. Column chromatography was conducted on silica gel (Kanto 60 N). The diethyl ether and anhydrous THF were purchased from Kanto Chemical Co., Inc., and used without further purification. Carbon dioxide (99.5%) was purchased from Sagami Acetylene Co., Ltd. Sodium sulfate anhydrous, diethyl aluminum chloride in *n*-hexane (ca. 1.0 M solution) and triethyl borane in *n*-hexane (ca. 1.0 M solution) were purchased from Kanto Chemical Co., Inc., and used without further purification. Diethylzinc in *n*-hexane (ca. 1.0 M solution) was purchased from Tokyo Chemical Industry Co., Ltd., and repackaged into a smaller size to avoid degradation, then used without further purification. Trimethylsilyldiazomethane in *n*-hexane (ca. 0.6 M solution) was purchased from Tokyo Chemical Industry Co., Ltd., and used without further purification. Unless otherwise noted, all reactor vessels and syringes were dried by heating before use.

Synthesis of the Starting Materials. The starting materials **1a**–**1i** and **1k**–**1m** were synthesized from the corresponding aldehydes by Wittig reaction or Horner–Wadsworth–Emmons reaction. The corresponding aldehydes of the substrates **1b**–**1f** and **1h** were prepared by a reported procedure.[23] The corresponding aldehyde of the substrate **1g** was prepared by a reported procedure.[24] Cinnamonitrile **1j** was purchased from Tokyo Chemical Industry Co., Ltd., and purified by silica gel column chromatography before use. The substrates **1n**–**1q** were synthesized from the butyrophenone or tetralone derivatives by a reported procedure.[25] The substrates **1r**–**1bb** were synthesized from the corresponding carboxylic acids via acid chloride intermediates. The corresponding carboxylic acids of the substrates **1r**–**1z**, **1ac**, **1ad**, **1ag**, **1aj**, and **1ak** were prepared from aldehydes by reported procedure.[26]

General Procedure for the Reductive Carboxylation. In a Schlenck flask filled with gaseous carbon dioxide, to a stirred THF (1.5 mL) solution of the α,β-unsaturated compound **1** (0.25 mmol) and bis(acetylacetonato)cobalt(II) (conditions A: 3.2 mg, 5 mol %; conditions B: 6.4 mg, 10 mol %) was added a 1.0 M *n*-hexane solution of diethylzinc (conditions A: 0.5 mL, 2 equiv; conditions B: 1.0 mL, 4 equiv) at 0 °C, then the reaction mixture was stirred at 20 °C for 1–48 h. After checking the completed reaction by TLC analysis, the reaction mixture was quenched with a 1.0 M hydrochloric acid diethyl ether solution (conditions A: 1.5 mL, 6 equiv; conditions B: 3.0 mL, 12 equiv) at 0 °C. The organic layer was extracted with diethyl ether, washed with brine, dried over sodium sulfate and concentrated in vacuum. The residue was purified by silica gel column chromatography (Hexanes:AcOEt:HCOOH = 1:1:0.003) to afford the desired carboxylic acid **2**. The resulting compound was diluted with a mixed solution (6.25 mL, diethyl ether:MeOH = 5:1) and methylated with trimethylsilyldiazomethane in *n*-hexane (ca. 0.6 M solution, (1.04 mL, 2.5 equiv)). After purification by chromatography on silica gel, the corresponding methyl carboxylate was isolated.

2-Cyano-5-phenylpentanoate Methyl Ester (3a): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76–1.90 (m, 2H), 1.93–2.03 (m, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 3.51 (t, $J = 7.1$ Hz, 1H), 3.81 (s, 3H), 7.16–7.23 (m, 3H), 7.30 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 29.2, 34.9, 37.2, 53.4, 116.3, 126.1, 128.3, 128.5, 140.7, 166.6; IR (KBr): 2954, 2251, 1766, 1733, 1263, 1212, 751, 701; HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{16}NO_2^+$, 218.1176; found, m/z 218.1178.

Procedure for the Synthesis of 4p: Using the same procedure as previously described, to a THF solution of **1p** (43.4 mg, 0.23 mmol) and the cobalt catalyst (10 mol %) was added a 1.0 M *n*-hexane solution of diethylzinc (1.0 mL, 4 equiv). After methylation and purification, the ethyl-substituted product at the β-position **4p** was isolated (9.4 mg, 12%).

Methyl 1-Cyano-2-ethyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate (4p): Colorless solid; mp: 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, $J = 7.6$ Hz, 3H), 1.60 (t, $J = 7.3$ Hz, 2H), 1.63–1.68 (m, 1H), 2.07–2.31 (m, 2H), 2.88 (dd, $J = 8.3$, 3.9 Hz, 2H), 3.78 (s, 3H), 3.88 (s, 3H), 6.66 (d, $J = 2.4$ Hz, 1H), 6.76 (dd, $J = 8.5$, 2.7 Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 23.8, 25.4, 29.1, 43.0, 53.7, 54.4, 55.3, 113.6, 114.2, 118.2, 123.3, 128.9, 137.9, 159.7, 170.2; IR (KBr): 2935, 2238, 1736, 1609, 1263, 1035, 597; HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{20}NO_3^+$, 274.1438; found, m/z 274.1433.

Methyl 2-Cyano-5-(*p*-tolyl)pentanoate (3b): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79–1.86 (m, 2H), 1.94–2.00 (m, 2H), 2.32 (s, 3H), 2.64 (t, $J = 7.6$ Hz, 2H), 3.50 (t, $J = 6.8$ Hz, 1H), 3.80 (s, 3H), 7.05–7.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 28.5, 29.3, 34.5, 37.3, 53.5,

116.3, 128.2, 129.2, 135.7, 137.6, 166.5; IR (KBr): 2928, 2250, 1750, 1259, 807, 543; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2^+$, 232.1333; found, m/z 232.1337.

Methyl 2-Cyano-5-benzyloxypentanoate (3g): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79–1.86 (m, 2H), 2.01–2.18 (m, 2H), 3.51–3.56 (m, 2H), 3.60 (dd, $J = 8.3$, 5.9 Hz, 1H), 3.81 (s, 3H), 4.50 (s, 2H), 7.28–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 27.1, 37.1, 53.4, 68.8, 73.0, 116.5, 127.6, 127.7, 128.4, 138.1, 166.6; IR (KBr): 2955, 2864, 2250, 1747, 1259, 1101, 742, 699; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{18}NO_3^+$, 248.1282; found, m/z 248.1283.

Methyl 2-Cyano-4-phenylbutanoate (3i): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25–2.32 (m, 2H), 2.77–2.94 (m, 2H), 3.46 (t, $J = 6.3$ Hz, 1H), 3.79 (s, 3H), 7.20–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.3, 32.6, 36.5, 53.5, 116.2, 126.8, 128.5, 128.8, 138.9, 166.5; IR (KBr): 2956, 2251, 1747, 1259, 750, 700; HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{14}NO_2^+$, 204.1020; found, m/z 204.1024.

Methyl 2-Cyano-4-phenylpropanoate (3j): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17–3.32 (m, 2H), 3.72–3.76 (m, 1H), 3.80 (s, 3H), 7.28–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7, 39.5, 53.6, 116.0, 127.8, 128.9, 129.0, 135.2, 166.0; IR (KBr): 3032, 2957, 2252, 1743, 1267, 1213, 750, 701; HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{12}NO_2^+$, 190.0863; found, m/z 190.0863.

Methyl 2-Cyano-2-methyl-5-phenylpentanoate (3k): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 3H), 1.68–2.01 (m, 4H), 2.66 (t, $J = 7.3$ Hz, 2H), 3.81 (s, 3H), 7.16–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 27.0, 30.9, 35.2, 37.7, 43.7, 53.5, 119.9, 126.1, 128.3, 128.5, 140.9; IR (KBr): 2955, 2244, 1743, 1262, 751, 701; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2^+$, 232.1333; found, m/z 232.1338.

Methyl 2-Cyano-3-methyl-5-phenylpentanoate (3l): Yellow oil; diastereomers mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 or 1.19 (d, $J = 6.8$ Hz, 3H), 1.67–1.86 (m, 2H), 2.26–2.32 (m, 1H), 2.53–2.78 (m, 2H), 3.48 or 3.58 (d, $J = 5.6$ or 4.8 Hz, 1H), 3.79 or 3.81 (s, 3H), 7.16–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 17.6, 32.9, 33.1, 34.0, 34.1, 34.8, 36.4, 43.6, 44.3, 53.3, 53.4, 115.1, 115.5, 126.1, 126.2, 128.3, 128.5, 128.6, 140.8, 166.2, 166.4; IR (KBr): 2933, 2249, 1747, 1257, 750, 701; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2^+$, 232.1333; found, m/z 232.1338.

Methyl 2-Cyano-4-methyl-5-phenylpentanoate (3m): Yellow oil; diastereomers mixture (diastereomer ratio = 53:47); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 or 0.96 (d, $J =$ 6.0 or 7.2 Hz, 3H), 1.71–1.78 or 1.83–1.89 (m, 1H), 1.96–2.11 (m, 2H), 2.43–2.70 (m, 2H), 3.49–3.52 or 3.55–3.59 (m, 1H), 3.80 (s, 3H), 7.14–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 19.4, 32.6, 32.9, 35.6, 35.7, 36.1, 36.5, 42.6, 43.3, 53.5, 53.5, 116.2, 116.5, 126.3, 126.3, 128.4, 129.1, 139.5, 139.5, 166.7, 166.9; IR (KBr): 2956, 2249, 1747, 1251, 746, 702; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2^+$, 232.1333; found, m/z 232.1339.

Methyl 2-Cyano-2-phenyl-pentanoate (3n): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.38–1.53 (m, 2H), 2.07–2.14 (m, 1H), 2.32–2.39 (m, 1H), 3.79 (s, 3H), 7.35–7.43 (m, 3H), 7.54–7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.9, 40.2, 53.9, 54.1, 118.4, 126.0, 128.8, 129.1, 134.5, 168.3; IR (KBr): 2964, 2245, 1751, 769, 730, 698; HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{16}NO_2^+$, 218.1176; found, m/z 218.1177.

Methyl 1-Cyano-1,2,3,4-tetrahydronaphthalene-1-carboxylate (3o): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98–2.07 (m, 2H), 2.38–2.53 (m, 2H), 2.87 (t, $J = 6.0$ Hz, 2H), 3.86 (s, 3H), 7.15–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 28.4, 32.9, 47.6, 53.9, 120.1, 126.9, 128.7, 129.0, 129.7, 130.1, 136.6, 169.4; IR (KBr): 2954, 2241, 1736, 1240, 1099, 1017, 759; HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{14}NO_2^+$, 216.1020; found, m/z 216.1023.

Methyl 1-Cyano-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate (3p): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.08 (m, 2H), 2.35–2.50 (m, 2H), 2.84 (t, $J =$ 6.3 Hz, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 6.65 (d, $J = 2.4$ Hz, 1H), 6.79 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.29 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 28.8, 32.9, 47.1, 53.8, 55.3, 113.4, 114.3, 120.2, 121.8, 129.9, 138.1, 159.7, 169.6; IR (KBr): 2955, 2240, 1743, 1609, 1244, 1124, 1038, 841; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{16}NO_2^+$, 246.1125; found, m/z 246.1129.

1-Ethyl 3-Methyl 2-(3-phenylpropyl)malonate (3r): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.3$ Hz, 3H), 1.61–1.69 (m, 2H), 1.95 (dd, $J = 15.9$, 7.6 Hz, 2H), 2.64 (t, $J = 7.6$ Hz, 2H), 3.36 (t, $J = 7.6$ Hz, 1H), 3.73 (s, 3H), 4.19 (q, $J = 7.0$ Hz, 2H), 7.16–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 28.4, 29.1, 51.8, 52.4, 61.4, 125.9, 128.2, 128.4, 141.7, 169.3, 169.9; IR (KBr): 2954, 1734, 1454, 1244, 1148, 1028, 750, 700; HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{21}O_4^+$, 265.1434; found, m/z 265.1433.

Methyl 2-[Methyl(phenyl)carbamoyl]-5-phenylpentanoate (3t): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49–1.53 (m, 2H), 1.84–1.96 (m, 2H), 2.49–2.54 (m, 2H), 3.30 (s, 3H), 3.34 (dd, $J = 8.3$, 6.3 Hz, 1H), 3.66 (s, 3H), 7.10–7.43 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1, 29.2, 35.6, 37.7, 49.0, 52.3, 125.8, 127.6, 128.2, 128.3, 128.4, 129.9, 141.9, 143.4, 169.0, 170.5; IR (KBr): 2950, 1747, 1661, 1453, 1383, 1201, 701, 563; HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{24}NO_3^+$, 326.1751; found, m/z 326.1750.

Methyl 2-(4-Methoxybenzyl)-3-[methyl(phenyl)amino]-3-oxopropanoate (3z): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (dd, $J = 13.4$, 5.1 Hz, 1H), 3.13–3.15 (m, 1H), 3.19 (s, 3H), 3.54 (dd, $J = 10.3$, 5.4 Hz, 1H), 3.70 (s, 3H), 3.81 (s, 3H), 6.79 (d, $J = 8.8$ Hz, 3H), 6.94 (d, $J = 8.3$ Hz, 2H), 7.27–7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.4, 37.4, 51.0, 52.4, 55.3, 113.7, 127.5, 128.0, 129.5, 130.2, 130.3, 143.2, 158.3, 168.5, 169.9; IR (KBr): 2953, 1747, 1655, 1513, 1442, 1248, 1035, 775, 549; HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{22}NO_4^+$, 328.1543; found, m/z 328.1544.

Methyl 2-[Methyl(phenyl)carbamoyl]butanoate (3ae): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, $J = 7.3$ Hz, 3H), 1.84–1.94 (m, 2H), 3.27 (t, $J = 7.3$ Hz, 1H), 3.32 (s, 3H), 3.67 (s, 3H), 7.23–7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 22.8, 37.6, 50.5, 52.2, 127.7, 128.2, 129.9, 143.5, 169.1, 170.5; IR (KBr): 2969, 1746, 1661, 1497, 1384, 1280, 1200, 1125, 776, 703, 563; HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{18}NO_3^+$, 236.1281; found, m/z 236.1281.

Methyl 2-(Morpholine-4-carbonyl)octanoate (3af): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, $J = 7.1$ Hz, 3H), 1.10–1.25 (br m, 8H), 1.79–1.89 (m, 2H), 3.31 (s, 3H), 3.33–

3.35 (m, 1H), 3.67 (s, 3H), 7.23 (d, $J = 8.3$ Hz, 2H), 7.35–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.3, 29.0, 29.5, 31.5, 37.7, 49.0, 52.2, 127.6, 128.2, 129.8, 143.5, 169.2, 170.7; IR (KBr): 2927, 2857, 1747, 1663, 1596, 1496, 1383, 1261, 1117, 1027, 775, 702, 563; HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{26}NO_3^+$, 292.1907; found, m/z 292.1904.

Methyl 2-(4-Methoxybenzyl)-3-morpholino-3-oxopropanoate (3ag): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19–3.23 (m, 4H), 3.40–3.65 (m, 6H), 3.72 (s, 3H), 3.78 (s, 3H), 3.82 (t, $J = 7.6$ Hz, 1H), 6.80–6.83 (m, 2H), 7.10–7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.3, 42.5, 46.5, 50.2, 52.5, 55.2, 66.3, 66.6, 113.9, 130.0, 130.1, 158.4, 166.9, 169.7; IR (KBr): 2957, 2858, 1743, 1641, 1514, 1437, 1247, 1114, 1033, 918, 847, 757, 564; HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{22}NO_5^+$, 308.1492; found, m/z 308.1493.

Methyl 2-(Morpholine-4-carbonyl)butanoate (3al): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.3$ Hz, 3H), 1.98 (dq, $J = 17.1$, 7.3 Hz, 2H), 3.45–3.69 (m, 9H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 22.5, 42.6, 46.4, 50.4, 52.4, 66.6, 66.8, 167.1, 170.3; IR (KBr): 2969, 2859, 1743, 1636, 1437, 1271, 1116, 1034, 865, 571; HRMS (ESI): $[M + H]^+$ calcd for $C_{10}H_{18}NO_4^+$, 216.1230; found, m/z 216.1226.

Methyl 2-(Morpholine-4-carbonyl)octanoate (3am): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.8$ Hz, 3H), 1.28 (s, 8H), 1.93 (s, 2H), 3.45–3.68 (m, 9H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.5, 29.0, 29.1, 31.5, 42.6, 46.4, 48.9, 52.5, 66.6, 66.8, 167.3, 170.4; IR (KBr): 3478, 2925, 2857, 1743, 1648, 1436, 1271, 1116, 1029; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{26}NO_4^+$, 272.1856; found, m/z 272.1858.

Methyl 2-Benzyl-3-[benzyl(methyl)amino]-3-oxopropanoate (3an): Colorless oil; regioisomers mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 or 2.90 (s, 3H), 3.21–3.37 (m, 2H), 3.70 or 3.74 (d, $J = 1.0$ Hz, 3H), 3.88 or 3.99 (dd, $J = 8.9$, 6.0 Hz, 1H), 4.25–4.71 (m, 2H), 6.86–7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 34.3, 35.1, 35.4, 50.6, 50.8, 51.2, 52.5, 52.5, 53.3, 99.6, 126.2, 126.6, 127.3, 127.5, 127.8, 128.5, 128.5, 128.8, 129.0, 129.2, 135.9, 136.6, 138.4, 155.9, 168.4, 169.8; IR (KBr): 3029, 2952, 1746, 1648, 1454, 1266, 753, 700; HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{22}NO_3^+$, 312.1594; found, m/z 312.1593.

Methyl 2-Methyl-3-[Methyl(phenyl)amino]-3-oxo-2-phenylpropanoate (3aq): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (br s, 3H), 3.24 (br s, 3H), 3.70 (s, 3H), 6.59 (s, 1H), 7.01–7.52 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 40.1, 52.3, 58.7, 126.5, 126.9, 127.5, 127.8, 128.1, 128.3, 128.8, 129.5, 170.9, 172.2; IR (KBr): 3002, 2950, 1740, 1655, 1447, 1372, 1247, 1198, 1106, 766, 699, 539; HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{20}NO_3^+$, 298.1438; found, m/z 298.1439.

Methyl 2-Methyl-3-morpholino-3-oxo-2-phenylpropanoate (3ar): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 3.01–3.66 (br m, 8H), 3.80 (s, 3H), 7.24–7.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 52.8, 58.5, 126.6, 127.4, 128.7, 139.7, 169.7, 172.4; IR (KBr): 2955, 2857, 1735, 1648, 1424, 1236, 1116, 1030, 857, 767, 701, 592; HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{20}NO_4^+$, 278.1387; found, m/z 278.1389.

Methyl 2-Methyl-2-[methyl(phenyl)carbamoyl]butanoate (3au): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, $J = 7.6$ Hz, 3H), 1.34 (s, 3H), 1.80 (br s, 2H), 3.24 (s, 3H), 3.50 (br s, 3H), 7.16–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 21.7, 29.8, 40.2, 51.8, 53.9, 128.3, 128.3, 128.8, 129.2, 171.1, 173.8; IR (KBr): 2948, 1736, 1655, 1496, 1455, 1361, 1243, 1146, 776, 704, 575; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{20}NO_3^+$, 250.1438; found, m/z 250.1435.

Methyl 2-Methyl-2-(morpholine-4-carbonyl)butanoate (3av): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $J = 7.6$ Hz, 3H), 1.40 (s, 3H), 1.80–2.02 (m, 2H), 3.62–3.64 (br m, 8H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 20.9, 29.6, 52.4, 52.6, 66.6, 169.9, 174.9; IR (KBr): 2974, 2857, 1422, 1302, 1251, 1117, 1040, 858, 593; HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{20}NO_4^+$, 230.1387; found, m/z 230.1387.

Methyl 2-(Morpholine-4-carbonyl)hexanoate (5bb): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.1$ Hz, 3H), 1.26–1.37 (m, 4H), 1.90–1.98 (m, 2H), 3.51–3.72 (m, 9H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 28.8, 29.7, 42.6, 46.4, 48.8, 52.5, 66.6, 66.8, 167.3, 170.4; IR (KBr): 3489, 2959, 2922, 2858, 1736, 1647, 1435, 1253, 1116, 1033; HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{22}NO_4^+$, 244.1543; found, m/z 244.1544.

Supporting Information

The material data, the ^{1}H NMR, ^{13}C NMR spectra data of the substrates and products are provided. These materials are available free of charge on J-STAGE.

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