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Attachment of carbonyl functionalities onto olefins via copper-promoted radical reaction of dichloromethylcyanides

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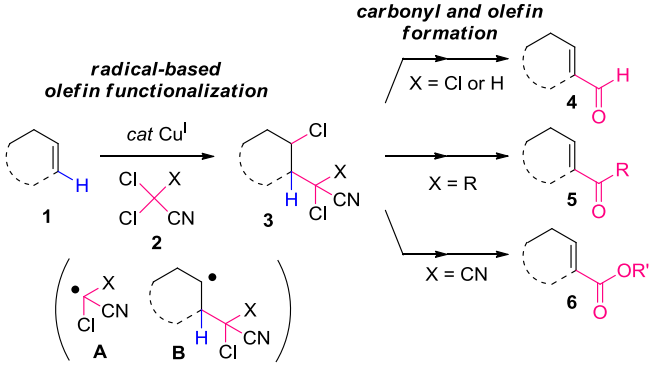
ABSTRACT

Chemo- and regioselective protocols for attachment of various carbonyl functionalities onto unactivated olefins have been developed. Atom transfer radical reactions of Cl_3CCN, $Cl_2C(R)CN$, and $Cl_2C(CN)_2$ were all promoted efficiently by a catalytic amount of CuCl and 1,1′-bis(diphenylphosphino)ferrocene to introduce chloromethylcyanide and chloride units to the C–C double bonds. Conversion of the chloromethylcyanide to the carbonyl functionalities (e.g., aldehydes, ketones and esters), and subsequent double bond reconstruction through elimination of HCl resulted in selective formation of the carbonyl-conjugated *E*-olefins.

1. Introduction

α,β-Unsaturated carbonyls function as extremely useful synthetic intermediates due to the electron-deficient and polarized nature of their olefins.[1] Consequently, there are abundant examples of the introduction of a carbon unit onto α,β-unsaturated carbonyls based on conjugated addition of carbanion nucleophiles. In contrast, installations of a carbon unit onto non-polarized olefins have been rather limited due to their inherently low reactivity.[1a,2] To provide such a strategy, we directed our attention to transition metal-catalyzed atom transfer radical reactions (Kharasch reactions).[3] In general, metal reagents promote formation of radical species under neutral conditions, and the resultant radicals can chemoselectively react with C–C π-bonds without affecting a wide array of polar functionalities such as carbonyl and alcohol moieties.[4] Here we report chemo- and regioselective Cu(I)-promoted addition of dichloromethylcyanide derivatives $Cl_2C(X)CN$ **2** to unactivated olefins **1** (Scheme 1). The resultant bis-functionalized product **3** can be efficiently converted to α,β-unsaturated carbonyl compounds **4**–**6** through carbonyl formation and HCl elimination. Therefore, the present protocols enable preparation of synthetically valuable activated olefins from their more readily available unactivated counterparts by using chloromethylcyanides as carbonyl surrogates.



Scheme 1. Attachment of carbonyl functionalities onto olefins.

2. Results and discussion

Dichloromethylcyanide derivatives **2** were selected as radical donors, because the highly electrophilic nature of the corresponding radical **A** was expected to possess high reactivity toward non-conjugated and relatively electron-rich olefins to produce intermediate **B** (Scheme 1).[5] To realize mild and general bis-functionalization of olefins, reaction conditions were first optimized using terminal olefin **1a** and **2a** (trichloroacetonitrile, Cl_3CCN) as substrates (Table 1).

After screening of metal catalysts, CuCl and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were found to effectively activate **2a**.[6] Treatment of **1a** with 5 equiv of **2a** and 10 mol % of CuCl/dppf at

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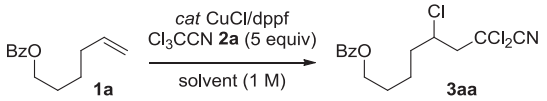
Table 1
Screening of reaction conditions for Cu-catalyzed addition of Cl_3CCN **2a** to olefin **1a**[a]



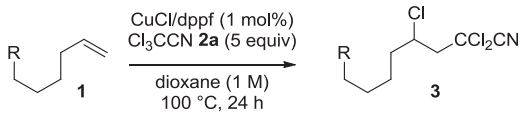
Entry	Solvent	CuCl (mol %)	dppf (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)
1	$(CH_2Cl)_2$	10	10	75	48	85[c]
2	Dioxane	10	10	75	48	82
3	PhCN	10	10	75	48	71
4	DMF	10	10	75	48	47[d]
5	*t*-BuOH	10	10	75	48	76
6	Dioxane	1	1	100	24	90[c]
7	Dioxane	0.1	0.1	100	72	79
8[e]	Dioxane	1	1	100	24	81

[a] Reaction conditions: olefin **1a**, Cl_3CCN **2a** (5 equiv), catalytic amount of CuCl/dppf, solvent (1 M) unless otherwise noted.
[b] Yield was determined by NMR analysis of the crude mixture.
[c] Isolated yield.
[d] Olefin **1a** was recovered in 40% yield.
[e] Cl_3CCN (2 equiv) was employed.

75 °C regioselectively generated product **3aa** in high yield (entry 1). The solvent polarity did not exhibit a significant influence on the reaction. Namely, the addition efficiently proceeded not only in aprotic polar solvents such as 1,2-dichloroethane (entry 1), 1,4-dioxane (entry 2), PhCN (entry 3), and DMF (entry 4), but also in protic *t*-BuOH (entry 5). The highest yield (90%) was obtained when olefin **1a** was treated with **2a** (5 equiv) in dioxane in the presence of 1 mol % of the copper catalyst at 100 °C for 24 h (entry 6). Further decrease of the amounts of the catalyst (0.1 mol %) or **2a** (2 equiv) slightly lowered the product yields (entries 7 and 8).

To examine the functional group compatibility of the present addition, various terminal olefins **1a**–**i** were subjected to the optimized conditions (Table 2). Protected alcohol derivatives having benzoyl (Bz, **1a**), mesyl (Ms, **1b**), methoxymethyl (MOM, **1c**), and (*t*-butyl)dimethylsilyl (TBS, **1d**) groups as well as alcohol group (**1e**) were applicable as starting materials to afford the corresponding adducts **3aa**–**ea** in 62–90% yield (entries 1–5). Nitrogen functionalities, such as carbamate (**1f**) and azide (**1g**), were tolerated under the reaction conditions, furnishing products **3fa** (82%) and **3ga** (54%), respectively (entries 6 and 7). The reactions of chloride **1h** and cyanide **1i** proceeded to give adducts **3ha** and **3ia**, respectively, in over 76% yields (entries 8 and 9). Interestingly, addition of molecular sieves (3 Å MS) was essential for clean conversion when the substrates had acid-sensitive functional groups (entries 3–6). It is most likely that the molecular sieves scavenged adventitious water as well as HCl generated in situ from the reaction between Cl_3CCN and water.[7]

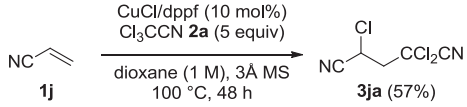
Table 2
Cu-catalyzed addition of Cl_3CCN to terminal olefins



Entry	R	Yield[a] (%)
1	OBz (**1a**)	90 (**3aa**)
2	OMs (**1b**)	88 (**3ba**)
3[b]	OMOM (**1c**)	62 (**3ca**)
4[b]	OTBS (**1d**)	70 (**3da**)
5[b]	OH (**1e**)	67 (**3ea**)
6[b]	NHBoc (**1f**)	82 (**3fa**)
7	N_3 (**1g**)	54 (**3ga**)
8	Cl (**1h**)	78 (**3ha**)
9	CN (**1i**)	76 (**3ia**)

[a] Isolated yield.
[b] The reaction was conducted in the presence of 3 Å MS (200 mg/0.5 mmol of **1**).

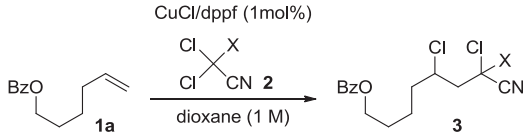
As expected, electron-deficient acrylonitrile **1j** was found to be a less reactive radical acceptor toward the electrophilic radical than non-conjugated terminal olefins **1a**–**i** (Scheme 2). Additional loading of the CuCl/dppf catalyst (10 mol %) and elongation of the reaction time were required to obtain a reasonable yield of adduct **3ja** from **1j** and **2a**.



Scheme 2. Cu-catalyzed addition of CCl_3CN to acrylonitrile.

Significantly, a variety of dichloromethylcyanide derivatives $Cl_2C(X)CN$ **2a**–**d** successfully added to **1a** in high yields using the same reaction system (Table 3). Compared to Cl_3CCN **2a** (entry 1), $Cl_2C(CN)_2$ **2b** exhibited even higher reactivity, giving **3ab** in 95% yield within 4 h (entry 2). It is noteworthy that the reduction of equivalents of **2b** from 5 to 1.5 did not change the product yield (entry 3). Although the reactivities of Cl_2CHCN **2c** (entry 4) and $Cl_2C(R)CN$ **2d** (entry 5) were revealed to be lower than those of **2a** and **2b**, the adducts **3ac** and **3ad** were formed in 95% and 93% yields, respectively, at elevated temperature (130 °C). These results clarified that more electron-withdrawing nature and less steric bulkiness of X both contributed to increase the reactivity of the radical **A** (•CClXCN).[8]

Table 3
Cu-catalyzed addition of various dichloromethylcyanides to olefin



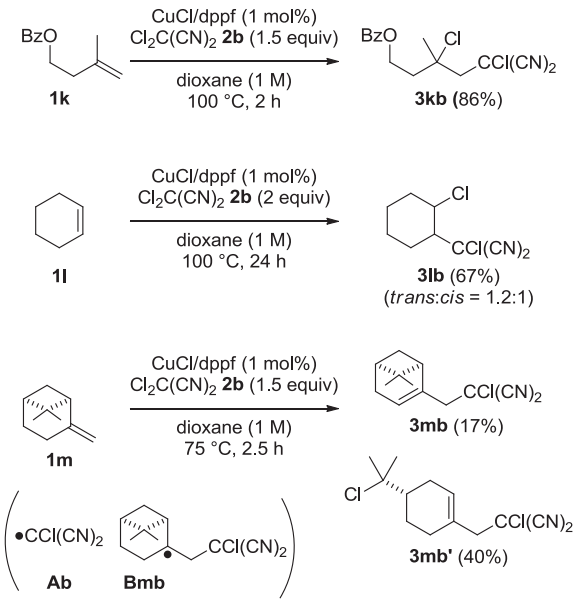
Entry	X	Equiv	Temperature (°C)	Time (h)	Yield[a] (%)
1	Cl (**2a**)	5	100	24	90 (**3aa**)
2	CN (**2b**)	5	100	4	95 (**3ab**)
3	CN (**2b**)	1.5	100	6	94 (**3ab**)
4	H (**2c**)	5	130	24	95 (**3ac**)
5	$Ph(CH_2)_2$ (**2d**)	5	130	48	93 (**3ad**)[b]

[a] Isolated yield.
[b] Compound **2d** was recovered in 45% yield.

By taking advantage of the most reactive $Cl_2C(CN)_2$ **2b**, we next investigated its reaction with the more sterically congested disubstituted olefins **1k**–**m** (Scheme 3). Adducts **3kb** and **3lb** were generated from 1,1- and 1,2-disubstituted olefins **1k** and **1l**, respectively. When β-pinene **1m** was employed, dehydrochlorinated product **3mb** as well as the monocyclic product **3mb′** were obtained. Ring-opening of the strained cyclobutane ring observed in the present reaction confirmed the intermediacy of radical **Bmb**, which was generated through regioselective addition of **Ab** to **1m**.

Next, we focused on the development of conversion methods to α,β-unsaturated carbonyl compounds from the radical adducts (Scheme 4). First, Cu-catalyzed addition of **2a**–**d** to olefin **1n** generated products **3na**–**nd** in high yields. It was anticipated that all the chloromethylcyanide moieties of **3na**–**nd** would be transformed to the carbonyl functionalities, including aldehyde **4**, ketone **5**, and ester **6a**, through their derivatization to cyanohydrin or chlorohydrin intermediates. However, despite the similarity of the structures, different reaction sequences were necessary to achieve formation of the carbonyl-conjugated *E*-olefins in high yields.[9]

Preparation of α,β-unsaturated aldehyde **4** was realized by treatment of chloromethylcyanide **3nc** with NaI, followed by water. The β-chloroaldehyde generated through the iodohydrin underwent elimination of HCl, leading to *E*-olefin **4** in one-pot. Alternatively, dichloromethylcyanide **3na** was converted to the same



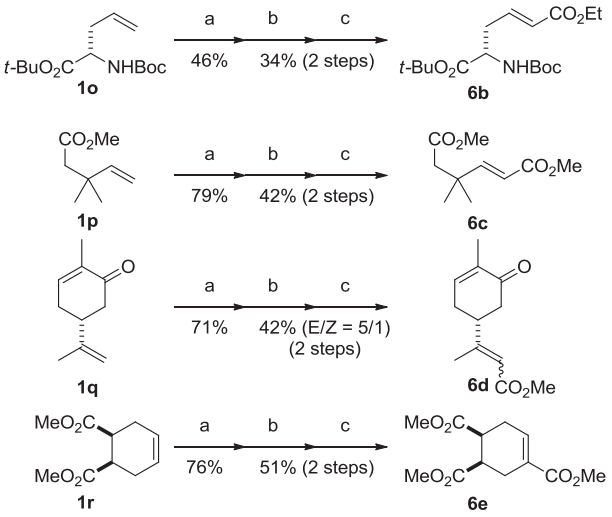
Scheme 3. Cu-catalyzed addition of dichloromalononitrile to disubstituted olefins.

aldehyde **4** after its reduction to **3nc** by using *n*-Bu_3P and subsequent aqueous work-up.[10]

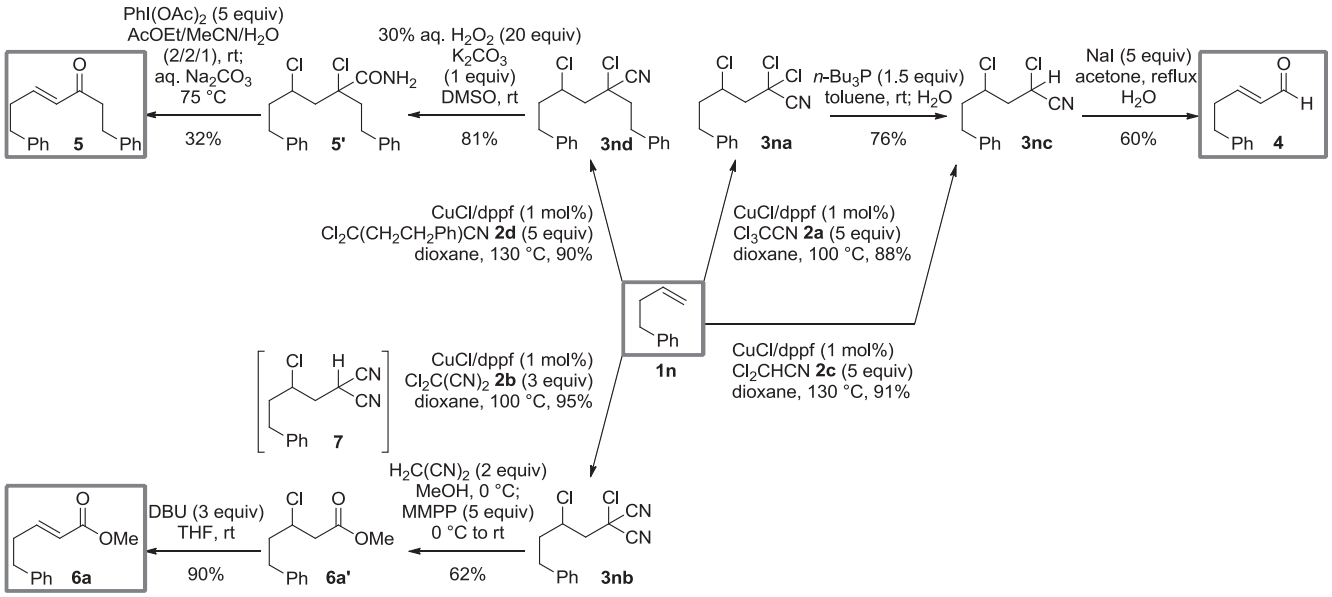
Synthesis of α,β-unsaturated ketone **5** was achieved via a two-step sequence starting from alkylated chloromethylcyanide **3nd**. When **3nd** was subjected to aqueous H_2O_2 under basic conditions, amide **5′** was produced. Hofmann rearrangement[11] of **5′** using $PhI(OAc)_2$ led to formation of the corresponding ketone, in situ treatment of which with aqueous Na_2CO_3 promoted HCl elimination to furnish enone **5**.

Two functional group manipulations from chloromalononitrile **3nb** resulted in formation of α,β-unsaturated ester **6a**. Reduction of the C–Cl bond of **3nb** to a C–H bond was successfully achieved by chloride transfer from **3nb** to malononitrile,[12] leading to dechlorinated **7**. Subsequent introduction of excess amounts of magnesium bis(monoperoxyphthalate) hexahydrate (MMPP) in the same flask promoted oxidation of the C–H bond,[13,14] giving rise to methyl ester **6a′** through the corresponding cyanohydrin. Elimination of HCl from **6a′** was achieved by DBU to furnish conjugated ester **6a**. Hence, three conjugated carbonyl compounds **4**, **5**, and **6a** were prepared from the common terminal olefin **1n** under mild conditions.

The three-step protocol developed for synthesis of α,β-unsaturated ester **6a** was applied to the more functionalized olefins **1o**–**r** (Scheme 5). Bis-functionalization of the terminal olefins of amino acid derivative **1o** and sterically congested substrate **1p** smoothly proceeded using $Cl_2C(CN)_2$ **2b** to provide the radical adducts, which were converted to conjugated *E*-olefins **6b**[15] and **6c**, respectively, in two steps. The same three-step sequence achieved stereoselective introduction of the ester group to the unactivated olefin of carvone **1q** in the presence of the conjugated olefin, affording *E*-olefin **6d** as a major product. Furthermore, the cyclic internal olefin of cyclohexene **1r** was successfully converted to trisubstituted olefin **6e**. Overall, the present protocol serves as a general method for attachment of the ester group to various olefins, and is complementary to other olefinations (e.g., cross-olefin metathesis[16] and oxidative olefin cleavage/Wittig reaction[17]) because of its characteristic chemo- and regioselectivity.



Scheme 5. Three-step conversion of olefins to α,β-unsaturated esters. Reagents and conditions: (a) dichloromalononitrile **2b** (1.5–2 equiv), CuCl/dppf (1 mol%), dioxane (1 M), 3 Å MS for **1o**; (b) malononitrile (2 equiv), EtOH for **1o** or MeOH for **1p**–**r** (0.1 M); then magnesium bis(monoperoxyphthalate) hexahydrate (MMPP, 5 equiv); (c) DBU (3 equiv), THF (0.1 M).



Scheme 4. Syntheses of conjugated carbonyl compounds **4**–**6** from terminal olefin **1n**.

3. Conclusions

We have developed a chemo- and regioselective Cu(I)-promoted bis-functionalization of unactivated olefins **1** using dichloromethylcyanide derivatives **2**. The adducts **3** were selectively converted to the carbonyl-conjugated *E*-olefins **4**–**6** through exchange of the chloromethylcyanide units of **3** to the carbonyl functionalities and subsequent reconstruction of the C–C double bonds by HCl elimination. It was also found that the more electron-deficient radical species derived from Cl_3CCN **2a** and $Cl_2C(CN)_2$ **2b** exhibited higher reactivity toward non-polarized olefins than those of Cl_2CHCN **2c** and Cl_2CRCN **2d**. The present protocol enables facile preparation of various synthetically useful α,β-unsaturated carbonyl compounds, which are not readily available via other strategies. Further synthetic applications of the developed protocol are ongoing in our laboratory.

4. Experimental section

4.1. General information

All reactions sensitive to air or moisture were carried out under argon atmosphere under anhydrous conditions unless otherwise noted. Analytical TLC was performed on E. Merck silica gel 60 F254 pre-coated plates. Flash column chromatography was performed by using 40–50 μm silica gel 60N (Kanto) or 75 μm activated alumina (Wako). The ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500 (500 MHz), JNM-ECA-500 (500 MHz), and JNM-ECS-400 (400 MHz) spectrometers. Chemical shifts are reported in δ (ppm) with reference to residual solvent signals [^1H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. HRMS were recorded on a Bruker Daltonics BioTOF-Q spectrometer (ESI).

4.2. General procedure for the Cu-catalyzed addition of dichloromethylcyanide derivatives 2 to olefins 1

To a solution of CuCl (0.5 mg, 5 μmol) and dppf (2.8 mg, 5 μmol) in dioxane (0.5 mL) were added 6-(benzoyloxy)-1-hexene **1a** (104.7 μL, 0.5 mmol) and trichloroacetonitrile **2a** (250.7 μL, 2.5 mmol). The reaction mixture was degassed by freeze–thaw for three times, purged with Ar, and stirred at 100 °C for 24 h. The mixture was then filtered through a silica gel short column (AcOEt), and the filtrate was concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 10:1–3:1) to give compound **3aa** in 90% yield (156.9 mg).

*4.2.1. 5,7,7-Trichloro-7-cyanoheptyl benzoate (**3aa**).* Colorless oil; IR (neat) 2239, 1715, 1602, 1584, 1452, 1275, 1115, 784, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–2.00 (6H, m), 2.88 (1H, dd, *J*=15.2, 3.6 Hz), 3.03 (1H, dd, *J*=15.2, 8.0 Hz), 4.23 (1H, m), 4.36 (2H, t, *J*=6.0 Hz), 7.45 (2H, dd, *J*=8.0, 7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 8.04 (2H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 28.0, 38.0, 55.1, 56.4, 64.3, 66.4, 115.1, 128.4, 129.5, 130.2, 133.0, 166.6; HRMS (ESI) calcd for $C_{15}H_{16}O_2NCl_3Na$ $[M+Na]^+$ 370.0144, found 370.0145.

*4.2.2. 5,7,7-Trichloro-7-cyanoheptyl methanesulfonate (**3ba**).* Colorless oil; IR (neat) 2246, 1350, 1333, 1172, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.98 (6H, m), 2.87 (1H, dd, *J*=10.4, 3.9 Hz), 3.02 (3H, s), 3.03 (1H, dd, *J*=10.4, 8.0 Hz), 4.18–4.25 (1H, m), 4.25 (2H, t, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 28.4, 37.4, 37.6, 55.0, 56.2, 66.3, 69.2, 115.1; HRMS (ESI) calcd for $C_9H_{14}O_3NCl_3SNa$ $[M+Na]^+$ 343.9652, found 343.9651.

*4.2.3. 2,2,4-Trichloro-8-(methoxymethoxy)octanenitrile (**3ca**).* Colorless oil; IR (neat) 2246, 1148, 1111, 1044, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52–1.72 (4H, m), 1.80–1.95 (2H, m), 2.86 (1H, dd, *J*=15.3, 3.5 Hz), 3.01 (1H, dd, *J*=15.3, 8.2 Hz), 3.35 (3H, s), 3.54 (2H, t, *J*=6.0 Hz), 4.21 (1H, dddd, *J*=8.2, 8.0, 4.7, 3.5 Hz), 4.61 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 28.9, 38.2, 55.0, 55.2, 56.5, 66.4, 67.2, 96.4, 115.1; HRMS (ESI) calcd for $C_{10}H_{16}O_2NCl_3Na$ $[M+Na]^+$ 310.0139, found 310.0143.

*4.2.4. 8-((tert-Butyldimethylsilyl)oxy)-2,2,4-trichlorooctanenitrile (**3da**).* Colorless oil; IR (neat) 2246, 1102, 836, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.50–1.68 (4H, m), 1.80–1.93 (2H, m), 2.86 (1H, dd, *J*=13.0, 3.0 Hz), 3.01 (1H, dd, *J*=13.0, 7.0 Hz), 3.63 (2H, t, *J*=5.0 Hz), 4.20 (1H, dddd, *J*=7.1, 7.0, 4.2, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 22.3, 25.9, 31.8, 38.2, 55.1, 56.6, 62.6, 66.5, 115.1; HRMS (ESI) calcd for $C_{14}H_{26}ONCl_3SiNa$ $[M+Na]^+$ 380.0741, found 380.0744.

*4.2.5. 2,2,4-Trichloro-8-hydroxyoctanenitrile (**3ea**).* Colorless oil; IR (neat) 3361 (br), 2247, 1055, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40–1.72 (5H, m), 1.81–1.96 (2H, m), 2.88 (1H, dd, *J*=15.5, 3.7 Hz), 3.01 (1H, dd, *J*=15.5, 8.0 Hz), 3.68 (2H, t, *J*=6.0 Hz), 4.22 (1H, dddd, *J*=8.5, 8.0, 4.9, 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 31.7, 38.1, 55.0, 56.5, 62.4, 66.4, 115.1; HRMS (ESI) calcd for $C_8H_{12}ONCl_3Na$ $[M+Na]^+$ 265.9877, found 265.9879.

*4.2.6. tert-Butyl (5,7,7-trichloro-7-cyanoheptyl)carbamate (**3fa**).* Colorless oil; IR (neat) 3351, 2246, 1701, 1271, 1250, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.50–1.65 (4H, m), 1.79–1.92 (2H, m), 2.82–2.88 (1H, m), 2.96–3.03 (1H, m), 3.09–3.20 (2H, m), 4.14–4.23 (1H, m), 4.50–4.62 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 28.4, 29.4, 37.9, 40.2, 55.0, 56.5, 66.4, 79.2, 115.1, 156.0; HRMS (ESI) calcd for $C_{13}H_{21}O_2N_2Cl_3Na$ $[M+Na]^+$ 365.0562, found 365.0561.

*4.2.7. 8-Azido-2,2,4-trichlorooctanenitrile (**3ga**).* Colorless oil; IR (neat) 2246, 2096, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52–1.74 (4H, m), 1.80–1.96 (2H, m), 2.87 (1H, dd, *J*=13.0, 3.0 Hz), 3.02 (1H, dd, *J*=13.0, 6.7 Hz), 3.33 (2H, t, *J*=6.3 Hz), 4.21 (1H, dddd, *J*=6.7, 6.7, 3.3, 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 28.1, 37.8, 51.1, 55.0, 56.3, 66.3, 115.1; HRMS (ESI) calcd for $C_8H_{11}N_4Cl_3Na$ $[M+Na]^+$ 290.9942, found 290.9934.

*4.2.8. 2,2,4,8-Tetrachlorooctanenitrile (**3ha**).* Colorless oil; IR (neat) 2246, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–1.96 (6H, m), 2.87 (1H, dd, *J*=13.0, 3.5 Hz), 3.02 (1H, dd, *J*=13.0, 7.0 Hz), 3.56 (2H, t, *J*=5.1 Hz), 4.21 (1H, dddd, *J*=7.0, 7.0, 3.5, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 31.6, 37.5, 44.4, 54.9, 56.2, 66.3, 115.0; HRMS (ESI) calcd for $C_8H_{11}NCl_4Na$ $[M+Na]^+$ 283.9538, found 283.9539.

*4.2.9. 2,2,4-Trichlorononanedinitrile (**3ia**).* Colorless oil; IR (neat) 2248, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–2.00 (6H, m), 2.39 (2H, t, *J*=6.5 Hz), 2.85 (1H, dd, *J*=10.5, 3.9 Hz), 3.02 (1H, dd, *J*=10.5, 8.0 Hz), 4.20 (1H, dddd, *J*=8.0, 8.0, 3.9, 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 24.6, 25.0, 37.3, 54.8, 56.0, 66.2, 115.0, 119.2; HRMS (ESI) calcd for $C_9H_{11}N_2Cl_3Na$ $[M+Na]^+$ 274.9880, found 274.9870.

*4.2.10. 2,2,4-Trichloropentanedinitrile (**3ja**).* Colorless oil; IR (neat) 2250, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22 (1H, dd, *J*=15.0, 6.5 Hz), 3.35 (1H, dd, *J*=15.0, 6.8 Hz), 4.86 (1H, dd, *J*=6.8, 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 51.5, 64.0, 113.7, 114.7; HRMS (ESI) calcd for $C_5H_3N_2Cl_3Na$ $[M+Na]^+$ 218.9254, found 218.9256.

*4.2.11. 5,7-Dichloro-7,7-dicyanoheptyl benzoate (**3ab**).* Colorless oil; IR (neat) 2254, 1738, 1438, 1206, 1180, 849, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62–1.96 (6H, m), 2.75 (1H, dd, *J*=15.1, 3.5 Hz), 2.91 (1H, dd, *J*=15.1, 9.6 Hz), 4.23 (1H, dddd, *J*=9.6, 7.6, 5.0, 3.5 Hz), 4.36 (2H, t, *J*=6.5 Hz), 7.45 (2H, dd, *J*=7.8, 7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 8.05 (2H, d, *J*=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5,

27.9, 37.7, 41.4, 49.2, 55.7, 64.2, 111.1, 111.8, 128.4, 129.5, 130.2, 133.0, 166.5; HRMS (ESI) calcd for $C_{16}H_{16}O_2N_2Cl_2Na$ $[M+Na]^+$ 361.0481, found 361.0482.

*4.2.12. 5,7-Dichloro-7-cyanoheptyl benzoate (**3ac**).* Ratio of diastereomers=ca. 1:1; colorless oil; IR (neat) 2250, 1717, 1601, 1451, 1277, 714, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.90 (6H, m), 2.36–2.57 (2H, m) 4.05–4.15 (1H, m), 4.35 (2H, t, J=6.1 Hz), 4.74–4.84 (1H, m), 7.45 (2H, dd, J=8.0, 8.0 Hz), 7.56 (1H, t, J=8.0 Hz), 8.03 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) detectable signals: δ 22.7, 22.9, 28.1, 37.4, 37.7, 39.8, 40.2, 44.3, 45.0, 57.7, 58.4, 64.3, 64.4, 116.2, 116.7, 128.4, 129.5, 130.2, 133.0, 166.5; HRMS (ESI) calcd for $C_{15}H_{17}O_2NCl_2Na$ $[M+Na]^+$ 336.0529, found 336.0533.

*4.2.13. 5,7-Dichloro-7-cyano-9-phenylnonyl benzoate (**3ad**).* Ratio of diastereomers=ca. 1:1; colorless oil; IR (neat) 2250, 1718, 1601, 1452, 1314, 1276, 749, 713, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–2.05 (6H, m), 2.25–2.70 (4H, m), 2.93–3.10 (2H, m) 4.25–4.40 (3H, m), 7.17–7.25 (3H, m), 7.30–7.40 (2H, m), 7.44 (2H, dd, J=7.8, 7.8 Hz), 7.58 (1H, t, J=7.8 Hz), 8.04 (2H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) detectable signals: δ 22.57, 22.58, 27.96, 27.98, 31.2, 31.5, 38.1, 38.6, 43.6, 45.0, 49.5, 50.1, 56.8, 57.3, 58.8, 59.0, 64.3, 64.4, 117.8, 118.3, 126.60, 126.63, 128.31, 128.32, 128.4, 128.7, 129.5, 130.21, 130.23, 132.86, 132.88, 139.0, 139.1, 166.5; HRMS (ESI) calcd for $C_{23}H_{25}O_2NCl_2Na$ $[M+Na]^+$ 440.1155, found 440.1155.

*4.2.14. 3,5,5-Trichloro-5-cyano-3-methylpentyl benzoate (**3kb**).* Colorless oil; IR (neat) 2252, 1719, 1601, 1451, 1274, 1114, 807, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s), 2.41 (1H, dt, J=15.0, 6.0 Hz), 2.48 (1H, dt, J=15.0, 6.0 Hz), 2.99 (1H, d, J=15.0 Hz), 3.10 (1H, d, J=15.0 Hz), 4.61 (2H, t, J=6.0 Hz), 7.46 (2H, dd, J=7.5, 7.5 Hz), 7.59 (1H, t, J=7.5 Hz), 8.02 (2H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 39.8, 43.4, 54.2, 60.7, 66.1, 111.7, 112.0, 128.5 (overlap of two carbon signals in the phenyl group), 129.5 (overlap of three carbon signals in the phenyl group), 133.3, 166.2; HRMS (ESI) calcd for $C_{15}H_{14}O_2N_2Cl_2Na$ $[M+Na]^+$ 347.03252, found 347.0322.

*4.2.15. trans-1-Chloro-2-(dichlorocyanomethyl)cyclohexane (trans-**3lb**).* Colorless oil; IR (neat) 2250, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34–1.46 (3H, m), 1.76–1.89 (2H, m), 1.92–1.97 (1H, m), 2.33–2.43 (2H, m), 2.52 (1H, ddd, J=11.5, 10.0, 3.8 Hz), 4.00 (1H, ddd, J=11.1, 10.0, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.3, 28.3, 37.4, 47.8, 52.7, 58.5, 111.5, 112.0; HRMS (ESI) calcd for $C_9H_{10}N_2Cl_2Na$ $[M+Na]^+$ 239.0113, found 239.0115.

*4.2.16. cis-1-Chloro-2-(dichlorocyanomethyl)cyclohexane (cis-**3lb**).* Colorless oil; IR (neat) 2251, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32–1.42 (1H, m), 1.60–1.69 (1H, m), 1.74–1.87 (2H, m), 1.95–2.11 (3H, m), 2.16–2.25 (1H, m), 2.42 (1H, ddd, J=11.5, 4.0, 3.0 Hz), 4.75 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 22.3, 24.8, 34.3, 47.2, 52.0, 57.1, 110.7, 111.5; HRMS (ESI) calcd for $C_9H_{10}N_2Cl_2Na$ $[M+Na]^+$ 239.0113, found 239.0112.

*4.2.17. 2,2-Dichloro-4-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)butanenitrile (**3mb**).* Colorless oil; IR (neat) 2250, 1643, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.22 (1H, d, J=7.5 Hz), 1.31 (3H, m), 2.11–2.15 (1H, m), 2.29–2.43 (3H, m), 2.49 (1H, dt, J=7.5, 4.9 Hz), 3.01 (1H, dd, J=11.0, 0.8 Hz), 3.04 (1H, dd, J=11.0, 0.8 Hz), 5.80–5.83 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.9, 31.7, 32.0, 38.2, 39.9, 42.8, 46.4, 49.1, 112.0, 112.1, 129.2, 138.1; HRMS (ESI) calcd for $C_{14}H_{19}ON_2ClNa$ $[M+MeOH+Na]^+$ 289.1078, found 289.1077.

*4.2.18. (S)-2,2-Dichloro-4-(4-(2-chloropropan-2-yl)cyclohex-1-en-1-yl)butanenitrile (**3mb′**).* Colorless oil; IR (neat) 2250, 1662, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (1H, dddd, J=12.0, 12.0, 12.0, 5.0 Hz), 1.57 (3H, m), 1.60 (3H, m), 1.75–1.82 (1H, m), 2.04–2.13 (2H, m), 2.24–2.30 (1H, m), 2.32–2.41 (1H, m), 3.03 (2H, s), 5.96 (1H, dd, J=2.6, 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 27.7, 29.96, 29.98, 30.5, 42.9, 45.5, 49.6, 73.5, 112.2, 112.3, 128.3, 132.3; HRMS (ESI) calcd for $C_{14}H_{20}ON_2Cl_2Na$ $[M+MeOH+Na]^+$ 325.0845, found 325.0841.

*4.2.19. 2,2,4-Trichloro-6-phenylhexanenitrile (**3na**).* Colorless oil; IR (neat) 2248, 1603, 1496, 1454, 779, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09–2.22 (2H, m), 2.81 (1H, ddd, J=12.0, 7.5, 6.0 Hz), 2.89 (1H, dd, J=13.0, 3.5 Hz), 2.94 (1H, ddd, J=12.0, 7.5, 4.5 Hz), 3.04 (1H, dd, J=13.0, 7.0 Hz), 4.18 (1H, dddd, J=7.0, 7.0, 3.5, 3.5 Hz), 7.20–7.25 (3H, m), 7.29–7.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 39.9, 55.0, 55.9, 66.3, 115.1, 126.4, 128.4, 128.6, 139.8; HRMS (ESI) calcd for $C_{12}H_{12}NCl_3Na$ $[M+Na]^+$ 297.9928, found 297.9930.

*4.2.20. 2-Chloro-2-(2-chloro-4-phenylbutyl)malononitrile (**3nb**).* Colorless oil; IR (neat) 2250, 1603, 1496, 1454, 751, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (2H, ddd, J=6.8, 5.5, 5.5 Hz), 2.72 (1H, dd, J=13.0, 2.9 Hz), 2.81 (1H, dt, J=12.0, 2.9 Hz), 2.91 (1H, dd, J=13.0, 8.0 Hz), 2.95 (1H, dt, J=12.0, 5.5 Hz), 4.17 (1H, dtd, J=8.0, 5.5, 2.9 Hz), 7.19–7.23 (3H, m), 7.30–7.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 39.8, 41.4, 49.2, 55.2, 111.1, 111.8, 126.6, 128.4, 128.7, 139.4; HRMS (ESI) calcd for $C_{13}H_{12}N_2Cl_2Na$ $[M+Na]^+$ 289.0270, found 289.0257.

*4.2.21. 2,4-Dichloro-6-phenylhexanenitrile (**3nc**).* Ratio of diastereomers=ca. 1:1; colorless oil; IR (neat) 2250, 1602, 1496, 1454, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07–2.13 (2H, m), 2.37–2.51 (2H, m), 2.75–2.83 (1H, m), 2.89–2.95 (1H, m), 4.04–4.11 (1H, m), 4.76–4.83 (1H, m), 7.19–7.23 (3H, m), 7.30–7.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 32.4, 39.5, 39.7, 39.8, 40.2, 44.3, 44.9, 57.2, 58.0, 116.1, 116.7, 126.3, 126.4, 128.36, 128.38, 128.6, 128.7, 139.9, 140.0; HRMS (ESI) calcd for $C_{12}H_{13}NCl_2Na$ $[M+Na]^+$ 264.0317, found 264.0316.

*4.2.22. 2,4-Dichloro-2-phenethyl-6-phenylhexanenitrile (**3nd**).* Ratio of diastereomers=ca. 1:1; colorless oil; IR (neat) 2242, 1603, 1496, 1454, 1496, 1454, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08–2.72 (6H, m), 2.76–2.86 (1H, m), 2.89–3.10 (3H, m), 4.14–4.30 (1H, m), 7.17–7.28 (6H, m), 7.30–7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) detectable signals: δ 31.2, 31.5, 32.1, 32.2, 40.1, 40.7, 43.6, 45.0, 49.5, 50.1, 56.3, 56.9, 58.7, 58.9, 117.9, 118.4, 126.31, 126.32, 126.6, 126.7, 128.40, 128.44, 128.49, 128.58, 128.59, 128.72, 139.0, 139.1, 140.1, 140.2; HRMS (ESI) calcd for $C_{20}H_{21}NCl_2Na$ $[M+Na]^+$ 368.0943, found 368.0942.

4.3. Procedure for the reduction of 3na to 3nc

To a solution of compound **3na** (29.2 mg, 0.10 mmol) in toluene (1.0 mL) was added *n*-Bu_3P (37.5 μL, 0.15 mmol). The reaction mixture was stirred at room temperature for 15 min under Ar. After the consumption of the starting material on TLC, the mixture was diluted with H_2O and extracted with AcOEt (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 30:1–10:1) to give compound **3nc** in 76% yield (18.3 mg).

4.4. Procedure for the transformation of 3nc to 4

To a solution of compound **3nc** (24.2 mg, 0.10 mmol) in acetone (5.0 mL) was added NaI (74.9 mg, 0.50 mmol). The reaction mixture was refluxed for 72 h under Ar. After the consumption of the starting material on TLC, the mixture was diluted with H_2O and

extracted with AcOEt (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 1:1–1:3) to give compound **4** in 60% yield (9.6 mg).

*4.4.1. (E)-5-Phenylpent-2-enal (**4**).*[18] CAS [33046-84-3]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (2H, td, J=6.5, 5.7 Hz), 2.84 (2H, ddd, J=6.5 Hz), 6.14 (1H, dd, J=13.2, 6.8 Hz), 6.86 (1H, dt, J=13.2, 5.7 Hz), 7.18–7.25 (3H, m), 7.29–7.34 (2H, m), 9.49 (1H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0, 34.2, 126.4, 128.3, 128.6, 133.4, 140.2, 157.3, 194.0.

4.5. Procedure for the hydration of 3nd to 5′

To a solution of compound **3nd** (34.6 mg, 0.10 mmol) in DMSO (1.0 mL) were added 30% aqueous H_2O_2 (161.9 μL) and K_2CO_3 (13.8 mg, 0.10 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 1 h. After the consumption of the starting material, the reaction was quenched with aqueous sodium thiosulfate and the mixture was extracted with AcOEt (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 1:1–1:2) to give compound **5′** in 81% yield (29.4 mg).

*4.5.1. 2,4-Dichloro-2-phenethyl-6-phenylhexanenitrile (**5′**).* Ratio of diastereomers=ca. 1:1; colorless oil; IR (neat) 3474, 1689, 1601, 1496, 1454, 749, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97–2.20 (4H, m), 2.45–3.00 (6H, m), 4.18–4.32 (1H, m), 5.50–5.65 (1H, br s), 6.70–6.90 (1H, br s), 7.20–7.28 (6H, m), 7.30–7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) detectable signals: δ 30.6, 30.9, 32.3 32.4, 40.3, 40.7, 44.2, 45.5, 49.2, 49.3, 57.8, 58.0, 75.45, 75.53, 126.06, 126.12, 126.16, 126.18, 128.42, 128.43, 128.45, 128.47, 128.48, 128.56, 140.4, 140.5, 140.7, 140.8, 172.4, 172.6; HRMS (ESI) calcd for $C_{20}H_{23}ONCl_2Na$ $[M+Na]^+$ 386.1049, found 386.1046.

4.6. Procedure for the transformation of 5′ to 5

To a solution of compound **5′** (17.5 mg, 0.048 mmol) in AcOEt/CH_3CN/H_2O (2/2/1, 3.2 mL) was added $PhI(OAc)_2$ (77.3 mg, 0.24 mmol), and the mixture was stirred for 1.5 h. Then, aqueous Na_2CO_3 (1.0 mL) was added, and the mixture was further stirred for 24 h at 75 °C. The reaction was quenched with aqueous NH_4Cl and the mixture was extracted with AcOEt (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 1:1–1:2) to give compound **5** in 32% yield (4.0 mg).

*4.6.1. (E)-1,7-Diphenylhept-4-en-3-one (**5**).*[19] CAS [79559-59-4]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49–2.56 (2H, t, J=7.8 Hz), 2.77 (2H, t, J=6.7 Hz), 2.82–2.86 (2H, m), 2.90–2.95 (2H, m), 6.11 (1H, dd, J=13.5, 1.0 Hz), 6.84 (1H, dt, J=13.5, 6.0 Hz), 7.15–7.23 (6H, m), 7.26–7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 34.1, 34.4, 41.7, 126.1, 126.2, 128.31, 128.35, 128.46, 128.50, 130.7, 140.7, 141.2, 146.3, 199.4.

4.7. Procedure for the transformation of 3nb to 6a′

To a solution of compound **3nb** (26.7 mg, 0.10 mmol) in MeOH (1.0 mL) was added malononitrile (13.2 mg, 0.20 mmol) at 0 °C, and the mixture was stirred for 10 min. Then, MMPP (246.3 mg, 0.50 mmol) was added, and the reaction mixture was gradually warmed to room temperature and stirred for 3 h. The mixture was then filtered through a silica gel short column (AcOEt), and the filtrate was concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 20:1–10:1) to give compound **6a′** in 62% yield (14.1 mg).

*4.7.1. Methyl 3-chloro-5-phenylpentanoate (**6a′**).* Colorless oil; IR (neat) 1741, 1603, 1496, 1454, 1246, 1169, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.15 (2H, m), 2.71–2.84 (3H, m), 2.91 (1H, ddd, J=13.5, 8.9, 5.2 Hz), 3.71 (3H, s), 4.27 (1H, m), 7.19–7.23 (3H, m), 7.27–7.33 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5, 39.6, 43.5, 51.9, 57.1, 126.2, 128.48, 128.54, 140.6, 170.5; HRMS (ESI) calcd for $C_{12}H_{15}O_2ClNa$ $[M+Na]^+$ 249.0653, found 249.0654.

4.8. Procedure for the transformation of 6a′ to 6a

To a solution of compound **6a′** (9.2 mg, 0.041 mmol) in THF (0.41 mL) was added DBU (18.2 mg, 0.12 mmol) at room temperature, and the mixture was stirred for 15 min. After the consumption of the starting material on TLC, the reaction was quenched with aqueous NH_4Cl and the mixture was extracted with Et_2O (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified with a flash column chromatography (SiO_2; hexane/Et_2O 3:1–2:1) to give compound **6a** in 90% yield (7.0 mg).

*4.8.1. (E)-Methyl 5-phenylpent-2-enoate (**6a**).*[20] CAS [26429-97-0]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (2H, ddd, J=6.5, 5.8, 1.2 Hz), 2.78 (2H, t, J=6.5 Hz), 3.72 (3H, s), 5.85 (1H, dd, J=13.5, 1.2 Hz), 7.00 (1H, dt, J=13.5, 5.8 Hz), 7.17–7.22 (3H, m), 7.27–7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 34.3, 51.4, 121.4, 126.2, 128.3, 128.5, 140.7, 148.4, 167.0.

*4.8.2. (S,E)-6-tert-Butyl 1-ethyl 5-((tert-butoxycarbonyl)amino)hex-2-enedioate (**6b**).*[15] CAS [81323-60-6]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.0 Hz), 1.43 (9H, s), 1.45 (9H, s), 2.55–2.66 (1H, m), 2.65–2.73 (1H, m), 4.17 (2H, q, J=7.0 Hz), 4.32 (1H, dt, J=7.0, 6.0 Hz), 5.11 (1H, br d, J=7.0 Hz), 5.87 (1H, d, J=15.0 Hz), 6.83 (1H, dt, J=15.0, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.0, 28.3, 35.5, 52.9, 60.3, 79.9, 82.6, 124.7, 142.6, 155.0, 165.9, 170.4; $[\alpha]_D^{25}$=+6.4 (c=0.82, EtOH).

*4.8.3. (E)-Dimethyl 4,4-dimethylhex-2-enedioate (**6c**).* Colorless oil; IR (neat) 1727, 1654, 1315, 1275, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, s), 2.38 (2H, m), 3.64 (3H, s), 3.73 (3H, s), 5.77 (1H, d, J=16.0 Hz), 7.01 (1H, d, J=16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 35.9, 45.9, 51.4, 51.5, 117.8, 156.3, 167.3, 171.4; HRMS (ESI) calcd for $C_{10}H_{16}O_4Na$ $[M+Na]^+$ 223.0941, found 223.0944.

*4.8.4. (R,Z)-Methyl 3-(4-methyl-5-oxocyclohex-3-en-1-yl)but-2-enoate (**Z-6d**).* Colorless oil; IR (neat) 1713, 1674, 1641, 1209, 1155, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (3H, d, J=1.5 Hz), 1.88 (3H, d, J=1.1 Hz), 2.33–2.38 (2H, m), 2.43–2.46 (2H, m), 3.67 (3H, s), 4.38–4.48 (1H, m), 5.72 (1H, d, J=1.1 Hz), 6.73–6.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 20.7, 30.1, 36.8, 41.6, 51.0, 117.4, 135.5, 144.3, 159.2, 166.1, 198.7; HRMS (ESI) calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0992, found 231.0992.

*4.8.5. (R,E)-Methyl 3-(4-methyl-5-oxocyclohex-3-en-1-yl)but-2-enoate (**E-6d**).* Colorless oil; IR (neat) 1716, 1675, 1647, 1227, 1157, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (3H, m), 2.18 (3H, d, J=1.0 Hz), 2.30–2.49 (3H, m), 2.57 (1H, ddd, J=15.5, 3.5, 1.5 Hz), 2.76–2.85 (1H, m), 3.70 (3H, s), 5.71 (1H, dq, J=1.0, 1.0 Hz), 6.73–6.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 16.8, 30.6, 42.2, 45.0, 51.0, 115.6, 135.7, 143.7, 159.4, 167.0, 198.4; HRMS (ESI) calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0992, found 231.0993.

*4.8.6. cis-Methyl 4,5-(dimethoxycarbonyl)cyclohex-1-ene-1-carboxylate (**6e**).* Colorless oil; IR (neat) 1735, 1722, 1653, 1258, 1204, 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48–2.64 (2H, m),

2.72–2.86 (2H, m), 3.00 (1H, dt, J=3.5, 3.1 Hz), 3.12 (1H, dt, J=5.5, 3.1 Hz), 3.69 (3H, s), 3.69 (3H, s), 3.73 (3H, s), 6.94–6.97 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.2, 39.0, 39.5, 51.7, 52.01, 52.04, 128.4, 137.3, 167.0, 173.00, 173.04; HRMS (ESI) calcd for $C_{12}H_{16}O_6Na$ $[M+Na]^+$ 279.0839, found 279.0841.

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Supplementary data

Images of NMR spectra for relevant compounds (PDF). Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.089.

References and notes

1. (a) Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4; (b) Perlmutter, P. *Conjugated Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
2. For a review, see: Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366.
3. For a review of transition metal-catalyzed radical reactions in organic synthesis, see: Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.
4. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; (b) Curran, D. P. In Ref. 1a, p 715.
5. For examples of olefin functionalizations using chloroacetonitrile derivatives, see: (a) Murai, S.; Tsutsumi, S. *J. Org. Chem.* **1966**, *31*, 3000; (b) Julia, M.; Le Thuillier, G.; Saussine, L. *J. Organomet. Chem.* **1979**, *177*, 211; (c) Pews, R. G.; Lysenko, Z. *J. Org. Chem.* **1985**, *50*, 5115; (d) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533; (e) Mori, M.; Kubo, Y.; Ban, Y. *Heterocycles* **1990**, *31*, 433; (f) Dneprovskii, A. S.; Kasatochkin, A. N.; Boyarskii, V. P.; Ermoshkin, A. A.; Yakovlev, A. A. *Russ. J. Org. Chem.* **2006**, *42*, 1120; (g) Thommes, K.; Fernández-Zúmel, M. A.; Buron, C.; Godinat, A.; Scopelliti, R.; Severin, K. *Eur. J. Org. Chem.* **2011**, 249.
6. Other catalysts containing Pd, Fe, Ru, and Rh as a metal center promoted the addition, however the product yield was lower than that observed from the Cu-catalyzed reaction.
7. For examples of application of molecular sieves as basic reagents, see: (a) Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, *16*, 3979; (b) Mizuno, M.; Kobayashi, K.; Nakajima, H.; Koya, M.; Inazu, T. *Synth. Commun.* **2002**, *32*, 1665.
8. For examples of addition reactions through the generation of malononitrile radicals, see: (a) Curran, D. P.; Thoma, G. *J. Am. Chem. Soc.* **1992**, *114*, 4436; (b) Kita, Y.; Gotanda, K.; Murata, K.; Suemura, M.; Sano, A.; Yamaguchi, T.; Oka, M.; Matsugi, M. *Org. Process Res. Dev.* **1998**, *2*, 250.
9. Standard basic conditions to convert the chloromethylcyanide moiety to carbonyl group gave a complex mixture of undesired products (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675; (b) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, *13*, 121.
10. (a) Kepler, J. A.; Carroll, F. I.; Garner, R. A.; Wall, M. E. *J. Org. Chem.* **1966**, *31*, 105; (b) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323; (c) Buchstaller, H.-P.; Ebert, H. M.; Anlauf, U. *Synth. Commun.* **2001**, *31*, 1001; (d) Vágó, I.; Greiner, I. *Tetrahedron Lett.* **2002**, *43*, 6039.
11. (a) Stevens, C. L.; Coffield, T. H. *J. Am. Chem. Soc.* **1951**, *73*, 103; (b) Zhang, L.-h.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918.
12. (a) Hata, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 547; (b) Fuchs, R. Ger. Offen. DE 19912243, 1999.
13. Förster, S.; Tverskoy, O.; Helmchen, G. *Synlett* **2008**, 2803.
14. Utilization of protected hydroxymalononitriles as acyl anion equivalent, see: (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515; (b) Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73; (c) Nemoto, H.; Kawamura, T.; Kitasaki, K.; Yatsuzuka, K.; Kamiya, M.; Yoshioka, Y. *Synthesis* **2009**, 1694.
15. Ramsamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42.
16. (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (b) For a review, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.
17. For reviews on the Wittig reaction, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863; (b) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283.
18. Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988.
19. Drummond, L. J.; Sutherland, A. *Tetrahedron* **2010**, *66*, 5349.
20. Poeylaut-Palena, A. A.; Testero, S. A.; Mata, E. G. *J. Org. Chem.* **2008**, *73*, 2024.