Conjugate Addition of Dialkylaluminum Chlorides to Alkylidenemalonic Acid Derivatives

Steffen Maas, Armin Stamm, Horst Kunz*

Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10–14, D–55128 Mainz, Germany
Fax +49(6131)394786; E-mail: hokunz@mail.uni-mainz.de

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Dedicated to Professor Herbert Meier on the occasion of his 60th birthday

Abstract: Complete regioselectivity is achieved in conjugate addition reactions of dialkylaluminum chlorides with alkylidenemalonic esters, alkylidenecyanoacetates, and alkylidenemalonodinitrile to give β-branched carboxylic acid derivatives. Sterically demanding products containing quaternary carbon atoms are obtained in good yields. In the case of diethylaluminum chloride, accompanying reductions of the substrates can be suppressed by application of boron trifluoride as an assisting Lewis acid.

Key words: Michael addition, organoaluminum halides, β-branched carboxylic acids and nitriles, regioselective addition to enolates, quaternary carbons, organometallic reagents

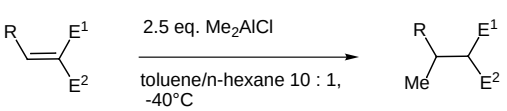
The 1,4-conjugate addition of carbanions to activated alkenes is an important carbon–carbon bond forming reaction. While the addition of stabilized carbanions, e.g. enolates (Michael addition) usually occurs with complete 1,4-regioselectivity,[1] addition reactions of organometallic compounds transferring non-stabilized alkyl (or aryl) groups to enones and enoate often suffer from accompanying side reactions. As a rule, organolithium compounds undergo 1,2-addition to α,β-unsaturated carbonyl compounds and carboxylic esters. With less reactive salts and secondary amides of cinnamic-type carboxylic acids, they produce mixtures of Michael and "contra-Michael" adducts.[2]

Like those of organolithium compounds, the reactions of Grignard reagents with α,β-unsaturated carbonyl compounds generally afford 1,2-addition products. Conjugate 1,4-addition of Grignard reagents occurs with unsaturated *N*,*N*-disubstituted amides as the substrates.[3] This reaction was extended to diastereoselective formations of β-branched carboxylic acid derivatives,[4] however, this strategy needs subsequent cleavage of the stable amide groups prior to further chemical transformations. Regioselective 1,4-addition was also reported for reactions of Grignard reagents with alkylidenemalonates and -cyanoacetates.[3,5,6] If ethyl- and higher alkylmagnesium halides are used, Grignard reduction occurs to a considerable extent.[5a,b] In the case of phenylmagnesium bromide, polymerization of the alkylidenemalonates was found to be a serious problem.[5] Organocopper intermediates are the reactive species in the copper-catalyzed Grignard additions to enones, enolates and doubly activated alkenes which often proceed with high 1,4-regioselectivity.[7,8] Organocuprates are the most widely applied reagents in order to achieve a selective 1,4- versus the 1,2-mode of addition to α,β-unsaturated carbonyl compounds,[9] although some limitations on their thermal stability and ligand transfer efficiency have been recognized.

The 1,4-addition of alkyl- or arylaluminum compounds to enones is only achieved under special conditions. The transfer of a methyl group from trimethylaluminum[10] or an aryl group from aryldimethylaluminum[11] requires catalytic amounts of low valent nickel, while the conjugate addition of tripropylaluminum to cyclohexenone needs photochemical activation.[12] Alkenyl- and alkynylaluminum reagents are more reactive and deliver the alkenyl[13] or alkynyl group[14] efficiently to Michael acceptors.

Conjugate 1,4-additions of alkyl and aryl groups have been achieved efficiently and with high diastereoselectivity in reactions of α,β-unsaturated *N*-acyloxazolidinones[15] and -oxazinones[16] with dialkyl- or diarylaluminum chlorides. A marked contrast between dimethyl- and higher dialkylaluminum chlorides was observed in these processes. While the latter react at –78°C in toluene/hexane or dichloromethane, dimethylaluminum chloride undergoes 1,4-addition only after photochemical activation or radical initiation.[15,16]

We report here on an efficient regioselective 1,4-addition of dialkylaluminum chlorides which neither needs special conditions nor *N*-acylurethanes as substrates. Alkylidenemalonic esters, alkylidenecyanoacetates and alkylidenemalonodinitrile are used as the acceptors to yield the corresponding β-branched alkyl derivatives which are useful precursors of β-branched carboxylic acids or nitriles and their conversion products. As shown in Scheme 1 for dimethylaluminum chloride, the 1,4-addition to these acceptors **1, 2** or **3** proceeds in toluene at –40°C to furnish the corresponding β-branched products **4, 5** or **6**, respectively, in high yield (Table 1).



1 $E^1 = E^2$ = COOEt
2 E^1 = CN; E^2 = COOEt
3 $E^1 = E^2$ = CN

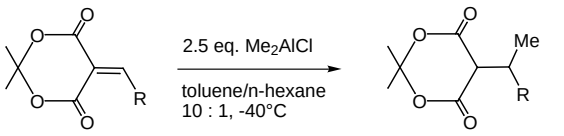
4 $E^1 = E^2$ = COOEt
5 E^1 = CN; E^2 = COOEt
6 $E^1 = E^2$ = CN

Scheme 1

Table 1 Conjugate Addition of Me_2AlCl to Malonic Acid Derivatives **1**, **2** and **3**

Substrate	R	Reaction Time (h)	Product	Yield (%)
1a	CH_3	15	**4a**	84
1b	CH_2CH_3	16	**4b**	79
1c	$CH(CH_3)_2$	20	**4c**	100
1d	$CH_2CH(CH_3)_2$	18	**4d**	79
1e	*c*-C_6H_{11}	15	**4e**	81
1f	$C(CH_3)_3$	18	**4f**	63
1g	C_6H_5	6	**4g**	100
2a	$CH(CH_3)_2$	16	**5a**	81
2b	$C(CH_3)_3$	18	**5b**	77
3	$CH(CH_3)_2$	17	**6**	73

In contrast to the corresponding reactions with the *N*-acylurethane-type acceptors, no photochemical activation, radical initiation or transition metal catalysis is required. Branching in γ-position (**1c**, **1e**, **2a**) does not hinder the conversion. Even with the *tert*-butyl substituted alkylidenemalonate **1f** and -cyanoacetate **2b**, the 1,4-adducts **4f** and **5b** are obtained in good yield. Benzylidenemalonate **1g** is slightly more reactive than the other alkylidenemalonates presumably because of its lower LUMO. The reactivity of the isobutylidenemalonodinitrile **3** is not significantly different from those of the corresponding malonate **1c** and cyanoacetate **2a**. Knoevenagel products of Meldrum acid **7** also smoothly undergo 1,4-addition of dimethylaluminum chloride to yield branched-chain compounds **8** in high yield (Scheme 2).



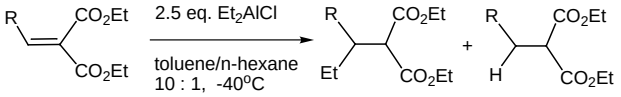
7a R = Ph
7b R = $CHMe_2$

8a R = Ph; 88%
8b R = $CHMe_2$; 93%

Scheme 2

The reaction of diethylaluminum chloride as an example of higher alkylaluminum chlorides with Michael acceptors **1** first was investigated under conditions identical to those applied in the addition reactions of dimethylaluminum chloride (Scheme 3).

Selective conjugate addition and high yields of 1,4-adducts are obtained with non-branched alkylidenemalonic esters (**1a, 1b**). Analogous conversions of substrates containing branching in γ-position (**1c, 1e, 1f**) result in accompanying formations of byproducts formed by β-hydride transfer and release of ethylene (Table 2).

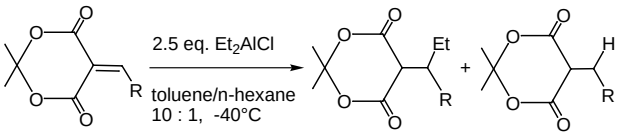


9 **10**

Scheme 3

The results given in Table 2 show that δ-branching in substrate **1d** also affects the selectivity of the addition reaction, while the phenyl group in benzylidenemalonate **1g** does not exert sterical hindrance. The (1-phenyl)propylmalonic ester **9g** is obtained almost quantitatively.

The reaction of diethylaluminum chloride to alkylidene-Meldrum acids **7** shows the same feature. Complete selective 1,4-addition occurs with benzylidene-Meldrum acid **7a**, whereas the reaction with the isobutylidene derivative **7b** produces a mixture of the 1,4-adduct **11b** and the reduced compound **12b** (Scheme 4).



7a,b

11a R = Ph; 83%
11b R = $CHMe_2$; 63%

12a
12b

ratio **11a**/**12a** 100:0
ratio **11b**/**12b** 77:23

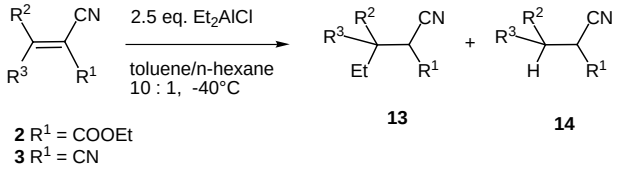
Scheme 4

Table 2 Conjugate Addition of Et_2AlCl to Alkylidene Malonic Esters **1**

Substrate	R	Reaction Time (h)	Product Ratio **9**/**10**[a]	Product	Yield (%)
1a	CH_3	14	100:0	**9a**	88
1b	CH_2CH_3	16	100:0	**9b**	82
1c	$CH(CH_3)_2$	22	33:67	**9c**/**10c**[c]	95
1d	$CH_2CH(CH_3)_2$	15	88:12[b]	**9d**/**10d**[c]	50
1e	*c*-C_6H_{11}	15	42:58[b]	**9e**/**10e**[c]	29
1f	$C(CH_3)_3$	16	38:62[b]	**9f**	19
1g	C_6H_5	21	100:0	**9g**	100

[a] Determined by ^1H NMR spectra.
[b] Additionally determined by gas chromatography.
[c] Not separable.

The most selective reaction is observed if alkylidenecyanoacetates **2** are used as the acceptors (Scheme 5). In no case (Table 3) was the formation of the reduced acceptor **14** found.



Scheme 5

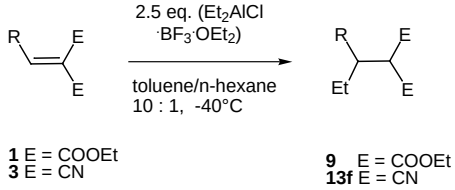
Results given in Table 3 also illustrate, that acceptors **2** carrying two substituents in β-position (**2c, 2d, 2e**) are converted completely selectively into the 1,4-adducts **13c**, **13d** or **13e**, respectively, all containing a newly formed quaternary carbon atom.

It appears particularly remarkable that the conjugate adduct **13e** which contains a γ-branching next to the quaternary carbon in β-position is formed without accompanying reduction of the substrate. Nevertheless, the sterical hindrance in this conjugate addition must be overcome by a long reaction time although excess of the diethylaluminum chloride is used.

In general, the described conjugate additions proceed with one equivalent of the organoaluminum chloride. In order to accelerate the reactions, 2.5 equivalents are uniformly applied. It is astonishing that isobutylidenemalonodinitrile **3** carrying two slim electron-withdrawing groups reacts with lower chemoselectivity compared to the cyanoacetates **2**.

In order to improve the ratio of the 1,4-addition versus reduction for alkylidenemalonic esters **1** and the dinitrile **3**, the influence of the solvent on the reaction of diethylaluminum chloride with isobutylidenemalonic ester **1c** was investigated. Addition of one equivalent of diethyl ether (related in the amount of) Et_2AlCl slightly changes the ratio of products **9c**/**10c** from 1:2 (Table 2) to 1:1. If the reaction is carried out in diethyl ether instead of toluene, preferred formation of the 1,4-addition product **9c** is achieved (ratio **9c**/**10c** = 4:1). The obvious influence of the donor quality of the solvent on the chemoselectivity of the conjugate addition can be rationalized by the breaking effect of Lewis basic donors on organoaluminum chloride aggregates present in non-polar solutions.[10] Complexation of the substrates **1** or **3** by boron trifluoride etherate prior to addition of the diethylaluminum chloride markedly improved the chemoselectivity of the reaction in favour of preferred formation of the 1,4-conjugate adducts. The β-ethyl branched malonate **9d** and malonodinitrile **13f** were formed with complete selectivity and isolated in yields of 73 and 92%, respectively. The more hindered malonates **1c, 1e** and **1f** gave ratios for **9**/**10** of about 10:1 to 20:1. In spite of this improved chemoselectivity the byproducts **10** have to be separated by chromatography in these cases.

Therefore, we were interested in a completely chemoselective 1,4-addition of diethylaluminum chloride even to these sterically more demanding alkylidenemalonates **1**. Because neither coordination of diethyl ether to the organoaluminum reagent nor that of boron trifluoride to the substrates resulted in the desired effect, diethylaluminum chloride itself was pretreated with equimolar amounts of boron trifluoride etherate in toluene at –40°C for 2 hours. After additon of the alkylidenemalonates **1** complete chemoselective 1,4-addition of the ethyl group is achieved (Scheme 6, Table 4).



Scheme 6

Table 3 Conjugate 1,4-Addition of Et_2AlCl to Alkylidene Cyanoacetates **2** and Malonodinitrile **3**

Substrate	R^1	R^2	R^3	Reaction Time (h)	Product Ratio **13**/**14**[a]	Product	Yield (%)
2a	CO_2Et	$CH(CH_3)_2$	H	16	100:0	**13a**	81
2b	CO_2Et	$C(CH_3)_3$	H	18	100:0	**13b**	85
2c	CO_2Et	CH_3	CH_3	40	100:0	**13c**	65
2d	CO_2Et	CH_2CH_3	CH_3	44	100:0	**13d**	88
2e	CO_2Et	$CH(CH_3)_2$	CH_3	168	100:0	**13e**	87
3	CN	$CH(CH_3)_2$	H	17	94:6	**13f**	67

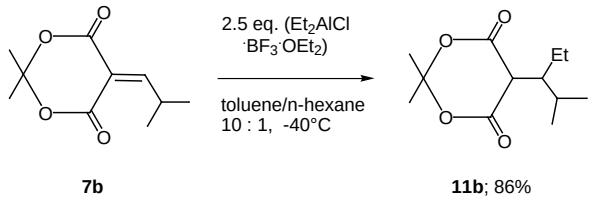
[a] Determined by ^1H NMR spectra.

Compared to the results obtained with diethylaluminum chloride alone (Table 2), the effect of boron trifluoride on the chemoselectivity is decisive. Without BF_3•OEt_2 (Table 2), the reaction of Et_2AlCl with all three acceptors **1c, 1e** and **1f** yields mixtures of 1,4-adduct **9** and prevailing reduction product **10**. In contrast, after pretreatment with BF_3•OEt_2 the conjugate additon of Et_2AlCl furnishes selectively the 1,4-adducts **9** (Table 4).

We assume that BF_3 forms heterodimeric complexes with Et_2AlCl and thus breaks the oligomeric structures of the organoaluminum reagents. The heterodimeric Et_2AlCl•BF_3 complexes are responsible for the chemo- and regioselective 1,4-addition of the dialkylaluminum chloride even to sterically hindered acceptors. This conclusion is confirmed by the reaction of Et_2AlCl•BF_3 with isobutylidene Medrum acid **7b** giving selectively the conjugate adduct **11b**.

Table 4 Conjugate 1,4-Addition of Et_2AlCl Pretreated with Equimolar $BF_3{\cdot}OEt_2$

Substrate	R	Reaction Time (h)	Product	Yield (%)
1c	$CH(CH_3)_2$	18	**9c**	93
1d	$CH_2CH(CH_3)_2$	16	**9d**	73
1e	*c*-C_6H_{11}	20	**9e**	93
1f	$C(CH_3)_3$	20	**9f**	87
3	$CH(CH_3)_2$	16	**13f**	92



7b **11b**; 86%

Scheme 7

Comparison of this result with that shown in Scheme 4 also illustrates the general efficiency of the novel reaction in this optimized modification for the conjugate addition of alkyl groups to alkylidenemalonic acid derivatives. The reactions are conveniently carried out in homogenous solution and do not need assistance by transition metal components. Compounds containing multiple branchings or quaternary carbon centers are efficiently accessible.

Toluene and Et_2O were dried before use by distillation from potassium/benzophenone ketyl. Alkylidenemalonic diethyl esters **1**, alkylidene-Meldrum acids **7**, ethyl alkylidenecyanoacetates **2** and isobutylidenemalonodinitrile **3** were synthesized according to published procedures.[17] Dimethyl- and diethylaluminum chloride were purchased from Aldrich and used as 1 M solutions in hexane. Petroleum ether refers to the fraction with bp 40–70°C. Flash chromatography was carried out using silica gel 60 (Merck, Darmstadt, Germany), 0.04–0.063 nm. TLC was performed on silica gel (Kieselgel 60 F_{254}, Merck, Darmstadt, Germany). Gas chromatography was carried out with a fused silica-column (PERMABOND SE-30-DF-0.25, 25m × 0.32mm ID, Machery & Nagel, Düren, Germany).

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 or on a Bruker AM 400 NMR spectrometer. All NMR spectra were recorded in $CDCl_3$ using TMS as the standard. Melting points are uncorrected. Satisfactory micoanalyses were obtained for all new compounds and those incompletely characterized in the literature.

Conjugate Addition of Dimethylaluminum Chloride or Diethylaluminum Chloride to Malonic Acid Derivatives 1, 2, or 3; General Procedure

Anhyd toluene (50 mL) was distilled into a two-neck flask under argon atmosphere. After addition of the alkylidenemalonic acid derivative **1**, **2**, **3** or **7**, respectively (3 mmol), the mixture was cooled to –40°C. The dialkylaluminum chloride (7.5 mmol; 7.5 mL of a 1 M solution in hexane) was injected by a syringe. After stirring for the reaction time given in Table 1, 2 or 3 (TLC monitoring), aq sat. NH_4Cl solution (100 mL) was added. After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with NH_4Cl solution (50 mL) and dried ($MgSO_4$). The solvent was removed by distillation and the crude product purified by flash chromatography using petroleum ether (PE)/EtOAc (20:1) as eluent (Tables 1–3).

Characteristic ^1H NMR signals of all malonic esters **4**, **9** and **10**: δ = 1.20–1.22 (t, 3 H, *J* = 7.0–7.2 Hz, C*H*$_3$CH$_2$O), 4.11–4.14 (q, 4 H, *J* = 7.0–7.2 Hz, CH$_3$C*H*$_2$O), and for cyanoacetic esters **5** and **13**: δ = 1.27–1.29 (t, 3 H, *J* = 7.0–7.3 Hz, C*H*$_3$CH$_2$O), 4.20–4.22 (q, 2 H, *J* = 7.1 Hz, CH$_3$C*H*$_2$O).

Diethyl Isopropylmalonate (4a)[19]
Colorless oil; R_f 0.36 (PE/EtOAc, 10:1).

^1H NMR: δ = 0.95 (d, 6 H, *J* = 6.8 Hz, CH_3), 3.05 [d, 1 H, *J* = 8.8 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 14.0 (*C*H$_3$CH$_2$O), 20.3 (CH*C*H$_3$), 28.6 (*C*HMe$_2$), 59.1 [*C*H(CO$_2$Et)$_2$], 60.9 (CH$_2$O), 168.7 (C=O).

Diethyl (1-Methylpropyl)malonate (4b)[18]
Colorless oil; R_f 0.49 (PE/EtOAc, 10:1).

^1H NMR: δ = 0.84 (t, 3 H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.91 (d, 3 H, *J* = 6.8 Hz, C*H*$_3$CH), 3.16 [d, 1 H, *J* = 8.3 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 11.1 (*C*H$_3$CH$_2$), 14.0 (*C*H$_3$CH$_2$O), 16.4 (*C*H$_3$CH), 57.5 [*C*H(CO$_2$Et)$_2$], 60.9, 61.0 (CH$_2$O), 168.7, 168.9 (C=O).

Diethyl (1,2-Dimethylpropyl)malonate (4c)[19]
Colorless oil; R_f 0.63 (PE/EtOAc, 5:1).

^1H NMR: δ = 0.79 [d, 3 H, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$], 0.85 [d, 3 H, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$], 0.92 (d, 3 H, *J* = 6.8 Hz, CHC*H*$_3$), 1.66 (m, 1 H, C*H*Me$_2$), 3.31 [d, 1 H, *J* = 9.4 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 11.4, 13.7, 16.3, 20.9 (CH$_3$), 60.7, 60.8 (CH$_2$O), 168.6, 168.8, (C=O).

Diethyl (1,3-Dimethylbutyl)malonate (4d)
Colorless oil, R_f 0.44 (PE/EE 10:1).

^1H NMR: δ = 0.83 and 0.84 each [d, 3 H, *J* = 6.5 Hz, CH(C*H*$_3$)$_2$], 0.92 (d, 3 H, *J* = 6.8 Hz, CHC*H*$_3$), 3.15 [d, 1 H, *J* = 7.9 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 14.1 (*C*H$_3$CH$_2$O), 17.0, 21.6, 23.6 (CH$_3$), 60.9, 61.0 (CH$_2$O), 168.8, 168.9 (C=O).

Diethyl (1-Cyclohexylethyl)malonate (4e)[20]
Colorless oil; R_f 0.40 (PE/EtOAc, 10:1).

^1H NMR: δ = 0.85 (d, 3 H, *J* = 6.9 Hz, CHC*H*$_3$), 2.12 (m, 1 H, C*H*Me), 3.34 [d, 1 H, *J* = 9.2 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 12.9 (CH$_3$), 14.1 (*C*H$_3$CH$_2$O), 26.4, 26.5, 26.7, 27.6, 31.5, 38.5 (*c*-C_6H_{11}), 60.9, 61.0 (CH$_2$O), 169.0 169.2 (C=O).

Diethyl (1,2,2-Trimethylpropyl)malonate (4f)[19]
Colorless oil; R_f 0.37 (PE/EtOAc, 10:1).

^1H NMR: δ = 0.84 [s, 9 H, C(CH$_3$)$_3$], 0.95 (d, 3 H, *J* = 7.3 Hz, CHC*H*$_3$), 3.45 [d, 1 H, *J* = 5.4 Hz, C*H*(CO$_2$Et)$_2$].

^{13}C NMR: δ = 12.0 (CH$_3$), 14.0 (*C*H$_3$CH$_2$O), 27.5 [C(*C*H$_3$)$_3$], 33.6 (*C*Me$_3$), 42.6 (*C*HMe), 60.8, 61.2 (CH$_2$O), 169.4, 170.1 (C=O).

Diethyl (1-Phenylethyl)malonate (4g)[18]
Colorless oil; R_f 0.60 (PE/EtOAc, 5:1).

^1H NMR: δ = 3.45–3.60 [m, 2 H, C*H*(CO$_2$Et)$_2$, C*H*Ph], 3.89 (q, 2 H, *J* = 7.2 Hz, CH$_2$O), 4.21 (q, 2 H, *J* = 7.2 Hz, CH$_2$O), 7.07–7.30 (m, 5 H, C_6H_5).

^{13}C NMR: δ = 13.7, 14.1 (*C*H$_3$CH$_2$O), 20.1 (CH$_3$), 40.0 (*C*HPh), 61.0, 61.4 (CH$_2$O), 143.2 (C-*ipso*, C_6H_5), 167.9, 168.4 (C=O).

Ethyl 2-Cyano-3,4-dimethylpentanoate (5a)
Colorless oil; R_f 0.32 (PE/EtOAc, 10:1); mixture of diastereomers.

^{1}H NMR: δ = 0.85 and 1.01 each (d, 3 H, *J* = 6.8 Hz, 3-CH_3), 0.93 [m, 6 H, CH(CH_3)$_2$], 1.62 (m, 1 H, H-3), 1.91 (m, 1 H, H-4), 3.35 and 3.60 each (d, 1 H, *J* = 4.7 and 7.6 Hz, C*H*CO_2Et].

^{13}C NMR: δ = 13.4, 13.9 (*C*H_3CH_2O), 42.1, 42.7 (*C*HCO_2Et), 62.4, 62.5 (CH_2O), 115.4, 116.1 (CN), 165.9, 166.4 (C=O).

Ethyl 2-Cyano-3,4,4-trimethylpentanoate (5b)[21]
Colorless oil; R_f 0.35 (PE/EtOAc, 10:1); mixture of diastereomers.

^{1}H NMR: δ = 0.94, 0.95 each [s, 9 H, C$(CH_3)_3$], 1.06 (d, 3 H, *J* = 7.0 Hz, CH_3CH), 1.99 and 2.12 each (dq, 1 H, *J* = 2.1 and 5.0 Hz, C*H*Bu-*t*), 3.47 and 3.66 each (d, 1 H, *J* = 2.1 and *J* = 5.0 Hz, C*H*CO_2Et).

^{13}C NMR: δ = 27.4, 27.6 C(*C*H_3)$_3$, 33.4, 33.9 *C*$(CH_3)_3$, 39.8, 40.4 (*C*HBu-*t*), 43.8, 44.7 (*C*HCO_2Et), 62.4, 62.7 (CH_2O), 116.1, 117.4 (CN), 166.4, 167.0 (C=O).

(1,2-Dimethylpropyl)malonodinitrile (6)
Colorless oil; R_f 0.26 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.93–1.01 [m, 6 H, CH(CH_3)$_2$], 1.20 (d, 3 H, *J* = 5.6 Hz, CHCH_3), 3.75 [dd, 1 H, ^3J = 5.6 Hz, ^4J = 1.2 Hz, CH$(CN)_2$].

^{13}C NMR: δ = 13.5, 18.0, 20.6 (CH_3), 27.5 (*C*HMe_2), 30.4 (C-β), 41.4 (CCN), 111.9, 112.8 (CN).

2,2-Dimethyl-5-(1-phenylethyl)1,3-dioxane-4,6-dione (8a)[22]
Yield: 88%; colorless crystals; mp 101°C (); R_f 0.25 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 3.68 [d, 1 H, *J* = 3.2 Hz, CH$(CO)_2$], 3.98 (dq, 1 H, *J* = 7.3, 3.0 Hz, C*H*Ph), 7.20–7.34 (m, 5 H, C_6H_5).

^{13}C NMR: δ = 17.8 (CH_3), 28.0, 28.3 [C(*C*H_3)$_2$], 38.7 (*C*HPh), 105.2 [*C*$(CH_3)_2$], 164.7, 165.0 (C=O).

2,2-Dimethyl-5-(1,2-dimethylpropyl)-1,3-dioxane-4,6-dione (8b)

Yield: 93%; colorless crystals; mp 89°C (PE/EtOAc); R_f 0.18 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.89 [d, 3 H, *J* = 7.1 Hz, CH(*C*H_3)$_2$], 0.91 [d, 3 H, *J* = 6.7 Hz, CH(CH_3)$_2$], 1.00 (d, 3 H, *J* = 6.7 Hz, CH_3), 1.69 and 1.70 each [s, 3 H, C$(CH_3)_2$], 2.02 (m, 1 H, C*H*Me_2), 2.16 (m, 1 H, C*H*CH_3), 3.55 [d, 1 H, *J* = 2.9 Hz, CH$(CO)_2$].

^{13}C NMR: δ = 15.1, 20.9, 21.3, (CH_3), 27.8, 28.2 [C(*C*H_3)$_2$], 41.3 (*C*HMe), 48.8 [*C*H$(CO)_2$], 104.6 (*C*Me_2), 164.7, 166.3 (C=O).

Diethyl (1-Methylpropyl)malonate (9a)
Identical to **4b**; R_f 0.49 (PE/EtOAc, 10:1).

Diethyl (1-Ethylpropyl)malonate (9b)[23]
Colorless oil; R_f 0.55 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.83 (t, 6 H, *J* = 7.5 Hz, C$H_3$$CH_2$CH), 2.00 (m, 1 H, C*H*$Et_2$), 3.34 [d, 1 H, *J* = 8.1 Hz, C*H*$(CO_2Et)_2$].

^{13}C NMR. δ = 10.8 (CH_3), 14.0 (*C*H_3CH_2O), 23.0 (CH_2), 40.9 (*C*HEt_2), 55.1 [*C*H$(CO_2Et)_2$], 60.9 (CH_2O), 169.0 (C=O).

Diethyl (1-Phenylpropyl)malonate (9g)[24]
Colorless oil; R_f 0.60 (PE/EtOAc, 5:1).

^{1}H NMR: δ = 0.68 (t, 3 H, *J* = 6.0 Hz, C$H_3$$CH_2$CH), 3.22 (dt, 1 H, *J* = 3.7, 10.9 Hz, C*H*Ph), 3.60 [d, 1 H, *J* = 11.0 Hz, C*H*$(CO_2Et)_2$], 3.84 (q, 2 H, *J* = 7.1 Hz, CH_2O), 4.19 (q, 2 H, *J* = 7.1 Hz, CH_2O), 7.11–7.26 (m, 5 H, C_6H_5).

^{13}C NMR: δ = 11.7 (CH_3), 13.6, 14.1 (*C*H_3CH_2O), 47.3 (*C*HPh), 61.0, 61.4 (CH_2O), 140.6 (C-*ipso*, C_6H_5), 167.8, 168.5 (C=O).

2,2-Dimethyl-5-(1-phenylpropyl)-1,3-dioxane-4,6-dione (11a)
Yield: 83%; colorless oil; R_f 0.46 (PE/EtOAc, 5:1).

^{1}H NMR: δ = 0.91 (t, 3 H, *J* = 7.3 Hz, C$H_3$$CH_2$), 1.09 [s, 3 H, $(CH_3)_2$C], 1.59 [s, 3 H, $(CH_3)_2$C], 3.62 (m, 1 H, C*H*Ph), 3.70 [d, 1 H, *J* = 3.2 Hz, C*H*$(CO)_2$], 7.15–7.31 (m, 5 H, C_6H_5).

^{13}C NMR: δ = 12.4 (CH_3), 25.6 (*C*H_2CH_3), 27.9, 28.3 [C(*C*H_3)$_2$], 48.1 (*C*HPh), 50.9 [*C*H$(CO)_2$], 105.3 (*C*Me_2), 139.5 (C-*ipso*, C_6H_5), 164.6, 165.8 (C=O).

2,2-Dimethyl-5-(1-ethyl-2-methylpropyl)-1,3-dioxane-4,6-dione (11b)
Separated from **12b** by flash chromatography; yield: 63%; colorless crystals; mp 54°C (PE/EtOAc); R_f 0.14 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.86–0.97 (m, 9 H, CH_3), 1.73 [s, 6 H, $(CH_3)_2$C], 2.18 (m, 1 H, C*H*Et), 3.49 [d, 1 H, *J* = 2.5 Hz, CH$(CO)_2$].

^{13}C NMR: δ = 15.1, 20.9, 21.3 (CH_3), 23.3 (CH_2), 27.6, 28.1 [C(*C*H_3)$_2$], 30.2 (*C*HMe_2), 46.2 (*C*HEt), 47.9 [*C*H$(CO)_2$], 104.7 (*C*Me_2), 166.1 (C=O).

2,2-Dimethyl-5-(2-methylpropyl)-1,3-dioxane-4,6-dione (12b)[22]
Separated from **11b**; yield: 23%; colorless crystals; mp 120°C (PE/EtOAc); R_f 0.18 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.89 (d, 6 H, *J* = 6.4 Hz, CH_3), 1.70 [s, 3 H, $(CH_3)_2$C], 1.75 [s, 3 H, $(CH_3)_2$C], 1.92–2.07 (m, 3 H, CH_2, C*H*Me_2), 3.42 [t, 1 H, *J* = 5.4 Hz, CH$(CO)_2$].

^{13}C NMR: δ = 22.1 (CH_3), 25.9 (*C*HMe_2), 26.8, 28.6 [C(*C*H_3)$_2$], 44.2 [*C*H$(CO)_2$], 35.3 (CH_2), 104.8 (*C*Me_2), 166.0 (C=O).

Ethyl 2-Cyano-3-ethyl-4-methylpentanoate (13a)
Colorless oil; mixture of diastereomers; R_f 0.30 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.87–0.97 (m, 9 H, CH_3) 1.25–1.95 (m, 4 H, C*H*Et, CH_2, C*H*Me_2), 3.59 and 3.60 each (d, 1 H, *J* = 5.4 and 6.8 Hz, C*H*CO_2Et).

^{13}C NMR: δ = 11.9, 12.1 (CH_3), 13.9 (*C*H_3CH_2O), 18.5, 19.2 (CH_3), 20.2, 21.2 (CH_3), 21.5, 22.6 (CH_2), 39.5, 40.3 (*C*HEt), 46.7, 46.8 (*C*HCO_2Et), 62.5, 62.6 (CH_2O), 115.9, 116.1 (CN), 166.8, 167.0 (C=O).

Ethyl 2-Cyano-3-ethyl-4,4-dimethylpentanoate (13b)
Colorless oil; mixture of diastereomers; R_f 0.35 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.87 (t, 3 H, *J* = 7.5 Hz, CH_3), 0.96 and 0.97 each [s, 9 H, C$(CH_3)_3$], 1.53–1.75 (m, 2 H, CH_2), 1.89–1.95 (m, 1 H, C*H*Bu-*t*), 3.61 and 3.69 each (d, 1 H, J = 1.0 and 3.0 Hz, C*H*CO_2Et).

^{13}C NMR: δ = 13.1, 13.2 (CH_3). 13.8, 13.9 (*C*H_3CH_2O) 20.9, 21.7 (CH_2), 27.8, 28.0 [C(*C*H_3)$_3$], 34.0, 34.4 (*C*Me_3), 37.8, 38.5 (*C*HBu-*t*), 50.7, 51.3 (*C*HCO_2Et), 62.6, 62.7 (CH_2O), 116.2, 116.6 (CN), 167.4, 167.6 (C=O).

Ethyl 2-Cyano-3,3-dimethylpentanoate (13c)
Colorless oil; R_f 0.35 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.86 (t, 3 H, CH_2CH_3),1.04 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.46 (m, 2 H, CH_2), 3.31 (s, 1 H, C*H*CO_2Et).

^{13}C NMR: δ = 8.1 (*C*H_3CH_2C) 14.0 (*C*H_3CH_2O), 24.1, 24.7 (CH_3), 33.0 (CH_2), 37.7 (Et*C*Me_2), 47.8 (*C*HCO_2Et), 62.3 (CH_2O), 116.0 (CN), 165.4 (C=O).

Ethyl 2-Cyano-3-ethyl-3-methylpentanoate (13d)
Colorless oil; R_f 0.41 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.83 (t, 3 H, *J* = 7.6 Hz, C$H_3$$CH_2$), 0.84 (t, 3 H, *J* = 7.3 Hz, C$H_3$$CH_2$), 1.04 (s, 3 H, CH_3), 1.39 (dq, 2 H, *J* = 7.5, 1.7 Hz, CH_2), 1.50 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.41 (s, 1 H, C*H*CO_2Et).

^{13}C NMR: δ = 7.6, 7.8 [(*C*$H_3CH_2)_2$C] 13.9 (*C*H_3CH_2O), 21.7 (CH_3), 28.8 (CH_2), 29.5 (CH_2), 40.3 (Et_2*C*Me), 46.1 (*C*HCO_2Et), 62.2 (CH_2O), 116.1 (CN), 165.5 (C=O).

Ethyl 2-Cyano-3-ethyl-3,4-dimethylpentanoate (13e)
Colorless oil; mixture of diastereomers; R_f 0.43 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.81–1.09 (m, 12 H, CH_3), 1.37–2.03 (m, 3 H, CH_2, C*H*Me), 3.46 and 3.49 each (s, 1 H, C*H*CO_2Et).

^{13}C NMR: δ = 8.3, 8.4 (*C*H_3CH_2). 14.0 (*C*H_3CH_2O), 17.2, 17.4, 17.6, 20.0, 20.9 (CH_3), 28.0, 29.3, 32.7, 34.2 (*C*HMe_2, CH_2), 42.9, 43.1 (*i*-Pr*C*MeEt), 44.8, 45.0 (*C*HCO_2Et), 62.9 (CH_2O), 116.7 (CN), 166.0 (C=O).

(1-Ethyl-2-methylpropyl)malonodinitrile (13f)
Yield: 67%; separated from **14** by flash chromatography; colorless oil; R_f 0.30 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 1.00 [d, 6 H, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$], 1.04, (t, 3 H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 1.52–2.05 (m, 4 H, CH_2, C*H*Et, C*H*Me_2), 3.82 (d, 1 H, *J* = 3.9 Hz, CHCN).

^{13}C NMR: δ = 11.8, 19.0, 19.8 (CH_3), 21.8 (CH_2), 24.7 (*C*HMe_2), 29.6 (*C*HEt), 47.4 (*C*HCN), 112.5, 112.9 (CN)

(2-Methylpropyl)malonodinitrile (14)
Separated from **13f**; yield: 5.6%; colorless oil; R_f 0.24 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.98 [d, 6 H, *J* = 6.4 Hz (CH(C*H*$_3$)$_2$], 1.78–1.97 (m, 3 H, CH_2, C*H*Me_2), 3.72 (t, 1 H, *J* = 7.3 Hz, CHCN).

^{13}C NMR: δ = 20.9 (CH_2), 21.5 [CH(CH_3)$_2$], 26.1 (CHMe_2), 39.0 (CCN), 112.9 (CN).

Conjugate Addition of Diethylaluminum Chloride Precoordinated to Boron Trifluoride Etherate to Alkylidenemalonic Esters 1,Isobutylidenemalonodinitrile 3 or Meldrum Acid Derivative 7b; General Procedure

Toluene (50 mL) was distilled into a two neck flask under argon atmosphere and cooled to –40°C. BF_3•OEt_2 (0.93 mL, 7.5 mmol) and Et_2AlCl (7.5 mmol, 7.5 mL of 1 M solution in hexane) were added by a syringe. After stirring for 2 h, the alkylidenemalonic ester **1**, dinitrile **3**, or Meldrum acid derivative **7b**, respectively, was added and the solution stirred for the time given in Table 4. The solution was then poured into aq satd NH_4Cl solution (100 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with aq satd NH_4Cl solution and dried ($MgSO_4$). The solvent was removed by distillation and the crude product purified by flash chromatography in petroleum ether/EtOAc (25:1) (Table 4).

Diethyl (1-Ethyl-2-methylpropyl)malonate (9c)[23]
Colorless oil; R_f 0.59 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.78–0.88 (m, 9 H, CH_3), 1.19 and 1.20 each (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.16–1.48 (m, 2 H, C*H*$_2$CH$_3$), 1.72 (m, 1 H, C*H*Me_2) 1.91 (m, 1 H, C*H*Et), 3.34 [d, 1 H, *J* = 7.8 Hz, C*H*(CO_2Et)$_2$].

^{13}C NMR: δ = 13.5 (*C*H_3CH_2), 14.0 (*C*H_3CH_2O), 18.6, 20.2 [CH(*C*H$_3$)$_2$], 29.5 (*C*HMe_2), 45.7 (*C*HEt), 54.6 [*C*H(CO_2Et)$_2$], 61.0, 61.1 (CH_2O), 169.3, 169.5 (C=O).

Diethyl (1-Ethyl-3-methylbutyl)malonate (9d)
Colorless oil; R_f 0.46 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.82 (t, 3 H, *J* = 7.3 Hz, CH_2C*H*$_3$), 0.83 (d, 6 H, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 1.00–1.66 (m, 5 H, C*H*$_2$CH$_3$, C*H*$_2$C*H*Me_2), 2.11 (m, 1 H, C*H*Et), 3.36 (d, 1 H, *J* = 7.3 Hz, C*H*(CO_2Et)$_2$].

^{13}C NMR: δ = 10.5 (*C*H_3CH_2), 14.1 (*C*H_3CH_2O), 22.0, 23.3, 23.7 (*C*H_2CH_3, CH_3), 25.3 (*C*H_2CHMe_2), 37.2 (*C*HMe_2), 40.1 (*C*HEt), 55.0 [*C*H(CO_2Et)$_2$], 61.0 (CH_2O), 169.1 (C=O).

Diethyl (1-Cyclohexylpropyl)malonate (9e)
Colorless oil; R_f 0.46 (PE/EtOAc, 10:1).

^{1}H NMR; δ = 0.87 (t, 3 H, *J* = 7.6 Hz, C*H*$_3$CH$_2$CH), 0.90–1.79 (m, 13 H, *c*-C_6H_{11}, CH_2), 1.23 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.95 (m, 1 H, C*H*Et), 3.42 [d, 1 H, *J* = 7.8 Hz, CH(CO_2Et)$_2$].

^{13}C NMR: δ = 13.7 (*C*H_3CH$_2$CH), 14.1 (*C*H_3CH_2O) 22.0, 26.6, 26.8, 26.9, 29.4, 30.8 (CH_2), 40.3 (CHEt*C*H), 45.5 (*C*HEt), 54.5 [*C*H(CO_2Et)$_2$], 61.0, 61.1 (CH_2O), 169.4 169.7 (C=O).

Diethyl (1-Ethyl-2,2-dimethylpropyl)malonate (9f)
Colorless oil; R_f 0.46 (PE/EtOAc, 10:1).

^{1}H NMR: δ = 0.86 [s, 9 H, C(CH_3)$_3$], 0.89 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$CH), 1.22 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.23 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.48–1.63 (m, 2 H, C*H*$_2$CH$_3$), 1.93 (m, 1 H, C*H*Et), 3.54 (d, 1 H, *J* = 4.2 Hz, C*H*(CO_2Et)$_2$).

^{13}C NMR: δ = 13.9 (*C*H_3CH_2O), 14.8 (*C*H_3CH_2), 20.4 (*C*H_2CH_3), 28.0 [C(*C*H$_3$)$_3$], 34.4 (*C*Me$_3$), 50.8 (*C*HEt), 52.3 [*C*H(COOEt)$_2$], 60.7, 61.2 (CH_2O), 169.5, 170.6 (C=O).

(1-Ethyl-2-methylpropyl)malonodinitrile (13f)
Colorless oil; R_f 0.30 (PE/EtOAc, 10:1). Identification vide supra.

2,2-Dimethyl-5-(1-ethyl-2-methylpropyl)-1,3-dioxane-4,6-dione (11b)
Yield: 86%; colorless crystals; mp 54°C (PE/EtOAc); R_f 0.14 (PE/EtOAc, 10:1). Identification vide supra.

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