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Tetrahedron 61 (2005) 1363–1374

Catalytic electronic activation as a tool for the addition of stabilised nucleophiles to allylic alcohols

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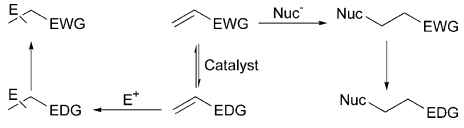
Received 31 May 2004; revised 8 September 2004; accepted 1 October 2004

Abstract—This paper describes the activation of 2-cyclohexen-1-ol (**1**) and 2-cyclopenten-1-ol (**11**) through the use of aluminium-catalysed transfer hydrogenation. The electronically activated substrates are demonstrated to undergo facile conjugate addition and, when the alcohol functional group is subsequently restored in a one-pot procedure, this leads to an indirect addition of nucleophiles to allylic alcohols. This novel methodology has been termed catalytic electronic activation.The aluminium *tert*-butoxide catalysed conversion of 2-cyclohexen-1-ol (**1**) into 2-(3-hydroxycyclohexyl)-2-methylmalononitrile (**18**) and 2-cyclopenten-1-ol (**11**) into 2-(3-hydroxycyclopentyl)-2-methylmalononitrile (**16**) in 90 and 60% yield, respectively has been demonstrated through an efficient domino Oppenauer/Michael addition/Meerwein–Ponndorf–Verley process.

1. Introduction

The reactivity of an alkene is highly dependent upon the nature of any nearby substituents. For example, whilst alkenes conjugated to electron-withdrawing groups can be susceptible to nucleophilic addition reactions, alkenes attached to electron-donating groups are more susceptible to electrophilic addition. Conversion of electron-donating groups and electron-withdrawing groups would achieve reversible catalytic electronic activation of the alkene, and enable a cross-over in the reactivity of alkene substrates (Scheme 1). Thus, alkenes attached to electron-withdrawing groups (EWG) could undergo indirect electrophilic addition, and alkenes attached to electron donating groups (EDG) could undergo indirect nucleophilic addition.



Scheme 1. Reversible crossover of alkene reactivity.

By designing a reaction whereby an alcohol is reversibly oxidised to a carbonyl compound, we have reported preliminary results which show that it is possible to effect indirect nucleophilic addition to allylic alcohols.[1] A related concept has been applied by this group to indirect Wittig reactions on alcohols[2,3] and other processes.[4–7]

Transfer hydrogenation reactions have been used widely in the reduction of carbonyl compounds, as well as the reverse process.[8–12] One of the hallmarks of these reactions is their reversibility, which has been exploited in the racemisation of secondary alcohols.[13] Whilst there are many reagents and catalysts capable of effecting a reversible oxidation/reduction sequence, we reasoned that the use of aluminium catalysts would be less likely to promote isomerisation of allylic alcohol substrates than many transition metal catalysts.[14,15]

2. Results and discussion

2.1. Use of malonate nucleophiles

Aluminium alkoxides have been used extensively to carry out reversible hydride transfer to a carbonyl acceptor.[16–18] The most commonly used reagent, aluminium isopropoxide, is available commercially and promotes both the Meerwein–Ponndorf–Verley (MPV) reduction and Oppenauer oxidation effectively under suitable reaction conditions, generally employing an excess of either oxidant (acetone, 2-butanone) or reductant (propan-2-ol).

It was envisaged that the catalytic electronic activation process would only require a catalytic amount of ketone added at the start of the reaction. Equilibrium would then be

Keywords: Aluminium; Catalytic electronic activation; Homogeneous catalysis; Hydrogenation; Michael addition.
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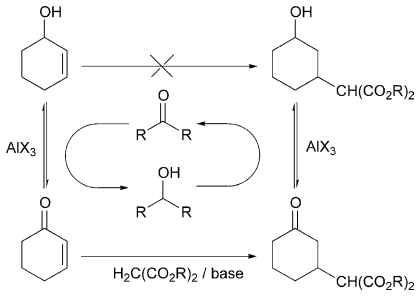
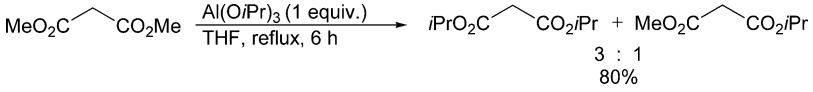
doi:10.1016/j.tet.2004.10.009



Scheme 2. Principal of catalytic domino Oppenauer/Michael addition/MPV reduction.

maintained between the alcohol and ketone components during the course of the reaction (Scheme 2).

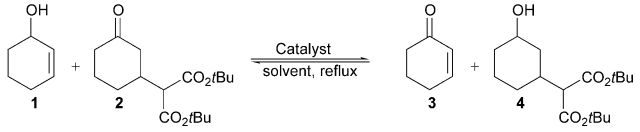
Preliminary studies indicated that both dimethyl malonate derived nucleophiles and the corresponding Michael addition adducts were susceptible to aluminium isopropoxide mediated *trans*-esterification (Scheme 3).[19,20] The labile methoxy ester groups are replaced readily by the isopropoxide ligands on the aluminium catalyst.



Scheme 3. Aluminium isopropoxide catalysed trans-esterification of dimethyl malonate.

In an attempt to block *trans*-esterification and base-catalysed hydrolysis reactions, the more robust *tert*-butyl ester was chosen; for these substrates *trans*-esterification proceeds almost exclusively through alkyl-oxygen cleavage.[21]

In order to ascertain the equilibrium position for the desired transfer hydrogen reaction, arguably the most important factor in catalytic electronic activation, a 1:1 mixture of 2-cyclohexen-1-ol (**1**) and ketone **2** was heated to reflux in solvent into which aluminium *tert*-butoxide was added dropwise (Scheme 4, Table 1).



Scheme 4. Aluminium catalysed Oppenauer/MPV crossover reaction.

Table 1. Results of malonate derived Oppenauer/MPV crossover reaction

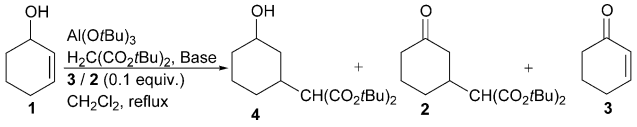
Entry	Catalyst (mol%)	Solvent[a]	*t* (h)	Conv. (%)[b]	Recovery (%)[c]
1	$Al(OtBu)_3$ (100)	THF	6	>95	96
2	$Al(OtBu)_3$ (100)	CH_2Cl_2	24[d]	>95	99
3	$Al(OtBu)_3$ (10)	CH_2Cl_2	24	>95	100
4	Na(O*i*Pr) (100)	CH_2Cl_2	24	<5	76

[a] The reactions were carried out on a 1 mmol scale in solvent (10 mL) at reflux.
[b] Analysed by ^{1}H NMR.
[c] Crude recovery upon work-up.
[d] Reaction reached completion in 6 h.

After 6 h, ^{1}H NMR analysis of the crude product indicated a >95% conversion into 2-cyclohexen-1-one (**3**) and alcohol **4** in both tetrahydrofuran and dichloromethane (Table 1, entries 1 and 2), thus proving conclusively that the equilibrium position for the transfer hydrogenation reaction lies firmly to the right, that is, towards the thermodynamically more favourable conjugated ketone. This is beneficial for ensuring a constant supply of enone ready for conjugate addition. Surprisingly, aluminium *tert*-butoxide also exhibited excellent activity at substoichiometric levels (Table 1, entry 3); a property not normally associated with MPV-type systems.[16] However, a repeat experiment conducted at room temperature gave no conversion into the desired products after 6 h, while the use of a sodium isopropoxide catalyst[22] (Table 1, entry 5) provided equally disappointing results.

The data collected thus far suggested that the following reaction scheme could be envisaged (Scheme 5).

A series of experiments was designed in order to test this hypothesis: the general procedure involved the addition of 2-cyclohexen-1-ol (**1**) and a catalytic amount of 2-cyclohexen-1-one (**3**) to a stirred solution of di-*tert*-butyl malonate (**5**) and base in dichloromethane. This solution was subsequently heated at reflux into which aluminium *tert*-butoxide was added slowly over 30 min (Table 2).



Scheme 5. Malonate derived domino Oppenauer/Michael addition/MPV process.

Table 2. Results of malonate derived domino Oppenauer/Michael addition/MPV process

Entry	Base[a] (mol%)	Malonate (mol%)	$Al(OtBu)_3$ (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	NaH (20)	200	100	1	12:14:1
2	NaH (20)	200	100	6	19:12:5
3	NaH (10)	200[c]	100	24	0:0:10
4	KO*t*Bu (10)	100[d]	100	24	0:0:10
5	NaH (30)	200	10	24	0:29:0
6	NaH (50)	500	100	24	0:43:0
7	NaH (20)	200	100	72	10:2:6

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (5–8 mL) at reflux.
[b] Analysed by ^{1}H NMR.
[c] Added portionwise over 7 h.
[d] Heated at 100 °C in an ACE pressure tube.

The initial results were rather disappointing: under a variety of experimental conditions, only low conversions (10–19%; Table 2, entries 1, 2 and 7) into alcohol **4** were obtained, even after 72 h. Of some concern was the presence of ketone **2** in

the reaction mixture (Table 2, entries 5 and 6). This suggested that the efficient aluminium catalysed transfer hydrogenation between ketone **2** and allylic alcohol **1** (Scheme 4) was inhibited by the presence of di-*tert*-butylmalonate (**5**).

Surprisingly, a repeat experiment using 10 mol% of ketone intermediate **2** as oxidant (Scheme 5) provided appreciably enhanced, yet still moderate, conversions into alcohol **4** (Table 3). We are not sure why the choice of ketone has such a pronounced effect on conversion, however a possible solution is postulated (vide infra).

Table 3. Results of domino Oppenauer/Michael addition/MPV process using catalytic ketone **2**

Entry	Solvent[a] (mL)	Malonate (mol%)	$Al(OtBu)_3$ (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	THF (10)	100	100	96	43:20:5
2	THF (10)	100[c]	10	24	29:67:0[d]
3	CH_2Cl_2 (10)	200	100	72	38:0:0
4	CH_2Cl_2 (5)	200	100	10	0:23:0
5	CH_2Cl_2 (5)	200	100	10	10:0:9
6	CH_2Cl_2 (25)[e]	120	100	24	24:0:1

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (5–25 mL) at reflux.
[b] Analysed by ^1H NMR.
[c] 0.1 equiv KO*t*Bu.
[d] Main product consistent with malonic acid dicyclohex-2-enyl ester.
[e] 5 mmol in CH_2Cl_2 at reflux.

Both Wilds[17] and Okano[23] have reported that β-diketones deactivate aluminium and lanthanide(III) catalysts by strong chelate formation. Furthermore, Okano and co-workers were able to isolate the acetylacetonate complex $gd(acac)_3$ from the reaction mixture which displayed no catalytic activity. It is therefore probable that the low conversions to date are attributed to an analogous complex formation (Fig. 1, A).

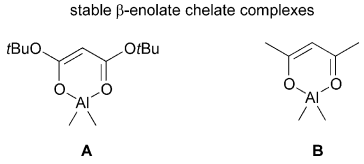


Figure 1. Comparison of proposed aluminium complex and aluminium acetylacetonate.

This idea is reinforced by the fact that aluminium acetylacetonate (Fig. 1, B) was demonstrated to be an ineffective promoter in the Oppenauer/MPV crossover reaction (Scheme 4, Table 4).

Snider[24] and more recently Node[25,26] demonstrated that dimethylaluminium chloride was able to catalyse both an Oppenauer/ene annelation and a domino Michael addition/MPV reduction, respectively. In each case, the reaction proceeded at room temperature to give the desired products in excellent yield.

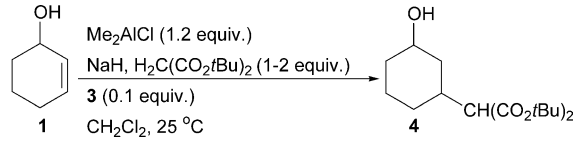
Table 4. Results of dimethylaluminium chloride catalysed Oppenauer/MPV crossover reaction

Entry	Catalyst[a] (mol%)	Temperature (°C)	Conv. (%)[b]
1	$Al(acac)_3$ (100)	44	<5
2	Me_2AlCl (10)	25	>95
3	Me_2AlCl (120)	25	>90

[a] The reactions were carried out on a 1 mmol scale in solvent (5 mL).
[b] Analysed by ^1H NMR.

In view of this evidence dimethylaluminium chloride appeared to be an excellent candidate for the domino Oppenauer/Michael addition/MPV process. Thus, the transfer hydrogenation capabilities of dimethylaluminium chloride were investigated for the crossover Oppenauer/MPV process (Scheme 4, Table 4).

These promising results prompted further investigation towards the domino Oppenauer/Michael addition/MPV process. The general procedure involved adding dimethylaluminium chloride to a nitrogen-purged dichloromethane solution of 2-cyclohexen-1-ol (**1**). After 20 min, a catalytic amount of 2-cyclohexen-1-one (**3**), di-*tert*-butyl malonate (**5**) and sodium hydride were added and the reaction maintained at room temperature (Scheme 6, Table 5).



Scheme 6. Dimethylaluminium chloride catalysed Domino Oppenauer/Michael addition/MPV reaction.

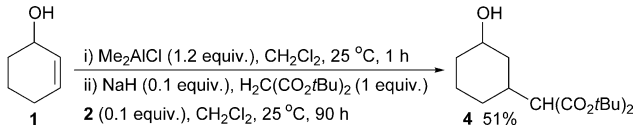
Table 5. Dimethylaluminium chloride catalysed Domino Oppenauer/Michael addition/MPV reaction

Entry	NaH (mol%)	Malonate[a] (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	10	100[c]	6	9:1:15
2	20	100[c]	6	22:12:11
3	10	100[d]	24	25:1:5
4	20	100[c]	72	11:1:20
5	20	200[c]	72	23:12:10

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (7–10 mL) at room temperature.
[b] Analysed by ^1H NMR.
[c] 2-Cyclohexen-1-one (0.2 equiv) and 4 Å MS were added.
[d] 2-Cyclohexen-1-ol and catalyst stirred for 1 h.

Unfortunately, the conversions into alcohol **4** were still low (9–25%), even after prolonged reaction times (Table 5, entries 4 and 5). However, the presence of unreacted 2-cyclohexen-1-one (**2**) (Table 5, entries 2 and 5), again suggests that the malonate salt may be forming an acac-type complex (Fig. 1, A) with the aluminium catalyst, inhibiting both the Michael addition and Meerwein–Ponndorf–Verley–Oppenauer (MPVO) chemistry.

Yager and co-workers[27] have demonstrated that the rates of MPVO reactions were affected directly by the degree of pre-association of the aluminium complex and the alcohol substrate. Thus, a final experiment was performed in order to discover whether prior reaction of cyclohexenol with the aluminium promoter could lead to an improved yield. Thus, reaction of 2-cyclohexen-1-ol (**1**) with dimethylaluminium chloride for 1 h presumably forms an aluminium cyclohexenyl alkoxide intermediate, and this was found to provide an increase in the rate of reaction (Scheme 7).

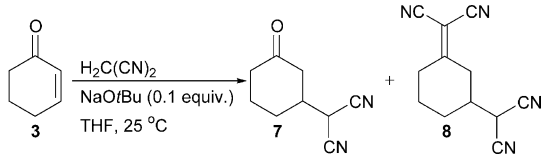


Scheme 7. In situ generated aluminium alkoxide domino Oppenauer/Michael addition/MPV reaction.

After 90 h an increased conversion into alcohol **4** (51%) was realised. The formation of the desired product, at room temperature, albeit at moderate conversion, was considered a notable improvement.

2.2. Use of malononitriles as nucleophiles

In order to realise high conversions in the allylic alcohol catalytic electronic activation procedure it was proposed that an alternative non-chelating nucleophile should be investigated. Malononitrile (**6**) is a useful building block in synthetic chemistry[28] and it is therefore an appealing substrate for the domino Oppenauer/Michael addition/MPV process. However competitive Knoevenagel condensation/dehydration was found to occur either preferentially or subsequent to the desired conjugate addition (Scheme 8, Table 6).[29,30]



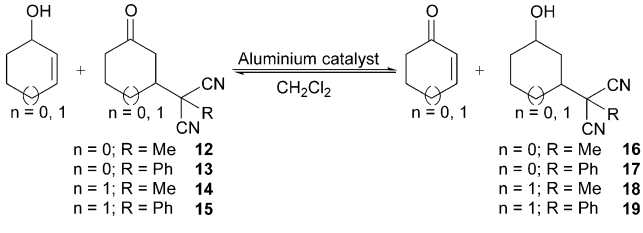
Scheme 8. Addition of malononitrile to 2-cyclohexen-1-one.

Table 6. Results of the addition of malononitrile to 2-cyclohexen-1-one

Entry	Malononitrile[a] (mol%)	*t* (h)	Conv. **7**:**8** (%)[b]
1	100	1	>90:0
2	200	4	43:57
3	100	8	29:71

[a] Reactions were performed on a 1 mmol scale in solvent (10–20 mL).
[b] Analysed by ^{1}H NMR.

It was proposed that a simple solution to prevent the aldol/dehydration reaction was to place a substituent at the acidic ($pK_a = 11.2$)[31] α-position of malononitrile (**6**). Thus, methylmalononitrile (**9**) and benzylmalononitrile (**10**) were synthesised according to a recent procedure reported by Díez-Barra and co-workers.[32] This procedure was adopted as other simple base-catalysed routes are known to lead to di-substituted products.



Scheme 9. Aluminium catalysed Oppenauer/MPV crossover reaction of malononitrile derived substrates.

The next objective was to establish the equilibrium position for the transfer hydrogenation reaction. Thus, dimethylaluminium chloride and aluminium *tert*-butoxide were investigated for their ability to effect transfer hydrogenation between 2-cyclohexen-1-ol (**1**), 2-cyclopenten-1-ol (**11**) and the corresponding ketone intermediates (Scheme 9, Table 7).

Table 7. Results of aluminium catalysed Oppenauer/MPV crossover reaction of malononitrile derived substrates

Entry	Substrate	Catalyst[a] (mol%)	Temperature (°C)	*t* (h)	Conv. (%)[b]
1	**14**	Me_2AlCl (10)	25	15	>95
2	**15**	$Al(OtBu)_3$ (10)	44	6	>95
3	**12**	$Al(OtBu)_3$ (10)	44	24	41
4	**13**	$Al(OtBu)_3$ (100)	44	24	68

[a] Reactions were performed on a 1 mmol scale in solvent (5 mL).
[b] Analysed by ^{1}H NMR.

Whilst the equilibrium position for the transfer hydrogenation reaction between cyclohexyl derivatives lies firmly to the right (Table 7, entries 1 and 2), the effect is not quite as pronounced for the cyclopentyl adducts (Table 7, entries 3 and 4). This suggests that the thermodynamic driving force to produce the conjugated ketone is less well defined. Feringa[33] and Pfaltz[34] have also observed an analogous significant difference in reactivity between 2-cyclohexen-1-one (**3**) and 2-cyclopenten-1-one (**20**) towards asymmetric conjugate addition.

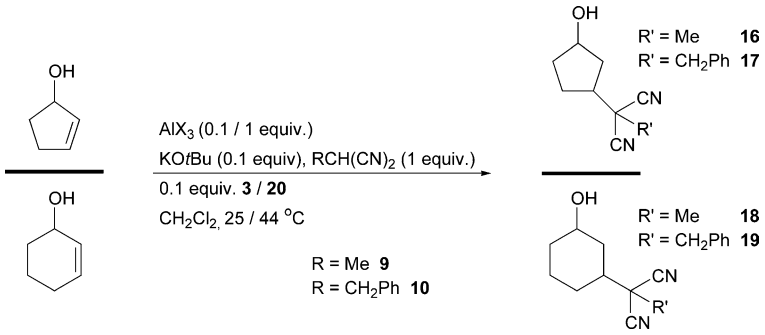
Based on the conditions needed for conjugate addition and for transfer hydrogenation an indirect nucleophilic addition of methylmalononitrile (**9**) and benzylmalononitrile (**10**) to 2-cyclohexen-1-ol (**1**) and 2-cyclopenten-1-ol (**11**) was attempted (Scheme 10, Table 8). These experiments employed the aluminium reagent in stoichiometric amounts.

These data demonstrated for the first time an efficient domino Oppenauer/Michael addition/MPV process (Table 8, entries 5 and 6); it is worth noting that the maximum expected yield is 90%. However, significantly poorer yields were obtained when using the dimethylaluminium chloride catalyst (Table 8, entries 1 and 2) and in the cyclopentyl system (Table 8, entries 7–9).

Nevertheless, it was hoped that a fully catalytic reaction could be employed. Thus, both aluminium *tert*-butoxide and dimethylaluminium chloride were investigated for their ability to effect a catalytic electronic activation process (Scheme 10, Table 9).

Poor results were obtained initially when using substoichiometric amounts of catalyst (Table 9, entries 1–3). To address these problems the reactions were studied at elevated temperatures using ACE pressure tubes (Table 9, entries 4–9). Thus we were able to realise the catalytic reaction within 8 h when the higher temperatures were employed; even when using 10 mol% of cyclohexanone as an alternative catalytic oxidant (Table 9, entry 5). Under the same conditions a 57% yield of alcohol **18** could be obtained using 5 mol% cyclohexanone.

The initial results for the attempted domino Oppenauer/



Scheme 10. Aluminium catalysed domino Oppenauer/Michael addition/MPV process using malononitrile derived substrates.

Table 8. Results of malononitrile derived domino Oppenauer/Michael addition/MPV process

Entry	Product	Catalyst[a]	Temperature (°C)	*t* (h)	Yield (%)[b]
1	**18**	Me_2AlCl	25	24	43
2	**18**	Me_2AlCl[c]	25	24	46
3	**18**	$Al(OiPr)_3$	44	24	78
4	**18**	$Al(OtBu)_3$	44	8	69
5	**18**	$Al(OtBu)_3$[d]	44	48	90
6	**19**	$Al(OtBu)_3$	44	24	81
7	**16**	$Al(OtBu)_3$	44	6	10
8	**16**	$Al(OtBu)_3$	44	24	31[e]
9	**17**	$Al(OtBu)_3$	44	24	19

[a] Reactions were performed on a 1 mmol scale in CH_2Cl_2 (5–10 mL).
[b] Yield of isolated product after flash-column chromatography.
[c] Tetrabutylammonium bromide (0.04 equiv) added to increase dissolution of malononitrile salt.
[d] Reaction carried out on a 5 mmol scale.
[e] NaO*t*Bu (0.1 equiv) used as base.

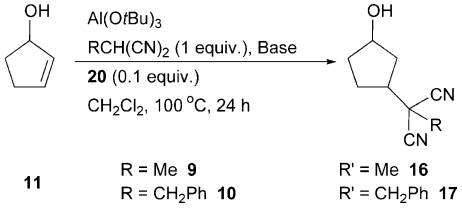
Table 9. Results of malononitrile derived catalytic domino Oppenauer/Michael addition/MPV process

Entry	Product	Catalyst[a] (mol%)	Temperature (°C)	*t* (h)	Yield (%)[b]
1	**18**	Me_2AlCl (10)	25	24	<5
2	**18**	Me_2AlCl (30)	25	24	37
3	**18**	$Al(OtBu)_3$ (10)[c]	44	24	<5
4	**18**	$Al(OtBu)_3$ (10)[c]	100	8	90
5	**18**	$Al(OtBu)_3$ (10)[c,d]	100	8	70
6	**19**	$Al(OtBu)_3$ (10)[c]	100	8	64
7	**16**	$Al(OtBu)_3$ (100)[c]	100	24	60
8	**16**	$Al(OtBu)_3$ (100)[c]	150	24	61
9	**17**	$Al(OtBu)_3$ (100)[c]	100	24	21

[a] Reactions were performed on a 1 mmol scale in CH_2Cl_2 (3–10 mL).
[b] Yield of isolated product after flash column chromatography.
[c] Reactions were performed on a 1 mmol scale in an ACE pressure tube.
[d] Cyclohexanone (0.1 equiv) used as oxidant.

Michael addition/MPV process between 2-cyclopenten-1-ol (**11**) and malononitrile derivatives were disappointing (Table 9, 7–9), although an increase in temperature does provide an appreciable enhancement in yield (Table 9, entries 7 and 8 cf. Table 8, entries 7–9). Nevertheless, these yields are moderate in comparison with the cyclohexyl system (vide supra) and require a stoichiometric amount of catalyst. Unidentified by-products were formed when 2-cyclopenten-1-ol (**11**) was employed as a substrate. This may be attributable to self-condensation of the enone, malononitrile or to Ritter or Pinner reactions on the nitrile. Spectroscopic analysis on the intractable mixtures was inconclusive.

In order to address these problems, two further approaches were explored: organic and fluoride bases (Scheme 11, Table 10).



Scheme 11. 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process.

Table 10. Results of 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

Entry	Product	$Al(OtBu)_3$ (mol%)[a]	Base (mol%)	Temperature (°C)	*t* (h)	Conv. (%)[b]
1	**16**	100	CsF (10)	100	20	71
2	**16**	10	CsF (100)	100	24	<5
3	**16**	100[c]	DBU[d] (10)	44	24	<5
4	**16**	100	MTBD[e] (10)	100	24	48[f]
5	**17**	100	—	100	24	44
6	**17**	100	—	100	72	60[f]

[a] Reactions were performed on a 1 mmol scale in an ACE pressure tube.
[b] Analysed by ^1H NMR.
[c] Reaction was performed on a 1 mmol scale in solvent at reflux.
[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[e] 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[f] Yield of isolated product after flash column chromatography.

Catalytic caesium fluoride (Table 10, entry 1) was demonstrated to be an excellent base in the domino Oppenauer/Michael addition/MPV process. Michael addition reactions using caesium fluoride do have literature precedent: Yamaguchi and co-workers[35] have reported previously the stereoselective addition of di-*tert*-butyl malonate (**5**) to 2-cyclohexen-1-one (**3**) catalysed by 20 mol% caesium fluoride. In addition, fluoride bases provided a very 'clean' reaction profile appearing to suppress the minor side-reactions which were previously observed. This trend was also reflected in the result obtained using the strong organic base, MTBD ($pK_a \sim 23$).[36] Whereas the weaker organic base DBU (pK_a 11–12), did not display any activity in the allylic alcohol catalytic electronic activation process (Table 10, entry 3), MTBD was

able to catalyse the reaction in moderate yield (Table 10, entry 4).

Whilst the yield of alcohol **17** was low at reflux and elevated temperatures (Tables 8 and 9, entries 9), a moderate yield was finally obtained through using a system in which the potassium *tert*-butoxide base was omitted (Table 10, entries 5 and 6). It therefore appeared that under the prolonged high temperatures, the aluminium catalyst was able to form the desired malononitrile nucleophile,[37] whilst not possessing sufficient basicity to facilitate the formation of base-catalysed by-products.

An issue not discussed thus far is product diastereoselectivity. For the cyclohexyl-derived substrates an approximate 60:40 ratio of product diastereomers was delivered, whereas the cyclopentyl-derived products displayed a moderate bias towards the *cis* configuration (Fig. 2). The ratio of diastereoisomers was established by analysis of the ^{1}H NMR spectra. Absolute stereochemistry was confirmed through X-ray crystallographic analysis of the individual diastereomers.

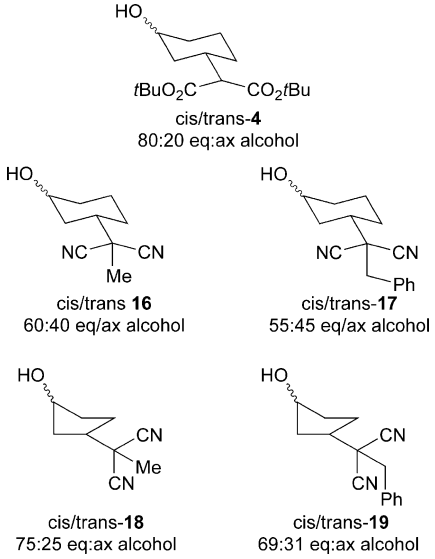


Figure 2. Axial/equatorial product ratios.

The thermodynamic product distribution was explored through the equilibration of pure axial alcohol (*trans*-**16**) in 1:1 acetone/propan-2-ol at reflux (Scheme 12).

Thus, the axial alcohol (*trans*-**16**) was converted into a thermodynamic product ratio (62:38 equatorial/axial) efficiently under aluminium *tert*-butoxide catalysis within 12 h. This is essentially the same ratio that is observed in the overall domino process.

The application of the current procedure towards acyclic substrates is, at present, unfulfilled. The required reaction was found to be fatally inhibited by both poor crossover transfer hydrogenation, and undesired cyclisation processes.[38]

3. Conclusion

In summary, it has been demonstrated that whilst nucleophiles will not normally add to allylic alcohols, this reaction becomes possible by a procedure involving catalytic electronic activation of the substrate.

The concept of temporarily oxidising alcohols to carbonyl compounds as an approach to catalytic electronic activation processes is under further investigation.

4. Experimental

4.1. General procedures

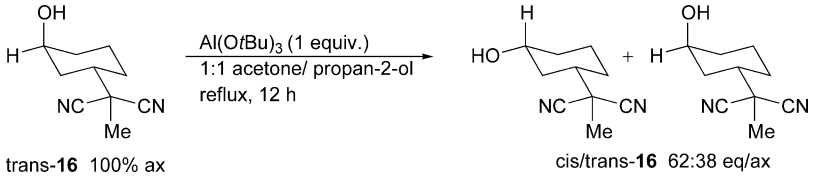
All reactions were performed under an atmosphere of dry nitrogen using oven-dried (150 °C) glassware. Dichloromethane was distilled from CaH_2 before use. THF was distilled from the anion of benzophenone ketyl radical. Unless preparative details are provided all chemicals were available commercially and were purchased from Acros, Fluka, Lancaster or Sigma-Aldrich. Methylmalononitrile (**9**) and benzylmalononitrile (**10**) were prepared by the method of Díez-Barra.[32] 2-Cyclopenten-1-ol (**11**) was prepared by the method of Larock.[39]

Melting points were recorded on a Büchii 535 Series instrument and are uncorrected.

IR spectra were recorded as thin films, solutions ($CDCl_3$) or KBr discs using a Perkin–Elmer 1600 Series FT-IR spectrophotometer in the range 4000–600 cm^{-1}, with internal background scan. Absorption maxima are recorded in wavenumbers (cm^{-1}).

Proton (δ ^{1}H) NMR spectra were run in $CDCl_3$ using either a Bruker AM-300 (300 MHz), Jeol (270 MHz), or Jeol (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm) as internal standard. Coupling constants (*J*) are given Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (br). Carbon-13 (δ ^{13}C) NMR spectra were run in $CDCl_3$ and were recorded using a Bruker WH-400 (100 MHz) or a Bruker AM-300 (75 MHz).

Mass spectra, including high-resolution spectra, were



Scheme 12. Equilibration of axial alcohol.

recorded on a Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+, *iso*-butane) ionisation, electrospray (ES+) ionisation and/or Fast Atom Bombardment (FAB+) ionisation.

Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser or an Exeter Analytical Inc. CE-440 Elemental Analyser.

4.1.1. Aluminium isopropoxide catalysed trans-esterification of dimethyl malonate. Dimethyl malonate (0.132 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) were heated to 62 °C in THF (8 mL). After 6 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give a mixture of *iso*-propylmethylmalonate and di-*iso*-propylmalonate (1:3) as yellow oil (80% conversion determined by ^{1}H NMR). An authentic sample of *iso*-propylmethylmalonate was prepared by the method of Wakasugi.[40]

4.1.2. Preparation of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2). 2-Cyclohexen-1-one (**3**) (1.00 g, 10 mmol) in THF (2 mL) was added dropwise to a suspension of sodium hydride (0.025 g, 1.0 mmol) and di-*tert*-butyl malonate (**5**) (2.25 g, 10 mmol) in THF (10 mL). After 6 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (2×50 mL). The aqueous phase was separated and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave **2** as a white crystalline solid (3.05 g, 94%) (Fig. 3).

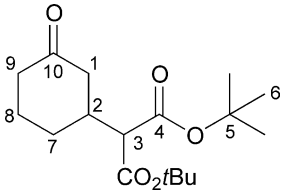


Figure 3.

Compound **2**. Mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=1.42 (br s, 9H, H_6), 1.42–1.75 (m, 2H), 1.94–2.03 (m, 1H), 2.04–2.12 (m, 1H), 2.20–2.32 (m, 2H), 2.36–2.50 (m, 3H), 3.09 (d, J=8 Hz, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=24.7, 28.0 (C_6), 28.0 (C_6), 37.9, 41.2, 45.2, 58.8 (C_3), 81.8 (C_5), 81.8 (C_5), 167.0 (C_4), 209.7 (C_{10}); IR ($CHCl_3$): ν (cm^{-1})=1740 (C=O), 1724 (C=O); MS (FAB+): *m/z* 313 [$M^{\cdot+}$]; HRMS (FAB+): $C_{17}H_{28}O_5$ requires 313.2015, found 313.2028; $C_{17}H_{28}O_5$ requires C 65.36%, H 9.03%, found C 65.60%, H 9.05%.

4.1.3. Preparation of *cis*/*trans*-2-(3-hydroxy-cyclohexyl)-malonic acid di-*tert*-butyl ester (4). 2-(3-Oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**4**) (0.312 g, 1.0 mmol) in anhydrous methanol (5 mL) was cooled to 0 °C whilst sodium borohydride (0.038 g, 1.0 mmol) was added gradually over 0.1 h. After 1 h, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash-column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave *cis*/*trans*-**5** as colourless oil (0.311 g, 99%, 80:20 *cis*/*trans*) (Fig. 4).

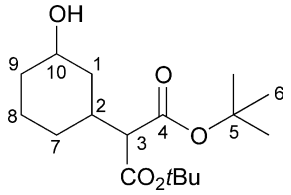


Figure 4.

Compound cis/*trans*-**4**. ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ=0.90–1.22 (m, 2H), 1.24–1.40 (m, 1H), 1.43 (br s, 18H), 1.50–1.64 (m, 3H), 1.66–1.77 (m, 1H), 1.78–1.83 (m, 1H), 1.93–2.11 (m, 1H), 2.98 (d, J=9 Hz, 1H, H_3), 2.98 (d, J=9 Hz, 1H, H_3), 3.59 (m, 1H, H_{10ax}), 4.09 (br s, 1H, H_{10eq}); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=23.6, 27.9 (C_6), 27.9 (C_6), 35.2, 35.9, 39.7, 59.5 (C_3), 70.0 (C_{10}), 81.3 (C_5), 81.3 (C_5), 167.5 (C_4), 167.6 (C_4); IR ($CHCl_3$): ν (cm^{-1})=3436 (O–H); 1750 (C=O); MS (FAB+): *m/z* 315 [$M^{\cdot+}$]; $C_{17}H_{30}O_5$ requires C 64.92%, H 9.62%, found C 64.40%, H 9.62%.

4.1.4. General procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2) (Scheme 4, Table 1). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise over a period of 30 min to a stirred solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.312 g, 1.0 mmol) in dichloromethane (8 mL) at 44 °C under nitrogen. After 24 h, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to give **3/4** as a yellow oil (0.387 g, 94% recovery, >95% conversion determined by ^{1}H NMR).

4.1.5. General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2) (Scheme 4, Table 4). Dimethylaluminium chloride (0.1 mL, 1.0 M solution in hexane, 0.1 mmol) was added to a nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 0.25 h followed by the addition of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.312 g, 1.0 mmol) in dichloromethane (2 mL). After 24 h, the reaction was quenched with

saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **3/4** as a yellow oil (0.369 g, 90% recovery, >95% conversion determined by ^1H NMR).

4.1.6. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 5, Table 2). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol) in dichloromethane (1 mL) were added to a suspension of di-*tert*-butyl malonate (**5**) (0.624 g, 2.0 mmol) and NaH (0.005 g, 0.2 mmol) in dichloromethane (5 mL) at room temperature. The solution was heated to 44 °C and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 6 h, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to give **4/2/3** as a yellow oil (0.673 g, 92% recovery, 19:12:5% conversion determined by ^1H NMR).

4.1.7. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 6, Table 5). Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol), 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol), di-*tert*-butyl malonate (**5**) (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL). After 24 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **4/2/3** as a yellow oil (0.309 g, 93% recovery, 25:1:5% conversion determined by ^1H NMR).

4.1.8. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 7). Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged (0.25 h) stirred solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) in dichloromethane (2 mL). After 1 h at room temperature, 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.031 g, 0.1 mmol), di-*tert*-butyl malonate (**5**) (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL) were added. After 90 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give (**4**) as a yellow oil (0.304 g, 91% recovery, 51% conversion determined by ^1H NMR).

4.1.9. Preparation of 2-(3-dicyanomethyl-cyclohexylidene)-malononitrile (8). 2-Cyclohexen-1-one (**3**) (0.192 g, 2.0 mmol) in THF (10 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.019 g, 0.2 mmol) and malononitrile (**6**) (0.264 g, 4.0 mmol) in THF (10 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with dichloromethane (50 mL) and washed with water (100 mL). The aqueous phase was separated and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **8** as a yellow gum (0.306 g, 67%) (Fig. 5).

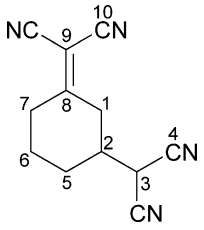


Figure 5.

Compound **8**. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.60–1.76 (m, 2H), 2.18–2.46 (m, 5H), 3.12–3.26 (m, 2H), 3.85 (d, J=5 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=25.4, 28.2, 28.8, 30.7, 40.0, 75.3 (C_3), 85.7 (C_9), 111.5 (C_4), 111.5 (C_{10}), 111.6 (C_4), 111.8 (C_{10}), 179.3 (C_8); IR ($CHCl_3$): ν (cm^{-1})=2339 (C≡N), 2232 (C≡N), 1598 (C=C); MS (EI+, 70 eV): m/z (%) 210 (23) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{12}H_{10}N_4$ requires 210.0906, found 210.0910.

4.1.10. Preparation of 2-(3-oxo-cyclohexyl)-malononitrile (7). 2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester[41] (1.00 g, 4.38 mmol) was stirred for 18 h in 35% aqueous NH_4OH (5 mL) at room temperature. The aqueous phase was concentrated in vacuo to give 2-(3-oxo-cyclohexyl)-malonamide as an off-white solid (0.966 g, 97% recovery). Phosphoryl chloride (0.91 mL, 9.75 mmol) was added to a stirred suspension of 2-(3-oxo-cyclohexyl)-malonamide in anhydrous acetonitrile (25 mL). After 5 h at 82 °C, the solution was filtered and concentrated in vacuo. The oily residue was dissolved in chloroform (100 mL) and extracted with a saturated solution of Na_2CO_3 (2×50 mL). The combined aqueous phases were neutralised with 10% v/v aqueous HCl and NaCl added until a saturated solution was obtained. The aqueous phase was extracted with chloroform (4×50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave 2-(3-oxo-

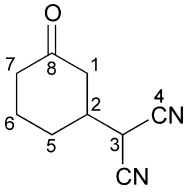


Figure 6.

cyclohexyl)-malononitrile (**7**) as a colourless oil (0.593 g, 75%) (Fig. 6).

Compound **7**. ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ=1.67–1.82 (m, 2H), 2.18–2.27 (m, 2H), 2.29–2.54 (m, 4H), 2.53–2.60 (m, 1H, H_2), 3.75 (d, J=5 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=24.0, 28.4, 39.7, 40.7, 44.6, 75.3 (C_3), 111.5 (C_4), 111.6 (C_4), 206.9 (C_8); IR (thin film): ν (cm^{-1})=2251 (C≡N), 1700 (C=O); MS (EI+, 70 eV): *m/z* (%) 162 (7) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_9H_{10}N_2O$ requires 162.0793, found 162.0790.

4.1.11. Preparation of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile (14). 2-Cyclohexen-1-one (**3**) (0.144 g, 1.50 mmol) in THF (3 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.014 g, 0.15 mmol) and methylmalononitrile (**9**) (0.120 g, 1.50 mmol) in THF (7 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave **14** as a white solid (0.202 g, 83%) (Fig. 7).

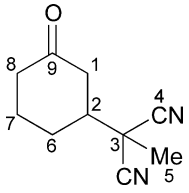


Figure 7.

Compound **14**. Mp 59–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.63–1.80 (m, 2H), 1.81 (s, 3H), 2.16–2.41 (m, 5H), 2.46–2.54 (m, 1H), 2.67–2.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=22.5 (C_5), 23.7, 27.2, 40.5, 42.7, 45.3 (C_3), 114.5 (C_4), 115.0 (C_4), 206.2 (C_9); IR ($CHCl_3$): ν (cm^{-1})=2360 (C≡N), 1700 (C=O); MS (EI+, 70 eV): *m/z* (%) 176 (32) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{10}H_{12}N_2O$ requires 176.0950, found 176.0952; $C_{10}H_{12}N_2O$ requires C 68.16%, H 6.86%, N 15.90%, found C 68.10%, H 6.88% N 15.80%.

4.1.12. Preparation of *cis/trans*-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile *cis/trans*-(18). 2-Methyl-2-(3-oxo-cyclohexyl)-malononitrile (**14**) (0.016 g, 0.71 mmol) in anhydrous methanol (15 mL) was cooled to 0 °C whilst sodium borohydride (0.027 g, 0.71 mmol) was added portionwise over 0.1 h. After 1 h, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave *cis/trans*-**18** as a white solid (0.037 g, 32%, 94:6 *cis/trans*) (Fig. 8).

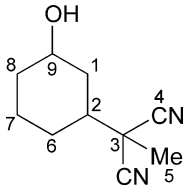


Figure 8.

Compound cis/trans-**18**. Mp 75–76 °C; ^{1}H NMR (300 MHz, $CHCl_3$, 25 °C): δ=1.20 (app dq, J=4, 16 Hz, 2H), 1.41 (app ddt, J=2, 4, 16 Hz, 2H), 1.55–1.80 (m, 3H), 1.71 (s, 3H, H_5), 1.89–2.10 (m, 2H), 2.22 (app ddt, J=3, 3, 12 Hz, 1H), 3.50–3.65 (m, 1H, H_{9ax}), 4.23 (br s, 1H, H_{9eq}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, single diastereomer): δ=22.7 (C_5), 23.2, 27.5, 35.0, 37.0, 37.4, 43.9 (C_3), 69.9 (C_9), 70.0 (C_9), 115.9 (C_4), 116.0 (C_4); IR ($CHCl_3$): ν (cm^{-1})= 3383 (O–H), 2249 (C≡N); MS (CI+): *m/z* (%) 179 (88) [MH^+]; HRMS (CI+): $C_{10}H_{15}N_2O$ requires 179.1184, found 179.1177.

4.1.13. General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile (14) (Scheme 9, Table 7). Carried out following the procedure described above. After 15 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **3/16** as a yellow solid (0.294 g, 100% recovery, >95% conversion determined by ^{1}H NMR).

4.1.14. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 8). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile (**9**) (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (5 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (3 mL) was added dropwise. After 24 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**18** as a white crystalline solid (0.153 g, 85%).

4.1.15. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 8). Dimethylaluminium chloride (1.0 mL, 1.0 M solution in hexane, 1.0 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol), 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol), methylmalononitrile (**9**) (0.080 g, 1.0 mmol) TBAB (0.012 g, 0.04 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (3 mL). After 24 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The

combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** as a white crystalline solid (0.076 g, 45%).

4.1.16. General procedure for the catalytic aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 9). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile (**9**) (0.080 g, 1.0 mmol), potassium *tert*-butoxide (0.012 g, 0.1 mmol) and aluminium *tert*-butoxide (0.025 g, 1.0 mmol) in dichloromethane (3 mL). The solution was heated to 100 °C in an ACE pressure tube. After 8 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** as a white crystalline solid (0.160 g, 90%).

4.1.17. Preparation of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile (15). 2-Cyclohexen-1-one (**3**) (0.096 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and benzylmalononitrile (**10**) (0.156 g, 1.0 mmol) in THF (3 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **15** as a cubic white solid (0.217 g, 86%) (Fig. 9).

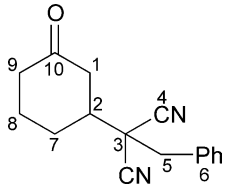


Figure 9.

Compound **15**. Mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.68 (dddd, J=2, 12, 12, 12 Hz, 1H), 1.83 (app dtq, J=1, 4, 12 Hz, 1H), 2.22–2.54 (m, 5H), 2.77–2.84 (m, 1H), 3.16 (d, J=14 Hz, 1H, H_5), 3.15 (d, J=14 Hz, 1H, H_5), 7.36–7.43 (m, 5H, H_6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=23.8, 27.5, 40.6, 43.2, 43.8, 44.7, 44.7, 113.6 (C_4), 114.0 (C_4), 128.9, 128.9, 129.0, 130.0, 130.0, 131.4, 206.2 (C_{10}); IR (thin film): ν (cm^{-1})=2241 (C≡N), 1716 (C=O); MS (EI+, 70 eV): *m*/*z* (%) 252 (37) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{16}H_{16}N_2O$ requires 252.1263, found 252.1251; $C_{16}H_{16}N_2O$ requires C 76.16%, H 6.39%, N 11.10%, found C 76.0%, H 6.41% N 11.10%.

4.1.18. Preparation of *trans*-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile (19). A solution of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile (**15**) (0.590 g, 2.34 mmol) in THF (2 mL) was added dropwise to a nitrogen-purged 1.0 M solution of L-Selectride (2.81 mL, 2.81 mmol) in THF (3 mL) at −78 °C. After 3 h, aqueous 3 M NaOH (0.17 mL, 0.5 mmol) was added dropwise followed by slow addition of 30% H_2O_2 (0.55 mL, 12.0 mmol). After a further 0.5 h stirring at room temperature the mixture was diluted with water (50 mL), extracted with ethyl acetate (5×30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *trans*-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile (**19**) as a white crystalline solid (0.244 g, 41%) (Fig. 10).

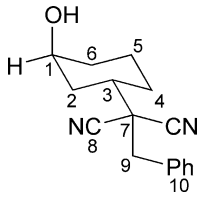


Figure 10.

Compound trans-**19**. Mp 106–108 °C; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ=0.35 (br s, 1H, O*H*), 0.81 (app. ddt, J=2, 4, 13.5 Hz, 1H, H_{6ax}), 0.96 (app. dq, J=4, 13 Hz, 1H, H_{4ax}), 1.12 (app. dt, J=2, 13 Hz, 1H, H_{2ax}), 1.17–1.21 (m, 1H, H_{5eq}), 1.25 (br d, J=14 Hz, 1H, H_{6eq}), 1.37 (app. tq, J=4, 13 Hz, 1H, H_{5ax}), 1.64 (br d, J=12.5 Hz, 1H, H_{4eq}), 1.70 (br d, J=13 Hz, 1H, H_{2eq}), 1.99 (app. tt, J=3, 12 Hz, 1H, H_{3ax}), 2.41 (d, J=14 Hz, 1H, H_7), 2.51 (d, J=14 Hz, 1H, H_7), 3.53 (br s, 1H, H_{1eq}), 7.02–7.25 (m, 5H, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=19.6, 28.7, 32.4, 35.3, 38.7, 40.9, 45.6, 66.0 (C_1), 66.1 (C_1), 115.0 (C_8), 129.1, 129.3, 130.6, 132.8; IR (C_6D_6): ν (cm^{-1})=3592 (O–H), 2282 (C≡N); MS (EI+, 70 eV): *m*/*z* (%) 254 [$M^{\cdot+}$], 91 (100) [$PhCH_2^+$]; $C_{16}H_{18}N_2O$ requires C 75.56%, H 7.13%, N 11.01%, found C 74.8%, H 7.34% N 11.30%.

4.1.19. Preparation of 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile (12). 2-Cyclopenten-1-one (**20**) (0.082 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and methylmalononitrile (**9**) (0.080 g, 1.0 mmol) in THF (3 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50

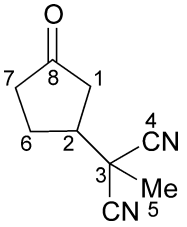


Figure 11.

petroleum ether/diethyl ether) gave **12** as a white solid after recrystallisation from acetonitrile (0.139 g, 86%) (Fig. 11).

Compound **12**. Mp 37–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=1.86 (br s, 3H, H_5), 1.90–2.02 (m, 1H), 2.22–2.39 (m, 2H), 2.41–2.50 (m, 1H), 2.52–2.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=23.5 (C_5), 25.8, 35.8 (C_3), 38.2, 40.6, 44.5 (C_2), 114.6 (C_4), 114.7 (C_4), 212.1 (C_8); IR (thin film): ν (cm^{-1})=2245 (C≡N), 1747 (C=O); MS (EI+, 70 eV): *m/z* (%) 162 (21) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_9H_{10}N_2O$ requires 162.0793, found 162.0795; $C_9H_{10}N_2O$ requires C 66.65%, H 6.21%, N 17.27%, found C 66.40%, H 6.22% N 17.26%.

4.1.20. Preparation of *cis/trans*-2-(3-hydroxy-cyclopentyl)-2-methyl-malononitrile (16). 2-Methyl-2-(3-oxo-cyclopentyl)-malononitrile (**12**) (0.415 g, 2.6 mmol) and aluminium *tert*-butoxide (0.640 g, 2.6 mmol) were heated to 82 °C in anhydrous propan-2-ol (10 mL). After 18 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**12** as pale yellow oil (0.401 g, 94%, 75:25 *cis/trans*) (Fig. 12).

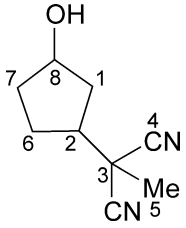


Figure 12.

Compound cis/trans-**12**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.50–1.70 (m, 1H), 1.72 (br s, 3H, H_5), 1.90–2.20 (m, 3H), 2.25–2.38 (m, 2H), 2.59–2.71 (m, 1H), 4.30–4.34 (m, 1H, H_{8eq}), 4.42–4.45 (m, 1H, H_{8ax}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=23.8 (C_5), 24.3 (C_5), 26.9, 26.9, 31.3, 31.3, 34.9, 36.1, 36.3, 39.1, 45.8, 46.3, 72.6 (C_3), 73.1(C_3), 115.0 (C_4), 115.1 (C_4), 115.2 (C_4), 116.1 (C_4); IR (thin film): ν (cm^{-1})=3610 (O–H), 2250 (C≡N); MS (CI+): *m/z* (%) 165 (100) [MH^+]; HRMS (CI+): $C_9H_{13}N_2O$ requires 165.1028, found 165.1026.

4.1.21. Preparation of 2-benzyl-2-(3-oxo-cyclopentyl)-malononitrile (13). 2-Cyclopenten-1-one (**20**) (0.164 g, 2.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.022 g, 0.1 mmol) and benzylmalononitrile (**10**) (0.312 g, 2.0 mmol) in THF (3 mL). After 6 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **13** as a cubic white solid (0.280 g, 61%) (Fig. 13).

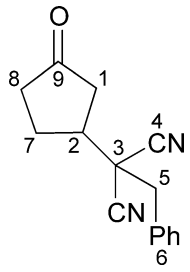


Figure 13.

Compound **13**. Mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.00–2.14 (m, 1H), 2.25–2.41 (m, 3H), 2.42–2.78 (m, 3H), 3.23 (d, J=14 Hz, 1H, H_5), 3.24 (d, J=14 Hz, 1H, H_5), 7.38–7.61 (m, 5H, H_6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=25.8, 37.8, 40.5, 41.6, 42.4, 43.6, 113.8 (C_4), 113.8 (C_4), 128.8, 129.0, 129.8, 131.5, 212.5 (C_9); IR (thin film): ν (cm^{-1})=2245 (C≡N), 1747 (C=O); MS (CI+): *m/z* (%) 239 (67) [MH^+]; HRMS (CI+): $C_{15}H_{15}N_2O$ requires 239.1184, found 239.1193; $C_{15}H_{14}N_2O$ requires C 75.61%, H 5.92%, N 11.76%, found C 74.80%, H 5.96% N 11.60%.

4.1.22. Preparation of *cis/trans*-2-benzyl-2-(3-hydroxy-cyclopentyl)-malononitrile (17). 2-Benzyl-2-(3-oxo-cyclopentyl)-malononitrile (**13**) (0.265 g, 1.11 mmol) and aluminium *tert*-butoxide (0.274 g, 1.11 mmol) were heated to 82 °C in anhydrous propan-2-ol (10 mL). After 13 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**17** as a white crystalline solid (0.214 g, 80%) (Fig. 14).

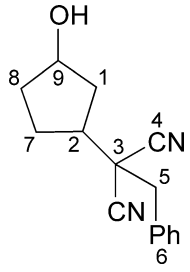


Figure 14.

Compound trans-**17**. Mp 84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.61–1.82 (m, 3H), 1.90–2.10 (m, 2H), 2.13–2.23 (m, 1H), 2.66–2.77 (m, 1H), 3.09 (d, J=14 Hz, 1H, H_5), 3.10 (d, J=14 Hz, 1H, H_5), 4.44 (br s, 1H, H_9), 7.24–7.60 (br s, 5H, H_6).

Compound cis-**17**. 4.26–4.35 (m, 1H, H_9); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, *cis/trans*-**17**): δ=27.2, 34.8, 35.2, 38.9, 39.3, 42.5, 42.8, 44.4, 44.6, 44.7, 72.5 (C_9), 72.9 (C_9), 115.3 (C_4), 115.3 (C_4), 129.2, 129.4, 130.5, 132.6, 132.7; IR (thin film): ν (cm^{-1})=3396 (O–H), 2245 (C≡N); MS (ES+): *m/z* 263 [MNa^+]; HRMS (CI+): $C_{15}H_{17}N_2O$

requires 241.1333, found 241.1335; $C_{15}H_{16}N_2O$ requires C 74.97%, H 6.71%, N 11.66%, found C 74.70%, H 6.79% N 11.60%.

4.1.23. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 11, Table 10). 2-Cyclopenten-1-ol (**11**) (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one (**20**) (0.008 g, 0.1 mmol) were added to a suspension of benzylmalononitrile (**10**) (0.156 g, 1.0 mmol) in dichloromethane (3 mL). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) was added and the solution heated to 100 °C in an ACE pressure tube. After 72 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**17** as a white crystalline solid (0.144 g, 60%).

4.1.24. Meerwein–Ponndorf–Verley equilibration of *trans*-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile *trans*-18. *trans*-2-(3-Hydroxy-cyclohexyl)-2-methyl-malononitrile *trans*-**18** (0.134 g, 0.75 mmol) and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) were heated to 82 °C in a 1:1 mixture of anhydrous propan-2-ol/acetone (10 mL). After 12 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** (62:38 *cis*/*trans*, determined by ^1H NMR) as a white crystalline solid (0.145 g, 100% recovery).

Acknowledgements

We wish to thank the University of Bath, Roche Discovery (P. J. B.), and the E. P. S. R. C. (M. G. E.) for their generous financial support.

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