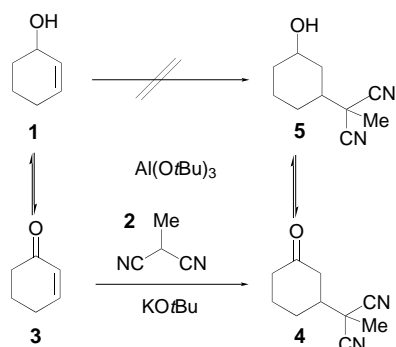


Catalytic Electronic Activation: Indirect Addition of Nucleophiles to an Allylic Alcohol**

Phillip J. Black, William Harris, and Jonathan M. J. Williams*

As a general principle, nucleophiles are able to add to electron-deficient alkenes, but are reluctant to react with electron-rich alkenes.^[1] This is readily demonstrated by a comparison of the reactivity of 2-cyclohexen-1-ol (**1**) and 2-cyclohexen-1-one (**3**) towards the nucleophile derived from methylmalononitrile (**2**).^[2] Whilst **1** was found to be unreactive even after 11 days, **3** underwent facile conjugate addition (4 h, RT, THF, 83%; see Scheme 1).

With increasing worldwide interest in domino and cascade reactions,^[3] we have considered the possibility of temporarily converting an unreactive allylic alcohol **1** into the electronically activated α,β -unsaturated ketone **3**. The electronically activated substrate would then undergo conjugate addition, followed by a restoration of the alcohol functional group from the conjugate addition product **4**. Overall this would lead to an indirect addition of nucleophiles to allylic alcohols to give the addition product **5** (Scheme 1).

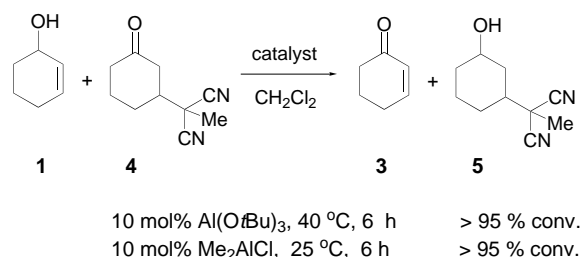


Scheme 1. Catalytic electronic activation of **1** permits conjugate addition followed by subsequent reduction.

For this one-pot approach to be successful, the following criteria must be met: 1) the interconversion of alcohol and ketone must be rapid and reversible; 2) the method for alcohol/ketone interconversion must be compatible with the conjugate addition reaction. The success of the overall

catalytic electronic activation principle depends on these requirements.

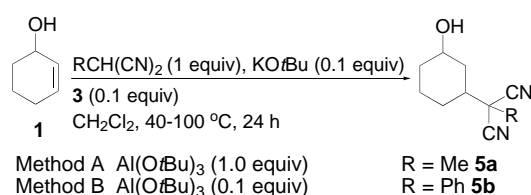
The most straightforward process for alcohol/ketone interconversion is arguably transfer hydrogenation and there is plenty of scope in this area for choice of catalyst.^[4] However, for some rhodium and ruthenium catalysts double-bond migration of allylic alcohols is a known process, affording the saturated ketone by isomerization.^[5] It is for this reason that we have chosen to explore aluminum (Meerwein–Ponndorf–Verley (MPV)) catalysts^[6] for their ability to effect transfer hydrogenation between 2-cyclohexen-1-ol (**1**) and ketone **4** (Scheme 2).



Scheme 2. Oppenauer/MPV crossover.

These data clearly demonstrate that the equilibrium position for the transfer hydrogenation reaction lies firmly to the right, that is towards the thermodynamically more favorable conjugated ketone. This is beneficial for ensuring a constant supply of enone ready for conjugate addition. Surprisingly, both catalysts exhibit excellent activities at substoichiometric levels; a property not normally associated with MPV-type systems.^[6d]

Based on the conditions needed for conjugate addition and for transfer hydrogenation we attempted an indirect nucleophilic addition of methylmalononitrile (**2**) and benzylmalononitrile (**6**)^[2] to 2-cyclohexen-1-ol (**1**) and 2-cyclopenten-1-ol (**7**) (Scheme 3, Method A; Table 1).



Scheme 3. Typical procedure for the domino Oppenauer/Michael addition/MPV process.

Although good yields were obtained for cyclohexyl-derived substrates (Table 1, entries 1 and 5), poor results occurred by using substoichiometric amounts of catalyst (Table 1, entries 2 and 4) and for the cyclopentyl system (Table 1, entries 6 and 7). To address these problems the reactions were studied at elevated temperatures using Ace-Pressure tubes (Scheme 3, Method B).

Therefore, we were delighted with the realization of a fully catalytic reaction (Table 2, entries 1 and 2) when higher reaction temperatures were employed; even when using

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Table 1. Indirect nucleophilic addition to cycloalkenols **1** and **7**.^[a]

Entry	Substrate	Nucleophile	Catalyst [mol %]	<i>t</i> ^[b] [h]	Yield ^[c,d] [%]
1	1	2	Al(<i>Or</i> Bu) ₃ (100)	24	90 ^[e]
2	1	2	Al(<i>Or</i> Bu) ₃ (10)	24	< 5
3	1	2	Me ₂ AlCl(100) ^[f]	24	45
4	1	2	Me ₂ AlCl(10)	24	< 5
5	1	6	Al(<i>Or</i> Bu) ₃ (100)	24	81
6	7	2	Al(<i>Or</i> Bu) ₃ (100)	24	27
7	7	6	Al(<i>Or</i> Bu) ₃ (100)	24	19

[a] The reactions were carried out on a 1 mmol scale in dichloromethane (5 mL) at reflux (Al(*Or*Bu)₃); or at room temperature (Me₂AlCl). [b] Rate studies indicated that the reaction reached near completion after 6–8 h. [c] Yield of isolated product after column chromatography. [d] The maximum expected yield is 90%. [e] Reaction carried out on a 5 mmol scale. [f] Tetrabutylammonium bromide (4 mol %) added to increase dissolution of methylmalononitrile salt.

Table 2. Catalytic indirect nucleophilic addition to cycloalkenols **1** and **7**.^[a]

Entry	Substrate	Nucleophile	Al(<i>Or</i> Bu) ₃ [mol %]	<i>t</i> [h]	Yield ^[b] [%]
1	1	2	10	24	90
2	1	2	10	24	70 ^[c]
3	1	6	10	24	64
4	7	2	100	24	60
5	7	6	100	24	21

[a] The reactions were carried out on a 1 mmol scale in dichloromethane (3 mL) at 100 °C. [b] Yield of isolated product after column chromatography. [c] Cyclohexanone (10 mol %) used as oxidant.

cyclohexanone as an alternative catalytic oxidant (Table 2, entry 2).

However, the increase in temperature does not provide an enhancement in the yields obtained for the cyclopentyl system that we would have anticipated (Table 2, entries 4 and 5). Further experiments using scandium triflate and cerium chloride heptahydrate additives to activate 2-cyclopenten-1-one proved equally unsuccessful. It is suspected that the lower recovered yield at these temperatures is attributed to a competing side reaction (e.g. Pinner^[7] reaction).

In summary, we have 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.^[8] We anticipate that the concept of catalytic electronic activation could be applied to other reactions that are more successful for electron-deficient alkenes than for electron-rich alkenes.

Experimental Section

Typical procedure for the domino Oppenauer/Michael addition/MPV process: Compounds **1** (0.098 g, 1.0 mmol) and **3** (0.009 g, 0.1 mmol) were added to a suspension of **6** (0.156 g, 1.0 mmol) and K*Or*Bu (0.011 g, 0.1 mmol) in CH₂Cl₂ (3 mL). The solution was heated to reflux under nitrogen and aluminum *tert*-butoxide (0.246 g, 1.0 mmol) in CH₂Cl₂ (2 mL) was added dropwise. 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, dried (MgSO₄), and concentrated in vacuo. Purification by flash column chromatography (SiO₂, 50% petroleum ether/diethyl ether) gave **5b** (0.206 g, 81% yield). **5b**_{axial alcohol}: m.p. 106–108 °C; ¹H NMR (500 MHz, C₆D₆, 25 °C): δ = 0.35 (br s, 1H; OH), 0.81 (app. ddt, ³J(H,H) = 2 Hz,

³J(H,H) = 4 Hz, ²J(H,H) = 13.5 Hz, 1H; H_{6ax}), 0.96 (app. dq, ³J(H,H) = 4 Hz, ²J(H,H) = 13 Hz, 1H; H_{4ax}), 1.12 (app. dt, ³J(H,H) = 2 Hz, ²J(H,H) = 13 Hz, 1H; H_{2ax}), 1.17–1.21 (m, 1H; H_{5eq}), 1.25 (br d, ²J(H,H) = 14 Hz, 1H; H_{6eq}), 1.37 (app. tq, ²J(H,H) = 4 Hz, ³J(H,H) = 13 Hz, 1H; H_{5ax}), 1.64 (br d, ²J(H,H) = 12.5 Hz, 1H; H_{4eq}), 1.70 (br d, ²J(H,H) = 13 Hz, 1H; H_{2eq}), 1.99 (app. tt, ³J(H,H) = 3 Hz, ³J(H,H) = 12 Hz, 1H; H_{3ax}), 2.41 (d, ²J(H,H) = 14 Hz, 1H; CHPh), 2.51 (d, ²J(H,H) = 14 Hz, 1H; CHPh), 3.53 (br s, 1H; H_{1eq}), 7.02–7.25 (m, 5H; Ph); IR (C₆D₆): ν̄ = 2282 (C≡N), 3592 cm⁻¹ (O–H); MS (70 eV): *m/z* (%): 254 [*M*⁺], 91 (100) [PhCH₂⁺].

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The tmbp Dianion in the Contact Ion Pair [(tmbp)Na₂(dme)_{1.5}]_n and in the Solvent-Separated Ion Pair [(tmbp)[(2.2.1)Li]₂]^{**}

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Multiple reductions of unsaturated π systems generally provide important information on delocalization processes. Furthermore they often yield fascinating structures that illustrate aggregation and solvation phenomena of cations,^[1] and constitute good models for the modification of solid

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