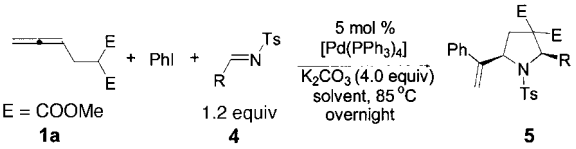
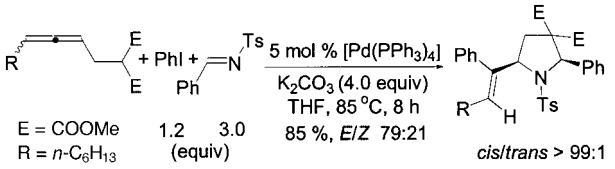
Table 3. [Pd(PPh$_3$)$_4$]-catalyzed tandem double-addition–cyclization of **1a** with PhI and different imines **4** in THF or 1,4-dioxane.[a]



Entry	R	Solvent[b]	5 Yield[%]	*cis*/*trans*	Yield of **2a** [%]
1	*p*-$O_2NC_6H_4$ (**4b**)	THF	89 (**5i**)	95:5	0
2	*p*-$O_2NC_6H_4$ (**4b**)	A	95 (**5i**)	97:3	0
3	*p*-$MeOC_6H_4$ (**4c**)	THF	52 (**5j**)	>99:1	42
4[c]	*p*-$MeOC_6H_4$ (**4c**)	THF	99 (**5j**)	>99:1	0
5	*p*-$MeOC_6H_4$ (**4c**)	A	52 (**5j**)	97:3	29
6	*p*-ClC_6H_4 (**4d**)	THF	95 (**5k**)	>98:2	0

[a] PhI (1.2 equiv) was used. [b] A = 1,4-dioxane; [c] Imine **4c** (3.0 equiv) was used.



Scheme 3. Synthesis of **5l** from **1b** and imine **4a**.

1H), 2.60 (dd, J = 13.70, 5.98 Hz, 1H), 2.39 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 170.04, 167.18, 147.84, 143.71, 139.88, 139.05, 139.04, 135.69, 129.34, 128.55, 128.51, 128.46, 128.38, 128.25, 128.08, 116.63, 68.14, 64.03, 63.83, 53.73, 52.62, 39.28, 21.79 ppm; MS (70 eV): *m*/*z* (%): 520 (14.32) $[M+H]^+$, 364 (100); IR (KBr): $\tilde{\nu}$ = 1749, 1729, 1635, 1597, 1493, 1350, 1165 cm^{-1}; elemental analysis: calcd for $C_{29}H_{29}NO_6S$ (%): C 67.03, H 5.63, N 2.70; found C 67.04, H 5.48, N 2.63.

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Revised: September 10, 2002 [Z19689]

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[15] X-ray data for compound **5a**: $C_{29}H_{29}NSO_6$, M_r = 519.61, triclinic, space group $P\bar{1}$ (#2), a = 10.228(2), b = 13.310(4), c = 9.980(2) Å, V = 1328.9(5) Å^3, α = 97.57(2)°, β = 96.13(2)°, γ = 96.17(2)°, T = 20.0 °C, Z = 2, $\mu(Mo_{K\alpha})$ 1.65 cm^{-1}, reflections collected 4926 (unique 4642), number of data with $I > 3.00\sigma(I)$ 3978, parameters 335, R_1 = 0.043, R_w = 0.057, R_{int} = 0.022. CCDC-189277 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Catalytic Electronic Activation: Indirect "Wittig" Reaction of Alcohols**

Michael G. Edwards and Jonathan M. J. Williams*

Tandem, domino, and cascade reactions have become increasingly popular in recent years, driven by the opportunity to simplify linear sequences and achieve otherwise unfeasible reactions.[1] Contributions from this group have involved the idea of "catalytic electronic activation", which temporarily enhances the electronic nature of a functional group to a given reaction. We have recently reported the indirect addition of

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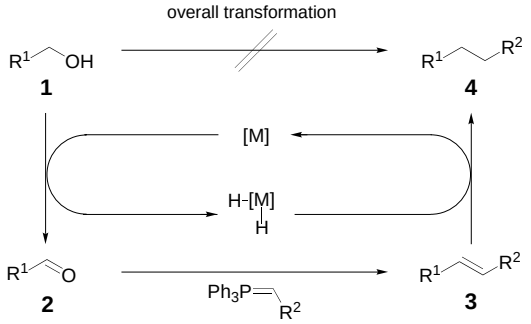
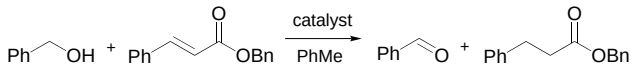
nucleophiles to allylic alcohols[2] and the directed asymmetric epoxidation of enals.[3] Here we report an extension of catalytic electronic activation to the indirect "Wittig" reaction of alcohols (Scheme 1).



Scheme 1. Indirect Wittig reaction of alcohols by catalytic electronic activation.

A substrate alcohol **1** can be activated by dehydrogenation to afford an intermediate carbonyl compound **2**, which will then readily undergo olefination. The sequence is completed by hydrogenation of intermediate alkene **3** to provide the alkane **4**. This domino reaction sequence affords alkane derivatives directly from the alcohol. An important feature of this method is that only one equivalent of alcohol is required where the hydrogen atoms "borrowed" during the oxidation step are subsequently returned in the hydrogenation of the alkene intermediate. Several research groups have reported in situ oxidation of alcohols coupled with Wittig olefination to afford alkene derivatives.[4] However, our system is unusual in that there is no net oxidation transformation. The one-pot sequence illustrated in Scheme 1 potentially offers an alternative to the traditional route involving conversion of alcohol into alkyl halides, malonate substitution and decarboxylation.

The starting point for our studies was to establish that the necessary oxidation and reduction steps were feasible. The crossover transfer hydrogenation reaction between benzyl alcohol and benzyl cinnamate was chosen to demonstrate this (Scheme 2, Table 1). These data indicated that judicious choice of catalyst enabled virtually complete conversion into benzaldehyde and benzyl dihydrocinnamate, respectively. The iridium-based catalyst system reported by Ishii and co-workers[5] (Table 1, entry 7) provided the optimal results, and was the system chosen for examination in the complete cycle.



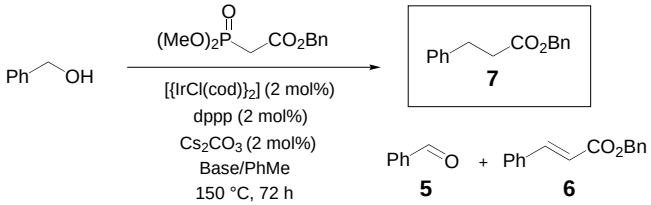
Scheme 2. Crossover transfer hydrogenation (CTH) of benzyl cinnamate with benzyl alcohol.

Table 1. Crossover transfer hydrogenation (CTH) studies.[a]

Entry	Catalyst (mol %)	T [°C]	t [h]	Conv. [%][b]
1	Raney-Ni (25)	110	24	33
2	Pd/C (25)	110	48	65[c]
3	$Al(OtBu)_3$ (100)	110	48	< 5
4	[Ru(η^6-*p*-cymene)(TsDPEN)][d] (5)	110	48	25
5	[Ir(cod)(Py)(PCy_3)]PF_6[e] (4)	150	72	58
6	[{IrCl(cod)}$_2$]/dppp/Cs_2CO_3[f] (2)	80	24	35
7	[{IrCl(cod)}$_2$]/dppp/Cs_2CO_3 (2)	150	72	92

[a] The reactions were carried out on a 0.5 mmol scale in toluene (1.5 mL). [b] Measured by ^{1}H NMR spectroscopy. [c] Reaction run in THF. [d] TsDPEN = (1*S*,2*S*)1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine. [e] Py = pyridine, Cy = cyclohexyl, cod = cycloocta-1,5-diene. [f] dppp = 1,2-bis(diphenylphosphanyl)propane.

An extensive selection of methods exists for the olefination of aldehydes, including several elegant methods reported recently.[6] The method of olefination investigated initially was the Horner–Wadsworth–Emmons (HWE) reaction; the water-soluble phosphate by-product is easily removed and the necessary phosphonates are readily available. Initial results were promising although conversion into the desired product was sluggish despite attempts to optimize the reaction conditions (Scheme 3, Table 2). The best result was obtained with the organic base MTBD (Table 2, entry 3). However, the



Scheme 3. Indirect Horner–Wadsworth–Emmons (HWE) reactions of alcohols.

Table 2. Indirect HWE reactions with benzyl alcohol.[a]

Entry	Phosphonate (equiv)	Base (equiv)	Conv. [%][b]	**5** [%]	**6** [%]	**7** [%]
1	1.0	Cs_2CO_3 (1.0)	59	11	25	23
2[c]	5.0	NaH (5.0)	67	8	11	48
3	1.0	MTBD[d] (1.0)	90	18	14	58
4[e]	1.0	Cs_2CO_3 (1.0)	30	5	3	22

[a] The reactions were carried out on a 0.5 mmol scale in toluene (1.5 mL) at 150 °C. [b] Total conversion of benzyl alcohol into compounds **5**, **6**, and **7** measured by ^{1}H NMR spectroscopy. [c] Na salt of HWE Phosphonate was preformed. [d] MTBD = 1-Methyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine. [e] With Crabtree's catalyst (2 mol %).

significant amount of intermediates **5** and **6** remaining is consistent with the presence of an alternative path for the loss of hydrogen. The coordination of β-carbonyl phosphonates (and derivatives) to metal centers is well known. In particular, they have been used for the extraction of radioactive metal cations.[7] In this respect the slow progression of the cycle is perhaps unsurprising.

We next focused upon the Wittig reaction[8] to achieve the necessary olefination step. It was anticipated that the use of stabilized Wittig ylides would prove to be more successful,

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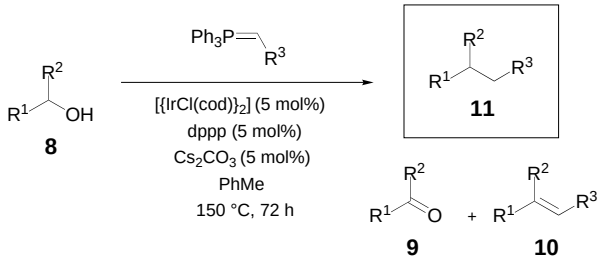
since the problem of chelation to the metal center should be removed (Scheme 4). We were therefore delighted to discover that these reactions proceeded to give the expected alkane products. Optimization of the reaction conditions (5 mol% catalyst, 1.1 equiv ylide) provided a system that was applicable to various benzylic alcohols (Table 3).



Scheme 4. Typical procedure for the domino crossover transfer hydrogenation–Wittig olefination process.

Table 3. Indirect Wittig reaction of alcohol substrates **8**.[a]

Entry	R^1	R^2	R^3	Conv. [%][b]	**9** [%]	**10** [%]	**11** [%][c]
1	Ph	H	CO_2Bn	100	5	12	79(71)[d]
2	Ph	H	CO_2Me	100	21	3	68(51)[d]
3	Ph	H	$CO_2(CH_2tBu)$	96	4	20	68(54)[d]
4	Ph	H	CONMe(OMe)	99	11	11	75(47)[d]
5	Ph	H	CN	84	7	7	70(56)
6	4-ClC_6H_4	H	CN	97	10	8	79(66)
7	2-naphthyl	H	CN	90	16	2	72(46)
8	1-pyrenyl	H	CN	98	25	6	67(52)
9	Ph	Me	CN	77	30	6	41(14)

[a] The reactions were carried out on a 2 mmol scale in toluene (6 mL) at 150 °C. [b] Total conversion of alcohol **8** into compounds **9**, **10**, and **11** measured by ^1H NMR spectroscopy. [c] Figures in brackets refer to the yield of isolated products after column chromatography. [d] Following oxidative removal of the alkene by-product.[11]

The results shown in Table 3 indicate that acceptable yields of the alkane products could be obtained (entries 1–4). Dihydrocinnamate derivatives were synthesized in 46–71% yield, although a small amount of transesterification (< 10%) occurred when the alternative ester ylides were employed. In this regard, the reaction with the cyano ylide was attractive. The reaction afforded only one reduced Wittig adduct, dihydrocinnamonitrile, in 56% yield (Table 3, entry 5). The use of the same nitrile ylide with alternative benzylic alcohols was probed (entries 6–8). Successful reactions with these alcohols yielded the products in 46–66%. Attempts to extend the scope of the reaction to both unactivated alcohols and secondary alcohols were only partly successful. Reaction with *n*-butanol produced less than 5% of the capronitrile product. Reaction with 2-phenylethanol (entry 9) resulted in a low yield of the desired product, 3-phenylbutanenitrile. This is entirely consistent with the lower reactivity of ketones towards Wittig olefination.[9]

In summary, we have developed new methodology for the one-pot conversion of alcohols to alkanes by catalytic electronic activation. We anticipate that application of a more active crossover transfer hydrogenation catalyst will enable the use of more amenable reaction conditions and allow extension of this methodology to a wider range of alcohols.

Experimental Section

Sample procedure:[10] To an argon-purged pressure tube containing [{IrCl(cod)}$_2$] (0.067 g, 0.1 mmol), dppp (0.041 g, 0.1 mmol), Cs_2CO_3 (0.033 g, 0.1 mmol) and benzyl (triphenylphosphoranylidene)acetate (0.782 g, 2.2 mmol) was added benzyl alcohol (0.212 g, 2.0 mmol, 197 μL), followed by anhydrous toluene (6 mL). The tube was sealed and then heated at 150 °C for 72 h. The resulting brown mixture was poured into water (50 mL) and extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with saturated brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 40:1 petroleum ether (b.p. 40–60 °C)/diethyl ether) afforded an inseparable 5.8:1 mixture of benzyl dihydrocinnamate and benzyl cinnamate. The cinnamate by-product was removed oxidatively by using the procedure of Von Rudloff.[11] The mixture was dissolved in 50 mL of a 0.005 M potassium permanganate/0.25 M sodium metaperiodate/0.1 M potassium carbonate solution in 3:2 water/*tert*-butyl alcohol and stirred for 2 h. The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts washed with 1 M sodium hydroxide (2 × 50 mL) and saturated brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford benzyl dihydrocinnamate,[12] a colorless liquid (0.341 g, 71% yield).

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A Straightforward Detection of Deprotonated Conformers of Malonic Acid by Solid-State ^{13}C NMR Spectroscopy

Roxane Colsenet, Carole Gardiennet, Bernard Henry, and Piotr Tekely*

There is wide interest in the study of dicarboxylic acids, which are known to be substrates of a large number of enzymes.[1] Very recently, it has also been reported that malonic acid based inhibitors of matrix metalloproteinases involved in tissue remodeling, and thus in various disease processes such as tumor development and joint destruction, reveal a unique mode of binding to the enzymes.[2] In view of the role of malonic acid in biological metabolism, and of the resulting chemistry, the detection of its deprotonated forms during various processes is of prime importance.

Herein we demonstrate, for the first time, that solid-state ^{13}C NMR spectroscopy permits information to be obtained in a straightforward manner about the presence and the nature of various deprotonated forms of malonic acid in lyophilizates prepared from parent solutions at different pH values. The clear advantage of solid-state over liquid-state NMR spectroscopy arises from the existence of well-separated, isotropic ^{13}C signals for protonated and deprotonated species in the lyophilizate as a result of a dramatic slowing down of inter- and intramolecular proton exchanges on the NMR time scale.[3–4] Another benefit of solid-state measurements results from easy access to the principal values of carbon chemical shift anisotropy (CSA) tensors, which, by virtue of their nature, are much more sensitive to the changes in the ionization state and the hydrogen-bonding interactions than the isotropic chemical shift.[5]

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Figure 1 shows the changes in the isotropic positions in high-resolution ^{13}C cross polarization magic-angle-spinning (CP/MAS) NMR spectra of malonic acid lyophilizates prepared from solutions at different pH values. The principal elements δ_{ii} of protonated and deprotonated carboxy CSA

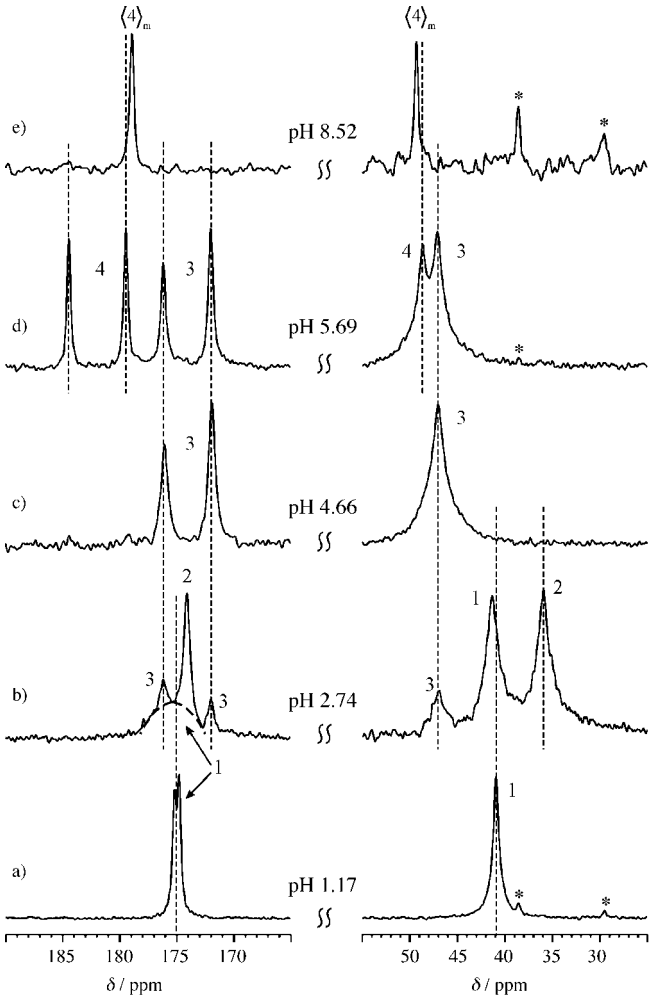

Figure 1. Evolution of isotropic positions in low-speed MAS ($\nu_r = 2.0$ kHz) ^{13}C NMR spectra of malonic acid lyophilized from solutions at pH 1.17 (a), 2.74 (b), 4.66 (c), 5.69 (d), and 8.52 (e). The numbered isotropic peaks refer to malonic acid (1), monoanion conformers (2) and (3), and double deprotonated rigid (4) as well as the motionally averaged ($\langle 4 \rangle_m$) form. For better visualization, the signals in (c) and (e) have been presented with equal height. The signals labeled as * are the isotropic positions of adamantane placed at the bottom of the rotor for the purpose of chemical shift calibration.

tensors were derived from spinning sideband manifolds (Figure 2). The isotropic chemical shifts δ_{iso} and the principal CSA elements δ_{ii} are reported in Table 1. The isotropic chemical shifts of hydroxy protons involved in hydrogen bonding, as revealed from high-speed ^{1}H MAS spectra (not shown), are also included.

The high-resolution ^{13}C spectra show that the successive steps of deprotonation are manifested by sharp changes in the δ_{iso}, δ_{11}, and δ_{22} values, which are significantly different for each species and for individual carboxy groups. We ascribe the two closely placed isotropic resonance peaks at pH 1.17 to

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