Transfer Hydrogenations of Alkenes with Formate on Pd/C: Synthesis of Dihydrocinchona Alkaloids

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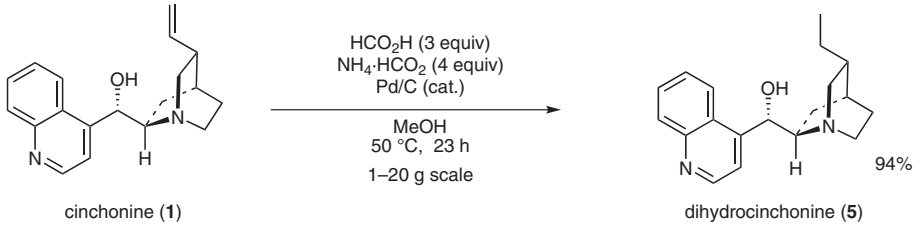
Received: 08.01.2013; Accepted after revision: 14.01.2013

PSP No 246

Abstract: Protocols for preparative (1–80 gram scale) transfer hydrogenations of alkenes over a palladium on carbon catalyst using formic acid/ammonium formate as hydrogen donor are presented. Cinchona alkaloids have been converted to their dihydro derivatives in >94% yield.

Key words: alkaloids, alkenes, catalysis, hydrogen transfer, hydrogenation, palladium



Scheme 1

The catalytic hydrogenation of alkenes over heterogeneous metal catalysts is an important transformation in organic chemistry.[1,2] Among the most common protocols[1,2] is the direct reaction with hydrogen gas over a palladium on carbon[3] catalyst, often at elevated pressure. Pressurized reactions require specialized equipment; in addition, installation of hydrogen cylinders and work with this potentially explosive gas may be subject to necessary, if laborious, safety measures as defined by house rules and local legislation. To reduce the risk of fire or explosion, reactant solutions should be degassed prior to the addition of catalyst and hydrogen.[1] Most of those specific requirements are absent when alkene hydrogenations are performed as transfer hydrogenations,[4] of which those using formic acid[5] or ammonium formate[6] as hydrogen donors are particularly simple and economic. A review on transfer hydrogenations with ammonium formate did not yet mention examples of simple alkenes as substrates.[6] In the meantime, such a procedure has been reported,[7] but was optimized only to the 1 mmol scale.[8] Over the past few years, we have occasionally hydrogenated alkenes on preparative scale and have unequivocally found that transfer hydrogenations with formate offer an operationally simple work-around to direct hydrogenations in pressure equipment. Reactions were performed on multi-gram scales and with up to 0.25 mol of the starting material. Specifically, in our work with cinchona alkaloids as chiral organocatalysts,[9,10] we found it desirable to convert the characteristic alkaloid vinyl to an ethyl group[11] as a simple means of catalyst structure variation.[12] For the basic alkaloids, the use of formic acid alone or with added ammonium formate recommended itself for catalytic transfer hydrogenation (Scheme 1). Reactions in aqueous acid were tested, but this led to precipitation of the alkaloids and incomplete reactions. Methanol was a suitable solvent to dissolve the alkaloids directly (quinine, quinidine) or after addition of formic acid (cinchonine, cinchonidine). Transfer hydrogenations over palladium on carbon proceed at room temperature, but are faster when heated. For safety reasons, reactions were always started at ambient temperature; namely, the addition of the catalyst to the concentrated formate solution induced evolution of gas, even in the absence of substrate (presumably according to $HCO_2H = H_2 + CO_2$). This reaction became quite vigorous at large scales and high concentrations of starting materials. A sufficiently large reaction vessel must be used to allow for some foaming of the reaction mixture at this stage.

Reaction parameters such as the excess of formic acid and ammonium formate, the catalyst quantity, and the reaction temperature were optimized in a series of reactions of increasing scale (100 mg, 500 mg, 1 g, 5 g alkaloid). Isolation of the dihydroalkaloid products from the filtered reaction mixtures by precipitation with aqueous ammonia

SYNTHESIS 2013, 45, 0888–0892
Advanced online publication: 14.02.2013
DOI: 10.1055/s-0032-1318156; Art ID: SS-2013-Z0022-PSP

was also optimized, such that products of satisfactory purity were obtained after washing the solids with water or aqueous methanol, with no need for chromatographic purification. The use of 3–6 equivalents each of formic acid and ammonium formate gave good results. The excess of reagents was lowered for larger-scale reactions. Occasionally, formic acid was combined with triethylamine rather than ammonium formate.[5] The catalyst quantity is an important parameter: a weight ratio of 1:10 (catalyst/substrate) was sufficient in most cases, whereas a ratio of 1:20 often was not. In case of incomplete conversion, the addition of more formate or the use of prolonged reaction times was not overly helpful, but the addition of additional catalyst (and formate) would usually solve the problem. Typically, a catalyst/substrate ratio of 1:15 (w/w) was chosen, or of 1:10 in nonoptimized cases with new substrates. All catalysts were commercial palladium on carbon products with 5–10% of Pd content,[13] some of considerable age. A few experiments were repeated with newly ordered commercial catalysts and gave equally good results, often in shorter reaction times.[13]

The examples shown in Table 1 have been optimized to minimize use of catalyst, reagents, and solvent, at the cost of prolonged reaction times. Faster reactions can be achieved by use of higher catalyst loading and excess formate. The reaction temperature is well below the boiling point of the solvent, thus simple air- rather than water-cooling of the reflux condenser is sufficient. All cinchona alkaloids **1**–**4** were hydrogenated satisfactorily at 5 or 10 gram scales (Table 1, entries 1–4), or in one case also at the 20 gram scale (cinchonine; not shown). The hydrogenation of cinchonidine was successfully repeated by undergraduate students in a synthetic laboratory course.[14] For quinine (entry 3), the reaction mixture was diluted with water, because the alkaloid/formic acid solution in methanol started to crystallize after addition of ammonium formate.

Table 1 Preparative-Scale Transfer Hydrogenations of Various Alkenes over Palladium on Carbon Catalyst[a]

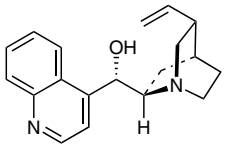
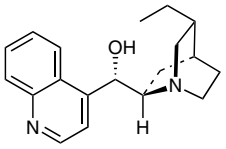
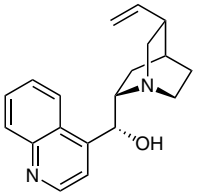
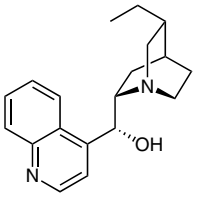
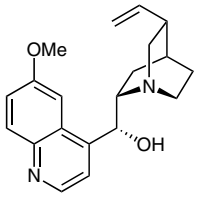
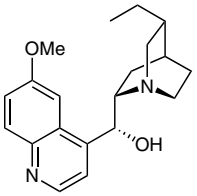
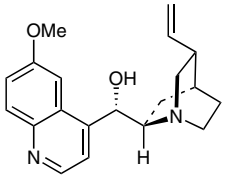
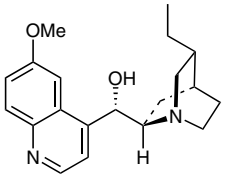
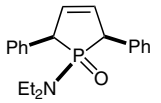
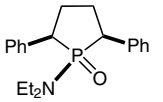
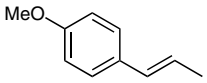
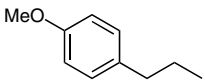
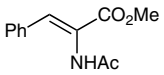
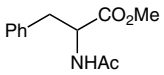
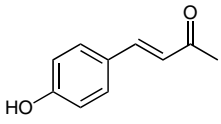
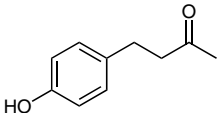
Entry	Substrate	Scale (g)	MeOH (mL)	Cat.[b] (w/w)	AF + FA[c] (equiv)	Temp (°C)	Time (h)	Product	Yield (%)[d]
1		10	50	1/15	4 + 3	50	23		94
	cinchonine (**1**)							**5**	
2		10	50	1/15	4 + 3	50	26		96
	cinchonidine (**2**)							**6**	
3		5	20 + 10 (H_2O)[e]	1/15	4 + 5	55	26		98
	quinine (**3**)							**7**	
4		5	50	1/15	4 + 3	50	23		95
	quinidine (**4**)							**8**	
5		81.3	150	1/16	3.8 + 3.2	45	4		96
	9							**10**	

Table 1 Preparative-Scale Transfer Hydrogenations of Various Alkenes over Palladium on Carbon Catalyst[a] (continued)

Entry	Substrate	Scale (g)	MeOH (mL)	Cat.[b] (w/w)	AF + FA[c] (equiv)	Temp (°C)	Time (h)	Product	Yield (%)[d]
6	 **11**	5	50	1/10	5 + 3	60	36	 **12**	85
7	 **13**	5	50	1/10	6 + 3	50	5	 **14**	90
8	 **15**	5	50	1/10	6 + 3	50	16	 **16**	(48)[f]

[a] Reactions were performed according to the general procedure with given amounts of reagents and solvents; see experimental part.
[b] Weight ratio of 10% Pd on carbon catalyst relative to starting material is given.
[c] AF = ammonium formate, FA = formic acid.
[d] Yield of materials directly crystallized or extracted from the reaction mixture with satisfactory purity, as documented by ^{1}H NMR spectra (see the Supporting Information).
[e] Addition of H_2O for complete solubilization of starting materials.
[f] Yield after TEMPO-oxidation of the crude product; see text.

The *meso*-2,5-dihydro-1*H*-phosphole-1-oxide (**9**) (entry 5), readily prepared by McCormack cycloaddition from Et_2NPCl_2, $AlCl_3$ and (*E*,*E*)-1,4-diphenylbuta-1,3-diene[10,15] is a useful starting material in the synthesis of phospholane ligands.[15] Hydrogenation over Pd/C to phospholane **10** at a pressure of 50 bar has been reported,[15] but we wished to develop a transfer hydrogenation instead. In view of the sensitivity of **9** to bases, which induce isomerization to conjugated 2-phospholenes, the presence of excess formic acid is advantageous to buffer the reaction medium. When ammonium formate is the exclusive hydrogen donor, it decomposes to CO_2 (*g*) and dissolved NH_3, generating a basic reaction medium. Ammonium carbonate is occasionally observed in such reactions since it crystallizes in the reflux condenser. In the presence of formic acid, **9** was successfully hydrogenated to **10**, initially at the 1 gram, then the 5 gram, and eventually at 80 gram scale (entry 5) without isomerization. The high concentration of starting material ensured a short reaction time.

Other compounds of interest were submitted to the transfer hydrogenation conditions, including anethole (**11**) (entry 6) and methyl α-acetamidocinnamate (**13**) (entry 7). A catalyst to substrate ratio of 1:10 was chosen with no further reaction optimization to give very satisfactory yields of **12** or **14**, respectively, with no need for chromatography. A limitation of the method became apparent in the hydrogenation of unsaturated ketone **15** to raspberry ketone **16**; the latter has recently been obtained by an elegant organocatalytic transfer hydrogenation.[16] Transfer hydrogenation of **15** with formate over palladium gave a mixture of product and over-reduced 4-arylbutan-2-ol; oxidation of the crude mixture with NaOCl/TEMPO gave the desired raspberry ketone **16**, albeit in unsatisfactory yield (entry 8). This was somewhat disappointing, since successful (transfer) hydrogenations of **15** over palladium have been reported.[17]

In conclusion, transfer hydrogenations of alkenes with formic acid/ammonium formate over a heterogeneous palladium on carbon catalyst are operationally simple when compared to hydrogenations with H_2 (*g*). They can be performed on preparative scales in simple glassware, at ambient pressure in air. Compared to homogeneous procedures,[8] both the reaction setup and the purification of products are very simple, while the catalyst loading with respect to palladium is similar (1–2 mol%). The dihydrocinchona alkaloids can be synthesized in a simple manner without the need for pressure equipment, and the method should have wider applicability. For new substrates, starting with a catalyst/substrate ratio of 1:10 (w/w), and use of 3–5 equivalents each of formic acid and ammonium formate is recommended.

All reactions were performed in round-bottom glass flasks with a mounted air-cooled reflux condenser open to air. Solvents were of technical quality and were distilled before use. Starting materials, reagents, and catalysts were commercial products unless otherwise mentioned. Technical quality formic acid (98%) and ammonium formate were used as received.

Caution! Dry, active Pd/C catalyst can produce sparks with solvent vapors. Use of wetted catalyst is recommended. The addition of the catalyst to the reaction mixture induces decomposition of formate, which can produce considerable foaming at large scales. Catalyst addition should always take place at r.t., and a reaction vessel with sufficient empty volume above the reaction mixture must be used. New reactions should be scaled up stepwise. Reaction vessels must not be closed tightly to prevent the building of overpressure.

Transfer Hydrogenation of Cinchona Alkaloids; General Procedure

To a stirred solution of the alkaloid (10.00 g, 34.0 mmol for cinchonine or cinchonidine; 30.8 mmol for quinine or quinidine) in MeOH (50 mL) was added formic acid (4.70 g, 102 mmol, 3 equiv) dropwise with vigorous stirring at r.t. Ammonium formate (8.60 g, 136 mmol, 4 equiv) and 10% Pd/C (667 mg) were then added consecutively. After 1 h, the reaction mixture was slowly heated to 50 °C and stirred at that temperature for 23–26 h. Reaction progress was followed by TLC (EtOAc–MeOH–Et_3N, 20:1:1–30:1:1). After cooling, formic acid (1.60 g, 34 mmol) was added dropwise to the mixture with vigorous stirring to dissolve the precipitated product. The mixture was filtered through a 1.5 cm layer of Celite in a 125 mL glass filter funnel and the filter was washed with MeOH (30 mL). The filtrate was evaporated to dryness (rotary evaporator) and H_2O (10 mL) was added to the residue. Concd (28–30%) aq ammonia (50 mL) was slowly dropped into the vigorously stirred suspension to complete precipitation of the product (warming). The mixture was stirred for 15 min with cooling to attain r.t. Filtration and washing of the solid with H_2O (50 mL; note a) gave a white powder, which was collected and dried to constant weight in a ventilated oven at 45 °C (note b).

Notes: a) The washing with H_2O was continued until the product represents a homogeneous fine powder. The washing removes formate salt and formamide impurities. b) Constant weight was attained after drying overnight.

Dihydrocinchonine (5)

Yield: 9.38 g (94%); white powder; mp 270.1–270.6 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.1 Hz, 3 H), 1.19–1.33 (m, 1 H), 1.35–1.42 (m, 2 H), 1.43–1.62 (m, 2 H), 1.70 (s, 1 H), 1.75–2.01 (m, 2 H), 2.68–2.80 (m, 1 H), 2.88–2.91 (m, 2 H), 3.12 (td, *J* = 9.2, 5.0 Hz, 2 H), 5.66 (d, *J* = 5.0 Hz, 1 H), 7.47–7.57 (m, 1 H), 7.60 (d, *J* = 4.5 Hz, 1 H), 7.65–7.76 (m, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 8.90 (d, *J* = 4.5 Hz, 1 H).

The low solubility of **5** in $CDCl_3$ prevented from obtaining a ^{13}C NMR spectrum.

Dihydrocinchonidine (6)

Yield: 9.63 g (96%); white powder; mp 232.0–232.5 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3 H), 1.14–1.33 (m, 2 H), 1.34–1.47 (m, 2 H), 1.47–1.59 (m, 1 H), 1.62–1.86 (m, 2 H), 2.35–2.41 (m, 1 H), 2.56–2.66 (m, 1 H), 2.95–3.21 (m, 2 H), 3.46 (m, 2 H), 5.64 (d, *J* = 4.1 Hz, 1 H), 7.44–7.50 (m, 1 H), 7.58 (d, *J* = 4.5 Hz, 1 H), 7.65–7.71 (m, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 8.12 (d, *J* = 8.5 Hz, 1 H), 8.87 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.1, 21.6, 25.6, 27.6, 28.4, 37.6, 43.3, 58.7, 60.2, 72.3, 118.2, 123.1, 125.8, 126.6, 129.0, 130.4, 148.3, 149.2, 150.2.

Dihydroquinidine (8)

Yield: 4.73 g (95%); white powder; mp 169.5–170.0 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 1.07–1.25 (m, 1 H), 1.41–1.45 (m, 2 H), 1.46–1.56 (m, 2 H), 1.70 (s, 1 H), 1.87–2.03 (m, 1 H), 2.17 (s, 2 H), 2.71–2.79 (m, 1 H), 2.82–2.96 (m, 2 H), 3.00–3.09 (m, 2 H), 3.87 (s, 3 H), 5.59 (d, *J* = 4.3 Hz, 1 H), 7.20 (d, *J* = 2.7 Hz, 1 H), 7.33 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.54 (d, *J* = 4.5 Hz, 1 H), 7.99 (d, *J* = 9.2 Hz, 1 H), 8.68 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (91 MHz, $CDCl_3$): δ = 12.0, 20.9, 25.1, 26.3, 27.1, 37.4, 50.2, 51.2, 55.5, 59.8, 71.9, 101.2, 118.4, 121.4, 126.6, 131.5, 133.4, 144.1, 147.5, 157.6.

Dihydroquinine (7)

Because of solubility reasons, the general reaction conditions were slightly varied: Formic acid (2.15 g, 48 mmol, 3 equiv) was added dropwise with stirring to a mixture of quinine (5.00 g, 15.4 mmol) and ammonium formate (3.90 g, 64 mmol, 4 equiv) in MeOH (20 mL). The resulting suspension was heated to 55 °C, then sufficient H_2O (10 mL) was added to the suspension to give a homogeneous solution. The mixture was cooled to r.t., and 10% Pd/C catalyst (333 mg) was added. After stirring for 1 h at r.t., the mixture was gradually heated to 50 °C and stirred for 26 h at that temperature. Reaction progress was followed by TLC (EtOAc–MeOH–Et_3N, 25:1:1). After cooling to r.t., formic acid (0.74 g, 16 mmol) was added dropwise to the mixture with vigorous stirring. The reaction mixture was filtered through a 1.5 cm layer of Celite in a 125 mL glass filter funnel and the filter was washed with MeOH (20 mL). The filtrate was evaporated (rotary evaporator) to leave a viscous liquid. To this was slowly added concd (28–30%) aq ammonia (30 mL) with stirring, and CH_2Cl_2 (50 mL) was added to the suspension after cooling to r.t. (note). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with concd aq ammonia (30 mL) and H_2O (2 × 30 mL), dried (Na_2SO_4), filtered, and the filtrate concentrated to give a slightly yellow solid (4.90 g, 98%); mp 171.0–171.5 °C.

Note: Isolation of dihydroquinine by filtration was not viable, since the product did not form a nicely crystalline precipitate. In such cases, isolation by extraction is generally recommended.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.3 Hz, 3 H), 1.16–1.32 (m, 2 H), 1.33–1.45 (m, 2 H), 1.46–1.56 (m, 1 H), 1.61–1.82 (m, 3 H), 2.32–2.40 (m, 1 H), 2.49–2.75 (m, 1 H), 2.91–3.18 (m, 2 H), 3.26–3.53 (m, 1 H), 3.76 (s, 1 H), 3.90 (s, 3 H), 5.49 (d, *J* = 4.3 Hz, 1 H), 7.25 (d, *J* = 2.7 Hz, 1 H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.48 (d, *J* = 4.5 Hz, 1 H), 7.96 (d, *J* = 9.2 Hz, 1 H), 8.62 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (91 MHz, $CDCl_3$): δ = 12.1, 21.4, 25.5, 27.7, 28.3, 37.5, 43.3, 55.7, 58.6, 59.7, 72.0, 101.4, 118.4, 121.4, 126.6, 131.4, 144.1, 147.5, 148.0, 157.7.

(1*s*,2*R*,5*S*)-1-(Diethylamino)-2,5-diphenylphospholane 1-Oxide (10)

In a 1 L round-bottom flask, ammonium formate (60.0 g, 0.95 mol) and formic acid (90%; 41.6 g, 0.80 mol) were added to MeOH (150 mL) with stirring. The 10% Pd/C catalyst (5.10 g) was added, which led to an immediate somewhat vigorous gas evolution. (1*s*,2*R*,5*S*)-1-(Diethylamino)-2,5-diphenyl-2,5-dihydro-1*H*-phosphole 1-oxide[10] (**9**; 81.345 g, 0.250 mol) was added and the reaction mixture slowly warmed to 30–35 °C over 1 h, such that gas evolution did not become overly vigorous. The temperature was further increased to 45 °C over 1 h and held at that temperature for 3 h, when the substrate had been fully consumed according to TLC (EtOAc). The reaction mixture was filtered over Celite and the filter washed with several portions of EtOH, H_2O, EtOAc, and again EtOH. The combined filtrates were evaporated in vacuum to remove organic solvents, and the product was extracted from the aqueous slurry with EtOAc (300 mL). The organic phase was collected and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with dil. aq NH_3 until the aqueous phase remained basic (i.e., the smell of NH_3 persists; use of pH indicator paper is recommended). The organic phase was washed with H_2O (3 × 100 mL) and evaporated to a small volume. The residual oil was diluted with a small volume of *t*-BuOMe (50 mL), overlayered with hexanes (200 mL), and set aside for crystallization at 4 °C. Filtration and washing gave **10** (74.79 g, 91%) as colorless needles. The mother liquor was evaporated and recrystallized from *t*-BuOMe–hexanes to give another 3.6 g of **10**; total yield: 78.4 g (96%); mp 109.5–110.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.25 (t, *J* = 7.1 Hz, 6 H), 2.34 (ψ-dq, *J* = 9.0, 7.1 Hz, 4 H), 2.46–2.62 (m, 4 H), 3.68 (dt, *J* = 22.6, 8.2 Hz, 2 H), 7.15–7.22 (m, 2 H_{Ar}), 7.27–7.36 (m, 8 H_{Ar}).

^{13}C NMR (75.4 Hz, $CDCl_3$): δ = 13.4 (d, $J_{P,C}$ = 2.4 Hz), 27.0 (d, $J_{P,C}$ = 13.1 Hz), 38.3 (d, $J_{P,C}$ = 2.7 Hz), 46.3 (d, $J_{P,C}$ = 71.5 Hz), 126.3 (d, $J_{P,C}$ = 2.7 Hz), 127.2 (d, $J_{P,C}$ = 4.8 Hz), 128.4 (d, $J_{P,C}$ = 2.3 Hz), 137.1 (d, $J_{P,C}$ = 5.6 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 67.7 (s).

MS (EI$^+$): *m/z* = 328 (21, $[M + H]^+$), 328 (55, $[M]^+$), 312 (44), 206 (20), 104 (100), 72 (80).

Anal. Calcd for $C_{20}H_{26}NOP$: C, 73.37; H, 8.00; N, 4.28. Found: C, 73.87; H, 7.86; N, 4.21.

1-Methoxy-4-propylbenzene (12)
To a solution of anethole (**11**; 5.00 g, 33.7 mmol) in MeOH (50 mL) was added formic acid (4.70 g, 102 mmol) with stirring. After addition of ammonium formate (10.60 g, 168 mmol) and 10% Pd/C (500 mg), the reaction mixture was stirred for 1 h at r.t., then slowly heated to 60 °C, and stirred at that temperature for 36 h. Reaction progress was monitored by TLC (Et_2O–pentane 1:4). After cooling to r.t., the mixture was filtered through Celite (1.5 cm layer in a 125 mL glass filter) and the filter washed was with MeOH (30 mL). The filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (3 × 20 mL), dried ($MgSO_4$), and filtered. Evaporation in vacuum gave a faint yellow oil (4.23 g, 85%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H), 1.61 (dq, *J* = 14.7, 7.3 Hz, 2 H), 2.41–2.68 (m, 2 H), 3.79 (s, 3 H), 6.68–6.95 (m, 2 H), 6.99–7.20 (m, 2 H).

^{13}C NMR (91 MHz, $CDCl_3$): δ = 13.8, 24.8, 37.2, 55.2, 113.6, 129.3, 134.8, 157.6.

Methyl 2-Acetamido-3-phenylpropanoate (14)
Methyl (*Z*)-2-acetamido-3-phenylacrylate (**13**; 5.00 g, 22.8 mmol) was dissolved in MeOH (50 mL). To the mixture was added formic acid (3.20 g, 69 mmol, 3 equiv) dropwise with vigorous stirring. Ammonium formate (8.60 g, 137 mmol, 6 equiv) and 10% Pd/C (500 mg) were added consecutively. The reaction mixture was stirred at r.t. for 1 h and then slowly heated to 50 °C, and stirred for 5 h at that temperature. Reaction progress was monitored by TLC (EtOAc–hexane, 1:2). After cooling, the mixture was filtered through a 1.5 cm layer of Celite in a 125 mL glass filter funnel and the filter was washed with EtOAc (100 mL). The filtrate was evaporated to dryness, the residue taken up in EtOAc (150 mL) and washed with aq 1 M HCl (15 mL). The organic phase was dried ($MgSO_4$), filtered, and the filtrate evaporated to dryness to give faint yellow crystals (4.50 g, 90%); mp 88.5–89.0 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.95–3.23 (m, 2 H), 3.70 (s, 3 H), 4.86 (dt, *J* = 7.7, 5.9 Hz, 1 H), 6.14 (d, *J* = 6.7 Hz, 1 H), 6.98–7.18 (m, 2 H), 7.19–7.40 (m, 3 H).

^{13}C NMR (91 MHz, $CDCl_3$): δ = 23.1, 37.8, 52.3, 53.1, 127.1, 128.6, 129.2, 135.8, 169.7, 172.1.

4-(4-Hydroxyphenyl)butan-2-one (16)
To a solution of (*E*)-4-(4-hydroxyphenyl)but-3-en-2-one (**15**; 5.00 g, 31 mmol) in MeOH (50 mL) was added formic acid (4.30 g, 93 mmol, 3 equiv) dropwise with stirring, followed by the addition of ammonium formate (11.70 g, 186 mmol, 6 equiv) and 10% Pd/C (500 mg). The reaction mixture was stirred for 1 h at r.t., then heated to 50 °C, and stirred at that temperature for 15 h. Reaction progress was monitored by TLC (EtOAc–hexane, 1:2). After cooling to r.t., the mixture was filtered through Celite, the filter was washed with EtOAc (100 mL), and the filtrate evaporated to dryness. The intermediate alcohol was then oxidized with TEMPO.[18] The residue was taken up in CH_2Cl_2 (50 mL). After addition of KBr (360 mg, 3 mmol; 10 mol%) and 4-NHAc-TEMPO (64 mg, 0.3 mmol; 1 mol%), the mixture was cooled to 0 °C in an ice bath with stirring. A aq solution of NaOCl (27 mL, 1.42 M) containing $NaHCO_3$ (1.1 g) as buffer was added dropwise to the vigorously stirred reaction mixture at 0 °C. After completion of the addition, the reaction mixture was stirred for 3 h at r.t. and monitored by TLC (EtOAc–hexane, 1:2). The organic layer was separated, washed with aq 1 M HCl (80 mL; containing 35.5 mg of KI), 10% aq $Na_2S_2O_3$ (30 mL), and brine (30 mL). After drying ($MgSO_4$), the organic layer was filtered and the filtrate evaporated to dryness to give a slightly yellow solid (2.40 g, 48%); mp 80.5–81.0 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 2.55–2.98 (m, 4 H), 5.73 (s, 1 H), 6.62–6.91 (m, 2 H), 6.91–7.16 (m, 2 H).

^{13}C NMR (91 MHz, $CDCl_3$): δ = 28.9, 30.2, 45.5, 115.4, 129.4, 132.6, 154.2, 209.7.

Acknowledgment

H.W. thanks the DAAD for a research stipend.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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