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A simple, catalytic H_2-hydrogenation method for the synthesis of fine chemicals; hydrogenation of protoporphyrin IX dimethyl ester

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Abstract—A conceptually simple H_2-hydrogenation protocol is introduced for the high-yield preparation of a natural product derivative. Protoporphyrin IX dimethyl ester is hydrogenated to the mesoporphyrin analogue in *N*,*N*-dimethylacetamide under H_2 (1 atm) at 80 °C within 30 min. The reaction is catalyzed by commercial $RuCl_3$, without the need for the use of phosphine- and/or carbene-based ligands.

Catalytic hydrogenations are key reactions for organic synthesis in both laboratory and industrial scales.[1–8] Because H_2 is the cleanest reducing agent, there has been a great deal of interest in developing robust homogeneous catalysts to attain efficient H_2-hydrogenations of a variety of C=C, C=O, and C=N functionalities.[1–11] Historically, the catalysts in these systems 'evolved' from simple late-transition metal salts to platinum metal-based complexes containing phosphine as ligands;[2,8,9] more recently, carbene-containing species have received attention due to their ability to mimic the reactivities of their phosphine counterparts.[12] This catalyst evolution was initially driven by interests in the organometallic chemistry of reaction intermediates and coincided with the development of very active catalysts such as the so-called Wilkinson's catalyst;[9] this represented the origins of the usual phosphine/platinum–metal combination that has dominated the hydrogenation literature since the mid-1960s.[1,2,8,9] Whereas in most of the hydrogenation systems the appropriate choice of the phosphine represents a means of controlling catalytic efficiency and/or selectivity,[1–11] the actual role of the phosphine ligands is not always obvious and, in some cases, these ligands may play no role.[13,14] Our group, for example, while studying the catalytic properties of some Ni(II)-phosphine complexes for hydrogen transfer hydrogenation of ketones, observed that simple NiX_2 salts had comparable (X = Cl) or even higher activity (X = Br, I) than Ni-phosphine complexes themselves.[13,14] Evidently, depending on the catalytic conditions (solvent, temperature, additives, substrate), efforts in designing ligand systems for metal complex catalysts may be unnecessary.

It was first reported in the 1960s that *N*,*N*-dimethylacetamide (DMA) solutions of $RuCl_3$ were able to perform H_2-hydrogenation of simple olefins (e.g., maleic and fumaric acids) under mild conditions.[15–22] Despite the intrinsic, conceptual advantages of the $RuCl_3$–DMA method, that is, no need to prepare ligands or their metal complexes and the low-cost of Ru (compared to the other platinum group metals), there has been no report on the use of this protocol for organic synthesis. In this communication, the convenience of this simple, phosphine-free, $RuCl_3$-based method is explored for the high-yield preparation of mesoporphyrin IX dimethyl ester (H_2mesoPIX-DME) via H_2-hydrogenation of protoporphyrin IX dimethyl ester (H_2PPIX-DME), which involves reduction of vinyl to ethyl groups (Scheme 1).

Because such reduction results in a more stable compound than the parent H_2PPIX,[23] H_2mesoPPIX and its metal complexes have been extensively used in a variety of chemical, biological, and clinical studies.[24–51] The choice of mesoPIX is sometimes dictated by the incompatibility of the vinyl groups of PPIX with the harsh conditions required for the synthesis of heme analogues.[24] Whereas mesoPIX complexes have been traditionally used for studies of reconstituted heme proteins and enzymes (e.g., myoglobin and horseradish

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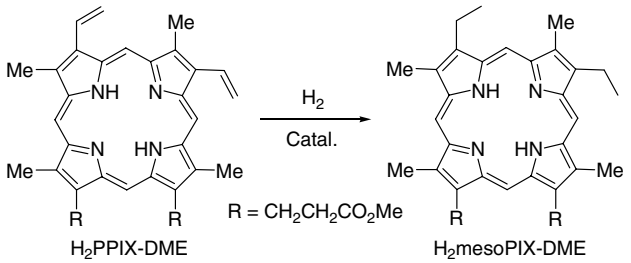


Scheme 1.

peroxidases),[24–36] mesoPIX derivatives have also been particularly useful in studying enzymes such as ferrochelatase[37–40] and heme oxygenase (HO),[41–43] in following heme trafficking within living cells,[44] and in understanding aspects of the synthesis of antihemostatics by blood-sucking insects.[45] The clinical use of a mesoPIX complex, Sn(mesoPIX)Cl_2, for the treatment of hyperbilirubinemia in infants (neonatal jaundice) relies on the potent inhibitory effect that this compound exerts on HO.[46,47] Such an effect has also been explored for functional imaging of HO gene expression in living animals.[48] Of note, Sn(mesoPIX)Cl_2 is a stronger HO inhibitor than is Sn(PPIX)Cl_2.[41]

The H_2-hydrogenation of H_2PPIX-DME, or its chloro-Fe(III) complex, has been traditionally accomplished by using one of three literature protocols (A,[52] B,[53,54] and C;[55] Table 1). In Method A, which is an optimized protocol[52] of Taylor's procedure,[57] Fe(PPIX)Cl is hydrogenated in 90% formic acid using wet PdO as catalyst, and quantitative demetalation of the protohemin occurs concomitantly; although the method affords H_2PPIX in relative high yields, it uses high loadings of Pd per vinyl group (Table 1). A modification uses Pd on carbon (Pd/C) as catalyst and anhydrous formic acid as solvent (Method B); the course of the reaction needs to be monitored spectrophotometrically as over-reduction may occur to yield a chlorin-type compound that shows a UV–vis band at ~650 nm.[54] In an attempt to prevent the formation of side-products that generally accompanied the earlier hydrogenations and contaminated the isolated products,[56] Baker et al.[55] proposed that the hydrogenation of Fe(PPIX)Cl be carried out in aqueous KOH solution (0.2 mol L^{-1}) catalyzed by PtO_2 (Method C); the crude hydrogenation product is then demetalated with concd H_2SO_4. Indeed, although over-reduction has not been observed in Method C[55] and the yield of H_2mesoPIX is comparable to those of Methods A and B (Table 1), the amount of Pt per vinyl group is almost stoichiometric and the 16 h reaction time is long (likely because of the low temperature used in this method).

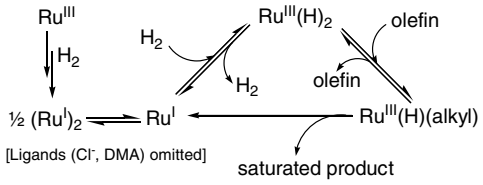
Method D emerged as an adaptation of the PtO_2-catalyzed reduction of '$RuCl_3$' by H_2 in DMF,[58] where the organic substrate H_2PPIX-DME replaced the inorganic substrate '$RuCl_3$'. In this Method, H_2PPIX-DME and PtO_2 in DMF were warmed at 60 °C for 30 min under H_2 (1 atm).[59] The end of the reaction was detected by the disappearance of the UV–vis bands for H_2PPIX-DME; the appearance of a small band at ~650 nm at high conversions indicated that reduction of the vinyl groups was accompanied also by some reduction at the ring as reported previously in Methods A and B;[54,57] the nature of this 'chlorin'-type compound was not investigated further, but the impurity can easily be removed by filtration through a neutral Al_2O_3 plug using $CHCl_3$ (containing 0.75% EtOH) as eluent. The compromise between heating time and product selectivity has been noted.[54,57] Nevertheless, the H_2mesoPIX yield in Method D is close to that of Method C, using ~5 times less catalyst load than that used in C; furthermore, the experimental setup for Method D is convenient as DMF and PtO_2 are used as received, and the work-up procedure is simple. Although no effort was made to recover the PtO_2 catalyst, in larger scale reactions PtO_2 may be filtered off after hydrogenation is completed. Of note, a drawback of Method D is that PtO_2 should not be exposed to mixtures of O_2 (air) and H_2 as a fire may occur; the experimental procedure thus requires flushing with N_2 at the beginning and at the end of the catalytic hydrogenation.[59]

Given that for the preparation of small quantities of H_2mesoPIX-DME on a laboratory-scale, recovery and recycling of the catalyst are not usually a concern, the use of a homogeneous catalyst (vs a heterogeneous one) is justified. The modification of the vinyl groups of H_2PPIX-DME and its Zn(II) or Ni(II) complexes via homogeneous catalysis has received some attention recently. For example, Pereira and coworkers[60,61] found that homogeneous hydroformylation of M(PPIX-DME) (M = H_2, Ni, Zn) can be efficiently accomplished by the use of Rh-phosphine catalysts, while Dolphin and coworkers[62] reported that olefins and M(PPIX-DME) (M = H_2, Zn) undergo cross-metathesis reactions catalyzed by Grubbs-type, Ru-phosphine/carbene catalysts.

Table 1. Catalytic hydrogenation of protoporphyrin IX derivatives under 1 atm H_2

Method	Catalyst (mmol metal)	Solvent (volume)	Vinyl group/catalyst	*T*/°C	*t*/min	% Yield	Ref.
A[a]	PdO (57.1)	HCO_2H (3 L)	2.15	96	60	82[c]	52
B[b]	Pd/C (0.705)	$HCO_2H_{(anhydrous)}$ (120 mL)	4.80	50	45	95[c,d]	53,54
C[a]	PtO_2 (8.81)	$KOH_{(aq)}$ (1.5 L)	1.39	25	960	85[e]	55
D[b]	PtO_2 (0.014)	DMF (50 mL)	7.43	60	30	81[c]	This work
E[b]	'$RuCl_3$' (0.008)	DMA (10 mL)	8.75	80	30	86[c]	This work

[a] Using Fe(PPIX)Cl as starting material; acidic demetalation of crude product mixture yields H_2mesoPIX.
[b] Using H_2PPIX-DME as starting material.
[c] Isolated as H_2mesoPIX-DME.
[d] Purity has been questioned.[56]
[e] Isolated as H_2mesoPIX.



Scheme 2.

Although Wilkinson-type catalysts, $RhCl(PPh_3)_3$ or $RuCl_2(PPh_3)_3$, are the usual choice for H_2-hydrogenation of terminal olefins,[1] the replacement of PtO_2 (Method D) by these phosphine complexes would result in the introduction of an extra step in the synthetic protocol for H_2-hydrogenation of H_2PPIX-DME, that is, the preparation and isolation or purchase of these expensive catalysts. In order to maintain the relative simplicity of Method D, an alternative, $RuCl_3$-based catalytic system was investigated. The ability of DMA or DMF solutions of $RuCl_3$ to catalyze the H_2-hydrogenation of simple olefins has long been recognized,[22] but applications in organic synthesis have remained unexplored. Whereas the kinetic and mechanistic aspects of this phosphine-free, $RuCl_3$-based hydrogenation system are relatively complex (Scheme 2),[15–21] the experimental one-pot procedure is simple: DMA solutions of $RuCl_3$ are warmed to 60–80 °C and reacted with H_2 (1 atm) for 1–2 h to generate a Ru(I)–DMA complex in situ; substrate hydrogenation is then initiated by addition of the olefin.[15,18] A successful H_2-hydrogenation of H_2PPIX-DME via this method (Method E; Table 1) was accomplished.[63] Indeed, Method E combines all the advantages listed for Method D with one additional feature: Ru is the cheapest of the platinum group metals, and indeed $RuCl_3$ can often be acquired free as 'on loan' material from several suppliers. Analogously to methods A, B, and D, formation of the over-reduced, chlorin-type product (band at ~650 nm) is observed at high conversion. The work-up procedure for Method E is identical to that of Method D and the isolated H_2mesoPIX-DME samples from either method are indistinguishable. The convenient and efficient H_2-hydrogenation of H_2PPIX-DME via Method E represents the first example of the use of the simple, phosphine-free, $RuCl_3$–DMA catalytic system in organic synthesis of fine chemicals.

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59. A 125 mL three-neck-round-bottom flask fitted with a reflux condenser and an oil-bubbler was charged with H_2PPIX-DME (30.9 mg, 0.052 mmol), PtO_2 (3.21 mg, 0.014 mmol), and DMF (50 mL), and the mixture was warmed to 60 °C with magnetic stirring. The purple solution was flushed with N_2 for 10 min before H_2 was introduced. The mixture was kept at 60 °C under a slow flow of H_2 for 30 min, when the UV–vis spectrum of a sample of the mixture showed complete conversion to H_2mesoPIX-DME (the 630 nm band of H_2PPIX-DME is replaced by the 620 nm band of H_2mesoPIX-DME[57]). The mixture was flushed with N_2 for 5 min, opened to the atmosphere, and concentrated to ~5 mL. Water (50 mL) was added and the suspension was then filtered through Celite. The purple solid was washed with H_2O, and then MeOH, and collected by elution with CH_2Cl_2; a black solid (presumably PtO_2) remained on the Celite pad. The CH_2Cl_2 solution was evaporated to dryness and the resulting solid was dissolved in ~5 mL of $CHCl_3$ (used as received, containing 0.75% EtOH). This solution was percolated through a neutral Al_2O_3 (Brockmann activity I) plug. The filtrate was collected and evaporated to dryness. The purple solid was further dried in an Abderhalden pistol (EtOH) overnight. Yield: 24.7 mg (81%). Characterization data are below.[63]
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63. The apparatus described above[59] was charged with '$RuCl_3$' (1.91 mg, 0.008 mmol in Ru) and DMA (10 mL), and the mixture was warmed to 80 °C with magnetic stirring. The resulting brownish-red solution was flushed 10 min with Ar and then a slow flow of H_2 was introduced at 80 °C for 1.5 h, during which time the color changed to pale yellow. H_2PPIX-DME (20.7 mg, 0.035 mmol), contained in a glass half-capsule, was then added. After 30 min, the UV–vis spectrum of a sample aliquot showed complete conversion. The mixture was cooled to room temperature, flushed with Ar for 5 min, opened to the atmosphere, and concentrated to ~5 mL. The work-up procedure for isolation of H_2mesoPIX-DME was identical to that described above,[59] except that Ru salts were eliminated in the H_2O/MeOH washings. Yield: 17.9 mg (86%). Anal. Calcd for H_2mesoPIX-DME, $C_{36}H_{42}N_4O_4$: C, 72.70; H, 7.12; N, 9.42. Found: C, 72.91; H, 7.11; N, 9.74. UV–vis (CH_2Cl_2): 398 nm ($\log\varepsilon$/L mol^{-1} cm^{-1}, 5.15), 498 (4.10), 532 (3.94), 568 (3.76), 620 (3.61). IR (KBr): 3314 cm^{-1} (ν_{NH}), 1735 (ν_{CO}). ^{1}H NMR ($CDCl_3$): δ 10.10, 10.09 (2 s, 4H, *meso*-H), 4.42 (t, 4H, $^3J_{HH} = 7.59$ Hz, $CH_2CH_2CO_2$), 4.08 (q, 4H, $^3J_{HH} = 7.62$, CH_2CH_3), 3.65 (s, 6H, CO_2CH_3), 3.64, 3.62 (2s, 12H, CH_3), 3.28 (t, 4H, $^3J_{HH} = 7.59$, CH_2CO_2), 1.85 (t, 6H, $^3J_{HH} = 7.62$, CH_2CH_3). ESI-MS (9:1 MeOH/CH_2Cl_2, positive mode): m/z 595 (100%, $[H_2$mesoPIX-DME$+H]^+$). Spectroscopic data agree with those reported.[52,54,64,65]
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