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Development of a Stepwise Reductive Deoxygenation Process by Ru-Catalysed Homogeneous Ketone Reduction and Pd-Catalysed Hydrogenolysis in the Presence of Cu Salts

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A stepwise catalytic reduction of ketone **1** to alcohol **2** and subsequently to aryl(imidazo[1,2-b]pyridazinyl)methane **3** is described, which provides synthetically useful chemoselectivity at acceptably low catalyst loadings. Undesired reactive sites include an aryl chloride, heteroarylchloride and benzylic amine group. The presence of these functional groups presents a significant challenge to chemoselectivity for both reduction steps. For selective C=O reduction of highly functionalised **1**, high chemoselectivity was observed at low catalyst loading by using Wills' tethered Ru transfer-hydrogenation catalyst **13**. The selective hydrogenolysis of **2** was then accomplished under acidic hydrogenation conditions by using a Pd/C catalyst in the presence of Cu salts. This procedure has been demonstrated on a multi-gram scale, which makes this approach a viable method to use a combination of homogeneous and heterogeneous catalysis.

Introduction

This work describes the development of an efficient two-step catalytic method for the reductive deoxygenation of ketone **1** to aryl(imidazo[1,2-b]pyridazinyl)methane **3**, which is a key building block in the preparation of LY2784544 (Scheme 1). LY2784544 is a JAK2 inhibitor currently undergoing clinical investigations for the treatment of myeloproliferative disorders.[1,2] To date, this deoxygenation has been accomplished in a single step by the treatment of **1** with six equivalents of triethylsilane in the presence of twelve equivalents of trifluoroacetic acid as a promoter and solvent.[2] Although the isolated yields and purity for this transformation are high, the desire to avoid large amounts of fluoride- and silicon-containing waste prompted us to investigate alternatives. We identified two alternative reductions for the single-step deoxygenation, but each had drawbacks. Trichlorosilane with triethylamine worked well,[3] but the volatile nature of trichlorosilane and a difficult reaction workup eliminated this method from contention. Hypophosphorus acid/iodine reductions were also effective,[4] but iodide-induced catalyst poisoning was encountered in the downstream chemistry,[2] which caused us to abandon this approach. Wolff–Kishner reduction and numerous other methods were found to be ineffective, which highlights the surprising difficulty of the desired transformation.

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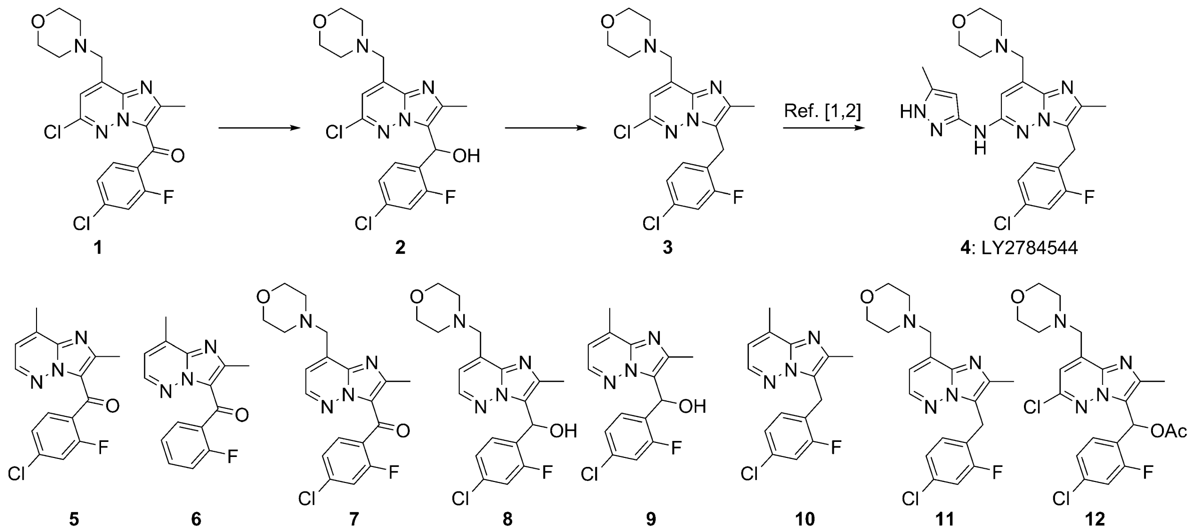
Experimental Results

The most direct catalytic approach to the target molecule would be the hydrogenation of **1** to **2** and the one-pot hydrogenolysis to **3** in the presence of heterogeneous catalysts.[5] A 5% Pd/C catalyst (Johnson Matthey (JM), Type 5R39) was chosen to test a broad range of reaction variables, which include choice of solvent (MeOH, THF, toluene, AcOH, THF/water and THF/AcOH), temperature (30–70 °C) and H_2 pressure (6–30 bar).[6] The consumption of starting material **1** was observed to varying extents but it invariably produced none of the desired product **3**, only traces of **2** and significant amounts of side-products that arise from morpholine cleavage along with dechlorination. The two main side-products were tentatively identified by using LC–MS as **5** and **6**.[6] It is known that additives that act as chloride sources help to suppress dechlorination side-reactions.[5] Hence several acids and salts (including, among others, HCl, NaCl, $ZnCl_2$,[7] $CuCl_2$ and $CuSO_4$) were tested without any noticeable improvement in conversion. Interestingly, $CuCl_2$ and $CuSO_4$ in THF or THF/water were found to reduce the formation of dechlorinated and morpholine-cleaved side-products, although their addition resulted in no conversion of **1**. When the screen was extended to other pre-



Scheme 1. LY2784544, key intermediates 1 and 3 and side-products identified by using LC–MS.

cious-metal catalysts on different supports and in different solvents, only Ir catalysts gave somewhat encouraging results with good selectivity for the reduction of **1** to **2**. $Ir/CaCO_3$ (JM, Type 30) gave a clean conversion to **2** in MeOH (80 °C, 5 bar H_2, 8 h, 5% dry weight catalyst loading) but the conversion remained moderate at best (up to 67% **2**) and the reaction could not be optimised into a preparative process.[6]

As a result of the chemoselectivity problems associated with the direct hydrogenation/hydrogenolysis of **1**, it was decided to switch the research focus to a two-step approach. Initially, **2** was easily prepared by the reduction of **1** with $NaBH_4$. As an alternative to $NaBH_4$, catalytic reductions of **1** with homogeneous transfer-hydrogenation catalysts (Table 1) and hydrogenation catalysts (Table 2) were examined. We exploited the fact that homogeneous catalysts, which operate under an entirely different mechanistic pathway from heterogeneous catalysts, can display much higher chemoselectivity towards carbonyl reduction versus dechlorination and hydrogenolysis.

Table 1. Homogeneous transfer hydrogenation of **1**.[a]

Entry	Catalyst	Hydride source	Amount	S/C	*t* [h]	**2**[b] [%]
1	**13**	NH_4OOCH	10 equiv.	1000:1	16	100
2[c]	**13**	NH_4OOCH	4 equiv.	5000:1	20	100
3	**13**	NH_4OOCH	4 equiv.	10000:1	16	99.5
4	**13**	NaOOCH	4 equiv.	5000:1	16	41
5	**14**	NH_4OOCH	10 equiv.	1000:1	16	60

[a] Reactions were performed at 80 °C in AcOEt/H_2O 4:1 for 16 h on a scale between 0.5 and 4 mmol (0.1–0.8 M). [b] By HPLC analysis, XBridge C18, 4.6×150 mm, 228 nm. [c] Reaction on a 14.2 mmol (6 g) scale.

Table 2. Homogeneous hydrogenation of **1**.[a]

Entry	Catalyst	S/C	*T* [°C]	Solvent	Base (5%)	**2**[b] [%]
1	**15**	100:1	50	MeOH	–	39
2	**16**	1000:1	50	*i*PrOH	*t*BuOK	4
3	**17**	1000:1	50	MeOH	*t*BuOK	3
4	**17**	1000:1	50	*i*PrOH	*t*BuOK	71
5	**17**	2000:1	60	*i*PrOH	*t*BuOK	36
6	**18**	1000:1	50	MeOH	*t*BuOK	100
7	**18**	2000:1	60	MeOH	*t*BuOK	99

[a] Reactions were carried out under H_2 (27 bar) for 16 h on a scale between 0.25 and 0.5 mmol (0.1–0.2 M). [b] By HPLC analysis, XBridge C18, 4.6×150 mm, 228 nm.

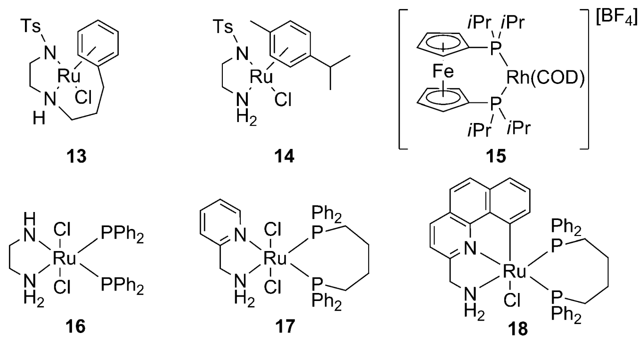


Figure 1. Homogeneous transfer-hydrogenation catalysts (**13** and **14**) and hydrogenation catalysts (**15**–**18**). COD = 1,5-cyclooctadiene.

Following the original work by Wills on tethered Ru chiral catalysts for asymmetric transfer hydrogenation,[8] we have recently developed an achiral version of the catalyst, **13** (Figure 1).[9] Initial tests indicated that different reducing agents were effective: formic acid/triethylamine (5:2 and 1:1 mixtures) as well as sodium formate and ammonium formate in a biphasic system of EtOAc/water. The biphasic system was found to be particularly convenient to facilitate workup and product isolation and rapidly allowed the reduction of the catalyst loading from S/C (equivalents S = substrate/C = catalyst) 1000:1 (Table 1, entry 1) to S/C 5000:1 (entry 2) and S/C 10000:1 (entry 3). Ammonium formate was a more efficient reducing agent than sodium formate (entry 4), and the reaction at S/C 5000:1 (w/w 4280:1, entry 2) was demonstrated on a multi-gram scale. After 20 h, full conversion was achieved to give **2** with a high isolated yield (97%). Although ammonium formate has been previously used with homogeneous transfer hydrogenation for the reductive amination of ketones,[10] selective conversion to **2** was obtained in this case. The non-tethered Noyori catalyst **14**[11] displayed a much lower activity under partially optimised reaction conditions (entry 5). These results confirmed the advantage of the tethered catalyst design already reported in the area of chiral catalysis.[8,9] The improved results are probably a consequence of increased catalyst robustness in the presence of poly-functionalised substrates.

As an alternative catalytic method for the ketone reduction to alcohol, homogeneous achiral hydrogenation catalysts were tested (Table 2, Figure 1). The Rh catalyst **15**,[12] known to reduce ketones, gave partial conversion at S/C 100:1 (Table 2, entry 1). Low conversion was obtained with Noyori's catalyst **16** (entry 2), which was used in *i*PrOH/*t*BuOK as generally required by this class of catalyst.[13] Baratta's catalyst **17**[14] provided up to 71% conversion to **2** at S/C 1000:1 in *i*PrOH/*t*BuOK (entry 4) and 36% conversion at S/C 2,000:1 (entry 5). Catalyst **18**[15] provided increased activity with full conversion at S/C 2000:1 in MeOH with 5% *t*BuOK (60 °C and 27 bar H_2). The higher activity associated with the use of a tridentate amine ligand may be again associated with increased catalyst stability in the presence of substrates that, such as **1**, are capable of various metal coordination modes.

Having in hand some options for a clean and efficient reduction of **1** to **2**, we set out to study the hydrogenolysis step (**2** to **3**), choosing again a 5% Pd/C catalyst (JM, Type 5R39) as the starting point (Table 3). No conversion was obtained in THF/water in the presence of excess NaCl (entry 1). When the reactions were conducted in a 4:1 mixture of THF and 2 N aqueous HCl (four equivalents of HCl to substrate), the main reaction products that could be identified by direct LC–MS analysis of these reactions were **8** and **9**, derived from dechlorination at the pyridazine ring and hydrogenolysis of the benzylic morpholine substituent, and **10**, from further hydrogenolysis of the benzylic alcohol (entry 2). Reduced reaction temperatures only led to increased selectivity towards **8** and **9** (entry 3).

The breakthrough came when it was observed that the addition of Cu salts, $CuCl_2$ and $CuSO_4$, (10% to **2**) had an extraordinary effect on the reaction selectivity (Table 3, entries 4 and 5) to produce for the first time significant amounts of **3**. Following these encouraging results, several solvents were tested in combination with 2 N aqueous HCl, and AcOH was chosen as the preferred solvent for further optimisation (entries 6–9). Alternative Cu salts were also tested, and in each case comparable results were obtained (entries 9–11). The amount of Cu salt additive was optimised in AcOH/aqueous HCl (entries 12–15) and it was found that between 0.5% and 1% $CuSO_4$ gave the highest reaction purity (entries 12 and 13). However, below the 0.5% threshold, an increasing amount of dechlorinated product **11** was formed (entries 14 and 15). Interestingly, when salt additives that did not contain Cu were tested in AcOH/aqueous HCl ($FeCl_2$, $NiCl_2$, $CeCl_3$, $CoCl_2$, $MgBr_2$, $Zn(OAc)_2$), **3** was not formed, and high amounts of dehalogenated product **11** (65–82%) together with minor amounts of **8** were observed (entries 16–21).

Further small-scale experimentation[6] in the presence of 1% $Cu(OAc)_2$ led to the adjustment of the amount of water from 20 to 30% of the total solvent volume (without taking into account that some water is introduced into the reaction from the catalyst; 5% Pd/C is a paste that contains ca. 50% water

Table 3. Small-scale hydrogenolysis of **2** with 5% Pd/C.[a]

Entry	Solvent	Additive [mol%]	Conv.[b] [%]	**3**[b] [%]	Side products
1	THF/H_2O	NaCl	3	–	–
2[c]	THF/HCl 80:20	–	–	–	53% **8** and **9**,[d] 21% **10**
3[e]	THF/HCl 80:20	–	–	–	96% **8** and **9**,[d]
4	THF/HCl 80:20	$CuSO_4$ (10)	43	41	–
5	THF/HCl 80:20	$CuCl_2$ (10)	31	27	–
6	Toluene/HCl 80:20	$CuSO_4$ (10)	94	52	–
7	AcOEt/HCl 80:20	$CuSO_4$ (10)	97	76	–
8	*i*PrOAc/HCl 80:20	$CuSO_4$ (10)	>99	76	–
9	AcOH/HCl 80:20	$CuSO_4$ (10)	>99.5	75	–
10	AcOH/HCl 80:20	$CuCl_2$ (10)	>99.5	76	[f]
11	AcOH/HCl 80:20	$Cu(OAc)_2$(10)	>99.5	78	[f]
12	AcOH/HCl 80:20	$CuSO_4$ (1)	>99	87	[f]
13	AcOH/HCl 80:20	$CuSO_4$ (0.5)	>99	86	[f]
14	AcOH/HCl 80:20	$CuSO_4$ (0.25)	>99	81	11% **11**
15	AcOH/HCl 80:20	$CuSO_4$ (0.125)	>99	50	37% **11**
16	AcOH/HCl 80:20	$FeCl_2$ (1)	>99	–	11% **8**,79% **11**
17	AcOH/HCl 80:20	$NiCl_2$ (1)	>99	–	8% **8**, 65% **11**
18	AcOH/HCl 80:20	$CeCl_3$ (1)	>99	–	12% **8**,78% **11**
19	AcOH/HCl 80:20	$CoCl_2$ (1)	>99	–	8% **8**, 69% **11**
20	AcOH/HCl 80:20	$MgBr_2$ (1)	>99	–	9% **8**, 82% **11**
21	AcOH/HCl 80:20	$Zn(OAc)_2$ (1)	>99	–	7% **8**, 72% **11**
22[g]	AcOH/HCl 70:30	$Cu(OAc)_2$(1)	>99	95	[f]

[a] All reactions were carried out under H_2 (5 bar) at 70 °C in a Biotage Endeavour reactor on a scale of 0.2–0.25 mmol of **2** (0.1 M), with 5% Pd/C 5R39 (5 wt% on a dry basis) for 8–16 h. [b] By HPLC analysis, XBridge C18, 4.6×150 mm, 228 nm. [c] 20 bar H_2 and 70 °C. [d] The HPLC method initially used (entries 1–3) did not separate products **8** and **9**. [e] 20 bar H_2 and 30 °C. The same result was obtained under 5 bar H_2. [f] Dimers were detected in variable amounts. [g] 5% Pd/C A405038 (5 wt% on a dry basis), HCl 1.33 N, [**2**] = 0.1 M, 80 °C, 27.5 bar H_2.

by weight) and to the identification of an alternative catalyst (5% Pd/C, JM, Type A405038). The reaction temperature was increased to 80 °C, the H_2 pressure was increased to 27.5 bar and, on a small scale, the reaction reproducibly gave **3** in 95–96% HPLC purity (from direct HPLC analysis of the crude reaction mixture) (Table 3, entry 22). The only significant side-products detected at this stage corresponded to late-eluting HPLC peaks. Structural assignments made by using a combination of LC–MS and ^{1}H NMR spectroscopy suggested the presence of dimers.[17]

The reaction required the presence of Cu in molar amounts similar to that of Pd (therefore, catalytic with respect to **2**), and there appeared to be an induction time for the formation of a more chemoselective catalyst with >50% of the total impurities formed in the first 2–3 h of the reaction.[6] Further analysis of the crude reaction solution after catalyst separation, indicated a significant reduction in the amount of solubilised Cu, approximately 75% reduction, calculated by comparison to a control reaction with no added Pd/C or substrate. In conjunction, analysis of the separated Pd/C catalyst indicated that a significant amount of Cu was present.[6] Additional experiments confirmed that no reaction occurred in the presence of Cu salts alone (without Pd/C) or by replacing Pd/C with $PdCl_2$ (1 mol%).[6] In the latter case only small amounts of O-acetylated derivative **12** (4%) were detected.[20]

Unfortunately, the reactions in AcOH/aqueous HCl were difficult to reproduce on a multi-gram scale (10–12 g). The best reaction conditions given in Table 3 were repeated in 25 and 50 mL stainless-steel autoclaves but gave reduced conversion to **3** (Table 4, entries 1 and 2). A combination of increased water content (AcOH/aqueous HCl 6 N), reduced reaction temperatures, and a move to Hastelloy Parr autoclaves increased the conversion to **3** (entries 3 and 4).[18] Finally, phosphoric acid was identified as an additional suitable reaction medium (entries 5–8), which appeared to have a slight advantage over acetic acid in terms of reproducibility and overall impurity profile, to provide a small but reproducible increase in the conversion to **3**.[19]

Table 4. Multi-gram-scale hydrogenolysis of **2**.[a]

Entry	Solvent	*t* [h]	*T* [°C]	Conv.[b] [%]	**3**[b] [%]	Yield **3** [%][c]
1[d]	AcOH/HCl 70:30	17	80	>99	60	–
2[d]	AcOH/HCl 70:30	8	70	98	70	–
3	AcOH/HCl 50:50	17	60	99.4	91.5	63 (98.4)
4	AcOH/HCl 50:50	46	50	98	92	72 (98.2)
5	H_3PO_4/HCl 50:50	18	60	99.7	94.2	67 (99.3)
6	H_3PO_4/HCl 50:50	24	60	99.8	94.9	76 (98.9)
7	H_3PO_4/HCl 50:50	24	50	97	92.7	80 (97)
8	H_3PO_4/HCl 50:50	24	60	99.7	94.3	80 (99)

[a] Reactions were carried out on a 10–12 g scale with 5% Pd/C JM 5R39 (5 wt% on a dry basis) and 1.4% $CuSO_4$ in an autoclave under 34.5 bar H_2. [b] By HPLC analysis, XBridge C18, 4.6×150 mm, 228 nm. [c] HPLC purity of isolated **3** in brackets. [d] Catalyst: 5% Pd/C A405038 (5 wt% on a dry basis), 1% $Cu(OAc)_2$, 20 bar H_2.

The optimised hydrogenolysis conditions were 5% Pd/C (5 wt% loading on a dry basis, JM, Type 5R39) with 1.4% $CuSO_4$ in 2.75 volumes of H_3PO_4, 2.75 volumes of 5 N HCl (six equivalents to substrate) in an autoclave under 34.5 bar (500 psi) of H_2 at 60 °C for 24 h (Table 4, entry 6). Although a reaction performed at 50 °C gave a slightly lower conversion (entry 7), the other reactions in H_3PO_4/aqueous HCl (entries 5 and 8) reliably resulted in >99.5% consumption of **2** and <6% area impurities by HPLC. The reaction was estimated to be completed in 14–15 h; little to no increase in impurity levels were observed upon prolonged exposure of the product to the hydrogenolysis conditions. The reaction workup involved catalyst filtration, adjustment of the pH of the aqueous phase with 50% NaOH to approximately 7 and the addition of toluene. Compound **3** was observed to partition into the organic layer. Partial distillation of the toluene layer followed by the addition of heptane resulted in the crystallisation of **3**. The isolated yields were typically 70–80%, with an additional 10–15% lost in the mother liquor.

Conclusions

A stepwise reduction of **1** to **2** and **2** to **3** has been demonstrated, which provides synthetically useful chemoselectivity at acceptably low catalyst loadings. In the presence of supported metal catalysts, **1** was mostly unreactive towards C=O reduction, although other undesired reactions took place more easily. However, we took advantage of the inherently higher chemoselectivity of homogeneous catalysts to overcome the otherwise intractable problem of the reduction of **1** to **2**. In particular, Wills' tethered Ru transfer-hydrogenation catalyst **13** and Baratta's pincer Ru hydrogenation catalyst **18** showed superior reactivity in the presence of highly functionalised **1**.

Substrate **2** became amenable to hydrogenolysis to **3** in the presence of Cu salts, an effect that, to the best of our knowledge, has never been reported. Several salts were tested as additives but only Cu salts prevented both dechlorination side-reactions and hydrogenolysis of the benzylic morpholine. The use of an excess of acids (e.g., HCl) is well established to accelerate the hydrogenolysis of benzylic alcohols as well as to prevent aromatic dechlorination.[5] An additional, well-established effect of the acidic environment is to protonate the basic heterocyclic sites of both substrate and products and to prevent catalyst deactivation.[5] On the contrary, the exact role of the Cu additives in such a complex catalytic system is only a matter of hypothesis. Cu salts completely inhibited the reduction of **1** but were necessary to achieve the chemoselective hydrogenolysis of **2**.

The use of Cu modifiers on supported Pd catalysts under hydrogenation conditions has some precedent in areas as different as selective dechlorination in the presence of C=C bonds,[21] denitration of water[22] and diastereoselective imine reduction.[23] Literature precedents usually employ pre-formed bimetallic Pd-Cu catalysts.[22,23] Depending on the application, it has been suggested that higher selectivity is associated with the presence of Cu^{II} or, more specifically, that a catalytic cycle occurs in which Cu(0) is oxidised to CuO (e.g., in the NO_2 to

NO reduction step), which is then reduced by activated hydrogen from the neighbouring Pd atom.[22] Based on literature data and our own analysis of the reaction mixture after separation of the catalyst, it can be envisaged that under the reaction conditions Cu precipitation occurs to form a metal layer, which acts as modifier of the Pd catalyst.

The current combination of homogenous achiral catalysts and Pd/C in the presence of Cu additives provides the basis for a viable process. Our results highlight the benefits of open-minded experimentation with both homogenous and heterogeneous hydrogenation technology for achiral transformations of synthetic importance.

Experimental Section

Reagents and catalysts: Heterogeneous catalysts are commercially available from Johnson Matthey.[24] Homogeneous catalysts[9,11–15] and **1**[1,2] were prepared according to literature procedures.

HPLC analysis: Waters XBridge C18 column, 4.6×150 mm, 3.5 μm particle size; flow rate = 1.5 mL min^{-1}; T = 30 °C; detection at 228 nm. Solvent A: NH_4OH in water (0.1 mL L^{-1}); Solvent B: NH_4OH in CH_3CN (0.1 mL L^{-1}). Gradient elution: 70% A at t = 0 min to 15% A at t = 8 min, 15% A at t = 15 min to 70% A at t = 16 min, 18 min total run time. Retention times: **2**: 7.4 min; **1**: 8.5 min, **3**: 9.7 min.

Synthesis of 2: A 100 mL round-bottomed flask with a magnetic stirrer bar was charged with **1** (6.0 g, 14.2 mmol), ammonium formate (3.57 g, 56.7 mmol) and **13** (1.4 mg, S/C 5000:1). The flask was purged with N_2, and H_2O (7.1 mL) and EtOAc (28 mL) were added. The slurry was heated to 80 °C for 20 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc (30 mL), and the aqueous phase was separated. The organics were washed with H_2O (3×10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (5.83 g, 97%) was obtained in >99% HPLC purity. Pale yellow powder; m.p. (toluene/heptane) = 133.0–134.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (t, ^3J(H,H) = 8.4 Hz, 1H; CH), 7.23 (s, 1H; CH), 7.21 (dd, ^3J(H,H) = 1.6, 8.4 Hz, 1H; CH), 7.04 (dd, ^3J(H,H) = 1.6, 10.4 Hz, 1H; CH), 6.56 (brs, 1H; CH), 4.01 (brd, ^3J(H,H) = 4.4 Hz, 1H; OH), 3.94 (s, 2H; CH_2), 3.77 (t, ^3J(H,H) = 4.4 Hz, 4H; CH_2), 2.58 (t, ^3J(H,H) = 4.4 Hz, 4H; CH_2), 2.31 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (d, J = 249 Hz), 146.5, 141.5, 138.5, 136.3, 134.4 (d, J = 10.3 Hz), 128.9 (d, J = 4.6 Hz), 126.4 (d, J = 12.0 Hz), 124.4 (d, J = 12.2 Hz), 116.2, 116.0, 115.7, 66.9 (2C), 61.5 (d, J = 3.0 Hz), 55.9, 53.8 (2C), 14.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −114.9 ppm (t, J = 9.4 Hz); IR (neat): $\tilde{\nu}$ = 3268 (br, OH), 2959 (w), 2863 (w), 1610 (m), 1579 (m), 1544 (s), 1486 (m), 1441 cm^{-1} (s); HRMS m/z: calcd for $C_{19}H_{20}Cl_2FN_4O_2$: 425.0942 [M+H]; found: 425.0940.

Synthesis of 3:[2] To a 160 mL Hastelloy Parr reactor were charged **2** (12.05 g, 26.97 mmol), $CuSO_4$ (61 mg, 0.38 mmol), wet Pd/C (1.44 g, JM 5R39, 5 wt% on a dry basis), phosphoric acid (32 mL) and HCl (32 mL, 5 N). The reactor was purged twice with N_2 and three times with H_2. The reaction was placed under 34.5 bar H_2 with stirring at 400 rpm and heated to 60 °C. After 24 h, the reaction mixture was cooled and purged with N_2. HPLC analysis showed 99.7% conversion of **2** and 5.4% area impurities. Toluene (50 mL) was added, and the slurry was stirred for 30 min. The slurry was then filtered through a bed of Hyflo® Super Cel® (filter aid, flux calcined, treated with Na_2CO_3), which was washed with water (36 mL) and then toluene (50 mL). The combined filtrates were added to water (20 mL) and toluene (20 mL). NaOH (35 mL, 50% solution) was then slowly added to the biphasic mixture (exothermic!) to adjust the pH to approximately 7. The organic layer was removed, and the aqueous layer extracted with additional toluene (50 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (0.5 M, 60 mL) and water (2×25 mL). Occasional heat was applied to the solutions to avoid haziness/product precipitation during the extractions. The toluene layer was then concentrated to a volume of approximately 36 mL in a 250 mL flask at 50–60 °C. The product solution was held at 60 °C while heptane (144 mL) was added dropwise over 45 min; 20 mL into the heptane addition, a small amount of seed crystals of **3** was added, which induced product crystallisation. When the heptane addition was complete, the slurry was cooled from 60 to 0 °C over 6 h, and stirred overnight. The solids were isolated by vacuum filtration and were washed with 20% toluene in heptane (36 mL). The solid was dried in vacuo to afford 8.95 g (81.1%). Quantitative HPLC analysis of the filtrate revealed a loss of 1.45 g (3.54 mmol, 13.2%).

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Keywords: hydrogenation · palladium · heterogeneous catalysis · ruthenium · homogeneous catalysis

[1] T. P. Burkholder, J. R. Clayton, L. Ma, Amino pyrazole compound. US Pat. Appl. Publ. US 20100152181A1 20100617; CAN 153:97762, AN 2010:753991.2010.
[2] D. Mitchell, K. P. Cole, P. M. Pollock, D. M. Coppert, T. P. Burkholder, J. R. Clayton, *Org. Process Res. Dev.* **2012**, *16*, 70–81.
[3] R. A. Benkeser, *Acc. Chem. Res.* **1971**, *4*, 94–100.
[4] a) L. D. Hicks, J. K. Han, A. J. Fry, *Tetrahedron Lett.* **2000**, *41*, 7817–7820; b) G. G. Wu, F. X. Chen, D. LaFrance, Z. Liu, S. G. Greene, Y.-S. Wong, J. Xie, *Org. Lett.* **2011**, *13*, 5220–5223; c) J. E. Milne, T. Storz, J. T. Coyler, O. R. Thiel, M. D. Seran, R. D. Larsen, J. A. Murry, *J. Org. Chem.* **2011**, *76*, 9519–9524.
[5] a) G. V. Smith, F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry*, Academic Press, San Diego, USA, **1999**; b) R. L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist*, Marcel Dekker, New York, **1996**; c) P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, USA, **1979**.
[6] Detailed experimental results are reported in the Supporting Information.
[7] G. Wu, M. Huang, M. Richards, M. Poirier, X. Wen, R. W. Draper, *Synthesis* **2003**, *11*, 1657–1660.
[8] a) A. M. Hayes, D. M. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318; b) D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem.* **2006**, *71*, 7035; c) F. K. Cheung, A. J. Clarke, G. J. Clarkson, D. J. Fox, M. A. Graham, C. Lin, A. Lorente Crivillé, M. Wills, *Dalton Trans.* **2010**, *39*, 1395–1402.
[9] K. E. Jolley, A. Zanotti-Gerosa, F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, I. Prokes, D. J. Morris, M. Wills, *Adv. Synth. Catal.* **2012**, *354*, 2545–2555.
[10] For example: J. S. D. Boggs, J. D. Cobb, K. J. Gudmundsson, L. A. Jones, R. T. Matsuoko, A. Millar, D. E. Patterson, V. Samano, M. D. Trone, S. Xie, X.-M. Zhou, *Org. Process Res. Dev.* **2007**, *11*, 539–545.
[11] a) Y. Crameri, K. Puentener, M. Scalone (F. Hoffman–La Roche AG), EP0915076 B1; b) The chiral version of the catalyst was first described by Noyori: S. Hashiguchi, A. Fujii, J. Takeara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; c) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288.
[12] a) M. J. Burk, T. G. P. Harper, J. R. Lee, C. Kalberg, *Tetrahedron Lett.* **1994**, *35*, 4963–4966; b) I. R. Butler, W. R. Cullen, T. J. Kim, *Synth. React. Inorg. Met.-Org. Chem.* **1986**, *75*, 109–116.

[13] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792 – 1796; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1703 – 1707.
[14] W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660 – 1669.
[15] W. Baratta, E. Herddtweck, K. Siega, M. Toniutti, P. Rigo, *Chem. Eur. J.* **2008**, *14*, 9148 – 9160.
[16] Optimised reaction conditions shown in Table 3 were re-tested with **1**, but resulted in no conversion.
[17] The mechanism by which these dimers are formed is unclear. Their formation was strongly impacted by the amount of Cu and H_2 pressure, and low pressures (<6.5 bar) resulted in higher levels of impurities. In the author's experience with other chemical transformations of the aryl-(imidazo[1,2-b]pyridazinyl)methane moiety, this is prone to oxidation especially under radical conditions, possibly because of the existence of a highly stabilised and delocalised radical or ionic reactive intermediate.
[18] Small-scale screening reactions were performed in glass-lined Biotage Endeavour reactors. However, upon performing the reactions in 25 mL 316 stainless-steel Parr reactors, etching and corrosion were observed on the surface of the metal reactor, which were associated with a greenish colour of the reaction mixture and to degradation of the reaction performance with higher levels of dimeric impurities being formed. Upon switching to Hastelloy Parr reactors, no further corrosion was noted.
[19] Acetic acid was felt to be potentially advantageous in the workup because of the possibility for distillative removal. Extraction of the desired free-base product from the phosphoric acid mixture was complicated by the necessary partial quenching of the phosphoric acid with base, which resulted in large quantities of inorganic solids unless a copious amount of water was employed.
[20] Independent preparation of the acetylated product **12** and its submission to standard hydrogenolysis conditions showed no higher conversion than the reaction that started from **2**. Although **12** may be reduced to **3**, there is no evidence that the formation of **12** is necessary for the catalytic cycle.
[21] T. Mallát, J. Petró, *Appl. Catal.* **1990**, *57*, 71 – 81. The improved selectivity of Pd/C catalysts in dehalogenation versus C=C hydrogenation in pyridine and in the presence of Et_3N and Cu salts was attributed to metal deposition on Pd, which partly modifies the active sites.
[22] J. Sá, N. Barrabé, E. Kleymenov, C. Lin, K. Föttinger, J. A. van Bokhoven, M. Nachtegaal, A. Urakawa, G. A. Crespo, G. Rupprechter, *Catal. Sci. Technol.* **2012**, *2*, 794 – 799 and references therein. Bimetallic Pt-Cu and Pd-Cu catalysts are used in water denitration.
[23] J. Müslehiddinoğlu, J. Li, S. Tummala, R. Deshpande, *Org. Process Res. Dev.* **2010**, *14*, 809 – 894. A bimetallic Pd-Cu/C catalyst (Johnson Matthey A701023-4) was used for the highly diastereoselective imine hydrogenation. The Pd-Cu/C catalyst gave a higher selectivity than Pd-Cu/Al_2O_3, which was attributed to the higher amount of Cu^{II} in the Pd-Cu/C catalyst.
[24] *Handbook of Pharmaceutical Catalysis*, **2009**, available at www.jmcatalysts.com/pharma.

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