

# Chemistry A European Journal

 **Chemistry  
Europe**  
European Chemical  
Societies Publishing

## Accepted Article

**Title:** Regioselective Partial Hydrogenation and Deuteration of Tetracyclic (Hetero)aromatic Systems Using a Simple Heterogeneous Catalyst

**Authors:** Roberta A Kehoe, Amy Lowry, Mark E Light, David J Jones, Peter Byrne, and Gerard P. McGlacken

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

**To be cited as:** *Chem. Eur. J.* **2024**, e202400102

**Link to VoR:** <https://doi.org/10.1002/chem.202400102>

## COMMUNICATION

# Regioselective Partial Hydrogenation and Deuteration of Tetracyclic (Hetero)aromatic Systems Using a Simple Heterogeneous Catalyst

Roberta A. Kehoe,<sup>[a,b],§</sup> Amy Lowry,<sup>[a],§</sup> Mark E. Light,<sup>[c]</sup> David J. Jones,<sup>[d]</sup> Peter Byrne<sup>[b,e]</sup> and Gerard P. McGlacken<sup>[a,b],\*</sup>

[a] R. A. Kehoe, Dr A. Lowry, Dr G. P. McGlacken  
School of Chemistry, Analytical and Biological Chemistry Research Facility  
University College Cork, Robert Kane Building  
Western Road, Cork  
E-mail: g.mcglacken@ucc.ie

[b] R. A. Kehoe, Dr P. Byrne, Dr G. P. McGlacken  
Synthesis and Solid State Pharmaceutical Centre (SSPC)  
University of Limerick, Limerick

[c] Dr M. E. Light  
Department of Chemistry,  
University of Southampton,  
SO17 1BJ, United Kingdom

[d] Dr D. J. Jones  
EaStCHEM School of Chemistry,  
University of Edinburgh, Joseph-Black Building  
David Brewster Road, Edinburgh  
EH9 3FJ, United Kingdom

[e] Dr P. Byrne  
Centre for Synthesis and Chemical Biology,  
School of Chemistry, University College Dublin  
Belfield, Dublin 4, Ireland

<sup>§</sup>Both Authors contributed equally. Supporting information for this article is given via a link at the end of the document.

**Abstract:** The introduction of added '3-dimensionality' through late-stage functionalisation of extended (hetero)aromatic systems is a powerful synthetic approach. The abundance of starting materials and cross-coupling methodologies to access the precursors allows for highly diverse products. Subsequent selective partial reduction can alter the core structure in a manner of interest to medicinal chemists. Herein, we describe the precise, partial reduction of multicyclic heteroaromatic systems using a simple heterogeneous catalyst. The approach can be extended to introduce deuterium (again at late-stage). Excellent yields can be obtained using simple reaction conditions.

## Introduction

Aromatic and extended aromatic compounds play a key role in many disciplines of chemistry, and have provided a molecular framework for pharmaceutical drug design in particular.<sup>[1]</sup> At least partially as a consequence of the success of catalytic C(*sp*<sup>2</sup>)-C(*sp*<sup>2</sup>) cross-coupling methodologies, there has been a predominant trend in drug design strategies (over several decades) to focus on rather planar compounds.<sup>[2]</sup> However, the associated 2D character of extended aromatic compounds is often not conducive to clinical success,<sup>[3]</sup> where 3D character is advantageous.<sup>[4]</sup> Indeed, molecules exhibiting greater levels of *sp*<sup>3</sup> character progress further through clinical trials (a trend attributed mainly to greater selectivity and solubility)<sup>[5]</sup> and many of the top selling pharmaceutical drugs contain saturated carbo- and/or heterocyclic ring systems.<sup>[4]</sup>

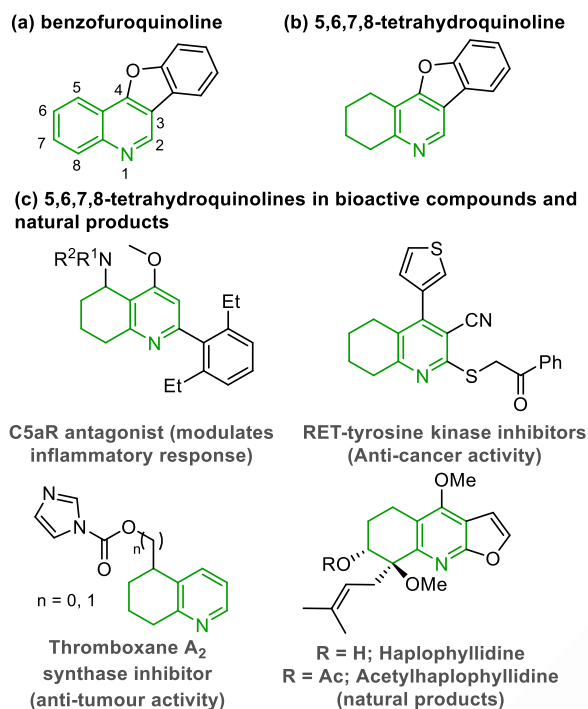
Uncovering new methodologies to form less planar, novel drug candidates is essential for the continued success of medicines through clinical trials. A highly attractive approach that can enable

synthetic access to compounds with a high degree of 3D character while harnessing the unparalleled scope and broad applicability of *sp*<sup>2</sup>-*sp*<sup>2</sup> cross-coupling reactions is to introduce 3D character through hydrogenation of aromatic compounds. As will be demonstrated below, this approach enables selective modification of highly functionalised planar aromatic compounds, and thus is highly suitable for late-stage modification of complex planar compounds of the type that are frequently encountered as precursors (or final products) in the latter stages of syntheses of pharmaceutical compounds.

Quinolines, pyridines and furans represent critically important molecule classes in medicinal and natural product chemistry.<sup>[6]</sup> The partially reduced quinoline motif, tetrahydroquinoline, is also a common pharmacophore and is found in many natural products and pharmacologically relevant therapeutics (**Figure 1 (c)**).<sup>[7]</sup> Benzofuroquinolines (see **Figure 1 (a)**) are biologically significant compounds in which quinoline and benzofuran systems are fused together in a planar tetracyclic aromatic system.<sup>[8]</sup> In the research described herein, we focused on generation of derivatives of these planar compounds containing significant additional 3D

## COMMUNICATION

character (see **Figure 1 (b)**), since non-planar derivatives (containing a higher proportion of  $sp^3$  centres) of fully aromatic bi-, tri- and tetracyclic rings systems frequently possess very different biological activity to their planar, fully aromatic analogues.<sup>[9]</sup>



**Figure 1.** (a) Fused quinoline (green) and benzofuran (black) rings to form the benzofuroquinoline scaffold; (b) carbocyclic reduced tetrahydroquinoline; (c) selected examples of reduced carbocyclic quinolines in bioactive compounds and natural products.

Conditions have been reported under which simple quinolines undergo hydrogenation at either (i) the heterocyclic ring, (ii) the carbocyclic ring, or (iii) both rings.<sup>[10]</sup> However, these conditions are typically harsh, requiring high pressures and temperatures, and the reactions often suffer from issues with selectivity (i.e., competitive reduction of heterocyclic and carbocyclic rings).<sup>[11]</sup> Chemoselective reduction of the carbocyclic ring in these systems is rare, emphasising the urgency for novel methodologies to access these core structures<sup>[10a, 12]</sup> and there is limited work in general on the selective reduction of polycyclic aromatic compounds.<sup>[13]</sup> Selective reduction of the heterocyclic or carbocyclic ring systems in bicyclic compounds mainly utilises specialised homogeneous Pt,<sup>[13a, 14]</sup> Ru,<sup>[15]</sup> and Rh<sup>[16]</sup> catalysis and requires harsh conditions such as strongly acidic solvent, high pressures and/or high temperatures. Although there have been significant advances in homogeneous hydrogenation catalysis,<sup>[17]</sup> heterogeneous catalysis is still at the forefront in industrial processes due to easier handling, separation and potential recyclability of the catalyst. In particular, Pd/C is a simple and accessible heterogeneous catalyst.<sup>[18]</sup>

There are few examples of quinolines undergoing selective hydrogenation using Pd/C using atmospheric hydrogen pressure currently in the literature. Shelke and co-workers selectively reduce the carbocyclic ring in a hydrofuroquinoline derivative using Pd/C (10 mol%), H<sub>2</sub> (atm.) in EtOAc at room temperature for 5 days.<sup>[19]</sup> In 2016, Comins used Pd/C (12 mol%), H<sub>2</sub> (atm.),

Li<sub>2</sub>CO<sub>3</sub> (1.2 eq.) in EtOH at room temperature for 5 days to also yield the reduced carbocycle of the respective 4-methoxyquinoline.<sup>[20]</sup> Recently, Tanaka and Usuki subjected unsubstituted quinoline to Pd/C (10 ml%), H<sub>2</sub> (atm.), AcOH at room temperature for 15 hours and achieved hydrogenation of both the carbo- and heterocycle of quinoline to form decahydroquinoline.<sup>[18d]</sup>

The work described here involves the highly selective partial dearomatisation of benzofuroquinolines using the widely available, simple Pd/C catalyst. Importantly, we also introduce deuterium into the carbocyclic ring through *ex situ* D<sub>2</sub> formation. Our deuterium-based experiments also revealed a surprising insight into the mechanistic pathway.

## Results and Discussion

### Optimisation Studies

We began our optimisation using unsubstituted benzofuroquinoline **1a**. We observed that tetrahydrobenzofuroquinoline **2a** could be formed from **1a** in very high yield using Pd/C (10 mol%) and H<sub>2</sub> (balloon) in AcOH after stirring at room temperature for 24 hours (**Table 1**, entry 1). Reduction of the amount of catalyst (to 5 mol%) also allowed for full conversion at 50 °C (entry 2). Further lowering of catalyst led to reduced amount of product (entries 3 and 4). Using hexafluoroisopropanol ( $pK_a = 9.3$  in H<sub>2</sub>O)<sup>[21]</sup> as solvent instead of AcOH ( $pK_a = 4.72$  in H<sub>2</sub>O)<sup>[22]</sup> resulted in just 9% conversion from **1a** to **2a** (entry 5). Use of trifluoroacetic acid ( $pK_a = -0.3$  in H<sub>2</sub>O)<sup>[23]</sup> also led to selective reduction of the A-ring of **1a** in excellent yield (entry 6).

**Table 1.** Initial optimisation of reaction conditions.

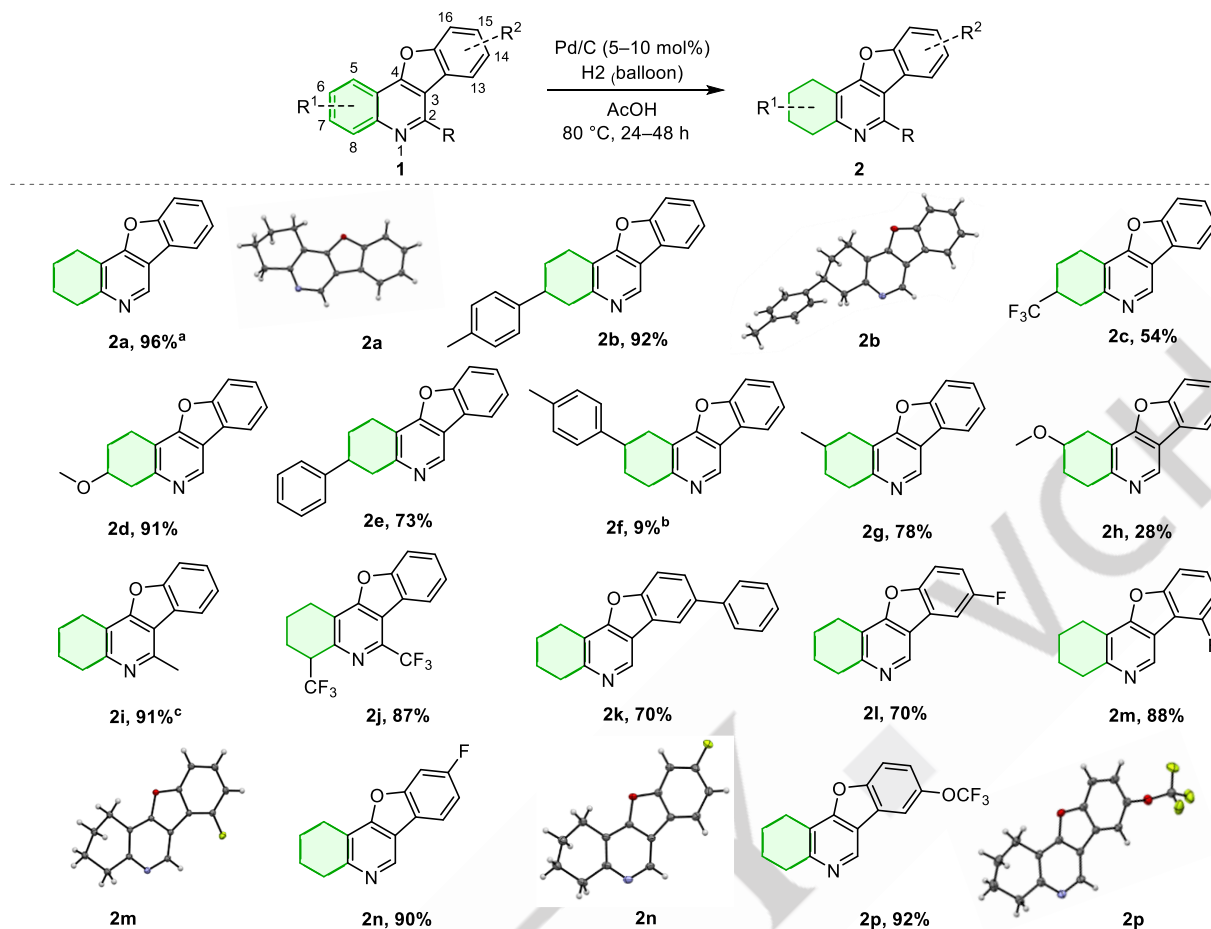
Entry	Pd/C (mol%)	Solvent	Temp. (°C)	% Conversion <sup>a</sup> (Isolated) <sup>b</sup>
1	10	AcOH	r.t.	100 (96)
2	5	AcOH	50	100 (94)
3	2	AcOH	80	75
4	2	AcOH	r.t.	5
5	10	HFIP	r.t.	9
6	10	TFA	r.t.	100 (95)

<sup>a</sup> Conversion determined using <sup>1</sup>H NMR analysis of **1a** and **2a**. <sup>b</sup> Isolated yield in parentheses. HFIP: hexafluoroisopropanol, TFA: trifluoroacetic acid, r.t.: room temperature

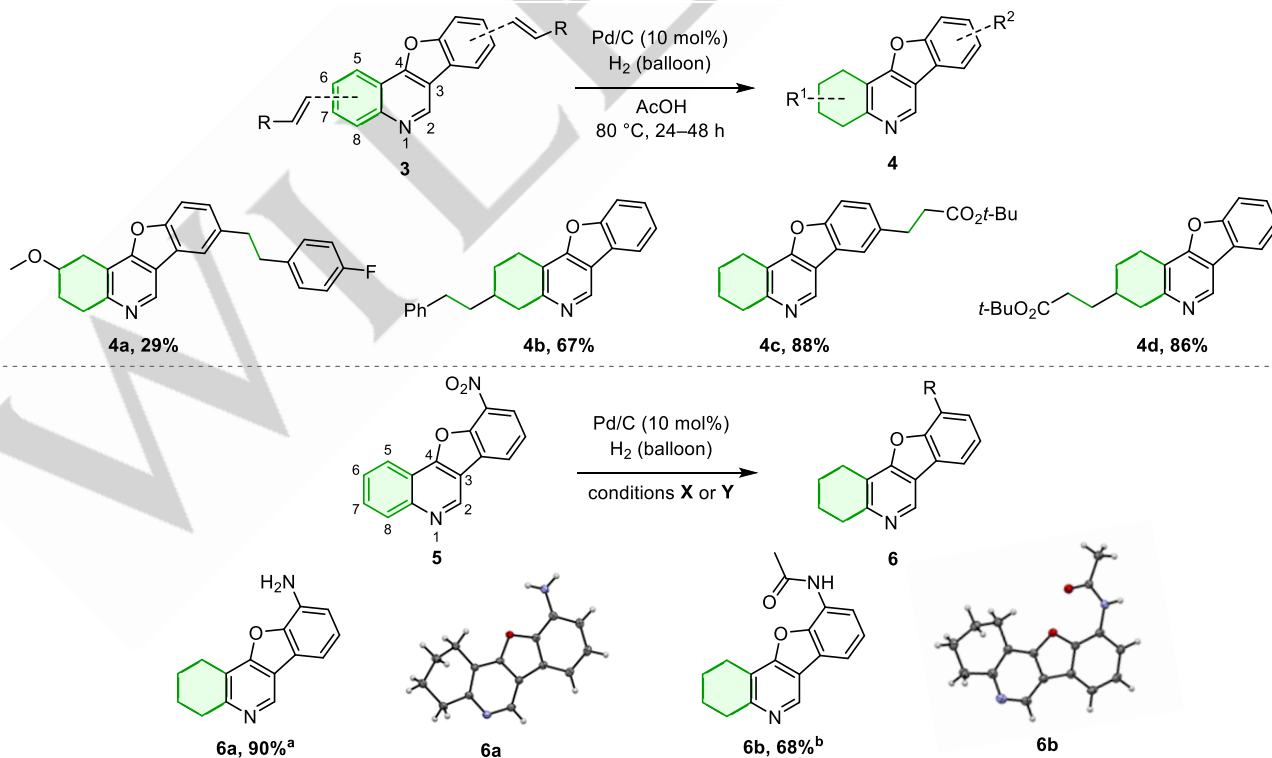
### Substrate Scope

Based on our success in the selective reduction of the A-ring of benzofuroquinoline **1a**<sup>[24]</sup> to **2a** (**Table 1**), we adopted 5 mol% Pd/C, 50 °C, and 24 hour reaction time in AcOH solvent (under a H<sub>2</sub> atmosphere provided through a balloon) as our standard

## COMMUNICATION



**Scheme 1.** Substrate scope with substitution on the A-ring, B-ring and D-ring. <sup>a</sup> Pd/C (5 mol%), 50 °C, 24 h. <sup>b</sup> Pd/C (10 mol%), 100 °C, 72 h. <sup>c</sup> Pd/C (10 mol%), 100 °C, 48 h.



**Scheme 2.** Extended Scope of Selectively Reduced Substituted Benzofuroquinolines. Conditions X: MsOH (2M, 3 eq.) in *i*PrOH, 80 °C, 24 h. Conditions Y: AcOH, 80 °C, 72 h. <sup>a</sup> Used conditions X. <sup>b</sup> Used conditions Y.

## COMMUNICATION

conditions. These conditions were applied in the selective reductions of a diverse array of substituted benzofuroquinolines. Substitution at C-7 of the benzofuroquinoline skeleton did not hinder product formation and selectively reduced products **2b–e** were obtained from the corresponding fully aromatic compounds (**1b–e**) in moderate to excellent yields (54–92%) (**Scheme 1**). 2-Methylbenzofuroquinoline **1i** required elevated temperature and extended time for full reduction of the A-ring. However, an excellent yield (91%) of **2i** was obtained.

Products bearing substituents at the C-6 position were, in some cases, formed in lowered yields (**2f**, **2h**). However, 6-methyl-substituted product **2g** was produced in a yield of 78%. The effect of C-8 substitution on the efficacy of selective A-ring hydrogenation was investigated through examination of the.

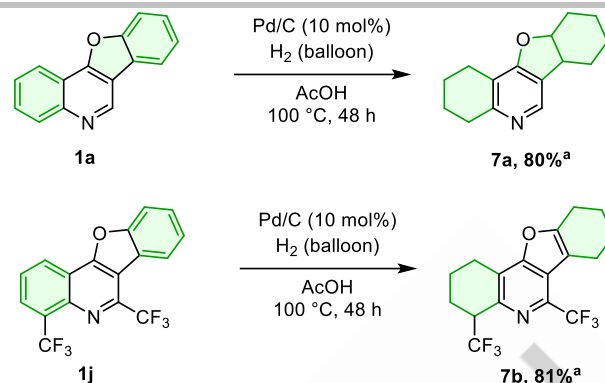
conversion of **1j** (incorporating the 2,8-bis(trifluoromethyl)quinoline motif commonly present in anti-malarial compounds)<sup>[25]</sup> to **2j**. Pleasingly, **2j** was isolated in 87% yield. D-ring substituted products **2k–o** were also obtained in good to excellent yields (68–92%). In several cases (**2a**, **2b**, **2m**, **2n**, **2p**, **3e** and **3f**), the structures of the products were verified by obtaining X-ray crystal structures of the crystalline products.

Next, substrates with olefin pendant groups (easily installed via a Heck-Mizoroki reaction)<sup>[24c]</sup> could have both the carbocyclic ring and the alkene functional group of the starting material reduced (**Scheme 2**), conveniently yielding alkylated products (**4a–4d**) in yields of 29–88% (again, the presence of a methoxy substituent at the 6-position resulted in a low yield for **4a** – cf. compound **2h** in **Scheme 1**). Additionally, we were pleased to find that the acid-labile *tert*-butyl esters in products **4c** and **4d** were retained. Next, the concomitant reduction of a nitro group in substrate **5** was investigated under our standard conditions. Surprisingly, a mixture of the amine product **6a** (ca. 56%) and *N*-acetylated product **6b** (ca. 44%) was observed initially. To achieve selective amine formation, we revisited alternative acids. Pleasingly, we found that using 3 equivalents of methanesulfonic acid (MsOH,  $pK_a = -2.6$  in  $H_2O$ )<sup>[22]</sup> in *i*PrOH allowed for selective formation of **6a** in 90% yield.

Selective hydrogenation of **1a** was also undertaken on larger (5 mmol, 1.10 g) scale, and gave an isolated yield of **2a** of 91% (using Pd/C (5 mol%), AcOH,  $H_2$ , 24 h, 50 °C).

Finally, when the substrates **1a** and **1j** were subjected to extended reaction times, yields of 80% and 81% of **7a** and **7b** respectively, could be obtained (see **Scheme 3**). Interestingly, reduction of three of the four rings in tetracycle **1a**, was observed, leaving the pyridine ring untouched, whereas with the bis-trifluoro compound **1j**, two of the four rings were reduced. For reference, hydrogenation of C2-methylated compound **1i** under the same conditions resulted in reduction of the A-ring only, i.e., in formation of compound **2i** (see **Scheme 1**). Multi-ring reduction products **7a** and **7b** represent new heterocyclic cores and will be the subject of future work.

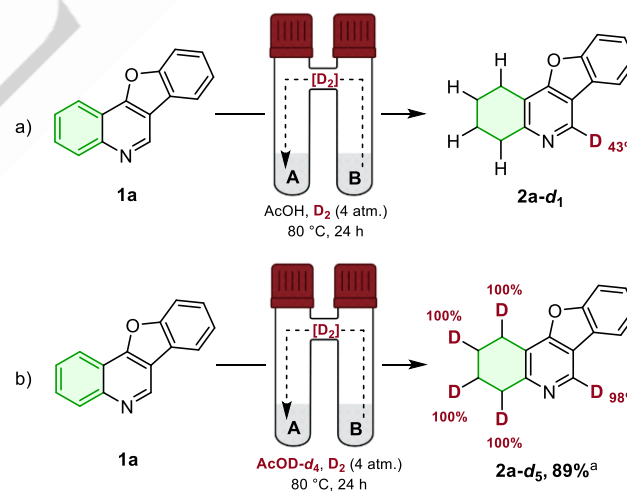
Some competition studies (see SI for details) show that substitution of the A-ring leads to reduced reactivity relative to **1a**. Bias then appears to favour electron donating groups, with **2d** formation outcompeting **2c**, for example (see SI for details).



**Scheme 3.** Highly unusual selectivity; double ring reduction products. <sup>a</sup>Isolated yields.

## Deuterium incorporation

Deuterated compounds have many important applications, and are extensively used in studies of reaction mechanisms and pharmacokinetics.<sup>[26]</sup> Additionally, in 2017, the first deuterium containing drug, deutetrabenazine, was approved by the FDA.<sup>[27]</sup> The difficulty in accessing  $D_2$  gas directly, can in some cases be circumvented by using the 'COWare' apparatus, which allows for *ex-situ* gas generation (**Scheme 4** and SI).<sup>[28]</sup> In our case, using DCI and Zn metal to generate  $D_2$  gas, we observed full reduction *but no deuterium incorporation* into the A-ring (**Scheme 4a**). The source of hydrogen was unclear to us. However when  $AcOD-d_4$  was used in conjunction with  $D_2$ , full incorporation of deuterium was observed (**Scheme 4b**)<sup>[29]</sup> In the latter case, 98% deuterium incorporation was also observed at the C-2 position (**Scheme 4b**).

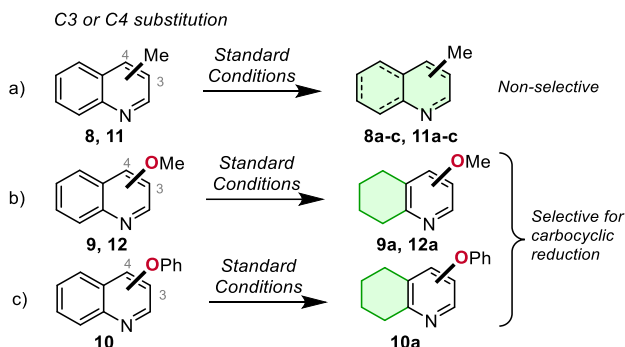


**Scheme 4.** Deuterium incorporation using COWare apparatus. <sup>a</sup>Isolated yield.

To gain an insight into the structural requirements for selective carbocyclic reduction, several carefully chosen substituted quinolines were subjected to the optimised hydrogenation conditions (**Scheme 5**). In reactions of quinolines bearing a methyl or phenyl group substituent at the 3- or 4-position, little or no selectivity was exhibited between hydrogenation of the carbocyclic ring and the heteroaromatic ring (**Scheme 5a**). In contrast, reactions of 3- or 4-methoxy or phenoxy-substituted quinolines exhibited exclusive carbocyclic ring hydrogenation (**Scheme 5b** and **5c**, see SI for conversions and more details).

## COMMUNICATION

This indicates that a more electron rich heterocyclic ring or improved nitrogen basicity impacts the selectivity of this reaction.



**Scheme 5.** Requirements for selective carbocyclic reduction. Standard Conditions: Pd/C (5 mol%), AcOH, H<sub>2</sub> (balloon), 50 °C, 24 h.

## Conclusions

Uncovering practical methodologies to effect small (yet significant) changes to the core structure of medicinally important compounds has recently gained traction, due to the urgent need for increased clinical success of drug candidates.<sup>[3d]</sup> With this type of approach (recently termed molecular editing),<sup>[30]</sup> selectivity is the key. In the work described here, the selective hydrogenation of substituted benzofuroquinolines was demonstrated, using a simple, highly accessible heterogeneous catalyst. This methodology demonstrates a great strategy for late-stage modification of complex heteroaromatic structures of the type that appear widely in existing, highly planar pharmaceutical compounds, thus providing straightforward access to analogues with a high degree of 3-dimensionality. In addition, deuterium could be introduced very conveniently through *in-situ* D<sub>2</sub> formation. The latter experiments suggested that the AcOD-*d*<sub>4</sub> was also a source of the deuterium for the reduction. Finally, the 'O' at the 4-position in these substrates helps control selectivity.

## Supporting Information

The authors have cited additional references within the supporting information.<sup>[31-42]</sup> Deposition Number(s) <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202400102">2115483 (for **2a**), 2288736 (for **2b**), 2304121 (for **2m**), 2267614 (for **2n**), 2288587 (for **2o**), 2298734 (for **6a**), 2267627 (for **6b**)</url> contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

## Acknowledgements

The authors would like to thank Dr Denis Lynch of University College Cork for providing NMR services, the Science Foundation Ireland (grant number SFI/12/IP/1315) and the Synthesis and Solid State Pharmaceutical Centre (SSPC) (SFI/12/RC/2275, SFI/12/RC/2275\_P2 and SFI/ (21/FFP-A/8784).

## Conflict of Interest

The authors declare no conflict of interest.

## References

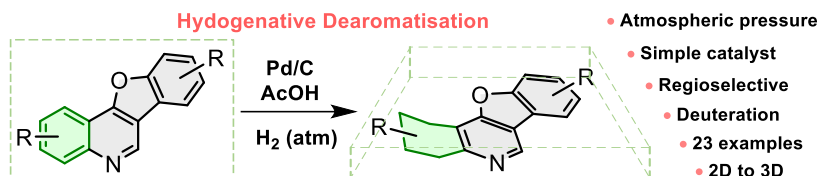
- [1] a) Y. Sanemitsu, S. Kawamura, *J. Pestic. Sci.* **2008**, *33*, 175-177; b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845-5859; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; d) P. Das, M. D. Delost, M. H. Qureshi, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2019**, *62*, 4265-4311.
- [2] a) W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.* **2011**, *54*, 6405-6416; b) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458.
- [3] a) J. A. Kramer, J. E. Sagartz, D. L. Morris, *Nat. Rev. Drug Discov.* **2007**, *6*, 636-649; b) F. Lovering, *MedChemComm* **2013**, *4*, 515-519; c) J. D. Hughes, J. Blagg, D. A. Price, S. Bailey, G. A. DeCrescenzo, R. V. Devraj, E. Ellsworth, Y. M. Fobian, M. E. Gibbs, R. W. Gilles, N. Greene, E. Huang, T. Krieger-Burke, J. Loesel, T. Wager, L. Whiteley, Y. Zhang, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872-4875; d) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756; e) M. Beckers, N. Fechner, N. Stiefl, *J. Chem. Inf. Model.* **2022**, *62*, 6002-6021.
- [4] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348-1349.
- [5] a) W. Wei, S. Cherukupalli, L. Jing, X. Liu, P. Zhan, *Drug Discov. Today* **2020**, *25*, 1839-1845; b) M. Ishikawa, Y. Hashimoto, *J. Med. Chem.* **2011**, *54*, 1539-1554.
- [6] a) M. Napiórkowska, M. Cieślak, J. Kaźmierczak-Barańska, K. Królewska-Golińska, B. Nawrot, *Molecules* **2019**, *24*, 1529-1545; b) B. S. Matada, R. Pattanashettar, N. G. Yernale, *Bioorg. Med. Chem.* **2021**, *32*, 115973-115997; c) E. Khan, *ChemistrySelect* **2021**, *6*, 3041-3064.
- [7] a) R. W. Hartmann, M. Frotscher, *Arch. Pharm.* **1999**, *332*, 358-362; b) C. Jacobs, M. Frotscher, G. Dannhardt, R. W. Hartmann, *J. Med. Chem.* **2000**, *43*, 1841-1851; c) J. K. Barbay, Y. Gong, M. Buntinx, J. Li, C. Claes, P. J. Hornby, G. Van Lommen, J. Van Wauwe, W. He, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2544-2548; d) W. Brandt, L. Mologni, L. Preu, T. Lemcke, C. Gambacorti-Passerini, C. Kunick, *Eur. J. Med. Chem.* **2010**, *45*, 2919-2927; e) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157-7259; f) Z. N. Mamadaliyeva, R. D. Siddikov, S. S. Sagdullaev, *Curr. Tradit. Med.* **2018**, *4*, 166-183.
- [8] a) Y. Long, Z. Li, J.-H. Tan, T.-M. Ou, D. Li, L.-Q. Gu, Z.-s. Huang, *Bioconjugate Chem.* **2012**, *23*, 1821-1831; b) Y. Lin, D. Xing, W.-B. Wu, G.-Y. Xu, L.-F. Yu, J. Tang, Y.-B. Zhou, J. Li, F. Yang, *Molecules* **2020**, *25*, 189-200.
- [9] a) H. Jo, M. Choi, A. S. Kumar, Y. Jung, S. Kim, J. Yun, J.-S. Kang, Y. Kim, S.-b. Han, J.-K. Jung, J. Cho, K. Lee, J.-H. Kwak, H. Lee, *ACS Med. Chem. Lett.* **2016**, *7*, 385-390; b) Ü. M. Koçyiğit, S. Ökten, O. Çakmak, G. Burhan, M. Ataş, P. Taslimi, İ. Gülçin, *ChemistrySelect* **2022**, *7*, e202203469.
- [10] a) M. Freifelder, in *Advances in Catalysis, Vol. 14* (Eds.: D. D. Eley, H. Pines, P. B. Weisz), Academic Press, **1963**, pp. 203-253; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557-2590; c) L. Shi, Y.-G. Zhou, in *Org. React.*, **2018**, pp. 1-228; d) R. Gunasekar, R. L. Goodyear, I. Proietti Silvestri, J. Xiao, *Org. Biomol. Chem.* **2022**, *20*, 1794-1827.
- [11] F. Foubelo, M. Yus, in *Arene Chemistry* (Ed.: J. Mortier), Wiley Online Library, **2015**, pp. 337-364.
- [12] a) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2008**, *47*, 8464-8467; b) Z.-J. Wang, H.-F. Zhou, T.-L. Wang, Y.-M. He, Q.-H. Fan, *Green Chem.* **2009**, *11*, 767-769; c) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878-9891.

## COMMUNICATION

- [13] a) F. W. Vierhapper, E. L. Eliel, *J. Org. Chem.* **1975**, *40*, 2729-2734; b) E. Bresó-Femenia, B. Chaudret, S. Castillón, *Cat. Sci. Technol.* **2015**, *5*, 2741-2751; c) B. Han, P. Ma, X. Cong, H. Chen, X. Zeng, *J. Am. Chem. Soc.* **2019**, *141*, 9018-9026.
- [14] a) F. W. Vierhapper, E. L. Eliel, *J. Am. Chem. Soc.* **1974**, *96*, 2256-2257; b) M. Hönel, F. W. Vierhapper, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933-1939; c) M. Hönel, F. W. Vierhapper, *J. Chem. Soc., Perkin Trans. 1* **1982**, 2607-2610; d) M. Hönel, F. W. Vierhapper, *Monatshefte für Chemie / Chemical Monthly* **1984**, *115*, 1219-1228; e) K. A. Skupinska, E. J. McEachern, R. T. Skerlj, G. J. Bridger, *J. Org. Chem.* **2002**, *67*, 7890-7893; f) A. Solladié-Cavallo, M. Roje, A. Baram, V. Šunjić, *Tetrahedron Lett.* **2003**, *44*, 8501-8503; g) M. Heitbaum, R. Fröhlich, F. Glorius, *Adv. Synth. Catal.* **2010**, *352*, 357-362.
- [15] R. Kuwano, R. Ikeda, K. Hirasada, *Chem. Commun.* **2015**, *51*, 7558-7561.
- [16] a) F. Fache, *Synlett* **2004**, *2004*, 2827-2829; b) F. Martínez-Espinar, P. Blondeau, P. Nolis, B. Chaudret, C. Claver, S. Castillón, C. Godard, *J. Catal.* **2017**, *354*, 113-127; c) S. Kim, F. Loose, M. J. Bezdek, X. Wang, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 17900-17908.
- [17] L. Lückemeier, M. Pierau, F. Glorius, *Chem. Soc. Rev.* **2023**, *52*, 4996-5012.
- [18] a) S. Nishimura, *Org. Process Res. Dev.* **2001**, *5*, 669-670; b) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 7450-7453; c) D.-T. D. Tang, K. D. Collins, J. B. Ernst, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 1809-1813; d) N. Tanaka, T. Usuki, *Eur. J. Org. Chem.* **2020**, *2020*, 5514-5522; e) Z. Mao, H. Gu, X. Lin, *Catalysts* **2021**, *11*, 1078-1104.
- [19] S. J. Gharpure, S. K. Nanda, P. A. Adate, Y. G. Shelke, *J. Org. Chem.* **2017**, *82*, 2067-2080.
- [20] S. V. Tsukanov, L. R. Marks, D. L. Comins, *J. Org. Chem.* **2016**, *81*, 10433-10443.
- [21] E. P. Serjeant, B. Dempsey, *Ionisation constants of organic acids in aqueous solution (IUPAC chemical data series)*, Pergamon Press Oxford, Oxford, **1979**.
- [22] A. T. Tran, J. Tomlin, P. H. Lam, B. L. Stinger, A. D. Miller, D. J. Walczyk, O. Cruz, T. D. Vaden, L. Yu, *ChemEngineering* **2019**, *3*, 81-94.
- [23] D. H. Ripin, D. A. Evans, "pKa values compilation", *can be found under* [http://ccc.chem.pitt.edu/wipf/MechOMs/evans\\_pKa\\_table.pdf](http://ccc.chem.pitt.edu/wipf/MechOMs/evans_pKa_table.pdf), (accessed 1 Nov 2023).
- [24] a) R. M. Shanahan, A. Hickey, F. J. Reen, F. O'Gara, G. P. McGlacken, *Eur. J. Org. Chem.* **2018**, *2018*, 6140-6149; b) R. M. Shanahan, A. Hickey, L. M. Bateman, M. E. Light, G. P. McGlacken, *J. Org. Chem.* **2020**, *85*, 2585-2596; c) R. A. Kehoe, M. E. Light, D. J. Jones, G. P. McGlacken, *Green Chem.* **2023**, *25*, 5654-5660.
- [25] A. R. Hamann, C. de Kock, P. J. Smith, W. A. L. van Otterlo, M. A. L. Blackie, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5466-5469.
- [26] a) J. Atzrodt, V. Derau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022-3047; b) T. Pirali, M. Serafini, S. Cargini, A. A. Genazzani, *J. Med. Chem.* **2019**, *62*, 5276-5297; c) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, *Chem. Rev.* **2022**, *122*, 6634-6718.
- [27] a) A. Mullard, *Nat. Rev. Drug Discov.* **2017**, *16*, 305-305; b) S. H. DeWitt, B. E. Maryanoff, *Biochemistry* **2018**, *57*, 472-473.
- [28] a) A. Modvig, T. L. Andersen, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem.* **2014**, *79*, 5861-5868; b) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, *49*, 594-605.
- [29] *For rational behind these conditions, see SI*
- [30] a) *C&EN Global Enterprise* **2021**, *99*, 41-41; b) J. Jurczyk, M. C. Lux, D. Adpressa, S. F. Kim, Y.-h. Lam, C. S. Yeung, R. Sarpong, *Science* **2021**, *373*, 1004-1012; c) S. H. Kennedy, B. D. Dherange, K. J. Berger, M. D. Levin, *Nature* **2021**, *593*, 223-227; d) C. Hui, Z. Wang, S. Wang, C. Xu, *Org. Chem. Front.* **2022**, *9*, 1451-1457.
- [31] X. Huang, J. Brubaker, W. Zhou, P. J. Biju, L. Xiao, N. Shao, Y. Huang, L. Dong, Z. Liu, R. Bitar, A. Buevich, J. Jung, S. L. Peterson, J. W. Butcher, J. Close, M. Martinez, R. N. MacCoss, H. Zhang, S. Crawford, K. D. McCormick, R. Aslanian, R. Nargund, C. Correll, F. Gervais, H. Qiu, X. Yang, C. Garlisi, D. Rindgen, K. M. Maloney, P. Siliphaivanh, A. Palani, *ACS Med. Chem. Lett.* **2018**, *9*, 679-684.
- [32] E. Landagaray, M. Ettaoussi, M. Rami, J. A. Boutin, D.-H. Caignard, P. Delagrance, P. Melnyk, P. Berthelot, S. Yous, *Eur. J. Med. Chem.* **2017**, *127*, 621-631.
- [33] S. Batsyts, R. Vedmid, J. C. Namyslo, M. Nieger, A. Schmidt, *Eur. J. Org. Chem.* **2019**, *2019*, 1301-1310.
- [34] Y.-Q. Fang, R. Karisch, M. Lautens, *J. Org. Chem.* **2007**, *72*, 1341-1346.
- [35] Y. Zhou, W. Yan, D. Cao, M. Shao, D. Li, F. Wang, Z. Yang, Y. Chen, L. He, T. Wang, M. Shen, L. Chen, *Eur. J. Med. Chem.* **2017**, *138*, 1114-1125.
- [36] S. Adam, *Tetrahedron* **1991**, *47*, 7609-7614.
- [37] F. Hong, Y. Chen, B. Lu, J. Cheng, *Adv. Synth. Catal.* **2016**, *358*, 353-357.
- [38] Y. Lin, D. Xing, W.-B. Wu, G.-Y. Xu, L.-F. Yu, J. Tang, Y.-B. Zhou, J. Li, F. Yang, *Molecules* **2020**, *25*.
- [39] *CrysAlisPro Software System, Rigaku Oxford Diffraction, 2022*.
- [40] G. Sheldrick, *Acta Crystallogr. Sect. A, Found. Crystallogr.* **2015**, *71*, 3.
- [41] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339.
- [42] G. M. Sheldrick, *Acta Crystallogr. Sect. C, Struct. Chem.* **2015**, *71*, 3.

## COMMUNICATION

## Entry for the table of contents



The introduction of added '3-dimensionality' through late-stage functionalisation is a powerful synthetic approach to biologically significant moieties. Herein, a hydrogenative, regioselective dearomatisation of extended (hetero)aromatic systems is described, using a simple Pd catalyst at atmospheric hydrogen pressure. Deuteration is also demonstrated and some initial mechanistic insights are revealed.