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A phosphine free, inorganic base free, one-pot tandem Mizoroki–Heck olefination/direct arylation/hydrogenation sequence, to give multicyclic alkylated heteroarenes†

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One-pot processes which facilitate a number of tandem reactions, represent an environmentally friendly approach to building molecular complexity. In addition, there are significant cost and time saving benefits. However, unearthing multiple reactions that display substrate, reagent and solvent compatibility across two or more reactions, is not straightforward. This is even more pronounced when using catalysts, which by their nature, are present in small amounts and thus susceptible to poisoning. Herein we describe a phosphine-free, inorganic base free, multi-step, one-pot reaction sequence which enables the rapid synthesis of complex, medicinally relevant heterocycles in excellent yields. This Pd-catalysed approach combines Heck olefination, C–H activation, and hydrogenation, and the same pre-catalyst is involved in the three mechanistically distinct processes. Quinolines as substrates are used in the main, but we also provide a neat extension to pyridines and simple aryl substrates. Deuterium (D₂) incorporation can be facilitated through use of the COWare apparatus in the reduction step. Favourable mass productivity (MP), environmental impact factor (EF), solvent intensity (SI) and process mass intensity (PMI) values are reported. While the motivation to avoid problematic additives (inorganic base and P-ligands) and problematic solvent (DMA and NMP) was driven by a green agenda, the removal of reagents and additives in the context of one-pot strategies might also serve to reduce the bad actors and improve yields in one-pot processes.

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Introduction

The design of one-pot, multi-step reaction sequences is highly desirable in the context of green organic synthesis, as molecular complexity is rapidly achieved, whilst avoiding wasteful isolation and purification of reaction intermediates.¹ Achieving substrate, reagent and solvent compatibility across two or more reactions is not straightforward and, thus,

unearthing multiple compatible reactions, which work together in a single medium, is very challenging. This problem is even more pronounced when considering transition metal-catalysed reactions, as catalytic performance can be dramatically influenced by the various reaction inputs and outputs. This presents a barrier to the optimisation of multi-step, one-pot processes as the structure of the initial catalyst is not static, and changes over the course of one or more steps due to interactions with intermediates and by-products. Consequently, individual reaction optimisation is less applicable and due regard must be given to the potential role of other upstream or downstream reaction components. Auto-tandem catalysis is defined as a domino reaction process in which one catalyst promotes two or more fundamentally distinct chemical transformations in a single reactor.² There has been tremendous progress in the development of Pd-catalysed auto-tandem processes, in a bid to develop greener synthetic methods. A key feature of this approach is that Pd acts as the catalyst in two sequential, one-pot reactions.³ Interestingly, extending this concept to the development of processes with three or more mechanistically distinct Pd-catalysed reactions

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†Electronic supplementary information (ESI) available: Full characterisation data on each isolated compound, further optimisation details and crystallographic data for nine novel compounds. CCDC 2143462, 2143446, 2204946, 2211708, 2204910, 2201481, 2204956, 2204818 and 2204795. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3gc01403g>



has proven challenging and examples are sparse in the literature.⁴

Fagnou and co-workers previously reported a rare example of a three-reaction process, wherein a series of benzochromenes were prepared in good yields (Scheme 1). While this exquisite example demonstrates the power of auto-tandem catalysis, there is clear potential for further green chemistry improvement and expansion.

Quinolines, pyridines and furans represent important molecule classes in medicinal and natural product chemistry.⁵ Core quinoline, pyridine and furan motifs are the 22nd, 2nd and 25th most abundant of the 351 ring systems present in FDA-approved drugs respectively.⁶ Direct arylation *via* C–H activation of these moieties has received significant attention in recent years, as the protocol avoids the introduction of activating groups, and the associated waste. Direct arylation *via* C–H activation also facilitates the introduction of new aryl groups which could be difficult using traditional (Het)Ar–(Het)Ar bond forming processes such as the Suzuki–Miyaura and Stille reactions.⁷ This is especially the case with intramolecular reactions, where the installation of halides and boronic acids (or stannanes) onto a single substrate is often difficult.

We posited that intramolecular direct arylation of quinolines could be coupled with a Mizoroki–Heck alkenylation and a hydrogenation in a one-pot sequence to give decorated tri- and tetra-cyclic quinolines with a built-in benzofuran. However, we were also aware that the quinoline nitrogen atom can ligate Pd^{8a} and thus effect a synergistic or deleterious effect on any of the three Pd-mediated process.⁸ In any case, we were keen to apply a ‘bottom-up’ green chemistry approach to develop tricyclic alkylated heterocycles, bearing key functionalities relevant to medicinal chemistry.

We set ourselves the specific challenges of (1) minimising catalyst loading (2) eliminating the need for a P-ligand (3) avoiding the use of toxic solvents such as DMA and NMP and (4) carrying out the reactions in air. Herein we describe the successful execution of these goals (Scheme 1). We expand the substrate scope from quinolinyl to pyridinyl and simple aryl ethers. Also, for the first time in these types of processes, we introduce deuterium *via* reduction of the Heck products using the COware apparatus (which circumvents the difficulty in

accessing D₂ gas). Finally, some initial investigation of the catalytic species required for each step is presented.

Results and discussion

Optimisation study

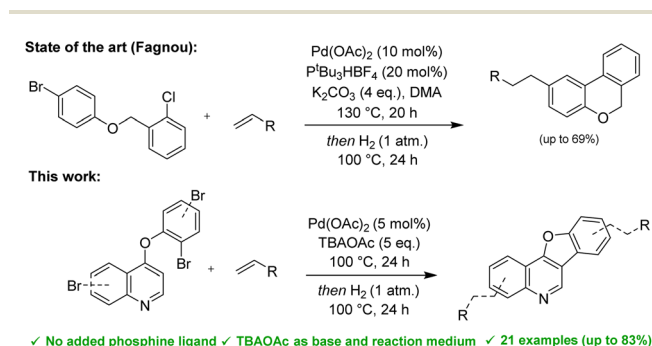
As a starting point, we revisited our previously reported one-pot, two-step methodology involving a Mizoroki–Heck/direct arylation sequence with a view toward obviating the need for *N*-methylpyrrolidone (NMP) as solvent.^{8a,9,10} We began our optimisation efforts with a number of more desirable solvents (Table 1 and ESI† for further information).¹⁰ Initially, we found that 1,4-dioxane gave rise to moderate conversion (Table 1, entry 1), which was improved slightly through the addition of 18-crown-6 as an additive (Table 1, entry 2). Jeffery and co-workers have previously shown that the use of quaternary ammonium salts as additives in Pd-catalysed olefination reactions led to superior reaction performance.^{11,12}

Gratifyingly, the use of tetrabutylammonium chloride (TBACl) in 2.00 equivalents in place of 18-crown-6 resulted in near quantitative formation of olefin **2a** (Table 1, entry 3). Conducting the reaction in the absence of base or using NaOAc in place of K₂CO₃ gave lower conversion (Table 1, entries 4 and 5). We also explored the use of tetrabutylammonium acetate (TBAOAc).¹³ Exchanging TBACl for TBAOAc resulted in similarly excellent results (Table 1, entry 6 *cf.* Table 1, entry 3). Encouraged by this initial result, we wondered whether TBAOAc could also act as the base for the reaction and replace K₂CO₃. We knew the acetate ion could act as base from previously tried NaOAc, which gave 77% conversion to the target compound (Table 1, entry 5). Using TBAOAc in the absence of K₂CO₃, these conditions gave rise to **2a** in good conversion (Table 1, entry 7), which was the rendered quanti-

Table 1 Optimisation of Heck olefination reaction

Entry	Solvent	Additive	Base	Conversion ^a
1	1,4-Dioxane	—	K ₂ CO ₃	65%
2	1,4-Dioxane	18-Crown-6	K ₂ CO ₃	73%
3	1,4-Dioxane	TBACl	K ₂ CO ₃	100% (80%)
4	1,4-Dioxane	TBACl	—	15%
5	1,4-Dioxane	TBACl	NaOAc	77%
6	1,4-Dioxane	TBAOAc	K ₂ CO ₃	98% (79%)
7	1,4-Dioxane	TBAOAc	—	84%
8 ^b	1,4-Dioxane	TBAOAc	—	98% (77%)
9 ^b	EtOAc	TBAOAc	—	100%
10 ^b	CPME	TBAOAc	—	98% (78%)
11 ^b	Cyrene	TBAOAc	—	98%
12 ^b	H ₂ O	TBAOAc	—	88%

^a Conversion to product **3a** determined by ¹H NMR analysis, isolated yields following chromatographic purification in parentheses. ^b 3.00 eq. TBAOAc used.



Scheme 1 Comparison to previous work from a green perspective.



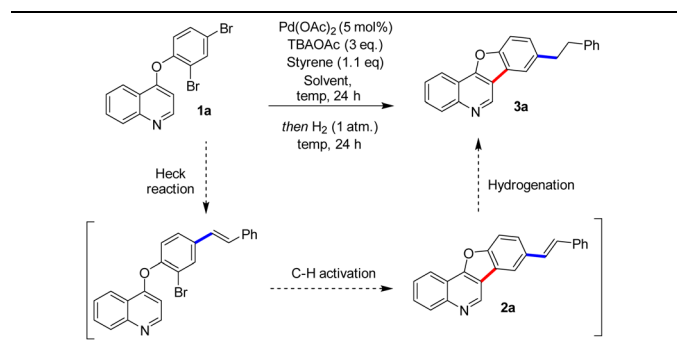
tative on increasing the equivalents of TBAOAc from 2.00 to 3.00 (Table 1, entry 8). Although preferable to NMP, 1,4-dioxane is still not an ideal solvent for this transformation from a green chemistry perspective. To our delight, the use of TBAOAc enabled this chemistry to proceed in several more desirable solvents, including EtOAc, CPME, Cyrene and water with 3.00 equivalents (Table 1, entries 9–12 and ESI† for further information).

With optimised conditions for the first two steps in hand, we next turned our attention to finding compatible conditions for the subsequent reduction step (Table 2). Alkene reduction with molecular hydrogen is ideal from a green chemistry perspective.¹⁴

Although conducting the reaction in CPME, Cyrene, EtOAc and 2-MeTHF typically led to excellent conversions to olefin **2a**, elevated temperatures were generally required to achieve quantitative hydrogenation (Table 2, entries 1–8). Furthermore, Cyrene appeared to polymerise during the course of the reaction, thus proving problematic.¹⁵ As TBAOAc melts at approximately 100 °C, we wondered whether molten TBAOAc could act as both base for the first two reactions and a reaction medium for the hydrogenation step.

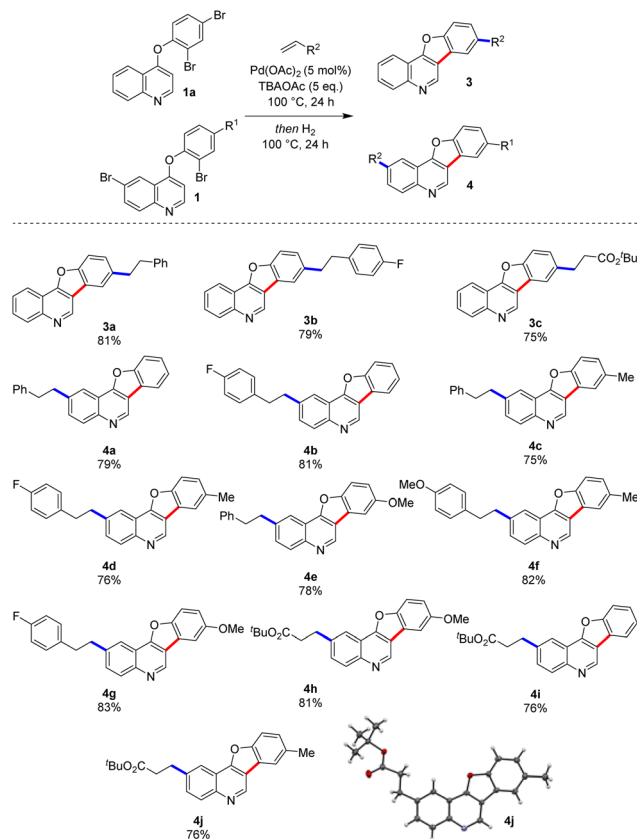
Indeed, quantitative formation of reduced product **3a** was recorded using TBAOAc at both 135 °C and 100 °C (Table 2, entries 9 and 10). Finally we attempted a number of transfer hydrogenation agents (in place of H₂) but with less success. See ESI for details.†

Table 2 Optimisation of three-step one-pot sequence



Entry	Solvent	Temperature	Conversion to 2a ^a	Conversion to 3a ^a
1	CPME	90 °C	28%	n.d.
2	CPME	110 °C	98%	100%
3	Cyrene	100 °C	74%	n.d.
4	Cyrene	135 °C	98%	100%
5	EtOAc	60 °C	n.d.	n.d.
6 ^b	EtOAc	90 °C	100%	n.a.
7	2-MeTHF	70 °C	14%	n.d.
8	2-MeTHF	90 °C	100%	50%
9 ^c	—	135 °C	100%	100%
10 ^c	—	100 °C	100%	100%

^a Conversion to products **2a** and **3a** determined by ¹H NMR analysis from starting material **1a**. ^b n.a. = not applicable: EtOAc did not support the hydrogenation step. ^c 5.00 eq. TBAOAc used as reaction medium; n.d. = not determined.

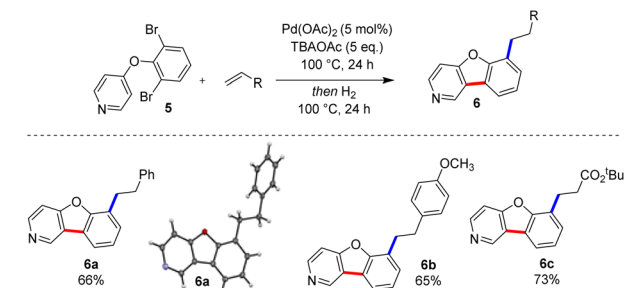


Scheme 2 Scope of phenoxyquinoline substrates.

Substrate scope

We then extended the scope of our optimised conditions to include several phenoxyquinoline substrates (Scheme 2). The products, prepared through our three-step, one-pot process were isolated in excellent yields following purification by column chromatography. The scope was established by varying the precursors for the Heck reaction. The reaction worked well irrespective of whether the aryl bromide Heck partner was on the pendant phenoxy-ring or the quinoline core. Both electron-rich and electron-poor olefin coupling partners were also well-tolerated.

Pyridines are often difficult substrates in direct arylation reactions.⁹ However, their prevalence in biologically active



Scheme 3 Scope of phenoxyquinoline substrates.



compounds⁶ prompted us to submit a series of phenoxy pyridines to our optimal conditions (Scheme 3). We were pleased that both electron-rich and electron poor olefins were compatible with the Heck-hydrogenation sequence, giving novel benzo-furopyridines **6a–6c** in good yields. Finally, we were interested in exploring the synthesis of benzofurans *via* this approach (Scheme 4). Benzofuran derivatives are ubiquitous in bioactive molecules and have well-established uses as antimicrobial and anticancer chemotherapeutics.¹⁶ This class of substrates also constitutes an interesting extension as they do not possess a

for this study, we used the 'COWare' apparatus developed by Skrydstrup (Scheme 5).¹⁹ This apparatus connects two chambers by a glass bridge which facilitates *ex situ* gas generation. Here D₂ was generated (by addition of DCl to zinc) and successfully incorporated into the final structure **4h-d₄** by addition across the double bond. The ability to isotopically label these densely functionalised molecules at a late stage in their preparation demonstrates the medicinal chemistry potential of this approach. Interestingly, some incorporation of D was observed at other locations on the quinoline, which might provide a rich avenue of further research.

Sequence of the direct arylation and olefination reactions

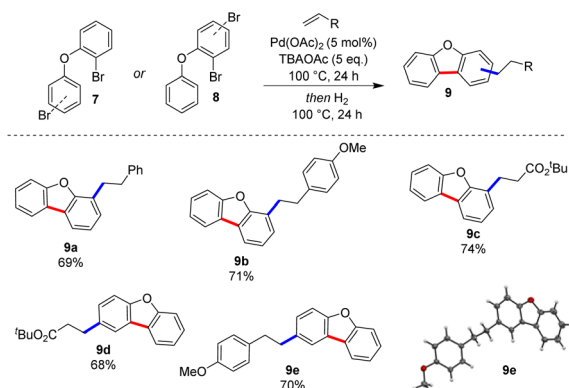
Initially, we were curious whether the direct arylation and Heck reactions took place concurrently or sequentially. ¹H NMR analysis of the reaction between dibromoquinoline **1b** and styrene, under the optimised conditions, revealed that the Heck reaction was significantly faster than the direct arylation reaction. This result suggests that oxidative addition to the less hindered quinoline Ar–Br bond is favoured over oxidative addition at the phenoxy Ar–Br. Indeed, we have previously observed a similar trend in reactivity when studying tandem Suzuki–Miyaura/C–H activation reactions on phenoxyquinoline substrates.^{8a}

Probing the catalytic species in the hydrogenation reaction

During the Heck olefination/C–H activation process, we observed the formation of palladium black, and we were interested to determine the speciation of Pd during the hydrogenation step. We considered it most likely that heterogeneous or soluble nanoparticulate Pd, formed *in situ*, was catalysing the hydrogenation reaction.^{3l,4c} To discern the impact of soluble Pd sources, we undertook a filtration test. Initially, we performed the first two reaction steps (Heck and C–H activation) using a dibromoquinoline and styrene as per our established reaction conditions (see ESI† for more information). However, before inserting the hydrogen balloon, we filtered the reaction mixture through a 2 μm PTFE syringe filter and placed the filtrate back into a clean reaction vial. The reaction mixture was then purged with hydrogen and allowed to stir for a further 24 hours at 100 °C. As the reaction mixture was rid of visible aggregates of palladium, it appeared as a brown homogenous solution. Complete conversion to the hydrogenated product was observed by ¹H NMR spectroscopy. Thus, interestingly, it appears that soluble Pd nanoparticles are active catalysts in the hydrogenation reaction.^{4c}

Analysis of green chemistry metrics

Finally, as we set ourselves the challenge to design a 'bottom-up' green chemistry approach to the polycyclic alkylated heterocycles in this study, we turned to calculating green metrics to evaluate the greenness of our reaction *versus* the current state-of-the-art reported by Fagnou (Scheme 1).^{4d} The metrics were determined as per previously reported calculations by Ma



Scheme 4 Scope of diaryl ether substrates.

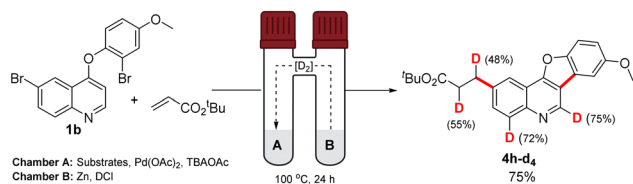
coordinating nitrogen atom. The reaction worked well with diaryl ether substrates (**9a–9e**).¹⁷

Deuterium incorporation and mechanistic studies

In a bid to better understand the underlying mechanistic processes which were operative in this complex transformation, we undertook a series of mechanistic studies.

Deuterium incorporation

Incorporating deuterium into target molecules has many important applications in the context of mechanistic studies (*e.g.*, kinetic isotope effects), but also by enhancing metabolic stability and pharmacokinetics, aiding ADME studies, bettering toxicity profiles in drugs and creating new chemical entities of commercial importance.¹⁸ To facilitate easy access to D₂



Scheme 5 Deuterium incorporation using COWare apparatus.



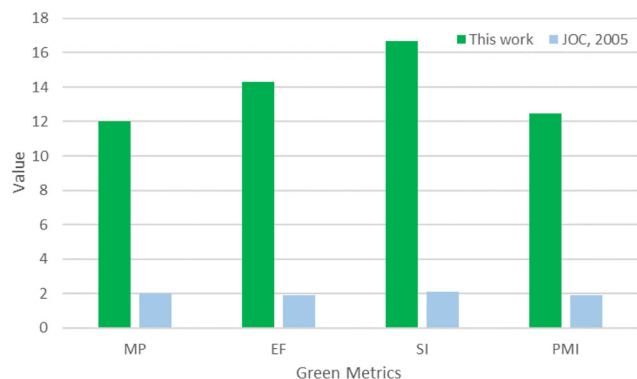


Fig. 1 Quantitative comparison of green chemistry metrics for this work and previous work by Fagnou.^{4d} For illustration purposes, EF, SI and PMI values were inverted and multiplied by 100 (calculation can be found in ESI†).

*et al.*²⁰ Analysis was conducted on atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE), process mass intensity (PMI), *E*-factor (EF), solvent intensity (SI) and water intensity (WI) (Fig. 1 and see ESI† for the definition of the metrics and methodology).

As shown in Fig. 1, our process constitutes a significant green chemistry improvement under these metrics due to our system not requiring an ancillary phosphine ligand, added base and excess solvent. For comparison, in green metric calculations, we input our quinoline substrate with Fagnou's conditions and input Fagnou's chromene substrate into our new conditions. Both metrics show the more favourable greenness of our conditions (see ESI†).

The MP of the average one-pot values of 12% is six times higher than that of Fagnou's process, which has a value of just 2%. MP is an important metric that indicates the level of resource consumption as it includes all benign and non-benign reagents such as catalysts, base and solvent.

Conclusions

Achieving substrate, ligand and solvent compatibility across three mechanistically distinct catalytic reactions is challenging. In the methodology described here, no P-ligand or inorganic base is added, with TBAOAc acting as both ionic liquid and base. Decorated tri- and tetra-cyclic alkylated heteroarenes are conveniently and rapidly formed. Our new methodology greatly improves on the current state-of-the-art and demonstrates superior green chemistry values across many of the key metrics.

Experimental

General information

All reagents and solvents were purchased from commercial suppliers and were used without further purification. Column

chromatography was carried out using 60 Å (35–70 μm) silica. ¹H NMR (600 MHz), ¹H NMR (500 MHz), ¹H NMR (400 MHz), and ¹H NMR (300 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers respectively. ¹³C NMR (150.9 MHz), ¹³C NMR (125 MHz), ¹³C NMR (100 MHz), and ¹³C NMR (75.5 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers respectively. Chemical shifts are reported in parts per million (ppm) downfield from TMS internal standard. Additional information on the COWare apparatus and setup is available in the ESI.†

General procedure for the synthesis of phenoxyquinoline starting materials

A mixture of the 4-chloroquinoline substrate **S1** (1 eq.), the phenol (3.5 eq.) and NaOH (1.5 eq., crushed pellets) was stirred at 120 °C until TLC analysis indicated the reaction was complete (2–24 hours). The reaction mixture was cooled to room temperature and 10% aqueous NaOH (10 mL) was added and stirred for 30 min. The aqueous layer was extracted with DCM (3 × 15 mL). The organic layers were combined and washed with 6 M NaOH (3 × 15 mL), water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Impure products were purified by column chromatography over silica gel using a gradient cyclohexane : EtOAc (70 : 30).

General procedure for the one-pot Mizoroki–Heck/direct arylation/hydrogenation reaction

To a screw capped vial was added the quinoline/pyridine/diaryl ether substrate (1 eq.), Heck coupling partner (1.1 eq.), palladium diacetate (5 mol%) and tetrabutylammonium acetate (5 eq.) which was stirred at 100 °C for 24 hours. The reaction mixture was then purged with hydrogen gas and stirred under a hydrogen atmosphere for a further 24 hours at 100 °C. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography. The benzofuroquinoline and benzofuopyridine products eluted in a gradient cyclohexane : EtOAc (70 : 30). The dibenzofuran products eluted in a gradient cyclohexane : EtOAc (90 : 10).

General procedure for the synthesis of deuterated benzofuroquinoline (4h-d₄)

To chamber 'A' of the 20 mL COWare^{19a} apparatus was added the benzofuroquinoline substrate (1 eq.), Heck coupling partner (1.1 eq.), palladium diacetate (5 mol%) and tetrabutylammonium acetate (5 eq.). To the second chamber 'B' was added zinc powder (3.65 eq.). Chamber 'A' was submerged into an oil bath and was stirred at 100 °C for 24 hours. DCl (4 M in D₂O, 7.3 eq.) was added *via* syringe to chamber 'B' which initiated the D₂ formation [CAUTION] and reaction was allowed to stir at 100 °C for a further 24 hours. The crude product was purified loaded directly onto silica gel for purification by column chromatography, eluting with a gradient cyclohexane : EtOAc (70 : 30).



Crystallographic data

X-ray crystallographic data for compounds **3a** [CCDC 2143462], **3b** [CCDC 2143446], **3c** [CCDC 2204946], **4d** [CCDC 2211708], **4h** [CCDC 2204910], **4j** [CCDC 2201481], **6a** [CCDC 2204956], **9a** [CCDC 2204818], **9e** [CCDC 2204795] (see ESI for details).†

Author contributions

RK, DJ and GM conceived the ideas and experiments. RK carried out the experiments. ML solved the single crystal structures. All contributed to the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- 1 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866.
- 2 (a) N. Shindoh, Y. Takemoto and K. Takasu, *Chem. – Eur. J.*, 2009, **15**, 12168; (b) F.-X. Felpin and E. Fouquet, *ChemSusChem*, 2008, **1**, 718; (c) J. E. Camp, *Eur. J. Org. Chem.*, 2017, 425.
- 3 (a) K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao and J. Chen, *Org. Lett.*, 2018, **20**, 3083; (b) A. A. Nechaev, P. R. Jagtap, E. Bažíková, J. Neumannová, I. Císařová and E. Matoušová, *Org. Biomol. Chem.*, 2021, **19**, 3434; (c) W. Hagui, N. Besbes, E. Srasra, T. Roisnel, J.-F. Soulé and H. Doucet, *Org. Lett.*, 2016, **18**, 4182; (d) J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *J. Org. Chem.*, 2007, **72**, 7650; (e) K. Geoghegan, S. Kelleher and P. Evans, *J. Org. Chem.*, 2011, **76**, 2187; (f) S. P. Mulcahy and J. G. Varelas, *Tetrahedron Lett.*, 2013, **54**, 6599; (g) H. Jong, S. T. C. Eey, Y. H. Lim, S. Pandey, N. A. B. Iqbal, F. F. Yong, E. G. Robins and C. W. Johannes, *Adv. Synth. Catal.*, 2017, **359**, 616; (h) L. Mayer, R. Kohlbecher and T. J. J. Müller, *Chem. – Eur. J.*, 2020, **26**, 15130; (i) G. A. Molander, S. L. J. Trice and S. M. Kennedy, *J. Org. Chem.*, 2012, **77**, 8678; (j) R. Barroso, M. Paraja, M.-P. Cabal and C. Valdés, *Org. Lett.*, 2017, **19**, 4086; (k) T. Watanabe, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2009, **74**, 4720; (l) F.-X. Felpin, O. Ibarguren, L. Nassar-Hardy and E. Fouquet, *J. Org. Chem.*, 2009, **74**, 1349; (m) L. Nassar-Hardy, S. Fabre, A. M. Amer, E. Fouquet and F.-X. Felpin, *Tetrahedron Lett.*, 2012, **53**, 338; (n) F.-X. Felpin, J. Coste, C. Zakri and E. Fouquet, *Chem. – Eur. J.*, 2009, **15**, 7238; (o) J. Barluenga, A. Jiménez-Aquino, M. A. Fernández, F. Aznar and C. Valdés, *Tetrahedron*, 2008, **64**, 778; (p) J. Laudien, E. Fouquet, C. Zakri and F.-X. Felpin, *Synlett*, 2010, 1539; (q) B. Gabriele, P. Plastina, G. Salerno, R. Mancuso and M. Costa, *Org. Lett.*, 2007, **9**, 3319; (r) R. Devlin, D. J. Jones and G. P. McGlacken, *Org. Lett.*, 2020, **22**, 5223.
- 4 (a) M. Szlosek-Pinaud, P. Diaz, J. Martinez and F. Lamaty, *Tetrahedron Lett.*, 2003, **44**, 8657; (b) A. Pinto, L. Neuville and J. Zhu, *Tetrahedron Lett.*, 2009, **50**, 3602; (c) J. Hitce and O. Baudoin, *Adv. Synth. Catal.*, 2007, **349**, 2054; (d) J.-P. Leclerc, M. André and K. Fagnou, *J. Org. Chem.*, 2006, **71**, 1711.
- 5 (a) B. S. Matada, R. Pattanashettar and N. G. Yernale, *Bioorg. Med. Chem.*, 2021, **32**, 115973; (b) E. Khan, *ChemistrySelect*, 2021, **6**, 3041; (c) M. Napiórkowska, M. Cieślak, J. Kaźmierczak-Barańska, K. Królewska-Golińska and B. Nawrot, *Molecules*, 2019, **24**, 1529.
- 6 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845.
- 7 (a) N. Miyaaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (b) J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508; (c) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1978, **100**, 3636; (d) T.-Y. Luh, M.-K. Leung and K.-T. Wong, *Chem. Rev.*, 2000, **100**, 3187; (e) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (f) Y. Nishihara, *Applied Cross-Coupling Reactions*, Springer Science & Business Media, 2012, vol. 80; (g) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (h) R. Cano, J. M. Pérez, D. J. Ramón and G. P. McGlacken, *Tetrahedron*, 2016, **72**, 1043.
- 8 (a) R. M. Shanahan, A. Hickey, L. M. Bateman, M. E. Light and G. P. McGlacken, *J. Org. Chem.*, 2020, **85**, 2585; (b) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 18570; (c) Y. He, Z. Wu, C. Ma, X. Zhou, X. Liu, X. Wang and G. Huang, *Adv. Synth. Catal.*, 2016, **358**, 375; (d) K. Mackey, D. J. Jones, L. M. Pardo and G. P. McGlacken, *Eur. J. Org. Chem.*, 2021, 495.
- 9 R. M. Shanahan, A. Hickey, F. J. Reen, F. O'Gara and G. P. McGlacken, *Eur. J. Org. Chem.*, 2018, 6140.
- 10 (a) P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro and L. Ackermann, *ACS Sustainable Chem. Eng.*, 2019, **7**, 8023; (b) H. L. Parker, J. Sherwood, A. J. Hunt and J. H. Clark, *ACS Sustainable Chem. Eng.*, 2014, **2**, 1739; (c) J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmer and A. J. Hunt, *Green Chem.*, 2016, **18**, 3990; (d) A. Jordan, C. G. J. Hall, L. R. Thorp and H. F. Sneddon, *Chem. Rev.*, 2022, **122**, 6749; (e) J. Sherwood, M. De bruyn, A. Constantinou, L. Moity, C. R. McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunt and J. H. Clark, *Chem. Commun.*, 2014, **50**, 9650.
- 11 F. Chen, T. Dong, T. Xu, X. Li and C. Hu, *Green Chem.*, 2011, **13**, 2518.



- 12 (a) T. Jeffery, *Tetrahedron Lett.*, 1999, **40**, 1673; (b) T. Jeffery, *Tetrahedron*, 1996, **52**, 10113; (c) T. Jeffery and M. David, *Tetrahedron Lett.*, 1998, **39**, 5751.
- 13 (a) V. Calò, A. Nacci, A. Monopoli, A. Detomaso and P. Iliade, *Organometallics*, 2003, **22**, 4193; (b) V. Calò, A. Nacci, A. Monopoli, A. Damascelli, E. Ieva and N. Cioffi, *J. Organomet. Chem.*, 2007, **692**, 4397; (c) B. C. Ranu, S. S. Dey and A. Hajra, *Tetrahedron*, 2003, **59**, 2417; (d) V. Calò, A. Nacci, L. Lopez and N. Mannarini, *Tetrahedron Lett.*, 2000, **41**, 8973; (e) V. Calò, A. Nacci, A. Monopoli, A. Fornaro, L. Sabbatini, N. Cioffi and N. Ditaranto, *Organometallics*, 2004, **23**, 5154; (f) G. Battistuzzi, S. Cacchi and G. Fabrizi, *Synlett*, 2002, 0439.
- 14 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.
- 15 P. Ray, T. Hughes, C. Smith, M. Hibbert, K. Saito and G. P. Simon, *Polym. Chem.*, 2019, **10**, 3334.
- 16 H. Khanam and Shamsuzzaman, *Eur. J. Med. Chem.*, 2015, **97**, 483.
- 17 For attempts at scale up see ESI.†.
- 18 (a) T. Pirali, M. Serafini, S. Cargnin and A. A. Genazzani, *J. Med. Chem.*, 2019, **62**, 5276; (b) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge and M. Beller, *Chem. Rev.*, 2022, **122**, 6634; (c) J. Atzrodt, V. Derdau, W. J. Kerr and M. Reid, *Angew. Chem., Int. Ed.*, 2018, **57**, 3022; (d) A. Mullard, *Nat. Rev. Drug Discovery*, 2017, **16**, 305.
- 19 (a) S. D. Friis, A. T. Lindhardt and T. Skrydstrup, *Acc. Chem. Res.*, 2016, **49**, 594; (b) A. Modvig, T. L. Andersen, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Org. Chem.*, 2014, **79**, 5861.
- 20 X. Ma, X. Zhang, J. M. Awad, G. Xie, W. Qiu and W. Zhang, *Green Chem.*, 2019, **21**, 4489.

