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Cyclometallated ruthenium catalyst enables late-stage directed arylation of pharmaceuticals

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Biaryls are ubiquitous core structures in drugs, agrochemicals and organic materials that have profoundly improved many aspects of our society. Although traditional cross-couplings have made practical the synthesis of many biaryls, C–H arylation represents a more attractive and cost-effective strategy for building these structural motifs. Furthermore, the ability to install biaryl units in complex molecules via late-stage C–H arylation would allow access to valuable structural diversity, novel chemical space and intellectual property in only one step. However, known C–H arylation protocols are not suitable for substrates decorated with polar and delicate functionalities, which are commonly found in molecules that possess biological activity. Here we introduce a class of ruthenium catalysts that display a unique efficacy towards late-stage arylation of heavily functionalized substrates. The design and development of this class of catalysts was enabled by a mechanistic breakthrough on the Ru(II)-catalysed C–H arylation of *N*-chelating substrates with aryl (pseudo)halides, which has remained poorly understood for nearly two decades.

The installation of the biphenyl fragment via cross-coupling reactions has become a staple of drug design[1,2]. Due to the pivotal role of aromatic non-covalent interactions in protein–ligand recognition[3], the placement of aryl motifs in drug candidates can lead to derivatives with higher activities[4–7]. Although during the past years some statistical studies have tried to start to rationalize the impact of aromatic ring count on drug developability[8–10], it is widely acknowledged that only a small portion of the available chemical space has been explored and that safe compounds can be identified outside the conventional drug-like chemical space[8,11,12]. Consequently, the development of reliable C–H arylation technologies would provide a more sustainable alternative to cross-coupling reactions[13] and grant access to a rapid and valuable exploration of the structural diversity via late-stage C–H arylation[14–17], which would make them extremely desirable within drug discovery and development.

The vast majority of drugs contain several polar functionalities, often as part of oxygen, nitrogen and sulfur heterocycles[18–20], that are essential to maximize the drug–target interaction and maintain acceptable levels of pharmacokinetics and toxicity[21]. However, despite the need to manipulate polar functionalities in medicinal chemistry, a statistical analysis revealed that "the more polar products in an array tended to systematically fail more often in synthesis", which may correlate with the crisis of productivity of the drug-discovery process[22]. Specifically, polar groups are often problematic in C–H activation as the presence of Lewis basic heteroatoms can promote catalyst poisoning or substrate decomposition[23–25]. Moreover, in directed C–H activation reactions, strongly coordinating moieties add a further challenge as they can outcompete the directing group (DG) for catalyst binding, and thus prevent its approach into the proximity of the targeted C–H bond[26]. Nonetheless, despite the historical bias towards *para*-substitution observed in medicinal chemistry, which favours the synthesis of 'flat' products[27], *ortho*-directed C–H activation protocols have the capability of expanding the chemical space. Due to the twisting and disruption of the planar structure, *ortho* regioisomers have different physicochemical properties relative to *para* and *meta* ones, and they may prove themselves valuable when exploring new target classes that necessitate different spatial arrangements to bind and attain the desired effect[2].

In the context of *ortho*-directed C–H arylation reactions with aryl (pseudo)halides, whereas palladium-catalysed processes are by far the most studied[13,28–33], the use of ruthenium often brings several benefits. In addition to being more than 15 times cheaper than palladium, electrophiles such as aryl chlorides, triflates and bromides can be coupled by ruthenium with similar levels of efficiency[13,34]. Since the pioneering work on the Ru(II)-catalysed C–H arylation of DG-containing arenes with aryl halides in 2001[35], tremendous efforts have been dedicated towards the establishment of more general and efficient reaction conditions[13,34,36–40]. However, state-of-the-art methodologies still require high temperatures and often a several-fold excess of the aryl (pseudo)halide (Fig. 1a). Furthermore, the exceptional binding affinity of the Ru(II) metal centre to sp^2 nitrogen atoms—widespread in *ortho* DGs—has not flourished as an in-built selection device able to discriminate between sp^2 nitrogens over other heteroatoms or functional groups that possess lesser coordinating abilities. Thus, directed Ru(II)-catalysed C–H activation reactions have yet to be shown to withstand polar sensitive groups, which are ubiquitous in pharmaceuticals and natural products. This is probably because the harsh working conditions commonly required in these methodologies facilitate detrimental reaction paths, either by preventing the desired DG–catalyst interaction or by initiating thermal decomposition of these delicate functionalities.

Here we report the discovery of a key catalytic species in the mechanism of the Ru(II)-catalysed C–H arylation of DG-containing arenes with aryl (pseudo)halides. For nearly two decades, this reaction has been proposed to operate via a catalytic cycle (Fig. 1b) that involves an initial C–H activation step to form cycloruthenated species **I**, which undergoes oxidative addition with the aryl halide to generate the Ru(IV) intermediate **II**. The latter, after the reductive elimination step, will then release the biaryl product, which restarts the cycle[13,34,41,42]. We speculate that this oversimplified mechanism has, to date, prevented the discovery of truly reactive catalysts. Contrary to previous postulations, our mechanistic investigations

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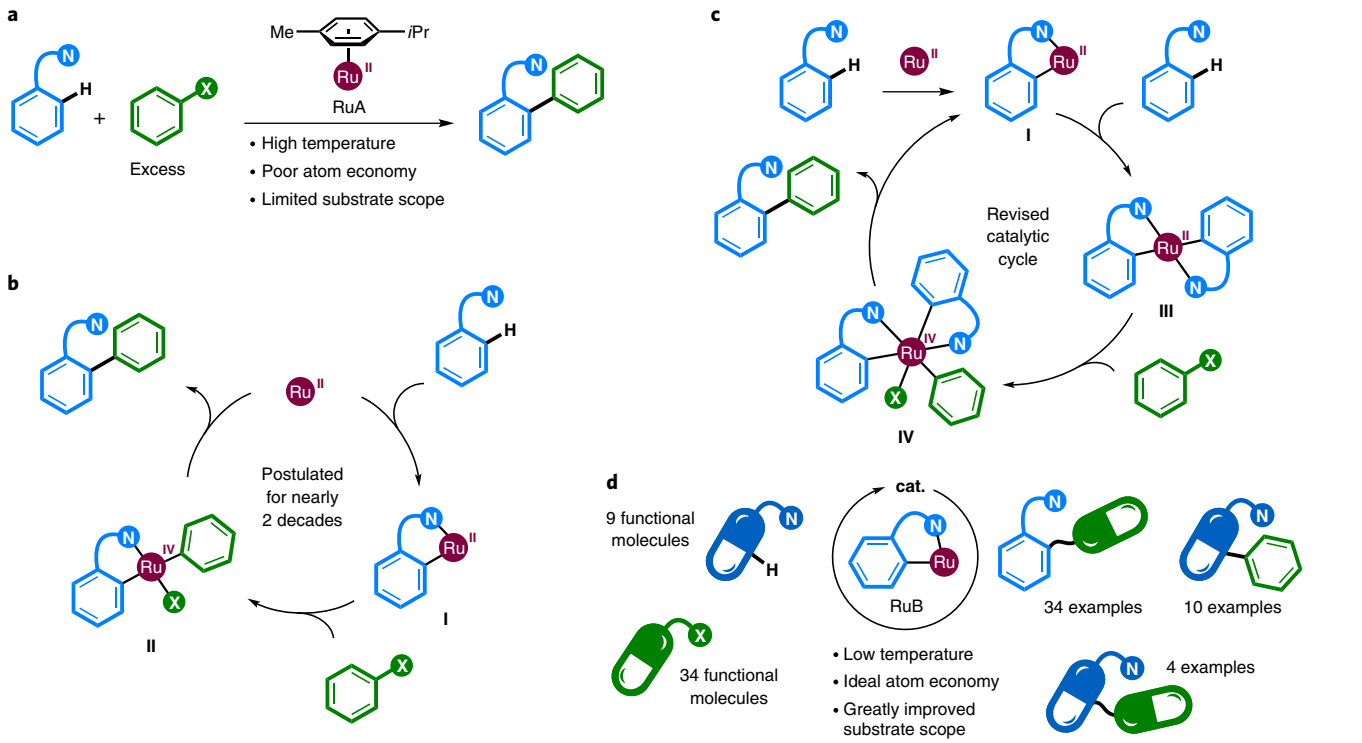

Fig. 1 | Ru(II)-catalysed C–H arylation of DG-containing arenes with aryl (pseudo)halides. a, State-of-the-art methodologies that rely on common Ru(II) catalysts still suffer from limited functional group compatibility and poor atom economy. **b**, Previously proposed catalytic cycle for the C–H arylation reaction (for clarity, not all of the ligands on ruthenium are shown). **c**, This revised catalytic cycle for the C–H arylation reveals the crucial formation of intermediate **III** prior to the oxidative addition step. **d**, Establishment of cyclometallated Ru(II) complexes (RuB) as superior catalysts, which enabled the coupling of complex functional molecules.

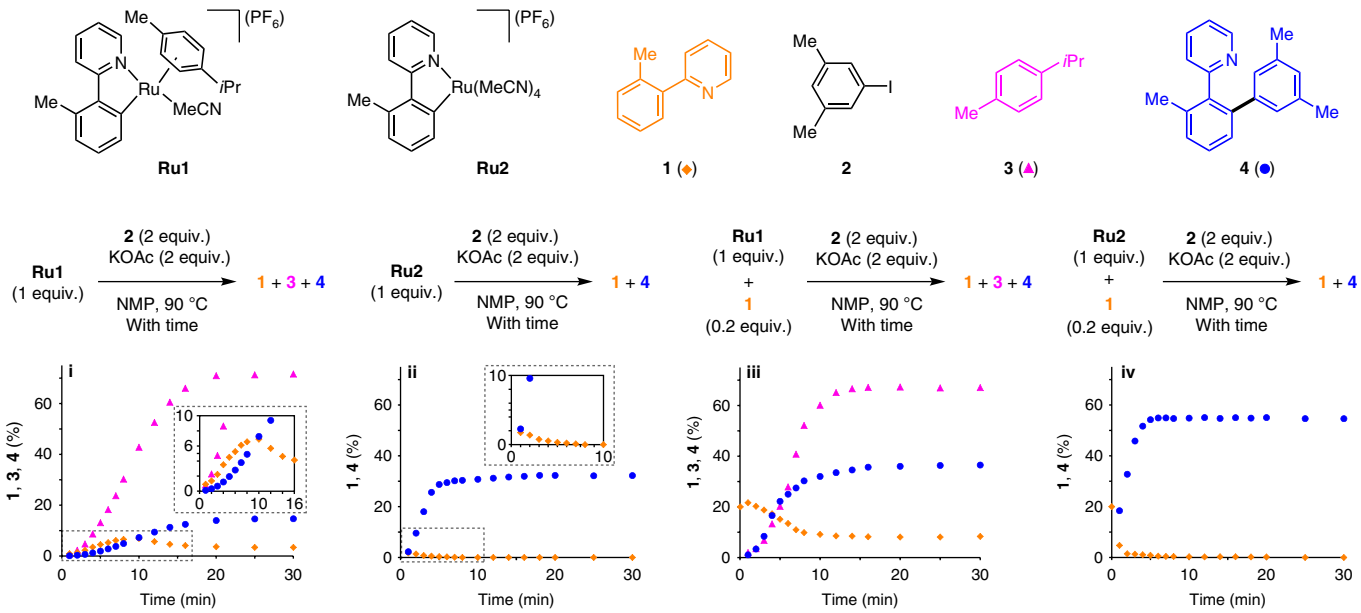

Fig. 2 | Kinetic evidence that supports the involvement of a bis-cycloruthenated intermediate in the Ru-catalysed C–H arylation of DG-containing arenes with aryl (pseudo)halides. Reaction kinetic profiles for the stoichiometric arylation of **Ru1** (**i** and **iii**) and **Ru2** (**ii** and **iv**) with 5-iodo-*m*-xylene **2** in the absence (**i** and **ii**) or in the presence (**iii** and **iv**) of 0.2 equiv. of 2-(*o*-tolyl)pyridine **1** show the evolution of free **3** (fuchsia triangles), free **1** (orange rhombi) and biaryl product **4** (blue dots). The reactions were analysed by gas chromatography–flame ionization detection (GC–FID) using hexadecane as the internal standard.

revealed that a second C–H activation event is required to form the bis-cyclometallated Ru(II) complex **III**, prior to the oxidative addition step that leads to the Ru(IV) species **IV** (Fig. 1c). The detection and characterization of the bis-cycloruthenated intermediate **III** was made possible by kinetic studies, which allowed us to hypothesize its fundamental role in the catalytic cycle. Furthermore, our

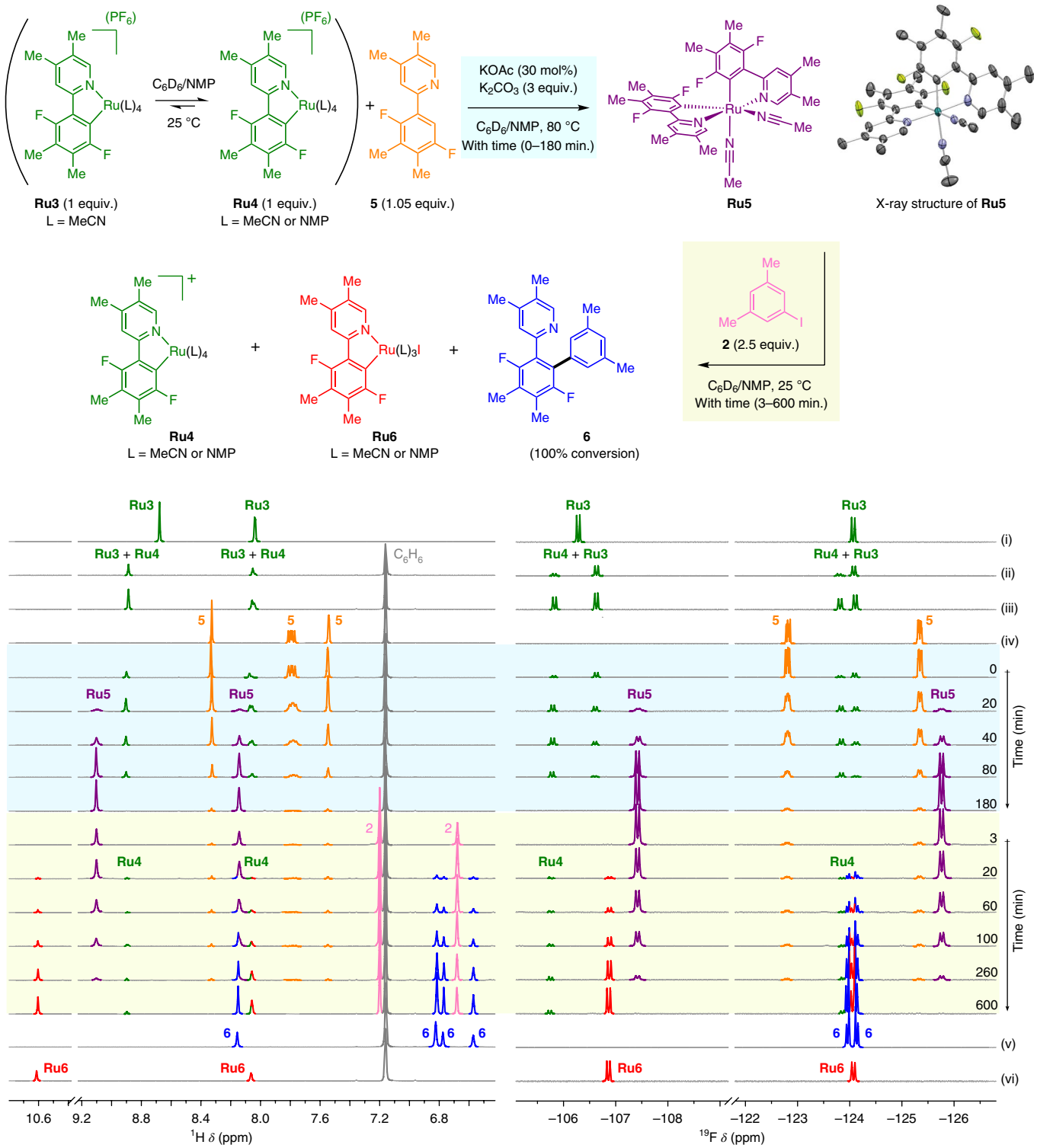

Fig. 3 | Detection, isolation and reactivity of the bis-cycloruthenated complex Ru5. In situ ^{1}H and ^{19}F NMR monitoring of the reaction between **Ru3** and **5** that generated **Ru5** is shown in the light blue box. In situ ^{1}H and ^{19}F NMR monitoring of the reaction between **Ru5** and **2** that produced **6**, **Ru6** and **Ru4** is shown in the light yellow box. ^{1}H and ^{19}F NMR spectra of: **Ru3** in CD_3CN (i); a freshly prepared sample of **Ru3** in C_6D_6/NMP that reveals the formation of **Ru4** (ii); a sample of **Ru3** in C_6D_6/NMP after 12 h (iii); **5** in C_6D_6/NMP (iv); **6** in C_6D_6/NMP (v); and a freshly prepared sample of **Ru3** + KI (excess) in C_6D_6/NMP that reveals the instantaneous formation of **Ru6** (vi) are also shown for clarity (Supplementary Section 4). The X-ray of **Ru5** is an ORTEP diagram at 60% probability ellipsoids; co-crystallized Et_2O molecules and hydrogen atoms are omitted for clarity (Supplementary Section 16).

studies reveal that cycloruthenated complexes like **I** (Fig. 1d, RuB) are able to catalyse the C–H arylation at remarkably low temperatures, with equimolar amounts of the aryl (pseudo)halide. Owing to the commercial and competitive aspects of drug discovery, robust and established methodologies are relentlessly preferred. Consequently, the uptake of new synthetic methods in medicinal chemistry is a function of the extents of the substrate scope presented in the methodology[43,44]. Therefore, with the aim to provide a

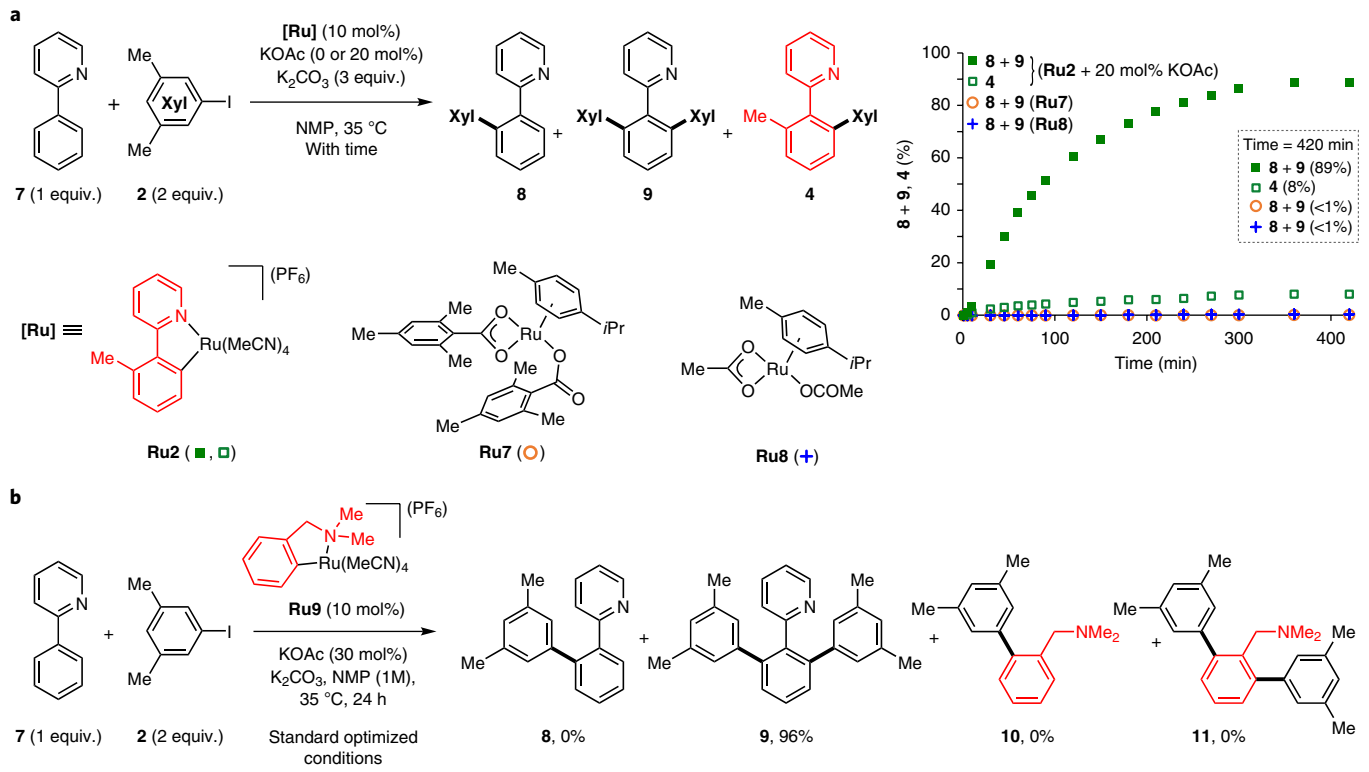

Fig. 4 | Cycloruthenated complexes as a superior class of catalysts for the C–H arylation of DG-containing arenes with aryl (pseudo)halides. a, Comparison of the catalytic activity of the system constituted by **Ru2** and KOAc with respect to **Ru7** and **Ru8**. The reactions were analysed by GC-FID using hexadecane as the internal standard. **b**, Establishment of **Ru9** as the catalyst of choice for the Ru(II)-catalysed directed C–H arylation. The reactions were analysed by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

truthful and solid platform to evaluate the possibility of implementing our technology in the synthesis of drug-like compounds, we targeted heavily functionalized molecules by performing late-stage arylation on pharmaceuticals, agrochemicals, natural products and organic electronic materials.

Results and discussion

Kinetic evidence that supports the involvement of a bis-cycloruthenated intermediate. Recently, we described the first Ru(II)-catalysed C–H arylation methodology for 'simple' electron-deficient arenes[45]. During the development of this methodology, we discovered that, contrary to previous hypotheses[41], the *p*-cymene ligand present in state-of-the-art ruthenium catalysts (Fig. 1a, RuA) is an inhibitor in the reaction. This disparity prompted a more thorough investigation of the general mechanism of Ru(II)-catalysed C–H arylation. We began our investigation by examining the mechanism of the directed arylation of 2-(*o*-tolyl)pyridine **1** with 5-iodo-*m*-xylene **2** to form **4** (Fig. 2). We assessed the reactivity of two proposed catalytic intermediates, **Ru1** and **Ru2** (corresponding to complex **I** in Fig. 1b,c), in their stoichiometric reaction with aryl iodide **2** in the presence of KOAc in NMP (*N*-methyl-2-pyrrolidone) at 90 °C (Fig. 2). Surprisingly, both **Ru1** and **Ru2** reacted sluggishly with **2**, which suggests that a more complex mechanism than that depicted in Fig. 1b was in operation. Specifically, the reaction profile of **Ru1** revealed: (1) a fast release of *p*-cymene **3**, (2) a rapid build-up of decomplexed 2-(*o*-tolyl)pyridine **1**, which then decreased over time, and (3) an induction period in the formation of biaryl **4** that correlated with the evolution of free **1** (Fig. 2, graph i). *p*-Cymene-free **Ru2** displayed a similar behaviour, albeit with a much faster arylation rate (Fig. 2, graph ii), which confirms the inhibitory role of the *p*-cymene ligand in this directed arylation. Importantly, the observed formation and consumption of free **1** is consistent with kinetics in which this species is a reaction intermediate in the arylation process. Thus, we hypothesized that a C–H activation step between an η^6-arene-free cycloruthenated species, such as **Ru2** and **I**, must happen before reaction with iodoarene **2** (for example, **I** to **III** in Fig. 1c). Indeed, when the concentration profiles for the arylation reactions of **Ru1** and **Ru2** were monitored after the addition of 0.2 equiv. of 2-(*o*-tolyl)pyridine **1**, a fast consumption of **1** and a significant increase in the arylation rate were observed (Fig. 2, graphs iii and iv). Furthermore, in agreement with the generation of a bis-cyclometallated complex like **III** (Fig. 1c), the omission of the base required for C–H activation, KOAc, substantially reduced the arylation rate[46] (Supplementary Section 3).

Detection and reactivity of the bis-cycloruthenated intermediate. To validate further this mechanistic hypothesis, we followed the reaction of cyclometallated complex **Ru3** with 2-arylpyridine **5** (Fig. 3, light blue shading) by ^{1}H and ^{19}F NMR spectroscopy. A rapid ligand exchange took place at room temperature between the acetonitrile ligands of **Ru3** and NMP to produce **Ru4** (Fig. 3, spectra i–iii). After 180 minutes at 80 °C, **Ru3**/**Ru4** had quantitatively reacted with **5** to form the predicted bis-cyclometallated Ru(II) species **Ru5**, whose structure was confirmed by X-ray analysis. Then, iodoarene **2** was added and the reaction was monitored at 25 °C (Fig. 3, light yellow shading). Over 600 minutes, **Ru5** quantitatively reacted with **2** to form the arylated product **6**, along with the cyclometallated complexes **Ru6** and **Ru4** derived from reductive elimination. This experiment is fully consistent with our mechanistic hypothesis, and provides strong evidence that the catalytic cycle reported in Fig. 1c is, indeed, operating.

Monocycloruthenated complexes as a superior class of catalysts. Having discovered evidence for the intermediacy of a bis-cycloru-

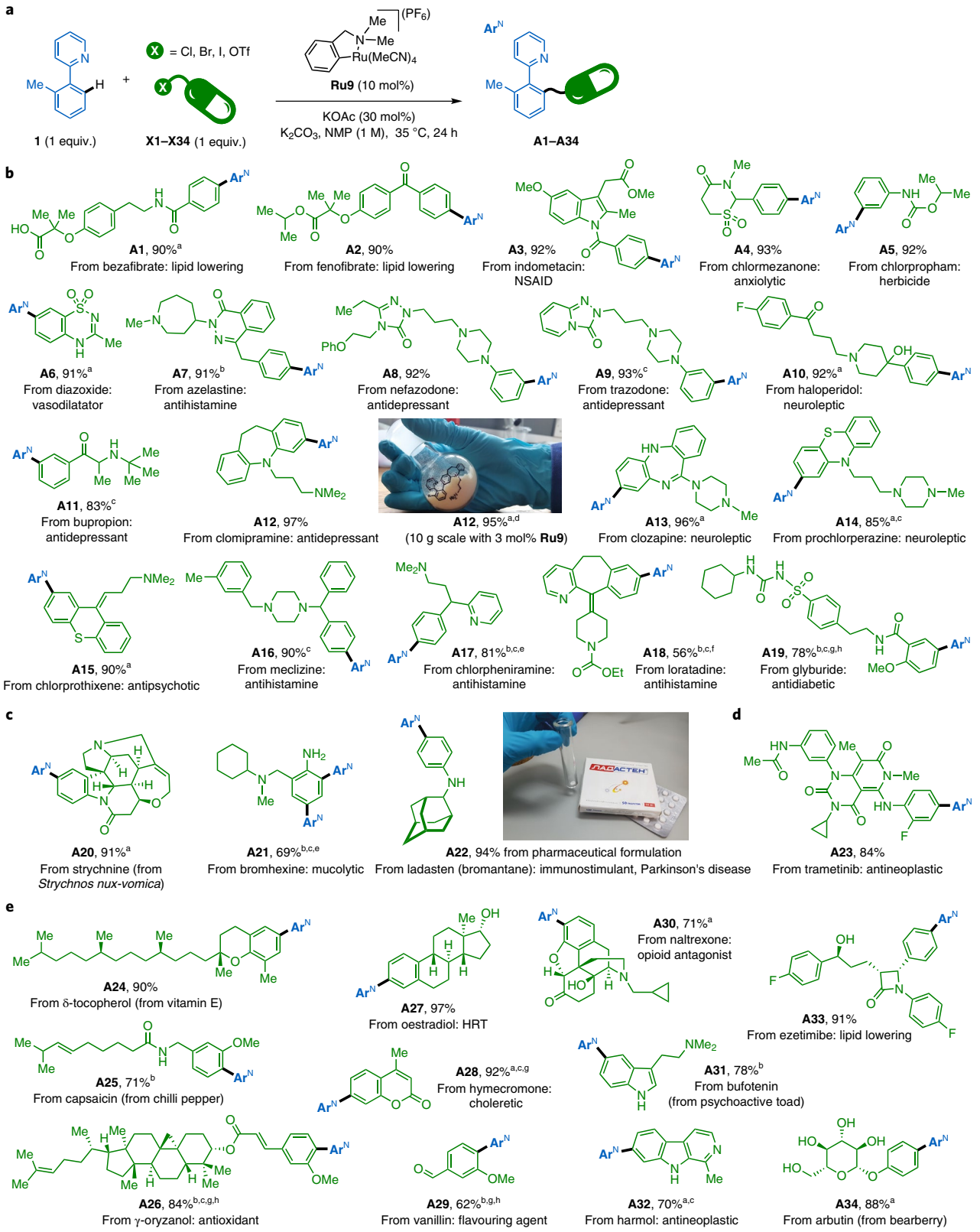

Fig. 5 | Substrate scope of the C–H arylation with respect to the aryl (pseudo)halide-containing drugs. The 2-(*o*-tolyl)pyridine **1** component (Ar^N) is shown in light blue and the aryl (pseudo)halide-containing drug part is shown in green. **a**, C–H arylation coupling of **1** with aryl (pseudo)halides. **b**, Coupling with chloride-containing drugs **X1**, **X2**, **X4** and **X6**–**X19**, chloride-containing drug derivative **X3** and chloride-containing agrochemical **X5**. **c**, Coupling with bromide-containing drugs **X21** and **X22** and bromide-containing natural product derivative **X20**. **d**, Coupling with iodide-containing drug **X23**. **e**, Coupling with triflate-containing drug derivatives **X27**, **X28**, **X30** and **X33** and triflate-containing natural product derivatives **X24**–**X26**, **X29**, **X31**, **X32** and **X34**. All of the yields are isolated yields. Reaction conditions: **Ru9** (10 mol%), KOAc (30 mol%), **1** (1 equiv.), **X1**–**X34** (1 equiv.), K_2CO_3 (2–4 equiv. (Supplementary Information)), NMP (1 M), 35 °C, Ar atmosphere, 24 h. [a]48 h. [b]72 h. [c]50 °C. [d]**X12** (1 equiv.), **1** (1.03 equiv.), **Ru9** (3 mol%). [e]**1** (2 equiv). [f]**1** (3 equiv). [g]KOBz used in replacement of KOAc. [h]NMP (0.5 M). HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

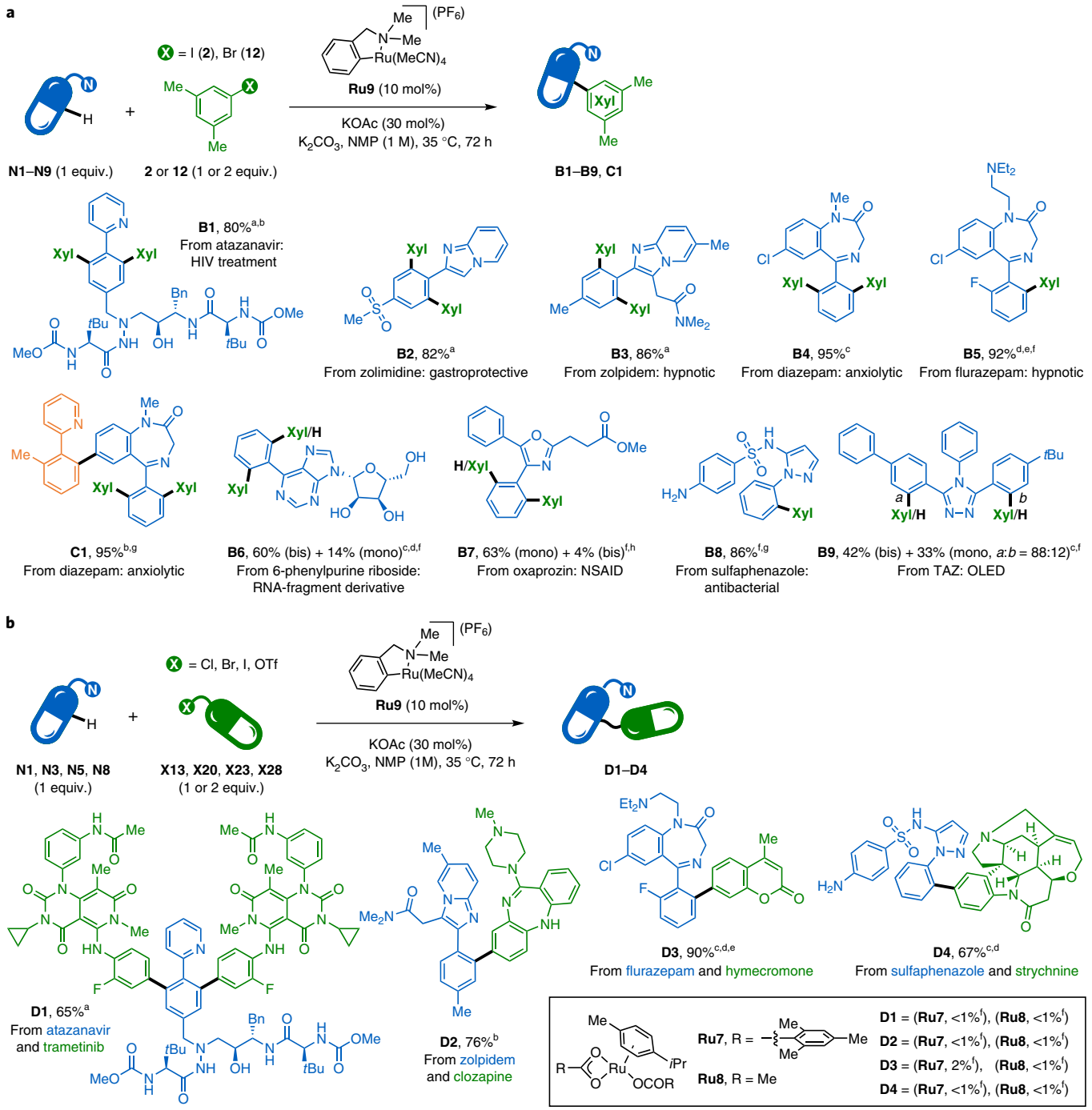

Fig. 6 | Substrate scope of the C–H arylation with respect to the DG-containing drugs and C–H arylation between DG-containing drugs and aryl (pseudo)halide-containing drugs. The DG-containing drug component is shown in light blue, whereas 5-bromo-*m*-xylene **12** or 5-iodo-*m*-xylene **2** (Xyl) (the aryl (pseudo)halide-containing drug part) is shown in green, and the 2-(*o*-tolyl)pyridine **1** component of **C1** is shown in orange. **a**, C–H arylation of DG-containing drugs **N1**–**N5**, **N7** and **N8**, DG-containing drug-like **N6** and DG-containing organic material **N9**. All of the yields are isolated yields. Reaction conditions: **Ru9** (10 mol%), KOAc (30 mol%), **N1**–**N9** (1 equiv.), **12** or **2** (1 or 2 equiv.), K_2CO_3 (2–4 equiv. (Supplementary Information)), NMP (1 M), 35 °C, Ar atmosphere, 72 h. [a]**12** (2 equiv). [b]NMP (0.5 M). [c]**2** (2 equiv). [d]48 h. [e]**2** (1 equiv). [f]50 °C. [g](i) **2** (2 equiv), 72 h; then (ii) **1** (1.5 equiv), 72 h. [h]**12** (1 equiv). **b**, C–H arylation of **N1**, **N3**, **N5** and **N8** with **X23**, **X13**, **X28** and **X20**, respectively. All of the yields are isolated yields. Reaction conditions: **Ru9** (10 mol%), KOAc (30 mol%), **N1**, **N3**, **N4** and **N8** (1 equiv.), **X23** (2 equiv.), **X13**, **X20** and **X28** (1 equiv.), K_2CO_3 (2–3 equiv. (Supplementary Information)), NMP (1 M), 35 °C, Ar atmosphere, 72 h. [a]NMP (0.5 M). [b]144 h. [c]48 h. [d]50 °C. [e]KOBz used instead of KOAc. [f]Reaction set up under identical optimized conditions for each particular case, but **Ru7** and **Ru8** were used instead of **Ru9** without KOAc or KOBz; the yield was evaluated by NMR spectroscopy. OLED, organic light-emitting diode.

thenated complex, we compared the rate of the reaction catalysed by **Ru2** and KOAc to the rates with **Ru7** and **Ru8**, which are the most widely employed state-of-the-art ruthenium catalysts[13,34,46,47] (Fig. 4a). Thus, the C–H arylation of 2-phenylpyridine **7** with 5-iodo-*m*-xylene **2** was monitored over time at 35 °C. Remarkably, although the cyclometallated **Ru2** catalyst afforded a combined yield of 89% of mono

(**8**) and diarylated (**9**) adducts in 420 minutes, **Ru7** and **Ru8** were essentially inactive. These results demonstrate that catalysts based on on-cycle intermediates, such as **I** (RuB in Fig. 1d), possess a far superior catalytic activity than the commonly employed Ru(II) species (RuA in Fig. 1a), which enables reactivity to occur at unprecedentedly low temperatures. However, 8% of biaryl **4**, derived from arylation of the cyclometallating ligand in **Ru2**, was also formed. A similar scenario was also observed with other aryl (pseudo)halides (Supplementary Section 6). It was hypothesized that this was due to the non-selective reductive elimination from a Ru(IV) complex that featured two different cyclometallated arenes, which implies that catalysts such as **Ru2** still suffered from a major drawback. In an attempt to overcome this limitation, we tested cycloruthenated complexes that featured different nitrogen ligands. Gratifyingly, the *N,N*-dimethylbenzylamine-containing **Ru9** provided diarylated adduct **9** in 96% yield and suppressed the undesired 'catalyst arylation' degradation pathway that produces **10** and **11** (Fig. 4b).

Investigation of the scope of the reaction with respect to the aryl (pseudo)halide coupling partners. Having identified **Ru9** as an ideal catalyst able to couple equimolar amounts of DG-containing arenes with aryl (pseudo)halides under exceptionally mild reaction conditions, we decided to demonstrate the synthetic utility of this catalytic system. Towards this aim, pharmaceuticals and natural products that possess an aromatic chloride, bromide, iodide or a phenol moiety transformed into its triflate derivative (**X1**–**X34**), were selected as coupling partners for the C–H arylation of 2-(*o*-tolyl)pyridine **1** (Fig. 5). The scope of the reaction is striking; many ubiquitous heterocycles and functional groups in medicinal chemistry[18–20] were well tolerated and provided good-to-excellent yields (**A1**–**A34**). O-, N-, S- and C-containing (hetero)cycles, such as piperidine (**A10** and **A18**), pyridine (**A17**, **A18** and **A32**), piperazine (**A8**, **A9**, **A13**, **A14** and **A16**), azepane (**A7**), indole (**A3** and **A31**), carbazole (**A32**), phenothiazine (**A14**), dihydrodibenzoazepine (**A12**), dibenzodiazepine (**A13**), thioxanthene (**A15**), triazolone (**A8** and **A9**), pyrimidinedione (**A23**), pyridone (**A23**), morphinan (**A30**), steroid (**A26** and **A27**), β-lactam (**A33**), glucose (**A34**), coumarin (**A28**), chromane (**A24**), phtalazinone (**A7**), benzothiadiazine (**A6**) and thiazinane (**A4**), were shown to be compatible with our system. More specifically, sensitive functional groups, which included tertiary (**A12**, **A15**, **A17**, **A20**, **A21** and **A31**) and secondary amines (**A11**), carbamates (**A5** and **A18**), a sulfonylurea (**A19**), alkenes (**A15**, **A18**, **A20**, **A25** and **A26**), acryloyl groups (**A26** and **A28**), benzylic (**A10**, **A33**), tertiary (**A10** and **A30**), secondary (**A27** and **A34**) and primary alcohols (**A34**), an acetal (**A34**), a thiohemiaminal derivative (**A4**), amidine derivatives (**A6** and **A13**), cyclopropyl groups (**A23**, **A26** and **A30**), an aniline (**A21**), a carboxylic acid (**A1**), an aldehyde (**A29**), amides (**A1**, **A19**, **A23** and **A25**), esters (**A2**, **A3** and **A26**), an α-amino ketone (**A11**) and ketones (**A2** and **A30**) were all tolerated. The efficiency of this catalytic system was also demonstrated by conducting the reaction with clomipramine **X12** on a 10 g scale with the catalyst loading lowered to 3 mol%. The corresponding product, **A12**, was yielded in 95% after a simple aqueous work-up. To highlight further the robustness of our method, bromantane could be used in its pharmaceutical formulation of Ladasten, **X22**, to provide **A22** in 94% yield despite the presence of possibly interfering excipients.

Investigation of the scope of the reaction with respect to the DG-containing arene coupling partners. We then turned our attention to the generality of this reaction with respect to the DG-containing coupling partner (Fig. 6a). Towards this purpose, we tested the 2-phenylpyridine derivative atazanavir **N1**, a peptidomimetic human immunodeficiency virus-1 protease inhibitor that features a complex azadipeptide isoester, which provided **B1** in 80% yield. This methodology is not limited to 2-arylpyridine analogues: other heterocycles with a sp^2-nitrogen DG, which include imidazopyridines (zolimidine to give **B2** and zolpidem to give **B3**), dihydrodibenzoazepin-2-ones (diazepam to **B4** and flurazepam to **B5**), purine (to **B6**), oxazole (oxaprozin to **B7**), pyrazole (sulfaphenazole to **B8**) and 1,2,4-triazole (TAZ (3-(biphenyl-4-yl)-5-(4-*t*-butylphenyl)-4-phenyl-4H-1,2,4-triazole) to **B9**) gave good-to-excellent yields of the corresponding *ortho*-arylated functional molecules (**B2**–**B9**). Consequently, more sensitive moieties, such as sulfonyl (**B2**), the hemiaminal ether of the purine riboside **B6**, sulfonamide (**B8**) and chloride (**B4** and **B5**) were also tolerated. Remarkably, the diazepam derivative **C1** was obtained in 95% yield in a one-pot fashion simply by the sequential addition of iodoarene **2** and 2-(*o*-tolyl)pyridine **1**. To illustrate further the power of our catalytic system, the coupling between two highly functionalized drugs was achieved (Fig. 6b). Atazanavir **N1**, zolpidem **N3**, flurazepam **N5** and sulfaphenazole **N8** were, respectively, reacted with trametinib **X23**, clozapine **X13**, hymecromone derivative **X28** and Br-strychnine **X20** and provided superb yields of the targeted compounds (**D1**–**D4**). Conversely, when the current state-of-the-art Ru(II) catalysts **Ru7** and **Ru8** were tested, neither catalyst afforded **D1**–**D4** in synthetically useful yields (Fig. 6b, bottom right).

Conclusion

Our study highlights the factors that promote oxidative addition at Ru(II) centres in C–H arylation processes of *N*–chelating substrates with aryl (pseudo)halides and demonstrates how comprehensive mechanistic studies can inform the development of more-efficient catalysts. In particular, we identified a bis-cycloruthenated species as the key intermediate that is required for the oxidative addition step to occur. Based on this knowledge, we designed a more-robust catalytic system capable of performing late-stage arylation on complex functionalized molecules and that tolerates functional groups generally considered incompatible with C–H arylation.

According to the PubChem database, there are 6.4 million (hetero)aromatic compounds with a sp^2 nitrogen suitable for *ortho*-ruthenation via a five-membered intermediate, and 22 million (hetero)aromatic chlorides, bromides, iodides and phenols that have biological activity. Owing to this impressive pool of potential coupling partners that bear diverse functionalities, our efficient and cost-effective technology promises to be a powerful and reliable tool for drug discovery and development. Finally, we anticipate that the presented mechanistic discovery could be extended to other C–H activation transformations under current development.

Methods

General procedure for C–H arylation. All of the liquid reagents and solvents were dried over 4 Å molecular sieves and degassed with three freeze–pump–thaw cycles prior to use. KOAc and K_2CO_3 were dried at 140 °C in a vacuum oven for 48 h prior to use. Unless otherwise indicated, in a glovebox, an oven-dried crimp-cap microwave vial equipped with a magnetic stirring bar was charged with **Ru9** (10 mol%), KOAc (30 mol%), K_2CO_3 (2–4 equiv.), the appropriate DG-containing arene (1 equiv.) and aryl (pseudo)halide (1 equiv.) and NMP (1 M). The vial was capped and stirred at 35 °C for 24 h. Upon completion, the vial was transferred out of the glovebox and the crude mixture was loaded onto a silica gel column and purified by flash chromatography.

Data availability. The data reported in this paper are available in the Supplementary Information. Metrical parameters for the structure of bis-cyclometallated complex **Ru5** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/data_request/cif) under reference number CCDC 1567316.

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Author contributions

M.S. and I.L. conceived the work and prepared the manuscript. M.S., D.M.C. and I.L. designed the experiments. M.S. and D.M.C. performed the experiments and analysed the data. X.J.-B., M.S. and D.M.C. prepared the Supplementary Information. I.J.V.-Y. acquired the X-ray of **Ru5**.

Competing interests

A patent protecting the findings disclosed in this manuscript has been filed by the University of Manchester (application number 1807672.9).

Additional information

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