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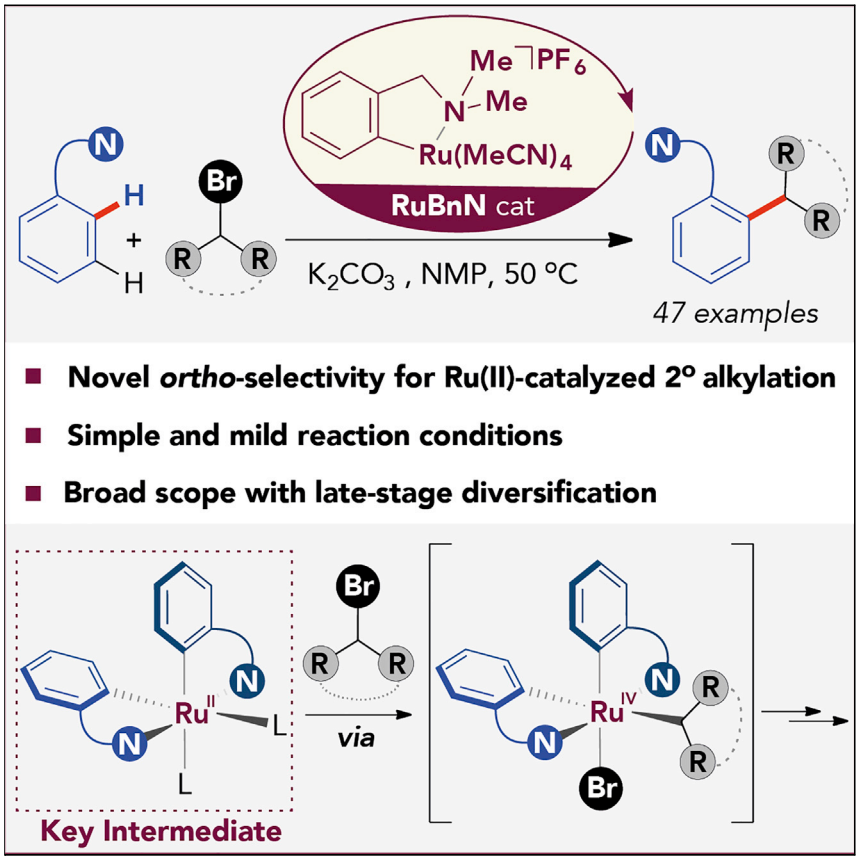
Cyclometalated Ruthenium Catalyst Enables *Ortho*-Selective C–H Alkylation with Secondary Alkyl Bromides



Here, we report the first *ortho*-selective sp^2 C–H bond alkylation with secondary alkyl bromides in the Ru catalytic platform, enabled by cyclometalated ruthenium(II) complex **RuBnN**. Mechanistic studies indicate that the formation of a bis-cycloruthenated intermediate enables an oxidative addition to occur, thus avoiding the single-electron transfer (SET) pathway associated with *meta*-selectivity in other Ru catalytic systems. The reaction is tolerant of a variety of medicinally relevant functional groups and has been used to modify existing pharmaceuticals.

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HIGHLIGHTS

Cyclometalated Ru-complex, **RuBnN**, used as the catalyst

Complete switch of *meta*- to *ortho* selectivity in sp^2 C–H bond alkylation

Bis-cycloruthenated intermediate enables S_N2-type oxidative addition

Late-stage functionalization and diversification of pharmaceutical compounds

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Cyclometalated Ruthenium Catalyst Enables *Ortho*-Selective C–H Alkylation with Secondary Alkyl Bromides

Gang-Wei Wang,[1,2] Matthew Wheatley,[1,2] Marco Simonetti,[1] Diego M. Cannas,[1] and Igor Larrosa[1,3,*]

SUMMARY

Although Ru-catalyzed *meta*-selective sp^2 C–H alkylation with secondary alkyl halides is well established, *ortho* selectivity has never been achieved. We demonstrate that the use of a cyclometalated Ru-complex, RuBnN, as the catalyst results in a complete switch of the inherent *meta*-selectivity to *ortho* selectivity in the Ru-catalyzed sp^2 C–H alkylation reaction with unactivated secondary alkyl halides. The high catalytic activity of RuBnN allows mild reaction conditions that result in a transformation of broad scope and versatility. Preliminary mechanistic studies suggest that a bis-cycloruthenated species is the key intermediate undergoing oxidative addition with the alkyl bromides, thus avoiding the more common SET pathway associated with *meta*-selectivity.

INTRODUCTION

The design of new catalysts exhibiting diverse and superior reactivity lies at the heart of modern synthetic method development. Their discovery is pivotal for improving both the efficiency and synthetic utility of existing chemical transformations, as well as unlocking previously inaccessible reaction pathways toward difficult-to-make compounds.[1–3] In this context, the development of catalytic systems for C–C bond formation through C–H functionalization has received significant attention over the last two decades.[4–8] Despite major advances in the formation of Csp^2–Csp^2 bonds through C–H activation,[9–12] comparatively few methods have been developed for the more challenging C–H alkylation of arenes, particularly with secondary alkyl halides.[13–16] Over the last decade, significant advances on Pd,[17] Ni,[18–22] Co,[23–28] Mn,[29] and Fe[30–32] catalyzed directed alkylations with secondary alkyl halides have been reported; however, important limitations still exist. For example, the majority of methods are limited to the *ortho*-alkylation of benzamides, use a large bidentate directing group, and require high temperatures (100°C–160°C). Those using Co, Mn, and Fe generally require 3–4 equiv of alkyl Grignard as additives, heavily reducing functional-group compatibility as well as in some cases leading to side Grignard-alkylation products. Ru-catalyzed alkylations with unactivated secondary alkyl halides have also been reported, displaying good compatibility with a wide variety of directing groups.[33–44] To date, every example of these Ru-catalyzed alkylations deliver exclusively the *meta*-alkylation product (Scheme 1A). This is in contrast to Ru-catalyzed alkylations by using primary alkyl halides and benzyl halides, which deliver *ortho*-alkylation.[45–47] The origin of *meta*-selectivity in these reactions has been attributed to a single-electron transfer (SET) process generating an alkyl radical that preferentially adds *para* to a Ru^{III}–C bond, rather than at the Ru center. Consequently, *ortho* selectivity with unactivated secondary alkyl halides is currently unknown on the Ru catalytic platform.

The Bigger Picture

Direct C–H functionalization is a powerful tool for milder and more environmentally friendly syntheses of biologically active compounds, as well as offering easy access to unexplored chemical space in drug discovery. However, major challenges remain for these methods to be widely applicable. The development of new catalysts with diverse and superior reactivity is key to address these challenges. Here, we show for the first time that cyclometalated Ru-complexes are able to catalyze the directed *ortho*-C–H alkylation of arenes with secondary alkyl bromides, enabling the late-stage functionalization and diversification of pharmaceuticals. The obtained regioselectivity is in stark contrast to that delivered by the commonly used arene-bound Ru-complexes, which afford exclusive *meta*-alkylation. Our work points a way to further rationally design next-generation Ru-catalysts with improved control over selectivity and reactivity, and a richer synthetic toolbox for chemists in the future.

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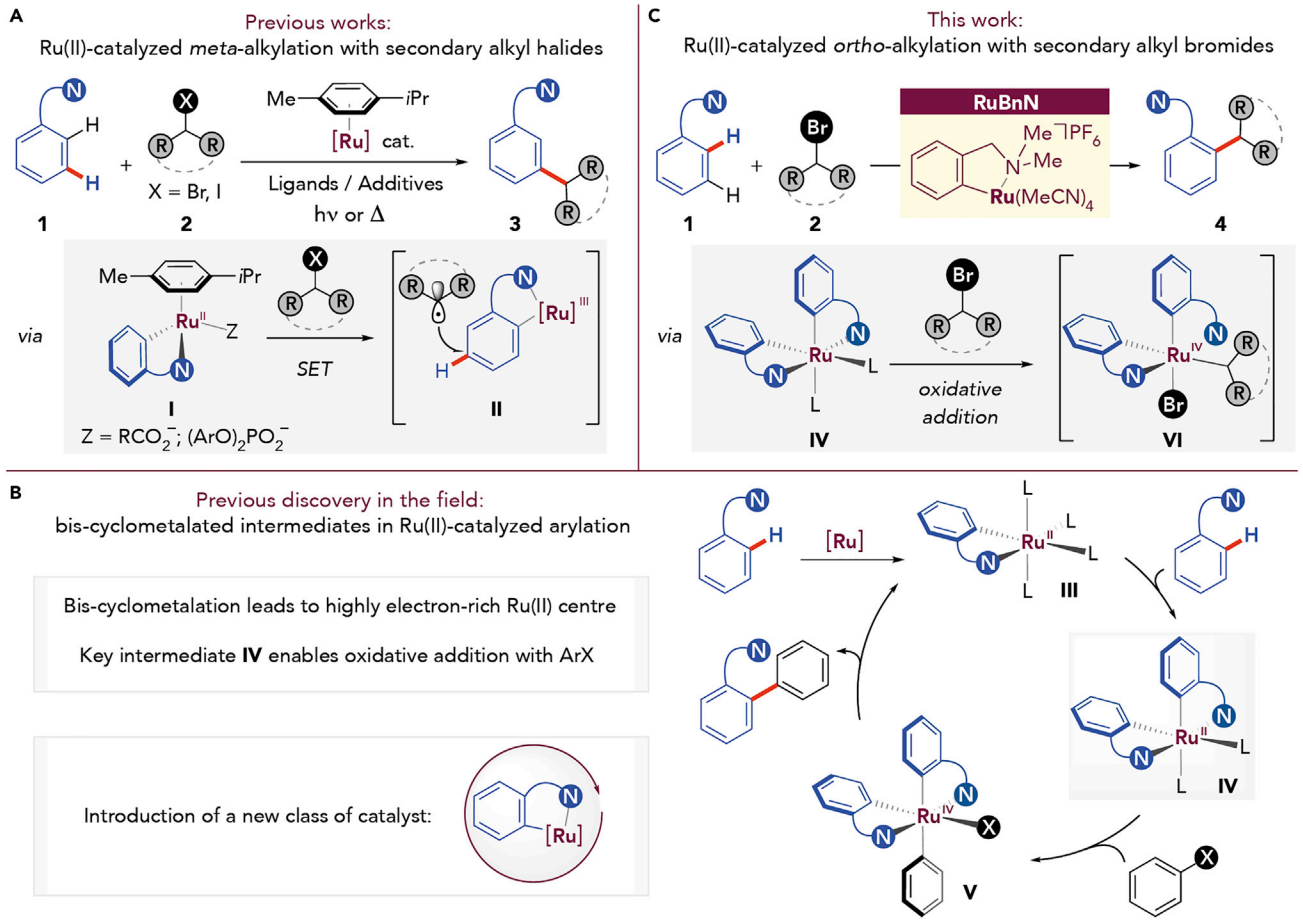

Scheme 1. Ru-Catalyzed C–H *Meta*-Alkylation with Secondary Alkyl Halides versus Proposed *Ortho*-Alkylation

Our group has recently reported mechanistic studies on the Ru-catalyzed C–H arylation of arenes that revealed a previously unknown key catalytic intermediate in these processes (Scheme 1B).[48–50] Our studies demonstrated that two units of substrate are needed in the active species, bis-cyclometalated Ru-intermediate **IV**, before oxidative addition with the aryl halide can occur. This mechanistic insight led to the development of a novel class of Ru-catalysts bearing a cyclometalated ligand instead of the otherwise ubiquitous η^6-coordinated *para*-cymene ligand.[50] We showed that the cyclometalated Ru-complex **RuBnN** was able to outperform the previous state-of-the-art catalysts in the arylation of arenes, realizing very mild conditions for the late-stage arylation and diversification of a large number of drug and drug-like molecules containing a breadth of delicate functionalities.

We envisaged that the coordinatively saturated nature of **I** was responsible for the observed SET pathway leading to meta-selectivity with secondary alkyl halides (Scheme 1A). Thus, we hypothesized that the highly electron-rich bis-cyclometalated Ru-intermediates, such as **IV**, with labile neutral ligands might be able to undergo oxidative addition at the Ru-center instead, leading to hitherto unachieved *ortho*-alkylation selectivity (Scheme 1C). However, this process might be considerably more difficult than the corresponding arylation because of the lower reactivity toward oxidative addition of secondary alkyl halides, originating from their relatively electron-rich C–X bond and increased steric bulk.[51–55]

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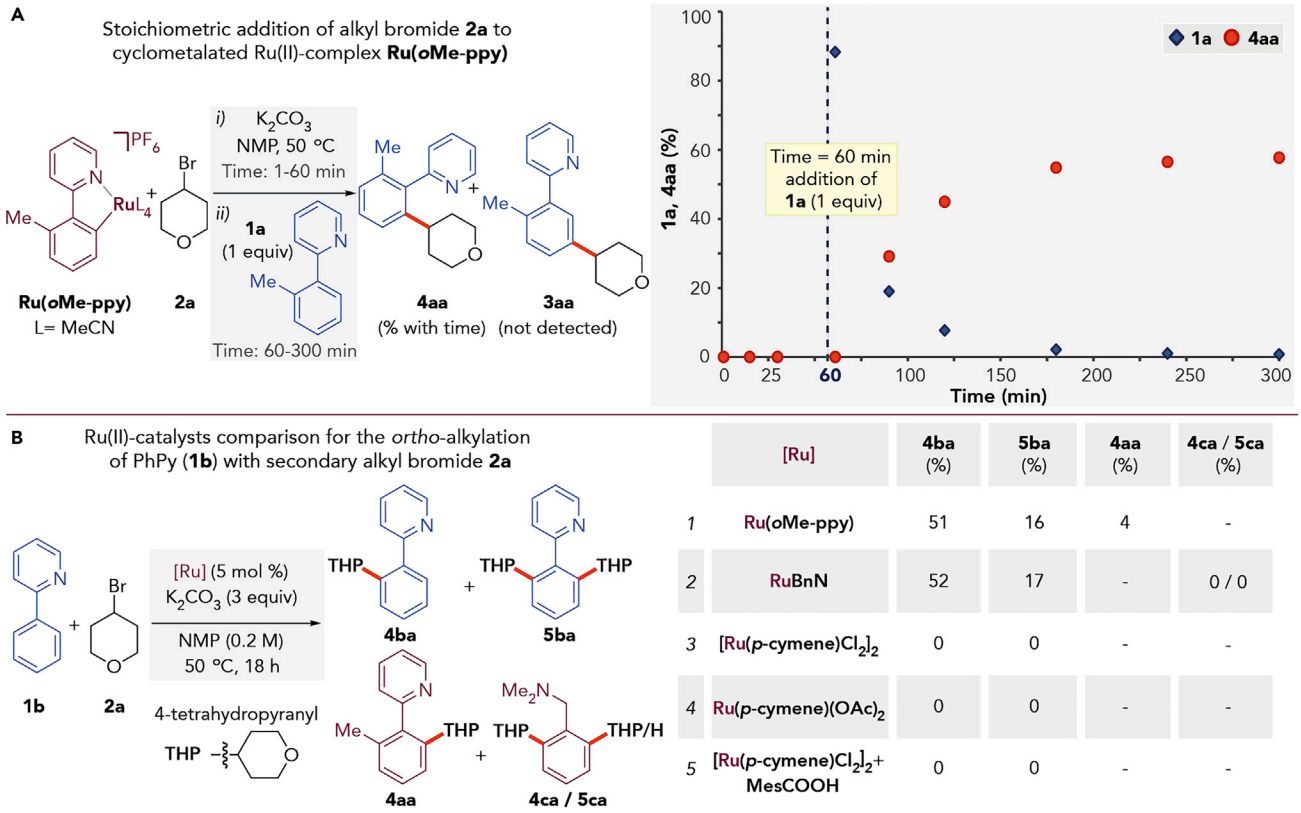

	[Ru]	4ba (%)	5ba (%)	4aa (%)	4ca / 5ca (%)
1	Ru(oMe-ppy)	51	16	4	-
2	RuBnN	52	17	-	0 / 0
3	[Ru(*p*-cymene)Cl_2]$_2$	0	0	-	-
4	Ru(*p*-cymene)$(OAc)_2$	0	0	-	-
5	[Ru(*p*-cymene)Cl_2]$_2$+ MesCOOH	0	0	-	-

Scheme 2. Preliminary Studies

RESULTS AND DISCUSSION

In order to test this hypothesis, we performed stoichiometric experiments using the cyclometalated ruthenium complex **Ru(oMe-ppy)** (Scheme 2A; Figures S1–S4). Similar to the previous observations with aryl halide coupling partners,[50] treatment of this complex with 4-bromotetrahydropyran **2a** revealed no formation of the alkylation product. Gratifyingly, upon addition of 1 equiv of 2-(*o*-tolyl)pyridine (**1a**), formation of the desired *ortho*-alkylation product **4aa** was observed, reaching 60% yield in 4 h. Remarkably, no *meta*-alkylation product was observed, suggesting that the SET pathway previously observed with other Ru-catalysts is not operative with this class of catalysts. Addition of pyridine (1 equiv) instead of **1a** did not afford any product formation as it failed to form the bis-cyclometalated intermediate (Scheme S3); this in turn, rules out the possibility that 2-(*o*-tolyl)pyridine (**1a**) only acts as a pyridine-type ligand to promote the reaction. These results are consistent with the hypothesized requirement for the formation of a bis-cycloruthenated complex of the type **IV** (Scheme 1C) in order to facilitate oxidative addition. Encouraged by the unprecedented formation of *ortho*-alkylation product **4aa**, we explored the development of a Ru-catalyzed alkylation process (Schemes 2B and S4). We were pleased to observe, when 5 mol % **Ru(oMe-ppy)** was employed as the catalyst in the alkylation of **1b** with **2a**, 67% of *ortho*-alkylation (**4ba** and **5ba**) was obtained, with no trace of *meta*-alkylation being formed (Scheme 2B, entry 1). However, a small amount of alkylated **4aa** was obtained as a by-product resulting from alkylation of the ligand in the Ru-catalyst. To our delight, when **RuBnN** was used as the catalyst, side-product formation was completely suppressed (Scheme 2B, entry 2). It is noteworthy that [Ru(*p*-cymene)Cl_2]$_2$ has been reported to deliver exclusive

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meta-alkylation of **1a** with secondary alkyl halides at 100°C.[34–39] However, under our reaction conditions, no alkylation products of **1a** were observed with *p*-cymene catalysts (Scheme 2B, entries 3–5). To the best of our knowledge, this is the first example of a *meta*-to-*ortho* selectivity switch of a C–H alkylation with unactivated secondary alkyl halides by changing the ligand environment at Ru.[56] **RuBnN** affords simple and mild conditions for *ortho*-alkylation, operating at only 50°C and using K_2CO_3 as the base, without the requirement for a carboxylate co-catalyst (Tables S2–S5).

With the optimized conditions in hand, we examined the substrate scope with respect to the heteroarene unit (Schemes 3A and S1). Substrates bearing electronically diverse substituents at different positions were efficiently transformed into the corresponding *ortho*-alkylated products in good-to-excellent yields. In addition to methyl esters and aryl chlorides, unprotected benzylic alcohols were tolerated (**4ga**, **4ha**, and **4ia**). Where symmetrical substrates were used, minimal or trace amounts of bis-*ortho*-alkylation product were obtained. Notably, the alkylation is highly selective for mono-alkylation with substrates bearing *meta*-substituents, and alkylation occurred exclusively at the less sterically hindered *ortho*-position (**4la** and **4ma**).[57] Other heteroarenes, such as quinolines and pyrimidines, were also found to be suitable directing groups, producing the corresponding *ortho*-alkylated products **4pa** and **4qa** in excellent yields.

After this, we investigated the scope of alkyl bromides (Schemes 3B and S2). Different bromo-substituted carbocycles exhibited high reactivity and yielded the products in excellent yield (**4nb–4nc**). Alkyl bromides bearing a wide variety of functional groups and heteroarenes were compatible with our catalytic system. Piperidine units are tolerated (**4nd–4ah**), a key structural motif in numerous natural products and pharmaceuticals.[58,59] Although free N–H are not tolerated, amines protected in the form of carbamate (**4nd**), benzyl amines (**4ne**), and amides (**4nf–4ah**) were all compatible with the reaction conditions leading to good-to-excellent yields of the corresponding products. Heteroaryls, such as furan (**4nf**), N-methyl-pyrrole (**4ng**),[60] and thiophene (**4ah**), were also supported motifs. Acyclic secondary alkyl bromides were also tested. Interestingly, 2-bromopropane **2i** led to *ortho*-alkylation product **4ni** in 50% yield, and a small amount of *meta*-alkylation was observed (Table S1), indicating a possible competition between oxidative addition to Ru and SET pathways for these substrates. Gratifyingly, the *meta*-alkylation products were suppressed when using *meta*-substituted phenyl pyridine substrates, leading to good yields of the desired *ortho*-alkylated products with a range of acyclic alkylating partners (**4mi–4mk**). It is noteworthy that in previously reported Ru-catalyzed C–H alkylation with secondary alkyl halides, *meta*-substituted phenyl pyridines afforded instead exclusively *meta*-alkylation or no reaction.[34,37,38]

Taking advantage of the mild reaction conditions of our new *ortho*-alkylation system, we attempted the late-stage diversification of a series of pharmaceuticals and natural products (Scheme 3C). Accordingly, a series of alkyl bromides was prepared either through conversion of an alcohol in the substrate or via amide coupling of a carboxylic acid with 4-bromopiperidine. The structurally complex cyclic alkyl bromides **2l** and **2m**, prepared from epiandrosterone and cholesterol, respectively, reacted smoothly to the corresponding *ortho*-alkylation products in good-to-excellent yields (**4dl** and **4am**). Notably, a single diastereoisomer was obtained in both cases (vide infra).

This reaction tolerates various functional groups relevant to medicinal chemistry, such as: amides; terminal, conjugated, and internal alkenes (**4an**, **4ao**, and **4ap**);

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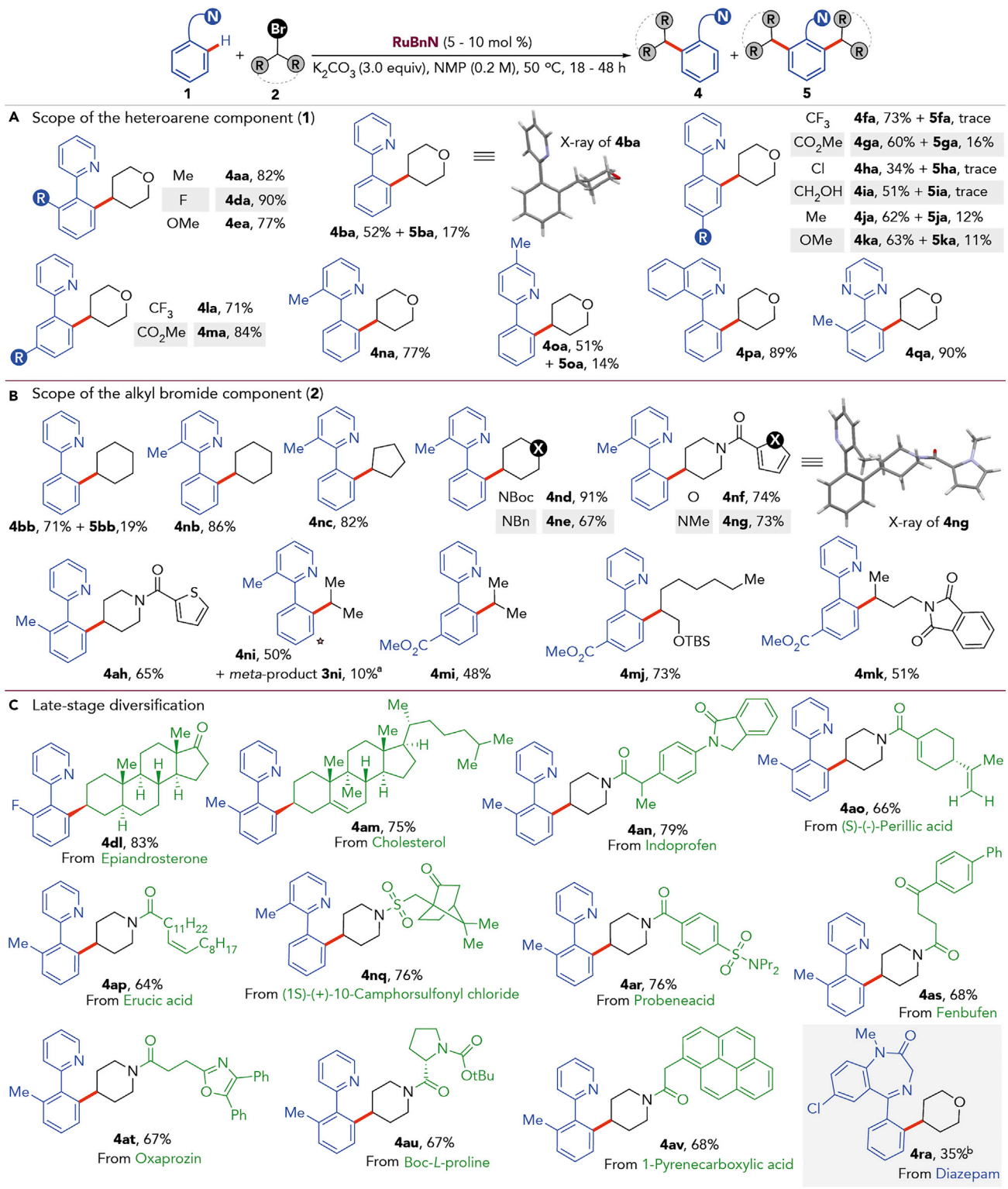

Scheme 3. Heteroarene-Directed *Ortho*-C–H Alkylation

Reactions carried out on a scale of 0.20 mmol of **1**. Isolated yields of **4** and **5** are given. [a]Reaction carried out at 30°C. [b]Reaction carried out for 72 h.

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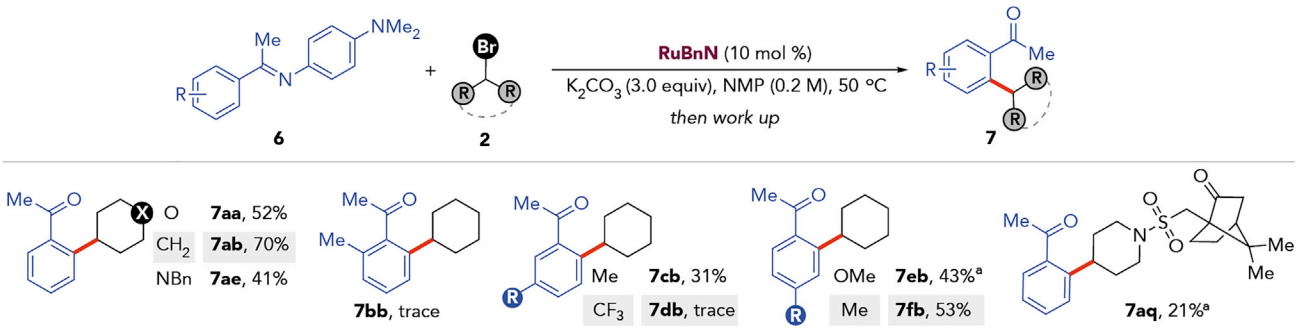

Scheme 4. Ketimine-Directed *Ortho*-C–H Alkylation

Reactions carried out on a scale of 0.20 mmol of **6**. Isolated yields of **7** are given. [a]A small amount of *meta*-alkylation product was obtained. See Supplemental Information for details.

sulfonamides (**4nq** and **4ar**); aryl and alkyl ketones (**4as** and **4dl**); oxazole (**4at**); and N-Boc-proline (**4au**), and the desired *ortho*-alkylated products formed in moderate to good yields. A pyrene[61] containing bromoalkane was also a suitable alkylating partner under our reaction conditions (**4av**). Furthermore, the late-stage functionalization of diazepam was achieved, leading to *ortho*-alkylated **4ra**. This result further demonstrated the applicability of our alkylation protocol and encouraged us to investigate its application to the synthetically versatile ketimine directing group (Scheme 4). Without any further optimization, ketimine-based substrate **6a** reacted smoothly with simple alkyl electrophiles, delivering the corresponding *ortho*-alkylated arylketones **7aa**, **7ab**, and **7ae** in good yields, after an *in situ* hydrolysis. Subsequently, different ketimines were examined in the reaction under the standard conditions. *Ortho*-substitution had a significant negative effect on the reaction (**7bb**), whereas *meta*-substitution could be tolerated (**7cb**). It is noteworthy that *ortho*- and *meta*-substituted ketimines have not been shown to be competent in Ru-catalyzed *meta*-alkylation manifolds.[37] Notably, the reaction performed better with ketimines bearing an electron-donating substituent at the *para* position, with **7eb** and **7fb** produced in 43% and 53% yields, respectively. However, lower yields were delivered when electron withdrawing substitutions were introduced.[62] Complex alkyl bromide **2q** was also successfully transformed into desired product **7aq** in the reaction, albeit in a lower yield.

Careful analysis of the stereochemical outcome of the alkylation reactions of deoxybromo-androsterone derivatives 3α-**2l** and 3β-**2l** revealed important differences between our method and previous methods involving radical intermediates. Indeed, when 3α-**2l** was submitted to the reaction conditions (Scheme 5A), 3β-**4dl** was obtained as the only stereoisomer in excellent yield (83%). Conversely, previously reported use of **2l** in radical mediated C–C bond-forming processes led to varying ratios from 1.4:1 to 6.7:1 of diastereomeric mixtures.[63–67] The analysis of the recovered starting material showed that 3β-**2l**, resulting from the epimerization of 3α-**2l**, was obtained in a significant amount. Intriguingly, when 3β-**2l** was used as the coupling partner, the overall reaction was more sluggish but led to the formation of the same equatorially substituted product 3β-**4dl** with epimerized 3α-**2l** detected only in a trace amount. This observation is consistent with a more hindered S_N2-based oxidative addition on the equatorial C–Br bond of 3β-**2l**.[68,69] Instead, we found that 3β-**2l** can slowly epimerize under the reaction conditions to 3α-**2l** (Schemes 5B and S5), which is then able to react smoothly to afford 3β-**4dl**. The detection of only a trace amount of epimerized 3α-**2l** in the catalytic reaction not only confirmed the slow epimerization of 3β-**2l**, but also indicated a fast

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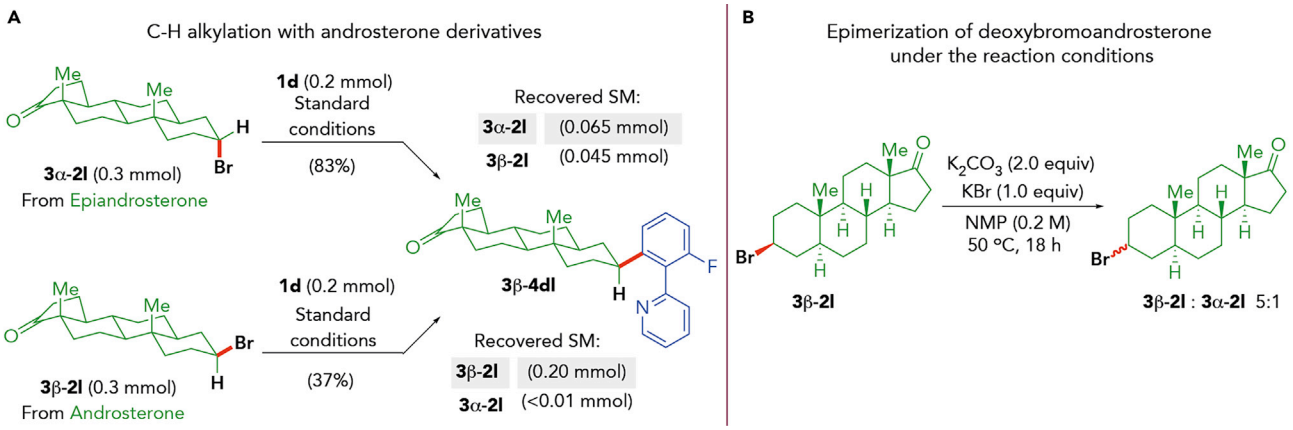

Scheme 5. Stereochemical Outcome of the Oxidative Addition Step

consumption of 3α-2l. These results, together with our preliminary stoichiometric experiments (Scheme 2), are consistent with an S_N2-type oxidative addition process, with inversion of configuration, at the bis-cycloruthenated species **IV**.

In summary, we have demonstrated that cyclometalated ruthenium catalyst **RuBnN** provides a distinct regiochemical outcome to previous non-cyclometalated (*p*-cymene)Ru(II)-catalysts. This work provides a new platform for *ortho*-alkylation with unactivated secondary alkyl bromides. Preliminary mechanistic studies are suggestive of a S_N2-type oxidative addition at a bis-cyclometalated Ru(II) intermediate. This is in stark contrast to previous Ru(II)-catalyzed alkylations which are proposed to proceed through an SET pathway and deliver *meta*-alkylated products. The transformation, realized under mild conditions, exhibits a broad substrate scope and shows excellent functional-group compatibility. Both heteroarenes and ketimines are suitable directing groups and the synthetic utility of this new catalyst has been demonstrated on the late-stage diversification and alkylation of pharmaceuticals and natural products.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Igor Larrosa (igor.larrosa@manchester.ac.uk).

Materials Availability

Unique and stable reagents generated in this study will be made available on request, but we may require a payment and/or a completed Materials Transfer Agreement if there is potential for commercial application.

Data and Code Availability

Metrical parameters for X-ray structures are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference numbers **4ba**: 1969096; **4ng**: 1969097.

Representative Method for *Ortho*-Alkylation Process

In a glove box, an oven-dried crimp-cap microwave vial equipped with a magnetic stirring bar was charged with **RuBnN** (5.44 mg, 0.01 mmol) and K_2CO_3 (82.8 mg,

0.6 mmol), followed by addition of substrates **1a** (33.8 mg, 0.20 mmol), **2a** (34.2 mg, 0.21 mmol), and *N*-methyl-2-pyrrolidone (1.0 mL). The vial was then capped, taken out of the glovebox, and stirred at 50°C for 18 h. The reaction was then allowed to cool to room temperature before being quenched with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (10% EtOAc/Hex) to yield the **4aa** (41.7 mg, 82%) as a colorless solid.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.04.006.

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AUTHOR CONTRIBUTIONS

M.S., D.M.C., and I.L. conceived the project. M.S. and D.M.C. carried out initial discovery work. G.-W.W. and M.W. contributed equally to the design of experiments, optimization of the methodology, and exemplification of the chemistry. I.L. secured the funding and directed the work. The manuscript was prepared with contributions from all authors.

DECLARATION OF INTERESTS

A patent protecting the findings disclosed in this manuscript has been filed by the University of Manchester.

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