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

Here, we report the first ortho-selective sp² 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.
Article

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

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SUMMARY

Although Ru-catalyzed meta-selective sp² 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 sp² 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 Csp²–Csp² 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 Fe30–32 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 (100–160 °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 alkylation 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 alkylation 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 RuIII–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.
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). 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 h\textsubscript{6}-coordinated para-cymene ligand. 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.

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

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https://doi.org/10.1016/j.chempr.2020.04.006
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, 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+ has been reported to deliver exclusive...
meta-alkylation of 1a with secondary alkyl halides at 100°C. 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. RuBnN affords simple and mild conditions for ortho-alkylation, operating at only 50°C and using K2CO3 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). 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. 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), 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.

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);
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. *Reaction carried out at 30°C. **Reaction carried out for 72 h.
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 pyrene61 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 stereoechemical 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_{n}2-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 5S), 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
consumption of 3α-2l. These results, together with our preliminary stoichiometric ex-
periments (Scheme 2), are consistent with an SN2-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-cym-
ene)Ru(II)-catalysts. This work provides a new platform for ortho-alkylation with un-
activated secondary alkyl bromides. Preliminary mechanistic studies are suggestive
of a SN2-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 excel-
 lent 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 Cam-
bridge 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 K2CO3 (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 H2O (10 mL) and extracted with Et2O (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na2SO4, 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.

ACKNOWLEDGMENTS
We gratefully acknowledge the Engineering and Physical Sciences Research Council (EPSRC, EP/S02011X/1) for funding and the European Research Council for an Advanced Grant (RuCat) to I.L. We are grateful to Iñigo J. Vitorica-Yrezabal (UoM) for X-ray crystallography.

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.

Received: February 21, 2020
Revised: March 23, 2020
Accepted: April 8, 2020
Published: May 4, 2020

REFERENCES
1. Freeze, J.G., Kelly, H.R., and Batista, V.S. (2019). Search for catalysts by inverse design: artificial intelligence, mountain climbers, and alchemists. Chem. Rev. 119, 6595–6612.
2. Houk, K.N., and Cheong, P.H.-Y. (2008). Computational prediction of small-molecule catalysts. Nature 455, 309–313.
3. Ahn, S., Hong, M., Sundararajan, M., Ess, D.H., and Baik, M.-H. (2019). Design and optimization of catalysts based on mechanistic insights derived from quantum chemical reaction modeling. Chem. Rev. 119, 6509–6560.
4. Bergman, R.G. (2007). Organometallic chemistry: C–H activation. Nature 446, 391–393.
5. Shilov, A.E., and Shul’pin, G.B. (1997). Activation of C–H bonds by metal complexes. Chem. Rev. 97, 2879–2932.
6. Gandeepan, P., and Ackermann, L. (2018). Transient directing groups for transformative C–H activation by synergistic metal catalysis. Chem 4, 199–222.
7. Lyons, T.W., and Sanford, M.S. (2010). Palladium-catalyzed ligand-directed C–H functionalization reactions. Chem. Rev. 110, 1147–1169.
8. He, J., Wasa, M., Chan, K.S.L., Shao, Q., and Yu, J.-Q. (2017). Palladium-catalyzed transformations of alkyl C–H bonds. Chem. Rev. 117, 8754–8786.
9. Alberico, D., Scott, M.E., and Lautens, M. (2007). Aryl–aryl bond formation by transition-metal-catalyzed direct arylation. Chem. Rev. 107, 174–238.
10. McGlacken, G.P., and Bateman, L.M. (2009). Recent advances in aryl–aryl bond formation by direct arylation. Chem. Soc. Rev. 38, 2447–2464.
11. Daugulis, O. (2010). Palladium and copper catalysis in regioselective, intermolecular coupling of C–H and C-Hal bonds. Top. Curr. Chem. 292, 57–84.
12. Simonetti, M., Cannas, D.M., and Larrosa, I. (2017). Biaryl synthesis via C–H bond activation: strategies and methods. In Advances in Organometallic Chemistry, P.J. Pérez, ed. (Elsevier), pp. 299–399.
13. Evano, G., and Theunissen, C. (2019). Beyond Friedel and Crafts: directed alkylation of C–H bonds in arenes. Angew. Chem. Int. Ed. 58, 7202–7236.
14. Evano, G., and Theunissen, C. (2019). Beyond Friedel and Crafts: innate alkylation of C–H bonds in arenes. Angew. Chem. Int. Ed. 58, 7558–7598.
15. Chen, Z., Rong, M.-Y., Nie, J., Zhu, X.-F., Shi, B.-F., and Ma, J.-A. (2019). Catalytic alkylation of unactivated Csp2–H bonds for Csp2–Csp3
bond formation. Chem. Soc. Rev. 48, 4921–4942.

16. Ackermann, L. (2010). Metal-catalyzed direct alkylation of heteroarenes via C–H bond cleavages with unactivated alkyl halides. Chem. Commun. (Camb.) 46, 4866–4877.

17. Zhang, S.-Y., Li, Q., He, G., Nacc, W.A., and Chen, G. (2015). Pd-catalyzed monoselective ortho-C–H alkylation of N-quinolinyl benzamides: evidence for stereoreorientive coupling of secondary alkyl oxidics. J. Am. Chem. Soc. 137, 531–539.

18. Song, W., Lackner, S., and Ackermann, L. (2014). Nickel-catalyzed C–H alkylation: direct secondary alkylation and trifluoroethylation of arenes. Angew. Chem. Int. Ed. 53, 2477–2480.

19. Ruan, Z., Lackner, S., and Ackermann, L. (2016). A general strategy for the nickel-catalyzed C–H alkylation of anilines. Angew. Chem. Int. Ed. 55, 3153–3157.

20. Ghorai, D., Finger, L.H., Zanoni, G., and Ackermann, L. (2018). Bimetallic nickel complexes for aniline C–H-alkylations. Angew. Chem. Int. Ed. 57, 9279–9283.

21. Soni, V., Jagtap, R.A., Gonnade, R.G., and Ackermann, L. (2016). Unified strategy for nickel-catalyzed C–2 alkylation of indoles Pd-catalyzed oxidation of aldehydes with aryl and alkyl halides. J. Org. Chem. 81, 9826–9830.

22. Shen, Z., Huang, H., Zhu, C., Warrat, S., and Ackermann, L. (2019). MnCl2-catalyzed C–H alkylation on azine heterocycles. Org. Lett. 21, 571–574.

23. Frueh, E.R., Monks, B.M., and Cook, S.P. (2014). A unified strategy for iron-catalyzed Ortho-alkylation of carboxamides. J. Am. Chem. Soc. 136, 13130–13133.

24. Ilies, L., Matsubara, T., Ichikawa, S., Asako, S., and Nakamura, E. (2014). Iron-catalyzed directed alkylation of aromatic and olefinic carboxamides with primary and secondary alkyl tosylates, mesylates, and halides. J. Am. Chem. Soc. 136, 13126–13129.

25. Cera, G., Haven, T., and Ackermann, L. (2016). Expedit C–H functionalization through assisted triazole. Angew. Chem. Int. Ed. 55, 293–296.

26. Ackermann, L., Novák, P., Vicente, R., and Hofmann, N. (2009). Ruthenium-catalyzed regioselective direct alkylation of arenes with unactivated alkyl halides through C–H bond cleavage. Angew. Chem. Int. Ed. 48, 6045–6048.

27. Ackermann, L., and Novák, P. (2009). Regioselective ruthenium-catalyzed direct benzylations of arenes through C–H bond cleavages. Org. Lett. 11, 4966–4969.

28. Ackermann, L., Hofmann, N., and Vicente, R. (2011). Carboxylate-aided ruthenium-catalyzed direct alkylations of ketones. Org. Lett. 13, 1875–1877.

29. Simonetti, M., Perry, G.J.P., Cambeiro, X.C., Juliá-Hernández, F., Arakonathan, J.N., and Larrosa, I. (2016). Ru-Catalyzed C–H arylation of fluoroarenes with aryl halides. J. Am. Chem. Soc. 138, 3596–3606.

30. Simonetti, M., Kunjil, R., Macgregor, S.A., and Larrosa, I. (2018). Benzolate cyclometalation enables oxidative addition of haloarenes to a Ru(II) center. J. Am. Chem. Soc. 140, 11836–11847.

31. Simonetti, M., Cannas, D.M., Just-Baringo, X., Vitorica-Yztrezabal, I.J., and Larrosa, I. (2018). Cyclometalated ruthenium catalyst enables late-stage directed arylation of pharmaceuticals. Nat. Chem. 10, 724–731.

32. Rudolph, A., and Landers, M. (2009). Secondary alkyl halides in transition-metal-catalyzed cross-coupling reactions. Angew. Chem. Int. Ed. 48, 2656–2670.

33. Aniafa, A., and Lin, Z. (2006). Understanding the relative easiness of oxidative addition of aryl and alkyl halides to palladium (0). Organometallics 25, 4030–4033.

34. Luh, T.Y., Leung Mk, M.K., and Wong, K.T. (2020). Transition-metal-catalyzed activation of aliphatic C-X bonds in carbon-carbon bond formation. Chem. Rev. 100, 3187–3204.

35. Frisch, A.C., and Beller, M. (2005). Catalysts for cross-coupling reactions with non-activated alkyl halides. Angew. Chem. Int. Ed. 44, 674–688.

36. Fu, G.C. (2017). Transition-metal catalysis of nucleophilic substitution reactions: a radical alternative to S N1 and S N2 processes. ACS Cent. Sci. 3, 692–700.

37. Ackermann and coworkers have recently shown a regioselectivity switch using primary benzyl halides as coupling partners. see: Korvorapun, K., Kunjil, R., and Ackermann, L. (2020). Late-stage diversification by selectivity switch in meta-C–H activation: evidence for singlet stabilization ACS Catal. 10, 435–440.
57. The Meta-OMe substituted 2-phenylpyridine derivative only yielded the desired product in a very low yield (<10% NMR yield).

58. Pinder, A.R. (1990). Pyrrolidine, piperidine, and pyridine alkaloids. Nat. Prod. Rep. 7, 447–455.

59. O’Hagan, D. (2000). Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. Nat. Prod. Rep. 17, 435–446.

60. CCDC number for 4ba: 1969096; CCDC number for 4ng: 1969097.

61. Figueira-Duarte, T.M., and Müllen, K. (2011). Pyrene-based materials for organic electronics. Chem. Rev. 111, 7260–7314.

62. See Supplemental Information for details.

63. Wang, C., and Dong, G. (2018). Direct β-alkylation of ketones and aldehydes via Pd-catalyzed redox cascade. J. Am. Chem. Soc. 140, 6057–6061.

64. Wang, G.Z., Shang, R., Cheng, W.M., and Fu, Y. (2017). Irradiation-induced heck reaction of unactivated alkyl halides at room temperature. J. Am. Chem. Soc. 139, 18307–18312.

65. Sargent, B.T., and Alexanian, E.J. (2016). Palladium-catalyzed alkoxycarbonylation of unactivated secondary alkyl bromides at low pressure. J. Am. Chem. Soc. 138, 7520–7523.

66. Xiao, B., Liu, Z.J., Liu, L., and Fu, Y. (2013). Palladium-catalyzed C—H activation/cross-coupling of pyridine N-oxides with nonactivated secondary alkyl bromides. J. Am. Chem. Soc. 135, 616–619.

67. Yan, X.B., Li, C.L., Jin, W.J., Guo, P., and Shu, X.Z. (2018). Reductive coupling of benzyl oxalates with highly functionalized alkyl bromides by nickel catalysis. Chem. Sci. 9, 4529–4534.

68. Elie, E.L., and Haber, R.G. (1959). Conformational analysis. VII. Reaction of alkylcyclohexyl bromides with thiophenolate. The conformational equilibrium constant of bromine. J. Am. Chem. Soc. 81, 1249–1254.

69. Hartwig, J.F. (2010). Oxidative addition of polar reagents. In Organotransition Metal Chemistry – From Bonding to Catalysis (University Science books), pp. 301–320.