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Sequential *meta*-/*ortho*-C–H Functionalizations by One-Pot Ruthenium(II/III) Catalysis

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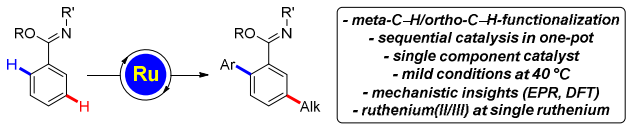
ABSTRACT: The sequential twofold *meta*-C–H/*ortho*-C–H functionalization was achieved by means of versatile ruthenium(II) biscarboxylate catalysis. The double C–H activation proved viable in a one-pot fashion by assistance of synthetically useful imidates. The operationally-simple twofold C–H functionalization occurred with high levels of positional selectivity control, and was conducted in a non-sequential manner by the judicious choice of the reaction temperature. Detailed experimental mechanistic studies, including unprecedented EPR experiments, provided strong support for a homolytic C–X cleavage and a facile C–H ruthenation, while a computational DFT analysis was supportive of a novel mechanistic scenario, involving synergistic catalysis via cyclometalated ruthenium(III) complexes as key intermediates.

KEYWORDS: *C–H activation, DFT, EPR, remote selectivity, ruthenium, sequential catalysis.*

C–H activation has emerged as a transformative platform for molecular syntheses, enabling the step- and atom-economical synthesis of organic compounds from easily accessible raw materials.[1] The sustainable nature of this approach has further been improved by the design of sequential one-pot processes, ideally exploiting a single[2] metal catalyst for two mechanistically-distinct transformations. Despite of considerable advances in the field, these multicatalytic single-component[3] C–H activations are thus far restricted to entropically-favored intramolecular reactions,[4] functionalizations of electronically-biased heteroarenes,[5] or proximity-induced *ortho*-C–H functionalizations.[6] In sharp contrast, the implementation of challenging remote *meta*-C–H functionalizations[7] into single-catalyst component[8] one-pot sequential[9] catalysis has thus far proven elusive,[10] which contrasts the notable recent progress in remote C–H functionalizations[7, 11] with ruthenium catalysts by inter alia Frost, Greaney and Ackermann, among others.[12] Within our program directed towards sustainable C–H activation,[13] we have now devised the first strategy for multicatalytic *meta*-C–H/*ortho*-C–H functionalizations, on which we report herein (Scheme 1). Notable features of our findings include (a) a versatile ruthenium(II) biscarboxylate catalyst for a positional-selective *meta*-C–H alkylation/*ortho*-C–H arylation[14,15] manifold, (b) synthetically-meaningful[16] imidates[17] for *meta*-C–H functionalizations, (c) mild reaction conditions of 40-60 °C, and (d) detailed mechanistic insights into homolytic C–X cleavage. Thus, first electron paramagnetic resonance (EPR) spectroscopic studies on remote C–H functionalizations and computational insights provided strong support for a novel ruthenium(II/III) catalysis manifold on a single ruthenium catalyst.

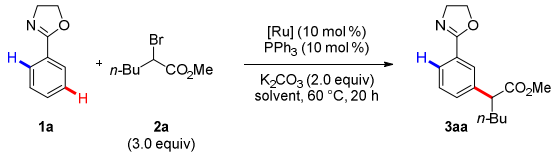


Scheme 1. Sequential *meta*-C–H/*ortho*-C–H functionalization

We commenced our studies by probing various reaction conditions for the envisioned *meta*-C–H functionalization of aryloxazoline **1a** (Table 1, and Table S-1 in the Supporting Information).[18] Carboxylate assistance[19] was found to be key to success for the remote-C–H alkylation process (entries 1-7), with best results being accomplished in 1,4-dioxane as the solvent (entries 5–8). The high catalytic efficacy of the ruthenium(II)biscarboxylate catalysis manifold was reflected by comparably high yields under rather mild reaction conditions,[20] featuring a mild base at a reaction temperature of only 40 °C (entry 9). Control experiments verified the key role of the carboxylate (entry

3) and phosphine additive (entry 10), illustrating the importance of a synergistic catalysis regime.

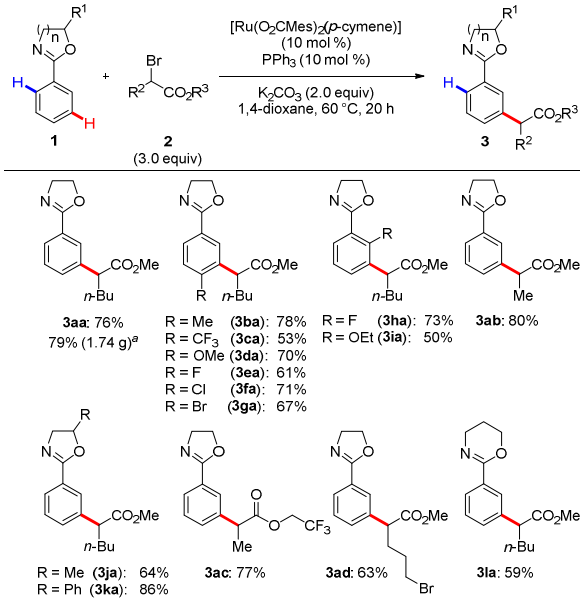
Table 1. *meta*-C–H-Alkylation by Oxazoline Assistance[a]



entry	[Ru]	Solvent	Yield (%)
1	-	1,4-dioxane	-
2	$Ru_3(CO)_{12}$	1,4-dioxane	-
3	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	(<5)
4	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	(<5)[b, c]
5	$[Ru(O_2CMes)_2(p\text{-cymene})]$	PhMe	(17)
6	$[Ru(O_2CMes)_2(p\text{-cymene})]$	1,2-DCE	(10)
7	**$[Ru(O_2CMes)_2(p\text{-cymene})]$**	**1,4-dioxane**	**76**
8	$[Ru(O_2CAd)_2(p\text{-cymene})]$	1,4-dioxane	73
9	$[Ru(O_2CMes)_2(p\text{-cymene})]$	1,4-dioxane	65[d]
10	$[Ru(O_2CMes)_2(p\text{-cymene})]$	1,4-dioxane	trace[b]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), [Ru] (10 mol %), PPh_3 (10 mol %), K_2CO_3 (1.0 mmol), solvent (2.0 mL), 60 °C, 20 h, isolated yield. Conversion of **3aa** in parentheses by ^{1}H-NMR with CH_2Br_2 as internal standard. [b] Without PPh_3. [c] $AgSbF_6$ (20 mol %). [d] 40 °C.

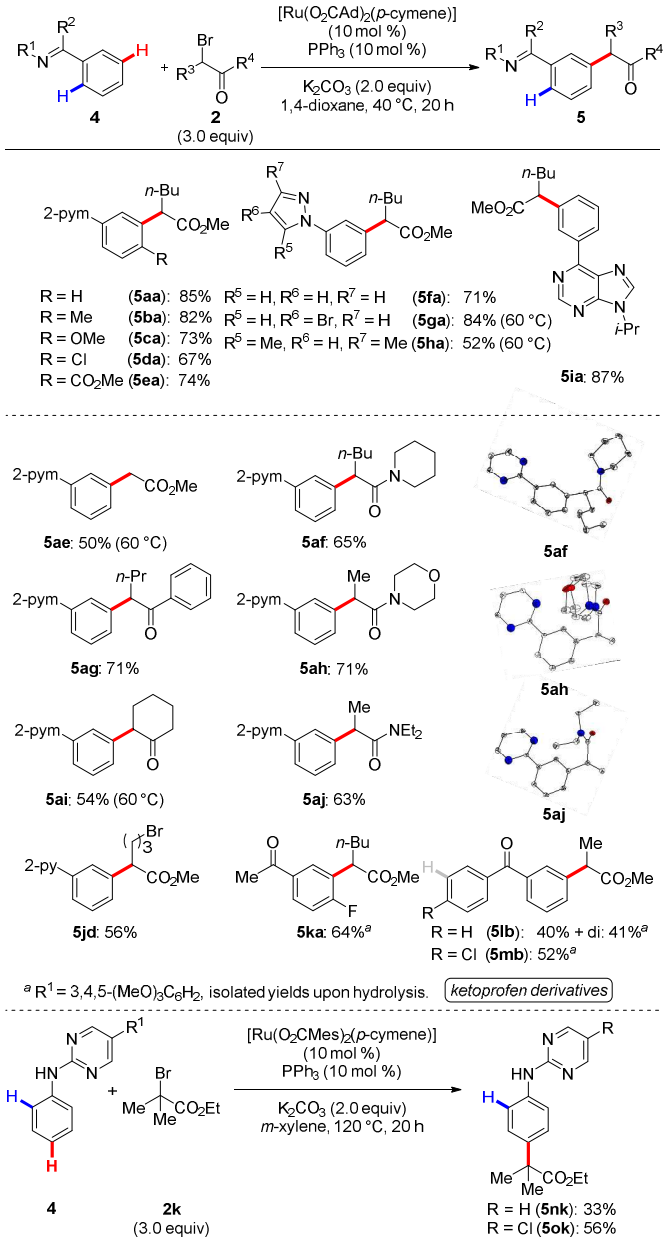
With the optimized ruthenium(II) biscarboxylate catalyst in hand, we initially explored its versatility in the remote C–H functionalization of synthetically useful arylimidates (Scheme 2). Thus, the ruthenium(II) catalysis proved broadly applicable, tolerating a wealth of valuable electrophilic functional groups, including ester, chloro and bromoarenes as well as primary alkyl bromides. The *meta*-C–H functionalization occurred with excellent levels of positional selectivity, exclusively leading to functionalization in the *meta*-position. Here, the *ortho*-substituted aryloxazolines **1h/i** delivered the more densely-1,2,3-substituted isomers **3ha/3ia** as the sole products. The robustness of the ruthenium(II) biscarboxylate catalyst was mirrored by the gram-scale synthesis of product **3aa**, at the same time featuring a reduced catalyst loading.



[a] $[Ru(O_2CMes)_2(p\text{-cymene})]$ (5 mol %) and PPh_3 (5 mol %).

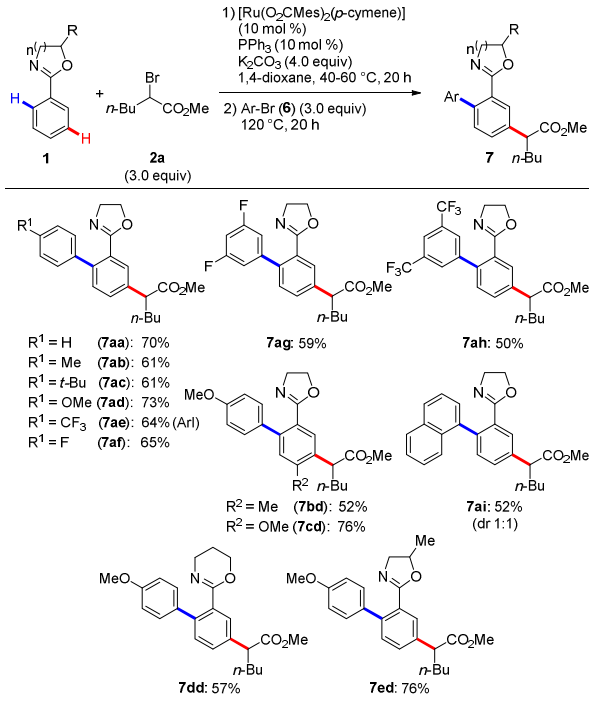
Scheme 2. *meta*-C–H-Alkylation of Aryloxazolines 1

The synergistic ruthenium(II)-catalyzed *meta*-C–H functionalization was not limited to the assistance of imidates **1** (Scheme 3). Indeed, the versatility of our strategy was mirrored by efficient *meta*-C–H alkylations with various organic electrophiles accomplished on arenes bearing pyrimidine, removable[21] pyrazoles, purine bases or ketimines. Here, the ruthenium(II) complex $[Ru(O_2CAd)_2(p\text{-cymene})]$[19] proved to be most generally applicable, allowing for high-yielding *meta*-C–H alkylations under exceedingly mild conditions at 40 °C. Thereby, α-bromo-substituted esters, amides and ketones were smoothly converted into the desired products **5**. In this context, it is noteworthy that secondary and primary alkyl groups could be installed in the *meta*-position, which among others set the stage for a step-economical approach to ketoprofen derivatives **5lb/5mb**. The connectivity of the thus obtained products was unambiguously confirmed by X-ray crystal structure analyses.[18] Moreover, it is noteworthy that 2-pyrimidylanilines delivered instead the *para*-substituted[22] products **5nk-5ok**,[18] most likely by an electrophilic mode of action (for detailed DFT calculations on the *para*-selectivity, see the Supporting Information).[18]



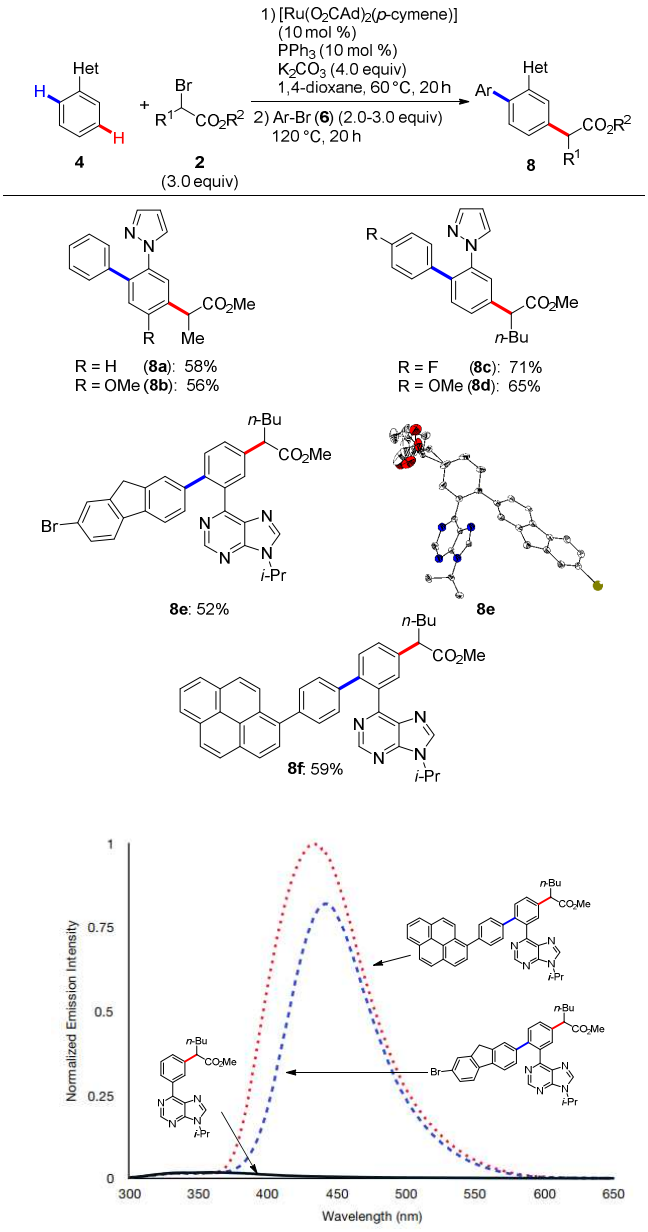
Scheme 3. Scope of *meta*- and *para*-C–H-Alkylation

After having established a general strategy for remote *meta*-C–H transformations on arylimidates **1**, we next explored the desired sequential *meta*-C–H/*ortho*-C–H functionalization through the action of a single ruthenium(II) catalyst in a sustainable one-pot operation. After considerable experimentation, we found that the operationally-simple addition of the second electrophilic aryl bromide **6** upon completion of the *meta*-C–H functionalization enabled the twofold one-pot C–H activation. Thereby, sequential *meta*-C–H/*ortho*-C–H functionalizations proved viable with complete positional selectivity control (Scheme 4). It is particularly noteworthy that a change of the catalyst or of the solvent was not required, significantly reducing the overall footprint of the sustainable C–H activation strategy. The mass balance was accounted for by *meta*-alkylated intermediate **3**. The sequential catalysis was found to be highly robust, delivering the desired arenes **7** with high catalytic efficacy and ample substrate scope.



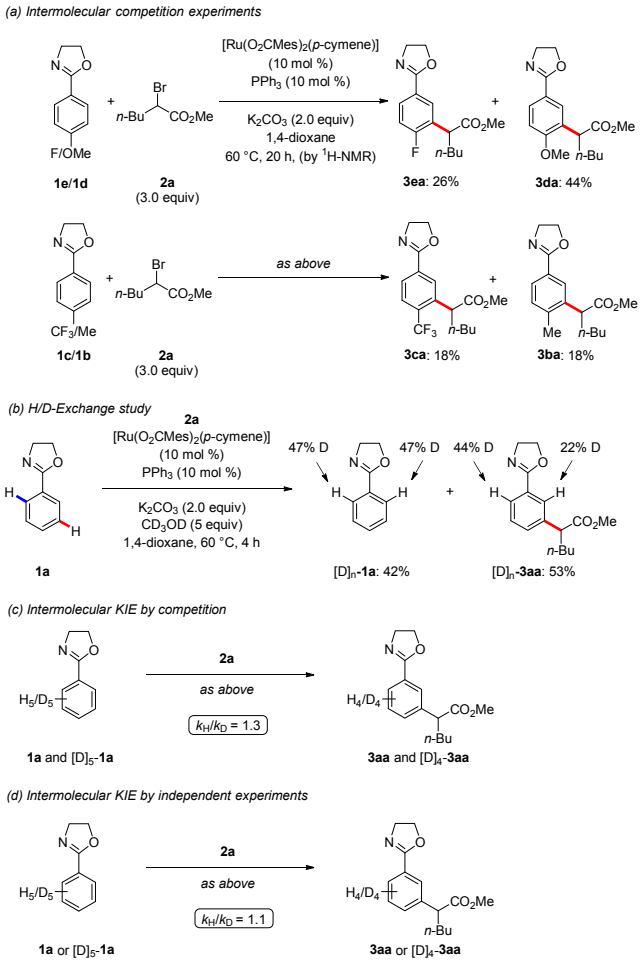
Scheme 4. Sequential *meta*-C–H-Alkylation/*ortho*-C–H-Arylation of Aryloxazolines 1

The one-pot *meta*-C–H/*ortho*-C–H functionalization strategy was not limited to arylimidates **1**, but further set the stage for the twofold C–H functionalization with useful pyrazoles and purine bases **4** (Scheme 5). Again, excellent levels of chemo and positional selectivity were observed, allowing among others for the late-stage fluorescence labeling on purine bases. The molecular structure of product **8e** was again established by X-ray crystal structure analysis.[18]



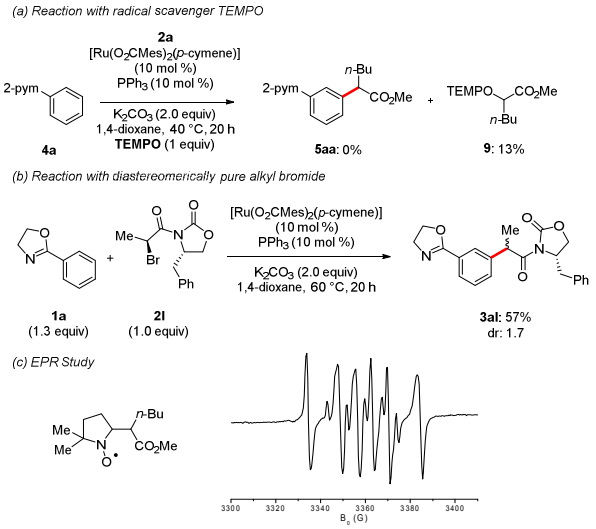
Scheme 5. Scope of sequential one-pot *meta*-C–H-Alkylation/*ortho*-C–H-Arylation

In order to elucidate the working mode of the ruthenium(II)-catalyzed *meta*-C–H activation we next conducted experimental mechanistic studies. To this end, intermolecular competition experiments showed only a minor electronic influence (Scheme 6a). Reactions with isotopically labeled cosolvent $[D]_4$-MeOH provided strong support for a facile reversible H/D-exchange, solely occurring in the *ortho*-position (Scheme 6b), while kinetic experiments with the substrates **1a** and $[D]_5$-**1a** suggested both of the C–H cleavages not to be kinetically relevant.



Scheme 6. Mechanistic Studies of *meta*-C–H-Alkylation by Oxazoline Assistance

Subsequently, we became attracted to better understanding the nature of the C–X cleavage event. The addition of the typically used radical trap TEMPO led to complete inhibition of the catalytic C–H activation (Scheme 7a). The isolation of the TEMPO-adduct **9** can thus be explained by a homolytic C–X cleavage. In good agreement with these findings, the stereochemically well-defined substrate **2l** highlighted a significant loss of stereochemical integrity at the alkyl bromide motif. This observation is again in good agreement with a single-electron-transfer (SET)-induced C–X cleavage. Further support for a radical reaction pathway was gained by first electron paramagnetic resonance (EPR) spectroscopic studies in remote C–H functionalization. Hence, the use of 5,5-dimethyl-1-pyrroline-*N*-Oxide (DMPO) as a spin trap label unraveled the *in-situ* generation of an alkyl radical (Scheme 7c).[18]



Scheme 7. Support for Radical Reaction Mechanism of *meta*-C–H-Functionalization

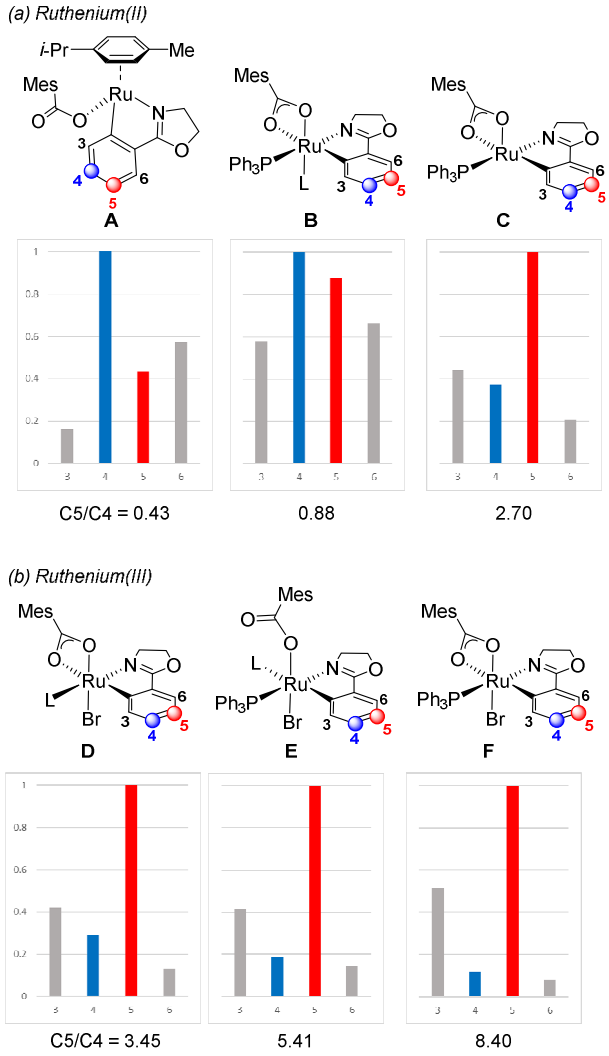
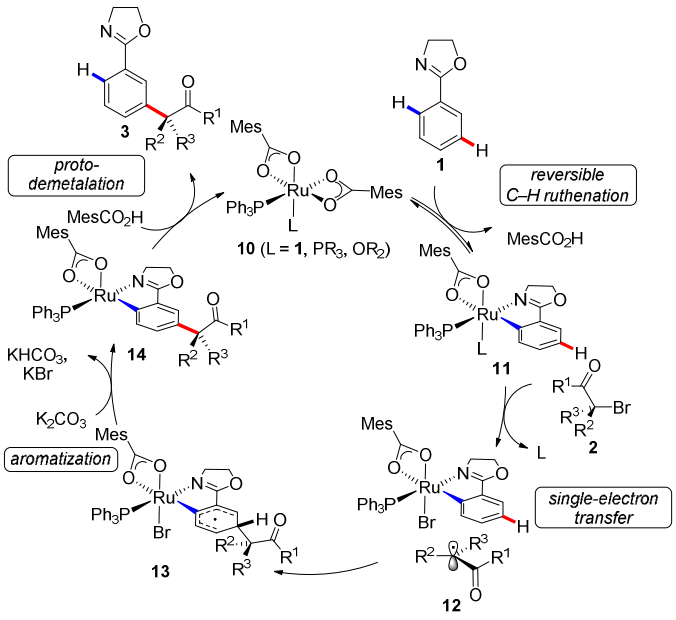


Figure 1. Calculated Relative Radical Fukui Indices at the B3LYP/def2-TZVP Level of Theory. L = 1,4-dioxane.

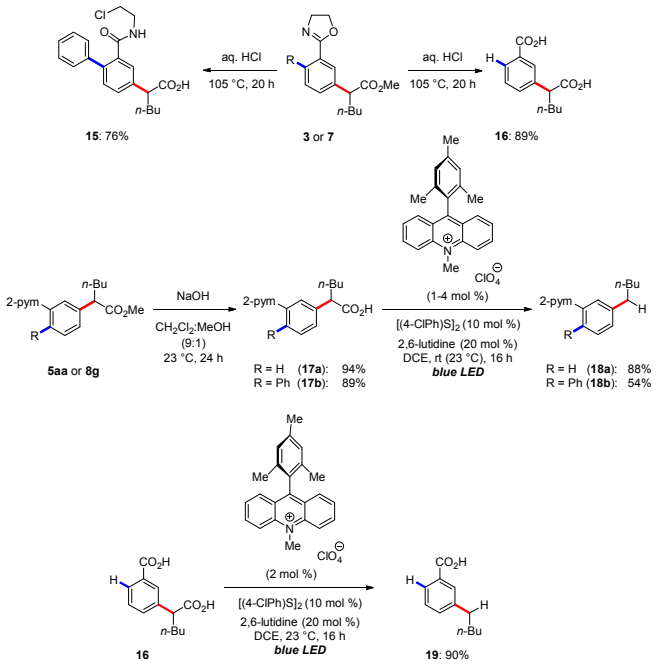
To rationalize the positional selectivity of the *meta*-C–C bond formation, computational studies were conducted by means of a Fukui indices[23a] analysis for proposed cyclometallated complexes. In this context it is noteworthy that nucleophilicity Fukui indices were largely employed in previous reports to rationalize the site-selectivity in C–H functionalizations.[12c,f, 23a] In stark contrast, we found that radical Fukui indices were better suited to rationalize the radical C–H functionalization which were obtained at the B3LYP/def2-TZVP level of theory (Figure 1).[23b-e] Thus, our computational studies are suggestive of an initial SET process to generate a ruthenium(III) species. Accordingly, we compared the pattern of various cyclometalated ruthenium(III) complexes. Since the C-3 and C-6 positions are significantly blocked by steric effects that are not well described by the computational analysis (for the full analysis, please, see the Supporting Information),[18] the schematic presentation in Figure 1b highlights the relative C-5/C-4 selectivities. Interestingly, the synergistic coordination of the phosphine and carboxylate ligands, the latter in a bidentate fashion, emerged to best reproduce the experimentally observed *meta*-selectivity in the C–C formation through attack of the radical species. It is noteworthy that the ruthenium(III)bromide complexes **D–F** are generally better suited to explain the observed positional selectivity as compared to the corresponding ruthenium(II) complexes **A–C**. Overall, our analysis supports the initial coordination of the phosphine ligand, along with a SET from the cyclometalated ruthenium to the alkyl halide, which upon halide transfer delivers the alkyl radical and the ruthenium(III) bromide.[24] Thus, a change of the arene ligand's hapticity or, preferentially, its dissociation is proposed to account for the observed synergistic ruthenium/phosphine effect. In this context it is noteworthy that arene-ligand-free ruthenium complexes were thus far employed for ruthenium-catalyzed *ortho*-C–H arylations.[6b, 25]

Based on our mechanistic findings, we propose a plausible catalytic cycle to commence by reversible carboxylate-assisted C–H ruthenation (Scheme 8). Thereafter, SET occurs from the ruthenium(II) complex **11** to the alkyl halide **2**, generating after halide transfer the cyclometalated ruthenium(III) intermediate **12**. Radical attack on the aromatic moiety then proceeds at the *para*-position to ruthenium, leading to species **13**, while the subsequent rearomatization furnishes ruthenacycle **14**. Finally, protodemetalation delivers the desired *meta*-substituted product **3**, which at the same time regenerates the catalytically active ruthenium(II) complex **10**.



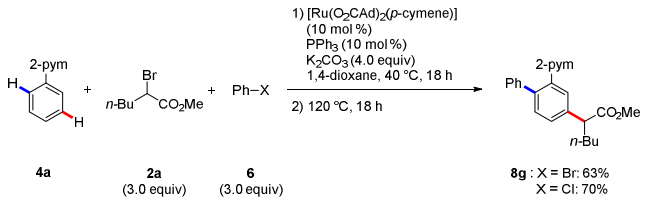
Scheme 8. Plausible catalytic cycle with ruthenium(III) intermediate

Finally, the power of our sequential *meta*-C–H/*ortho*-C–H functionalization strategy was illustrated by the facile late-stage modification of the thus obtained arylimidates **3** and **7** (Scheme 9). Thus, the efficient transformation of the imidates to carboxylic derivatives **15** and **16** proved viable. Moreover, we accomplished the chemo-selective decarboxylation of the aliphatic carboxylic acids through a visible-light photoredox[26] catalysis reduction manifold.



Scheme 9. Late-stage modification

The user-friendly nature of the *meta*-C–H-alkylation/*ortho*-C–H-arylation was reflected by performing the desired double C–H functionalization in a one-pot fashion. Thus, the complex mixture of substrate **4a** and electrophiles **2a** and **6** delivered the tri-substituted product **8g** using either the aryl bromide or the aryl chloride **6** by the judicious choice of the reaction temperature control (Scheme 10).



Scheme 10. One-pot *meta*-C–H-alkylation/*ortho*-C–H-arylation by temperature control

In summary, we have reported on the twofold *meta*/*ortho*-C–H functionalizations by a single ruthenium(II) biscarboxylate catalyst. The well-defined single-component catalyst proved broadly applicable with excellent levels of positional selectivity. The three-component reaction could be achieved in a non-sequential fashion by the judicious temperature control. Detailed mechanistic studies, including EPR[27] findings and computational radical Fukui indices analysis, provided strong support for a facile C–H cleavage under mild reaction conditions, which is followed by radical attack on cyclometalated ruthenium(III) intermediates.

ASSOCIATED CONTENT

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Author Contributions

K.K. and N.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds; DFT calculations; crystal structure analysis.

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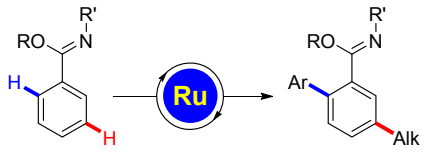

- meta-C–H/ortho-C–H-functionalization
- sequential catalysis in one-pot
- single component catalyst
- mild conditions at 40 °C
- mechanistic insights (EPR, DFT)
- ruthenium(II/III) at single ruthenium