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Late-Stage Diversification by Selectivity Switch in *meta*-C–H Activation: Evidence for Singlet Stabilization

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ABSTRACT: The full control of site selectivity in C–H activation is paramount for the programmed late-stage functionalization of structurally complex structures. During the past decade, directing groups have revolutionized molecular synthesis in terms of *ortho*-selective C–H activation. In sharp contrast, a selectivity switch that guides the typical *ortho*- to remote *meta*-C–H activation has thus far proven elusive. Herein, we describe the realization of such a concept for a robust selectivity-control in ruthenium-catalysis. The distal C–H transformation was guided by key mechanistic insights into the mild, synergistic action of carboxylates and phosphines in ruthenium(II) catalysis. Our findings allowed remote selectivity in broadly-effective late-stage diversification of structurally complex drugs and natural product molecules, tolerating sensitive fluorescent dyes, drugs, lipids, peptides, nucleosides and carbohydrates.

KEYWORDS: *C–H activation, ruthenium, meta-selectivity, remote functionalization, late-stage diversification, DFT, purines*

INTRODUCTION

The transformation of otherwise inert C–H bonds has emerged as an increasingly powerful tool in molecular sciences, with transformative applications to among others material sciences, drug discovery, crop protection and pharmaceutical industries.[1] The key towards the development of synthetically useful C–H transformation is the full control of site selectivity.[2] In this regard, chelation assistance has been identified as a particularly effective approach towards proximity-induced *ortho*-C–H functionalization.[3] In sharp contrast, considerably more challenging remote C–H functionalizations continue to be in high demand.[4] In this context, notable recent progress was accomplished through ruthenium catalysis,[5] with *meta*-benzylations being underdeveloped.[5h, 5i] Particularly, the distal late-stage diversification of bioactive compounds[6] bears unique potential for the identification of novel therapeutic agents of relevance to agrochemical and pharmaceutical industries.[7] While the effect of phosphate[5a, 5i, 8] and phosphine[5c-e, 5l, 5m] additives has been noted, a mechanistic rationale for the *meta*-selectivity has proven elusive. Based on detailed mechanistic insights into the cooperative action of carboxylates and phosphines in ruthenium[9] catalysis, we have now unravelled a uniquely versatile manifold for the chemo-selective late-stage modification of structurally complex molecules (Figure 1a). Notable features of our findings include (i) the cooperative action of ruthenium(II) biscarboxylates and phosphines for a programmable *ortho*- to *meta*-C–H functionalization switch, (ii) mild reaction conditions, (iii) tolerance of a broad range of functional groups, and (iv) bioorthogonal late-stage C–H conjugation of biorelevant motifs, including monosaccharides, nucleotides, amino acids, peptides, and triglycerides, as well as BODIPY labels for fluorescence spectroscopy (Figure 1b).

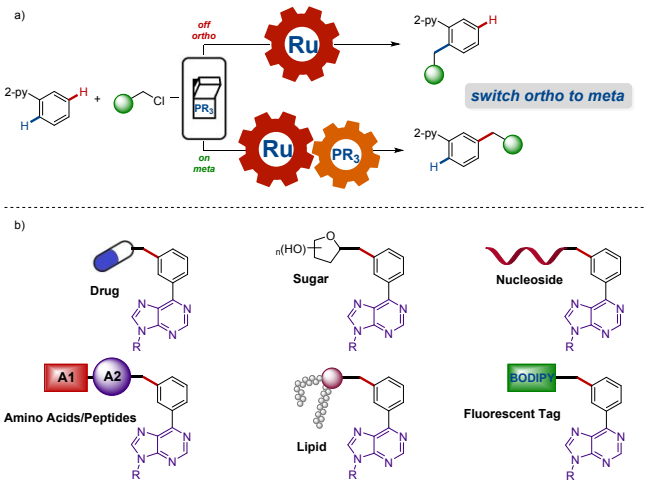
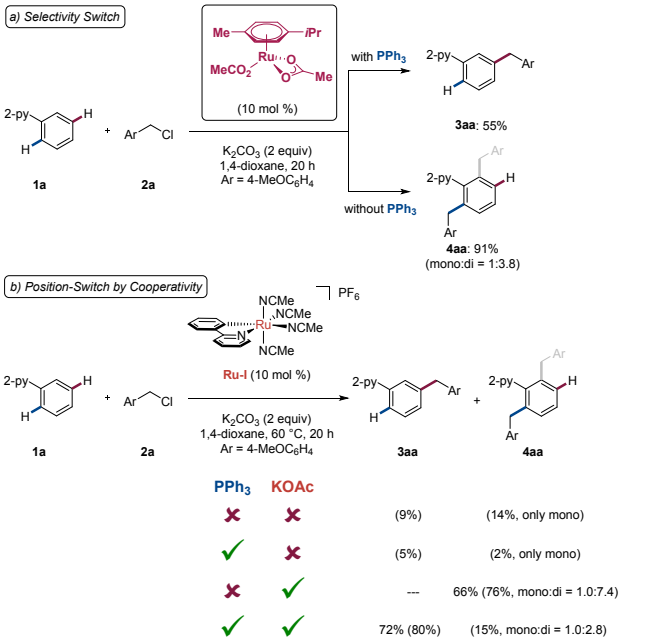


Figure 1. Site selectivity control by *ortho*- to *meta*-selective ruthenium-catalyzed C–H functionalization switch. a) Mechanistic insights enable a general platform for site-selective C–H benzylation by phosphine/carboxylates cooperation in ruthenium catalysis. b) Transformative ruthenium-catalyzed remote *meta*-C–H functionalizations of biorelevant molecules, featuring saccharides, nucleosides, amino acids, peptides, triglycerides, and fluorescence labeling.

RESULTS AND DISCUSSION

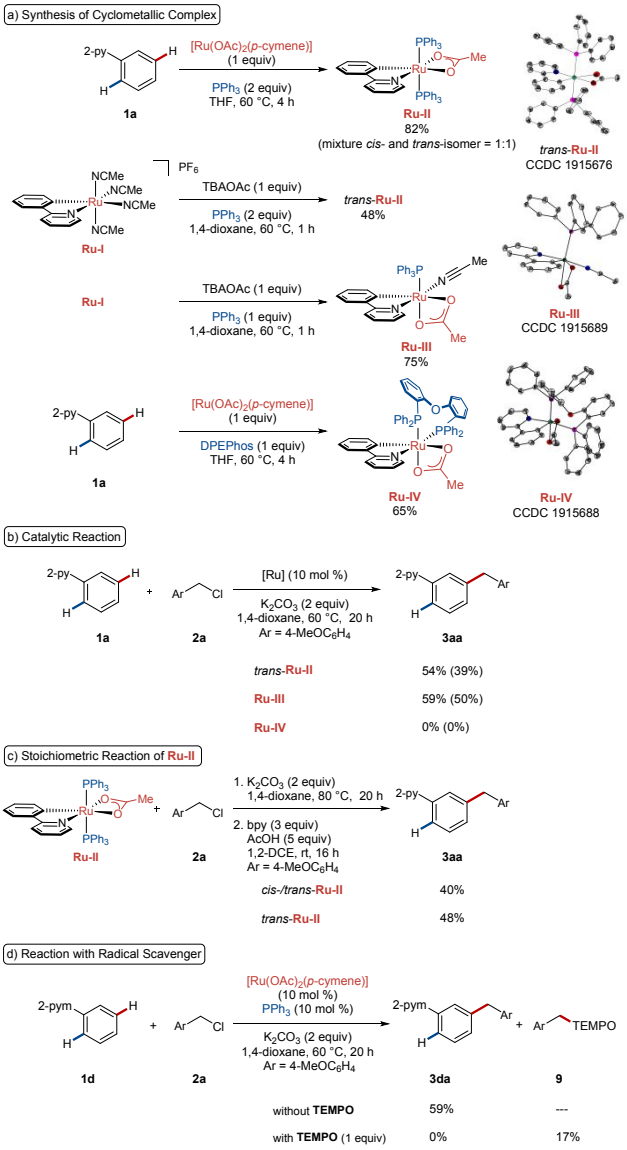
Given the unique potential of ruthenium catalysis for remote arene functionalization, we set out to delineate the coordination environment of the key C–H activated ruthenacycles towards *meta*-selective C–H functionalization (Scheme 1). The cooperation of [Ru(OAc)$_2$(*p*-cymene)] with a phosphine[10] ligand resulted in the *meta*-benzylated product **3aa** (Scheme 1a).[11] In the absence of the phosphine ligand, the selectivity completely switched from *meta* to *ortho*, yielding **4aa**. Likewise, the ruthenium complex **Ru-I** gave by carboxylate

assistance the *ortho*-substituted products **4aa** (Scheme 1b). In sharp contrast, the cooperative action of carboxylates and phosphines led again to a switch in site-selectivity to furnish the *meta*-decorated arene **3aa** upon the judicious addition of phosphine. The sole action of phosphine complexes gave unsatisfactory results.



Scheme 1. Switching selectivity. a) Switch of site selectivity by carboxylate and phosphine cooperation. b) Identification of synergistic carboxylate/phosphine assistance with well-defined complex **Ru-I**. The conversion in parentheses was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Given this switch in selectivity, we became intrigued to prepare a series of well-defined ruthenacyles **Ru-I**–**Ru-V**, among others the novel ruthenium(II) complexes **Ru-II**, **Ru-III**, and **Ru-IV**. All new complexes were fully characterized, including X-ray diffraction analysis, as depicted in Scheme 2a. Here, the unique selectivity of the carboxylate and phosphine synergistic cooperation was reflected by the efficacy of ruthenacycles **Ru-II** and **Ru-III** with two and one phosphines, respectively (Scheme 2a), both of which were effective in catalytic transformations (Scheme 2b). In contrast, the ruthenacycle **Ru-IV** with a bidentate bisphosphine failed to provide the desired product **3aa**.[12] The stoichiometric experimentation further reflected the central importance of carboxylate and phosphine additives for the *meta*-selective C–H functionalization manifold (Scheme 2c). These findings are in good agreement with an analysis of the optimal metal to ligand stoichiometry that featured an ideal ruthenium to phosphine ratio of 1:1, with an excess of phosphine being beneficial.[12] The typically used radical scavenger[12] (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) fully inhibited the ruthenium-catalyzed *meta*-C–H functionalization (Scheme 2d). Instead, the TEMPO-adduct was isolated, being indicative of homolytic C–X scission by single-electron-transfer to deliver an alkyl radical.



Scheme 2. Mechanistic Studies. a) Synthesis of ruthenacycles **Ru-II**–**Ru-IV**. b) Catalytic *meta*-C–H functionalization. The yield in parentheses was obtained in the absence of KOAc. c) Stoichiometric transformations of ruthenacycles. d) Reaction with radical scavenger.

We have previously studied site-selectivity of the *meta*-C−C formation by means of Fukui indices analysis.[5d, 5e] In stark contrast, we here probed the nature of the thus-formed key intermediate by DFT calculation at the PBE0-D3(BJ)/def2-TZVP+SMD(1,4-dioxane)//TPSS-D3(BJ)/def2-TZVP level of theory (Figure 2).[12] Our detailed orbital analysis unravel for the first time a mechanistic rational for the site-selective C–C formation *para* to ruthenium. Thus, the highly reactive triplet radical is significantly stabilized as the singlet metallacycle **C** by 20 kcal mol^{-1} *via* ligand-to-metal charge transfer.

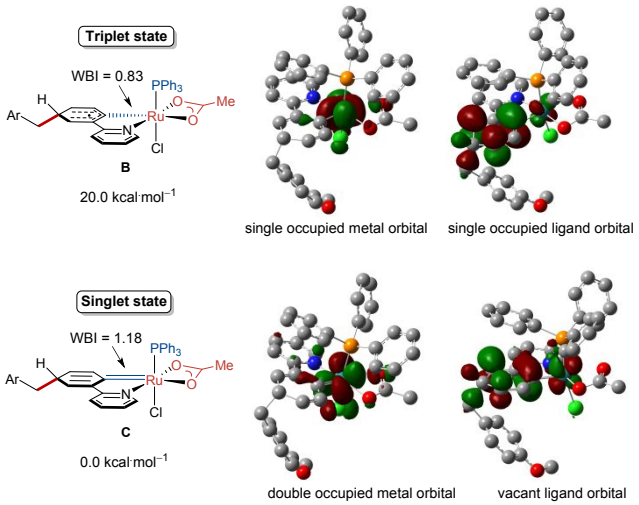


Figure 2. Computational DFT analysis unravels significant stabilization of the singlet ruthenacycle by 20 kcal mol^{-1}. WBI = Wiberg Bond Indices.

Moreover, cyclic voltammetry studies of ruthenacycles **Ru-I**, **Ru-II**, **Ru-III**, and **Ru-IV** showed reversible redox processes at $E_{1/2}$ = 0.75 V (**Ru-I**), $E_{1/2}$ = 0.32 V (*trans*-**Ru-II**), $E_{1/2}$ = 0.47 V (**Ru-III**), and $E_{1/2}$ = 0.44 V (**Ru-IV**) *versus* Ag/AgCl, respectively (Figure 3). Contrarily, the *p*-cymene-coordinated ruthenacycle **Ru-V** exhibited an irreversible oxidation event at E = 0.81 V.

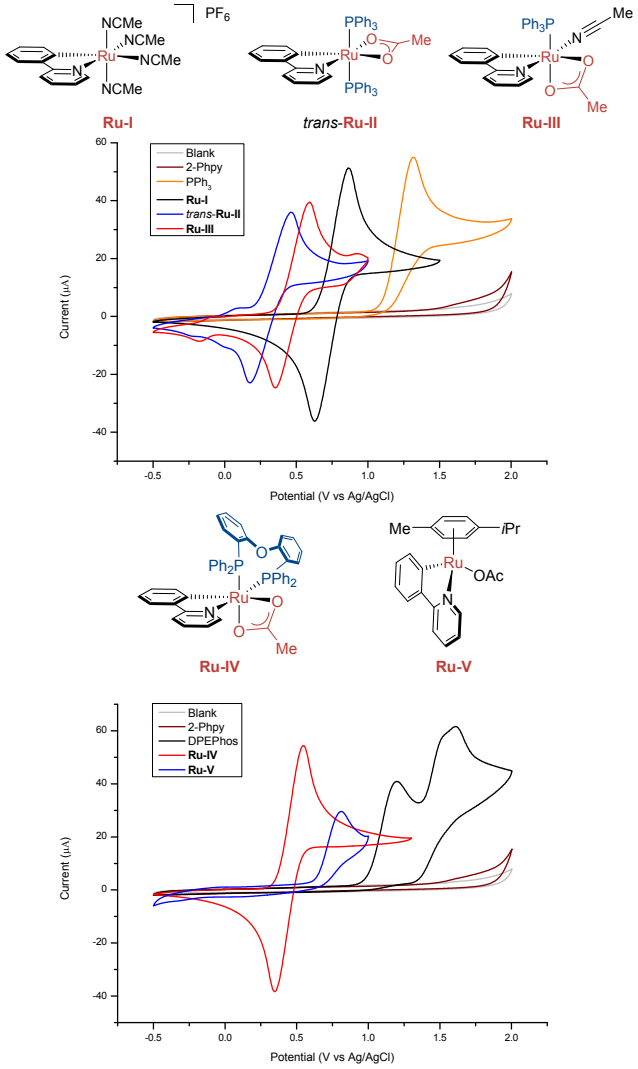
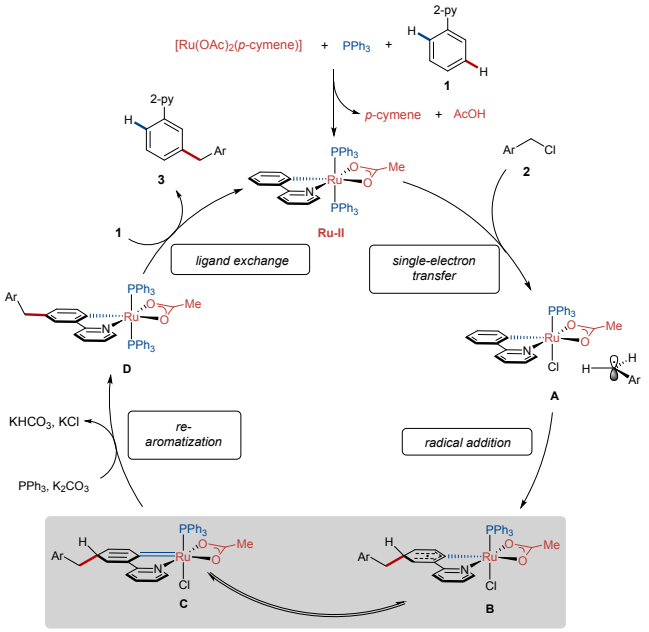


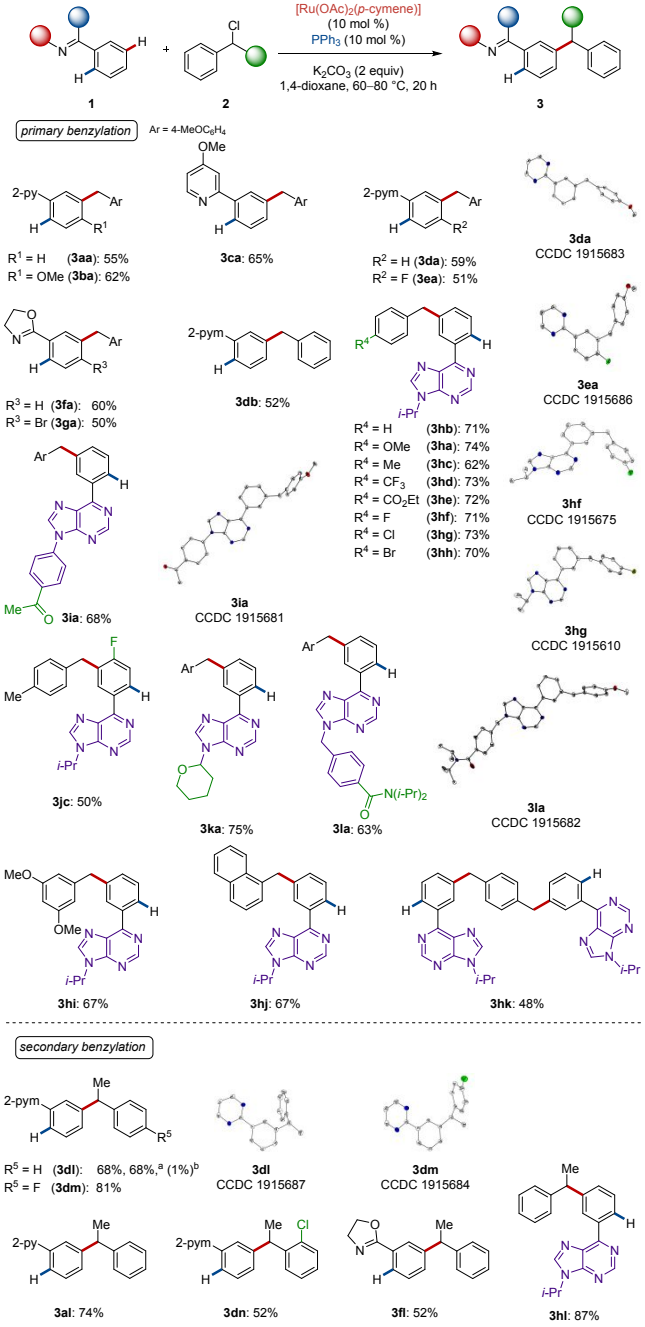
Figure 3. Cyclic voltammetry studies in 1,2-DCE containing 0.1 mol L^{-1} nBu$_4$NPF$_6$, scan rate 100 mV s^{-1}.

A plausible catalytic cycle, hence, features carboxylate-assisted *ortho*-C–H ruthenation to generate complex **Ru-II** (Scheme 3). Then, single-electron-transfer (SET) from the ruthenium(II) complex **Ru-II** to the benzyl halide **2**, generates the ruthenium-(III) intermediate **A**. The benzyl radical attacks on the arene moiety at the position *para* to ruthenium, providing triplet species **B**. Next, ligand-to-metal charge transfer leads to the significantly stabilized singlet ruthenacycle **C**. Finally, re-aromatization and ligand exchange delivers the desired *meta*-benzylated product **3** and regenerates ruthenium(II) complex **Ru-II**.



Scheme 3. The proposed catalytic cycle highlights *meta*-selective C–H functionalization by singlet stabilization *para* to ruthenium.

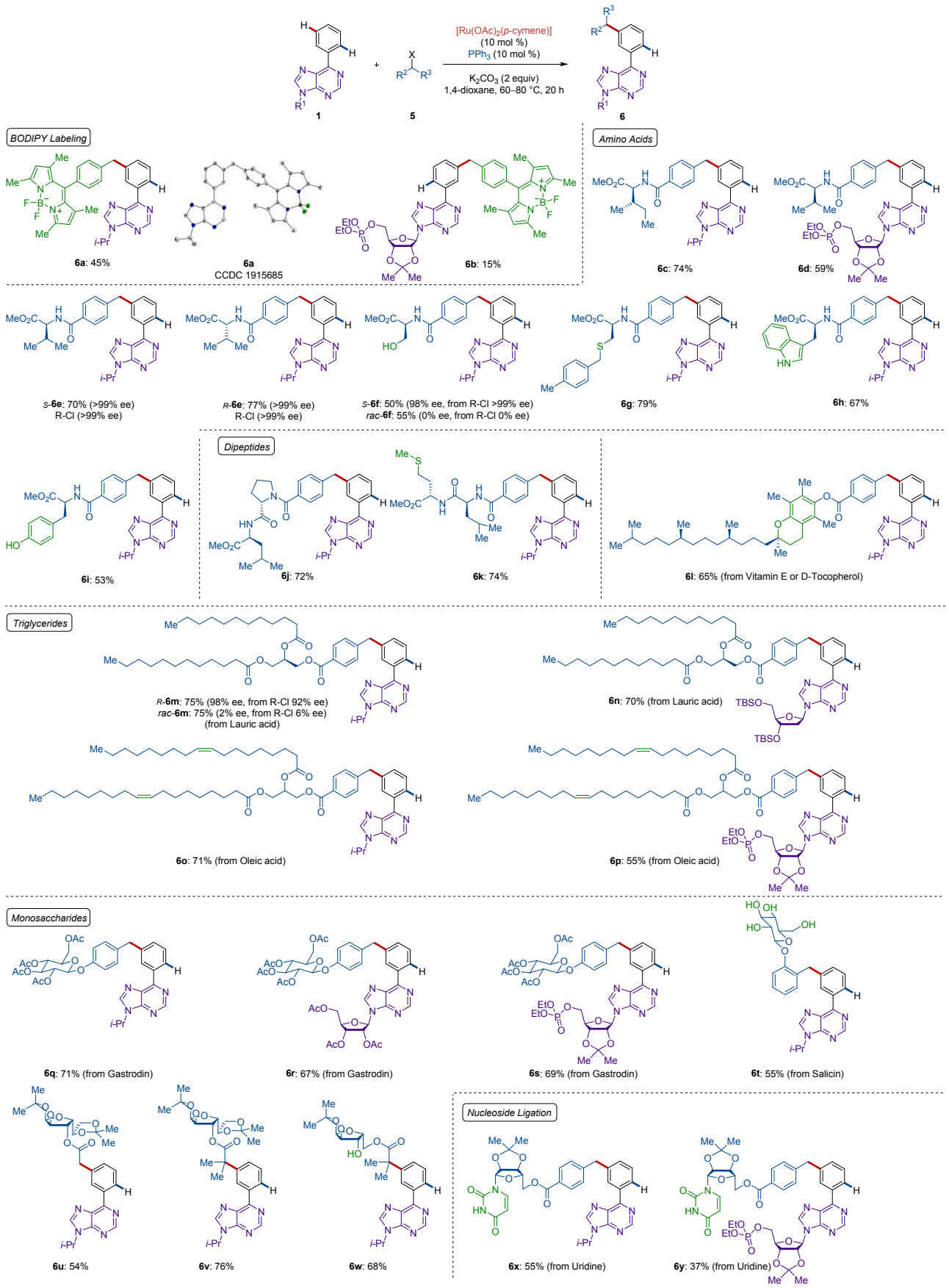
To explore the synthetic utility of the carboxylate-phosphine cooperation, we probed its robustness with a representative set of arenes **1** and electrophiles **2** under the optimized reaction conditions (Scheme 4). Our strategy proved to be generally applicable for primary and secondary *meta*-benzylations, leading to monobenzylated products without the observation of dialkylated products. The ruthenium catalyst was not limited to pyridine guidance, but indeed also allowed for the use of transformable oxazolines and biorelevant purine bases.[13] The mild reaction conditions were mirrored by fully tolerating sensitive functional groups, including ester (**3he**), halides (**3hf**–**3hh**),[14] ketone (**3ia**), and amide (**3la**). Likewise, twofold *meta*-C–H functionalization proved to be viable, providing bis-purine hybrid **3hk**. The connectivities of the *meta*-products **3** were unambiguously confirmed by two-dimensional nuclear magnetic resonance (2D-NMR) spectroscopy and X-ray crystal structure analyses for select compounds.



Scheme 4. Ruthenium-catalyzed remote *meta*-C–H functionalization by carboxylate-phosphine cooperation occurs with ample substrate scope in a programmable manner. [a] With $Ru(OAc)_2(PPh_3)_2$ (10 mol %) as the catalyst at 100 °C. [b] Without PPh_3, determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

The singlet stabilization manifold was not restricted to synergistic cooperation towards simple electrophile transformations. Instead, the transformative potential of our approach was harnessed for the late-stage diversification with fluorescence labels of relevance to spectroscopy (Scheme 5). Thus, purine bases were directly transformed with BODIPY labels by the singlet stabilization in carboxylate-phosphine ruthenium catalysis (**6a** and **6b**). Electrophiles bearing amino acids were efficiently converted to *meta*-products **6c**–**6i** with high levels of chemo-selectivity without any evidence for

racemization. Thereby, otherwise reactive free hydroxyl groups in serine and tyrosine as well as free *NH*-indole in tryptophan were fully tolerated. Even more structurally complex peptides underwent the desired chemical ligation[15] towards products **6j** and **6k**, featuring among others sensitive methionine. The synergistic ruthenium(II) catalyst proved also fully compatible with vitamin D-*a*-tocopherol (**6l**), and triglycerides derived from saturated and unsaturated fatty acids (**6m**–**6p**). Particularly, the chemo-selectivity of the *meta*-C–H transformation in the presence of unsaturated fatty acids is noteworthy, since they are normally prone to olefinic and allylic functionalizations. Importantly, the late-stage modification of marketed drugs was accomplished, including transformations of neuroprotective agent gastrodin, and the fully anti-inflammatory salicin. The ruthenium catalysis was not restricted to benzylic electrophiles, but synthetically useful monosaccharide bromoesters furnished the desired *meta*-products **6u**–**6w** with high catalytic efficacy. Notably, hybrids **6x** and **6y** were obtained by the synergistic catalysis *via* unprecedented nucleoside ligation. It is noteworthy that for the first time fully unprotected *OH*-free monosaccharides proved to be amenable substrates (**6t**).



Scheme 5. Carboxylate-phosphine cooperation allows for late-stage diversification by singlet stabilization in terms of *meta*-C–H functionalization of arenenucleobases with fluorescence tags, peptides, lipids, drugs, unprotected sugars and nucleosides.

CONCLUSIONS

Mechanistic insights into the working mode of ruthenium-catalyzed *meta*-C–H functionalization have unraveled a carboxylate-phosphine synergistic manifold for effective singlet stabilization. Thereby, a uniquely effective catalytic system for remote arene functionalization was identified for remote C–H functionalization, fully tolerating purine and uridine nucleobases, sensitive lipids, functionalized amino acids and peptides, fluorescent tags as well as unprotected sugar motifs. The high levels of site- and chemo-selectivity of our robust, synergistic ruthenium catalysis should prove invaluable for enabling late-stage modifications of biorelevant compounds in academia as well as by practitioners in agrochemical and pharmaceutical industries.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Cost-effective triphenylphosphine (PPh_3) was selected from 23 different phosphine ligands in the synergistic ruthenium(II) *meta*-C–H benzylation. See the supporting information for more details.

(11) $Ru(OAc)_2(PPh_3)_2$ as the catalyst was effective in the remote functionalization at 100 °C, while it failed to give conversion at a lower reaction temperature of 60 °C.

(12) For detailed information, see the Supporting Information.

(13) Under identical reaction conditions, azobenzenes, *O*-methyloximes, 2-phenoxypyrimidines, and *N*-pyrimidylaniline gave unsatisfactory results.

(14) Sensitive aryl chloride **3hg** or bromide **3hh** did not give any by-products.

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