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Recyclable Ruthenium Catalyst for Distal *meta*-C–H Activation

Isaac Choi,[a,†] Valentin Müller,[a,†] Yanhui Wang,[b] Kai Xue,[c] Rositha Kuniyil,[a] Loren B. Andreas,[c] Volker Karius,[d] Johan G. Alauzun,[b] and Lutz Ackermann*[a]

[a] Isaac Choi, Valentin Müller. Dr. Rositha Kuniyil, and Prof. Dr. Lutz Ackermann
Institut für Organische und Biomolekulare Chemie and Wöhler Research Institute for Sustainable Chemistry (WISCh)
Georg-August-Universität Tammanstraße 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de/index.html
[b] Dr. Yanhui. Wang, Dr. Johan. G. Alauzun
Institut Charles Gerhardt Montpellier, UMR 5253, CNRS-Université de Montpellier-ENSCM, Montpellier Cedex 5 34095 (France)
[c] Dr. Kai. Xue, Dr. Loren. B. Andreas
Max Planck Institute for Biophysical Chemistry Am Faßberg 11, 37077 Göttingen (Germany)
[d] Dr. V. Karius
Geowissenschaftliches Zentrum Georg-August-Universität Göttingen Goldschmidtstraße 3, 37077 Göttingen (Germany)

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Abstract: We disclose the unprecedented hybrid-ruthenium catalysis for distal *meta*-C–H activation. The hybrid-ruthenium catalyst was recyclable, as was proven by various heterogeneity tests, and fully characterized with various microscopic and spectroscopic techniques, highlighting the physical and chemical stability. Thereby, the hybrid-ruthenium catalysis proved broadly applicable for *meta*-C–H alkylations of among others purine-based nucleosides and natural product conjugates. Additionally, its versatility was further reflected by *meta*-C–H activations through visible-light irradiation, as well as *para*-selective C–H activations.

Introduction

Methods for achieving position-selective functionalizations of specific C–H bonds have surfaced as transformative tools for molecular science.[1] Thus, a plethora of *ortho*-selective arene C–H functionalizations has been accomplished by proximity-induced C–H activation through chelation assistance.[2] In sharp contrast, distal C–H functionalizations continue to be challenging with considerable momentum gained by steric control,[3] template assistance,[4] weak hydrogen bonding,[5] or transient mediator[6] (Figure 1aI–IV). Recently, Greaney,[7] Frost,[8] and Ackermann[9] among others[10] developed site-selective homogeneous C–H functionalization *via* ruthenium-catalyzed σ-activation, allowing *meta*- and *para*-functionalization to the metal center (Figure 1aV).[11] In spite of recent notable progress, the realm of C–H functionalizations was thus far considerably limited to homogeneous catalysis. This approach impedes challenging catalyst separation and reuse, directly translating into trace metal impurities in the target molecules. While classical heterogeneous catalysts – a metal catalyst dispersed on a solid surface – have been previously reported for C–H functionalizations,[12] hybrid catalysts,[13] namely a homogeneous catalyst immobilized with an organic linker on a solid support, add unique properties to the design of the reusable catalysts.[14] Thereby, numerous heterogenized homogeneous catalysts, namely hybrid catalysts, have been devised particularly by Jones[15] and Sawamura[16] among others.[17] In sharp contrast to this advance in hybrid catalysis, recyclable polymer-based[18] hybrid-ruthenium catalyst for remote C–H alkylations *via* σ-activation has as of yet unfortunately proven elusive.

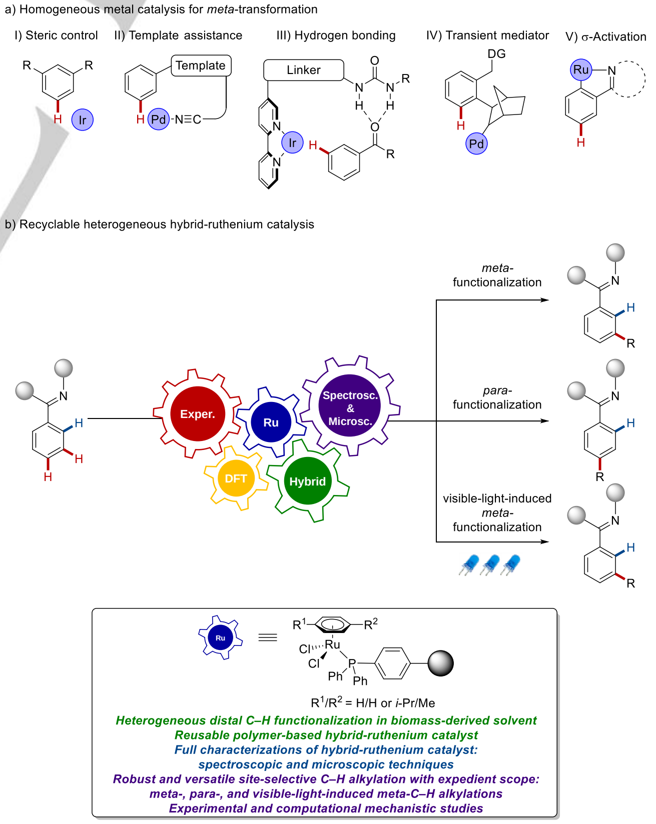

Figure 1. Towards heterogeneous distal C–H functionalization

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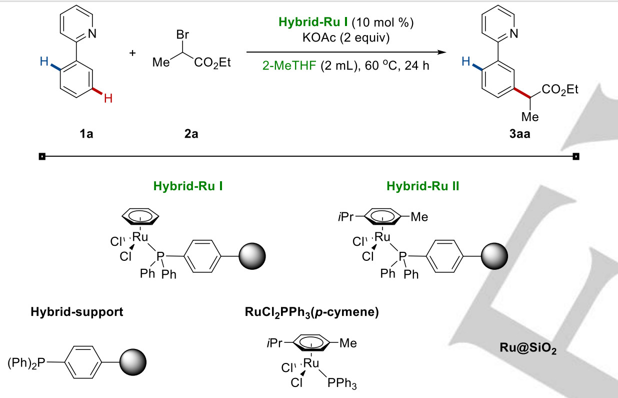
Within our program on sustainable C–H activation,[19] we have now unravelled an unprecedented recyclable hybrid-ruthenium catalyst for remote C–H alkylations in a biomass-derived solvent,[20] on which we report herein (Figure 1b). Salient features of our strategy include a) the first hybrid-ruthenium catalysis for distal C–H alkylations, b) robust hybrid-ruthenium catalyst for *meta*-C–H functionalization, c) full characterizations of the recyclable hybrid-ruthenium catalyst for remote C–H alkylation, d) expedient position-selective C–H alkylations with ample scope, ranging from purine-based nucleosides to natural product conjugates with the aid of typical heterocyclic groups and alkylating reagents in an eco-friendly solvent, and e) experimental and computational mechanistic insights.

Results and Discussion

We initiated our studies by probing various reaction conditions for the envisioned recyclable ruthenium-catalyzed *meta*-C–H alkylation of arene **1a** (Table 1).[21] The amount of ruthenium in the hybrid-ruthenium catalysts were determined by detailed inductive coupled plasma-optical emission spectrometry (ICP-OES) analysis.[21]

Table 1. Establishing *meta*-C–H functionalization by hybrid-ruthenium catalyst.

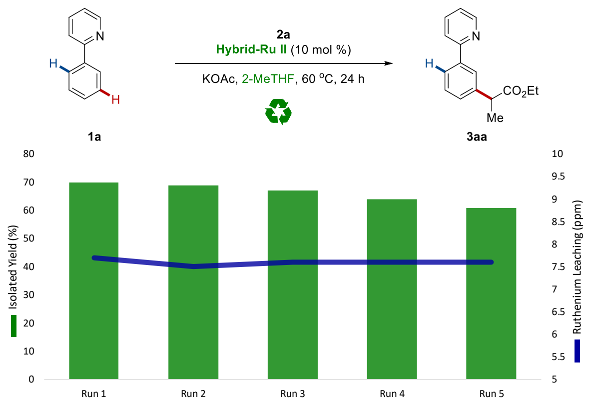


Entry	Deviation from above	Yield [%][a]	
		1st run	2nd run
1	none	66	64
2	$RuCl_2PPh_3$(*p*-cymene) instead of Hybrid-Ru **I**	81	0
3	Hybrid-Ru **II** instead of Hybrid-Ru **I**	70	69
4	Without Hybrid-Ru **I**	0	--
5	Only Hybrid-support	0	--
6	1,4-dioxane instead of 2-MeTHF	63	--
7	$PhCMe_3$ instead of 2-MeTHF	45	--
8	80 °C instead of 60 °C	61	--
9	Ru@SiO_2[b] instead of Hybrid-Ru **I**	0	--

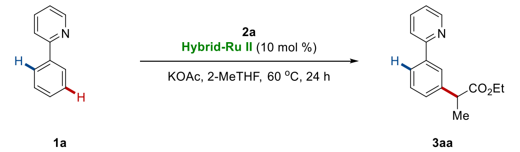
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), catalyst (10 mol %), KOAc (2 equiv), 2-MeTHF (2.0 mL), 60 °C, 24 h, isolated yield. [b] See the reference 22. "--" indicates that the reaction is not performed.

After considerable experimentations, we were delighted to obtain the *meta*-alkylated product **3aa** with KOAc as the base in biomass-derived 2-MeTHF at 60 °C, and observe the reusability of hybrid-ruthenium catalysts (entries 1 and 2). Fine-tuning the hybrid-ruthenium catalyst by changing the arene ligands highlighted the pivotal role of the designable hybrid catalysts, giving a higher yield and improved reusability (entry 3). Control experiments confirmed the essential role of the recyclable hybrid-ruthenium catalyst, suggesting a simple electrophilic aromatic substitution less likely to be operative (entries 4–5). Furthermore, conventional solvents for *meta*-C–H alkylation proved to be less effective, while an elevated reaction temperature gave unsatisfactory results (entries 6–8). Having shown slightly higher reactivity and recyclability than the Hybrid-Ru **I**, Hybrid-Ru **II** was chosen as a better candidate for distal C–H functionalizations and further characterizations to elucidate its mode of action. Notably, one heterogeneous catalyst was reported for *meta*-C–H bromination.[22a] However, the previously employed catalyst fell short in delivering the desired *meta*-alkylated product (entry 9).[21] To obtain detailed understanding of the hybrid-ruthenium-catalyst, we became intrigued to further probe its reusable nature (Scheme 1).[21] We were hence delighted to observe that the hybrid-ruthenium featured excellent reusability, enabling practical access to *meta*-C–H alkylated arenes (Scheme 1a). Practitioners in pharmaceutical, agrochemical and chemical industries performing large scale reactions or flow applications in homogeneous catalysis are mainly concerned with the removal of metal impurities, which are detrimental to synthetic and economic efficiency, while well-designed heterogeneous catalysts help to avoid additional process by a simple separation. It is noteworthy that less than 8 ppm of ruthenium was detected by detailed ICP-OES studies of the reaction mixture, reflecting negligible leaching of the transition metal. The sustainable feature of the hybrid-ruthenium catalysis was also mirrored by a gram-scale reaction, maintaining high efficiency along with position-selectivity and reusability of hybrid-ruthenium catalyst (Scheme 1b).

a) Reuse test of hybrid-ruthenium catalysis and ICP-OES analysis of trace metal impurities



b) Recyclability test with gram-scale reaction



First run: 80% (2.04 g)
Second run: 76% (1.94 g)

Scheme 1. Recyclability and reusability of hybrid-ruthenium catalyst

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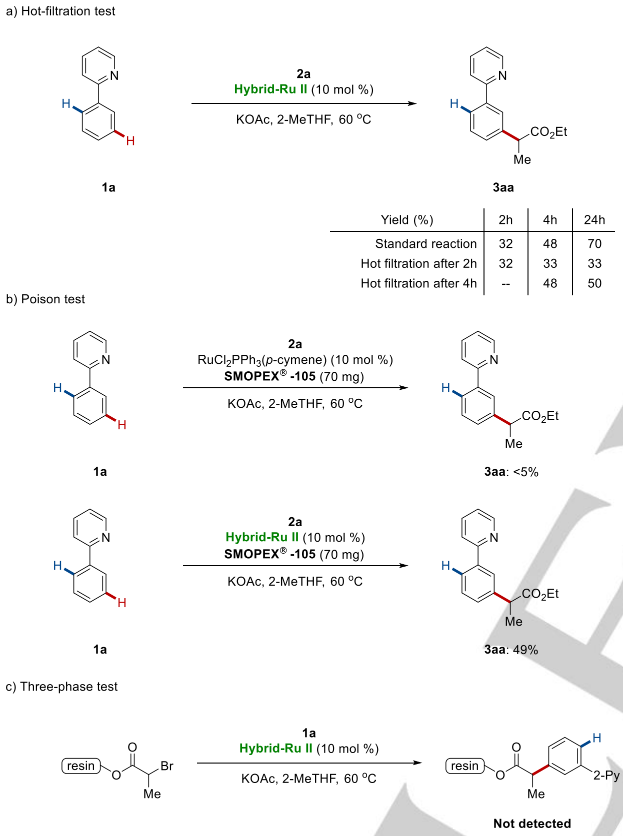
As the reusability and recyclability of the hybrid-ruthenium catalyst were demonstrated, we became attracted to further delineating its heterogeneous nature (Scheme 2). A hot-filtration test demonstrated that the physical removal of the hybrid-ruthenium catalyst completely inhibited the hybrid catalysis for *meta*-C–H alkylations (Scheme 2a). In addition, we performed a poisoning test with SMOPEX®-105, of which the role was clearly shown to inhibit the homogeneous ruthenium catalysis. In contrast, the hybrid catalysis occurred in the presence of the metal scavenger (Scheme 2b). Furthermore, a three-phase test clearly illustrated the heterogeneous mode of the hybrid-ruthenium catalyst, rendering homogeneous catalysis unlikely to be operative (Scheme 2c).



Yield (%)	2h	4h	24h
Standard reaction	32	48	70
Hot filtration after 2h	32	33	33
Hot filtration after 4h	--	48	50

Scheme 2. Heterogeneity tests.

Given the unique features of recyclable and reusable hybrid-ruthenium catalyst, we sought to determine its chemical and physical properties. It is noteworthy that the hybrid-ruthenium catalyst has not been yet characterized by any means of spectroscopic or microscopic tools, whereas a metathesis reactivity was reported.[23] To shed light on the characteristic features, we firstly conducted detailed solid-state NMR spectroscopic studies of the Hybrid-support, RuCl$_2$PPh$_3$(p-cymene), Hybrid-Ru **II** and reused Hybrid-Ru **II** (Figure 2a and 2b).[21] Interestingly, ^{13}C and ^{31}P-NMR spectra showed similar chemical shifts among RuCl$_2$PPh$_3$(p-cymene), the Hybrid-Ru **II**, and the reused Hybrid-Ru **II**, providing a strong evidence that coordination of the ruthenium by phosphorus remained stable during the course of the hybrid-ruthenium catalysis. X-ray photoelectron spectroscopy (XPS) was also employed to determine the oxidation state of ruthenium from hybrid-ruthenium catalyst and the reused one (Figure 2c). The peak of Ru 3d5/2 at 281.1 eV from the surface of both catalysts corresponds to ruthenium(II) species.[24] Furthermore, the powder X-ray powder diffraction (PXRD) patterns of the Hybrid-Ru **II** identified two very wide peaks around 10° and 20° showing the amorphous support, whereas the formation of crystalline ruthenium compounds such as ruthenium oxide was not detected (Figure 2d).[21] The PXRD patterns from the reused Hybrid-Ru **II** confirmed crystalline KBr (JCPDS 730381) as an insoluble byproduct in 2-MeTHF while the residue was proven to be innocuous to the reusability of the hybrid-ruthenium catalyst.

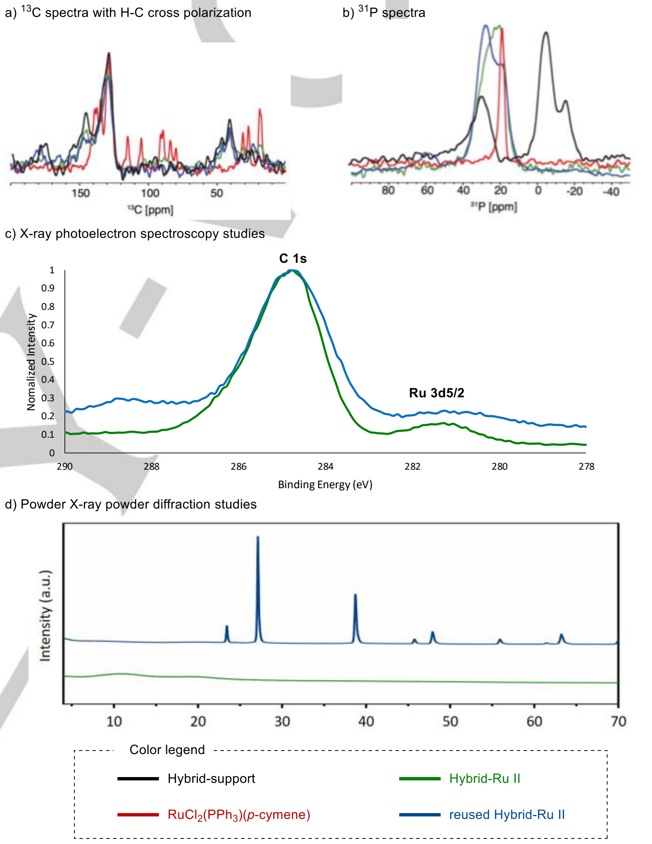


Figure 2. Characterizations of the hybrid-ruthenium catalysts.

Additionally, we performed detailed microscopic studies including scanning electron microscopy (SEM), transmission electron microscopy (TEM) and transmission electron microscopy energy-dispersive X-ray spectroscopy (TEM-EDX) studies of the Hybrid-Ru **II** and the reused one (Figure 3).[21] SEM analysis of the Hybrid-Ru **II** revealed non-aggregated spheres up to 100 µm in diameter with relatively smooth surface (Figure 3a). The reused Hybrid-Ru **II** in SEM studies showed innocent KBr on the surface previously detected by PXRD. TEM analysis of the Hybrid-Ru **II** and the reused Hybrid-Ru **II** revealed that both hybrid catalysts have homogeneous non-porous amorphous morphology (Figure 3b). This reflected the durability of hybrid catalyst, enabling outstanding reuses in *meta*-C–H functionalization. TEM-EDX mapping studies also confirmed the excellent stability of coordination between phosphourus (yellow) and ruthenium (red) with homogeneous dispersion (Figure 3c).

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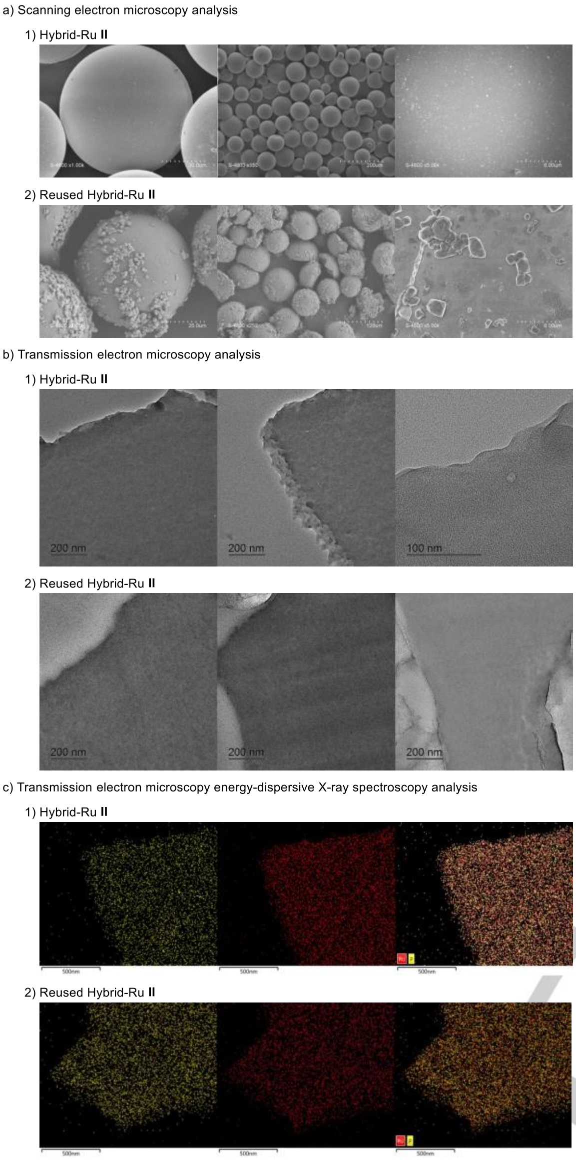
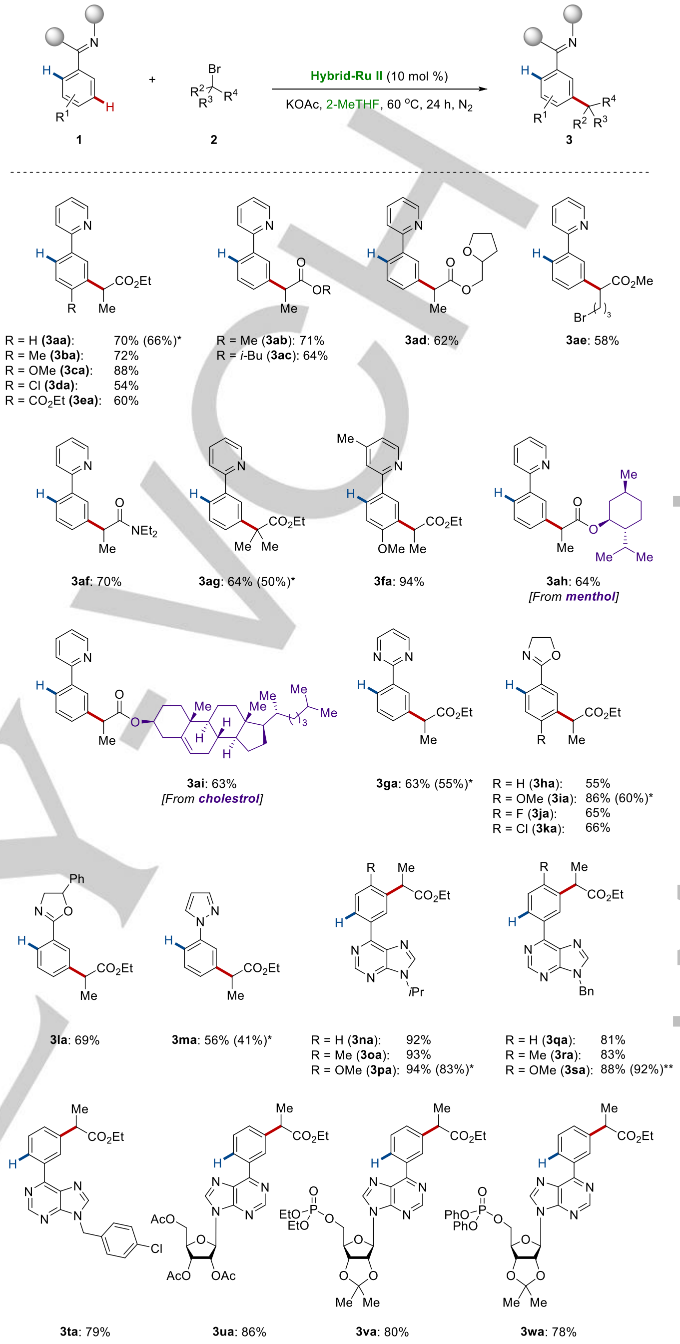


Figure 3. Detailed microscopic analysis of the hybrid-ruthenium catalysts.

The thus established reactivity and recyclability together with full characterization of hybrid-ruthenium catalyst allowed us to explore its unique catalytic performance. We commenced the exploration by hybrid-ruthenium-catalyzed *meta*-C–H functionalization with a set of representative arenes (Scheme 3). The robust heterogeneous *meta*-C–H alkylations were not limited to pyridinyl arenes, but arenes having pyrimidine, oxazoline, pyrazole, and purine groups were also found to be viable. Also, differently substituted arenes **1** bearing electron-deficient and electron-rich functional groups were position-selectively transformed to the desired *meta*-functionalized products **3**. Distal *meta*-C–H alkylation by the Hybrid-Ru **II** tolerated various alkyl bromides **2**, including valuable functional groups, featuring halides, ethers, esters, and amides, while natural product derivatives were converted without racemization.



* The yield in a parenthesis was obtained with **Hybrid-Ru I**.

** The yield in a parenthesis was obtained in the gram-scale reaction.

Scheme 3. Robustness of hybrid-ruthenium catalysis for *meta*-C–H functionalization.

Hence, the Hybrid-Ru **I** was identified as a powerful hybrid-ruthenium catalyst for *meta*-C–H alkylations, showing comparable reactivities (**3aa**, **3ag**, **3ga**, **3ia**, **3ma**, and **3pa**). It is noteworthy that the robust nature of the hybrid-ruthenium catalysis was mirrored by the gram-scale *meta*-C–H functionalization of purine (**3sa**). In contrast, alternative attempted alkylating reagents led thus far to less satisfactory results.[21]

As photocatalysis enables valuable chemical transformations,[25] visible-light-induced homogeneous ruthenium-catalyzed C–H functionalization was realized,[26] but yet explored with

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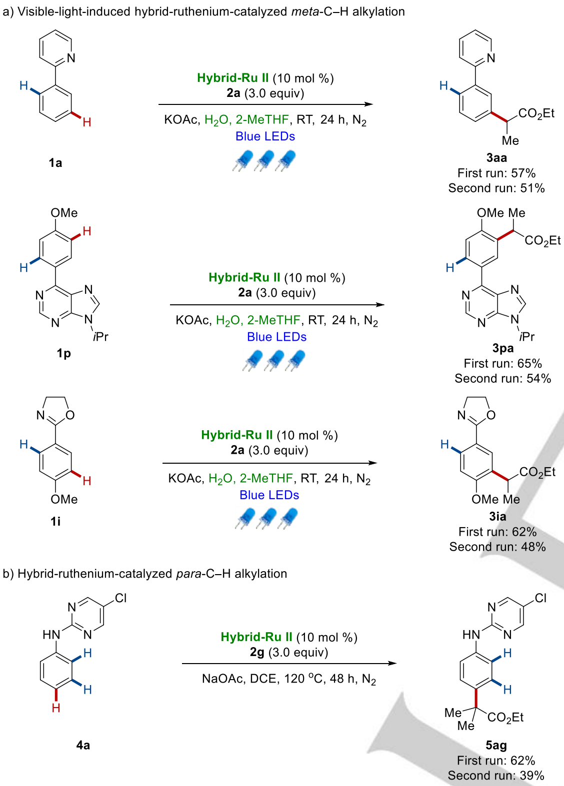
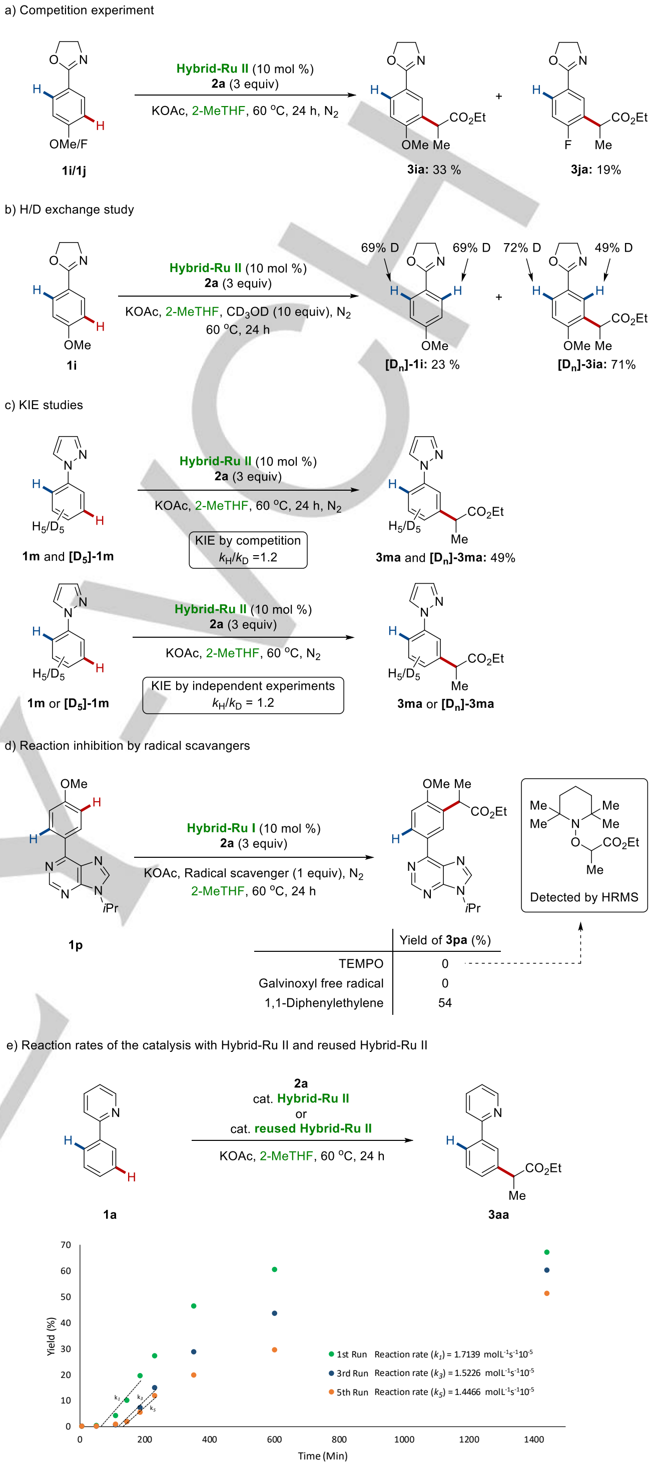
heterogeneous ruthenium catalyst. Interestingly, experiments with hybrid-ruthenium catalyst provided *meta*-C–H alkylated products at room temperature in a reusable manner (Scheme 4a). While accessing *para*-selective C–H functionalization was typically achieved by the substrate's inherent substitution pattern[27] or template-based directing groups,[28] homogeneous ruthenium catalysts enabled distal functionalization of arenes.[29, 9b,c] Delightfully, hybrid-ruthenium catalyst also efficiently accomplished *para*-C–H alkylation under slightly modified reaction condition (Scheme 4b). Indeed, the robust and versatile hybrid-ruthenium-catalyst allowed for distal C–H transformation with excellent level of site-selectivity, exclusively leading to functionalization at the *meta* or *para* position in both thermal and mild light-induced conditions. Importantly, the versatile hybrid-ruthenium catalysis set the stage for novel position-selectivity as compared to the homogeneous[30] ruthenium catalysis.[21]



Scheme 4. Versatility of hybrid-ruthenium catalysis.

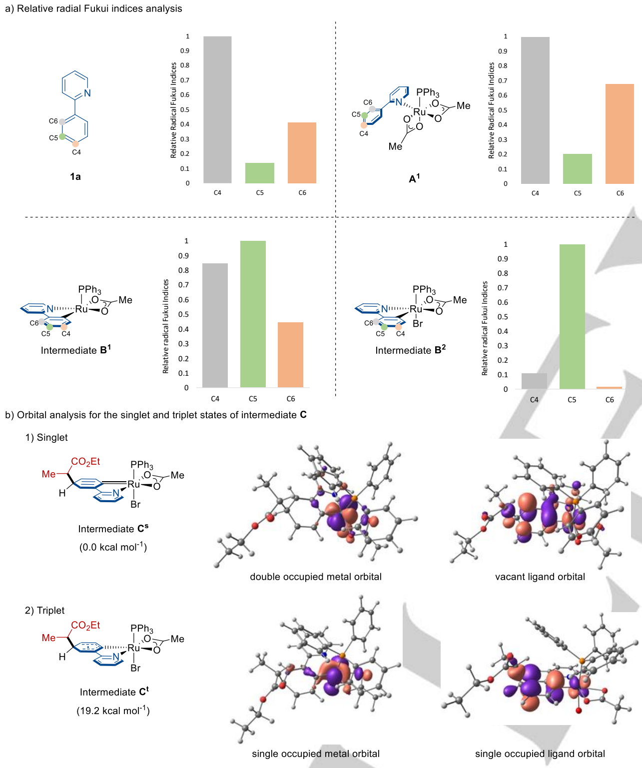
Furthermore, we performed mechanistic studies to elucidate the hybrid-ruthenium catalyst's mode of action (Scheme 5).[21] Notably, we made mechanistic observations comparable to those of our homogeneous catalysis,[31] reflecting that hybrid catalysis is characterized by predictable reactivity and selectivity that are in accordance with the homogeneous realm.



Scheme 5. Experimental key mechanistic findings.

To this end, an intermolecular competition experiments revealed that the electron-rich arene **1i** was preferentially reacted (Scheme 5a). *meta*-C–H activations in the presence of isotopically labelled CD_3OD provided strong support for facile and reversible C–H activation solely at the *ortho* position (Scheme 5b), while kinetic experiments indicated a secondary isotope effect, being suggestive of C–H cleavages at the *ortho* and *meta* position are not kinetically relevant (Scheme 5c). Furthermore, we examined a SET-type regime by the use of the typical radical scavengers TEMPO, Galvinoxyl free radical, and 1,1-diphenylethylene, resulting in a significant inhibition of *meta*-C–H alkylation catalyzed by the Hybrid-Ru **I** (Scheme 5d). Kinetic studies demonstrated similar initial rates of the hybrid catalyst Hybrid-Ru II upon reuse, albeit featuring an extended induction period (Scheme 5e). Additionally, free *p*-cymene was observed by ^{1}H NMR spectroscopy and gas chromatographic study.[21]

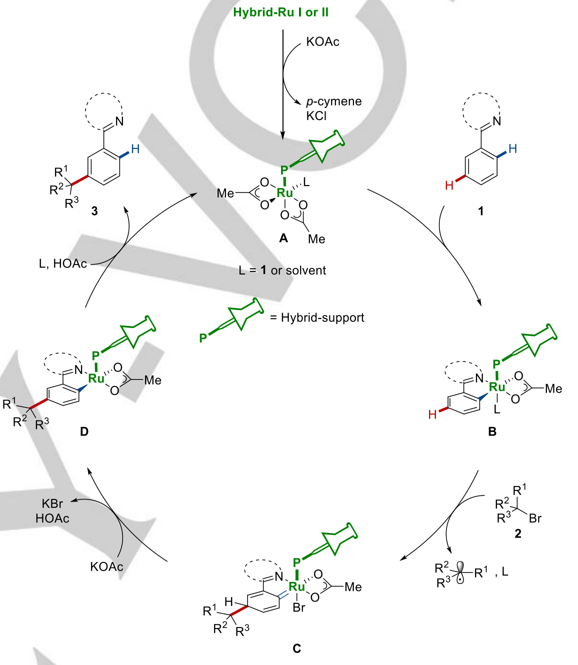
Additionally, the positional selectivity of the hybrid-ruthenium-catalyzed *meta*-C–H functionalization was further probed by means of radical Fukui indices[9b] for the ruthenacycle complexes **B^1** and **B^2** at the PBE0-D3(BJ)/def2-TZVP,SDDAll(Ru)+SMD(THF)//TPSS-D3(BJ)/def2-SVP,SDDAll(Ru) level of theory and with PPh_3 (Scheme 6a).[21] While the intermediate **A^1**, ruthenium(II) complex **B^1**, and **1a** did not show site-selectivity, we could observe that ruthenium(III) complex **B^2** only showed a significant *meta*-selectivity, providing support for a SET oxidation process on the ruthenium(II) center for *meta*-selectivity through σ-activation by *ortho*-C–H metalation.



Scheme 6. Computational mechanistic studies.

Furthermore, we carried out detailed orbital analysis for the singlet and the triplet state of complex (**C^s** and **C^t**) at the same level of theory (Scheme 6b).[21] The triplet state **C^t** bears single occupied ligand and metal orbitals whereas the singlet state **C^s** has a double occupied metal orbital and a vacant ligand orbital, showing a clear evidence of stabilization of the singlet state by the charge transfer from the ligand to the metal.[9a]

On the basis of our detailed experimental and computational mechanistic studies along with the spectroscopic and microscopic characterization of the hybrid-ruthenium catalyst, a plausible catalytic cycle for the heterogeneous *meta*-C–H alkylation was proposed (Scheme 7). The mechanistic rationale commences by a carboxylate-assisted C–H ruthenation.[32] Subsequently, ruthenium(III) intermediate is generated *via* single electron transfer from the ruthenium(II) complex **B** to the alkyl halide **2**. The alkyl radical attacks aromatic moiety at the position *para* to ruthenium, rendering intermediate **C**. Thereafter, protodemetallation followed by aromatization delivers the desired *meta*-alkylated product **3** and regenerates the catalytically active ruthenium(II) complex **A** as confirmed by various characterization of reused hybrid-ruthenium catalyst.



Scheme 7. Proposed catalytic cycle.

Conclusion

In summary, we have reported on a recyclable catalyst for remote C–H functionalizations within a hybrid-ruthenium catalysis manifold. Full characterizations by microscopic and spectroscopic analysis illustrated the outstanding physical and chemical stability of the hybrid-ruthenium catalysts for position selective C–H functionalization. The modular hybrid-ruthenium catalyst featured remarkable robustness towards *meta*-C–H alkylation in a reusable manner without significant loss of catalytic efficacy. Its versatility was further mirrored by *meta*-C–H alkylations under photo-induced conditions and selective *para*-C–H alkylations. Detailed experimental and computational mechanistic studies provided strong support for high position-selectivity enabled by a reusable hybrid catalyst.

Acknowledgements

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Keywords: heterogeneous catalysis • C–H activation • alkylation • *meta*-selectivity • photocatalysis

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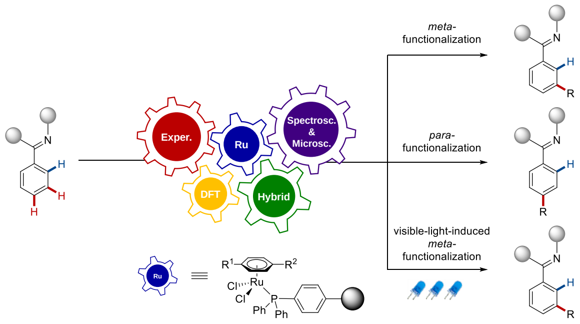

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