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Ruthenium(II)-catalyzed C–H functionalizations on benzoic acids with aryl, alkenyl and alkynyl halides by weak-*O*-coordination†

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C–H arylations of weakly coordinating benzoic acids were achieved by versatile ruthenium(II) catalysis with ample substrate scope. Thus, user-friendly ruthenium(II) biscarboxylate complexes modified with tricyclohexylphosphine enabled C–H functionalizations with aryl electrophiles. The unique versatility of the ruthenium(II) catalysis manifold was reflected by facilitating effective C–H activations with aryl, alkenyl and alkynyl halides.

Transformations of unactivated C–H bonds have emerged as an attractive alternative to conventional cross-coupling approaches, enabling step-economical biaryl syntheses with reduced by-product formation.[1] Major progress has been accomplished by means of ruthenium(II)-catalyzed reactions with easily accessible electrophilic[2–6] aryl halides,[7–10] with transformative applications in material sciences,[11] as well as agrochemical[12] and pharmaceutical industries,[13,14] among others.[7,8] Despite these undisputable advances, ruthenium(II)-catalyzed C–H arylations with organic electrophiles continue to be limited to strongly coordinating nitrogen-containing directing groups,[7,8] which are difficult to remove[15] or modify (Fig. 1a).[16] Within our ongoing program on ruthenium-catalyzed C–H functionalizations,[17,18] we have now developed the unprecedented ruthenium(II)-catalyzed C–H arylations of benzoic acids,[19] on which we report herein (Fig. 1b). The key to success was represented by using a tricyclophosphine-derived ruthenium(II) complex, which we have previously developed for C–H functionalizations guided by strong *N*-coordination.[20] Notable features of our approach include (i) first ruthenium-catalyzed C–H arylations of weakly *O*-coordinating[21,22] benzoic acids, (ii) mechanistic insights on facile carboxylate-assisted C–H activation, and (iii) a versatile ruthenium(II) catalysis regime that set the stage for expedient C–H transformations with challenging aryl, alkenyl and alkynyl halides.

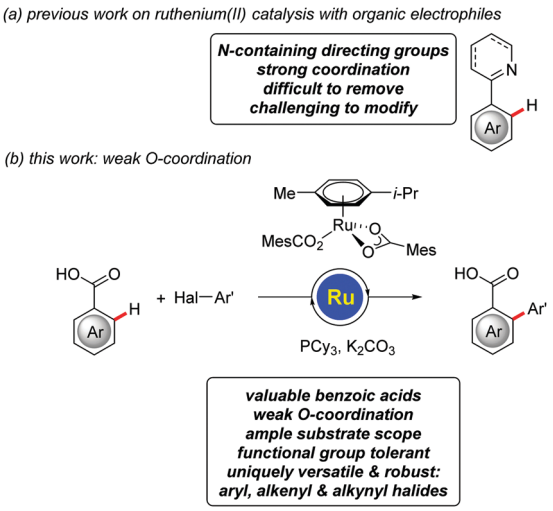

Fig. 1 Ruthenium(II)-catalyzed C–H arylation by weak coordination.

At the outset of our studies, we explored reaction conditions for the envisioned ruthenium(II)-catalyzed C–H arylation of weakly *O*-coordinating benzoic acids **1a** (Table 1 and Table S1 in the ESI†).[23] While typical phosphine or N-heterocyclic carbene ligands fell short in providing access to any arylated benzoic acid products (entries 1–8), a PCy_3-derived catalyst – previously exploited for strongly *N*-coordinating 1,2,3-triazoles[20] – enabled the challenging C–H arylation process (entries 9 and 10). It is noteworthy that the well-defined [$RuCl_2(PCy_3)$(*p*-cymene)] was also identified as a user-friendly single component catalyst, allowing for the preparation of the *ortho*-arylated benzoic acid **3aa** with comparable levels of efficacy (entry 11). The catalytic performance was further significantly improved by exploiting carboxylate[24] assistance with the aid of the well-defined ruthenium(II)biscarboxylate complex **4**[25] (entries 12–14).

With the optimized catalyst in hand, we probed its versatility in the C–H arylation of differently substituted aryl halides **2** (Scheme 1).

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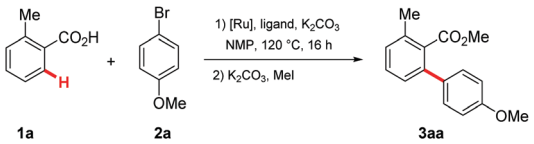
‡ RM and CZ contributed equally.

Table 1 Optimization of ruthenium(II)-catalyzed C–H arylation with benzoic acid **1a**[a]

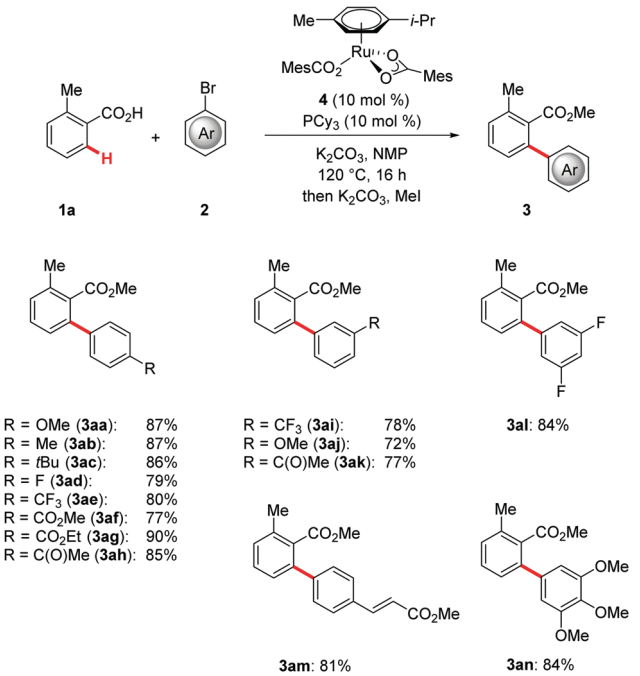


1a 2a 3aa

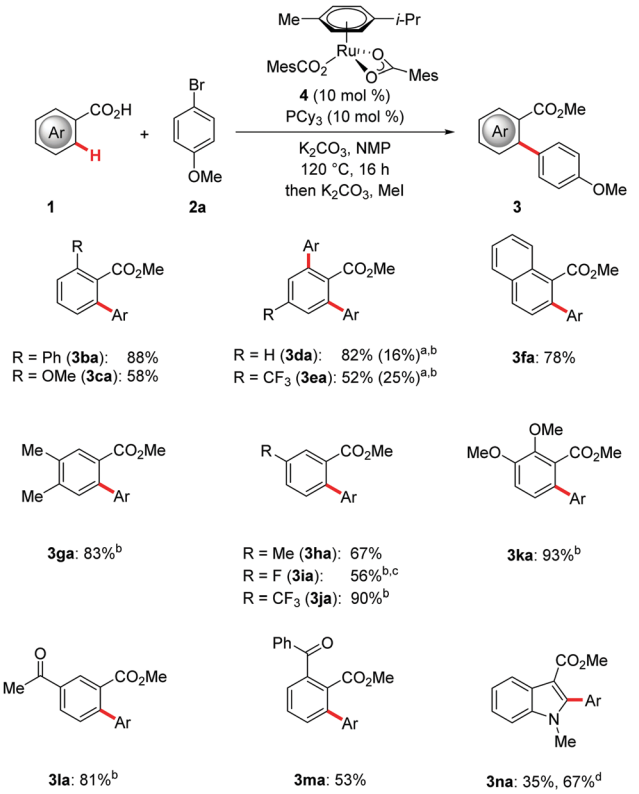
Entry	[Ru]	Ligand	3aa[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	—	(11)
2	$[RuCl_2(p\text{-cymene})]_2$	IPrHCl	(<5)
3	$[RuCl_2(p\text{-cymene})]_2$	IMesHCl	(<5)
4	$[Ru(MesCO_2)_2(p\text{-cymene})]$	X-Phos	(7)
5	$[RuCl_2(p\text{-cymene})]_2$	DavePhos	(<5)
6	$[RuCl_2(p\text{-cymene})]_2$	JohnPhos	(8)
7	$[RuCl_2(p\text{-cymene})]_2$	$(t\text{Bu})_2\text{POH}$	(20)
8	$[RuCl_2(p\text{-cymene})]_2$	$P(t\text{Bu})_3$	(22)
9	$[RuCl_2(p\text{-cymene})]_2$	PCy_3	81
10	$[RuCl_2(p\text{-cymene})]_2$	PCy_3	—[c]
11	$[RuCl_2(PCy_3)(p\text{-cymene})]$	—	75
12	$[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)	PCy_3	(32)[d]
13	$[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)	PCy_3	54[e]
14	$[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)	PCy_3	87

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Ru] (10 mol%), additive (10 mol%), K_2CO_3 (2.0 equiv.), NMP (2.0 mL), 120 °C, 16 h; then K_2CO_3 (3.0 equiv.), MeI (5.0 equiv.), MeCN (3.0 mL), 50 °C, 2 h. [b] Yields of isolated product; in parentheses: GC conversion after esterification with 1,3,5-trimethoxybenzene as the internal standard. [c] Without K_2CO_3. [d] DMPU (2.0 mL) as the solvent. [e] DMA (2.0 mL) as the solvent.

Here, a representative set of synthetically meaningful functional groups, such as halides, activated alkenes, esters or enolizable ketones, was well tolerated by the optimized catalyst at different positions of the organic electrophile **2**. Moreover, the robustness of the ruthenium(II) catalyst was reflected by efficiently converting



Scheme 1 C–H activation of weakly *O*-coordinating benzoic acid **1a** with aryl bromides **2**.

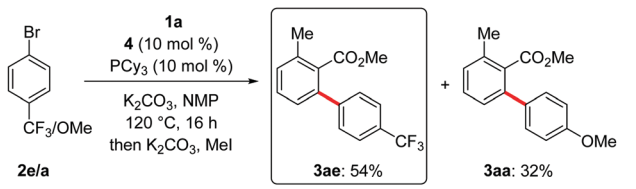


Scheme 2 C–H arylation of benzoic acids **1** by ruthenium(II) catalysis. [a] Isolated yield of the mono-arylated product. [b] With ArI instead of **2a**. [c] 9% of the di-arylated product isolated. [d] JohnPhos (10 mol%) instead of PCy_3.

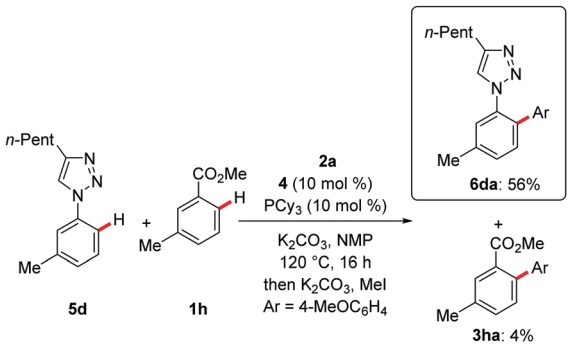
both electron-deficient as well as more demanding electron-rich aryl halides **2**.

Subsequently, we probed the scope of viable benzoic acids in the ruthenium(II)-catalyzed C–H arylation manifold (Scheme 2). Thus, we were delighted to observe that various weakly-coordinating acids **1** could be converted with high catalytic efficacy and excellent positional selectivity by the phosphine-modified biscarboxylate complex **4**. Importantly, the versatile ruthenium(II) catalyst was not restricted to arenes. Indeed, the biscarboxylate complex **4** also allowed for the site-selective C–H arylation of synthetically useful indole **1n**. Interestingly, the ligand JohnPhos outcompeted PCy_3 in the heteroarene diversification.

In consideration of the unique efficiency of the ruthenium(II) catalysis regime, we became intrigued by rationalizing its mode of action. To this end, intermolecular competition experiments revealed electron-deficient aryl bromides to react preferentially (Scheme 3).



Scheme 3 Intermolecular competition experiment.



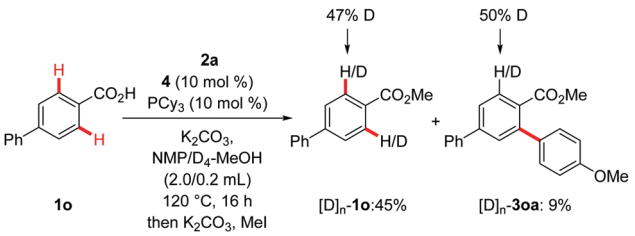
Scheme 4 Intermolecular competition experiment.

The challenging nature of the C–H arylation with weakly coordinating benzoic acids became apparent by an intermolecular competition experiment between benzoic acid **1h** and arene **5d** displaying the strongly *N*-coordinating 1,2,3-triazole (Scheme 4).

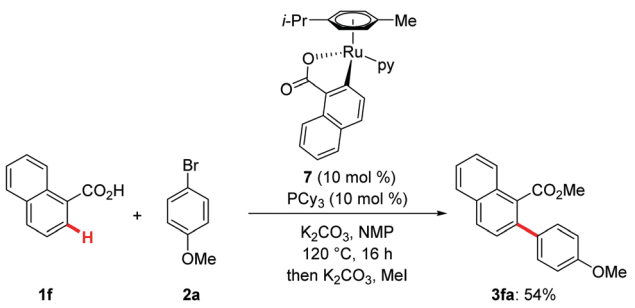
Moreover, we observed a significant H/D scrambling upon the addition of an isotopically labeled cosolvent under otherwise identical reaction conditions. The deuterium incorporation in the reisolated substrate $[D]_n$–**1o** and product $[D]_n$–**3oa** is supportive of a reversible C–H metalation event (Scheme 5).

The well-defined ruthenacycle **7**, that we had previously employed for oxidative alkyne annulations,[26] was shown to be catalytically competent (Scheme 6), being indicative of an organometallic mode of C–H activation.

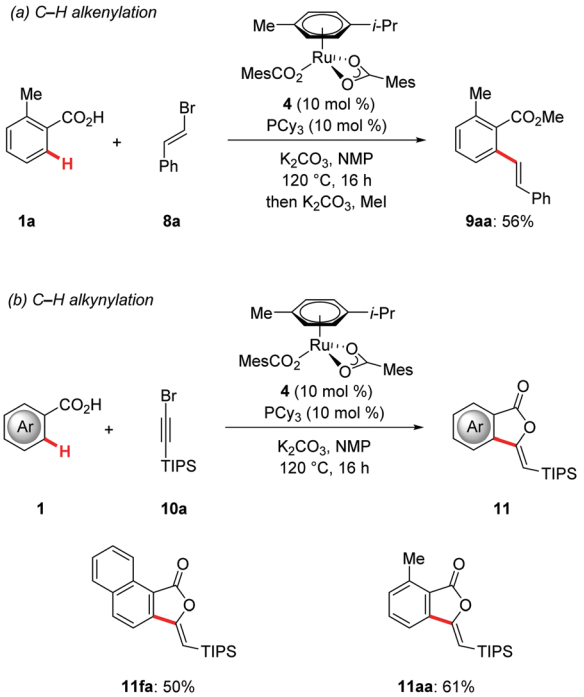
Finally, the unique versatility of the ruthenium(II) catalysis was illustrated by the phosphine-modified catalyst **4** enabling the unprecedented olefination and alkynylation of benzoic acids **1** by alkenyl and alkynyl halides **8** and **10**, respectively (Scheme 7). Both types of C–H functionalization occurred by



Scheme 5 Facile C–H arylation in the presence of isotopically labeled cosolvent.



Scheme 6 Ruthenacycle **7** for C–H arylation.



Scheme 7 Weak *O*-coordination for (a) C–H alkenylation and (b) C–H alkynylation.

weak *O*-coordination with excellent levels of positional selectivities, thereby providing access to *ortho*-alkenylated benzoic acids **9** and phthalide[27,28] derivatives **11** – key structural motifs of naturally occurring compounds.[29]

In summary, we have developed the first ruthenium(II)-catalyzed C–H functionalization of weakly *O*-coordinating arenes with organic halides. Thus, a versatile phosphine-modified[30] ruthenium(II) biscarboxylate catalyst enabled C–H arylations of benzoic acids with excellent positional selectivity and ample scope. The facile C–H ruthenation manifold enabled the direct arylation of aromatic and heteroaromatic carboxylic acids. Furthermore, the unique synthetic utility of the ruthenium(II) catalysis regime also set the stage for site-selective C–H olefinations and C–H alkynylations of benzoic acids under otherwise identical reaction conditions. Further studies on ruthenium(II)-catalyzed C–H functionalization by weak coordination are ongoing in our laboratories and will be reported in due course.

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