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Ligand-Enabled *ortho*-Arylation of (hetero)Aromatic Acids with 2,6-Disubstituted Aryl Halides

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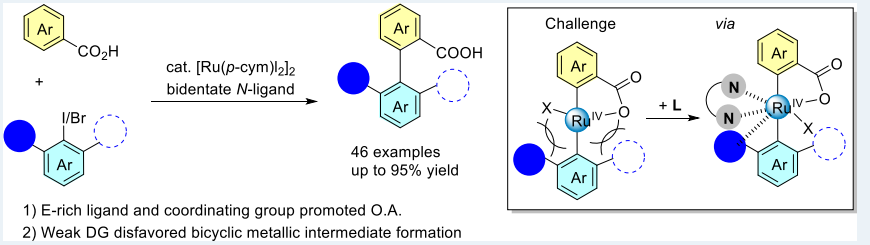

ABSTRACT: Directed C−H arylations have proven to be some of the most advantageous strategies for the synthesis of biaryls. However, their sensitivity toward steric hindrance is a key limitation. Couplings of 2,6-disubstituted aryl halides with arenes have so far been elusive. This weakness is overcome by a ruthenium 3,4,7,8-tetramethyl-1,10-phenanthroline catalyst. It allows the selective *ortho*-C−H arylation of widely available (hetero)aromatic acids with bulky aryl halides in up to 95% isolated yield. 46 examples of tri-substituted (hetero)biaryls, all outside the scope of established catalyst systems, demonstrate the efficiency of the protocol. Computational and experimental studies illustrate how this unique combination of carboxylate directing group and chelating *N*-ligand facilitates the selectivity determining C−H activation step. The preference for oxidative addition of the aryl halide over competing benzoic acid coordination is decisive to suppress unwanted dehydrogenative homocoupling.

KEYWORDS: *Ru-catalysis, ligand enabled, 2,6-disubstituted aryl halides, aromatic acid, C−H arylation*

The development of efficient methods to construct biaryls is of high importance due to the prevalence of this moiety in functional materials, pharmaceuticals, and agrochemicals.[1] Biaryls bearing multiple ortho-substituents are of particular interest in drug discovery (Scheme 1a)[1] since these forces the aromatic systems out of planarity, inducing a three-dimensionality in the structures. 2,6-Disubstituted biaryls even allow the introduction of axial chirality, which can be exploited in the synthesis of chiral ligands/catalysts.[2] *Ortho*-substituted biaryls are traditionally synthesized via transition-metal-catalyzed cross couplings of aryl metal reagents with aryl electrophiles.[3] The groups of Fu,[4] Buchwald,[5] Glorius,[6] Organ,[7] Tang,[8] Gooßen,[9] and others[10] have developed highly efficient catalyst systems that allow to access even tri- and tetra-ortho-substituted biaryls. However, the limited availability and the high price of aryl metal reagents have triggered intense research activities on alternative methods to construct biaryl moieties.

As an alternative synthesis of biaryl moieties, *ortho*-C−H arylations of donor-functionalized arenes have received particular attention. Several transition-metal catalysts are known to promote *ortho*-C−H arylations by coupling with aryl halides.[11] Among them, ruthenium and palladium are widely employed due to their unique reactivity toward C−H bond activation even when directed by weakly coordinating groups and mild bases and the ability of the resulting metallacycles to undergo oxidative addition with non-activated aryl halide electrophiles (Scheme 1b, right). A considerable number of palladium[12] or ruthenium[11c,d,13]-catalyzed C−H arylations have been developed, with major contributions being made by Yu,[12c,d] Ackermann,[11c,13b−d] Dixneuf,[11d,13f] Larrosa,[12b,13g,h] and Gooßen.[13i] It is believed that these reactions proceed via base-assisted concerted deprotonation/metalation of the donor-functionalized arene, followed by oxidative addition of aryl halides, forming the high valent metal species of the general structure **II**, from which the biaryl product is liberated via reductive elimination (Scheme 1b, right).

In contrast, hindered aryl halides act as oxidants rather than aryl sources, leading to redox reactions. Ackerman,[14] Chen,[15] and Gaunt[16] even made synthetic use of this low reactivity by developing dehydrogenative homocouplings and cyclizations. According to the proposed mechanisms, rather than the monometallacycles **II**, bicyclic metallic intermediates of the

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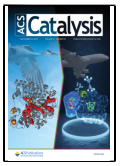

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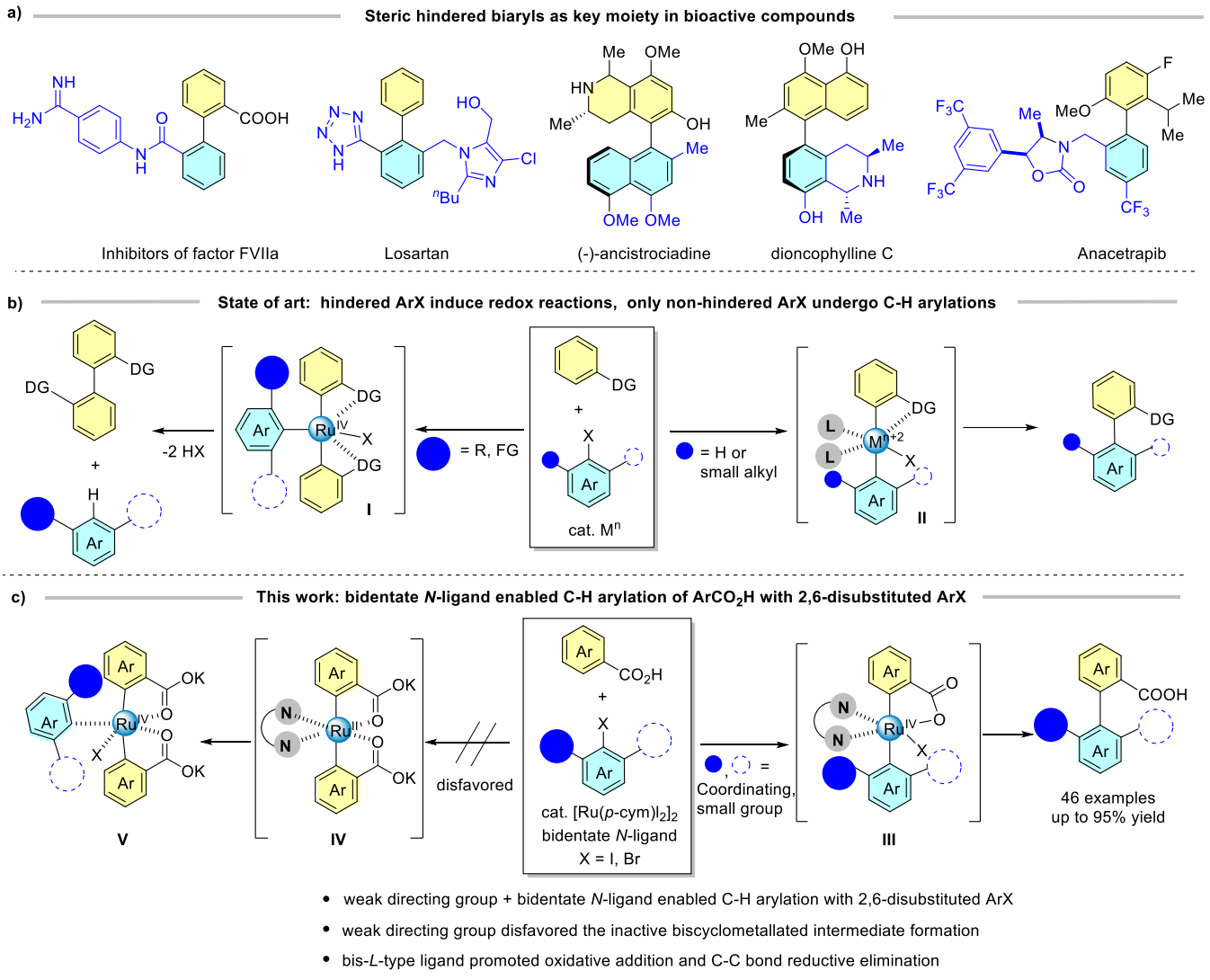
Scheme 1. (a) Steric Hindered Biaryls as the Key Moiety in Bioactive Compounds; (b) State of Art: Steric Hindered ArX-Induced Redox Reactions and Non-Steric Hindered ArX Undergo C−H Arylation; (c) This Work: Bidentate *N*-Ligand Enabled C−H Arylation of $ArCO_2H$ with 2,6-Disubstituted ArX



general structure **I** are formed. These facilitate homocoupling of the bicyclic metallic arenes rather than cross-coupling with the aryl halide (Scheme 1b, left). Several strategies had been devised to facilitate the arylation pathway over the oxidative homocoupling by promoting the oxidative addition over the competing second cyclometallation step. The nucleophilicity of cyclometallated intermediates has been increased by ligands,[13i,17] by metallacycle,[13g,18] and by photo excitation.[13d,e] However, C−H arylations with *ortho*-functionalized aryl halides have only been sporadically reported,[19] and C−H arylations using 2,6-disubstituted aryl halides have so far remained elusive, altogether.

In the context of a synthetic project, we became interested in the synthesis of polysubstituted biaryls bearing several *ortho*-amide substituents. Biaryls with *ortho*-amide groups are inhibitors of tissue factor FVIIa complex,[1c] potent inhibitors of *Tb*GalE[1d] and fluorene inhibitors of BoNT/E.[1e] However, we found these compounds to be outside the scope even of the best-known *ortho*-arylation protocols due to the steric bulk of the ortho-substituted aryl halide substrates.[14b] A dedicated reaction protocol was clearly required.

We hypothesized that the limitation to non-hindered substrates may be overcome by employing chelating ligands with strong nitrogen donors in combination with weakly coordinating, charged carboxylate-directing groups (Scheme 1c). The use of carboxylate as directing group has been reported to reduce the tendency toward a second cyclometallation.[20] Blocking reactive sites by a chelating *N*-ligand should render the formation of the bicyclic metallic intermediate **IV** even less favorable. This would block the access to unwanted oxidative homocoupling processes via species of the type **V**. In contrast, the nitrogen donors of the ligand should increase the electron density of the Ru-center to an extent that sequential cyclometallation and oxidative addition steps with formation of complexes of the type **III** might become feasible even for sterically highly demanding bis-ortho-functionalized aryl halides.

This hypothesis was evaluated upfront by preliminary DFT calculations: the formation of coordinatively saturated bicyclic metallic ruthenium complexes of the type **IV** was confirmed to be unfavorable for the example of naphthoic acid by as much as 35.3 kcal/mol, and the formation of a mono-cyclometallated

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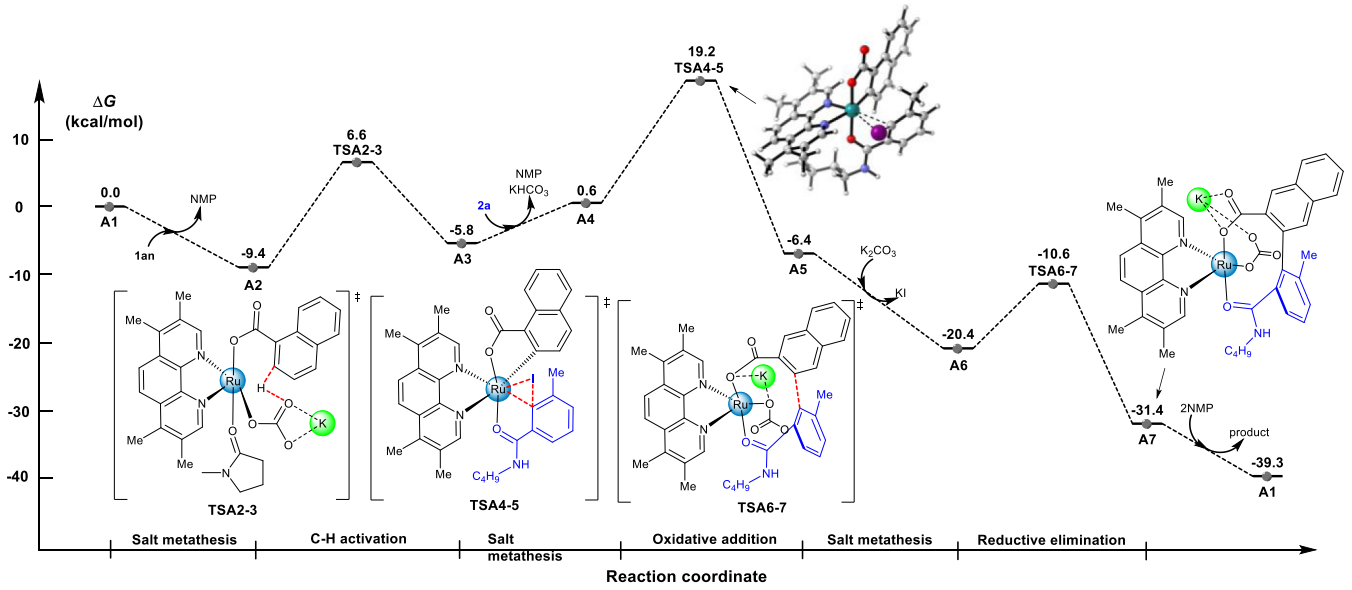
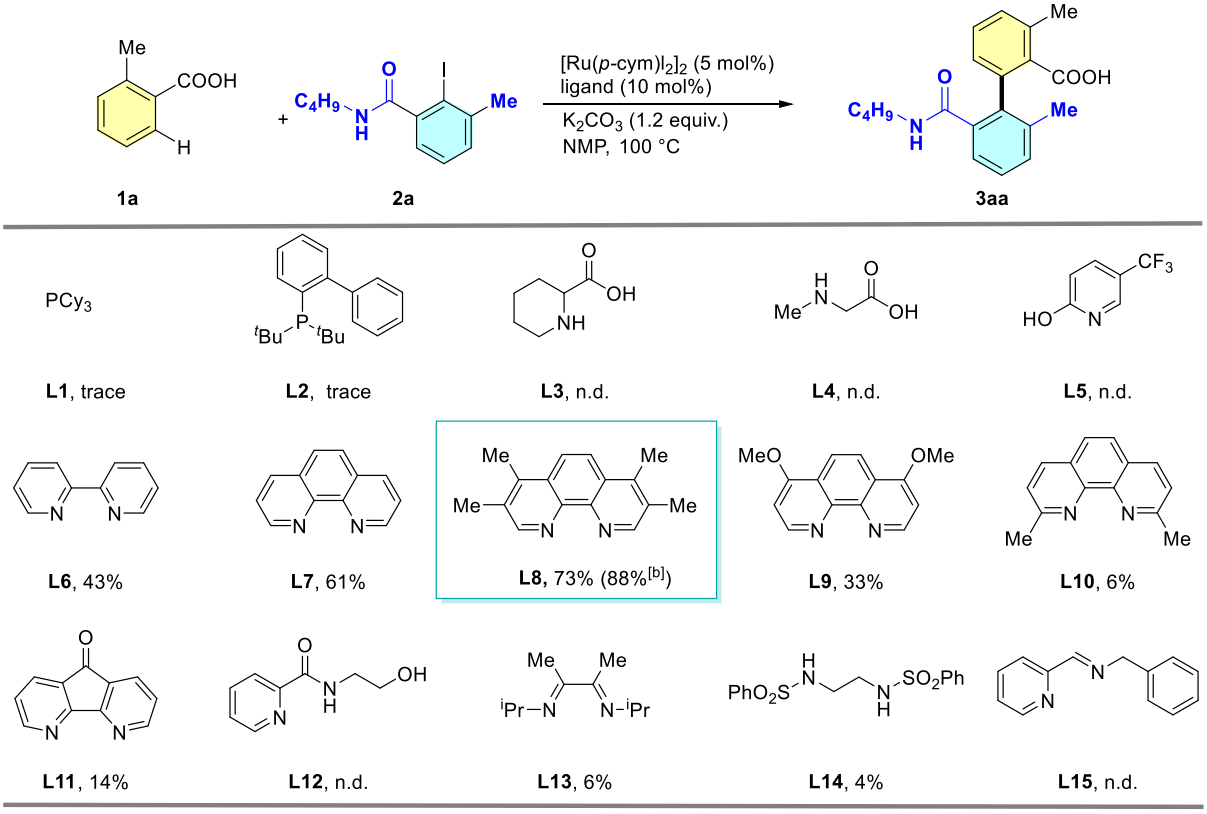


Figure 1. Gibbs free-energy profiles of the carboxylate-assisted C−H arylation with 2,6-disubstituted aryl halides catalyzed by Ru-complex A1 (unit: kcal/mol).

Table 1. Optimization of the Reaction Conditions for C−H Arylation with 2,6-Disubstituted Aryl Halide 2a[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Ru(p\text{-cym})I_2]_2$ (5 mol %), ligand (10 mol %), K_2CO_3 (1.2 equiv), NMP (1.0 mL), 100 °C, 24 h, N_2 atmosphere. Yields of the corresponding methyl esters determined by GC analysis after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP using *n*-tetradecane as the internal standard. Yields of isolated products are given in parentheses. [b]At 120 °C.

oxidative addition complexes of the type **II** was also found to endergonic by 33.5 kcal/mol with the traditionally used ligand L = PCy_3. However, when a bidentate *N*-ligand and ortho-coordinating aryl halides were coordinated to the ruthenium center, the oxidative addition of aryl halides to form ruthenium complexes of the desired type **III** was predicted to be exergonic by as much as 28.6 kcal/mol (for details, see Figure 1 and Figures S4 and S6 of the Supporting Information). Based on these considerations and our experience in developing carboxylate-directed C−H functionalization,[21] we systematically screened Ru complexes with bidentate *N*-ligands, until we found a catalyst that efficiently promotes the *ortho*-C−H

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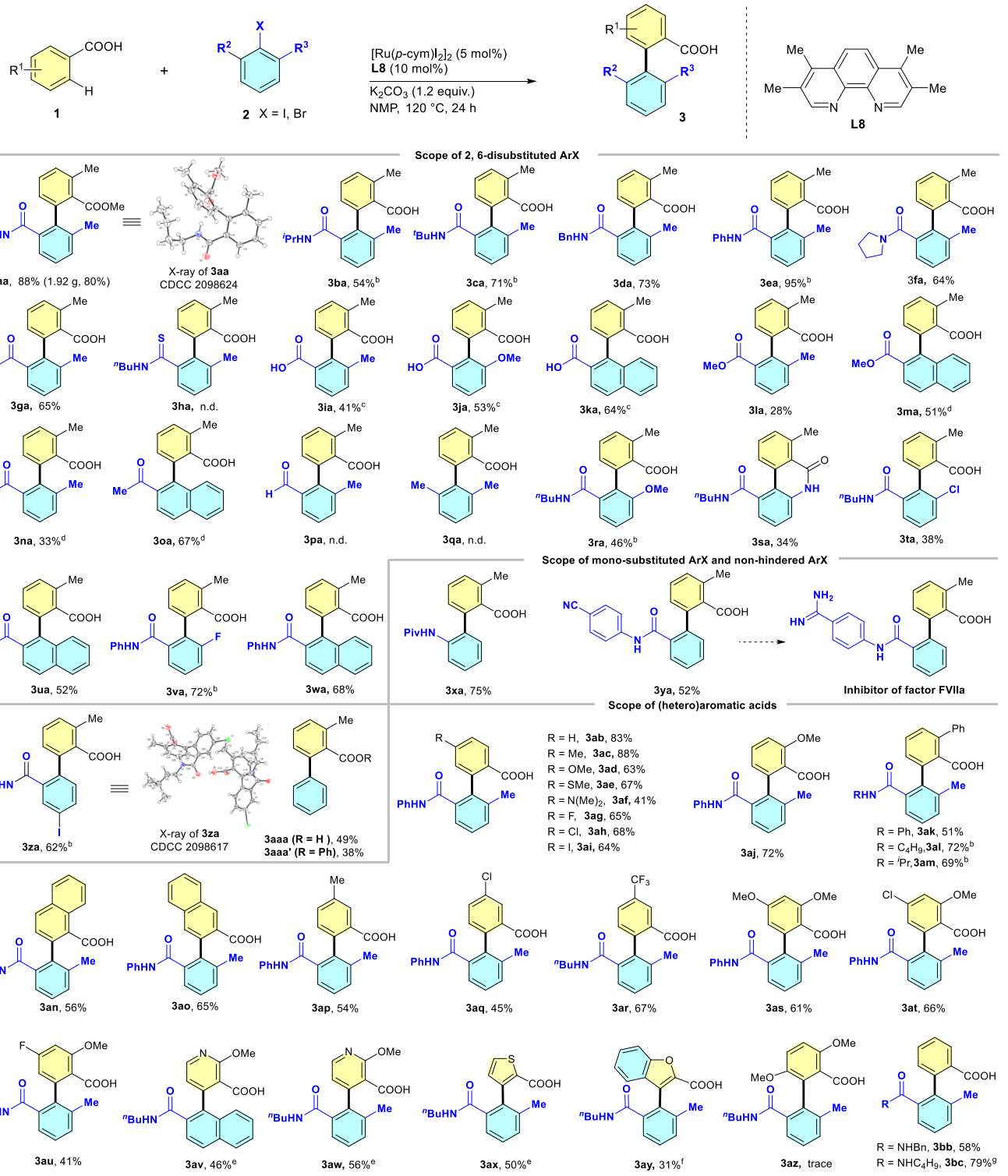
Table 2. Scope of 2,6-Disubstituted Aryl Halides and (hetero)Aromatic Acids[a]



[a]Conditions: **2ka**, **2ma**, **2ra**, **2ua**, and **2wa** were coupled with aryl bromides, all other products were generated from aryl iodides. **1** (0.3 mmol), **2** (0.45 mmol), $[Ru(p\text{-cym})I_2]_2$ (5 mol %), **L8** (10 mol %), and K_2CO_3 (1.2 equiv) were stirred in NMP (2 mL at 120 °C for 24 h under an N_2 atmosphere. Yields correspond to the isolated amounts of methyl esters following in situ esterification with K_2CO_3 (2 equiv) and MeI (5 equiv). [b]Isolated as the free acid. [c]K_2CO_3 (3.0 equiv). [d]Ru-cat (7.5 mol %), **L8** (15 mol %), 130 °C. [e]Use $Ru(p\text{-cym})(dtbpy)Cl_2$ (5 mol %) instead of $[Ru(p\text{-cym})I_2]_2$ and dtbpy. [f]$[Ru(p\text{-cym})I_2]_2$ (7.5 mol %), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) (15 mol %). [g]Use $Ru(p\text{-cym})(\mathbf{L8})Cl_2$ (10 mol %) instead of $[Ru(p\text{-cym})I_2]_2$ (5 mol %) and **L8** (10 mol %).

arylation of arene carboxylic acids with sterically highly demanding 2,6-disubstituted aryl halides.

We chose the sterically crowded aryl iodide **2a**, bearing an amide and a methyl group in its ortho-position as a model substrate, and investigated its coupling with *o*-toluic acid in the

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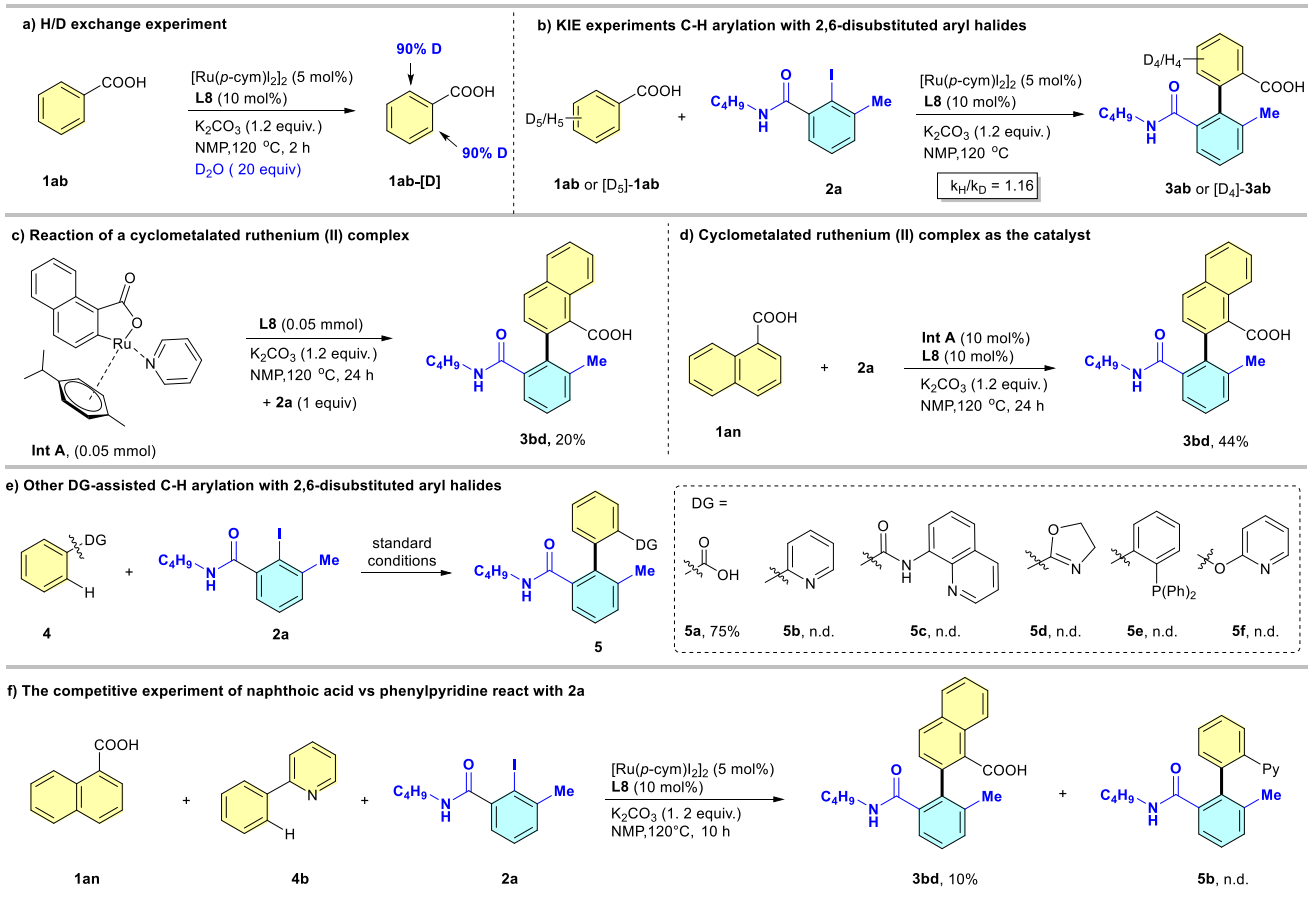
Scheme 2. Mechanistic Studies and Control Experiments[a]



[a](a) H/D exchange experiment; (b) KIE experiments C−H arylation with 2,6-disubstituted aryl halides; (c) reaction of a cyclometalated ruthenium(II) complex; (d) cyclometalated ruthenium(II) complex as the catalyst; (e) other DG-assisted C−H arylation with 2,6-disubstituted aryl halides; and (f) competitive experiment of naphthoic acid vs phenylpyridine react with **2a**.

presence of various catalysts (Table 1). The results detailed in Tables 1 and S1 show that state-of-the art catalysts for C−H arylations of aromatic acids proved to be ineffective in this challenging test reaction. *p*-Cymene-ruthenium halide complexes in combination with mono-dentate phosphines such as PCy_3 or JohnPhos, which are highly effective for *ortho*-arylations of non-sterically hindered aryl halides,[13c,i,21c] gave at best traces of the desired product **3a**. Many other ligand classes were tested including amino acids (**L3**−**4**) and pyridine derivative (**L5**), and all were ineffective. In contrast, bipyridine (**L6**) directly gave the product in moderate yields. Following up on this lead structure, a series of chelating nitrogen ligands were evaluated, and 3,4,7,8-tetramethyl-1,10-phenanthroline (**L8**) was found to be most effective. Substituents ortho to the nitrogen-donor atoms strongly reduce the ligand efficiency. The phenanthroline scaffold was found to be optimal, other bidentate nitrogen ligands (**L12**−**15**) gave unsatisfactory results. Further experiments confirmed K_2CO_3 as the optimal base, $[Ru(p\text{-cym})I_2]_2$ as the optimal precatalyst, NMP as the best solvent, and revealed that the reaction is best conducted over 24 h at 120 °C (see Table 1). Under the optimal conditions, the model reaction proceeded in 88% yield with near exclusive selectivity for the cross-coupling over dehalogenation/homocoupling products. It was successfully brought to a gram scale for the example of compound **3aa**. A single-crystal X-ray diffraction analysis confirmed the structure of this representative product.

Having established an effective catalyst system, we surveyed the scope of aryl halides, placing a focus on 2, 6-disubstituted aryl halides that are outside the scope of existing protocols (Table 2). Starting from compound **2a**, we first varied the amide substituent and found that the protocol is widely applicable to our target structures, *ortho*-amide functionalized biaryls (**3aa**−**3ga**). Solely thioamides could not be converted. The amide substituent was successfully replaced by acid, ester, and keto groups.

However, the aldehyde-substituted substrate failed. We speculate that aldehyde has a weaker coordination ability with ruthenium catalysts, making their oxidation addition more challenging. Interestingly, 2,6-dimethylphenyl iodide did not give any conversion, which suggested that at least one of the ortho-substituents must bear a coordinating functionality. A control experiment revealed that the coupling of *N*-^{n}Bu-2, 5-diiodobenzamide proceeded with exclusive regioselectivity in favor of the more hindered biaryl **3za** bearing an *ortho*-amide functionality. The structure of **3za** was confirmed by single-crystal X-ray analysis. In combination with an amide group in one ortho position, the other ortho substituent can be varied greatly (**3ra**−**3wa**). Even unprotected amino group was tolerated, which was easily condensed with an intramolecular

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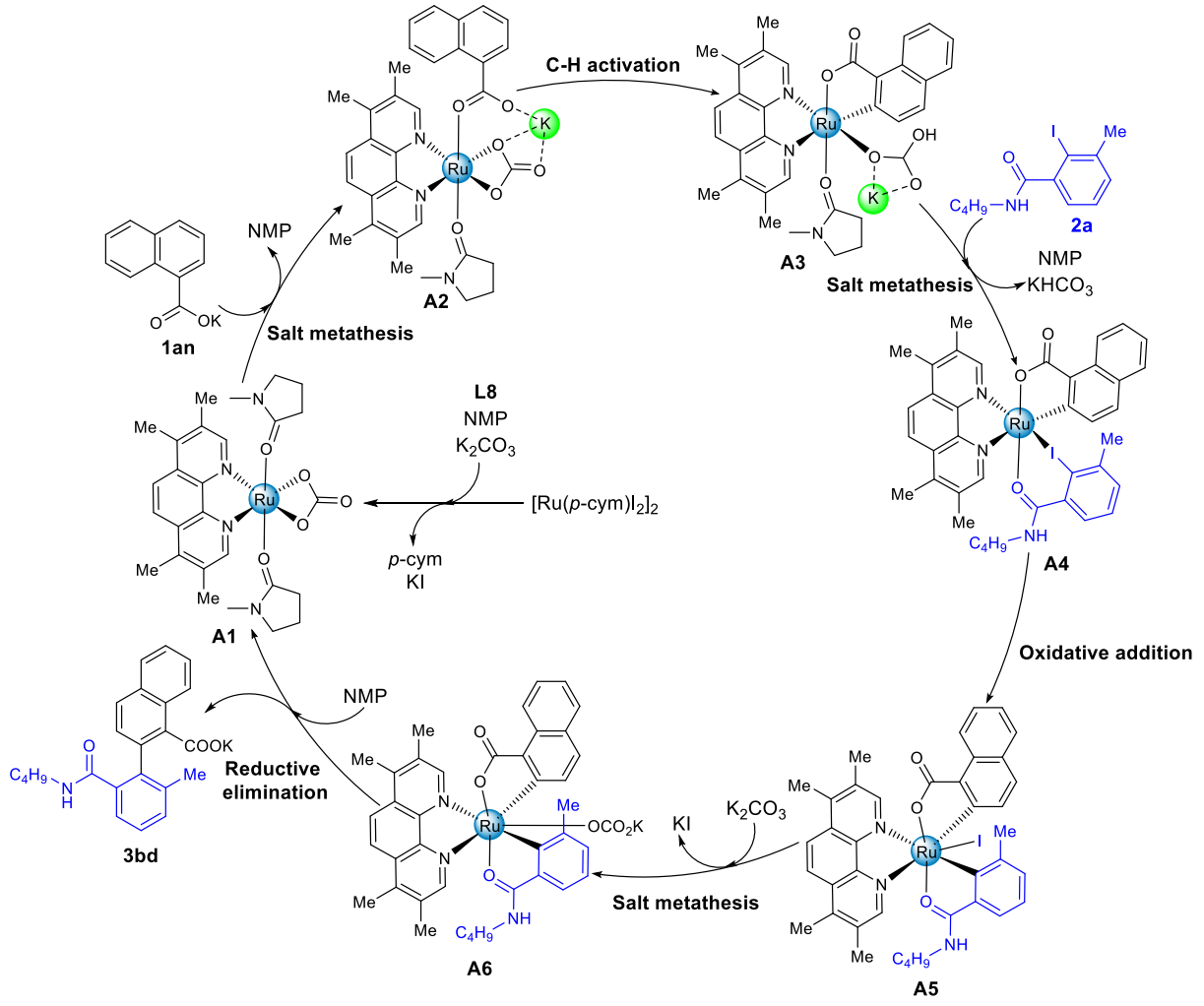
Scheme 3. Proposed Reaction Mechanism for $[Ru(p\text{-cym})I_2]_2$-Catalyzed Carboxylate-Assisted C−H Arylation with 2,6-Disubstituted Aryl Iodide



carboxylate group to synthesize a bioactive phenanthridinones skeleton product (**3sa**).[22] It should be mentioned that the catalyst, although developed specifically for sterically hindered aryl halides, also allowed the coupling of mono- and unsubstituted aryl iodides. The synthetic value of the protocol was demonstrated by the synthesis of *a* factor FVIIa inhibitor via compound **3ya**.[1c] However, for non-hindered substrates, competing C−O bond arylation was observed as side reaction (**3aaa** and **3aaa′**).[23]

On the side of the carboxylic acid, various functional groups were tolerated, including −Me, −OMe, −SMe, and $-N(Me)_2$, as well as halogen atoms such as −F, −Cl, and even −I. This sets the stage for orthogonal follow-up reactions. In all cases, the selectivity for mono-arylation products was high (**3ab**−**3ai**). This indicated that the axial rotation was restricted in the tri-ortho-substituted biaryl products. In addition to mono-substituted aromatic carboxylic acids, multi-substituted aromatic carboxylic acids (**1as**−**1au**) and various heterocycles carboxylic acids (**1av**−**ay**) were also tolerated. The performance limit of the reaction was reached for tetra-ortho-substituted biaryl product **3az**, which was only observed in trace amounts.

A series of control experiments were conducted to shed some light on the reaction mechanism (Scheme 2). Treating **1ab** with D_2O under standard reaction conditions for 2 h in the absence of an aryl halide led to deuteration in both ortho positions (Scheme 2a). This suggests that the *ortho*-cycloruthenation is the first step of the catalytic cycle and that it is reversible. Parallel kinetic experiments using **1ab** and its D_5-deuterated analogue as substrates gave a KIE of 1.16, which indicates that this initial C−H activation is not rate-determining (Scheme 2b). This interpretation is supported by a series of kinetic experiments with varying amount of **1ab**, which showed almost identical reaction rates. Analogous experiments revealed that the reaction follows a first-order kinetic with regard to the aryl halide substrate **2a** (for details, see the Supporting Information). This suggests that the oxidative addition of the aryl halide is the rate-determining step.

Preformed ruthenacycle **Int A** was smoothly converted into the product **3bd** in a stoichiometric reaction, and it was also found to be an effective catalyst (Scheme 2c,d). This suggests that **Int A** is a likely intermediate in the catalytic cycle. A comparative study of various directing groups that are commonly used in Ru-catalyzed *ortho*-C−H arylations revealed that carboxylates are uniquely reactive at the optimized reaction conditions. Arenes with nitrogen- or phosphine-based directing groups did not give any conversion when treated with the 2,6-disubstituted aryl halide **2a** under the standard conditions. Neither the C−H arylation product nor homocoupling products were detected, and the starting materials (**4b**−**f**) were fully recovered (Scheme 2e). In a competition experiment, naphthoic

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acid **1an** and phenylpyridine **4b** were allowed to react with **2a** under standard reaction conditions for 10 h. The carboxylate arylation product **3bd** was obtained only in 10% yield, whereas no phenylpyridine arylation product **5b** was detected. Most of the starting material **4b** was recovered, which suggests that pyridine directing group traps the catalyst without leading to *ortho*-C−H arylation, thus hampering the competing carboxylate-directed *ortho*-C−H arylation (Scheme 2f).

Based on these experimental studies, it is reasonable to assume that the phenanthroline-ligated ruthenium catalyst mediates the carboxylate-assisted C−H arylation of aryl halides along the pathway outlined in Scheme 3. The catalytic species **A1** is formed by reaction of the catalyst $[Ru(p\text{-cym})I_2]_2$ with the ligand **L8**, the base K_2CO_3, and the coordinating solvent NMP. In the initial step of the catalytic cycle, the ruthenium carboxylate **A2** is formed via salt metathesis with potassium carboxylate **1an**, liberating NMP. Intramolecular, base-assisted C−H activation gives rise to the metalacyclic intermediate **A3**. The aryl iodide **2a** then coordinates to the Ru center to form complex **A4**, releasing one molecule of $KHCO_3$ and NMP, and oxidatively adds to the ruthenium complex with formation of complex **A5**. Following salt metathesis of K_2CO_3, the resulting complex **A6** undergoes reductive elimination, releasing the product **3bd**, thereby closing the catalytic cycle by regenerating species **A1**.

This mechanism was fully supported by DFT calculations.[24] As shown in Figure 1, the initiating salt metathesis of **A1** with potassium carboxylate **1an** is exergonic by 9.4 kcal/mol. The C−H activation step via **TSA2-3** has only a low barrier of 16.0 kcal/mol. Coordination of the aryl iodide is endergonic by 6.4 kcal/mol, and the transition state of the oxidative addition **TSA4-5** adds another 18.6 kcal/mol to the barrier for the uptake of the sterically demanding aryl iodide. With an overall barrier of 25.0 kcal/mol, the oxidative addition step is clearly rate-determining. However, it is exergonic by 7.0 kcal/mol and leads to an exergonic (14.0 kcal/mol) salt metathesis step. The barrier **TSA6-7** for the reductive elimination step is low (9.8 kcal/mol). These calculations correspond well with the experimental findings. We also calculated an alternative catalytic cycle, in which two molecules of aromatic carboxylic acids react with formation of a bicyclic metallic intermediate. However, the second C−H insertion and the oxidative addition of the aryl halide both have unrealistically high energy barriers of 36.3 and 31.7 kcal/mol, respectively. It is safe to assume that this alternative pathway does not contribute to the reaction progress (see more details in Figures S4 and S5 of the Supporting Information).

In summary, the feasibility of directed C−H functionalization using sterically demanding, functionalized aryl halides was demonstrated for the example of carboxylate-directed arylations of (hetero)aromatic carboxylic acids. The successful strategy of using a weakly coordinating, anionic directing group in combination with an electron-rich, chelating ligand to steer the ruthenium catalysts toward cross-coupling rather than redox couplings might turn out to be an enabling concept for related couplings. The reaction protocol, which is based on inexpensive, easy-to-handle $[Ru(p\text{-cym})I_2]_2$ and 3,4,7,8-tetramethyl-1,10-phenanthroline, opens up a convenient access to pharmaceutically meaningful multi-ortho-substituted biaryls bearing various functional groups. Experiments and DFT calculation allow an understanding why the broadly available carboxylate moiety is so uniquely effective as the directing group, and they point toward the oxidative addition of the 2,6-disubstituted aryl halides as the rate-determining step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c03168.

Detailed experimental procedures, characterization data, crystallographic data for **3aa** (CIF) and **3za** (CIF), details of DFT calculation, and copies of ^{1}H NMR and ^{13}C NMR spectra for all isolated compounds (PDF)

Accession Codes

CCDC 2098624 and CCDC 2098617 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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