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Ruthenium-catalysed decarboxylative unsymmetric dual *ortho*-/*meta*-C–H bond functionalization of arenecarboxylic acids†

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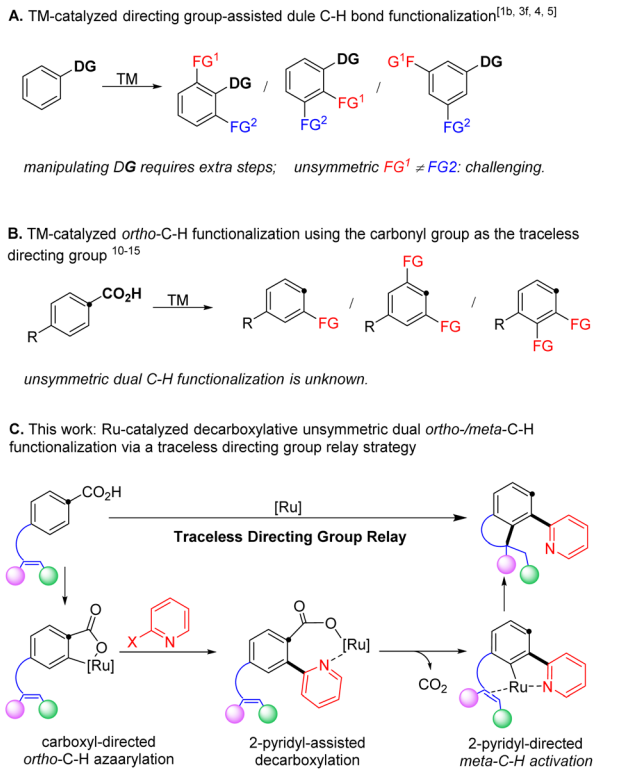
Here, we describe a ruthenium-catalysed decarboxylative unsymmetric *ortho*-C–H azaarylation/*meta*-C–H alkylation *via* a traceless directing group relay strategy. The installation of a 2-pyridyl functionality *via* carboxyl directed *ortho*-C–H activation is critical to promote decarboxylation and enable *meta*-C–H bond alkylation to streamline the synthesis of 4-azaaryl-benzo-fused five-membered heterocycles. This protocol is characterized by high regio- and chemoselectivity, broad substrate scopes, and good functional group tolerance under redox-neutral conditions.

Introduction

Polysubstituted arenes are frequently encountered in pharmaceuticals, agrochemicals, and functional materials,[1–3] and thus their synthesis is of paramount interest in the community of synthetic chemistry.[4–7] In recent decades, transition metal-catalysed C–H bond activation has become a powerful tool to selectively install various functionalities (Scheme 1A).[2,8–13] Using this tactic, a number of dual C–H bond functionalization reactions have been achieved by repeated reaction with the same compounds in one step.[2,13–17] In contrast, a method for selectively replacing multiple aryl C–H bonds with different functionalities remains challenging and highly desirable to streamline the synthesis of diversely functionalized aromatic compounds.[9–11,18–23]

The employment of coordinating directing groups in transition metal-catalysed C–H bond functionalization is the predominant strategy to achieve regioselectivity.[24–38] However, utilizing directing groups often adds additional synthetic steps for their installation and/or removal, thus reducing the overall synthetic economy. In this context, the carboxyl functionality represents a desirable directing group, because it is readily accessible[39] and widely utilized to direct *ortho*-C–H bond functionalization,[40–43] and can be completely removed to allow complementary regioselectivities in products (Scheme 1B).[43–48] Indeed, utilizing the carboxyl functionality as a deciduous directing group has enabled a number of C–H bond functionalization reactions of arenecarboxylic acids with *in situ* elimination of CO_2.[49–60] Specifically, the recent advance in ruthenium catalysis, pioneered by Zhao and Hartwig,[61] Goo-ßen[62] and Ackermann,[63] has enabled mild decarboxylative *ortho*-C–H bond alkenylation under redox neutral conditions, which eliminates the requirement of substrate activation and additives to facilitate decarboxylation in previous examples. However, so far, ruthenium catalysis is limited to C–H addition to unsaturated bonds such as alkynes,[61–65] alkenes,[66–70] and isocyanates.[71] Besides, dual C–H bond functionalization is only applicable to repeated



Scheme 1 Synthesis of polysubstituted arenes *via* C–H bond functionalization.

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incorporation of the same functionality.[72,73] Therefore, it is desirable to design new strategies to exploit the traceless carboxyl group that might selectively functionalize multiple C–H bonds with various functionalities to access polysubstituted arenes.

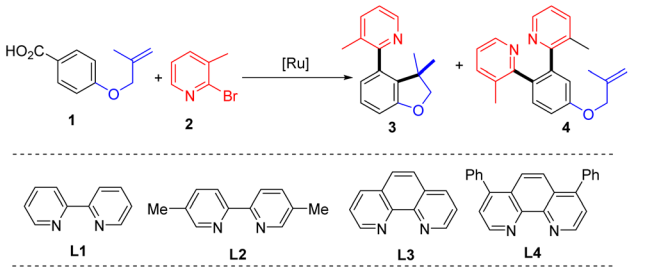
We hypothesized that an unsymmetric dual *ortho*-/*meta*-C–H bond functionalization would be achieved *via* a directing group relay strategy by taking advantage of the traceless carboxyl group. Specifically, catalytic decarboxylative *ortho*-C–H bond azaarylation would install a 2-pyridyl functionality, which will serve as the directing group to assist the catalyst to functionalize the *meta*-C–H bond *via* an intramolecular alkene hydroarylation, furnishing chemo- and regio-selective unsymmetric dual C–H bond functionalization (Scheme 1C). We chose the 2-pyridyl group as the relay directing group because (**1**) a cyclic ruthenium carboxylate could be formed *via* coordinating to the nitrogen atom, which is expected to promote decarboxylation and avoid di-*ortho*-C–H azaarylation;[12,16,61,80] (**2**) the 2-pyridyl group has been unambiguously demonstrated as a strong directing group in various *ortho*-C–H functionalization reactions, which will provide broad opportunities for the next C–H bond activation to introduce a different functionality.[18] Following this design, we herein disclose a ruthenium-catalysed decarboxylative unsymmetric dual *ortho*-/*meta*-C–H bond functionalization of alkene-tethered arenecarboxylic acids *via* a directing group relay strategy. This protocol, for the first time, enables decarboxylative *ortho*-C–H azaarylation offering a new method for the construction of aryl-azaaryl structures, and streamlines the synthesis of 4-azaaryl-benzo-fused five-membered saturated heterocycles, which are privileged structural motifs in various natural products and pharmaceuticals.[1,74]

Results and discussion

To verify our hypothesis, 4-((2-methylallyl)oxy)benzoic acid (**1**) and 2-bromo-3-methylpyridine (**2**) were selected as the model substrates to evaluate the reaction parameters. After extensive exploration (Tables S1–S6†), 73% of the desired 4-(2-pyridyl)-2,3-dihydrobenzofurane with a C3 quaternary carbon center (**3**) was obtained in the presence of 4 mol% of $[Ru(p\text{-cymene})Cl_2]_2$, 8 mol% of bathophenanthroline (**L4**), and 5 mol% of ZnI_2 and KOAc in 1,4-dioxane after 20 hours of reaction at 120 °C (entry 1). In the test of ligands, 2,2′-bipyridine (**L1**), 5,5′-dimethyl-2,2′-bipyridine (**L2**) and 1,10-phenanthropline (**L3**) led to inferior yields of **3** (entries 2–4). The effects of solvent show that NMP is also suitable and provides **3** in 57% yield (entry 5 and Table S1†). The reaction performed at 100 °C gave 63% of **3** (entry 6). A series of control experiments were conducted to elucidate the necessity of each component in the optimal system (Table S6†). The catalyst and base were proved indispensable for the reaction (entries 7 and 8), while the ligand played an essential role to get a high yield (Table 1, entry 9). In addition, ZnI_2 is found to be capable of suppressing bis-2-pyridination product **4** (Table S5†).

With the evaluated reaction conditions, we next explored the scope of alkene-tethered arenecarboxylic acids with 2-bromo-3-methylpyridine (**2**) (Table 2A). The linkage to the alkene unit could also be amine, ester and amide, affording the corresponding indoline (**5**), furanone (**6**), and oxindole (**7**) in good to high yields. Remarkably, substrates with amide linkers exhibit high reactivity

Table 1 Evaluation of reaction parameters[a]



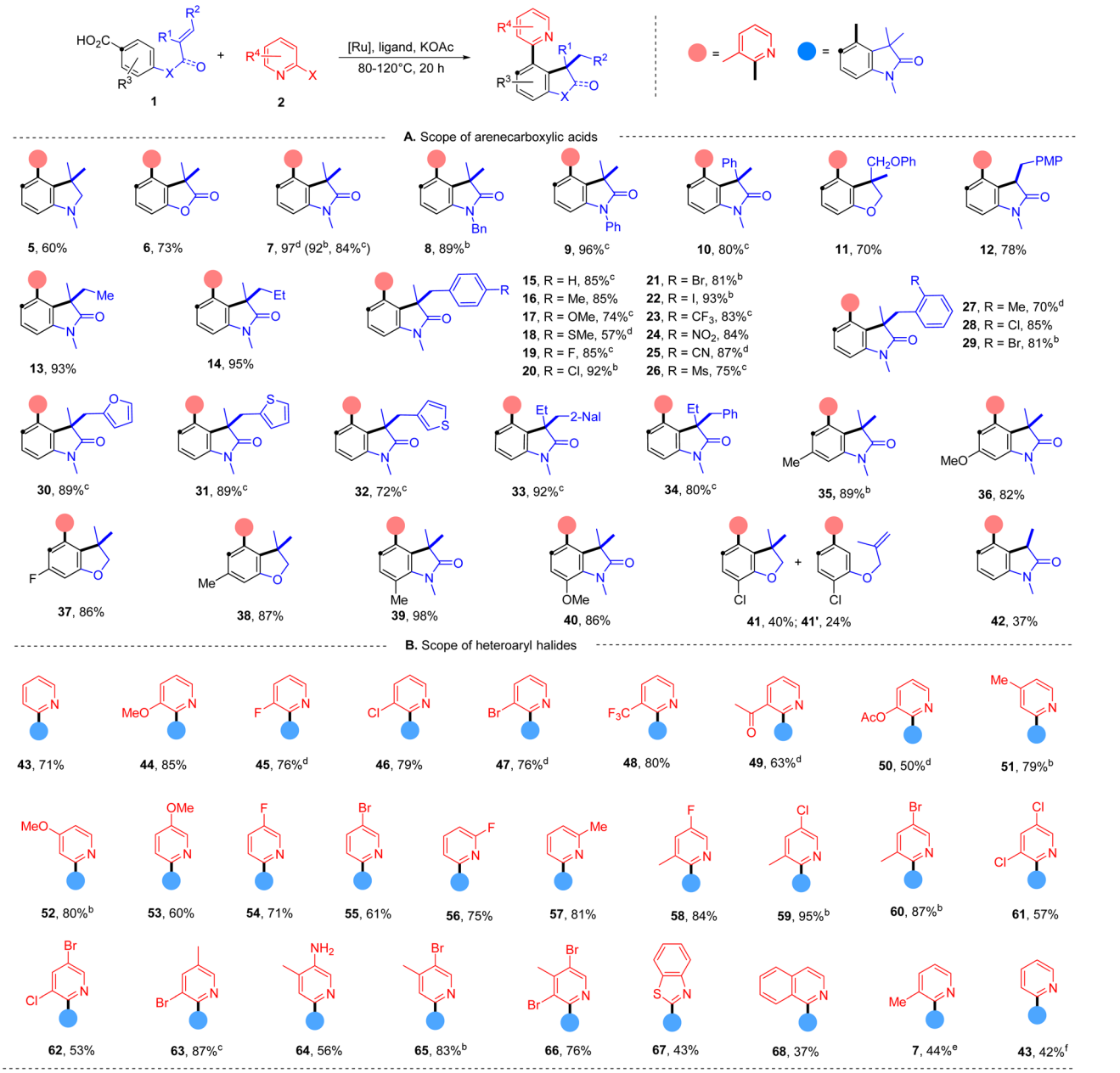
Entry	Deviations	3[a] (%)	4 (%)
1	None	71 (73)	Trace
2	**L1** instead of **L4**	30	Nd
3	**L2** instead of **L4**	43	5
4	**L3** instead of **L4**	64	5
5	NMP as solvent	57	Nd
6	At 100 °C	63	Trace
7	Without $[Ru(p\text{-cymene})Cl_2]_2$	0	Nd
8	Without KOAc	0	Nd
9	Without **L4**	8	Nd
10	Without ZnI_2	67	13

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), KOAc (0.36 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (4 mol%), bathophenanthroline (8 mol%), ZnI_2 (5 mol%), 1,4-dioxane (2 mL), under argon, 120 °C, 20 hours. GC yields. Isolated yield in the parentheses. Nd: not detected.

and could produce oxindoles in high yields under much milder conditions (Table S7†). For example, 84% of **7** was obtained at 80 °C with a lower catalyst loading and simple 2,2′-bipydine ligand (**L1**) in the absence of ZnI_2. Besides *N*-methyl amide, benzyl and phenyl-substituted amides were also suitable linkers producing **8** and **9** in high yields. Substrates with phenyl (**10**), phenoxymethyl (**11**), and ethyl (**33** and **34**) substituted alkene fragments also afforded high yields of products. In addition to substrates with 1,1-disubstituted alkenes, those with 1,2-disubstituted alkene are also amenable to the reaction giving 78% of **12**. While those with 1,1,2-trisubstituted alkenes can efficiently deliver products in good to high yields (**13–34**). A wide range of functional groups with diverse electronic characters in different substitution patterns on the phenyl group of alkene were tolerated, including electron-donating methyl (**16**), methoxyl (**17**), methylthio (**18**) groups and electron-withdrawing trifluoromethyl (**23**), nitro (**24**), cyano (**25**), and mesyl (**26**) groups, furnishing products in good to high yields (57–93%). Aryl halides, including fluoride (**19**), chloride (**20** and **28**), bromide (**21** and **29**) and even iodide (**22**) remained intact during the reaction and delivered products in high yields (85–93%), highlighting the excellent chemoselectivity of this protocol and providing valuable handles to further functionalization.

Additionally, substrates with heteroaryl alkene fragments, such as 2-furyl (**30**), 2-thiophenyl (**31**), and 3-thiophenyl (**32**), were tolerated and underwent reaction with high efficiency. Oxindoles with a more crowed quaternary carbon center are also accessed in high yields (**33** and **34**). *ortho*-Substitutions to the carboxyl group were not detrimental to the reaction furnishing high yields of

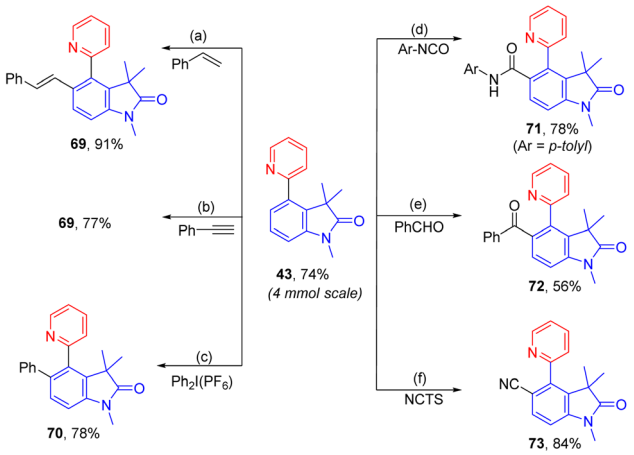
Table 2 Substrate scopes[a]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.20 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol%), **L4** (8 mol%), KOAc (0.36 mmol, 1.8 equiv.), ZnI_2 (5 mol%), 1,4-dioxane (2 mL) under argon, 120 °C, 20 hours, isolated yields. [b] [Ru(*p*-cymene)Cl_2]$_2$ (3 mol%), **L1** (6 mol%), KOAc (1.5 equiv.), dioxane (1 mL), 100 °C. [c] [Ru(*p*-cymene)Cl_2]$_2$ (3 mol%), **L1** (6 mol%), KOAc (0.3 mmol), dioxane (1 mL), 80 °C. [d] [Ru(*p*-cymene)Cl_2]$_2$ (3 mol%), **L1** (6 mol%), KOAc (0.3 mmol), dioxane (1 mL), 120 °C. [e] With 2-chloro-3-methylpyridine. [f] With 2-iodo-3-methylpyridine.

polysubstituted arenes (**35–38**). The effects of *ortho*-substitution to the tethered-alkene were found substrate-dependent. Those with the amide-linker gave high yields of oxindoles (**39** and **40**), and those with the ether-linker delivered 40% of benzodihydrofuran **41** with 24% of 2-arylpyridine **41′** indicating a hindered alkene hydroarylation.

Next, the scope of azaaryl halides was explored with 4-(*N*-methylmethacrylamido)benzoic acid (Table 2B). The reaction proved to be general providing a series of diversely functionalized 4-(2-pyridyl)oxindole structures in good to high yields (**42–60**). A broad array of functional groups in various substitution patterns is compatible, including methoxyl (**44**, **52** and **53**), fluoride (**45**, **54** and **56**), chloride (**46**, **59**, **61** and **62**), bromide (**47**, **55**, **62**, **63**, **65** and **66**), acyloxyl (**50**), trifluoromethyl (**48**), acetyl (**49**), acyloxy (**50**), and unprotected amino groups (**64**). Notably, only halide at the *ortho*-position of



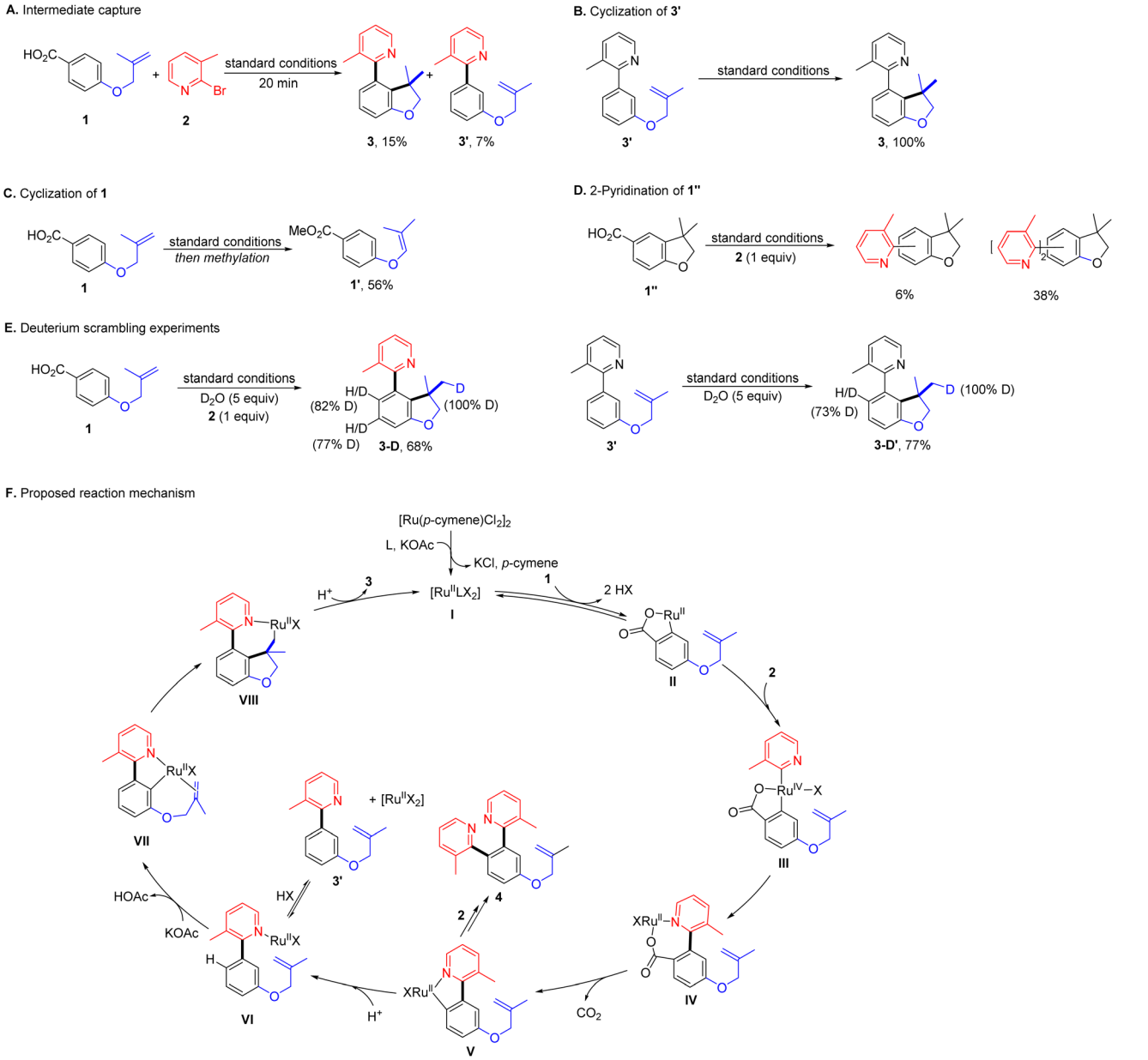
Scheme 2 Scaleup reaction and derivatization for synthesizing polysubstituted arenes ([a] styrene (1.5 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), DMF, 100 °C, 24 h; [b] ethynylbenzene (1.5 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (15 mol%), AcOH (0.1 M), 100 °C, 24 h; [c] (c) Ph_2IPF_6 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), AcOH, 100 °C, 24 h; [d] 4-Me-PhNCO (1.8 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), 2-NO_2-$PhCO_2H$ (30 mol%), DCE, 50 °C, 24 h; [e] PhCHO (1.5 equiv.), *t*-BuOOH (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), MeCN, r.t., 24 h; [f] NCTS (2.0 equiv.), $[Cp^*RhCl_2]_2$ (1 mol%), $AgSbF_6$ (10 mol%), PhMe, 120 °C, 24 h.).

the nitrogen atom participates in the reaction, and both chloride and bromide substituents at other positions remained intact (**45–47**, **54–56**, **58–62**, **65** and **66**), providing opportunities for orthogonal manipulations. Multi-substituted 2-bromopyridines also worked well (**57–66**, 50–95%). Other heterocyclic substrates, 2-bromo-benzothiazole and 1-bromo-isoquinoline, could also undergo the reaction, albeit with lower efficiency (**67** and **68**). Apart from azaaryl bromides, the corresponding chloride and iodide are also applicable in this transformation though leading to lower yields of products (**7** and **43**).

To demonstrate the practicability, a scaleup reaction with **1** and 2-bormopyridne was conducted and produced **43** in 74% yield. In addition, the synthetic applicability of this reaction was demonstrated by derivatization of **43** by a series of 2-pyridyl-directed *ortho*-C–H bond functionalization reactions (Scheme 2). Through a Rh-catalysed hydroarylation of terminal alkynes, **69** was produced from reaction with phenylacetylene in 91%.[75] **69** could also be obtained from rhodium-catalysed *ortho*-vinylation with styrene.[76] *ortho*-Arylation of **43** was achieved by palladium catalysis with diphenyliodonium salt giving **70** in 78%.[77] Additionally, *via* a ruthenium-catalysed C–H amidation with aryl isocyanate, **71** was obtained in 78% yield.[78] The palladium-catalysed decarboxylative C–H benzoylation with benzoylformic acid introduced an *ortho*-benzoyl group forming **72** in 56%.[79] At last, *ortho*-C–H cyanation was accomplished by a rhodium catalysis with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) affording **73** in 84%.

While the mechanistic hypothesis guided our thinking in the design of this system, further mechanistic investigations will be necessary to evaluate its validity (Scheme 3). To identify the intermediate, the reaction with **1** and **2** under optimal conditions was halted at the early stage. Aside from **3** (15%), **3′** was detected in 7% yield without hydroarylation of the tethered alkene (Scheme 3A). A significant amount of this type of byproduct **41′** was also observed when cyclization was hindered (Table 2). Then **3′** was subjected to the standard conditions, giving **3** quantitatively (Scheme 3B). These results suggest that **3′** is likely to be the intermediate connecting successive C–H bond functionalization, while, under identical conditions, **1** failed intramolecular hydroarylation, but gave an alkene isomerization product **1′** (56%, Scheme 3C). Moreover, the standard reaction with **1″** and **2** produced a mixture of isomers of mono- and di-azaarylation products (Scheme 3D). These results suggest the unsymmetric dual C–H bond functionalization is a tandem process *via* a directing group relay. When the reaction of **1** and **2** was carried out in the presence of D_2O, the *meta*- and *ortho*-C–H bonds to the 2-pyridyl substituent in **3-D** were found to be highly deuterated (Scheme 3E). When **3′** was subjected to the same reaction conditions, **3-D′** was obtained with 73% of deuterium decoration of the *ortho*-C–H bond These results illustrate reversible C–H bond activation directed by the carboxyl and 2-pyridyl groups. Moreover, the absence of 2-pyridyl arenecarboxylic acids in all reactions implies a swift decarboxylation, as expected from the design of the formation of the 2-pyridyl coordinated cyclic ruthenium carboxylate intermediate.

Based on the results from mechanistic studies, we proposed a plausible reaction mechanism for this ruthenium-catalysed decarboxylative unsymmetric dual *ortho*-/*meta*-C–H bond functionalization as shown in Scheme 3F. At the beginning, the ruthenium catalyst precursor, the ligand and the base would generate an active catalytic complex, $[Ru^{II}LX_2]$. In the catalytic cycle, the dinitrogen ligand would be omitted and the anion would be labelled as X to get a clear view of reaction. The arenecarboxylic acid **1** would exchange with X to coordinate to the ruthenium, followed by a reversible *ortho*-C–H bond activation generating a five-membered ruthenium carboxylate **II**. Then **II** undergoes oxidative addition with **2** presumably facilitated by the coordinating nitrogen atom, and affords the high valent ruthenium complex **III**. Subsequent reductive elimination produces a seven-membered ruthenium carboxylate **IV**, which possesses the favourable structure for decarboxylation.[61,80] In the next step, a five-membered ruthenacycle **V** is generated after elimination of CO_2. There are two possible reaction paths of **V**, one would lead to the bis-2-pyridination product by reacting with **2** producing **4**. The other would deliver intermediate **3′** *via* protonation completing the decarboxylative *ortho*-2-azaarylation. Next, the 2-pyridyl group serves as the directing group and assists the catalyst to activate the *meta*-C–H bond reversibly. The resulting ruthenacycle-**VI** undergoes migratory insertion with the tethered alkene furnishing a seven-membered alkyl ruthenium complex **VII**. Finally, protonation of **VII** yields the desired product **3** and completes the catalytic cycle.



Scheme 3 Mechanistic investigations and proposed reaction mechanism.

Conclusions

In summary, we have developed a ruthenium-catalysed decarboxylative unsymmetric dual *ortho*-/*meta*-C–H functionalization of arenecarboxylic acids *via* a traceless directing group relay strategy. This transformation includes the first example of transition metal-catalysed decarboxylative *ortho*-C–H bond azaarylation, which is ascribed to the formation of a seven-membered ruthenium carboxylate assisted by the 2-pyridyl group. This protocol provides a streamlined path to a series of 4-azaaryl-benzo-fused five-membered heterocycles with a C3 quaternary center and features high regio- and chemo-selectivity, broad substrate scope and excellent functional group tolerance. We expect this protocol would inspire more efforts to exploit the deciduous carboxyl group to develop methods for the synthesis of polysubstituted arenes.

Data availability

All experimental procedures and characterization for this study, can be found in the ESI.†

Author contributions

Xiankai Li and Xiaofei Wang conducted and analyzed the synthetic experiments. Xiankai Li and Jing Zhang planned the project. Jing Zhang designed and directed the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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