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A facile method for Rh-catalyzed decarbonylative *ortho*-C–H alkylation of (hetero)arenes with alkyl carboxylic acids†

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A facile and effective method for Rh-catalyzed direct *ortho*-alkylation of C–H bonds in (hetero)arenes with commercially available carboxylic acids has been developed. This strategy was initiated by *in situ* conversion of carboxylic acids to anhydrides which, without isolation, underwent Rh-catalyzed direct decarbonylative cross-coupling of aryl carboxamides containing 8-aminoquinoline. The reaction proceeds with high regioselectivity and exhibits a broad substrate scope as well as functional group tolerance.

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Alkylation of (hetero)arenes[1] is one of the most fundamental reactions in synthetic chemistry, leading to ubiquitous alkylated scaffolds and revealing itself to be of great significance with widespread application in fine chemicals, pharmaceuticals, agrochemicals and so forth. One of the classical methods for the C–H alkylation of arenes is the Friedel–Crafts reaction,[2] one of the oldest organic transformations and still a commonly used protocol nowadays which, however, suffers from severe limitations such as poor reactivity of electron-poor aromatic substrates, undesired cationic rearrangement, and low chemo- and/or regioselectivity. Recently, oxidative decarboxylative coupling of aliphatic carboxylic acids[3,4] has provided complementary access to Friedel–Crafts reactions with opposite reactivity and selectivity. However, in this decarboxylative coupling, the substrate scopes of carboxylic acids were mainly restricted to arylacetic acids, secondary and tertiary alkyl acids, or alkyl acids with a stabilized atom (such as N, O, S) at the α-position of the carboxyl group. Additionally, regioselectivity in simple (hetero)arenes remains challenging.

These well-established limitations have encouraged the development of alternative metal-catalyzed directed alkylation of (hetero)arenes C–H bonds,[5] one of the most accurate and effective tools, therein, highly regioselectivity mostly relies on the use of a directing group by allowing the metal center proximally close to the target C–H bonds in the starting (hetero) arenes. To date, this directed C–H alkylation of (hetero)arenes undergoes with diverse alkylating agents within which alkenes[5j,l,p] and alkyl halides[5c] are mostly used reagents. To avoid the multiple steps or limitations in synthesis of these agents from available starting materials, as well as to reduce the discharge of poisonous by-products, there is a need to explore novel and convenient alkyl donors beyond these commonly used reagents. Carboxylic anhydrides[6] thereof have attracted considerable attention not only owing to their low cost and nontoxicity, but also the easy obtainment from commercially available carboxylic acids. Driven by their electron deficiency, the activated anhydrides may serve as potent alkylating sources in the metal-catalyzed direct decarbonylative coupling reaction of (hetero) arenes which is triggered by metal-catalyzed oxidative addition of a C(acyl)–O bond. Notably, this direct decarbonylative alkylation no longer confined to the use of *ortho*-substituted aromatic carboxylic acids which are required in conventional decarboxylative cross-coupling reactions.[7] Following their first example of the decarbonylative methylation of arenes with benzoic acids *via* $Rh^{I}/(tBuCO)_2O$ catalytic system,[6c] Z.-J. Shi and co-workers further extended this concept to afford alkylated products, enabling to introduce methyl, ethyl, benzyl and phenethyl groups onto cyclic enamines,[6d] and later achieved methylation of indoles.[6e] In their research, the presence of a monodentate N-directing groups and the *in situ* generation of mixed anhydrides were crucial. Using a similar protocol, Z. Shi and co-workers developed Rh-catalyzed methylation of indoles with Ac_2O in the presence of a P^{III}-directing groups.[6g] P. Walsh and co-workers demonstrated an analogous access to Rh-catalyzed C6-alkylated 2-pyridones with the assist of pyridine as the directing group, installing long chains and cyclic rings onto N-heteroarenes (Scheme 1a).[6h] Despite these significant progresses in recent years, there is still much room for improvement of this decarbonylative alkylation, particularly in terms of substrate scopes and functional group tolerance for both the starting (hetero)arenes and alkyl sources.

Encouraged by Daugulis's pioneering work and others' previous studies,[5] herein we select 8-aminoquinoline (AQ), an excellent *N*,*N*-bidentate directing group in catalytic

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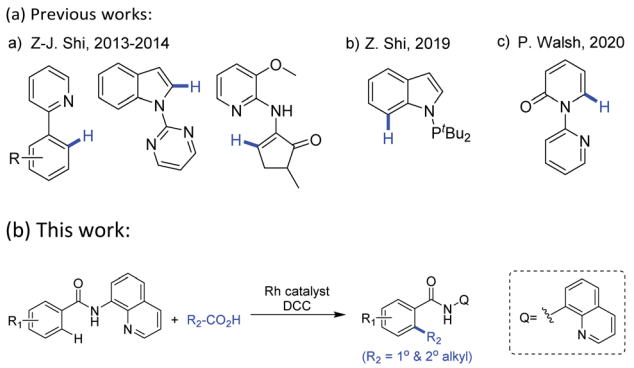


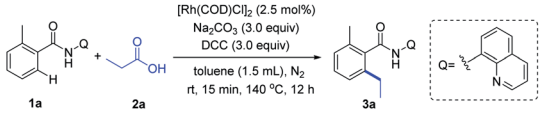
Scheme 1 Transition-metal-catalyzed chelation-assisted decarbonylative alkylation reactions of (hetero)arenes with alkyl carboxylic acids or anhydrides.

functionalization of C–H bonds,[8,9] as the installed moiety on the starting (hetero)arenes, and expect to develop a general method for Rh-catalyzed decarbonylative C–H alkylation of (hetero)arenes with *in situ* generated alkyl carboxylic acid anhydrides (Scheme 1b).

Based on our knowledge, we initially chose *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the additive for the stoichiometric conversion of alkyl carboxylic acids into the corresponding anhydrides,[10] and began our studies with a thorough optimization for this Rh-catalyzed C–H alkylation of AQ-substituted benzamide **1a** with propionic acid **2a** (Table 1). To our delight, the desired *ortho*-alkylated product **3a** was delivered in the presence of 2.5 mol% $[Rh(COD)Cl_2]$ as the catalyst, DCC (3 equiv.) and Na_2CO_3 (3 equiv.) under N_2 in toluene (1.5 ml) at 140 °C for 12 h (entry 1). The control experiments revealed that $[Rh(COD)Cl_2]$, DCC and Na_2CO_3 all were essential to this reaction (entries 2–4). Compared with other frequently employed Rh^I catalysts, $[Rh(COD)Cl_2]$ exhibited the most satisfied efficiency (see Table S1 in the ESI†). Na_2CO_3 was identified as potent base when compared with $NaHCO_3$ and K_2CO_3 (entries 5 and 6). Using *N*,*N*′-diisopropylcarbodiimide (DIC) as an additive in the activation of carboxylic acid led to a drop in yield (entry 7). Lowing the reaction temperature hindered the reaction, probably because the high temperature was required for the decarbonylation step (entries 8 and 9). The use of polar solvent such as 1,4-dioxane gave a decreased yield (entry 10). Interestingly, this reaction still occurred in air, albeit with a lower yield, indicating its promising application in the practical synthesis (entry 11).

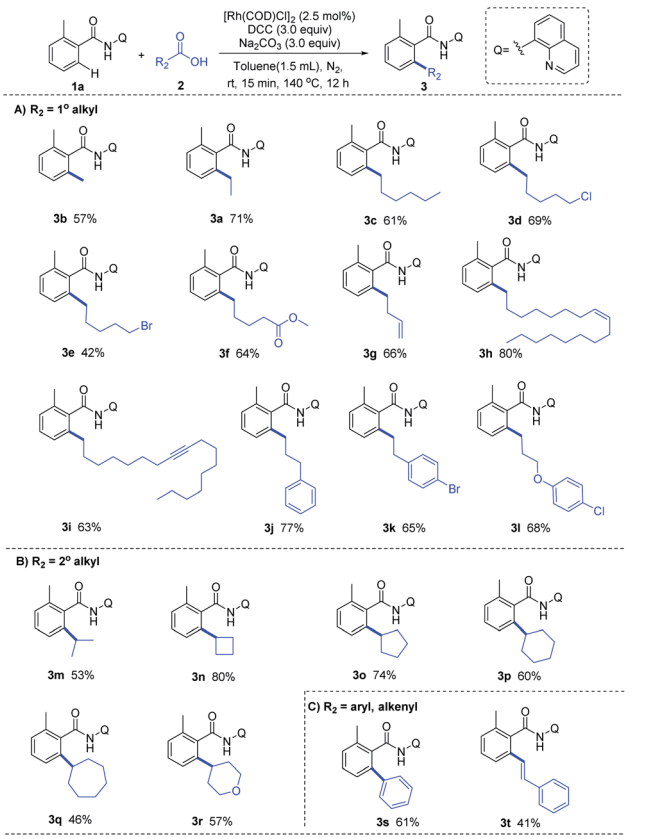
With the optimized reaction condition in hand, we next examined the generality of this method by exploring the substrate scopes of alkyl carboxylic acids and 8-AQ-containing benzamides (Scheme 2). Gratifyingly, this protocol afforded expected alkylation and successfully introduced a vast set of primary and secondary alkyl chains on the *ortho*-position of the benzamide motif (**3a–3r**). Various functional groups on the scaffolds of linear aliphatic carboxylic acids, including chloro (**3d**), bromo (**3e**), ester (**3f**), alkenyl (**3g**, **3h**) and alkyne (**3i**), were all compatible. It's worth noting that terminal C–Cl, C–Br and C=C bonds in alkyl carboxylic acids hydrides remained intact (**3d**, **3e**, **3g**), indicating that hydrides might be applied as complementary alkylating agents to the commonly used alkyl halides or alkenes at present. Though metal-catalyzed cross-

Table 1 Selected results from optimization of reaction conditions[a]



Entry	Variation from the standard conditions	Yield[b] (%)
1	None	75 (71[c])
2	Without $[Rh(COD)Cl]_2$	NA
3	Without DCC	NA
4	Without Na_2CO_3	NA
5	$NaHCO_3$ instead of Na_2CO_3	60
6	K_2CO_3 instead of Na_2CO_3	34
7	DIC instead of DCC	57[c]
8	130 °C instead of 140 °C	52
9	120 °C instead of 140 °C	31
10	1,4-Dioxane as the solvent	54
11	Air instead of N_2	59

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol). [b] GC yield of **3a**. [c] Yield of isolated **3a**. DCC (0.6 mmol, *N*,*N*′-dicyclohexylcarbodiimide) DIC (0.6 mmol, *N*,*N*′-diisopropylcarbodiimide).



Scheme 2 Substrate scope of carboxylic acids.

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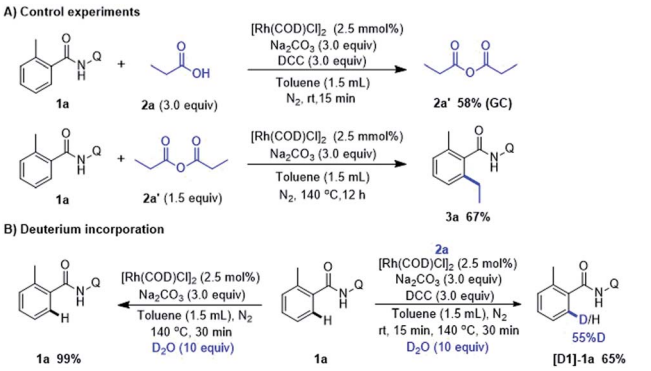
coupling with alkyl carboxylic acid derivatives bearing β-hydrogens are rather challenging,[11] to our delight, no C–H alkenylation occurred in this Rh-catalyzed decarbonylative coupling of **1a** with **3g**, **3j**, **3k** and **3l** which are inclined to form stable conjugated side products *via* β-hydride elimination process, ruling out the possible β-H elimination pathway in this catalytic cycle. The use of 8-AQ might be the key in this transformation which occupies the site of coordinative unsaturation on the metal *cis* to the alkyl group by flexible ligand association/dissociation and thus suppresses the possible β-H elimination.[12] Besides, secondary alkyl carboxylic acids, including branched acids (**3m**) and cyclic acids with different ring size (**3n–3r**), delivered the desired alkylation products in moderate to good yield. Interestingly, this protocol was not limited to C–H alkylation of aryl benzamides, direct C–H arylation (**3s**) and alkenylation (**3t**) were also achieved under the standard conditions, demonstrating its promising utility in synthetic chemistry. Moreover, as shown in Scheme 3, this Rh-catalyzed method enabled *ortho*-C–H ethylation of diversely 8-AQ decorated amides containing electron-donating and electron-withdrawing substitutes on the arene rings (**4b–4f**), and tolerated C–Cl and C–Br bonds (**4g**, **4h**). Polycyclic arene (**4i**) and heteroaryl arenes (**4j–4l**) also proved to be compatible with satisfactory yield. Thus, this protocol exhibits its broad substrate scope and implies its potential application.

To gain insight of this Rh-catalyzed decarbonylative coupling reaction, a series of experiments was carried out (Scheme 4). In order to observe and verify the formation anhydride, the control experiment was conducted with amide (**1a**) and propionic acid (**2a**) under standard condition. The reaction was quenched after 15 min pre-stirring at room temperature and 58% yield of propionic anhydride (**2a′**) was detected. Then we performed experiment with **1a** and possible intermediates **2a′** to confirm whether the alkylation product **3a** could be formed. Notwithstanding a slightly drop in yield when compared with the output under the standard conditions (67% in Scheme 4A *vs.* 71% in Scheme 2, **3a**). It consists with the hypothesis that *in situ*

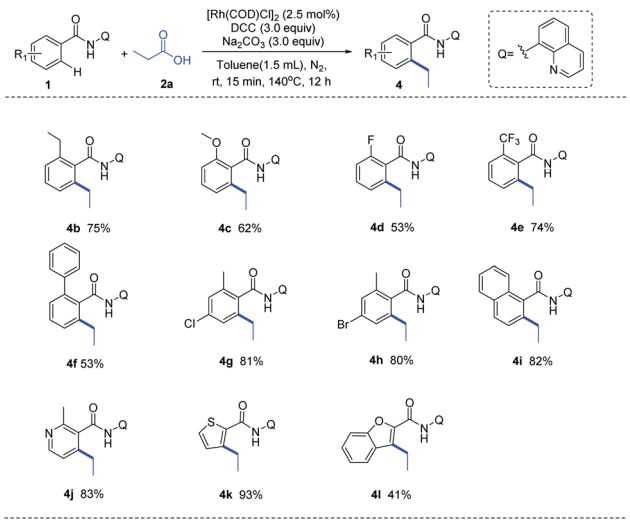


Scheme 4 Mechanistic studies.

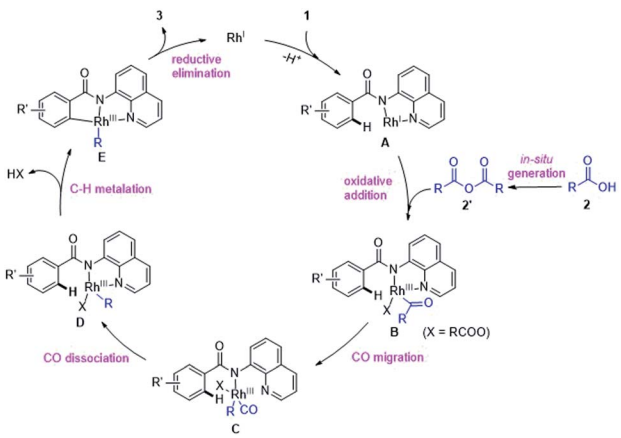
conversion of carboxylic acid into anhydride comprises the basic steps of this Rh-catalyzed alkylation reaction. When **1a** was reacted with D_2O for 30 min under otherwise standard conditions (Scheme 4B), we observed a significant difference of H/D exchange with or without **2a**, which indicating the fact that Rh^I species did not react with *ortho*-C–H bond of **1a** *via* catalyzed C–H activation even with the assistance of bidentate directing group. Instead, *ortho*-C–H bond of **1a** was activated by Rh^{III} complex which was formed by Rh^I oxidatively inserting into C(acyl)–O bond in anhydride.

Thus, we propose a plausible catalytic pathway different from the previous researches,[6c–e,g] which likely involves: (i) *in situ* conversion of carboxylic acid **2** into anhydride **2′**, (ii) oxidative addition of C(acyl)–O bond in **2′** by Rh^I species **A**, (iii) decarbonylation, (iv) chelation-assisted C–H cyclometalation and (v) C–C bond-forming reductive elimination to release the product **3** and regenerates Rh^I to propagate the reaction cycle (Scheme 5).

In conclusion, we have developed a facile method for Rh-catalyzed direct *ortho*-C–H alkylation of (hetero)arenes with readily available carboxylic acids, which involving an initial step of *in situ* conversion of carboxylic acids to the corresponding anhydrates and the subsequent Rh-catalyzed decarbonylative cross-coupling of the resultant anhydrates with (hetero)arenes.



Scheme 3 Substrate scope of aromatic amides.



Scheme 5 Plausible mechanism.

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This reaction proceeds in highly regioselectivity by identifying 8-aminoquinoline as the efficient bidentate directing group embedded on the starting (hetero)arenes. Enabling a diversity of primary and secondary carboxylic acids as well as various benzamide derivatives as the cross-coupling substrates, our strategy reveals its promising utility in synthetic chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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