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.

Alkylation of (hetero)arenes 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, 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 chemoselectivity. Recently, oxidative decarbonylative coupling of aliphatic carboxylic acids has provided complementary access to Friedel–Crafts reactions with opposite reactivity and selectivity. However, in this decarbonylative 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, 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 and alkyl halides 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 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 decarbonylative cross-coupling reactions. Following their first example of the decarbonylative methylation of arenes with benzoic acids via RhI/(tBuCO)2O catalytic system, 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 and later achieved methylation of indoles. 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 Ac2O in the presence of a P3-directing groups. 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). 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, herein we select 8-aminoquinoline (AQ), an excellent N,N-bidentate directing group in catalytic
functionalization of C–H bonds, 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,N0-dicyclohexylcarbodiimide (DCC) as the additive for the stoichiometric conversion of alkyl carboxylic acids into the corresponding anhydrides, 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)Cl2] as the catalyst, DCC (3 equiv.) and Na2CO3 (3 equiv.) under N2 in toluene (1.5 ml) at 140 °C for 12 h (entry 1). The control experiments revealed that [Rh(COD)Cl2], DCC and Na2CO3 all were essential to this reaction (entries 2–4). Compared with other frequently employed Rh1 catalysts, [Rh(COD)Cl2] exhibited the most satisfied efficiency (see Table S1 in the ESI†). Na2CO3 was identified as potent base when compared with NaHCO3 and K2CO3 (entries 5 and 6). Using N,N0-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-

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**Table 1** Selected results from optimization of reaction conditions

| Entry | Variation from the standard conditions | Yield (%) |
|-------|---------------------------------------|-----------|
| 1     | None                                  | 75 (71°)  |
| 2     | Without [Rh(COD)Cl2]                  | NA        |
| 3     | Without DCC                           | NA        |
| 4     | Without Na2CO3                         | NA        |
| 5     | NaHCO3 instead of Na2CO3              | 60        |
| 6     | K2CO3 instead of Na2CO3               | 34        |
| 7     | DIC instead of DCC                    | 57°       |
| 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 N2                     | 59        |

° Reaction conditions: 1a (0.2 mmol), 2a (0.6 mmol). 1 GC yield of 3a. 2 Yield of isolated 3a. DCC (0.6 mmol, N,N0-dicyclohexylcarbodiimide) DIC (0.6 mmol, N,N0-diisopropylcarbodiimide).

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**Scheme 2** Substrate scope of carboxylic acids.
coupling with alkyl carboxylic acid derivatives bearing β-hydrogens are rather challenging,\textsuperscript{13} to our delight, no C–H alkenylation occurred in this Rh-catalyzed decarboxylative 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.\textsuperscript{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 substituents on the arene rings (4b–4l), 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 decarboxylative 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 conversion of carboxylic acid into anhydride comprises the basic steps of this Rh-catalyzed alkylation reaction. When 1a was reacted with D₂O 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\textsuperscript{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\textsuperscript{II} complex which was formed by Rh\textsuperscript{II} oxidatively inserting into C(acyl)-O bond in anhydride.

Thus, we propose a plausible catalytic pathway different from the previous researches,\textsuperscript{5b–e–f} 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\textsuperscript{I} species A, (iii) decarboxylation, (iv) chelation-assisted C–H cyclometalation and (v) C–C bond-forming reductive elimination to release the product 3 and regenerates Rh\textsuperscript{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 anhydrides and the subsequent Rh-catalyzed decarboxylative cross-coupling of the resultant anhydrides with (hetero)arenes.

![Scheme 3](image-url)  
**Scheme 3** Substrate scope of aromatic amides.

![Scheme 4](image-url)  
**Scheme 4** Mechanistic studies.

![Scheme 5](image-url)  
**Scheme 5** Plausible mechanism.
This reaction proceeds in highly regioselectivity by identifying 8-aminooquinoline 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.

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Notes and references
1 For selective reviews on C–H alkylation, see: (a) W. R. Gutekunst and P. S. Baran, Chem. Soc. Rev., 2011, 40, 1976; (b) J. Yamaguchi, A. D. Yamaguchi and K. Itami, Angew. Chem., Int. Ed., 2012, 51, 8960; (c) E. J. E. Caro-Díaz, M. Urbano, D. J. Buzard and R. M. Jones, Bioorg. Med. Chem. Lett., 2016, 26, 5378; (d) G. Evano and C. Theunissen, Angew. Chem., Int. Ed., 2019, 58, 7558.
2 (a) R. M. Roberts and A. A. Khalaf, Friedel-Crafts Alkylation Chemistry: A Century of Discovery, Marcel Dekker, New York, 1984; (b) M. Bandini, A. Melloni and A. Umani-Ronchi, Angew. Chem., Int. Ed., 2004, 43, 550; (c) T. B. Poulsen and K. A. Jorgensen, Chem. Rev., 2008, 108, 2903.
3 For selective reviews on oxidative decarboxylative cross-coupling of alkyl carboxylic acids, see: (a) J. Xuan, Z. G. Zhang and W. J. Xiao, Angew. Chem., Int. Ed., 2015, 54, 15632; (b) M. O. Konev and E. R. Jarvo, Angew. Chem., Int. Ed., 2016, 55, 11340; (c) P. Liu, G. Zhang and P. Sun, Org. Biomol. Chem., 2016, 14, 10763; (d) H. Bao, Y. Li, L. Ge and M. Muhammad, Synthesis, 2017, 49, 5263; (e) T. Patra and D. Maiti, Chem., 2017, 23, 7382.
4 For the selective examples of oxidative decarboxylative cross-coupling of alkyl carboxylic acids, see: (a) F. Yin, Z. Wang, Z. Li and C. Li, J. Am. Chem. Soc., 2012, 134, 10401; (b) M. Rueda-Becerril, O. Mahe, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis and G. F. Paquin, J. Am. Chem. Soc., 2014, 136, 2637; (c) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. MacMillan, Science, 2014, 345, 437; (d) Q. Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L. Q. Lu and W. J. Xiao, Angew. Chem., Int. Ed., 2015, 54, 11196; (e) Z. J. Liu, X. Lu, G. Wang, L. Li, W. T. Jiang, Y. D. Wang, B. Xiao and Y. Fu, J. Am. Chem. Soc., 2016, 138, 9714; (f) C. P. Johnston, R. T. Smith, S. Allmendinger and D. W. MacMillan, Nature, 2016, 536, 322.
5 The selective reviews on metal-catalyzed directed alkylation of (hetero)arenes, see: (a) D. A. Colby, R. G. Bergman and J. A. Ellman, Chem. Rev., 2010, 110, 624; (b) L. Ackermann, Chem. Commun., 2010, 46, 4866; (c) G. Rouquet and N. Chatani, Angew. Chem., Int. Ed., 2013, 52, 11726; (d) F. Zhang and D. R. Spring, Chem. Soc. Rev., 2014, 43, 6906; (e) M. Zhang, Y. F. Zhang, X. M. Jie, H. Q. Zhao, G. Li and W. P. Su, Org. Chem. Front., 2014, 1, 843; (f) O. Daugulis, J. Roane and L. D. Tran, Acc. Chem. Res., 2015, 48, 1053; (g) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, Chem. Rev., 2017, 117, 9333; (h) G. Zhang, F. Jia and L. J. Goossen, Chem., 2018, 24, 4537; (i) N. Chatani, Bull. Chem. Soc. Jpn., 2018, 91, 211; (j) C. Sambiagiò, D. Schonbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnurch, Chem. Soc. Rev., 2018, 47, 6603; (k) T. Bhattacharya, S. Pimparkar and D. Maiti, RSC Adv., 2018, 8, 19456; (l) P. Gandeepan and L. Ackermann, Chem., 2018, 4, 199; (m) G. Evan and C. Theunissen, Angew. Chem., Int. Ed., 2019, 58, 7202; (n) S. Rej, Y. Ano and N. Chatani, Chem. Rev., 2020, 120, 1788; (o) S. B. Ankade, A. B. Shabade, V. Soni and B. Punji, ACS Catal., 2021, 11, 3268; (p) T. Yamaguchi, S. Natsui, K. Shibata, K. Yamazaki, S. Rej, Y. Ano and N. Chatani, Chem.–Eur. J., 2019, 25, 6915.
6 The selective examples of decarboxylative cross-coupling with anhydrides or carboxylic acids, see: (a) E. M. O’Brien, E. A. Bercot and T. Rovis, J. Am. Chem. Soc., 2003, 125, 10498; (b) W. Jin, Z. Yu, W. He, W. Ye and W. J. Xiao, Org. Lett., 2009, 11, 1317; (c) F. Pan, Z. Q. Lei, H. Wang, H. Li, J. Sun and Z. J. Shi, Angew. Chem., Int. Ed., 2013, 52, 2063; (d) Z.-Z. Lei, J.-H. Ye, J. Sun and Z.-J. Shi, Org. Chem. Front., 2014, 1, 634; (e) L. Zhang, X. Xue, C. Xu, Y. Pan, G. Zhang, L. Xu, H. Li and Z. Shi, ChemCatChem, 2014, 6, 3069; (f) C. Liu, C. L. Ji, X. Hong and M. Szostak, Angew. Chem., Int. Ed., 2018, 57, 16721; (g) X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan and Z. Shi, Angew. Chem., Int. Ed., 2019, 58, 1504; (h) H. Zhao, X. Xu, H. Yu, B. Li, X. Xu, H. Li, L. Xu, Q. Fan and P. J. Walsh, Org. Lett., 2020, 22, 4228.
7 The studies on ortho-substituent effect on metal-catalyzed decarboxylation, see: (a) J. Corrêa, C. Sanchez, D. Banawa and I. Larrosa, Chem. Commun., 2009, 46, 7176; (b) L. Xue, W. Su and Z. Lin, Dalton Trans., 2011, 40, 11926; (c) R. Grainger, J. Corrêa, D. C. Blakemore, I. Larrosa and J. M. Campanera, Chem.–Eur. J., 2014, 20, 16680.
8 The selective examples of 8-aminooquinoline-directed C–H functionalization, see: (a) V. G. Zaitsev, D. Shashabov and O. Daugulis, J. Am. Chem. Soc., 2005, 127, 13154; (b) Y. Aihara and N. Chatani, J. Am. Chem. Soc., 2013, 135, 5308; (c) S. Asako, L. Ilies and E. Nakamura, J. Am. Chem. Soc., 2013, 135, 17755; (d) W. Song, S. Lackner and L. Ackermann, Angew. Chem., Int. Ed., 2014, 53, 2477; (e) E. R. Fruchey, B. M. Monks and S. P. Cook, J. Am. Chem. Soc., 2014, 136, 13130; (f) L. Ilies, T. Matsubara, S. Ichikawa, S. Asako and E. Nakamura, J. Am. Chem. Soc., 2014, 136, 13126; (g) B. M. Monks, E. R. Fruchey and S. P. Cook, Angew. Chem., Int. Ed., 2014, 53, 11065; (h) S. Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, J. Am.
9 The selective examples of directed C–H functionalization of (hetero)arenes, see: (a) Y. H. Cheng, S. J. Yu, Y. H. He, G. H. An, G. M. Li and Z. Y. Yang, Chem. Sci., 2021, 12, 3216; (b) C. Tian, Q. Wang, X. Wang, G. H. An and G. M. Li, J. Org. Chem., 2019, 84, 14241; (c) K. Korvorapun, N. Kaplaneris, T. Rogge, S. Warratz, A. C. Stückl and L. Ackermann, ACS Catal., 2018, 8, 886.

10 D. G. Stark, L. C. Morrill, D. B. Cordes, A. M. Slawin, T. J. O’Riordan and A. D. Smith, Chem.–Asian J., 2016, 11, 395.

11 The selective examples of conversion of alkyl acid derivates into alkenes via β-H elimination, see: (a) L. J. Goossen and N. Rodriguez, Chem. Commun., 2004, 724; (b) Y. Liu, S. C. Virgil, R. H. Grubbs and B. M. Stoltz, Angew. Chem., Int. Ed., 2015, 54, 11800; (c) A. John, M. O. Miranda, K. Ding, B. Dereli, M. A. Ortuño, A. M. LaPointe, G. W. Coates, C. J. Cramer and W. B. Tolman, Organometallics, 2016, 35, 2391; (d) J. Hu, M. Wang, X. Pu and Z. Shi, Nat. Commun., 2017, 8, 14993; (e) X. Zhang, F. Jordan and M. Szostak, Org. Chem. Front., 2018, 5, 2515.

12 The studies on ligands suppressing β-H elimination for cross-coupling of alkyl nucleophiles, see: (a) J. S. Zhou and G. C. Fu, J. Am. Chem. Soc., 2003, 125, 14726; (b) J. Breitenfeld, O. Vechorkin, C. m. Corminboeuf, R. Scopelliti and X. Hu, Organometallics, 2010, 29, 3686.