JOC The Journal of Organic Chemistry

Note

Rhodium(III)-catalyzed decarboxylative aminomethylation of glycine derivatives with indoles via C-H activation

Ruixing Liu, Yin Wei, and Min Shi

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03365 • Publication Date (Web): 06 Jan 2020

Just Accepted

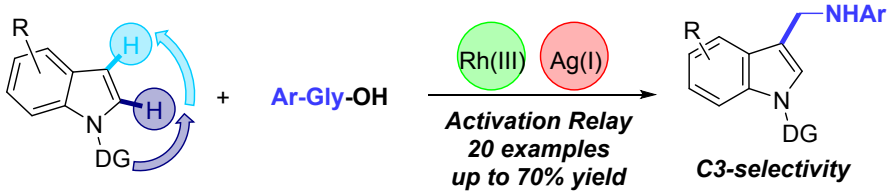
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Rhodium(III)-catalyzed decarboxylative aminomethylation of glycine derivatives with indoles via C−H activation

Ruixing Liu,[a] Yin Wei[a,*] and Min Shi[a,b]

[a]State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Science, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032 China. Email: weiyin@sioc.ac.cn.

[b]Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen, Guangdong 518000, China.



Abstract: A rhodium(III)-catalyzed decarboxylative aminomethylation of glycine derivatives with indoles bearing a pyrimidine directing group has been developed via C−H activation, exclusively affording the corresponding aminomethylated products with *C3* selectivity. In this synthetic protocol, easily available and resourceful arylglycines were utilized as aminomethyl functional moieties.

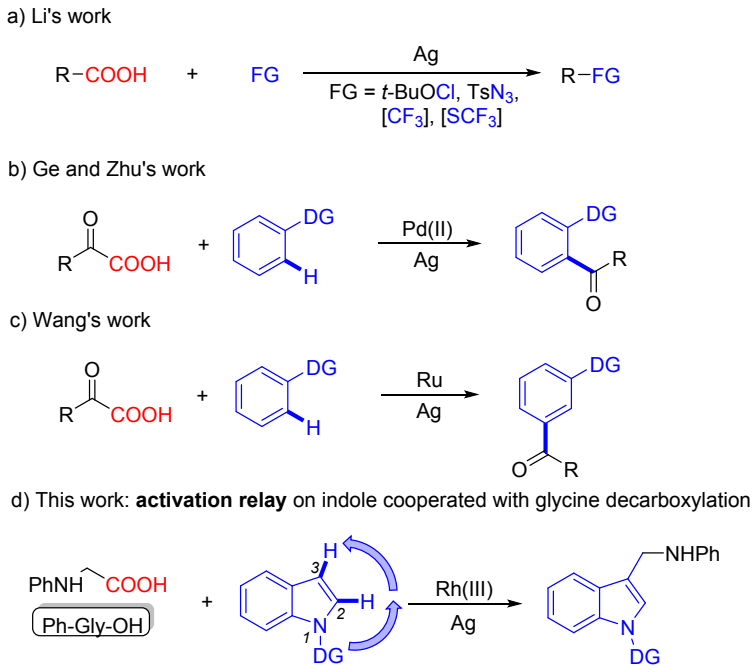
In recent years, decarboxylative cross-coupling has been established as a modern strategy for the formation of C–C and C–heteroatom bond.[1] Inexpensive and readily available carboxylic acids are used as an alternative to expensive organometallic reagents and halides. On the other hand, due to the worldwide abundance of biomass that incorporates carboxylate functionality (e.g., amino acids, α-hydroxy acids, fatty acids etc), there is a strong impetus to invent or discover chemical transformations that target carboxylic acids as chemoselective leaving groups for new and valuable C−C bond forming reactions.

Decarboxylative C–H functionalization has emerged as a fascinating field in organic synthesis. In this realm, silver salt played a pivotal role in the decarboxylative process since Hunsdicker reaction has been discovered in 1942.[2] The seminal studies of Goossen have demonstrated decarboxylative couplings as a powerful strategy to form C–C or C–heteroatom bonds starting from carboxylic acids.[3] In recent years, Li's group developed a series of silver-catalyzed decarboxylative functionalization reactions (Scheme 1a).[4] On the basis of their transformations, various functional groups such as halide, azide, CF_3 and SCF_3, can be introduced into the molecules accompanied with decarboxylative process.

C-H bond activation of arenes by transition-metal catalyzed reaction has been extensively developed as an important synthetic method to provide complex molecular structures.[5] Currently, as a highly efficient method to introduce functional groups, C-H bond functionalizations have

significant advantages to construct polycyclic compounds. However, decarboxylation cooperated in C-H activation paradigm still needs a further exploration. Recently, the groups of Ge and Zhu have independently displayed the successful exploration of pyruvic acid as the cross-coupling partners in transition metal (TM)-catalyzed C−H functionalization (Scheme 1b).[6] Wang and co-workers also reported an example of ruthenium-catalyzed decarboxylative *meta*-selective C−H acylation with pyruvic acid (Scheme 1c).[7] Although *meta*-selectivity makes this realm rejuvenating again, the pyruvic acid derivatives are still an obvious limitation of this reaction.

Scheme 1. Examples of carboxylic acid as coupling partners in the decarboxylative functionalization and C-H activation as well as this work.

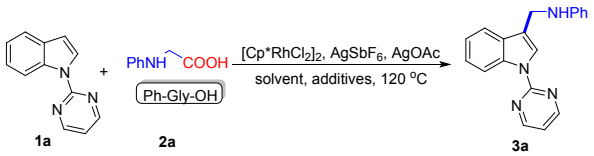


Previously, we reported an example of C-H aminomethylation with triphenylhexahydrotriazine (THT) under photocatalysis and rhodium catalysis.[8] In this finding, we revealed a new activation relay mode in indole substrate bearing a pyrimidine directing group, in which the reactivity of indole's C3 position was enhanced due to the rhodium coordination at the C2 position. Distinct from C3-cyanation,[9] C3-formylation,[10] C3-alkynylation[11] and C3-alkenylation[12] of indole with its inherent C3 nucleophilicity, this protocol requires a rhodium catalyst to activate its C2 position. We wonder whether there is a new coupling pattern between decarboxylative species and cyclometallated intermediate derived from C-H activation. In this report, we present the coupling of *N*-pyrimidylindole derivatives with glycine derivatives via a new Rh(III)-catalyzed C-H activation process to exclusively afford the aminomethylated products with *C3* selectivity through a decarboxylative process in the presence of silver salt (Scheme 1d).

The reaction was carried out with *N*-pyrimidylindole **1a** and *N*-phenylglycine **2a** by using [Cp*Rh^{III}] complex (4 mol%) and $AgSbF_6$ (20 mol%) as the catalyst combination, AgOAc as an oxidant (2.0 equiv), acetic acid (2.0 equiv) as the additive in DMF at 120 °C, providing the desired aminomethylation product **3a** in 70% yield (Table 1, entry 1). Noteworthy, the C2 product was not detected at all. The use of pivalic acid, benzoic acid or adamantanecarboxylic acid as additive

afforded **3a** in lower yield and only 6% of **3a** was formed in the absence of additive, suggesting that the addition of acetic acid was crucial to this reaction (Table 1, entries 2-5). Then, we screened several solvents in this transformation and found that the yield of **3a** decreased in acetonitrile and dichloroethane (Table 1, entries 6 and 7). In addition, none of **3a** was obtained if this reaction was carried out in ethanol (Table 1, entry 8). Finally, we extended reaction time to 30 hours, and identified that **3a** was obtained in 61% yield under otherwise identical conditions, indicating that the product **3a** may decompose in the acidic media under heating condition (Table 1, entry 9). It should be mentioned here that the starting materials could not be completely converted when the reaction was quenched after 12 h, giving the desired product in moderate yield. With regard to the sensitivity test for this protocol,[13] we tested the influences of reaction temperature and under dark condition (for a more detailed condition screening, see Tables S1 and S2 in the Supporting Information). The reaction could not take place smoothly at 20 °C and 70 °C (see Table S2, entries 1-2 in Supporting Information); slightly modified reaction temperature from 120 °C to 110 °C and 130 °C led to slight yield decreasing (see Table S2, entries 3-5 in Supporting Information). Under the dark condition, the yield was not affected (see Table S2, entry 13 in Supporting Information).

Table 1 Optimization of the reaction conditions for the reaction of *N*-pyrimidylindole **1a** and *N*-phenylglycine **2a**.

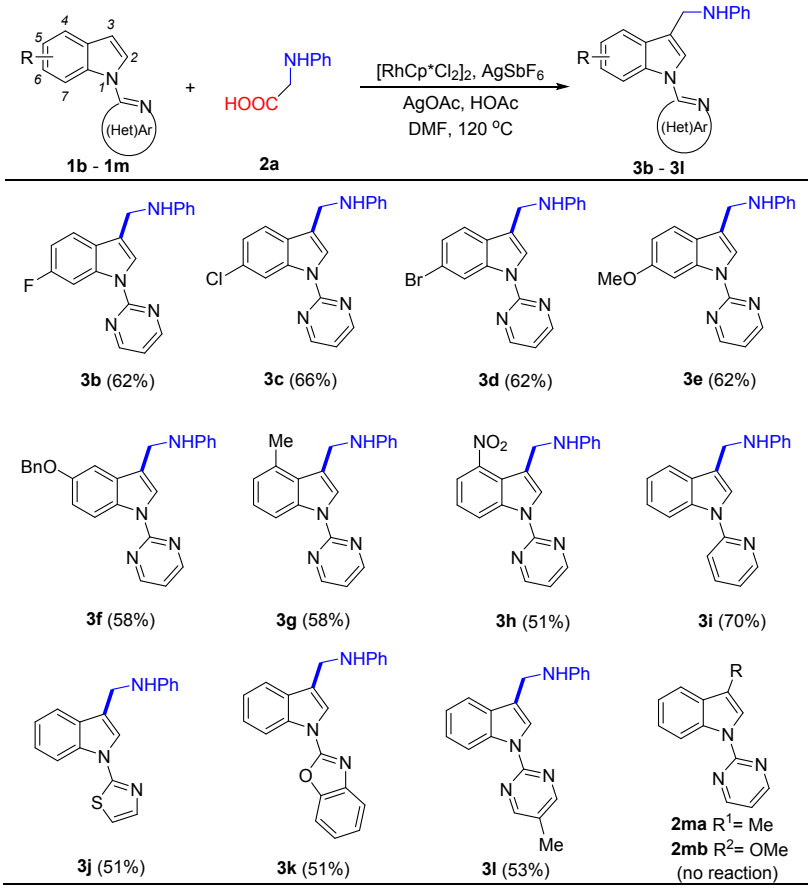


entry[a]	solvent	additives	yield of **3a** (%)
1	DMF	HOAc	70
2	DMF	PivOH	53
3	DMF	PhCOOH	45
4	DMF	AdCOOH	51
5	DMF	-	6
6	DCE	HOAc	48
7	MeCN	HOAc	46
8	EtOH	HOAc	-
9[b]	DMF	HOAc	61

[a] Substrate **1a** (0.10 mmol), **2a** (0.15 mmol), HOAc (0.20 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (20 mol %), AgOAc (0.20 mmol), additives (2 equiv) were added. All the reactions were carried out in a 0.10 mmol scale in solvent (1.0 mL) at 120 °C for 12 h. [b] The reaction was carried out for 30 hrs.

After the optimal reaction conditions were established, the substrate scope of various substituted indoles **1** was subsequently explored, and the results are shown in Scheme 2. When indole was introduced halide (substrates **1b - 1d**) and methoxy group (substrate **1e**) at C6 position, the reaction could proceed smoothly, giving the desired products in 62% to 66% yields. When indole's C5-position was substituted with an OBn group (substrate **1f**), the reaction also performed very well to furnish the corresponding product **3f** in 58% yield. This aminomethylation protocol was compatible with substrate **1g** and substrate **1h** as well, in which the methyl substituent or nitro substituent was incorporated at indole's C4-position. We next inspected different directing groups for this newly developed C-H activation process. The pyrimidine group could be replaced by pyridine (substrate **1i**), thiazole (substrate **1j**) and benzoxazole (substrate **1k**), affording the desired products **3i-3k** in moderate yields ranging from 51% to 70%. A methyl group could be

introduced into pyrimidine directing group (substrate **1l**), affording **3l** in 53% yield. Its electronic property or substrate conformation probably affected the coordination of rhodium and substrate. For substrates **2ma** and **2mb** having a substituent at C3 position, the reaction did not give the desired products because the reaction site has been blocked out by the methyl group, and neither of C2 products were obtained.

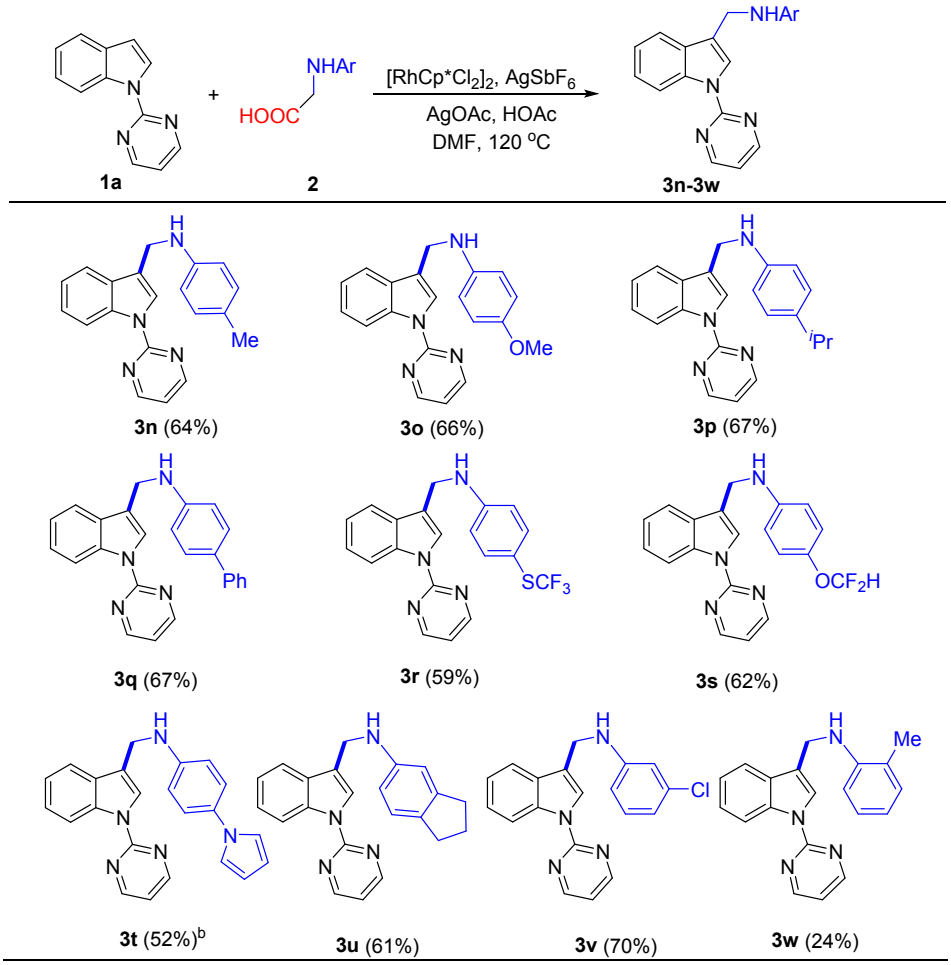


Scheme 2. Substrate scope of different indole derivatives.[a]

[a] Substrate **1** (0.10 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (20 mol %), AgOAc (0.20 mmol), HOAc (0.20 mmol), DMF (1.0 mL). All the reactions were carried out in a 0.10 mmol scale in DMF (1.0 mL) at 120 °C for 12 h.

Since amino acids are a huge feed stock in the synthetic chemistry, we next investigated the substrate scope for a varity of substituted *N*-phenylglycines. The results are demonstrated in Scheme 3. Various phenyl-substituted glycines bearing electron-donating or electron-withdrawing groups coupled smoothly with **1a** at indole's C3 position, affording the corresponding aminomethyl products in moderate yields. For example, methyl group (**2n**), methoxy group (**2o**), isopropyl group (**2p**) and phenyl group (**2q**) could be introduced into the *para* position of phenylglycines, giving the desired products **3n-3q** in moderate yields ranging from 64% to 67%. To our delight, trifluoromethylthio group (**2r**) and difluoromethoxy group (**2s**) substituted glycines were also tolerated, affording the corresponding products **3r** and **3s** in 62% and 59% yields, respectively. For pyrrole tethered phenylglycine (**2t**), the product **3t** could be isolated in 52% yield at 100 °C for 10 h with 6 mol% rhodium(III) catalyst. Furthermore, the *meta*-substituted phenylglycines were also tested, affording the corresponding indane derivative **3u** and

chlorine-substituted product **3v** in 61% and 70% yields, respectively. Using ortho substituted glycine **2w**, the reaction could took place; however, the corresponding product **3w** was obtained in 24% yield.



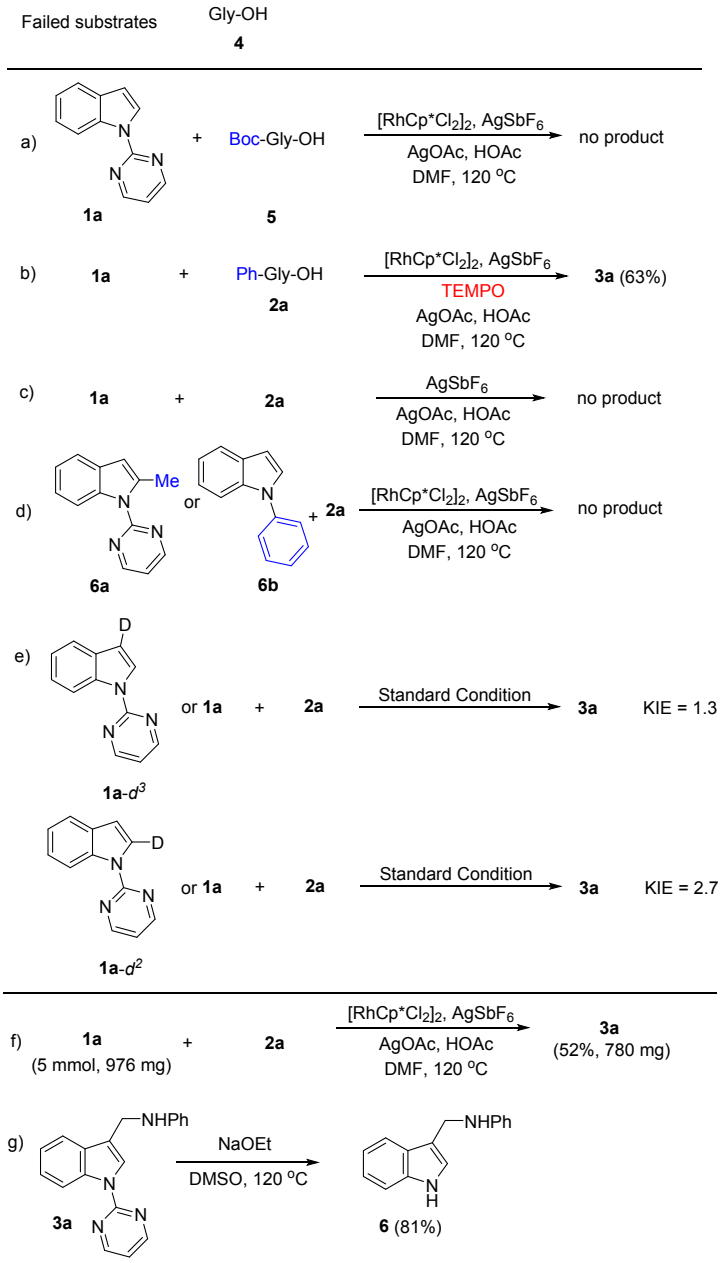
Scheme 3 Substrate scope of different indole *N*-phenylglycine derivatives.[a]

[a] **1a** (0.10 mmol), **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (20 mol %), AgOAc (0.20 mmol), HOAc (0.20 mmol), DMF (1.0 mL). All the reactions were carried out in a 0.10 mmol scale in DMF (1.0 mL) at 120 °C for 12 h. [b] The reactions were carried out at 100 °C for 10 h with $[Cp^*RhCl_2]_2$ (6 mol %)

We also tried plain glycine, but it did not give the desired product under the standard condition. This observation may reveal the different mechanism from the previously reported decarboxylative reactions. To further clarify the reaction scope, we attempted to replace the aryl group with Boc protecting group in our reaction and found that using Boc protected glycine **5** as substrate[14] did not give the coupling product under the standard condition, suggesting the essential of an aryl group in glycine (Scheme 4a). The control experiment confirmed that this C-H activation reaction under the optimized conditions was not affected by the addition of the radical inhibitors such as TEMPO (1.0 equiv), rendering unlikely the intervention of a radical pathway (Scheme 4b). The control experiments also indicated that none of the desired product was formed in the absence of rhodium(III) catalyst (Scheme 4c). Using indole substrate **6a** or **6b** having a methyl substituent at C2 position, this C-H activation process was completely interrupted, illustrating that the C-H activation step is indispensable in this synthetic protocol (Scheme 4d).

The KIE was determined to be k_H/k_D = 2.7 for the parallel reactions using **1a** and **1a**-d^2 at a low conversion while the KIE is 1.3 using **1a** and **1a**-d^3. This value indicates that the C2–H cleavage step is probably involved in the turnover-limiting process (Scheme 4e). Without the co-catalyst $AgSbF_6$, the reaction also failed.[8] A large-scale reaction was carried out to demonstrate the practical value on synthesis. The yield can be obtained up to 52% in 5 mmol scale (Scheme 4f). Removal of directing group was achieved upon treatment with NaOEt in DMSO to afford corresponding product **6** in 81% yield (Scheme 4g).

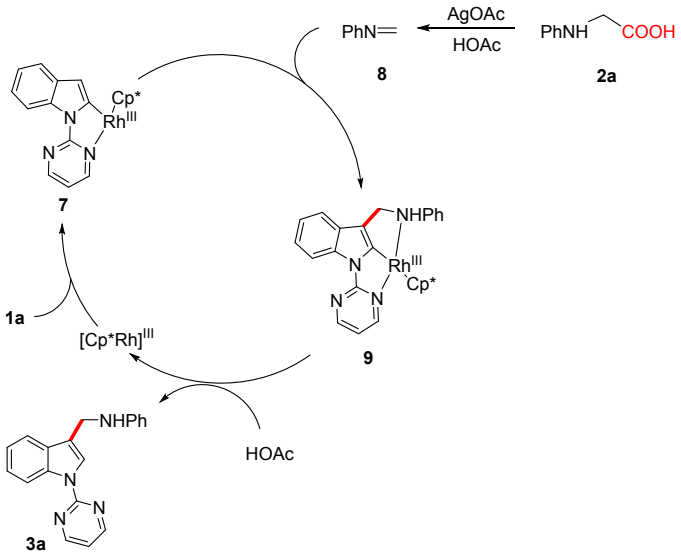
Scheme 4 Control experiments and synthetic transformations.



Based on the above results and the previous reports, a plausible catalytic cycle has been shown in Scheme 5. In the presence of $AgSbF_6$, the cationic [Cp*Rh^{III}] complex is initially generated, which coordinates with substrate **1a**, giving a metallacyclic intermediate **7**. The

N-phenylglycine **2a** undergoes decarboxylation to afford *N*-methyleneaniline **8** in the presence of AgOAc and HOAc. For intermediate **7**, the reactivity of C3 position has been enhanced due to the cyclometallation at C2 position.[15] The electrophilic addition of **7** on the reactive Mannich acceptor **8**[16] affords the key intermediate **9**. Protodemetallation from intermediate **9** produces the aminomethylation product **3a**. The activation of Rh(III) enhanced the nucleophilicity of indole. Species **8** is a small and highly active imine. The two key factors as cyclometallation at C2 position and formation of active species **8** induce the exclusive C3 site selectivity. The reaction could not take place if the directing group was changed. This selectivity is irrelevant with directing group. During optimization of reaction conditions, we found that the loading amount of AgOAc affected the product yield (see Table S1 in the Supporting Information). AgOAc probably plays an important role on decarboxylation from **2a** to **8**. These two parts constitute a relay catalysis.[17]

Scheme 5 A plausible mechanism.



In summary, a novel rhodium(III)-catalyzed decarboxylative aminomethylation of glycine derivatives with indoles via C−H activation is developed, which exclusively produces C3 aminomethylation indole products. In this reaction, resourceful arylglycines were utilized as aminomethyl functional moieties in this rhodium(III)-catalyzed C-H activation. Investigations on expanding this rhodium-catalyzed cross coupling reaction and application of this method to synthesize other heterocycles are undergoing in our laboratory.

Experimental Section

General information. ^{1}H NMR spectra were recorded on Agilent and Varian 400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; coupling constants *J* are given in Hz. ^{13}C NMR spectra were recorded on Agilent and Varian 400 spectrophotometers (100 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: 77.0 ppm). Mass and HRMS spectra were recorded by DART method. Organic solvents used were dried by standard methods when necessary. Infrared spectra were recorded on a Thermofisher spectrometer with

absorption in cm^{-1}. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using silica gel at increased pressure. All the derivatives of **1** and **2** were prepared by the reported methods.[17]

General procedure for the preparation of compound 3a: To a Schlenk tube with a magnetic stirring bar was added 1-(pyrimidin-2-yl)-1H-indole **1a** (0.10 mmol, 19.5 mg), phenylglycine **2a** (0.15 mmol, 47.2 mg), $[RhCp^*Cl_2]_2$ (4 mol%, 2.5 mg), $AgSbF_6$ (20 mol%, 6.8 mg) and AgOAc (0.20 mmol, 33.4 mg). Then, DMF (1.0 ml) was injected to the reaction mixture and HOAc (0.20 mmol, 12.0 mg) was added. The reaction was carried out at 120 °C in the oil bath. After the reaction was completed, the solution was concentrated under reduced pressure and the residue was purified with a silica gel column chromatography to afford the product (petroleum ether / ethyl acetate = 10 / 1).

Procedure for Scale-Up Preparation of 3a: To a Schlenk tube with a magnetic stirring bar was added 1-(pyrimidin-2-yl)-1H-indole **1a** (5.0 mmol, 975 mg), phenylglycine **2a** (7.5 mmol, 2.36 g), $[RhCp^*Cl_2]_2$ (4 mol%, 124 mg), $AgSbF_6$ (20 mol%, 343 mg) and AgOAc (10 mmol, 1.67 g). Then, DMF (25 ml) was injected to the reaction mixture and HOAc (10 mmol, 600 mg) was added. The reaction was carried out at 120 °C in the oil bath. After the reaction was completed, the reaction mixture was filtered through a celite to remove the salts. The solution was concentrated under reduced pressure and the residue was purified with a silica gel column chromatography to afford the product (petroleum ether / ethyl acetate = 10 / 1).

N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3a).[9] yellow oil (21.0 mg, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.00 (s, 1H), 4.51 (s, 2H), 6.72 – 6.80 (m, 3H), 7.01 (dd, *J* = 4.8 Hz, 1H), 7.22 – 7.31 (m, 3H), 7.40 (dd, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 8.26 (s, 1H), 8.67 (d, *J* = 4.8 Hz, 2H), 8.83 (d, *J* = 8.4 Hz, 1H).

N-((6-fluoro-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3b).[9] yellow oil (19.7 mg, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.97 (s, 1H), 4.47 (s, 2H), 6.71 – 6.81 (m, 3H), 6.99 – 7.06 (m, 2H), 7.25 (dd, *J* = 7.8 Hz, 2H), 7.56 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.21 (s, 1H), 8.57 (dd, *J* = 11.1, 2.4 Hz, 1H), 8.61 – 8.71 (m, 2H).

N-((6-chloro-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3c).[9] yellow oil (22.1 mg, 66%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.97 (s, 1H), 4.44 (s, 2H), 6.68 – 6.82 (m, 3H), 7.02 (dd, *J* = 4.8 Hz, 1H), 7.17 – 7.29 (m, 3H), 7.53 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 8.64 (d, *J* = 4.8 Hz, 2H), 8.84 (s, 1H).

N-((6-bromo-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3d).[9] yellow oil (23.5 mg, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.95 (s, 1H), 4.45 (s, 2H), 6.70 – 6.80 (m, 3H), 7.03 (dd, *J* = 4.8 Hz, 1H), 7.23 (dd, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 8.19 (s, 1H), 8.66 (d, *J* = 4.8 Hz, 2H), 9.01 (s, 1H).

N-((6-methoxy-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3e).[9] yellow oil (20.5 mg, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.95 (s, 3H), 4.46 (s, 2H), 6.68 – 6.83 (m, 3H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.99 (dd, *J* = 4.4 Hz, 1H), 7.24 (dd, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 8.15 (s, 1H), 8.46 (s, 1H), 8.65 (d, *J* = 4.9 Hz, 2H).

N-((5-(benzyloxy)-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3f).[9] yellow oil (23.6 mg, 58%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.94 (s, 1H), 4.47 (s, 2H), 5.11 (s, 2H), 6.71 – 6.79

(m, 3H), 7.01 (dd, *J* = 4.8 Hz, 1H), 7.07 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.18 – 7.26 (m, 3H), 7.33 (dd, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 2H), 8.23 (s, 1H), 8.66 (d, *J* = 4.8 Hz, 2H), 8.71 (d, *J* = 9.1 Hz, 1H).

N-((4-methyl-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3g).[9] yellow oil (18.2 mg, 58%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.71 (s, 3H), 3.94 (s, 1H), 4.56 (s, 2H), 6.70 – 6.80 (m, 3H), 7.00 – 7.07 (m, 2H), 7.21 – 7.30 (m, 3H), 8.24 (s, 1H), 8.63 – 8.81 (m, 3H).

N-((4-nitro-1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3h).[9] yellow oil (17.6 mg, 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.07 (s, 1H), 4.57 (s, 2H), 6.72 – 6.80 (m, 3H), 7.16 (dd, *J* = 4.8 Hz, 1H), 7.22 (dd, *J* = 7.6 Hz, 2H), 8.23 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.41 (s, 1H), 8.59 (d, *J* = 2.3 Hz, 1H), 8.74 (d, *J* = 4.8 Hz, 2H), 8.91 (d, *J* = 9.2 Hz, 1H).

N-((1-(pyridin-2-yl)-1H-indol-3-yl)methyl)aniline (3i).[9] yellow oil (21.0 mg, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.98 (s, 1H), 4.52 (s, 2H), 6.68 – 6.80 (m, 3H), 7.15 (dd, *J* = 7.1, 5.1 Hz, 1H), 7.18 – 7.27 (m, 3H), 7.34 (dd, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 10.2 Hz, 2H), 7.79 (dd, *J* = 7.8 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J* = 3.9 Hz, 1H).

N-((1-(thiazol-2-yl)-1H-indol-3-yl)methyl)aniline (3j).[9] yellow oil (15.5 mg, 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.96 (s, 1H), 4.50 (s, 2H), 6.68 – 6.79 (m, 3H), 7.03 (d, *J* = 2.9 Hz, 1H), 7.20 (dd, *J* = 7.5 Hz, 2H), 7.27 (dd, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 2.8 Hz, 1H), 7.63 – 7.72 (m, 2H), 8.29 (d, *J* = 8.3 Hz, 1H).

N-((1-(benzo[d]oxazol-2-yl)-1H-indol-3-yl)methyl)aniline (3k).[9] yellow oil (17.3 mg, 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.01 (s, 1H), 4.52 (s, 2H), 6.69 – 6.79 (m, 3H), 7.18 – 7.39 (m, 6H), 7.43 – 7.53 (m, 2H), 7.67 (dd, *J* = 8.3 Hz, 2H), 7.83 (s, 1H), 8.55 (d, *J* = 8.3 Hz, 1H).

N-((1-(5-methylpyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3l).[9] yellow oil (16.6 mg, 53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.31 (s, 3H), 3.99 (s, 1H), 4.51 (s, 2H), 6.69 – 6.79 (m, 3H), 7.20 – 7.29 (m, 3H), 7.37 (dd, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 8.51 (s, 2H), 8.79 (d, *J* = 8.3 Hz, 1H).

4-methyl-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3n).[9] yellow oil (20.1 mg, 64%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.26 (s, 3H), 4.50 (s, 2H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.99 – 7.08 (m, 3H), 7.25 (dd, *J* = 5.7 Hz, 1H), 7.38 (dd, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 8.26 (s, 1H), 8.69 (d, *J* = 4.6 Hz, 2H), 8.82 (d, *J* = 8.7 Hz, 1H).

4-methoxy-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (3o).[9] yellow oil (21.8 mg, 66%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.75 (s, 3H), 4.46 (s, 2H), 6.68 – 6.73 (m, 2H), 6.78 – 6.83 (m, 2H), 7.02 (dd, *J* = 4.8 Hz, 1H), 7.22 – 7.28 (m, 1H), 7.34 – 7.40 (m, 1H), 7.64 – 7.70 (m, 2H), 8.24 (s, 1H), 8.67 (d, *J* = 4.8 Hz, 2H), 8.81 (d, *J* = 8.4 Hz, 1H).

4-isopropyl-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (**3p**). yellow oil (22.9 mg, 67%), petroleum ether/ethyl acetate = 10:1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.22 (d, *J* = 6.8 Hz, 6H), 2.82 (hept, *J* = 6.9 Hz, 1H), 3.86 (s, 1H), 4.49 (s, 2H), 6.65 – 6.73 (m, 2H), 7.03 (d, *J* = 4.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.37 (dd, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 2H), 8.81 (d, *J* = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 24.3, 33.2, 40.4, 113.0, 116.1, 116.5, 118.3, 119.1, 122.1, 123.9, 124.1, 127.2, 130.2, 136.0, 138.1, 146.5, 157.7, 158.1. IR (neat) ν 3301, 2924, 2853, 1575, 1509, 1454, 1432, 1413, 1381, 1310, 1211, 1112, 1044 cm^{-1}. HRMS (DART-FTICR) m/z [M-H]$^+$ Calcd. for $C_{22}H_{21}N_4$ 341.1761, Found: 341.1758.

N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)-[1,1'-biphenyl]-4-amine (**3q**). yellow oil (25.2 mg, 67%), petroleum ether/ethyl acetate = 10:1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.06 (br,

1H), 4.55 (s, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 4.8 Hz, 1H), 7.28 (dd, *J* = 8.0 Hz, 2H), 7.38 (dd, *J* = 7.7 Hz, 3H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 1H), 8.27 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 2H), 8.82 (d, *J* = 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*) δ 40.1, 113.2, 116.1, 116.6, 117.9, 119.1, 122.2, 124.0, 124.2, 126.1, 126.4, 128.0, 128.7, 130.2, 130.5, 136.0, 141.3, 147.8, 157.6, 158.2. IR (neat) ν 3379, 3034, 2811, 1609, 1577, 1560, 1527, 1453, 1430, 1382, 1345, 1324, 1244, 1222, 1207, 1162 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{25}H_{19}N_4$ 375.1604, Found: 375.1602.

N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)-4-((trifluoromethyl)thio)aniline (**3r**). yellow oil (23.6 mg, 59%), petroleum ether/ethyl acetate = 10:1. ^1H NMR (400 MHz, Chloroform-*d*) 4.30 (s, 1H), 4.52 (s, 2H), 6.63 – 6.74 (m, 2H), 7.01 – 7.09 (m, 1H), 7.22 – 7.32 (m, 2H), 7.33 – 7.42 (m, 1H), 7.43 – 7.51 (m, 2H), 7.57 – 7.67 (m, 1H), 8.26 (s, 1H), 8.69 (d, *J* = 8.0 Hz, 2H), 8.82 (d, *J* = 8.0 Hz, 1H). $^{19}F\{^1H\}$ NMR (377 MHz, Chloroform-*d*) δ -44.5. $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*) δ 39.6, 109.8, 113.2, 116.3, 116.6, 117.0, 118.9, 122.3, 124.1, 124.3, 129.8 (q, *J* = 307 Hz), 129.9, 136.0, 138.3, 150.3, 157.6, 158.2. IR (neat) ν 3298, 1570, 1509, 1454, 1433, 1384, 1312, 1135, 1111, 1087, 1042 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{20}H_{14}F_3N_4S$ 399.0886, Found: 399.0881.

4-(difluoromethoxy)-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (**3s**). yellow oil (22.7 mg, 62%), petroleum ether/ethyl acetate = 10:1. ^1H NMR (400 MHz, Chloroform-*d*) δ 3.97 (br, 1H), 4.46 (s, 2H), 6.38 (t, *J* = 74.9 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.94 – 7.06 (m, 3H), 7.21 – 7.32 (m, 1H), 7.32 – 7.43 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 8.23 (s, 1H), 8.67 (d, *J* = 4.8 Hz, 2H), 8.81 (d, *J* = 8.4 Hz, 1H). $^{19}F\{^1H\}$ NMR (377 MHz, Chloroform-*d*) δ -80.0, -79.8. $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*) δ 40.3, 113.5, 116.2, 116.58, 116.64 (t, *J* = 257 Hz), 117.7, 119.0, 121.5, 122.2, 123.9, 124.2, 130.1, 136.0, 142.6, 146.3, 157.6, 158.2. IR (neat) ν 3319, 2913, 2845, 1570, 1508, 1453, 1432, 1413, 1381, 1310, 1210, 1132, 1110, 1086, 1066 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{20}H_{15}F_2N_4O$ 365.1208, Found: 365.1203.

N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)-4-(1H-pyrrol-1-yl)aniline (**3t**). yellow oil (19.0 mg, 52%), petroleum ether/ethyl acetate = 10:1. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.07 (br, 1H), 4.54 (s, 2H), 6.32 (d, *J* = 1.9 Hz, 2H), 7.06 (dd, *J* = 2.0 Hz, 2H), 7.06 (dd, *J* = 4.8 Hz, 1H), 7.22 – 7.26 (m, 4H), 7.39 (dd, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 8.28 (s, 1H), 8.70 (d, *J* = 4.8 Hz, 2H), 8.83 (d, *J* = 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*) δ 40.3, 109.4, 113.4, 116.2, 116.6, 117.8, 119.0, 119.8, 122.2, 122.5, 124.0, 124.2, 130.1, 132.1, 136.0, 146.6, 157.6, 158.2. IR (neat) ν 2922, 2852, 1577, 1561, 1508, 1442, 1428, 1381, 1311, 1266, 1209, 1179, 1134, 1083, 1042 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{23}H_{18}N_5$ requires (M^+-H): 364.1557, Found: 364.1553.

N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)-2,3-dihydro-1H-inden-5-amine (**3u**). yellow oil (20.7 mg, 61%), petroleum ether/ethyl acetate = 10:1. ^1H NMR (400 MHz, Chloroform-*d*) δ 2.00 – 2.11 (m, 2H), 2.79 – 2.90 (m, 4H), 3.73 (br, 1H), 4.50 (s, 2H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 7.00 – 7.10 (m, 2H), 7.27 (d, *J* = 9.9 Hz, 2H), 7.38 (dd, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 8.69 (d, *J* = 4.7 Hz, 2H), 8.82 (d, *J* = 8.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*) δ 25.8, 32.0, 33.2, 40.6, 109.1, 111.4, 116.1, 116.5, 118.3, 119.1, 122.1, 123.9, 124.1, 124.8, 130.3, 133.3, 136.0, 145.5, 147.3, 157.7, 158.1. IR (neat) ν 3356, 2997, 1578, 1561, 1470, 1452, 1434, 1381, 1330, 1311, 1211, 1137, 1121, 1107, 1083 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{22}H_{19}N_4$ 339.1604, Found: 339.1600.

3-chloro-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (**3v**). yellow oil (23.4 mg, 70%),

petroleum ether/ethyl acetate = 10:1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.04 (br, 1H), 4.48 (s, 2H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.67 – 6.75 (m, 2H), 7.03 (dd, *J* = 4.8 Hz, 1H), 7.11 (dd, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.40 (dd, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 8.25 (s, 1H), 8.68 (d, *J* = 4.7 Hz, 2H), 8.83 (d, *J* = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 39.9, 111.2, 112.5, 116.2, 116.6, 117.3, 117.4, 119.0, 122.2, 124.0, 124.2, 130.0, 130.3, 135.1, 135.9, 149.4, 157.6, 158.2. IR (neat) ν 3426, 3126, 1567, 1507, 1472, 1449, 1437, 1428, 1379, 1338, 1329, 1313, 1293, 1267, 1247, 1222, 1206, 1177, 1100, 1069, 1043 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{19}H_{14}ClN_4$ 333.0900, Found: 333.0899.

2-methyl-N-((1-(pyrimidin-2-yl)-1H-indol-3-yl)methyl)aniline (**3w**). colorless oil (7.5 mg, 24%), petroleum ether/ethyl acetate = 10:1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.11 (s, 3H), 3.79 (s, 1H), 4.51 (s, 2H), 6.69 (dd, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 4.7 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.16 (dd, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 7.5 Hz, 1H), 7.37 (dd, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 8.62 (d, *J* = 4.7 Hz, 2H), 8.81 (d, *J* = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 17.7, 40.2, 110.1, 116.2, 116.7, 117.3, 118.1, 119.2, 122.2, 122.3, 124.2, 124.3, 127.4, 130.2, 130.4, 136.1, 146.5, 157.7, 158.2. IR (neat) ν 3445, 3361, 2845, 1603, 1580, 1560, 1510, 1455, 1444, 1426, 1380, 1347, 1307, 1261, 1230, 1211, 1137, 1084 cm^{-1}. HRMS (DART-FTICR) m/z $[M-H]^+$ Calcd. for $C_{20}H_{17}N_4$ 313.1448, Found: 313.1449.

Supporting Information Available: Optimization of Reaction Conditions, KIE experiment, Procedure for Removing Directing Group and NMR spectra for compounds **3** are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment

We are grateful for the financial support from the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), the National Natural Science Foundation of China (21572052, 21772226, 21772037, 21861132014 and 91956115) and the Shenzhen Nobel Prize Scientists Laboratory Project.

References

1. (a) Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C–H Functionalization. *Chem. Rev.* **2017**, *117*, 8864-8907; (b) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chem. Rev.* **2011**, *111*, 1846-1913; (c) Huang, H.; Jia, K.; Chen, Y. Radical Decarboxylative Functionalizations Enabled by Dual Photoredox Catalysis. *ACS Catal.* **2016**, *6*, 4983-4988; (d) Schwarz, J.; König, B. Decarboxylative reactions with and without light - a comparison. *Green Chem.* ***2018,*** *20*, 323-361; (e) Bloom, S.; Liu, C.; Kölmel, D. K.; Qiao, J. X.; Zhang, Y.; Poss, M. A.; Ewing, W. R.; MacMillan, D. W. C. Decarboxylative alkylation for site-selective bioconjugation of native proteins via oxidation potentials. *Nat. Chem.* **2017**, *10*, 205-211; (f) Liang, Y.; Zhang, X.; MacMillan, D. W. C. Decarboxylative sp^3 C–N coupling via dual copper and photoredox catalysis. *Nature,* **2018**, *559*, 83-88.

2. Tan, X.; Song, T.; Wang, Z.; Chen, H.; Cui, L.; Li, C. Silver-Catalyzed Decarboxylative Bromination of Aliphatic Carboxylic Acids. *Org. Lett.* **2017**, *19*, 1634-1637.

3. (a) Goossen, L. J. Pd-catalyzed synthesis of arylacetic acid derivatives from boronic acids. *Chem. Commun.* **2001**, 669-670; (b) Goossen, L. J.; Ghosh, K. A new practical ketone synthesis directly from carboxylic acids:

first application of coupling reagents in palladium catalysis. *Chem. Commun.* **2001**, 2084-2085; (c) Goossen, L. J.; Paetzold, J. Pd-Catalyzed Decarbonylative Olefination of Aryl Esters: Towards a Waste-Free Heck Reaction. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237–1241; (d) Goossen, L. J.; Paetzold, J.; Winkel, L. Pd-Catalyzed Decarbonylative Heck Olefination of Aromatic Carboxylic Acids Activated in situ with Di-tert-butyl Dicarbonate. *Synlett*, **2002**, 1721-1723; (e) Goossen, L. J.; Paetzold, J. Decarbonylative Heck Olefination of Enol Esters: Salt-Free and Environmentally Friendly Access to Vinyl Arenes. *Angew. Chem. Int. Ed.* **2004**, *43*, 1095-1098; (f) Goossen, L. J.; Döhring, A. Lewis Acids as Highly Efficient Catalysts for the Decarboxylative Esterification of Carboxylic Acids with Dialkyl Dicarbonates. *Adv. Synth. Catal.* **2003**, *345*, 943-947; (g) Goossen, L. J.; Ghosh, K. Palladium-Catalyzed Synthesis of Aryl Ketones from Boronic Acids and Carboxylic Acids Activated in situ by Pivalic Anhydride. *Eur. J. Org. Chem.* **2002**, 3254-3267.

4. a) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. Silver-Catalyzed Decarboxylative Chlorination of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2012**, *134*, 4258-4563; (b) Liu, C.; Wang, X.; Li, Z.; Cui, L.; Li, C. Silver-Catalyzed Decarboxylative Radical Azidation of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2015**, *137*, 9820-9823; (c) Yin, F.; Wang, Z.; Li, Z.; Li, C. Silver-Catalyzed Decarboxylative Fluorination of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 10401-10404; (d) Liu, X.; Wang, Z.; Cheng, X.; Li, C. Silver-Catalyzed Decarboxylative Alkynylation of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 14330-14333. (e) Hua, A. M.; Mai, D. N.; Martinez, R.; Baxter, R. D. Radical C−H Fluorination Using Unprotected Amino Acids as Radical Precursors. *Org. Lett.* **2017**, *19*, 2949-2952.
5. (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C-H Bond Activation. *Chem. Rev.* **2010**, *110*, 624-655; (b) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. -Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754-8786; (c) Song, G.; Li, X. Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.* **2015**, *48*, 1007-1020; (d) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem. Eur. J.* **2010**, *16*, 11212-11222; (e) Song, G.; Wang, F.; Li, X. C–C, C–O and C–N bond formation via rhodium(iii)-catalyzed oxidative C–H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651-3678; f) Kuhl, N.; Schröder, N.; Glorius F. Formal S_N-Type Reactions in Rhodium(III)-Catalyzed C-H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443; (g) Gulías, M.; Mascareñas, J. L. Metal-Catalyzed Annulations through Activation and Cleavage of C−H Bonds. *Angew. Chem. Int. Ed.* **2016**, *55*, 11000-11019; (h) Ye, B.; Cramer, N. Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C–H Functionalizations. *Acc. Chem. Res.* **2015**, *48*, 1308-1318; (i) Meyer, T. H.; Finger, L. H.; Gandeepan, P.; Ackermann, L. Resource Economy by Metallaelectrocatalysis: Merging Electrochemistry and CH Activation. *Trends Chem.* **2019**, *1*, 63-76.
6. (a) Fang, P.; Li, M.; Ge, H. Room Temperature Palladium-Catalyzed Decarboxylative ortho-Acylation of Acetanilides with α-Oxocarboxylic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 11898-11899; (b) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. Palladium-catalyzed decarboxylative C2-acylation of indoles with α-oxocarboxylic acids. *Chem. Commun.* **2013**, 2933-2955; (c) Hossian, A.; Manna, M. K.; Manna, K.; Jana, R. Palladium-catalyzed decarboxylative, decarbonylative and dehydrogenative C(sp^2)–H acylation at room temperature. *Org. Biomol. Chem.* **2017**, *15*, 6592-6603; (d) Penteado, F.; Lopes, E. F.; Alves, D.; Perin, G.; Jacob, R. G.; Lenardao, E. J. α-Keto Acids: Acylating Agents in Organic Synthesis. *Chem. Rev.* **2019**, *119*, 7113-7278.
7. Jing, K.; Li, Z.; Wang, G. -W. Direct Decarboxylative Meta-Selective Acylation of Arenes via an Ortho-Ruthenation Strategy. *ACS Catal.* **2018**, *8*, 11875-11881.

8. Liu, R.; Liu, J.; Wei, Y.; Shi, M. Activation Relay on Rhodium-Catalyzed C–H Aminomethylation in Cooperation with Photoredox Catalysis. *Org. Lett.* **2019**, *21*, 4077-4081.

9. (a) Ren, X.; Chen, J.; Chen, F.; Cheng, J. The palladium-catalyzed cyanation of indole C–H bonds with the combination of NH_4HCO_3 and DMSO as a safe cyanide source. *Chem. Commun.* **2011**, 6725-6727; (b) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. Palladium-Catalyzed Direct Cyanation of Indoles with $K_4[Fe(CN)_6]$. *Org. Lett.* **2010**, *12*, 1052-1055; (c) Ding, S.; Jiao, N. Direct Transformation of N,N-Dimethylformamide to −CN: Pd-Catalyzed Cyanation of Heteroarenes via C–H Functionalization. *J. Am. Chem. Soc.* **2011**, 133, 12374-12377; (d) Xu, S.; Huang, X.; Hong, X.; Xu, B. Palladium-Assisted Regioselective C–H Cyanation of Heteroarenes Using Isonitrile as Cyanide Source. *Org. Lett.* **2012**, *14*, 4614-4617.

10. (a) Wu, W.; Su, W. Mild and Selective Ru-Catalyzed Formylation and Fe-Catalyzed Acylation of Free (N–H) Indoles Using Anilines as the Carbonyl Source. *J. Am. Chem. Soc.* **2011**, *133*, 11924-11927; (b) Chen, J.; Liu, D.; Liu, B.; Liu, S.; Cheng, J. The Copper-Catalyzed C-3-Formylation of Indole C-H Bonds using Tertiary Amines and Molecular Oxygen. *Adv. Synth. Catal.* **2012**, *354*, 2438-2442.

11. (a) Brand, J. P.; Charpentier. J.; Waser, J. Direct Alkynylation of Indole and Pyrrole Heterocycles. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346-9349; (b) Gu. Y.; Wang, X. Direct palladium-catalyzed C-3 alkynylation of indoles. *Tetrahedron Lett.* **2009**, *50*, 763-766.

12. (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective C-H Functionalization. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125-3129; (b) Xiang, S. -K.; Zhang, B.; Zhang, L. -H.; Cui, Y.; Jiao, N. Morpholine catalyzed direct C3 alkenylation of indoles with α,β-unsaturated aldehydes. *Chem. Commun.* **2011**, 8097-8099; (c) Chen, W. -L.; Gao, Y. -R.; Mao, S.; Zhang, Y. -L.; Wang, Y. -F.; Wang, Y. -Q. Palladium-Catalyzed Intermolecular C3 Alkenylation of Indoles Using Oxygen as the Oxidant. *Org. Lett.* **2012**, *14*, 5920-5923; (d) Yu, H.; Yu, Z. Direct Alkenylation of Indoles with α-Oxo Ketene Dithioacetals: Efficient Synthesis of Indole Alkaloids Meridianin Derivatives. *Angew. Chem. Int. Ed.* **2009**, *48*, 2929-2933.

13. Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem. Int. Ed.* **2019**, *58*, 8572-8576.

14. (a) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of α-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257-5260; (b) Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. Conjugate Addition-Enantioselective Protonation of N-Aryl Glycines to α-Branched 2-Vinylazaarenes via Cooperative Photoredox and Asymmetric Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 6083-6087.

15. (a) Leitch, J. A.; Frost, C. G. Ruthenium-catalysed σ-activation for remote meta-selective C–H functionalisation. *Chem. Soc. Rev.* **2017**, *46*, 7145-7153; (b) Leitch, J. A.; Heron, C. J.; Mcknight, J.; Kociok-Köhn, G.; Bhonoah, Y.; Frost, C. G. Ruthenium catalyzed remote C4-selective C–H functionalisation of carbazoles via σ-activation. *Chem. Commun.* **2017**, 13039-13042.

16. Li, Z. -L.; Sun, K. -K.; Wu, P. -Y.; Cai, C. Iron-Catalyzed Regioselective α-C–H Alkylation of N-Methylanilines: Cross-Dehydrogenative Coupling between Unactivated $C(sp^3)$–H and $C(sp^3)$–H Bonds via a Radical Process. *J. Org. Chem.* **2019**, *84*, 6830-6839.

17. (a) Patil, N. T.; Shinde, V. S.; Gajula, B. A one-pot catalysis: the strategic classification with some recent examples. *Org. Biomol. Chem.* **2012**, *10*, 211-224; (b) Pellissier, H., Recent developments in enantioselective multicatalysed tandem reactions. *Tetrahedron*, **2013**, 69, 7171-7210;

18. (a) Wang, Q.; Xie, F.; Li, X. Rh(III)-Catalyzed Trifluoromethylthiolation of Indoles via C–H Activation. *J. Org. Chem.* **2015**, 80, 8361-8366; (b) Petry, N.; Vanderbeeken, T.; Malher, A.; Bringer, Y.; Retailleau, P.;

Bantreil, X.; Lamaty, F. Mechanosynthesis of sydnone-containing coordination complexes. *Chem. Commun.* 2019, 9495-9498.