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Rh-Catalyzed Intermolecular Carbenoid Functionalization of Aromatic C−H Bonds by α-Diazomalonates

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Supporting Information

ABSTRACT: A Rh-catalyzed intermolecular coupling of diazomalonates with arene C−H bonds is reported. The reaction is initiated by electrophilic C−H activation, which is followed by coupling of the arylrhodium(III) complex with the diazomalonate. In most cases, arenes with oximes, carboxylic acids, and amines as directing groups cross-couple with diazomalonates with excellent regioselectivities and functional group tolerance, and thus, this reaction offers a new route to α-aryl carbonyl compounds for specific applications.

Catalytic site-selective functionalization of unactivated C−H bonds offers an innovative route for atom-economical C−C and C−heteroatom bond formations.[1] Over the past years, Pd-catalyzed C−H bond functionalizations have achieved enormous successes.[1c−h] However, the Pd catalysis is limited in its substrate scope, must use a high catalyst loading, and often requires forcing conditions. Recently, several investigations revealed that $[Cp^*Rh^{III}Cl_2]_2$ and $[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ complexes are promising catalysts for direct arene functionalizations under mild conditions.[1i−l] It has been established that $[Cp^*Rh^{III}Cl_2]_2$ undergoes chelation-assisted electrophilic metalation of the ortho $C(sp^2)$−H bond to form arylrhodium complexes,[2] which couple with a variety of reagents such as isocyanates,[3a] aldehydes/imines,[3b,c] alkenes, and alkynes. Recently, the research groups of Glorius,[4a,b] Ma,[4c] and Miura[4d] achieved the dehydrogenative coupling reaction of allenes and arenes with arylrhodium(III) complexes using [Cp*Rh] catalysis. Glorius[5] and we[6b] also independently achieved [Cp*Rh]-catalyzed direct aryl C−H amination with excellent regioselectivity and functional group compatibility.

To explore new C−H bond functionalizations, we have been interested in the coupling reactions of metal−aryl complexes with carboradicals, nitrenes, and carbenes as unconventional coupling partners.[6] We found that the reactions of arylpalladium complexes with carboradicals and nitrenes result in C−C and C−N bond formations. Earlier works by the research groups of Van Vranken, Barluenga, and Wang demonstrated the Pd-catalyzed cross-coupling reactions of aryl halides with carbenoid reagents for C=C bond formation.[7] We also accomplished the Pd-catalyzed oxidative coupling of arylboronic acids with α-aryldiazoacetates to furnish (*E*)-diarylacrylates with excellent stereoselectivity.[8] Recently, we achieved the Rh(I)-catalyzed one-pot coupling of arylboronates with α-aryldiazoacetates and alkyl halides to afford quarternary heterodiaryl carboxylic acids.[8a] Migratory carbene insertion is believed to be the principal step in these carbenoid coupling reactions.

Prompted by these achievements, we anticipated that direct carbenoid cross-couplings with arene C−H bonds via migratory carbene insertion should be possible. Reactive metal−carbene complexes are known to insert into saturated C−H bonds with excellent regio- and enantiocontrol,[9] but their reactivity toward C−H insertion exhibits an order of reactivity of tertiary C−H > secondary C−H ≫ primary C−H. Notably, direct carbene functionalization of aryl C−H bonds has limited precedent in the literature. Recently, Wang, Satoh, and Miura independently reported the metal-catalyzed C−H bond cross-coupling of 1,3-azoles with *N*-tosylhydrazones.[10] However, these reactions are limited to heteroarene C−H bonds, and excess LiO*t*Bu and high temperatures (110 °C) are required for success. Herein we report the [Cp*Rh^{III}]-catalyzed direct aryl C−H bond coupling of diazocarbonyl compounds. This *base-free* diazo coupling reaction occurs under mild conditions with excellent regioselectivity and functional group compatibility. The reaction is likely initiated by electrophilic C−H metalation, which is followed by coupling of the diazo compound with the arylrhodium complex.

To begin, **1a** (1 equiv) was treated with $[Cp^*RhCl_2]_2$ (2.5 mol %), AgOAc (15 mol %), and diazomalonate **2a** (1 equiv) in MeOH (1.5 mL) at 60 °C overnight, and the desired α-aryl malonate **3a** was obtained in 98% yield (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallography. The reaction was equally effective at room temperature under air, although longer reaction times were required for complete reaction (entry 2). No product formation was observed with AgOAc alone *in the absence of the Rh catalyst* (entry 3). It is likely that AgOAc provides the acetate ligand for catalytic turnovers. As expected, effective transformation was observed when $[Cp^*Rh(OAc)_2]$ was employed as the catalyst (entry 4).

Other alcoholic solvents such as EtOH and *t*BuOH were not suitable for the C−H coupling reaction, and carbene O−H insertion products were isolated as the major products (entries 5 and 6).[11] Little or no product formation was observed with 1,2-dichloroethane (DCE), acetonitrile, tetrahydrofuran (THF), or toluene as the solvent.[12,13] Some acetate additives were tested; good product yields were obtained with $Cu(OAc)_2$, but poor results were obtained with NaOAc (entries 7 and 8). Lowering the Rh catalyst loading to 1.25 mol % and the

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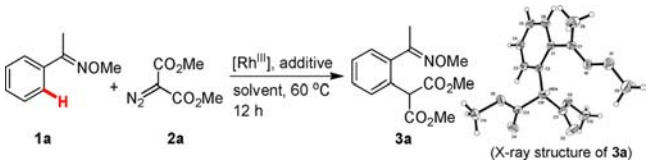
Table 1. Reaction Optimization[a]



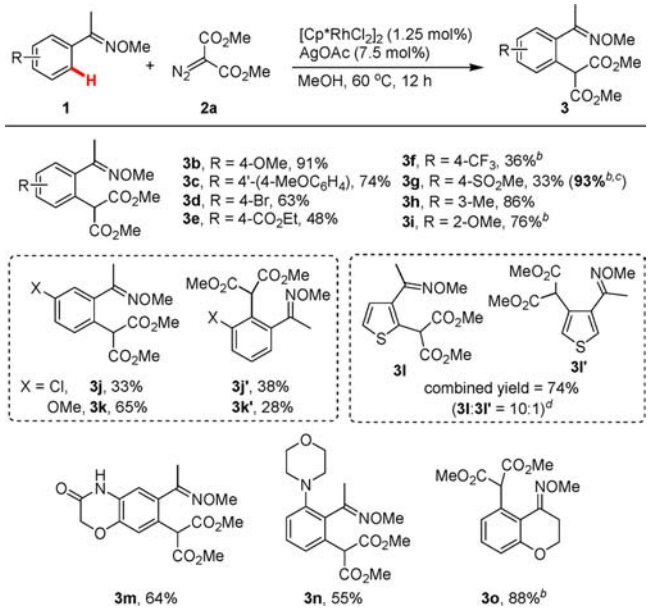
entry	[Rh] (mol %)	additive (mol %)	solvent	yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (2.5)	AgOAc (15)	MeOH	98
2[c]	$[Cp^*RhCl_2]_2$ (2.5)	AgOAc (15)	MeOH	93
3	none	AgOAc (15)	MeOH	0
4	$Cp^*Rh(OAc)_2$ (2.5)	none	MeOH	85
5	$[Cp^*RhCl_2]_2$ (2.5)	AgOAc (15)	EtOH	31
6	$[Cp^*RhCl_2]_2$ (2.5)	AgOAc (15)	*t*BuOH	0
7	$[Cp^*RhCl_2]_2$ (2.5)	$Cu(OAc)_2$ (15)	MeOH	70
8	$[Cp^*RhCl_2]_2$ (2.5)	NaOAc (15)	MeOH	10
9	$[Cp^*RhCl_2]_2$ (1.25)	AgOAc (7.5)	MeOH	96[d]
10	$[Cp^*RhCl_2]_2$ (0.5)	AgOAc (3)	MeOH	90

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [Rh], and additives in solvent (1.5 mL) at 60 °C overnight. [b]Yields were determined by ^1H NMR analysis using 1,2-dibromoethane as an internal standard. [c]Reaction was run at room temperature. [d]Isolated yield.

AgOAc additive to 7.5 mol % gave the optimal reaction conditions, with an excellent isolated yield of 96% (entry 9).

For the substrate scope study (Table 2), acetophenone oximes bearing electron-releasing and -withdrawing substituents were found to be effective substrates, giving **3b–i** in 33–91% yield. Notably, the 4-bromo-substituted substrate afforded the expected product in this Rh-catalyzed reaction. The lower yields for substrates bearing CF_3, CO_2Et, and SO_2Me can be attributed to their electron-withdrawing properties, which slowed the electrophilic C–H activation by the [Cp*Rh] complex. However, when **1g** was treated with **2a** via dropwise addition, **3g** was obtained in 93% yield. With the assistance of the oxime directing groups, the ortho C–H bond was exclusively functionalized. Nevertheless, the reactions of some meta-substituted acetophenone oximes produced regiomeric products. For instance, the reactions of **1j** (3-Cl) afforded a mixture of **3j** (33%) and **3j′** (38%); likewise, the reaction of **1k** (3-OMe) gave **3k** and **3k′** in 65 and 28% yield, respectively.

Table 2. [Cp*Rh^{III}]-Catalyzed C–H Coupling of Aryl Ketone Oximes with Diazomalonate[a]

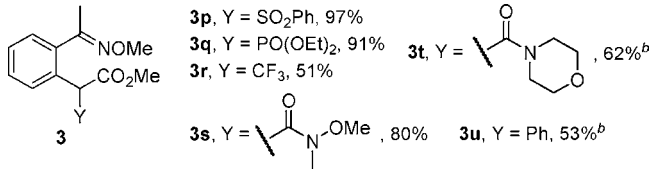


[a]See the Supporting Information (SI) for experimental details. [b]Catalyst loading = 2.5 mol %; AgOAc = 15 mol %; **1** = 0.4 mmol; **2a** = 0.2 mmol. [c]**2a** (0.2 mmol) was added dropwise over 10 h under N_2. [d]The regioisomeric ratio was determined by NMR analysis.

According to the literature, rhodium carbenoids can react with oxygen, nitrogen, and sulfur atoms to afford ylides, which can undergo a diverse number of chemical tranformations.[11] In this work, when acetothiophene oxime (**1l**) was treated with **2a** (1 equiv) and the [Cp*Rh] catalyst, the C–H insertion products **3l** and **3l′** were formed exclusively in 74% overall yield, yet ylide formation was not observed.[14] Similarly, substrates bearing heterocyclic scaffolds were effectively transformed into their corresponding products (e.g., **3m**, 64%; **3n**, 55%; **3o**, 88%).

The scope of the diazoester coupling partner was also investigated. With **1a** as the substrate, the Rh-catalyzed C–H coupling reactions with diazoesters **2p–t** bearing substituents such as phenylsulfone, diethyl phosphonate, CF_3, and amide furnished the desired products **3p–t** in 51–97% yield (Scheme 1). Similarly, the facile reaction of methyl phenyldiazoacetate (**2u**) gave the product **3u** in 53% yield under the standard reaction conditions.

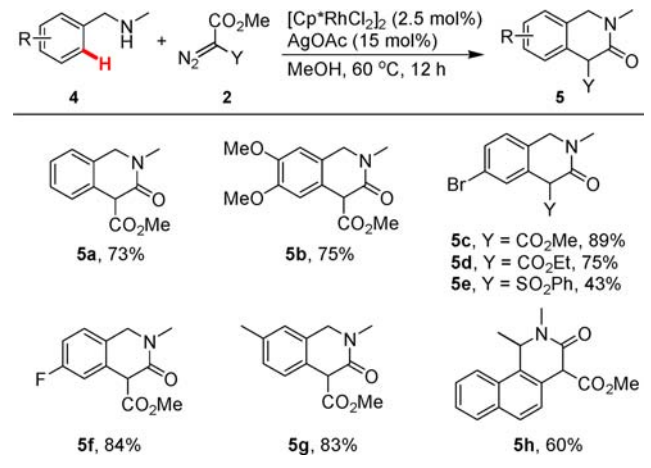
Scheme 1. Scope of Diazoesters[a]



[a]See the SI for experimental details. [b]Catalyst loading = 2.5 mol %; AgOAc = 15 mol %; **1a** = 0.4 mmol; **2** = 0.2 mmol.

To expand the substrate scope further, we examined the carbenoid C–H coupling reactions of unprotected benzylamines. As shown in Table 3, treatment of *N*-benzylmethyl-

Table 3. [Cp*Rh^{III}]-Catalyzed C–H Coupling of *N*-Benzylmethylamines with Diazomalonates[a]



[a]See the SI for experimental details.

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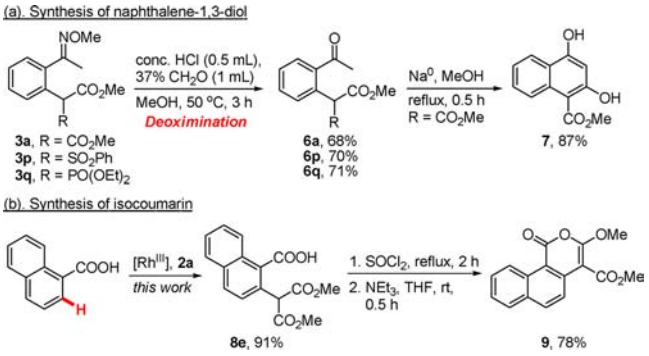
amine derivatives **4** with diazoesters under the standard conditions afforded isoquinolones **5a–h** in 43–89% yield with excellent functional group compatibility. Isoquinolone nuclei are ubiquitous motifs in bioactive alkaloids.[15]

α-Aryl malonates are useful intermediates for organic synthesis. In this work, **3a**, **3p**, and **3q** were deoximinated by treatment with concentrated HCl/formaldehyde (Scheme 2a),

Scheme 2. Synthetic Applications



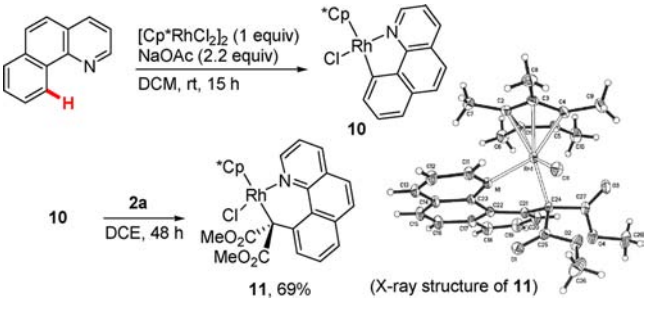
and the corresponding ketones **6** were obtained in good yields (68–71%). Carboxylate naphthalene-1,3-diol **7** was prepared in 87% yield by the intramolecular Dieckmann condensation of **6a**.[16]

Likewise, isocoumarins are important structural units in pharmaceutical compounds such as some serine protease inhibitors.[17] In this work, we prepared benzoic acid **8e** by the Rh-catalyzed diazomalonate coupling of 2-naphthoic acid.[18] Treatment of **8e** with excess thionyl chloride followed by cyclization of the acid chloride in a basic medium produced isocoumarin **9** in 78% yield (Scheme 2b).

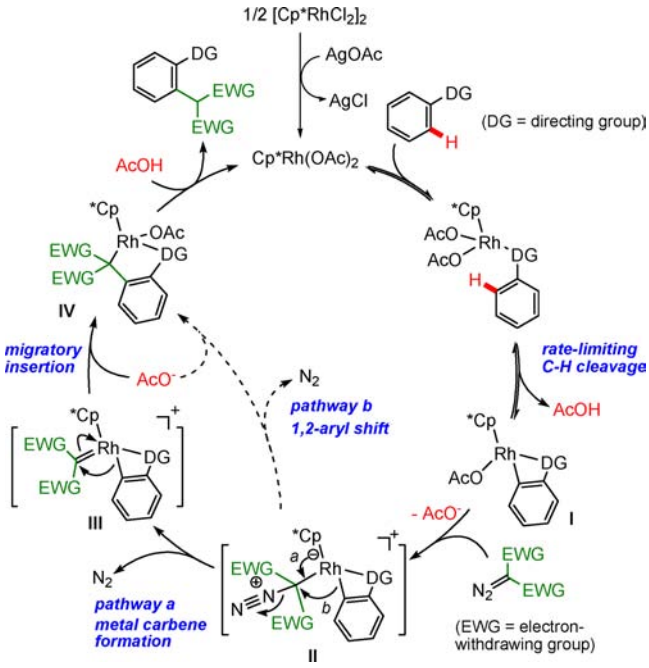
The carbenoid C–H coupling reaction probably involves rate-limiting C–H bond cleavage by the Cp*Rh(III) complex, since a notable primary kinetic isotope effect (KIE) of k_H/k_D = 3.0 was observed in a competitive experiment using equimolar amounts of **1a** and **1a**-d_5.[19] Treatment of benzo[*h*]quinoline with $[Cp^*RhCl_2]_2$ afforded cyclometalated Rh(III) complex **10**, which reacts with **2a** in DCE to afford σ-alkyl–Rh(III) complex **11** in 69% yield (Scheme 3). The structure of **11** was determined by X-ray crystallography.

A plausible reaction mechanism is shown in Scheme 4. First, $[Cp^*RhCl_2]_2$ undergoes ligand exchange with AgOAc to give the cationic acetate-ligated species, which undergoes electrophilic C–H bond cleavage to form a rhodacyclic intermediate.[20] Coordination of the diazo compound with **I** may form the diazonium intermediate **II**. At this stage, two pathways are

Scheme 3. Characterization of the Alkylrhodacycle Intermediate



Scheme 4. Proposed Mechanism



possible. In pathway a, extrusion of N_2 from **II** would afford Rh–carbene **III**, which would subsequently undergo migratory insertion to afford **IV**. Alternatively, intramolecular 1,2-migratory insertion of the aryl group would give **IV** (pathway b).[21] The detailed mechanism of the diazo coupling with the arylrhodium complexes remains unclear. Finally, protonolysis of **IV** would generate the desired alkylated product and the active Rh catalyst.

In summary, we have developed a mild Rh(III)-catalyzed carbenoid ortho C–H cross-coupling reaction with diazomalonates. Except for some meta-substituted substrates, arenes such as acetophenone oximes, benzoic acids, 2-phenylpyridines, and unprotected benzylamines can be functionalized in high yields with excellent regioselectivities and functional group tolerance. This carbenoid coupling reaction does not require a strongly basic medium and gives benign N_2 as the only byproduct. The arylated products can readily be converted into other useful compounds (e.g., naphthalenes and isocoumarins) for specific applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) See Tables S3 and S4 in the SI for detailed optimization of the reaction conditions.

(13) We noted that the analogous reactions of 2-phenylpyridine in MeOH gave mono- (67%) and dialkylation (12%) products. However, the same reaction in DCE afforded the monoalkylation product (85%) exclusively (Table S2). To account for the overalkylations, we speculated that the [Cp*Rh^{III}] complex should form a rather stable metallacycle with 2-phenylpyridine. Compared with DCE, the active [Cp*Rh(OAc)]$^+$ complex would turnover more readily in MeOH by protonation of the alkylrhodacycle intermediates. Therefore, the higher availability of the [Cp*Rh(OAc)]$^+$ complex should favor further alkylation of the 2-phenylpyridine.

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(18) Benzoic acids are effective substrates for Rh-catalyzed diazomalonate C−H bond couplings. See Table S1 for a detailed substrate scope study.

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