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Cp*Rh(III)-Catalyzed Cross-Coupling of Alkyltrifluoroborate with α-Diazomalonates for C(sp^3)−C(sp^3) Bond Formation

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Ⓢ *Supporting Information*

ABSTRACT: A Cp*Rh(III)-catalyzed cross-coupling of alkyltrifluoroborate with α-diazomalonates was developed; the C(sp^3)−C(sp^3) bond coupled products were formed in up to 97% yields. The reaction tolerates some useful functional groups, including ketone, ester, amide, ether, sulfonyl, and thiophene. Electrospray ionization mass spectrometry (ESI-MS) analysis revealed the formation of a distinct molecular species corresponding to σ-alkylrhodium(III) complexes. The successful diazo coupling reaction may be attributed to coordination of the amide group that promotes stability of the alkylrhodium(III) complex through the formation of a five-membered metallacycle.

The use of diazo compounds for transition-metal-catalyzed cross-coupling reactions has recently received much attention.[1] Pioneered by van Vrenken,[2] Barluenga[3] and Wang,[4] arylpalladium(II) complexes have been extensively investigated for diazo coupling reactions for synthesis of aryl-substituted alkenes.[5−8] The diazo coupling reaction is believed to involve reactive arylpalladium−carbene complexes, and migratory carbene insertion would afford an σ-alkylpalladium(II) complex characterized by a quaternary stereocenter. Owing to the high propensity of the d^8 σ-alkylpalladium(II) to undergo β-hydride elimination, further functionalization of the σ-alkyl complexes has met limited success.[9]

Our recent findings revealed that organorhodium-mediated diazo cross-coupling reactions would offer a unique point of entry to synthesis of functionalized sp^3 carbon centers.[6c−f] For instance, arylrhodium(III) complexes of 1,2,3,4,5-pentamethylcyclopentadienyl (Cp*) ligand were found to couple with diazomalonates to form σ-alkylrhodium(III) complexes by migratory carbene insertion. With benzoquinoline as the substrate for the diazomalonate coupling reaction, the σ-alkylrhodium(III) complex has been structurally characterized.[6d] While protonolysis of the σ-alkylrhodium(III) would lead to C−H bond formation,[6d] the analogous alkyl complexes derived from benzohydroxamic acids would react by intramolecular N−O bond cleavage to effect C−N bond formation.[6e] Recently, we achieved a [Cp*Rh(III)]-catalyzed cascade arylation−chlorination of diazomalonates for the synthesis of α-aryl-α-chlorocarbonyl compounds.[6f] The cascade reaction should occur via migratory carbene insertion of the arylrhodium(III) to form a 1,3-diketonate complex, followed by chlorination with *N*-chlorosuccinimide.

Despite the facile C(aryl)−C(sp^3) bond formation by the diazo cross-coupling reactions, the analogous diazo reactions with σ-alkylmetal complexes for C(sp^3)−C(sp^3) bond formation are rare.[1,10,11] Recently, Szabó and co-workers reported a copper-catalyzed cross-coupling of substituted allylboronic acids with diazoketones for effective C(sp^3)−C(sp^3) bond formation.[12] Nevertheless, σ-alkyl−transition metal complexes bearing a β-hydrogen are reactive toward β-hydride elimination, and the development of broadly applicable catalytic alkyl−alkyl cross-coupling reactions remains a formidable challenge. Here, we report a successful [Cp*Rh(III)]-catalyzed cross-coupling reaction of α-diazomalonates with primary alkyltrifluoroborates bearing β-hydrogens; up to 97% C(sp^3)−C(sp^3)-coupled alkane was obtained.

At the outset, potassium alkyltrifluoroborate **1a** was employed as the model substrate for the Rh-catalyzed diazo-coupling reaction.[13] Compound **1a** was prepared by copper(I)-catalyzed β-boration of α,β-unsaturated carbonyl compounds according to a literature method.[14] When **1a** (0.2 mmol) was treated with diazomalonate **2a** (0.2 mmol), $[\mathrm{Cp^*RhCl_2}]_2$ (2.5 mol %), and AgOAc (15 mol %) in MeOH (1.5 mL) at 60 °C for 20 h,[6d] the desired C(sp^3)−C(sp^3)-coupled product was formed in 96% isolated yield (entry 1, Table 1). In the absence of AgOAc, the "**1a** + **2a**" coupling reaction still afforded **3aa** in 85% isolated yield (entry 2). Changing solvent to aprotic solvents, such as THF, dioxane, toluene, DCE, and CH_3CN [combined with water in a ratio of 20:1 (v/v)] resulted in lower product yields (51−85% NMR yield; entries 3−7).

The structural requirements of the alkyltrifluoroborate for effective diazo-coupling reactions have been examined. First, when **1b** containing a Weinreb amide moiety was employed as substrate, the diazomalonate coupling afforded **3ba** in 71% isolated yield (entry 8, Table 1). Notably, the related keto (**1c**) and ester (**1d**) derivatives were poor substrates for the diazo-coupling reaction with <10% yield of the desired products

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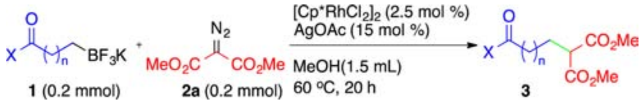
Table 1. Reaction Optimization and Substrate Scope Studies[a]



entry	n	X	solvent	yield (%)
1	1	NMe_2 (**1a**)	MeOH	96[b]
2	1	NMe_2 (**1a**)	MeOH	85[c] (93)[d]
3	1	NMe_2 (**1a**)	THF/H_2O (20:1)	85[d]
4	1	NMe_2 (**1a**)	dioxane/H_2O (20:1)	61[d]
5	1	NMe_2 (**1a**)	toluene/H_2O (20:1)	80[d]
6	1	NMe_2 (**1a**)	DCE/H_2O (20:1)	80[d]
7	1	NMe_2 (**1a**)	CH_3CN/H_2O (20:1)	51[d]
8	1	N(OMe)Me (**1b**)	MeOH	71[b]
9	1	Et (**1c**)	MeOH	5[d]
10	1	*t*BuO (**1d**)	MeOH	8[d]
11	2	NMe_2 (**1e**)	MeOH	6[d]
12	3	NMe_2 (**1f**)	MeOH	<3[d]

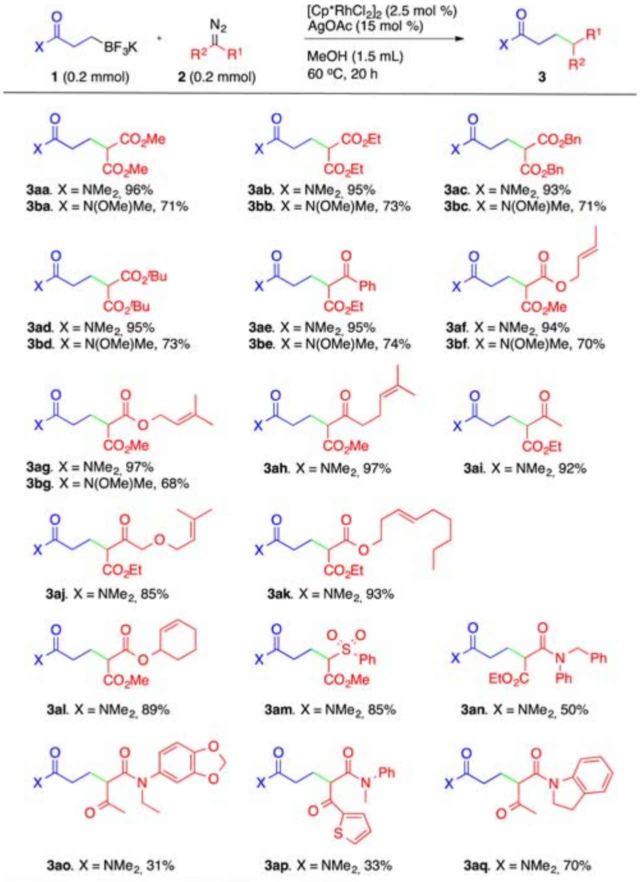
[a] Reaction conditions: potassium alkyltrifluoroborate **1** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), AgOAc (15 mol %), solvent (1.5 mL) at 60 °C for 20 h under N_2 atmosphere. [b] Isolated yield. [c] Isolated yield without AgOAc as additive. [d] Detected by ^1H NMR spectroscopy using 0.1 mmol of dibromomethane as internal standard.

being formed on the basis of ^1H NMR analysis of the reaction mixture (entries 9 and 10). Interestingly, side products dimethyl malonate (**4a**) and malonate dimer **4b** were detected.[15] Moreover, with *N,N*-dimethylamido moiety as the terminal group, the effect of chain length has also been studied. While the coupling of **1a** with diazomalonate **2a** afforded **3aa** in 96% yield, the analogous reactions of the alkyltrifluoroborates with a longer carbon chain [$n = 2$ (**1e**); $n = 3$ (**1f**)][16] gave negligible product yields. Notably, dimethyl malonate **4a** was found to be the major side product (entries 11 and 12, see the Supporting Information for details). To account for the above findings, coordination of the amide group should promote stability of the putative alkylrhodium(III) complex through formation a five-membered metallacycle.[17]

We next turned to examine the diazomalonate substrate scope (Scheme 1). The coupling reaction using amide substrate **1a** always gave better yields than the substrates bearing Weinreb amide (**1b**).[18] Changing the ester group from methyl to ethyl, benzyl, and *tert*-butyl was tolerated under the standard conditions, and the corresponding products were obtained in excellent (**3aa−ad**) and good (**3ba−bd**) yields. Similar to our previous findings,[6f] both disubstituted (**3af**, **3bf**, **3ak**, and **3al**) and trisubstituted C═C bonds (**3ag**, **3bg**, **3ah**, and **3aj**) were tolerated under the Rh^{III}-catalyzed conditions. Assuming the alkylrhodium(III) intermediate, this finding suggested that migratory carbene insertion is kinetically more competitive than intramolecular cyclopropanation. The Rh(III)-catalyzed reaction is also compatible with functional groups such as ether, sulfonyl, and thiophene, and the corresponding products (**3aj**, **3am**, and **3an**) were formed in 85%, 85%, and 33% yield, respectively.

For the reactions of some amide-containing diazo compounds, lower coupling yields (**3an−aq**, 31−50%) were encountered for **2n**, **2o**, and **2p**, each containing an *N*-Ar group. Notably, 70% cross-coupled product was obtained for **2q** bearing a dihydroindole moiety.

Scheme 1. Substrate Scope Study of Diazomalonate[a,b]



[a] Reaction conditions: potassium alkyltrifluoroborate **1a**,**b** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), AgOAc (15 mol %), MeOH (1.5 mL) at 60 °C for 20 h under N_2 atmosphere. [b] Isolated yield.

It is plausible that the diazo coupling reaction is initiated by transmetalation with the alkyltrifluoroborate to form a σ-alkylrhodium(III) complex **A**. In this work, the reaction of **1a** with $[Cp^*Rh(OAc)_2]$ was analyzed by the ESI-MS technique. As shown in Figure 1, a prominent peak at $m/z = 338.0984$ was observed (full scan). More detailed analysis of the peak

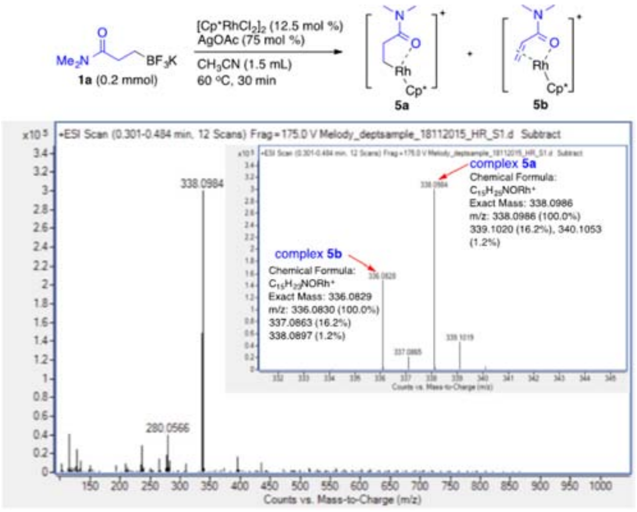
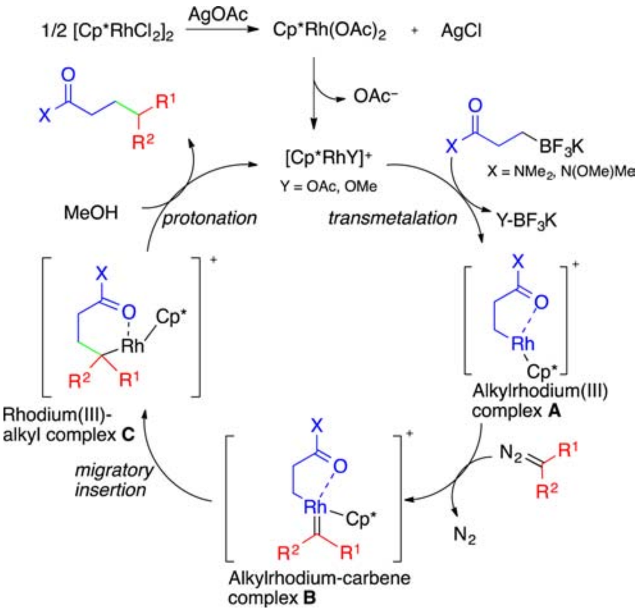


Figure 1. ESI-MS analysis of the reaction of $[Cp^*Rh(OAc)_2]$ with **1a** in MeCN.

composition revealed two distinct molecular ion species with maximum *m*/*z* peak intensity at 338.0984 and 336.0828. These ion species are assigned, respectively, as the σ-alkylrhodium(III) complex **5a** and π-acrylamide−rhodium(III) complex **5b** based on isotope simulation studies.[19]

Scheme 2 depicts a plausible mechanism for the diazo-coupling reaction. The alkylrhodium(III) complex **A** generated by transmetalation from the organoborate would then react with diazo carbonyl compound, presumably via formation of rhodium−carbene **B**. Subsequent migratory carbene insertion would afford alkylrhodium complex **C**. However, a concerted alkyl migration−dinitrogen elimination pathway cannot be ruled out. Complex **C** should undergo protonolysis with MeOH to furnish the alkane product.

Scheme 2. Plausible Reaction Mechanism



In summary, the first Rh(III)-catalyzed cross-coupling reaction of alkyltrifluoroborate with α-diazomalonates for $C(sp^3)-C(sp^3)$ bond formation is developed. The present strategy brings about $C(sp^3)-C(sp^3)$ bond formation in moderate to excellent yields under operationally simple and mild reaction conditions. Importantly, the chelation of the carbonyl oxygen to the Rh center through a five-membered metallacycle should stabilize the alkylmetal intermediate to avoid spontaneous β-hydride elimination. Furthermore, the Rh-coupling reaction tolerates various functional groups such as ketone, ester, amide, ether, sulfonyl, thiophene, etc. Further exploration of this reaction for multicomponent reactions is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00283.

Detailed experimental procedures, analytical data, and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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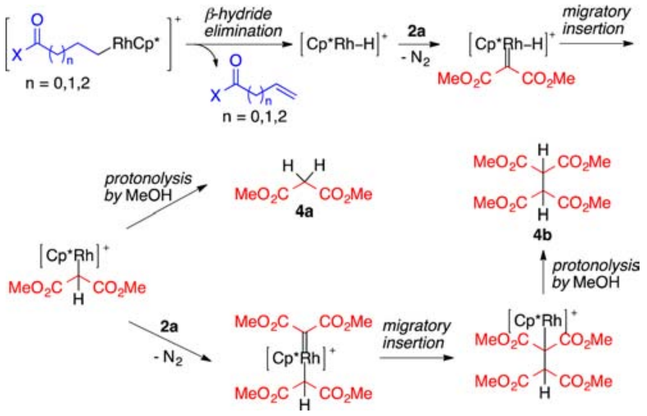

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