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A novel catalytic decarbonylative Heck-type reaction and conjugate addition of aldehydes to unsaturated carbonyl compounds

Luo Yang, Camille A. Correia, Xiangyu Guo, Chao-Jun Li *

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec, Canada H3A 2K6

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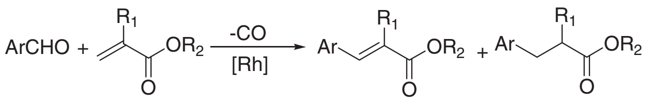
ABSTRACT

A novel rhodium-catalyzed decarbonylative reaction of aldehydes with unsaturated carbonyl compounds was discovered to generate Heck-type reaction product and conjugate addition product.

The transition metal-catalyzed Heck-type reactions[1] and conjugate addition reactions[2] are among the most important reactions in modern synthetic organic chemistry. Numerous biological compounds, natural products, and fine chemicals have been synthesized by these reactions.[3] However, an archetypical requirement of such reactions is the pre-generation of organic halides or organometallic reagents. Recently, through the work of Gooβen,[4] Myers,[5] Tunge[6] and others including us,[7] decarboxylation reactions which utilize pre-existing carboxylic acid as readily available and convenient functional group amenable for various C–C bond formation reactions have been developed. On the other hand, the alternative decarbonylation of aldehydes, which has been frequently used for the removal of aldehdye,[8] has never been used for C–C bond formation purposes until our recently reported decarbonylative addition of aldehyde to alkyne,[9] providing a novel olefin synthesis. The success of this reaction encouraged us to explore the potential application of decarbonylation for the Heck and conjugate additions. Herein, we will report the preliminary success of such reactions catalyzed by rhodium (Scheme 1).

During the past decade, rhodium-catalyzed conjugate additions of organoboron, tin, silicon, bismuth, lead, titanium, zinc, and zirconium reagents have been shown to be highly effective by us[10] and others[11] even under aqueous conditions. Furthermore, through the work of Hayashi and many others[12] various highly efficient asymmetric conjugate addition of organoboronic acids has also been developed. To begin our study, we examined the reaction between 4-methoxybenzaldehyde and butyl methacrylate by using $(CO)_2Rh^I(acac)$, which has been shown to be a robust catalyst for the conjugate additions of organometallic compounds. However, only a trace amount of the Heck-type reaction product **3a** was detected after 24 h in toluene (Table 1, entry 1). Since the presence of water was crucial for some rhodium-catalyzed coupling reactions,[10,13] water was added as a cosolvent and the yield was increased to 12% (entry 2).

Based on these initial results, a detailed optimization was carried out. We found that a small amount of $Ni^{II}(acac)_2$ was beneficial to the reaction, and the yield was improved further from 24% to 72% after the addition of 10 mol % K_2CO_3 (entries 3 and 4). Other bases such as Na_2CO_3 and cesium pivalate were also tested but were not as effective as K_2CO_3 (entries 5–7). Fe, Co, and Cu salts bearing acetylacetonate anion were also examined; only $Co^{III}(acac)_3$ provided a moderate yield (entries 8–10). Notably, this decarbonylative coupling occurred in a common solvent system composed of toluene and water (15:1). Other solvent such as chlorobenzene, dichloroethane, and benzene lead to decreased yields and 1,4-dioxane was not viable in this reaction (entries 11–14). The substrate concentration was also examined and the best yield was obtained when the concentration of the aldehyde was ca. 0.33 M (entries 4, 15 and 16). Finally, the relatively high reaction



Scheme 1. Rhodium-catalyzed decarbonylative coupling reaction of aldehyde with acrylate.

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* Corresponding author. Tel.: +1 514 398 8457; fax: +1 514 398 3797.
E-mail address: cj.li@mcgill.ca (C.-J. Li).

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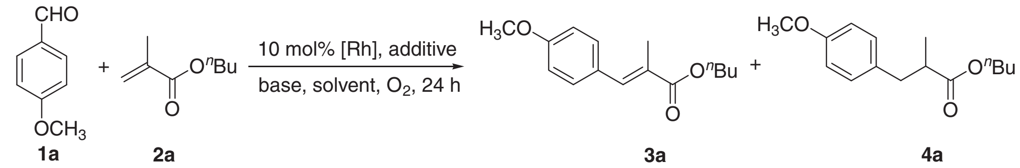
Table 1

Optimization for the Rh-catalyzed decarbonylative coupling reaction[a]



Entry	Rh catalyst	Additive (mol %)	Base (mol %)	Solvent	Yield (%) **3a** + **4a**	Ratio[b] **3a**/**4a**
1	$(CO)_2Rh^I(acac)$	–	–	Toluene	5%	ND
2	$(CO)_2Rh^I(acac)$	–	–	Toluene + H_2O	12%	ND
3	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	–	Toluene + H_2O	24%	60:40
4	**$(CO)_2Rh^I(acac)$**	**$Ni^{II}(acac)_2$ (20)**	**K_2CO_3 (10)**	**Toluene + H_2O**	**72%**	**65:35**
5	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (20)	Toluene + H_2O	63%	56:44
6	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	Na_2CO_3 (10)	Toluene + H_2O	28%	41:59
7	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	CsOPiv (20)	Toluene + H_2O	24%	62:38
8	$(CO)_2Rh^I(acac)$	$Fe^{III}(acac)_3$ (20)	K_2CO_3 (10)	Toluene + H_2O	Trace	ND
9	$(CO)_2Rh^I(acac)$	$Co^{III}(acac)_3$ (10)	K_2CO_3 (10)	Toluene + H_2O	50%	60:40
10	$(CO)_2Rh^I(acac)$	$Cu^{II}(acac)_3$ (20)	K_2CO_3 (10)	Toluene + H_2O	22%	36:64
11	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	PhCl + H_2O	9%	54:46
12	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Dioxane + H_2O	0	ND
13	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	DCE + H_2O	45%	66:34
14	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Benzene + H_2O	40%	67:33
15	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O[c]	63%	56:44
16	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O[d]	49%	73:27
17	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O	16%[e]	44:56
18	$(CO)_2Rh^I(acac)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O	14%[f]	ND
19	$(PPh)_4Rh^IH$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O	23%	34:66
20	$(COD)_2Rh^I(BF_4)$	$Ni^{II}(acac)_2$ (20)	K_2CO_3 (10)	Toluene + H_2O	50%	55:45

[a] Conditions: **1a** (0.1 mmol), **2b** (0.4 mmol), 10 mol % [Rh], additive, solvent (0.3 mL), H_2O (0.02 mL), 150 °C, 24 h, under O_2 atmosphere, unless otherwise noted.

[b] Yields and the ratios were determined by ^1H NMR analysis of the crude reaction mixture using an internal standard.

[c] Toluene, 0.2 mL.

[d] Toluene, 0.4 mL.

[e] Reacted at 140 °C.

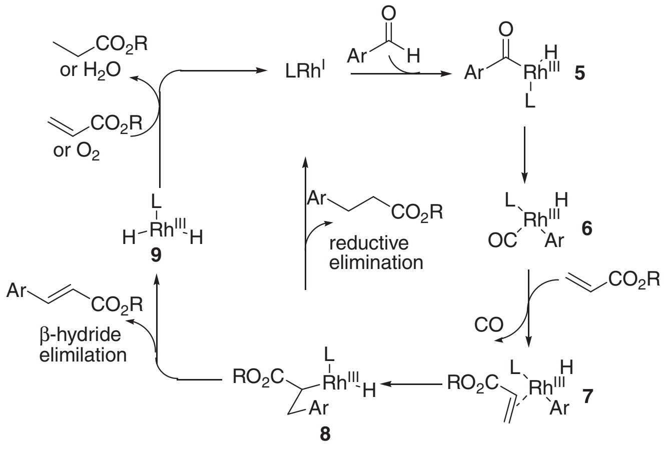
[f] Reacted under argon.

temperature was important, decreasing the reaction temperature gave a much lower yield (entries 4 and 18). Besides $(CO)_2Rh^I(acac)$, this decarbonylative coupling reaction can also be catalyzed by $(PPh)_4Rh^IH$ and $(COD)_2Rh^I(BF_4)$, providing the target products in 23% and 50% total yields, respectively. It is worth noting that an excess of butyl methacrylate was required to serve as a sacrificial hydrogen acceptor[13c] (Scheme 2, proposed mechanism).

Having established the standard reaction conditions, the substrate scope of this novel decarbonylative coupling reaction was explored. As shown by the results in Table 2, various aromatic aldehydes reacted with butyl methacrylate **2a** smoothly. Electron-rich aromatic aldehydes, with an alkoxyl or dimethylamino substituent at the *para*-position, decarbonylatively coupled with **2a** efficiently to furnish the corresponding Heck-type and conjugate addition products in 71% and 56% total yields, respectively (Table 2, entries 1 and 2). 4-Phenylbenzaldehyde was also applicable to this reaction and provided **3c** and **4c** in moderate yields (entry 3). Fluorinated aryl groups are highly useful building blocks in biomedical studies.[14] Thus, 4-fluoro benzaldehyde was tested and low yields of the corresponding products were obtained (entry 4). Furthermore, both α- and β-naphthaldehydes could take part in this decarbonylative coupling reaction (entries 5 and 6). Under the same reaction conditions, the decarbonylative coupling reaction of aliphatic aldehydes such as hydrocinnaldehyde **1f** and butyl methacrylate were examined (entry 7), and only a trace amount of the corresponding coupling products can be detected by GC–MS.

Apart from butyl methacrylate **2a,** both ethyl methacrylate **2b** and *tert*-butyl acrylate **2c** could also undergo decarbonylative coupling with aromatic aldehyde smoothly, to give the corresponding products (entries 7 and 8).

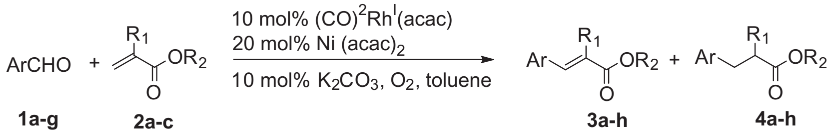
A tentative mechanism to explain the product formation is illustrated in Scheme 2. First, low valent rhodium catalyst undergoes oxidative addition with the aromatic aldehyde C–H bond to produce acylrhodium hydride **5**, which decarbonylates to give arylrhodium hydride **6**. Second, coordinated carbon monoxide is replaced by acrylate as a ligand to rhodium catalyst to form complex **7**. Subsequently, insertion of C=C into complex **7** generates **8**, which undergoes reductive elimination to yield the conjugate addition product and regenerates the low valent rhodium catalyst or β-hydride elimination to yield the Heck-type product and rhodium complex **9**. Rh(I) active catalyst is regenerated from

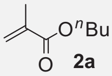
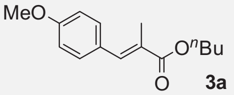
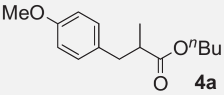
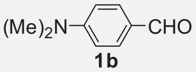
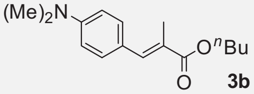
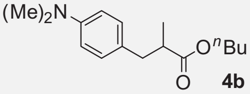
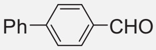
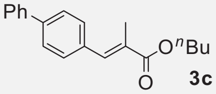
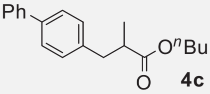
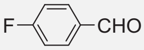
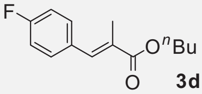
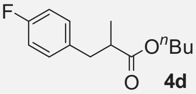
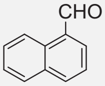
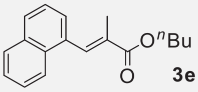
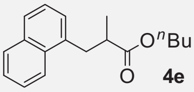
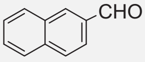
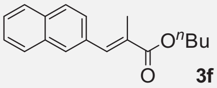
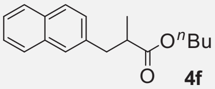
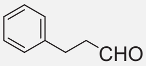
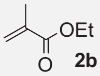
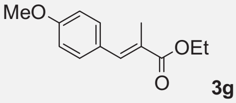
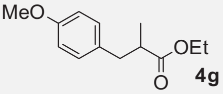
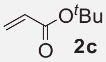
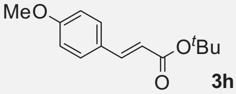
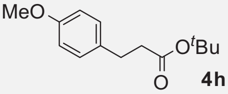


Scheme 2. Tentative mechanism for the rhodium-catalyzed decarbonylative coupling reaction.

Table 2

Rh-Catalyzed decarbonylative coupling reaction of aldehydes with acrylates[a]



Entry	Aldehyde	Acrylate	Product		Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	 **4a**	71 **3a**/**4a** = 65:35
2	 **1b**	**2a**	 **3b**	 **4b**	56 **3b**/**4b** = 82:18
3	 **1c**	**2a**	 **3c**	 **4c**	51 **3c**/**4c** = 74:26
4	 **1d**	**2a**	 **3d**	 **4d**	38 **3d**/**4d** = 70:30
5	 **1e**	**2a**	 **3e**	 **4e**	73 **3e**/**4e** = 87:13
6	 **1f**	**2a**	 **3f**	 **4f**	63 **3f**/**4f** = 60:40
7	 **1g**	**2a**	–	–	Trace
8	**1a**	 **2b**	 **3g**	 **4g**	54 **3h**/**4h** = 60:40
9	**1a**	 **2c**	 **3h**	 **4h**	52 **3h**/**4h** = 65:35

[a] Conditions[15]: **1** (0.2 mmol), **2** (0.8 mmol), 10 mol % (CO)$_2$Rh^I(acac), 20 mol % Ni(acac)$_2$, 10 mol % K_2CO_3, toluene (0.6 mL), H_2O (0.04 mL), 150 °C, 24 h, under O_2 atmosphere.

[b] Isolated yields after flash silica gel chromatograph and the ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

complex **9** assisted by the excessive acrylate[13c] or dioxygen. Alternatively, the activation of aldehyde and subsequent decarbonylation were catalyzed by rhodium and the arylrhodium hydride **6** undergoes transmetalation to produce the corresponding arylnickel species to take part in the Heck-type reaction and conjugate addition reaction.

In conclusion, we have discovered the first decarbonylative Heck-type reaction and conjugate addition of aldehyde with unsaturated carbonyl compounds. Efforts to increase the efficiency of the reaction as well as to further tune the reaction into selective Heck-type or conjugate addition is undergoing in our laboratory.

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15. *A general experimental procedure for the decarbonylative coupling is described as following*: An oven-dried reaction vessel was charged with 4-methoxybenzaldehyde **1a** (29.8 mg, 0.2 mmol), butyl methacrylate **2a** (0.8 mmol, 114 mg, 4 equiv), $(CO)_2Rh^I(acac)$ (5.1 mg, 0.02 mmol, 10 mol %) and $Ni(acac)_2$ (10.2 mg, 0.04 mmol, 20 mol %), K_2CO_3 (2.8 mg, 0.02 mmol, 10 mol %), vacuumed, and refilled with argon. Then toluene (0.6 mL) and water (0.04 mL) were added by syringe and the vessel was sealed and heated at 150 °C (oil bath temperature). After 24 h, the resulting mixture was cooled to rt, transferred to silica gel column directly, and eluted with hexanes and ethyl acetate (95:5) to give pure products **3a** and **4a**.

    Compound **3a**: oil; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 7.63 (s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 4.21 (t, J = 6.5 Hz, 2H), 3.84 (s, 3H), 2.13 (s, 3H), 1.68–1.73 (m, 2H), 1.41–1.49 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ (ppm) 169.2, 159.8, 138.5, 131.7, 130.1, 114.0, 113.9, 64.9, 55.5, 31.0, 19.5, 14.3, 14.0. HRMS (ESI) *m/z*: $[M+1]^+$ calcd for $C_{15}H_{21}O_3$, 249.1485; found: 249.1480.

    Compound **4a**: oil; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 7.08 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.03 (t, J = 6.5 Hz, 2H), 3.78 (s, 3H), 2.95 (dd, J = 7.0, 13.0 Hz, 1H), 2.59–2.70 (m, 2H), 1.51–1.57 (m, 2H), 1.28–1.33 (m, 2H), 1.14 (d, J = 6.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ (ppm) 176.5, 158.3, 131.6, 128.7, 126.7, 64.4, 55.4, 42.0, 39.1, 30.8, 19.3, 17.0, 13.9. HRMS (ESI) *m/z*: $[M+1]^+$ calcd for $C_{15}H_{23}O_3$, 251.1642; found: 258.1635.