Coupling Reactions

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Selective 1:2 Coupling of Aldehydes and Allenes with Control of Regiochemistry**

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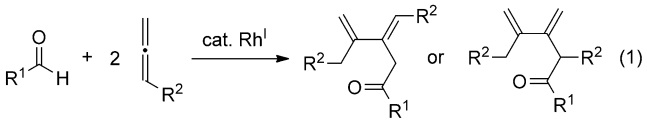
Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

Transition-metal-catalyzed coupling reactions of aldehydes with unsaturated compounds provide useful methods for the synthesis of alcohols and ketones by C–C bond formation.[1] Allenes are often employed as the reactive coupling partner. Their two orthogonal π-systems possess comparable potential to participate in the coupling reactions, and the regiochemistry associated with unsymmetrical allenes results in wide structural variations in the products. A nickel(0)-catalyzed reductive coupling reaction of aldehydes, allenes, and silanes affords allylic alcohol derivatives.[2] In contrast, homoallylic alcohols are produced by a nickel(0)-catalyzed alkylative coupling reaction using organozinc compounds instead of silanes.[3,4] A hydrogenative coupling reaction of aldehydes with allenes is catalyzed by iridium(I) and ruthenium(II) complexes and leads to the formation of homoallylic alcohols.[5] A rhodium(I)-catalyzed coupling reaction of thio-substituted aldehydes with allenes proceeds through oxidative addition of an aldehydic C–H bond to furnish β,γ-unsaturated ketones.[6,7] We recently found a rhodium(I)-catalyzed dimerization reaction of allenes;[8] this discovery led us to study a rhodium(I)-catalyzed coupling reaction of aldehydes with allenes.[9] Herein is described a new coupling reaction of one molecule of aldehyde and two molecules of allene to give β,γ-dialkylidene ketones.[10] Either one of two constitutional isomers is selectively obtained depending on the counterion of the employed rhodium(I) catalyst [Eq. (1)].

Initially, 2-naphthaldehyde (**1a**) was treated with 1.1 equiv of 5-phenylpenta-1,2-diene (**2a**) in the presence of



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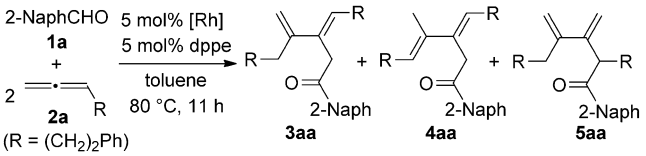
[{RhCl(cod)}$_2$] (5 mol% of Rh) and dppe (5 mol%) in toluene (Table 1, entry 1). After the reaction mixture was heated at 80°C for 11 h, 40% of the aldehyde **1a** was consumed and the other portion of **1a** remained intact. While the formation of a 1:1 coupling product of **1a** with **2a** was not observed, an isomeric mixture of 1:2 coupling products of **1a** with **2a** was formed. Chromatographic purification afforded a 93:7 mixture of the products **3aa** and **4aa** in 33% combined yield along with a trace amount (ca. 2%) of the product **5aa**. When the ratio **2a**/**1a** was increased to 3.5:1, the aldehyde **1a** was quantitatively transformed into the β,γ-dialkylidene ketones (**3aa**:**4aa**:**5aa** = 90:6:4; Table 1, entry 2). Analogous rhodium bromide and rhodium iodide complexes gave results inferior to the chloride complex in terms of both yield and product selectivity (Table 1, entries 3 and 4).[11] A slightly better result was obtained with the use of [{RhCl(nbd)}$_2$] (**3aa**:**4aa**:**5aa** = 91:6:3; Table 1, entry 5; conditions A).

To our surprise, completely different product selectivity was observed when cationic rhodium(I) complexes were

Table 1: Rhodium(I)-catalyzed coupling reaction of **1a** and **2a**: Screening of rhodium(I) complexes.[a]



No.	[Rh]	Total yield [%][b]	**3aa**/**4aa**/**5aa**[c]
1	[{RhCl(cod)}$_2$][d]	41 (33)[e]	89:7:4
2	[{RhCl(cod)}$_2$]	99 (84)[e]	90:6:4
3	[{RhBr(cod)}$_2$]	72	83:8:9
4	[{RhI(cod)}$_2$]	51	72:9:19
5	**[{RhCl(nbd)}$_2$]**	**100 (87)[e]**	**91:6:3**
6	[Rh(cod)$_2$]BF$_4$	35	13:0:87
7	[Rh(cod)$_2$]PF$_6$	59	9:0:91
8	[Rh(cod)$_2$]OTf	75	6:0:94
9	**[Rh(cod)$_2$]OTf[f]**	**100 (79)[g]**	**5:0:95**

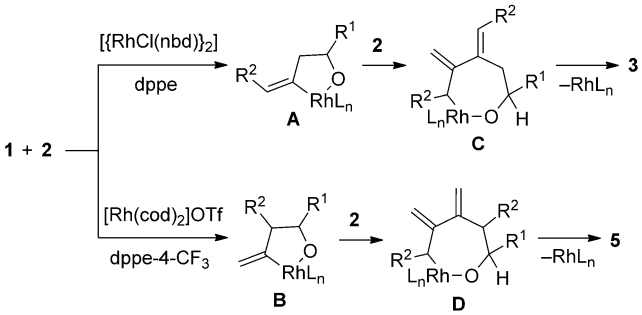
[a] **1a** (0.2 mmol) and **2a** (0.7 mmol, 3.5 equiv) in toluene (1 mL) were heated at 80°C for 11 h in the presence of [Rh] (10 μmol) and dppe (10 μmol) unless otherwise noted. [b] Total yield of **3aa**, **4aa**, and **5aa** determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Product ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Using **1a** (0.2 mmol) and **2a** (0.22 mmol, 1.1 equiv). [e] The combined yield of **3aa** and **4aa** after chromatographic purification is in parentheses. [f] Using dppe-4-CF$_3$ (10 μmol) at 40°C for 24 h. [g] Yield of isolated **5aa** after chromatographic purification in parenthesis. cod = cyclooctadiene, dppe = 1,2-bis(diphenylphosphino)-ethane, 2-Naph = 2-naphthyl, nbd = norbornadiene, Tf = trifluoromethanesulfonyl.

examined. The isomer **5aa** became the major product when $[Rh(cod)_2]BF_4$ was used instead of $[\{RhCl(nbd)\}_2]$ (Table 1, entry 6). The selectivity was affected by the counterion, and the triflate complex $[Rh(cod)_2]OTf$ showed better yield and selectivity (Table 1, entry 8). The highest yield and selectivity of **5aa** (79%, **3aa**:**4aa**:**5aa** = 5:0:95) were attained when dppe-4-CF_3 (1,2-bis(di(4-trifluoromethylphenyl)phosphino)-ethane) was used as the additional ligand (Table 1, entry 9; conditions B). Thus, either of the two constitutional isomers **3** and **5** was selectively prepared from the same starting materials by using a suitable rhodium catalyst.

The results obtained with different combinations of aldehydes and allenes under conditions A ($[\{RhCl(nbd)\}_2]$/dppe) are shown in Table 2. A diverse array of aldehydes **1b–h** reacted well with **2a** to afford the corresponding 1:2 coupling products **3ba–ha** in moderate to good yield with good product selectivity (Table 2, entries 1–7). The reaction of **1a** with monosubstituted allenes **2b–g** having various primary alkyl groups proceeded efficiently to demonstrate good functional group compatibility (Table 2, entries 8–13). On the other hand, the allenes possessing cyclohexyl and *tert*-butyl groups failed to undergo the coupling reaction with **1a**, probably because of steric reasons.

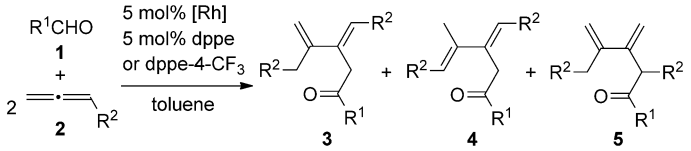
The coupling reaction was carried out also under conditions B ($[Rh(cod)_2]OTf$/dppe-4-CF_3) and the results are shown in Table 2. The reaction of various aldehydes **1b–h** with **2a** under conditions B afforded the corresponding isolated products **5ba–ha** in yields ranging from 45% to 78% (entries 1–7). Functional groups such as benzyloxy, siloxy, hydroxy, and 1,3-dioxoisoindolin-2-yl were tolerated in the alkyl chain, as was the case with conditions A (Table 2, entries 10–13). Higher product selectivity was generally observed with the reaction under conditions B than with the reaction under conditions A. In particular, the formation of the isomer **4** was not observed under conditions B.

Although it is difficult to delineate a single mechanistic pathway leading to β,γ-dialkylidene ketones **3** and **5** from aldehyde **1** and allene **2**, a plausible mechanism is depicted in Scheme 1.[12] Initially, intermolecular oxidative cyclization of **1** and **2** occurs on rhodium(I) to give five-membered ring oxarhodacyclic intermediates **A** and **B**.[3] The counterion of the employed rhodium complexes dictates the regiochemistry of this step. The neutral rhodium(I) chloride complex favors the coupling at the terminal sp^2 carbon of the allene to form **A**. On the other hand, the cationic rhodium(I) triflate complex favors the coupling at the internal sp^2 carbon to form **B**, although the reason for this change in reactivity is unclear. Subsequent insertion of another molecule of **2** into the Rh–C_{sp^2} bond at the internal C–C double bond[13] expands the five-membered ring oxarhodacycles **A** and **B** to seven-membered ring oxarhodacycles **C** and **D**, respectively. β-Hydride elimination furnishes a carbonyl group and reductive elimination follows to give the products **3** and **5** together with the catalytically active rhodium(I) complex.



Scheme 1. Proposed mechanism for the rhodium(I)-catalyzed synthesis of **3** and **5** from **1** and **2**.

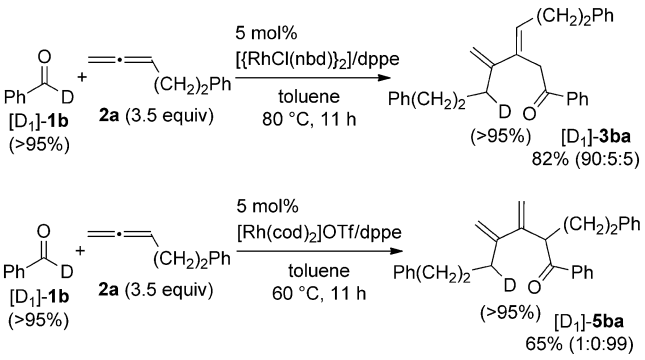
Table 2: Rhodium(I)-catalyzed coupling reaction of **1** and **2**.[a]



No.	**1** (R^1)	**2** (R^2)	Conditions A yield [%] **3**+**4**[b]	**3**/**4**/**5**[c]	Conditions B yield [%] **5**[d]	**3**/**4**/**5**[c]
1	**1b** (Ph)	**2a** ($(CH_2)_2Ph$)	82	87:7:6	67[h]	1:0:99
2	**1c** (4-tol)	**2a**	76	86:7:8	62[h]	1:0:99
3	**1d** (2-tol)	**2a**	79	90:8:2	45[h]	1:0:99
4	**1e** (4-$CF_3C_6H_4$)	**2a**	82	90:7:3	78	6:0:94
5	**1f** (4-$MeOC_6H_4$)	**2a**	68[e]	88:7:5	47[h]	1:0:99
6	**1g** (2-furyl)	**2a**	68[f]	81:6:13	77	1:0:99
7	**1h** (Cy)	**2a**	63	90:7:3	61	5:0:95
8	**1a** (2-naphthyl)	**2b** (*n*Hex)	75	89:6:5	82	3:0:97
9	**1a**	**2c** (CH_2Cy)	79	90:6:4	79	7:0:93
10	**1a**	**2d** ($(CH_2)_4OBn$)	82	88:7:5	82	3:0:97
11	**1a**	**2e** ($(CH_2)_4OTBS$)	77	89:7:4	80	4:0:96
12	**1a**	**2f** ($(CH_2)_4OH$)	57[g]	89:7:4	56[i]	3:0:97
13	**1a**	**2g** ($(CH_2)_4N$(phth))	97	89:7:4	85	3:0:97

[a] Conditions A: **1** (0.2 mmol) and **2** (0.7 mmol, 3.5 equiv) in toluene (1 mL) were heated at 80°C for 11 h in the presence of $[\{RhCl(nbd)\}_2]$ (5 μmol) and dppe (10 μmol) unless otherwise noted. Conditions B: **1** (0.2 mmol) and **2** (0.7 mmol, 3.5 equiv) in toluene (1 mL) were heated at 40°C for 24 h in the presence of $[Rh(cod)_2]OTf$ (10 μmol) and dppe-4-CF_3 (10 μmol) unless otherwise noted. [b] Combined yield of **3** and **4** after chromatographic purification. [c] Product ratios determined by ^1H NMR analysis. [d] Yield of isolated **5**. [e] 24 h. [f] Using **2a** (0.9 mmol, 4.5 equiv) in the presence of $[\{RhCl(nbd)\}_2]$ (7.5 μmol) and dppe-4-CF_3 (15 μmol). [g] Using **2f** (0.9 mmol, 4.5 equiv) in the presence of $[\{RhCl(nbd)\}_2]$ (7.5 μmol) and dppe (15 μmol). [h] Using dppe (10 μmol) at 60°C for 11 h. [i] Using **2f** (0.9 mmol, 4.5 equiv). Bn = benzyl, phth = phthaloyl, TBS = *tert*-butyldimethylsilyl.

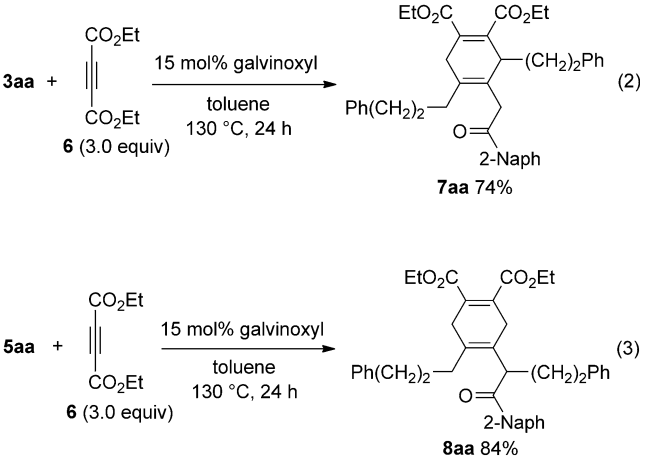
We carried out the coupling reaction using deuterated benzaldehyde (PhCDO; Scheme 2). Products $[D_1]$-**3ba** and $[D_1]$-**5ba** had a deuterium atom incorporated at the allylic position; this result is consis-



Scheme 2. Deuterium-labeling studies.

tent with the β-hydride elimination/reductive elimination path from **C** and **D**.

β,γ-Dialkylidene ketones can act as a diene in the Diels–Alder reaction [Eq. (2) and Eq. (3)]. Treatment of **3aa** and **5aa** with diethyl acetylenedicarboxylate (**6**) in the presence of galvinoxyl afforded cyclic adducts **7aa** and **8aa**, respectively.



In summary, a new rhodium-catalyzed coupling reaction of one molecule of aldehyde and two molecules of allene was developed, and gives selectively either of two constitutional isomers of β,γ-dialkylidene ketones that are difficult to synthesize by other methods. Interestingly, the regioselectivity of the reaction depends on the counterion of a rhodium(I) complex. Further studies to elucidate the mechanism of this reaction and to expand its utility are in progress.

Experimental Section

Typical procedure for the coupling reaction of aldehydes with allenes using $[\{RhCl(nbd)\}_2]$/dppe as the catalyst (Table 1, entry 5; conditions A): To a side-arm tube equipped with a stirrer bar was added **1a** (31.2 mg, 0.2 mmol, 1.0 equiv), $[\{RhCl(nbd)\}_2]$ (2.3 mg, 5.0 μmol; 5 mol% of Rh), and dppe (4.0 mg, 10 μmol, 5 mol%). The tube was evacuated and refilled with argon three times. Then, **2a** (100.9 mg, 0.7 mmol, 3.5 equiv) and toluene (1.0 mL) were added via a syringe and the tube was closed. After being heated at 80 °C for 11 h, the reaction mixture was cooled to room temperature. The resulting mixture was passed through a pad of Florisil and eluted with ethyl acetate (40–50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel; *n*-hexane/ether = 10:1) to give the products **3aa** and **4aa** (77.1 mg, 0.17 mmol, 87% combined yield, **3aa**/**4aa** = 94:6).

Typical procedure for the coupling reaction of aldehydes with allenes using $[Rh(cod)_2]OTf$/dppe-4-CF_3 as the catalyst (Table 1, entry 9; conditions B): To a side-arm tube equipped with a stirrer bar was added **1a** (31.2 mg, 0.2 mmol, 1.0 equiv), $[Rh(cod)_2]OTf$ (4.7 mg, 5.0 μmol; 5 mol% of Rh), and dppe-4-CF_3 (6.7 mg, 10 μmol, 5 mol%). The tube was evacuated and refilled with argon three times. Then, **2a** (100.9 mg, 0.7 mmol, 3.5 equiv) and toluene (1.0 mL) were added via a syringe and the tube was closed. After being heated at 40 °C for 24 h, the reaction mixture was cooled to room temperature. The resulting mixture was passed through a pad of Florisil and eluted with ethyl acetate (40–50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel; *n*-hexane/Et_2O = 10:1) and gel permeation chromatography (GPC; $CHCl_3$) to give the product **5aa** (70.3 mg, 0.158 mmol, 79% yield).

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[13] The minor isomer **4** could be formed through the insertion of **2** into the Rh–C_{sp^2} bond of **A** at the terminal C–C double bond and subsequent β-hydride elimination/reductive elimination.

