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The Ullmann coupling reaction catalyzed by a highly reactive rhodium-aryl complex derived from Grignard reagent and its application

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Abstract

A novel Rh-catalyzed one-pot Ullmann homo-coupling reaction of Grignard reagents was achieved. The reaction with bromobenzenes having an electron-donating group or halogen group gave the corresponding homo-coupling products in good yields, although heterocyclic or aliphatic bromides did not give the products. A highly reactive

Rh(III)-bis(aryl) complex would play an important role in giving the homo-coupling products in this reaction. The reaction was applied to the integrin inhibitor that was being developed in parallel. As the result, we synthesized a novel inhibitor for integrins which is critical for several diseases.

Keywords

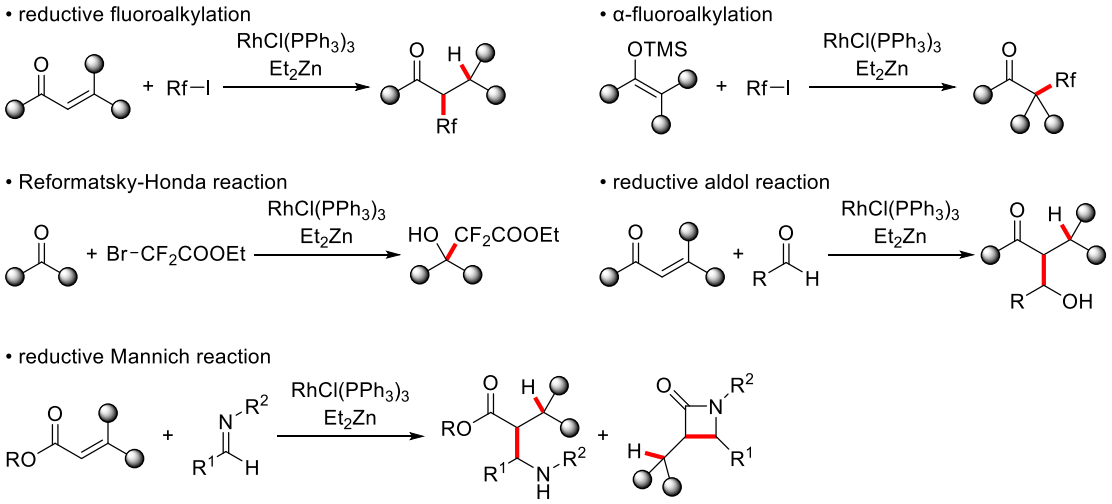
Ullmann reaction; rhodium catalyst; homo-coupling; biphenyltetracarboxylic acid; integrin inhibitor

Introduction

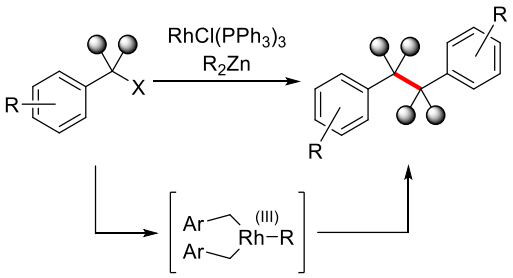
The Ullmann reaction is a coupling reaction of aryl halides using copper, traditionally using metallic copper-bronze alloy, and has been used as one of the methods for obtaining homo-coupling biaryl compounds.[1,2] Starting from this work, various modified Ullmann-type coupling reactions have been developed.[3,4] However, the reaction usually required high temperatures and the yield was not very high. Therefore, the reaction has led to the development of various homo-coupling reactions using transition metal catalysts such as palladium, nickel, and iron.[5–11] In recent years, transition metal-free coupling reactions have also been developed for environmentally benign synthetic applications.[12–16]

Even though the development of green organic reactions is also important, there is no doubt a transition metal catalyzed carbon-carbon (C–C) bond formation, especially coupling reaction, is one of the most powerful tools in organic synthetic chemistry. Among the transition metal catalysts, there are a number of reactions using a rhodium catalyst such as aldol-type reaction, 1,4-addition reaction, hydroacylation, and carbocyclization.[17–20] Furthermore, Rh-catalyzed coupling reactions have

undergone intense study, and it is even possible to insert a sp^3 carbon (Csp^3) into a molecule for the C–C bond formation.[21–25] We also reported an effective formation of a highly reactive rhodium-alkyl complex and its applications to reductive fluoroalkylation,[26,27] α-fluoroalkylation,[28–32] Reformatsky-Honda reaction,[33–39] reductive α-acylation,[40–42] reductive aldol reaction,[43–45] and reductive Mannich reaction (Scheme 1).[46,47] Moreover, we reported a new Rh-catalyzed Csp^3–Csp^3 homo-coupling reaction of benzyl halides, which was concerning a rhodium-bis(benzyl) complex derived from dialkylzinc (R_2Zn) and $RhCl(PPh_3)_3$ (Scheme 2).[48] Following these outcomes, as part of a research program aimed at a wide range of Rh catalyzed C–C bond formation reactions, in this paper, we would like to report the Ullmann-type reaction catalyzed by a highly reactive rhodium-bis(aryl) complex derived from aryl Grignard reagents.



Scheme 1: Previous works on Rh catalyzed C–C bond formation reactions.

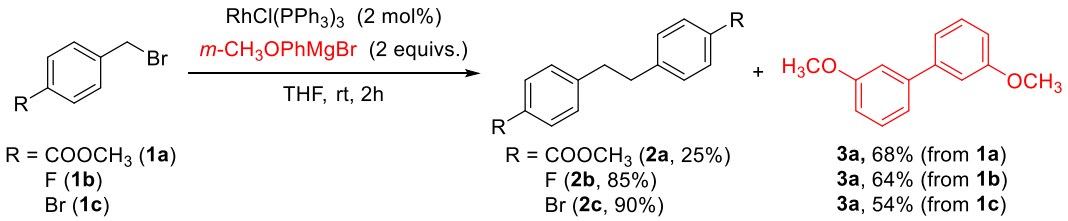


Scheme 2: Rh catalyzed homo-coupling reaction of benzyl halides.

Results and Discussion

Methodology development:

In our work towards Rh-catalyzed homo-coupling reactions of benzyl halides, we observed that a similar rhodium-bis(benzyl) complex can also be formed from benzyl halide by using a Grignard reagent instead R_2Zn in the presence of $RhCl(PPh_3)_3$ to subsequently give the desired dibenzyl product. For example, the reaction gave the desired dibenzyl product (**2a**) in 25% along with the corresponding biphenyl product (**3a**) in 68%, when methyl 4-(bromomethyl)benzoate (**1a**) was treated with 2.0 equivs. of 3-methoxyphenylmagnesium bromide in the presence of 2 mol% of $RhCl(PPh_3)_3$ in THF as shown in Scheme 3. In addition, similar reactions using 4-fluorobenzyl bromide (**1b**) or 4-bromobenzyl bromide (**1c**) gave the desired dibenzyl products (**2b** or **2c**) along with **3a** in 64% or 54%, respectively.

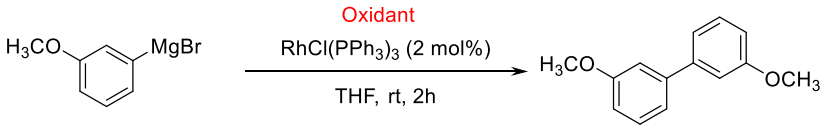


Scheme 3: Rh catalyzed homo-coupling reaction by using Grignard reagents.

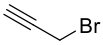
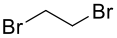
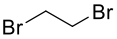
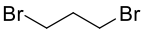
Mechanistically, the benzyl halide works as an oxidizing agent, so various alkyl halides to replace the benzyl halides were investigated in this reaction (Table 1). Allyl bromide, propargyl bromide, and carbon tetrabromide did not work well as shown in entries 1, 2, and 6. On the other hand, other alkyl halides gave the product in moderate to good yields, especially 1,2-dibromoethane was the best oxidant. The reaction proceeded in

good yield, even if 0.5 equivs. of 1,2-dibromoethane was used in this reaction, as shown in entries 7 and 8. However, it has been confirmed that this reaction did not proceed when alkyl halide was not added to the reaction mixture (entry 10).

Table 1: Examination of various alkyl halides as an oxidant.

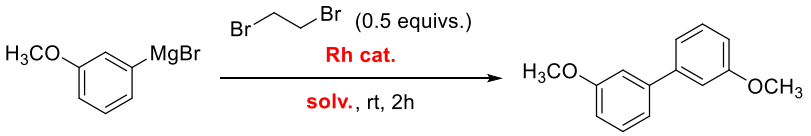


4a **3a**

entry	oxidant	(equiv.)	yield (%)	entry	oxidant	(equiv.)	yield (%)
1		(1)	18	6	CBr_4	(1)	nd
2		(1)	10	7		(1)	66
3		(1)	42	8		(0.5)	73
4	CH_3I	(1)	41	9		(1)	40
5	CH_2Br_2	(1)	36	10	none		trace

Next, we investigated various Rh catalysts and solvents, and the results were summarized in Table 2. All Rh catalysts that were examined in this reaction gave the product in good yields, although the absence of Rh catalyst failed the reaction as shown in entries 1-8. In addition, there was no need to prolong the reaction time (entry 3). Therefore, Rh catalyst was absolutely essential in this reaction, and $RhCl(PPh_3)_3$ was the best catalyst because of its availability. In the examination of the reaction solvents, the use of THF led to the highest yield. It is interesting that the reaction proceeded without adding the oxidant (1,2-dibromoethane) when 1,2-dichloroethane was used as the solvent, although a slight decrease in yield was observed (entry 14). Based on these results, we decided the best condition is entry 1 in which the reaction used $RhCl(PPh_3)_3$ as the Rh catalyst and THF as the solvent.

Table 2: Examination of various Rh catalysts and solvents.

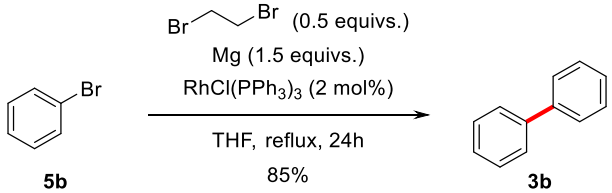


4a **3a**

entry	Rh cat. (mol%)	solv.	yield (%)	entry	Rh cat. (mol%)	solv.	yield (%)
1	$RhCl(PPh_3)_3$ (2)	THF	73	9	$RhCl(PPh_3)_3$ (1)	Et_2O	48
2	$RhCl(PPh_3)_3$ (1)	THF	67	10	$RhCl(PPh_3)_3$ (1)	1,4-dioxane	48
3[a)]	$RhCl(PPh_3)_3$ (1)	THF	67	11	$RhCl(PPh_3)_3$ (1)	toluene	65
4	$RhCl(PPh_3)_3$ (0.5)	THF	64	12	$RhCl(PPh_3)_3$ (1)	DCM	66
5	$RhCl(CO)(PPh_3)_2$ (1)	THF	61	13	$RhCl(PPh_3)_3$ (1)	DCE	67
6	$[Rh(cod)Cl]_2$ (1)	THF	65	14[b)]	$RhCl(PPh_3)_3$ (1)	DCE	58
7	$Rh(CO)_2acac$ (1)	THF	65	15	$RhCl(PPh_3)_3$ (1)	DMF	trace
8	none	THF	trace				

a) The reaction was carried out for 13h.
b) The reaction was carried out without oxidant.

We found the use of the commercially available Grignard reagent (**4a**) gave the corresponding homo-coupled product (**3a**) in a short time at room temperature. Subsequently, for the purpose of expansion of the scope of substrates, we examined the preparation of Grignard reagent *in situ* followed by the homo-coupling reaction. Various conditions were examined, biphenyl (**3b**) was obtained in 85% as the one-pot reaction, when bromobenzene (**5b**) was treated with 1.5 equivs. of Mg (Turnings, Grade for Grignard Reaction) under the reflux condition of THF for 24h in the presence of $RhCl(PPh_3)_3$ (Scheme 4).

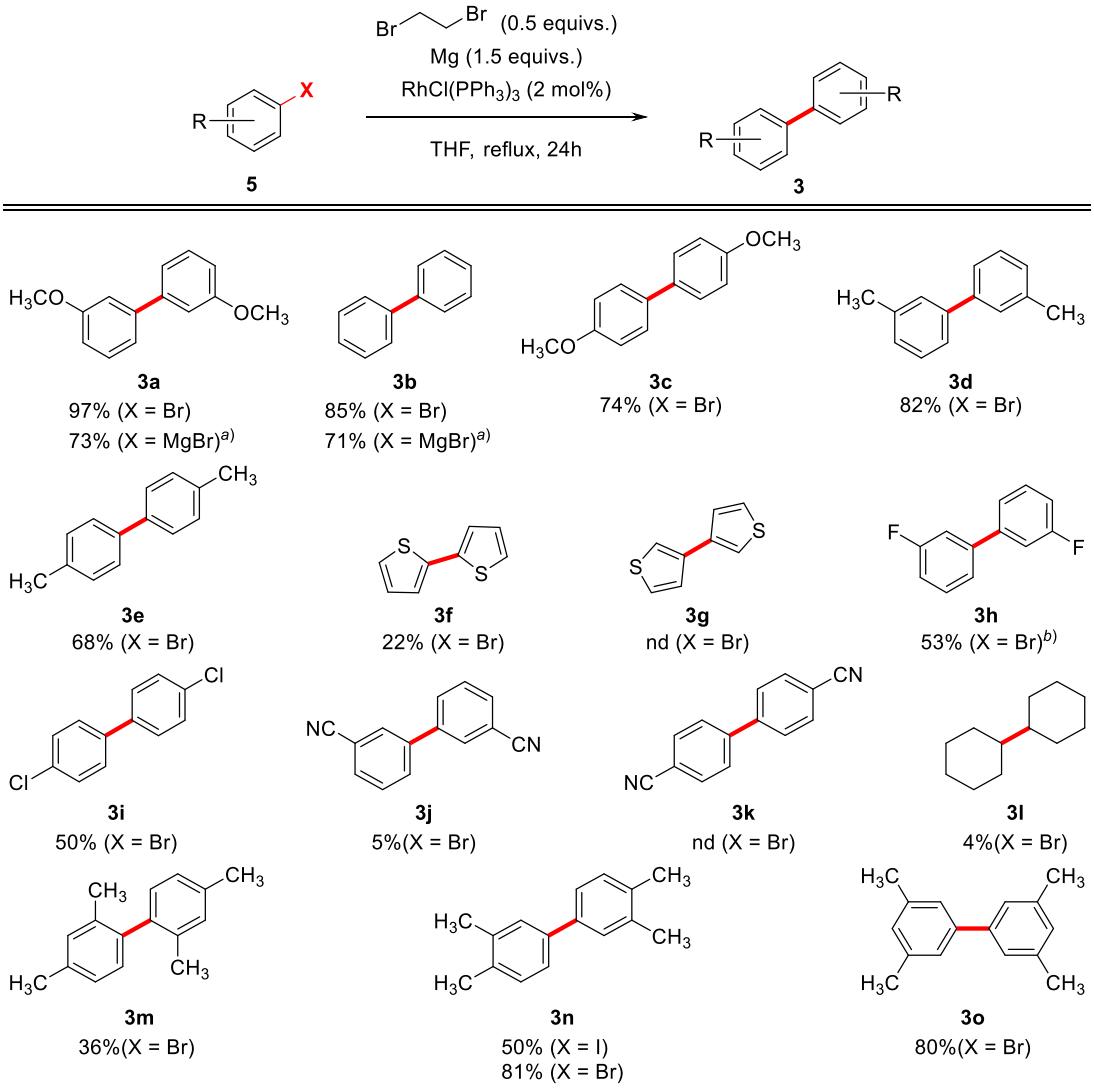


5b **3b**

Scheme 4: Rh-catalyzed one-pot Ullmann reaction with bromobenzene by using optimization of the condition.

According to the above conditions, Rh-catalyzed one-pot Ullmann reaction was investigated by using various substrates, and the results are summarized in Table 3. In the reaction with bromobenzenes bearing an electron-donating group such as bromotoluene and bromoanisole, the corresponding homo-coupling products (**3a**, **3c**-**3e**) were obtained in good yields. In addition, reactions with substrates having halogen substituents also gave the products (**3h** and **3i**) in moderate yields. It is interesting the reaction using 3-bromofluorobenzene (**5h**) gave a small amount of side product, 3,3''-difluoro-1,1':3',1''-terphenyl (**6h**), that might derive from S_NAr reaction of **3h** with the Grignard reagent of **5h**. Moreover, bromoxylenes (**5m**-**5o**) also gave the corresponding products (**3m**-**3o**) respectively, although the position of substituents affected the yields. On the other hand, using the bromothiophenes (**5f** and **5g**), bromobenzonitriles (**5j** and **5k**), or cyclohexyl bromide (**5l**) were not suitable for this reaction.

Table 3: Scope and limitations for the Rh-catalyzed one-pot Ullmann reaction.



a) The reaction was carried out at rt for 1-3h without Mg.
b) The side product (**6h**) by S_NAr reaction onto **3h** was obtained in 8%.

We propose the reaction mechanism as shown in Fig. 1. In the initial step, Rh catalyst reacted with Grignard reagent **4** to give Rh(I)-aryl complex **7**. Oxidative addition of 1,2-dibromoethane onto **7** generated Rh(III)-aryl complex **8**, then further transmetalation between the complex **8** and another Grignard reagent gave Rh(III)-bis(aryl) complex **9**. Finally, reductive elimination gave the desired homo-coupling product **3** along with elimination of ethylene and regenerated Rh catalyst. Unfortunately, we have not clarified the reason why a cross-coupling product such as ethylarenes or styrenes was not formed from Rh(III) complexes **8** or **9**. At this stage, we speculate that the

elimination rate of ethylene and reductive elimination rate of **3** might be enough fast in this reaction.

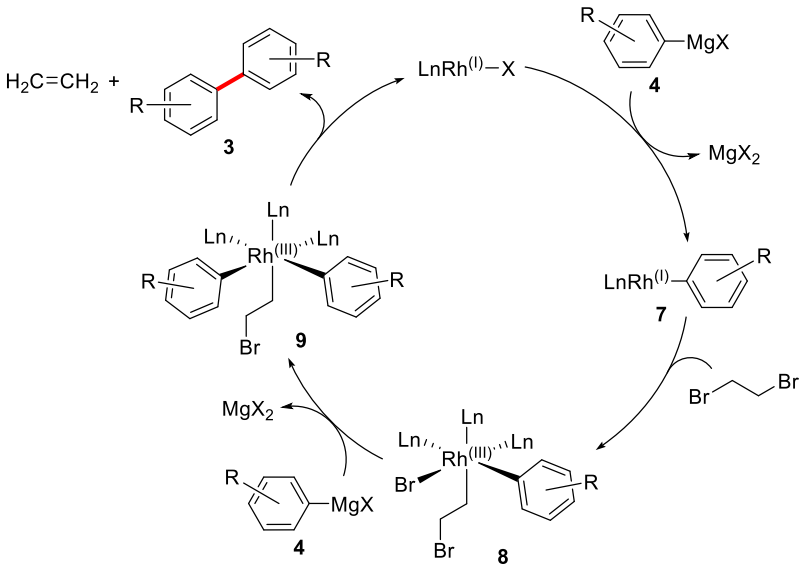


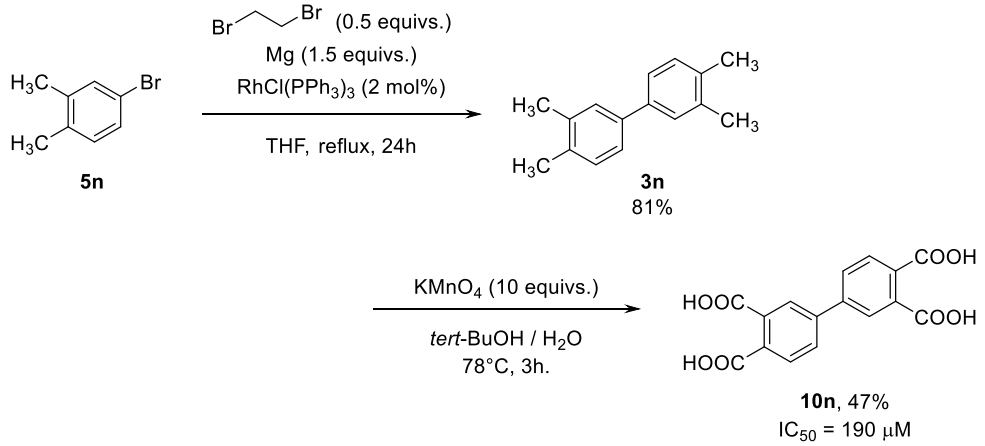
Fig. 1: Tentative reaction mechanism.

Medicinal chemistry application:

Integrins are transmembrane heterodimers, each consisting of α and β subunits, that mediate cell–cell and cell–matrix adhesion involved in normal and pathological processes. Bidirectional signaling through integrins regulate cell shapes, motility and cell cycle progression.[49] The integrin complexes are extremely important for performing various cellular functions, such as cell proliferation, migration, and morphological changes.[50,51] Consequently, the integrin inhibitors have received great attention as novel candidates for the treatment of several intractable diseases.[52–54]

In the process of developing novel inhibitors of integrin function, we identified a drug candidate (**10n**) through high throughput screening (HTS) that inhibits the integrin complex formation, which is an important step for integrin activation. The binding inhibitor **10n** was effective as IC_{50} of 190 μM in AlphaScreen system, and we thought

that the Rh-catalyzed Ullmann homo-coupling reaction would be optimal for the synthesis of **10n** from the chemical structure. The successful Rh-catalyzed Ullmann homo-coupling reaction of **5n** was followed by oxidation by $KMnO_4$ to give **10n** in 38% in two steps (Scheme 5).



Scheme 5: Synthesis of a candidate for the integrin inhibitor.

Conclusion

In conclusion, we have developed a novel Rh-catalyzed one-pot Ullmann homo-coupling reaction of Grignard reagents. The use of commercially available Grignard reagents gave the Ullmann homo-coupling products even if it was carried out at room temperature for 1h. On the other hand, since the preparation of Grignard reagents derived from haloarenes with Mg *in situ* required heating for and long time, we decided to use heating conditions in one-pot homo-coupling reaction. Most homo-coupling products were obtained in this reaction, although the product yield decreased when using substrates that are difficult to react with Mg to make Grignard reagents. Furthermore, we successfully synthesized a candidate of integrin inhibitor by using Rh-catalyzed Ullmann-type homo-coupling reaction as the key disconnection. The integrin inhibitor was effective as IC_{50} of 190 μM in AlphaScreen system, and we believe that

further QSAR studies of analogs of the inhibitor will lead to the discovery of novel potential therapeutics for the treatment of several intractable diseases.

Experimental

See Supporting Information File for full experimental data.

Supporting Information

General procedures and analytical data, including copies of ^{1}H NMR and ^{13}C NMR spectra.

Supporting Information File 1: A25_Supplementary Materials_v1.docx

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