Carbonylative Coupling

Rh^I-Catalyzed Intramolecular Carbonylative C—H/C—I Coupling of 2-Iodobiphenyls Using Furfural as a Carbonyl Source

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Abstract: Synthesis of fluoren-9-ones by a Rh-catalyzed intramolecular C–H/C–I carbonylative coupling of 2-iodobiphenyls using furfural as a carbonyl source is presented. The

Introduction

Fluoren-9-one and its derivatives are recognized as highly useful structural motifs that can be found in a wide variety of natural products, drug candidates, and optoelectronic materials.^[1] The frameworks of these compounds involve the linkage of the 2- and 2'-positions of biaryl derivatives. Because of the ready availability of both biaryl and carbonyl moieties, the intramolecular carbonylative coupling of 2-halobiphenyl derivatives with carbon monoxide or its isoelectronic isocyanides has recently emerged as an accessible method (Scheme 1 a).^[2] The reaction involves the palladium-catalyzed C–H bond cleavage of the biaryl as an essential key step. From the viewpoints of safety and ease of operation, we reported on the Pd-catalyzed C–H carbonylation of 2-bromobiphenyls with paraformalde-hyde, which acts as a carbonyl source through decarbonylation, leading to the formation of fluoren-9-ones.^[3] In such reac-



Scheme 1. C-H cyclocarbonylation to fluore-9-ones.

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Supporting information for this article can be found under http://

Supporting information for this article can be found under http:// dx.doi.org/10.1002/asia.201600802.

Chem. Asian J. **2016**, 00, 0-0

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findings indicate that the rate-determining step is not a C–H bond cleavage but, rather, the oxidative addition of the C–I bond to a $\rm Rh^{1}$ center.

tion, the use of formaldehyde as a carbonyl source led to the hydrodebromination of the substrates, resulting in only moderate yields of the desired products,^[4] whereas aromatic aldehydes failed to participate in the reaction, probably due to the low activity of phosphane-ligated Pd catalysts for the decarbonylation of aromatic aldehydes.^[5a] With the intent to improve the reaction, we focused on the use of rhodium complexes as catalysts instead of palladium complexes, because they have a high ability to (i) abstract a carbonyl moiety from various aldehydes (decarbonylation),^[5b,c,6] (ii) cleave and functionalize a C-H bond,^[7] and (iii) introduce a carbonyl moiety into various organic substrates (carbonylation).^[8] We herein report on the Rh-catalyzed intramolecular carbonylative C-H/ C-I coupling of 2-iodobiphenyls utilizing a CO gas-free carbonylation method with aromatic aldehydes (Scheme 1 b). To the best of our knowledge, a Rh-catalyzed direct carbonylative coupling of a C-H bond in an arene derivative with a C-X bond of an aryl halide has not yet been reported.^[9]

Results and Discussion

In the present study, furfural was selected as an aromatic aldehyde due to its availability from biomass resources.^[10] We first examined the Rh-catalyzed carbonylation of 2-iodobiphenyl (1a) with furfural under the following basic conditions: 1a (0.25 mmol), furfural (1.25 mmol), [{RhCl(cod)}₂] (0.0125 mmol), and Na₂CO₃ (0.30 mmol) in xylene (1 mL) at 130 °C for 48 h. As shown in Scheme 2, the combination of [{RhCl(cod)}₂] and 1,3bis(diphenylphosphino)propane (DPPP) resulted in a higher activity than the use of [{RhCl(cod)}₂] on its own, and the amount of added DPPP had a significant effect on the yield of fluoren-9-one (2a). When the amount of DPPP was increased, ranging from 0 to 2 equivalents to that of [{RhCl(cod)}₂], 1.5 equivalent of DPPP to [{RhCl(cod)}₂] resulted in the highest yield to give 2a (89%). These results indicate that both DPPP-ligated and -free Rh species are generated in the reaction mixture under the conditions used, and that they play an essential role in the decarbonylation of furfural and the cyclocarbonylation of 1a,



Scheme 2. Optimization of amount of DPPP used (the values in parentheses are the yields of recovered 1 a).

respectively, and function in a cooperative manner.^[11] Furthermore, we investigated the influence of bidentate phosphane derivatives as ligands on the yield of **2***a*, since they have been shown to be effective for the decarbonylation of carbonyl compounds.^[6,12] Consequently, the addition of DPPP afforded the highest yield among the examined phosphanes: DPPP (72%), DPPE (62%), DPPB (43%), BINAP (56%), and BIPHEP (40%) for a reaction time of 24 h.

We then explored the scope of the intramolecular C–H carbonylation of 2-halobiphenyls with furfural under the optimal conditions and the results are summarized in Table 1. The reaction of 2-bromobiphenyl (4), instead of **1 a** as a substrate, gave a poor yield of the product (entry 2). 2-lodobiphenyls possess-



[a] Reaction conditions: 1 (0.25 mmol), [{RhCl(cod)}₂] (0.0125 mmol), DPPP (0.0188 mmol), Na₂CO₃ (0.3 mmol), furfural (1.25 mmol), and xylene (1 mL) at 130 °C for 48 h. [b] Isolated yield. [c] Reaction was carried out at 150 °C. [d] **2a** was obtained in 18% yield.

ing both electron-donating and -withdrawing groups at the 4'position (1b-1g) were converted into the corresponding fluoren-9-ones (2b-2g) in good yields (entries 3–8). The influence of the substituent at the 2'-position on the reaction was investigated. 2'-Fluoro-2-iodobiphenyl (1h) also underwent the transformation in 61% yield (entry 9). On the other hand, the reaction of 2'-methyl- and 2'-bromo-2-iodobiphenyls (1i and 1j) proceeded slowly even at 150 °C to produce 2i and 2j in low yield, probably because of the steric hindrance of the substituent (entries 10–12).

The reaction of 2-iodobiphenyls containing a substituent at the 3'-position proceeded in an exclusive regioselective manner. The high regioselective reaction resulted in the formation of 2k and 2l in moderate yields (Scheme 3).^[13] These results are in contrast to the Pd-catalyzed reaction of 2k and 2lwith carbon monoxide or isocyanides, in which fluoren-9-one derivatives, generated from 3'-substitutesd 2-halobiphenyls, were obtained as a mixture of regioisomers.^[2]



Scheme 3. The reaction of 3'-substituted 2-iodobiphenyls (the values in parentheses are the yields of recovered 2-iodobiphenyls).

In an attempt to elucidate the mechanistic aspects of the reaction, especially the effect of DPPP, on the present cyclocarbonylation, some experiments using gaseous carbon monoxide were carried out. It should be noted that the active species for the C-H intramolecular carbonylation of iodobiphenyls has not been clarified, whereas the use of a combination of Rh and DPPP is known to be a high performance catalytic system for the decarbonylation of aldehydes.^[5b,c] In the reactions of **1a** with gaseous carbon monoxide in the presence of a catalytic amount of [{RhCl(cod)}₂], the combination of [{RhCl(cod)}₂] and DPPP, and [{Rh(dppp)₂}Cl] was used under the standard conditions (Scheme 4). The higher was the amount of DPPP to the rhodium center, the lower was the yield of 2 a. Thus, the DPPPfree rhodium complex appears to be more important for the cyclocarbonylation step. The reactions were then carried out by varying the compositions of nitrogen and carbon monoxide (Scheme 5). Increasing the partial pressure of carbon monoxide from 0.05 to 0.5 atm resulted in a smoother reaction. Interestingly, the reaction proceeded sluggishly under atmospheric carbon monoxide and only 4% of 2a was produced after 48 h. In other words, a large amount of carbon monoxide in situ interferes with the reaction. This phenomenon suggests that a [RhCl(CO)₂] complex is ineffective for the present carbonylation and the timely release of the carbonyl source from furfural is highly decisive in terms of the efficiency of the carbonylation reaction.

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Scheme 4. The reaction using gaseous carbon monoxide.



Scheme 5. Effect of partial pressure of carbon monoxide on the reaction.

During the course of our studies on the nature of the actual catalytic species, it was found that when the carbonylation reaction is carried out under the above standard conditions A (Figure 1), it involves an induction period. After the pretreat-



Figure 1. Reaction profiles for the carbonylation of **1a** with furfural. Plots are the concentration of product **2a**. Condition A: heating the mixture after all the reagents are added; condition B: pretreating a mixture of [{RhCl(cod)}₂] and DPPP with Na₂CO₃ at 130 °C prior to the addition of **1a** and furfural.

ment of $[{RhCl(cod)}_2]$ and DPPP with Na₂CO₃ in xylene at 130 °C for 2 h (condition B), the reaction of 2-iodobiphenyl (**1 a**) with furfural led to no observable induction period. This result suggests that a rhodium carbonate complex is the actual catalytic species for the reaction.^[14]

Lastly, deuterium labelling experiments using $1 a - d_5$ was conducted (Scheme 6). A comparison of the initial rates of the reactions of 1 a and $1 a - d_5$ with furfural resulted in a $k_{\rm H}/k_{\rm D}$ of 0.97 (a). A similar ratio was also observed in the reaction with gaseous carbon monoxide ($k_{\rm H}/k_{\rm D} = 0.98$) (b). These findings suggest that the cleavage of the C–H bond at the 2'-position



Scheme 6. Deuterium-labelling experiments.

is not involved in the rate-determining step.^[15] Taking into account the fact that 2-bromobiphenyl and biphenyl derivatives contain substituents that exert steric hindrance around the C–I bond were converted into the desired fluoren-9-ones in very low yields (Table 1), we propose that the rate-determining step is the oxidative addition of the C–I bond. Indeed, it is well known that the oxidative addition and cyclization are frequent-ly rate-determining steps in other carbonylation reactions catalyzed by Rh.^[16] This speculation is supported by the fact that more carbonyl moieties inhibit the reaction (Scheme 5).

Based on previous studies by others^[5f,17,18] and the above observations, a proposed mechanism for the Rh-catalyzed carbonylation is shown in Scheme 7. After the generation of complex **A** from [{RhCl(cod)}₂], DPPP, and Na₂CO₃, 2-iodobiphenyl (**1a**) adds oxidatively to complex **A** to form complex **B** or **B'**. This step can be considered as the rate-determining step. Subsequently, the cleavage of the C–H bond at the 2'-position leads to the formation of rhodafluorene **C**. The migratory insertion of the carbonyl moiety, which is produced through the decarbonylation of furfural catalyzed by DPPP-ligated Rh complex, then affords the rhodacycle **D**. Finally, the desired product (**2a**) is released by the reductive elimination, and the active Rh¹ species is regenerated to complete the catalytic cycle.

Conclusions

In summary, we reported on the Rh-catalyzed intramolecular carbonylative C–H/C–I coupling of 2-iodobiphenyls with furfural leading to the formation of fluoren-9-one derivatives. Compared with the analogous Pd-catalyzed reaction with paraformaldehyde, the present Rh-catalyzed C–H carbonylation gave higher yields of fluoren-9-ones. Furthermore, a high degree of regioselectivity of the reaction with 3'-substituted 2-iodobiphenyl was achieved.

Experimental Section

General procedure for the Rh-catalyzed cyclocarbonylation of 2-iodobiphenyl with furfural

A 5 mL two-necked flask equipped with a stir bar was charged with $[{RhCl(cod)}_2]$ (0.0125 mmol, 6.16 mg), DPPP (0.0188 mmol, 7.73 mg), and Na₂CO₃ (0.3 mmol, 31.80 mg). The central neck of the flask was equipped with a reflux condenser and N₂ balloon (2 L) that was connected by a three-way stopcock at the top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N₂ (three times). Xylene (1.0 mL), fur-

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Scheme 7. Proposed reaction mechanism.

fural (1.25 mmol, 120.11 mg), and 2-iodobiphenyl 1a (0.25 mmol, 70.03 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N₂. The mixture was placed in an oil bath, which had been preheated to 130°C for 48 h. After cooling to room temperature, the resulting solution was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica-gel to afford 2a in 89% yield as a yellow solid (gradient elution with hexane/AcOEt = 100/0-30/1; R_{f} : 0.22 (Hexane/AcOEt = 20/1); ¹H NMR (500 MHz, CDCl₃): δ = 7.29 (td, 2 H, J = 1.0, 7.5 Hz), 7.47-7.53 (m, 4H), 7.66 ppm (dd, 2H, J=1.0, 7.5 Hz); ¹³C NMR (125 MHz, $CDCl_3$): $\delta = 120.4$, 124.4, 129.2, 134.2, 134.8, 144.5, 194.1 ppm.^[19]

Acknowledgements

This study was partially supported by the NAIST Presidential Special Fund. We also thank Ms. Yoshiko Nishikawa and Mr. Kazuo Fukuda for the HRMS measurements.

Keywords: carbonylation · C-H functionalization · fluoren-9one · furfural · rhodium

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Manuscript received: June 9, 2016 Accepted Article published: Final Article published:

Chem. Asian J. 2016, 00, 0-0

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◆1st Rh-cat. C-H/C-X carbonylative coupling ◆CO gas-free ◆High yields (up to 89%)

Synthesis of fluoren-9-ones by a Rhcatalyzed intramolecular C–H/C–I carbonylative coupling of 2-iodobiphenyls using furfural, which is readily available from biomass, as a carbonyl source has been developed (see scheme). The findings indicate that the rate-determining step is not a C–H bond cleavage but, rather, the oxidative addition of the C–I bond to a Rh¹ center.

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