Doctoral Dissertation

Study on Development of Novel Carbonylation with Furfural Involving Cleavage of Inert Bonds

(フルフラールを用いた不活性結合の切断を含む新規カルボニル化反応の開発に関する研究)

Takuma Furusawa

March 2017

Graduate School of Materials Science,

Nara Institute of Science and Technology (NAIST)

TABLE OF CONTENTS

List of Abbreviations ii

Chapter 1 General Introduction 1

Chapter 2 Intramolecular Carbonylative Coupling of 2-Iodobiphenyls 20

Chapter 3 Three-component Carbonylative Annulation Involving *Ortho*-C-H Bond Cleavage 57

Chapter 4 Three-component Carbonylative Annulation through C-C Bond Cleavage 91

Chapter 5 General Conclusion 114

List of Publications 116

Acknowledgements 121

LIST OF ABBREVIATIONS

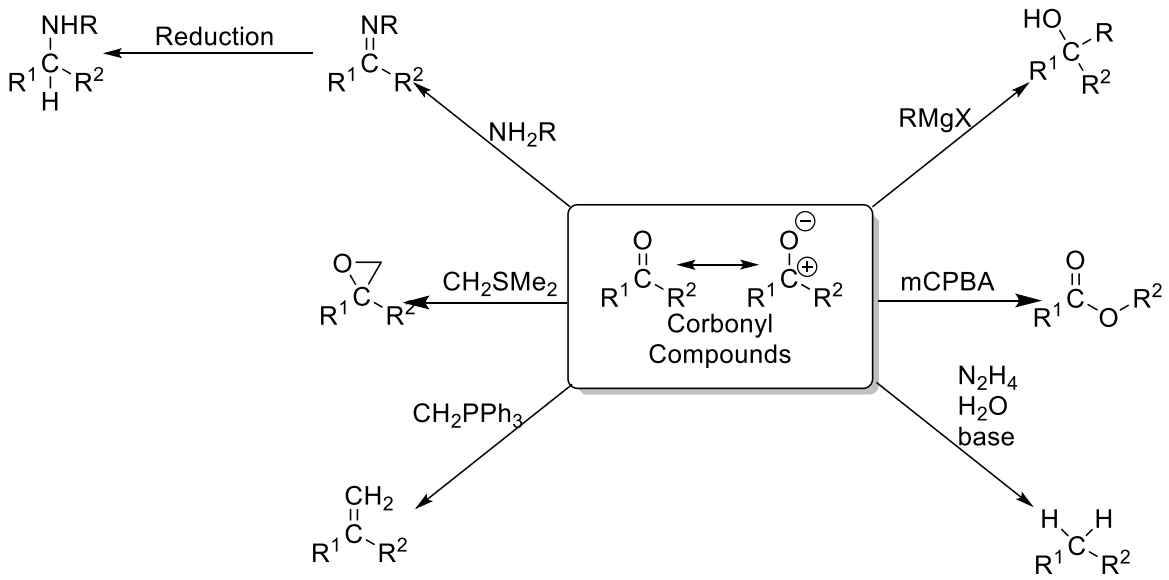
Ac	acetyl
acac	acetylacetonate
AChE	acetylcholine esterase
Ar	aryl
atm	atmosphere
BINAP	2,2'- bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEP	2,2’-bis(diphenylphospino)-1,1’-biphenyl
Bn	benzyl
Bu	butyl
cbz	benzyloxycarbonyl group
cod	1,5-cyclooctadiene
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
δ	chemical shift of NMR signal in ppm
DBA	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPB	1,4-bis(diphenylphosphino)butane
DPPBz	1,2-bis(diphenylphosphino)benzene
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1’-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
EI	electron impact ionization
Eq.	equation
equiv.	equivalent
Et	ethyl
GC	gas chromatography
h	hour(s)
HRMS	high-resolution mass specra
i	iso
IC_{50}	50% inhibitory concentration
IR	infrared absorption spectrometry
J	coupling constant in NMR

KIE	kinetic isotope effect
m	multiplet
mCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	mesitylene
MS	mass spectrometry
n	normal
nbd	2,5-norbornadiene
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
o-	ortho
Ph	phenyl
Piv	pivaloyl
Pr	propyl
Py	2-pyridyl
R_f	retention factor
rt	room temperature
s	singlet
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3- benzodioxole
t	triplet
t-	tertiary
Temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
THF	tetrahydrofuran
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1 General Introduction

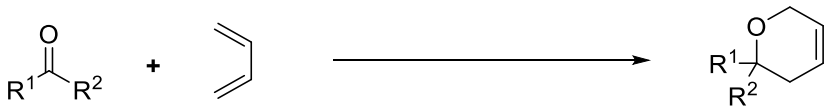
1.1 Carbonyl Compounds

Compounds having C-O double bond, namely carbonyl compounds, such as ketones have been one of the most important synthons in organic synthesis.[1] Because they have highly electrophilic carbon atom, the reactions shown in Scheme 1-1 occur through the addition of various nucleophiles to the carbon atom of the carbonyl group leading to carbon-carbon and –heteroatom bond formation.



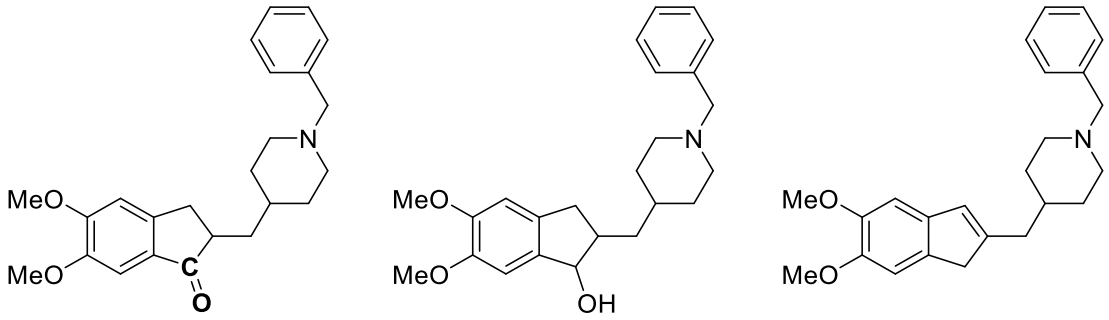
Scheme 1-1. Reactions of carbonyl compounds.

They are also employed in several cycloadditions such as Hetero Diels-Alder reaction to construct oxygen containing heterocycles.[2]



Scheme 1-2. Hetero Diels-Alder reaction.

Furthermore, the carbonyl group itself is indispensable in many organic compounds including bioactive natural products and medicines.[3] For example, donepezil hydrochloride (Aricept®), which is used as a medicine for the treatment of patients with Alzheimer's disease, involves the indanone framework.[4] It is noteworthy that the absence of the carbonyl group remarkably diminishes anti-AChE activity (Scheme 1-3). The carbonyl group of the indanone moiety only interacts with AChE by van der Waals forces and hydrogen bonding.[4b]



IC_{50} (nM) 6.7 300 4400

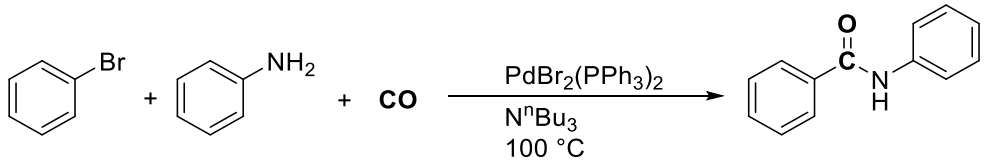
Scheme 1-3. Donepezil hydrochloride.

Therefore, developing the efficient synthetic methods of compounds containing the carbonyl groups is highly desirable in both organic synthesis and medicinal chemistry.

1.2 Transition metal-catalyzed carbonylation

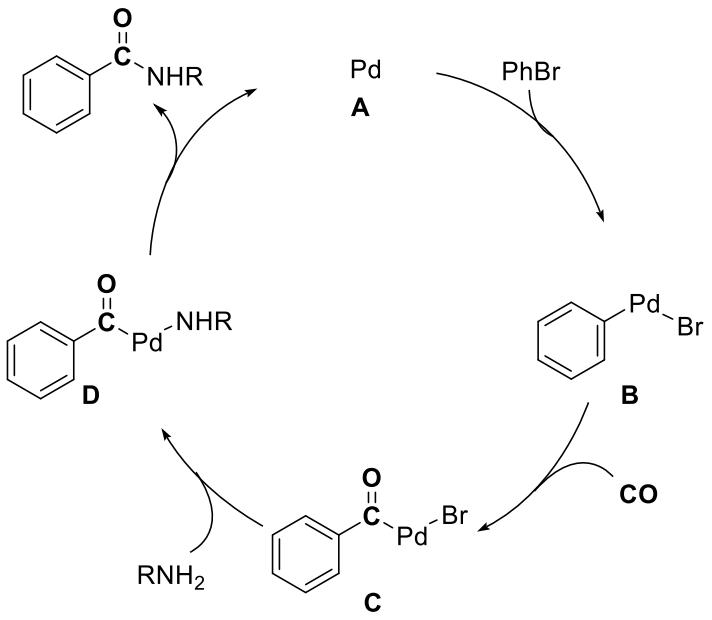
The transition metal-catalyzed carbonylation using gaseous carbon monoxide has long been recognized as a powerful tool for the synthesis of a wide variety of carbonyl compounds; for example, hydroformylation to aldehydes (Oxo process), hydrocarboxylation to carboxylic acids (Reppe carbonylation), and methanol carbonylation to acetic acid (Monsanto or Cativa process).[5]

In 1974, Heck and Schoenberg developed the palladium-catalyzed aminocarbonylation of aryl halides with amines and carbon monoxide leading to the efficient synthesis of aromatic amides (Scheme 1-4).[6]



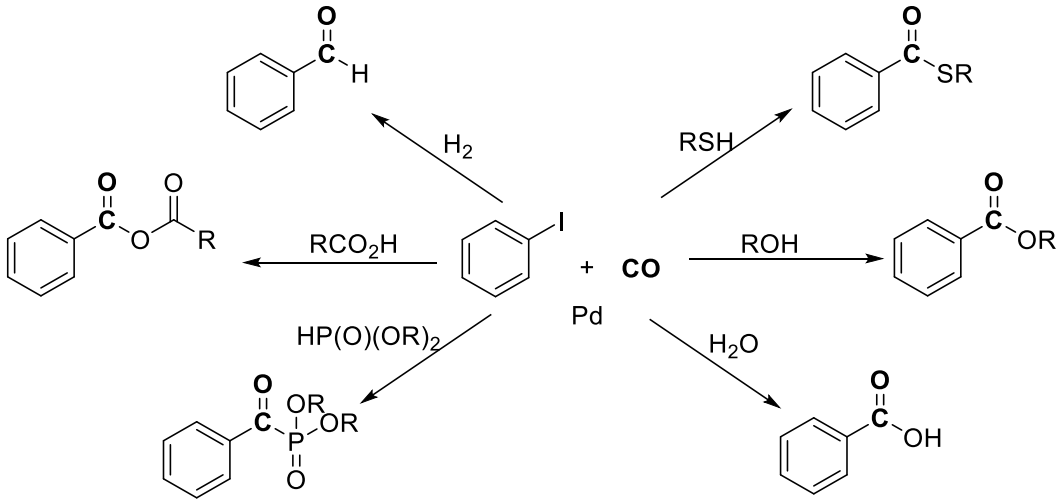
Scheme 1-4. Palladium-catalyzed aminocarbonylation.

A general catalytic cycle for the palladium-catalyzed aminocarbonylation is shown in Scheme 1-5. The oxidative addition of aryl bromide to the palladium(0) species **A** and the subsequent migratory insertion of carbon monoxide into **B** afford the acyl palladium species **C**. Then, **C** reacts with amines forming the desired amides.



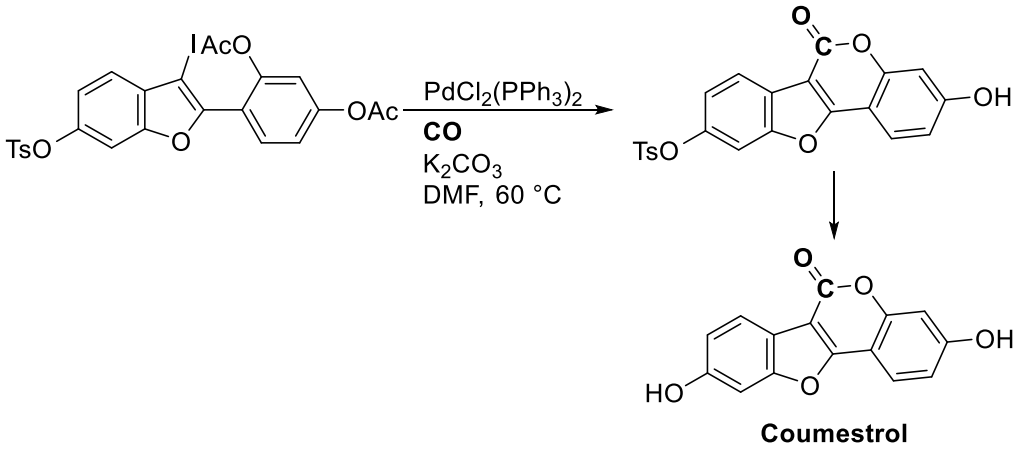
Scheme 1-5. General catalytic cycle for the aminocarbonylation.

This breakthrough opened up the possibility of the synthesis of various aromatic carbonyl compounds by changing amines to suitable nucleophiles. Indeed, the efficient syntheses of carboxylic acids (with water), esters (with alcohols), thioesters (with thiols), acid anhydrides (with carboxylic acids), acylphosphonates (with phosphonates), acid halides (with inorganic halides), and aldehydes (with hydrogen or hydrosilanes), have been achieved (Scheme 1-6).[7]

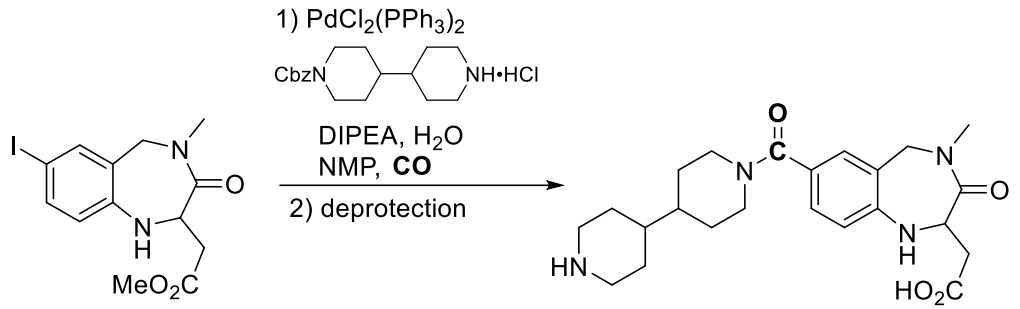


Scheme 1-6. Carbonylative coupling of aryl halides with nucleophiles.

As these carbonylations usually tolerate a great variety of functional groups, they are often employed in total synthesis of natural products and pharmaceutical synthesis (Scheme 1-7 and 1-8).[7,8]

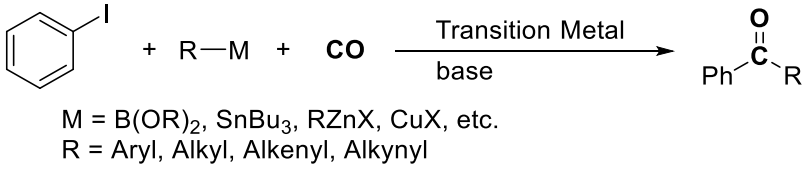


Scheme 1-7. The application of carbonylations in total synthesis.



Scheme 1-8. The application of carbonylations in pharmaceutical synthesis.

Although ketones can also be produced using organometallic reagents such as organoboron, organozinc, organotin, organosilane, and organocopper compounds as nucleophiles (Scheme 1-9),[7,9] there is an inevitable problem that they generally do not occur in nature and require multiple steps for their preparation.



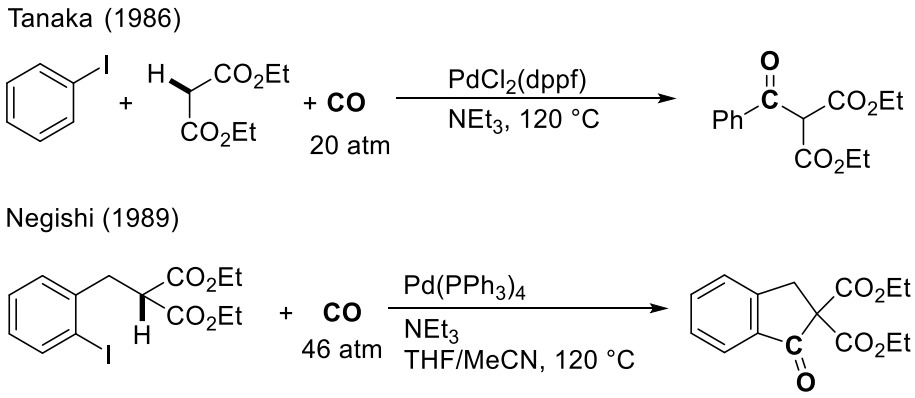
Scheme 1-9. Carbonylative coupling for the synthesis of ketones.

1.3 Catalytic Carbonylation of Ubiquitous Bond in Organic Molecule for Synthesis of Ketones

Because carbon-hydrogen and carbon-carbon bonds are contained in almost all organic compounds, the direct carbonylation of these bonds is an ideal protocol for the synthesis of ketones in terms of atom- and step-economy, and waste generation.[10] Therefore, some efforts have been devoted to developing the direct catalytic carbonylation of ubiquitous C-H and C-C bonds.

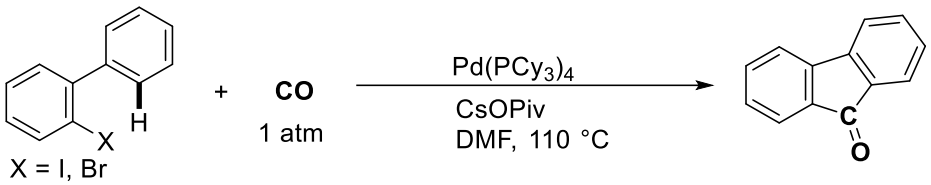
1.3.1 Carbonylation of C-H Bond with Aryl Halides Using Gaseous Carbon Monoxide

In the 1980s, Tanaka's group[11a] and Negishi's group[11b] reported the carbonylative coupling of aryl halides with C-H bond at the activated methylene, which is highly reactive compared with the conventional C-H bond (Scheme 1-10).



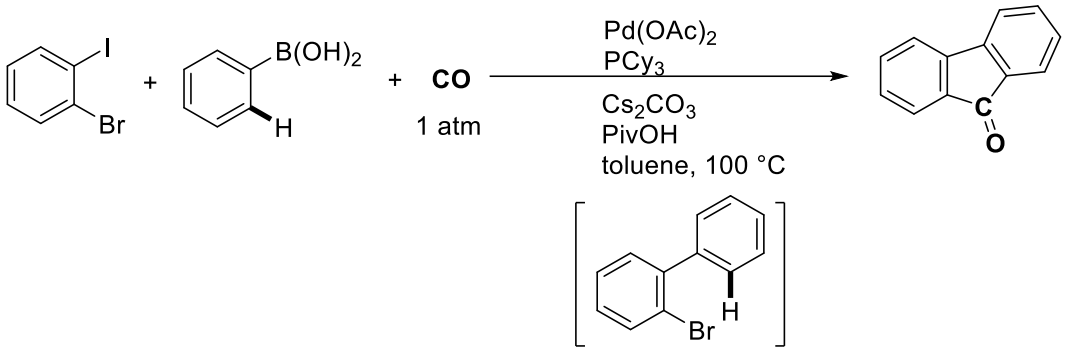
Scheme 1-10. Palladium-catalyzed carbonylative coupling of aryl halides with C-H bond at the activated methylene.

In 2000, the palladium-catalyzed cyclocarbonylation of 2-halobiphenyls, which is the first example of a direct carbonylation of inert C-H bond with aryl halides, was reported by Larock and Campo (Scheme 1-11).[12]



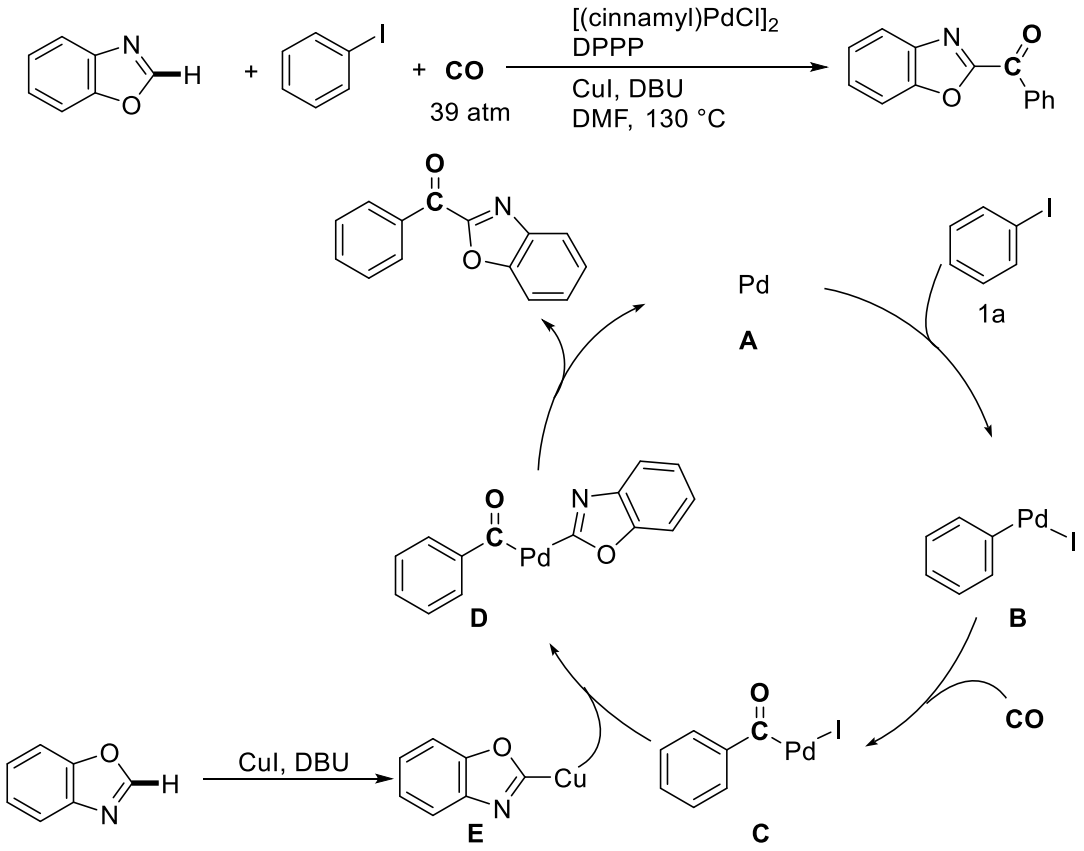
Scheme 1-11. Palladium-catalyzed carbonylation of 2-halobiphenyls through the cleavage of inert C-H bond.

Afterwards, Song, Liu, and Xie reported the three component carbonylation of 1,2-dihalobenzenes and arylboronic acids under atmospheric carbon monoxide.[13] As shown in Scheme 1-12, this reaction consists of the cross coupling of 1,2-dihalobenzenes and arylboronic acids leading to the formation of 2-halobiphenyls and the subsequent intramolecular C-H carbonylation.



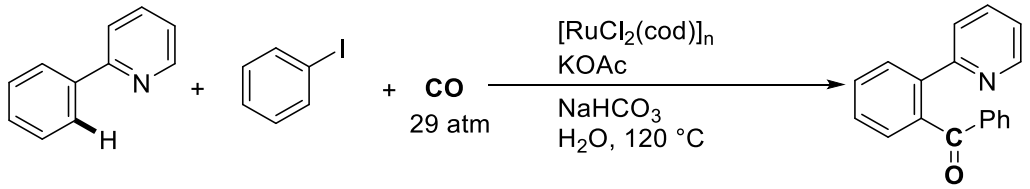
Scheme 1-12. Palladium-catalyzed three component carbonylation.

In 2010, Beller's group demonstrated that the palladium complex catalyzed the intermolecular carbonylative coupling of aryl halides with five-membered heteroarenes in the presence of a stoichiometric amount of copper(I) complex.[14] As illustrated in Scheme 1-13, the reaction proceeded via C-H bond cleavage of heteroarenes mediated by copper complex, followed by the transmetalation between acyl palladium intermediate **C** and heteroaryl copper species **E**.



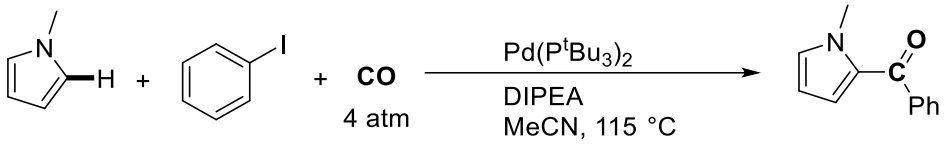
Scheme 1-13. Palladium-catalyzed direct carbonylative coupling of aryl iodides with five-membered heteroarenes assisted by copper.

Although the above system has made enormous impact, there are still some drawbacks that the presence of a stoichiometric amount of copper is essential and this protocol is not applicable to the reaction of simple benzene derivatives. Thus, Beller and co-workers developed the ruthenium-catalyzed C-I/C-H intermolecular carbonylative coupling of aryl iodides with 2-phenyl pyridines (Scheme 1-14).[15]



Scheme 1-14. Ruthenium-catalyzed carbonylative coupling of aryl iodides with 2-phenylpyridines.

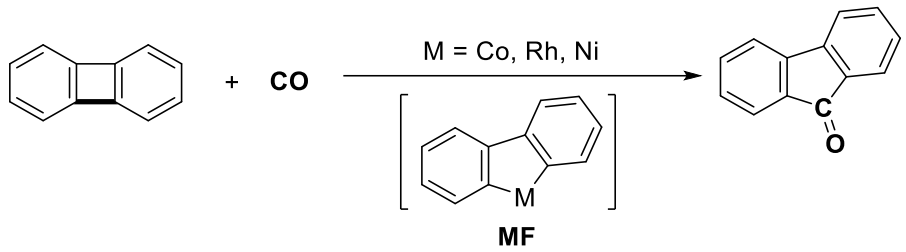
Moreover, Arndtsen reported that the intermolecular carbonylative coupling of aryl iodides and five-membered heteroarenes could proceed by using $Pd(P^tBu_3)_2$ catalysis in the absence of copper complex (Scheme 1-15).[16]



Scheme 1-15. Palladium-catalyzed copper-free carbonylative coupling of aryl iodides with heteroarenes.

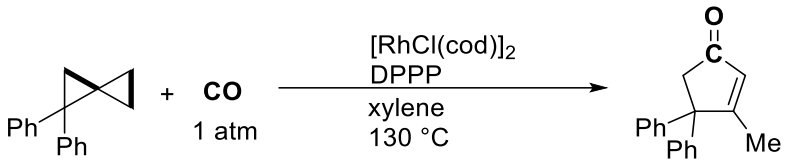
1.3.2 Carbonylation of C-C bond Using Gaseous Carbon Monoxide

The direct carbonylation of C-C bond involved in small ring molecules provides the convenient synthesis of cyclic ketones. Jones and co-workers reported the formation of metallafluorene (**MF**) via the oxidative addition of biphenylene to the metal complex and the subsequent migratory insertion of carbon monoxide leading to the carbonylative synthesis of fluoren-9-one (Scheme 1-16).[17]



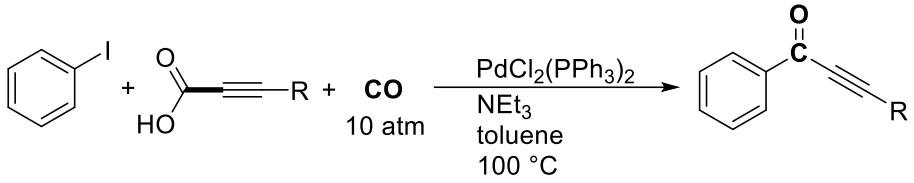
Scheme 1-16. Synthesis of fluoren-9-one through carbonylation of biphenylene.

The elegant work from Murakami revealed that the carbonylation of spiropentanes was catalyzed by the combination of $[RhCl(cod)]_2$ and DPPP to afford cyclopentenones involving double C-C bond cleavages (Scheme 1-17).[18]



Scheme 1-17. Rhodium-catalyzed carbonylation of spiropentanes involving double C-C bond cleavages.

Compared with the reaction of small ring molecules, unstrained C-C bond has been rarely employed in carbonylation chemistry. In 2011, the intermolecular decarboxylative alkynyl-carbonylation of aryl iodides with alkynyl carboxylic acids, which is the only example of C-C/C-I carbonylation, was reported by Lee (Scheme 1-18).[19]



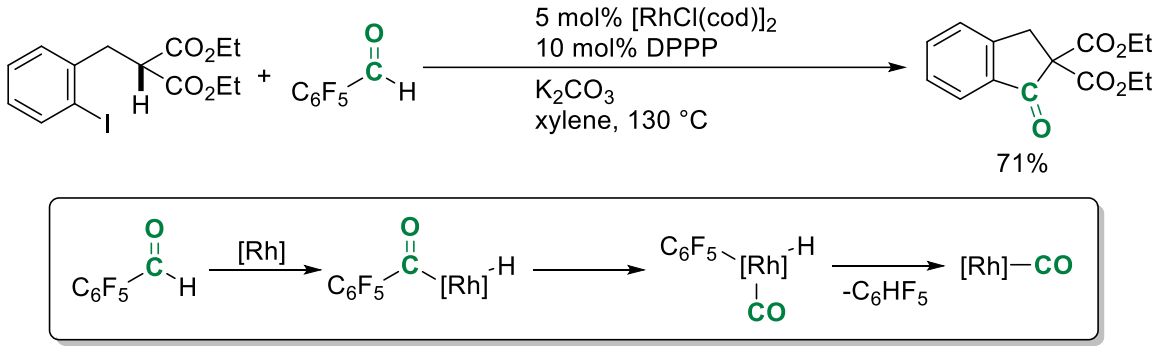
Scheme 1-18. Palladium-catalyzed decarboxylative alkynylcarbonylation of aryl iodides with alkynyl carboxylic acids.

1.3.3 Slow Progress in Carbonylation Chemistry: Drawbacks of Carbon Monoxide

Although gaseous carbon monoxide is an inexpensive, atomeconomical, and readily available C1 feedstock, the following drawbacks associated with the chemical, physical, and biological properties of carbon monoxide have resulted in much slower progress in carbonylations at inert bonds, compared to other functionalizations such as arylation[20]; 1) it is a colorless, odorless, and highly flammable gas, and is highly toxic to humans, 2) therefore, special equipment such as autoclave and safe handling are required, and 3) it often interferes with the coordination of substrates[21] and reactions such as the oxidative addition[22] on the metal because of its strong coordination to metal center.

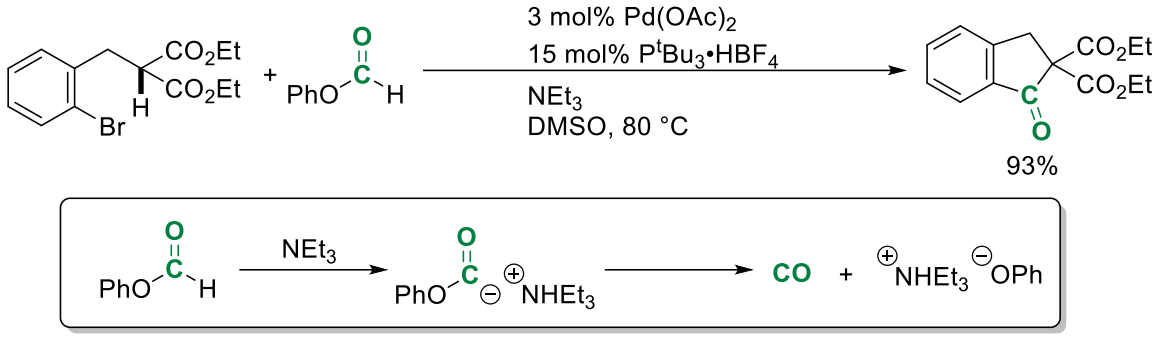
1.4 Catalytic Carbonylation of C-H and C-C bonds Using Carbonyl Surrogates

In order to overcome above problems, CO gas-free carbonylation techniques using carbonyl surrogates such as aldehydes, formates, acid chlorides, and metal carbonyls, which are lower toxicity and easy-to-handle, have been attracted considerable attention.[23] In 2007, the first report, the rhodium-catalyzed intramolecular cyclocarbonylation of aryl halides having the activated methyne moiety with aldehydes as a carbonyl surrogate, was published by Morimoto and Kakiuchi.[24] In this reaction, the carbonyl moiety was generated via the rhodium-catalyzed decarbonylation of aldehydes (Scheme 1-19).



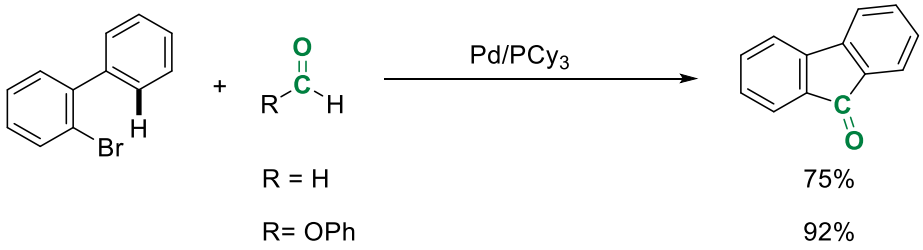
Scheme 1-19. Rhodium-catalyzed carbonylation of aryl halides having the activated methyne moiety with aldehydes.

Later, Manabe's group demonstrated that phenyl formate can be employed as a carbonyl surrogate for the palladium-catalyzed cyclocarbonylation under relatively mild conditions (Scheme 1-20).[25] The generation of carbon monoxide from phenyl formate was mediated by NEt_3.



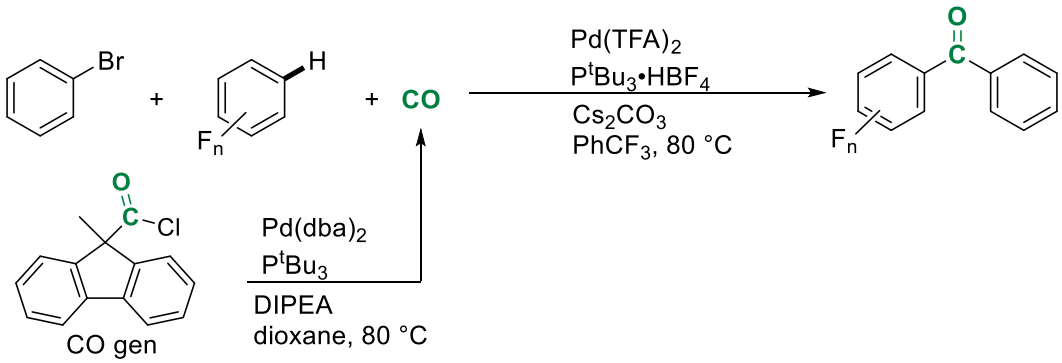
Scheme 1-20. Palladium-catalyzed carbonylation of aryl halides having the activated methyne moiety with phenylformate.

My group[26] and Manabe's group[27] independently demonstrated that the CO gas-free protocol was applicable to the palladium-catalyzed C-H carbonylation of 2-bromobiphenyls reported by Larock (Scheme 1-21).



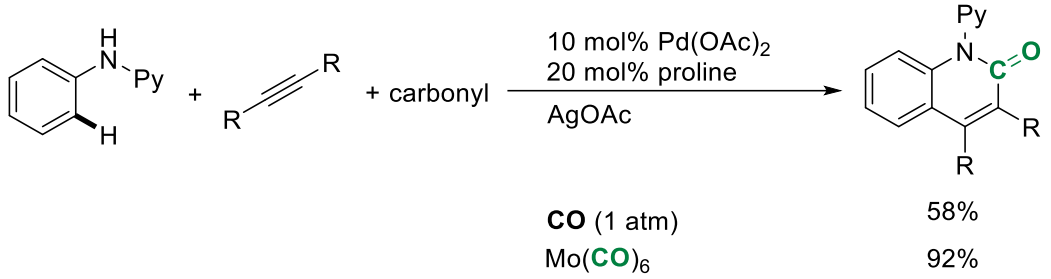
Scheme 1-21. CO gas-free protocols for the carbonylation of 2-bromobiphenyls.

In 2015, Skrydstrup and co-workers developed the novel palladium-catalyzed carbonylative C-H arylation of perfluoroarenes with aryl bromides using CO gas-free carbonylaion technique (Scheme 1-22).[28]



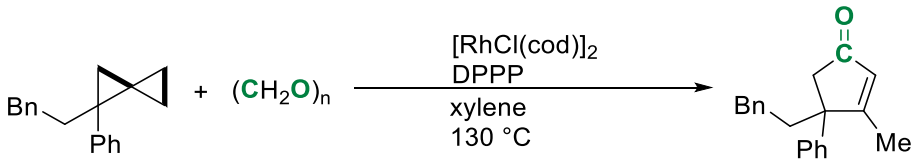
Scheme 1-22. Pd-catalyzed carbonylative coupling of aryl bromides with perfluoroarenes.

Furthermore, some groups have proved that $Mo(CO)_6$ worked as a superior carbonyl source than atmospheric carbon monoxide for the palladium-catalyzed aminocarbonylation involving C-H bond cleavage (Scheme 1-23).[29] This fact indicates that the existence of excess amounts of carbon monoxide results in the decomposition or deactivation of palladium(II) complex via reduction or saturation of the metal coordination sphere.



Scheme 1-23. C-H aminocarbonylation using $Mo(CO)_6$.

To the best of my knowledge, there is only one report of CO gas-free carbonylation of C-C bond. Paraformaldehyde worked well as a carbonyl surrogate in the carbonylation of spiropentanes reported by Murakami (Scheme 1-24).[18]

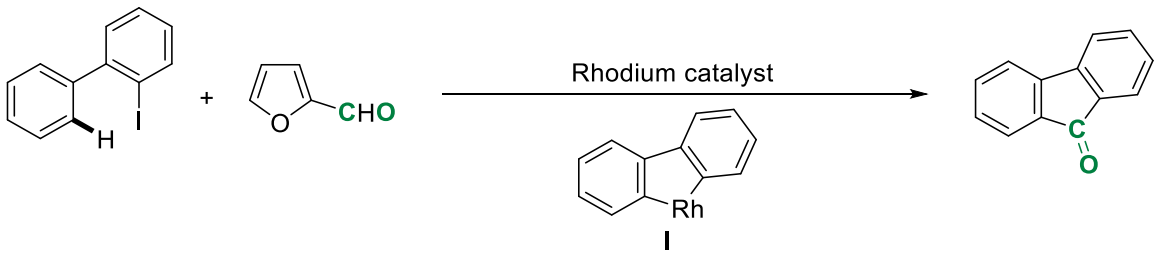


Scheme 1-24. Carbonylation of spiropentanes using paraformaldehyde.

1.5 Purpose of This Dissertation

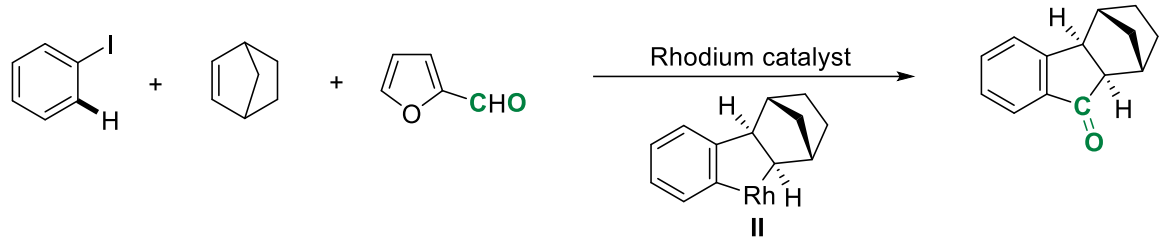
As described in previous sections, the direct carbonylation of C-H and C-C bonds with carbonyl surrogates has emerged as a reliable method for the synthesis of various carbonyl compounds. Nevertheless, there are still few reports because carbonyl surrogates used in reported protocols are far more expensive than carbon monoxide. Moreover, much of the studies depend on palladium catalysts and the use of other transition metals including rhodium was rarely studied. The prime object described in this dissertation is to develop the novel carbonylation catalyzed by rhodium complex of inert C-H and C-C bonds using furfural, which is industrially produced from biomass resources such as xylose and is inexpensive.[30]

In chapter 2, I investigated the use of furfural in the rhodium-catalyzed intramolecular carbonylative coupling of 2-iodobiphenyls which are representative substrates in C-H cyclization (Scheme 1-25).



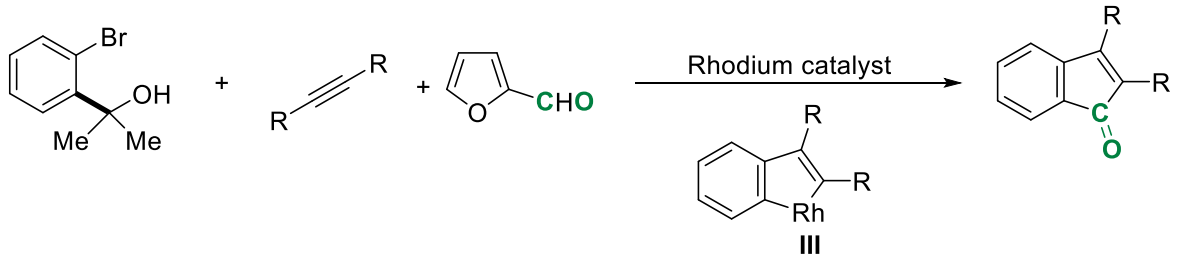
Scheme 1-25. Intramolecular carbonylative coupling of 2-iodobiphenyls.

In chapter 3, I then envisioned that the intermediate **II** similar to the rhodafluorene **I** should be generated from the reaction of iodobenzenes, π-unsaturated hydrocarbons, and a rhodium complex, leading to the three-component carbonylative annulation (Scheme 1-26).



Scheme 1-26. Carbonylative annulation of iodobenzene, 2-norbornene, and furfural.

In chapter 4, I developed the carbonylative annulation of α,α-dimethyl-(2-bromophenyl)methanols and internal alkynes with furfural leading to indenones involving C-C bond cleavage (Scheme 1-27).



Scheme 1-27. Carbonylative annulation involving C-C bond cleavage.

In chapter 5, I summarize my studies described in this doctoral dissertation and describe the prospective of carbonylations using furfural.

References and Notes

1. (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (d) Pu, L.; Yu, H.-B. *Chem. Rev*. **2001**, *101*, 757.
2. Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093.
3. (a) Forbis, R. M.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 5003. (b) Claassen, G.; Brin, E.; Crogan-Grundy, C.; Vaillancourt, M. T.; Zhang, H. Z.; Cai, S. X.; Drewe, J.; Tseng, B.; Kasibhatla, S. *Cancer Lett*. **2009**, *274*, 243. (c) Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner, F. S. *J. Med. Chem.* **2009**, *52*, 1639. (d) Shi, Y.; Gao, S. *Tetrahedron* **2016**, *72*, 1717.
4. (a) Sugimoto, H.; Ogura, H.; Arai, Y.; Iimura, Y.; Yamanishi, Y. *Jpn. J. Pharmacol.* **2002**, *89*, 7. (b) Kryger, G.; Silman, I.; Sussman, J. L. *Structure* **1999**, *7*, 297.
5. (a) Jones, J. H. *Platinum Metals Rev.* **2000**, *44*, 94. (b) Kiss, G. *Chem. Rev*. **2001**, *101*, 3435. (c) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675.
6. Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
7. Beller, M.; Wu, X. -F. *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C-X Bonds*; Springer: Amsterdam, 2013.
8. (a) Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177.

9. (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 4986.

10. (a) Li, B.-J.; Shi, Z.-J. *Homogeneous Catalysis for Unreactive Bond Activation*; Shi, Z.-J., Ed.; John Wiley & Sons: NJ, 2015; pp 498−521. (b) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (c) Gadge, S. T.; Gautam, P.; Bhanage, B. M. *Chem. Rec.* **2016**, *16*, 835.

11. (a) Kobayashi, T.; Tanaka, M. *Tetrahedron Lett.* **1986**, *27*, 4745. (b) Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018.

12. (a) Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675. (b) Campo, M. A.; Larock, R. C. *J. Org. Chem*. **2002**, *67*, 5616.

13. Song, J.; Wei, F.; Sun, W.; Li, K.; Tian, Y.; Liu, C.; Li, Y.; Xie, L. *Org. Lett.* **2015**, *17*, 2106.

14. Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7316.

15. Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293.

16. Tjutrins, J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2015**, *137*, 12050.

17. (a) Perthuisot, C.; Edelbach, B. E.; Zubris, D. L.; Jones, W. D. *Organometallics* **1997**, *16*, 2016. (b) Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **1999**, *18*, 4040.

18. Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc*. **2007**, *129*, 12596.

19. (a) Park, A.; Park, K.; Kim, Y.; Lee, S. *Org. Lett.* **2011**, *13*, 944. (b) Kim, W.; Park, K.; Park, A.; Choe, J.; Lee, S. *Org. Lett.* **2013**, *15*, 1654.

20. (a) Yu, J.-Q. ; Shi, Z. *C-H Activation*, Springer, Heidelberg, 2010. (b) Dong, G. *C-C Bond Activation*, Springer, Heidelberg, 2014.

21. (a) Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73. (b) Shibata, T.; Toshida, N.; Yamazaki, M.; Maekawa, S.; Takagi, K. *Tetrahedron* **2005**, *61*, 9974. (c) Kim, D. E.; Kim, I. S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Jeong, N. *J. Org. Chem.* **2008**, *73*, 7985.

22. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

23. For reviews and accounts of carbonylation with CO surrogates, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 5580. (b) Larhed, M.; Odell, L.; Russo, F. *Synlett* **2012**, *23*, 685. (c) Wu, L.; Liu, Q.; Lackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 6310. (d) Konishi, H.; Manabe, K. *Synlett* **2014**, *25*, 1971. (e) Gautam, P.; Bhanage, B. M. *Catal. Sci. Technol*. **2015**, *5*, 4663. (f) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594. (g) Cao, J.; Zheng, Z.-J.; Xu, Z.; Xu, L.-W. *Coord. Chem. Rev.* **2017**, *336*, 43. (h) Peng, J.-B.; Qi, X.; Wu, X.-F. *Synlett* **2017**, *28*, 175.

24. Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Organomet. Chem.* **2007**, *692*, 625.

25. Konishi, H.; Nagase, H.; Manabe, K. *Chem. Commun*. **2015**, *51*, 1854.

26. Furusawa, T.; Morimoto, T.; Oka, N.; Tanimoto, H; Nishiyama, Y.; Kakiuchi, K. *Chem. Lett.* **2016**, *45*, 406.

27. Konishi, H. *The Research Reports of the Uehara Memorial Foundation* **2014**, *28*, 1.

28. Lian, Z.; Friis, S. D.; Skrydstrup, T. *Chem. Commun.* **2015**, *51*, 1870.

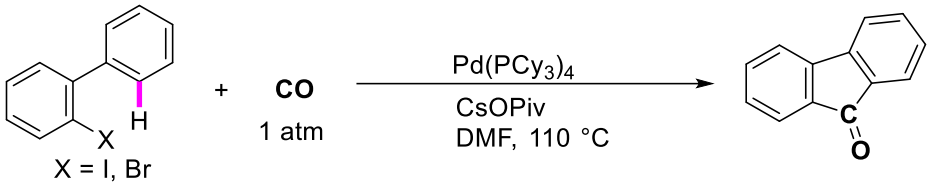
29. (a) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu, X.-F. *Chem. Eur. J.* **2014**, *20*, 14189. (b) Hernando, E.; Villalva, J.; Martinez, A. M.; Alonso, I.; Rodriguez, N.; Arrayás, R. G.; Carrentero, J. C. *ACS Catal.* **2016**, *6*, 6868.

30. (a) Dutta, S.; De, S.; Saha, B.; Alam, M. I. *Catal. Sci. Technol.* **2012**, *2*, 2025. (b) Cai, C. M.; Zhang, T.; Kumar, R.; Wyman, C. E. *J. Chem. Technol. Biotechnol.* **2014**, *89*, 2. (c) Peleteiro, S.; Rivas, S.; Alonso, J. A.; Santos, V.; Parajó, J. C. *Bioresource Techonology*, **2016**, *202*, 181. (d) Li, C.-L.; Qi, X.; Wu, X.-F. *J. Mol. Catal. A: Chem.* **2015**, *406*, 94.

Chapter 2 Intramolecular Carbonylative Coupling of 2-Iodobiphenyls

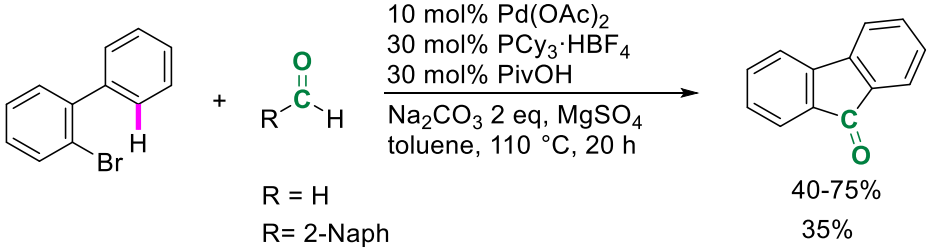
2.1 Introduction

Ever since the pioneering study from Larock and Campo,[1] several protocols of the palladium-catalyzed intramolecular carbonylation of 2-halobiaryls via C-H bond cleavage at 2'-position have been reported in the literature (Scheme 2-1).[2]



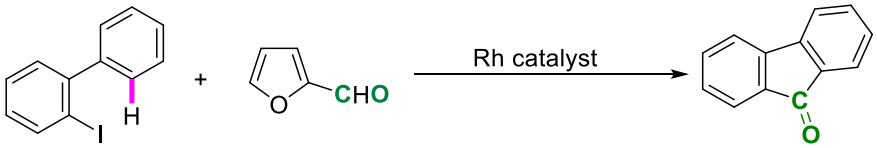
Scheme 2-1. Carbonylation of 2-halobiphenyls.

From the viewpoints of safety and ease of operation, I reported the palladium-catalyzed C-H carbonylation of 2-bromobiphenyls with paraformaldehyde, which has great advantages in terms of cost and atom economy in comparison with other reported carbonyl surrogates.[3] In this reaction, however, the use of formaldehyde led to the hydrodebromination of the substrates,[4] resulting in low to moderate yields of the desired products, while aromatic aldehydes such as 2-naphthaldehyde failed to participate efficiently in the reaction, probably due to the low activity of phosphane-ligated palladium catalysts for the decarbonylation of aromatic aldehydes (Scheme 2-2).[5]



Scheme 2-2. Cyclocarbonylation of 2-bromobiphenyls using aldehydes.

With the intent to improve the reaction, I focused on the use of rhodium complexes, because they have a high ability to (i) abstract a carbonyl moiety from various aldehydes (decarbonylation),[6] (ii) cleave and functionalize an inert C-H bond at arenes,[7] and (iii) introduce a carbonyl moiety into various organic substrates (carbonylation).[8] In this chapter, I describe the rhodium-catalyzed intramolecular carbonylative C-H/C-I coupling of 2-iodobiphenyls with furfural (Scheme 2-3). To the best of my knowledge, the rhodium-catalyzed direct carbonylative coupling of a C-H bond in an arene derivative with a C-X bond of aryl halides has not yet been reported.



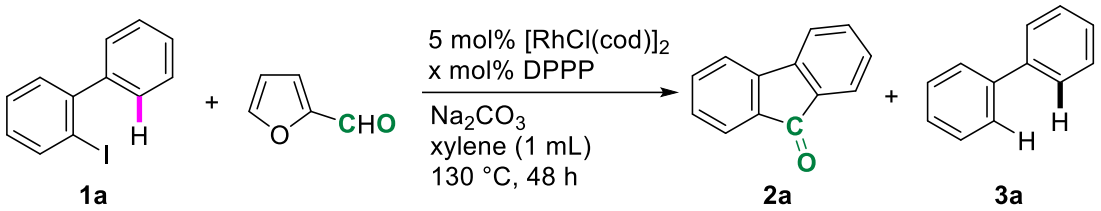
Scheme 2-3. Rhodium-catalyzed cyclocarbonylation of 2-iodobiphenyls using furfural.

2. 2 Results and Discussions

2. 2. 1 Optimization of Reaction Conditions

I first examined the rhodium-catalyzed carbonylation of 2-iodobiphenyl (**1a**) with furfural under the following conditions: **1a** (0.25 mmol), furfural (1.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), and Na_2CO_3 (0.30 mmol) in xylene (1 mL) at 130 °C for 48 h (Table 2-1, entry 1). As a result, the desired fluoren-9-one (**2a**) was obtained in 22% yield and 60% of **1a** was recovered from the reaction mixture. I hypothesized that the decarbonylation of furfural proceeds slowly due to low activity of $[RhCl(cod)]_2$. Hence, the addition of DPPP, which is known as an efficient ligand for the decarbonylation of aromatic aldehydes,[6] was investigated. As expected, the combination of $[RhCl(cod)]_2$ and DPPP resulted in a higher activity than the single use of $[RhCl(cod)]_2$, and the amount of added DPPP had a significant effect on the yield of fluoren-9-one (**2a**) (entries 2-7). 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** (entry 5). These results indicate that both DPPP-ligated and –free rhodium 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** respectively and function in a cooperative manner.[9] Removal of rhodium catalyst from the catalytic system for the present carbonylation resulted in no formation of the desired product (entry 8).

Table 2-1. Optimization of amount of DPPP.[a]



1a **2a** **3a**

Entry	DPPP (x mol%)	Conv. (%)[b]	**2a** (%)[b]	**3a** (%)[b]
1	0.0	40	22	tr
2	2.5	69	53	3
3	5.0	89	67	5
4	7.0	94	84	3
5	**7.5**	**96**	**89**	**2**
6	8.0	92	81	2
7	10.0	86	75	3
8[c]	7.5	<2	0	0

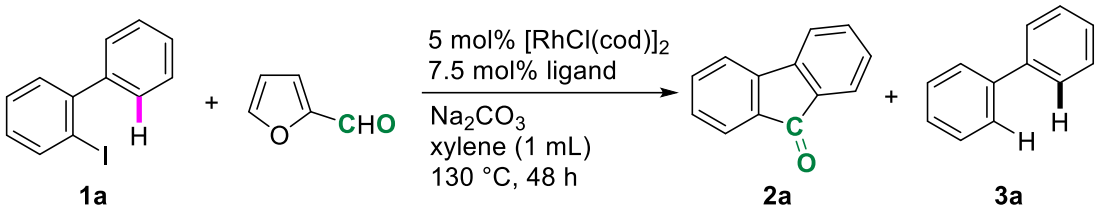
[a]Reaction conditions: **1a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), DPPP (as indicated), Na_2CO_3 (0.3 mmol), and furfural (1.25 mmol).

[b]Isolated yield. [c]Without rhodium complex.

Next, the influence of bidentate phosphane derivatives as ligands on the yield of **2a** was investigated, since they have been shown to be effective for the decarbonylation of carbonyl compounds (Table 2-2).[6,10] 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 (entries 1-5). With monodentate phosphane such as PPh_3, the carbonylative coupling proceeded slowly (entry 6).

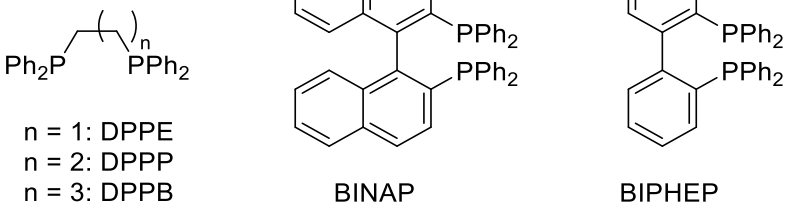
It is well known that added base affects remarkably the C-H bond cleavage efficiency.[11] Therefore, I examined various bases (Table 2-3), but the use of other inorganic carbonates and sodium carboxylates in place of Na_2CO_3 led to lower yields of the desired product.

Table 2-2. Optimization of phosphane ligands.[a]



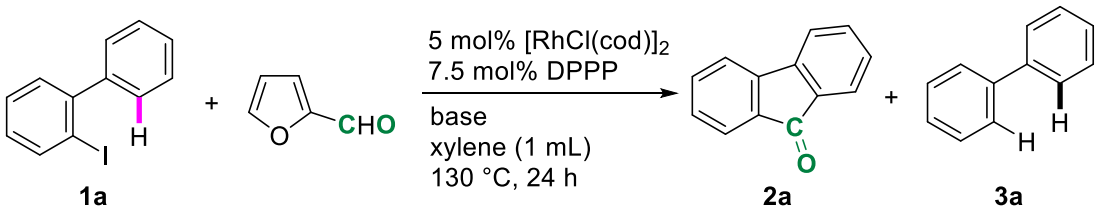
1a **2a** **3a**

Entry	Ligand	Conv. (%)[b]	**2a** (%)[b]	**3a** (%)[b]
1	**DPPP**	**80**	**72**	**2**
2	DPPE	71	62	2
3	DPPB	51	43	tr
4	BINAP	60	56	tr
5	BIPHEP	43	40	tr
6	PPh_3[c]	30	14	2



[a]Reaction conditions: **1a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), ligand (0.0188 mmol), Na_2CO_3 (0.3 mmol), and furfural (1.25 mmol). [b]Isolated yield. [c]PPh_3 (0.0375 mmol).

Table 2-3. Optimization of bases.[a]



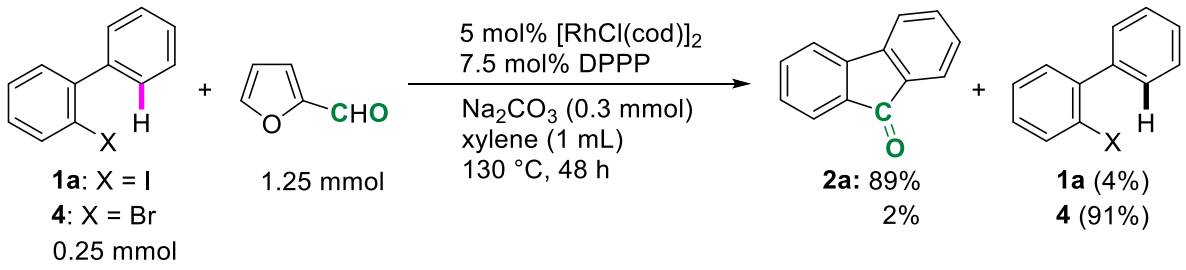
1a **2a** **3a**

Entry	Base	Conv. (%)[b]	**2a** (%)[b]	**3a** (%)[b]
1	**Na_2CO_3**	**80**	**72**	**2**
2	Li_2CO_3	29	22	tr
3	K_2CO_3	91	41	tr
4	NaOPiv	52	44	6
5	NaOAc	41	36	4

[a]Reaction conditions: **1a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), DPPP (0.0188 mmol), base (0.3 mmol), and furfural (1.25 mmol). [b]Isolated yield.

2. 2. 2. Substrate Scope

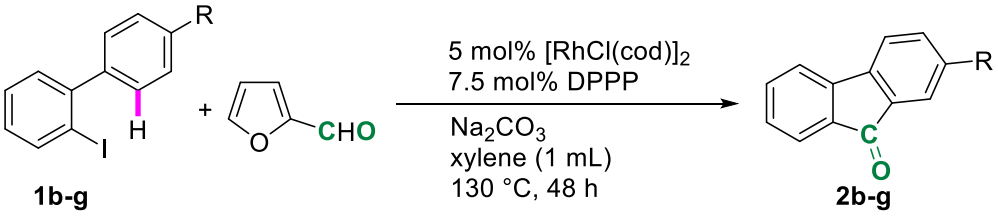
I then explored the scope of the intramolecular C-H carbonylation of 2-halobiphenyls with furfural under the optimal conditions. The reaction of 2-bromobiphenyl (**4**) gave a poor yield of **2a** and 91% of **4** was recovered from the reaction mixture (Scheme 2-4).[12]



Scheme 2-4. Reaction of 2-halobiphenyl.

2-Iodobiphenyls possessing both electron-donating and electron-withdrawing groups at the 4'-position (**1b**-**1g**) were converted into the corresponding fluoren-9-ones (**2b**-**2g**) in good yields (Table 2-4).

Table 2-4. Scope of 4-substituted 2'-iodobiphenyls.[a]

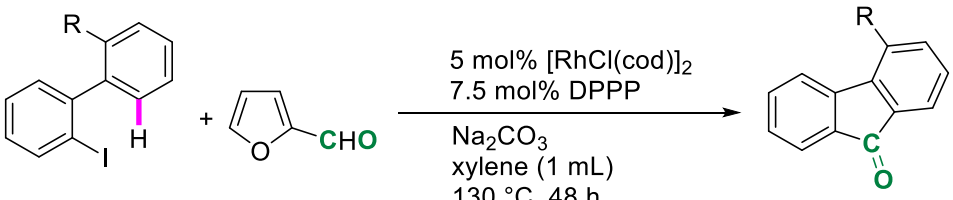


Entry		Conv. (%)[b]		Yield (%)[b]
1	**1b**: R = Me	95	**2b**	84
2	**1c**: R = OMe	98	**2c**	82
3	**1d**: R = ^{t}Bu	85	**2d**	73
4	**1e**: R = CF_3	85	**2e**	71
5	**1f**: R = F	89	**2f**	74
6	**1g**: R = Cl	81	**2g**	70

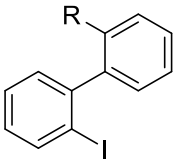
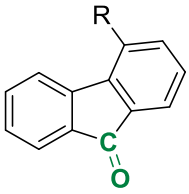
[a]Reaction conditions: **1b-g** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), DPPP (0.0188 mmol), Na_2CO_3 (0.3 mmol), and furfural (1.25 mmol).
[b]Isolated yield.

The influence of the substituent at the 2'-position on the reaction was then investigated. 2-Fluoro-2'-iodobiphenyl (**1h**) also underwent the transformation to furnish **2h** in 61% yield (Table 2-5, entry 1). 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 2-4).

Table 2-5. Scope of 2-substituted 2'-iodobiphenyls.[a]

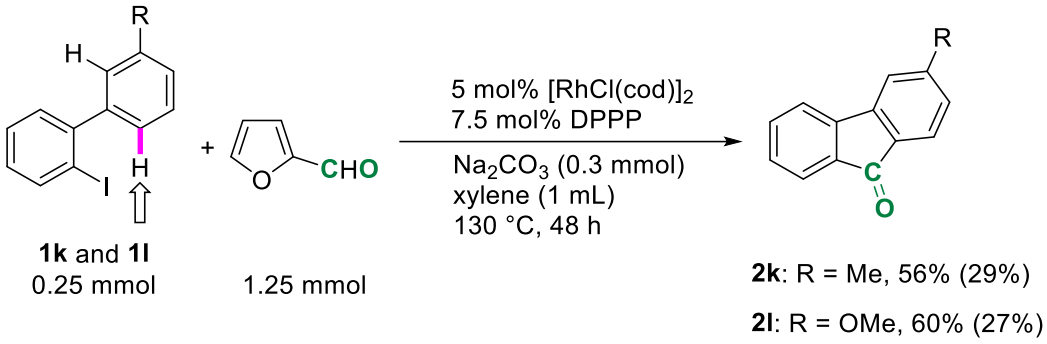


1h-j **2h-j**

Entry		Conv.		Yield (%)[b]
1	**1h**: R = F	72	**2h**	61
2	**1i**: R = Me	38	**2i**	17
3[c]	**1i**: R = Me	70	**2i**	40
4[c,d]	**1j**: R = Br	68	**2j**	31

[a]Reaction conditions: **1h-j** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), DPPP (0.0188 mmol), Na_2CO_3 (0.3 mmol), and furfural (1.25 mmol).
[b]Isolated yield. [c]Reaction was carried out at 150 °C.
[d]**2a** was obtained in 18% yield.

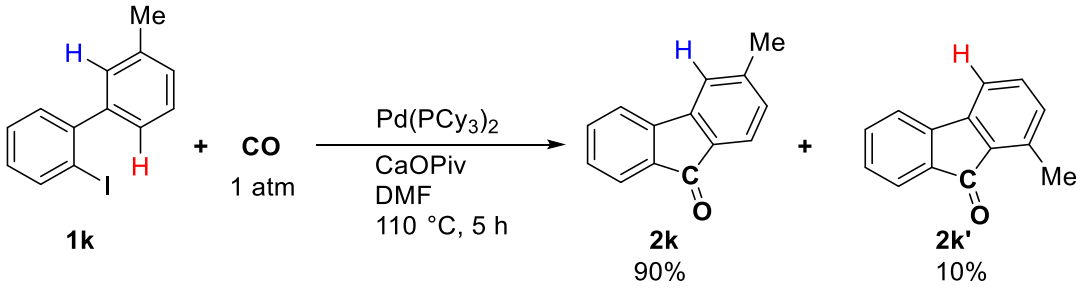
The reaction of 2-iodobiphenyls containing a substituent at the 3'-position proceeded in an exclusive regioselective manner. The high regioselective reaction resulted in the formation of **2k** and **2l** in moderate yields (Scheme 2-5). The similar result was found in the intramolecular acylation of biphenyl-2-carboxylic acids reported by Fukuyama and Ryu.[13]



The values in the parentheses are recovered 2-iodobiphenyls.

Scheme 2-5. The reaction of 2-iodobiphenyls containing a substituent at the 3'-position.

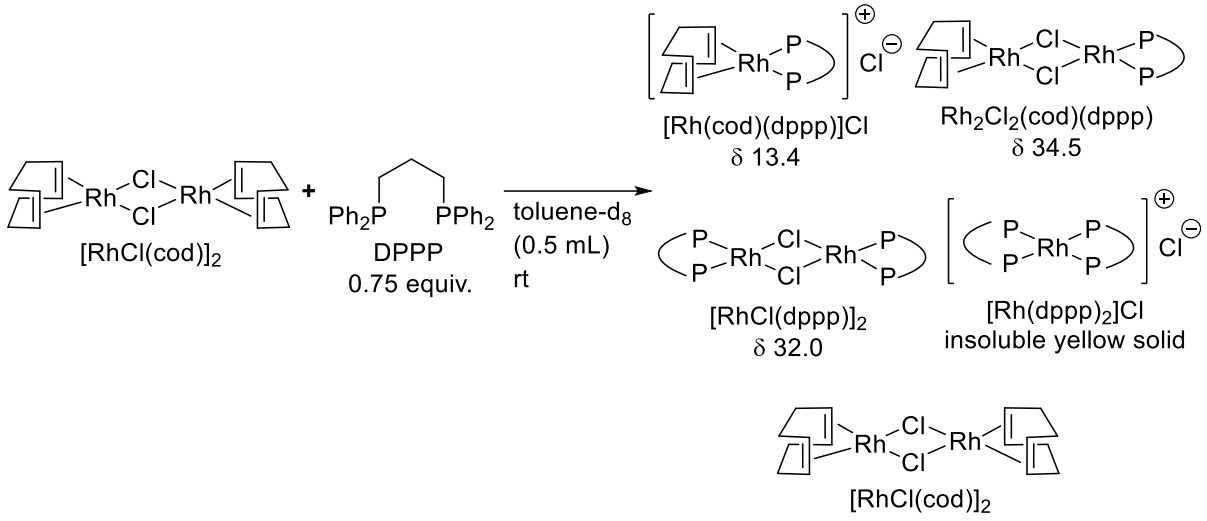
These results are in contrast to the palladium-catalyzed reaction of **1k** and **1l** with carbon monoxide[1] or isocyanides,[14] in which fluoren-9-one derivatives, generated from 3'-substitutesd 2-halobiphenyls, were obtained as a mixture of regioisomers (Scheme 2-6).



Scheme 2-6. Palladium-catalyzed reaction of 2-iodobiphenyl **1k** with carbon monoxide.

2. 2. 3. Mechanistic Study

In an attempt to elucidate the mechanistic aspects of the reaction, especially the effect of DPPP, on the present cyclocarbonylation, some experiments were carried out. Firstly, I conducted ^{31}P NMR experiment to identify the active species (Scheme 2-7 and Figure 2-1). ^{31}P NMR spectum of the mixture of $[RhCl(cod)]_2$ and 0.75 equivalent of DPPP to the rhodium center showed signals at 13.4, 32.0, and 34.5 ppm, which are assigned to [Rh(cod)(dppp)]Cl, $[RhCl(dppp)]_2$, and $Rh_2Cl_2(cod)(dppp)$, respectively.[15] This mixture at room temperature gave the insoluble yellow solid, which is attributed to $[Rh(dppp)_2]Cl$. Furthermore, phosphane-free complex, $[RhCl(cod)]_2$, would exist in this mixture because of the addition of a short amount of DPPP to the rhodium center.



Scheme 2-7. ^{31}P NMR experiment.

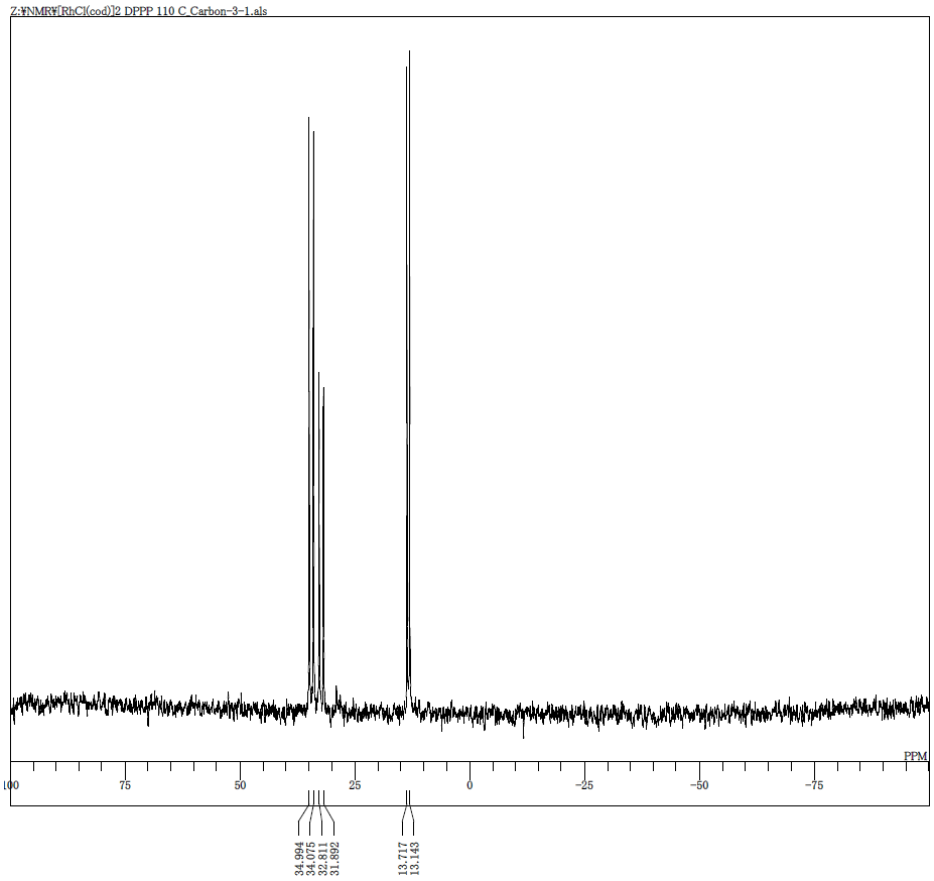
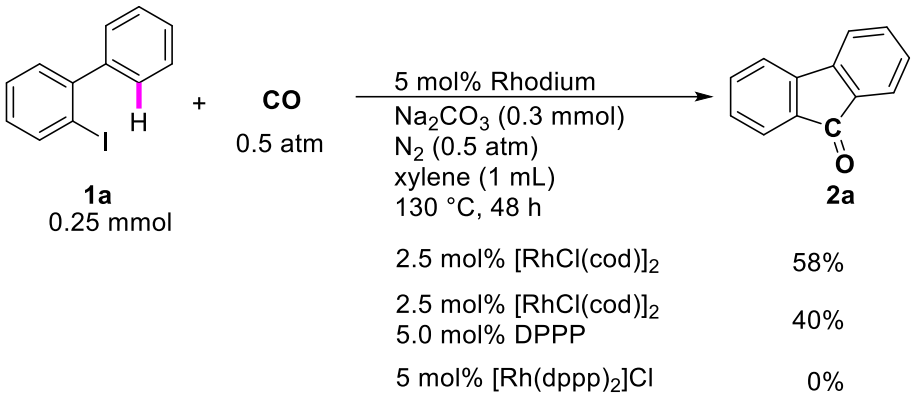


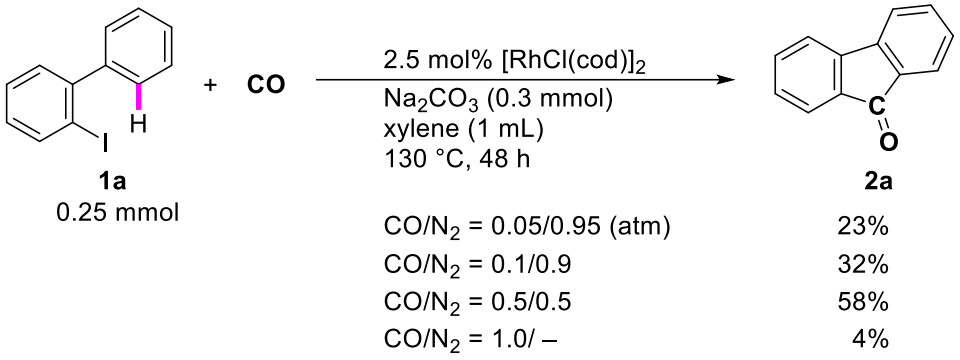
Figure 2-1. ^{31}P NMR spectrum of the mixture of $[RhCl(cod)]_2$ and DPPP.

It should be noted that the active species for the present C-H intramolecular carbonylation of 2-iodobiphenyls has not been clarified. On the basis of the result of ^{31}P NMR experiment, some catalyst systems were examined to identify the active species for the carbonylation step using gaseous carbon monoxide (Scheme 2-8). In this experiment, the combination of $[RhCl(cod)]_2$ and DPPP in place of three complexes, [Rh(cod)(dppp)]Cl, $[RhCl(dppp)]_2$, and $Rh_2Cl_2(cod)(dppp)$, were employed because they are difficult to isolate. The higher was the amount of DPPP to the rhodium center, the lower was the yield of **2a**. Thus, the DPPP-free rhodium complex appears to be more important for the cyclocarbonylation step.



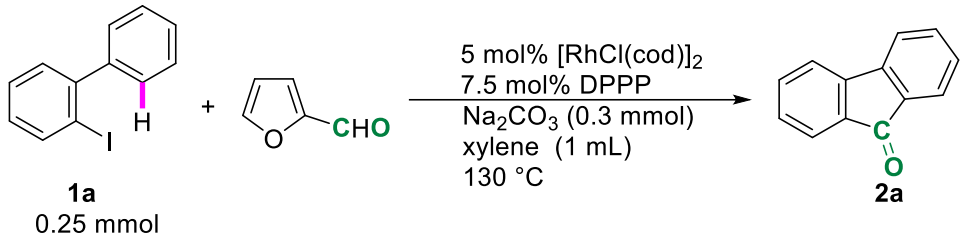
Scheme 2-8. Reactions using gaseous carbon monoxide.

The reactions were then carried out by varying the compositions of nitrogen and carbon monoxide (Scheme 2-9). 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.[16] 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 because of the inhibition of the coordination and the oxidative addition of substrate[17] and the timely release of the carbonyl source from furfural is highly decisive in terms of the efficiency of the carbonylation reaction.



Scheme 2-9. Partial pressure of carbon monoxide.

During the course of my studies on the nature of the actual catalytic species, it was found that, when the carbonylation reaction under the above standard conditions A (Figure 2-2), it involves an induction period. After the pretreatment of $[RhCl(cod)]_2$ and DPPP with Na_2CO_3 in xylene at 130 °C for 2 h (condition B), the reaction of 2-iodobiphenyl (**1a**) with furfural led to no observable induction period. These results suggest that a rhodium carbonate complex formed by the ligand exchange between the rhodium chloride and Na_2CO_3 is the actual catalytic species for the reaction.[18]



Condition A: standard conditions
Condition B: Pretreating a mixture of $[RhCl(cod)]_2$ and DPPP with Na_2CO_3 in xylene at 130 °C for 2 h prior to the addition of **1a** and furfural.

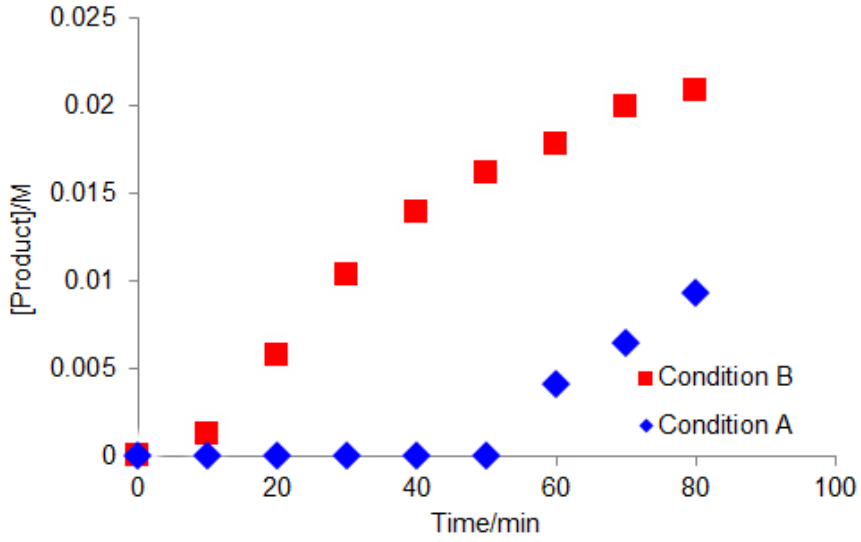
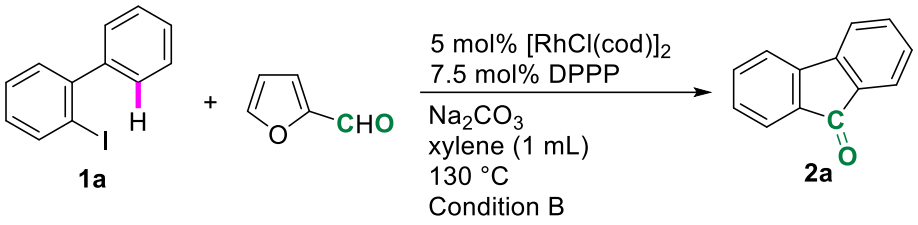


Figure 2-2. Reaction profiles for the carbonylation of **1a** with furfural under Condition A or Condition B.

Next, kinetic studies were done by using the initial rate method under condition B described in Figure 2-2, and the results are summarized in Table 2-6. While the rate dependence on the substrate (**1a**) concentration over the range of 0.20 to 0.25 M was found (entries 1-3), the value of k_{obs} decreased with increasing $[furfural]_0$ (entries 3-5). Furthermore, it is known that both stoichiometric[19] and catalytic[20] carbonyl transfer take place easily even at ambient temperature. Despite the need for further examinations, these would imply that the rate-determining step under the optimal conditions is involved in the carbonylation cycle.

Table 2-6. Kinetic data in the carbonylation of 2-iodobiphenyl (**1a**) with furfural.[a]

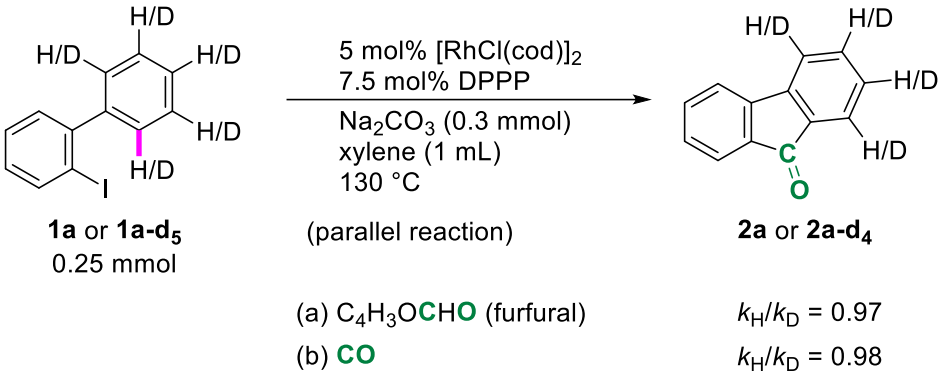


Entry	$[\mathbf{1a}]_0$ [M]	$[\mathbf{Furfural}]_0$ [M]	$k_{obs} \times 10^{-4}$(Mmin^{-1})
1	0.20	1.25	1.3
2	0.225	1.25	2.0
3	0.25	1.25	3.1
4	0.25	1.00	3.2
5	0.25	1.50	2.7

[a]Reaction conditions: **1a** (0.20-0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), DPPP (0.0188 mmol), Na_2CO_3 (0.3 mmol), and furfural (1.0-1.5 mmol).

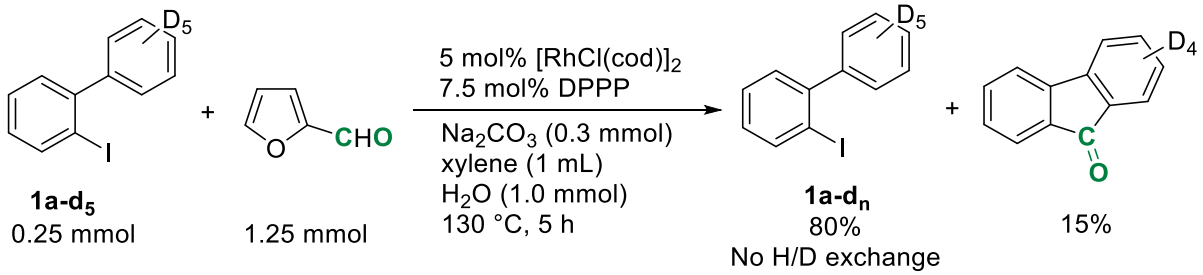
Lastly, deuterium labelling experiments using **1a**-d_5 was conducted. A comparison of the initial rates of the reactions of **1a** and **1a**-d_5 with furfural resulted in a k_H/k_D of 0.97 (a). A similar ratio was also observed in the reaction with gaseous carbon monoxide (k_H/k_D = 0.98) (b) (Scheme 2-10). These findings suggest that the cleavage of the C-H bond at the 2'-position is not involved in the rate-determining step.[21] 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 (Scheme 2-4 and Table 2-5), I propose that the rate-determining step is the oxidative addition of the C-I bond. Indeed, it is well known that oxidative addition and cyclization are frequently rate-determining steps in other carbonylation catalyzed by rhodium.[17] This speculation is supported by the fact that more carbonyl moieties inhibit the reaction (Scheme 2-9).[22]



Scheme 2-10. KIE experiments.

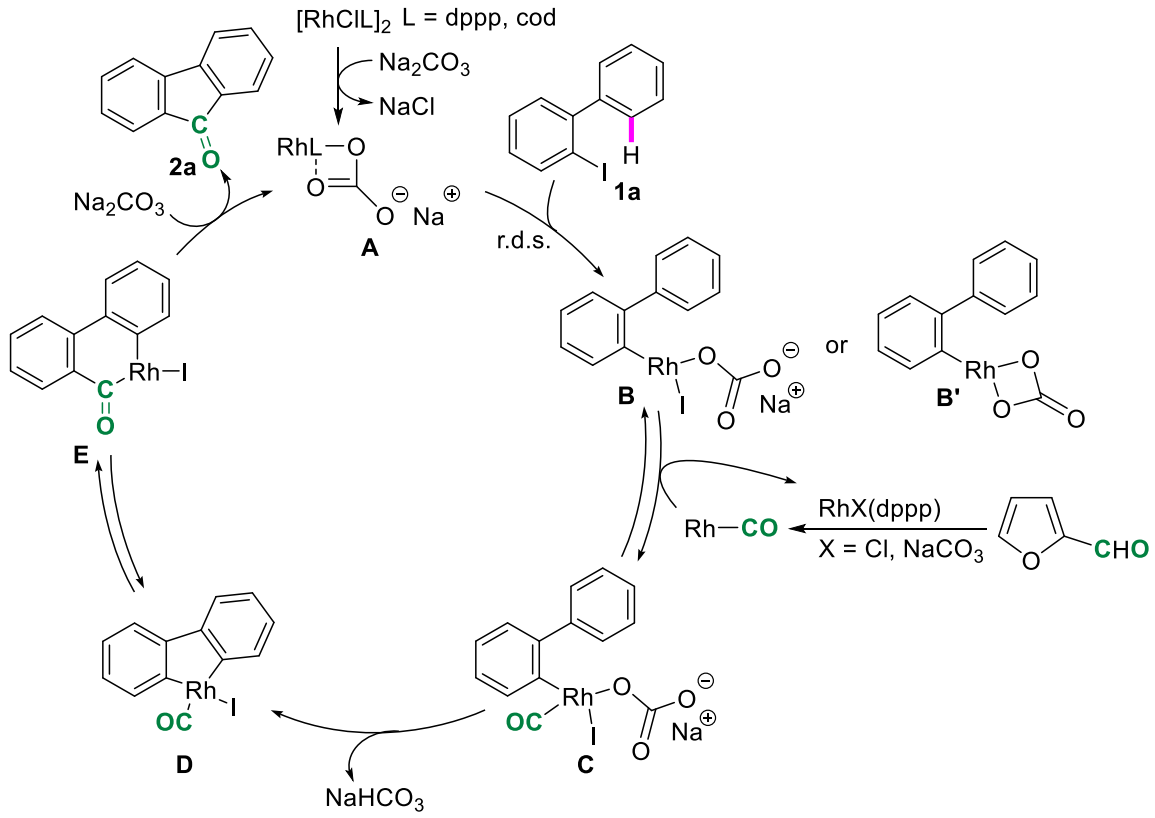
No H/D exchange in the desired product and the recovered starting material was observed even in the presence of H_2O (Scheme 2-11). This result suggests that the oxidative addition of C-I bond is earlier event than C-H bond cleavage which is irreversible step.[23,24]



Scheme 2-11. Deuterium labelling experiments.

Based on previous studies by others[1,6,24] and the above observations, a proposed mechanism for this rhodium-catalyzed carbonylation is shown in Scheme 2-12. After the

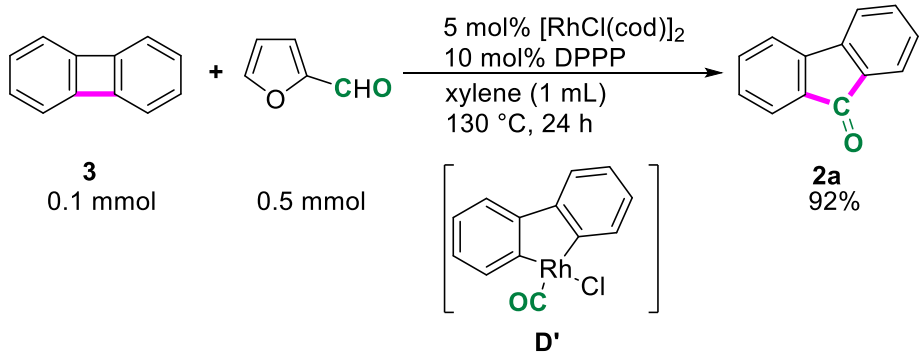
generation of complex **A** from $[RhCl(cod)]_2$, DPPP, and Na_2CO_3, 2-iodobiphenyl (**1a**) adds oxidatively to complex **A** to form 2-biphenyl rhodium(III) **B** or **B'**. This step can be considered to be the rate-determining step. The carbonyl ligand, which is produced through the decarbonylation of furfural catalyzed by DPPP-ligated rhodium complex, is then directly transferred to **B** giving complex **C**. Subsequently, the cleavage of C-H bond at the 2'-position leads to the formation of rhodafluorene **D**.[24] The migratory insertion of the carbonyl moiety then affords the six-membered rhodacycle **E**. Finally, the desired fluoren-9-one (**2a**) is released by the reductive elimination, and the active species **A** is regenerated to complete the catalytic cycle.



Scheme 2-12. Proposed reaction mechanism.

2. 2. 4. Carbonylation of Biphenylene

Jones's group reported the rhodium-catalyzed direct carbonylation of biphenylene through the formation of rhodafluorene, which is accordance with complex **D** in Scheme 2-12, involving the oxidative addition of C-C bond.[25] To my delight, the present approach was applicable to the reaction of biphenylene (**3**) to afford **2a** in good yield (Scheme 2-13).



Scheme 2-13. Carbonylation of biphenylene (**3**) through the cleavage of C-C bond.

2. 3 Conclusion

In summary, I found the rhodium-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 palladium-catalyzed reaction with paraformaldehyde, the present rhodium-catalyzed C-H carbonylation gave higher yields of fluoren-9-ones. Furthermore, a high degree of regioselectivity of the reaction with 3'-substituted 2-iodobiphenyls was achieved. 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 rhodium(I) center. Importantly, the exchange of furfural into atmospheric carbon monoxide resulted in retarding the formation of the desired fluoren-9-one, suggesting that the key to success of the present carbonylation is the timely release of the carbonyl moiety from furfural. Furfural also worked well as a carbonyl source in the carbonylation of biphenylene through the oxidative addition of C-C bond.

2. 4 Experimental Section

I. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer in $CDCl_3$ using $CHCl_3$ (proton: 7.26 ppm, carbon: 77.16 ppm) as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), integration, and interpretation. The products were analyzed by a gas chromatography (SHIMADZU GC-2025), equipped using a flame ionization detector. Column chromatography was performed using a SiO_2 (MERCK Silica gel 60).

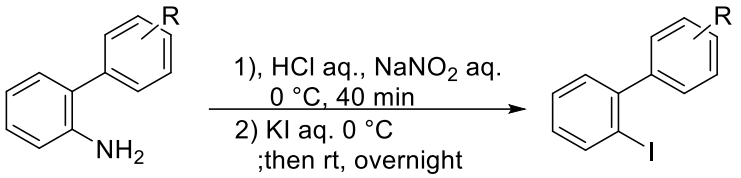
II. Materials.

$[RhCl(cod)]_2$,[26] $[Rh(dppp)_2]Cl$,[27] NaOPiv,[28] 2-iodobiphenyls **1b, c, e-g, i**-1,[29] **1a**-d_5,[30] and biphenylene **3**[31] were prepared using a previously reported method. Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, and NaOAc were purchased from Wako Pure Chemical Industries, Ltd. and dried over P_2O_5 under a vacuum prior to use. $NaNO_2$, KI, HCl, and Furfural were purchased from Wako Pure Chemical Industries, Ltd and used directly without further purification. PPh_3 was purchased from Wako Pure Chemical Industries, Ltd. and recrystallized from ethanol. DPPE, DPPP, DPPB, and 2-iodobiphenyl **1a** were purchased from Tokyo Chemical Industry Co., Ltd. and were used directly without further purification. BIPHEP was purchased from Strem Chemicals Inc. and was used directly without further purification. BINAP was purchased from

Kanto Chemical. and was used directly without further purification. Anhydrous xylene was purchased from Wako Pure Chemical Industries, Ltd. dried by storage over 4A molecular sieves, and degassed by N_2 bubbling prior to use. .

III. Procedure and Spectroscopic Data for Starting Materials

The spectroscopic data for **1b**, **c**, **e-g**, **i-l** can be found in the literature.[29]

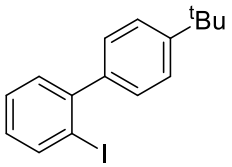


R = 4'-^{t}Bu: **S1d**
R = 2'-F: **S1h**

R = 4'-^{t}Bu: **1d**
R = 2'-F: **1h**

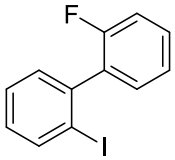
A typical procedure is as follows; an aqueous $NaNO_2$ solution (0.75 M, 4.0 mL) was added dropwise into a reaction mixture of **S1**[32] (2.0 mmol) and 35% aqueous HCl (0.6 mL), and the resulting mixture was stirred at 0 °C for 40 min. After adding a solution consisting of KI (5.0 mmol, 830.00 mg) and water (1.0 mL), the combined reaction solution was stirred at room temperature overnight. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 10% aqueous $Na_2S_2O_3$ solution (2 x 10 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude product was purified by flash column chromatography on silica-gel to afford **1.**

1d: 4-Tert-butyl-2'-iodobiphenyl



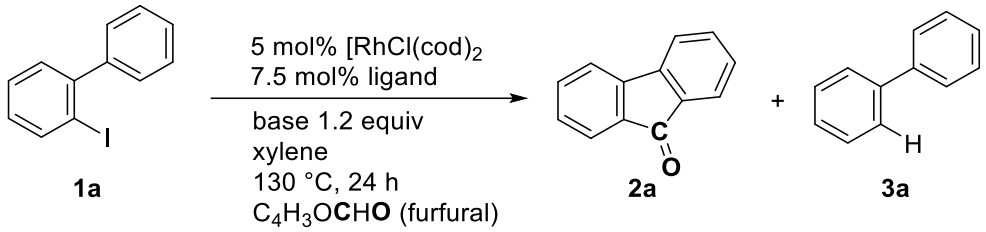
Colorless liquid; R_f: 0.34 (Hexane); Isolated yield = 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 9H), 7.02 (dt, 1H, J = 2.0, 8.0 Hz), 7.28–7.32 (m, 3H), 7.38 (t, 1H, J = 7.5 Hz), 7.44 (d, 2H, J = 8.0 Hz), 7.96 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.5, 34.8, 98.8, 125.0, 128.2, 128.7, 129.0, 130.4, 139.7, 141.3, 146.6, 150.6.; IR (neat) 3051, 3029, 2964, 2902, 2866, 1910, 1462, 1395, 1362, 1269, 1001, 834, 742, 679, 641, 579, 541.; HRMS (EI) calcd. for $C_{16}H_{17}I$ [M]+ 336.0375, found 336.0359.

1h: 2-Fluoro-2'-iodobiphenyl



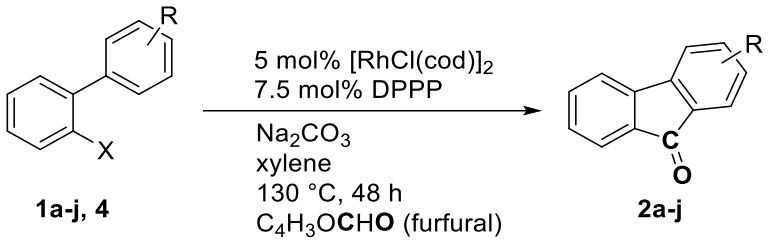
Colorless liquid; R_f: 0.29 (Hexane); Isolated yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dt, 1H, J = 1.0, 8.0 Hz), 7.14–7.25 (m, 3H), 7.30 (d, 1H, J = 6.5 Hz), 7.38-7.43 (m, 2H), 7.96 (dd, 1H, J = 1.0, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.7, 115.9 (d, J = 21.5 Hz), 124.0 (d, J = 3.6 Hz), 128.1, 129.6, 130.0 (d, J = 7.2 Hz), 130.7, 131.6 (d, J = 2.4 Hz), 132.0 (d, J = 16.7 Hz), 139.3, 141.4, 159. 2 (d, J = 247.1 Hz).; IR (neat) 3052, 1581, 1497, 1463, 1155, 1004, 824, 648, 569.; HRMS (EI) calcd. for $C_{12}H_8FI$ [M]+ 297.9655, found 297.9657.

IV. Optimization Study of Rhodium-Catalyzed Intramolecular Carbonylation of 2-Iodobiphenyl



A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(cod)]_2$ (0.0125 mmol, 6.16 mg), bidentate phosphane ligand (0-0.025 mmol), and base (0.3 mmol). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL), furfural (1.25 mmol, 120.1 mg), and 2-iodobiphenyl **1a** (0.25 mmol, 70.0 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that had been preheated to 130 °C for 24 or 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** and **3a** (gradient elution with hexane/AcOEt = 100/0 - 30/1).

V. General Procedure for the Rhodium-Catalyzed Cyclocarbonylation of 2-Iodobiphenyl with Furfural (Condition A).

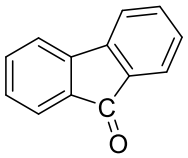


A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(cod)]_2$ (0.0125 mmol, 6.16 mg), DPPP (0.0188 mmol, 7.73 mg), and Na_2CO_3 (0.3 mmol, 31.8 mg). The central neck of the flask was equipped with a reflux condenser having an a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL), furfural (1.25 mmol, 120.1 mg), and 2-iodobiphenyl **1a** (0.25 mmol, 70.0 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that 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).

VI. Spectroscopic Data for Products

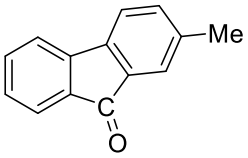
All fluoren-9-ones[33] shown here were reported previously and identified by comparing the ^{1}H NMR and ^{13}C NMR data.

2a: *9H*-Fluoren-9-one [486-25-9]



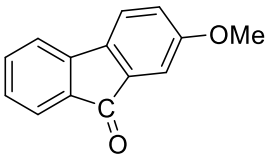
Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (td, 2H, J = 1.0, 7.5 Hz), 7.47–7.53 (m, 4H), 7.66 (dd, 2H, J = 1.0, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.4, 124.4, 129.2, 134.2, 134.8, 144.5, 194.1.

2b: 2-Methyl-*9H*-fluoren-9-one [2840-51-9]



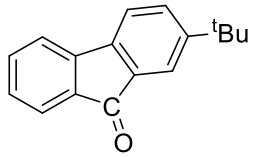
Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.22–7.27 (m, 2H), 7.37 (d, 1H, J = 7.5 Hz), 7.43–7.45 (m, 3H), 7.61 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 120.1, 120.3, 124.3, 125.1, 128.7, 134.4, 134.5, 134.8, 135.2, 139.4, 141.9, 144.7, 194.4.

2c: 2-Methoxy-*9H*-fluoren-9-one [3314-07-1]



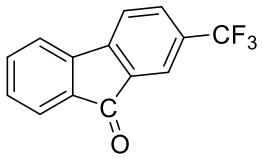
Yellow-orange solid; R_f: 0.13 (Hexane/AcOEt = 20/1); Isolated yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.99 (dd, 2H, J = 2.5, 8.0 Hz), 7.19–7.22 (m, 2H), 7.39–7.44 (m, 3H), 7.60 (d, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.8, 109.5, 119.7, 120.3, 121.4, 124.4, 128.0, 134.4, 134.9, 136.0, 137.1, 145.0, 160.9, 193.94.

2d: 2-*tert*-Butyl-9*H*-fluoren-9-one [58775-11-4]



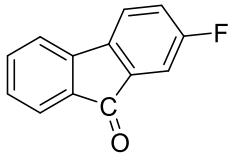
Yellow solid; R_f: 0.23 (Hexane/AcOEt = 20/1); Isolated yield = 73%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 7.24-7.26 (m, 1H), 7.43–7.52 (m, 4H), 7.64 (d, 1H, J = 7.5 Hz), 7.72 (d, 1H, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 35.2, 120.1, 120.2, 121.7, 124.3, 128.7, 131.6, 134.3, 134.6, 134.7, 141.9, 144.6, 152.9, 194.5.

2e: 2-Trifluoromethyl-9*H*-fluoren-9-one [22052-25-1]



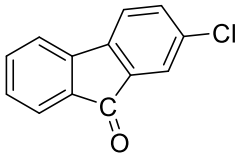
Yellow solid; R_f: 0.18 (Hexane/AcOEt = 20/1); Isolated yield = 71%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.39 (m, 1H), 7.53–7.57 (m, 3H), 7.68–7.74 (m, 2H), 7.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.6, 121.2, 121.3 (q, $J_{C\text{-}F}$ = 3.5 Hz), 123.8 (q, $J_{C\text{-}F}$ = 270.6 Hz), 124.9, 130.3, 131.4 (q, $J_{C\text{-}F}$ = 32.8 Hz), 131.7 (q, $J_{C\text{-}F}$ = 3.5 Hz), 134.4, 134.5, 135.3, 143.1, 147.5, 192.3.

2f: 2-Fluoro-*9H*-fluoren-9-one [343-01-1]



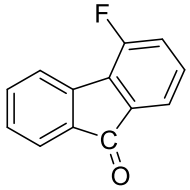
Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 74%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, 1H, *J* = 2.5, 8.5 Hz), 7.27–7.29 (m, 1H), 7.34 (dd, 1H, *J* = 2.5, 7.5 Hz), 7.47–7.49 (m, 3H), 7.66 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.1 (d, $J_{C\text{-}F}$ = 22.6 Hz), 120.3, 121.1 (d, $J_{C\text{-}F}$ = 23.9 Hz), 121.7 (d, $J_{C\text{-}F}$ = 8.4 Hz), 124.8, 128.9, 134.4, 135.2, 136.4 (d, $J_{C\text{-}F}$ = 7.1 Hz), 140.3, 144.0, 163.7 (d, $J_{C\text{-}F}$ = 249.1 Hz), 192.6 (d, $J_{C\text{-}F}$ = 2.4 Hz).

2g: 2-Chloro-*9H*-fluoren-9-one [3096-47-7]



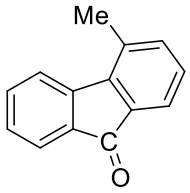
Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, 1H, *J* = 2.5, 8.5 Hz), 7.29–7.32 (m, 1H), 7.43 (s, 2H), 7.48-7.51 (m, 2H), 7.59 (s, 1H), 7.65 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.5, 121.5, 124.6, 124.7, 129.4, 134.0, 134.3, 135.0, 135.1, 135.7, 142.6, 143.7, 192.6.

2h: **4-Fluoro-*9H*-fluoren-9-one [1514-18-7]**



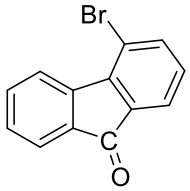
Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 61%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, 1H, J = 9.0 Hz), 7.26–7.30 (m, 3H), 7.33 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.67–7.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.2 (d, $J_{C\text{-}F}$ = 2.4 Hz), 122.7 (d, $J_{C\text{-}F}$ = 21.5 Hz), 124.1 (d, $J_{C\text{-}F}$ = 4.8 Hz), 124.6, 129.2, 130.0 (d, $J_{C\text{-}F}$ = 15.5 Hz), 130.9 (d, $J_{C\text{-}F}$ = 6.0 Hz), 133.7, 135.2, 136.7 (d, $J_{C\text{-}F}$ = 3.5 Hz), 141.6, 157.8 (d, $J_{C\text{-}F}$ = 252.8 Hz), 192.7 (d, $J_{C\text{-}F}$ = 2.4 Hz).

2i: **4-Methyl-*9H*-fluoren-9-one [4269-05-0]**



Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 40%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.18 (t, 1H, J = 7.5 Hz), 7.24-7.29 (m, 2H), 7.46-7.53 (m, 2H), 7.61 (d, 1H, J = 7.5 Hz), 7.67 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 122.1, 123.5, 124.4, 128.5, 128.9, 133.8, 134.5, 134.6, 134.8, 137.5, 142.3, 145.4, 194.4..

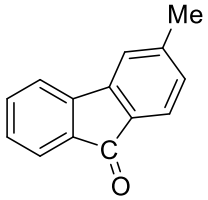
2j: **4-Bromo-*9H*-fluoren-9-one [4269-17-4]**



Yellow solid; R_f: 0.21 (Hexane/AcOEt = 20/1); Isolated yield = 31%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, 1H, J = 7.5 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.62 (t,

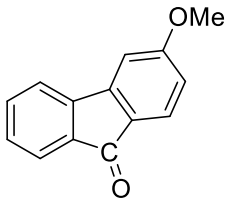
2H, *J* = 7.5 Hz), 7.70 (d, 1H, *J* = 7.5 Hz), 8.36 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.7, 123.2, 123.7, 124.6, 129.7, 130.2, 134.2, 134.9, 136.9, 139.6, 142.5, 143.9, 192.7.

2k: **3-Methyl-*9H*-fluoren-9-one [1705-89-1]**



Yellow solid; R_f: 0.22 (Hexane/AcOEt = 20/1); Isolated yield = 56%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.09 (d, 1H, *J* = 7.5 Hz), 7.27–7.30 (m, 1H), 7.33 (s, 1H), 7.45-7.50 (m, 2H), 7.55(d, 1H, *J* = 7.5 Hz), 7.64 (dd, 1H, *J* = 1.0, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 120.2, 121.3, 124.3, 124.4, 129.1, 129.7, 131.9, 134.5, 134.8, 144.4, 144.9, 145.9, 193.7.

2m: 3-Methoxy-*9H*-fluoren-9-one [15144-82-8]

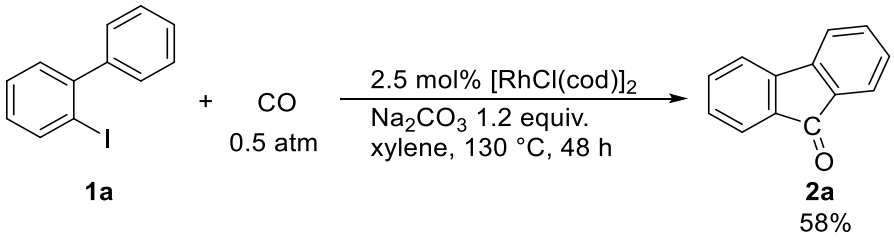


Yellow solid; R_f: 0.14 (Hexane/AcOEt = 20/1); Isolated yield = 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.74 (dd, 1H, *J* = 2.5, 8.5 Hz), 7.03 (s,1H), 7.30 (dt, 1H, *J* = 2.0, 7.5 Hz), 7.45-7.49 (m, 2H), 7.61-7.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ55.9, 107.2, 113.1, 120.3, 124.0, 126.4, 127.3, 129.4, 134.3, 135.5, 143.5, 147.2, 165.5, 192.7.

VII. NMR Experiment.

A J. Young NMR tube was charged with $[RhCl(cod)]_2$ (0.0125 mmol, 6.16 mg), DPPP (0.0188 mmol, 7.73 mg), and 0.5 mL of toluene-d_8 in a glove box under a nitrogen atmosphere. After mixing at room temperature, the ^{31}P NMR spectrum of this solution was measured.

VIII. Procedure for the Reaction of 2-Iodobiphenyl (1a) Using Carbon Monoxide.



A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(cod)]_2$ (0.0625 mmol, 3.08 mg) and Na_2CO_3 (0.3 mmol, 31.8 mg). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL), and 2-iodobiphenyl **1a** (0.25 mmol, 70.0 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with a mixture of N_2/CO prepared in the gas-bag (1:1, 2 L). The mixture was placed in an oil bath that had been preheated to 130 °C for 48 h. After cooling to room temperature, the resulting solution was filtered through a pad

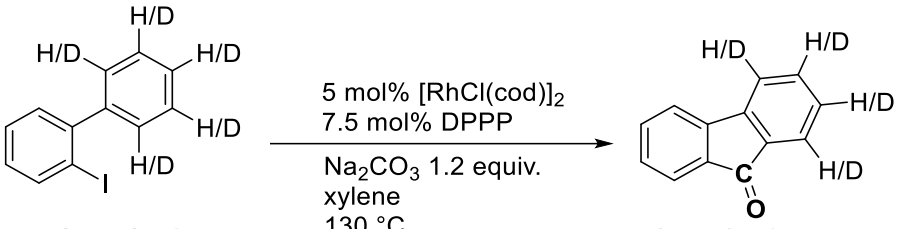
of celite, and the filtrate was concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica-gel to afford **2a** in 58% yield as a yellow solid (gradient elution with hexane/AcOEt = 100/0 - 30/1).

IX. Procedure for Condition B Described in Figure 2-2.

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), Na_2CO_3 (0.3 mmol, 31.8 mg), and octadecane (internal standard, 25.0 mg). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL) was then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that had been preheated to 130 °C for 2 h. After cooling to room temperature, 2-iodobiphenyl **1a** (0.25 mmol, 70.0 mg) and furfural (1.25 mmol, 120.1 mg) were added to the resulting mixture. The flask was degassed and was filled with N_2 by the above method again. Then, the reaction mixture was stirred at 130 °C. The reaction was monitored by GC at 10 min intervals.

X. Kinetic Isotope Effect study: Determination of the Initial Rate of the Reaction.

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), Na_2CO_3 (0.3 mmol, 31.8 mg), and octadecane (internal standard, 25.0 mg). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL) was then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that had been preheated to 130 °C for 2 h. After cooling to room temperature, 2-iodobiphenyl **1a** or **1a-d$_5$** and furfural (if furfural was used as a carbonyl source) were added to the resulting mixture. After degassing the reaction mixture by the freeze-pump-thaw method three times, the flask was filled with N_2 (if using furfural as a carbonyl source) or a mixed gas of N_2/CO (1/1) (if gaseous carbon monoxide was used as a carbonyl source) again. The mixture was stirred at 130 °C. The reaction was monitored by GC at 10 min intervals. The KIE value (k_H/k_D = 0.97 or 0.98) was determined by the rate of formation of **2a** or **2a-d$_5$**.

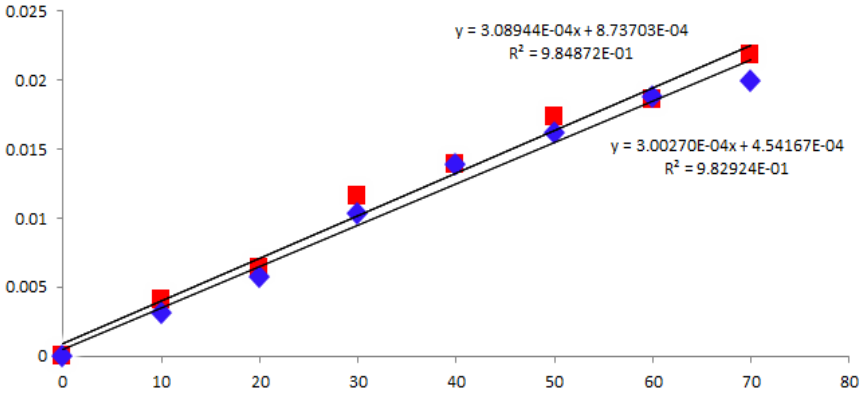


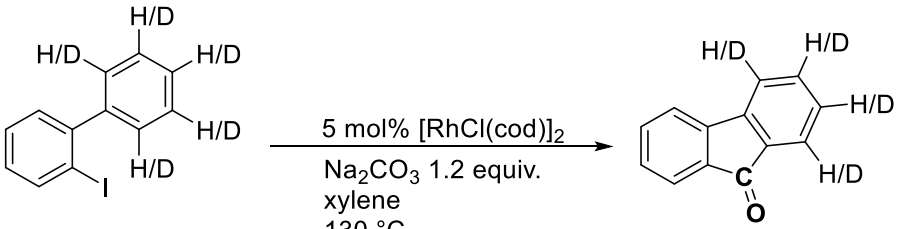
1a or **1a-d$_5$**
parallel reaction

$C_4H_3O\mathbf{C}H\mathbf{O}$ (furfural)

2a or **2a-d$_4$**

k_H/k_D = 0.97



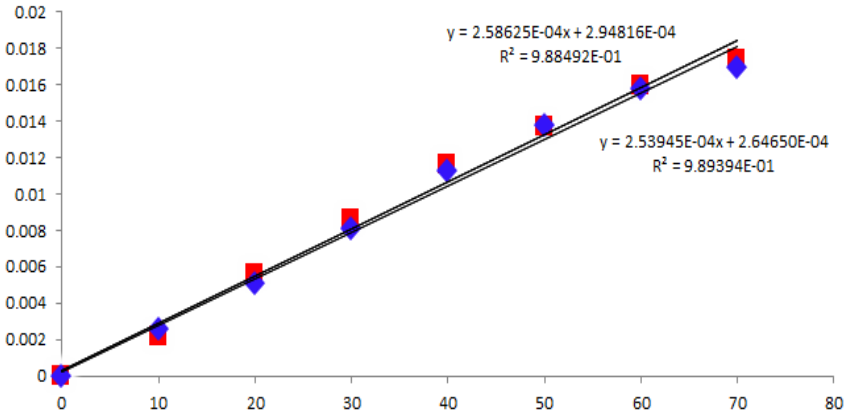


1a or **1a-d$_5$**
parallel reaction

CO (0.5 atm)

2a or **2a-d$_4$**

k_H/k_D = 0.98



XI. Procedure for the Carbonylation of Biphenylene.

A 5 mL dry two-necked flask equipped with a stir bar was charged with $[RhCl(cod)_2]_2$ (0.005 mmol, 2.47 mg), DPPP (0.01 mmol, 4.14 mg), and biphenylene **3** (0.1 mmol, 15.2 mg). The flask was evacuated and backfilled with N_2. 1.0 mL of xylene and furfural (0.5 mmol, 48.1 mg) were added. After the reaction mixture was degassed by the freeze-pump-thaw method with three times, the flask was refilled with N_2. The mixture was placed in an oil bath preheated at 130 °C for 24 h. The resulting solution was concentrated *in vacuo.* The resulting crude product was purified by flash column chromatography on silica-gel to afford **2a** (hexane/AcOEt = 30/1).

References and Notes

1. (a) Campo, M. A.; Larock, R. C. *Org*. *Lett*. **2000**, *2*, 3675. (b) Campo, M. A.; Larock, R. C. *J*. *Org*. *Chem*. **2002**, *67*, 5616. (c) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677.

2. (a) Lu, B.; Wu, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 11598. (b) Song, J.; Wei, F.; Sun, W.; Li, K.; Tian, Y.; Liu, C.; Li, Y.; Xie, L. *Org. Lett*. **2015**, *17*, 2106. (c) Zhang, J.; Zhang, X.; Fan, X. *J. Org. Chem*. **2016**, *81*, 3206. (d) Liu, S.; Shi, X.; Hu, Y.; Zhang, X.; Sun, W.; Qi, Y.; Fu, N.; Zhao, B.; Huang, W. *Tetrahedron Lett*. **2016**, *57*, 4452.

3. Furusawa, T.; Morimoto, T.; Oka, N.; Tanimoro, H.; Nishiyama, Y.; Kakiuchi, K. *Chem. Lett.* **2016**, *45*, 406.

4. Pyo, A.; Kim, S.; Kumar, M. R.; Byeun, A.; Eom, M. S.; Han, M. S.; Lee, S. *Tetrahedron Lett.* **2013**, *54*, 5207.

5. Modak, A.; Deb, A.; Patra, T.; Rana, S.; Maity, S.; Maiti, D. *Chem. Commun.* **2012**, *48*, 4253.

6. (a) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2007**, *46*, 9331. (c) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206. For early reports on the utilization of the decarbonylation of aldehydes as a carbonyl-donation process in carbonylation reaction, see: (d) Morimoto, T.;

Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806. (e) Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* **2002**, *4*, 1619.

7. (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev*. **2012**, *41*, 3651. (d) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31.
8. (a) Wu, X.-F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447. (b) Feng, J.-B.; Wu, X.-F. in *Transition Metal Catalyzed Carbonylative Synthesis of Heterocycles* (Eds.: Wu, X.-F.; Beller, M.), Springer, Heidelberg, 2016, pp. 25−54.
9. My group previously reported that phosphane ligated- and free-Rh catalyzed carbonylation with paraformaldehyde as a carbonyl source. See: (a) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777. (b) Wang, C.; Morimoto, T.; Kanashiro, T.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K.; Artock, L. *Synlett* **2014**, *25*, 1155.
10. Whittaker, R. E.; Dong, G. *Org. Lett.* **2015**, *17*, 5504.
11. (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Kefalidis, C. E.; Baudoin, O.; Clot, E. *Dalton Trans.* **2010**, *39*, 10528.
12. (a) Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980. (b) Brennfu¨hrer, A.;

Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.

13. Fukuyama, T.; Maetani, S.; Miyagawa, K.; Ryu, I. *Org. Lett.* **2014**, *16*, 3216.

14. Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem*. **2010**, *75*, 4835.

15. (a) Slack, D. A.; Greveling, I.; Baird, M. C. *Inorg. Chem*. **1979**, *18*, 3125. (b) Garrou, P. E. *Chem. Rev*. **1981**, *81*, 229.

16. (a) Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73. (b) Shibata, T.; Toshida, N.; Yamazaki, M.; Maekawa, S.; Takagi, K. *Tetrahedron* **2005**, *61*, 9974. (c) Kim, D. E.; Kim, I. S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Jeong, N. *J. Org. Chem.* **2008**, *73*, 7985.

17. (a) Fulford, A.; Hickey, C. E.; Maitlis, P. M. *J. Organomet. Chem.* **1990**, *398*, 311. (b) Pitcock, W. H. J.; Lord, R. L.; Baik, M.-H. *J. Am. Chem. Soc*. **2008**, *130*, 5821.

18. Pollice, R.; Schnurch, M. J. *J. Org. Chem*. **2015**, *80*, 8268.

19. (a) Barluenga, J.; Vicente, R.; Lopez, L. A.; Rubio, E.; Tomas, M.; Alvarez-Rua, C. *J. Am. Chem. Soc*. **2004**, *126*, 470. (b) Makado, G.; Morimoto, T.; Sugimoto, Y.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K. *Adv. Synth. Catal.* **2010**, *352*, 299.

20. Furusawa, T.; Morimoto, T.; Ikeda, K.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K.; Jeong, N. *Tetrahedron* **2015**, *71*, 875.

21. Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

22. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

23. Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677.

24. Miura and Satoh demonstrated that rhoda- and iridafluorene were produced from 2-biphenyl Rh(III) and Ir(III), respectively. See: a) Nagata, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 8960. b) Nagata, T.; Satoh, T.; Nishii, Y.; Miura, M. *Synlett* **2016**, *27*, 1707.

25. (a) Perthuisot, C.; Edelbach, B. E.; Zubris, D. L.; Jones, W. D. *Organometallics* **1997**, *16*, 2016. (b) Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **1999**, *18*, 4040. (c) Iverson, C. N.; Jones, W. D. *Organometallics* **2001**, *20*, 5745.

26. Giordano, G.; Crabtree, R. H. *Inorg. Synth.* **1979**, *19*, 218.

27. James, B. R.; Mahajan, D. *Can. J. Chem.* **1979**, *57*, 180

28. Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201.

29. (a) Iwasaki, M.; Iino, S.; Nishihara, Y. *Org. Lett*. **2013**, *15*, 5326. (b) Campo, M. A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R. D.; Huang, Q.; Zhao, J.; Jenks, W. S.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 6298. (c) Leroux, F. R.; Bonnafoux, L.; Heiss, C.; Colobert, F.; Lafranchi, D. A. *Adv. Synth. Catal.* **2007**, *349*, 2705.

30. Shi, G.; Chen, D.; Jiang, H.; Zhang, Y.; Zhang, Y. *Org. Lett.* **2016**, *18*, 2958.

31. Iyoda, M.; Kabir, S. M. H.; Vorasingha, A.; Kuwatani, Y.; Yoshida, M. *Tetrahedron Lett.* **1998**, *39*, 5393.

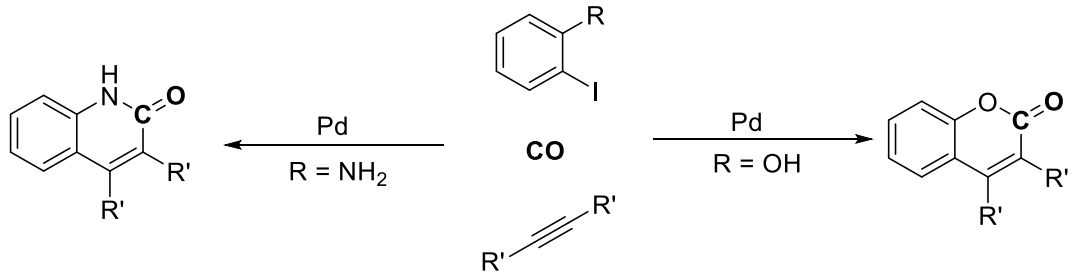
32. Stokes, B. J.; Jovanovic, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225.

33. (a) Wan, J.-C.; Huang, J.-M.; Jhan, Y.-H.; Hsieh, J.-C. *Org. Lett*. **2013**, *15*, 2742. (b) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928.

Chapter 3 Three-component Carbonylative Annulation Involving *Ortho*-C-H Bond Cleavage

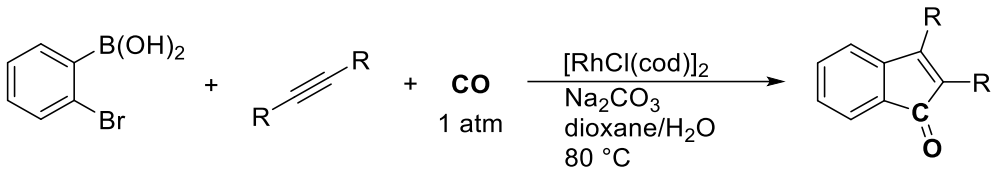
3. 1 Introduction

The transition metal-catalyzed three-component carbonylative annulation of *ortho*-functionalized aryl halides, π-unsaturated compounds, such as alkynes and olefins, and carbon monoxide is an attractive method for preparing cyclic carbonyl-containing compounds (Scheme 3-1),[1,2] which are found in a wide variety of natural products.[3]



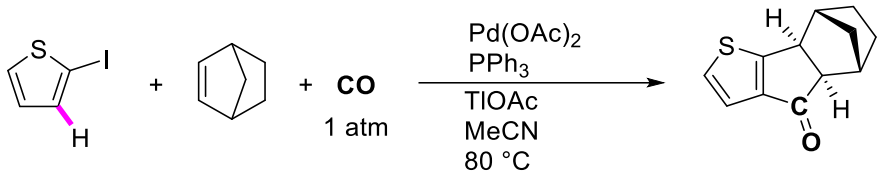
Scheme 3-1. Carbonylative annulation of *ortho*-functionalized aryl halides and alkynes.

While significant efforts have been devoted to developing the concise synthesis of heterocyclic carbonyl compounds, only a few examples of three-component carbonylative annulation for the synthesis of carbocyclic carbonyl compounds such as indenones and indanones have been reported in the literature.[4] In 2007, the first report, the rhodium-catalyzed carbonylative cyclization of 2-halophenylboronic acids with internal alkynes or 2-norbornene under atmospheric carbon monoxide, was published by Chatani's group (Scheme 3-2).[5] Later, Morimoto and Kakiuchi demonstrated that paraformaldehyde can be used as a carbonyl source in this transformation.[6]



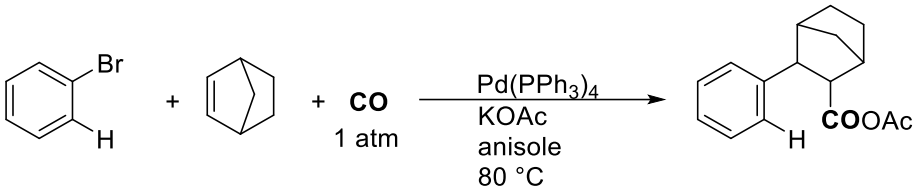
Scheme 3-2. Carbonylative cyclization of 2-halophenylboronic acids and alkynes.

Although high yields of the desired products could be achieved, these procedures have problem from the viewpoint of atom- and step-economy, and waste generation; the preparation of 2-halophenylboronic acids is generally a multistep.[7] Therefore, the straightforward functionalization at a C-H bond of simple haloarenes is an extremely ideal method.[8] In this context, Grigg reported on the fact that 2-iodothiophene reacts with 2-norbornene and carbon monoxide in the presence of a palladium catalyst to furnish the cyclic carbonyl compound through C-H metalation at the C3-position of the thiophene (Scheme 3-3).[9]



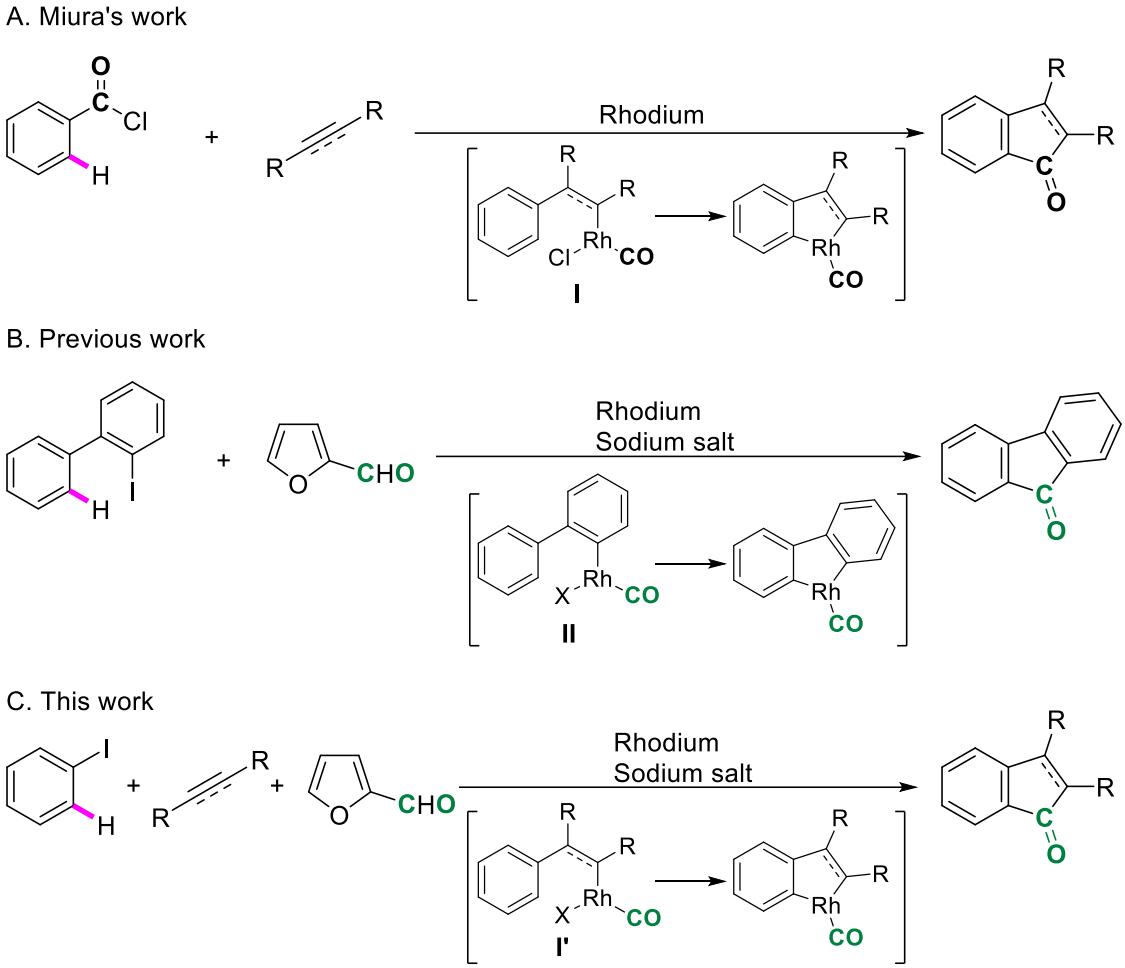
Scheme 3-3. Carbonylative annulation of 2-iodothiophene through C-H bond cleavage.

Even though the palladacycle formation and the subsequent transformation have been extensively studied,[10] the reaction of halobenzene and 2-norbornene with carbon monoxide failed to produce an annulated carbonyl compound (Scheme 3-4).[11] To date, the carbonylative annulation of halobenzenes with π-unsaturated compounds via C-H bond cleavage remains an undeveloped area.



Scheme 3-4. Carbonylation of bromobenzene with 2-norbornene.

An elegant work by Miura and co-workers showed that the rhodium complex catalyzes the direct C-H cyclization of benzoyl chlorides with internal alkynes and 2-norbornene (Scheme 3-5, A).[12] In that report, the complex **I** was proposed as the key intermediate for the cleavage of C-H bond. As described in previous chapter, I developed the intramolecular carbonylative coupling of 2-iodobiphenyl with furfural produced from biomass resources[13] as a carbonyl source via the formation of 2-rhodabiphenyl **II**, which is analogous to complex **I**, to give fluoren-9-one (B). These findings encouraged me to investigate the three-component carbonylative annulation of iodobenzenes, unsaturated hydrocarbons, and a carbonyl moiety using a rhodium catalyst (C). The present chapter describes the successful demonstration of this transformation.



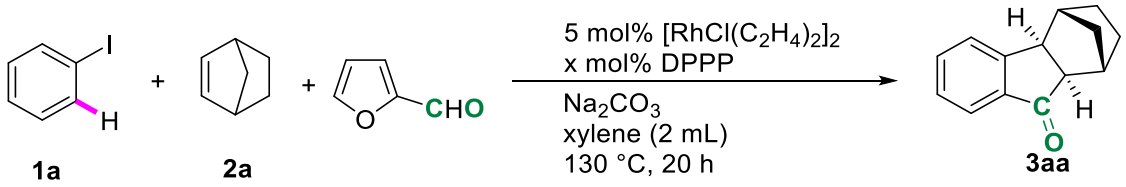
Scheme 3-5. Carbonylative annulation through C-H bond cleavage.

3. 2 Results and Discussions

3. 2. 1 Optimization of Reaction Conditions

Based on the reaction of 2-iodobiphenyls, varying amounts of DPPP from 0 to 10 mol% were initially examined. As shown in Table 3-1, the addition of 0.5 equivalent of DPPP to the rhodium center gave the highest yield of **3aa** (entry 4), suggesting that both phosphane-ligated and -free rhodium species play a crucial role in the decarbonylation of furfural and the subsequent carbonylative annulation of **1a** with **2a**, respectively.

Table 3-1. Optimization of amount of DPPP.[a]



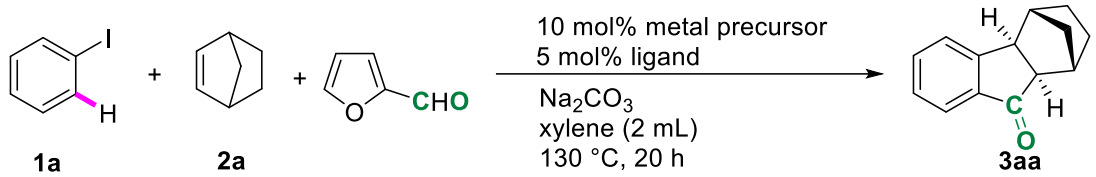
Entry	DPPP (mol%)	**3aa**[b] (%)
1	0	8
2	2	24
3	4	28
4	**5**	**41**
5	6	32
6	8	10
7	10	2

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), furfural (2.5 mmol), $[RhCl(C_2H_4)_2]_2$ (0.025 mmol), DPPP (as indicated), and Na_2CO_3 (1.0 mmol).
[b]Isolated yield.

I subsequently examined transition metal precursors and phosphane ligands. Using rhodium complexes having diene ligands, the product yields slightly diminished (entries 2-4).[12] It is noteworthy that the rhodium complex was found to be necessary to promote the

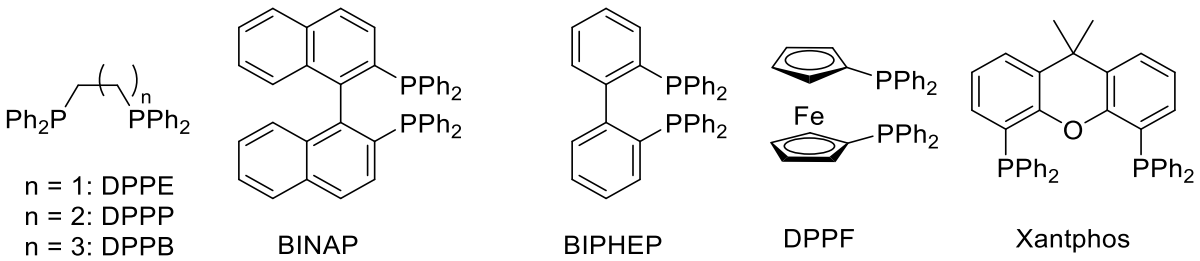
present carbonylation (entries 5-9). The screening of bidentate phosphane ligands, which are effective for the decarbonylation of carbonyl compounds,[14] showed that BINAP was the optimal ligand for this reaction (entries 10-15).

Table 3-2. Optimization of catalytic synstems.[a]



1a **2a** **3aa**

Entry	Metal precursor	Ligand	**3aa**[b] (%)
1	$[RhCl(C_2H_4)_2]_2$	DPPP	41
2[c]	$[RhCl(cod)_2]_2$	DPPP	30
3	$[RhCl(nbd)_2]_2$	DPPP	36
4	$[Rh(cod)_2]OTf$	DPPP	27
5	None	DPPP	0
6	$Pd(PPh_3)_4$		0
7	$Ru_3(CO)_{12}$		0
8	$CoBr_2$	DPPP	0
9	$[IrCl(cod)]_2$	PPh_3	0
10	$[RhCl(C_2H_4)_2]_2$	DPPE	45
11	$[RhCl(C_2H_4)_2]_2$	DPPB	18
12	$[RhCl(C_2H_4)_2]_2$	DPPF	20
13	**$[RhCl(C_2H_4)_2]_2$**	**BINAP**	**48**
14	$[RhCl(C_2H_4)_2]_2$	BIPHEP	30
15	$[RhCl(C_2H_4)_2]_2$	Xantphos	31

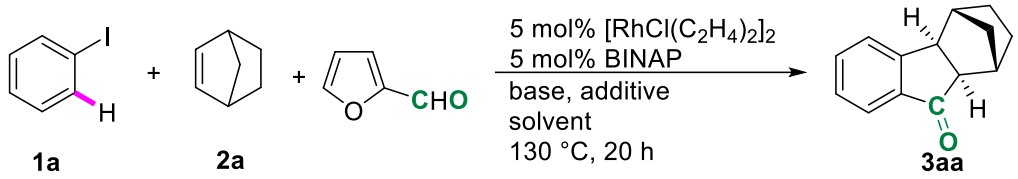


[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), furfural (2.5 mmol), metal precursor (0.05 mmol of metal), ligand (0.025 mmol), and Na_2CO_3 (1.0 mmol).

[b]Isolated yield.

Further optimization of the reaction parameters, such as base, additive, and solvent, was conducted, and the results are summarized in Table 3-3. Other inorganic carbonates were less effective than Na_2CO_3 (entries 1-4). The presence of LiCl promoted the progress of the reaction (entries 5 and 6). It can be assumed that the rhodate species generated by the coordination of a chloride to the rhodium center permits a more facile oxidative addition of the C-I bond.[15] The reaction in 1mL of xylene provided somewhat improved yield (entries 5, 7, and 8). Among the various sodium salts examined, NaOPiv was found to be the best choice

Table 3-3. Optimization of base, additive, and solvent.[a]



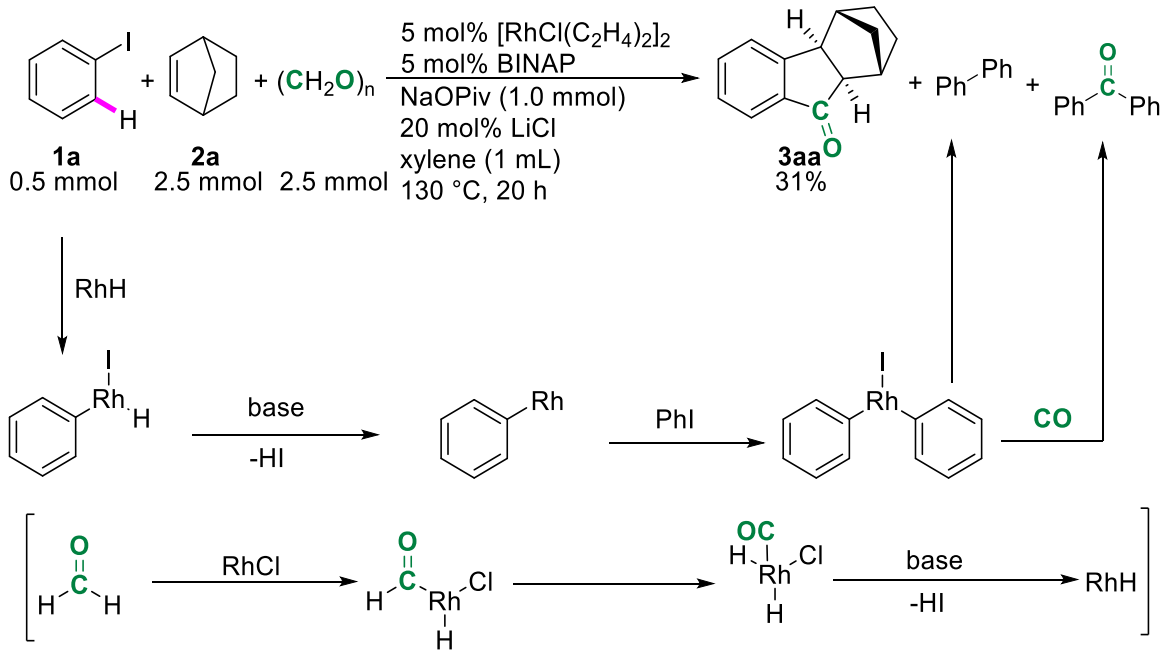
1a **2a** **3aa**

Entry	Base	Additive	Solvent (mL)	**3aa**[b] (%)
1	Na_2CO_3		Xylene (2)	48
2	Li_2CO_3		Xylene (2)	18
3	K_2CO_3		Xylene (2)	42
4	Cs_2CO_3		Xylene (2)	27
5	Na_2CO_3	LiCl (0.1)	Xylene (2)	55
6	Na_2CO_3	LiCl (1.0)	Xylene (2)	57
7	Na_2CO_3	LiCl (0.1)	Xylene (3)	45
8	Na_2CO_3	LiCl (0.1)	Xylene (1)	60
9	NaOAc	LiCl (0.1)	Xylene (1)	48
10	**NaOPiv**	**LiCl (0.1)**	**Xylene (1)**	**80**
11	$MesCO_2Na$	LiCl (0.1)	Xylene (1)	70
12	None	LiCl (0.1)	Xylene (1)	20
13	NaOPiv	LiCl (0.1)	Dioxane (1)	40
14[c]	NaOPiv	LiCl (0.1)	Toluene (1)	77

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), furfural (2.5 mmol), $[RhCl(C_2H_4)_2]_2$ (0.025 mmol), BINAP (0.025 mmol), base (1.0 mmol), LiCl (as indicated), and solvent (1.0-3.0 mL). [b]Isolated yield. [c]At 100 °C

(entries 9-11). In sharp contrast to Miura's report, it was necessary to add a base in order to achieve an efficient reaction (entry 12).[12] Changing the solvent away from xylene led to a significant loss in the efficiency of the reaction (entry 13). The reaction also proceeded smoothly in toluene at 100 °C to afford the corresponding compound in 77% yield (entry 14).

Paraformaldehyde, which has great advantages in terms of cost and atom economy in comparison with other reported carbonyl surrogates,[16,17] was tested as a carbonyl source. However, the formation of substantial amounts of side products, such as biphenyl, benzophenone, and benzoic acid, triggered by rhodium hydride (RhH) caused a low yield of the desired product **3aa** (Scheme 3-6).[18]

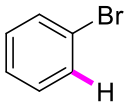
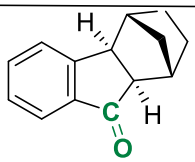
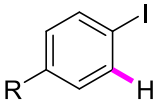
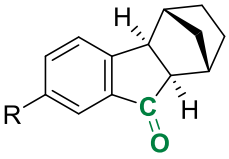
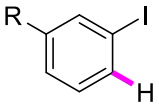
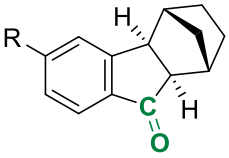
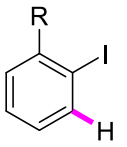
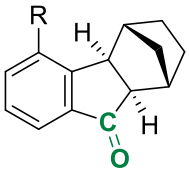
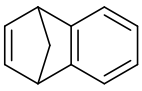
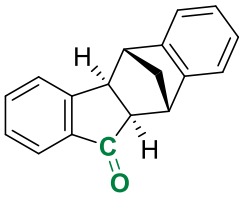
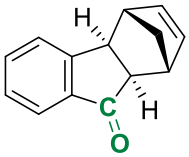


Scheme 3-6. Carbonylation with paraformaldehyde

3. 2. 2 Substrate Scope

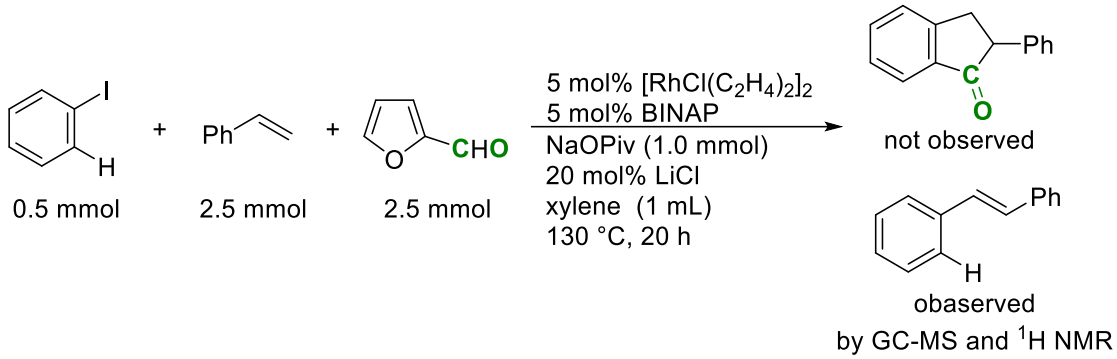
Having optimized the reaction conditions, I investigated the scope and limitation of halobenzenes and strained olefins (Table 3-4). Bromobenzene (**1b**) showed a much lower reactivity for this carbonylation (entry 1).[19] 4-Substituted iodobenzenes (**1c**-**e**) were allowed to react with **2a** to produce the corresponding indanones in moderate to good yields (entries 2-4). The carbonylative annulation of 3-substituted iodobenzenes (**1f** and **g**) also proceeded efficiently with exclusive site selectivity (entries 5 and 6). On the other hand, 2-substituted iodobenzenes such as 2-iodotoluene (**1h**) and 2-iodoanisole (**1i**) were barely converted into the desired products under standard reaction conditions, probably due to steric hindrance. The use of Na_2CO_3, which is an effective base for the intramolecular carbonylation of 2-iodobiphenyls, in place of NaOPiv gave **3ha** in 16% yield. Furthermore, when 2-substituted iodobenzenes were reacted with **2a** and furfural at 150 °C, **3ha** and **3ia** were obtained in moderate yields (entries 7 and 8). Benzonorbornadiene (**2b**) was applicable to the transformation to afford **3ab** in 74% yield (entry 9). Unfortunately, the reaction of **1a** with 2,5-norbornadiene (**2c**) provided an unidentified and inseparable complex mixture (entry 10). It is probably due to the stabilization of rhodium by 2,5-norbornadiene.[20]

Table 3-4. Scope of the rhodium-catalyzed carbonylative annulation.[a]

Entry	1	2	3	Yield (%)[b]
				
1	**1b**	**2a**	**3aa**	10%
				
2	R = Me: **1c**	**2a**	**3ca**	75%
3	R = Br: **1d**	**2a**	**3da**	66% (72%)[c]
4	R = NO_2: **1e**	**2a**	**3ea**	52%
				
5	R = OMe: **1f**	**2a**	**3fa**	74%
6	R = Me: **1g**	**2a**	**3ga**	76%
				
7[d,e]	R = Me: **1h**	**2a**	**3ha**	44%
8[d,e]	R = OMe: **1i**	**2a**	**3ia**	40%
9[f]	**1a**			74%
		2b	**3ab**	
10	**1a**			0%
		2c	**3ac**	

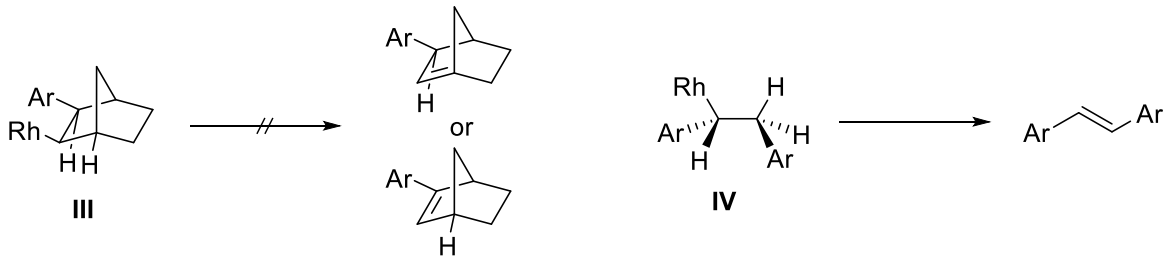
[a]Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), furfural (2.5 mmol), $[RhCl(C_2H_4)_2]_2$ (0.025 mmol), BINAP (0.025 mmol), NaOPiv (1.0 mmol), LiCl (0.1 mmol), and xylene (1 mL) at 130 °C. [b]Isolated yield. [c]At 100 °C. [d]Na_2CO_3 instead of NaOPiv was employed. [e]At 150 °C. [f]**2b** (1.5 mmol) was employed.

In reactions with typical olefins such as cyclohexene and styrene, Mizoroki-Heck-type reaction took place leading to no formation of indanone products (Scheme 3-7).[15b]



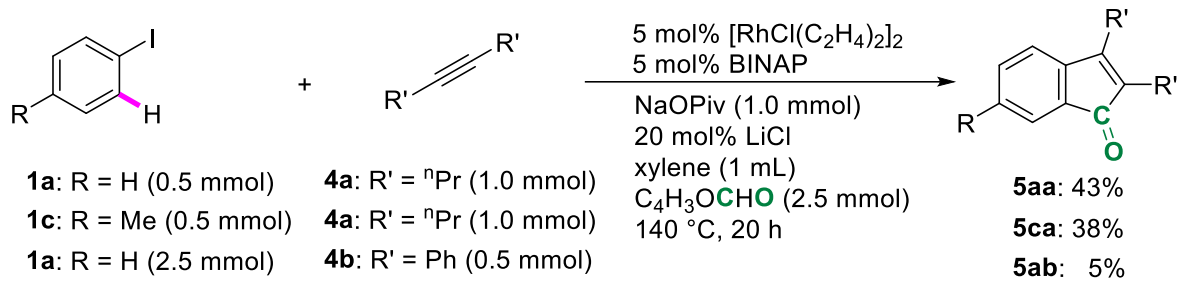
Scheme 3-7. Reaction of iodobenzene with styrene.

Because β-hydrogen elimination from **III**, which does not have a hydrogen atom in a *syn*-relationship to rhodium in contrast to **IV**, would be suppressed,[10d] the reaction with 2-norbornene proceeded efficiently to give the indanone products (Scheme 3-8).

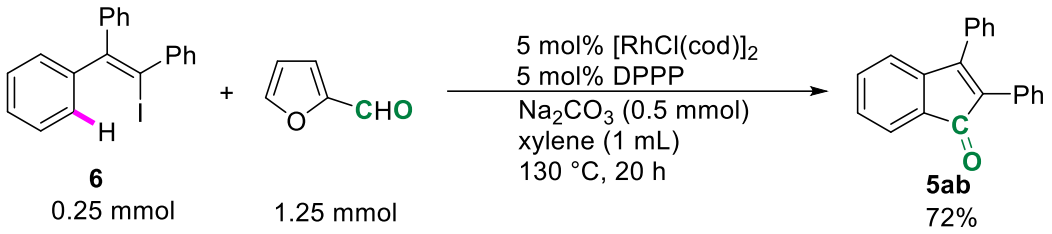


Scheme 3-8. β-Hydrogen elimination.

The synthesis of 2,3-dipropylinden-1-ones (**5aa** and **ca**) was also achieved when 4-octyne (**4a**) was employed in place of **2a** (Scheme 3-9). However, the formation of naphthalene derivatives[12b,21] as side reaction products led to moderate yields of the desired indenones. The use of diphenyl acetylene (**4b**) dramatically lowered the efficiency of the reaction, and 63% of **4b** was recovered from the reaction mixture, although 2-iodo-1,1,2-triphenylethylene (**6**) reacted with furfural to produce **5ab** in 72% yield (Scheme 3-10).[22]

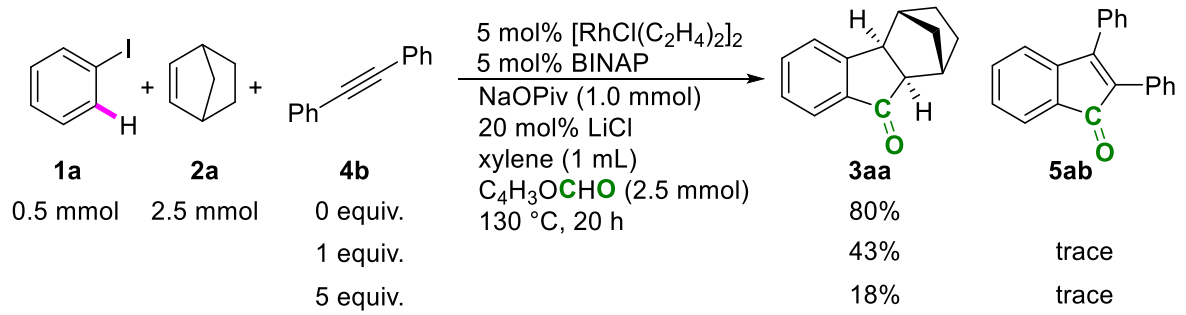


Scheme 3-9. Synthesis of inden-1-ones using alkynes.



Scheme 3-10. Synthesis of indenones via the reaction of 2-iodo-1,1,2-triphenylethylene (**6**).

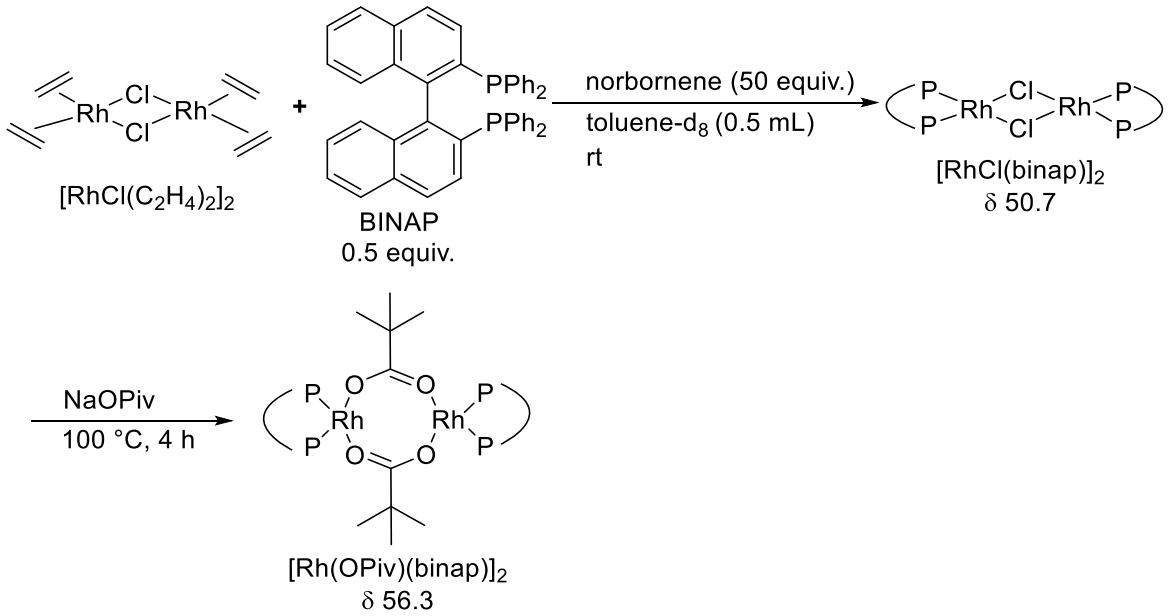
Furthermore, intermolecular competition reactions were conducted between diphenyl acetylene (**4b**) and 2-norbornene (**2a**). As a result, **3aa** was obtained although trace amount of **5ab** was detected in both cases (Scheme 3-11). In general, the insertion of acetylene having electron withdrawing group is faster than that of alkyne having electron donating group and olefins. In this reaction, however, diphenyl acetylene (**4b**) reacted more slowly. These results indicate that the stronger back donation from rhodium to **4b** than **2a** and **4a** results in the stabilization of the rhodium(I) complex to inhibit the oxidative addition of iodobenzene.



Scheme 3-11. Intermolecular competition reaction.

3. 2. 3 Mechanistic study

I then conducted some experiments to determine the active catalyst for the present carbonylative annulation. ^{31}P NMR spectrum of the mixture containing $[RhCl(C_2H_4)_2]_2$, 50 equivalent of 2-norbornene (**2b**), and 0.5 equivalent of BINAP in toluene-d_8 showed sole signal at δ 50.7 which correspond to $[RhCl(binap)]_2$.[23] After this solution was treated with NaOPiv and the resulting solution allowed to stand at 100 °C for 4 h, ^{31}P NMR spectrum showed the appearance of a new complex which was assigned to $[Rh(OPiv)(binap)]_2$ (δ 56.3 (d, $J_{Rh\text{-}P}$ = 194.93 Hz)) (Scheme 3-12 and Figure 3-1). It was suggested that both $[Rh(OPiv)(nbe)_2]_2$ and $[Rh(OPiv)(binap)]_2$ worked cooperatively in the reaction.



Scheme 3-12. ^{31}P NMR experiments.

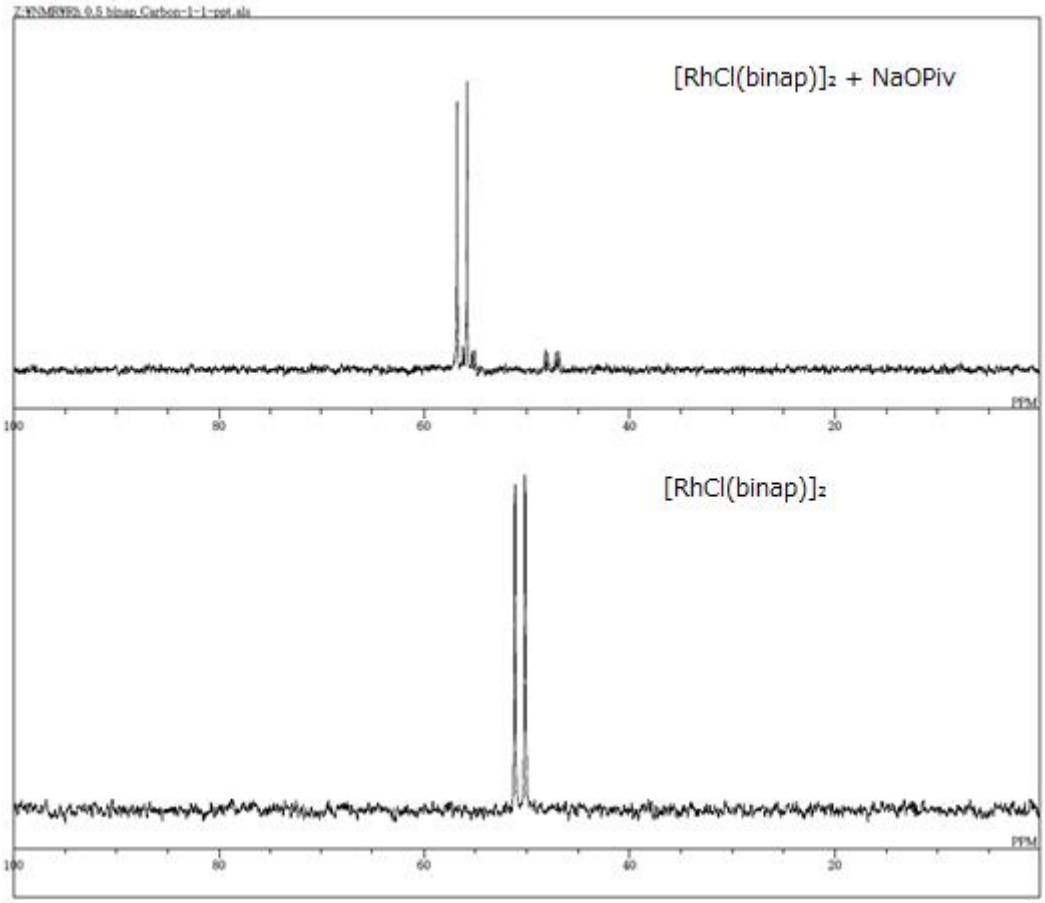
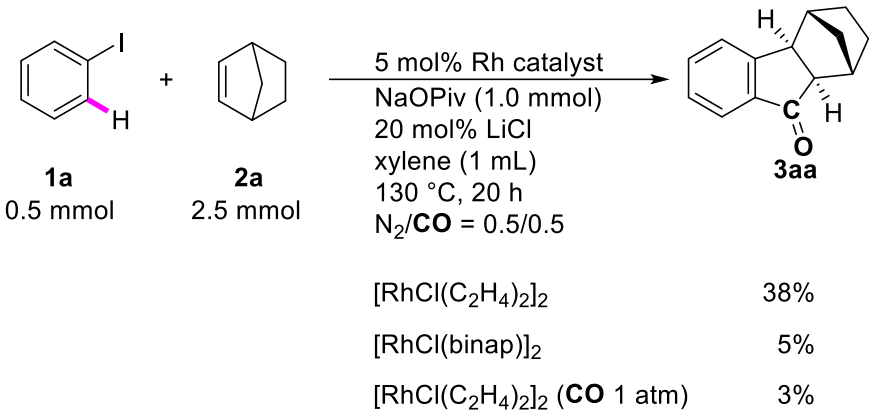


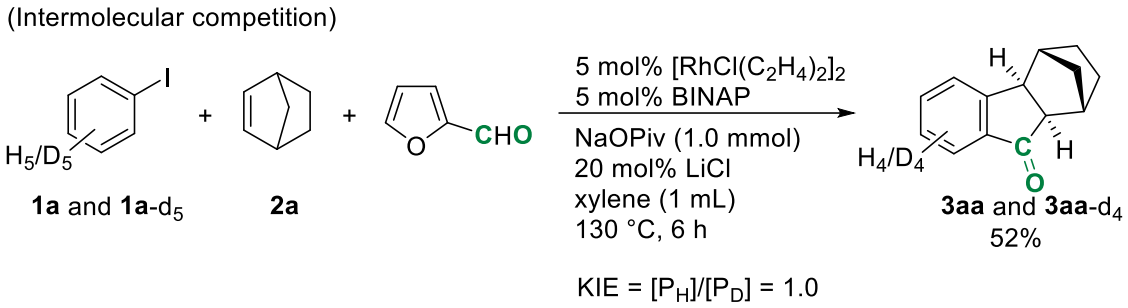
Figure 3-1. ^{31}P NMR spectra of the mixture containing $[RhCl(C_2H_4)_2]_2$, 2-norbornene (**2b**), and BINAP (below), and the treatment with NaOPiv (above).

Thus, the carbonylative annulation of **1a** and **2a** under a partial pressure of 0.5 atm of CO and 0.5 atm of N_2 was examined using $[RhCl(C_2H_4)_2]_2$ and $[RhCl(binap)]_2$ (Scheme 3-13). While $[RhCl(C_2H_4)_2]_2$ gave the desired product **3aa** in 38% yield, $[RhCl(binap)]_2$ was found to be catalytically ineffective for this reaction. According to my initial expectations, the reaction under atmospheric carbon monoxide catalyzed by $[RhCl(C_2H_4)_2]_2$ was considerably slower. This phenomenon suggests that the timely release of the carbonyl moiety from furfural plays highly decisive role in the efficient reaction, consistent with findings in a previous chapter.



Scheme 3-13. Reaction with carbon monoxide.

Next, KIE was investigated by means of an intermolecular competition experiment between **1a** and **1a**-d_5 (Scheme 3-14 and Figure 3-2). KIE value ($[P_H]/[P_D]$) of 1.0 was obtained, indicating that the cleavage of C-H bond is not the rate-determining step.[24,25] Considering the experimental observations and the results of the previous chapter, I propose that the oxidative addition of the C-I bond is involved in the rate-determining step.



Scheme 3-14. Deuterium labelling experiment.

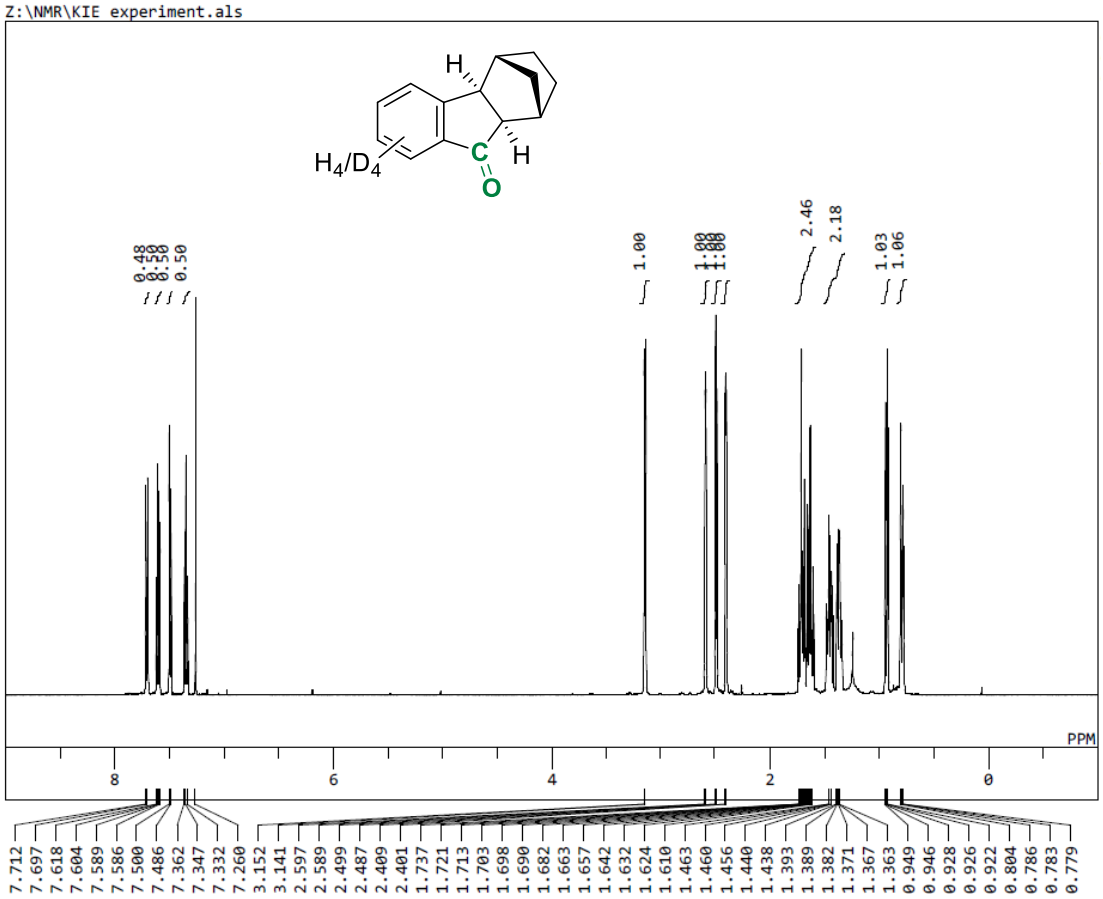
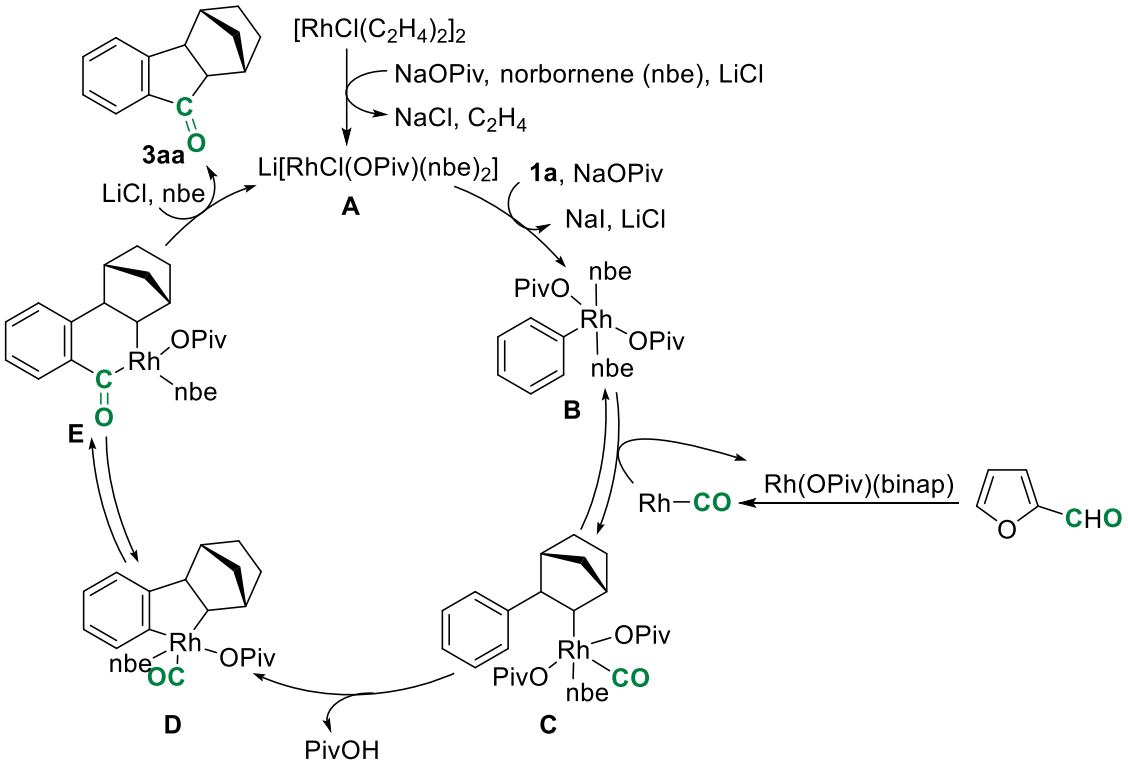


Figure 3-2. ^{1}H NMR spectrum of deuterium labelling experiment.

A plausible catalytic cycle for the present reaction with 2-norbornene is illustrated in Scheme 3-15.[12] The rhodium(III) species **B** is generated via the oxidative addition of an iodobenzene to $[Rh(OPiv)(nbe)_2]_2$ **A**, which is generated in situ from $[RhCl(C_2H_4)_2]_2$ and NaOPiv in the presence of 2-norbornene. The migratory insertion of the 2-norbornene, followed by the transfer of a carbonyl moiety via the decarbonylation of furfural catalyzed by the $[Rh(OPiv)(binap)]_2$ complex, generates the key intermediate **C**. This undergoes the cleavage of C-H bond at *ortho*-position, furnishing the five-membered rhodacycle **D**. Although details of the C-H bond dissociation are unclear at present,[26] it is likely that the pivalate as a ligand assists in the cleavage of C-H bond.[27] The incorporation of the carbonyl

moiety into **D** gives the acyl species **E**. Finally, **3aa** is liberated from **E** to complete the catalytic cycle.



Scheme 3-15. Plausible catalytic cycle.

3. 3 Conclusion

In summary, I described the carbonylative annulation of iodobenzenes, strained olefins or 4-octyne, and furfural as the carbonyl source via *ortho*-C-H bond cleavage, leading to the formation of indanone and indenone derivatives. This carbonylative annulation represents the first example of the three component carbonylative annulation of iodobenzenes with unsaturated hydrocarbons involving C-H cleavage. In accordance with the reaction of 2-iodobiphenyls shown in previous chapter, the rate-determining step is not involved in a C−H bond cleavage. Importantly, furfural rather than gaseous carbon monoxide served well as the carbonyl source.

3. 4 Experimental Section

I. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer in $CDCl_3$ using $CHCl_3$ (proton: 7.26 ppm, carbon: 77.16 ppm) as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), integration, and interpretation. The products were analyzed by a gas chromatography (SHIMADZU GC-2025), equipped using a flame ionization detector. Column chromatography was performed using a SiO_2 (MERCK Silica gel 60).

II. Materials.

$[RhCl(cod)]_2$,[28] NaOPiv,[29] 1**a**-d_5,[30] **1g**,[31] **2b**,[32] and **6a**[33] were prepared by previously reported methods. $[RhCl(C_2H_4)_2]_2$, xantphos, **1d**, and **1e** were purchased from Sigma-Aldrich Chemical Co. $[RhCl(nbd)]_2$, $[Rh(cod)_2]OTf$, and BIPHEP were purchased from Strem Chemicals Inc. and was used directly without further purification. **6b**, LiCl, K_2CO_3, Li_2CO_3 Cs_2CO_3, Na_2CO_3, and NaOAc were purchased from Wako Pure Chemical Industries, Ltd. and dried over P_2O_5 under a vacuum prior to use. Furfural, **1a**, **1f**, **1h**, and **4** were purchased from Wako Pure Chemical Industries, Ltd. and were used directly without further purification. DPPE, DPPP, DPPB, **1c**, and 2-norbornene were purchased from Tokyo Chemical Industry Co., Ltd. and were used directly without further purification. BINAP was purchased from

Kanto Chemical. and was used directly without further purification. Anhydrous xylene and dioxane were purchased from Wako Pure Chemical Industries, Ltd. and dried by storage over 4A molecular sieves, and degassed by N_2 bubbling prior to use.

III. Optimization Study

A 10-mL dry sealed-tube equipped with a stir bar was charged with Rh precursor (0.025 mmol), bidentate phosphane ligand (0-0.05 mmol), base (1.0 mmol), additive, and norbornene (2.5 mmol, 235.4 mg) under a N_2 flow. Solvent (1-3 mL), iodobenzene **1a** (0.5 mmol, 102.0 mg), and furfural (2.5 mmol, 240.2 mg) were then added. After degassing the reaction mixture by the freeze-pump-thaw method three times, the tube was filled with N_2. The mixture was then placed in an oil bath preheated at 130 °C for 20 h. After cooling to room temperature, the resulting solution was filtered through a celite pad, and the filtrate was concentrated *in vacuo.* The resulting crude product was purified by flash column chromatography on silica-gel to afford **3aa** (hexane/AcOEt = 20/1).

IV. General Procedure for Rh-Catalyzed Carbonylative Annulation of Iodobenzenes, Norbornenes, and Furfural.

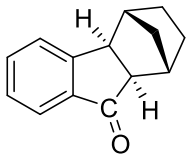
A 10-mL dry sealed-tube equipped with a stir bar was charged with $[RhCl(C_2H_4)_2]_2$ (0.025 mmol, 9.72 mg), BINAP (0.025 mmol, 15.6 mg), NaOPiv (1.0 mmol, 124.1 mg), LiCl (0.1 mmol, 4.24 mg), and norbornene (2.5 mmol, 235.4 mg) under a N_2 flow. Xylene (1 mL),

iodobenzenes (0.5 mmol), and furfural (2.5 mmol, 240.2 mg) were then added. After degassing the reaction mixture by the freeze-pump-thaw method three times, the tube was filled with N_2. The mixture was then placed in an oil bath preheated at 130 °C for 20 h. After cooling to room temperature, the resulting solution was filtered through a celite pad, and the filtrate was concentrated *in vacuo.* The resulting crude product was purified by flash column chromatography on silica-gel to afford **3**.

IV. Spectroscopic Data for Products

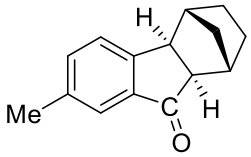
All hexahydrofluoren-9-ones[34] and inden-1-one[6] shown here were reported previously and identified by comparing the ^{1}H NMR and ^{13}C NMR data.

3aa: 1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



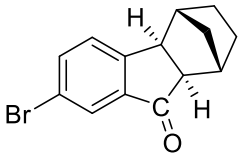
R_f : 0.16 (Hexane/AcOEt = 20/1); Isolated yield = 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79-0.81 (m, 1H), 0.93-0.96 (m, 1H), 1.37-1.47 (m, 2H), 1.61-1.73 (m, 2H), 2.41 (d, 1H, J = 4.0 Hz), 2.50 (d, 1H, J = 5.5 Hz), 2.60 (d, 1H, J = 4.0 Hz), 3.15 (d, 1H, J = 6.5 Hz), 7.35 (t, 1H, J = 7.5 Hz), 7.50 (dd, 1H, J = 1.0, 7.5 Hz), 7.61 (dt, 1H, J = 1.0, 7.5 Hz), 7.71 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7, 28.9, 32.2, 40.4, 41.2, 48.0, 55.8, 123.1, 126.2, 127.4, 135.0, 139.0, 157.3, 209.0.

3ca: 7-methyl-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



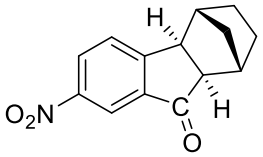
R_f : 0.16 (Hexane/AcOEt = 20/1); Isolated yield = 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-0.81 (m, 1H), 0.91-0.94 (m, 1H), 1.35-1.45 (m, 2H), 1.60-1.72 (m, 2H), 2.37-2.39 (m, 4H), 2.48 (d, 1H, J = 6.0 Hz), 2.58 (d, 1H, J = 4.0 Hz), 3.09 (d, 1H, J = 6.0 Hz), 7.37-7.43 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.7, 28.9, 32.2, 40.4, 41.2, 47.7, 56.3, 123.1, 125.9, 127.4, 136.3, 137.4, 139.3, 154.8, 209.0.

3da: 7-bromo-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



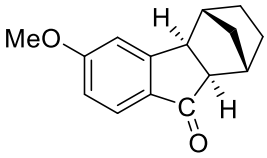
R_f : 0.15 (Hexane/AcOEt = 20/1); Isolated yield = 66%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-0.80 (m, 1H), 0.95-0.98 (m, 1H), 1.36-1.46 (m, 2H), 1.60-1.74 (m, 2H), 2.39 (d, 1H, J = 4.0 Hz), 2.52 (d, 1H, J = 6.5 Hz), 2.60 (d, 1H, J = 4.0 Hz), 3.10 (d, 1H, J = 6.5 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.70 (dd, 1H, J = 2.0, 8.0 Hz), 7.82 (d, 1H, J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7, 28.9, 32.4, 40.6, 41.3, 47.8, 56.3, 121.9, 126.3, 127.9, 137.8, 141.0, 155.8, 207.5.

3ea: 7-nitro-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



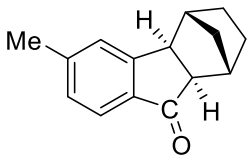
R_f : 0.16 (Hexane/AcOEt = 6/1); Isolated yield = 52%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77-0.79 (m, 1H), 1.02-1.04 (m, 1H), 1.40-1.52 (m, 2H), 1.65-1.79 (m, 2H), 2.49 (d, 1H, *J* = 5.0 Hz), 2.63-2.68 (m, 2H), 3.26 (d, 1H, *J* = 6.5 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 8.46 (dd, 1H, *J* = 2.5, 8.0 Hz), 8.51 (d, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.6, 29.0, 32.6, 40.9, 41.6, 48.4, 56.6, 118.7, 127.4, 129.3, 140.2, 148.0, 162.3, 206.7.

3fa: 6-methoxy-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



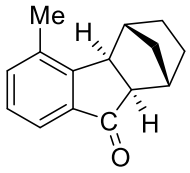
R_f : 0.26 (Hexane/AcOEt = 10/1); Isolated yield = 74%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.85 (m, 1H), 0.93-0.96 (m, 1H), 1.35-1.44 (m, 2H), 1.61-1.71 (m, 2H), 2.39 (d, 1H, *J* = 4.0 Hz), 2.48 (d, 1H, *J* = 6.5 Hz), 2.58 (d, 1H, *J* = 4.0 Hz), 3.08 (d, 1H, *J* = 6.5 Hz), 3.89 (s, 3H), 6.87-6.91 (m, 2H), 7.64 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7, 28.9, 32.3, 40.2, 41.3, 48.0, 55.7, 56.3, 109.2, 115.4, 124.9, 132.5, 160.3, 165.6, 207.0.

3ga: 6-methyl-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



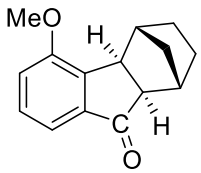
R_f : 0.16 (Hexane/AcOEt = 20/1); Isolated yield = 76%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80–0.94 (m, 2H), 1.33-1.47 (m, 2H), 1.60-1.73 (m, 2H), 2.39 (d, 1H, *J* = 4.0 Hz), 2.44 (s, 3H), 2.48 (d, 1H, *J* = 6.5 Hz), 2.58 (d, 1H, *J* = 4.0 Hz), 3.09 (d, 1H, *J* = 5.5 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.28 (s, 1H), 7.60 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 28.8, 29.0, 32.3, 40.4, 41.3, 48.0, 56.2, 123.1, 126.6, 128.8, 136.9, 146.3, 157.9, 208.6.

3ha: 5-methyl-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



R_f : 0.16 (Hexane/AcOEt = 20/1); Isolated yield = 44%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.97 (m, 2H), 1.37-1.50 (m, 2H), 1.62-1.76 (m, 2H), 2.45-2.51 (m, 4H), 2.63 (d, 1H, *J* = 3.5 Hz), 3.12 (d, 1H, *J* = 6.5 Hz), 7.28 (d, 1H, *J* = 7.0 Hz), 7.41 (d, 1H, *J* = 7.0 Hz), 7.56 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 28.6, 29.3, 32.5, 39.0, 41.4, 47.4, 56.2, 120.9, 127.8, 135.9, 136.0, 139.2, 155.6, 209.5.

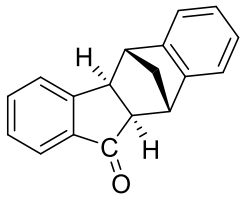
3ia: 5-methoxy-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one



R_f : 0.25 (Hexane/AcOEt = 10/1); Isolated yield = 40%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-0.94 (m, 2H), 1.35-1.46 (m, 2H), 1.60-1.70 (m, 2H), 2.46 (d, 1H, *J* = 6.5 Hz), 2.59 (dd, 2H, *J* = 4.0, 9.0 Hz), 3.15 (d, 1H, *J* = 6.5 Hz), 3.91 (s, 3H), 7.28 (dd, 1H, *J* = 2.0, 7.0 Hz),

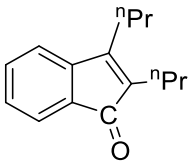
7.29-7.34 (m, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.7, 29.1, 32.4, 38.7, 40.4, 45.7, 55.5, 55.9, 114.9, 115.4, 129.1, 140.8, 145.6, 157.2, 209.3.

3ab: 4b,5,10,10a-tetrahydro-5,10-methanobenz[b]fluoren-11-one



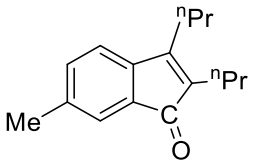
R_f : 0.16 (Hexane/AcOEt = 20/1); Isolated yield = 74%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33-1.35 (m, 1H), 1.65-1.67 (m, 1H), 2.72 (d, 1H, J = 6.0 Hz), 3.37 (d, 1H, J = 6.0 Hz), 3.43 (s, 1H), 3.66 (s, 1H), 7.12-7.43 (m, 5H), 7.62-7.68 (m, 2H), 7.77 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.9, 46.9, 48.2, 48.3, 55.6, 121.4, 121.5, 123.8, 126.2, 126.2, 126.3, 128.0, 135.3, 140.8, 147.4, 148.2, 156.2, 206.8.

5aa: 2,3-dipropyl-*1H*-inden-1-one



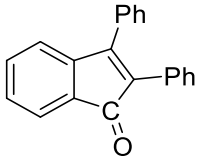
R_f : 0.34 (Hexane/AcOEt = 20/1); Isolated yield = 43%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.5 Hz), 1.03 (t, 3H, J = 7.5 Hz), 1.45-1.53 (m, 2H), 1.58-1.60 (m, 2H), 2.24 (t, 2H, J = 7.5 Hz), 2.52 (t, 2H, J = 7.5 Hz), 7.03 (d, 1H, J = 7.0 Hz), 7.15 (dt, 1H, J = 1.0, 7.5 Hz), 7.31 (dt, 1H, J = 1.0, 7.5 Hz), 7.37 (d, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 14.6, 21.4, 22.7, 25.0, 28.4, 119.1, 121.8, 128.0, 131.3, 133.3, 134.9, 145.8, 157.8, 198.8.

5ca: 6-methyl-2,3-dipropyl-*1H*-inden-1-one



R_f : 0.33 (Hexane/AcOEt = 20/1); Isolated yield = 38%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.02 (t, 3H, *J* = 7.5 Hz), 1.44-1.51 (m, 2H), 1.58-1.67 (m, 2H), 2.21 (t, 2H, *J* = 7.5 Hz), 2.31 (s, 3H), 2.50 (t, 2H, *J* = 7.5 Hz), 6.91 (d, 1H, *J* = 7.5 Hz), 7.09 (d, 1H, *J* = 7.5 Hz), 7.19 (s, 1H).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 14.5, 21.4, 22.7, 25.0, 28.5, 31.1, 119.0, 123.0, 131.6, 133.1, 134.3, 138.1, 143.0, 158.2, 199.1.

5ab: 2,3-diphenyl-*1H*-inden-1-one



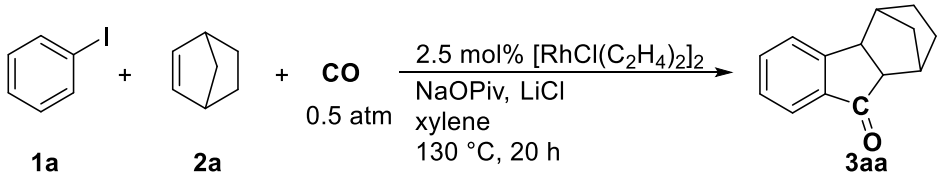
R_f : 0.24 (Hexane/AcOEt = 18/1); Isolated yield = 5%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, 1H, *J* = 7.0 Hz), 7.24-7.29 (m, 6H), 7.34-7.41 (m, 6H), 7.58 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.4, 123.1, 127.9, 128.2, 128.6, 128.9, 129.1, 129.4, 130.1, 130.8, 132.5, 132.8, 133.6, 145.3, 155.4, 196.6.

V. NMR Experiment

A J. Young NMR tube was charged with $[RhCl(C_2H_4)_2]_2$ (0.0125 mmol, 4.86 mg), BINAP (0.0125 mmol, 7.78 mg), 2- norbornene (1.25 mmol, 117.7 mg), and toluene-d_8 in a glove box under a nitrogen atmosphere. After the ^{31}P NMR spectrum of this solution was measured, this

mixture was treated with NaOPiv (0.5 mmol, 62.1 mg) and placed at 100 °C for 4 h, and the ^{31}P NMR spectrum of the mixture was measured. $[RhCl(binap)]_2$: δ 50.7 (J_{Rh-P} = 194.93 Hz). $[Rh(OPiv)(binap)]_2$: δ 56.3 (J_{Rh-P} = 194.93 Hz).

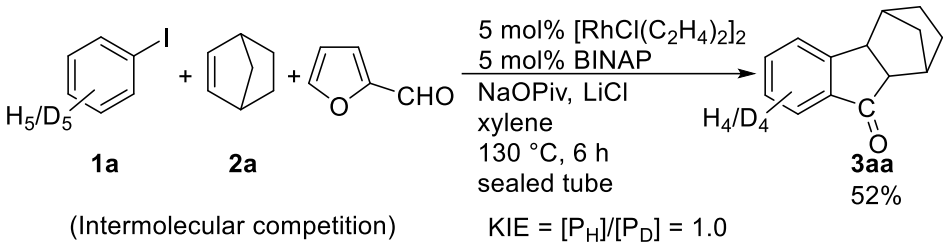
VI. Procedure for the Reaction of 2-Iodobiphenyl (1a) Using Carbon Monoxide.



A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(C_2H_4)_2]_2$ (0.00625 mmol, 2.43 mg), NaOPiv (1.0 mmol, 124.1 mg), and LiCl (0.1 mmol, 4.24 mg). The central neck of the flask was equipped with a reflux condenser having a gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). A solution containing xylene (1.0 mL) and norbornene (2.5 mmol, 235.4 mg), furfural (2.5 mmol, 240.2 mg), and iodobenzene **1a** (0.5 mmol, 120.0 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with a mixture of N_2/CO prepared in the gas-bag (1:1, 2 L). The mixture was placed in an oil bath that had been preheated to 130 °C for 20 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 **3aa** in 38% yield (hexane/AcOEt = 20/1).

VII. Kinetic Isotope Effect Study.



A 10-mL dry sealed-tube equipped with a stir bar was charged with $[RhCl(C_2H_4)_2]_2$ (0.025 mmol, 9.72 mg), BINAP (0.025 mmol, 15.6 mg), NaOPiv (1.0 mmol, 124.1 mg), LiCl (0.1 mmol, 4.24 mg), and norbornene (2.5 mmol, 235.4 mg) under a N_2 flow. Xylene (1 mL), iodobenzene **1a** (0.25 mmol, 51.0 mg), **1a**-d_5 (0.25 mmol, 52.3 mg), and furfural (2.5 mmol, 240.2 mg) were then added. After degassing the reaction mixture by the freeze-pump-thaw method three times, the tube was filled with N_2. The mixture was then placed in an oil bath preheated at 130 °C for 6 h. After cooling to room temperature, the resulting solution was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica-gel to afford **3aa** (hexane/AcOEt = 20/1). The ratio of two compounds was determined by ^{1}H NMR of **3aa** and **3aa**-d_4 to give intermolecular kinetic isotopic effect (KIE) $[P_H]/[P_D] = 1.0$.

References and Notes

1. For recent issue and review, see: (a) Wu, X.-F.; Neumann, H.; Beller. M. *Chem. Rev.* **2012**, *113*, 1. (b) Wu, X.-F.; Neumann, H.; Beller, M. in *Domino Reactions: Concepts for Efficient Organic Synthesis* (Ed.: Tietze, L. F.), Wiley-VCH: Weinheim, 2014, pp. 7-30. (c) Wu, X.-F.; Beller, M. *Transition Metal Catalyzed Carbonylative Synthesis of Heterocycles*, Springer, Heidelberg, 2016.

2. (a) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772.

3. (a) Forbis, R. M.; Rinehart Jr., K. L. *J. Am. Chem. Soc.* **1973**, *95*, 5003. (b) Claassen, G.; Brin, E.; Crogan-Grundy, C.; Vaillancourt, M. T.; Zhang, H. Z.; Cai, S. X.; Drewe, J.; Tseng, B.; Kasibhatla, S. *Cancer Lett*. **2009**, *274*, 243. (c) Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner F. S. *J. Med. Chem.* **2009**, *52*, 1639. (d) Shi, Y.; Gao, S. *Tetrahedron* **2016**, *72*, 1717.

4. For papers on other types of the three component carbonylative synthesis of carbocyclic carbonyl compounds, see: (a) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647. (b) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12868. (c) Artok, L.; Kus, M.; Aksin-Artok, O.; Dege, F. N.; Ozkihnc, F. Y. *Tetrahedron* **2009**, *65*, 9125.

5. Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766.

6. Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777.

7. Although some concise methods for preparing 2-halophenylboronic acid pinacol esters have been reported, there is still room for improving the yields and selectivities. For selected papers, see: (a) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura M. *J. Am. Chem. Soc*. **2009**, *131*, 5058. (b) Qiu, D.; Mo, F.; Zheng, Z.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5474. (c) Takaya, J.; Ito, S.; Nomoto, H.; Saito, N.; Kirai, N.; Iwasawa, N. *Chem. Commun*. **2015**, *51*, 17662.

8. For recent issues and reviews on the C-H bond functionalization reactions, see: (a) Yu, J.-Q.; Shi, Z. *C-H Activation*, Springer, Heidelberg, 2010. (b) Beller, M.; Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C−X bonds*, Springer: Heidelberg, 2013. (c) Li, B.-J.; Shi, Z.-J. in *Homogeneous Catalysis for Unreactive Bond Activation* (Ed.: Shi, Z.-J.), John Wiley & Sons: NJ, 2015; pp. 498−521. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (f) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (g) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (h) Gadge, S. T.; Gautam, P.; Bhanage,

B. M. *Chem. Rec*. **2016**, *16*, 835. (i) Gulıás, M.; Mascareñas, J. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 2.

9. Grigg, R.; Khalil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett.* **1994**, *35*, 3197.

10. (a) Catellani, M. *Pure Appl. Chem.* **2002**, *74*, 63. (b) Catellani, M. *Synlett* **2003**, 298. (c) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (d) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem*. **2010**, *292*, 1. (e) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863. (f) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389.

11. (a) Catellani, M.; Chiusoli, G. P.; Peloso, C. *Tetrahedron Lett*. **1983**, *24*, 813. (b) Dalcanale, E.; An, Z.; Battaglia, L. P.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, *437*, 375.

12. (a) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Adv. Synth. Catal.* **2004**, *346*, 1765. (b) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941.

13. (a) Dutta, S.; De, S.; Saha, B.; Alam, M. I. *Catal. Sci. Technol.* **2012**, *2*, 2025. (b) Cai, C. M.; Zhang, T.; Kumar, R.; Wyman, C. E. *J. Chem. Technol. Biotechnol.* **2014**, *89*, 2. (c) Peleteiro, S.; Rivas, S.; Alonso, J. A.; Santos, V.; Parajó, J. C. *Bioresource Techonology*, **2016**, *202*, 181. (d) Li, C.-L.; Qi, X.; Wu, X.-F. *J. Mol. Catal. A: Chem.* **2015**, *406*, 94.

14. (a) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed*.

2007, *46*, 9331. (c) Dermenci, A.; Whittaker, R. E.; Dong, G. *Org. Lett.* **2013**, *15*, 2242. (d) Whittaker, R. E.; Dong, G. *Org. Lett.* **2015**, *17*, 5504.

15. The addition of LiCl often has a profound effect on the yield. For selected papers, see: (a) Larock, R. C. *J. Organomet. Chem*. **1999**, *576*, 111. (b) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4672.
16. (a) Wu, X.-F. *Adv. Synth. Catal.* **2015**, *357*, 3393. (b) Cao, J.; Zheng, Z.-J.; Xu, Z.; Xu, L.-W. *Coord. Chem. Rev.* **2017**, *336*, 43.
17. For recent examples, see: Pd: (a) Mahendar, L.; Satyanayarana, G. *J. Org. Chem.* **2016**, *81*, 7685. (b) Chen, J.; Natte, K.; Wu, X.-F. *J. Organomet. Chem.* **2016**, *803*, 9. (c) Liu, Q.; Yuan, K.; Arockiam, P.-B.; Franke, R.; Doucet, H.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 4493. (d) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed*. **2014**, *53*, 10090. (e) Li, W.; Wu, X.-F. *J. Org. Chem*. **2014**, *79*, 10410. Rh: (f) Midya, S. P.; Sahoo, M. K.; Landge, V. G.; Rajamohanan, P. R.; Balaraman, E. *Nat. Commun.* **2015**, *6*, 8591. (g) Furusawa, T.; Morimoto, T.; Ikeda, K.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K.; Jeong, N. *Tetrahedron* **2015**, *71*, 875. Ru: (h) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. *ChemCatChem* **2014**, *6*, 2805.
18. Biphenyl and benzophenone were produced even in the absence of 2-norbornene. This result indicates that their production do not occur through Catellani-type reaction.
19. (a) Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980. (b) Brennfu¨hrer, A.;

Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.

20. Landesberg, J. M.; Sieczkowski, J. *J. Am. Chem. Soc*. **1971**, *93*, 972.

21. (a) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc*. **2002**, *124*, 12680. (b) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem*. **2003**, *68*, 6836.

22. The yield was decreased to 48% when BINAP was employed as a ligand in accordance with the intramolecular carbonylative coupling of 2-iodobiphenyls.

23. Bunten, K. A.; Farrar, D. H.; Poë, A. J.; Lough, A.; *Organometallics* **2002**, *21*, 3344.

24. For KIE study on the formation of palladacycle, see: Chai, D. I.; Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2011**, *17*, 8175.

25. Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2012**, *51*, 3066.

26. In the palladacycle formation from halobenzenes and 2-norbornene, it is believed that the metalation of C-H bond at *ortho*-position occurs via an electrophilic aromatic substitution (S_EAr). See: Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem*. **1992**, *425*, 151.

27. Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

28. Giordano, G.; Crabtree, R. H. *Inorg. Synth*. **1979**, *19*, 218.

29. Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201.

30. Ghorai, D.; Choudhury, J. *Chem. Commun*. **2014**, *50*, 15159.

31. Niu, L.; Zhang, H.; Yang, H.; Fu, H. *Synlett* **2014**, *25*, 995.

32. Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett*. **2004**, *6*, 1589.

33. Iwasaki, M.; Araki, Y.; Iino, S.; Nishihara, Y. *J. Org. Chem*. **2015**, *80*, 9247.

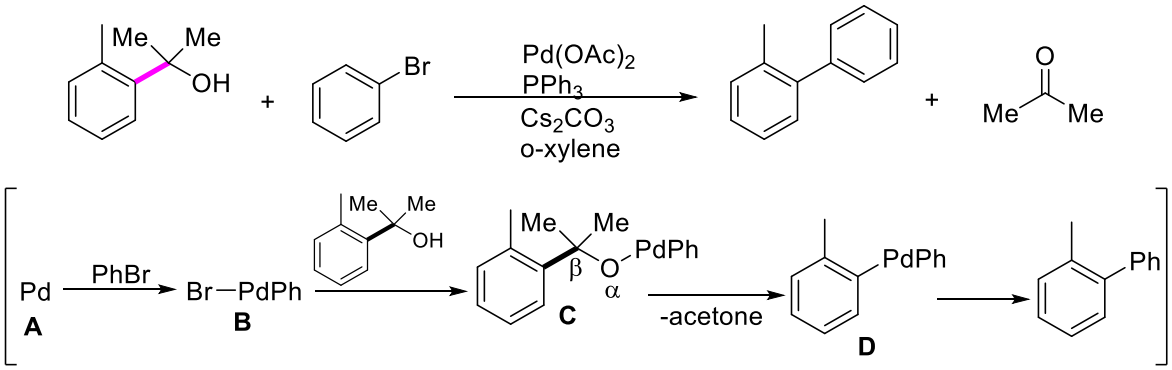
34. Pletnev, A. A.; Tian, Q. P.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276. (b) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4308.

Chapter 4 Three-component Carbonylative Annulation through C-C Bond Cleavage

4. 1 Introduction

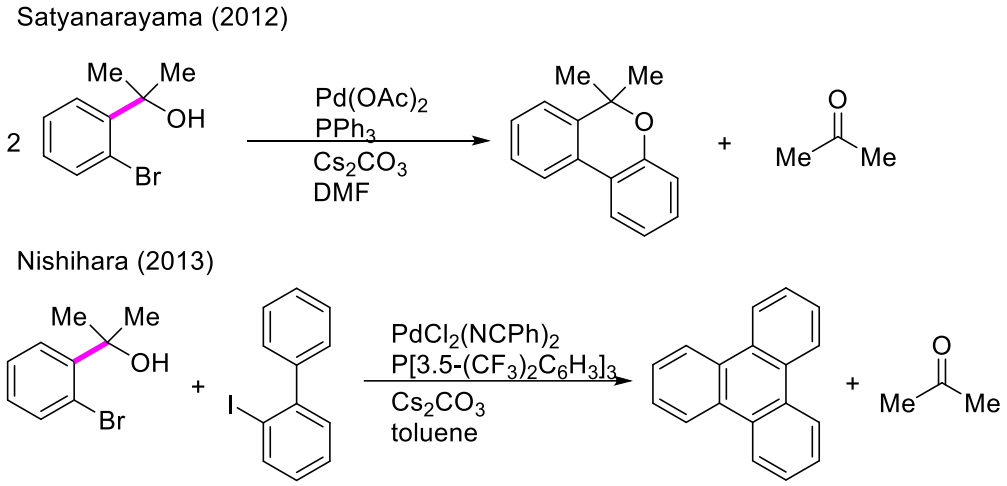
Over the past decades, the transition metal-catalyzed transformation involving carbon-carbon bond cleavage has attracted great interest from organic chemists as well as C-H bond functionalization because of their ubiquity in organic molecules.[1,2] Although C-C bond activation in strained molecules, such as cyclopropanes, cyclobutanes, and biphenylenes has been extensively studied, the cleavage of unstrained C-C single bonds and the subsequent transformation are still central challenging.

Ever since the pioneering report from Miura and co-workers,[3] unstrained (tertiary) benzylic alcohols have been applied to various reactions for forming new carbon-carbon bonds including the arylation with aryl halides (Scheme 4-1)[4] and the addition to unsaturated compounds.[5] In these reactions, they react with transition metal complexes to give aryl-transition metal species via ipso C-C bond cleavage, that is β-aryl elimination.



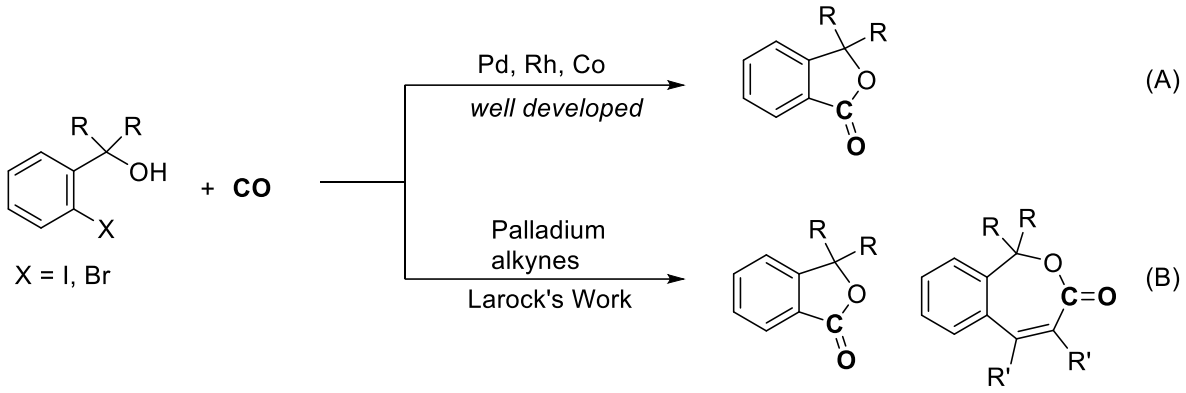
Scheme 4-1. Arylation of benzylic alcohol with aryl halides through C-C bond cleavage.

Furthermore, Satyanarayana[6a] and Nishihara[6b] recently demonstrated that α,α-dialkyl-(2-bromoaryl)methanols in the presence of palladium catalysts underwent the annulative coupling with the liberation of ketones (Scheme 4-2).



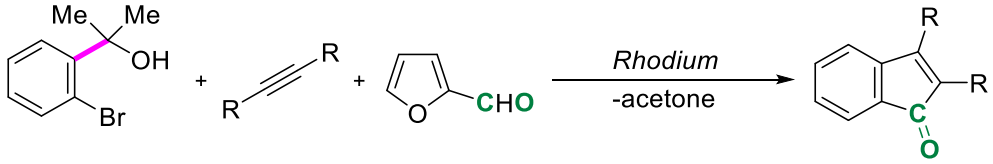
Scheme 4-2. Cyclization of α,α-dialkyl-(2-bromoaryl)methanols through C-C bond cleavage.

Even though several carbonylations of 2-halo-(tertiary) benzylic alcohols have also been reported in the literature (Scheme 4-3, A),[7] to the best of my knowledge, there have been no reports on the carbonylative transformation through C-C bond cleavage, probably due to more rapid addition of the alcohol moiety to the acyl metal complex (M-C(=O)-R) than other elementary reactions including C-C bond cleavage. Indeed, Larock's work revealed that 2-iodobenzylic alcohols reacted with carbon monoxide in the presence of 5 equivalent of 4-octyne to give five- and seven-membered lactones without formation of the C-C bond cleaved products (Scheme 4-3, B).[8]



Scheme 4-3. Reported carbonylation of *o*-halobenzylic alcohols.

I hypothesized that the timely release of the carbonyl moiety from carbonyl surrogates[9] results in the novel carbonylation involving C-C bond cleavage. In this Chapter, I demonstrate the first carbonylative annulation of α,α-dimethyl-(2-bromoaryl)methanols, internal alkynes, and furfural[10] through C-C bond cleavage (Scheme 4-4).

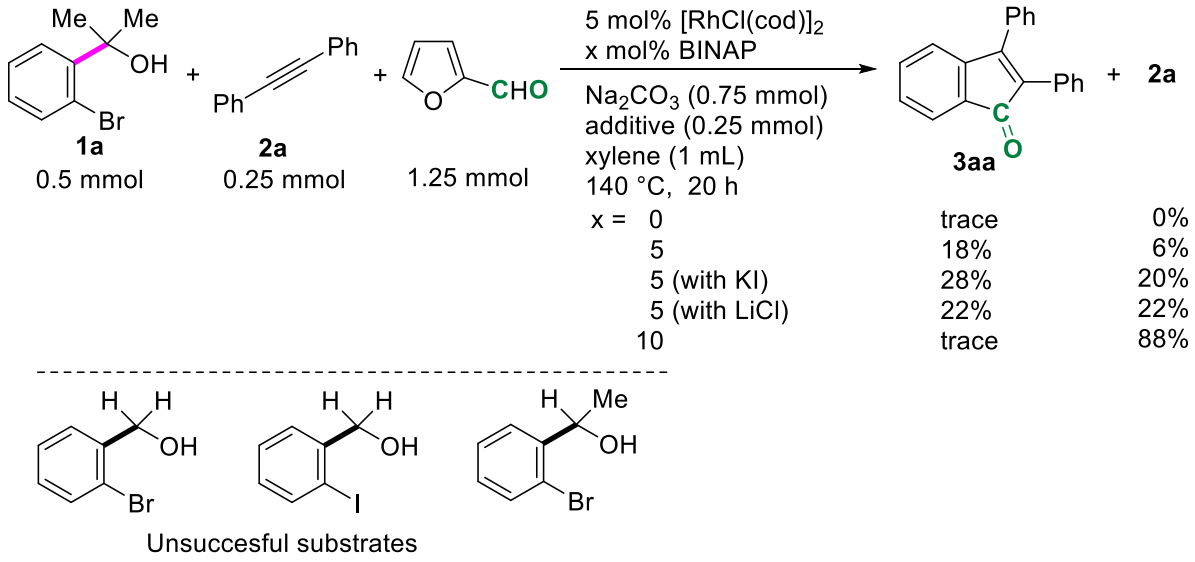


Scheme 4-4. Carbonylative annulation of α,α-dimethyl-(2-bromoaryl)methanols through C-C bond cleavage.

4. 2 Results and Discussions

4. 2. 1 Optimization of Reaction Conditions

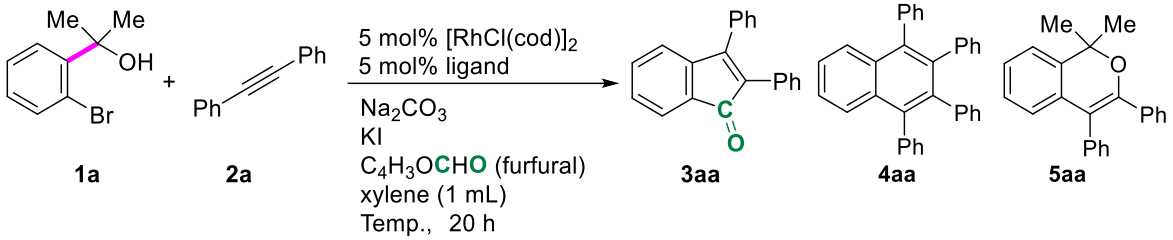
I initially carried out the reaction of α,α-dimethyl-(2-bromophenyl)methanol (**1a**) and diphenyl acetylene (**2a**) with furfural in the presence of 5 mol% of $[RhCl(cod)]_2$ and 5 mol% of BINAP yielding 18% of the desired indenone (**3aa**). In accordance with my previous results, the carbonylative annulation was catalyzed by neither $[RhCl(cod)]_2$ nor $[RhCl(binap)]_2$. The presence of 1 equivalent of KI or LiCl improved the yield.[7c,11] KI was more effective than LiCl, probably because of the acceleration of the ligand exchange between RhIX (X = I, Br, or Cl) and **1a**.[12] The absence of rhodium complexes did not afford indenone product (**3aa**). The present carbonylative annulation was not catalyzed by 10 mol% of palladium and iridium complexes. The reaction of simpler 2-halobenzylic alcohols led to no formation of **3aa** due to the elimination of not β-carbon but rather β-hydrogen.



Scheme 4-5. Initial optimization of reaction conditions.

Then, the reaction of α,α-dimethyl-(2-bromophenyl)methanol (**1a**, 0.75 mmol), diphenyl acetylene (**2a**, 0.25 mmol), and furfural (1.75 mmol) in the presence of 5 mol% of $[RhCl(cod)]_2$ and 5 mol% of BINAP afforded the corresponding indenone (**3aa**) in 39% isolated yield accompanied by 24% of 1,2,3,4-tetraphenylnaphthalene (**4aa**)[13] and 13% of the isochromene derivative (**5aa**)[14] (determined by ^{1}H NMR) (Table 4-1, entry 1). Other bidentate

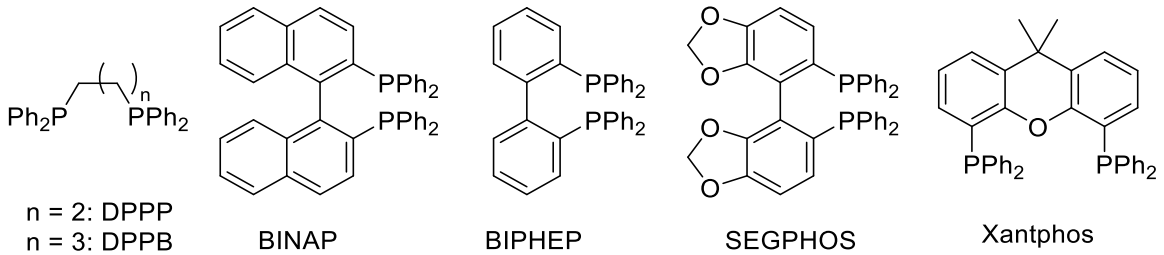
Table 4-1. Optimization of reaction conditions.[a]



Entry	Ligand	Temp.	Conv. (%)[b]	**3aa** (%)[b]	**4aa** (%)[c]	**5aa** (%)[c]
1	**BINAP**	**140**	**100**	**39**	**24**	**13**
2	BIPHEP	140	100	11	ND[d]	ND[d]
3	SEGPHOS	140	30	18	ND[d]	ND[d]
4	DPPP	140	93	18	28	14
5	DPPB	140	90	23	26	14
6	Xantphos	140	88	23	25	13
7	PPh_3[e]	140	100	tr	43	29
8	BINAP	130	33	18	5	5
9	BINAP	150	100	21	30	12

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), ligand (0.0125 mmol), Na_2CO_3 (1.0 mmol), KI (0.25 mmol), and furfural (1.75 mmol).

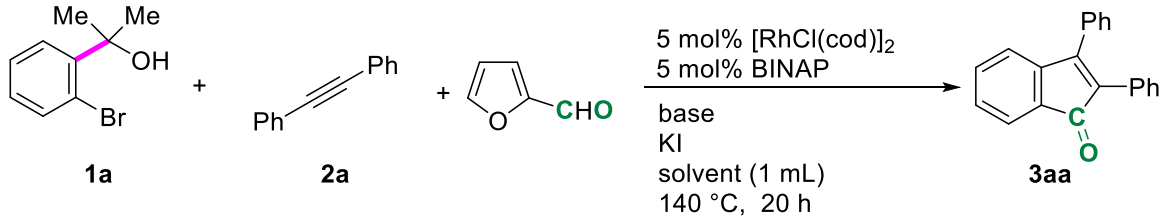
[b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Not determined. [e]PPh_3 (0.025 mmol).



phosphanes[15] such as BIPHEP, SEGPHOS, DPPE, DPPP, DPPB, DPPBz, and Xantphos, and monodentate phosphanes such as PPh_3, PCy_3, and $PCyp_3$ did not improve the yield of the desired indenone (**3aa**) (entries 2-7). The reaction at 130 °C proceeded slowly leading to low conversion of **2a** (entry 8). The yield of **4aa** increased at higher temperature (entry 9).

While using K_2CO_3, K_3PO_4, KO^{t}Bu, Cs_2CO_3, and $Na_3PO_4 \cdot 12H_2O$ as a base gave the complex mixture, Li_2CO_3 resulted in slower progress of the reaction (Table 4-2, entries 1-7). The reactions in anisole, in octane, and in 1,4-dioxane significantly diminished the yield of **3aa** (entries 8-10).

Table 4-2. Optimization of bases and solvents.[a]



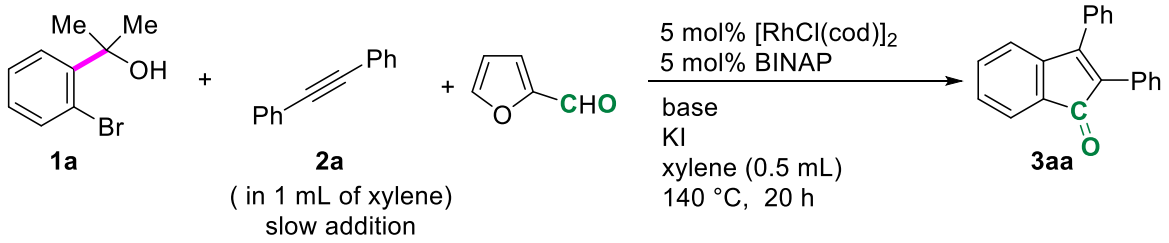
Entry	Base	Solvent	Conv. (%)[b]	**3aa** (%)[b]
1	**Na_2CO_3**	**Xylene**	**100**	**39**
2	Li_2CO_3	Xylene	68	23
3	K_2CO_3	Xylene	100	tr
4	Cs_2CO_3	Xylene	100	tr
5	$Na_3PO_4 \cdot 12H_2O$	Xylene	100	8
6	K_3PO_4	Xylene	100	tr
7	KO^{t}Bu	Xylene	100	0
8	Na_2CO_3	Anisole	88	23
9	Na_2CO_3	Octane	32	15
10	Na_2CO_3	Dioxane	10	tr

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), BINAP (0.0125 mmol), base (1.0 mmol), KI (0.25 mmol), and furfural (1.75 mmol).

[b]Isolated yield.

To suppress the formation of 1,2,3,4-tetraphenyl naphthalene (**4aa**), **2a** dissolved in xylene was added slowly using a syringe pump over 8 h, and then the mixture was stirred for 12 h. Unlike my expectation, the yield of **3aa** did not improve because of low conversion of **2a** (Table 4-3).

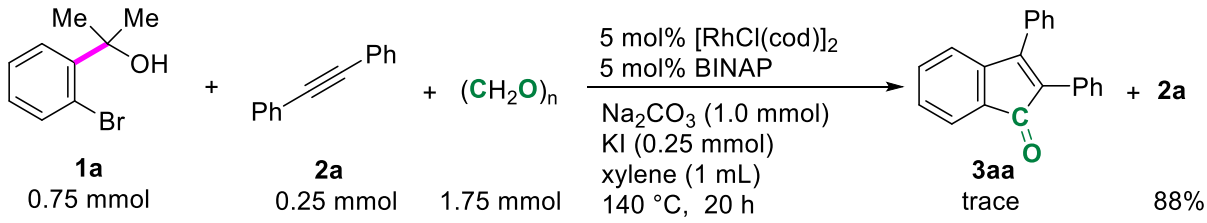
Table 4-3. Reaction using a syringe pump.[a]



Entry	Base	Conv. (%)[b]	**3aa** (%)[b]
1	Na_2CO_3	46	18
2	$Na_3PO_4 \cdot 12H_2O$	40	tr
3	K_2CO_3	62	tr
4	K_3PO_4	ND[c]	tr

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), BINAP (0.0125 mmol), base (1.0 mmol), KI (0.25 mmol), furfural (1.75 mmol), and total amount of xylene (1.5 mL). [b]Isolated yield. [c]Not determined.

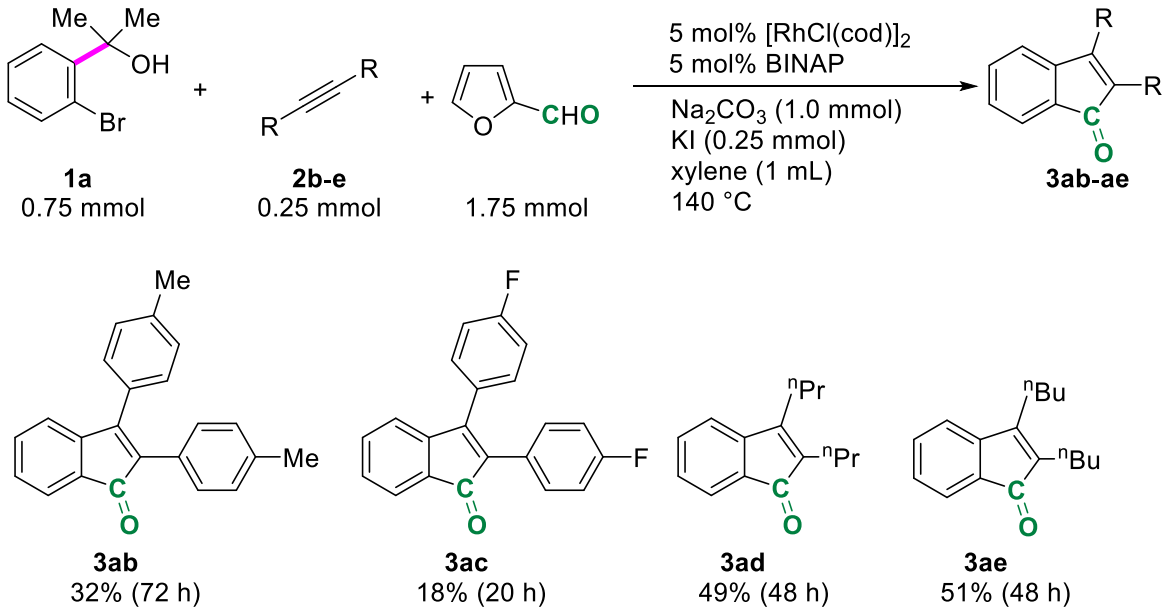
In general, the production of the carbonyl source from formaldehyde is more rapid than aromatic aldehydes.[9g,16] Hence, I tested paraformaldehyde, but it hardly served as a carbonyl source in the present carbonylative annulation (Scheme 4-6).



Scheme 4-6. Carbonylative annulation with paraformaldehyde.

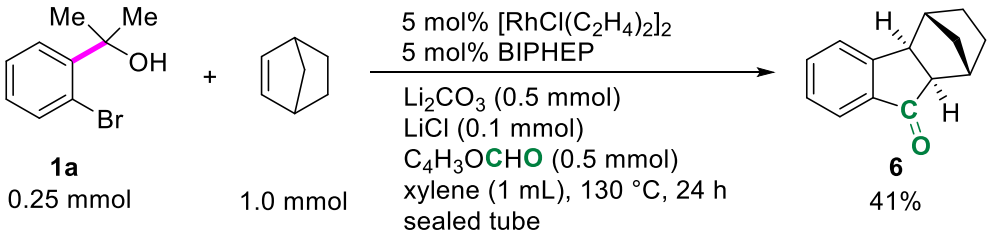
4. 2. 2 Substrate Scope

The scope of the reaction with respect to internal alkynes was examined using **1a** (Scheme 4-7). Alkynes bearing both aromatic (**2b** and **2c**) and aliphatic substituents (**2d** and **2e**) were converted into the corresponding indenones (**3ab-ae**), albeit in low to moderate yields.



Scheme 4-7. Scope of internal alkynes

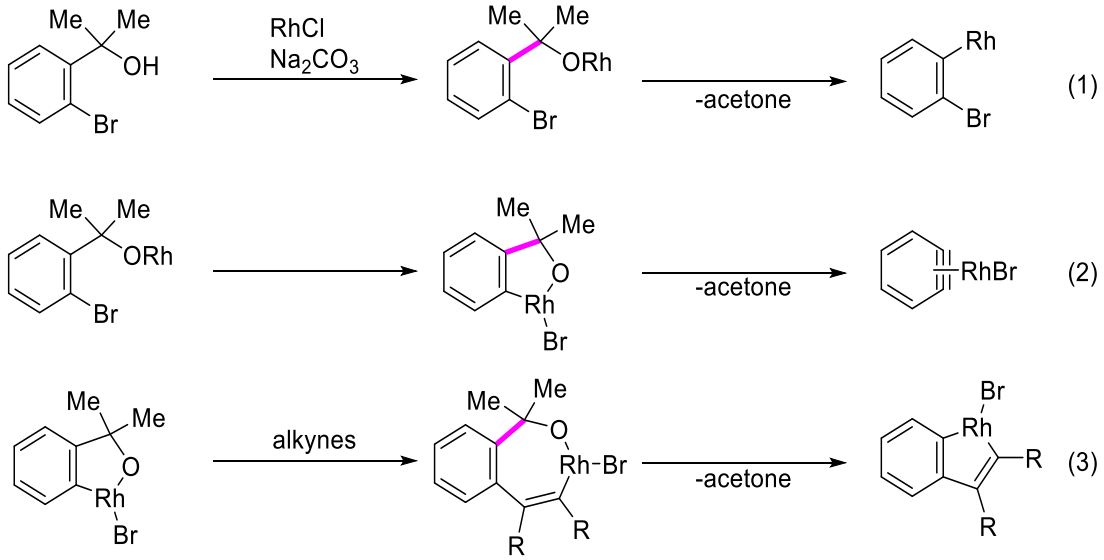
After some optimizations, the indanone derivative (**6**) was obtained through the reaction of **1a** with 2-norbornene catalyzed by $[RhCl(C_2H_4)_2]_2$ and BIPHEP (Scheme 4-8).



Scheme 4-8. Carbonylative annulation with 2-norbornene

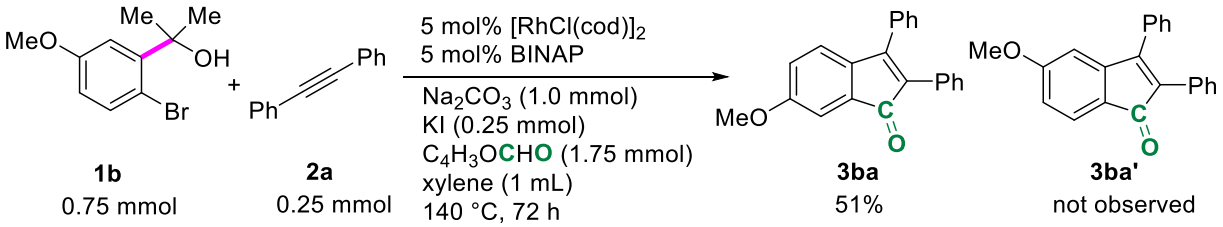
4. 2. 3 Investigation of Reaction Pathway

In the present carbonylation, three possible C-C bond cleavage steps can be proposed, as depicted in Scheme 4-9. To examine the feasibility of each reaction pathways, I performed several experiments.



Scheme 4-9. Three possible pathways of C-C bond cleavage step.

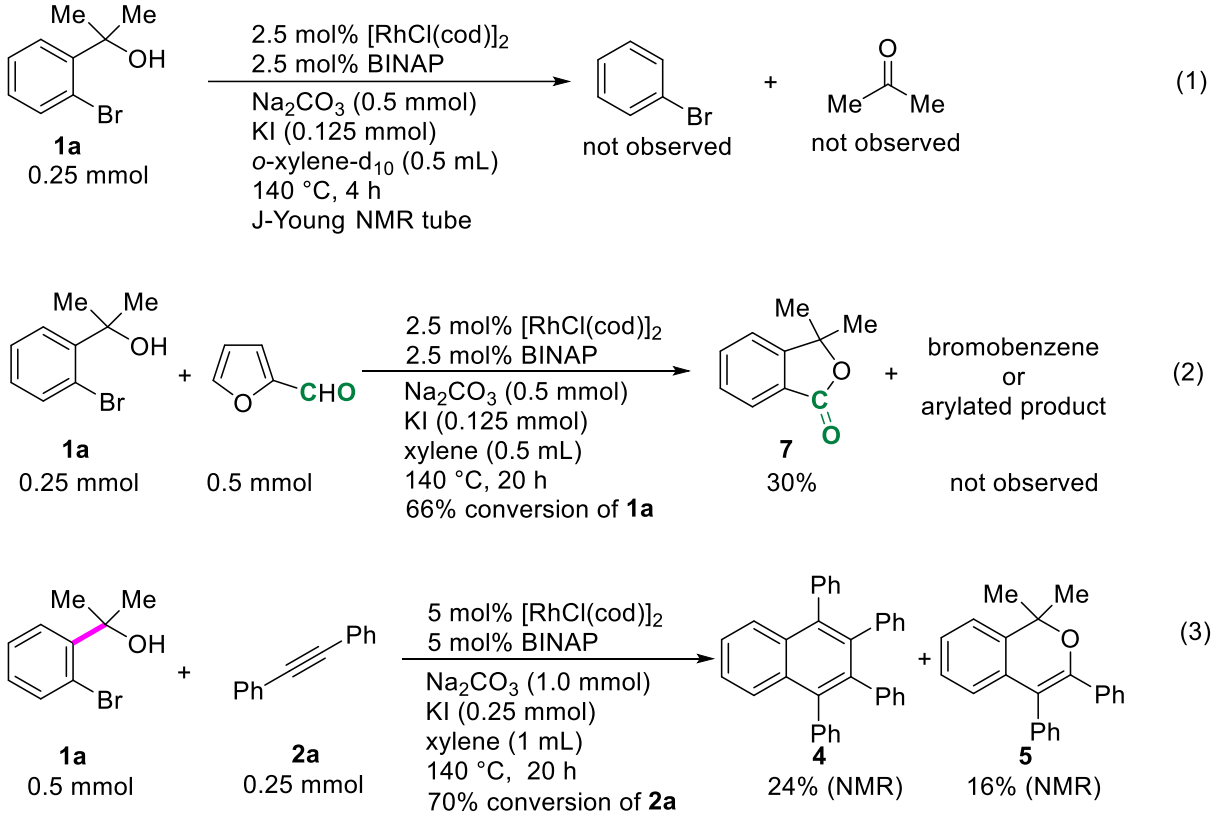
When **2a** was treated with **1b** under optimal conditions, 6-methoxy-2,3-inden-1-one (**3ba**) was generated in 51% yield as a single isomer (Scheme 4-10). Thus, the pathway (2) through the production of arynes from **1**, followed by [2+2+1] cyclocarbonylation, was completely ruled out.[17]



Scheme 4-10. Carbonylative annulation of **1b**.

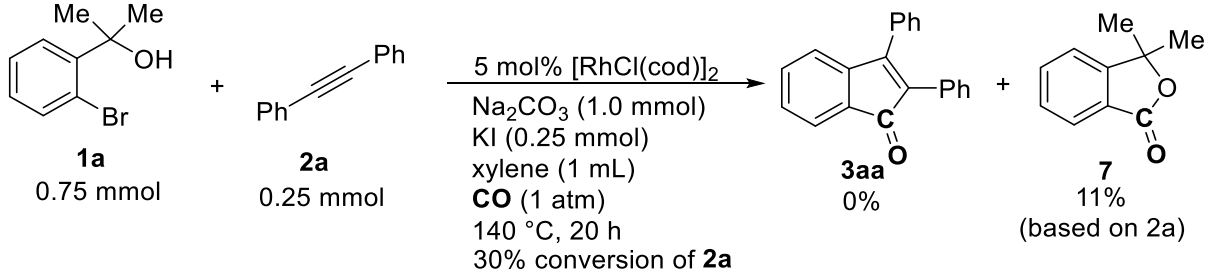
To gain further insights into the reaction pathway, several control experiments were conducted. While the removal of alkynes from this reaction system led to no formation of C-C

bond cleaved products (Scheme 4-11, Eq. 1 and 2),[18] the annulation proceeded in the presence of **2a** leading to the formation of the naphthalene derivative (Eq. 3). These results suggest that alkynes are necessary for the C-C bond cleavage step.[13]



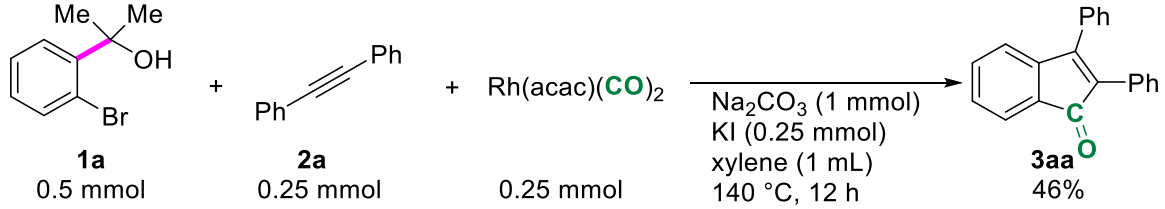
Scheme 4-11. Control experiments.

Consistent with my hypothesis, the reaction under atmospheric carbon monoxide did not give the desired indenone at all (Scheme 4-12). However, this result could also imply that the carbonyl ligand do not involve in the synthesis of indenones.



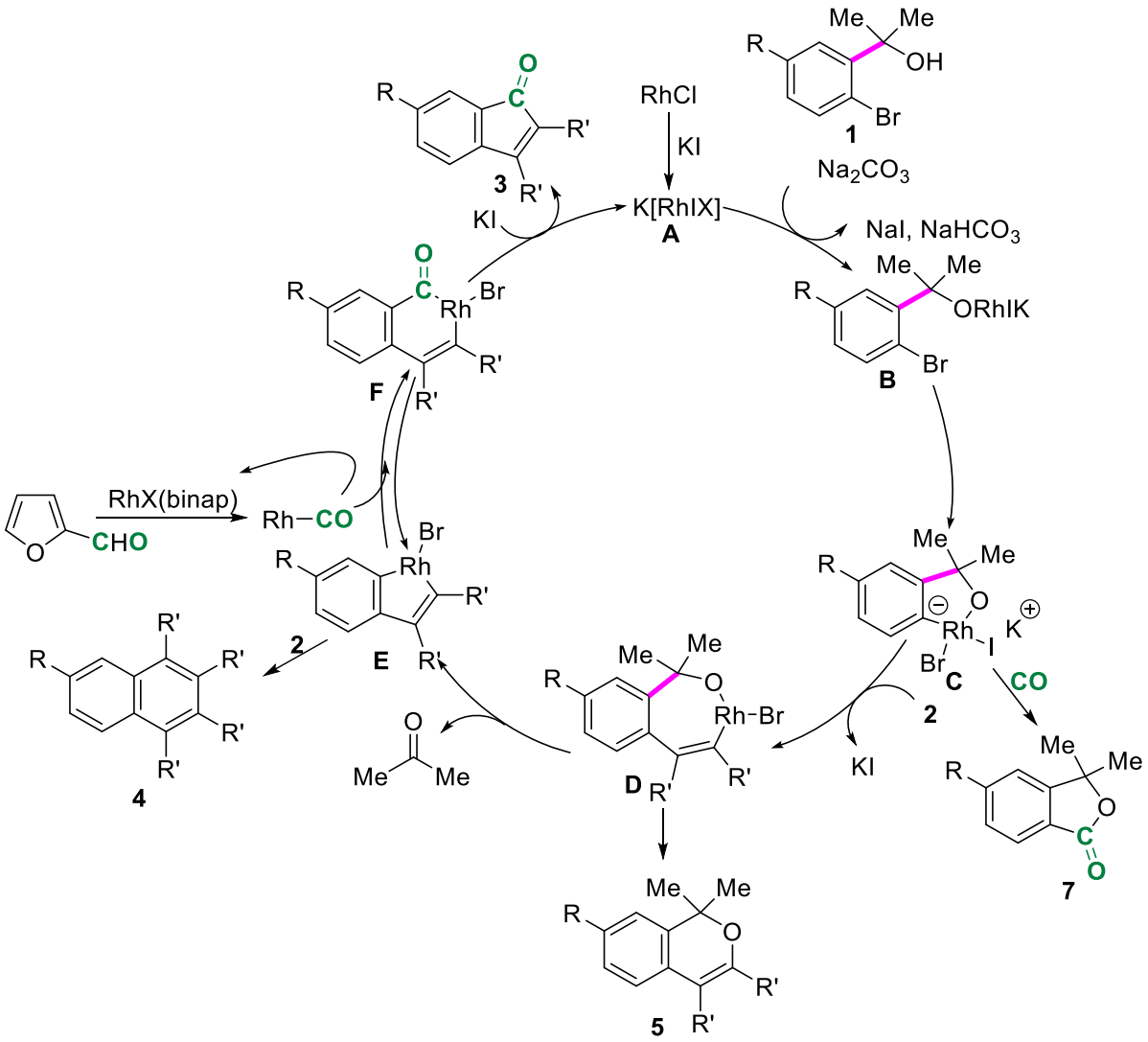
Scheme 4-12. Reaction with carbon monoxide.

As shown in Scheme 4-13, its migratory insertion was supported by the fact that the stoichiometric reaction of **1a** with **2a** mediated by $Rh(acac)(CO)_2$ in the absence of furfural gave **3aa** in 46% yield. This indicates that the timely release of the carbonyl moiety via the decarbonylation of furfural plays highly decisive role in the present carbonylative annulation in agreement with previous chapters.



Scheme 4-13. Stoichiometric reaction using $Rh(acac)(CO)_2$.

Although more mechanistic studies are needed to understand the details of the present carbonylation, the current proposed catalytic cycle based on the above findings is outlined in Scheme 4-14. The ligand exchange of complex **A** with the benzylic alcohol (**1**) produced alkoxorhodium **B**, which took place the intramolecular oxidative addition of Ar-Br bond accelerated by KI.[11b] The migratory insertion of an alkyne into **C**, followed by C-C bond cleavage of **D**, resulted in the formation of rhodaindene **E**.[13] Then, the carbonyl moiety generated from the decarbonylation of furfural was incorporated into **E** giving the six-membered acyl species **F**. Finally, the annulated carbonyl product (**3**) is liberated from **F** to close the catalytic cycle.



Scheme 4-14. Proposed catalytic cycle.

4. 3 Conclusion

In summary, I described the carbonylative annulation through C-C bond cleavage of α,α-dimethyl-(2-bromophenyl)methanols and internal alkynes with furfural. To the best of my knowledge, this is the first example of the carbonylative transformation of tertiary benzylic alcohols via C-C bond cleavage. Based on results obtained from control experiments, I proposed that the alkyne assists the cleavage of C-C bond. Most importantly, it was found that the reaction under atmospheric carbon monoxide did not provide the desired indenone at all although the involvement of the carbonyl ligand on the rhodium complex in the indenone synthesis was proved by the reaction of **1a** with **2a** mediated by $Rh(acac)(CO)_2$. Therefore, the timely release of the carbonyl moiety from furfural plays highly decisive role in the present carbonylative annulation.

4. 4 Experimental Section

I. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer in $CDCl_3$ using $CHCl_3$ (proton: 7.26 ppm, carbon: 77.16 ppm) and TMS (proton: 0.00 ppm) as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), integration, and interpretation. Column chromatography was performed using a SiO_2 (MERCK Silica gel 60).

II. Materials.

$[RhCl(cod)]_2$,[19] **2b**, **c**,[20] and **1a**, **b**,[6] were prepared by previously reported methods. BIPHEP and $Rh(acac)(CO)_2$ were purchased from Strem Chemicals Inc. and was used directly without further purification. Paraformaldehyde, LiCl, KI, K_2CO_3, Li_2CO_3 Cs_2CO_3, KO^tBu, K_3PO_4 and Na_2CO_3 were purchased from Wako Pure Chemical Industries, Ltd. and dried over P_2O_5 under a vacuum prior to use. $Na_3PO_4 \cdot 12H_2O$, **2d**, and **2e** were purchased from Wako Pure Chemical Industries, Ltd. and were used directly without further purification. PPh_3 was purchased from Wako Pure Chemical Industries, Ltd. and recrystallized from ethanol. Furfural was purchased from Wako Pure Chemical Industries, Ltd. and was distilled from Na_2CO_3. It was kept in a brown bottle. **2a**, DPPE, DPPP, DPPB, DPPBz, $PCy_3 \cdot HBF_4$, and 2-norbornene were purchased from Tokyo Chemical Industry Co., Ltd. and were used directly without further

purification. Xantphos and $PCyp_3 \cdot HBF_4$ were purchased from Sigma-Aldrich Chemical Co. and was used directly without further purification. BINAP was purchased from Kanto Chemical. and was used directly without further purification. Anhydrous xylene and dioxane were purchased from Wako Pure Chemical Industries, Ltd. and dried by storage over 4A molecular sieves. Anhydrous anisole was purchased from sigma-Aldrich Chemical Co. and dried by storage over 4A molecular sieves. Octane was purchased from Wako Pure Chemical Industries, Ltd., washed with conc. H_2SO_4, and then was distilled over sodium.

III. Optimization Study

A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(cod)]_2$ (0.0125 mmol, 6.16 mg), bidentate phosphane ligand (0-0.025 mmol), **2a** (0.25 mmol), KI (0.25 mmol), and base (1.0 mmol). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Solvent (1.0 mL), **1a** (0.75 mmol, 161.3 mg), and furfural (1.75 mmol, 168.2 mg), were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that had been preheated to 130-150 °C for 20 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 **3aa** (hexane/AcOEt = 40/1).

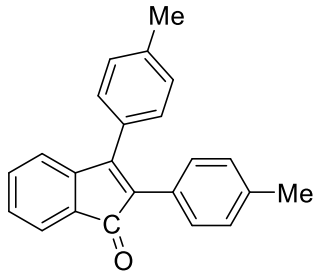
IV. General Procedure for Rhodium-Catalyzed Carbonylative Annulation.

A 5-mL two-necked flask equipped with a stir bar was charged with $[RhCl(cod)]_2$ (0.0125 mmol, 6.16 mg), BINAP (0.0125 mmol, 7.78 mg), **2a** (0.25 mmol, 44.6 mg), KI (0.25 mmol, 41.5 mg), and Na_2CO_3 (1.0 mmol, 106.0 mg). The central neck of the flask was equipped with a reflux condenser having a N_2 gas-bag (2 L), which was connected by a three-way stopcock at its top, and a rubber septum was inserted into the side neck. The flask was evacuated and backfilled with N_2 (three times). Xylene (1.0 mL), **1a** (0.75 mmol, 161.3 mg), and furfural (1.75 mmol, 168.2 mg), were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the flask was filled with N_2. The mixture was placed in an oil bath that had been preheated to 140 °C for 20 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 **3aa**

V. Spectroscopic Data for Products

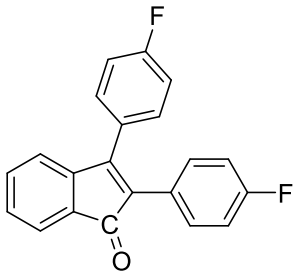
All inden-1-ones[21] and phthalide **7**[8] shown here were reported previously and identified by comparing the ^{1}H NMR and ^{13}C NMR data.

3ab: 2,3-bis(4-methylphenyl)-*1H*-inden-1-one



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.41 (s, 3H), 7.08 (d, 2H, J = 8.0 Hz), 7.15-7.30 (m, 8H), 7.35-7.37 (m, 1H), 7.57 (d, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.7, 121.3, 122.9, 128.0, 128.6, 128.9, 129.0, 129.6, 130.0, 131.0, 132.1, 133.4, 137.7, 139.5, 145.5, 154.9, 197.0.

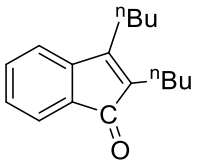
3ac: 2,3-bis(4-fluorophenyl)-*1H*-inden-1-one



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96-7.00 (m, 2H), 7.11-7.15 (m, 3H), 7.22-7.25 (m, 2H), 7.29-7.32 (m, 1H), 7.36-7.39 (m, 3H), 7.59 (d, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.5 (d, J = 7.0 Hz), 116.3 (d, J = 7.0 Hz), 121.2, 123.3, 126.6 (d, J = 7.0 Hz), 128.6 (d, J =

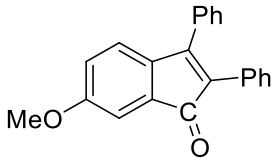
7.0 Hz), 129.3, 130.6, 130.7 (d, J = 7.0 Hz), 131.6, 131.9 (d, J = 7.0 Hz), 133.7, 145.0, 154.3, 161.5, 162.3, 163.5, 164.3, 196.4.

3ad: 2,3-dibutyl-*1H*-inden-1-one



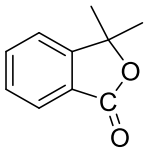
Yellow oil; R_f: 0.35 (Hexane/EtOAc = 18/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz), 1.32-1.47 (m, 6H), 1.55-1.62 (m, 2H), 2.25 (t, 2H, J = 7.5 Hz), 2.53 (t, 2H, J = 7.5 Hz), 7.03 (d, 1H, J = 7.0 Hz), 7.15 (t, 1H, J = 7.0 Hz), 7.31 (t, 1H, J = 7.0 Hz), 7.36 (d, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.8, 22.9, 23.2, 26.2, 30.1, 31.6, 119.1, 121.8, 128.0, 131.3, 133.3, 134.9, 146.8, 157.9, 198.8.

3ba: 6-methocy-2,3-diphenyl-*1H*-inden-1-one



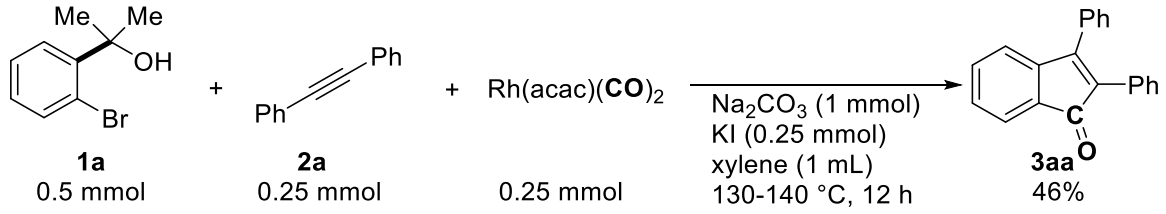
Red-purple solid; R_f: 0.1 (Hexane/EtOAc = 18/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.78-6.80 (m, 1H), 7.04 (d, 1H, J = 8.0 Hz), 7.19-7.26 (m, 5H), 7.36-7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.0, 110.7, 116.4, 122.4, 127.6, 128.2, 128.6, 128.9, 129.4, 130.0, 131.1, 131.5, 133.1, 133.1, 137.1, 156.5, 161.2, 196.3.

7: 3,3-dimethyl-*3H*-isobenzofuran-1-one



White solid; R_f: 0.19 (Hexane/EtOAc = 6/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 6H), 7.40 (d, 1H, J = 7.5 Hz), 7.50 (t, 1H, J = 7.5 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.85 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 85.6, 120.8, 125.4, 125.9, 129.0, 134.2, 155.1, 170.0.

VI. Stoichiometric Reaction mediated by Rh(acac)(CO)$_2$.



A 10-mL dry sealed-tube equipped with a stir bar was charged with Rh(acac)(CO)$_2$ (0.25 mmol), **2a** (0.25 mmol, 44.6 mg), KI (0.25 mmol, 41.5 mg), and Na_2CO_3 (1.0 mmol, 106.0 mg) under a N_2 flow. Xylene (1.0 mL) and **1a** (0.5 mmol, 107.5 mg) were then added. After degassing the reaction mixture three times by the freeze-pump-thaw method, the tube was filled with N_2. The mixture was placed in an oil bath that had been preheated to 140 °C for 12 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 **3aa**.

References and Notes

1. For recent issues and reviews on the C-C bond activation, see: a) Dong, G. *C-C Bond Activation*, Springer, Heidelberg, 2014. (b) Murakami, M.; Chatani, N. *Cleavage of Carbon−Carbon Single Bonds by Transition Metals*, Wiley-VCH: Weinheim, 2016. (c) Li, B.-J.; Shi, Z.-J. in *Homogeneous Catalysis for Unreactive Bond Activation* (Ed.: Shi, Z.-J.), John Wiley & Sons: NJ, 2015; pp. 575−617. (d) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613. (e) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 414. (g) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410.
2. For recent issues and reviews on the C-H bond functionalization reactions, see: (a); Yu, J.-Q.; Shi, Z. *C-H Activation*, Springer, Heidelberg, 2010. (b) Beller, M.; Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C−X bonds*, Springer: Heidelberg, 2013. (c) Li, B.-J.; Shi, Z.-J. in *Homogeneous Catalysis for Unreactive Bond Activation* (Ed.: Shi, Z.-J.), John Wiley & Sons: NJ, 2015; pp. 498−521. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (f) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (g) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (h) Gadge, S. T.; Gautam, P.; Bhanage, B. M. *Chem. Rec*. **2016**, *16*, 835. (i) Gulıás, M.; Mascareñas, J. L. *Angew. Chem., Int. Ed*. **2016**, *55*, 11000.

3. Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

4. (a) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236. (b) Nakano, M.; Satoh, T.; Miura. M. *J. Org. Chem.* **2006**, *71*, 8309. (c) Biro, A. B.; Kotschy, A. *Eur. J. Org. Chem.* **2007**, 1364.

5. (a) Terao, Y.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2004**, *69*, 6942. (b) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem., Int. Ed*. **2007**, *46*, 4937.

6. (a) Mahendar, L.; Krishna, J.; Reddy, A. G. K.; Ramulu, B. V.; Satyanarayana, G. *Org. Lett.* **2012**, *14*, 628. (b) Iwasaki, M.; Iino, S.; Nishihara, Y. *Org. Lett.* **2013**, *15*, 5326.

7. (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (b) Brunet, J.-J.; Sidot, C.; Caubere, P. *J. Org. Chem.* **1983**, *48*, 1166. (c) Fujioka, M.; Morimoto, T.; Tsumagari, T.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K. *J. Org. Chem*. **2012**, *77*, 2911. (d) Mahendar, L.; Satyanayarana, G. *J. Org. Chem.* **2016**, *81*, 7685.

8. (a) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem*. **2003**, *68*, 9423. (b) Kadnikov, D. V.; Larock, R. C. *Mendeleev Commun.* **2007**, *17*, 74.

9. For reviews and accounts of carbonylation with CO surrogates, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 5580. (b) Larhed, M.; Odell, L.; Russo, F. *Synlett* **2012**, *23*, 685. (c) Wu, L.; Liu, Q.; Lackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 6310. (d) Konishi, H.; Manabe, K. *Synlett* **2014**, *25*, 1971. (e) Gautam, P.;

Bhanage, B. M. *Catal. Sci. Technol*. **2015**, *5*, 4663. (f) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594. (g) Cao, J.; Zheng, Z-.J.; Xu, Z.; Xu, L-.W. *Coord. Chem. Rev.* **2017**, *336*, 43.

10. (a) Dutta, S.; De, S.; Saha, B.; Alam, M. I. *Catal. Sci. Technol.* **2012**, *2*, 2025. (b) Cai, C. M.; Zhang, T.; Kumar, R.; Wyman, C. E. *J. Chem. Technol. Biotechnol.* **2014**, *89*, 2. (c) Peleteiro, S.; Rivas, S.; Alonso, J. A.; Santos, V.; Parajó, J. C. *Bioresource Techonology*, **2016**, *202*, 181. (d) Li, C.-L.; Qi, X.; Wu, X.-F. *J. Mol. Catal. A: Chem.* **2015**, *406*, 94.
11. (a) Larock, R. C. *J. Organomet. Chem*. **1999**, *576*, 111. (b) Perry, R. J.; Wilson, B. D. *J .Org. Chem.* **1996**, *61*, 7482.
12. Coe, B. J.; Glenwright, S. J. *Coord. Chem. Rev*. **2000**, *203*, 5.
13. Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 298.
14. Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548.
15. (a) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. (b) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2007**, *46*, 9331. (c) Dermenci, A.; Whittaker, R. E.; Dong, G. *Org. Lett.* **2013**, *15*, 2242. (d) Whittaker, R. E.; Dong, G. *Org. Lett.* **2015**, *17*, 5504.
16. (a) Wu, X.-F. *Adv. Synth. Catal.* **2015**, *357*, 3393. For recent examples, see: Pd: (b) Chen, J.; Natte, K.; Wu, X.-F. *J. Organomet. Chem.* **2016**, *803*, 9. (c) Liu, Q.; Yuan, K.;

Arockiam, P.-B.; Franke, R.; Doucet, H.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 4493. (d) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed*. **2014**, *53*, 10090. (e) Li, W.; Wu, X.-F. *J. Org. Chem*. **2014**, *79*, 10410. Rh: (f) Midya, S. P.; Sahoo, M. K.; Landge, V. G.; Rajamohanan, P. R.; Balaraman, E. *Nat. Commun.* **2015**, *6*, 8591. (g) Furusawa, T.; Morimoto, T.; Ikeda, K.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K.; Jeong, N. *Tetrahedron* **2015**, *71*, 875. Ru: (h) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. *ChemCatChem* **2014**, *6*, 2805.

17. Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12868.
18. There are several studies on C-C bond cleavage of benzylic alcohols by rhodium(I): see. (a) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3124. (b) Xue, L.; Ng, K. C.; Lin, Z. *Dalton Trans*. **2009**, 5841.
19. Giordano, G.; Crabtree, R. H. *Inorg. Synth.* **1979**, *19*, 218.
20. Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199.
21. Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3948.

Chapter 5 General Conclusion

Transition metal-catalyzed the direct carbonylation of C-H and C-C bonds at arene, which are ubiquitous in organic molecules, is an ideal protocol for the synthesis of ketones. However, some drawbacks arising from properties of carbon monoxide resulted in much slower progress in this area, compared to other C-H and C-C functionalizations such as arylation. In this doctoral dissertation, I have demonstrated that furfural can provide effectively the carbonyl moiety via the decarbonylation catalyzed by rhodium complex leading to the novel rhodium-catalyzed carbonylations of inert C-H and C-C bonds at arenes.

In chapter 2, I described the carbonylative coupling of 2-iodobiphenyls with furfural through the cleavage of C-H bond at 2'-position. This is the first report on the rhodium-catalyzed C-H carbonylation of aryl halides and arenes. The present protocol was applicable to the reaction of biphenylene via the oxidative addition of C-C bond. In chapter 3, I investigated the carbonylative annulation of iodobenzenes, strained olefins and 4-octyne, and furfural through *ortho*-C-H bond cleavage leading to the convenient synthesis of indanone and indenone derivatives. In chapter 4, I studied the carbonylative annulation of *o*-bromobenzylic alcohols and alkynes involving C-C bond cleavage. This is the first example of the carbonylation of benzylic alcohols through β-aryl elimination.

It is notable that the reactions described here hardly proceeded under atmospheric carbon monoxide. This fact suggests that the timely release of the carbonyl moiety from furfural

plays highly decisive role in the present carbonylative annulation. The outcome of the present study promises that the method depending on furfural enables the development of novel carbonylation reactions which are difficult to achieve by the traditional method using gaseous carbon monoxide.

List of Publications

学位論文の主たる部分を公表した論文

1. “Rh(I)-Catalyzed Intramolecular Carbonylative C-H/C-I Coupling of 2-Iodobiphenyls Using Furfural as a Carbonyl Source”

   Takuma Furusawa, Tsumoru Morimoto, Yasuhiro Nishiyama, Hiroki Tanimoto, and Kiyomi Kakiuchi,

   Chem. Asian J. **2016**, *16*, 2312.

2. “Rhodium(I)-Catalyzed Carbonylative Annulation of Iodobenzenes with Strained Olefins and 4-Octyne in the Presence of Furfural Involving *Ortho*-C-H Bond Cleavage”

   Takuma Furusawa, Hiroki Tanimoto, Yasuhiro Nishiyama, Tsumoru Morimoto, and Kiyomi Kakiuchi,

   Adv. Syn. Catal. **2017**, *359*, 240.

3. “Rhodium-Catalyzed Carbonylative Annulation of *o*-Bromobenzyl Alcohols and Alkynes with Furfural via β-Aryl Elimination”

   Takuma Furusawa, Tsumoru Morimoto, Hiroki Tanimoto, Yasuhiro Nishiyama, and Kiyomi Kakiuchi,

   Manuscript in preparation.

参考論文

1. “Palladium-Catalyzed Hydroxymethylation of Aryl− and Heteroarylboronic Acids using Aqueous Formaldehyde”

   Tetsuya Yamamoto, Azamat Zhumagazin, **Takuma Furusawa**, Ryoji Tanaka, Tetsu Yamakawa, Yohei Oe, and Tetsuo Ohta,

   Adv. Syn. Catal. **2014**, *356*, 3525.

2. “Palladium-catalyzed arylation of aldehydes with bromo-substituted 1, 3-diaryl-imidazoline carbene ligand”

   Tetsuya Yamamoto, **Takuma Furusawa**, Azamat Zhumagazin, Tetsu Yamakawa, Yohei Oe, and Tetsuo Ohta,

   Tetrahedron **2015**, *71*, 19.

3. “Asymmetric Pauson–Khand-type reactions of 1, 6-enynes using formaldehyde as a carbonyl source by cooperative dual rhodium catalysis”

   Takuma Furusawa, Tsumoru Morimoto, Keiichi Ikeda, Hiroki Tanimoto, Yasuhiro Nishiyama, Kiyomi Kakiuchi, and Nakcheol Jeong,

   Tetrahedron **2015**, *71*, 875.

4. “Pd(0)-Catalyzed CO Gas-Free Carbonylation of 2-Bromobiphenyls with Formaldehyde as a Carbonyl Surrogate through the Cleavage of a CH Bond”

   Takuma Furusawa, Tsumoru Morimoto, Nagato Oka, Hiroki Tanimoto, Yasuhiro Nishiyama, and Kiyomi Kakiuchi,

   Chem. Lett. **2016**, *45,* 406.

   Selected as “New Synthetic Methods” in *J. Synth. Org. Chem. Jpn.* **2016**, *74*, 1143.

   .

学会発表

国際学会発表

1. “Asymmetric Pauson-Khand-Type Reactions of Enynes Using Formaldehyde as a Carbonyl Source by Cooperative Dual Rhodium Catalysis”
   Tsumoru Morimoto, **Takuma Furusawa**, Kiyomi Kakiuchi, and Nakcheol Jeong
   ICOMC 2014 Post-Symposium in Osaka, Osaka University, Japan, July, 2014.

2. “Enantioselective Pauson-Khand-type Reactions of Enynes Using Formaldehyde as a Carbonyl Source under Milder Conditions by Dual Rhodium Catalysts”
   Tsumoru Morimoto, **Takuma Furusawa**, Kiyomi Kakiuchi, and Nakcheol Jeong
   ICCC41, suntec singapore convention and exhibition centre, Singapore, July, 2014.

3. “Dual Rh(I)&Pd(0)-Catalyzed Cyclocarbonylation Reaction of C-Nuclephile-Tethered Bromoarenes with Aldehydes”
   Tsumoru Morimoto, **Takuma Furusawa**, Ai Tomiie, Kiyomi Kakiuchi
   The 2nd International Conference on Organometallics and Catalysis (OM&Cat-2014), Todaiji temple, Japan, October, 2014.

国内会議

1. 「非対称 NHC-Pd 触媒を用いるアリールボロン酸のカルボニル化合物への求核付加反応」

   山本哲也，古澤拓馬, 大江洋平, 山川　哲, 太田哲男

   日本化学会第 93 春季年会、1F6-55、立命館大学・草津キャンパス、2013 年 3 月

2. ”NHC-Palladacycle Catalyzed Hydroxymethylation of Arylboronic Acids”

   山本哲也，Zhumagazin Azamat，古澤拓馬，山川　哲

   第 60 回有機金属化学討論会、P3A-14、学習院大学、2013 年 9 月.

3. 「ロジウム複合触媒の協働作用による穏和な条件下でのエンイン類の不斉環化カルボニル化反応」

   森本積、古澤拓馬、垣内喜代三、Nakcheol Jeong

   日本化学会第 94 春季年会、2D4-27、名古屋大学 ・東山キャンパス、2014 年 3 月

4. 「ホルマリンを用いるアリールホウ素化合物の触媒的ヒドロキシメチル化反応」

   山本哲也，Zhumagazin Azamat，古澤拓馬，山川　哲

   日本プロセス化学会サマーシンポジウム、2P-15、タワーホール船堀、2015 年 7 月

5. 「ロジウム複合触媒の協働作用による穏和な条件下でのエンイン類の不斉環化カルボニル化反応」

   森本積、古澤拓馬、垣内喜代三、Nakcheol Jeong

   58th 香料、テルペンおよび精油化学に関する討論会、2AII-4、和歌山大学、2014 年 9 月

6. 「ロジウム複合触媒の協働作用によるホルムアルデヒドを用いた 1,6-エンイン類の不斉環化カルボニル化反応」

古澤拓馬、森本積

第 7 回公開シンポジウム（新学術領域研究「有機分子触媒」合同シンポジウム）、PM-09、北海道大学、2014 年 6 月

7. “Asymmetric Pauson-Khand-Type Reactions of 1,6-Enynes Using Formaldehyde as a Carbonyl Source by Cooperative Dual Rhodium Catalysis”

森本積、古澤拓馬、垣内喜代三、Nakcheol Jeong

第 61 回有機金属化学討論会、P2C-08、九州大学、2014 年 9 月

8. “Rhodium(I)-Catalyzed Carbonylative Ar-H/Ar-X Annulation Coupling with Furfural as a Carbonyl Source”

古澤拓馬、森本積、垣内喜代三

第 63 回有機金属化学討論会、P2-21、早稲田大学、2016 年 9 月

ACKNOWLEDGEMENTS

The studies described in this dissertation have been carried out under the guidance of Professor Kiyomi Kakiuchi at Synthetic Organic Chemistry laboratory of the Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST), from April, 2014 to March, 2017. First of all, I would like to sincerely thank Professor Kiyomi Kakiuchi for his continuous guidance, valuable suggestion, encouragement, and great support. I am extremely grateful to Associate Professor Tsumoru Morimoto, Assistant Professor Hiroki Tanimoto, and Assistant Professor Yasuhiro Nishiyama for their inspiring suggestions and valuable comments. Furthermore, I would also like to offer sincere thanks to my co-supervisors, Associate Professor Tsuyoshi Ando and Professor Jun-ichi Kikuchi for their helpful discussions, comments and judging of this dissertation.

I owe a very important debt to Ms. Hisayo Fujiki and Ms. Yurika Fujita for their kind help and support with infinite tenderness throughout my research life at NAIST. I am also grateful to members of Kakiuchi's laboratory, Dr. Kimitada Terao, Dr. Yuuki Yanagisawa, Dr. Chuang Wang, Dr. Huan Zhang, Dr. Yasuo Sasaki, Dr. Yusuke Mizutani, Ms. Ai Tomiie, Mr. Nagato Oka, Mr. Takahiro Sugiura, Mr. Kosei Nishida, Mr. Keiichi Yokoyama, Mr. Tomohiko Nagao, amongst others. I would like to express my special gratitude to Mr. Makoto Abe for his experimental assistance in the research on the rhodium-catalyzed cyclohydroformylation of 1,6-enynes with formaldehyde.

I thank Ms. Yoshiko Nishikawa and Mr. Kazuo Fukuda for the measurement of mass spectra, and Mr. Fumio Asanoma for his assistance with ^{31}P NMR experiments.

I wish to express grate gratitude to Assistant Professor Tetsuya Yamamoto, *Tokyo Denki University*, Dr. Tetsu Yamakawa, *Sagami Chemical Research Institute*, and Professor Yasuhiro Mazaki, *Kitasato University*, for their kind suggestions.

I would like to deeply acknowledge Professor Jun Okuda, *RWTH Aachen University*, for accepting me as a visiting student researcher and his great advices.

The studies described in this dissertation were partially supported by the NAIST Presidential Special Fund for funding.

Finally, I would like to express my greatest thankfulness to my family for their support and encouragement.

Takuma Furusawa

March, 2017