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이학석사 학위논문

Rhodium-catalyzed reactions using alcohol as a carbon monoxide, nucleophile, hydration and alkylating source

로듐촉매를 사용하여 알코올을 일산화탄소와 친핵체, 수화 및 알킬화 공급원으로 이용하는 반응 연구

2017년 8월

서울대학교 대학원

화학부 무기화학전공

박 하 원

Rhodium-catalyzed reactions using alcohol as a carbon monoxide, nucleophile, hydration and alkylating source

Supervisor : Professor Young Keun Chung

By

Hawon Park

A Thesis for M.S. Degree

In Inorganic Chemistry

08-2017

Department of Chemistry

Graduate School

Seoul National University

Rhodium-catalyzed reactions using alcohol as a carbon monoxide, nucleophile, hydration and alkylating source

지도교수 정 영 근

이 논문을 이학석사 학위논문으로 제출함

2017년 8월

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박 하 원

박하원의 석사학위논문을 인준함

2017년 8월

위 원 장 _____ (인)

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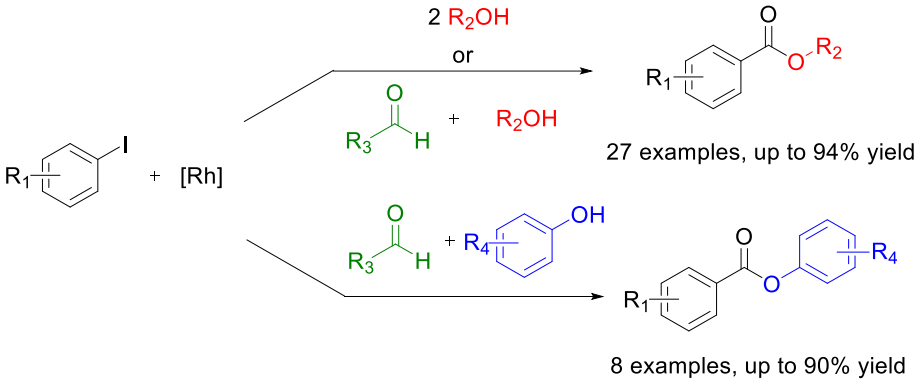
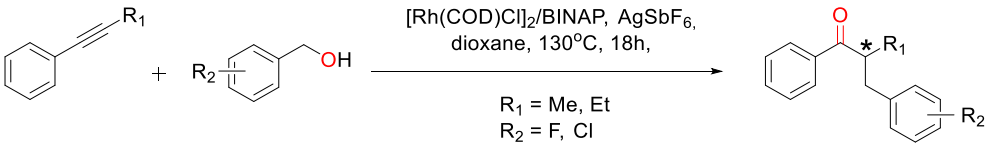
Abstract



R_1 = H, Alkyl, Alkoxy, Aryl, Halogen, Naphtyl
R_2 = 1°,2° and 3° alkyl, Benzyl
R_3 = Benzyl, Alkyl
R_4 = H, Alkyl, Alkoxy, Halogen, Nitro
condition : $[Rh(COD)Cl]_2$/DPEPhos, TMP, toluene, 120°C, 6-18h

A CO-gas-free rhodium-catalyzed alkoxycarbonylation of aryl iodide with alcohols has been developed. Alcohols, with/without the aid of an aldehyde, were used as a carbon monoxide and nucleophile source.



Moreover, atom economic rhodium-catalyzed synthesis of chiral α-alkylated ketone from alkyne with benzyl alcohols has been developed. Benzyl alcohols were used as a hydration and alkylation source.

Keywords: rhodium, ester, alcohol, alkyne, carbonylation, chiral, α-alkylated ketone, hydration, alkylation, addition reaction

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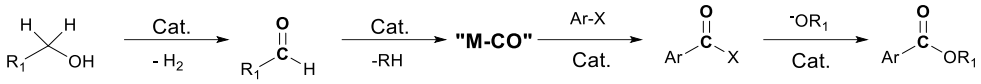
Chapter 1. Rhodium-catalyzed synthesis of esters from aryl halides using alcohols as carbon monoxide and nucleophile sources.

1.1. Introduction

Since the first report by Heck et al. on the palladium-catalyzed reaction of carbon monoxide with aryl halides and alcohols or amines,[1] transition metal catalyzed cross-coupling reactions have been developed as a valuable method for creating carbon-carbon bonds.[2] In particular, the Rhodium-catalyzed carbonylation with a variety of substrate has been studied.[3] These reactions require the addition of CO to the substrate, and are typically carried out with carbon monoxide gas. However, the use of carbon monoxide is not recommendable due to its toxicity and difficulty to handle. Thus, the use of CO-releasing reagents, such as formic acid derivatives[4], oxiranes,[5] and aldehyde[6] has been studied. Recently, Jun et al. reported[7] the Pd/C-catalyzed carbonylative esterification of a primary alcohol with aryl chlorides in the presence of NaF. Previously, We reported the use of an alcohol as a CO source in the rhodium-catalyzed Pauson-Khand reaction of enynes[8] and as a source of hydrogen in the Rh-catalyzed reductive cyclization of enynes.[9] Thus, in the presence of a rhodium catalyst, an alcohol can be used as a CO or hydrogen source as well as a reaction medium. We therefore decided to explore the use of an alcohol as a CO and nucleophile

source, in a reaction with aryl iodides, during the synthesis of esters (Scheme 1.1.).

Scheme 1.1. Proposed catalytic process in esterification

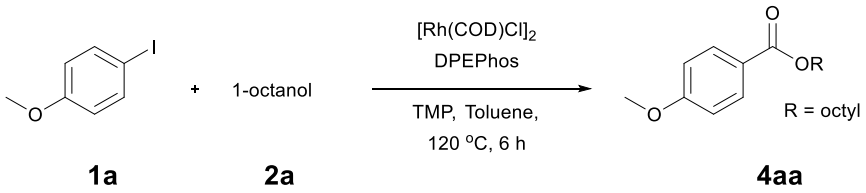


We studied the alkoxycarbonylation of an aryl iodide with an alcohol in the presence of a base and a rhodium catalyst. This led to the discovery of a rhodium−catalyzed, CO−gas−free alkoxycarbonylation reaction of aryl iodide. The reaction occurred in the presence of an alcohol with/without an aldehyde. The alcohol acted as both a CO and nucleophile source to afford an alkoxycarbonylated product. We herein report our preliminary results.

1.2. Result and Discussion

The reaction of 4-iodoansiole (**1a**) with 1-octanol (**2a**) in the presence of $[Rh(COD)Cl]_2$ (2 mol%) and DPEPhos [DPEPhos = (Oxydi-2,1-phenylene)bis(diphenylphosphine)] (4 mol%) at 70 °C was chosen as the synthetic model. This afforded the alkoxycarbonylation product, octyl 4-methoxybenzoate (**4aa**).

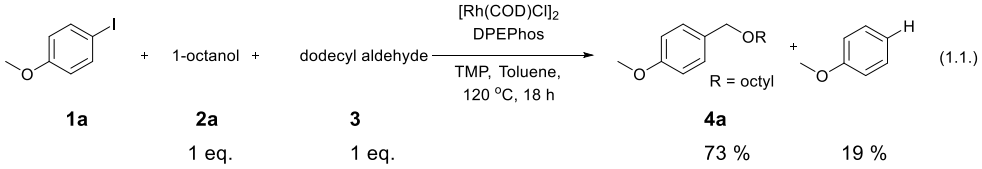
Table 1.1. Screening the reaction conditions[a]



entry	Variation from initial conditions	Yield[b]
1	None	50
2	DIPEA instead of TMP	3
3	Xantphos instead of DPEPhos	13
4	With benzoquinone	Trace
5	$RhCl_3$ instead of $[Rh(COD)Cl]_2$	40
6	With p-chlorobenzaldehyde	90
7	Without $[Rh(COD)Cl]_2$	trace
8	Without alcohol	N.R.

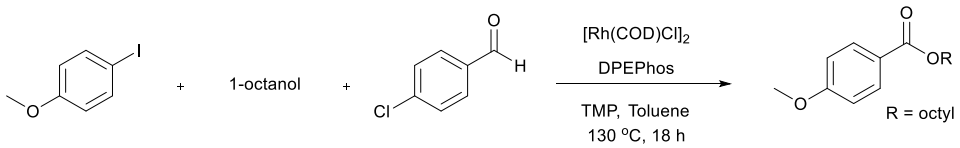
[a] Reaction conditions: 0.5 mmol of **1a**, 2 mol% of $[Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP (Tetramethylpiperidine), 3 equiv. of **2a** and 1.5 mL of toluene. [b] GC yield using 1,3,5-trimethylbenzene as an internal standard.

A yield of 50% was achieved with TMP (2,2,6,6-tetramethylpiperidine) and DPEPhos as the base and ligand, respectively (reaction conditions: $[Rh(COD)Cl]_2$ catalyst in toluene at 120 °C for 6 h). We next screened different bases and ligands (Table 1.1.). The use of DIPEA (*N*,*N*-Diisopropylethylamine) or xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) did not aid the yield of the reaction (entries 2 and 3). In addition, dehalogenated anisole was observed as a by-product in various yields depending on the reaction conditions. We attributed the formation of anisole to the presence of an Rh-hydride intermediate. Thus, a variety of hydrogen acceptor and oxidant were screened (entry 4). However, no noticeable enhancement in yield was observed. Other rhodium precatalysts, such as $RhCl_3$ and $Rh(OAc)_2$, had no effect on the product yield (entry 5). The addition of an aldehyde enhanced the reaction, resulting in a large increase in yield (entry 6). This was highly dependent upon the aldehyde used. The compound 4-chlorobenzaldehyde afforded the best results. For example, 1 equiv 4-chlorobenzaldehyde and 1 equiv 1-octanol afforded the ester and the anisole products in 90% and 6% yields, respectively (entry 6). In the case of the dodecyl aldehyde, the ester and anisole were isolated in 73% and 19% yields, respectively (eq 1.1.). We therefore concluded that the addition of an aldehyde aided the formation of rhodium-carbonyl intermediate, and increased the rate of the reaction between the intermediate and the alkoxide to afford the ester. No product was formed in the absence of the alcohol or the rhodium catalyst (entries 7 and 8).



Initially, we expected the aldehyde to act as a carbon monoxide surrogate. To examine the role of the aldehyde in the alkoxycarbonylation of the aryl iodide more closely, We studied the relation between the yield of the reaction and the ratio of octanol to 4-chlorobenzaldehyde (Table 1.2.).

Table 1.2. Yield dependence upon the ratio of 1-octanol to 4-chlorobenzaldehyde[a]

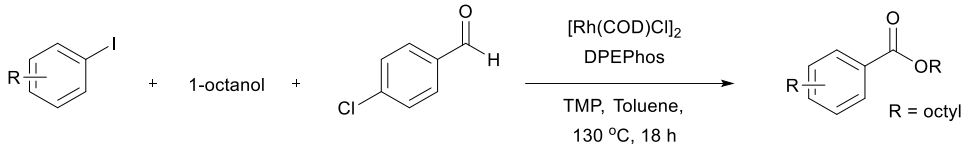


entry	Alcohol (x eq.)	Aldehyde (y eq.)	Yield[b]
1	1	0	28
2	2	0	44
3	3	0	44
4	0	1	N.R.
5	1	0.7	56
6	1	1	76
7	1	1.3	72
8	1.3	1.3	82
9	2	2	80

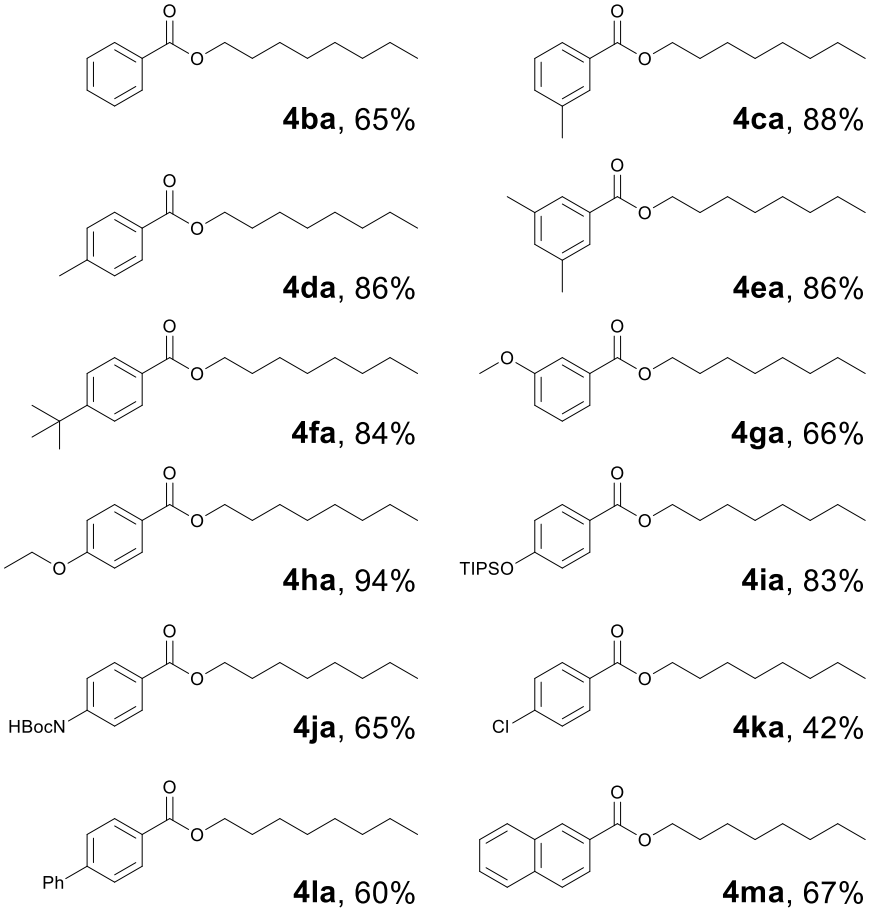
[a] Reaction conditions: 0.5 mmol of **1a**, 2 mol% of $Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, x equiv. of **2a,** y equiv. of **3a** and 1.5 mL of toluene. [b] Isolated yield.

In the presence of 1 equiv. octanol, the expected ester was isolated in 28% yield (entry 1). As the amount of octanol was increased to 2 equiv, the yield also increased to 44% (entry 2). Following this, an additional increase in octanol did not lead to a further increase in yield (entry 3). As expected, no reaction was observed in the absence of octanol (entry 4). When 1.0 equiv octanol and 0.7 equiv 4-chlorobenzaldehyde were used, the yield increased to 56% (entry 5). When equal amounts (1.0 equiv) of octanol and 4-chlorobenzaldehyde were employed, the yield increased to 76% (entry 6). A further increase in aldehyde to 1.2 equiv, with 1.0 equiv octanol, led to a slight decrease in yield (entry 7, 72%). The highest yield (82%) was observed when 1.3 equiv of both octanol and 4-chlorobenzaldehyde were used (entry 8). When 2.0 equiv of both octanol and 4-chlorobenzaldehyde were employed, the yield decreased slightly to 80% (entry 9). This observation suggests that the presence of an aldehyde aids the alkoxycarbonation reaction of the aryl iodide in the presence of an alcohol. From these results, the optimum conditions were established as follows: 0.5 mmol of aryl iodide, 2 mol% of $[Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1.3 equiv 4-chlorobenzaldehyde, 1.3 equiv octanol, 1 equiv TMP, and 1.5 mL of toluene, at 130 °C, for 18 h.

Table 1.3. Esters from aryl iodides and 1−octanol [a,b]



1 **2a** **3a** **4**

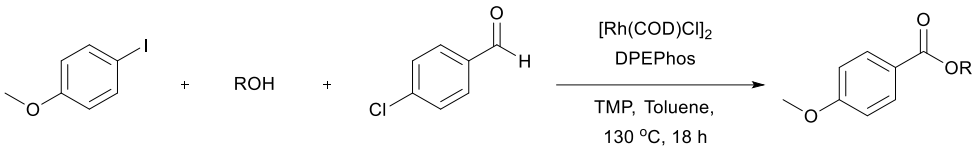


[a] Reaction conditions: 0.5 mmol of **1**, 2 mol% of Rh(COD)Cl]$_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, 1.3 equiv. of **2a**, 1.3 equiv. of **3a** and 1.5 mL of toluene. [b] Isolated yield. [c] p−tolualdehyde used instead of p−chlorobenzaldehyde. [d] Some octyl ester impurities. [e] dppp (1,3−bis(diphenylphosphino)propane) as a ligand.

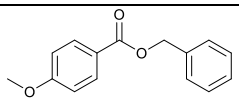
With the optimum reaction conditions in hands, the substrate scope was studied next (Table 1.3.).

Aryl halides with an electron−donating group were found to be good substrates (**4ba–4ha**). The highest yield (94%) was observed for the substrate with an ether group. In the cases of substrates having an electron−accepting group (**4ka−4la**), the yields were rather low, and in some cases no reaction was observed. An aryl halide bearing a chloro group afforded the corresponding product in < 50% (**4ka**). Moreover, < 60% of the expected product was isolated when 4−iodo−1,1'−biphenyl was used (**4la**). No reaction was observed for aryl iodides having an ester or formyl group. Aryl iodides bearing a hydroxy or amine group did not afford expected product, presumably due to a reaction the rhodium catalyst. However, when the functional groups were blocked, the expected products were isolated in reasonable yields (**4ia−4ja**). Steric effects were observed in some cases; when a methyl group was located at the meta− or para−position, the corresponding ester was isolated in high yields (**4ca−4da**). However, in the case of 1−iodo−2−methylbenzene, no reaction was observed. Similarly, 1−iodonaphthalene did not afford any products in the presence of the ligand DPEPhos. However, when this ligand was substituted with dppp, 67% of the expected product was isolated (**4ma**).

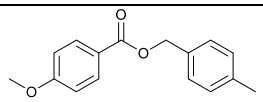
Table 1.4. Esters from aryl iodides and various alcohols[a,b]



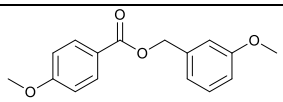
1a **2** **3a** **4**



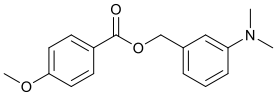
4ab, 82%



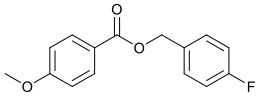
4ac, 74%



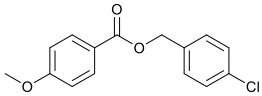
4ad, 70%



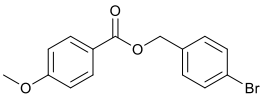
4ae, 60%



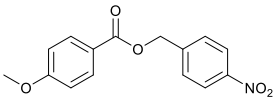
4af, 70%



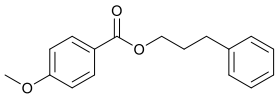
4ag, 76%



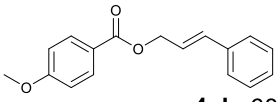
4ah, 70%



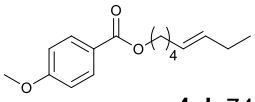
4ai, 70%



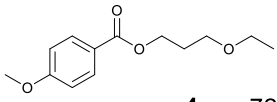
4aj 70%



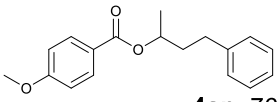
4ak, 68%



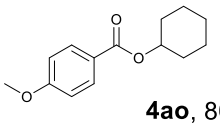
4al, 74%



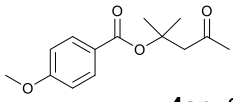
4am, 72%



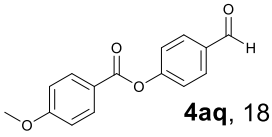
4an, 76%



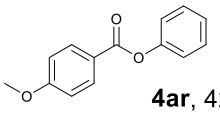
4ao, 80%



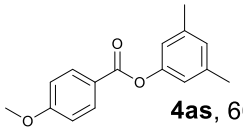
4ap, 24%



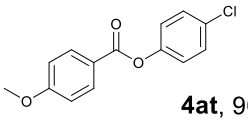
4aq, 18%



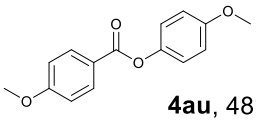
4ar, 42%



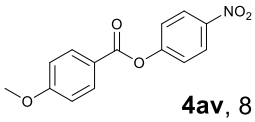
4as, 60%



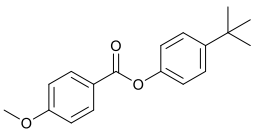
4at, 90%



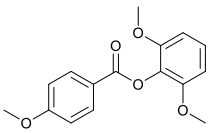
4au, 48%



4av, 81%



4aw, 30%



4ax, 74%

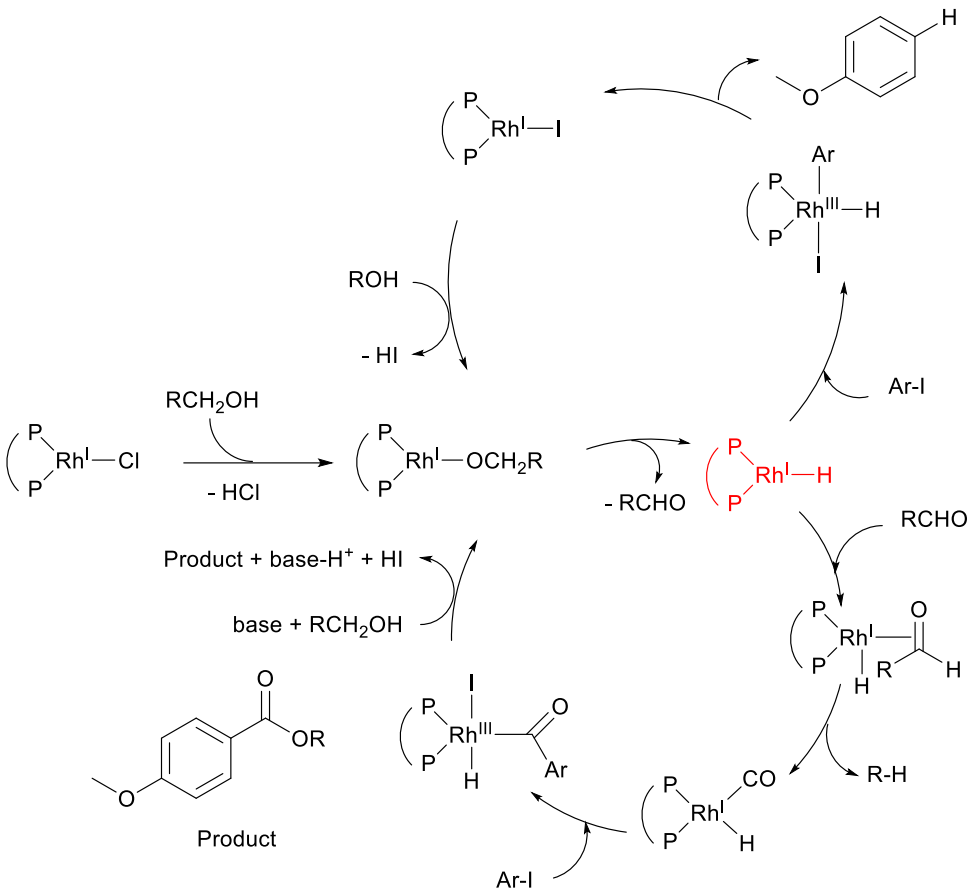
[a] Reaction conditions: 0.5 mmol of **1a**, 2 mol% of Rh(COD)Cl]$_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, 1.3 equiv. of **2**, 1.3 eq. of **3a** and 1.5 mL of toluene. [b] Isolated yield.

Next, We examined the reaction of the aryl iodide with other alcohols (Table 1.4.). Primary alcohols were studied first. Benzyl alcohols bearing electron-donating (Me, OMe, NMe_2) or electron-withdrawing (F, Cl, Br, NO_2) functional groups were found to be good substrates (**4ab-4ai**), and high yields (60 – 82%) were observed. Lengthening the chain between the phenyl and hydroxyl groups to three carbons did not have any influence on the yield (**4aj**). An internal double bond survived during the reaction (**4ak-4al**). When (*E*)-3-phenylpropanol or *(E)*-oct-5-en-1-ol were used as an alcohol, the expected product was isolated in 68% and 74% yields, respectively. In the case of *(E)*-oct-5-en-1-ol, the product was a mixture of regioisomers. Unfortunately, these could not be separated by conventional separation methods. The ether group retained its position during the reaction (**4am**). For secondary alcohols, including 4-phenylbutanol and cyclohexanol, high yields (76% and 80%, respectively) were observed (**4an-4ao**, respectively). However, the tertiary alcohol 4-hydroxy-4methylpentan-2-one afforded a poor yield (24%) (**4ap**).

When the alcohol used was 4-(hydroxymethyl)phenol, a phenol that bears two kinds of hydroxyl groups, the product (4-Formylphenyl 4-methoxybenzoate)[10] was isolated in 18% yield (**4aq**). The phenyl hydroxyl group was more reactive than the benzyl hydroxyl group. In

the phenoxycarbonylation reaction, the aldehyde acted as the sole source of carbon monoxide. This observation prompted us to study the phenoxycarbonylation of other phenols under the same reaction conditions. Seven more phenols were tested as substrates (**4ar–4ax**). The corresponding products were isolated in the reasonable to high yields (42–88%). Electron–deficient phenols are more reactive than electron–rich phenols. Thus, phenols, that are less reactive in the carbonylation reaction,[11] are suitable reaction partners in the catalytic reaction. Phenyl esters could therefore serve as useful acylating reagents for the production of other carboxylate derivatives.[12]

Scheme 1.2. Proposed reaction mechanism



On the basis of the experimental results, together with previously studies,[8,9,13] a plausible reaction mechanism can be drawn for the alkoxycarbonylation of an aryl halide, in the presence of a rhodium compound, with an alcohol and aldehyde (Scheme 1.2.). Two catalytic cycles may be operated under our reaction conditions, namely, a reduction path via a rhodium−hydride intermediate, and an alkoxycarbonylation through a rhodium−carbonyl intermediate. The rhodium−carbonyl intermediate reacts with the aryl iodide in the

presence of an alkoxide, leading to the formation of an ester. The rhodium−hydride intermediate reacts with the aryl halide to afford the reduced product as a minor pathway. We predict that the addition of an aldehyde would aid the formation of the rhodium−carbonyl intermediate, and increase the rate of the reaction.

1.3. Conclusion

In conclusion, We have developed a CO-gas-free alkoxycarbonylation of aryl iodide in the presence of an $[Rh(COD)Cl]_2$/DPEPhos catalytic system and an alcohol with/without an aldehyde. Without the aldehyde, the alcohol acted as both a CO and a nucleophile source to afford the alkoxycarbonylated product in moderate yield. In the presence of both the alcohol and aldehyde, high yields of the alkoxycarbonylated product were isolated. This occurred because the aldehyde assisted the carbonylation reaction. When phenols were used instead of alcohols, phenoxycarbonylation products were also isolated in high yields. Thus, simple aldehydes and primary alcohols could be converted to a useful CO source without any additives. Further mechanistic studies and optimization of the reaction conditions are in progress.

1.4. Experimental Section

1. Chemicals and Reagents

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Sigma−Aldrich and Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane, and acetone). Toluene were dried over Na and distilled under nitrogen. *n*−Hexane, diethyl ether, and ethyl acetate were used without further purification. Reagents were purchased from Sigma−Aldrich, Alfa Aesar, or TCI and were used as received. $[Rh(COD)Cl]_2$ were purchased from Pressure Chem. DPEPhos((oxybis(2,1−phenylene))bis(diphenylphosphane)) were purchased from Alfa Aesar. Reactions were monitored by thin−layer chromatography on 0.25 mm E. Merck silica gel plates (60F−254). The TLC plates were visualized by UV−light (254 nm) and treatment with acidic *p*−anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

2. Physical Methods

^{1}H and ^{13}C NMR spectra were recorded with Agilent 400−MR DD2 (400 MHz and 100 MHz, respectively) spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (7.26 ppm)

and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass Selective detector. Analytical condition – initial temperature: 50 °C, raising temperature 10 °C / min, final temperature : 280 °C, He gas, Pressure : 7.56 psi, Total flow : 53.7 mL / min.

3. Experimental Procedures

A. General Procedure for the entries reported Table 1.1. from aryl iodide and alcohol .

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 5 mg (c.a. 2 mol%) of catalyst, 10 mg of ligand (4 mol%) 0.5 mmol of aryl iodide, 1 equiv (86 uL) of base, 3 equiv of 1-octanol and 1.5 mL of toluene. The mixture was stirred at 120 °C for 18 h. The reaction mixture was extracted with aqueous NH_4Cl solution and diethyl ether and dried over anhydrous $MgSO_4$, filtered, and finally evaporated under reduced pressure. The concentrated reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

4. Characterization Data for Isolated Products

Octyl benzoate: colorless liquid (Table 1.3., **4ba**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2 H), 7.47 (t, J = 7.4 Hz, 1 H), 7.36 (t, J = 7.7 Hz, 2 H), 4.24 (t, J = 6.7 Hz, 2 H), 1.83 – 1.59 (m, 2 H), 1.57 – 1.32 (m, 2 H), 1.24 (m, 8 H), 0.81 (t, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 132.7, 130.5, 129.5, 128.3, 65.1, 31.7, 29.2, 29.1, 28.7, 26.0, 22.6, 14.1. IR (ATR): 1723 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{22}O_2, M]^+$ 234.1620, found 234.1620

Octyl 3−methylbenzoate: colorless liquid (Table 1.3., **4ca**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.7 Hz, 2 H), 7.25 (m, 2 H), 4.23 (t, J = 6.7 Hz, 2 H), 2.32 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.40 – 1.33 (m, 2 H), 1.28 – 1.19 (m, 8 H), 0.81 (t, J = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 138.0, 133.5, 130.4, 130.0, 128.2, 126.6, 65.1, 31.8, 29.22, 29.16, 28.7, 26.0, 22.6, 21.2, 14.1. IR (ATR): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 248.1776, found 248.1777

Octyl 4−methylbenzoate: colorless liquid (Table 1.3., **4da**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 2 H), 7.15 (d, J = 8.0 Hz, 2 H), 4.22 (t, J = 6.7 Hz, 2 H), 2.33 (s, 3 H), 1.72 – 1.63 (m, 2 H), 1.41 – 1.32 (m, 2 H), 1.24 (m, 8 H), 0.81 (t, J = 6.7 Hz, 3

H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.4, 129.5, 129.0, 127.8, 64.9, 31.8, 29.23, 29.17, 28.7, 26.0, 22.6, 21.6, 14.1. IR (ATR): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 248.1776, found 248.1777

Octyl 3,5−dimethylbenzoate: colorless liquid. (Table 1.3., **4ea**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 2 H), 7.09 (s, 1 H), 4.21 (t, *J* = 6.7 Hz, 2 H), 2.27 (s, 6 H), 1.71 – 1.65 (m, 2 H), 1.39 – 1.32 (m, 2H), 1.27 – 1.16 (m, 8 H), 0.80 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 137.9, 134.4, 130.4, 127.2, 65.0, 31.8, 29.23, 29.16, 28.7, 26.0, 22.6, 21.1, 14.1. IR (ATR): 1719 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{26}O_2, M]^+$ 262.1933, found 262.1933

Octyl 4−(tert−butyl)benzoate: colorless liquid. (Table 1.3., **4fa**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 4.22 (t, *J* = 6.6 Hz, 2 H), 1.68 (dd, *J* = 14.2, 7.1 Hz, 2 H), 1.39 – 1.32 (m, 2 H), 1.26 (s, 9 H), 1.29 – 1.22 (m, 8 H), 0.81 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.4, 129.4, 127.7, 125.2, 64.9, 35.0, 31.8, 31.1, 29.23, 29.18, 28.7, 26.0, 22.6, 14.1. IR (ATR): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{19}H_{30}O_2, M]^+$ 290.2246, found 290.2246

Octyl 3−methoxybenzoate: colorless liquid. (Table 1.3., **4ga**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 1 H), 7.49 (s, 1 H), 7.26 (t, *J* = 8.4 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 4.23 (t, *J* = 7.3 Hz, 2 H), 3.77 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.35 (m, 2 H), 1.22 (m, 8 H), 0.80 (t, *J* = 5.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 159.5, 131.8, 129.4, 121.9, 119.2, 114.0, 65.2, 55.4, 31.8, 29.21, 29.16, 28.7, 26.0, 22.6, 14.1. IR (ATR): 1700 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 264.1725, found 264.1727

Octyl 4−ethoxybenzoate: colorless liquid. (Table 1.3., **4ha**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 4.18 (t, *J* = 6.6 Hz, 2 H), 3.96 (q, *J* = 6.9 Hz, 2 H), 1.68 – 1.61 (m, 2 H), 1.34 – 1.30(m, 5 H), 1.28 – 1.12 (m, 8 H), 0.79 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.5, 131.4, 122.6, 113.8, 64.7, 63.5, 31.7, 29.17, 29.11, 28.7, 26.0, 22.5, 14.5, 14.0. IR (ATR): 1717 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{26}O_3, M]^+$ 278.1882, found 278.1884

Octyl 4−((triisopropylsilyl)oxy)benzoate: colorless liquid. (Table 1.3., **4ia**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 4.20 (t, *J* = 6.7 Hz, 2 H), 1.71 – 1.63 (m, 2H), 1.40 – 1.32 (m, 2H), 1.23 (m, 10 H), 1.04 (s, 9 H), 1.02 (s, 7 H), 0.81 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 160.3, 131.5, 123.3, 119.6, 64.8, 31.8, 29.26, 29.20, 28.8, 26.1, 22.6, 17.9, 14.1,

12.7. IR (ATR): 1705 cm^{-1}, HRMS (EI) calc. for $[C_{24}H_{42}O_3Si, M]^+$ 406.2903, found 406.2906

Octyl 4-((tert-butoxycarbonyl)amino)benzoate: colorless liquid. (Table 1.3., **4ja**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 6.86 (s, 1 H), 4.21 (t, *J* = 6.6 Hz, 2 H), 1.70 – 1.63 (m, 2 H), 1.43 (s, 9 H), 1.37 – 1.33 (m, 2 H), 1.23 – 1.20 (m, 8 H), 0.79 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 152.2, 142.7, 130.8, 124.6, 117.3, 81.0, 64.9, 31.7, 29.19, 29.13, 28.7, 28.2, 26.0, 22.6, 14.0. IR (ATR): 1704 cm^{-1}, HRMS (EI) calc. for $[C_{20}H_{31}O_4N, M]^+$ 349.2253, found 349.2255

Octyl 4-chlorobenzoate: colorless liquid. (Table 1.3., **4ka**) with octyl ester impurities

^{1}H NMR (400 MHz, $cdcl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 4.23 (t, *J* = 6.7 Hz, 2 H), 1.72 – 1.64 (m, 2 H), 1.38 – 1.32 (m, 2 H), 1.23 – 1.20 (m, 8 H), 0.81 (t, *J* = 4.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 139.2, 130.9, 128.9, 128.6, 65.4, 31.8, 29.20, 29.15, 28.6, 26.0, 22.6, 14.1. IR (ATR): 1700 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{21}O_2Cl, M]^+$ 268.1230, found 268.1233

Octyl [1,1'−biphenyl]−4−carboxylate: colorless liquid. (Table 1.3., **4la**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.57 (dd, *J* = 13.8, 7.8 Hz, 4 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 4.27 (t, *J* = 6.6 Hz, 2 H), 1.76 – 1.67 (m, 2 H), 1.42 – 1.35 (m, 2 H), 1.31 – 1.18 (m, 8 H), 0.82 (t, *J* = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 166.6, 145.5, 140.1, 130.0, 129.3, 128.9, 128.1, 127.3, 127.0, 65.2, 31.8, 29.26, 29.20, 28.8, 26.1, 22.6, 14.1. IR (ATR): 1720 cm^{-1}, HRMS (EI) calc. for $[C_{21}H_{26}O_2, M]^+$ 310.1933, found 310.1934

Octyl 1−naphthoate: colorless liquid. (Table 1.3., **4ma**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 8.6 Hz, 1 H), 8.08 (d, *J* = 6.9 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 1), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.41 (dt, *J* = 14.1, 7.6 Hz, 2 H), 4.32 (t, *J* = 6.6 Hz, 2 H), 1.78 – 1.68 (m, 2 H), 1.42 – 1.35 (m, 2 H), 1.31 – 1.15 (m, 8 H), 0.80 (t, *J* = 5.8 Hz, 3 H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 167.6, 133.8, 133.1, 131.3, 130.0, 128.4, 127.6, 127.4, 126.1, 125.8, 124.4, 65.2, 31.7, 29.20, 29.15, 28.7, 26.1, 22.6, 14.0. IR (ATR): 1716 cm^{-1}, HRMS (EI) calc. for $[C_{19}H_{24}O_2, M]^+$ 284.1776, found 284.1779

Benzyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4ab**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 7.33 – 7.22 (m, 3 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.26 (s, 2 H), 3.77 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.4, 136.3, 131.7, 128.5, 128.10, 128.06, 122.5, 113.6, 66.4, 55.4. IR (ATR): 1715 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{14}O_3, M]^+$ 242.0943, found 242.0941

4−Methylbenzyl 4−methoxybenzoate: white crystal. (Table 1.4., **4ac**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 7.7 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 5.19 (s, 2 H), 3.72 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.3, 137.9, 133.2, 131.6, 129.1, 128.2, 122.6, 113.5, 66.3, 55.4, 21.1. IR (ATR): 1708 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_3, M]^+$ 256.1099, found 256.1102, m.p. 38.4 °C

3−Methoxybenzyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4ad**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2 H), 7.20 (t, *J* = 7.9 Hz, 1 H), 6.98 – 6.85 (m, 2 H), 6.85 – 6.71 (m, 3 H), 5.21 (s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.4, 159.7, 137.8, 131.7, 129.5, 122.4, 120.2, 113.6, 113.5, 113.6, 66.2, 55.3, 55.2. IR (ATR): 1712 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_4, M]^+$ 272.1049, found 272.1051

3−(Dimethylamino)benzyl 4−methoxybenzoate: dark green liquid. (Table 1.4., **4ae**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.70 (d, *J* = 7.8 Hz, 2 H), 6.60 (d, *J* = 8.5 Hz, 1 H), 5.19 (s, 2 H), 3.73 (s, 3 H), 2.85 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.3, 150.7, 137.0, 131.7, 129.2, 122.6, 116.2, 113.5, 112.2, 112.1, 67.0, 55.3, 40.5. IR (ATR): 1709 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{19}O_3N, M]^+$ 285.1365, found 285.1366

4−Fluorobenzyl 4−methoxybenzoate: white solid. (Table 1.4., **4af**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2 H), 7.31 (dd, *J* = 8.5, 5.5 Hz, 2 H), 6.96 (t, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.9 Hz, 2 H), 5.19 (s, 2 H), 3.74 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 163.8, 163.4, 161.3, 132.11, 132.08, 131.7, 130.9, 130.02, 122.4, 115.5, 115.3, 113.6, 65.6, 55.4. IR (ATR): 1711 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3F, M]^+$ 260.0849, found 260.0850, m.p.: 54 °C

4−Chlorobenzyl 4−methoxybenzoate: white solid. (Table 1.4., **4ag**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2 H), 7.24 (q, *J* = 8.6 Hz, 4 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.18 (s, 2 H), 3.73 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 134.7, 133.9, 131.6,

129.4, 128.6, 122.2, 113.6, 65.4, 55.3. IR (ATR): 1712 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3Cl, M]^+$ 276.0553, found 276.0552, m.p. : 86 °C

4-Bromobenzyl 4-methoxybenzoate: white solid. (Table 1.4., **4ah**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2 H), 7.39 (d, *J* = 8.3 Hz, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.81 (d, *J* = 8.9 Hz, 2 H), 5.17 (s, 2 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 135.3, 131.64, 131.61, 129.7, 122.2, 122.1, 113.6, 65.5, 55.3.

IR (ATR): 1713 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3Br, M]^+$ 320.0048, found 320.0049, m.p. : 94 °C

4-Nitrobenzyl 4-methoxybenzoate: yellow crystal. (Table 1.4., **4ai**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 8.6 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.33 (s, 2 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 163.6, 147.5, 143.6, 131.7, 128.1, 123.7, 121.7, 113.7, 64.8, 55.4. IR (ATR): 1714 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_5N, M]^+$ 287.0794, found 287.0795, m.p. : 132 °C

3−Phenylpropyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4aj**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 7.0 Hz, 2 H), 7.10 (d, *J* = 6.5 Hz, 3 H), 6.80 (d, *J* = 8.2 Hz, 2 H), 4.20 (t, *J* = 6.1 Hz, 2 H), 3.72 (s, 3 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 1.98 (t, *J* = 5.2 Hz 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.2, 141.2, 131.6, 131.5, 128.3, 125.9, 122.7, 113.5, 63.9, 55.3, 32.2, 30.3. IR (ATR): 1716 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{18}O_3, M]^+$ 270.1256, found 270.1253,

Cinnamyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4ak**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.29 (dt, *J* = 13.1, 6.3 Hz, 1 H), 4.84 (d, *J* = 6.2 Hz, 2 H), 3.72 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.3, 136.2, 133.9, 131.6, 128.5, 127.9, 126.5, 123.5, 122.5, 113.5, 65.1, 55.3. IR (ATR): 1709 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{16}O_3, M]^+$ 268.1099 found 268.1097

(E)−Oct−5−en−1−yl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4al**) with regioisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 5.42 – 5.20 (m, 2 H), 4.20 (t, *J* = 6.5 Hz, 2 H), 3.75

(s, 6 H), 2.04 – 1.92 (m, 4 H), 1.73 – 1.63 (m, 2 H), 1.45 – 1.37 (m, 2 H), 0.87 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.2, 132.1, 131.4, 128.4, 122.8, 113.4, 64.5, 55.3, 28.2, 26.6, 26.1, 20.5, 14.3. IR (ATR): 1702 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{22}O_3, M]^+$ 262.1569 found 262.1568

3-Ethoxypropyl 4-methoxybenzoate: colorless liquid. (Table 1.4., **4am**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2 H), 6.81 (d, J = 8.1 Hz, 2 H), 4.29 (t, J = 6.0 Hz, 2 H), 3.75 (s, 3 H), 3.47 (t, J = 5.9 Hz, 2 H), 3.40 (d, J = 6.8 Hz, 2 H), 1.98 – 1.90 (m, 2 H), 1.10 (t, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.2, 131.4, 122.7, 113.4, 67.0, 66.1, 61.8, 55.3, 29.1, 15.0. IR (ATR): 1713 cm^{-1}, HRMS (EI) calc. for $[C_{13}H_{18}O_4, M]^+$ 238.1205 found 238.1206

4-Phenylbutan-2-yl 4-methoxybenzoate: colorless liquid. (Table 1.4., **4an**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.7 Hz, 2 H), 7.16 (t, J = 7.4 Hz, 2 H), 7.08 (d, J = 7.5 Hz, 3 H), 6.81 (d, J = 8.7 Hz, 2 H), 5.06 (dd, J = 12.4, 6.2 Hz, 1 H), 3.73 (s, 3 H), 2.68 – 2.56 (m, 2 H), 2.02 – 1.94 (m, 1 H), 1.86 – 1.79 (m, 1 H), 1.26 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.2, 141.5, 131.4, 128.3, 128.2, 125.8, 123.1, 113.5, 70.7, 55.3, 37.7, 31.8, 20.1. IR (ATR):

1700 cm^{-1}, HRMS (EI) calc. for $[C_{18}H_{20}O_3, M]^+$ 284.1412 found 284.1414

Cyclohexyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4ao**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 4.94 – 4.85 (m, 1 H), 3.74 (s, 3 H), 1.87 – 1.83 (m, 2 H), 1.73 – 1.65 (m, 2 H), 1.53 – 1.44 (m, 3 H), 1.38 – 1.22 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.1, 131.4, 123.3, 113.4, 72.5, 55.3, 31.6, 25.4, 23.6. IR (ATR): 1704 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{18}O_3, M]^+$ 234.1256 found 234.1258

2−Methyl−4−oxopentan−2−yl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4ap**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 5.3 Hz, 2 H), 6.82 (d, *J* = 5.3 Hz, 2 H), 3.77 (s, 3 H), 3.09 (s, 2 H), 2.08 (s, 3 H), 1.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 165.6, 163.2, 131.4, 123.8, 113.5, 80.4, 55.4, 52.4, 31.7, 26.6. IR (ATR): 1703 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{18}O_4, M]^+$ 250.1205 found 250.1205

4−Formylphenyl 4−methoxybenzoate: colorless liquid. (Table 1.4., **4aq**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1 H), 8.08 (d, *J* = 8.7 Hz, 2 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 164.2, 164.1, 155.8, 133.9, 132.4, 131.2, 122.6, 121.1, 114.0, 55.5. IR (ATR): 1724, 1695 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{12}O_4, M]^+$ 256.0736 found 256.0733

Phenyl 4-methoxybenzoate: pale brown crystal. (Table 1.4., **4ar**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 6.7 Hz, 2 H), 7.18 – 7.09 (m, 3 H), 6.89 (d, *J* = 7.7 Hz, 2 H), 3.78 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.8, 151.0, 132.2, 129.4, 125.6, 121.8, 121.7, 113.8, 55.4. IR (ATR): 1732 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{12}O_3, M]^+$ 228.0786 found 228.0782, m.p.: 74 °C

3,5-Dimethylphenyl 4-methoxybenzoate: pale brown solid. (Table 1.4., **4as**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.78 (s, 1 H), 6.72 (s, 2 H), 3.76 (s, 3 H), 2.23 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.7, 150.9, 139.1, 132.1, 127.4, 121.9, 119.3, 113.7, 55.4, 21.2. IR (ATR): 1725 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_3, M]^+$ 256.1099 found 256.1103, m.p.: 62 °C

4−Chlorophenyl 4−methoxybenzoate: pale brown crystal. (Table 1.4., **4at**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 5.7 Hz, 2 H), 7.23 (d, J = 5.6 Hz, 2 H), 7.02 (d, J = 5.6 Hz, 2 H), 6.84 (d, J = 5.8 Hz, 2 H), 3.74 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.9, 149.4, 132.2, 130.9, 129.3, 123.1, 121.3, 113.8, 55.4. IR (ATR): 1728 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{11}O_3Cl, M]^+$ 262.0397 found 262.0400, m.p.: 96 °C

4−Methoxyphenyl 4−methoxybenzoate: pale brown crystal. (Table 1.4., **4au**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.6 Hz, 2 H), 7.02 (d, J = 8.7 Hz, 2 H), 6.85 (dd, J = 16.4, 8.7 Hz, 4 H), 3.77 (s, 3 H), 3.70 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.7, 157.1, 144.4, 132.1, 122.4, 121.8, 114.4, 113.7, 55.46, 55.40. IR (ATR): 1728 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{14}O_4, M]^+$ 258.0892 found 258.0890, m.p.: 124 °C

4−Nitrophenyl 4−methoxybenzoate: pale brown crystal. (Table 1.4., **4av**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 2 H), 8.07 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 9.0 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.9, 155.9,

145.2, 132.5, 125.2, 122.6, 120.7, 114.0, 55.6. IR (ATR): 1735 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{11}O_5N, M]^+$ 273.0637 found 273.0639, m.p.: 167 °C

4-(tert-Butyl)phenyl 4-methoxybenzoate: pale brown crystal. (Table 1.4., **4aw**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 2 H), 7.34 (d, J = 7.6 Hz, 2 H), 7.04 (d, J = 7.4 Hz, 2 H), 6.89 (d, J = 7.9 Hz, 2 H), 3.79 (s, 3 H), 1.25 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.8, 148.6, 148.4, 132.2, 126.3, 122.0, 121.0, 113.7, 55.4, 34.4, 31.4. IR (ATR): 1729 cm^{-1}, HRMS (EI) calc. for $[C_{18}H_{20}O_3, M]^+$ 284.1412 found 284.1411, m.p.: 103 °C

2,6-Dimethoxyphenyl 4-methoxybenzoate: pale brown crystal. (Table 1.4., **4ax**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 163.6, 152.5, 132.4, 128.9, 126.1, 121.7, 113.6, 104.9, 56.1, 55.4. IR (ATR): 1734 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_5, M]^+$ 288.0998 found 288.0999, m.p.: 119 °C

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Chapter 2. Rhodium−catalyzed synthesis of chiral α−alkylated ketones from alkynes with benzyl alcohols.

2.1. Introduction

The α−alkylation of ketones is one of the most attractive method for creating a new carbon−carbon bond. Aryl ketone is important in pharmaceutical and bioactive chemistry field.[1] Especially, α−alkylated ketone has more significance due to its possibility of possessing a chirality center to the α−position of the ketone group. In recent years, significant efforts have been devoted to synthesize α−alkylated ketones from alkyne with alkylating agents.[2] However, only terminal alkyne could be directly functionalized to form α−alkylated ketone.[3]

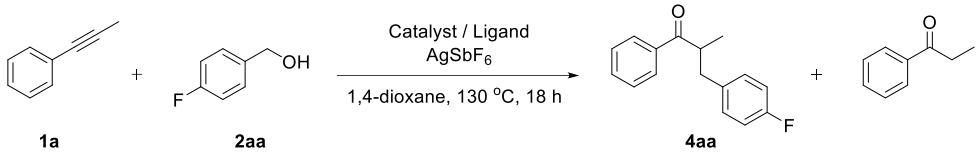
Therefore, owing to such that limitation, we have focused on the development of a direct functionalization of alkyne including internal alkyne. As a consequence, our research suggests that atom economic direct functionalization of alkyne using alcohol as a both hydration and alkylation source.

2.2. Result and Discussion

The reaction of 1-phenyl-1-propyne (**1a**) with 4-fluorobenzyl alcohol (**2aa**) in the presence of $[Rh(COD)Cl]_2$ (2 mol%), BINAP [BINAP = (±)-bis(diphenylphosphino)-1,1'-binaphthyl] (4 mol%) and silver hexafluoroantimonate (20 mol%) at 130 °C was chosen as the synthetic model. This afforded the α-alkylated ketone product, 3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one (**4aa**).

We screened different metals and ligands (Table 2.1.). Without metal and ligand, the reaction did not occur (entry 1). Other metal catalysts, such as $Cu(OAc)_2$, $NiCl_2$ and $[Ir(COD)Cl]_2$, had no effect on the product yield (entries 3 ~ 5). The use of bidentate ligands such as dppm and DPEPhos did not aid the yield of the reaction (entries 10 and 11). Therefore we chose (±)-BINAP as the optimized ligand for its chirality that might give chiral selectivity to the ketone's α-position (entry 8). However, the chiral character of the ligand did not have an effect on chiral selectivity of the product (entry 9). In addition, hydrated propiophenone was observed as a by-product. It seemed that the presence of water might hydrate alkyne to form propiophenone.

Table 2.1. Catalyst and ligand screening data[a]

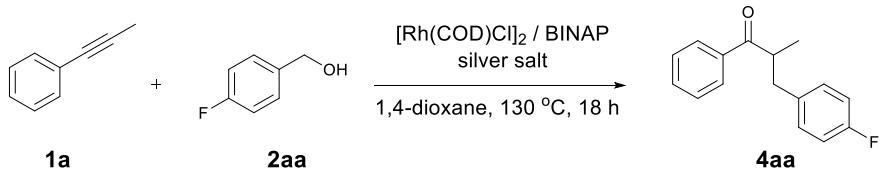


entry	Catalyst	Ligand	Yield[b]
1	none	none	trace
2	none	(±)−BINAP	trace
3	$Cu(OAc)_2$ 4 mol%	(±)−BINAP	11
4	$NiCl_2$ 4 mol%	(±)−BINAP	25
5	$[Ir(COD)Cl]_2$ 2 mol%	(±)−BINAP	38
6	$Pd(OAc)_2$ 4 mol%	(±)−BINAP	43
7	$PtCl_2$ 4 mol%	(±)−BINAP	47
8	$[Rh(COD)Cl]_2$ 2 mol%	(±)−BINAP	52
9	$[Rh(COD)Cl]_2$ 2 mol%	(S)−BINAP	53 (50:50) [c]
10	$[Rh(COD)Cl]_2$ 2 mol%	dppm[d]	50
11	$[Rh(COD)Cl]_2$ 2 mol%	DPEPhos[e]	40

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (2 mol%), (±)−BINAP [(±)−BINAP = (±)−Bis(diphenylphosphino)−1,1'−binaphthyl] (4 mol%), 0.5 mmol of **1a**, 1 equiv. of **2aa**, 0.2 equiv. of $AgSbF_6$, and 1.5 mL of 1,4−dioxane. [b] Isolated yield. [c] The ratio of chiral coumpounds separated by a chiral HPLC.(see Figure 2.5 in experimental section) [d] dppm = 1,1−Bis(diphenylphosphino)methane, [e] DPEPhos = Bis[(2−diphenylphosphinophenyl] ether.

We next screened different silver salts and the amount of them (Table 2.2.). The use of silver salt was essential (entry 1). Other silver salts such as $AgBF_4$, Ag_2CO_3, silver p−tolusulfonate, and $AgPF_6$ did not afford the product (entries 2 ~ 5). Only $AgNTf_2$ and $AgSbF_6$ could afford the desired product (entries 6 and 8). We assumed that silver salt was used for anion exchange of the catalyst. However, excess silver salt had an effect on the product yield (entries 7 ~ 9). Hence, we could assume that silver salt acts as not only exchanging an anion of the catalyst, but also mediating other effect during the reaction.

Table 2.2. Silver salt screening data[a]



entry	Silver salt	Yield[b]
1	none	N.R.
2	$AgBF_4$ 20 mol%	N.R.
3	Ag_2CO_3 20 mol%	N.R.
4	Silver p−tolusulfonate 20 mol%	N.R.
5	$AgPF_6$ 20 mol%	N.R.
6	$AgNTf_2$ [c] 20 mol%	36
7	$AgSbF_6$ 5 mol%	trace
8	$AgSbF_6$ 10 mol%	40
9	$AgSbF_6$ 20 mol%	52

[a] Reaction conditions: $[Rh(COD)Cl]_2$ 2 mol%, (±)−BINAP 4 mol%, 0.5 mmol of **1a**, 1 equiv. of **2aa**, 1.5 mL of 1,4−dioxane. [b] Isolated

yield. [c] $AgNTf_2$: (silver bis(trifluoromethanesulfonyl)imide)

We next screened various solvents and reaction temperatures (Table 2.3.). The noticeable thing was that only ether solvents like 1,4-dioxane and diglyme could afford the product (entries 5 and 10). Also, the reaction requires at least above 100 °C (entry 7).

Table 2.3. Solvent and Temperature screening data[a]

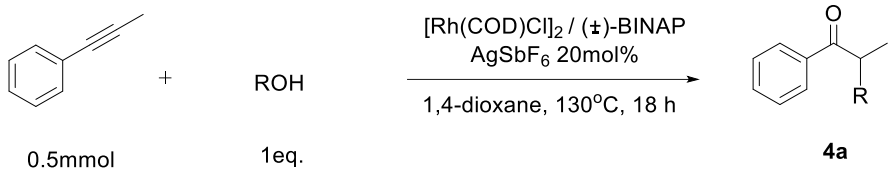
entry	Solvent	Temperature (℃)	Yield[b]
1	DMA	130	N.R.
2	DMF	130	N.R.
3	DMSO	130	N.R.
4	toluene	130	N.R.
5	diglyme [c]	130	21
6	1,4-dioxane	90	N.R.
7	1,4-dioxane	100	17
8	1,4-dioxane	110	38
9	1,4-dioxane	120	47
10	1,4-dioxane	130	52

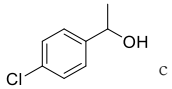
[a] Reaction conditions: $[Rh(COD)Cl]_2$ 2 mol%, (±)-BINAP 4 mol%, 0.5 mmol of **1a**, 1 equiv. of **2aa**. [b] Isolated yield. [c] diglyme = diethylene glycol dimethyl ether

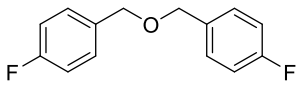
We next screened various alcohols to figure out the mechanism of the reaction (Table 2.4.). No product was formed with both 1° and 2° alcohols (entries 1 ~ 3). Also, we observed that the only benzyl alcohol could afford the product even if the alcohol is the secondary alcohol (entries 2 and 5). It reveals that the catalytic cycle requires a benzylic position during the reaction. Especially, an aliphatic alcohol converted an alkyne to propiophenone and remained as a dehydrated ether compound itself (entries 1 and 3). The c-hexanol formed hydrated propiophenone and remained as a dehydrated form of c-hexene (entry 2). These observations suggest that the reaction undergoes via an ether intermediate derived from an alcohol. We next synthesized 4,4'-(oxybis(methylene))bis(fluorobenzene) (2ab) to figure out the role of the ether intermediate. We used 2ab instead of 4-fluorobenzyl alcohol and added 0.5 equivalent of water to assist the action of the generated water during the ether formation (entry 6). The desired product was formed and the yield of the product decreased slightly due to its high initial concentration of the water. Even without the addition of the water, the desired product was formed (entry 7). We assumed that the trace amount of the moisture in 1,4-dioxane assisted the reaction. Thus, we added activated molecular sieve(4Å, 50mg) to remove moisture in 1,4-dioxane and water produced during the reaction (entry 8). No product was formed in the presence of the molecular sieve. Moreover, the same result was obtained when the molecular sieve was added to the optimal conditions, with 4-fluorobenzyl alcohol (entry 9). Therefore, we concluded that the formation of ether intermediate from alcohol

precedes and the water produced in that process is used as a hydrating source to make an alkyne to a ketone.

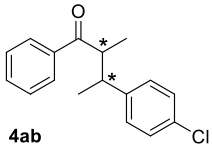
Table 2.4. Alcohol screening data[a]



entry	ROH	Additive	Yield[b]
1	1−Octanol		N.R.
2	c−Hexanol		N.R.
3	Phenethyl alcohol		N.R.
4	4−Fluorobenzyl alcohol		**4aa**, 52
5	 c		**4ab**, 12
6	**2ab** (0.5 eq.)	H_2O(0.5eq.)	**4aa**, 46
7	**2ab** (0.5 eq.)	none	**4aa**, 51
8	**2ab** (0.5 eq.)	MS [d]	N.R.
9	4−Fluorobenzyl alcohol	MS	N.R.



2ab

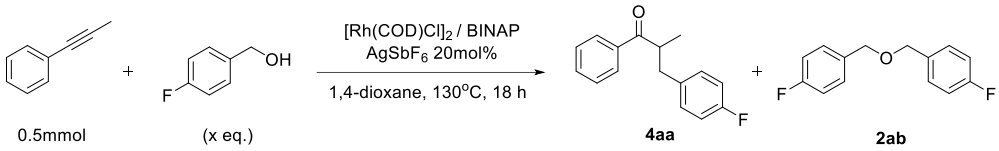


4ab

[a] Reaction conditions: $[Rh(COD)Cl]_2$ 2mol%, (±)−BINAP 4 mol% and 1.5ml of 1,4−dioxane. [b] Isolated yield. [c] 1−(4−Chlorophenyl)−ethanol. [d] MS = powder−type molecular sieve, 4Å.

To examine the role of an alcohol more closely, we studied the relation between the yield of the reaction and the ratio of 4-fluorobenzyl alcohol (Table 2.5.). As the amount of 4-fluorobenzyl alcohol was increased to 1.5 equiv., the yield also increased to 68%(entry 2). A further increase in 4-fluorobenzyl alcohol led to a slight decrease in yield (entry 3). We could observe residual ether compound that remained after the reaction when 2 equiv. of 4-fluorobenzyl alcohol was used. This observation suggests that the concentration of the alcohol could accelerate the rate of forming an ether compound and it could be used as a hydrating and alkylating source until all of the alkyne is consumed.

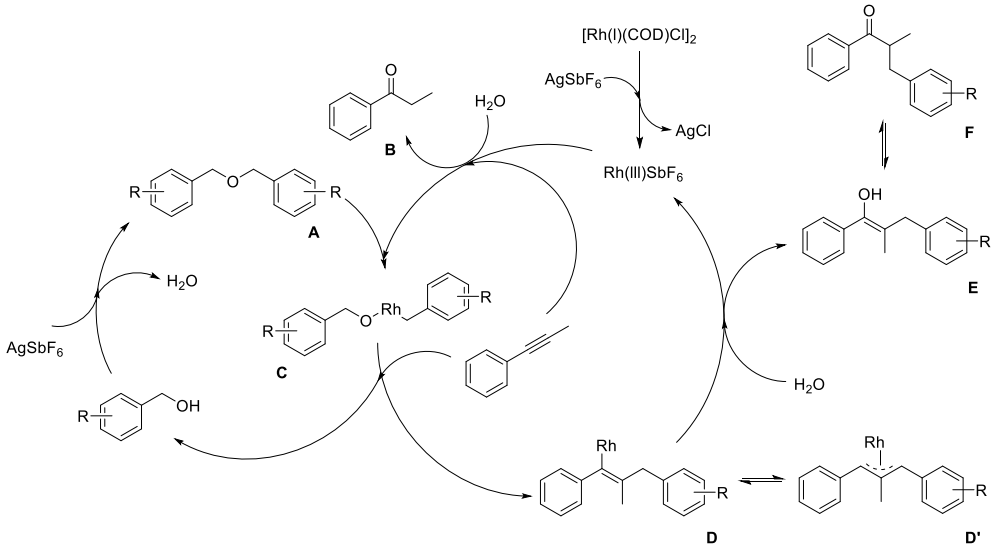
Table 2.5. Yield dependence upon the ratio of 4-fluorobenzyl alcohol[a]



entry	4-Fluorobenzyl alcohol (x eq.)	Yield[b]
1	1.0	52
2	1.5	68
3	2.0	60[c]

[a] Reaction conditions: 2 mol% of $[Rh(COD)Cl]_2$, 4 mol% of (±)-BINAP, and 1.5 mL of 1,4-dioxane. [b] Isolated yield. [c] **2ab** was observed

Scheme 2.1. Proposed reaction mechanism



On the basis of the experimental results, together with previous studies[4], a plausible reaction mechanism can be drawn in Scheme 2.1 for the synthesis of α−alkylated ketone from an alkyne with benzyl alcohols in the presence of an $[Rh(COD)Cl]_2$/DPEPhos catalytic system with an assistance of $AgSbF_6$. It is known that the ether intermediate (A) could be formed from a benzyl alcohol with the assistance of metal and silver salts.[4] In this pathway, however, water released during the formation of an ether intermediate might be used to make only hydrated ketone (B) as a by−product if it reacts with unactivated alkyne first. In the presence of the rhodium/silver catalytic system, we expect that the rhodium catalyst mediates the cleavage of ether compound as an intermediate(C). The alkylation might occur because the rhodium−ether intermediate activates the alkyne. Subsequently, intermediate π−allene complexes (D and D') react with water leading to the formation of an enol compound (E).

For that reason, the product(F) loses its chiral selectivity through a keto-enol tautomerization.

2.3. Conclusion

We have developed an atom economic synthetic method of chiral α-alkylated ketones from alkynes with benzyl alcohols in the presence of an $[Rh(COD)Cl]_2$/DPEPhos catalytic system with an assistance of $AgSbF_6$. With a silver salt, the benzyl alcohols form an ether intermediate itself as they release water. The water released during the reaction, it was used to hydrate the alkyne to ketone. Moreover, ether intermediate cleavages itself again and was used to alkylate the α-position of the ketone. Only in the presence of both silver salt and the rhodium catalyst, high yields of the α-alkylated ketone product was isolated. This occurred because the silver salt assisted the formation of ether and a rhodium catalyst mediated the cleavage of ether to activate the alkyne during the reaction. When aliphatic alcohols were used instead of benzyl alcohols, α-alkylated ketone product was not isolated. Thus, various benzyl alcohols and alkyne substrates are expected to synthesize diverse α-alkylated ketone product. Further mechanistic studies and optimization of the reaction conditions are in progress.

2.4. Experimental Section

1. Chemicals and Reagents

Solvents utilized in this work were obtained from Sigma-Aldrich and Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane, and acetone). 1,4-Dioxane was used with a sure-sealed product from Sigma-Aldrich. *n*-Hexane, diethyl ether, and ethyl acetate were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. $[Rh(COD)Cl]_2$ were purchased from Pressure Chem. (S)-BINAP ((S)-Bis(diphenylphosphino)-1,1'-binaphthyl) were purchased from Strem Chemicals. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

2. Physical Methods

^1H and ^{13}C NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz and 100 MHz, respectively) and Varian (500 MHz and 125 MHz, respectively) spectrometer. ^1H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (7.26 ppm) and reported

as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass Selective detector. Analytical condition – initial temperature: 50 °C, raising temperature 10 °C / min, final temperature : 280 °C, He gas, Pressure : 7.56 psi, Total flow : 53.7 mL / min. Chiral High Performance Liquid Chromatography analysis was performed with a HP-1100 series with a Chiralcel® OD-H column.

3. Experimental Procedures

B. General Procedure for the entries reported Table 2,1, from alkyne and benzyl alcohol.

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 5 mg (c.a. 2 mol%) of catalyst, 12.5 mg of ligand (4 mol%) 0.5 mmol of alkyne, 1.5 equiv (83 uL) of benzyl alcohol, 0.2 equiv of $AgSbF_6$ and 1.5 mL of 1,4-dioxane. The mixture was stirred at 130 °C for 18 h. The reaction mixture was filtered with celite and finally evaporated under reduced pressure. The concentrated reaction

mixture was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether) to afford the product.

4. Characterization Data for Isolated Products

3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one (Table 2.1. **4aa**)

Transparent liquid ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.12 – 7.01 (m, 2H), 6.85 (t, J = 8.5 Hz, 2H), 3.70 – 3.56 (m, 1H), 3.06 (dd, J = 13.8, 6.7 Hz, 1H), 2.60 (dd, J = 13.8, 7.4 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H). ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.65, δ 161.58 (d, J_{C-F} = 244.1 Hz), 136.12 (d, $^{4}J_{C-F}$ = 106.4 Hz), 133.12, 130.58 (d, $^{3}J_{C-F}$ = 7.9 Hz), 128.79, 128.36, 115.25 (d, $^{2}J_{C-F}$ = 21.2 Hz), 42.97, 38.64, 17.67. ; **HRMS** (EI^{+}): m/z calcd for $[C_{16}H_{15}FO]^{+}$: 242.1107, found 242.1110.

3-(4-chlorophenyl)-2-methyl-1-phenylbutan-1-one (Table 2.4. **4ab**)

White crystal ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01, 8.00, 7.61, 7.59, 7.58, 7.51, 7.50, 7.48, 7.30, 7.29, 7.26, 7.18, 7.17, 3.65, 3.63, 3.62, 3.61, 3.60, 3.59, 3.20, 3.18, 3.17, 3.16, 3.15, 3.14, 1.19, 1.18, 0.94, 0.93. ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.42, 143.58, 137.40,

133.29, 132.19, 129.21, 128.89, 128.74, 128.40, 47.27, 42.72, 21.07, 17.38.

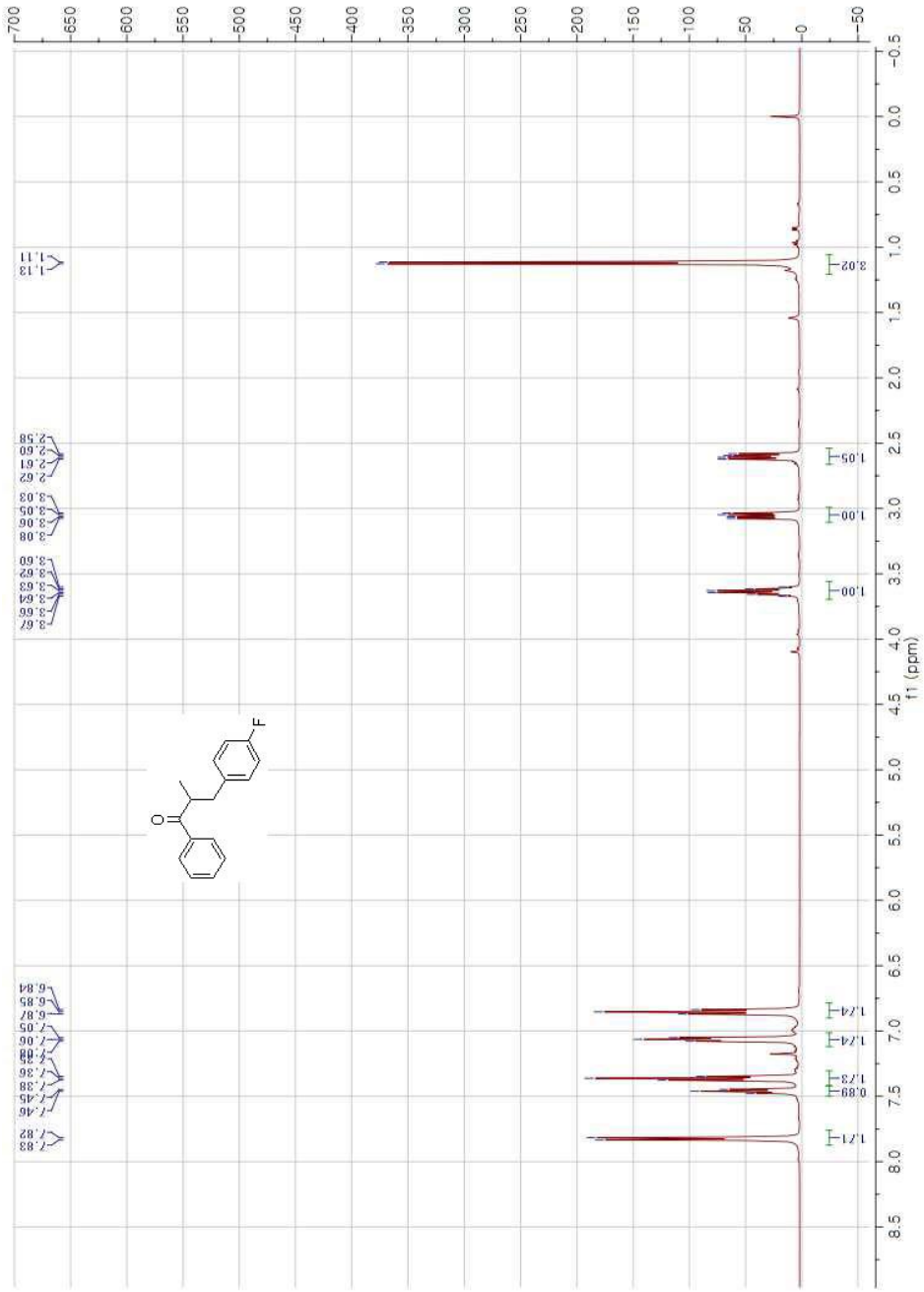


Figure 2.1. ^{1}H NMR specrta of 3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one (**4aa**)

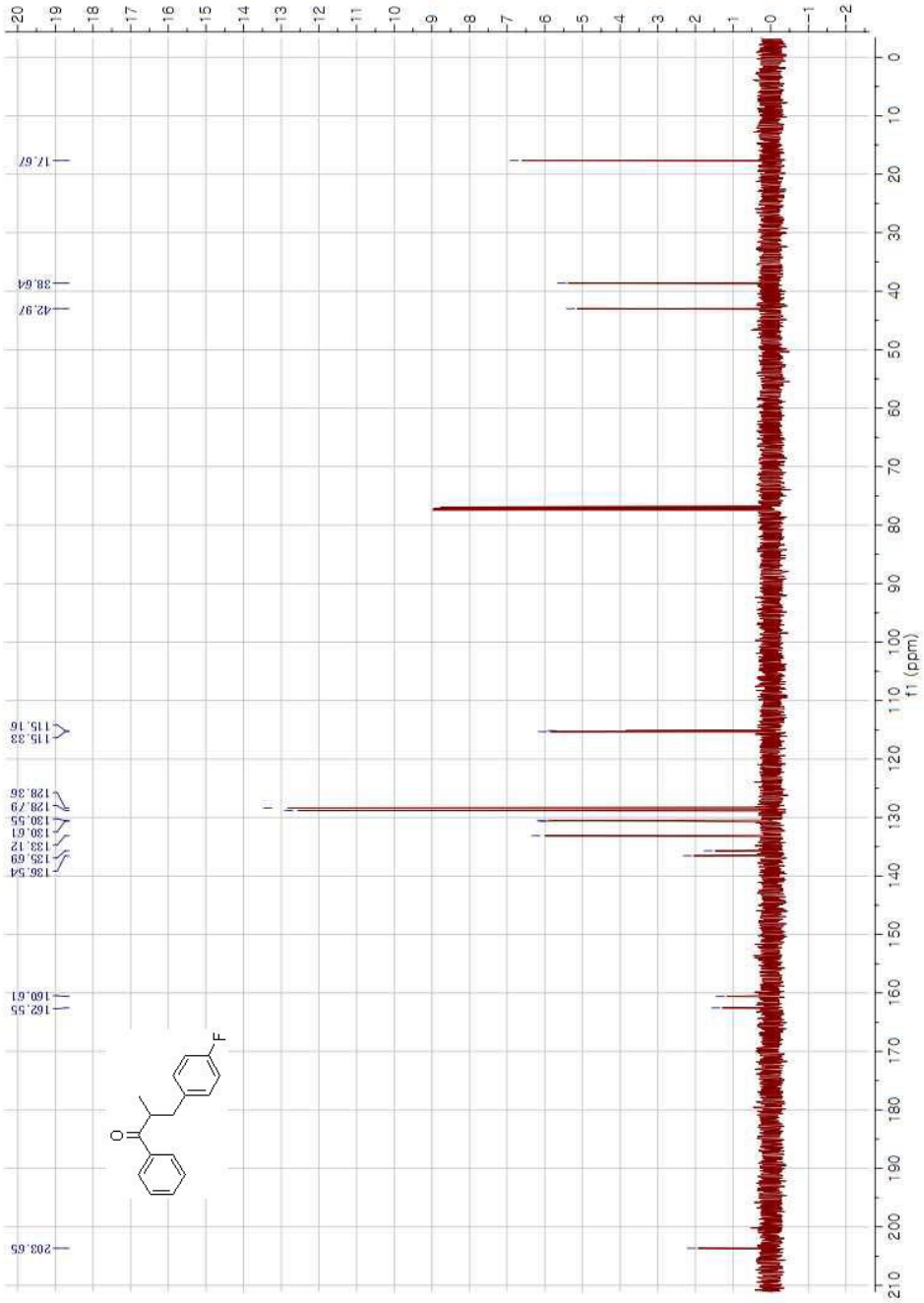


Figure 2.2. ^{13}C NMR specrta of 3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one (**4aa**)

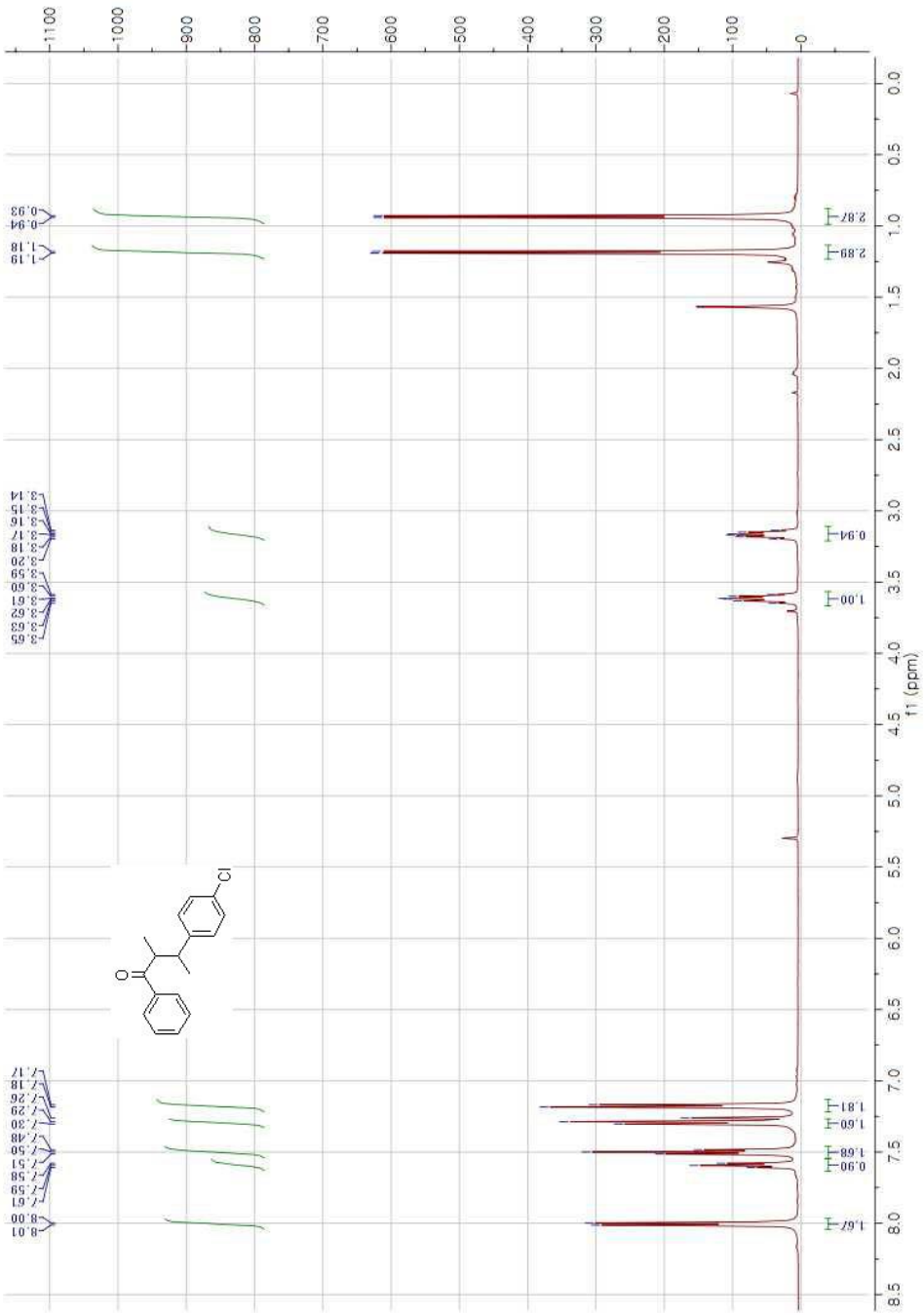


Figure 2.3. ^{1}H NMR specrta of 3-(4-chlorophenyl)-2-methyl-1-phenylbutan-1-one (Table 2.4. **4ab**)

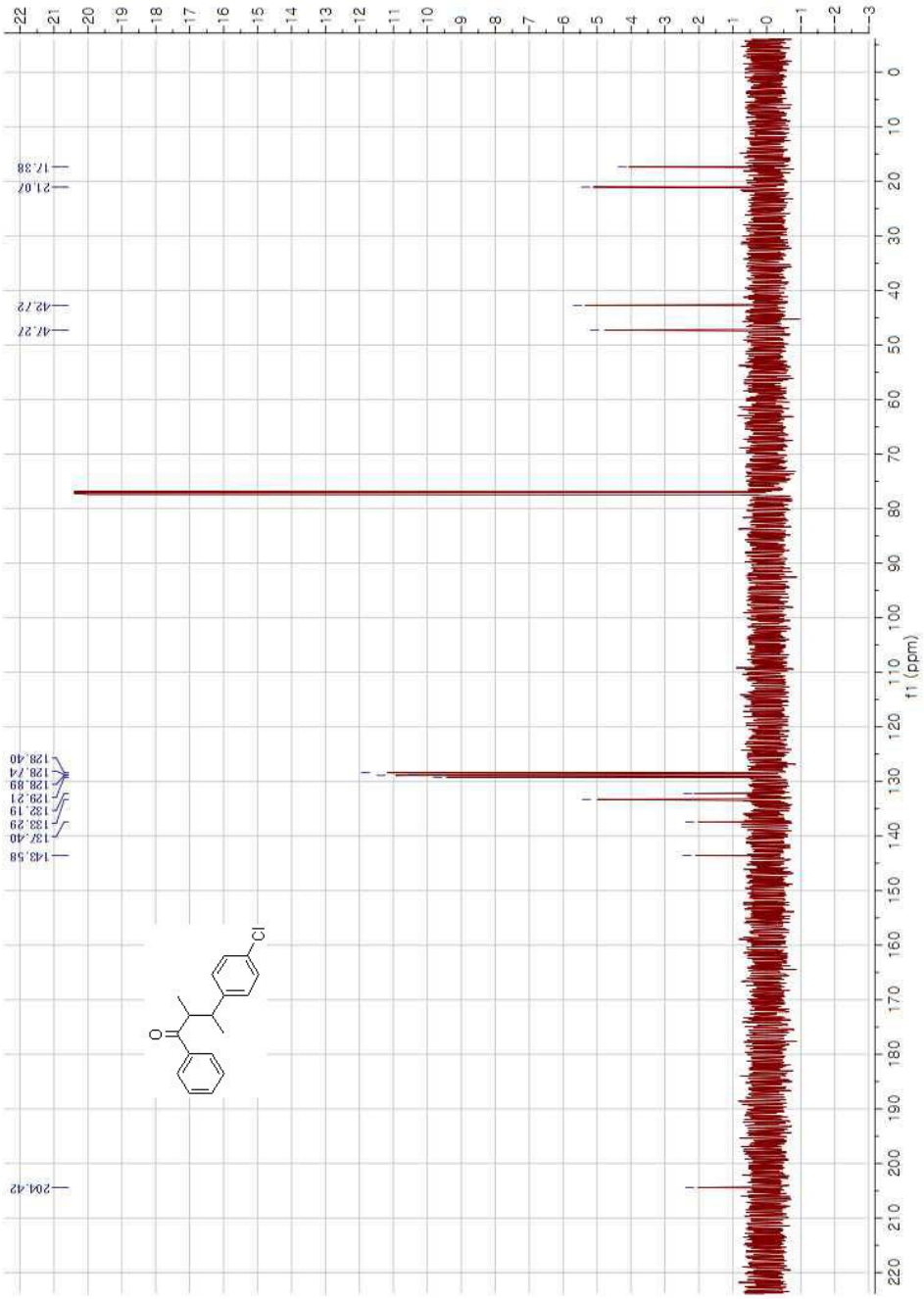
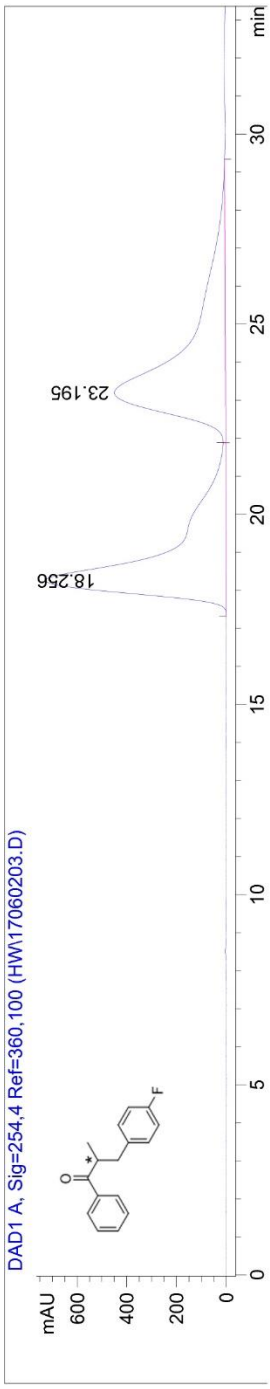


Figure 2.4. ^{13}C NMR specrta of 3-(4-chlorophenyl)-2-methyl-1-phenylbutan-1-one (**4ab**)

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                         Area Percent Report
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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width    Area      Height     Area
  #   [min]      [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|---------|
   1  18.256 BB   1.0492 5.32963e4   725.35150  50.3302
   2  23.195 BB   1.6825 5.25969e4   446.44159  49.6698

Totals :                1.05893e5  1171.79309

 Results obtained with enhanced integrator!
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Figure 2.5. ^{13}C NMR specrta of 3-(4-chlorophenyl)-2-methyl-1-phenylbutan-1-one (**4ab**)

2.5. Reference

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국문초록

로듐 촉매를 사용한 아릴할라이드 화합물의 알콕시카르보닐화 반응을 개발하였다. 이때에 알데하이드의 보조 혹은 없이 알코올을 일산화탄소 와 친핵체 공급원으로 사용하였다. 이 반응을 통해 유해한 일산화탄소를 사용하지 않고 카르보닐화 반응을 보낼 수 있었고, 알데하이드의 보조와 함께 다양한 페놀을 사용한 페녹시카보닐레이션 반응 또한 일어남을 확인하였다.

또한, 로듐 촉매를 사용하여 벤질알코올을 물과 알킬화 공급원 모두로 이용해 알카인으로부터 알파 위치에 알킬기가 치환된 키톤 화합물을 합성하는 방법을 개발하였다. 반응은 은 화합물의 존재 하에 알코올로부터 에테르 중간체를 거쳐 반응이 일어남을 확인할 수 있었다.

Keywords: 로듐, 에스터, 카르보닐화 반응, 알코올, 알카인, 카이랄, 알파탄소가 친핵체화된 카르보닐기, 수화 반응, 알킬화 반응, 첨가반응

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