Accepted Manuscript

RhCl(CO)(PPh₃)₂ catalyzed α -alkylation of ketones with alcohols

Rui Wang, Lina Huang, Zhengyin Du, Hua Feng

PII: S0022-328X(17)30370-4

DOI: 10.1016/j.jorganchem.2017.05.055

Reference: JOM 19981

To appear in: Journal of Organometallic Chemistry

Received Date: 14 February 2017

Revised Date: 22 May 2017

Accepted Date: 26 May 2017

Please cite this article as: R. Wang, L. Huang, Z. Du, H. Feng, RhCl(CO)(PPh₃)₂ catalyzed α -alkylation of ketones with alcohols, *Journal of Organometallic Chemistry* (2017), doi: 10.1016/j.jorganchem.2017.05.055.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Graphical Abstract

 $RhCl(CO)(PPh_3)_2$ catalyzed α -alkylation of ketones with alcohols

Rui Wang, Lina Huang and Zhengyin Du*

A simple and efficient method for α -alkylation of ketones with primary alcohols catalyzed by RhCl(CO)(PPh₃)₂ without additional additives under mild conditions is developed. It has a wide substrate scope, a high atom-efficiency and chemoselectivity. It is an environmentally friendly method to build C-C bond because water is the only byproduct.



n=1,2

ACCEPTED MANUSCRIPT **RhCl(CO)(PPh₃)₂ catalyzed α-alkylation of ketones with** alcohols

Rui Wang,[†] Lina Huang,[†] Zhengyin Du* and Hua Feng*

Key Laboratory of Eco-Environment Related Polymer Materials of Ministry of Education, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. China.

* Phone and Fax: +86-931-7971989; E-mail: clinton du@126.com

[†] They contributed equally to this work.

Abstract. A simple and efficient method for α -alkylation of ketones with primary alcohols catalyzed by RhCl(CO)(PPh₃)₂ without additional additives under mild conditions is developed. It has a wide substrate scope, high atom-efficiency and chemoselectivity. It is an environmentally friendly method to build C-C bond because water is the only byproduct.

Keywords: Alkylation; Ketones; Alcohols; Hydrogen transfer; Cross coupling

1. Introduction

α-Alkylation of ketones has been known as a pivotal method for a carbon-carbon bond formation in organic synthesis.^[1,2] Transition metal-catalyzed cross-coupling reaction between ketones and alcohols is the most attractive strategy for the α -alkylation of ketones not only from its high atom efficiency but also from water as only byproduct, which is in accordance with sustainable development in views of economy and environment.^[3,4] This reaction is regarded as proceeding via hydrogen transfer strategy and alcohols are the source of hydrogen, which has been paid much attention in recent years.^[5] In connection with this strategy, many transition metals, such as ruthenium^[6] and iridium complexes^[7] have been successfully used as homogeneous catalysts in this transformation and good results were obtained. Supported heterogeneous palladium catalysts, such as Pd/C,^[8] Pd NPs/AlO(OH),^[9] Pd NPs/viologen,^[10] $Pd(II)/SiO_2^{[11]}$ are also applied for α -alkylation of ketones with primary alcohols. Most of these catalysts can be recycled and reused for several times. For instance, Ni NPs^[12] and Ag/Mo oxides^[13] are reported to be good and efficient reusable catalysts for this reaction. However, harsh reaction temperature of up to 140 °C was required^[7a,11] and over-reduction of target products and substrates was often observed.^[8] Also, an additional hydrogen acceptor, 1-dodecene or 1-decene, must be added to promote the reaction.^[8] In order to overcome these disadvantages and to realize regioselective α -alkylation of methyl ketone derivatives with primary alcohols, Yus et al^[14] reported an osmium catalyzed α -alkylation of methyl ketones with alcohols through borrowing hydrogen

methodology under mild conditions and satisfactory results were achieved. This cross coupling reaction can also be catalyzed by iron complex^[15] and Fe(OTf)₃^[16] to produce aimed product selectively. Besides, metal-free organocatalysis of N-heterocyclic carbenes and a large number of t-BuOLi were demonstrated to be efficient for a-alkylation of ketones with primary alcohols.^[17] Whatever, this kind of reaction always suffered from excess base usage, long reaction time consumption, and innert atmosphere requirement.

Compared with other heavy metal salts, rhodium has been proved to be low toxic and rhodium complexes bearing NHCs have also been widely used as catalysts for transfer hydrogenation and crosscoupling reaction in organic synthesis.^[18] In 2013, tris(acetylacetonato)rhodium(III) was used as a catalyst for the α -alkylation of ketones with primary alcohols followed by transfer hydrogenation to furnish reductive coupling products in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as ligand.^[19] Unfortunately, the reaction cannot be stopped on the stage of alkylated ketone products. In 2014, Donohoe and coworkers^[20] reported a [Cp*RhCl₂]₂ catalyzed ketone methylation reaction using methanol as alkylating reagent to form α -branched products under mild conditions. Except the above-mentioned references, few literature in connection with rhodium catalyst for α -alkylation of ketones was reported.

With our continuous interest in transitional metalcatalyzed efficient cross coupling reaction^[21] and alkylation reaction with alcohols as green alkylating reagents,^[22] we herein report a simple and efficient α alkylation coupling reaction of ketones with primary alcohols catalyzed by RhCl(CO)(PPh₃)₂ in the

presence of KOH as base and 1,4-dioxane as solvent at 95 °C. The corresponding alkylated ketones as unique products were obtained in good yields. To the best of our knowledge, this is the fisrt example of Rh (I) complex-catalyzed α -alkylation of ketones with primary alcohols to form alkylated ketones exclusively.

2. Results and discussion

We initiated our studies with the screen of reaction conditions in the coupling of acetophenone (1a) with benzyl alcohol (2a), as seen in Table 1.

Table 1. Optimization of the reaction conditions^{a)}

		~				
	+	∫ `OH _ B	Catalyst			
1a	ž	2a		3a	\checkmark	
Entry	Catalyst	Base	Solvent	Time	Yield	_
-	-			(h)	(%)	
1	FeCl ₃	K ₂ CO ₃	Toluene	20		_
2	NiCl ₂	K_2CO_3	Toluene	20	16	
3	$CuCl_2$	K_2CO_3	Toluene	20	20	
4 ^{b)}	Cu NPs	K_2CO_3	Toluene	20	9	
5	$PdCl_2$	K_2CO_3	Toluene	15	_	
6	$PdCl_2$	Cs_2CO_3	Toluene	18	25	7
7	Pd NPs	Cs_2CO_3	PEG-2000	15	63	
8	RhCl(CO	KOH	1,4-	10	81	
	$)(PPh_3)_2$		Dioxane			
9	RhCl(CO	KOtBu	1,4-	8	56	
	$(PPh_3)_2$		Dioxane			
10	RhCl(CO	Et ₃ N	1,4-	8	\rightarrow	
	$)(PPh_3)_2$		Dioxane			
11 ^{c)}	RhCl(CO	KOH	1,4-	9	91	
	$(PPh_3)_2$		Dioxane			
12 ^{d)}	RhCl(CO	KOH	1,4-	9	91	
	$(PPh_3)_2$		Dioxane			
13 ^{e)}	RhCl(CO	KOH	1,4-	12	87	
	$(PPh_3)_2$		Dioxane			
14 ^{c)}	RhCl ₃ ·3	KOH	1,4-	12	36	
	H_2O		Dioxane			

^{a)} Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst (2 mol%), base (1.0 mmol), solvent (3 mL), 95 °C. Yield is isolated yield. ^{b)} Cu NPs (10 mol%). ^{c)} **2a** (1.5 mmol), base (2.0 mmol). ^{d)} **2a** (1.5 mmol), base (2.0 mmol), catalyst (3 mol%). ^{e)} **2a** (1.5 mmol), base (1.5 mmol).

At first, we chosed different Lewis acids as catalysts (2 mol%) and K_2CO_3 as a base to conduct this reaction in toluene at 95 °C. The results show that FeCl₃ has no catalytic effect despite extending the reaction time tremendously (Table 1, entry 1). When NiCl₂ and CuCl₂ were used as catalysts, 16% and 20% yields of the aimed product **3a** were obtained, respectively (Table 1, entries 2 and 3). When replacing CuCl₂ with 10 mol% of copper nanoparticles (Cu NPs), only 9 % yield of **3a** was obtained (Table 1, entry 4). Then PdCl₂ was used as

the catalyst and it is found that there was no reaction took place (Table 1, entry 5). However, when potassium carbonate was replaced by cesium carbonate, 25% yield of 3a was obtained (Table 1, entry 6). When the reaction was catalyzed by palladium nanoparticles (Pd NPs), in situ generated from palladium chloride in PEG-2000^[21,23] at 95 °C, a moderate yield of 63% was achieved and there is no improvement of the yield when increasing the amount of Pd NPs and the reaction time (Table 1, entry 7). So we have to screen other transition metal catalysts. Surprisingly, when the reaction was catalyzed by 2 mol% of RhCl(CO)(PPh₃)₂, a satisfying yield of 81% was given in the presence of KOH in 1,4-dioxane at 95 °C (Table 1, entry 8). To investigate the base influence, potassium tert-butoxide and triethylamine were also examined and unsatisfactory results were obtained (Table 1, entries 9 and 10). Subsequently, we explored the effect of substrates ratio and the amount of the catalyst and the base. It is found that the use of 1.5 equivalents of benzyl alcohol and 2 equivalents of KOH resulted in an higher product yield (91%) in shorter reaction time (Table 1, entry 11). Increasing the amount of the catalyst from 2 mol% to 3 mol% could not improve the product yield (Table 1, entry 12) whereas decreasing the amount of the base to 1.5 equivalents caused a slight decrease of 3a (Table 1, entry 13). Rhodium (III) chloride hydrate was also employed as a catalyst for the reaction but only 36% yield of 3a was gained under the same reaction conditions (Table 1, entry 14). It is evident that ligands play a very important role in this reaction. In comparison with other catalysts, the good catalysis of RhCl(CO)(PPh₃)₂ might be due to the good exchange ability betwween hydrogen atom and ligand to form rhodium hydride complex which is key active species in catalytic cycle.

Under the optimized conditions, we tried to extend this methodology to a series of ketones and alcohols. The results are listed in Table 2. It is obvious that our catalytic system works well for the coupling reactions of various α-methyl(methylene)ketones with alcohols to achieve the corresponding α -alkylated ketone products in moderate to excellent yield. Electron-rich and electron-deficient acetophenones, such as 4methyl-, 4-chloro-, 4-bromo-, 2-methyl-, and 3methoxyacetophenone, could react smoothly with benzyl alcohol, 4-methyl- and 4-fluorobenzyl alcohols to form a series of α -benzylated acetophenones with good yields in range of 61-84% (Table 2, entries 2-10). Exchanging the substitution on the aryl ring of arylmethylketones and benzyl alcohols has no significant influence on the yield of aimed products. To examine the reactivity of aliphatic alcohols, we used ethanol and 1-butanol as alkylating reagents to react with acetophenone and 4-methylacetophenone, respectively, and found that the corresponding

CCEPTED MANUSCRIPT

coupling products 3k and 3l were obtained in the yield of 56% and 52%, respectively (Table 2, entries 11 and 12). These results proved that the hydrogen transfer reactivity of aliphatic alcohols is inferior to that of benzyl alcohols. To investigate the scope of ketones in this reaction, cyclopentanone and cycohexanone were also studied under the same reaction conditions to furnish the corresponding α alkylation of cycloketones with benzyl alcohol. The obtained moderate product yields (63% of 3m and 58% of **3n**) showed that the reactivity of arylmethylketones is superior to that of cyclanones. (Table 2, entries 13 and 14). It is need to emphasize that, in all cases, water is the exclusive byproduct and deeply reductive products, ketals and hemiketals of aalkylated ketones were not found.

Table 2. α -Alkylation of methyl ketone derivatives with alcohols catalyzed by RhCl(CO)(PPh₃)₂^{a)}

O U						
	+ R ₂ OH	Dioxane, 95		\sim R ₂		
R'1	2		~	3		
Entry	Ketone	Alcohol	Product	Yield		
				(%)		
1	© ↓	ОН		91		
2	, C	ОН	Ja o o	84		
3		ОН		63		
4	, solution of the second secon	F		61		
5	ci -	ОН		74		
6	CI C	ОН	3f	68		
7	Br	Стон	Br J	66		
8	Br	С	Br 3h	64		
9	o L	ОН		72		
10	H ₃ CO	ОН		78		
11 ^{b)}	o C	∕∩он		56		
			3k			



^{a)} Ketone (1.0 mmol), alcohol (1.5 mmol), RhCl(CO)(PPh₃)₂ (2 mol%), KOH (2.0 mmol), 1,4-dioxane (3 mL) at 95 °C for 9 h. Yield is isolated yield. ^{b)}Alcohol (2.0 mmol).

For the reaction mechanism of α -alkylation of ketones with primary alcohols, based on previous report,^[24] a transitional metal-catalyzed hydrogen transfer process is proposed with the reaction of acetophenone and benzyl alcohol as an example, as seen in Scheme 1. At first, benzyl alcohol is catalytically dehydrogenated to form benzaldehyde and the deprived active hydrogens are transferred to the catalyst to form rhodium hydride complex [RhH₂]. Then, the Aldol condensation occurs between acetophenone and benzaledyde to give chalcone. Finally, chalcone is further hydrogenated by [RhH₂] species to afford the aimed coupling product. The detailed mechanism of this reaction is still under investigation.



Scheme 1. Mechanism of Rh-catalyzed α -alkylation of acetophenone with benzyl alcohol.

3. Conclusion

In summary, we have developed a simple and efficient method on RhCl(CO)(PPh₃)₂-catalyzed α -alkylation of α -methyl(methylene) ketones with primary alcohols under mild conditions. This method has been proved to have a wide substrate scope and broad functional group tolerance. More importantly, the reaction is highly atomeconomical and chemoselective. There are no deeply reductive coupling and ketalization byproducts found in our reaction and completely no need for the addition of any auxiliary hydrogen donors, acceptors and additives in this protocol. It is a potentially useful method to build C-C bond in organic synthesis.

4. Experimental

Ketones (1.0 mmol), alcohols (1.5 mmol), RhCl(CO)(PPh₃)₂ (2 mol%) and bases (2.0 mmol) were added into dioxane (3 mL). The reaction mixture was stirred at 95 °C for completion monitored by TLC. Then the solution was filtered by suction and the solvent was evaporated under reduced pressure. The residue was passed through flash column chromatography on silica gel to give the pure products.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (20702042, 21262028) for financial support.

References

- [1] D. Seebach, Angew. Chem. Int. Ed. 29 (1990) 1320-1367.
- [2] D. H.Camacho, I. Nakamura, B. H. Oh, S. Saito, Y. Yamamoto, Tetrahedron Lett. 43 (2002) 2903-2907.
- [3] J. F. Jenck, F. Agterberg, M. J. Droescher, Green Chem. 6 (2004) 544-556.
- [4] G. W. V. Cave, C. L. Raston, J. L. Scott, Chem. Commun. 21 (2001) 2159-2169.
- [5] (a) Y. Obora, ACS Catal. 4 (2014) 3972-3981; (b) K.
 Shimizu, Catal. Sci. Technol. 5 (2015) 1412-1427.
- [6] (a) C. S. Cho, B. T. Kim, T. J. Kim, S. C. Shim, Tetrahedron Lett. 43 (2002) 7987-7989; (b) R. Martínez, D. J. Ramon, M. Yus, Tetrahedron 62 (2006) 8988-9001; (c) R. Martínez, G. J. Brand, D. J. Ramón, M. Yus, Tetrahedron Lett. 46 (2005) 3683-3686; (d) T. Kuwahara, T. Fukuyama, I. Ryu, Org. Lett. 14 (2012) 4703-4705; (e) F. X. Yan, M. Zhang, X. T Wang, F. Xie, M. M. Chen, H. Jiang, Tetrahedron 70 (2014)1193-1198; (f) O. O. Kovalenko, H. Lundberg, D. Hübner, H. Adolfsson, Eur. J. Org. Chem. 30 (2014) 6639-6642.

[7] (a) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, J. Am. Chem. Soc. 126 (2004) 72-74. (b) D. Wang, K. Zhao, P. Ma, C. Xu, Y. Ding, Tetrahedron Lett. 55 (2014) 7233-7235; (c) S. Bhat, V. Sridharan, Chem. Commun. 48 (2012) 4701-4703; (d) C. Xu, X.-M. Dong, Z.-Q. Wang, X.-Q. Hao, Z. Li, L.-M. Duan, B.-M. Ji, M.-P. Song, J. Organomet. Chem. 700 (2012) 214-218; (e) F. Li, J. Ma, N. Wang, J. Org. Chem. 79 (2014) 10447-10455.

- [8] C. S. Cho, J. Mol, Catal. A: Chem. 240 (2005) 55-60.
- [9] M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala, J. Park, Angew. Chem. 117 (2005) 7073-7075.
- [10] (a) Y. M. A. Yamada, Y. Uozumi, Org. Lett. 8 (2006)
 1375-1378; (b) Y. M. A. Yamada, Y. Uozumi, Tetrahedron 63 (2007) 8492-8498.
- [11] T. T. Dang, S. P. Shan, B. Ramalingam, A. M. Seayad, RSC Adv. 5 (2015) 42399-42406.
- [12] (a) M. Yus, P. Rient, F. Alonso, Synlett. 12 (2007)
 1877-1880; (b) M. Yus, P. Riente, F. Alonso, Eur. J. Org. Chem. 29 (2008) 4908-4914.
- [13] X. Cui, Y. Zhang, F. Shi, Y. Deng, Chem. Eur. J. 17 (2011) 1021-1028.
- [14] M. L. Buil, M. A. Esteruelas, J. Herrero, S. Izquierdo,I. M. Pastor, M. Yus, ACS Catal. 3 (2013) 2072-2075.
- [15] S. Elangovan, J. B. Sortais, M. Beller, C. Darcel, Angew. Chem. Int. Ed. 54 (2015) 14483-14486.
- [16] X. Pan, M. Li, Y. Gu, Chem. Asian J. 9 (2014) 268-274.
- [17] (a) Y.-F. Liang, X.-F. Zhou, S.-Y. Tang, Y.-B Huang, Y.-S. Feng, H.-J Xu, RSC Adv. 3 (2013) 7739-7742;
 (b)Y. Zhu, C. Cai, G. Lu, Helvetica Chim. Acta. 97 (2014) 1666-1671.
- [18] (a) D. Wang, D. Astruc, Chem. Rev. 115 (2015) 6621-6686; (b) D. A. Colby, R. G. Bergman, J. A. Ellman, Chem. Rev. 110 (2010) 624-655.
- [19] (a) P. Satyanarayana, G. M. Reddy, H. Maheswaran,
 M. L. Kantam, Adv. Synth. Catal. 355 (2013) 1859-1867; (b) C. S. Cho, H. J. Seok, S. C. Shim, J. Heterocycl. Chem. 42 (2005) 1219-1222.
- [20] (a) L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy,
 T. J. Donohoe, Angew. Chem. Int. Ed. 53 (2014) 761-

CEPTED MANUSCRIPT

765; (b) X. Yu, Q. Y. Wang, Q. J. Wu, D. W. Wang Russ. J. Gen. Chem. 86 (2016) 178-183.

- [21] (a) F. Gang, G. Xu, T. Dong, L. Yang. Z. Du, Chin. J. Org. Chem. 35 (2015) 1428-1440; (b) G. Xu, Y. Zhang, K. Wang, Y. Fu, Z. Du, J. Chem. Res. 39 (2015) 399-402; (c) W. Zhen, Z. Du, X. Li, Chin. J. Catal. 34 (2013) 679-683; (d) Z. Du, W. Zhou, L. Bai, F. Wang, J.-X. Wang, Synlett 3 (2011) 369-372; (e) Z. Du, W. Zhou, F. Wang, Tetrahedron 67 (2011) 4914-4918. (f) Z. Du, Y. Li, F. Wang, W. Zhou, J.-X. Wang, Tetrahedron Lett. 51 (2010) 1745-1747.
- [22] (a) Z. Du, Y. Yan, Y. Fu, K. Wang, Asian J. Org. Chem. 5 (2016) 812-818; (b) H. Wu, J. Wu, Z. Du, Chin. J. Org. Chem. 37 (2017), DOI:10.6023/cjoc201610034; (c) M. Trifonidou, C. G. Kokotos, Eur. J. Org. Chem. 2012 (2012) 1563-1568.
- [23] T. M. Razler, Y. Hsiao, F. Qian, R. Fu, R. K. Khan, W. Doubleday, J. Org. Chem. 74 (2009) 1381-1384.
- [24] F. Huang, Z. Liu, Z. Yu, Angew. Chem. Int. Ed. 55 (2016) 862-875.

out the second

$RhCl(CO)(PPh_{3})_{2}$ catalyzed $\alpha\mbox{-alkylation}$ of ketones with alcohols

Rui Wang,[†] Lina Huang[†] and Zhengyin Du*

Key Laboratory of Eco-Environment Related Polymer Materials of Ministry of Education, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. China.

* Phone and Fax: +86-931-7971989; E-mail: clinton_du@126.com

[†]They contributed equally to this work.

Highlights

The first example of Rh(I)-catalyzed α -alkylation of ketones with primary alcohols.

Aryl methyl ketons, cyclonones, benzyl and aliphatic alcohols are compatible.

Any auxiliary hydrogen donor, acceptor and additive were not needed.

No deeply reductive coupling and ketalization byproducts were found.

It is an environmentally friendly, high atom-efficiency and chemoselective method.