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Regioselective Intermolecular Coupling Reaction of Arylketones and Alkenes Involving C-H Bond Activation Catalyzed by an In-Situ Formed Cationic Ruthenium-Hydride Complex

Chae S. Yi and **Do W. Lee**
Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201−1881

Abstract

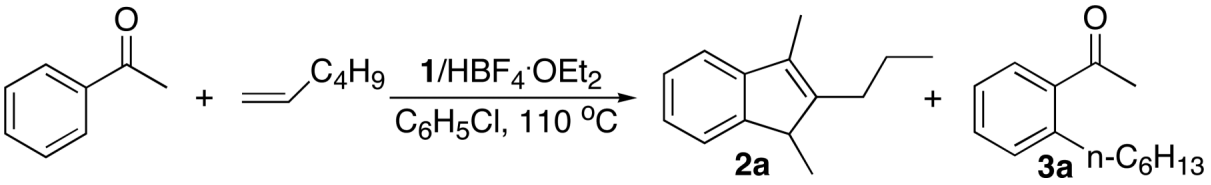
The cationic ruthenium-hydride complex, formed *in-situ* from the treatment of the tetranuclear ruthenium-hydride complex {[$(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)$} with $HBF_4{\cdot}OEt_2$, was found to be a highly effective catalyst for the intermolecular coupling reaction of arylketones and 1-alkenes to give the substituted indene and *ortho*-C–H insertion products. The formation of the indene products was resulted from the initial alkene isomerization followed by regioselective *ortho*-C–H insertion of 2-alkene and the dehydrative cyclization. The preliminary mechanistic studies revealed a rapid and reversible *ortho*-C–H bond activation followed by the rate-limiting C–C bond formation step for the coupling reaction.

Electrophilic late transition metal complexes have been found to be highly effective in mediating unreactive C–H and C–C bond activation reactions, the activity and selectivity patterns of which are often complementary to their neutral counterparts.[1] In a series of seminal reports, electrophilic Pt, Hg and Pd catalysts have been successfully developed and utilized for Shilov's C–H oxidation and functionalization reactions of alkanes and other hydrocarbons.[2] Extensive research on electrophilic Pd and Pt complexes have also led to a detailed mechanistic understanding on the alkane oxidation reaction,[3] as well as to the applications in the synthesis of complex organic molecules.[4] Most notably, electrophilic Pd and Pt catalysts have been found to be effective for a number synthetically useful coupling reactions involving C–H bond activation.[5] Remarkable activity of cationic Ru and Ir complexes toward C–C bond activation reactions have also been demonstrated under stoichiometric conditions.[6]

Our own interest in electrophilic late metal catalysts stemmed from the recent discoveries that cationic ruthenium-hydride catalysts are highly effective in promoting both hydrogenation reactions,[7] as well as for selective coupling reactions involving C–H and N–H bond activation.[8] We have been searching for suitable ways to generate catalytically active electrophilic ruthenium-hydride complexes and to explore their activity for the C-H bond activation reactions. This report delineates *in-situ* generation of the cationic ruthenium-hydride catalyst from the protonation reaction of tetranuclear ruthenium complex {[$(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)$} (**1**),[9] and its unusual activity and selectivity pattern toward the coupling reaction of arylketones and alkenes involving C-H bond activation.

chae.yi@marquette.edu.

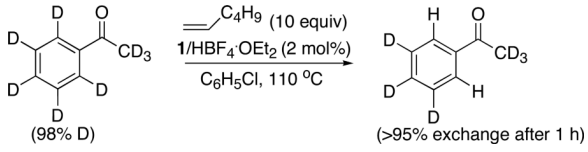
Supporting Information **Available:** Experimental procedures and spectroscopic data of organic products (25 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.



(1)

Initially, catalytic activity of electrophilic ruthenium complexes was surveyed for the coupling reaction of acetophenone and 1-hexene. 1-Hexene was chosen because it is normally not considered a suitable substrate for the chelate-assisted *ortho*-C–H insertion reaction pioneered by Murai and coworkers (eq 1).[10] Remarkably, the catalytic activity of **1** was "turned-on" upon the addition of $HBF_4{\cdot}OEt_2$ (2 equiv/Ru atom) to give a ~1:1 mixture of the substituted indene product **2a** and the *ortho*-C–H insertion product **3a** (Table 1).[11] Other selected ruthenium and rhenium catalysts were ineffective for the coupling reaction, giving only acid-catalyzed aldol condensation products. The structure of the coupling product **2a** revealed an unusual alkene insertion regioselectivity. The product **2a**, whose structure was completely established by 2-D NMR techniques, showed two methyl groups with 2-propyl group on the indenyl ring, even though 1-hexene was used as the substrate. While a conceptually similar dehydrative coupling reaction of imines and alkenes was reported by Takai and co-workers,[12] to the best of knowledge, the formation of substituted indenes from the coupling reaction of ketones and alkenes has not been achieved before.

The scope of the coupling reaction was explored by using **1**/$HBF_4{\cdot}OEt_2$ catalytic system (Table 2). Arylketone with an electron-withdrawing group was found to marginally favor the formation of the indene product **2** (entry 2), while the ketone with sterically demanding group tended to increase the formation of the *ortho*-C–H insertion product **3** (entry 4, 5). The coupling reaction with both ethylene and 2-butene formed the same products **2j** and **3j** rapidly within 1 h (entry 10, 11), and this observation can be rationalized by the ethylene dimerization and 1-butene to 2-butene isomerization prior to the coupling reaction. In all cases, high regioselectivity in forming the substituted indene product **2**, and a mixture of the double bond isomers is formed for unsymmetric products such as **2h**, **2i** and **2l** (entry 8, 9 and 13). In contrast, the coupling reaction with styrene predominantly gave the *ortho*-alkenyl product **4k** (entry 12), which is likely resulted from the vinyl C–H bond activation. The reaction with a benzocyclic ketone such as α-tetralone gave the *ortho*-C–H insertion product **3o** exclusively (entry 16).



(2)

The following experiments were performed to gain mechanistic insights on the coupling reaction. (1) The treatment acetophenone-d_8 with 1-hexene (10 equiv) led to a rapid and extensive H/D exchange on the ortho positions of acetophenone-d_8 within 1 h at 110 °C prior to the product formation (eq 2, Figure S2 in the Supporting Information). Also, a negligible isotope effect of k_H/k_D = 1.13±0.05 at 110 °C was obtained from the coupling reaction of acetophenone vs acetophenone-d_8 with 1-hexene. These results indicate a rapid and reversible *ortho*-C–H bond activation step. (2) Carbon isotope effect was measured from the coupling reaction of 2-acetonaphthone and 1-hexene by employing Singleton's isotope measurement

technique at natural abundance.[13] The $^{12}C/^{13}C$ ratio of unreacted 2-acetonaphthone isolated at 71% conversion was compared with the virgin sample. The most pronounced carbon isotope effect was observed at the *ortho*-arene carbon atom of 2-acetonaphthone ($^{12}C/^{13}C$ at $C^{(3)}$ = 1.020 with $C^{(7)}$ as the internal standard, average of 3 runs) (Table S1, Supporting Information).

(3) A catalytically relevant ruthenium-hydride species was detected from the reaction mixture of **1** and $HBF_4{\cdot}OEt_2$. Thus, the treatment of **1** (20 mg, 12 μmol) with $HBF_4{\cdot}OEt_2$ (6.5 μL, 2 equiv per Ru) in C_6D_6 at 20 °C led to a clean formation of the ruthenium-hydride complex, whose spectroscopic features are characterized by the Ru–H signal at δ −10.79 (d, J_{PH} = 25.8 Hz) by ^1H NMR and a single phosphine peak at δ 73.8 by $^{31}P\{^1H\}$ NMR. We tentatively formulate the structure of the cationic Ru–H species as $[(L)_3(PCy_3)(CO)RuH]^+$ on the basis of these spectroscopic data. Furthermore, the *in-situ* formed complex was found to be an active catalyst for the coupling reaction.

While details of the reaction mechanism remain unclear, these preliminary results suggest a mechanism involving a rapid and reversible *ortho*-C–H bond activation followed by the rate-limiting olefin insertion step for the coupling reaction (Scheme 1). We propose that the cationic *ortho*-metalated complex **5**, formed from the *ortho*-C–H bond activation of an arylketone and the reductive elimination of an alkane, is the key species for the coupling reaction.[14] The regioselective insertion of 2-alkene to **5** and the subsequent cyclization and dehydration sequence can be envisioned for the formation of **2**. The observation of significant carbon isotope effect on the *ortho*-arene carbon of an arylketone substrate supports the notion that the C-C bond-forming step involving the migratory insertion of 2-alkene to the *ortho*-metalated species **5** is the rate-limiting step of the coupling reaction.

Electrophilic nature of the ruthenium-hydride catalyst appears to be an important factor in mediating the coupling reaction, in that the cationic ruthenium catalyst would promote the dehydrative cyclization steps by facilitating strong dative bonding interaction with the ketone oxygen atom. Heteroatomchelated *ortho*-metalated late transition complexes have been widely considered to be the key intermediate species in both Murai-type of C-H/olefin insertion and oxidative C-H arylation reactions.[15] The cationic nature of the ruthenium-hydride catalyst would also be proficient in mediating the isomerization of terminal alkenes, and in this regard, the activity of electrophilic ruthenium catalysts towards alkenes isomerization and other coupling reactions has been well-documented in the literature.[16] Detailed kinetic and mechanistic investigations are currently underway to further discern the electrophilic nature of the ruthenium-hydride catalyst on the coupling reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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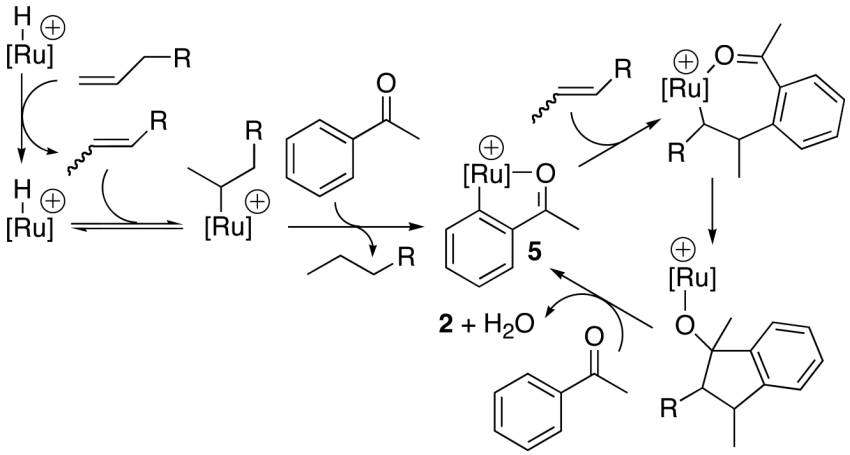


Scheme 1.
Proposed Mechanism for the Formation of **2**.

Table 1

Catalyst Survey for the Coupling Reaction of Acetophenone and 1-Hexene.[a]

entry	catalyst	additive	yield[b]	2a:3a
1	**1**	--	0	--
2	**1**	$HBF_4{\cdot}OEt_2$	44	43:57
3	$RuHCl(CO)(PCy_3)_2$	--	0	--
4	$RuHCl(CO)(PCy_3)_2$	$HBF_4{\cdot}OEt_2$	19	43:57
5	$RuH_2(CO)(PPh_3)_3$	--	7	0:100
6	$RuH_2(CO)(PPh_3)_3$	$HBF_4{\cdot}OEt_2$	0	--[c]
7	$RuCl_2(PPh_3)_3$	$HBF_4{\cdot}OEt_2$	5	100:0[c]
8	$RuCl_3{\cdot}3H_2O$	$HBF_4{\cdot}OEt_2$	0	--[c]
9	$[RuCl_2(COD)]_x$	$HBF_4{\cdot}OEt_2$	0	--[c]
10	$Ru_3(CO)_{12}$	NH_4PF_6	0	--
11[d]	$[RuH(CO)(PCy_3)_2(S)_2]^+BF_4^-$	--	0	--
12	$Re(CO)_3(THF)_2Br$	$HBF_4{\cdot}OEt_2$	0	--[c]
13	$BF_3{\cdot}OEt_2$	--	0	--[c]
14	$HBF_4{\cdot}OEt_2$	--	0	--[c]

[a] Reaction conditions: acetophenone (1.0 mmol), 1-hexene (10 mmol), catalyst (5 metal atom mol%), additive (2 equiv), C_6H_5Cl (1 mL), 110−120 °C, 15 h.

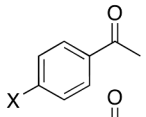
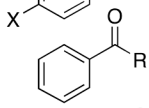
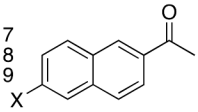
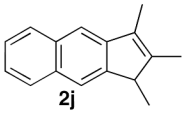
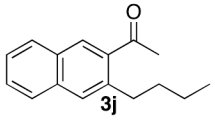
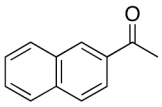
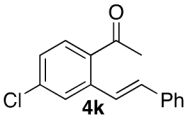
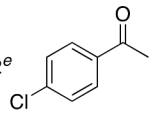
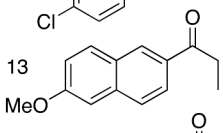
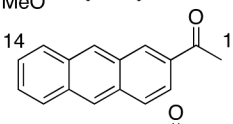
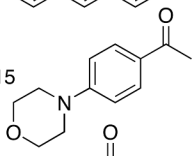
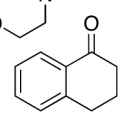
[b] GC yields based on acetophenone.

[c] 10−15% of the aldol products was formed.

[d] S = CH_3CN.

Table 2

Coupling Reaction of Arylketones and Alkenes.[a]

entry	ketone	alkene	product ratio (**2**:**3**)	convn (%)[b]	yd (%)[c]
1		1-hexene	X = H **2a**:**3a** = 41:59	57	47
2			X = Cl **2b**:**3b** = 56:44	67	61
3			X = OMe **2c**:**3c** = 33:67	47	40
4		1-hexene	R = Et **2d**:**3d** = 35:65	45	38
5			R = i-Pr **2e**:**3e** = 27:73	59	50
6			R = Ph **2f**:**3f** = 45:55	68	59
7		1-hexene	X = H **2g**:**3g** = 48:52	72	67
8			X = Me **2h**:**3h** = 50:50	73	65
9			X = OMe **2i**:**3i** = 45:55	84	75
	 **2j**				
	 **3j**				
10[d]		ethylene	**2j**:**3j** = 83:17	95	85
11[d]		2-butene	**2j**:**3j** = 71:29	99	90
	 **4k**				
12[e]		styrene	**2k**:**4k** = 10:90	47	35
13		1-hexene	**2l**:**3l** = 36:64	84	75
14		1-hexene	**2m**:**3m** = 35:65	88	82
15		1-hexene	**2n**:**3n** = 10:90	46	40
16		1-hexene	**2o**:**3o** = 0:100	76	72

[a] Reaction conditions: ketone (1.0 mmol), alkene (10 mmol), **1** (30 mg, 1.75 mol%, 7.0 Ru mol%), $HBF_4{\cdot}OEt_2$ (20 μL, 2 equiv per Ru), C_6H_5Cl (3 mL), 110 °C, 15 h. [b] Determined by GC based on ketone. [c] Combined isolated yield of **2** and **3**. [d] 4 atm of alkene was used. [e] 130 °C, 5 h.