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Intermolecular Dehydrative Coupling Reaction of Aryl Ketones with Cyclic Alkenes Catalyzed by a Well-Defined Cationic Ruthenium−Hydride Complex: A Novel Ketone Olefination Method via Vinyl C−H Bond Activation

Chae S. Yi* and Do W. Lee

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201-1881

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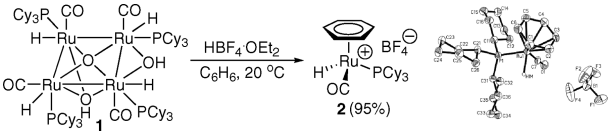
Summary: The cationic ruthenium−hydride complex $[(\eta^6\text{-}C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ *was found to be a highly effective catalyst for the intermolecular olefination reaction of aryl ketones with cycloalkenes. The preliminary mechanistic analysis revealed that an electrophilic ruthenium−vinyl complex is the key species for mediating both vinyl C−H bond activation and the dehydrative olefination steps of the coupling reaction.*

The Wittig reaction constitutes one of the most versatile olefination methods, and its synthetic prowess has been immensely demonstrated over the years in both laboratory-scale and industrial processes.[1] Despite its synthetic versatility, however, Wittig and related Peterson and Horner−Emmons olefination methods require stoichiometric amounts of ylides (or carbanion equivalents), which pose debilitating problems of the formation and removal of byproducts, especially for large-scale industrial applications. The Perkin and related aldol-type condensation/dehydration reactions have also been commonly used as carbonyl olefination methods, but these also suffer from similar restricted functional group compatibility and the formation of copious amounts of byproducts.[2] Considerable research progress has been achieved in the development of transition-metal-based carbonyl olefination methods that are more functional group tolerant and environmentally compatible, including Tebbe's and Petasis Ti reagents,[3] carbonyl-to-diazo coupling,[4] decarbonylative coupling reactions of aldehydes and alkynes,[5] and Pd-catalyzed coupling reactions.[6] From both synthetic and environmental points of view, the development of a catalytic version of the carbonyl olefination methods from the intermolecular coupling of carbonyl compounds with unactivated olefins would be highly desirable, but this still largely remains an elusive goal. Inspired by the recent progress on electrophilic C−H activation methods,[7] we have been exploring the coupling reactions of ketones and amines by using cationic ruthenium catalysts.[8] This report delineates a catalytic ketone olefination method that occurs from the intermolecular dehydrative coupling reaction of aryl ketones and cyclic alkenes involving vinyl C−H bond activation.

We have devised a convenient method to synthesize a cationic ruthenium−hydride complex from the protonation reaction of $\{[(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)\}$ (**1**) (eq 1).[9] Thus, the treatment of **1** (200 mg, 0.12 mmol) with $HBF_4\cdot OEt_2$ (64 μL) in C_6H_6 at room temperature cleanly led to the formation of the cationic ruthenium−hydride complex **2**, which was isolated as an ivory-colored solid in 95% yield. The ^{1}H NMR of **2** in CD_2Cl_2 showed the Ru−H signal at δ −10.39 (d, J_{PH} = 25.9 Hz), and a single phosphine peak was observed at δ 72.9 ppm by $^{31}P\{^1H\}$ NMR. The molecular structure of **2** as established from X-ray crystallography showed a three-legged piano-stool geometry, which is capped by a η^6-benzene moiety.[10]



(1)

Having a well-defined cationic ruthenium−hydride complex **2** in hand, we next explored its catalytic activity for the coupling reaction of aryl ketones and alkenes. We initially anticipated the formation of the ortho C−H insertion product **3**, in light of the reported results on the chelate-directed coupling reaction of aryl ketones and alkenes.[11] Instead, the

*To whom correspondence should be addressed. E-mail: chae.yi@marquette.edu.

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Scheme 1

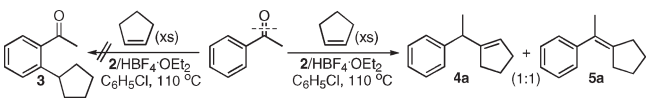


Table 1. Catalyst Survey for the Coupling Reaction of Acetophenone and Cyclopentene[a]

entry	catalyst	additive	**4a**:**5a**	conversn (%)[b]
1	**1**			0
2	**1**	$HBF_4 \cdot OEt_2$	1:1	50
3	$RuHCl(CO)(PCy_3)_2$			0
4	$RuHCl(CO)(PCy_3)_2$	$HBF_4 \cdot OEt_2$		6
5	**2**			12[c]
6	**2**	$HBF_4 \cdot OEt_2$	1:1	60
7	$RuH_2(CO)(PPh_3)_3$	$HBF_4 \cdot OEt_2$		8
8	$RuCl_2(PPh_3)_3$	$HBF_4 \cdot OEt_2$		< 5
9	$RuCl_3 \cdot 3H_2O$	$HBF_4 \cdot OEt_2$		0
10	$Ru_3(CO)_{12}$	NH_4PF_6		0
11[d]	$[RuH(CO)(PCy_3)_2(S)_2]^+BF_4^-$	$HBF_4 \cdot OEt_2$		0
12	$Re(CO)_3(THF)_2Br$	$HBF_4 \cdot OEt_2$		< 5
13	$Au(PPh_3)_3Cl$	$HBF_4 \cdot OEt_2$		< 5
14	$HBF_4 \cdot OEt_2$			0
15	$Cy_3PH^+BF_4^-$			0

[a] Reaction conditions: acetophenone (0.1 mmol), cyclopentene (2.0 mmol), catalyst (10 mg, 5 mol %), additive (2 equiv to catalyst), C_6H_5Cl (2 mL), 110 °C, 15 h. [b] Conversion was determined by GC on the basis of acetophenone. [c] Three different double bond isomers formed from dehydrogenation of **3**. [d] S = CH_3CN.

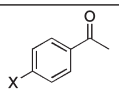
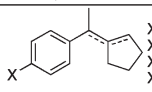
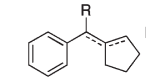
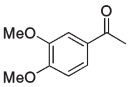
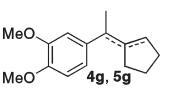
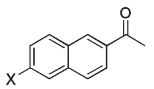
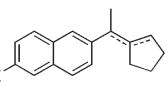
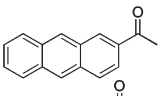
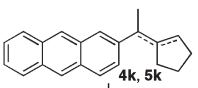
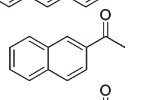
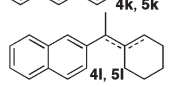
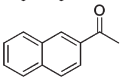
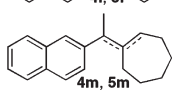
treatment of acetophenone with excess cyclopentene in the presence of **2**/$HBF_4 \cdot OEt_2$ (5 mol %) in C_6H_5Cl cleanly produced a ~1:1 ratio of double bond isomers of the olefination products **4a** and **5a**, without forming any ortho C−H insertion product **3** (Scheme 1).

The preliminary survey of ruthenium catalysts showed that both in situ formed **1**/$HBF_4 \cdot OEt_2$ and the isolated catalyst **2**/$HBF_4 \cdot OEt_2$ exhibited uniquely high activity for the coupling reaction (Table 1). The addition of $HBF_4 \cdot OEt_2$ was found to be critical for giving the olefination products, since the catalyst **2** alone exhibited a modest activity for the ortho C−H insertion products (entries 5 and 6).[12] One of the most remarkable features of the coupling reaction is that a direct ketone olefination has been achieved from the intermolecular dehydrative coupling reaction of aryl ketones and unactivated alkenes without employing any reactive reagents.

The scope of the olefination reaction was explored by using **2**/$HBF_4 \cdot OEt_2$ catalyst (Table 2). Aryl ketones with a para electron-donating group were found to modestly promote the coupling reaction (entries 2 and 3), while both terminal and internal olefins such as 1-hexene and 2-hexenes yielded the C−H insertion products **3** under similar conditions.[8b] Both cyclopentene and cyclohexene were found to be suitable substrates, but sterically demanding cyclic alkenes such as cyclooctene and methylcyclopentene as well as trisubstituted olefins yielded < 5% of the coupling products. A considerably higher conversion was achieved for naphthyl-substituted ketones (entries 8−11). In most cases, high selectivity for the olefination products of the types **4** and **5** was observed over the ortho C−H insertion product of type **3**, where the formation of a nearly 1:1 ratio of the double-bond isomers of **4** and **5** was observed in the crude product mixture. To obtain combined isolated yields, the hydrogenation reaction was performed on the crude product mixture. Thus, the treatment of a product

(12) See the Supporting Information for the experimental details.

Table 2. Coupling Reaction of Aryl Ketones and Cyclic Alkenes[a]

entry	ketone	alkene	products	convn (%)[b]	yd (%)[c]
1			 X = H (**4a**, **5a**)	60	52
2			X = Me (**4b**, **5b**)	65	55
3			X = OMe (**4c**, **5c**)	70	65
4			X = Cl (**4d**, **5d**)	36	30
5			 R = Et (**4e**, **5e**)	42	34
6[d]			R = CH_2Ph (**4f**, **5f**)	30	23
7			 **4g**, **5g**	53	45
8			 X = H (**4h**, **5h**)	92	84
9			X = Me (**4i**, **5i**)	84	75
10			X = OMe (**4j**, **5j**)	97	86
11			 **4k**, **5k**	92	84
12[e,f]			 **4l**, **5l**	50	40[g]
13[f]			 **4m**, **5m**	26	19

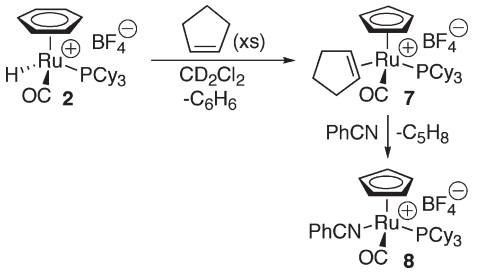
[a] Reaction conditions: ketone (0.7 mmol), alkene (14 mmol), **2** (20 mg, 5 mol %), $HBF_4 \cdot OEt_2$ (10 μL, 2 equiv), C_6H_5Cl (2 mL), 110 °C, 15 h. [b] Determined by GC on the basis of ketone. [c] Combined isolated yield of **4** and **5** determined from the hydrogenation product **6**. [d] Contained 28% of $PhCH_2CH_2Ph$. [e] A 4:1 ratio of **4l** and **5l** was formed in the crude product mixture. [f] 10 mol % of **2** was used. [g] ~10% of the ortho C−H insertion product **3** was also formed.

mixture of **4** and **5** with H_2 (2 atm) at 110 °C in the presence of **2**/$HBF_4 \cdot OEt_2$ (5 mol %) in C_6H_5Cl cleanly led to the olefin-hydrogenated product **6**, which was isolated by column chromatography on silica gel. The isolated yield of **6** is given in Table 2.

The following experiments were performed to gain mechanistic insights into the olefination reaction. First, the deuterium-labeling pattern was examined from the treatment of acetophenone-d_8 (90 mg, 0.7 mmol) with excess cyclopentene (0.95 g, 14 mmol) and **2**/$HBF_4 \cdot OEt_2$ (5 mol %). Extensive H/D exchange was found to occur on the methyl group of both **4a** and **5a** as well as on cyclopentene, without significant exchange on the ortho positions of the phenyl group as examined by ^1H and ^2H NMR.[12] The coupling reaction of acetophenone with a 1:1 mixture of 1-hexene and cyclopentene under the competitive conditions yielded the olefination products **4a** and **5a** predominantly over the C−H insertion product type **3** (**4a** + **5a**:**3** = 11:1). These results indicate that the vinyl C−H activation is rapid and reversible and that this step is favored over the arene ortho C−H activation for the cyclopentene case.

To discern the nature of catalytically relevant species, the reaction of **2** with cyclopentene was monitored by NMR. The treatment of **2** (20 mg, 35 μmol) with excess cyclopentene (24 mg, 10 equiv) in CD_2Cl_2 slowly formed the new cationic complex $[CpRu(CO)(PCy_3)(c\text{-}C_5H_8)]^+BF_4^-$ (**7**) within 3 h at 100 °C, along with $Cy_3PH^+BF_4^-$, free benzene, and cyclopentane. The structure of **7** was tentatively assigned on the basis of NMR spectroscopic data. Trapping of **7** with PhCN resulted in the stable nitrile complex $[CpRu(CO)(PCy_3)(NCPh)]^+BF_4^-$ (**8**) (Scheme 2).[12] The formation of cyclopentadienyl complex **8** can be readily rationalized from the dehydrogenation of cyclopentene and the elimination of cyclopentane.

Scheme 2



Though details of the coupling reaction still remain to be established, we propose a mechanistic rationale that invokes both olefinic C−H bond activation and dehydrative carbonyl olefination steps (Scheme 3). We propose that the electrophilic Ru−vinyl complex **9**, initially generated from the vinyl C−H activation of cycloalkene, is the key species for the coupling reaction. The dative coordination of ketone substrate followed by the alkenyl group migration to the electrophilic carbonyl carbon would yield the alcohol product after transfer of a hydrogen obtained from vinyl C−H activation of a coordinated alkene to the alkoxide ligand. While the formation of metal−vinyl species has been well documented in the C−H bond activation literature,[13] its synthetic utility has not been fully exploited in catalytic coupling reactions. The detailed mechanistic steps for the formation of the olefin products **4** and **5** from the alcohol are not clear at the present time, but it can be envisaged from an acid-catalyzed reductive dehydration of the alcohol, in light of the well-known alcohol dehydration reactions.

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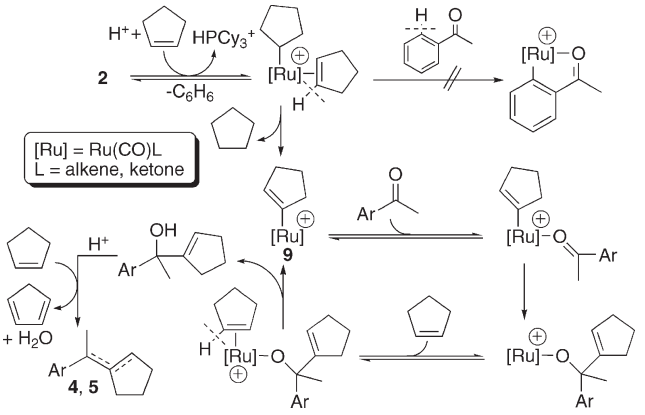
Scheme 3. Mechanistic Rationale for the Ketone Olefination



In summary, a novel catalytic ketone olefination method has been developed from the intermolecular coupling reaction of aryl ketones with cyclic alkenes. The electrophilic nature of the ruthenium catalyst **2** seems to be an essential feature for mediating both vinyl C−H bond activation and the subsequent dehydrative coupling steps of the reaction. The scope and synthetic efficacy of the catalytic method are currently being investigated.

Acknowledgment. Financial support from the National Institutes of Health, General Medical Sciences (Grant No. R15 GM55987) is gratefully acknowledged.

Supporting Information Available: Text, tables, figures, and a CIF file giving experimental procedures, spectroscopic data for organic products, and X-ray crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.