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Ruthenium Chloride as an Efficient Catalytic Precursor for Hydroarylation Reactions via C−H bond Activation

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ABSTRACT

A very simple and efficient catalytic system for the hydroarylation of olefins by aromatic ketones and Michael acceptors using simple and inexpensive ruthenium trichloride as a ruthenium source is described. These very mild conditions (dioxane at 80 °C) appeared to be highly compatible, tolerant, and selective toward various functional groups, and the ease of the protocol is highly convenient for synthetic purposes.

Carbon−carbon bond-forming reactions involving carbon−hydrogen bond activation catalyzed by transition-metal complexes have arisen as a very powerful methodology to build complex molecules.[1] These reactions allow the use of readily available substrates, since no preliminary functionalization is needed, and lead to clean reactions with atom economy.[2] Several transition-metal complexes like ruthenium, rhodium, iridium, and palladium have demonstrated a high activity for such catalytic reactions,[3] and among them, ruthenium complexes were revealed to be of high interest in term of cost and efficiency.

More particularly, hydroarylation reactions, have been developed using low-valent ruthenium complexes such as $RuH_2(CO)(PPh_3)_3$, $RuH_2(PPh_3)_4$, $Ru(CO)_2(PPh_3)_3$, $Ru_3(CO)_{12}$, and $RuH_2(H_2)_2(PCy_3)_2$, for example.[4,5] However, these catalysts are generally air and moisture sensitive and must be stored under inert atmosphere at low temperature to prevent decomposition. Moreover, they usually require several

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(3) For selected recent examples, see: (a) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (d) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (e) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (f) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (g) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (h) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (i) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (j) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (k) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179.

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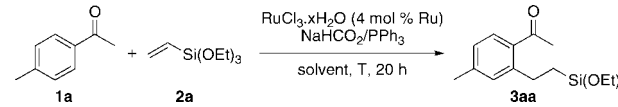
preparation and purification steps from commercial ruthenium chloride, and their fixed structure does not allow the steric and electronic properties of the catalytic active ruthenium species to be tuned by a proper choice of the ligand. We recently developed an alternative and more convenient protocol[6] consisting of the in situ generation of the ruthenium active catalyst from a stable and commercial ruthenium source $[RuCl_2(p\text{-cym})]_2$ (*p*-cym = *p*-cymene), sodium formate as a reducing agent, and a phosphane ligand. This catalytic system turned out to be very efficient for the hydroarylation of styrenes and vinylsilanes by aromatic ketones and imines[6,7] and for the hydroalkenylation of vinylsilanes by Michael acceptors.[8]

We wondered whether ruthenium chloride could be used as the ruthenium source in our catalytic system. Besides the practical advantages of such a precursor, its cost (2.7 €/mmol) would represent a significant benefit owing to the prohibitive price of commonly used ruthenium catalysts: $RuH_2(CO)(PPh_3)_3$ (87 €/mmol), $RuH_2(PPh_3)_4$ (160 €/mmol), $Ru_3(CO)_{12}$ (38 €/mmol), and $[RuCl_2(p\text{-cym})]_2$ (21 €/mmol).[9]

Ruthenium chloride has often been used as an in situ precursor in hydrogenation reactions,[10] but in the field of carbon−carbon bond formation, only a few examples have been reported.[11] We describe here the first example of alkylation of aromatic ketone by ortho carbon−hydrogen bond activation (Murai reaction)[4] starting from ruthenium chloride as a ruthenium source.

The main challenge consists of the reduction of ruthenium(III) to ruthenium(II) which would then likely undergo the same evolution as $[RuCl_2(p\text{-cym})]_2$ to generate the ruthenium-active species for the hydroarylation reaction.[7b] We first examined the role of the solvent on the reaction of 4-methylacetophenone (**1a**) and triethoxyvinylsilane (**2a**) in the presence of $RuCl_3{\cdot}xH_2O$, sodium formate, and triphenylphosphane at 80 °C for 20 h (Table 1). The use of nonpolar solvents (toluene or cyclohexane, entries 1 and 2), which were particularly adapted using a similar system but starting from ruthenium(II) precursor, resulted in low conversion. The use of 2-propanol as solvent[7c] led to the hydroarylation product **3aa** though with a moderate 73% conversion along with 5% of acetophenone reduction product (entry 3). As expected, the use of a 1:1 mixture of 2-propanol/acetone inhibited the formation of the reduction byproduct but did not increase the conversion (entry 4).[12] On the other hand, conducting the reaction in refluxing dioxane allowed the formation of **3aa** with a high 92% conversion (entry 5). Moreover, the reaction temperature could be reduced to 80 °C, and the expected hydroarylation product **3aa** was isolated in 80% yield.

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	solvent	temp (°C)	conversion[b] (%)
1	toluene	reflux	67
2	cyclohexane	reflux	52[c]
3	*i*-PrOH	reflux	78[c]
4	*i*-PrOH/acetone 1:1	reflux	71
5	dioxane	reflux	92
6	dioxane	80	99 (80)[d]

[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), $RuCl_3.xH_2O$ (4 mol % of Ru), $NaHCO_2$ (30 mol %), and PPh_3 (15 mol %) for 20 h at the indicated temperature. [b] Conversions were determined by GC using an internal standard. [c] Including 5% of acetophenone reduction product. [d] Isolated yield is shown in parentheses.

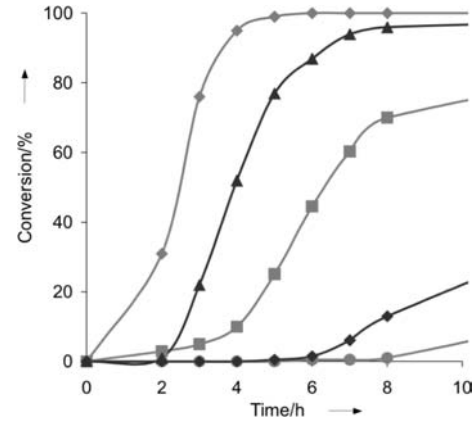


Figure 1. Influence of the ligand (12 mol %) in the reaction of **1a** with **2a** using in situ generated ruthenium catalyst from $RuCl_3{\cdot}xH_2O$ (4 mol % Ru) at 80 °C in dioxane: $(4\text{-}CF_3C_6H_4)_3P$, gray diamonds; $(4\text{-}ClC_6H_4)_3P$, black triangles; $[3,5\text{-}(CF_3)_2C_6H_4]_3P$, gray squares; Ph_3P, black diamonds; $(4\text{-}MeOC_6H_4)_3P$, gray circles.

Taking advantage of the versatility of this catalytic system, the role of the phosphane ligand was then investigated. Several triarylphosphane derivatives were evaluated (Figure 1), and we

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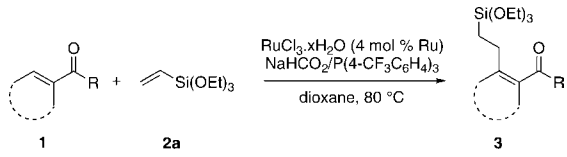
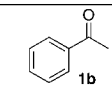
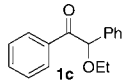
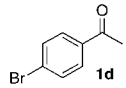
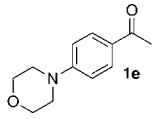
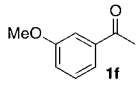
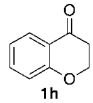
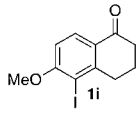
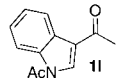
(9) Lowest prices quoted from Aldrich Chemistry, Alfa Aesar, and Strem Chemicals, 2009.

Table 2. Scope of the Reaction[a]



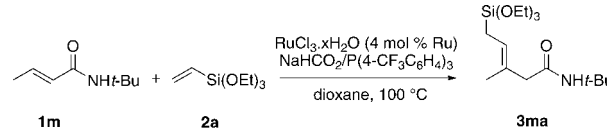
entry	1	yield (%)[b]
1	 1b	91 (82/18)
2	 1c	90 (100/0)
3	 1d	77 (69/31)
4	 1e	80 (77/23)
5	 1f	83[c]
6	 1g	67
7	 1h	92
8	 1i	89
9	 1j	87
10	 1k	90
11[d]	 1l	54

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), $RuCl_3{\cdot}xH_2O$ (4 mol % Ru), $NaHCO_2$ (30 mol %) and $P(4\text{-}CF_3C_6H_4)_3$ (15 mol %) in dioxane at 80 °C for 20 h. [b] Yields of isolated products; mono- and disubstituted ratio given between parentheses. [c] Formation of the 1,2 regioisomer. [d] The reaction was conducted for 68 h.

observed that the ligand significantly influenced the reaction rates since a complete conversion was obtained within 6 h with $P(4\text{-}CF_3C_6H_4)_3$, whereas PPh_3 led to less than 10% conversion in the same time. Therefore, electron-deficient ligands seemed to be more appropriate in this reaction as we noticed before when using $[RuCl_2(p\text{-cym})]_2$.[7b] Moreover, variable induction periods were observed depending on the electronic structure of the ligand (e.g., 1 h for $P(4\text{-}ClC_6H_4)_3$ and more than 5 h for PPh_3), which are consistent with the likely decisive role of the ligand in the reduction of ruthenium(III) precursor that has already been proposed.[11c,13]

These optimized conditions, using $P(4\text{-}CF_3C_6H_4)_3$ as ligand and dioxane as solvent, were tested in the reaction of a variety of aromatic ketone substrates with triethoxyvinylsilane and proved to be very general (Table 2). Acetophenone (**1b**) was efficiently alkylated in the presence of 5 mol % of ruthenium chloride hydrate in dioxane at 80 °C with 91% yield (entry 1). Ethoxybenzyl-substituted ketone **1c** reacted readily (entry 2), which contrasts with previous results at 140 °C in toluene where a poor conversion was obtained, presumably due to side reactions at such higher temperature.[6] Hydroarylation with para-substituted aromatic ketones proceeds easily with either electron-donating (entry 4) or -withdrawing (entry 3) substituents. With 3-methoxyacetophenone (**1f**), activation occurred selectively at the most hindered position, as was already reported, due to the chelating properties of the methoxy group.[4,6,7] The reaction with ortho-substituted ketones offered good yields (entries 6 and 7) such as the functionalized tetralone derivative **1i** (entry 8). Interestingly, the presence of bromo (entry 3) and even iodo (entry 8) substituents on the aromatic groups did not interfere with the C−H activation process, affording substrates that could be further functionalized by cross-coupling reactions. Various heteroaromatic ketones, including 2-acetylfuran (**1j**) (entry 9), 2-acetylthiophene (**1k**) (entry 10), and *N*-acetyl-3-acetylindole (**1 L**) (entry 11), participated in the reaction, affording moderate to good yields of hydroarylation products.

Scheme 1. Activation of the β C−H Bond of *tert*-Butylcrotonamide Leading to Allylsilane



[a] 15% of conjugated adduct were also formed

The activation of the β C−H bond of *tert*-butylcrotonamide **1m** was also achieved very efficiently leading to the corresponding allylsilane **3ma** with a satisfactory yield of 78% (Scheme 1), which constitutes an improved yield compared to that obtained using the previous catalytic system.[8]

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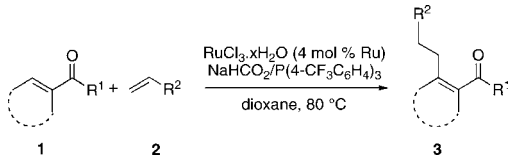
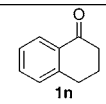
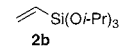
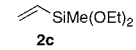
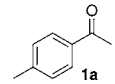
(12) For the use of acetone as hydride acceptor in rhodium-catalyzed processes, see: (a) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (b) Mora, G.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1180. (c) Martinez, R.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213. (d) Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* **2008**, *73*, 7800.

Table 3. Hydroarylation of Other Olefins[a]



entry	1	2	yield[b] (%)
1	 1n	 2b	92
2	1n	 2c	87
3[c]	1n	 2d	100
4[d]	 1a	 2e	97 (90)[e]

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), $RuCl_3 \cdot xH_2O$ (4 mol % of Ru), $NaHCO_2$ (30 mol %), and $P(4\text{-}CF_3C_6H_4)_3$ (15 mol %) in dioxane at 80 °C for 20 h. [b] Yields of isolated products. [c] Reaction conducted at 100 °C. [d] The reaction was carried out at 140 °C with 3 equiv of styrene. [e] Proportion of the *anti*-Markovnikov product between parentheses.

The reaction of other compatible olefins was also investigated (Table 3). α-Tetralone (**1n**) reacted with vinylsilanes derivatives (entries 1−3) leading to the alkylated product with very good yields. The reaction of styrene (**2e**) was also evaluated with 4-methylacetophenone (entry 4), and the *anti*-Markovnikov (linear) adduct was obtained in a high yield and with 90% selectivity, results which are similar to what we previously reported.[7a]

In conclusion, we have developed a very simple catalytic system for the hydroarylation of olefins by aromatic ketones and Michael acceptors. This catalytic system generates in situ an active ruthenium species from inexpensive ruthenium chloride hydrate, sodium formate, and tri(4-trifluoromethylphenyl)phosphane. These very mild conditions (dioxane at 80 °C) appeared to be highly compatible, tolerant, and selective toward various functional groups, and the ease of the protocol would make it very convenient for synthetic purposes. The mechanism for the generation of the active ruthenium species from ruthenium chloride is still unclear and is currently under investigation.

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Supporting Information Available: Experimental procedures and compound descriptions. This material is available free of charge via the Internet at http://pubs.acs.org.

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