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## A Versatile Ruthenium Catalyst for C–C Bond Formation by C–H Bond Activation\*\*

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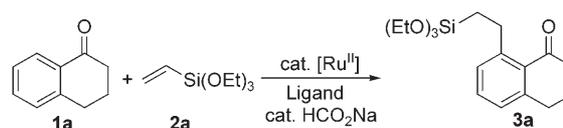
Catalytic processes involving C–H bond activation<sup>[1]</sup> are highly desirable as they allow the functionalization of more-easily available starting materials (atom economy concept<sup>[2]</sup>) and also because they produce clean reactions (reduced amounts of salts). In the field of C–C bond formation by C–H activation, several catalytic reactions have been developed recently involving mainly low-valent transition metals,<sup>[1]</sup> such as palladium, rhodium, and particularly ruthenium complexes, which have been extensively used in this field.<sup>[3]</sup>

The most active catalysts involve low-valent ruthenium complexes with oxidation states 0 or II, such as [Ru(cod)-(cot)] (cod = cyclooctadiene, cot = cyclooctatetraene), [Ru<sub>3</sub>(CO)<sub>12</sub>], [RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub>], and [RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub>], because of their high activity both in stoichiometric and catalytic reactions.<sup>[3]</sup> However, these low-valent catalyst precursors have low activity and/or are generally air- and moisture-sensitive and must therefore be stored under an inert atmosphere at low temperature to prevent their decomposition. Moreover, their synthesis is generally not obvious and requires several preparative and purification steps from commercially available RuCl<sub>3</sub>. Furthermore, their preparation does not allow the complexation of a large variety of ligands, which limits their scope. The generation of low-valent active ruthenium species in situ under mild conditions would therefore be a highly desirable improvement in terms of simplicity, flexibility, and scope of these catalytic systems.

We tested the feasibility of this approach in one of the most efficient ruthenium(0)-catalyzed processes involving C–H bond activation, namely the Murai reaction.<sup>[4]</sup> This reaction, and its subsequent variations,<sup>[5,6]</sup> involves C–H bond activation in the *ortho* position of an electron-withdrawing substituent, such as oxo, imino, or cyano, and subsequent insertion of an alkene. The ruthenium complex [RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub>] has been found to be the most active in

such processes, along with, in certain cases, [Ru<sub>3</sub>(CO)<sub>12</sub>].<sup>[7]</sup> No other ruthenium complexes with such high catalytic activity have been found even though several attempts have been made to prepare analogous compounds.<sup>[8]</sup> One exception concerns the use of the highly reactive and unstable complex [RuH<sub>2</sub>(H<sub>2</sub>)(PCy<sub>3</sub>)<sub>2</sub>] (Cy = cyclohexyl) developed by Chaudret et al.<sup>[9]</sup>

We report herein the generation of low-valent and flexible ruthenium catalysts in situ that are highly active in C–H bond activation, particularly in the Murai reaction. Our initial idea was to generate {RuH<sub>2</sub>} species as precursors to the ruthenium(0) catalyst<sup>[10]</sup> from commercial or easily available ruthenium(II) sources by reaction with a hydride donor. The activity of various catalytic systems was evaluated by the reaction of  $\alpha$ -tetralone (**1a**) with triethoxyvinylsilane (**2a**) in toluene at 140 °C (Scheme 1).



**Scheme 1.** Use of an in situ generated ruthenium catalyst in the Murai reaction.

We were pleased to find that the reaction between easily available [{Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>] and a formate salt generated a highly active catalyst that provided the expected coupling adduct in quantitative yield in the presence of triphenylphosphane as ligand (Table 1, entry 2). Among the various possible counter cations for the formate salts,<sup>[11]</sup> sodium and thallium were found to be the best as they gave faster initial reaction rates. However, because of the high toxicity of thallium derivatives, only the sodium salt was used in subsequent studies. Thus, reaction of ketone **1a** with tri-

**Table 1.** Ligand screening in the Murai-type reaction.<sup>[a]</sup>

Entry	Ligand	Conversion [%] <sup>[b]</sup>	
		after 3 h	after 21 h
1	none	0	0
2	PPh <sub>3</sub>	99	100
3	P( <i>p</i> -tolyl) <sub>3</sub>	3	94
4	P( <i>m</i> -tolyl) <sub>3</sub>	97	100
5	P( <i>o</i> -tolyl) <sub>3</sub>	0	0
6	P(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	90	93
7	P(4-MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	54	94
8	P(2-furyl) <sub>3</sub>	16	55
9	PCyPh <sub>2</sub>	1	62
10	PCy <sub>2</sub> Ph	2	8
11	PCy <sub>3</sub>	2	5
12	P(OEt) <sub>3</sub>	0	0
13	P(OPh) <sub>3</sub>	0	0
14	dppe	0	0
15	dppf	0	0

[a] Reactions conducted with 1 mmol of **1a**, 2 equiv of **2a**, 2.5 mol% [{Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>], and 3 equiv of ligand compared to Ru for monodentate ligands (1 equiv for bidentate ligands), in toluene at 140 °C. [b] Conversion determined by GC. dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1'-bis(diphenylphosphino)ferrocene.

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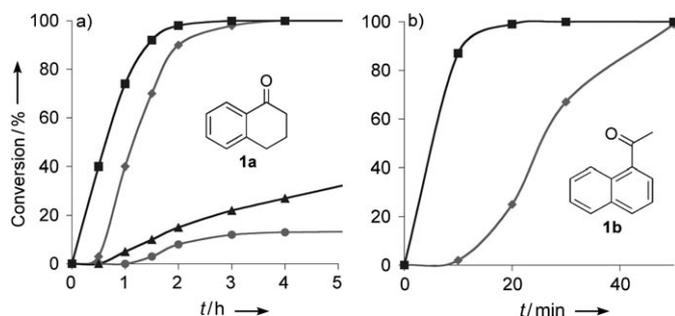
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ethoxyvinylsilane (**2a**) in the presence of 5 mol%  $[\{\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2\}_2]$ , 15 mol% triphenylphosphane, and 30 mol%  $\text{NaHCO}_2$  in toluene at  $140^\circ\text{C}$  afforded the expected product in quantitative yield in less than two hours, a result that compares well with those obtained with the classical complex  $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ .

We next decided to conduct a ligand screening to further improve the reactivity of this catalytic system and to demonstrate its versatility (see Table 1 for selected examples). From these results, it appears that only a few ligands are suitable, mainly tri(aryl)phosphanes (Table 1, entries 2–7). The bidentate ligands tested did not produce any catalytic activity (Table 1, entries 14 and 15) and the highest conversions were achieved with triphenylphosphane (Table 1, entry 2). It is also of note that the degree of steric hindrance provided by the phosphane ligand has a strong influence on the reaction course (the reactivity decreases with an increase of the cone angle<sup>[12]</sup>). Thus, tri(*o*-tolyl)phosphane (Table 1, entry 5) did not allow the formation of the expected adduct, whereas quantitative conversion was achieved under identical conditions with the *meta* or *para* isomers (Table 1, entries 3 and 4). The electronic nature of the ligand also greatly influences the kinetic course of the reaction, with electron-donating substituents retarding the coupling (Table 1, compare entries 6 and 7). Indeed, from these preliminary results it appears that electron-poor and nonhindered tri(aryl)phosphane ligands are the most suitable for this reaction.

We next turned our attention to determining the optimal ratio between the triphenylphosphane ligand and the ruthenium(II) precursor, with  $\alpha$ -tetralone (**1a**) as the aromatic ketone (Figure 1 a). The reaction conducted with one equiv-



**Figure 1.** Influence of the amount of triphenylphosphane on the reaction profile for ketones **1a** (a) and **1b** (b). Gray circles: 1 equiv; gray rhombi: 2 equiv; black squares: 3 equiv; black triangles: 4 equiv.

alent of  $\text{PPh}_3$  led to partial decomposition of the catalyst and low conversion. At least two equivalents of triphenylphosphane were needed, with optimal reaction rates being achieved with three equivalents of ligand. This result can be compared with that obtained with the most active ruthenium catalyst described for this reaction, namely  $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ .<sup>[4]</sup> Indeed, we have demonstrated that only the triphenylphosphane ligand, in the stoichiometry described above, is a requisite as CO is mainly a spectator ligand in the  $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$  catalyst precursor.<sup>[13]</sup> The stoichiometry of the added ligand compared to ruthenium was further

confirmed by the reaction with another aromatic ketone, namely 1-acetonaphthone (**1b**; Figure 1 b). Once again, a very fast reaction was achieved with three equivalents of triphenylphosphane, whereas with two equivalents an induction period was observed. It is also of note that ketone **1b** is even more reactive than **1a**—100% conversion was obtained in less than 20 minutes.

Under these optimal conditions, very high yields of coupling products were achieved for a variety of aromatic methyl ketones (Table 2). All reactions were conducted with two equivalents of alkene, which explains the formation of disubstituted products, but, by careful control of the number of equivalents, it was possible, in many cases, to obtain the mono-substituted acetophenones exclusively. As shown in Table 2, these conditions are compatible with a bromo-

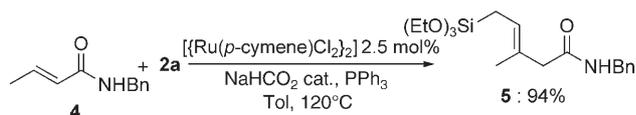
**Table 2:** The Murai reaction with the herein presented in situ generated ruthenium catalyst.<sup>[a]</sup>

Entry	2	Product	Time [h]	Yield [%] <sup>[b]</sup>
1	a		1	100 (85/15)
2	a		2	92 (50/50)
3	a		0.5	100 (75/25)
4	a		20	70 <sup>[c]</sup> (100/0)
5	a		1.5	99 <sup>[d]</sup> (100/0)
6	a		4	85
7	a		2	100
8	b		5	97
9	c		20	89

[a] Reactions conducted with 1 mmol of ketone **1**, 2 equiv of vinylsilane **2**, 2.5 mol%  $[\{\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2\}_2]$ , and 15 mol% of  $\text{PPh}_3$ , in toluene at  $140^\circ\text{C}$ . [b] Yields of isolated product, with the percentages of mono- and disubstituted products in parentheses. [c] Regioselectivity 85/15. [d] With 3 equiv of **2a**.

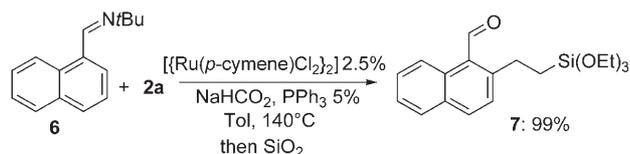
substituent (Table 2; entry 4, no oxidative addition is observed) and with heterocyclic ketones (Table 2; entries 6 and 7). Moreover, a high regioselectivity was observed with *meta*-substituted acetophenones (Table 2; entries 4 and 5), with a complexing substituent (Table 2; entry 5) or steric effects (Table 2; entry 4) also influencing the regioselectivity.<sup>[5]</sup> Other alkenylsilanes participated equally well in the reaction (Table 2, entries 8 and 9).

The present reaction conditions are not limited to acetophenones. For example, the  $\alpha,\beta$ -unsaturated amide **4** reacts with vinylsilane **2a** at 120 °C to afford amide **5** in high yield (Scheme 2).<sup>[14]</sup> The double bond in adduct **5** has been isomerized to the  $\beta,\gamma$ -position, with an 85/15 isomeric ratio of this bond in favor of the (*E*) isomer.



**Scheme 2.** The Murai reaction with an  $\alpha,\beta$ -unsaturated amide.

The versatility of this in situ generated catalyst was further confirmed by extending the reaction to other substrates, particularly to imine derivatives. Indeed, under standard Murai conditions, that is, with  $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$  as catalyst, aromatic imines fail to react and the use of  $[\text{Ru}_3(\text{CO})_{12}]$  has proved to be more appropriate.<sup>[4,15,16]</sup> A rapid screening of substrates revealed that aromatic aldimines react well with our catalytic system. Indeed, reaction of **6** and vinylsilane **2a** in the presence of only one equivalent of triphenylphosphane (instead of the usual three equivalents) compared to ruthenium afforded the expected imine in 100% conversion and, after hydrolysis, the expected aldehyde **7** in quantitative yield (Scheme 3), with the reaction being 10-times faster than with  $[\text{Ru}_3(\text{CO})_{12}]$  under identical conditions.

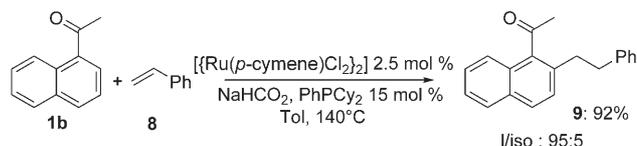


**Scheme 3.** C–H bond activation of aldimines.

To further demonstrate the versatility of the catalytic system, we turned our attention to the extension of this reaction to other alkenes. As reported previously, one of the main limitations of the Murai reaction is the low number of compatible alkenes and the lack of regioselectivity with other alkenes.<sup>[5]</sup> For example, the reaction of ketone **1b** with styrene (**8**) affords the coupled product with a 60/40 linear/branched product ratio (*l*/*iso*) using our catalyst (with three equivalents of  $\text{PPh}_3$ ).<sup>[17]</sup> Once again a ligand screening proved to be fruitful, and we were pleased to find that the use of dicyclohexylphenylphosphane instead of triphenylphosphane in the reaction of **1b** with **8** gave the coupled product **9** in 92%

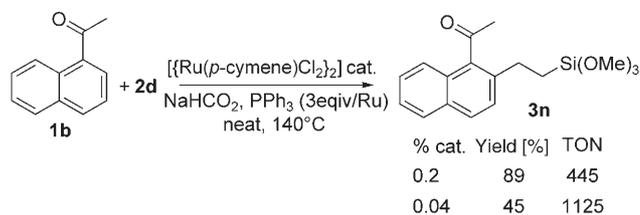
yield with high regioselectivity, the anti-Markovnikov adduct being formed for the first time in a 95/5 ratio (Scheme 4).

It is also noteworthy that the reaction can be conducted under solvent-free conditions, which makes it attractive from



**Scheme 4.** Coupling with styrene.

an environmental point of view, and it can be scaled-up easily without altering the yields (Scheme 5). Indeed, reaction of 50 mmol of **1b** (7.6 mL) with three equivalents of trimethoxyvinylsilane (**2d**, 23 mL) without any solvent afforded a 45% yield of pure **3n** with only 0.04 mol% of ruthenium (turnover number (TON) = 1125). Adduct **3n** was obtained directly by distillation from the reaction mixture.



**Scheme 5.** A large-scale C–H bond activation reaction under solvent-free conditions.

In summary, we have demonstrated for the first time the possibility of generating a highly active ruthenium catalyst for C–H bond activation in situ from stable and easily available ruthenium(II) sources and that this catalyst has a similar or higher activity than the Murai catalyst, depending on the substrates. The versatility of this catalytic system lies in the fact that the electronic and steric properties of the catalyst can be fine-tuned by varying the ligands, thus allowing the functionalization of various substrates. Further work is underway to extend the applications of this catalytic system, and to determine the nature of the active ruthenium species generated under these conditions.

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- [1] Reviews: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) F. Kakiuchi, S. Murai in *Topics in Organometallic Chemistry, Vol. 3* (Ed.: S. Murai), Springer, Berlin, **1999**, pp. 47–79; c) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; d) Y. Guari, S. Sabo-Etienne, B. Chaudret, *Eur. J. Inorg. Chem.* **1999**, 1047–1055; e) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639; f) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**,

- 102, 1731–1769; g) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; h) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2339–2463.
- [2] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; d) M. Eissen, R. Mazur, H.-G. Quebbemann, K.-H. Pennemann, *Helv. Chim. Acta* **2004**, *87*, 524–535.
- [3] a) M. A. Bennett, T. W. Matheson in *Comprehensive Organometallic Chemistry*, Vol. 4 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, p. 931; b) D. F. Shriver, M. I. Bruce in *Comprehensive Organometallic Chemistry II*, Vol. 7 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**; c) T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599–2660; d) T. Mitsudo, T. Kondo, *Synlett* **2001**, 309–321; e) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067–2096; f) *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; g) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788–6825; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630–6666.
- [4] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529–530.
- [5] a) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62–83; b) M. Sonoda, F. Kakiuchi, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117–3128; c) review: F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834.
- [6] For the ruthenium-catalyzed coupling of aromatic ketones with aryl boronates see: a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699; b) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706–2707.
- [7] One rhodium complex has also shown some interesting catalytic activity, see: C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1999**, *121*, 6616–6623.
- [8] H. Kawano, R. Tanaka, T. Fujikawa, K. Hiraki, M. Onishi, *Chem. Lett.* **1999**, 401–402.
- [9] a) Y. Guari, S. Sabo-Etienne, B. Chaudret, *J. Am. Chem. Soc.* **1998**, *120*, 4228–4229; b) Y. Guari, A. Castellanos, S. Sabo-Etienne, B. Chaudret, *J. Mol. Catal. A* **2004**, *212*, 77–82; c) J. Matthes, S. Gründemann, A. Toner, Y. Guari, B. Donnadieu, J. Spandl, S. Sabo-Etienne, E. Clot, H.-H. Limbach, B. Chaudret, *Organometallics* **2004**, *23*, 1424–1433; d) M. Grellier, L. Vendier, B. Chaudret, A. Albinati, S. Rizzato, S. Mason, S. Sabo-Etienne, *J. Am. Chem. Soc.* **2005**, *127*, 17592–17593, and references therein.
- [10] Studies on the Murai reaction mechanism: a) see ref. [5a]; b) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1998**, *120*, 12692–12693; c) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *Organometallics* **2000**, *19*, 2318–2329; d) R. F. R. Jazzar, M. F. Mahon, M. K. Whittlesey, *Organometallics* **2001**, *20*, 3745–3751.
- [11] Only the zinc, cesium, thallium, and sodium formate salts resulted in complete conversion.
- [12] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.
- [13] For a discussion on the influence of the CO ligand see: B. M. Trost, K. Imi, I. W. Davies, *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372.
- [14] C–H bond activation of  $\alpha,\beta$ -unsaturated esters and amides (one example) has already been reported, see ref. [13].
- [15] a) F. Kakiuchi, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.* **1996**, 111–112; b) F. Kakiuchi, T. Sato, T. Tsujimoto, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.* **1998**, 1053–1054; c) N. Chatani, A. Kamitani, S. Murai, *J. Org. Chem.* **2002**, *67*, 7014–7018.
- [16] For a related rhodium-catalyzed process see: a) C.-H. Jun, J.-B. Hong, Y.-H. Kim, K.-Y. Chung, *Angew. Chem.* **2000**, *112*, 3582–3584; *Angew. Chem. Int. Ed.* **2000**, *39*, 3440–3442; b) C.-H. Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.* **2002**, *8*, 485–492; c) S.-G. Lim, J.-A. Ahn, C.-J. Jun, *Org. Lett.* **2004**, *6*, 4687–4690; d) R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 7192–7193.
- [17] Similar results were obtained with the Murai catalyst  $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$  (*l*/iso = 70/30): see ref. [5].