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C−C Bond Formation via C−H Bond Activation Under Protic Conditions: On the Role of Phosphane Ligand and Cosolvent

Marc-Olivier Simon, Rémi Martinez, Jean-Pierre Genet, and Sylvain Darses*

Laboratoire Charles Friedel (UMR 7223, CNRS), Ecole Nationale Supérieure de Chimie de Paris, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France

sylvain-darses@chimie-paristech.fr

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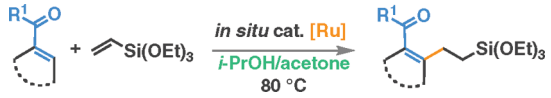

Effective conditions for the hydroarylation of vinylsilanes, allowing functionalization of various aromatic ketones in good yields at low temperature, using isopropanol, a protic solvent, are reported. Moreover, conducting this C−C bond-forming reaction under conditions similar to those used for hydride transfer reduction, the reduction of the ketone could be suppressed, simply by using acetone cosolvent as hydride acceptor. This reaction, conducted with an inexpensive and nontoxic solvent, constitutes the first C(sp^2)−H activation under protic conditions with low-valent ruthenium complexes.

To develop environmentally friendly processes for C−C bond formation, much attention has been paid to green and sustainable reactions. Among them, catalytic reactions involving C−H bond activation are highly desirable, not only because they allow the functionalization of more easily available starting materials (atom economy concept[1]) but also because they produce clean reactions (reduced amounts of salts).[2] In the field of C−C bond formation via C−H activation,[2] several catalytic reactions have been recently developed,[3] and hydroarylation reactions, allowing the functionalization of alkenes with a total atom economy, appear quite promising.[2,4]

Another point of concern in the development of green processes is the reaction solvent. Even if solvent-free reactions are highly desirable, the use of less hazardous and less toxic solvents is also an attractive alternative.[5] Hydroarylation reactions, involving low-valent active transition metal complexes (except electrophilic Pd(II)) are generally conducted in inert toxic hydrocarbon solvents like toluene or benzene.[2,4]

We report here, for the first time, that hydroarylation reactions involving C(sp^2)−H activation can be conducted in isopropanol, a protic solvent,[6] with higher efficiency and at moderate temperature (Scheme 1).

We recently reported an effective catalytic system, generated from an easily available ruthenium(II) source, allowing either the hydroarylation of alkenes (Murai type reaction)[7−9] or the formation of functionalized allysilanes via C−H bond activation.[10] The catalytically active ruthenium species was generated in situ from the reaction of inexpensive [$RuCl_2$-(*p*-cym)]$_2$ (*p*-cym = *p*-cymene) and sodium formate, in association with a phosphane ligand, but the reaction has to be

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
(2) Reviews: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (f) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (g) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (h) Kakiuchi, F. *Top. Organomet. Chem.* **2007**, *24*, 1. (i) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.
(3) For some recent examples of coupling reactions involving C−H bond activation, 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) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (d) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (e) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (f) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (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) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (j) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (k) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179.
(4) For some recent hydroalkylation reactions see: (a) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414. (b) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316. (c) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974. (d) McKeown, B. A.; Foley, N. A.; Lee, J. P.; Gunnoe, T. B. *Organometallics* **2008**, *27*, 4031. (e) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772. (f) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409. (g) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (h) Luedtke, A. T.; Goldberg, K. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 7694. (i) Vasylyev, M.; Alper, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1287. (j) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153.
(5) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (b) Sherman, J.; Chin, B.; Huibers, P. D. T.; Garcia-Valls, R.; Hatton, T. A. *Environ. Health Perspect.* **1998**, *106* (Suppl 1), 253. (c) Horváth, I. T. *Green Chem.* **2008**, *10*, 1024. (d) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31.
(6) For a review of C−H bond activation in water, see: (a) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. For recent examples of palladium-catalyzed C−H bond activation under protic conditions, see: (b) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (c) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.
(7) (a) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232. (b) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887.
(8) For ruthenium-catalyzed hydroarylation processes (Murai reaction) see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (c) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117. (d) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.
(9) Martinez, R.; Genet, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855.
(10) Simon, M.-O.; Martinez, R.; Genet, J.-P.; Darses, S. *Adv. Synth. Catal.* **2009**, *351*, 153.

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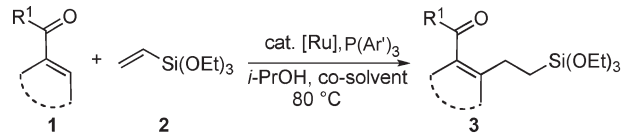
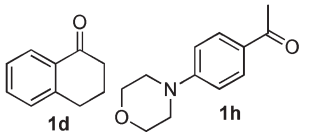
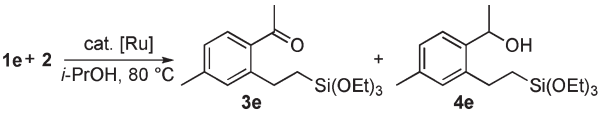
SCHEME 1. Ruthenium-Catalyzed C−C Bond Formation under Protic Conditions



ArCOMe, Ar = C_6H_5 (**1a**), 4-MeC_6H_4 (**1e**), 4-$MeOC_6H_4$ (**1f**), 4-FC_6H_4 (**1g**), 2-MeC_6H_4 (**1i**), 3-FC_6H_4 (**1j**), 3-$MeOC_6H_4$ (**1k**), 3-MeC_6H_4 (**1l**), 2-furyl (**1m**), 2-thienyl (**1n**)
$C_6H_5COR^1$, R^1 = Cy (**1b**), Et (**1c**),



SCHEME 2. Catalyst System Evaluation for the C−H Bond Activation in Isopropanol[a]



(a)	76%	12%
(b)	95%	4%
(c)	93%	5%

[Ru] cat.: (a) $[RuCl_2(p\text{-cym})]_2$ 2.5 mol %, NaOCOH 30 mol %, PPh_3 15 mol %. (b) $[Ru(OCOH)_2PPh_3(p\text{-cym})]$ 5 mol %, PPh_3 10 mol %. (c) Same as (a), using acetone as co-solvent.

[a]Reagents and conditions: [Ru] cat.: (a) $[RuCl_2(p\text{-cym})]_2$ (2.5 mol %), NaOCOH (30 mol %), PPh_3 (15 mol %); (b) $[Ru(OCOH)_2PPh_3(p\text{-cym})]$ (5 mol %), PPh_3 (10 mol %); and (c) same as (a), using acetone as co-solvent.

conducted at high temperature with toluene as solvent. We have also shown that the active ruthenium species was more efficiently generated in isopropanol compared to toluene, the reaction solvent used for the reaction.[7b] We wondered if this protic solvent would be more suited to conduct the hydroarylation reaction.

We were pleased to find that, using our previously described ruthenium catalytic system generated in situ from the reaction of $[RuCl_2(p\text{-cym})]_2$ with sodium formate and a phosphane ligand, the reaction of 4-methylacetophenone (**1e**) with vinyltriethoxysilane (**2**) afforded the expected hydroarylation product **3e** with 76% conversion, conducting the reaction in isopropanol at only 80 °C (Scheme 2). However, the reaction product was contaminated with byproduct, arising from the reduction of acetophenone (**4e**, 12%) and from intramolecular trans-alkoxylation of the silane moiety.[11] We reasoned that the reduction of acetophenone originated from ruthenium-catalyzed reduction via hydride transfer, because the reaction was conducted with a slight excess of the basic sodium formate, classical condition for such reduction reactions.[12] Moreover, the reduction product was minimized to 4% by using our recently described ruthenium complex $[Ru(OCOH)_2PPh_3(p\text{-cym})]$,[7b] and consumption of **1e** was quantitative (Scheme 2). As judged by the results obtained for several aromatic ketones (Table 1, conditions A), these new conditions proved to be quite general and compared favorably to those previously reported, all the more so since a reaction temperature as low as 80 °C allowed the C−C bond formation, compared to the 140 °C used for the reaction conducted in toluene.[7]

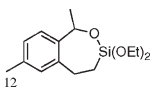
TABLE 1. Ruthenium-Catalyzed Ortho-Alkylation of Aromatic Ketones under Protic Conditions[a]

entry	product	conditions A[b,d]	conditions B[c,d]
1	**3a**	93 (98:2)	91 (89:11)
2	**3b**		98 (84:16)
3	**3c**		84 (83:17)
4	**3d**	95	89
5	**3e**		83 (72:28)
6	**3f**	83[e] (40:60)	81 (41:59)
7	**3g**	70[e] (63:37)	70 (50:50)
8	**3h**	96[e] (55:45)	77 (66:34)
9	**3i**	46	49
10	**3j**	70 (94:6)	81 (100:0)
11	**3k**	89[e] (87:13)	90 (90:10)
12	**3l**	89 (8:92)	84 (0:100)
13	**3m**		82
14	**3n**		70

[a]Reaction conducted with 1 mmol of **1** and 2 mmol of **2** at 80 °C for 4 to 20 h. [b]Conditions A: $[Ru(OCOH)_2PPh_3(p\text{-cym})]$ (5 mol %) and PPh_3 (10 mol %) in isopropanol. [c]Conditions B: $[RuCl_2(p\text{-cym})]_2$ (5 mol % Ru), $(4\text{-}CF_3C_6H_4)_3P$ (15 mol %), and NaOCOH (30 mol %) in isopropanol/acetone (1:1). [d]Yields of mono- and disubstituted adducts. The proportion of mono-/disubstituted adducts for 4-substituted substrates and selectivity for 6- and 2-substituted products for 3-substituted substrates are given in parentheses. [e]With 3 equiv of **2**.

Despite the efficiency of the catalytic system employed, it was not satisfactory since it necessitated the preparation and isolation of $[Ru(OCOH)_2PPh_3(p\text{-cym})]$. The use of an in situ generated catalyst would be more desirable but, as noticed previously, under these conditions, byproduct issued from the reduction of ketone, of either starting material or product, under hydride-transfer conditions was obtained.[12] To suppress the reduction of the keto functional group, we envisaged to introduce a sacrificial hydride acceptor in the reaction medium. We were pleased to find that the simple use of acetone as cosolvent suppressed, to a large extent, the reduction of acetophenone.[13] Indeed, reaction of **1e** with **2**, catalyzed by in situ-generated ruthenium catalyst from $[RuCl_2(p\text{-cym})]_2$ with sodium formate and triphenylphosphane, afforded the expected product **3e** with 93% conversion, along with only 5% of reduction product (Scheme 2). Evaluation of several phosphane ligands revealed that the use of $(4\text{-}CF_3C_6H_4)_3P$ as ligand for ruthenium, afforded the fastest reactions and completely suppressed the reduction of the substrates (Figure 1). Moreover, it appeared that the most effective ligands in that reaction were generally electron-deficient ones. Indeed, reaction of **1e** with **2** in a 1:1

(11) Formation of 3,3-diethoxy-1,7-dimethyl-1,3,4,5-tetrahydrobenzo-[*e*][1,2]oxasilepine:



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(12) Reviews: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (c) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300.

(13) For the use of acetone as hydride acceptor in other reactions, 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) Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* **2008**, *72*, 7800.

(14) The second substitution of the starting material is occurring concomitantly to the first one, that is before complete consumption of the starting material for several substrates, preventing the isolation of only monosubstituted adduct.

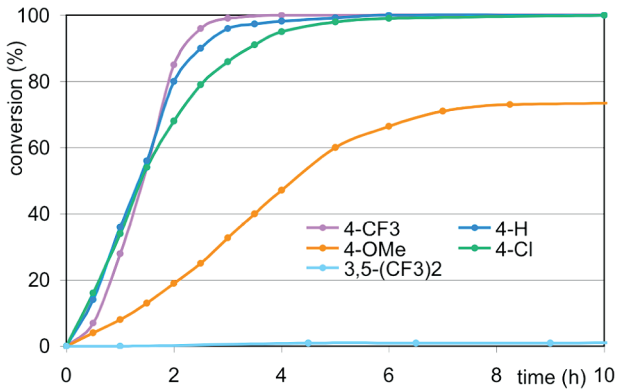

FIGURE 1. Effect of the ligand, $P(XC_6H_4)_3$, in the ruthenium-catalyzed arylation of **1e** with **2** in isopropanol/acetone mixture as solvent (conditions B).

mixture of acetone/isopropanol at 80 °C, catalyzed by in situ generated ruthenium catalyst from $[RuCl_2(p\text{-cym})]_2$ (5 mol %) with sodium formate and $(4\text{-}CF_3C_6H_4)_3P$ (15 mol %) (conditions B), afforded the alkylation adduct **3e** in 83% yield (Table 1, entry 5). These conditions proved to be general and various acetophenones were functionalized with high yield (Table 1).

In most of the examined reactions with para-substituted acetophenones, disubstituted adducts were also formed, leading to mixtures of mono- and disubstituted products.[14] The proportion of these products varies according to the substitution of acetophenones and the reaction times: the disubstituted product being favored by electron releasing substituents and prolonged reaction time. In the case of meta-substituted acetophenones, the two ortho positions of the acetyl group are not equivalent and two isomers may be obtained depending on the regioselectivity of the activation. Indeed, the activation process occurs at the less hindered position except in the presence of potential complexing substituent (entries 10−12). A similar regioselectivity was observed with $RuH_2(CO)(PPh_3)_3$ complex[8] and in the anti-Markovnikov hydroarylation of styrenes,[9] suggesting that a second complexation on the meta oxygen to ruthenium could direct the activation to the most congested side.

We have thus described improved conditions for the hydroarylation of vinylsilanes, allowing functionalization of various aromatic ketones in good yields, using isopropanol, a protic solvent. Moreover, even conducting this C−C bond forming reaction under conditions similar to those used for hydride transfer reduction, the reduction of the keto functional group could be suppressed, simply by using acetone cosolvent as hydride acceptor. This reaction, conducted with an inexpensive and nontoxic solvent, constitutes the first $C(sp^2)$−H (a quite inert bond) activation under protic conditions with low-valent ruthenium complexes.

Experimental Section

General Procedure for the Hydroarylation Reaction (Conditions B): Preparation of Cyclohexyl-{2-[(2-triethoxysilyl)-ethyl]phenyl}methanone (3b) (Table 1, entry 2). A septum-capped vial was charged with $[RuCl_2(p\text{-cym})]_2$ (15.3 mg, 25 μmol, 2.5 mol %), triphenylphosphane (39.3 mg, 150 μmol, 15 mol %), and sodium formate (20.4 mg, 300 μmol, 30 mol %). The vial was placed under vacuum for 15 min then under argon. Degassed 2-propanol (0.5 mL) and acetone (0.5 mL) were added, and then cyclohexylphenylketone (1 mmol, 188 mg) and triethoxyvinylsilane (423 μL, 2 mmol, 2 equiv) were added. The vial was placed in a preheated oil bath at 80 °C and the mixture was stirred until completion of the reaction (followed by GC analysis). After concentration under reduced pressure, the crude mixture was purified by silica gel chromatography affording **3b**, as a light yellow oil (270 mg). R_f 0.79 (cyclohexane/ethyl acetate 4:1). GC (DB-1701, program B): t_R = 8.3 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (1H, d, J = 7.5 Hz), 7.27−7.34 (2H, m), 7.18−7.22 (H, m), 3.84 (6H, q, J = 7.0 Hz), 2.95−3.01 (1H, m), 2.75−2.81 (2H, m), 1.29−1.89 (10H, m), 1.24 (9H, t, J = 7.0 Hz), 0.95−1.01 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0, 143.7, 138.9, 130.4, 130.0, 127.0, 125.4, 58.4, 49.4, 28.9, 26.8, 25.9, 25.8, 18.2, 13.3. MS (EI, m/z): 378 ($M^{+\bullet}$, 0.3%), 332 (81%), 163 (73%), 135 (100%). HRMS: calcd for $C_{21}H_{35}O_4Si$ (M + H) 379.2305, found 379.2311.

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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.