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Palladium-Catalyzed Intramolecular Hydroalkylation of Unactivated Olefins with Dialkyl Ketones

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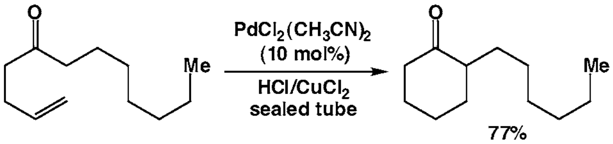
ABSTRACT



Treatment of 3-butenyl heptyl ketone with substoichiometric amounts of $PdCl_2(CH_3CN)_2$ (10 mol %), HCl (0.1 equiv), and $CuCl_2$ (0.3 equiv) in dioxane at 70 °C for 12 h in a sealed tube formed 2-hexylcyclohexanone in 77% isolated yield. A number of alkyl 3-butenyl ketones underwent hydroalkylation under these conditions to form 2-substituted cyclohexanones in moderate to good yield.

The direct addition of the α-C−H bond of a dialkyl ketone across the C═C bond of an unactivated olefin (hydroalkylation) is a transformation of considerable synthetic potential, but for which no effective procedure exists. For example, intramolecular hydroalkylation of γ-, δ-, ϵ-, or ζ-alkenyl alkyl ketones occurs thermally but requires temperatures of ≥ 350 °C.[1] Radical-mediated olefin hydroalkylation occurs under relatively mild conditions but suffers from poor site selectivity for radical generation, poor product selectivity, and slow chain transfer.[2] Lewis acid-catalyzed intramolecular olefin hydroalkylation occurs at room temperature but suffers from limited generality, is restricted to activated methylene compounds, and involves carbocationic intermediates.[3] Transition metal-catalyzed hydroalkylation has been restricted to the addition of activated methylene compounds to reactive unsaturated groups such as allenes,[4] alkynes,[5] and conjugated dienes.[6]

We recently reported the hydroalkylation of 3-butenyl β-diketones catalyzed by $PdCl_2(CH_3CN)_2$ (**1**) to form 2-acylcyclohexanones (eq 1),[7,8] which represent the first examples of the transition metal-catalyzed hydroalkylation of unactivated olefins with carbon nucleophiles.[9−11] Unfortunately, efficient hydroalkylation was initially restricted to β-diketones, which are $\geq 10^{11}$ more acidic and possess an equilibrium enol content $\geq 10^8$ greater than do to dialkyl ketones.[12,13] Through our efforts to expand the scope of palladium-catalyzed hydroalkylation, we noted that the reactivity of alkenyl β-keto esters toward **1** increased significantly in the presence of Me_3SiCl, which we attributed to the in situ generation of a reactive silyl enol ether.[14] For example, the

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[1] (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Moinet, G.; Brocard, J.; Conia, J. M. *Tetrahedron Lett.* **1972**, 4461.

[2] (a) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. (b) Curran, D. P. *Synthesis* **1988**, *417*, 489. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

[3] Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96.

[4] (a) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (b) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019.

[5] Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699.

[6] Goddard, R.; Hopp, G.; Jolly, P. W.; Kruger, C.; Mynott, R.; Wirtz, C.*J. Organomet. Chem.* **1995**, *486*, 163.

[7] Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290.

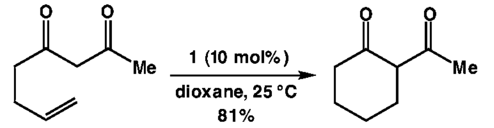
[8] For examples of the palladium-catalyzed oxidative alkylation of alkenyl β-diketones, see: Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648.

[9] Transition metal-catalyzed olefin hydroarylation[10] and alkenylation[11] via C−H bond activation has also been reported.

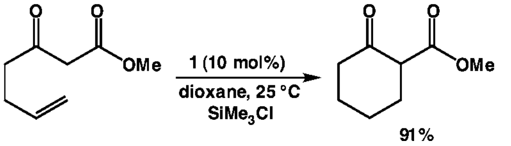
[10] (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (c) Lim, Y. G.; Kim, Y. H.; Kang, J. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2267. (d) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778.

10.1021/ol034879+ CCC: $25.00

yield of the palladium-catalyzed conversion of methyl 3-oxo-6-heptenoate to 2-carbomethoxycyclohexanone increased from 21 to 91% upon addition of Me_3SiCl to the reaction mixture (eq 2). Here we report that continued study in this area has led to the identification of HCl as the active promoter in palladium-catalyzed, silane-mediated hydroalkylation and to the development of the first effective transition metal-catalyzed procedure for the hydroalkylation of an unactivated olefin with a simple dialkyl ketone.



eq 1

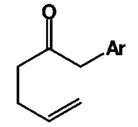
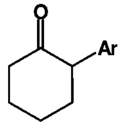
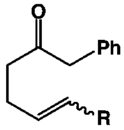
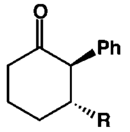
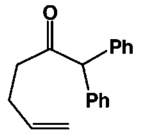
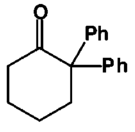
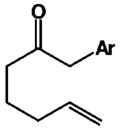
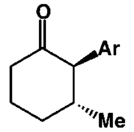


eq 2

The pK_a and $K_{enol/ketone}$ of α-aryl ketones lie roughly midway between the corresponding values for β-keto esters and dialkyl ketones,[12,13] and for this reason, we initially focused our attention on the cyclization of alkenyl α-aryl ketones. Surprisingly, a number of α-aryl 3-butenyl and 4-pentenyl ketones underwent efficient intramolecular hydroalkylation under conditions similar to those employed for the cyclization of alkenyl β-keto esters, albeit under more forcing conditions (Table 1). For example, treatment of benzyl 3-butenyl ketone (**2**) with a catalytic amount of **1** (10 mol %) in the presence of Me_2SiCl_2 (2.5 equiv) and $CuCl_2$ (1 equiv) at 70 °C for 18 h led to isolation of 2-phenyl cyclohexanone in 78% yield (Table 1, entry 1).[15] Unfortunately, this silane-mediated protocol required a 2- to 3-fold excess of the chlorosilane and failed in the case of both electron-rich α-aryl ketones and dialkyl ketones. For example, attempted cyclization of 3-butenyl heptyl ketone (**3**) or 1-(4-methoxyphenyl)-5-hexene-2-one (**4**) employing these conditions gave the desired cyclohexanone in ≤15% GC yield.

We initially hypothesized that Me_3SiCl promoted the palladium-catalyzed hydroalkylation of alkenyl ketones via in situ formation of a reactive silyl enol ether.[14] To test this assumption and gain insight into the role of the chlorosilane in palladium-catalyzed hydroalkylation, a dioxane-d_8 solution of **2**, Me_3SiCl, and **1** (0.1 equiv) was analyzed by ^1H NMR spectroscopy. In contrast to our expectations, no evidence for formation of the silyl enol ether of **2** was obtained, and instead, partial hydrolysis of Me_3SiCl with adventitious moisture generated a mixture of hexamethyldisiloxane and HCl. On the basis of this observation, we considered that perhaps HCl, rather than Me_3SiCl, was the active promoter of palladium-catalyzed olefin hydroalkylation. Consistent with this hypothesis, treatment of **2** with substoichiometric amounts of **1** (10%), HCl (0.1 equiv), and $CuCl_2$ (0.3 equiv) in a sealed tube for 12 h at 70 °C led to the isolation of 2-phenylcyclohexanone in 79% yield (Table 2, entry 1).[16]

Table 1. Cyclization of Alkenyl α-Aryl Ketones Catalyzed by **1** (10 mol %) in the Presence of Me_3SiCl (2−3 equiv) and $CuCl_2$ (1 equiv) at 70 °C in Dioxane

entry	ketone	cyclohexanone	yield (%)
			
1	Ar = Ph (**2**)		78[a]
2	Ar = 4-C_6H_4Br		80
3	Ar = 3-$C_6H_4CF_3$		76
4	Ar = 1-naphthyl		74
			
5	*cis*-Et		83[b]
6	*trans*-Et		77[b]
7			69
			
8	Ar = Ph		83[b]
9	Ar = 4-C_6H_4F		78[b]
10	Ar = 4-C_6H_4Br		67[b]
11	Ar = 2-naphthyl		75[b]

[a] Dichlorodimethylsilane employed in place of Me_3SiCl. [b] Thermodynamic isomer ratio ≥50:1.

Identification of HCl as the active promoter in the palladium-catalyzed hydroalkylation of **2** was significant because the procedure based on this knowledge proved to be effective for the hydroalkylation of alkyl alkenyl ketones (Table 2). Noteworthy was the formation of a quaternary carbon atom in the cyclization of 3-butenyl cyclohexyl ketone (Table 2, entry 7). Likewise, a 3-butenyl methyl ketone, which is ~100-fold less acidic than an ethyl ketone, underwent intramolecular hydroalkylation in moderate yield (Table 2, entry 12). This silane-free procedure was also effective for the intramolecular hydroalkylation of electron-rich α-aryl ketones such as **4** (Table 2, entry 6).

On the basis of deuterium-labeling experiments, we have proposed a mechanism for the palladium-catalyzed hydroalkylation of an alkenyl ketone involving attack of the pendant enol on the palladium-complexed olefin of **I** to form

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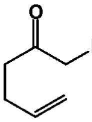
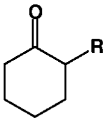
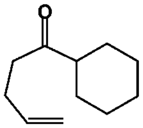
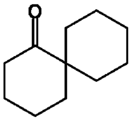
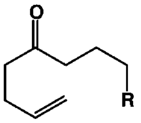
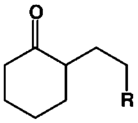
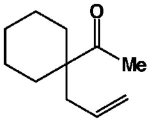
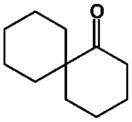
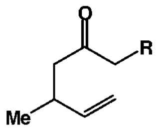
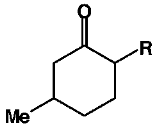
(11) (a) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc*. **1995**, *117*, 5371. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2001**, *123*, 2685.

(12) pK_a values for 2,4-pentanedione, ethyl acetoacetate, benzyl methyl ketone, and ethyl methyl ketone in DMSO are 13.3, 14.2, 19.9, and 24.8, respectively. Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456.

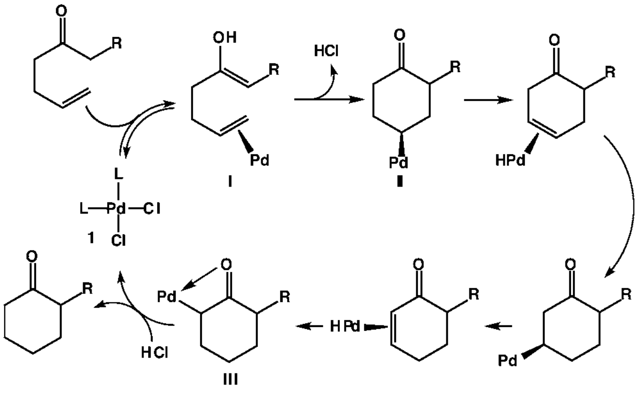
(13) $K_{enol/ketone}$ values for 2,4-pentanedione, ethyl acetoacetate, benzyl methyl ketone, and ethyl methyl ketone are 3.2, 0.9, 8×10^{-5}, and 5×10^{-9}, respectively. Guthrie, J. P. *Can. J. Chem*. **1979**, *57*, 1177.

(14) Pei, T.; Widenhoefer, R. A. *Chem. Commun*. **2002**, 650.

Table 2. Cyclization of α-Aryl and Alkyl 3-Butenyl Ketones Catalyzed by **1** (10 mol %) in the Presence of $CuCl_2$ (0.3 equiv) and HCl (0.1 equiv) at 70 °C in Dioxane in a Sealed Tube

entry	alkenyl ketone	cyclohexanone	yield (%)
			
1	R = Ph (2)		79
2	R = *n*-hexyl (3)		77
3	R = *n*-Bu		65
4	R = Bn		76
5	R = Cy		61
6	R = 4-C_6H_4OMe (4)		73
7			59
			
8	R = CO_2Me		82
9	R = Cl		55
10	R = OPh		72
11	R = OMe		60
12			55
			
13	R = *n*-hexyl	trans:cis = 3:1	44

Scheme 1



the palladium cyclohexyl species **II** (Scheme 1).[17] Isomerization of **II** via iterative *β*-hydride elimination/addition forms the metastable palladium enolate species **III**, which undergoes protonolysis to form the cyclohexanone with regeneration of **1** (Scheme 1). All available evidence points to C−C bond formation (**I** → **II**, Scheme 1) as the turnover-limiting step of catalysis. Because only the enol tautomer of palladium olefin intermediate **I** can presumably undergo cyclization and because enolization of an α-aryl ketone or dialkyl ketone is slow in the absence of an acid catalyst,[18] we propose that HCl facilitates the palladium-catalyzed hydroalkylation of alkenyl ketones by catalyzing enolization of the palladium olefin intermediate **I**.

In summary, we have identified HCl as the active promoter in palladium-catalyzed, silane-mediated hydroalkylation and have developed the first effective procedure for the hydroalkylation of an unactivated olefin with a dialkyl ketone based on this knowledge. We are currently working toward the identification of more effective methods for promoting enolization of alkenyl ketones and toward expanding the scope of palladium-catalyzed hydroalkylation with respect to ring size and substitution.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds and cyclohexanones. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) $CuCl_2$ stabilized the Pd(II) catalyst with respect to reduction/decomposition. Cyclization in the absence of $CuCl_2$ led to incomplete conversion.[14]

(16) Me_3SiCl also served as an effective source of HCl in this transformation. No reaction was observed in the absence of **1**.

(17) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056.

(18) Keefe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1990; pp 451−453.