Synthetic Methods

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Recyclable Palladium Catalyst for Highly Selective α Alkylation of Ketones with Alcohols**

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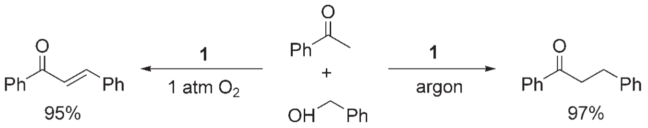
Carbon–carbon bond-forming reactions are fundamental in organic synthesis. The α alkylation of enolates derived from ketones with electrophiles such as alkyl halides is the conventional method to form C–C bonds.[1] The metal-catalyzed α alkylation of ketones with alcohols is attracting much attention because of its critical advantage over the conventional α-alkylation method, which suffers from problems with waste salts. Recently, several groups have reported the use of homogeneous catalysts for the α alkylation of ketones with alcohols.[2] However, these catalytic systems often suffer from low yield, low product selectivity, and/or the need for additives and strong bases. As a related C–C coupling reaction, Kaneda and co-workers developed an α alkylation of nitriles with primary alcohols using a Ru-grafted hydrotalcite as the catalyst.[3] Herein, we report a heterogeneous and recyclable palladium catalyst, which does not require ligands or additives, for the α alkylation of ketones with primary alcohols. Furthermore, our catalyst is active in the presence of oxygen and can produce enones selectively under 1 atm O_2, whereas ketones are the major product under argon (Scheme 1).



Scheme 1. Palladium-catalyzed coupling of acetophenone and benzyl alcohol.

Recently, we reported a heterogeneous palladium catalyst, Pd/AlO(OH) (**1**), that is composed of palladium nanoparticles entrapped in aluminum hydroxide[4] and is highly active for both alkene hydrogenation and aerobic alcohol oxidation. We envisioned that **1** would be applicable to the α alkylation of ketones with primary alcohols as it is able to produce aldehydes from primary alcohols and hydrogenate intermediate enones formed from the coupling of aldehydes and ketones in the presence of a base.[2d] In fact, 1,3-diphenylpropan-1-one was obtained in 97 % yield in the reaction of acetophenone with 1.2 equivalents of benzyl alcohol in the presence of **1** (0.2 mol % of Pd) and K_3PO_4 (3 equiv) for 8 h at 80 °C under argon. Notably, the same reaction under 1 atm O_2 produced chalcone in 95 % yield after 20 h.

The reaction conditions were optimized for the alkylation of acetophenone with benzyl alcohol through variation of the base, temperature, and solvent. Among the bases tested, K_3PO_4 was found to be the best. Strong bases such as KOH, NaOH, and CaH_2 dissolved the aluminum hydroxide matrix, whereas the alkylation product was not detected in reactions with weak bases, such as K_2HPO_4, K_2CO_3, Na_2CO_3, and triethylamine. The reaction rate was affected by the amount of K_3PO_4;[5] thus, three equivalents were needed to complete the reaction within 8 h at 80 °C. The temperature was also an important factor for the reaction rate: as the temperature was raised to 110 °C, the alkylation was completed in 2.5 h. Studies on the effect of the solvent revealed that toluene is more effective than trifluorotoluene, *n*-heptane, 1,4-dioxane, or water.

The high efficiency of **1** for the coupling of acetophenone and benzyl alcohol relative to commercially available catalysts and the α-alkylation catalysts reported previously was shown clearly (Table 1). Low selectivities (< 71 %) and yields (< 55 %) of 1,3-diphenylpropan-1-one (**2**) were observed for the reactions with commercially available heterogeneous palladium catalysts (entries 2–4). The reaction with $[RuCl_2(PPh_3)_3]$ requires the addition of 1-dodecene to increase the selectivity.[2c] The production of 1,3-diphenylpropane-1-ol increases as the amount of benzyl alcohol is increased for the reactions with $[RuCl_2(PPh_3)_3]$ and $[Ru(dmso)_4]Cl_2$ (dmso = dimethyl sulfoxide),[2f] and phosphine ligands were needed with $[\{IrCl(cod)\}_2]$ (cod = cyclooctadiene).[2e] The ruthenium-grafted hydrotalcite is a notable catalyst for α alkylation in the absence of a base, although a long reaction time at high temperature is required.[3]

The main advantage of **1**, besides its selectivity, is its recyclability—it can be recovered by filtration or decantation (Table 2). To the best of our knowledge, **1** is the first recyclable catalyst for the α alkylation of ketones with alcohols.[9] When the recovered catalyst was used without any treatment, the reaction rate decreased considerably (entry 2), whereas the addition of K_3PO_4 lead to resumption of the rate. Therefore, for each successive use, one equivalent of K_3PO_4 relative to acetophenone was added. Catalyst **1** retained its activity even during its sixth use, as **2** was prepared in 96 % yield after 20 h.

With suitable reaction conditions established, a series of ketones and alcohols were employed to investigate the scope of the reaction (Table 3). Our catalytic system was effective for a wide combination of ketones and alcohols that produced the corresponding α-alkylated products under anaerobic conditions. It was also effective for the selective production of *trans* enones under 1 atm O_2, although the reaction rates

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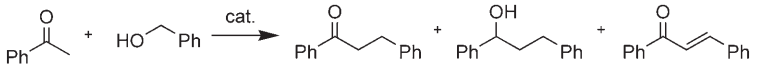
Table 1: Catalytic activity comparison.[a]



2 3 4

Entry	Catalyst	Metal [mol %]	Base (equiv)	T [°C]	t [h]	Conv. [%][b]	Product yield [%][c] 2	3	4
1	**1**	0.2	K_3PO_4 (3)	80	8	> 99	97	2	0
2	5 % Pd/C[d]	0.2	K_3PO_4 (3)	80	8	78	55	4	10
3	5 % Pd/Al_2O_3[d]	0.2	K_3PO_4 (3)	80	8	47	21	2	17
4	5 % $Pd/BaCO_3$[d]	0.2	K_3PO_4 (3)	80	8	30	11	0	12
5	$[RuCl_2(PPh_3)_3]$	2.0	KOH (1)	80	20	84	82	2	[e]
6	$[Ru(dmso)_4]Cl_2$	2.0	KOH (1)	80	[e]	[e]	72	[f]	[e]
7	[{Ir(cod)Cl}$_2$]	1.0	KOH (0.1)	100	4	[e]	86	10	[e]
8	Ru/HT	0.75	none	180	20	85	85	[e]	[e]

[a] A solution of acetophenone (1.0 mmol) and benzyl alcohol (1.2 mmol) in toluene (2 mL) was heated under argon. [b] Conversion of acetophenone. [c] Determined by GC. [d] Commercially available catalysts. [e] No report. HT = hydrotalcite.

Table 2: Recycling **1** for the coupling of acetophenone and benzyl alcohol.[a,b]

Use	T [°C]	t [h]	Yield [%][c]
1	80	8	97
2	80	8	30[d]
3	80	8	97
4	80	8	92
5	80	8	87
6	80	20	96

[a] A solution of acetophenone (1.0 mmol) and benzyl alcohol (1.2 mmol) in toluene (2 mL) was heated at 80 °C in the presence of **1** (0.2 mol % of Pd) under argon. [b] K_3PO_4 (1 equiv) was added for the reuse of **1**. [c] Determined by GC. [d] Without the addition of K_3PO_4.

were relatively slow (entries 5, 11, and 13). The alkylation of 4′-(trifluoromethyl)acetophenone was somewhat less selective, as the expected ketone was obtained in 87 % yield along with the corresponding alcohol in 6 % yield (entry 6).[6] Indanone was alkylated successfully at the α-methylene position (entry 7). Acetophenone was also alkylated by aliphatic alcohols in high yield (entries 8 and 9). Furthermore, aliphatic ketones were alkylated by an aliphatic alcohol as well as by aromatic alcohols in high yields and with high selectivities (entries 10–15). Alkylation occurred almost exclusively at the methyl positions, and the coupling of acetone with 1-butanol produced undecan-6-one in 92 % yield (entry 16). The reactions of aliphatic primary alcohols were slower than those of aryl methanol derivatives. In particular, the coupling between an aliphatic ketone and an aliphatic alcohol required a reaction time about eight times longer than for the coupling between aryl methyl ketones and aryl methanol derivatives (entry 15). A noticeable example is the coupling of 5-pregnen-3β-ol-20-one with benzyl alcohol,[7] as the secondary hydroxy group and the C=C bond are compatible with the coupling conditions (entry 17). Furthermore, the epimerization at C17 was negligible.[8]

In summary, we have demonstrated a highly efficient α alkylation of ketones with primary alcohols by the use of a recyclable palladium catalyst that is easily prepared from readily available reagents. We are currently investigating

Table 3: α Alkylation of ketones with primary alcohols.[a]

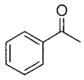
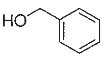
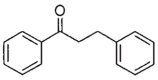
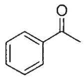
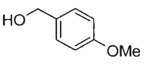
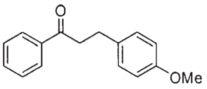
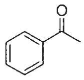
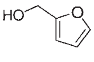
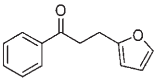
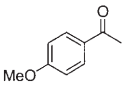
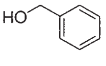
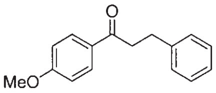
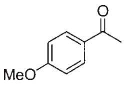
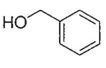
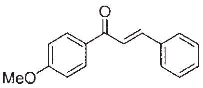
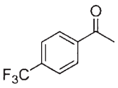
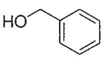
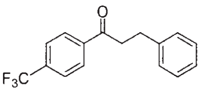
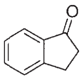
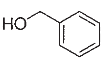
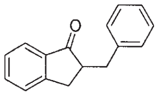
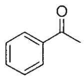
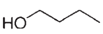
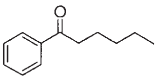
Entry	Ketone	Alcohol	t [h]	Product	Yield [%][b]
1			2.5		97 (92)[c]
2			2.5		96
3			2.5		96
4			2.5		98 (90)[c]
5			20[d]		87 (80)[c]
6			3		87[e]
7			3		97
8			12[f]		95 (88)[c]

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Table 3: (Continued)

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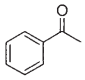
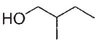
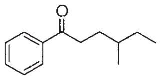
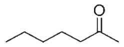
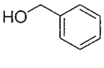
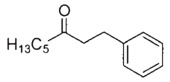
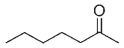
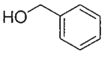
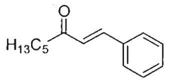
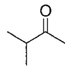
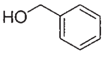
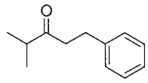
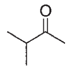
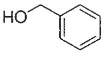
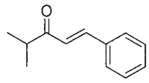
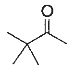
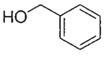
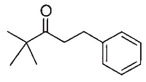
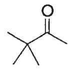
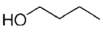
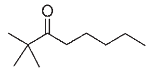
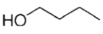
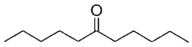
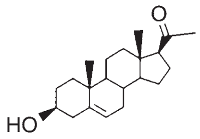
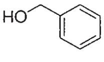
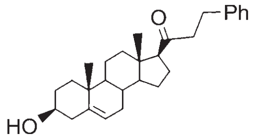
9			14[f]		95
10			3		97(90)[c]
11			20[d]		85[c]
12			3		97
13			20[d]		82[c]
14			3		98(94)[c]
15			20		94
16			48[f]		92
17			5		84[c]

[a] A solution of ketone (1.0 mmol) and alcohol (1.2 mmol) in toluene (2 mL) was heated in the presence of **1** (0.2 mol% of Pd) and K_3PO_4 (3 mmol) at 110°C under argon. [b] Determined by GC. [c] Yield of isolated product. [d] Under 1 atm O_2. [e] 3-Phenyl-1-(4-trifluoromethyl)phenylpropanol was formed in 6% yield. [f] Excess 1-butanol (4 mmol) was used.

other one-pot multicatalytic reactions based on the versatile activity of the palladium catalyst.

Experimental Section

Coupling of acetophenone and benzyl alcohol: Acetophenone (120 mg, 1.00 mmol), benzyl alcohol (130 mg, 1.20 mmol), **1** (24 mg, 0.2 mol% of Pd), K_3PO_4 (636 mg, 3.00 mmol), and toluene (2 mL) were placed in a 20-mL flask under argon at 80°C for 8 h. The catalyst was separated by filtration, and the filtrate was purified by column chromatography (ethyl acetate/hexane 1:9) to give 1,3-diphenylpropan-1-one (193 mg) in 92% yield.[10]

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[1] a) D. Caine in *Comprehensive Organic Synthesis, Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1–63; b) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem.* **2005**, *117*, 2282–2285; *Angew. Chem. Int. Ed.* **2005**, *44*, 2242–2245; c) *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**.

[2] a) C. S. Cho, B. T. Kim, M. J. Lee, T.-J. Kim, S. C. Shim, *Angew. Chem.* **2001**, *113*, 984–986; *Angew. Chem. Int. Ed.* **2001**, *40*, 958–960; b) C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim, *J. Org. Chem.* **2001**, *66*, 9020–9022; c) C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim, *Tetrahedron Lett.* **2002**, *43*, 7987–7989; d) C. S. Cho, B. T. Kim, H.-S. Kim, T.-J. Kim, S. C. Shim, *Organometallics* **2003**, *22*, 3609–3610; e) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2004**, *126*, 72–73; f) R. Martínez, G.-J. Brand, D.-J. Ramón, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 3683–3686.

[3] K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2004**, *126*, 5662–5663.

[4] M. S. Kwon, N. Kim, C. M. Park, J. S. Lee, K. Y. Kang, J. Park, *Org. Lett.* **2005**, *7*, 1077–1079.

[5] The coupling reaction was completed in 16 h (10 h) when one equivalent (2 equiv) of K_3PO_4 was used.

[6] The major product is the corresponding alcohol when $[Ru(dmso)_4]Cl_2$ is used as the catalyst; see ref. [2f].

[7] Pregnenolone is a main precursor of steroid hormones: K. Tsutsui, H. Sakamoto, K. Ukena, *J. Steroid Biochem. Mol. Biol.* **2003**, *85*, 311–321.

[8] According to ^{1}H NMR spectroscopic analysis, no diastereomer of the major coupling product was formed in significant yield.

[9] Palladium was not detected in the filtrate with inductively coupled plasma (ICP) analysis.

[10] The NMR spectroscopic data for the coupling products shown in Table 3 and the experimental procedures for the preparation of **1**, *E*-1,3-diphenyl-2-propen-1-one, and 21-benzylpregnenolone are contained in the Supporting Information.

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