



Bimetallic Pt–Sn/ γ -Al₂O₃ catalyzed β -alkylation of secondary alcohols with primary alcohols under solvent-free conditions



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ABSTRACT

Heterogeneous bimetallic Pt–Sn/ γ -Al₂O₃ (0.5 wt% Pt, molar ratio Pt:Sn = 1:3) was successfully utilized as the catalyst for direct β -alkylation of secondary alcohols with primary alcohols under solvent-free conditions. β -Alkylated secondary alcohols were obtained in moderate to high yields with water formed as the by-product through a hydrogen borrowing pathway. The present protocol provides a concise atom-economical and environmentally benign method for C–C bond formation.

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Alcohols are very important in organic synthesis and chemical industry. Traditional routes to access β -alkylated alcohols from secondary alcohols usually require a multistep process involving oxidation of the secondary alcohols, alkylation with alkyl halides, and reduction of β -alkylated ketones. Alkylation of alcohol by means of another alcohol as the alkylating agent has been considered as a green and direct method to attain β -alkylated alcohols.¹ In the absence of a hydrogen acceptor or donor, such a process can occur through a hydrogen borrowing pathway.² Homogeneous transition-metal catalysts such as ruthenium,³ iridium,⁴ palladium,⁵ and copper⁶ complexes have been reported to catalyze direct C–C cross-coupling of secondary alcohols with primary alcohols to form β -alkylated alcohols or β -alkylated ketones without using any hydrogen acceptor or donor, but the systems usually suffer from limited scope of alcohols, difficulty in recycling the catalyst, and need of a large amount of base. In order to overcome some of the drawbacks of homogeneous catalysts, development of efficient heterogeneous transition-metal catalyst systems has recently been paid much attention for hydrogen borrowing processes.⁷ Heterogeneous Ni/CeO₂⁸ and Pt/CeO₂⁹ exhibited high catalytic activity for self-coupling of aliphatic alcohols to β -alkylated ketones in the absence of additives. Ag/Al₂O₃ promoted the cross-alkylation of secondary alcohols with primary alcohols to afford β -alkylated ketones in the presence of a catalytic amount of Cs₂CO₃.¹⁰ β -Alkylation of secondary alcohols can also be

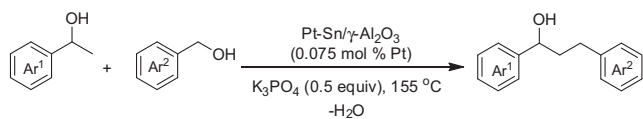
achieved using Ag₆Mo₁₀O₃₃,¹¹ IrO₂/Fe₃O₄,¹² and SBA-15-supported Ir/NHC complex¹³ catalysts under hydrogen borrowing conditions.

Recently, heterogeneous bimetallic catalysts have become attractive in this area. Cao et al. reported Au–Pd/HT (Au: Pd = 13:1) catalyzed synthesis of β -alkylated ketones from primary and secondary alcohols through a facile hydrogen borrowing pathway in the absence of basic additives.¹⁴ Such a catalyst could be easily separated from the reaction mixture and reused for at least three times without loss of its catalytic activity. Heterogeneous bimetallic catalyst Pt–Sn/ γ -Al₂O₃ has been well known for alkane dehydrogenation, reforming processes, and hydrogenation in petroleum industry.¹⁵ We found that Pt–Sn/ γ -Al₂O₃ catalyst can be efficiently applied for the hydrogen-borrowing *N*-alkylation of amines with alcohols or amines.¹⁶ Thus, we reasonably envisioned that this catalyst might be utilized to promote the cross-coupling between secondary and primary alcohols for the construction of C–C bonds. Herein, we disclose direct β -alkylation of secondary alcohols with primary alcohols through a hydrogen borrowing pathway using a Pt–Sn/ γ -Al₂O₃ catalyst¹⁶ for the first time (Scheme 1).

Initially, the reaction of 1-phenylethanol (**1a**) with benzyl alcohol (**2a**) was carried out to optimize the reaction conditions (Table 1). Using heterogeneous Pt–Sn/ γ -Al₂O₃ (**1**) (0.5 wt% Pt, Pt/Sn = 1:1) (0.075 mol% Pt) as the catalyst and K₃PO₄ (0.5 equiv) as the base at 145 °C in a sealed Pyrex glass screw-cap tube under solvent-free conditions, 42% conversion was reached for **1a** to form the target β -alkylated product **3a** as the major product and ketone **4a** as the minor product (Table 1, entry 1). Increasing the Pt/Sn molar ratio from 1:2 to 1:9 further improved the conversion of

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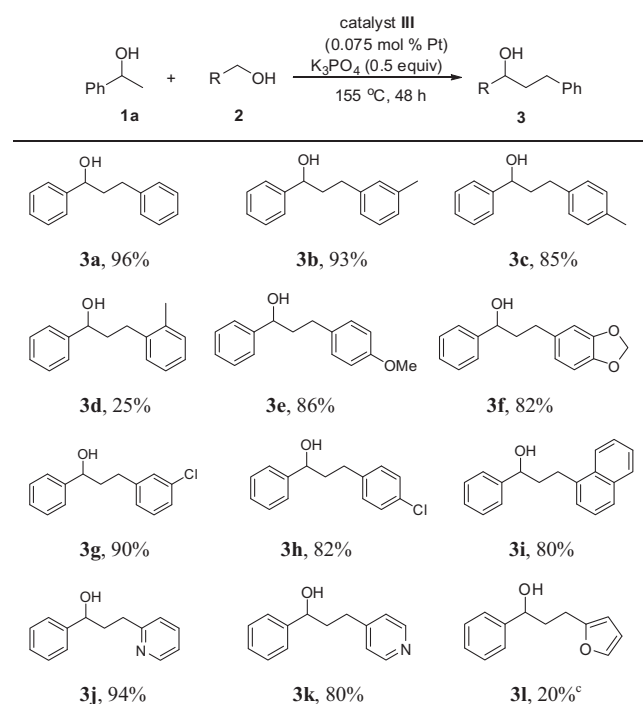


Scheme 1. Pt-Sn/ γ -Al₂O₃ catalyzed direct β -alkylation of secondary alcohols with primary alcohols through a hydrogen borrowing pathway.

1a, and the best result (99% conversion for **1a** with a 99:1 ratio of **3a**:**4a**) was obtained using a Pt/Sn ratio of 1:3 (Table 1, entries 2–6). The best result was obtained with catalyst **III** (Pt/Sn = 1:3), rendering formation of **3a** in 93% isolated yield (Table 1, entry 3). The high tin content in catalysts **IV–VI** (Pt/Sn = 1:5–1:9) may partially block exposure of the Pt (0) metal surface required for the hydrogen borrowing process, resulting in a lower reaction efficiency (Table 1, entries 4–6). Elevating the reaction temperature to 155 °C led to **3a** in 96% isolated yield (Table 1, entry 7). Lowering the base amount to 0.3 equiv slightly deteriorated the conversion of **1a** (Table 1, entry 8). It was noted that the selectivity was remarkably decreased by conducting the reaction in *o*-xylene solvent (Table 1, entry 9). Other bases such as NaO^tBu and KOAc were not effective for the desired reaction (Table 1, entries 10 and 11). Somehow, both PtCl₂ and Pt/ γ -Al₂O₃ did not show any catalytic activity for the reaction (Table 1, entries 12 and 13). It should be noted that the reaction did not occur in the absence of K₃PO₄ base (Table 1, entry 14).

Under the optimal conditions the reactions of **1a** with a variety of primary alcohols **2** were investigated (Table 2).¹⁷ Variation of the methyl substituent at 3- and 4-positions on the aryl backbone of **2** did not obviously affect formation of the target products **3b** and **3c** (85–93%), while 2-methylbenzyl alcohol could not efficiently undergo β -alkylation with **1a** due to the increased steric hindrance and the reaction only afforded **3d** in 25% yield. Benzyl alcohols bearing an electron-donating methoxy or 3,4-methylene-dioxy substituent reacted with **1a** to form products **3e** (86%) and **3f** (82%), respectively. Chlorobenzyl alcohols, that is, 3- and

Table 2
Scope of primary alcohols (**2**)^{a,b}



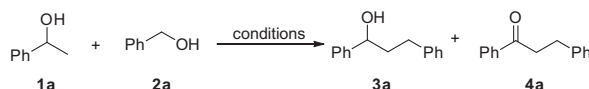
^a Conditions: **1a** (5 mmol), **2** (5 mmol), catalyst **III** (0.075 mol % Pt), K₃PO₄ (0.5 equiv), 155 °C, 0.1 MPa N₂, 48 h.

^b Yields refer to the isolated products.

^c Determined by GC analysis.

4-chlorobenzyl alcohols, also smoothly reacted with **1a** to afford products **3g** (90%) and **3h** (80%). The reaction of **1a** with 1-naphthylmethanol efficiently occurred, forming **3i** in 80% yield. Although 2- and 4-pyridylmethanols efficiently underwent the

Table 1
Screening of reaction conditions^a



Entry	Catalyst	Pt/Sn (molar ratio) ^b	Conv. of 1a (%)	3a : 4a ^c
1	Pt-Sn/ γ -Al ₂ O ₃ (I)	1:1	42	93:7
2	Pt-Sn/ γ -Al ₂ O ₃ (II)	1:2	90	94:6
3	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	99	99:1 (93) ^d
4	Pt-Sn/ γ -Al ₂ O ₃ (IV)	1:5	78	99:1
5	Pt-Sn/ γ -Al ₂ O ₃ (V)	1:7	74	99:1
6	Pt-Sn/ γ -Al ₂ O ₃ (VI)	1:9	74	99:1
7 ^e	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	>99	99:1 (96) ^d
8 ^f	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	98	99:1 (92) ^d
9 ^g	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	>99	73:27
10 ^{g,h}	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	29	88:12
11 ^{g,i}	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	n.r.	
12	PtCl ₂		n.r.	
13	Pt/ γ -Al ₂ O ₃		n.r.	
14 ^j	Pt-Sn/ γ -Al ₂ O ₃ (III)	1:3	n.r.	

^a Conditions: **1a** (5 mmol), **2a** (5 mmol), catalyst (0.075 mol % Pt), K₃PO₄ (0.5 equiv), 145 °C, 0.1 MPa N₂, 48 h. n.r. = no reaction.

^b The Pt content in all of the heterogeneous catalysts is 0.5 wt%.

^c Determined by GC analysis.

^d Isolated yield of **3a** given in parentheses.

^e 155 °C.

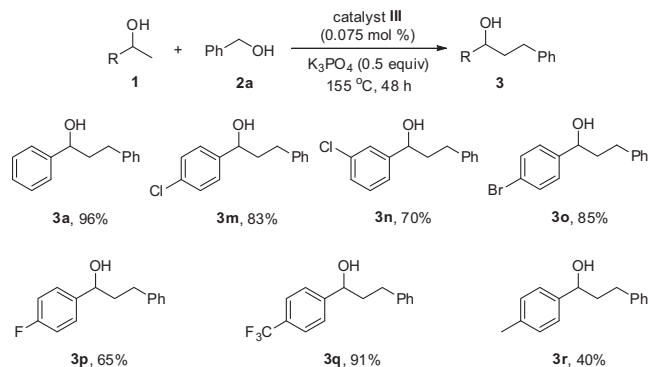
^f K₃PO₄ (0.3 equiv).

^g **1a** (1 mmol), **2a** (1 mmol), catalyst (0.5 mol % Pt), K₃PO₄ (0.5 equiv), *o*-xylene (3 mL), 155 °C, 0.1 MPa N₂, 48 h.

^h Using NaO^tBu (0.5 equiv) instead of K₃PO₄.

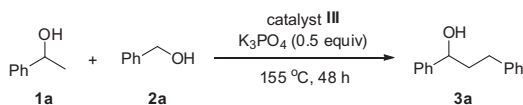
ⁱ Using KOAc (0.5 equiv) instead of K₃PO₄.

^j No base was used.



Scheme 2. Scope of secondary alcohols (**1**). Conditions: **1** (5 mmol), **2a** (5 mmol), catalyst **III** (0.075 mol % Pt), K_3PO_4 (0.5 equiv), 155 °C, 0.1 MPa N_2 , 48 h. Yields refer to the isolated products.

Table 3
Recycling of catalyst **III** from the reaction of **1a** with **2a**^a



Run	Conversion of 1a ^b (%)	Yield ^c (%)
1	>99	96
2	>99	92
3	94	90
4	90	85
5	60	53

^a Conditions: **1a** (5 mmol), **2a** (5 mmol), catalyst **III** (0.075 mol % Pt), K_3PO_4 (0.5 equiv), 155 °C, 0.1 MPa N_2 , 48 h.

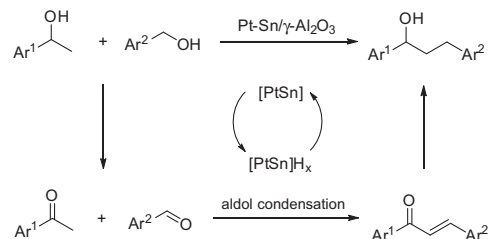
^b Determined by GC analysis.

^c Isolated yield.

β -alkylation with **1a** to afford the corresponding target products **3j** and **3k** (80–94%), 2-furfurylmethanol only demonstrated a poor reactivity to form **3l** in 20% yield. It is noteworthy that other heteroarylmethyl alcohols such as 3-pyridylmethanol and 2-thiophenemethanol, and 2-phenylethanol did not undergo the reactions with **1a** under the same conditions.

Next, the scope of secondary alcohols **1** was explored by means of the reaction with benzyl alcohol (**2a**) (Scheme 2). The present catalytic system could be tolerant with various functional groups such as chloro, bromo, fluoro, trifluoromethyl, and methyl. Secondary alcohols bearing a 4- or 3-Me group underwent the reaction to form the target products **3m** and **3n** (70–83%). 4-Bromo- and 4-fluorobenzyl alcohols reacted to afford **3o** (85%) and **3p** (65%), respectively. Unexpectedly, 4-trifluoromethyl-benzyl alcohol efficiently underwent the reaction to form **3q** in 91% yield. However, electron-donating 4-methyl-substituted secondary benzyl alcohol exhibited a low reactivity to yield the target product **3r** in 40% yield.

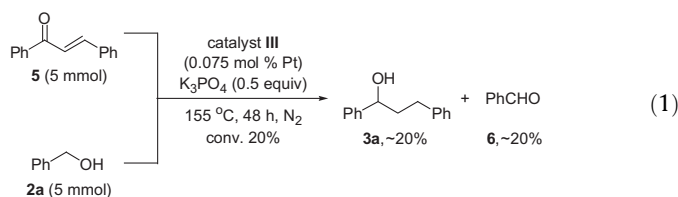
Then, the recyclability of the heterogeneous Pt–Sn/ γ - Al_2O_3 catalyst was evaluated (Table 3). After the first run reaction of **1a** with **2a** was finished, catalyst **III** was filtered, washed with water to remove K_3PO_4 salt, and subjected to calcination in air at 450 °C for 4 h. The recovered catalyst was then reused in the second run β -alkylation of **1a** with **2a** under the standard conditions. It should be noted that after each run reaction was complete, the catalyst was treated in the same fashion for the next run use. For the first two run reactions, the catalyst almost remained the same catalytic activity (Table 3, entries 1 and 2). In the third run obvious loss of catalytic activity was observed, achieving 94% conversion for **1a** and 90% yield for **3a**. In the fourth and fifth runs, the catalyst further lost activity (Table 3, entries 4–5). Analysis of the supernatant from



Scheme 3. Proposed mechanism.

the reaction mixture by ICP-AES technology revealed no Pt metal leaching into the liquid phase in each run reaction. A decrease in the catalytic activity of catalyst **III** after recycling is attributed to the aggregation of Pt nanoparticles on the γ - Al_2O_3 support during the reaction, which reduces the available bare surface of Pt particles catalytically active for the hydrogen borrowing process.

To gain insight into the reaction mechanism, a controlled experiment was conducted (Eqn 1). Under the standard conditions the 1:1 molar ratio reaction of chalcone (**5**) and benzyl alcohol (**2a**) achieved 20% for the starting substrates and formed nearly equimolar amounts of the reduction product **3a** (~20%) and benzaldehyde (**6**, ~20%) by 1H NMR analysis of the reaction mixture. Thus, the reaction of **1** with **2** can be considered to occur through a hydrogen borrowing pathway.



A simplified mechanism is proposed in Scheme 3. Initially, the precatalyst promotes oxidation of the secondary and primary alcohols to the corresponding ketone and aldehyde by generation of the $[PtSn]H_x$ hydride species. Then base-mediated cross-aldol condensation of the *in-situ* formed ketone and aldehyde occurs to form α,β -unsaturated ketone intermediate. Subsequent transfer hydrogenation with $[PtSn]H_x$ species yields the target alcohol.

In summary, an efficient heterogeneous bimetallic Pt–Sn/ γ - Al_2O_3 catalyzed β -alkylation of secondary alcohols with primary alcohols has been realized through a hydrogen borrowing strategy. The present protocol provides a concise and environmentally benign method for C–C bond formation.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.07.037>.

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17. A typical experimental procedure for the β -alkylation of secondary alcohols with primary alcohols – synthesis of **3a**: Under nitrogen atmosphere, to a 15-mL Pyrex glass screw-cap tube were added 1-phenylethanol (**1a**: 0.613 g, 5 mmol), benzyl alcohol (**2a**: 0.543 g, 5 mmol), K_3PO_4 (531 mg, 2.5 mmol), and Pt–Sn/ γ - Al_2O_3 (catalyst **III**: 147 mg, 0.075 mol% Pt). The resultant mixture was stirred in the sealed tube at 155 °C for 48 h. After cooled to ambient temperature, the catalyst and base were removed by centrifugation and washed with Et_2O (2×5 mL). The combined supernatant was condensed under reduced pressure and subject to purification by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording product **3a** as a white solid (1.018 g, 96%).