C–C Cross-Coupling of Primary and Secondary Benzylic Alcohols Using Supported Gold-Based Bimetallic Catalysts

Xiang Liu, Ran-Sheng Ding, Lin He, Yong-Mei Liu, Yong Cao,* He-Yong He, and Kang-Nian Fan[a]

The formation of C–C bonds,[11] a vital approach to increase the molecular complexity of a simple organic substrate, is one of the central themes in modern synthetic chemistry. Although a plethora of methods have been developed, the search for new, mild, efficient, and straightforward routes that minimize waste generation continues to be an active and challenging subject.[12] An elegant method such as the Guerbet reaction for C–C bond construction is the transition-metal-catalyzed direct cross-coupling of alcohols[3–7] by a borrowed hydrogen atom (BH, also known as hydrogen autotransfer).[8] In such a process, readily available, green alcohols undergo sequential dehydrogenation/aldol condensation/transfer hydrogenation to afford higher alcohols or ketones with only water and/or H2 as by-products. To date, relevant studies have largely focused on various Ru- or Ir-based homogeneous systems.[13–15] However, the inherent problems of nonreusability and the necessity of special handling precautions for air-sensitive metal complexes have restricted the utility of these procedures. These limitations reinforce the need for a ligand-free, reusable catalyst system for this type of transformation. In the only two related precedents to this work, Pd/C and Ag/Al2O3 were used as efficient catalysts for direct C–C cross-coupling of secondary and primary alcohols.[9] However, either a sacrificial hydrogen acceptor and/or a considerable amount of inorganic base was required to achieve a high selectivity. From a green and economic viewpoint, there is a great incentive to develop new simple and efficient catalytic protocols that can facilitate direct alcohol cross-coupling under mild, additive-free conditions.

Over the last decade, supported Au nanoparticles (NPs) have emerged as promising new catalytic materials for green organic transformations.[16–18] Au was originally considered to be chemically inert and hence a poor catalyst. However, if small Au particles or clusters are dispersed on a suitable support, Au becomes a highly active and selective catalyst capable of facilitating a broad range of synthetic reactions, which include selective oxidation,[19] chemoselective reduction,[20] and one-pot multistep reactions.[13,14a,b,15] Very recently, from our continuing studies on Au catalysis,[14] we discovered an excellent heterogeneous Au-catalyzed BH strategy that allows rapid and highly selective C–N bond construction by the direct coupling of alcohols with amines under mild, clean conditions.[18] Herein, we demonstrate that bimetallic Au–Pd NPs in combination with a basic layered clay of hydrotalcite (HT)[16] can work as a robust and efficient multitask catalyst for the direct C–C cross-coupling of equimolar amounts of primary and secondary alcohols under additive-free conditions. To the best of our knowledge, this new one-pot, Au-based bimetallic catalytic protocol constitutes the first base-free, recyclable solid catalytic system for clean and efficient C–C bond construction through alcohol cross-coupling.

In a preliminary experiment, a model aldol condensation reaction between benzaldehyde and acetophenone, the key step to form the desired C–C bond, was performed over various noble-metal-free solid materials, and the results are summarized in Table 1. Mg–Al/HT, TiO2, and MgO showed high activities for the desired aldol condensation, and the yields of the target product 1,3-diphenyl-2-propan-1-one (3a) were 92–97% (Table 1, entries 1–3). CeO2 catalyzed the aldol condensation moderately to give 3a in 87% yield (Table 1, entry 4). Other inorganic solid materials, such as Al2O3, ZrO2, SiO2, and La2O3, had far inferior activities toward 3a (Table 1, entries 5–8). To rationalize these results, the surface acidity and basicity of the catalysts were measured by CO2 and NH3 temperature-programmed desorption (CO2/NH3-TPD, Figure S1 a–b and Table S1). In general, the solids that feature prominent surface...
basicity (HT, MgO, CeO₂) can effectively promote the aldol reactions. Interestingly, surface-neutral TiO₂ also exhibits excellent activity for this reaction. However, most importantly and relevantly, after loading with Au, Pt, or Pd, only the highly basic HT is the most appropriate material that can catalyze the desired aldol condensation (Figure S1c and Tables S1 and S2).

Based on these results, we focused on combining the capability of HT-supported metals to facilitate the dehydrogenation of alcohols as well as the subsequent autotransfer reduction of the C=C bond involved in the titrated reaction. To this end, two equivalents of benzyl alcohol (1a) was employed to promote the reduction of the C=C bond of 3a in the presence of a series of HT-supported metal catalysts (see the Supporting Information) under N₂. As can be seen in Table 2, Au/HT has a distinct advantage over other supported noble metals. Notably, Au/HT can effectively catalyze the chemoselective transfer hydrogenation of 3a to give an 83 % yield of the desired product 1,3-diphenyl-propan-1-one (4a; Table 2, entry 1). Ag/HT and Ru/HT also converted 3a, but their activities for this transfer reduction transformation were much lower than that of Au/HT (Table 2, entries 3 and 4). In the presence of Rh/HT or Pt/HT, the yields of 4a were very low (Table 2, entries 5 and 6). A high conversion of 1a was observed with Pd/HT as the catalyst (Table 2, entry 2), however, only a moderate yield of 3a was obtained because a substantial amount of toluene (6a) was produced through the undesired hydrogenolysis of 1a.

Having established suitable conditions for each step of the sequential reaction, we were interested in the use of Au/HT to promote the direct coupling of primary and secondary alcohols to afford the corresponding higher ketones. For this purpose, the reaction between 1-phenylethanol (2a) and 1a was performed in p-xylene under N₂. Gratifyingly, Au supported on HT, which possesses beneficial surface redox and basic properties, gave an impressive conversion of 1a and 2a to achieve 4a in a high yield of 85 % at 120 °C after 5 h (Table 3, entry 1). As metal loading is especially influential for supported metal catalysts, three Au/HT samples with different Au loadings were prepared to explore the optimal catalyst. Interestingly, 0.50 wt % Au/HT gave the highest yield of 4a, and higher or lower Au loadings both decreased the yield of 4a (Table S3).

These results show that an optimal balance between the Au NPs and the basic sites of the HT surface is essential to promote the desired reaction. Thus, the most active and selective 0.50 wt % Au/HT catalyst was selected for further study. Subsequent experiments focused on the effect of the reaction temperature, which revealed that the reaction rate increased dramatically as the reaction temperature increased from 80 to 110 °C but leveled off at 120–135 °C (Table S4, entries 12 and 13). Among the solvents tested, p-xylene was the best, and changing the solvent to mesitylene, o-xylene, and dioxane decreased the yield of 4a to 13, 8, and 2 %, respectively.

To explore the reaction performed with Au/HT in detail, the product evolution of the cross-coupling of 2a and 1a in p-xylene under the conditions of entry 1 in Table 3 was followed by continuous sampling by using GC. As shown in Figure 1A, the desired product 4a was the main product in the initial stage of the reaction. In addition, 2–11 % of 5a was detected during the whole course of the reaction, and there was still approximately 12 % of intermediate 3a present in the final stage of the reaction. Taken together, these results demonstrate that the present Au/HT-catalyzed cross-coupling may proceed through the sequential reaction pathway depicted in Scheme 1. Furthermore, we have confirmed by a set of kinetic experiments that the initial reaction rates for each step of the overall sequential reaction decreases in the order: \( r_1 > r_3 > r_5 > r_6 \).
that used Ag/Al₂O₃,[9a] in which the rate-determining step of the alcohol coupling reaction. In contrast to a previous study amounts of benzaldehyde and chalcone intermediates during (Scheme S1), which accounts for the presence of appreciableScheme 1.

Figure 1. Reaction profiles for the direct cross-coupling of 1a with 2a over Au/HT (A) and Au–Pd(13:1)/HT (B). Reaction conditions: 1a (1 mmol), 2a (1 mmol), p-xylene (3 mL), catalyst (metal: 1 mol%), 120 °C, 5 h under N₂.

(Scheme S1), which accounts for the presence of appreciable amounts of benzaldehyde and chalcone intermediates during the alcohol coupling reaction. In contrast to a previous study that used Ag/Al₂O₃[9a] in which the rate-determining step of the overall reaction was the initial alcohol dehydrogenation mediated by supported Ag clusters, it seems that the controlling step in the present Au/HT-catalyzed system is the transfer reduction of intermediate 3a by the gold hydride (Scheme 1, step c).

In an effort to further improve the selectivity towards 4a, we selected metallic Pd as a promoter for the Au/HT catalyst. Pd was chosen because Pd NPs are well known to catalyze a wide range of reductive transformations, which include dehydrogenation and transfer hydrogenation.[6a,7d,e,g,9b] Given that monometallic Pd/HT appears to be too active but not selective for the desired transformation, we designed a series of Pd-containing bimetallic Au–Pd/HT catalysts with various Au/Pd atomic ratios (13:1–5:2), which were prepared by following the same procedures used for the monometallic Au/HT catalyst. Notably, the addition of a very small amount of Pd dramatically improves the yield of 4a from 85 to 97% (Table 3, entry 3). With an increasing Pd/Au atomic ratio from 1:13 to 2:5 (Table 3, entries 3, 6–8), a gradual decrease in the yield of 4a from 97 to 87% was observed. This may simply be because the undesirable formation of toluene from the disproportionation of 1a is favored at higher Pd loadings. Thus, a 13:1 mixture of Au/Pd provides the most effective catalyst for the titled reaction, which exhibited both excellent selectivity and activity towards the formation of 4a (Figure 1B). The advantage of the Au–Pd(13:1)/HT catalyst becomes clear if the reaction profiles obtained with the Au/HT catalyst (Figure 1A) and the Pd catalyst (Figure S2) are compared. The XRD pattern and TEM image of Au–Pd(13:1)/HT are shown in Figures S3 and S4, respectively, which indicate that the metallic particles are finely dispersed on the surface of HT and that most of the particles are 1–4 nm in diameter. The energy-dispersive X-ray (EDX) spectrum (Figure S5) of a single NP shows the presence of both Au and Pd on a single NP. EDX spectroscopy also shows that some of the NPs are monometallic Au. X-ray photoelectron spectroscopy (XPS) confirmed that the small Pd entities affect the electron densities of Au and the binding energy of Au 4f 7/2 for Au–Pd(13:1)/HT shifts to a higher energy than that of Au/HT by 0.1 eV (Figure S6). Although it is difficult to clarify whether a bulk alloy is formed between Au and Pd, the improved performance of the bimetallic Au–Pd catalyst can be ascribed to the beneficial role of a small amount of Pd to promote the transfer hydrogenation of 3a (Scheme 1, step c).

Au–Pd/HT can be easily separated by filtration after the reaction. Inductively coupled plasma (ICP) analysis confirmed that no Au or Pd was present in the filtrate, which indicates that the catalysis is truly heterogeneous in nature. Moreover, Au–Pd/HT can be reused at least three times and still maintains a complete conversion of 1a to give 4a in up to 96% yield under the same reaction conditions (Table 3, entry 4), in which the average turnover frequency (TOF) and the turnover number (TON, based on total metal) reached up to 20 h⁻¹ and 300, respectively. These values are one or two orders of magnitude greater than those in catalyst systems reported previously, such as Ag/Al₂O₃ (TOF = 0.5 h⁻¹ and TON = 25 at 115 °C).[19a] XRD, TEM, EDX, and XPS results showed no change in the dispersion of the Au NPs or the metallic state of Au before and after reuse, which is in good agreement with the excellent retention of activity (Figures S3–S6).[19a]

Building on these results, we extended this direct Au–Pd-mediated C–C coupling protocol to a wider range of primary and secondary alcohols to produce higher ketones. (Figure 1B)
The substituents were CH₃, CH₃O, F, and Cl. Again, the primary substrate was kept constant (i.e., only synthesis of ketones, the primary substrate was kept constant (i.e., only 1a synthesis of ketones, the primary substrate was kept constant (i.e., only 1a)).

In the second strategy employed for the direct cross-coupling of 1a and 2a to produce the corresponding chalcone 3a, which is known to have a diverse array of biological properties, such as antimalarial, anti-inflammatory, antileishmanial, and anticancer activities, with a high yield under 1 bar O₂ (ca. 90%; Scheme 2).

![Scheme 2. Aerobic cross-coupling reaction of 1a with 2a under O₂.](image)

In conclusion, we have demonstrated the noteworthy features of solid multifunctional Au–Pd/HT for direct and effective C–C cross-coupling of primary and secondary alcohols through a facile BH pathway. This process has prominent advantages compared with previous alcohol cross-coupling methods: (a) high catalytic activity and selectivity, (b) no external H₂ or other sacrificial agent is necessary, (c) no need to apply a base, and (d) no stabilizing ligands and/or co-catalysts are necessary. The reaction chemistry demonstrated herein will promote the application of the BH strategy in clean and atom-economical chemical processes.

### Experimental Section

**Preparation of Au/HT catalysts:** HT was synthesized according to a literature procedure. A modified deposition–precipitation (DP) procedure was employed to prepare Au/HT. HT (1.0 g) was dispersed in an aqueous solution of HAuCl₄·4H₂O (50 mL, 1.0 M), 1 bar N₂; n.r. = no reaction; n.d. = not detected. (b) Conversion and yield based on alcohol consumption. Numbers in parenthesis refer to yields of isolated products.

**Table 4. Reaction of primary and secondary alcohols.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>t [h]</th>
<th>Conversion [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>5</td>
<td>100</td>
<td>97 (95)</td>
</tr>
<tr>
<td>2</td>
<td>p-MeC₆H₄</td>
<td>Ph</td>
<td>5</td>
<td>100</td>
<td>93 (90)</td>
</tr>
<tr>
<td>3</td>
<td>p-CIC₆H₄</td>
<td>Ph</td>
<td>5</td>
<td>100</td>
<td>90 (85)</td>
</tr>
<tr>
<td>4</td>
<td>m-CIC₆H₄</td>
<td>Ph</td>
<td>8</td>
<td>100</td>
<td>87 (84)</td>
</tr>
<tr>
<td>5</td>
<td>p-MeOC₆H₄</td>
<td>Ph</td>
<td>8</td>
<td>100</td>
<td>80 (77)</td>
</tr>
<tr>
<td>6</td>
<td>o-MeOC₆H₄</td>
<td>Ph</td>
<td>8</td>
<td>100</td>
<td>72 (69)</td>
</tr>
<tr>
<td>7</td>
<td>p-PrC₆H₄</td>
<td>Ph</td>
<td>8</td>
<td>100</td>
<td>89 (85)</td>
</tr>
<tr>
<td>8</td>
<td>p-C₆H₄Cl</td>
<td>Ph</td>
<td>8</td>
<td>100</td>
<td>71 (68)</td>
</tr>
<tr>
<td>9</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>36</td>
<td>100</td>
<td>82 (78)</td>
</tr>
<tr>
<td>10</td>
<td>2-pyridyl</td>
<td>Ph</td>
<td>20</td>
<td>100</td>
<td>82 (77)</td>
</tr>
<tr>
<td>11</td>
<td>nBu</td>
<td>Ph</td>
<td>24</td>
<td>n.r.</td>
<td>n.d.</td>
</tr>
<tr>
<td>12</td>
<td>n-pentyl</td>
<td>Ph</td>
<td>24</td>
<td>n.r.</td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>p-MeC₆H₄</td>
<td>8</td>
<td>100</td>
<td>91 (88)</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>p-MeOC₆H₄</td>
<td>8</td>
<td>100</td>
<td>86 (83)</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>p-FC₆H₄</td>
<td>8</td>
<td>100</td>
<td>81 (77)</td>
</tr>
<tr>
<td>16</td>
<td>Ph</td>
<td>p-C₆H₄Cl</td>
<td>8</td>
<td>100</td>
<td>83 (76)</td>
</tr>
</tbody>
</table>

(a) Reaction conditions: primary alcohol (1 mmol), secondary alcohol (1 mmol), p-xylene (3 mL), Au-Pd (1 mol%), 120 °C, 1 bar N₂; n.r. = no reaction; n.d. = not detected. (b) Conversion and yield based on alcohol consumption. Numbers in parenthesis refer to yields of isolated products.

The reaction chemistry demonstrated herein will promote the application of the BH strategy in clean and atom-economical chemical processes.

**Experimental Section**

The applicability of the heterogeneous Au–Pd/HT-based protocol is highlighted by the one-pot synthesis of 4a by the direct cross-coupling of 1a and 2a under solvent-free conditions. Notably, the in situ C–C bond formation on a 10 mmol scale proceeds smoothly at 130 °C, and 4a was obtained in an impressive yield of 89% in the presence of Au–Pd/HT.

**Preparation of Au/HT catalysts:** HT was synthesized according to a literature procedure. A modified deposition–precipitation (DP) procedure was employed to prepare Au/HT. HT (1.0 g) was dispersed in an aqueous solution of HAuCl₄·4H₂O (50 mL, 1.02 × 10⁻⁵ M) with vigorous stirring. After agitation for 2 h at 25 °C, the mixture was filtered and washed thoroughly with deionized water until no Cl⁻ was detected in the filtrate by using AgNO₃. The resulting compound was dried for 12 h under vacuum at rt and reduced by using 5 % H₂/Ar at 300 °C for 2 h. Elemental analysis revealed that the Au loading of Au/HT was 0.5 wt%.

**General procedure for the direct cross-coupling of alcohols:** A mixture of primary alcohol (1 mmol), secondary alcohol (1 mmol), catalyst (1 mol % metal), p-xylene (3 mL), and n-dodecane (10 µL) as an internal standard was vigorously stirred at 120 °C under N₂ (1 bar). The product was identified by GC–MS, and the
spectra obtained were compared with those of standards. The conversion and product selectivity were determined by using a GC-17 A equipped with an HP-FFAP column (30 m x 0.25 mm) and a flame ionization detector (FID). For isolation, the combined organic components were concentrated under reduced pressure and purified by using silica-gel column chromatography.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20873026 and 21073042), New Century Excellent Talents in the University of China (NCET-09-0305), the National Basic Research Program of China (2009CB623506), and the Science and Technology Commission of Shanghai Municipality (08DZ2270500 and 12ZR1401500).

Keywords: alcohols · cross-coupling · gold · ketones · palladium


Received: October 25, 2012
Published online on March 26, 2013

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
ChemSusChem 2013, 6, 604 – 608 608