

Efficient and Clean Gold-Catalyzed One-Pot Selective N-Alkylation of Amines with Alcohols

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The N-alkylation of primary amines to secondary amines is of fundamental importance in organic synthesis, granting access to valuable N-alkylamines that are widely used as pharmacophores in numerous biologically active compounds, dyes, agrochemicals and functionalized materials.^[1] The most commonly used method for N-alkylation is the coupling of amines with alkyl halides^[2] in the presence of stoichiometric amounts of bases. This procedure, however, can be problematic due to overalkylation, the toxic nature of many alkyl halides, as well as the concomitant formation of large quantities of undesired waste. An alternative environmentally-benign approach is the N-alkylation of amines with readily available alcohols via hydrogen autotransfer,^[3] also known as hydrogen-borrowing process.^[4] The application of alcohols as alkylating agents has the benefit of high atom efficiency and the formation of water as the only side product. Until now, reports are largely focused on Ru-^[5] or Ir-^[6] based homogeneous systems, which are not practically useful because of the problem of reusability and/or the indispensable use of large amounts of additives or co-catalysts. Although there are several reports on the cross-coupling of amines and alcohols using heterogeneous catalysts,^[7] most of them suffer from harsh reaction conditions, low turnover numbers (TONs) and frequencies (TOFs), limited substrate scope, and/or the use of excess alcohols/amines to achieve high yields.

Catalysts based on supported gold nanoparticles (NPs) have shown their efficiency in a broad range of transformations.^[8] We and others have recently reported that supported gold NPs acted as robust catalysts for the transfer hydroge-

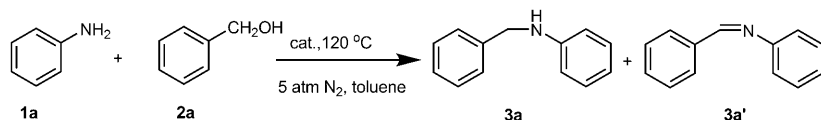
nation (TH) of carbonyl compounds with 2-propanol^[9] and oxidant-free dehydrogenation of alcohols under mild conditions.^[10] The excellent performance of gold catalysts for hydride transfer has led us to investigate the possibilities offered by Au catalysts for one-pot N-alkylation of amines using alcohols as alkylating agents. Herein, we present a simple and versatile gold-catalyzed system for highly selective N-alkylation of amines under mild conditions. The catalytic system described here is one promising candidate for the direct coupling of amines and alcohols because of the following advantages: i) extremely high atom-economical system achieved by the employment of equimolar amounts of starting materials with water as the sole by-product; ii) high catalytic activity and selectivity; iii) without any additives and/or cocatalysts, and iv) the reaction can proceed smoothly under a 100 mmol scale solvent-free conditions. To the best of our knowledge, this new heterogeneous Au-mediated catalysis is greener than any of the known alternatives and involves an easy work up.

Initially, the catalytic activity and selectivity for the additive-free reaction of equimolar amounts of aniline (**1a**) and benzyl alcohol (**2a**) to give *N*-phenylbenzylamine (**3a**) were compared by using various catalysts (Table 1). The titania supported gold catalysts such as Au/TiO₂-WGC (provided by the World Gold Council) and Au/TiO₂-VS (very small Au NPs ca. 1.8 nm, see Supporting Information) showed high activities for the transformation (entries 1–3); in particular, the reaction with Au/TiO₂-VS gave **3a** in 92% yield with high selectivity (entry 1). In this case, the average TOF and the TON reached up to 13.1 h⁻¹ and 184, respectively. There are very few catalysts that are effective under such benign conditions, the most prominent of which is a homogeneous [Cp*IrCl₂]₂ complex in the presence of a large excess of NaHCO₃ (TOF: 5.5 h⁻¹, TON: 94).^[6b] In the absence of the catalyst, the desired secondary amine **3a** was not produced. No formation of **3a** was observed in the presence of just TiO₂ (entry 12). Under the conditions described in Table 1, Au deposited on other supports as well as Pd, Ru catalysts supported on TiO₂ were not effective (entries 4–

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Table 1. Direct N-alkylation of aniline with benzyl alcohol (1:1 molar ratio) by various catalysts.^[a]



Entry	Catalyst	<i>t</i> [h]	Conv. [%] ^[c,d]	Yield [%] ^[d]		Others
				3a	3a'	
1	Au/TiO ₂ -VS	14	>99	92	7.5	<0.5
2 ^[b]	Au/TiO ₂ -VS	19	>99	91	8	<1
3	Au/TiO ₂ -WGC	14	71	64	6	1
4	Au/Al ₂ O ₃	14	49	36	11	2
5	Au/MgO	14	36	16	16	4
6	Au/ZnO	14	38	22	13	3
7	Au/HAP	14	29	21	6	2
8	Au/CeO ₂	14	24	15	8	1
9	Au/SiO ₂	14	19	6	12	1
10	Pd/TiO ₂	14	41	22	17	2
11	Ru/TiO ₂	14	22	16	5	1
12	TiO ₂ (P25)	14	n.r.	–	–	–

[a] Reaction conditions: aniline (1.5 mmol), benzyl alcohol (1.5 mmol), toluene (1 mL), catalyst (metal: 0.5 mol %), 120 °C, 5 atm N₂. n.r. = no reaction. [b] Third run. [c] Conversions based on benzyl alcohol consumption. [d] Determined by GC using *n*-dodecane as the internal standard.

11), although Au/Al₂O₃ gave moderate yield of **3a**, the undesirable **3a'** was also produced as a by-product (entry 4).

The reaction was completely terminated by the removal of Au/TiO₂-VS from the reaction mixture after 40 % conversion of **1a** at 120 °C. Further treatment of the filtrate under the same reaction conditions did not give any products. Moreover, ICP analysis of the filtrate confirmed that the Au content was below the detection limit (<0.10 ppm). Additionally, the recovered Au/TiO₂-VS could be reused at least three runs without appreciable loss of the original catalytic activity (Table 1, entry 2). These results indicate that the observed catalysis is truly heterogeneous.

Next, the scope of the present Au/TiO₂-VS catalyzed system with regard to various combinations of amines and alcohols (1:1 molar ratio for all examples) was examined. Table 2 showed that the catalyst system was surprisingly versatile. Structurally diverse alcohols, including aromatic, aliphatic ones react with aniline to

give the desired products in excellent yields (Table 2, entries 1–11). Benzyl alcohols with electron-donating groups react smoothly (entries 2–4), while substitution of electron-withdrawing group on the benzene ring decreases the reactivity (entry 5). The notoriously difficult secondary alcohols (entries 6, 8 and 9) were successfully converted without any additives, which has no precedent in the literature. Moreover, transformation of other nonactivated aliphatic alcohols proceeded smoothly to produce the corresponding secondary amines in high yields (entries 10, 11). The most noteworthy example is the reaction of phenethyl alcohol with aniline to give a 2-phenylethanamine derivative (entry 7),

Table 2. Au/TiO₂-VS-catalyzed amine alkylation with alcohols.^[a]

$R^1NH_2 + R^2R^3CHOH (R^2OH) \xrightarrow[5 \text{ atm } N_2, \text{ toluene}]{Au/TiO_2-VS} R^1NH-CHR^2R^3$					
Entry	Amine	Alcohol	<i>t</i> [h]	Conv. [%] ^[c]	Yield [%] ^[d]
1			14	>99	92 (90)
2			12	>99	92
3			5	>99	98 (95)
4			13.5	>99	95
5 ^[b]			42	97	87
6 ^[b]			36	98	93 (90)
7 ^[b]			19	>99	96
8 ^[b]			40	97	94
9 ^[b]			43	98	92
10 ^[b]			48	98	96 (92)
11 ^[b]			45	96	93

Table 2. (Continued)

Entry	Amine	Alcohol	<i>t</i> [h]	Conv. [%] ^[e]	Yield [%] ^[f]
12			24	> 99	93
13			28	> 99	96
14			20	> 99	96
15			36	98	95
16			20	> 99	90 (87)
17 ^[c]			31	> 99	85
18 ^[c]			26	> 99	86
19 ^[d]			49	71	51 ^[h]
20 ^[d]			55	74	53 ^[h]
21 ^[d]			63	69	50 ^[h]

[a] Reaction conditions: amine (1.5 mmol), alcohol (1.5 mmol), toluene (1 mL), 0.5 mol % Au, 120 °C, 5 atm N₂. [b] Amine (1.5 mmol), alcohol (1.5 mmol), toluene (1 mL), 1 mol % Au, 140 °C, 5 atm N₂. [c] Amine (0.5 mmol), alcohol (0.5 mmol), toluene (1 mL), 2 mol % Au, 140 °C, 5 atm N₂. [d] Amine (0.15 mmol), alcohol (0.15 mmol), toluene (1 mL), 5 mol % Au, 140 °C, 5 atm N₂. [e] Conversions based on alcohols consumption. Determined by GC using *n*-dodecane as the internal standard. [f] Numbers in parenthesis refer to yields of isolated products. [h] In these cases, not only alcohols serve as alkylating agents, but also amines themselves can act as alkylating agents, leading to undesired formation of appreciable amount of self-coupling products.

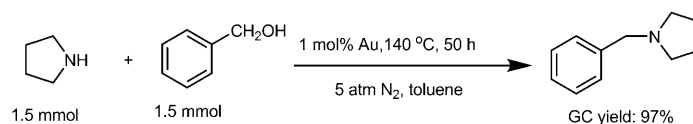
a common structural feature found in many medicinal drugs such as Piriton^[11] and Tripeleminam.^[12]

Furthermore, the reaction also proceeds successfully with a number of other primary amines. The transformation of substituted anilines with benzyl alcohol afforded the corresponding secondary amines in high yields (entries 12–16). Aliphatic amines, which are difficult to react, could also proceed smoothly to generate the corresponding amines (entries 17, 18). In the more challenging reactions employing aliphatic amines and aliphatic alcohols as the reactants, relatively larger amounts of the Au catalyst were required to obtain moderate yields (entries 19–21). Nevertheless, the performance was still encouraging since these transformations by using heterogeneous catalysts were scarcely described in the literature. Inspired by these results we became interested in the synthesis of tertiary amine by N-alkylation of secondary amines with alcohols. Pyrrolidine is chosen as the starting amine as it is one of the simplest alkaloid structures^[13] in many important nat-

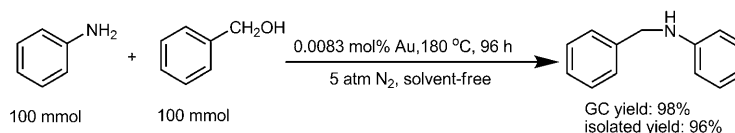
ural products, for example, proline, as well as pharmaceuticals such as retronecine and opioid receptor agonists (CJ-15161). The reaction of this cyclic amine with benzyl alcohol gave the desired tertiary amine in excellent yield after 50 h at 140 °C (see Scheme 1).

A heterogeneous direct N-alkylation without solvents would be more desirable for practical applications. Notably, the Au/TiO₂-VS catalyst system can facilitate the 100 mmol-scale selective N-alkylation of aniline with benzyl alcohol under neat conditions at 180 °C (see Scheme 2). After completion of the reaction, an impressive selectivity (98 %) was achieved and 17.6 g of the corresponding benzylphenylamine (isolated yield ca. 96 %) could be isolated in high purity via a simple work up.^[14]

In analogy to previously reported homogeneous systems,^[3a,5,7] the present Au-catalyzed N-alkylation may proceed through a sequential reaction pathway in which three elemen-



Scheme 1. Au/TiO₂-VS-catalyzed N-alkylation of pyrrolidine with benzyl alcohol.



Scheme 2. 100 mmol scale N-alkylation of aniline with benzyl alcohol under solvent-free conditions.

tary steps (alcohol dehydrogenation, imine formation and hydrogenation) are involved. Nevertheless, several unusual phenomena have been observed for the present heterogeneous Au-mediated system: i) The reaction between aniline and benzaldehyde in the presence of a hydrogen donor (2-propanol) under the same conditions led to exclusive formation of the corresponding imine with no desired amine prod-

uct generation; ii) the treatment of *N*-benzylideneaniline with benzyl alcohol under identical reaction condition resulted in the formation of only a trace amount of *N*-phenylbenzylamine, and iii) during aniline alkylation with benzyl alcohol, a small portion of imine (<7.5%) released from the catalyst, which became the main byproduct and can not be converted into the desired product by extending the reaction time (see Figure S3). Thus, being different from previously reported systems (for example, [Ru(*p*-cymene)Cl₂]₂,^[5] Ru(OH)_x/Al₂O₃,^[7a] Pd/MgO^[7c]), the results described in the present work show clearly a unique character of the TiO₂ supported Au for N-alkylation of amine with alcohols. Most importantly, it turns out that the present gold-catalyzed amine alkylation with alcohol does not involve the free imine/aldehyde species.

Although detailed mechanistic studies remain to be carried out, an initial β-hydride elimination of the alcohol may be involved in the rate-determining step based on the negative Hammett ρ value as found for the competitive N-alkylation of aniline with various substituted benzyl alcohols (ρ = -1.32, r² = 0.99, see Figure S4). Taking into account the superior hydrogen transfer activity previously established for the titania supported Au system,^[9] this may well explain the enhanced N-alkylation activity as observed for Au/TiO₂-VS (see Table 1). In this context, one may assume that the reaction could be further facilitated by the addition of a weak base, which can promote the initial alcohol dehydrogenation step.^[9] Nevertheless, a significantly retarded formation of the desired secondary amine has been identified when the reaction was conducted with Au/TiO₂-VS in the presence of Cs₂CO₃.^[15] Note that this result agrees very well with the work of Ishida et al.,^[16] who found that gold supported on TiO₂ gave similar selectivity (approx. 30%) for the formation of *N*-phenylbenzylamine under identical basic conditions. Therefore, it seems that other factors such as the delicate interaction of the Au/TiO₂-VS with the involved substrates or intermediates might also be a prerequisite for the desired reaction pathway. Indeed, we have observed that the presence of higher concentration of benzaldehyde would strongly inhibit the final formation of desired *N*-phenylbenzylamine with the present gold-catalyzed system.^[17]

In summary, very small gold nanoparticles supported on titania acts as an efficient heterogeneous catalyst for the clean and atom-efficient N-alkylation of amines with alcohols in excellent yields under mild and base-free conditions. This new catalytic system can provide a versatile and environmentally benign protocol for the economic synthesis of amines.

Experimental Section

General procedure for the direct N-alkylation of alcohols and amines: A mixture of amine (1.5 mmol), alcohol (1.5 mmol), metal catalysts (0.5 mol% metal), toluene (1 mL), and *n*-dodecane (10 μL) as internal standard were placed into a Teflon-lined autoclave (4 mL capacity). The resulting mixture was vigorously stirred at 120 °C under N₂ atmosphere (5 atm) for given reaction time. The product was identified by GC-MS

and the spectra obtained were compared with the standard spectra. The conversion and product selectivity were determined by GC-17A gas chromatograph equipped with a HP-FFAP column (30 m × 0.25 mm) and a flame ionization detector (FID). For isolation, the combined organic layer was dried over anhydrous Na₂SO₄, concentrated, and purified by silica gel column chromatography.

Direct N-alkylation of pyrrolidine with benzyl alcohol by using Au/TiO₂-VS: A mixture of pyrrolidine (1.5 mmol), benzyl alcohol (1.5 mmol), Au/TiO₂-VS (1 mol% Au), toluene (1 mL) and *n*-dodecane (10 μL) as internal standard were placed into a Teflon-lined autoclave (4 mL capacity). The resulting mixture was vigorously stirred at 140 °C under N₂ atmosphere (5 atm) for given reaction time. The product was identified by GC-MS.

100 mmol scale N-alkylation of aniline with benzyl alcohol under solvent-free conditions: A mixture of aniline (100 mmol, 9.3 g), benzyl alcohol (100 mmol, 10.8 g), and Au/TiO₂-VS (0.0083 mol% Au) were placed into an autoclave (50 mL capacity). The resulting mixture was vigorously stirred at 180 °C under N₂ atmosphere (5 atm) for given reaction time. For isolation, the combined organic layer was dried over anhydrous Na₂SO₄, concentrated, and purified by silica gel column chromatography to yield the corresponding benzylphenylamine (17.6 g, isolated yield ca. 96%).

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Keywords: alcohols • alkylation • gold • nanoparticles • N-alkylation

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- [14] Although Pd/MgO reported by Corma et al. (see ref. [7c]) showed a higher activity at 180 °C, the system suffers from low yield (for example, 79% for *N*-phenylbenzylamine, 35% for *N*-octylbenzylamine) and the use of excess amines to achieve high activity (alcohol/amine 1:3 for most cases).
- [15] Reaction conditions: aniline (1.5 mmol), benzyl alcohol (1.5 mmol), Cs₂CO₃ (1.5 mmol), toluene (1 mL), Au/TiO₂-VS (Au: 0.5 mol%), 120 °C, 5 atm N₂. Under identical conditions, conversion based on benzyl alcohol is ≈20% after 14 h with 30% selectivity for *N*-phenylbenzylamine. The undesirable imine (*N*-benzylideneaniline) was produced as a main by-product in high selectivity (≈50%).
- [16] Very recently, N-alkylation of primary amine with alcohol to afford secondary amines by Au/Al-MIL53 ([Al(OH)(bdc)], bdc=benzene-1,4-dicarboxylate) and Au/TiO₂ systems (in presence of basic CsCO₃) was demonstrated by Ishida et al. (see ref. [7d]), but the yield of *N*-phenylbenzylamine never exceeded 50%. In addition, the recycled reuse of the Au/Al-MIL53 was difficult, due to the severe aggregation of Au clusters to form larger NPs (>10 nm) after the reaction.
- [17] A crossover experiment was carried out with benzyl alcohol (0.75 mmol) and benzaldehyde (0.75 mmol), which were reacted with aniline (1.5 mmol) in the presence of Au/TiO₂-VS (0.5 mol% Au). Under these conditions, the aldehyde was immediately converted into the imine, while the alcohol reacted slowly to form the corresponding amine with about only 5% yield after 14 h.

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