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Formation of imines by selective gold-catalysed aerobic oxidative coupling of alcohols and amines under ambient conditions

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The formation of imines by aerobic oxidative coupling of mixtures of alcohols and amines was studied using gold nanoparticles supported on titanium dioxide, TiO_2, as a heterogeneous catalyst. The reactions were performed at ambient conditions (room temperature and atmospheric pressure) and occurred with excellent selectivity (above 98%) at moderate conversion under optimized conditions. The effect of catalytic amounts of different bases was studied, along with reaction temperature and time. Utilisation of a selective catalyst system that uses dioxygen as an oxidant and only produces water as by-product represents a new green reaction protocol for imine formation.

Introduction

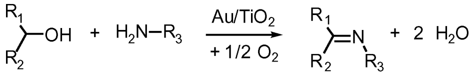
In recent years there has been a rising demand for efficient heterogeneously catalysed processes for the oxidation of alcohols for production of both fine and bulk chemicals.[1] So far, these industrially important oxidations have often been carried out using stoichiometric amounts of high-valent inorganic reagents, such as chromate or permanganate, which inevitably leads to the generation of large amounts of metal waste.[2]

In order to avoid undesirable waste formation, considerable effort has been put into the development of aerobic oxidation methods using molecular oxygen as the stoichiometric reagent. These methods represent a much greener and highly atom-efficient alternative, as oxygen is a cheap and abundant oxidant that produces water as the only by-product. Efficient aerobic oxidation is, however, strongly dependent on a good heterogeneous catalyst which readily provides oxygen activation.[3]

Dissolved gold metal has rich coordination and organometallic chemistry.[4] In contrast, bulk gold metal is chemically inert and the element has therefore often been regarded as a poor catalyst. Fundamental studies by Bond *et al.*,[5] Hutchings,[6] Haruta *et al.*[7] and Prati and Rossi[8] have triggered renewed interest in heterogeneous gold catalysis, and during recent years it has been shown that supported gold nanoparticles (typically with particle sizes of 1–5 nm) are surprisingly active and selective catalysts in a number of oxidation reactions of organic substrates.[9-11] For instance, gold nanoparticles have been successfully used in the oxidation of alcohols to aldehydes,[12] carboxylic acids[8,13,14] or esters,[15,16] in the oxidation of aldehydes to esters[17,18] or acids,[19,20] and in the epoxidation of alkenes.[21,22]

In addition to the above-mentioned oxidations, interesting studies have also recently been performed on oxidation of amines and mixtures of amines and alcohols or aldehydes. Thus, supported gold nanoparticles have been used in oxidation of amines to amides,[23,24] azo-compounds,[25] and – prior to this study – in formation of imines[26,27] and secondary amines.[28] So far, the application range of supported gold is still limited in organic chemistry, and the increasing number of reports on oxidation of nitrogen-containing hydrocarbons thus represents a very interesting development in this emerging field.

In this work, we show that gold nanoparticles supported on titanium dioxide, TiO_2, are an active and highly selective heterogeneous catalyst in the oxidative coupling of alcohols (particularly benzylic alcohols) with amines to form the corresponding imines, as depicted in Scheme 1. The employed oxidising agent was molecular oxygen and the reactions were conducted under ambient conditions (room temperature and atmospheric pressure). The effect of adding catalytic amounts of different bases was studied along with the effect of reaction temperature and time. Catalytic and selective synthesis of imines at ambient condition with dioxygen and a catalytic amount of base is an attractive extension of current "green" oxidations.



Scheme 1 Au-catalysed formation of imines by oxidative coupling of a primary or secondary alcohol and a primary amine.

The oxidation procedure was performed successfully with a number of primary and secondary benzylic alcohols and primary amines, demonstrating the benign reaction protocol to be versatile and applicable to a broad range of substrates. This makes the method an attractive alternative to previously reported approaches, including the recently reported synthesis route by Gnanaprakasam *et al.*[29] using a homogeneous ruthenium-based catalyst.

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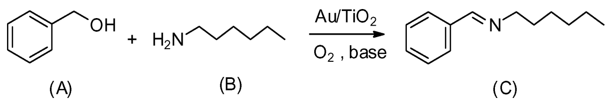
Results and discussion

Initially, benzyl alcohol (A) and 1-hexylamine (B) were used as substrates to study the effects of different reaction parameters in the synthesis of *N*-benzylidenehexan-1-amine (C), see Scheme 2.



Scheme 2 Synthesis of *N*-benzylidenehexan-1-amine (C) from benzyl alcohol (A) and 1-hexylamine (B) by oxidative coupling in the presence of Au/TiO_2 catalyst.

The results in Table 1 show the effect on conversion and selectivity after a reaction time of 24 h by addition of different bases to the reaction. Methanol solutions of lithium methoxide, sodium methoxide, and potassium methoxide were purchased and applied as base reagents. In principle, however, the solid methoxides or corresponding hydroxides could also have been utilised directly.

As is evident from Table 1, it proved possible to couple benzyl alcohol and 1-hexylamine at ambient conditions, forming *N*-benzylidenehexan-1-amine in very high selectively (97–98%). Only small amounts of *N*-hexylbenzamide were formed (confirmed by GC-MS). The gold-catalysed formation of amides from alcohols and amines has previously been reported by Christensen *et al.*[23] at high temperatures, *i.e.* >90 °C. The formation of amides was, however, suppressed at lower temperature and only the imines were formed at room temperature.

The presence of a catalytic amount of base was found to be essential for the conversion of substrate (Table 1, entry 1–3), since no reaction occurred in the absence of base (Table 1, entry 4). Additionally, the yield of imine was apparently dependent on the alkaline metal applied in the methoxide base. Hence, lithium methoxide resulted in an overall imine yield of 17%, sodium methoxide in 39% and potassium methoxide in 49%, under identical reaction conditions. This observation suggests a possible interference of the alkali ions with the gold catalysts resulting in a promoting effect. Promoted gold catalysts with alkali or alkaline earth metal have previously been reported in the literature for carbon monoxide oxidation.[30,31]

Carrying out the reaction with pure TiO_2 (Table 1, entry 5) did not result in any conversion, which verified that the gold nanoparticles were required to obtain catalytic activity.

The effect of potassium methoxide was further investigated by altering the catalytic amount from 0% to 30% (mole base/mole alcohol). Table 2 shows the yield of *N*-benzylidenehexan-1-amine formed as a function of the amount of potassium methoxide added, after 24 h of reaction.

Table 1 Synthesis of *N*-benzylidenehexan-1-amine from benzyl alcohol and 1-hexylamine using different bases.[a]

Entry	Catalyst	Base	Conversion [%]	Selectivity [%]
1	Au/TiO_2	$LiOCH_3$	18	97
2	Au/TiO_2	$NaOCH_3$	40	98
3	Au/TiO_2	$KOCH_3$	51	98
4	Au/TiO_2	None	1	97
5	pure TiO_2	$KOCH_3$	0	0

[a] All reactions were carried out at room temperature under atmospheric pressure of oxygen for 24 h using 10 mol% base (mole base/mole alcohol).

Table 2 *N*-benzylidenehexan-1-amine formation from oxidative coupling of benzyl alcohol and 1-hexylamine as a function of the amount of base added.[a]

Entry	Catalyst	Added $KOCH_3$ [mol%][b]	Yield [%]
1	Au/TiO_2	0	1
2	Au/TiO_2	5	45
3	Au/TiO_2	10	49
4	Au/TiO_2	20	52
5	Au/TiO_2	30	52

[a] All reactions were carried out at room temperature under atmospheric pressure of oxygen for 24 h. [b] As mole base/mole alcohol.

Table 3 Yield of *N*-benzylidenehexan-1-amine formed from oxidative coupling of benzyl alcohol and 1-hexylamine as a function of the reaction temperature.[a]

Entry	Catalyst	T [°C]	Yield [%]
1	Au/TiO_2	20	49
2	Au/TiO_2	40	56
3	Au/TiO_2	60	57
4	Au/TiO_2	65	44

[a] All reactions were carried out under atmospheric pressure of oxygen for 24 h using 10 mol% $KOCH_3$ (mole base/mole alcohol).

The yield of imine increased significantly from around 1% with no added base, to a yield of 49% at 10 mol% potassium methoxide, clearly signifying the requirement for having base present during the reaction, as shown previously for other Au-catalysed oxidations.[16,17] Further increase of the amount of base to 20 or 30 mol% had little effect on the yield. It is worth noting that the reaction selectivity remained high and unaffected by the amount of base in all reactions.

Table 3 shows the effect on formation of *N*-benzylidenehexan-1-amine by varying the reaction temperature. The temperature effect was investigated by maintaining the amount of base at 10 mol% potassium methoxide and the reaction time at 24 h.

As shown in Table 3, the yield only increased slightly from 49% at room temperature to 56% at 40 °C and to 57% at 60 °C, respectively. However, at 65 °C (boiling point of methanol) the yield dropped to 44%, suggesting that the rate of formation was possibly reduced due to inadequate oxygen solubility. Importantly, the increased temperatures had no effect on the selectivity and the only by-product formed was *N*-hexylbenzamide in yields less than 2–3%.

In order to investigate if oxygen solubility was rate-limiting (also at lower temperatures), a reaction was performed in a thoroughly stirred autoclave at room temperature at 10 bars of oxygen in presence of 10 mol% potassium methoxide. Under these conditions the amount of dissolved oxygen in the methanol solvent was expected to be significantly higher than at ambient pressure. After a reaction time of 24 h 47% of the 1-hexylamine was converted into *N*-benzylidenehexan-1-amine with 92% selectivity, corresponding to an overall imine yield of 43%. This showed that an increased amount of dissolved oxygen had no significant effect on the conversion, but that the selectivity was decreased somewhat as more amide was formed.

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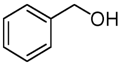
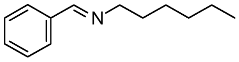
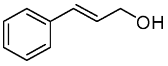
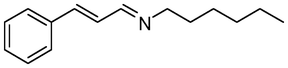
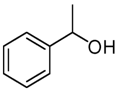
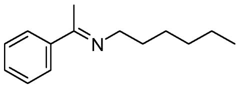
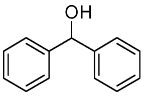
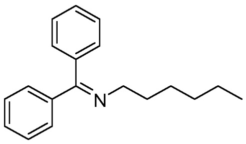
Table 4 Conversion and selectivity obtained in the oxidative couplings of 1-hexylamine (B) and different alcohols (see Scheme 1 and Scheme 2).[a]

Entry	Alcohol	Product	Conversion [%]	Selectivity [%]
1			51	98
2			63	99
3			14	99
4			0	—

[a] Reactions were carried out at room temperature under atmospheric pressure of oxygen for 24 h using 10 mol% $KOCH_3$ (mole base/mole alcohol).

Thus, the limited increase in yield as a function of temperature could not be directly related to the amount of dissolved oxygen.

In an attempt to increase the yield of *N*-benzylidenehexan-1-amine formation, the reaction was also performed using ten times more catalyst, *i.e.* 875 mg of catalyst (0.2 mol%) instead of 87.5 mg (0.02 mol%) as used in the prior experiments. Product formation in analogous reactions with different amounts of catalysts was followed as a function of the reaction time, shown in Fig. 1.

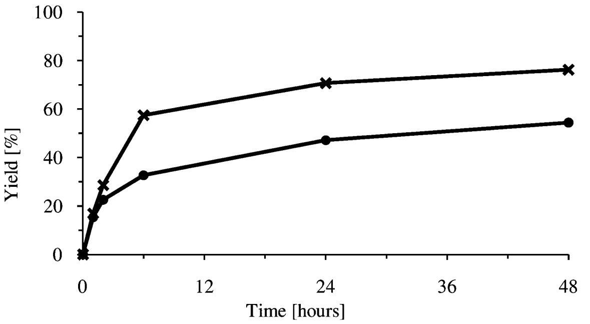


Fig. 1 Yield of *N*-benzylidenehexan-1-amine formed from oxidative coupling of benzyl alcohol and 1-hexylamine as a function of the reaction time. Reactions were carried out at room temperature under atmospheric pressure of oxygen using 10 mol% $KOCH_3$ with 87.5 mg (0.02 mol%) (●) and 875 mg (0.2 mol%) (×) of Au/TiO_2 catalyst, respectively.

As expected, the yield increased with both reaction time and the amount of added catalyst. Hence, for the reaction containing 0.02 mol% (87.5 mg) of catalyst the yield of imine increased from 49% after 24 h to 53% after 48 h, whereas the yield increased from 71 to 76% after 24 and 48 h, respectively, for the reaction containing 0.2 mol% (875 mg) of catalyst. Notably, the initial reaction rates were found to be practically identical for the two reactions despite the much higher content of catalyst in the latter reaction. This observation indicated that reaction progression was governed by the substrate availability.

The protocol for the oxidative coupling of alcohol and amine mixtures was extended to investigate imine formation more generally. A number of alternative alcohols and amines were therefore used instead of benzyl alcohol and 1-hexylamine, including a range of primary and secondary benzyl alcohols and different types of primary amines; see Table 4 and Table 5. All reactions were performed by the general oxidation procedure, *i.e.* 0.02 mol% catalyst (87.5 mg), 10 mol% potassium methoxide, room temperature, ambient pressure oxygen, 24 h of reaction time (no optimisation was attempted). Table 4 compiles the conversion and selectivity results obtained in the oxidative couplings of 1-hexylamine and different alcohols.

All the examined alcohol substrates: benzyl alcohol, cinnamyl alcohol, and the secondary alcohol 1-phenylethanol, were oxidised and coupled with 1-hexylamine to produce the desired imine products (Table 4, entry 1–3) in high selectivity. However, the more sterically demanding alcohol diphenylmethanol (Table 4, entry 4) surprisingly failed to undergo oxidation. Recently Mitsudome *et al.*[32] showed that it is possible to oxidize both 1-phenylethanol and diphenylmethanol to the ketone with gold nanoparticles. Accordingly, it seems therefore likely that the coupling reaction with the amine was the demanding step in the performed reaction with diphenylmethanol. Of the examined alcohol substrates, the conversion of cinnamyl alcohol (Table 4, entry 2) was the highest, with an overall yield of 62%.

Table 5 shows the conversion and selectivity obtained when benzyl alcohols were reacted with different amines. As seen in Table 5, all of the applied amine substrates reacted with high selectivity (above 98%) with benzyl alcohol to give the desired products. 3-Pentylamine (Table 5, entry 1) underwent comparable conversion as to 1-hexylamine, whereas the aromatic aniline (Table 5, entry 2) and benzyl amine (Table 5, entry 3) experienced lower conversion than both aliphatic amines. Similar results have also recently been reported by Sun *et al.*[27] who suggested

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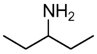
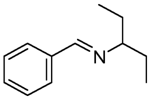
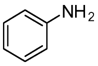
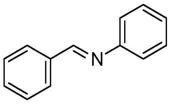
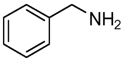
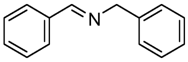
Table 5 Conversion and selectivity obtained in the oxidative couplings of benzyl alcohol (A) and different amines (see Scheme 1 and Scheme 2).[a]

Entry	Amine	Product	Conversion [%]	Selectivity [%]
1			53	99
2			7	99
3			23	100

[a] Reactions were carried out at room temperature under atmospheric pressure of oxygen for 24 h using 10 mol% $KOCH_3$ (mole base/mole alcohol).

that the high basicity of aliphatic amines facilitates the proton abstraction step in the oxidation of the alcohol, which is believed to be the first and rate-determining step in the overall reaction.

Conclusions

In this work we have shown that gold nanoparticles supported on titanium dioxide very selectively (above 98%) catalyse the oxidative coupling of alcohols and amines to form the corresponding imines. The reactions were conducted at room temperature with atmospheric pressure of dioxygen. Only limited effect on the reaction progression was found when increasing the temperature and increasing the catalyst amount, indicating the substrate availability to be limiting in the reactions. Furthermore, the necessity of adding a catalytic amount of base was proven. Different alkaline metal methoxides were applied as a base for the reaction and potassium methoxide was shown to be the best, thus suggesting a promoting effect of the cation. This aspect will be examined in detail in future studies.

The introduced oxidative coupling reaction was applied to a number of different alcohols and amines to demonstrate the versatility of the reaction protocol to a broader range of substrates. Furthermore, the reactions were intentionally carried out at relatively high substrate concentration under benign reaction conditions to comply with some of the most important principles of green and sustainable chemistry.

Experimental

Materials

All chemicals and reagents were purchased from commercial sources and used without further purification; anisole (99%, Sigma-Aldrich), benzyl alcohol (>99%, Aldrich), 1-hexylamine (99%, Aldrich), lithium methoxide ($LiOCH_3$, 1.0 M in methanol, Aldrich), sodium methoxide ($NaOCH_3$, 25 wt% in methanol, Sigma-Aldrich), potassium methoxide ($KOCH_3$, 25 wt% in methanol, Aldrich), methanol (>99.6%, Sigma-Aldrich), diphenylmethanol (>99%, Fluka), 1-phenylethanol (98%, Aldrich), cinnamyl alcohol (98%, Aldrich), aniline (97%, BDH Chemicals), 3-pentylamine (97%, Aldrich), benzylamine (98%, Fluka), oxygen (>99.9%, Air Liquide).

The employed gold catalyst was commercial gold on titanium dioxide (1 wt% Au/TiO_2, supplied by Mintek) with a Brunauer–Emmett–Teller (BET) surface area of 49 $m^2\ g^{-1}$. The size of the gold nanoparticles has previously been determined to be 4–8 nm by means of transmission electron microscopy (TEM).[20]

Oxidation procedure

In a typical experiment, alcohol (20 mmol), amine (20 mmol), anisole (internal standard, 1 mmol), base (alkaline metal methoxide, 2 mmol) and methanol (50 mmol) were charged into a 25 ml two-necked, round-bottomed flask equipped with a condenser and a stirring bar. The reactor system was connected to a manifold providing molecular O_2 for the oxidation (atmospheric pressure). The system was flushed with O_2 and 87.5 mg of the catalyst was added, corresponding to an Au/substrate molar ratio of 1/4500 (*i.e.* 0.02 mol% Au). The reaction mixture was either kept at ambient temperature (around 293 K) or heated using an oil bath for 24 h.

Product analysis

During the oxidation reactions samples of 0.1 ml were periodically collected, filtered and analysed by GC-FID and GC-MS using a HP-5 column from Agilent Technologies Inc. The amounts of substrates and reaction products were quantified using anisole as an internal standard.

Conversions and selectivities were calculated based on converted amine. The reported values converged with ±5% (abs.) with the analogous values calculated based on converted alcohol.

Acknowledgements

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