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Titania-Supported Gold Nanoparticles Catalyze the Selective Oxidation of Amines into Nitroso Compounds in the Presence of Hydrogen Peroxide

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Dedicated in memory of Prof. Yiannis Elemes, remembering the stimulating scientific discussions and friendship.

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Abstract: In this article, the catalytic activity of titania-supported gold nanoparticles (Au/TiO_2) was studied for the selective oxidation of amines into nitroso compounds using hydrogen peroxide (H_2O_2). Gold nanoparticles deposited on Degussa P25 polymorphs of titania (TiO_2) have been found to promote the selective formation of a variety of nitroso arenes in high yields and selectivities, even in a large-scale synthesis. In contrast, alkyl amines are oxidized to the corresponding oximes under the examined conditions. Kinetic studies indicated that aryl amines substituted with electron-donating groups are oxidized faster than the corresponding amines bearing an electron-withdrawing functionality. A Hammett-type kinetic analysis of a range of *para*-X-substituted aryl amines implicates an electron transfer (ET) mechanism ($\rho = -1.15$) for oxidation reactions with concomitant formation of the corresponding *N*-aryl hydroxylamine as possible intermediate. We also show that the oxidation protocol of aryl amines in the presence of 1,3-cyclohexadiene leads in excellent yields to the corresponding hetero Diels–Alder adducts between the diene and the in situ formed nitrosoarenes.

Keywords: gold nanoparticles; heterogeneous catalysis; hydrogen peroxide; nitrosoarenes; selective oxidation; titania

Introduction

Nitroso compounds are highly valuable chemical intermediates[1] widely used in various biological metabolic processes and synthetic chemical transformations, such as nitroso aldol[2] and ene reactions,[3] cycloadditions,[4,5] additions of Grignard reagents[6] and synthesis of indoles[7] and azoarenes.[8] Moreover, these intermediates could be easily reduced[9] or oxidized[10] to the respective amine and nitro derivatives. Therefore, the last years nitroso compounds chemistry plays a pivotal role in asymmetric catalysis.[4,5,11] Since the first synthesis of nitrosobenzene,[12] much research effort has been directed to the development of catalytic methods for the production of C-nitroso arenes as primary products.[1,13] Examples include nitrosation of arenes and organometallic (incl. organoborate) compounds,[14] addition reactions to C=C double bonds, oxidation of primary amines and hydroxylamines,[15] and reduction of nitroarenes.[13] Nevertheless, a simple yet high-yielding procedure for the direct formation of C-nitroso arenes remains a considerable challenge. This is because the C-nitroso compounds are very unstable and easily oxidized to the corresponding dimeric, azo and/or azoxy arenes through condensation reactions.

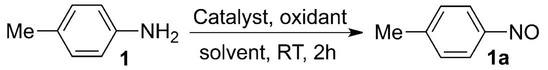
The transition metal-catalyzed oxidation of primary amines by hydrogen peroxide (H_2O_2)[13,15,16] or molecular oxygen (O_2),[17] are the most common routes to synthesize C-nitroso compounds. However this methodology often suffers from low chemoselectivity due to the formation of the corresponding azo and azoxy arenes or over-oxidation to the nitro compounds. Recently, we studied the oxidation of aryl amines into nitrosoarenes catalyzed by polyoxometalates anions (e. g. $W_{10}O_{32}^{4-}$ or $PW_{12}O_{40}^{3-}$) supported on mesoporous titania or under homogeneous conditions.[15e] In all cases, good to high catalytic activities were observed. Herein, following our interest in use of supported gold nanoparticles (AuNPs)[18] as catalysts in organic transformations,[19] we describe the chemoselective oxidation of amines into nitrosoarenes, employing AuNPs supported on TiO_2 as solid catalysts and H_2O_2 as oxidant under ambient conditions, which is a hitherto unknown transformation under Au-catalysis conditions. We also demonstrate through appropriate selection of the supported catalysts that amine oxidation reactions are strongly affected by the crystal phase of the titania support. Kinetic analysis of the oxidation of various *para*-X-substituted aryl amines shows that an electron-transfer (ET) mechanism operates, leading to the formation of an *N*-hydroxyl aryl amines as possible intermediate in the formation of nitrosoarene compounds. The Au/TiO_2 catalyst is also highly effective for the hetero Diels–Alder (HDA) cycloaddition of the in situ formed nitrosoarenes with 1,3-cyclohexadiene. Our oxidative approach is complementary to that of aniline's oxidation with heterogeneous Au-based catalysts, in which, however, primarily azoarenes were formed.[20]

Results and Discussion

A series of different gold supported catalysts, such as the commercially available Au/TiO_2, Au/Al_2O_3 and Au/ZnO nanoparticles, and as prepared Au-loaded Degussa P25 TiO_2 (Au/P25) nanoparticles and mesoporous Au-loaded TiO_2 nanoparticle assemblies (Au/MTA), were used for the oxidation of anilines. All commercial catalysts feature a ~1 wt% Au loading and exhibit an average gold crystallite size of about 2–3 nm. To produce the mesoporous Au/MTA, we utilized a surfactant-assisted aggregating assembly of titanium compounds, $Ti(OPr)_4$ and $TiCl_4$, followed by template removal by calcination. Gold nanoparticles was then deposited on the surface of MTA mesostructure by using a deposition–precipitation method.[19d] The obtained material possesses a three-dimensional network of tightly connected gold and anatase TiO_2 nanoparticles and exhibits large internal surface area ($115\ m^2 g^{-1}$) and narrow pore size distribution (ca. 7.5 nm), according to transmission electron microscopy (TEM) and N_2 physisorption measurements; these results are reported elsewhere[19d] (see Supporting Information, Figure S1). TEM analysis confirms that Au particles have an average size of 4–5 nm. The average size of titania particles was estimated using the Guinier approximation on the low-*q* range of the small angle X-ray scattering (SAXS) data and was found to be about 8 nm (see Supporting Information, Figure S2). N_2 adsorption–desorption isotherms indicated that the BET surface area of commercially available Au/TiO_2 and as-prepared Au/P25 catalysts is 47 and $36\ m^2 g^{-1}$, respectively (see Supporting Information, Figure S3). The crystallinity of these materials was examined with X-ray diffraction (XRD). The XRD patterns, shown in Figure S4 of the Supporting Information, indicated that both Au/TiO_2 and Au/P25 samples consist of a mixture of anatase and rutile TiO_2 particles (ca. 70/30 wt%), in agreement with previous studies.[21,22]

The herein presented catalytic protocol arose while studying the oxidation of aryl amines by hydrogen peroxide (H_2O_2) in the presence of metal oxide catalysts. Precedent is the first work by Kosswing who investigated the transformation of aniline into azoxybenzene on Ti^{IV} substances using *t*BuOOH.[16a] Later on, Tuel and co-worker studied the oxidation of aniline with H_2O_2 and *tert*-butyl hydroperoxide (*t*BuOOH) in the presence of various titanium silicalite catalysts. However in these reactions a mixture of nitrosobenzene and azoxybenzene was observed with the latter as the major one at late reaction times.[16b] Recently, Sudalai and co-workers presented the selective oxidation of anilines into nitroarenes catalyzed by titanium-type zeolites and Ti(O*i*Pr)$_4$ using H_2O_2 as oxidant.[16c] These reports demonstrate the potential use of TiO_2-based materials for the selective transformation of amines. In this work, our initial experiments indicated that oxidation of *p*-toluidine (**1**) with H_2O_2 on Degussa P25 and Hombikat UV-100 TiO_2 nanoparticles produces the corresponding azoxyarene as the major product (Table 1, entries 1 and 2), while in the absence of catalyst no reaction took place (Table 1, entry 3). These findings are in agreement with previous results.[16] At this point we were curious whether Au nanoparticles supported on titania have a beneficial effect on reaction outcome and selectivity as there are preceding literature reports.[23] Following various catalytic experiments, an almost quantitatively oxidation of **1** to the nitrosoarene **1a** was observed in the presence of Au/TiO_2 (0.8 mol%) in MeOH using H_2O_2 (3 equiv) as oxidant, in 2 h (Table 1, entry 8). The addition of equimolar amount of H_2O_2 (with respect to **1**) resulted in incomplete oxidation of **1**, while in the presence of 2 equiv of H_2O_2, a prolonged reaction time is required for the reaction completion. Among the solvents studied, high conversion of **1** was obtained using more polar solvents, especially ethanol and methanol (Table 1, entries 4–8). Meanwhile, no reaction was observed when *t*BuOOH and molecular oxygen (O_2) were used as oxidants under the same conditions (Table 1, entries 9 and 10). For comparison,

Table 1. Oxidation of *p*-toluidine (**1**) into 4-methylnitrosobenzene (**1a**) using various catalysts.



Entry	Catalyst[a]	Solvent	Oxidant[b]	Conv.[c]
1	Degussa (P25)	MeOH	H_2O_2	83 %[d]
2	Hombikat	MeOH	H_2O_2	5 %[d]
3	No catalyst	MeOH	H_2O_2	NR[e]
4	Au/TiO_2	DCM	H_2O_2	15 %
5	Au/TiO_2	CH_3CN	H_2O_2	65 %
6	Au/TiO_2	Acetone	H_2O_2	39 %
7	Au/TiO_2	EtOH	H_2O_2	89 %
8	Au/TiO_2	MeOH	H_2O_2	96 %[f]
9	Au/TiO_2	MeOH	*t*BuOOH	NR
10	Au/TiO_2	MeOH	O_2	NR
11	Au/Al_2O_3	MeOH	H_2O_2	16 %
12	Au/ZnO	MeOH	H_2O_2	37 %
13	Au/MTA	MeOH	H_2O_2	99 %[g]
14	Au/P25	MeOH	H_2O_2	97 %[f]
15	$AuCl_3$	MeOH	H_2O_2	7 %[h]
16	$AuCl_3$/AgOTf	MeOH	H_2O_2	14 %[h]
17	$Ph_3PAuNTf_2$	MeOH	H_2O_2	5 %[h]

[a] *p*-Toluidine (0.3 mmol) and 50 mg of the solid catalysts.
[b] 3.0 equiv
[c] Based on the consumption of **1** determined by ^{1}H NMR.
[d] Azoxyarene was formed as major product.
[e] NR = no reaction.
[f] The corresponding product was isolated in $>94\%$ yield.
[g] A mixture of the corresponding hydrazo, azo, azoxy, and nitroso compounds was observed by ^{1}H NMR with the former as the major one.
[h] A mixture of the corresponding nitroso, azoxy and azo compounds was observed by ^{1}H NMR with the former as the major product (40–60 % relative yield). In all cases, 3 mol % of Au catalyst have been used.

the Au-loaded Degussa TiO_2 nanoparticles (Au/P25) have been found to catalyze the oxidation of **1** to nitrosoarene **1a** in 93 % yield within shorter reaction time (Table 1, entry 14). Interestingly, mesoporous assemblies of gold and anatase TiO_2 nanoparticles (Au/MTA), in contrast, promotes the activation of **1**, giving hydrazoarene as the major product accompanying with small amounts of the corresponding azo-, azoxy- and nitrosoarene, according to the NMR spectroscopy (Table 1, entry 13). These results are consistent with previous studies showing improved activity towards the selective oxidation of cinnamyl alcohol to cinnamaldehyde[24a] when using titania-supported gold particles of 3–5 nm size.[19e,24] Au nanoparticles loaded on basic supports, like Au/Al_2O_3 and Au/ZnO, showed lower conversion of **1** (16 and 37 % yields, respectively) leading to the corresponding nitrosoarene **1a** ($>95\%$ selectivity), as shown in Table 1, entries 11 and 12). In stark contrast, the use of $AuCl_3$, $AuCl_3$/AgOTf and $Ph_3PAuNTf_2$ leads to a mixture of nitroso, azoxy and azo compounds even at low conversion levels of **1** (4–15 %), under similar conditions (Table 1, entries 15–17). These results clearly indicate that a fast and selective oxidation of *p*-toluidine (**1**) to the corresponding nitrosoarene (**1a**) took place only on the Au particles supported on P25 (anatase and rutile) polymorphs of TiO_2, such as the commercial available Au/TiO_2 and as-prepared Au/P25 materials.

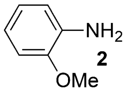
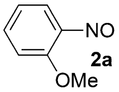
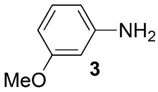
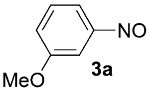
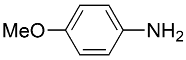
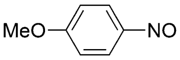
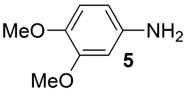
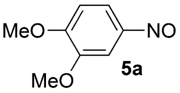
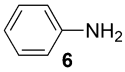
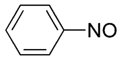
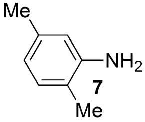
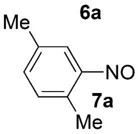
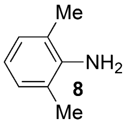
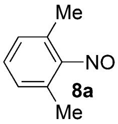
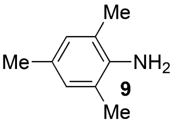
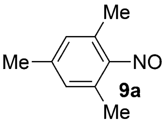
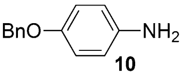
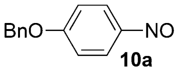
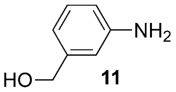
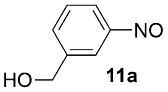
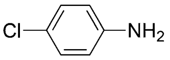
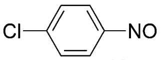
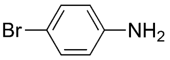
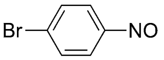
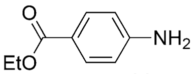
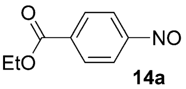
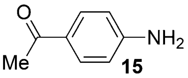
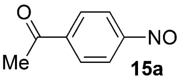
To study the limitation of the above oxidation process, a series of substituted anilines (**2**–**15**) were examined. Table 2 summarizes the results obtained using Au/TiO_2 catalyst. In all cases the corresponding nitrosoarenes (**2a**–**15a**) were formed with good to high isolated yields (ca. 57–98 %) and selectivity ($>95\%$). It is worth noting that electron rich aromatic amines (**2**–**10**) are oxidized faster to the corresponding nitrosoarenes, in high yields ($>94\%$, in 1–3 h), compared to the electron deficient amines (**14** and **15**) (ca. 57–61 % yield, in 28–30 h). It is noted that, only a small amount of the corresponding nitro- ($<5\%$) and azoxyarene ($<11\%$) compounds were detected by ^{1}H NMR analysis of the crude mixtures (results not shown).

Remarkably, oxidation of substituted anilines by Au/TiO_2 does not affect the chemical functionality of the phenyl ring. In particular, the benzyloxy, hydroxymethyl, chloro and bromo groups of anilines **10**–**13**, respectively, remain intact under the present oxidation conditions, giving the corresponding *para*-substituted nitrosoarenes **10a**–**13a** as the only products.[25] For comparison, oxidation of **4**, **6**, **12**, **13** and **14** anilines in the presence of Degussa P25 TiO_2 was also studied. Spectroscopic analysis (^{1}H and ^{13}C NMR) of the reaction mixture showed that, the corresponding azoxyarenes are formed as the major products, accompanying with small amount of hydrazoarenes, *N*-aryl hydroxylamines and nitrosoarenes (see Supporting Information, Figure S5–S10). This clearly suggests that gold particles are essential for the chemoselective oxidation to nitrosoarenes. Furthermore, primary alkyl amines **16**–**18**, were also effectively converted to the corresponding oximes (**16a**–**18a**) in 41–53 % isolated yields, accompanied by a small amount ca. 10 % of the corresponding azoxy-compounds and the unreactive amine. Oximes **16a** and **18a** were formed with a *E*/*Z* isomers ratio of ~4:1 as determined by NMR spectroscopy, by integrating the appropriate imines proton signals CH = NOH (see Supporting Information). However, an excess of H_2O_2 (6–8 equiv) and prolonged reaction times are required to reach completion (see Scheme S1 of the Supporting Information).

The Au/TiO_2 catalyst can be easily separated from the reaction mixture by simple filtration and reused for the next catalytic run. The stability of the Au/TiO_2 catalyst with the present conditions was examined by multi-cycle reactions. As shown in Figure S11 of the Supporting Information, the catalyst can be used at

Table 2. Selective oxidation of aryl amines **2–15** into nitrosoarenes **2a**–**15a** with H_2O_2 catalyzed by Au/TiO_2.

$$\text{R-NH}_2 \xrightarrow[\text{H}_2\text{O}_2\text{, MeOH, RT}]{\text{Au/TiO}_2\text{ (0.8\% mol)}} \text{R-NO}$$

Entry	Reactant	Product	Time/Yield[a]
1	 **2**	 **2a**	2h / 97%
2	 **3**	 **3a**	1h / 94%
3	 **4**	 **4a**	1h / 98%
4	 **5**	 **5a**	1h / 97%
5	 **6**	 **6a**	2h / 97%
6	 **7**	 **7a**	2h / 96%
7	 **8**	 **8a**	3h / 95%
8	 **9**	 **9a**	3h / 94%
9	 **10**	 **10a**	1h / 94%
10	 **11**	 **11a**	5h / 90%
11	 **12**	 **12a**	1h / 95%
12	 **13**	 **13a**	2h / 94%
13	 **14**	 **14a**	30h / 57%[b]
14	 **15**	 **15a**	28h / 61%[b]

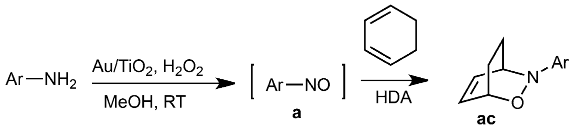
[a] Isolated yields. In all reactions the nitrosoarenes selectivity was >95%.

[b] The corresponding nitrosoarene was formed as major product.

least seven times, for the **1** oxidation, without a significant loss of its catalytic activity and selectivity (> 97% yield of **1a**, >99% selectivity). XRD analysis showed no change in the chemical composition and the porous structure of the reused Au/TiO_2 sample as compared to fresh one, thereby, indicating high durability and recyclability (see Figure S4 of the Supporting Information). Additionally, after stirring slurry of Au/TiO_2 and H_2O_2 in methanol for several hours, we observed that the supernatant solution is totally inefficient in promoting oxidation of **1**. Indeed, ICP analysis revealed that the gold content in the supernatant is extremely low (~0.9 ppb).[26] Based on these encouraging results, the Au/TiO_2 catalyst was further tested for possible large-scale production of nitroso arenes from aryl amines. For this reason, 6 mmol of aryl amine **4** were oxidized in the presence of Au/TiO_2 (0.3 mol%) with 3 equiv of H_2O_2 in 20 mL MeOH. After completion of the reaction (~7 h based on TLC analysis), the mixture was filtered upon silica gel, washed with ethanol and purified by column chromatography to afford the corresponding nitrosoarene **4a** in 89% isolated yield. This result corresponds to a high turnover number (TON) of 297 and turnover frequency (TOF) value of 43 h^{-1}. Furthermore, Au/TiO_2 has been found to promote the selective formation of the nitrosoarene **4a** in good isolated yield (78%) and high selectivity (>93%), even in a larger scale synthesis using 24 mmol of aryl amine **4**, 5 equiv of H_2O_2 and 0.3% mol of AuNPs; yet prolonged reaction time was required (50 h). It is noted that in the present conditions no oxidative polymerization of anilines was observed, based on NMR analysis of the relative integrations of the aromatic protons and the measured isolated yields.[27]

The general applicability of the present Au/TiO_2 catalytic system was verified by performing one-pot hetero Diels–Alder (HDA) reaction of the in situ formed nitrosoarenes with 1,3-cyclohexadiene. In general, nitrosoarenes are widely used as external additives in organocatalytic and acid-catalyzed asymmetric reactions.[3–5,11] Because of the instability of these compounds, the HDA reaction of nitrosoarenes that are produced by the oxidation of **1**, **4**, **6**, **12** and **15** aryl anilines was conducted in the presence of 1,3-cyclohexadiene (1 equiv) at ambient conditions. The catalytic results, shown in Scheme 1, indicated that the corresponding 1,4-cycloadducts were formed in good to high isolated yield (57–97%) and with a short reaction time (for product characterization see Supporting Information).

To rationalize a possible mechanism for the present catalytic system, we investigated the kinetic parameters of oxidation of various *para*-X-substituted anilines. Initially, the oxidation of *para*-anisidine (**4**, 0.3 mmol**)** was carried out with Au/TiO_2 (50 mg) using different concentrations of H_2O_2, that is, from 0.3 to



	Ar	HDA Time/Conversion[a]	Yield[b]
1ac	4-MeC$_6$H$_4$	2 h / 97%	95%
4ac	4-MeOC$_6$H$_4$	4 h / 75%	57%[c]
6ac	C$_6$H$_5$	2 h / 98%	95%
12ac	4-ClC$_6$H$_4$	0.5 h / 98%	94%
15ac	4-MeCOC$_6$H$_4$	1.5 h / 99%	97%

[a] Based on the nitrosoarene amount.

[b] Isolated yields, based on the initial amine amount.

[c] The cycloaddition product was unstable on column chromatography

Scheme 1. One-pot consequent HDA reaction between the 1,3-cyclohexadiene and in situ formed nitrosoarenes in the presence of Au/TiO$_2$ catalyst.

1.5 mmol. In all cases, the kinetic values were determined by monitoring the consumption of **4** by integrating the aromatic proton signals in ^{1}H NMR spectra. With excess of H_2O_2 (i.e., more than 3 equivalents based on aniline amount), the % consumption of aniline as a function of time was found to be constant (see Supporting Information, Figure S12), reflecting a pseudo-zero-order dependence at high H_2O_2 concentration. Thus, all further kinetic studies were conducted with 4 equiv of H_2O_2 using the following conditions: maintained Au/TiO$_2$ amount constant and varied **4** concentration and vice-versa. In both cases, kinetic plots were made of -ln(x) versus time and the relative rate constants (k) were obtained from the slopes of regression lines, as shown in Figure S13 and S14 of the Supporting Information. In this analysis, a plot of –ln(x) versus time can be fit by the following expression:

$$-\ln(x) = kt \quad (1)$$

where k is the rate constant and x is the consumption of **4** at reaction time t.

Next, a Hammett-type kinetic analysis of the reactivity of *para*-substituted anilines was performed. Specifically, the kinetic values were determined by monitoring the consumption of various *para*-X-substituted aryl amines [X=4-Me (**1**), 4-MeO (**4**), 3,4-diMeO (**5**), H (**6**), Cl (**12**) and COOEt (**14**)] with ^{1}H NMR, by integrating the aromatic proton signals. Catalytic reactions were carried out as follows: each respective amine (0.3 mmol), Au/TiO$_2$ catalyst (0.8 mol%) and H_2O_2 as oxidant (4 equiv) were stirred in [D$_4$]MeOH (1 mL), and 100 μL aliquots of the mixture were taken at appropriate times. After completion, the reaction mixture was filtered through a short pad of Celite and silica gel to withhold the catalyst and washed with $CDCl_3$ (~1 mL).[28] Each reaction was repeated at least three times and the average values are depicted in Figures S15 and S16 of the Supporting Information. On the basis of these results, plot of –ln(x) as a function of time yields a straight line indicating that the overall reaction followed a pseudo first-order kinetic model.

As shown in Figure 1 the kinetic activity of **1**, **4**, **5**, **6**, **12** and **14** aryl amines is remarkably affected by the nature of the *para*-X-substituent group, in which the oxidation proceeds faster as the electron-donating ability of the X-substituent group increases. For example, the oxidation rate of **4** (4-MeO) and **5** (3,4-diMeO) is approximately two times faster than the corresponding oxidation of the unsubstituted aniline **6** (X=H), as indicated by the relative rate constant ratios $k_{\mathrm{MeO}}/k_{\mathrm{H}} = 1.7$ and $k_{\mathrm{diMeO}}/k_{\mathrm{H}} = 2.2$ (see Supporting Information, Figure S15). On the other hand, anilines **12** (4-Cl) and **14** (4-COOEt) bearing an electron-withdrawing substituent in the *para* position were oxidized with a slower reaction rate (see Supporting Information, Figure S15); $k_{\mathrm{Cl}}/k_{\mathrm{H}} = 0.9$ and $k_{\mathrm{COOMe}}/k_{\mathrm{H}} = 0.3$. In addition to these results, a Hammett-type correlation in the competition of *para*-X-substituted aryl amines [X=MeO (**4**), Me (**1**), Cl (**12**) and COOEt (**14**)] versus aniline **5** gave negative slopes, i.e., $\rho \approx -0.71$ (using $\sigma+$ values) and $\rho \approx -1.15$ (using σ values) (see Supporting Information, Figure S17). This suggests that a nucleophilic attack (or electron transfer) of ani-

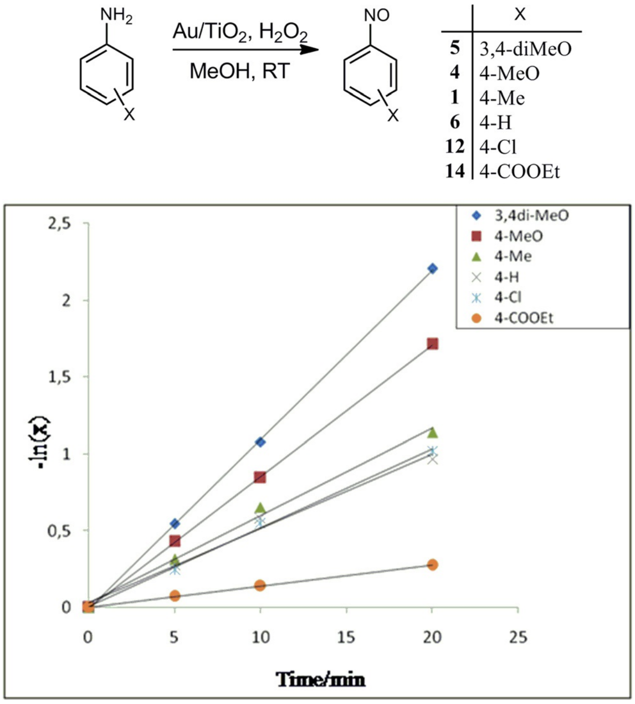
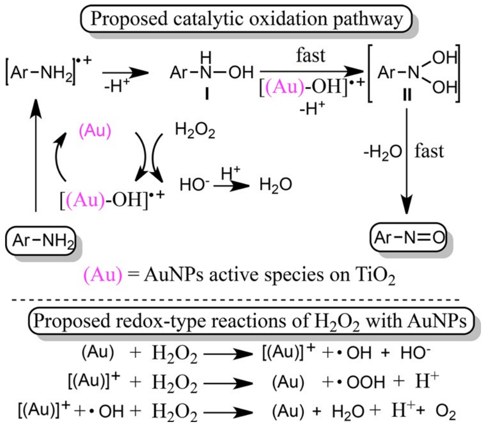


Figure 1. Kinetic analysis of the Au/TiO$_2$-catalyzed oxidation of various *para*-X-substituted aryl amines [X=3,4-diMeO (**5**), 4-MeO (**4**), 4-Me (**1**), 4-H (**6**), 4-Cl (**12**) and 4-COOEt (**14**)] with H_2O_2.

line nitrogen-pair electrons on the gold active species (possibly $[(Au)\text{-}OH]^{\bullet +}$ see below)[24a,b] of this catalyst is taking place in the rate-controlling step of the reaction with the parallel formation of a radical-cation intermediate in the transition state, which is better stabilized by an electron-donating substituent. This results found support from previous studies by Tada and co-workers,[24a,b] in which gold nanoparticles have been proposed to catalyze the chemoselective oxidation of cinnamyl alcohol to cinnamaldehyde in the presence of H_2O_2.

Our previous observation that anilines containing electron-donating substituents are oxidized faster than those with electron-withdrawing groups implies that these reactions proceed mainly via an electron transfer (ET) process. It is reported that decomposition of H_2O_2 into HO^- and $HO^\bullet$ radicals over Au-loaded TiO_2 is an one-electron redox reaction, as shown in Scheme 2.[24] Here, the in situ formed hydroxyl radicals are probably adsorbed on the surface of the AuNPs producing the reactive species $[(Au)\text{-}OH]^{\bullet +}$,[24a] which in turn catalyze the oxidation of aniline via possible formation of an *N*-aryl hydroxylamine **I** intermediate. Subsequent fast oxidation of the electron rich *N*-aryl hydroxylamine (**I**) under a second catalytic cycle produces the corresponding *N*-aryl dihydroxylamine **II** intermediate, which undergoes a fast dehydration process to form the desired nitrosoarenes.[15j] The active species of gold nanoparticles can be regenerated by the reaction with the H_2O_2, producing H_3O^+ and O_2 (redox-type reactions in Scheme 2).[24a–c]

To shed light on the above hypothesis, the catalytic oxidations of electron-donating **1** and **4** and electron-withdrawing **12** and **14** *p*-X-substituted anilines, were also separately conducted in CD_3OD using Au/TiO_2. Each reaction process was monitored directly by ^1H NMR spectroscopy. As shown in Figure S18–S21 of the Supporting Information, Au/TiO_2 catalyze the production of the corresponding nitrosoarenes **1a**, **4a**, **12a** and **14a** in excellent yields, accompanying with small amount of the unreacted aryl amines. However, when *N*-aryl hydroxyl amines **1d** and **12d** are synthesized and oxidized under similar conditions, a mixture of the corresponding nitrosoarenes **1a** and **12a** and azoxyarenes **1b** and **12b** were obtained, as shown by NMR spectroscopy, with the former as the major one (results not shown). Since the *N*-aryl hydroxyl amine oxidation is about two order of magnitude faster than that of the corresponding *N*-aryl amine (Scheme 2),[15j] it is difficult to detect *N*-aryl hydroxyl amines as intermediates. Remarkably, no reaction was observed when azoxybenzene (**6b**) was used as substrate, while hydrazobenzene (**6c**) is readily oxidized to azobenzene under similar conditions (results not shown).



Scheme 2. Proposed mechanism for the anilines oxidation by H_2O_2 catalyzed by Au/TiO_2.

It is interesting to note that a higher yield of the produced nitrosobenzene **1a** was measured when oxidation of **1** was performed in MeOH compared to CH_3CN, although methanol traps hydroxyl radicals with high rate, $k \sim 10^9\,\mathrm{M}^{-1}\,s^{-1}$.[29] Furthermore, 1-phenylethanol (**19**), 4-methoxy-1-phenylethanol (**20**) and 4-amino-1-phenylethanol (**21**) were oxidized under the same conditions in both solvents. While aromatic alcohols **19** and **20** were found to be unreactive at the initial reaction times, small amounts of the corresponding carbonyl compounds were detected by NMR at prolonged reaction times (ca. 24 h, see Supporting Information, Figures S24 and S25). In the case of 4-amino-1-phenylethanol (**21**), the corresponding nitrosoarene (**21a**) was formed as the major product (see Supporting Information, Figure S26). This suggests that under our reaction conditions no homogeneous oxidation process takes place by the excess amount of H_2O_2 or the proposed in situ formed hydroxyl radicals.[24c,d] Subsequent investigations showed that, unlike Au/TiO_2, Degussa P25 TiO_2 nanoparticles could oxidize **1** and **4** producing azoxyarenes **1b** and **4b** in high yields, according to NMR data (see Supporting Information, Figures S22 and S23). These findings are consistent with the above mentioned reaction mechanism, in which AuNPs catalyze the transformation of aryl amines to the corresponding nitrosoarenes, possibly via an ET mechanism, as shown in Scheme 2.

Conclusions

In conclusion, we have shown for the first time that titania-supported gold nanoparticles can catalyze the oxidation of a series of aryl amines into nitrosoarenes employing H_2O_2 as oxidant. The catalyst was found to be highly chemoselective to nitrosoarenes even for large-scale reactions. In addition, hetero Diels–Alder reaction between the in situ formed nitrosoarenes and 1,3-cyclohexadiene was achieved with high isolated yields. Kinetic analysis indicated that aryl amine oxidation proceeds mainly via an ET pathway, in which the corresponding nitrosoarenes are produced through a fast catalytic oxidation of the initially formed *N*-aryl hydroxyl amines intermediate. Gold nanoparticle active species found to be responsible for this catalytic process and no oxidation was observed under homogeneous conditions. The present Au/TiO_2–H_2O_2 catalytic system represents an expeditious approach towards a large-scale production of nitrosoarenes from aryl amines in excellent yields and selectivity.

Experimental Section

Catalysts preparation

The mesoporous titania-supported gold catalyst Au/MTA was prepared via a deposition–precipitation method over mesoporous TiO_2 nanoparticle assemblies (MTA),[30] according to the procedure reported previously.[19d,e] Briefly, a weighed amount of $Au(en)_3Cl_3$, corresponding to a 1 wt% gold loading based on TiO_2 support, was dissolved in 5 mL water and the pH of the resulting solution was adjusted to 9–10 with 1M NaOH. Then, 0.1 g of MTA was dispersed into the gold solution with vigorous stirring for 1 h and the precipitate was recovered by filtration, washed with deionized water and dried at 40 °C under vacuum. Reduction of gold species on the surface of MTA was achieved by reacting the Au/MTA solid (0.1 g) with $NaBH_4$ (0.45 mmol) in ethanol (10 mL) for 30 min. The purple-colored material was then recovered by filtration, washed with water and ethanol, and dried in a vacuum oven at 80 °C. For comparison, Au/P25 catalyst was also prepared in a similar procedure to Au/MTA, but depositing 1 wt% gold on commercially available TiO_2 Degussa P25 NPs (particle size ~20–30 nm).[21] The Au loadings of the samples was determined by elemental X-ray analysis (EDS).

Physical characterization

Small-angle X-ray scattering (SAXS) measurements were performed on a JJ X-ray system (Denmark) equipped with a Rigaku Helium-3 detector and a Cu ($\lambda = 1.54098$ Å) rotating anode operated at 40 kV and 40 mA. The sample-to-detector distance and the center of beam were precisely determined by calibration with the Ag-behenate ($d_{001} = 58.38$ Å) standard. The average size of spherical-shaped TiO_2 particles was determined from the scattering data, using the Guinier approximation: $I(q) = A\cdot\exp(q^{2}{}_{g}{}^{2}/3)$, where I is the scattering intensity, q ($= 4\cdot\pi\cdot\sin\theta/\lambda$, with 2θ being the scattering angle) is the scattering vector and R_g is the radius of gyration.[31a] X-ray diffraction (XRD) patterns were collected on a PAN analytical X'pert Pro MPD X-ray diffractometer using Cu Kα radiation (45 kV and 40 mA) in Bragg–Brentano geometry. Nitrogen adsorption and desorption isotherms were measured at −196 °C using a Quantachrome NOVA 3200*e* volumetric analyzer. Before analysis, the samples were degassed at 120 °C under vacuum ($< 10^{-5}$Torr) for 12 h to remove the moisture. The specific surface area was calculated using the Brunauer-Emmett-Teller (BET) method[31b] on the adsorption data in the 0.05–0.22 relative pressure (P/P_o) region. The pore size distribution of the Au/MTA sample was determined by applying the nonlocal density functional theory (NLDFT) method on the adsorption data. Transmission electron microscopy (TEM) analysis was conducted using a JEOL JEM-2100 electron microscope (LaB_6 filament) operating at an accelerating voltage of 200 kV. Elemental microprobe analysis was conducted on a JEOL JSM-6390 LV scanning electron microscope (SEM) equipped with an Oxford INCAPantaFET-x3 energy dispersive X-ray spectroscopy (EDS) detector. Data acquisition was performed at an accelerating voltage of 20 kV and 60 s accumulation time.

General Au/TiO_2 catalyzed oxidations

Into a sealed tube containing the aryl amine (0.3 mmol) and methanol (1 mL), 0.9 mmol of H_2O_2 (30 wt% in H_2O) and 50 mg of Au/TiO_2 (0.8 mol% Au) catalyst were added. The reaction mixture was vigorously stirred at room temperature for selected time and the oxidation process was monitored by thin layer chromatography (TLC). After completion, the slurry was filtered under reduced pressure through a short pad of Celite and silica gel to withhold the catalyst and excess of H_2O_2 using ethanol (~5 mL) as an eluent. The filtrate was then evaporated under vacuum to give the corresponding nitrosoarene in high purity. Product analysis was conducted by ^1H and ^{13}C NMR spectroscopy (Bruker AM 300 and Agilent AM 500). Mass spectra were recorded on an LCMS-2010 EV instrument (Shimadzu) under electrospray ionization (ESI) conditions.

Oxidation reactions in deuterated solvent

In a typical reaction, 0.3 mmol of H_2O_2 (30 wt% in H_2O) and 17 mg of Au/TiO_2 (0.8 mol% Au) catalyst were placed in a sealed tube containing 0.1 mmol *p*-toluidine and 0.5 mL $[D_4]$MeOH. Then the reaction mixture was vigorously stirred at room temperature for the appropriate time. After the reaction, the catalyst was removed by filtration through a short pad of Celite using CD_3OD or $CDCl_3$ (~1 mL) as an eluent, and the filtrate was analyzed directly by ^1H NMR spectroscopy.

Procedure for Hetero Diels–Alder (HDA) reactions

In a typical reaction Au/TiO_2 (1 mol% Au) catalyst was placed in a 5 mL glass reactor, followed by the addition of methanol (1 mL), aniline (0.3 mmol) and H_2O_2 (0.9 mmol), and the reaction mixture was stirred at room temperature for a selected time. Then, an equimolar amount of cyclohexadiene (0.3 mmol) was added, and the mixture was stirred at ambient conditions for the appropriate time, until the consumption of the nitrosoarene, based on TLC. The slurry was filtered under low pressure through a short pad of Celite and silica gel with the aid of ethanol (~5 mL) to withhold the catalyst. The filtrate was evaporated under vacuum to afford a mixture containing the HDA product as the major one accompanying with small amount of unreactive aniline. Further purification on column chromatography gave the corresponding HDA adduct in high isolated yield.

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[28] The reason for using deuterated solvents is to avoid the fast condensation reactions occurring under solvent evaporation conditions between the unreactive anilines and the produced nitroso or *N*-hydroxyl amines, giving the corresponding dimers azo-and azoxy-arenes. Indeed, we mixed nitrosobenzene and aniline in methanol for 10 min, and after solvent evaporation significant amount of the azobenzene was observed by ^{1}H NMR, while mix of *N*-hydroxyl aniline and nitrosobenzene gave the corresponding azoxy-benzene.

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