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## A residue-free production of biaryls using supported gold nanoparticles

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## ABSTRACT

Small gold nanoparticles in the presence of  $O_2$  are able to cleave C—H bonds of non-activated arenes and facilitate catalytic formation of biaryls under mild conditions. This procedure avoids the common requirement of iodine, acids, bases, and/or other stoichiometrical additives to accomplish multiple turnovers and results in a zero-waste synthetic process. A number of unactivated arenes such as benzene, toluene, p-xylene, nitrobenzene, chlorobenzene, or phenol are selectively converted to the corresponding biaryls, with accumulated turnover numbers greater than 600. Kinetic measurements, in combination with IR, HRTEM, and STEM-HAADF data, suggest that the reaction takes place on gold atoms that are metallic in character, with the highest C—C bond formation rate provided by gold nanoparticles of approximately 3 nm of diameter. A radical-free reaction mechanism is postulated on the basis of the kinetic measurements. The results represent a first stone for the waste-free preparation of biaryls using supported gold catalysts.

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## 1. Introduction

Biaryls are ubiquitous building blocks with application in agrochemistry, pharmacy, electronics, conductors, polymers, and liquid crystals, among others [1–4]. The industrial demand of biaryls is prominent, but the process to accomplish the formation of the C-C bond is, in general, costly. The high costs are in part derived from the difficulty of cleaving the Ar-H bond directly, which results in additional operations to pre-activate the arene prior to the coupling step. These processes typically involve aryl halides that are not ecofriendly to prepare (Friedel–Craft processes, [5] using metal-halide salts, and the Sandmayer reaction, [6] starting from aniline, hydrochloric acid and sodium nitrite are some examples). The aryl halide is then coupled with a second activated arene in the presence of a metal catalyst (e.g., Suzuki [7] or Stille [8] couplings). Stoichiometric amounts of additives such as bases in solution [7] or metals such as Sn [8] are usually needed to facilitate the removal of the halide from the metal and enable multiple turnovers. The base/halide or metal/halide residues cause further increment of the costs in operations for purification of the downstream effluents. The atom efficiency of the coupling step is, in this scenario, often <30%, corresponding to approximately 2.3 kg of waste per kilogram of desired product. Aware of these problems, chemists have sought methods that limit the generation of residues, for example through reactions where only one of the aromatic counterparts is functionalized [9,10], or upon substitution of iodine by lighter chlorine [11] or boronic acid group [12].

A major breakthrough would be brought by catalysts able to couple arenes that have not been activated in any manner before reaction and that operate without the necessity of other additives in the solution. In this sense, "unactivated arenes" react and yield biaryls in the presence of some metal catalysts and oxygen donors. although the number of examples is, up-to-date, scarce, For example, gold salts in acidic solutions used in tandem with iodine oxidants such as PhI(OAc)2 or PhI(OH)OTs activate the Ar-H moiety and catalyze some coupling reactions [13,14]-but the use of iodine, and acids in solution is not yet avoided; Pd<sup>2+</sup> facilitates the coupling of unactivates arenes with O<sub>2</sub> as the oxidant and water as the residue-but then the biaryl formation occurs with reduction of  $Pd^{2+}$  to  $Pd^{0}$ , which is an inactive species [15]. To complete multiple turnovers, Pd must be re-oxidized before precipitation as palladium particles, usually in the presence of acids and/or a second metal that allow Pd to shuttle in between oxidation states [16–20]. Even then, the number of turnovers per active site is low, typically <100 [16,17], and often <10 [20,21], while significant amounts of hazardous wastes are generated.

To our knowledge, there is no precedent of a catalyst that affords multiple turnovers in the coupling of unactivated arenes without the generation of residues such as acids, bases, iodine derivatives, metals salts, or other stoichiometrical additives. In other words, we have not seen a catalyst that cleaves directly the Ar—H bond and subsequently forms a new C—C bond with O<sub>2</sub> as the only co-reagent and water as the only by-product.





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In the present investigation, we report such a catalyst, prompted by the realization that gold is active for a number of C—C bond formation reactions not only when is present in the form of a soluble metal salt, but also when arranged as small nanoparticles [22–26], and that the latter work notably better in processes that involve  $O_2$  dissociation [27–32]. Our results demonstrate another remarkable feature of gold in heterogeneous catalysis [33–37].

## 2. Experimental methods

## 2.1. Catalysts preparation

1 wt% Au/TiO<sub>2</sub>, 1 wt% Au/Al<sub>2</sub>O<sub>3</sub>, and 1 wt% Au/ZnO catalysts were used as received from STREM (AUROliteTM catalysts). The catalysts can be prepared following a deposition–precipitation method from HAuCl<sub>4</sub>, as described elsewhere [32].

Pt/Al<sub>2</sub>O<sub>3</sub>, Rh/TiO<sub>2</sub>, Ni/TiO<sub>2</sub>, and Pd/TiO<sub>2</sub> samples were prepared by incipient wetness technique. H<sub>2</sub>PtCl<sub>6</sub> (hexahydrate, Aldrich, >37.5 as Pt), Ni(NO<sub>3</sub>)<sub>2</sub> (hexahydrate, Fluka, >98.5%), RhCl<sub>3</sub> (Aldrich, Rh content 40%) and PdCl<sub>2</sub> (Aldrich, 99%) were used to impregnate TiO<sub>2</sub> (Degussa P-25) in water. As an example, 20 mL of an aqueous solution containing 13.27 mg of H<sub>2</sub>PtCl<sub>6</sub>·6H<sub>2</sub>O was contacted with 1 g of TiO<sub>2</sub> to prepare the 0.5 wt% Pt/TiO<sub>2</sub> catalyst. After a perfect mixing of the corresponding slurries, samples were dried at 373 K during 12 h. Some samples were reduced in flow of H<sub>2</sub> at 723 K for 3 h before reaction, as specified in Table 1.

To prepare Au/TiO<sub>2</sub> catalysts with variable particle sizes, HAuCl<sub>4</sub> was deposited on TiO<sub>2</sub> at a controlled pH. This method allows controlling the degree of metal aggregation by choice of the metal loading, the pH of the deposition, and the activation conditions, as reported [38]. Table S1 (below) provides details of the synthesis of Au/TiO<sub>2</sub> catalysts characterized by average particle sizes of 7.2 and 14.4 nm, respectively.

The bimetallic Au@Pd/TiO<sub>2</sub> catalyst was synthesized by impregnation of the Au/TiO<sub>2</sub> catalyst with a solution of PdCl<sub>2</sub> to have a final Au/Pd mol ratio of approximately 1. This catalyst was thoroughly washed with deionized water and dried at 373 K for 12 h before reaction.

The following information guides the identification of each of the samples in Fig. 2: (A) c, 1 wt%  $Au/TiO_2$  sample supplied by

#### Table 1

Catalytic performance of several metal-based samples for the  $\rm O_2\textsc{-}assisted$  coupling of benzene at 413 K and 12 bar.

Entry	Catalyst	% Me <sup>d</sup> (mol)	$TOF^{e}(h^{-1})$	TON <sup>f</sup> (mol/mol)
1	1%Au/TiO2ª	0.022	382	230
2	1% Pd/TiO <sub>2</sub> <sup>b</sup>	0.041	0.21	<1
3	1% Pd/TiO <sub>2</sub> <sup>c</sup>	0.041	0	0
4	0.5% Pt/TiO2 <sup>c</sup>	0.014	0	0
5	1% Ni/TiO2 <sup>c</sup>	0.075	0	0
6	5% Rh/TiO2 <sup>b</sup>	0.298	0	0
7	TiO <sub>2</sub> <sup>b</sup>	-	0	0
8	1% Au@0.5% Pd/TiO2 <sup>b</sup>	0.043	0.02	<1
9	1% Au/Al <sub>2</sub> O <sub>3</sub> <sup>a</sup>	0.022	244	164
10	1% Au/ZnO <sup>a</sup>	0.022	254	158
11	HAuCl <sub>4</sub>	0.01	0	0
12	$(CH_3)Au(PPh_3)$	0.01	0	0

Turnovers calculated per metal atom on the external surface of the nanoparticles [33]. Experimental details provided in SI.

<sup>a</sup> Supplied by STREM (AUROlite<sup>™</sup> catalysts).

<sup>b</sup> Dried at 373 K before reaction.

- <sup>c</sup> Preactivated in H<sub>2</sub> at 723 K before reaction.
- <sup>d</sup> Mol of metal  $\times$  mol of benzene<sup>-1</sup>  $\times$  100.
- $^{e}~$  Turnover frequency (mol of benzene converted  $\times$  mol of metal  $^{-1}\times h^{-1}$  ).
- <sup>f</sup> Turnover number (mol of benzene converted  $\times$  mol of metal<sup>-1</sup>).

STREM (AUROliteTM); d, the preceding catalyst after being used in the coupling of benzene at 413 K and 12 bar for 100 h; e, sample c after deposition of 0.5 wt% Pd by incipient wetness technique; f, 3 wt% Au/TiO<sub>2</sub> sample prepared by deposition-precipitation of HAuCl<sub>4</sub> at pH = 9 and calcined under static atmosphere of air at 673 K. (B) Particle size distributions, as determined from the corresponding HAADF-STEM and/or HRTEM images, of the preceding catalysts and the following: a, sample c treated in 50 mL/min of air at 1 bar and 673 K; b, sample d treated in 50 mL/min of air at 1 bar and 673 K; g, 3 wt% Au/TiO<sub>2</sub> sample prepared by deposition-precipitation of  $HAuCl_4$  at pH = 6 and calcined under static atmosphere of air at 673 K. (C) Dependence of the TOF per external gold atom on the average particle size during the solvent-free coupling of benzene at 12 bar of O<sub>2</sub> and 413 K for the series of catalysts in (B). The selectivity to biphenyl was always >98%. Experimental details are provided in SI.

## 2.2. Oxidative coupling of arenes

Catalytic testing was performed in a reinforced glass reactor (2 mL volume) equipped with a temperature and pressure control and stirred magnetically. Catalytic testing was performed in a reinforced glass reactor (2 mL volume) equipped with a temperature and pressure control and stirred magnetically. The reactor vessel was bought to Supelco (Reference 2-7037) and modified to allow pressurization and/or extraction of liquids through a gas-tight needle. A 100  $\mu$ L gas-tight syringe was used to get 15–20  $\mu$ L aliquots at the various reaction times.

Before each experiment, all the material was washed with abundant acetone and dried at 383 K for >5 h. It is important to avoid acetone and other polar molecules in the reaction mixture to get optimal results. In a typical experiment, 891 mg of the aromatic compound was placed in the reactor together with 30-70 mg of catalyst and 9 mg of dodecane as an internal standard. Reactants were obtained from Sigma-Aldrich with purities above 99% and used as received. The reactor atmosphere was purged with  $O_2$  at room temperature, pressurized with 12 bar of  $O_2$  and placed into a silicon oil bath pre-heated at the desired reaction temperature. We systematically assigned time = 0 (start of the kinetic experiment) 30 s after the reactor had been immersed into the silicon oil bath. During the experiment, the pressure was kept at 12 bar, and the stirring rate was fixed at 700 r.p.m. Aliquots were taken at different times until the end of the experiment. The composition of these aliquots was determined with a gas chromatograph equipped with a FID detector and a 30 m HP-5 capillary column. Conversions and selectivities were calculated from the GC areas of the products corrected with the response factors determined experimentally. The products were identified by mass spectrometry using a GC/MS device (Agilent MDS-5973) equipped with a quadrupole electron-impact ionization detector (spectra provided in SI). Pure, commercially available compounds were used to compare the biaryls mass spectra and their GC retention times. We also performed HPLC analyses to evaluate the potential presence of heavier compounds. A Varian ProStar 240 device equipped with a column Mediterranea C18 (5  $\mu$ m, 25  $\times$  0.46 mm) was used; the mobile phase was acetonitrile/ethanol in a 30:70 ratio, and the flow was 0.5 mL/min; and detection was done using a PDA UV–Vis detector at a wavelength of 254 nm.

Some reactions were scaled-up (15 g of substrate) and the products purified by removal of the starting reactants in a rotatory evaporator at temperatures in the range 313–333 K. Isolated yields were calculated and are reported in the SI. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub> with tetramethylsilane as the internal standard at 298 K on a Bruker Avance 300 (spectra provided in SI).

Table 2Catalytic performance of Au/TiO2 for the O2-assisted coupling of various arenes at 12 bar.								
Sustrate	<i>T</i> <sup>a</sup> (K)	% Au <sup>b</sup> (mol)						

Sustrate	$T^{\rm a}$ (K)	% Au <sup>b</sup> (mol)	$TOF^{c}(h^{-1})$	TON <sup>d</sup> (mol/mol)	$S_{\text{Biaryl}}^{\text{e}}$ (%)
Benzene	413	0.022	382	230	98.5
Toluene	373	0.026	176	206	97.6
p-Xylene	373	0.030	18	71	98.1
1,2,4-Trimethylbenzene	373	0.034	6	8	98.4
Chlorobenzene	413	0.032	368	88	98.7
Nitrobenzene	413	0.035	176	175	98.6
Phenol	373	0.027	85	336	80.3

Turnovers calculated per metal atom on the external surface of the nanoparticles. Experimental details provided in SI.

<sup>a</sup> Reaction temperature.

<sup>b</sup> Mol of metal  $\times$  mol of benzene<sup>-1</sup>  $\times$  100.

 $^{c}\,$  Turnover frequency (mol of benzene converted  $\times$  mol of metal  $^{-1}\times h^{-1}$  ).

 $^{\rm d}$  Turnover number (mol of benzene converted imes mol of metal $^{-1}$ ).

<sup>e</sup> Selectivity to the biaryl.



**Fig. 1.** Activity (TON, blue bars; and TOF, red bars) of various catalysts in the  $O_2$ -assisted coupling of benzene at 413 K and 12 bar. The insert shows the performance (TON, blue bars; TOF, red bars; and selectivity to the corresponding substituted biaryls, green bars) of Au/TiO<sub>2</sub> (3.2 nm average diameter) in the coupling of various arenes. Details of experimental conditions provided in SI. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 2.3. Electron microscopy

The experiments have been performed in a JEOL-JEM-2010F microscope with a LaB6 electron gun operated at 200 kV both in scanning-transmission mode (STEM). This microscope has a structural resolution of 0.19 nm and allows forming, in STEM mode, electron probes with diameters down to 0.5 nm suitable for high-spatial resolution analytical investigation. STEM images were obtained using a High Angle Annular Dark Field detector (HAADF), which allows Z-contrast imaging. Analytical electron microscopy was performed with an ATW type EDS detector and the INCA Energy TEM platform. EDS spectra were collected at specific points of the samples and along electron-beam paths going from vacuum through surface positions of the metal particles and the support. Particle size distributions were determined upon measurement of, at least, 200 particles per sample.

Samples for electron microscopy studies were prepared by depositing small amounts of the powders directly onto holey-carbon coated Cu grids. Excess powder was removed from the grids by gentle blowing of air with a nozzle.

## 2.4. FTIR experiments

Fourier transform infrared (FTIR) spectra have been obtained on a Biorad FTS-40A spectrometer equipped with a DTGS detector. The experiments have been carried out in a homemade IR cell able to work in the high- and low (77 K)-temperature range. Prior to CO adsorption experiments, the sample has been evacuated at 298 K in a vacuum ( $10^{-6}$  mbar) for 1 h. In one case, the catalyst has been treated in a 4% CO/He flow at 298 and 373 K for 1 h prior to the CO adsorption experiment. CO adsorption experiments have been performed at 77 K in the 0.2–20 mbar range. Spectra were recorded once complete coverage of CO at the specified CO partial pressure has been achieved.

## 3. Results and discussion

# 3.1. Aerobic-coupling of arenes by gold and other supported metal catalysts

When benzene is contacted with gold nanoparticles on TiO<sub>2</sub>  $(Au/TiO_2)$  in the presence of O<sub>2</sub> at 413 K and 12 bar under solvent-free conditions, a turnover frequency (TOF) and turnover number (TON) of 382 h<sup>-1</sup> and 230, respectively, are obtained (reaction time = 118 h). TOF and TON are calculated here per surface atom in the supported gold nanoparticles, as estimated from the HAADF-STEM and HRTEM micrographs given in Figure S1 [39-41]. Gold nanoparticles on other supports such as ZnO and Al<sub>2</sub>O<sub>3</sub> are also active for the O<sub>2</sub>-assisted coupling of benzene (Table 1), but gold species such as HAuCl<sub>4</sub> or (CH<sub>3</sub>)(PPh)<sub>3</sub>Au in solution are not under the same reaction conditions. The selectivity to biphenyl with the supported gold nanoparticles is close to 99%, and blank experiments with TiO<sub>2</sub> show that the support is inactive. To further check that gold species in solution, leached from the catalyst surface during the reaction, are not responsible for the C-C bond formation, we removed the Au/TiO<sub>2</sub> catalyst from the reaction solution after several turnovers, which resulted in cessation of the catalytic activity (Figure S2). Catalyst removal was carried out by filtration at the reaction temperature (413 K).

The catalytic behavior of gold nanoparticles for coupling of benzene appears to be quite unique, since other metals such as Rh, Pt, Pd, or Ni supported on TiO<sub>2</sub> are not active for the formation of biphenyl. Only the TiO<sub>2</sub>-supported Pd catalyst gives trace amounts of the coupling product provided that the sample has not been reduced in H<sub>2</sub> before reaction. Nevertheless, the TON of supported Pd was lower than 1 after a 24 h reaction (Table 1). We infer that Pd<sup>2+</sup> species in the unreduced Pd/TiO<sub>2</sub> sample are responsible for a stoichiometric transformation of benzene into biphenyl, as has been reported previously [15]. In fact, when adding Pd to Au/ TiO<sub>2</sub>, the activity of the gold catalyst drops from 382 h<sup>-1</sup> to 0.02 h<sup>-1</sup> (TOF measured at 413 K and 12 bar of O<sub>2</sub>). This is due to the incorporation of Pd onto the gold surface in a core–shell conformation (Fig. 2e and Figure S3), with Pd, we infer, acting as a catalyst poison.

#### 3.2. Influence of gold particle size on catalytic performance

We have found that the particle size of supported gold strongly influences the activity of Au/TiO<sub>2</sub>, being the TOF greater as the gold crystallite size decreases (Fig. 2). Notice, however, that a maximum of activity is observed for a 3 nm diameter, approximately, with a decrease in activity for further size decrease. We infer, thus, that most dispersed forms of gold (small clusters or isolated atoms) are less effective than gold crystallites of ~3 nm diameter for this reaction, as it also occurs with the homocoupling of iodobenzene [42]. To test this hypothesis, Au/TiO<sub>2</sub> with a 3.2-nm average particle size was treated with iodomethane. This treatment has been reported to generate gold clusters and isolated gold atoms [43]. The resulting material gives almost no activity for the coupling of benzene. We stress, nevertheless, that some iodine remains adsorbed on the catalyst surface,[43] which may also poison the active sites [42,44].

Fig. 3A shows the number of turnovers as a function of the reaction time in the coupling of benzene with the 3-nm average size  $Au/TiO_2$  catalyst. The kinetic curve evidences that the rate of formation of biphenyl is highest at the shortest contact times, decreasing substantially afterward. Fig. 3, thus, evidences the occurrence of catalyst deactivation. However, the reaction rate stabilizes after approximately 5 h and is fairly sustained for the next 120 h, indicating the approach to a steady state situation.

## 3.3. Catalyst regenerability

To elucidate the origin of the catalyst deactivation, the catalyst was recovered after reaction, and characterized by HAADF-STEM microscopy. The images evidence that the average particle size increases from approximately 3.2 nm to approximately 4.5 nm after reaction, with the formation of a significant fraction of nanoparticles in the range 7–12 nm (Fig. 3D) that are, in contrast, negligible in the fresh Au/TiO<sub>2</sub> catalyst (Fig. 3B). Nevertheless, taking into account the correlation between the catalytic activity (per external gold atom) and the average particle size (Fig. 2), it is evident that the activity of the used catalyst is much lower than that

expected for a fresh catalyst of a similar average particle size. Thus, while some sintering is observed, this can only be partially responsible for the observed catalytic activity decay.

At this point, the reacted catalyst was characterized by IR spectroscopy after being dried to remove the excess of physisorbed benzene. The results in Figure S4 evidence the accumulation of aromatic compounds on the catalyst surface, as inferred from the growth of IR bands at 3034 and 3066  $\text{cm}^{-1}$ , ascribed to the =C–H stretch in arenes, and the appearance of other bands in the range 1400–1600 cm<sup>-1</sup>, typical of the C–C stretching vibrations in aromatics. When the reacted catalyst was subsequently probed with CO at 77 K, no IR bands attributable to metallic Au<sup>0</sup> species were observed, in contrast to the spectra of the fresh Au/TiO<sub>2</sub> catalyst, which shows intense bands in the range 2096–2125 cm<sup>-1</sup> region characteristic of Au<sup>0</sup> species in this class of materials [45-47]. These results suggest the presence of aromatic compounds on top of the gold nanoparticles, and we point to these surface species blocking the Au<sup>0</sup> sites as potentially responsible for the observed catalyst deactivation.

The aromatic compounds can be removed from the catalyst surface without further aggregation of the gold nanoparticles by calcination in air at 673 K for 3 h. TEM of the regenerated sample shows, in fact, that gold redisperses, to some extent, over the TiO<sub>2</sub> support when calcined at 673 K (Figure S1, G vs. H). Interestingly, the regenerated catalyst behaves nearly identically with fresh benzene from conversion and selectivity standpoints, as shown in Fig. 2 and Figure S5 along three consecutive runs. The number of turnovers achieved with the AuTiO<sub>2</sub> catalyst after three recycles is >600. We note that due to the high arene/gold ratio in our batch experiments (~4500), and because of the occurrence of catalyst deactivation, the conversion generally achieved with the supported gold catalysts is low after a single run ( $\sim$ 2%). The conversion can be increased to  ${\sim}4\%$ , and the reaction time shortened, by removal of the deactivated catalyst and addition of regenerated material every few hours (Fig. 4). This makes the Au/TiO<sub>2</sub> catalyst to complete a similar number of transformations ( $\sim 0.4$ vs. ~0.7 mmol) than with the HAuCl<sub>4</sub>/PhI(OAc)<sub>2</sub>/HOAc/benzene system (0.02/1/17.5/20, mol ratio),[13] but with a remarkably



**Fig. 2.** (A) HRTEM micrographs of some representative gold catalysts used for the coupling of non-activated arenes in  $O_2$  (image *e* corresponds to a bimetallic Pd@Au catalyst). (B) Particle size distributions of several supported gold catalysts used in the present work. (C) Dependence of the TOF per external gold atom on the average particle size during the solvent-free coupling of benzene at 12 bar of  $O_2$  and 413 K for the series of catalysts in (B). The selectivity to biphenyl was always >98%. Experimental details are provided in SI and in the Section 2.



Fig. 3. (A) Evolution of the TON (per external gold atom of the fresh catalyst) with time during the solvent-free coupling of benzene in O<sub>2</sub> at 413 K and 12 bar, using an Au/ TiO<sub>2</sub> sample (AUROlite<sup>™</sup>). The selectivity to biphenyl was >98%. (B and D) Particle size distributions of the preceding catalyst before and after a 100 h reaction, respectively. (C and E) IR spectra of the fresh and used catalyst, respectively, using CO as a probe molecule.

greater TON ( ${\sim}240\,$  vs.  ${\sim}35,$  per total gold atoms used) and no iodine, acids or bases needed.

## 3.4. Effect of arene substituents

The 3.2 nm Au/TiO<sub>2</sub> catalyst provides high selectivity to the corresponding substituted biaryls from arenes that incorporate one or several methyl groups, chloride, nitro, or hydroxyl substituents, provided that the reaction temperature is properly selected. Methyl groups in mono-, di-, and tri-substituted benzenes (toluene, *p*-xylene, and 1,2,4-trimethylbenzene) underwent oxidation to aldehydes and carboxylic acids when the temperature was 413 K, with selectivities to dimethylbiphenyl, tetramethylbiphenyl, and hexamethylbiphenyl, respectively, lower than 80%. The selectivity to coupling products, however, increases remarkably (>98%) if the reaction is performed at a milder temperature (373 K, Table 2). This result is consistent with earlier reports showing that gold nanoparticles catalyze the oxidation of alkylbenzenes, even toward full combustion, when the reaction temperature is sufficiently high [48,49]. At lower temperatures, and in solventfree conditions, in contrast, biaryls that retain the substituents of the starting arenes are obtained. Interestingly, recent reports show that toluene in the absence of a solvent oxidizes to benzaldehyde, benzoic acid, and benzyl benzoate on bimetallic Au/Pd catalysts at 353–433 K, without formation of biaryl products [50]. This result



**Fig. 4.** Conversion vs. time curves for the solvent-free oxidative coupling of toluene catalyzed by Au/TiO<sub>2</sub>. Open symbols refer to a single catalytic experiment over approximately 210 h. Solid circles refer to conversion accumulated along several shorter consecutive runs (approximately 24 h duration) with the catalyst regenerated in air at 673 K in between each run. Reaction conditions stated in Table 2.

agrees well with our observation that palladium hinders the activity of gold for establishment of a new C—C bond, as depicted hereinabove (Fig. 2 and Table 1).

At 373 K, the C–C formation rate on our Au/TiO<sub>2</sub> catalyst is largely determined by the number of methyl substituents, which defines the degree of sterical hindrance. Benzene and toluene yield the corresponding biaryls at similar rates, whereas a notable decrease in activity is observed for the di- and, especially, the trisubstituted methylbenzenes (Fig. 1, insert). In contrast, we do not observe a straightforward dependence of the reactivity of substituted arenes with the electron-withdrawing character of the substituent. For example, despite the presence of the deactivating halide function in chlorobenzene, this molecule reacts at a rate comparable to that of toluene (368  $h^{-1}$  vs. 356  $h^{-1}$ , respectively), whereby the  $-CH_3$  group acts as a moderately activating group. With nitrobenzene, which incorporates a strongly deactivating -NO<sub>2</sub> group, the reaction rate is only 2-fold lower than that of toluene (176  $h^{-1}$  vs. 356  $h^{-1}$ , respectively), and no reaction at all is observed with the relatively less deactivated iodobenzene. The presence of the activating -OH group in phenol does not result in an increase in the coupling activity with regard to toluene  $(85 h^{-1} vs. 176 h^{-1})$  (see Fig. 1, insert). We remark that Au/TiO<sub>2</sub> catalyzes the O<sub>2</sub>-assisted conversion of the strongly deactivated nitrobenzene into dinitrobiphenyls at 413 K with high selectivity (>98%), a TOF of 176 h<sup>-1</sup> and, at least, 175 turnovers completed, improving recent results with Pd salts in the presence of trifluoroacetic acid (approximately 5 turnovers, and a TOF <  $0.2 h^{-1}$  at 378 K) [17].

On the other hand, we observe a mixture of the six possible regioisomers during the transformation of toluene, chlorobenzene, and nitrobenzene that cannot be rationalized according to the classical electrophilic substitution pattern, in contrast to the results with soluble Au salts in the presence of iodine oxidants [13].

## 3.5. Reaction mechanism: first insights from kinetic data

The coupling reaction should require, on the one hand, the dissociation of  $O_2$  and, on the other hand, the C—H bond scission. Since we have not observed any regioselectivity during the coupling of, for example, toluene, a working hypothesis is that the C—C bond formation involves carbon radicals. The homolytic sequestration of H has been identified as a reaction step in a number of gold-catalyzed oxidation reactions, such as the alcohol oxidation [51,52], or in the oxidative coupling of anilines to azobenzenes [53], although the investigation of the Ar—H cleavage



**Fig. 5.** Influence of the pressure of O<sub>2</sub> (A) and the concentration of arene (B) in the initial rate of benzene coupling at 373 K and 413 K, respectively. The selectivity to biphenyl was always >98%. Experiment A was performed under solvent-free conditions, and experiment B at a pressure of O<sub>2</sub> of 12 bar.

by gold nanoparticles is scarce. However, the electron-induced dissociation of benzene to phenyl radicals and subsequent observation of biaryl products have been demonstrated [54]. Consistent with the radical mechanism, when we introduce radical scavengers such as hydroquinone into the reaction, the initial benzene to biphenyl coupling rate falls from  $382 h^{-1}$  to  $<0.02 h^{-1}$  on the 3.2-nm average size Au/TiO<sub>2</sub> catalyst.

Concerning the  $O_2$  activation, gold nanoparticles on various metal oxides have been shown to catalyze a number of reactions that involve  $O_2$  dissociation. [28,30,32,53–56] We emphasize, however, that other noble metals, exemplified by palladium, are also good oxidation catalysts, but they are not catalytically active for the  $O_2$ -assisted coupling reaction of non-activated aromatic, as demonstrated here, even at temperatures and pressures markedly higher than those strictly needed to form biaryls with the Au nanoparticles (Fig. 1).

To find out which is the rate-determining reaction step on the supported gold catalysts, initial rates were measured at variable partial pressures of  $O_2$  while keeping constant the concentration of benzene, and *vice versa*. In the latter case, benzene was diluted in decane, a solvent that does not react under our reaction conditions and is expected to interact weakly with the gold nanoparticles. Solvents such as acetone, ethanol, dichloroethane, or acetic acid were found to be, in contrast, unsuitable (no biaryl formation observed).

These experiments show that the initial coupling rate of benzene is little influenced by the  $O_2$  pressure in the range 1–12 bar (Fig. 5B), although no activity is observed in the total absence of  $O_2$ . At 373 K and 1 bar of  $O_2$ , for example, more than 175 turnovers toward biphenyl can be accomplished with the 3.2-nm average size Au/TiO<sub>2</sub> catalyst, a result that greatly differs from the high  $O_2$  pressures (35–50 bar) often required with Pd salts in the additional presence of acids and other metal functions to provide just a few catalytic turnovers [18–20].

On the other hand, the rate of biphenyl formation increases linearly with the concentration of benzene in the solution (Fig. 5A), and we infer, thus, that the C—C formation rate is not controlled by the activation of  $O_2$ , but controlled by the activation of the arene, with Au—O species potentially playing a role during the Ar—H cleavage.

### 4. Conclusions

In summary, our results provide valuable insights on a new process for the formation of biaryls in  $O_2$  using re-usable solid gold catalysts. Further work is needed to understand the exact mode of action of supported gold nanoparticle in the coupling of unactivated arenes, so that more efficient catalysts that, for example, circumvent deactivation issues, can be designed. Nonetheless, we consider this advance an important achievement on route toward a waste-free production of biaryls.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2014.04.004.

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