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Direct reductive amination of aldehydes with nitroarenes using bio-renewable formic acid as a hydrogen source†

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Reductive amination (RA) is one of the most important transformations in organic chemistry. A versatile and sustainable gas-free RA of aldehydes carried out directly with cheaply available nitroarenes using stoichiometric amounts of non-toxic and entirely renewable formic acid (FA) as the terminal reductant is described herein. A single phase rutile titania supported gold (Au/TiO₂-R) catalyst is shown to catalyse efficiently this FA-based direct RA in neat water under mild reaction conditions. The broad scope, mild and neutral conditions, together with CO₂ and water as environmental harmless byproducts, make this transformation very useful. Moreover, straightforward examples of the direct construction of bioactive heterocyclic compounds containing a benzimidazole motif were achieved through this protocol.

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Introduction

The pursuit of sustainable chemistry has stimulated the development of new strategies and technologies to access organic compounds with higher values in a safe, compact and energy-efficient manner. In this regard, the reduction of imines, which can be formed *in situ* by the reaction of carbonyl compounds with amines, offers an attractive method to access higher functionalized amines, compounds that are of great interest for industrial applications.¹ Although tremendous success has been achieved by the reductive amination (RA) of aldehydes or ketones with amines,² the development of a novel catalytic system for the direct RA (DRA) from stable and readily available substrates still remains a major challenge. Considering that nitroarenes are cheap and readily available organic compounds and the reduction of nitro groups is a common method for preparing amines,³ the DRA of carbonyl compounds with nitroarenes in a domino fashion is an important alternative. Such a reaction would be especially attractive given the use of nitroarenes as more straightforward and flexible feedstocks as well as the step economy as compared to traditional RA procedures. Despite the evident potential of this particular DRA strategy, only a few examples dealing with DRA between nitroarenes and carbonyl compounds have appeared.⁴

Unfortunately, the applications of these procedures are constrained by their limited functional-group tolerance, the need for organic solvents, as well as potential explosion hazards posed by the use of molecular hydrogen gas as a reducing agent. Furthermore, special handling of the air-sensitive or pyrophoric Pd-based supported catalysts is required in most cases. Therefore, the development of new efficient, mild and general catalytic methods offering more eco-friendly and operationally simple reaction conditions is highly appreciated.

Transfer hydrogenative DRA is obviously a compelling approach in this regard, in which the use of a reductant other than H₂ allows for reductions under ambient conditions; thus advantageously no special high-pressure equipment is needed.⁵ This is of special interest for organic synthesis as well as fine chemical production in batch processes. Until recently, studies on transfer hydrogenative reductions have mostly concentrated on the use of homogeneous catalysis, with reductants ranging from Hantzsch esters,^{2g} isopropanol^{5d} and silanes^{5g} to formic acid (FA).^{5h} FA is currently produced industrially by the hydrolysis of methyl formate and also easily accessible *via* CO₂ hydrogenation.⁶ Particularly given that it is one of the major by-products formed in biomass processing, and has high energy density, non-toxicity and excellent stability, FA represents an economical, safe and easy-to-handle liquid hydrogen carrier for renewable energy storage.⁷ In this context, the DRA of nitroarenes using green and versatile FA is exceedingly attractive, as it represents a mild, one-step construction of higher amines from a mixture of cheaply available compounds, which is of intense current interest with regard to sustainable use of both renewable and non-renewable natural

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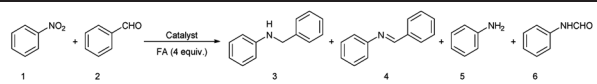
resources. Even more appealing is the use of stoichiometric amounts of FA for this reaction sequence, which signifies a more atom-efficient utilization of the raw materials. Despite these envisioned benefits, the implementation of such a truly convenient and green approach for DRA of carbonyl compounds with nitroarenes remains elusive, largely due to the lack of an efficient catalyst capable of suitably activating FA under transfer hydrogenative conditions as well as the perceived problems of the formation of multiple products.

In recent years, catalysts based on supported gold nanoparticles (NPs) have emerged as new promising nitro reduction materials owing to their high intrinsic selectivity toward the formation of the desired amino compounds.⁸ This was initiated by Corma's discovery that TiO₂ supported gold NPs can deliver an exceptionally high level of selectivity control for the hydrogenation of nitroarenes in the presence of other reducible functional groups.^{8a} As a part of our effort in this area, we demonstrated the remarkable abilities of CO/H₂O,^{8b} HCOONH₄^{8c} or HCOOH^{8d} as alternative reducing agents for Au-catalyzed nitro-to-amine reductions under ambient conditions. Meanwhile, from our continuing study on supported Au catalysis, we have discovered that ZrO₂ supported Au NPs can efficiently catalyze the dehydrogenation of FA at temperatures as low as 25 °C.⁹ Given the prominent efficiency of the gold system for low temperature FA activation, we became interested in exploring the Au-FA-based reduction strategy for DRA with nitroarenes. Herein we wish to report that chemoselective transfer hydrogenative DRA of aldehydes with nitroarene derivatives can be carried out efficiently in neat water in the presence of a single phase rutile titania supported gold catalyst using FA as the hydrogen donor, and good to excellent yields have been obtained for a range of substrates. The present procedure possesses the following noteworthy features: (i) use of a robust and reusable heterogeneous catalyst, (ii) use of entirely renewable and stoichiometric amounts of FA as the terminal reductant, (iii) use of water as a solvent and ease of phase-separation of water-insoluble products in the work-up procedure,¹⁰ (iv) use of readily available starting materials, and (v) formation of CO₂ and water as environmentally harmless byproducts.

Results and discussion

We began our research by examining the DRA of benzaldehyde (2) with an equimolar amount of nitrobenzene (1) as a benchmark system. In the first stage of our study, the experiments were carried out in neat water at a metal loading of 1 mol%, by using 4 equivalents of FA and a temperature of 80 °C. We initially investigated a zirconia supported gold catalyst system composed of small Au NPs (approx. 1.8 nm) deposited on ZrO₂ (Au/ZrO₂); it has previously been identified as a very efficient catalyst for low temperature dehydrogenation of FA.⁹ However, we found that this catalyst was not selective for the formation of the desired secondary amine, *N*-benzylaniline (3). After 3 h of reaction, only ca. 70% of 1 can be converted into 3 (Table 1, entry 1). It is worth noting that benzyl alcohol, one of the most

Table 1 The direct RA of benzaldehyde and nitrobenzene to *N*-benzylaniline^a



Entry	Catalysts	T [°C]	t [h]	Conv. ^b [%]	Yield ^b [%]			
					3	4	5	6
1	Au/ZrO ₂	80	3	>99	70	4	26	0
2	Au/TiO ₂ -P25	80	3	>99	76	6	18	0
3	Au/TiO ₂ -R	80	3	>99	97	1	2	0
4	Au/TiO ₂ -A	80	3	>99	78	9	13	0
5 ^c	Au/TiO ₂ -R	90	20	98	94	2	2	0
6	Au/CeO ₂	80	3	89	27	15	47	0
7	Au/Al ₂ O ₃	80	3	>99	68	10	22	0
8	Au/C	80	3	4	1	1	2	0
9	Pd/TiO ₂ -R	80	3	6	1	2	2	1
10	Pt/TiO ₂ -R	80	3	n.r.	—	—	—	—
11	Ir/TiO ₂ -R	80	3	n.r.	—	—	—	—
12	Ru/TiO ₂ -R	80	3	n.r.	—	—	—	—
13	Au/TiO ₂ -R	100	1.5	>99	92	8	0	0
14	Au/TiO ₂ -R	60	6	>99	95	4	1	0
15 ^d	Au/TiO ₂ -R	25	16	>99	94	5	1	0
16 ^e	Au/TiO ₂ -R	80	3	>99	96	1	3	0
17 ^f	Au/TiO ₂ -R	80	3	91	24	33	34	0
18 ^g	Au/TiO ₂ -R	80	3	>99	2	3	2	28

^a Nitrobenzene (1 mmol), benzaldehyde (1 mmol), FA (4 mmol), H₂O (5 mL), metal (1 mol%), N₂ (1 atm), n.r. = no reaction. ^b Conversions (Conv.) based on nitrobenzene, Conv. and yields determined by GC using *n*-dodecane as the internal standard. ^c Nitrobenzene (20 mmol), benzaldehyde (20 mmol), FA (80 mmol), water (10 mL), Au (0.05 mol%). ^d Au (4 mol%). ^e Under an air atmosphere. ^f FA (3 mmol). ^g FA (6 mmol), 65% yield of *N*-benzyl-*N*-phenylformamide was obtained.

unwanted by-products for metal-catalyzed DRA reactions, was not observed in this case. A careful analysis of the reaction products showed the formation of 26% of aniline (5) and 4% of imine intermediate *N*-benzylidenebenzylamine (4) as the byproducts. Running the reaction for extended periods did not produce an increase of 3 formation (Table S1†). Catalysts favouring the crucial imine formation and its subsequent reduction would be highly beneficial. We therefore examined a series of gold deposited on other mineral supports such as Al₂O₃, CeO₂, and activated carbon. The preparation procedure of these catalysts and relevant characterization data are provided in the ESI.† These catalysts, however, can only deliver the desired 3 with an even lower selectivity in the range of 1–68% (Table 1, entries 6–8). Interestingly, when applying a commercial biphasic nanocrystalline titania (Evonik P25) supported gold catalyst (Au/TiO₂-P25, Au mean particle size ~2.2 nm), which has been widely studied and proven to be highly effective for a variety of organic transformations including chemoselective nitro reduction,^{8b,c} alkyne semihydrogenation¹¹ and nitrile hydration,¹² appreciable levels of DRA selectivity were achieved, thus furnishing the desired 3 in a yield of 76% (Table 1, entry 2).

With the aim to further improve the catalytic efficiency, we examined an additional set of Au catalysts composed of gold NPs with identical average particle size (ca. 2 nm, for details see the ESI†) supported on TiO₂ with different polymorphic

structures. Much to our delight, when gold was deposited on single-phase rutile TiO_2 , the selectivity for **3** increased significantly. In contrast to the sample in which gold is loaded on single phase anatase ($\text{Au}/\text{TiO}_2\text{-A}$), an excellent yield of **3** (97%) was obtained at 80 °C after 3 h when using a $\text{Au}/\text{TiO}_2\text{-R}$ sample (Table 1, entry 3). These results further confirm that the support material plays a key role in the selectivity of this reaction. At this juncture, it should be mentioned that the reaction with various TiO_2 supports or unsupported Au NPs alone did not proceed at all (Table S1†). Note that $\text{Au}/\text{TiO}_2\text{-R}$ successfully promoted the DRA reaction even at room temperature (entry 15), conditions under which other supported metals, such as Pd, Pt, Ir and Ru, are totally inefficient (entries 9–12). Remarkably, the Au loading could be decreased to 0.05 mol% without affecting the conversion (entry 5). Thus, in a gram-scale reaction of **1** and **2** (20 mmol scale-up) for 20 h, 94% yield of **3** was obtained. In this case, no traces of *N*-formyl derivative (<0.5%), an unwanted by-product that usually formed in appreciable levels with traditional FA-based protocols under mild conditions, are observed during the reaction. Furthermore, the recovered $\text{Au}/\text{TiO}_2\text{-R}$ can also be reused at least five times without loss of activity on this scale (Fig. S1†). The transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS) and X-ray diffraction (XRD) measurements revealed almost no change in the dispersion of the Au or metallic state of Au before and after reuse (Fig. S2–S4†). Moreover, by filtering off the $\text{Au}/\text{TiO}_2\text{-R}$ catalyst after conducting the DRA reaction for 1 h, we observed no additional product during the next 2 h under the above conditions (Scheme S1†), indicating that the heterogeneous reaction involves minimal catalyst leaching and mechanisms entailing homogeneous reactions are not likely operating.

Significantly more interesting is the observation that this catalytic system can also afford near quantitative formation of **3** under an air atmosphere (Table 1, entry 16), thus offering clear and compelling advantages over existing methods to establish a more convenient and viable FA-based DRA process. Encouraged by these promising results, a more detailed study of the proposed process has been carried out with the $\text{Au}/\text{TiO}_2\text{-R}$ catalyst. We confirmed in control experiments that the reaction did not proceed in the absence of a catalyst and the reaction practically did not occur when H_2 was applied instead of FA as a reductant (Table S3†). Meanwhile, analysis of the head-space gases at the end of a typical reaction (Table 1, entry 3) showed the mere presence of CO_2 . These results indicate that the present Au-mediated DRA catalysis is entirely a transfer hydrogenation process. A further indication that our process does not proceed *via in situ* generation of H_2 by FA decomposition came from the observation that the sole FA decomposition did not occur to any practical degree in the absence of **1** and **2** (Table S3†). A subsequent investigation that was focused on the amount of FA revealed that 4 equivalents of FA were enough to obtain the optimal reaction activity. When the reaction was conducted with three equivalents of FA, the conversion decreased and formation of more byproducts was observed (entry 17). In contrast, significant formation of

unwanted *N*-formyl derivatives resulting from a further formylation of **3** as the intermediate was observed when 6 equiv. of FA were employed (Table 1, entry 18). The most interesting aspect, however, is that water was found to be the best solvent to promote the DRA efficiently, and lower yields were obtained using inorganic solvents (Table S2†). This is unexpected, as imine formation is thought to be greatly retarded in the presence of a large excess of water.^{2f,g}

To examine in detail the DRA reaction performed with $\text{Au}/\text{TiO}_2\text{-R}$, a kinetic experiment for the reaction of **1** with **2** was monitored by utilizing continuous sampling by gas chromatography. As can be seen in Fig. 1, **5** and **4** were initially formed followed by the formation of **3**. During the whole reaction process, the carbonyl group of benzaldehyde remains unaffected and the level of selectivity for **4** never exceeded 20%. Furthermore, it was confirmed in separate experiments that the direct and complete conversion of **1** to **5** in the presence of 3 equiv. of FA occurred rapidly in the first 15 min, while the hydrogenation of **4** readily proceeded to give **3** in 98% yield in 3 h in the presence of 1 equiv. of FA as a hydrogen donor (Tables S4 and S6†). These results indicate that the direct synthesis of **3** would proceed through a series of consecutive steps in a cascade mode, in which the initial step must be the transfer hydrogenation (TH) of **1** to aniline. Then the aniline readily reacts with a starting carbonyl compound to form the corresponding imine, which is presumably the rate-determining step of the overall process, followed by a final transfer hydrogenation to afford the corresponding secondary amine. To gain a deeper insight into the origin of the enhanced DRA performance achieved by using single-phase $\text{TiO}_2\text{-R}$ as a support, the direct condensation of benzaldehyde with aniline in neat water, as well as the direct reduction of **1** with FA and direct RA of aniline and **2** with FA, has been investigated for Au NPs deposited on different supports (Tables S4,

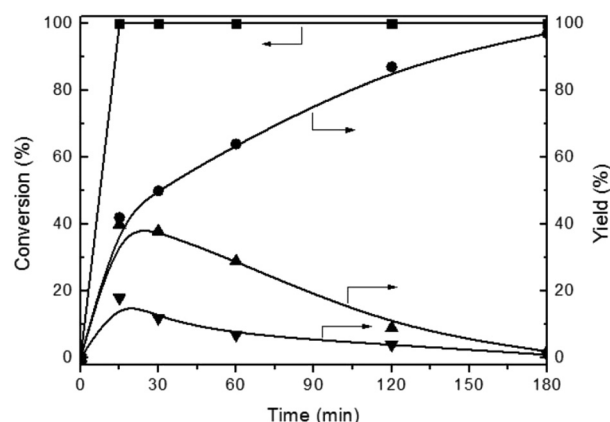












Fig. 1 . Reaction profile for *N*-benzylaniline formation from nitrobenzene and benzaldehyde. (■) Conversion of nitrobenzene, (●) yield of *N*-benzylaniline, (▲) yield of aniline, (▼) yield of *N*-benzylidenebenzylamine. Reaction conditions: nitrobenzene (1 mmol), benzaldehyde (1 mmol), FA (4 mmol), water (5 mL), $\text{Au}/\text{TiO}_2\text{-R}$ (Au: 1 mol%), N_2 (1 atm), 80 °C.

S5 and S7†). It is revealed that all relevant reactions, in particular the direct condensation of benzaldehyde with aniline (Table S5†) over Au/TiO₂-R, occurred with much higher rates than that over other catalysts. To clarify the essential role of Au/TiO₂-R in promoting the crucial direct condensation of benzaldehyde with aniline, we characterized the various supports by using NH₃- and CO₂-temperature-programmed desorption (NH₃/CO₂-TPD). It is revealed in Fig. S5† that TiO₂-R shows a much lower abundance of surface acidic and basic sites relative to other supports. It is therefore reasonable to conclude that an optimal cooperation between Au and TiO₂-R, in which rutile TiO₂ affords mild acid/base sites and Au furnishes suitable TH activity, is essential to facilitate the desired DRA reaction in a domino fashion.¹³

Building upon these results, we set out to examine the scope and limitations of this Au-FA-mediated DRA reaction. We started by studying the effect of substituents on the aromatic ring of the benzaldehyde substrate. As revealed in Table 2, various aldehydes were reductively aminated with nitrobenzene in the presence of 4 equiv. of FA. The aldehydes used for this study included aromatic and aliphatic examples. Irrespective of the electronic nature of the substituent, aromatic aldehydes reacted smoothly to give the desired secondary amine products in excellent yields (Table 2, entries 2–6). For instance, mixing nitrobenzene with 4-methylbenzaldehyde, or 4-chlorobenzaldehyde, in water at 80 °C for 4–5 h resulted in the formation of the corresponding secondary amines in 98 and 96% yields, respectively (Table 2, entries 2 and 4) and no dehalogenation of the chloride group is observed. Substituted 4-hydroxy and 4-methoxy-benzaldehydes also gave the

Table 2 Catalytic synthesis of secondary amines from nitrobenzene and different aldehydes^a













Entry	Aldehydes	T [h]	Conv. ^b [%]	Yield ^b [%]
1		3	>99	97 (94)
2		4	>99	98 (95)
3		4	>99	94 (92)
4		5	>99	96 (92)
5		4	>99	95 (90)
6		5	>99	94 (91)
7		5	>99	93 (90)
8		8	>99	85 (82)
9		9	>99	87 (85)
10		11	>99	83 (80)

^a Nitrobenzene (1 mmol), aldehyde (1 mmol), FA (4 mmol), H₂O (5 mL), Au/TiO₂-R (Au: 1 mol%), N₂ (1 atm), 80 °C. ^b Conv. and yields determined by GC using *n*-dodecane as the internal standard. The numbers in parentheses indicate yields of isolated products.

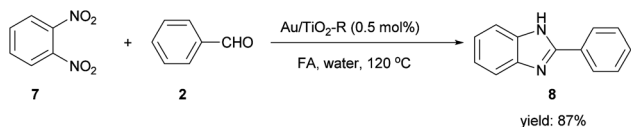
corresponding products in high yields (Table 2, entries 5 and 6). Notably, all the aromatic aldehydes generated the corresponding secondary amines as the primary products. A hetero-aromatic aldehyde, furfural (Table 2, entry 7), also underwent DRA with nitrobenzene smoothly and gave the corresponding secondary amine in good yield. As more challenging examples, aliphatic aldehydes (Table 2, entries 8–10) can also be converted with aniline to form higher amines in high yields, albeit with a prolonged reaction time.

The generality of this methodology has been extended to various substituted aromatic nitroarenes and benzaldehydes to produce corresponding secondary amines under mild reaction conditions. Table 3 compiles the conversion and selectivity results obtained in the reductive amination of benzaldehyde and different nitro-compounds. The electronic effect on the aromatic ring was not significant; nitrobenzene substituted with electron-donating or -withdrawing groups could undergo reductive coupling to the corresponding secondary amines with high yields (Table 3, entries 2–12). For instance, coupling of benzaldehyde with *p*-methyl-nitrobenzene (Table 3, entry 2) or 1-fluoro-4-nitrobenzene (Table 3, entry 5) gave desired secondary amines in excellent yields of 96 and 95%, respect-

Table 3 Catalytic synthesis of secondary amines from benzaldehyde and different nitroarenes^a

Entry	Nitroarenes	T [h]	Conv. ^b [%]	Yield ^b [%]
1		3	>99	97 (94)
2		3	>99	96 (93)
3		4	>99	97 (93)
4		9	>99	95 (91)
5		6	>99	95 (92)
6		5	>99	94 (91)
7		5	>99	94 (90)
8		10	98	86 (82)
9		9	>99	93 (90)
10		5	>99	92 (88)
11		4	>99	91 (87)
12		6	>99	95 (92)

^a Nitro compound (1 mmol), benzaldehyde (1 mmol), FA (4 mmol), H₂O (5 mL), Au/TiO₂-R (Au: 1 mol%), N₂ (1 atm), 80 °C. ^b Conv. and yields determined by GC using *n*-dodecane as the internal standard. The numbers in parentheses indicate yields of isolated products.



Scheme 1 Gold-catalyzed one-pot reductive amination for the synthesis of benzimidazole.

ively. Of note is that the reducible function groups such as alkene and ketone groups were remained intact during the reduction of nitrobenzene (Table 3, entries 10 and 11). In the transformation of methyl-nitrobenzene, the lower rate of *o*- and *m*-methyl relative to *p*-analogues indicated a steric effect (Table 3, entries 2–4). Again, no dehalogenation of the fluorine or chloride group is observed. Notably, all these results showed the high efficiency of the Au/TiO₂-R-catalyzed RA of nitro compounds and benzaldehyde mixtures to generate desired secondary amines.

Lastly, we investigated the potential of this method to generate N-heterocycles containing a benzimidazole motif, which are prevalent in natural products and pharmaceutical agents and are important synthetic targets for drug discovery and development.¹⁴ We anticipated that the *o*-dinitroarene substrate could be employed to furnish the desired N-heterocyclic ring construction. Gratifyingly, treatment of equimolar amounts of *o*-dinitroarene (1.0 g, 6 mmol, 7) and benzaldehyde (0.63 g, 6 mmol) with 6 equiv. of FA in the presence of 0.5 mol% Au/TiO₂-R in water at 120 °C for 6 h provided the 2-phenylbenzimidazole product (8) in 87% isolated yield (Scheme 1). This appears to be the most efficient method for accessing this type of compound, in terms of cost, effectiveness, practicability and scalability. It is also worth noting that for the reaction illustrated in Scheme 1, the work-up simply involves a facile filtration of the catalyst followed by direct separation of the organic phase of the filtrate, due to the low solubility of benzimidazole in aqueous solution.

Conclusions

In summary, we have developed a new catalytic system for DRA in water by using easily handled TiO₂ supported gold NPs as a catalyst with renewable FA as a hydrogen source. This mild and operationally easy amination employs cheaply available nitroarenes and aldehydes, exhibits a broad substrate scope, and liberates CO₂ as the only byproduct. By saving energy and additional steps, our process illustrates the general potential for conducting gas-free reductive condensation reactions in a less costly, simpler and greener manner.

Experiments

General procedure for DRA of aldehydes with nitroarenes

Nitroarene (1 mmol), aldehyde (1 mmol), FA (4 mmol), water (5 mL), *n*-dodecane (1 mmol, as the internal standard) and the

Au/TiO₂-R catalyst (Au: 1 mol%) were placed into a three-necked round-bottom flask (50 mL capacity) fitted with a reflux condenser. The resulting mixture was vigorously stirred (1000 rpm) at 80 °C under a N₂ atmosphere (1 atm) for a given reaction time. The conversion and product selectivity were determined by using an Agilent 7820A gas chromatograph equipped with a HP-FFAP column (30 m × 0.25 mm) and a flame ionization detector (FID). After completing the reaction, the resulting mixture was allowed to cool to room temperature. The catalyst was collected by filtration. The filtrate was extracted with dichloromethane and washed with a brine solution. The organic phase was collected, dried with anhydrous Na₂SO₄, and concentrated by rotary-evaporation. The residue was purified by silica flash column chromatography with PE : EA as the eluent.

Procedure for a gram-scale DRA of benzaldehyde with nitrobenzene

Nitrobenzene (20 mmol), benzaldehyde (20 mmol), FA (80 mmol, added by a peristaltic pump over the course of 15 h), water (10 mL), *n*-dodecane (5 mmol, as the internal standard) and the Au/TiO₂-R catalyst (Au: 0.05 mol%) were placed in a three-necked round-bottom flask (150 mL capacity) fitted with a reflux condenser. The resulting mixture was vigorously stirred (1000 rpm) at 90 °C under a N₂ atmosphere (1 atm) for 20 h. The conversion and product selectivity were determined by using an Agilent 7820A gas chromatograph equipped with a HP-FFAP column (30 m × 0.25 mm) and a flame ionization detector (FID).

Recovery and reuse of Au/TiO₂-R

The reused catalyst was recovered by filtering the solid Au/TiO₂-R catalyst from the liquid phase after the reaction. The recovered catalyst was washed several times with ethanol. The catalyst was then dried under vacuum at room temperature overnight before the next recycle run.

Procedure for the synthesis of 2-phenylbenzimidazole

o-Dinitro-benzene (1.00 g, 6 mmol), benzaldehyde (0.63 g, 6 mmol), FA (36 mmol), water (10 mL), *n*-dodecane (2 mmol, as the internal standard) and the Au/TiO₂-R catalyst (Au: 0.5 mol%) were charged into a 50 mL Hastelloy-C high pressure Parr reactor and stirred at a rate of 1000 rpm at 120 °C under an air atmosphere for 6 h. The mixture was stirred for 15 min at room temperature before adding Au/TiO₂-R. The conversion and product selectivity were determined by using an Agilent 7820A gas chromatograph equipped with a HP-FFAP column (30 m × 0.25 mm) and a flame ionization detector (FID). After completing the reaction, the mixture was allowed to cool to room temperature. The catalyst was collected by filtration. The filtrate was extracted with dichloromethane and washed with brine solution. The organic phase was collected, dried with anhydrous Na₂SO₄, and concentrated by rotary-evaporation. The residue was purified by silica flash column chromatography with PE:EA as the eluent.

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