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COMMUNICATION

Direct one-pot reductive imination of nitroarenes using aldehydes and carbon monoxide by titania supported gold nanoparticles at room temperature†

Jun Huang, Lei Yu, Lin He, Yong-Mei Liu, Yong Cao* and Kang-Nian Fan

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The direct one-pot reductive imination of nitroarenes with various aldehydes by a titania supported gold catalyst at room temperature using CO/H_2O as a reducing agent is illustrated. This method is simple, economic, general and environmentally benign, thus resulting in practical advantages for the synthesis of imines and their derivatives.

The formation of carbon–nitrogen bonds is one of the most important transformations in organic chemistry.[1] In particular, imines are highly desirable, owing to their versatile applications as electrophilic reagents in many organic reactions, such as reductions, additions, condensations, and cycloadditions.[2,3] Traditionally, imines are synthesized from the dehydrative condensation of amines and carbonyl compounds in the presence of an acid catalyst.[4] Imines can also be prepared by a number of catalytic and non-catalytic procedures, such as the self-condensation of amines upon oxidation,[5a,5b] the oxidation of secondary amines[5c,5d] or directly from alcohols and amines *via* several tandem catalytic processes,[5e,5f,6] mostly with homogeneous systems. However, many of these methods entail important practical drawbacks regarding the difficulty for resue, the use of expensive amines as starting materials, long reaction time, low selectivities, high temperature, tedious work-up procedures, and/or concomitant formation of large amounts of wasteful salts. In these regards, there is a strong incentive to develop an alternative heterogeneous-based method that can employ simpler starting materials, as well as mild and environmentally benign conditions.

Nitroarenes are inexpensive and readily available organic compounds, and the reduction of nitro compounds is a key step in the preparation of many pharmaceutical agents and fine chemicals.[7] Despite numerous established procedures for the reduction of nitro compounds, the development of catalytic methodologies that afford high chemo- and regio-selectivity under mild reaction conditions is still a challenging problem.[8] As for the synthesis of imines, the direct use of nitroarenes as starting materials is highly attractive, especially when an efficient and reusable catalytic system can be employed. Compared to the great progress being made in the imination of amines with aldehydes or ketones,[9] there are scarcely any available reports dealing with the direct reductive imination of nitroarenes with carbonyl compounds. A number of transition-metal-catalyzed carbonylative reductions of nitroarenes and aldehydes with CO and water to afford imines have been reported since the early 1970s.[10a–e] However, these homogeneous systems are problematic in terms of the recovery/recycling of the catalyst and the special handling of metal complexes. Recently, the direct synthesis of imines from nitroarenes and carbonyl compounds was realized using Au/TiO_2[11a] or Ni/SiO_2[11b] as a catalyst in the presence of molecular H_2, or using the hydrogen gas produced from the aqueous-phase reforming of methanol as an *in situ* reductant over a bimetallic Au–Pd/Al_2O_3[11c] catalyst. Despite their utility, clear drawbacks of these methods are the requirement of harsh reaction conditions, such as high temperatures (>110 °C), elevated pressures and prolonged reaction times, which made them far from ideal for both synthetic and large-scale applications. In this respect, the development of a new practical and efficient one-pot process that can allow the direct synthesis of imines from aromatic nitro compounds under mild conditions still remains a major challenge.

The use of supported gold nanoparticles (NPs) as catalysts for green organic transformations is an area of growing interest.[12] Recently, from our continuing studies on supported gold NPs catalysis,[5e,13] we have discovered an excellent Au-catalyzed reduction strategy that can allow the rapid and chemoselective reduction of polysubstituted nitro and carbonyl compounds under very mild conditions.[14] This process can circumvent the limited hydrogen delivery rate that has plagued previously reported Au-catalyzed hydrogenation processes.[8a,15] The reductant used in this green alternative methodology was CO and H_2O (rather than H_2), where the transient Au^0–H formed by the CO-induced H_2O reduction is believed to be the key active species for nitro reduction. An interesting feature of the Au–CO/H_2O-catalyzed reaction is that it tolerates a

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Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University, Shanghai, 200433, P. R. China. E-mail: yongcao@fudan.edu.cn; Fax: (+86-21) 65643774

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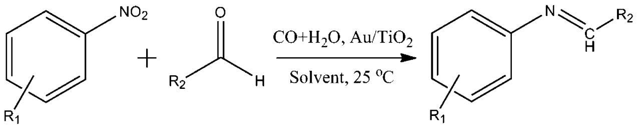
Table 1 Synthesis of *N*-benzylidenebenzenamine from nitrobenzene and benzaldehyde in different solvents[a]

Entry	Solvent	Water [equiv][b]	Con. [%][c]	Sel.[%][c] Imine	Aniline	Nitrone[d]
1	Ethanol/Water (v/v = 2 : 1)	33	100	27	65	8
2	Ethanol	0	25	78	2	20
3	Ethanol	0.5	71	74	8	18
4	Ethanol	1	90	72	13	15
5	Ethanol	2	100	64	23	13
6	Ethanol	10	100	43	47	10
7	Acetonitrile	1	43	53	28	19
8	DMF	1	34	50	35	15
9	Toluene	1	78	79	10	11
10	Tetrahydrofuran	1	100	85	10	5
11	Triethylamine	1	100	95	5	0
12[e]	Triethylamine	1	97	93	7	0
13[f]	Triethylamine	1	n.r.	—	—	—

[a] Reaction conditions: 1 mmol nitrobenzene, 1 mmol benzaldehyde, Au/TiO_2-VS (1 mol% Au), 2 mL solvent, 5 atm CO, 25 °C, 1 h. [b] Relative to that of nitrobenzene. [c] GC conversion and selectivity obtained by using anisole as an internal reference. [d] Confirmed by GC/MS. [e] 1 atm CO, 5 h. [f] H_2 (5 atm) as the hydrogen source, n.r. = no reaction.

diverse range of reducible functional groups, including alkenes, alkynes, halogens, ketones, aldehydes, esters, and nitriles.[14] Furthermore, this reaction can be carried out under atmospheric CO at room temperature. In view of the prominent efficiency of the gold system for chemoselective reduction of the nitro functionality, we envisioned that the CO/H_2O-mediated Au-catalyzed reduction strategy could afford a green and efficient protocol for the direct synthesis of substituted imines from nitroaromatics under mild conditions.

Herein, we report for the first time that direct reductive imination of nitroarenes with aldehydes *via* a simple CO-mediated one-pot strategy could efficiently be promoted by small gold NPs supported on titania (Au/TiO_2-VS). With the procedure presented here, nitroarenes are directly used as the starting reactants and undergo a selective reduction process to form anilines, which condense *in situ* with the aldehydes to provide the final imines through a cascade-type reaction (Scheme 1). Of note is that this particular transformation can proceed very effectively at ambient temperature under 5 atm CO atmosphere, these are the mildest reaction conditions ever reported for the direct reductive transformation of nitroarenes and aldehydes for the preparation of substituted imines. Thanks to the chemoselectivity of the CO–Au/TiO_2-VS system during the reduction of nitro aromatics, this methodology is found to be applicable to both aromatic and aliphatic aldehydes and a wide range of nitroaromatics. Compared with the known protocols from the literature,[11] the present Au-catalyzed CO-mediated one-pot direct reductive imination system has the following advantages: i) unprecedentedly high activity under very mild conditions; ii) high selectivity towards very sensitive competing groups; and iii) the use of safe and easy-to-handle catalysts and reducing reagents.



Scheme 1 The imination of nitroarenes using aldehydes and carbon monoxide by supported gold nanoparticles at room temperature.

We began our study by examining the direct coupling of nitrobenzene and benzaldehyde at 25 °C, as this is expected to represent the easiest scheme for the proposed reductive imination. First of all, the direct imination of nitrobenzene with an equimolar amount of benzaldehyde under 5 atm of CO in aqueous ethanol (ethanol/water 2 : 1) in the presence of Au/TiO_2-VS (1% mol of Au) was investigated. In line with our previous results in CO/H_2O-mediated Au-catalyzed nitro reduction, the initial reduction of the nitro functionality was complete after 1 h of the reaction.[14a] However, only very small amounts of *N*-benzylidenebenzenamine could be detected in this case (Table 1, entry 1), probably due to the lack of conversion in the consecutive imine formation step. As a result of the presence of a large excess of water in the reaction system, there still was an appreciable amount of aniline left in the reaction mixture. Surprisingly, a significant amount of nitrone was also observed as a by-product. Nitrones are highly versatile and valuable synthetic intermediates in organic synthesis and are extensively used in the synthesis of biologically active compounds.[16] The most frequent routes to prepare nitrones include the condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines or the oxidation of hydroxylamines or imines.[17] As the chemoselective reduction of nitroaromatics catalyzed by supported gold catalysts is believed to involve the formation of hydroxylamine as the key intermediate species,[8d,18] it is likely that the transient hydroxylamine thus formed might then react further with benzaldehyde, giving rise to the corresponding nitrones product.

In an attempt to facilitate the desired consecutive imine formation, a systematic study of the reductive imination was then accomplished in aqueous ethanol with decreasing water content. As expected, the reaction run using standard non-dry ethanol as the solvent (under otherwise the same conditions as the preliminary experiment) led to significantly improved imine selectivity but had the opposite effect on the conversion of nitrobenzene (Table 1, entry 2). This latter result can be rationalized by assuming that the formation of transient

Au^0–H species,[19] which are responsible for the superior activity of the CO/H_2O-mediated Au-catalyzed nitro reduction, is severely limited under water-deficient conditions.[20] Upon increasing the water content from 0.5 to 10 equiv (relative to that of nitrobenzene), the reaction proceeds to completion along with a progressive decrease in the selectivity of the desired product (Table 1, entry 3–6). Thus, of the various conditions examined here, the use of 1 equiv of H_2O affords the optimal catalytic performance (entry 4). In light of these results, the use of 1 equiv of H_2O was chosen as the suitable parameter to study the influence of the nature of the solvent on this particular transformation. Whereas changing the solvent to acetonitrile and DMF significantly lowered the imine selectivity to a level of *ca.* 50% (Table 1, entries 7 and 8), the use of toluene, THF and triethylamine as the solvents can afford the formation of imine with an excellent selectivity up to 95% (Table 1, entries 9–11). Of particular note is the lack of formation of nitrone when triethylamine was used as the solvent.[21] Thus, of the various solvents screened for this reaction, triethylamine is shown to be the solvent of choice (Table 1, entry 11).[22]

At this point it is interesting to note that the direct reductive coupling of nitrobenzene and benzaldehyde to afford imine with Au/TiO_2-VS in triethylamine could be carried out smoothly even under 1 atm of CO (Table 1, entry 12), although a much longer reaction time is required for reaction completion. Such mild reaction conditions had never been demonstrated for the direct synthesis of imines from nitroarenes and carbonyl compounds. As the choice of the support plays an important role in gold catalysis, we also evaluate gold supported on Fe_2O_3 (Au/Fe_2O_3), CeO_2 (Au/CeO_2), silica (Au/SiO_2) and activated carbon (Au/C). However, all these catalysts were significantly less active for the reductive imination reaction under similar reaction conditions (see Table S3†). Note that this fact is in complete agreement with our previous study about the role of support for the Au-catalyzed reduction of nitroarenes with CO/H_2O.[14a] Therefore, among the various catalysts examined here, TiO_2 supported Au (Au/TiO_2-VS) affords, by far, the best catalytic performance.

To examine the reaction performed in triethylamine in detail, a kinetic experiment for the reaction of nitrobenzene with benzaldehyde was monitored by utilizing continuous sampling by gas chromatography. As can be seen in Fig. 1, it is possible to obtain *N*-benzylideneaniline with 95% selectivity at complete nitrobenzene conversion after 1 h of reaction by using Au/TiO_2-VS as the catalyst. The high yield of the desired product obtained shows that both the carbonyl group of benzaldehyde and the C═N group of the product imine remain unaffected during the reduction of nitrobenzene.[23] The most important finding, however, is the lack of formation of *N*-phenylbenzylamine, even after prolonged reaction times, inferring that the undesirable imine reduction pathway is practically inhibited in this case. Note that this behavior is much better in terms of conversion and selectivity than those recently reported through a Au/TiO_2-catalyzed sequential nitro-hydrogenation-condensation pathway using H_2 as the reductant,[11a] in which a strict monitoring of the hydrogen uptake to avoid over-reduction of imine is required.

Given the observed high activity and selectivity, it is of interest to clarify the essential role of Au/TiO_2-VS in the final imine formation step, which is known as a process promoted by soluble Lewis or Brønsted acids.[4a,11c] By using the direct condensation between benzaldehyde and aniline in triethylamine as a standard reaction, several control experiments were performed with both the presence/absence of Au/TiO_2-VS or in the presence of bare TiO_2 for comparative purposes (other conditions were the same as those given in entry 11 of Table 1). As can be seen from Table S1†, the best result was obtained with Au/TiO_2-VS. Whereas the catalytic performance of Au-free TiO_2 closely resembles that using Au/TiO_2-VS as the catalyst, a substantially lower yield of the desired imine has been observed for the case without using any catalyst. Therefore, it seems that the mild acidity of the TiO_2 support surface[11a,24] plays a significant role in accelerating the subsequent imine formation step during the present one-pot reductive imination process.

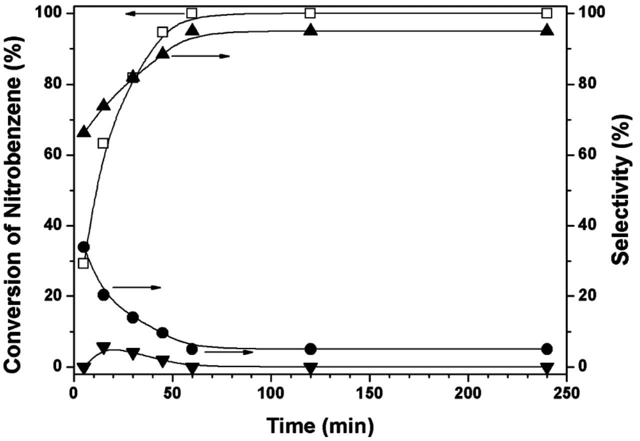
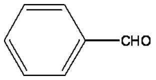
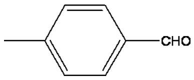
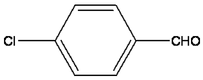
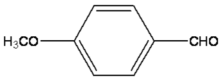
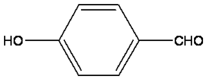
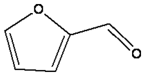
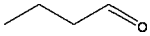
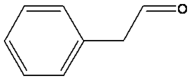


Fig. 1 Time course of *N*-benzylidenebenzenamine formation from nitrobenzene and benzaldehyde. (□) conversion of nitrobenzene, (●) selectivity of aniline, (▲) selectivity of imine, (▼) selectivity of nitrone. Reaction conditions: 1 mmol nitrobenzene, 1 mmol benzaldehyde, Au/TiO_2-VS (1 mol% Au), 2 mL triethylamine, 1 mmol H_2O, 5 atm CO, 25 °C.

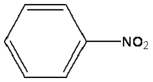
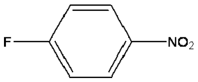
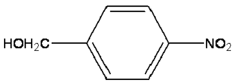
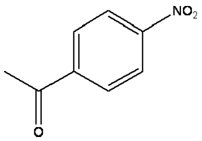
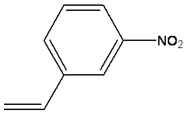
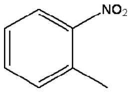
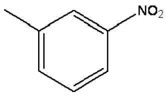
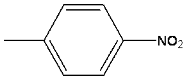
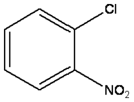
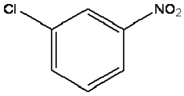
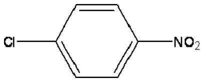
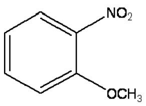
Under the optimized reaction conditions (Table 1, entry 11), the scope of the reaction was explored with structurally and electronically diverse aldehydes with a wide range of nitroarenes. As revealed in Table 2, various aldehydes were reductively iminated with nitrobenzene under 5 atm of CO. The aldehydes 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 imine products in excellent yields (Table 2, entries 2–5). For instance, mixing nitrobenzene with 4-methylbenzadlehyde, or 4-chlorobenzaldehyde, in triethylamine at 25 °C for 1 h resulted in the formation of the corresponding imines in 97 and 96% yields, respectively (Table 2, entries 2 and 3) and no dehalogenation of the chloride group is observed. Substituted 4-methoxy and 4-hydroxybenzaldehydes also gave the corresponding products in high yields (Table 2, entries 4 and 5). Notably, all the aromatic aldehydes generated the corresponding imines as the primary products. However, alphatic aldehydes (Table 2, entries 6–8) were more difficult to convert with aniline to form imines. For example, a much longer reaction time is required to gain good yields. The reaction of furfural with nitrobenzene led to the corresponding imine in good yield (Table 2, entry 6). GC analysis showed that 13% of the intermediate aniline was unreacted. Lower conversion of the intermediate aniline was observed in the reaction of

Table 2 Catalytic results of the synthesis of imines from nitrobenzene and different aldehydes[a]

Entry	Aldehyde	Time [h]	Con. [%][b]	Yield [%][b,c]
1		1	> 99	95 (91)
2		1	> 99	97
3		1	> 99	96 (92)
4		1	> 99	93
5		1	> 99	92 (89)
6		1 4	> 99 > 99	27 87 (80)
7		1 6	> 99 > 99	15 75
8		1 9	> 99 > 99	8 64

[a] Reaction conditions: 1 mmol nitrobenzene, 1 mmol aldehyde, Au/TiO_2-VS (1 mol% Au), 2 mL triethylamine, 1 mmol H_2O, 5 atm CO, 25 °C. [b] GC conversion and selectivity obtained by using anisole as an internal reference. Numbers in parentheses refer to yields of isolated products. [c] Aniline was the sole by-product.

Table 3 Catalytic results of synthesis of imines from benzaldehyde and different nitroarenes[a]

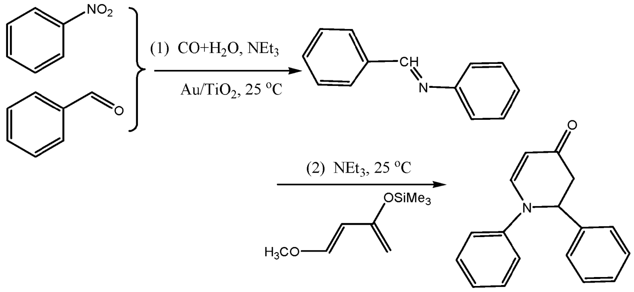
Entry	Nitro-compound	Time [h]	Con. [%][b]	Yield [%][b,c]
1		1	> 99	95 (91)
2		1	> 99	98 (95)
3		3	> 99	97
4		1	> 99	91 (88)
5		3	> 99	89 (84)
6		3.5	98	71
7		3.5	> 99	85
8		3.5	> 99	91 (89)
9		1 6	> 99 > 99	35 65
10		1	> 99	85
11		1	> 99	93 (90)
12		3 12	> 99 > 99	52 65

[a] Reaction conditions: 1 mmol nitro-compound, 1 mmol benzaldehyde, Au/TiO_2-VS (1 mol% Au), 2 mL triethylamine, 1 mmol H_2O, 5 atm CO, 25 °C. [b] GC conversion and selectivity obtained by using anisole as an internal reference. Numbers in parentheses refer to yields of isolated products. [c] The corresponding aniline was the sole by-product.

2-phenylacetaldehyde with nitrobenzene, which led to the imine in 64% yield by GC analysis (Table 2, entry 8).

The generality of this methodology has been extended to various substituted aromatic nitroarenes and benzaldehyde to produce corresponding imines under mild reaction conditions. Table 3 compiles the conversion and selectivity results obtained in the reductive imination of benzaldehyde and different nitrocompounds. 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 imines with high yields (Table 3, entries 2–5, 8 and 11). For instance, coupling of benzaldehyde with 1-fluoro-4-nitro benzene (Table 3, entry 2) or *p*-methyl-nitrobenzene (Table 3, entry 8) gave the desired imines in excellent yields with 98 and 91%, respectively. Of note is that the reducible function groups, such as alkene, ketone as well as the C═N group, remained intact during the reduction of nitrobenzene (Table 3, entries 4 and 5). In the transformation of methyl and chloronitroarenes, the lower rate of *o*- and *m*-methyl and chloronitroarenes relative to *p*-analogues indicated a steric effect (Table 3, entries 6–8 and entries 9–11). Again, no dehalogenation of the fluorine or chloride group is observed. Notably, all these results showed the high efficiency of the Au/TiO_2-VS reductive coupling of nitrocompounds and benzaldehyde mixtures to generate the desired imines.

The applicability of the Au/TiO_2-VS-catalyzed one-pot reductive imination reaction is highlighted by an aza Diels–Alder reaction of the imine (Scheme 2). After the coupling reaction of nitrobenzene and benzaldehyde under a CO atmosphere, the reactor was depressurized. Danishefsky's diene was then admitted into the reaction system to allow a reaction with the resulting imine. Purification of the aza Diels–Alder product by column chromatography provided 1,2-diphenyl-2,3-dihydropyridin-4-one through desilylation in a good yield of 85%. Given that the dihydropyridone derivatives thus obtained are prominent core scaffolds in biologically active compounds,[25] this atom-economical strategy towards aza-cycles opens up new possibilities for the application of ligand-free supported gold catalysts to the green synthesis of pharmaceutically important compounds.



Scheme 2 One-pot two-step aza Diels–Alder reaction.

The Au/TiO_2-VS catalyst was stable and can be easily reused in the reductive imination of nitrobenzene with benzaldehyde to afford *N*-benzylidenebenzenamine (Table 2, entry 1). After the first reaction, the catalyst was separated from the reaction mixture by filtration, thoroughly washed with ethanol and water, and then reused as catalyst for the next run under the same conditions. As shown in Fig. 2, the yield of target imine remained essentially constant during a period of five successive cycles, reflecting the high stability and reusability of the catalyst.

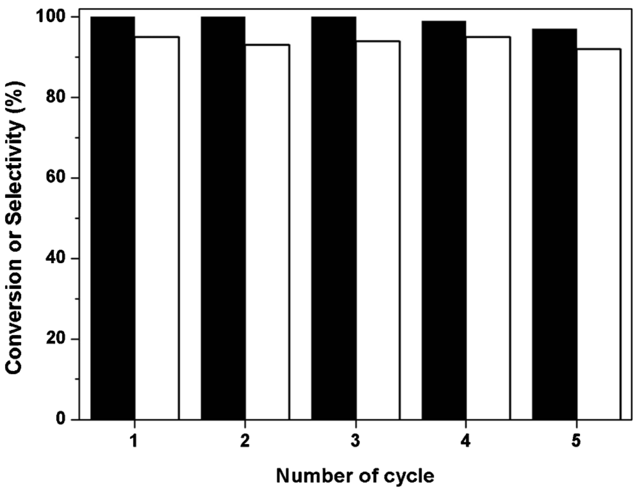


Fig. 2 Recycling of the catalyst for the synthesis of *N*-benzylidenebenzenamine from nitrobenzene and benzaldehyde. Reaction conditions: 1 mmol nitrobenzene, 1 mmol benzaldehyde, Au/TiO_2-VS (1 mol% Au), 2 mL solvent, 1 mmol H_2O, 5 atm CO, 25 °C, 1 h. (■) conversion, (□) selectivity of *N*-benzylidenebenzenamine.

In conclusion, we have demonstrated a simple and efficient heterogeneous TiO_2 supported gold-catalyzed protocol for the synthesis of imines *via* a facile one-pot nitro-reduction-direct reductive imination sequence, which proceeds at room temperature using cheap and easily accessible CO and H_2O as the hydrogen source. This protocol can be used to generate a diverse range of substituted imines in good to excellent yields. The operational simplicity and the mild reaction condition of our new catalyst system is expected to contribute to its utilization for the development of benign chemical processes and products.

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Notes and references

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21 It was confirmed that there is only a weak relationship between the imine yield and the pK_a value of solvents (See Table S2†), indicating that solvent basicity is not the key factor determining the catalytic performance of the present reductive imination process.

22 The use of 5 atm H_2 in place of CO did not initiate the reductive imination reaction at all (Table 1, entry 13), owing to the inability of gold to dissociate hydrogen under such mild conditions.

23 It was verified that the sole reduction of benzaldehyde did not proceed under the same reaction conditions (see Supporting Information for details†), which permit the rationalization of the high selectivity of this procedure as seen in Fig. 1.

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