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One-Pot Synthesis of Indoles and Aniline Derivatives from Nitroarenes under Hydrogenation Condition with Supported Gold Nanoparticles

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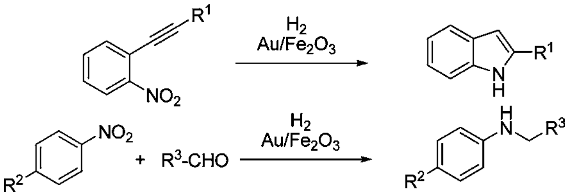
ABSTRACT



One-pot sequences of hydrogenation/hydroamination to form indoles from (2-nitroaryl)alkynes and hydrogenation/reductive amination to form aniline derivatives from nitroarenes and aldehydes were catalyzed by Au nanoparticles supported on Fe_2O_3. Nitro group selective hydrogenations and successive reactions were efficiently catalyzed under the conditions.

Nitroarenes are one of the most readily available starting materials in organic synthesis because nitration of aromatic rings by electrophilic substitution is a versatile method to introduce nitro groups. One of the major pathways of the transformation of nitroarenes is reduction including hydrogenation into anilines,[1] and then further transformation is carried out by alkylation, reductive alkylation, hydroamination, etc. to obtain their derivatives including heterocyclic compounds. However, when the other unsaturated functional group is located on the aromatic rings or on the substituent with the nitro group, selective reduction of the nitro group by hydrogenation is somewhat difficult.[1] Therefore stoichiometric reagents such as, $SnCl_2$[2a,c,g] and electrochemically generated Ni,[2b] Fe,[2d] $SnCl_2/NaBH_4$,[2e] Zn,[2f] PPh_3,[2h] etc. were used for selective reduction of the nitro group. The reduction of (2-nitroaryl)alkynes to (2-aminoaryl)alkynes with stoichiometric reducing agents followed by cyclization to form indoles,[2c,e−i] which is an important class of biologically

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(1) (a) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121–136. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151. (c) Corma, A.; Serna, P.; Concepcion, P.; Calvino, J. J. *J. Am. Chem. Soc.* **2008**, *130*, 8748–8753. (d) Reis, P. M.; Royo, B. *Tetrahedron. Lett.* **2009**, *50*, 949–952.

(2) (a) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839–842. (b) Yasuhara, A.; Kasano, A.; Sakamoto, T. *J. Org. Chem.* **1999**, *64*, 2301–2303. (c) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699–7702. (d) Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **2003**, *46*, 2436–2445. (e) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136. (f) Tarshits, D. L.; Tarasov, S. Y.; Buyanov, V. N. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 2586–2589. (g) Park, J. G.; Sill, P. C.; Makiyi, E. F.; Garcia-Sosa, A. T; Millard, C. B.; Schmidt, J. J.; Pang, Y.-P. *Bioorg. Med. Chem.* **2006**, *14*, 395–408. (h) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857–9865. (i) Kim, J. S.; Han, J. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Tetrahedron Lett.* **2008**, *49*, 3733–3738.

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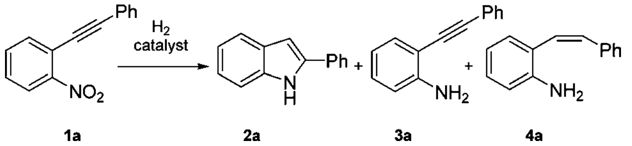
active compounds, is one of the major routes to access them. Obviously, the requirement of stoichiometric reducing agent and tedious manipulation for the product isolation and purification is a major drawback of two-step syntheses. Lately, the first one-pot synthesis of indoles through this route was reported by the use of In−HI as reagent.[2i] However, the reaction requires 4 equiv of expensive indium and the substrates are limited to 1-aryl(2-nitroaryl)alkynes giving only moderate yield (up to 64%).

Recently, we have been interested in unique catalytic activities and selectivities of Au nanoparticle catalysts[3] and involved in their application to organic synthesis. We have developed Au/Co_3O_4-catalyzed hydroformylation[4a,b] and amidocarbonylation[4c] (Wakamatsu reaction), where Au acts as a cocatalyst to generate Co^0 active species.

In the present work, we have investigated the Au-catalyzed chemoselective hydrogenation of nitro groups[5] and have applied this reaction to one-pot synthesis of indoles and aniline derivatives[6] by successive hydroamination, dehydration, and reductive amination.

The result of a one-pot synthesis of indoles from (2-nitroaryl)alkynes catalyzed by Au/Fe_2O_3 under hydrogenation conditions is shown in Table 1. As a model substrate, 1-nitro-2-(2-phenylethynyl)benzene (**1a**) was selected for this study. Hydrogenation of **1a** with 2.3 mol % of Au/TiO_2 (Au atom per substrate) was carried out at 120 °C under 1.2 MPa H_2 and afforded 2-phenylindole (**2a**) in 63% yield (Table 1, entry 1). Uncyclized aniline (**3a**) and overreduced aniline (**4a**) were obtained in yields of 5.7% and 2.8%, respectively. When Au/Fe_2O_3 was used as catalyst, a slightly better yield (69%) of **2a** was observed (entry 2). Au nanoparticles on another support such as Au/Co_3O_4 gave lower yields (<10%), thus Au/Fe_2O_3 was used as the optimized catalyst for this study. The reaction with higher temperature gave lower yield of **2a** (51% at 160 °C, entry 3), but higher H_2 pressure (2.0 MPa) brought a better result (67%, entry 4). Further higher pressure did not improve the yield of **2a**. The reaction with various temperatures was carried out between 40 and 160 °C (entries 4−11), and it was found that the most favorable temperature was 110 °C giving the highest yield (77%) of **2a** under a one-pot, one-step condition (entry 7). In this series of reactions, a combined yield of **2a** and **3a** reached maximum around 60−80 °C (83−84%, entries 9 and 10), because this condition minimized the amount of other byproduct such as hydroxylamine derivatives. Therefore, if uncyclized **3a** can be converted into **2a** without overreduction, the yield of **2a** will be improved. Thus, a second cyclization step was carried out separately under lower H_2 pressure and higher temperature as a one-pot, two-step synthesis.

Table 1. One-Pot, One-Step Synthesis of Indole **2a** by Supported Au Catalysts under Hydrogenation Condition

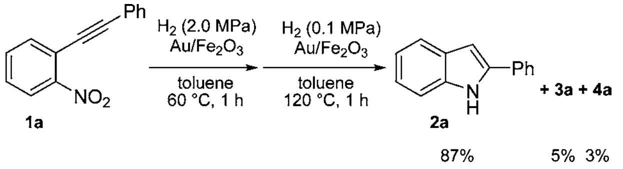


entry	cat.	t (°C)	P (MPa)	convn (%)	2a (%)[c]	3a (%)[c]	4a (%)[d]
					yield (%)		
1[a]	Au/TiO_2	120	1.2	100	62.5	5.7[d]	2.8
2[b]	Au/Fe_2O_3	120	1.2	100	69.0	0	6.5
3[b]	Au/Fe_2O_3	160	1.2	97.4	50.6	0	3.8
4[b]	Au/Fe_2O_3	160	2.0	100	66.5	0	16.2
5[b]	Au/Fe_2O_3	140	2.0	100	72.7	0	13.9
6[b]	Au/Fe_2O_3	120	2.0	100	73.0	0	12.7
7[b]	Au/Fe_2O_3	110	2.0	100	77.3	0	14.2
8[b]	Au/Fe_2O_3	100	2.0	100	75.9	2.6[d]	13.4
9[b]	Au/Fe_2O_3	80	2.0	100	59.8	24.4	3.1
10[b]	Au/Fe_2O_3	60	2.0	100	32.2	50.7	1.0
11[b]	Au/Fe_2O_3	40	2.0	38	2.6	30.4	1.0

[a] **1a** (0.5 mmol), toluene (2.0 mL), 1 h, Au/TiO_2 (1.2 atom % Au/(Au + Ti), 2.3 mol % Au/**1a**). [b] Au/Fe_2O_3 (5.0 atom % Au/(Au + Fe), 2.3 mol % Au/**1a**). [c] Isolated yield. [d] GC yield.

An optimized condition of this method is depicted in Scheme 1. The first step was performed at 60 °C, 2.0 MPa H_2 for 1 h, then H_2 was released to atmospheric pressure (0.1 MPa), then the system was closed and heated at 120 °C for 1 h. The isolated yield of **2a** reached 87%. Change in the reaction time (1−2 h) of the first and second step and catalyst loadings (1.2 to 4.6 atom % Au for substrate) did not bring a significant effect on yield of **2a** (>80%).

Scheme 1. One-Pot, Two-Step Synthesis of **2a** by Supported Au Catalysts under Hydrogenation Condition



The applicability of this one-pot indole synthesis was explored to several substrates (Table 2). Method A represents a one-pot, one-step condition (2.0 MPa H_2, 120 °C, 1 h), and method B represents a one-pot, two-step condition as shown in Scheme 1. In general, method B gave slightly better yields. When an electron-deficient 4-$CF_3C_6H_4$ group was used as R^1 substituent (**1e**), alkyne hydrogenation was enhanced (33%), which brought about a decreased yield of **2e** (43%, entry 10). The substrate with the aliphatic R^1 group also gave the indoles in good yield (entries 11−14,17, and 18). A sterically hindered *tert*-butyl group (**1g**) gave 81% yield but the trimethylsilyl group (**1h**) considerably decreased

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(3) (a) Haruta, M. *Chem. Rec.* **2003**, *3*, 75–87. (b) Hashmi, A. S. K.; Hutcings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936. (c) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358–4361.

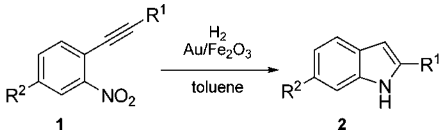
(4) (a) Liu, X.; Haruta, M.; Tokunaga, M. *Chem. Lett.* **2008**, *37*, 1290–1291. (b) Liu, X.; Hu, B.; Fujimoto, K.; Haruta, M.; Tokunaga, M. *Appl. Catal., B.* DOI: 10.1016/j.apcatb.2009.08.021. (c) Hamasaki, A.; Liu, X.; Tokunaga, M. *Chem. Lett.* **2008**, *37*, 1292–1293.

(5) (a) Corma, A.; Serna, P. *Science* **2006**, *313*, 332–334. (b) Corma, A.; Concepciń, P.; Serna, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7266–7269.

(6) (a) Santos, L. L.; Serna, P.; Corma, A *Chem.−Eur. J.* **2009**, *15*, 8196–8203. (b) Climent, M. J.; Corma, A.; Iborra, S.; Santos, L. L. *Chem.−Eur. J.* **2009**, *15*, 8834–8841.

the rate of the cyclization step. Thus **3h** was formed as a major product (84%). A substituent on the meta-position of the aromatic ring did not affect the yield (entries 19 and 20).

Table 2. Synthesis of Indoles by Supported Au Catalysts under Hydrogenation Condition[a]

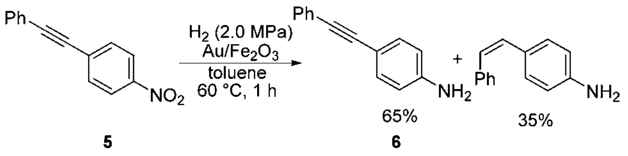


entry	substrate	R^1	R^2	method[b]	yield of **2** (%)
1	**1a**	Ph	H	A	73
2	**1a**	Ph	H	B	87
3	**1b**	$\text{4-MeC}_6\text{H}_4$	H	A	67
4	**1b**	$\text{4-MeC}_6\text{H}_4$	H	B	87
5	**1c**	$\text{4-FC}_6\text{H}_4$	H	A	66
6	**1c**	$\text{4-FC}_6\text{H}_4$	H	B	86
7	**1d**	$\text{4-MeOC}_6\text{H}_4$	H	A	75
8	**1d**	$\text{4-MeOC}_6\text{H}_4$	H	B	81
9	**1e**	$\text{4-CF}_3\text{C}_6\text{H}_4$	H	A	20
10	**1e**	$\text{4-CF}_3\text{C}_6\text{H}_4$	H	B	43
11	**1f**	cyclohexenyl	H	A	77
12	**1f**	cyclohexenyl	H	B	94
13	**1g**	*tert*-butyl	H	A	66
14[c]	**1g**	*tert*-butyl	H	B	81
15	**1h**	SiMe_3	H	A	0
16	**1h**	SiMe_3	H	B	0
17	**1i**	$n\text{-C}_6\text{H}_{13}$	H	A	56
18	**1i**	$n\text{-C}_6\text{H}_{13}$	H	B	75
19	**1j**	Ph	Me	A	45
20	**1j**	Ph	Me	B	81

[a] **1** (0.5 mmol), toluene (2.0 mL), Au/Fe_2O_3 (5.0 atom % Au/(Au + Fe), 2.3 mol % Au/**1**). [b] Method A: one-pot, one-step condition (2.0 MPa H_2, 120 °C, 1 h). Method B: one-pot, two-step condition (2.0 MPa H_2, 60 °C, 1 h, then 0.1 MPa H_2, 120 °C, 1 h). [c] H_2 pressure of the first step was 1.0 MPa.

A 5.0 mmol (1.1 g) scale reaction was carried out with substrate **1a**. The reaction was somewhat affected by the stirring efficiency, therefore longer reaction time (2 h) was required for the first hydrogenation step and 81% isolated yield (0.79 g) was achieved.

Chemoselectivity of the hydrogenation of the catalytic system was examined with a para-substituted substrate (**5**) and found that the selectivity of **6** is moderate (65%). This result indicates Au-catalyzed cyclization by hydroamination[7] is faster or comparable when ortho-substituted substrates were used under the condition.



Transmission electron microscopic (TEM) images of the Au/Fe_2O_3 catalysts showed gold particles of average 2−3 nm mean deiameter (Figure 1). The sizes of the gold particles were slightly increased after the catalytic reaction (Figure 2). Actually, the recycled catalysts showed somewhat lower activities and afforded **2a** in 30−46% yields. The slight change of the catalyst state including the gold particle size might decrease the performance.

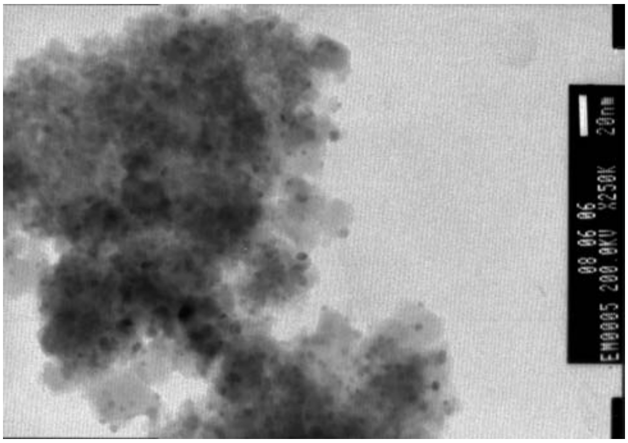


Figure 1. TEM image of Au/Fe_2O_3.

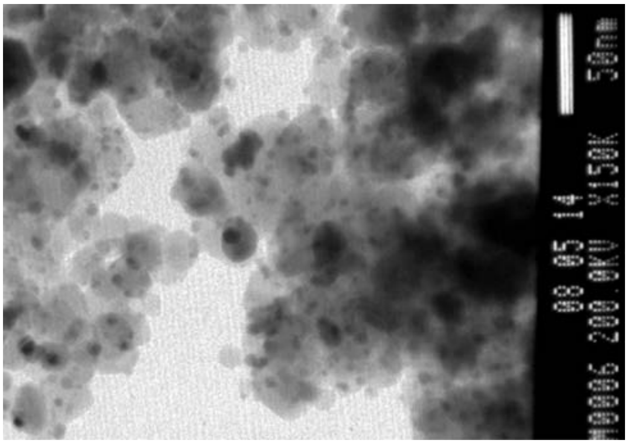


Figure 2. TEM image of Au/Fe_2O_3 after the reaction.

An atomic absorption spectrometry measurement of Au was performed for a supernatant of a reaction mixture of the reaction and found no detectable Au (Figure S-1 in the Supporting Information).

For the hydrogenation of the nitro group, a similar mechanism is expected to the Au/TiO_2-catalyzed one.[5b] On the other hand for hydroamination, the origin of soft Lewis acidity to promote the reaction is a subject of discussion[7] and future works should address this issue.

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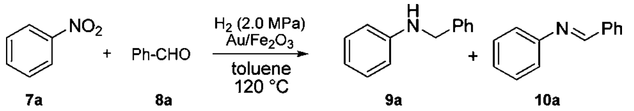
(7) (a) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799. (b) Corma, A.; Concepción, P.; Domínguez, I.; Fornés, V.; Sabater, M. J. *J. Catal.* **2007**, *251*, 39–47. (c) Miyazaki, Y.; Kobayashi, S. *J. Comb. Chem.* **2008**, *10*, 355–357. (d) Kitahara, H.; Kamiya, I.; Sakurai, H. *Chem. Lett.* **2009**, *38*, 908–909.

Next, intermolecular reductive amination of aldehydes with nitroarenes was examined with Au/Fe_2O_3 catalysts. Although the reductive alkylation of amines with aldehydes is a common process, few reports have been made on reductive alkylation from nitrocompounds. To the best of our knowledge, only one paper describes the reaction under hydrogenation condition with Pd/C,[8] but the reported substrate scope is limited in small aliphatic aldehydes. Very recently, Corma reported imine formation from aldehydes and nitroarenes with Au/TiO_2 catalysts.[6a] Table 3 shows our result. The chemoselective hydrogenation of the nitro groups of **7a** followed by imine (**10a**) formation with **8a** and further hydrogenation gave amine **9a**. When the reaction was carried out with 1 mol % of Au/Fe_2O_3 at 120 °C for 6 h, **10a** was the major product (62%) and **9a** was formed only in 10% (Table 3. entry 1). A longer reaction time (24 h) slightly improved the yield of **9a** (34%, entry 2). Higher catalyst loadings are also effective for improvement of the yield, sufficiently high selectivity of **9a**:**10a** was obtained with 3 mol % of catalyst (entries 3 and 4). When the ratio of **7a**:**8a** was changed from 1:1 to 1.5:1 or 1:1.5, a slight excess of the aldehyde **8a** gave a favorable result giving 80% yield of **9a** (entries 5 and 6). Thus we have concluded that entry 6 is the optimized condition. The reactions with the conditions for a longer (15 h) and shorter (1 h) time did not improve the yield (entries 7 and 8).

Table 3. One-Pot Reductive Amination of Benzaldehyde with Nitrobenzene with Au Catalysts



				yield (%)[b]	
entry[a]	**7a**:**8a**	cat. (mol %)	time (h)	**9a**	**10a**
1	1:1	1.0	6	10	62
2	1:1	1.0	24	34	33
3	1:1	2.0	6	41	30
4	1:1	3.0	6	59	4
5	1.5:1	3.0	6	42	2
6	1:1.5	3.0	6	80	2
7	1:1.5	3.0	15	78	0
8	1:1.5	3.0	1	28	62

[a] **7** (1.0−1.5 mmol), **8** (1.0−1.5 mmol), toluene (2.0 mL), Au/Fe_2O_3 (5.0 atom % Au/(Au + Fe), 1−3 mol % Au/**1**). [b] GC yield.

The reductive amination was carried out with several different nitroarenes and aldehydes (Table 4). Aliphatic aldehydes gave slightly lower yields: cyclohexanecarbaldehyde and isopentyl aldehyde gave amines **9b** and **9c** in 77% and 58% yields, respectively (entries 2 and 3). Electron-donating substituents on nitroarenes afforded the product amines in very high yield (entries 4 and 5), while electron-withdrawing substituents slightly decrease the yield (entry 6).

Scheme 2. One-Pot Formation of Indole from 2-(2-Nitrophenyl)acetaldehyde with Au Catalysts

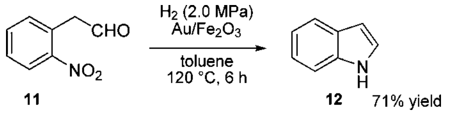
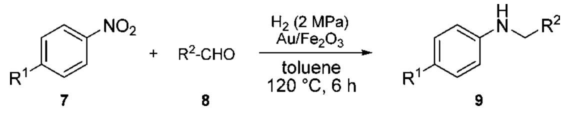


Table 4. One-Pot Reductive Amination of Aldehydes with Nitroarenes with Au Catalysts



entry[a]	R^1	R^2	product	yield (%)[b]
1	H	Ph	**9a**	86
2	H	cyclohexyl	**9b**	77
3[c]	H	isobutyl	**9c**	58
4	Me	Ph	**9d**	96
5	MeO	Ph	**9e**	95
6[d]	F	Ph	**9f**	71

[a] **7** (1.0 mmol), **8** (1.5 mmol), toluene (2.0 mL), 6 h, Au/Fe_2O_3 (5.0 atom % Au/(Au + Fe), 3 mol % Au/**1**). [b] Isolated yield. [c] **7c** (1.0 mmol), **8c** (2.0 mmol). [d] Reaction time 24 h.

When an intramolecular version of the reductive amination was performed with **11**, indole **12** was formed in 71% yield (Scheme 2). Further reduction into 2,3-dihydroindole was not observed under the condition due to the stability of the indole ring.[9]

In conclusion, we have developed one-pot sequences of hydrogenation/hydroamination to form indoles and hydrogenation/reductive amination to form aniline derivatives using a Au/Fe_2O_3 catalyst.

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Supporting Information Available: Experimental procedure, spectral data, and NMR charts for all products and synthesized substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Sydnes, M. O.; Isobe, M. *Tetrahedron Lett.* **2008**, *49*, 1199–1202.

(9) (a) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066–2069. (b) Moormann, A. E.; Pitzele, B. S.; Jones, P. H.; Gullikson, G. W.; Albin, D.; Yu, S. S.; Bianchi, R. G.; Sanguinetti, E. L.; Rubin, B.; Grebner, B.; Monroy, B.; Kellar, P.; Casler, J. *J. Med. Chem.* **1990**, *33*, 614–626.