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Exclusive Chemoselective Reduction of Imines in the Coexistence of Aldehydes Using AuNPore Catalyst

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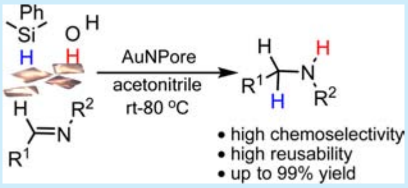
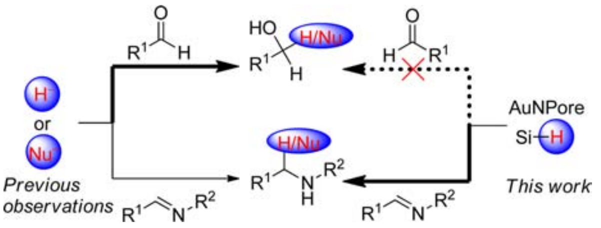
S Supporting Information

ABSTRACT: Aldimines ($R^1HC{=}NR^2$) were reduced in the coexistence of aldehydes (R^1CHO) with 100% chemoselectivity by the use of AuNPore giving corresponding amines ($R^1H_2C\text{-}NHR^2$) in high chemical yields.



It is widely accepted in the organic community that *nucleophilic addition (including hydride) to an aldehyde takes place much easier than that to the corresponding imine.* Actually, a C-13 chemical shift of the aldehyde carbon of benzaldehyde appears at δ 192.61 ppm, and the carbon of the corresponding imine, PhCH=NPh, appears at δ 160.64 ppm (see the Supporting Information), indicating that benzaldehyde is more electrophilic than the imine under ordinary conditions. We have found that aldimines ($R^1HC{=}NR^2$) were reduced in the coexistence of aldehydes ($R^1CH{=}O$) with exclusive chemoselectivity using an AuNPore catalyst/$PhMe_2SiH$/water system (Scheme 1).

Scheme 1. Exclusively Chemoselective Reduction of Imines in the Co-existence of Aldehydes



In recent years, the nanoporous gold (AuNPore) skeleton catalyst proved to be an efficient and robust catalyst for a variety of organic reactions,[1] and its well-defined structure was also established.[2] In the research of liquid phase reactions using robust, easily available, and reusable nanoporous gold (AuNPore) catalyst, we reported an AuNPore/silane system for reduction of *carbon–carbon* multiple bonds for selective reduction of alkynes to alkenes[3] and quinolines to tetrahydroquinolines.[4] We were interested in investigating the reduction of *carbon–heteroatom* multiple bonds, such as C=O and C=N, through this new reducing system, and we accidentally discovered that reduction of imines took place exclusively in the coexistence of aldehydes. The reduction of a 1:1 mixture of benzaldehydes **2** and the corresponding imines **1** is summarized in Table 1.

The reactions with $NaBH_4$, $LiAlH_4$, and homogeneous Pd catalyst $Pd(OAc)_2$, under conditions B–D, favored reduction of the C=O bond rather than the C=N bond. Use of 0.25 equiv of $NaBH_4$ resulted in 30% selectivity toward reduction of C=N and ca. 70% selectivity toward C=O bond, while use of 0.25 equiv of $LiAlH_4$ resulted in 1% selectivity for reduction C=N bond and nearly 99% selectivity for reduction of C=O bond (entry 1, conditions B and C). Even use of an excess of these reagents showed still higher selectivity toward a C=O bond than a C=N bond. The use of $Pd(OAc)_2$ and 10 bar of H_2 gas proved less efficient for the reduction of the C=N bond (all the entries), and additionally, in a certain case parent aniline was also isolated (entry 2, conditions D). Remarkably, totally different results were observed in the case of the AuNPore/$PhMe_2SiH$ system; only imines could undergo reduction, and aldehydes could not undergo hydrogenation at all (entries 1–6, condition A). Further, it should be mentioned that reduction of imine **1a** using a *gold homogeneous catalysts*/$PhMe_2SiH$ system resulted in very low yield (7–10%) of the desired product.[5]

This exclusive imine reduction property of nanoporous gold was further extended to a variety of imines. Accordingly, imine **1a** was treated with 5 mol % of AuNPore catalyst, 1.2 equiv of $PhMe_2SiH$, and 1.2 equiv of H_2O in acetonitrile as a solvent (Table 2). After being stirred for 5 h at room temperature, the desired product could be obtained in 90% yield. It is noteworthy to mention that even the use of PdNPore as a catalyst gave the desired product in 65% yield, but the use of PdNPore was avoided for further study owing to its leaching property.[6] Among other imines studied, those having electron-donating or weak electron-withdrawing groups at the aromatic ring resulted

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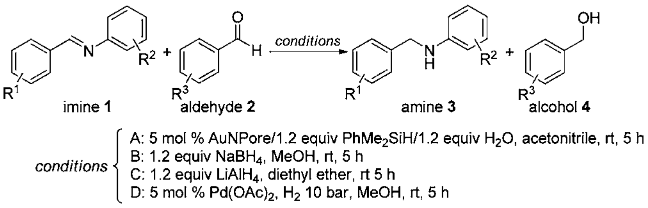
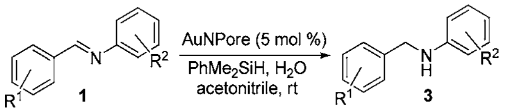
Table 1. Chemoselectivities in the Reduction of Imines and Aldehydes with Representative Reducing Reagents/Catalysts[a]



entry	imine 1	aldehyde 2		product	
				3 (%)[b]	**4** (%)[c]
1	**1a**, $R^1 = H$ $R^2 = H$	**2a**, $R^3 = H$	A	**3a**, 89	**4a**, 0
			B	**3a**, 58[d]	**4a**, 60[d]
			C	**3a**, 34[e]	**4a**, 83[e]
			D	**3a**, 29	**4a**, 93
2	**1b**, $R^1 = H$ $R^2 = OMe$	**2a**	A	**3b**, 98	**4a**, 0
			B	**3b**, 91	**4a**, 89
			C	**3b**, 63	**4a**, 87
			D	**3b**,trace[f]	**4a**, 72
3	**1c**, $R^1 = H$ $R^2 = Me$	**2a**	A	**3c**, 99	**4a**, 0
			B	**3c**, 85	**4a**, 85
			C	**3c**, 80	**4a**, 89
			D	**3c**, 23	**4a**, 73
4	**1d**, $R^1 = 4\text{-}Cl$ $R^2 = H$	**2b**, $R^3 = 4\text{-}Cl$	A	**3d**, 92	**4b**, 0
			B	**3d**, 65	**4b**, 84
			C	**3d**, 69	**4b**, 71
			D	**3d**, 81	**4b**, 97
5	**1e**, $R^1 = 4\text{-}Br$, $R^2 = H$	**2c**, $R^3 = 4\text{-}Br$	A	**3e**, 96	**4c**, 0
			B	**3e**, 92	**4c**, 95
			C	**3e**, 76	**4c**, 82
			D	**3e**, 35	**4c**, 89
6	**1f**, $R^1 = 3,4\text{-}(OMe)_2$ $R^2 = H$	**2d**, $R^3 = 3,4\text{-}(OMe)_2$	A	**3f**, 95	**4d**, 0
			B	**3f**, 86	**4d**, 91
			C	**3f**, 72	**4d**, 83
			D	**3f**, 36	**4d**, 81

[a] Reaction conditions: a mixture of **1** (0.5 mmol) and **2** (0.5 mmol) was treated with the representative reagents and catalysts under four different sets of conditions (A–D). [b] Isolated yield calculated on the basis of **1**. [c] Isolated yield calculated on the basis of **2**. [d] Use of 0.25 equiv of $NaBH_4$ resulted in **3a** in 29% yield and **4a** in 66% yield. [e] Use of 0.25 equiv of $LiAlH_4$ resulted **3a** in <1% yield and **4a** in 82% yield. [f] Parent aniline (4-methoxyaniline) was isolated in 58% yield.

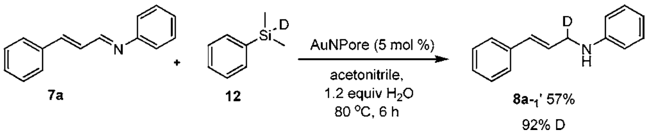
Table 2. Reduction of Simple Imines Using AuNPore/$PhMe_2SiH$[a]



entry	subtrate **1**	time (h)	product **3**	yield of **3** (%)[b]
1	**1a**, $R^1 = H$; $R^2 = H$	5	**3a**	90
2	**1b**, $R^1 = H$; $R^2 = 4\text{-}OMe$	3	**3b**	99
3	**1d**, $R^1 = 4\text{-}Cl$; $R^2 = H$	5	**3d**	92
4	**1e**, $R^1 = 4\text{-}Br$; $R^2 = H$	4	**3e**	99
5	**1g**, $R^1 = H$; $R^2 = 4\text{-}Br$	3	**3g**	95
6[c]	**1h**, $R^1 = H$; $R^2 = 4\text{-}COOH$	7	**3h**	76
7[c]	**1i**, $R^1 = H$; $R^2 = 4\text{-}COOMe$	7	**3i**	73
8[c]	**1j**, $R^1 = 4\text{-}OH$; $R^2 = H$	5	**3j**	98
9	**1k**, $R^1 = 4\text{-}NMe_2$; $R^2 = H$	4	**3k**	98

[a] Reaction conditions: **1** (0.5 mmol), AuNPore (5 mol %), $PhMe_2SiH$ (0.6 mmol), H_2O (0.6 mmol), acetonitrile (2.0 mL), at rt. [b] Isolated yield. [c] Reactions were carried out at 80 °C.

Scheme 2. Deuterium Labeling Experiment in the Reduction of Enimine



Scheme 3. Plausible Pathway for Imine Reduction

in good to excellent yields of desired amines, while strong electron-withdrawing groups such as −COOH and −COOMe resulted in moderate yields of the respective products (entries 6 and 7). Notably, these acid and ester groups were tolerated under the reaction conditions and did not undergo reduction.

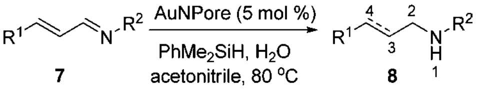
Encouraged by these results, we next examined the scope of this reducing system for enimine reduction to examine whether allylamines[7] can be obtained selectively (Table 3). The enimine **7a** was reduced by AuNPore/$PhMe_2SiH$ at 80 °C to give 75% yield of **8a** (as a 9:1 mixture of 1,2-reduction **8a-$_1$** and complete reduction **8a-$_2$**). Electron-donating groups on the aryl group attached to N (R^2 group) led to good yields of the desired products (entries 2−5 and 7), while electron-donating groups at R^1 did not exert significant effect on the yield or even gave a bit lower yields in some cases (entries 9−12). A bromine substituent at R^2 or a benzyl group gave high chemical yields (entries 8 and 14). However, bulky substitutions at R^2 resulted in lower yields of the desired products (entries 6 and 14). It should be noted that tosyl-protected enimine **7m** underwent 1,2 reduction without problem (entry 13).

After establishing the intermolecular chemoselectivity and scope of selective imine reduction, we were interested in the intramolecular selectivity using representative reducing agents. Accordingly, we treated enimines **9** with three different conditions: AuNPore/silane, $NaBH_4$, and $LiAlH_4$ (Table 4). To our delight, use of AuNPore resulted in selective reduction of imine groups, and no other functional groups such as ketones or esters were reduced (entry 1). However, use of $NaBH_4$ or $LiAlH_4$ as a reducing agent resulted in a mixture of products (entry 2 and 3).

Catalyst reusability of AuNPore catalyst was tested, and remarkably, the catalyst activity did not show any change even after the fifth use (see the Supporting Inforamtion). Generally, the catalyst was recovered by picking up with tweezers, washing 5 times with acetone, and drying under vacuum. It was used without further activation.

We carried out the deuterium-labeling experiment using deuterated silane **12** (Scheme 2). α-Deuterated amine **8a-$_1$′** was obtained in 57% yield with 92% deuterium labeling.

Table 3. Allylamines from Enimines via Reduction Using AuNPore/$PhMe_2SiH$[a]



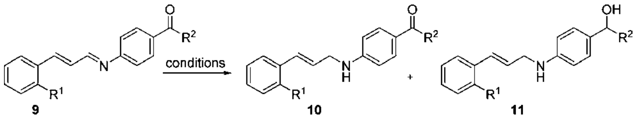
entry	subtrate 7	yield of 8 (%)[b]	selectivity (1,2 reduction/complete reduction
1	**7a**, $R^1 = C_6H_5$; $R^2 = C_6H_5$	75	**8a-**$_1$/**8a-**$_2$ = 90/10
2	**7b**, $R^1 = C_6H_5$; R^2 = 4-Me-C_6H_4	85	**8b-**$_1$/**8b-**$_2$ = 77/23
3	**7c**, $R^1 = C_6H_5$; R^2 = 3-Me-C_6H_4	85	**8c-**$_1$/**8c-**$_2$ = ~100/-
4[c]	**7d**, $R^1 = C_6H_5$; R^2 = 3,4-$(Me)_2$-C_6H_3	75	**8d-**$_1$/**8d-**$_2$ = 89/11
5[c]	**7e**, $R^1 = C_6H_5$; R^2 = 4-MeO-C_6H_4	75	**8e-**$_1$/**8e-**$_2$ = ~100/-
6[c]	**7f**, $R^1 = C_6H_5$; R^2 = 1-naphthyl	67	**8f-**$_1$/**8f-**$_2$ = 99/1
7	**7g**, $R^1 = C_6H_5$; R^2 = 4-EtO-C_6H_4	85	**8g-**$_1$/**8g-**$_2$ = 92/8
8	**7h**, $R^1 = C_6H_5$; R^2 = 4-Br-C_6H_4	90	**8h-**$_1$/**8h-**$_2$ = 99/1
9	**7i**, R^1 = 2-MeO-C_6H_4; $R^2 = C_6H_5$	67	**8i-**$_1$/**8i-**$_2$ = ~100/-
10	**7j**,R^1= 2-MeO-C_6H_4; R^2 = 4-MeO-C_6H_4	68	**8j-**$_1$/**8j-**$_2$ = ~100/-
11	**7k**, R^1 = 3-HO-C_6H_4; $R^2 = C_6H_5$	71	**8k-**$_1$/**8k-**$_2$ = ~100/-
12	**7l**, R^1 = 3-Me-C_6H_4; $R^2 = C_6H_5$	68	**8l-**$_1$/**8l-**$_2$ = 84/16
13	**7m**, $R^1 = C_6H_5$; R^2 = Ts	72	**8m-**$_1$/**8m-**$_2$ = 83/17
14	**7n**, $R^1 = C_6H_5$; $R^2 = CH_2C_6H_5$	89	**8n-**$_1$/**8n-**$_2$ = ~100/-
15[d]	**7o**, $R^1 = C_6H_5$; R^2 = 2-I-C_6H_4	20	**8o-**$_1$/**8o-**$_2$ = ~100/-

[a] Reaction conditions: **7** (0.5 mmol), AuNPore (5 mol %), $PhMe_2SiH$ (0.6 mmol), H_2O (0.6 mmol), acetonitrile (2.0 mL), 80 °C, 5 h. [b] Isolated yield. [c] Reaction time was increased to 7 h. [d] Reaction time was increased to 10 h.

On the basis of this deuterium-labeling experiment a plausible pathway for the reduction of imine is shown in Scheme 3. Adsorption of silane and water on AuNPore would result in $[\text{AuNPore–H}]^-$ species.[3,4] It was interesting to know that no H_2 bubbling was observed in this reaction, while it was observed clearly in the absence of amine additives.[3] This strongly suggests that the N atom of imine holds the other proton of water to avoid rapid elimination of H_2 gas. The resulting protonated imine further abstracts hydride from Au–H species to give the product via regeneration of the AuNPore catalyst. In the case of aldehyde, the oxygen atom of C═O would not be strong enough to hold the proton of water, compared to N atom of imine, leading to no reduction of aldehyde.

In conclusion, we have presented an exclusive chemoselectivity of AuNPore catalyst/$PhMe_2SiH$/water system toward imine reduction. In contrast to the previous catalyst/reagents, such as $Pd(OAc)_2$, $LiAlH_4$, and $NaBH_4$, AuNPore showed 100% selectivity toward reduction of imines in coexistence of aldehydes and other reducible groups. The catalyst can be reused several times without any loss in activity.

Table 4. Intramolecular Selective Reduction Study[a]



entry	conditions	substrate 9	yield of 10 (%)[b]	yield of 11 (%)[b]
1	AuNPore[c]	**9a**, R^1 = H; R^2 = Me	**10a**, 63	**11a**, 0
		9b, R^1 = OMe R^2 = Me	**10b**, 65	**11b**, 0
		9c, R^1 = H R^2 = OMe	**10c**, 71	**11c**, 0 (R^2= H)
2	$NaBH_4$[d]	**9a**	**10a**, 3	**11a**, 40
		9b	**10b**, 10	**11b**, 41
		9b[e]	**10b**, 4[e]	**11b**, 56[e]
		9c	**10c**, 69	**11c**, 0 (R^2= H)
3	$LiAlH_4$[f]	**9a**	**10a**, 12	**11a**, 30
		9b	**10b**, 10	**11b**, 26
		9c	**10c**, 20	**11c**, 23 (R^2= H)
		9c[g]	**10c**, 5[g]	**11c**, 60[g] (R^2= H)

[a] Reaction conditions: **9** (0.5 mmol) were treated with the reducing reagents under the mentioned conditions. [b] Isolated yield. [c] AuNPore (5 mol %), $PhMe_2SiH$ (0.6 mmol), H_2O (0.6 mmol), acetonitrile (2.0 mL), at 80 °C, 5 h. [d] $NaBH_4$ (0.25 mmol), methanol (2.0 mL), rt, 10 h. [e] $NaBH_4$ (0.6 mmol), methanol (2.0 mL), at 60 °C, 10 h. [f] $LiAlH_4$ (0.25 mmol), diethyl ether (2.0 mL), rt, 10 h. [g] $LiAlH_4$ (0.6 mmol), diethyl ether (2.0 mL), rt, 10 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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