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Highly Efficient Heterogeneous Gold-catalyzed Direct Synthesis of Tertiary and Secondary Amines from Alcohols and Urea

Lin He, Yue Qian, Ran-Sheng Ding, Yong-Mei Liu, He-Yong He, Kang-Nian Fan, and Yong Cao^{*[a]}

The transformation of simple and readily available raw materials into chemically complex and high-value-added molecules is one of the central priorities in chemistry. In this context, ammonia is one of the basic feedstocks of the industrial chemistry, and its low cost and widespread availability make it a highly attractive, environmentally benign nitrogen source in organic synthesis. For example, the use of NH_3 as a coupling partner in catalytic amination reactions allows the direct synthesis of substituted amines from simple substrates such as alkyl halides.^[1] However, there are practical difficulties associated with the use of NH_3 , including its storage, handling, and transportation. Urea, which is one of the most abundant (over 100 million tons per year) and least expensive organic compounds,^[2] is an appealing alternative to avoid these drawbacks, and is currently being considered as a convenient carrier of NH_3 in industry (e.g., in applications involving control of automotive emissions).^[3] Given its high nitrogen content of (46% of its total weight), urea offers great potential to establish new sustainable procedures for the synthesis of valuable nitrogen-containing compounds.

Tertiary and secondary amines are important building blocks in organic synthesis and routinely serve as synthons for pharmaceuticals, herbicides, agricultural chemicals, and functionalized materials.^[4] The synthesis of tertiary and secondary amines is traditionally carried out with (mostly multistep) procedures such as *N*-alkylation of amines with alkyl halides,^[5] reductive amination of carbonyl compounds,^[6] or hydroamination of unsaturated hydrocarbons with amines.^[7] In spite of their utility, clear drawbacks of these methods include the use of expensive starting materials, tedious workup procedures, low selectivities, and the concomitant formation of large amounts of wasteful salts. Alternatively, transition-metal-catalyzed alkylation of amines (including ammonia) by alcohols via a facile hydrogen-borrowing (also known as hydrogen autotransfer) strategy^[8] has been attracting considerable attention, since alcohols are inexpensive, readily available, nontoxic, and theoretically water is the only byproduct; thus, the overall reaction is intrinsically environmentally friendly.

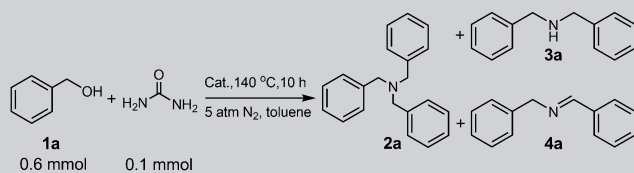
Compared to the impressive progress being made in the alkylation of organic amines with alcohols, reports dealing with the direct synthesis of tertiary or secondary amines from alcohols and urea are only scarcely available.^[9] In a precedent relat-

ed to this work, $\text{Ru}(\text{OH})_x$ supported on TiO_2 proved to be an efficient catalyst for the direct amination of alcohols with urea. One critical limitation associated with this process, however, is that a large excess of relatively expensive alcohols (alcohol/urea = 10:1) was required to obtain high yields of the desired substituted amines. From a synthetic and economic point of view, an atom-efficient catalytic transformation that can be carried out using stoichiometric amounts of alcohol and urea is preferred.

On the basis of our ongoing interest in the unique catalytic properties of supported gold nanoparticles (NPs)^[10] and their applications to green and sustainable organic synthesis,^[11] we have recently discovered that very small Au NPs (mean size ca. 1.8 nm) supported on acid-tolerant TiO_2 (Au/ TiO_2 -VS, see Supporting Information) can promote selective *N*-alkylation of amines with alcohols under mild conditions.^[12] A wide range of secondary amines were obtained with high atom efficiency by the employment of equimolar amounts of starting materials. In view of the excellent performance of the gold system for the alkylation of amines with alcohols, we reasoned that the heterogeneous Au-mediated hydrogen-borrowing strategy could afford a sustainable protocol for the amination of alcohols with urea. Herein, we report for the first time that gold catalysis enables the clean and selective formation of tertiary or secondary amines from the direct amination of stoichiometric amounts of alcohols with urea. By using this method, the reactions of primary alcohols with urea exclusively gave tertiary amines, while those of secondary alcohols selectively afforded secondary amines.

We initially investigated the direct coupling of stoichiometric amounts of benzyl alcohol (**1a**) and urea (6:1 molar ratio) in the presence of Au/ TiO_2 -VS (1.5 mol% of Au, see Supporting Information) for 10 h at 140 °C under N_2 atmosphere. To our delight, the corresponding tertiary amine, tribenzylamine (**2a**), was obtained in an excellent yield of ca. 92%, (Table 1, entry 1). This result underscores the significantly greater performance of supported gold relative to $\text{Ru}(\text{OH})_x/\text{TiO}_2$ (35% yield of **2a** when stoichiometric amounts of **1a** and urea were employed),^[9b] and thus highlights the synthetic potential of this new urea-mediated alcohol amination protocol. After the reaction, the Au/ TiO_2 -VS catalyst could be easily separated by filtration; inductively coupled plasma (ICP) analysis confirmed that the Au content of the filtrate was below the detection limit (<0.10 ppm). Furthermore, the recovered Au/ TiO_2 -VS could be used in at least three runs without appreciable loss of the original catalytic activity (Table 1, entry 2). These results rule out any contribution to the observed catalysis from gold species that had leached into the reaction solution, and show that the observed catalysis is heterogeneous.

[a] L. He, Y. Qian, R.-S. Ding, Dr. Y.-M. Liu, Prof. Dr. H.-Y. He, Prof. K.-N. Fan, Prof. Dr. Y. Cao
Department of Chemistry
Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials
Fudan University
Handan Road 220, Shanghai 200433 (PR China)
Fax: (+86)21-65643774
E-mail: yongcao@fudan.edu.cn

Table 1. Direct stoichiometric amination of benzyl alcohol (**1a**) with urea (alcohol/urea=6:1), using various catalysts.^[a]

Entry	Catalyst	Conv. [%] ^[b]	Yield. [%] ^[b]			
			2a	3a	4a	other ^[c]
1	Au/TiO ₂ -VS	98	92	2	1	3
2 ^[d]	Au/TiO ₂ -VS	97	90	3	2	2
3	Au/Fe ₂ O ₃	23	12	2	0.5	8.5
4	Au/Al ₂ O ₃	94	50	n.d.	n.d.	44
5	Au/CeO ₂	40	22	4	6	8
6	Au/ZnO	8	n.d.	n.d.	n.d.	8
7	Au/C	35	n.d.	n.d.	n.d.	35
8	TiO ₂	5	n.d.	1	2	2
9	HAuCl ₄	n.r.	–	–	–	–
10	Au ₂ O ₃	n.r.	–	–	–	–
11	Au ⁰ powder	n.r.	–	–	–	–
12	Pt/TiO ₂	9	1	3	2	3
13	Pd/TiO ₂	32	n.d.	6	17	9
14	Ag/TiO ₂	9	n.d.	n.d.	6	3
15	Ru/TiO ₂	41	19	11	4	7

[a] Reaction conditions: benzyl alcohol (0.6 mmol), urea (0.1 mmol), toluene (1.5 mL), catalyst (metal: 1.5 mol%), 140 °C, 0.5 MPa N₂, 10 h, n.r.=no reaction, n.d.=not detected. [b] Conversion and yield based on benzyl alcohol consumption. Determined by GC using *n*-dodecane as the internal standard. [c] The main by-products were benzaldehyde, benzylamine, and benzyl carbamate. [d] Third run.

The high efficiency of Au/TiO₂-VS for the direct amination of **1a** with urea relative to other supported gold catalysts was clear (Table 1). Au/Fe₂O₃, Au/CeO₂, Au/ZnO, and Au/C gave poor yields, whereas Au/Al₂O₃ afforded a moderate yield (entries 3–7). In control experiments with Au-free supports as catalysts under similar conditions, the decomposition of urea to NH₃ was promoted by TiO₂.^[13] This result suggests that the inherent nature of the underlying support is critical in mediating the in situ formation of NH₃ involved in the direct amination process. On the other hand, **2a** was hardly observed in the presence of pure TiO₂ (entry 8), further confirming that the highly dispersed gold NPs are indispensable for the desired transformation. In addition, the use of the catalyst precursor HAuCl₄, and other Au species including Au₂O₃ and bulk Au⁰ powder (average particle size, ca. 150 nm), did not promote the reaction at all (entries 9–11). Moreover, other metals (Pt, Pd, Ag, and Ru) supported on TiO₂ showed only very limited activity and selectivity towards amination of **1a** under present conditions (entries 12–15).

To obtain an insight into the origin of the superior performance achieved with Au/TiO₂-VS as catalyst, we examined a series of Au/TiO₂ samples with different average Au particle sizes. As determined by transmission electron microscopy (TEM), the mean diameter of the Au NPs ranged from 1.8 to 8.0 nm (see Supporting Information, Figure S1). By assuming that the Au NPs can be modeled as hemispherical particles,^[14] the number of surface Au atoms for each catalyst was estimated according to the method developed by Abad et al.^[15] The turnover frequency (TOF) per surface Au site versus the aver-

age particle size is shown in Table S1. Clearly, Au NPs with a smaller particle size have a higher intrinsic activity.

To demonstrate the usefulness of this Au-mediated amination system, we explored the reactions of various alcohols (Table 2). Structurally diverse primary alcohols, including benzylic, aliphatic linear, and aliphatic cyclic ones reacted with urea (alcohol/urea=6:1) to give the desired tertiary amines in good to excellent yields. Benzyl alcohols with electron-donating groups reacted smoothly, while substitution of electron-withdrawing groups on the benzene ring decreased the reactivity (entries 1–9). Notably, halogenated alcohols including 4-fluoro-, 4-chloro-, and 3-chloro benzyl alcohols resulted in excellent yields of the corresponding tertiary amines without any dehalogenation (entries 5–7). Aliphatic primary alcohols, which are difficult to react,

could also be successfully converted into the corresponding aliphatic tertiary amines in good yields (entry 10).

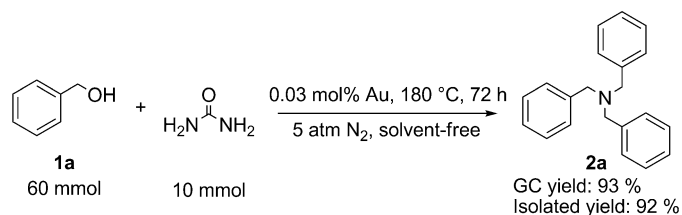
Secondary amines were obtained from reactions with secondary alcohols (alcohol/urea=4:1). Various types of secondary alcohol, including benzylic, aliphatic cyclic, and aliphatic linear ones, reacted smoothly with urea (Table 2, entries 11–14). Even with the alcohol/urea ratio set at 6:1, the corresponding secondary amines still formed selectively, and tertiary amines were detected in very small amounts,^[16] which is likely due to steric hindrance of the secondary alcohols or secondary amines produced. This result agrees very well with previous reports on homogenous iridium-catalyzed *N*-alkylation of NH₄BF₄ with secondary alcohols^[17] and Ru(OH)_x/TiO₂-catalyzed direct amination of alcohols with urea.^[9a]

The applicability of the synthetic protocol was highlighted by a 60 mmol-scale amination of stoichiometric amounts of **1a** with urea in the presence of Au/TiO₂-VS (0.03 mol% Au) under solvent-free conditions at 180 °C (see Scheme 1). After completion of the reaction, an impressive yield (93%) was achieved, and 5.28 g of the corresponding **2a** could be isolated in high purity after simple manipulation of the reaction mixture (isolated yield ca. 92%).

The time–conversion plot for the Au/TiO₂-VS-catalyzed direct amination of benzyl alcohol (**1a**) with urea provides useful information on the reaction pathway. As depicted in Figure 1, benzylamine (**5a**, <0.5% yield) could be detected, and initially formed imine (**4a**) was converted into secondary amine (**3a**) with subsequent *N*-alkylation to produce the desired tribenzylamine (**2a**). Moreover, it was confirmed in a separate experi-

Table 2. Au/TiO ₂ -VS-catalyzed direct amination of alcohols with urea. ^[a]				
Entry	Substrate	Product	t [h]	Conv. [%] ^[b] Yield [%] ^[b]
1			10	98 92 (91)
2			6	99 95 (93)
3			8	99 90 (86)
4			9	99 92 (90)
5			20	96 88 (83)
6			12	99 91 (85)
7			22	97 86 (82)
8			10	94 85 (80)
9			18	91 86 (80)
10			21	90 81 (79)
11 ^[c]			20	93 87 (82)
12 ^[c]			12	98 80 (74)
13 ^[c]			14	91 85 (81)
14 ^[c]			18	99 86 (81)

[a] Reaction conditions: alcohol (0.6 mmol), urea (0.1 mmol), toluene (1.5 mL), 1.5 mol% Au, 140 °C, 0.5 MPa N₂. [b] Conversion and yield based on alcohol consumption. Numbers in parenthesis refer to yields of isolated products. [c] Alcohol (0.6 mmol), urea (0.15 mmol), toluene (1.5 mL), 1.5 mol% Au, 140 °C, 0.5 MPa N₂.



ment that the direct conversion of **5a** and **3a** with **1a** over Au/TiO₂-VS resulted in high yields of **2a**. These results indicate that the direct synthesis of tertiary or secondary amines proceeds through a cascade of three (or two) *N*-alkylation reactions (see Scheme 2). In the first *N*-alkylation, the dehydrogena-

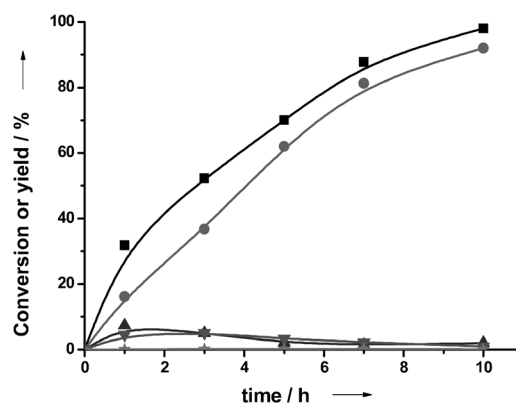
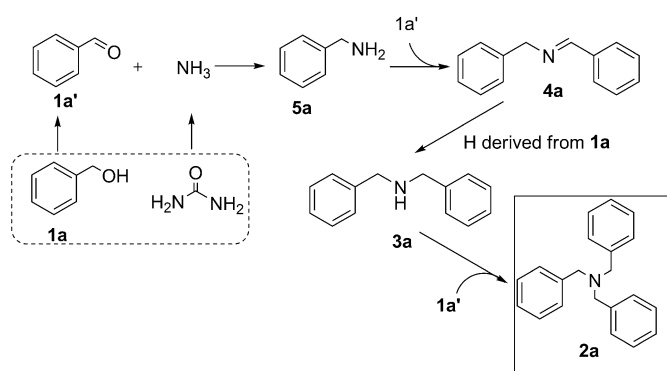


Figure 1. Time-conversion plot for the transformation of **1a** to **2a** in the presence of Au/TiO₂-VS. ■: Conversion of **1a**, ●: yield of **2a**, ▲: yield of **3a**, ▼: yield of **4a**, ★: Yield of **5a**.



Scheme 2. Direct synthesis of tertiary and secondary amines through a cascade of *N*-alkylation reactions.

tion of the alcohol initially gives the corresponding carbonyl compound, the reaction of which with the NH₃ produced by urea hydrolysis leads to the formation of an imine intermediate. Subsequent hydrogen transfer of the resultant imine yields the corresponding primary amine. In the overall reaction, the second and third *N*-alkylations proceed by similar processes. During this domino reaction sequence, the dehydrogenation of alcohols could be involved in the rate-determining step, based on the negative Hammett ρ value ($\rho = -0.51$, $R^2 = 0.99$) found for the competitive amination of benzyl alcohol against substituted benzyl alcohols with urea (see Figure S2).^[18]

In summary, we demonstrate a new, versatile, and environmentally benign catalytic route for the direct synthesis of tertiary or secondary amines by direct amination of alcohols with inexpensive and readily available urea as a convenient nitrogen source. A preliminary study using NH₄HCO₃ and (NH₄)₂CO₃ as alternative surrogates shows that the present Au-mediated protocol is not limited to the amination of alcohols with urea (see Table S2). Compared to protocols known from literature, the main advantage of the heterogeneous gold-catalyzed strategy, besides its recyclability, is its high atom efficiency by the employment of stoichiometric amounts of safe and convenient starting materials.

Experimental Section

Preparation of Au/TiO₂-VS catalysts: A slightly modified deposition-precipitation (DP) procedure was used to prepare the 0.5 wt% Au/TiO₂-VS sample. TiO₂ (1.0 g, Evonik P25, specific surface area: 45 m² g⁻¹ nonporous, 70% anatase and 30% rutile, purity > 99.5%) was added to 100 mL of an appropriate amount of aqueous solution of chloroauric acid (HAuCl₄) at a fixed pH 8 adjusting with 0.2 M NaOH. The mixture was aged for 2 h at 80 °C under vigorous stirring, after which the suspension was cooled to room temperature. Extensive washing with 0.2 M NH₄NO₃ and then deionized water followed to remove Na⁺ and Cl⁻. The sample was dried under vacuum at room temperature for 12 h before calcination at 300 °C for 2 h in static air. All preparations were performed in the absence of light. The Au/TiO₂ catalyst as-prepared with very small Au NPs (ca. 1.8 nm, see TEM data in Figure. S1) was denoted as Au/TiO₂-VS.

General procedure for the direct amination of alcohols with urea: A mixture of alcohol (0.6 mmol), urea (0.1 mmol for primary alcohol, 0.15 mmol for secondary alcohol), metal catalysts (1.5 mol% metal), toluene (1.5 mL), and *n*-dodecane (10 μL) as internal standard were placed into an autoclave (10 mL). The mixture was vigorously stirred at 140 °C under N₂ atmosphere (0.5 MPa) for a given reaction time. The product was identified by GC-MS, and the obtained spectra were compared to standard spectra. Conversion and product selectivity were determined by GC-17A gas chromatograph equipped with a HP-FFAP column (30 m × 0.25 mm) and a flame ionization detector (FID). For isolation, the product was extracted with dichloromethane, the resulting combined organic layers were dried over anhydrous Na₂SO₄, concentrated, and purified by silica gel column chromatography (eluent: *n*-hexane until elution of toluene, then ethyl acetate).

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Keywords: alcohols • amination • amines • gold • nanoparticles

- [1] a) K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, **1997**; b) D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1–27.
- [2] J. H. Meessen, H. Petersen, *Urea*, in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., Wiley-VCH, Weinheim **2000**.
- [3] a) M. Iwamoto, H. Yahiro, K. Tanda, N. Mizuno, Y. Mine, S. Kagawa, *J. Phys. Chem.* **1991**, *95*, 3727–3730; b) K. C. Taylor, *Catal. Rev. Sci. Eng.* **1993**, *35*, 457–481; c) R. Burch, J. P. Breen, F. C. Meunier, *Appl. Catal. B* **2002**, *39*, 283–303.
- [4] a) K. P. C. Vollhardt, N. E. Schore, *Organic Chemistry: Structure and Function*, 3rd ed., W. H. Freeman and Company, USA, **1999**; b) S. A. Lawrence, *Amines: Synthesis Properties, and Applications*, Cambridge University, Cambridge, **2004**; c) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154–3156.
- [5] a) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785–7811; b) C. B. Singh, V. Kavala, A. K. Samal, B. K. Patel, *Eur. J. Org. Chem.*

- 2007**, 1369–1377; c) C. Chiappe, P. Piccioli, D. Pieraccini, *Green Chem.* **2006**, *8*, 277–281.
- [6] G. Hughes, P. N. Devine, J. R. Naber, P. D. O'Shea, B. S. Foster, D. J. McKay, R. P. Volante, *Angew. Chem.* **2007**, *119*, 1871–1874; *Angew. Chem. Int. Ed.* **2007**, *46*, 1839–1842.
- [7] a) J. J. Brunet, N. C. Chu, M. Rodriguez-Zubiri, *Eur. J. Inorg. Chem.* **2007**, 4711–4722; b) K. Alex, A. Tillack, N. Schwarz, M. Beller, *ChemSusChem* **2008**, *1*, 333–338; c) K. C. Hultzsich, D. V. Gribkov, F. Hampel, *J. Organomet. Chem.* **2005**, *690*, 4441–4452.
- [8] a) A. Tillack, D. Hollmann, K. Mevius, D. Michalik, S. Bähn, M. Beller, *Eur. J. Org. Chem.* **2008**, 4745–4750; b) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *2*, 403–410; c) A. Tillack, D. Hollmann, D. Michalik, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8881–8885; d) S. I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229–232; e) G. Bitsi, E. Schleiffer, F. Antoni, G. Jenner, *J. Organomet. Chem.* **1989**, *373*, 343–352; f) N. Tanaka, M. Hatanka, Y. Watanabe, *Chem. Lett.* **1992**, 575–578; g) M. H. S. A. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725–727; h) K.-I. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525–3528; i) A. J. A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635–636; j) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555–1575; k) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641; l) M. Ernst, B. W. Hoffer, J. P. Melder, *WO 2009027249*, **2009**; m) N. Okajima, M. Nakazawa, *JP 05301846*, **1993**; n) H. Lyle A, *US 3384667*, **1968**.
- [9] a) J. L. He, J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2009**, *121*, 10072–10076; *Angew. Chem. Int. Ed.* **2009**, *48*, 9889–9893; b) K. Yamaguchi, J. L. He, T. Oishi, N. Mizuno, *Chem. Eur. J.* **2010**, *16*, 7199–7207; c) J. L. He, K. Yamaguchi, N. Mizuno, *Chem. Lett.* **2010**, *39*, 1182–1183.
- [10] a) G. Schmid, *Nanoparticles: From Theory to Application*, Wiley-VCH, Weinheim, **2004**; b) H. Tsunoyama, H. Sakurai, Y. Negishi, T. Tsukuda, *J. Am. Chem. Soc.* **2005**, *127*, 9374–9375; c) C. M. Y. Yeung, K. M. K. Yu, Q. J. Fu, D. Thompsett, M. I. Petch, S. C. Tsang, *J. Am. Chem. Soc.* **2005**, *127*, 18010–18011; d) M. Haruta, *Nature* **2005**, *437*, 1098–1099.
- [11] a) W. H. Fang, Q. H. Zhang, J. Chen, W. P. Deng, Y. Wang, *Chem. Commun.* **2010**, 1547–1549; b) L. He, L. C. Wang, H. Sun, J. Ni, Y. Cao, H. Y. He, K. N. Fan, *Angew. Chem.* **2009**, *121*, 9702–9705; *Angew. Chem. Int. Ed.* **2009**, *48*, 9538–9541; c) F. Z. Su, Y. M. Liu, L. C. Wang, Y. Cao, H. Y. He, K. N. Fan, *Angew. Chem.* **2008**, *120*, 340–343; *Angew. Chem. Int. Ed.* **2008**, *47*, 334–337; d) H. Sun, F. Z. Su, J. Ni, Y. Cao, H. Y. He, K. N. Fan, *Angew. Chem.* **2009**, *121*, 4454–4457; *Angew. Chem. Int. Ed.* **2009**, *48*, 4390–4393; e) A. Corma, P. Serna, *Science* **2006**, *313*, 332–334.
- [12] L. He, X. B. Lou, J. Ni, Y. M. Liu, Y. Cao, H. Y. He, K. N. Fan, *Chem. Eur. J.* **2010**, *16*, 13965–13969.
- [13] Confirmed by TG analyses, the contents of water in TiO₂ were approximately 1.5 wt% (at 140 °C).
- [14] G. C. Bond, D. T. Thompson, *Catal. Rev. Sci. Eng.* **1999**, *41*, 319–388.
- [15] A. Abad, A. Corma, H. Garcia, *Chem. Eur. J.* **2008**, *14*, 212–222.
- [16] Similar conversion and selectivity to secondary amines were obtained when alcohol/urea ratio was set at 6:1 for secondary alcohols.
- [17] R. Yamaguchi, S. Kawagoe, C. Asai, K.-I. Fujita, *Org. Lett.* **2008**, *10*, 181–184.
- [18] We examined the relationship between the relative rates and the Brown-Okamoto (σ^+) parameter for the competitive reaction of substituted benzyl alcohols with urea (see Figure S2 in the Supporting Information). The order of reactivity for various benzyl alcohols was *p*-CH₃O > *p*-CH₃ > *p*-H > *p*-Cl. There is a good linearity with a negative slope (Hammett value $\rho = -0.51$, $R^2 = 0.99$), indicating a positively charged transition state, which could be involved in the rate-determining step.

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