# Stable and Inert Cobalt Catalysts for Highly Selective and Practical Hydrogenation of C≡N and C=O Bonds

Feng Chen, Christoph Topf, Jörg Radnik, Carsten Kreyenschulte, Henrik Lund, Matthias Schneider, Annette-Enrica Surkus, Lin He, Kathrin Junge, and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein Straße 29a, Rostock 18059, Germany

S *Supporting Information*

ABSTRACT: Novel heterogeneous cobalt-based catalysts have been prepared by pyrolysis of cobalt complexes with nitrogen ligands on different inorganic supports. The activity and selectivity of the resulting materials in the hydrogenation of nitriles and carbonyl compounds is strongly influenced by the modification of the support and the nitrogen-containing ligand. The optimal catalyst system ([Co(OAc)$_2$/Phen@α-Al$_2$O$_3$]-800 = Cat. E) allows for efficient reduction of both aromatic and aliphatic nitriles including industrially relevant dinitriles to primary amines under mild conditions. The generality and practicability of this system is further demonstrated in the hydrogenation of diverse aliphatic, aromatic, and heterocyclic ketones as well as aldehydes, which are readily reduced to the corresponding alcohols.
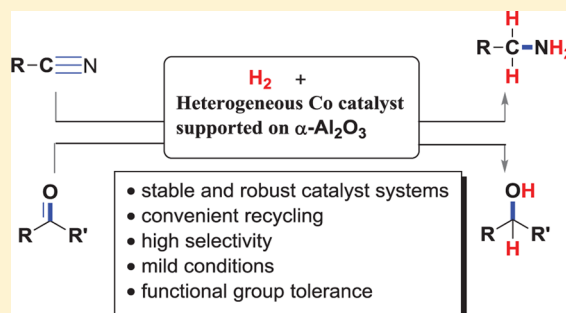
INTRODUCTION

Amines represent an important class of compounds in organic chemistry, especially for the pharmaceutical and agrochemical industries. In particular, primary amines represent valuable building blocks because of their structural diversity and straightforward valorization. Naturally, numerous methodologies have been reported for the synthesis of primary amines, including reductive aminations of carbonyl compounds,[1] hydroaminations,[2] and direct amination of alcohols.[3] Furthermore, the reduction of readily available nitriles is well-established and can be performed using hydrosilanes[4] or hydrogen.[5] Obviously, the latter reaction represents an attractive and sustainable approach.[6] Unfortunately, this process is usually accompanied by formation of secondary and tertiary amines as well as other byproducts.[7] In order to solve these problems and to improve known homogeneous catalysts mainly based on Ru[8] but also Ir,[9] Rh,[10] Re,[11] and Fe,[12] ongoing interest exists to develop novel systems. As recent examples, the works of Elsevier and de Bruin[13a] as well as Milstein[13b,c] using homogeneous cobalt catalysts are worth noting.

In general on an industrial scale, heterogeneous catalysis is preferred for the production of amines from nitriles. In this case, noble metal catalysts based on Pt, Pd, and Rh as well as nonprecious metal catalysts especially Ni or Co are commonly used.[7] Undoubtedly, the latter are more attractive owing to their abundance and low price. Indeed, prominent Raney nickel and Raney cobalt are well-known for nitrile hydrogenations. Unfortunately, the preparation and application of these Raney catalysts are difficult owing to their sensitivity and instability. Additionally, high pressure and/or temperature are needed for

these materials to develop sufficient catalytic activity and the substrate scope is limited. Hence, the development of active cobalt and nickel catalysts, which can be easily applied and allow for general hydrogenation of nitriles to primary amines, is still challenging and rewarding.
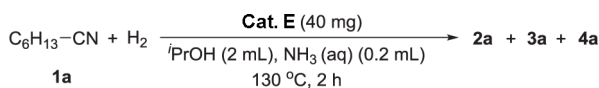
In addition to amines, alcohols are also important building blocks for polymers and constitute crucial intermediates in the pharmaceutical, agrochemical, and fine-chemical industry.[14] Typically, they are prepared directly from the corresponding carbonyl compounds. In this respect, stoichiometric reducing agents such as NaBH$_4$, LiAlH$_4$, boranes, and silanes are common for laboratory-scale synthesis of alcohols from ketones and aldehydes. However, generation of undesired waste and inconvenient operation conditions restrict their usage, especially in industry.[15] Therefore, in the past decades elegant and efficient transition metal catalyzed hydrogenations of C=O bonds have been developed.[6,16]

Typically, the selective hydrogenation of functionalized aldehydes and ketones is realized with homogeneous organometallic catalysts based on precious metals, although recently several base metal complexes, e.g. Fe, have been actively developed.[17] However, to the best of our knowledge, so far only few cobalt catalysts have been reported for the selective hydrogenation of C=O bonds. For example, Hanson and co-workers developed PNP-stabilized cobalt(II)-alkyl catalysts for the C=O hydrogenation.[18] Very recently, the group of Kempe reported PN$_{3-5}$P−Co complexes for the C=O bond hydrogenation under mild conditions.[19] Meanwhile, also Wolf and

Scheme 1. Hydrogenation of C≡N and C=O Bonds

co-workers reported an arene-cobalt catalytic system.[20] In addition to these sophisticated molecular-defined catalysts,[21] we thought the development of more stable and inert heterogeneous cobalt catalysts offers an attractive option for selective C=O bond hydrogenations.[22]

Recently, our group and others developed syntheses of novel nanostructured heterogeneous catalysts modified by N-doped graphenes based on the adsorption of metal amine complexes onto commercially available supports and subsequent pyrolysis.[23] Depending on the used nitrogen ligands, the pyrolysis temperature, the metal, and the support, the formation of active particles can be tuned and the activity of the resulting materials significantly varies. Herein, we report for the first time the application of stable and easily synthesized nanostructured cobalt catalysts for the hydrogenation of nitriles, ketones, and aldehydes to the corresponding amines or alcohols under mild conditions. Crucial for the activity of these novel materials is the use of specific α-Al$_2$O$_3$ as support.

■ RESULTS AND DISCUSSION

Hydrogenation of C≡N Bonds. We commenced our studies using heptanenitrile **1a** as model substrate which was hydrogenated at 40 bar hydrogen and 130 °C in the presence of cobalt catalysts on different supports (**Cat. A**: carbon; **Cat. B**: MgO, **Cat. C**: SiO$_2$, **Cat. D**: B$_4$C and **Cat. E**: α-Al$_2$O$_3$).

As shown in Table 1, the catalysts based on carbon and magnesium oxide gave low conversion (<10%), and only traces

Table 1. Hydrogenation of Heptanenitrile[a]

Entry	Metal precursor	Ligand	Support		Conversion (%)	Yield (%)[b]	
						2a	3a+4a
1	Co(OAc)$_2$•4H$_2$O	1,10-phen	Carbon	Cat. A	5	1	3
2	Co(OAc)$_2$•4H$_2$O	1,10-phen	MgO	Cat. B	9	1	trace
3	Co(OAc)$_2$•4H$_2$O	1,10-phen	Silica	Cat. C	66	17	22
4	Co(OAc)$_2$•4H$_2$O	1,10-phen	B$_4$C	Cat. D	100	37	20
5	**Co(OAc)$_2$•4H$_2$O**	**1,10-phen**	**α-Al$_2$O$_3$**	**Cat. E**	**100**	**62**	**30**

[a]The catalyst was pyrolyzed at 800 °C under argon atmosphere for 2 h. [b]GC yield using dodecane as an internal standard.

of the desired heptan-1-amine **2a** were detected by GC-FID (Table 1, entries 1−2). For the catalyst supported on silica improved activity was observed, but the selectivity was poor owing to the formation of secondary amine **3a**, imine **4a**, and some other byproducts (Table 1, entry 3). Interestingly, full conversion for the hydrogenation of heptanenitrile was enabled

by the catalysts immobilized on boron carbide and alumina, respectively. However, the aluminum oxide outperforms the boron congener in terms of selectivity (2:1) and yield (62%; Table 1, entries 4−5). To our delight, the addition of ammonia (25% aqueous solution, 0.1 mL) to the reaction mixture greatly improved the selectivity (>99:1) in the latter case and only traces of byproducts were detected. In addition, hydrogenations in the presence of H$_2$O or NH$_3$ (2 M) in ^{i}PrOH were performed. As shown in Figure 1 kinetic data indicate that both

Figure 1. Concentration/time diagram for the hydrogenation of heptanenitrile.

H$_2$O and NH$_3$ accelerate the hydrogenation process, thus reducing the reaction time. However, when H$_2$O was used as sole additive a large amount of unwanted byproducts (diheptylamine and N-heptylheptan-1-imine) were formed. In case of ammonia as additive only traces of such byproducts were detected (Figure 1). It is known that N-heptylheptan-1-imine (**4a**) is formed from the reaction of heptan-1-amine (**2a**) with heptan-1-imine via elimination of ammonia. Hence, the equilibrium between **4a** and heptan-1-imine can be shifted toward the desired heptan-1-imine by the addition of ammonia[6b,24] (see the SI).

Next, various α-Al$_2$O$_3$ supported cobalt catalysts prepared from different ligands were tested for the hydrogenation of heptanenitrile in the presence of ammonia. In agreement with previous results 1,10-phenanthroline (**L1**) proved to be best ligand whereas catalysts prepared from 2,2′-bipyridine (**L2**) and 2,2′:6′,2″-terpyridine (**L3**) provided lower yields (Table 2, entries 1−3). The influence of the pyrolysis temperature on the catalytic performance was also investigated and catalysts were prepared at 1000 °C, 900 °C, 800 °C, 600 and 400 °C (Table 2, entries 1 and 4−7). The material pyrolyzed at 400 °C did not exhibit catalytic activity for the nitrile hydrogenation whereas the other catalysts allowed for nearly full conversion. The highest product selectivity was observed in the presence of the catalyst treated at 800 °C. Notably, materials obtained upon pyrolysis of pure α-Al$_2$O$_3$ and Co(OAc)$_2$/α-Al$_2$O$_3$ were inactive for the nitrile hydrogenation (Table 2, entries 8 and 9). Moreover, the material Co(OAc)$_2$/1,10-phenanthroline/α-Al$_2$O$_3$ which was not pyrolyzed after support impregnation did not display any catalytic activity (Table 2, entry 10).

Table 2. Catalyst Screening for the Hydrogenation of Heptanenitrile

$$\text{C}_6\text{H}_{13}-\text{CN} + \text{H}_2 \xrightarrow[\substack{^i\text{PrOH (2 mL), NH}_3 \text{ (aq) (0.2 mL)} \\ 130\ ^\circ\text{C, 2 h}}]{\textbf{Cat. E} \text{ (40 mg)}} \textbf{2a} + \textbf{3a} + \textbf{4a}$$

1a

entry	metal precursor	ligand	support	pyrolyzed T (°C)	conv. (%)	yield (%)[a]	
						2a	**3a + 4a**
1	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$	800	100	99	trace
2	Co(OAc)$_2$·4H$_2$O	L2	α-Al$_2$O$_3$	800	12	10	0
3	Co(OAc)$_2$·4H$_2$O	L3	α-Al$_2$O$_3$	800	63	62	0
4	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$	1000	99	68	trace
5	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$	900	100	96	4
6	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$	600	99	94	5
7	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$	400	2	2	0
8		L1	α-Al$_2$O$_3$	800	0	0	0
9			α-Al$_2$O$_3$	800	0	0	0
10[b]	Co(OAc)$_2$·4H$_2$O	L1	α-Al$_2$O$_3$		0	0	0

[a]GC yield using dodecane as an internal standard. [b]4 mol % cobalt was used.

The most active cobalt material supported on alumina was characterized in detail (see the SI). The active catalyst shows a Co content of 3.10 wt % and contents of C and N of 16.86% and 0.24%, respectively. In the scanning transmission electron microscopy (STEM) measurement different types of cobalt containing structures were detected (Figure S2, c-d). The fresh catalyst shows metallic cobalt nanoparticles which are covered by several graphitic layers (Figure S2, e-f). In addition, Co$_x$O$_y$ particles without graphitic surrounding are observed which are in close contact to the metallic cobalt particles. Furthermore, highly disperse cobalt species and oxygen within the carbon phase could be detected, too (Figure S3, c, d and S4).

In order to understand the influence of the support in more detail, X-ray photoelectron spectroscopy (XPS) of the materials which are prepared with α-Al$_2$O$_3$, MgO, SiO$_2$, carbon, and B$_4$C have been recorded. As shown in Figure 2 depending on the support pyridinic, pyrrolic, or with Co bonded N could be observed. Notably, the latter two species cannot be well distinguished due to similar binding energies. For a good performance in the catalytic model reaction pyrrolic or more

Figure 2. XPS measurement (N 1s) of materials with different supports: (a) α-Al$_2$O$_3$; (b) MgO; (c) SiO$_2$; (d) carbon; and (e) B$_4$C. The binding energies were correlated to the different N species according refs 23 and 25.

likely with the Co bonded N seems to be crucial. Hence, for the inactive catalyst with MgO support only pyridinc N was observed. In agreement with previous works,[23a,25] the catalyst with carbon as support is inactive. We explain this behavior by the low Co/N ratio found for this sample (see Table S4). Comparing the SiO$_2$ and B$_4$C supported catalysts with similar N species a higher Co content in the near-surface region leads to a higher activity, whereas the α-Al$_2$O$_3$ supported catalysts with a relatively high Co content and with only the beneficial N species showed highest activity and the best selectivity for heptanenitrile hydrogenation.

In order to further improve the best catalyst **Cat. E** variations of the reaction conditions were performed. Parameters such as amount of added ammonia or H$_2$O, hydrogen pressure, temperature, as well as reaction time were investigated, and the results are summarized in Table 3. Comparing the effect of ammonia and water, in the presence of the later compound byproducts were always detected (Table 3, entries 2−4). In the presence of ammonia, full conversion was achieved even when the pressure was decreased to 5 bar albeit with concomitant increase of byproduct formation. We were pleased, that 98% yield was obtained and only 2% of byproducts were detected at 85 °C in the presence of an optimal amount of ammonia (Table 3, entry 9). Obviously, no conversion occurred when the reaction was conducted under a nitrogen atmosphere. Hence, this heterogeneous Co catalyst does not facilitate a transfer hydrogenation of nitriles (Table 3, entry 12).

Both stability as well as recyclability are important parameters for the application of any type of heterogeneous catalysts. Hence, we reused the catalytic material **Cat. E** for the hydrogenation of heptanenitrile up to eight times. As depicted in Figure 3, the desired product heptan-1-amine was obtained in a 99% yield even after eight runs and no loss of activity was observed. The selectivity stayed very good and only traces of byproducts were detected by GC-FID. These results evidently demonstrate that our catalyst is highly stable during the course of nitrile hydrogenation. Furthermore, this nanocomposite is conveniently handled on air without any deactivation compared to the classical Raney cobalt catalyst.

Notably, ICP-MS measurements of the recycling experiments indicated that no undesired leaching processes occurred during the course of the catalytic transformation. STEM character-ization of the used catalyst exposed the formation of new carbon phases with enrichments of cobalt and oxygen (Figure
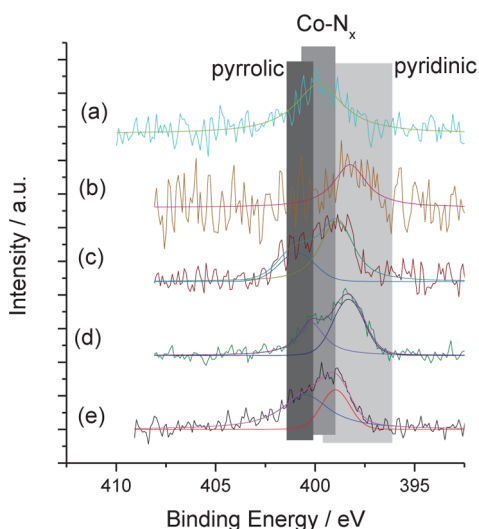
Table 3. Hydrogenation of Heptanenitrile.[a]

$$C_6H_{13}-CN + H_2 \xrightarrow[{}^{i}\text{PrOH (2 mL), additive}]{\text{Cat. E (4 mol\%)}} 2a + 3a + 4a$$

1a

entry	H$_2$ (bar)	additive (mL)	T (°C)	t (h)	conversion (%)	yield (%)[a]	
						2a	3a + 4a
1	40	NH$_3$ (aq) (0.1)	130	2	100	99	trace
2	40	H$_2$O (0.05)	130	2	100	85	11
3	40	H$_2$O (0.1)	130	2	100	87	10
4	40	H$_2$O (0.1)	130	1	71	56	7
5	30	NH$_3$ (aq) (0.1)	130	2	100	96	4
6	20	NH$_3$ (aq) (0.1)	130	2	100	95	5
7	10	NH$_3$ (aq) (0.1)	130	20	100	93	7
8	5	NH$_3$ (aq) (0.2)	130	20	100	89	11
9	5	NH$_3$ (aq) (0.3)	85	24	100	98	2
10	5	NH$_3$ (aq) (0.1)	85	24	100	96	4
11	2	NH$_3$ (aq) (0.3)	100	24	90	55	27
12	0	NH$_3$ (aq) (0.1)	130	2	0	0	0

[a]GC yield using dodecane as an internal standard.
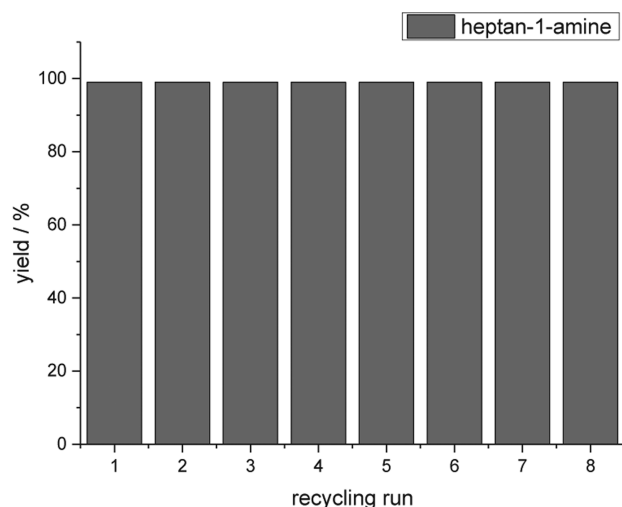
Figure 3. Recycling experiments using the Cat. E.

S5−S6), while the metallic cobalt nanoparticles surrounded by graphitic layers stayed unaffected (Figure S5e and f).

With the best conditions in hand, the substrate scope for the nitrile hydrogenation in the presence of the optimized heterogeneous catalyst was explored (Scheme 2). Initially, various (hetero)aromatic nitriles were tested under standard conditions. Aromatic nitriles containing electron-donating as well as electron-withdrawing groups are compatible with the catalytic system and good to excellent yields of the desired primary amines were obtained. Nevertheless, the selectivity of substrates bearing electron-withdrawing groups is better compared to nitriles with electron-donating groups in that secondary amines were formed in 10% - 15% for the latter. In general, no dehalogenation products were detected for fluoro- and chloro-substituted substrates whereas a small amount

Scheme 2. Hydrogenation of Aromatic Nitriles[a]

$$\text{Ar}-\text{CN} + H_2 \xrightarrow[\substack{{}^{i}\text{PrOH (2 mL), NH}_3\text{(aq)} \\ then\ 1.25\ \text{M HCl}_{\text{MeOH}}}]{\text{Cat. E (4 mol\%)}} \text{Ar}-\overset{+}{\text{CH}_2\text{NH}_3}\ \overset{-}{\text{Cl}}$$

5   6

5a 98% (98%[b,c]) 5b 86% (75%[b,c]) 5c 90%[c] 5d 80% (90%[b,c]) 5e 96%

5f 90% 5g 90% 5h 75% 5i 76%

5j 94% 5k 89% 5l 98% 5m 99%[c] 5n 90%

5o 97% 5p 89%[c] 5q 93%[c] 5r 82%[c,d] 5s 0%
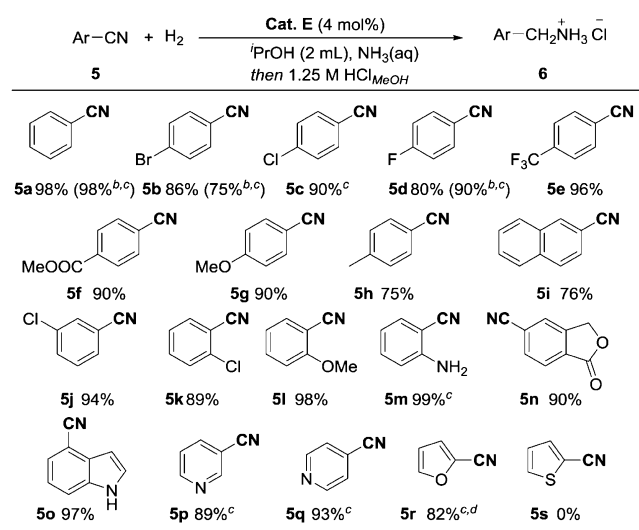
[a]Reaction conditions: nitrile (0.5 mmol) under 40 bar H$_2$ for 2 h. [b]5 bar H$_2$ at 85 °C. [c]GC yield using dodecane as an internal standard. [d]8 mol % catalyst was used. (The yield given below the structure refers to the primary amine or its hydrochloride salt.)

(10%) of dehalogenation product was observed for bromide-substituted substrates. The chloro-substituent in para-, meta-, and ortho- position does not exert an obvious effect for this catalytic transformation. Further substrates with trifluoromethyl, ester, and amine groups on the aromatic ring also afforded the desired products in good yields. In addition, nitrogen- or oxygen-containing heteroaromatic nitriles including indole, pyridine and furan are compatible and were readily converted into the corresponding primary amines with both high yields and selectivity.

To expand the scope further on, we tested the Co catalyst for less reactive aliphatic nitriles (Table 4). Fortunately, those

Table 4. Hydrogenation of Aliphatic Nitriles

$$\text{R}-\text{CN} + H_2 \xrightarrow[\substack{{}^{i}\text{PrOH (2 mL), NH}_3\text{ (aq)} \\ then\ 1.25\ \text{M HCl}_{\text{MeOH}}}]{\text{Cat. E (4 mol\%)}} \text{R}-\overset{+}{\text{CH}_2\text{NH}_3}\ \overset{-}{\text{Cl}}$$

1   2

entry	substrate		H$_2$ (bar)	NH$_3$(aq) (mL)	T (°C)	t (h)	yield (%)[a]
1	(adamantyl-CN)	(1b)	40	0.1	130	2	94
2			5	0.3	85	24	98
3	(isobutyl-CN)	(1c)	40	0.1	130	2	99[b]
4	(pentyl-CN)	(1d)	40	0.1	130	2	99[b]
5			5	0.3	85	24	97[b]
6	(cyclohexyl-CH$_2$CN)	(1e)	40	0.1	130	2	99[b]
7			5	0.3	85	24	96[b]
8	(benzyl-CN)	(1f)	40	0.1	130	2	91
9	(MeO-benzyl-CN)	(1g)	40	0.1	130	2	85
10	CH$_3$(CH$_2$)$_{17}$CN	(1h)	40	0.2	130	2	84
11	CH$_3$(CH$_2$)$_{15}$CN	(1i)	40	0.2	130	2	93
12	CH$_3$(CH$_2$)$_{15}$CN	(1i)	45	10	130	2.5	96[b,c]

[a]Isolated yield as hydrochloride salt. [b]GC yield using dodecane as an internal standard. [c]25 mmol scale.

substrates were converted into the desired amines with good to excellent yield (up to 99% yield) and selectivity. For instance, long chain fatty amines such as heptadecan-1-amine and nonadecan-1-amine were produced in high yields from the corresponding fatty acid nitriles. Notably, high activity under milder conditions (5 bar of H_2 at 85 °C for 24 h) was observed for selected substrates (**5a**, **5b**, **5d**, **1b**, **1d**, and **1e**), which were converted into the corresponding primary amines effectively.

Finally, hydrogenation of dinitriles **7** was also explored (Scheme 3). The prominent 1,6-hexamethylenediamine **8a**

Scheme 3. Hydrogenation of Dinitriles[a]
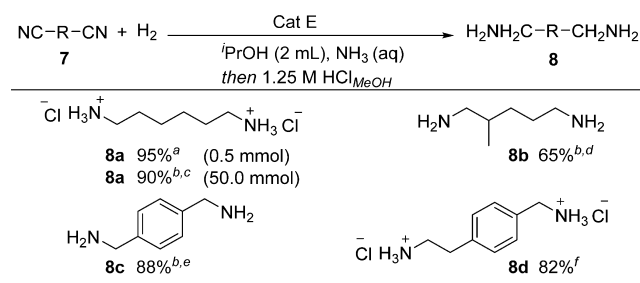
^{a}Dinitrile (0.5 mmol) with 60 mg Cat. E and 0.1 mL NH_3 (aq) under 50 bar H_2 at 140 °C for 3 h. ^{b}GC yield using dodecane as an internal standard. ^{c}With 60 mg Cat. E and 0.1 mL NH_3 (aq) under 55 bar H_2 for 4 h. ^{d}With 60 mg Cat. E and 0.2 mL NH_3 (aq) under 50 bar H_2 at 140 °C for 2 h. ^{e}With 80 mg Cat. E and 0.3 mL NH_3 (aq) under 50 bar H_2 at 150 °C for 4 h. ^{f}With 40 mg Cat. E and 0.2 mL NH_3 (aq) under 40 bar H_2 at 140 °C for 4 h.

(1,6-HMD) which is an essential building block for the production of Nylon-6,6 was obtained via hydrogenation of adipodinitrile (**7a**) in 95% isolated yield. In addition, a branched aliphatic dinitrile **7b** was hydrogenated to the corresponding diamine in moderate yield. Aromatic dinitriles such as terephthalodinitrile (**7c**) and 4-(cyanomethyl)benzonitrile (**7d**) furnished the desired amines in 88% and 82% yield, respectively. To demonstrate the usefulness of the catalyst on a preparative scale, experiments on 25−50 mmol scale were performed with adipodinitrile (Scheme 3) and heptadecanenitrile (Table 4, entry 12). As expected the corresponding amines are obtained in excellent yields and selectivity similar to the standard catalytic testing.

Hydrogenation of C=O Bonds. Due to the positive results for the nitrile reduction, we became interested in testing this heterogeneous cobalt catalyst **Cat. E** for the hydrogenation of other carbonyl compounds. Here, 6-methylhept-5-en-2-one (**9a**) was selected as model substrate to explore the catalyst

activity for C=O bonds. Initially, the various heterogeneous cobalt catalysts were tested in ethanol as solvent with hydrogen (20 bar) at 100 °C. In addition to the ligand also the support shows a major influence on the activity and selectivity of the respective heterogeneous catalyst.

For example, in the presence of cobalt catalysts supported on carbon, SiO_2 and MgO only low activity is observed (Table 5, entries 1−3). Again, the material prepared on B_4C showed improved activity and hydrogenated 6-methylhept-5-en-2-one to 6-methylhept-5-en-2-ol in 58% yield (Table 5, entry 4). To our delight, full conversion and 90% yield is obtained for the cobalt nanoparticles supported on α-Al_2O_3 (Table 5, entry 5). In this case the saturated alcohol **11a** is formed in 10% yield, too. It should be noted that this behavior is in contrast to the hydrogenation of nonconjugated enones with traditional PtO_2, Pd/C, and Raney Ni catalysts, in which the reduction of C=C bond is preferred compared to the C=O bond.[26] The Co catalyst on α-Al_2O_3 with a relatively high Co content and with only the beneficial N species showed high activity for the C=O bond hydrogenation.

With suitable conditions in hand, the general applicability of this heterogeneous cobalt catalyst **Cat. E** for hydrogenation of different carbonyl compounds was explored (Table 6). Aliphatic ketones are hydrogenated to the corresponding alcohols in excellent yields; however, higher pressure of hydrogen (>30 bar) and temperature (>100 °C) are necessary for full conversion of cycloheptanone and cyclooctanone (Table 6, entries 1−4). γ-Valerolactone (GVL), an important biomass-derived platform chemical, is obtained through selective hydrogenation of methyl 4-oxopentanoate (Table 6, entry 5). Similarly, the C=O bond of 4,4-dimethyldihydrofuran-2,3-dione is selectively hydrogenated to give the alcohol **10g** in almost quantitative yield (Table 6, entry 6).

Notably, the heterocyclic substrate 1-benzylpiperidin-4-one is converted into alcohol **10h** in 98% isolated yield, despite the possibility of hydrogenolysis (Table 6, entry 7). Related substitued acetophenones led to the corresponding alcohols in high yields (Table 6, entries 8−10). Similarly, α-CF_3-acetophenone is highly selectively hydrogenated into 2,2,2-trifluoro-1-phenylethan-1-ol in 95% isolated yield (Table 6, entry 11). Due to their importance as building blocks, several pyridine-based ketones were investigated in more detail. Here, 1-(pyridin-2-yl)ethan-1-one, 1-(pyridin-3-yl)ethan-1-one, 1-(pyridin-4-yl)ethan-1-one were converted into the corresponding alcohols in excellent yield without formation of any hydrodeoxygenation products (Table 6, entries 12−14). Even di(pyridin-2-yl)methanone was compatible with this catalyst

Table 5. Hydrogenation of 6-Methylhept-5-en-2-one: Variation of Catalysts and Conditions[a]

entry	metal precursors	ligand	support	t (h)	convertion	yield (%)[b]		
						10a	**11a**	**12a**
1	Co(OAc)$_2$·4H$_2$O	1,10-Phen	carbon	15	0	0	0	0
2	Co(OAc)$_2$·4H$_2$O	1,10-Phen	silca	15	0	0	0	0
3	Co(OAc)$_2$·4H$_2$O	1,10-Phen	MgO	15	0	0	0	0
4	Co(OAc)$_2$·4H$_2$O	1,10-Phen	B_4C	15	62	58	0	trace
5	Co(OAc)$_2$·4H$_2$O	1,10-Phen	α-Al$_2$O$_3$	15	100	90	10	0

^{a}6-Methylhept-5-en-2-one (0.5 mmol) with catalyst under H_2. ^{b}GC yield using dodecane as an internal standard.

Table 6. Hydrogenation of Different Ketones and Aldehydes[a]

$$R^1\text{-CO-}R^2 \;\; \mathbf{9} \;+\; H_2 \xrightarrow[\text{EtOH, T, t}]{\textbf{Cat. E} (4\ mol\%)} R^1\text{-CH(OH)-}R^2 \;\; \mathbf{10}$$

Entry	Substrate 9	H$_2$ (bar)	T (°C)	t (h)	Products 10	Yield (%)[b]
1	[nonan-5-one]	30	120	15	10b	(96)
2	[cyclic ketone]	15	120	10	10c n = 1	98
3		30	130	18	10d n = 2	(98)
4		40	130	20	10e n = 3	(97)
5	[keto ester]	20	100	15	10f	70
6	[dioxo lactone]	20	120	20	10g	98
7	[N-benzyl piperidinone]	20	100	20	10h	(98)
8	[aryl ketone, R]	20	100	12	10i R = Et	(98)
9		20	100	15	10j R = F	97
10		20	100	15	10k R = Cl	82
11	[trifluoroacetophenone]	20	100	15	10l	(95)
12	[2-acetylpyridine]	30	120	16	10m	(99)
13	[3-acetylpyridine]	20	100	20	10n	98
14	[4-acetylpyridine]	20	100	15	10o	(95)
15	[di(2-pyridyl) ketone]	30	130	18	10p	85
16	[HMF aldehyde]	30	120	15	10q	60
17	[citronellal]	20	100	20	10r	(98)

[a]Substrate (0.5 mmol) with 40 mg catalyst. [b]GC yield using dodecane as an internal standard (isolated yield in parentheses).

system to give sensitive di(pyridin-2-yl)methanol in 85% yield (Table 6, entry 15).

In addition, hydrogenations of aldehydes were explored in the presence of this heterogeneous cobalt catalyst. For example, carbohydrate-derived 5-(hydroxymethyl)furan-2-carbaldehyde gave the corresponding sensitive diol in 60% yield (Table 6, entry 16). Furthermore, naturally occurring citronellal (3,7-dimethyloct-6-enal) led to the corresponding primary alcohol in excellent yield. Notably, in this latter case no hydrogenation of the C=C double bond is occurring under these conditions (Table 6, entry 17).

In order to demonstrate the utility of this novel catalyst for reductions of pharmaceutically relevant molecules, the hydrogenation of four different oxo-steroids was investigated. Notably, hydroxysteroids are important intermediates for the metabolism of natural steroids. They constitute essential building blocks for natural products, synthetic pharmaceuticals, and various biologically active compounds. In fact, 16 steroid

derivatives were among the top 200 pharmaceuticals by U.S. retail sales in 2012.[27] Noteworthy, important steroids were smoothly hydrogenated into the corresponding hydroxysteroids (Table 7). For instance, estrone, pregnenolones and

Table 7. Catalytic Hydrogenation of Oxo-Steroids[a]

Entry	Substrate	Catalyst (mol%)	H$_2$ (bar)	T (°C)	Product	Yield (%)[b]
1	13	4	20	100	14	98
2	15	6	30	120	16	99
3	17	6	30	120	18	98
4	19	6	30	120	20	97

[a]Steroids (0.5 mmol) with 40–60 mg catalyst. [b]Isolated yield.

dehydroepiandrosterone gave almost quantitative yields of the two reduced stereoisomers (43:57–33:66), which are easily obtained through simple filtration. In agreement with the results vide supra, no olefin hydrogenation was observed.

■ CONCLUSION

We developed a novel heterogeneous cobalt catalyst system on α-Al$_2$O$_3$. This inexpensive and easily handled cobalt catalyst facilitates the formation of primary amines from nitriles and the products are formed with both high activity and selectivity. Aromatic as well as aliphatic nitriles are converted under mild conditions and the catalyst assembly displays a wide functional group tolerance. Furthermore, industrially relevant dinitriles were also hydrogenated into the corresponding diamines efficiently. In addition, they allow for selective hydrogenation of ketones and aldehydes to give the corresponding alcohols in high yield, even in the presence of C=C bonds. Commercialization of these heterogeneous cobalt catalysts is currently under way.

■ EXPERIMENTAL SECTION

Preparation of Heterogeneous Co Catalyst on α-Al$_2$O$_3$ (Cat. E). Co(OAc)$_2$·4H$_2$O (1.27 g, 5.0 mmol) and 1,10-phenanthroline (1.82 g, 10.0 mmol) (Co:phenanthroline =1:2 molar ratio) were stirred in ethanol (250 mL) for approximately 15 min at room temperature. Then the whole reaction mixture was agitated at 60 °C for 1 h. The support α-Al$_2$O$_3$ (6.91 g) was then added and the mixture was stirred at room temperature overnight. Then the ethanol was removed in vacuo and leaving behind a pale brown solid that was dried at the pump. The sample was grinded to a fine powder which was then transferred to a ceramic crucible and placed in the oven. The latter was evacuated to ca. 5 mbar and then flushed with argon three times. The furnace was heated to 800 °C at a rate of 25 °C per minute and held at 800 °C for 2 h under argon atmosphere. After the heating was switched off the oven was allowed to reach room temperature. During the whole process argon was constantly passed through the oven.

Catalytic Hydrogenation of Nitriles (Preparative Scale). In a 300 mL autoclave, heptadecanenitrile **5h** (25.0 mmol) with **Cat. E** (2.0 g) were mixed in 100 mL of 2-propanol and ammonia solution (25%,

10 mL). The autoclave was flushed with hydrogen gas twice and pressurized with hydrogen (45 bar). After the reaction was complete after 2.5 h at 130 °C, the autoclave was cooled to room temperature and the hydrogen was released. The ammonia was removed under vacuum conditions. Then to the crude reaction mixture was added hydrochloride solution (25 mL, 1.25 M in methanol). The solvent was removed and the corresponding salt **6h** was obtained.

General Procedure for Hydrogenation of Ketones and Aldehydes. In a reaction vial (5 mL), ketone or aldehyde **9** (0.5 mmol) with **Cat. E** (40 mg) were mixed in 2 mL of EtOH. The closed reaction vials were placed into a 300 mL autoclave via a prepared metal plate. The autoclave was flushed with hydrogen gas twice and pressurized with hydrogen. After the reaction was complete, the autoclave was cooled to room temperature and the hydrogen was released. The crude reaction mixture was purified by short flash chromatography on silicon gel (eluent: acetone) to afford corresponding alcohol **10**. For some substrates, the crude reaction mixture was added dodecane (50 μL) and analyzed by GC-FID.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03439.

    Additional experimental results, procedures and characterization data. (PDF)

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: Matthias.Beller@catalysis.de
Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055. (b) Ogo, S.; Uehara, K.; Abura, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 3020. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Núñez Magro, A. A.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun.* **2007**, 3154.

(2) (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(3) (a) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661. (b) Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126. (c) Pingen, D.; Müller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8130. (d) Imm, S.; Bähn, S.; Zhang, M.; Neubert, L.; Neumann, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7599. (e) Ye, X.; Plessow, P. N.; Brinks, M. K.; Schelwies, M.; Schaub, T.; Rominger, F.; Paciello, R.; Limbach, M.; Hofmann, P. *J. Am. Chem. Soc.* **2014**, *136*, 5923.

(4) (a) Corriu, R. J. P.; Moreau, J. J. E.; Pataud-Sat, M. *J. Organomet. Chem.* **1982**, *228*, 301. (b) Laval, S.; Dayoub, W.; Favre-Reguillon, A.; Berthod, M.; Demonchaux, P.; Mignani, G.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 7005. (c) Gutsulyak, D. V.; Nikonov, G. I. *Angew. Chem., Int. Ed.* **2010**, *49*, 7553. (d) Bornschein, C.; Werkmeister, S.; Junge, K.; Beller, M. *New J. Chem.* **2013**, *37*, 2061.

(5) For recent reviews on hydrogenation of nitriles see: (a) Werkmeister, S.; Junge, K.; Beller, M. *Org. Process Res. Dev.*
2014, *18*, 289. (b) Bagal, D. B.; Bhanage, B. M. *Adv. Synth. Catal.* **2015**, *357*, 883.

(6) (a) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007. (b) Enthaler, S.; Junge, K.; Addis, D.; Erre, G.; Beller, M. *ChemSusChem* **2008**, *1*, 1006. (c) *Catalysis without Precious Metals*; Bullock, R. M., Ed.; Wiley-VCH: Weinheim, Germany, 2010. (d) *Hydrogenation*; Karamé, I., Ed.; InTech: Rijeka, Croatia, 2012. (e) *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*; Dunn, P. J., Hii, K. K., Krische, M. J., Williams, M. T., Eds.; John Wiley & Sons: Hoboken, NJ, 2013.

(7) (a) de Bellefon, C.; Fouilloux, P. *Catal. Rev.: Sci. Eng.* **1994**, *36*, 459. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, 2001; p 254. (c) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (d) Hegedűs, L.; Máthé, T. *Appl. Catal., A* **2005**, *296*, 209.

(8) (a) Li, T.; Bergner, I.; Haque, F. N.; Zimmer-De Luliis, M.; Song, D.; Morris, R. H. *Organometallics* **2007**, *26*, 5940. (b) Enthaler, S.; Addis, D.; Junge, K.; Erre, G.; Beller, M. *Chem. - Eur. J.* **2008**, *14*, 9491. (c) Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. *J. Am. Chem. Soc.* **2010**, *132*, 7854. (d) Gunanathan, C.; Hölscher, M.; Leitner, W. *Eur. J. Inorg. Chem.* **2011**, *2011*, 3381. (e) Miao, X.; Bidange, J.; Dixneuf, P. H.; Fischmeister, C.; Bruneau, C.; Dubois, J.-L.; Couturier, J.-L. *ChemCatChem* **2012**, *4*, 1911. (f) Werkmeister, S.; Junge, K.; Wendt, B.; Spannenberg, A.; Jiao, H.; Bornschein, C.; Beller, M. *Chem. - Eur. J.* **2014**, *20*, 4227. (g) Choi, J.-H.; Prechtl, M. H. G. *ChemCatChem* **2015**, *7*, 1023.

(9) Chin, C.; Lee, B. *Catal. Lett.* **1992**, *14*, 135.

(10) Yoshida, T.; Okano, T.; Otsuka, S. *J. Chem. Soc., Chem. Commun.* **1979**, 870.

(11) Rajesh, K.; Dudle, B.; Blacque, O.; Berke, H. *Adv. Synth. Catal.* **2011**, *353*, 1479.

(12) Bornschein, C.; Werkmeister, S.; Wendt, B.; Jiao, H.; Alberico, E.; Baumann, W.; Junge, H.; Junge, K.; Beller, M. *Nat. Commun.* **2014**, *5*, 4111.

(13) (a) Korstanje, T. J.; van der Vlugt, J. I.; Elsevier, C. J.; de Bruin, B. *Science* **2015**, *350*, 298. (b) Mukherjee, A.; Srimani, D.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2015**, *137*, 8888. (c) Chakraborty, S.; Leitus, G.; Milstein, D. *Chem. Commun.* **2016**, *52*, 1812.

(14) (a) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346. (b) Blaser, H.-U.; Pugin, B.; Spindler, F. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1. (c) *Common Fragrance and Flavor Materials*; Surburg, H., Panten, J., Eds.; Wiley-VCH: Weinheim, Germany, 2006. (d) *Flavors and Fragrance Ingredients*; Berger, R. G., Ed.; Springer: Berlin, 2007. (e) Saudan, L. A. *Acc. Chem. Res.* **2007**, *40*, 1309. (f) Behr, A. in *Angewandte homogene Katalyse*; Wiley-VCH: Weinheim, Germany, 2008; pp 509−525.

(15) (a) Forrest, T. P.; Dauphinee, D. A.; Deraniyagala, S. A. *Can. J. Chem.* **1985**, *63*, 412. (b) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395. (c) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.

(16) For reviews on carbonyl hydrogenation see: (a) Gallezot, P.; Richard, D. *Catal. Rev.: Sci. Eng.* **1998**, *40*, 81. (b) Mäki-Arvela, P.; Hájek, J.; Salmi, T.; Murzin, D.Yu. *Appl. Catal., A* **2005**, *292*, 1. (c) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282. (d) Pritchard, J.; Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. *Chem. Soc. Rev.* **2015**, *44*, 3808. (e) Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. *Acc. Chem. Res.* **2015**, *48*, 2587.

(17) Recent examples of Fe-catalyzed carbonyl hydrogenation: (a) Sui-Seng, C.; Freutel, F.; Lough, A. J.; Morris, R. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 940. (b) Lagaditis, P. O.; Sues, P. E.; Sonnenberg, J. F.; Wan, K. Y.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 1367. (c) Chakraborty, S.; Lagaditis, P. O.; Förster, M.; Bielinski, E. A.; Hazari, N.; Holthausen, M. C.; Jones, W. D.; Schneider, S. *ACS Catal.* **2014**, *4*, 3994. (d) Li, Y.; Yu, S.; Wu, X.; Xiao, J.; Shen, W.; Dong, Z.; Gao, J. *J. Am. Chem. Soc.* **2014**, *136*, 4031. (e) Zell, T.; Milstein, D. *Acc. Chem. Res.* **2015**, *48*, 1979. (f) Zuo, W.;

Prokopchuk, D. E.; Lough, A. J.; Morris, R. H. *ACS Catal.* **2016**, *6*, 301.

(18) (a) Zhang, G.; Scott, B. L.; Hanson, S. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12102. (b) Zhang, G.; Hanson, S. K. *Chem. Commun.* **2013**, *49*, 10151. (c) Zhang, G.; Vasudevan, K. V.; Scott, B. L.; Hanson, S. K. *J. Am. Chem. Soc.* **2013**, *135*, 8668.

(19) Rösler, S.; Obenauf, J.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 7998.

(20) Gärtner, D.; Welther, A.; Rad, B. R.; Wolf, R.; Wangelin, A. J. v. *Angew. Chem., Int. Ed.* **2014**, *53*, 3722.

(21) For recent examples of other cobalt-based hydrogenation catalysts see: (a) Federsel, C.; Ziebart, C.; Jackstell, R.; Baumann, W.; Beller, M. *Chem. - Eur. J.* **2012**, *18*, 72. (b) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science* **2013**, *342*, 1076. (c) Jeletic, M. S.; Mock, M. T.; Appel, A. M.; Linehan, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 11533. (d) Jeletic, M. S.; Helm, M. L.; Hulley, E. B.; Mock, M. T.; Appel, A. M.; Linehan, J. C. *ACS Catal.* **2014**, *4*, 3755.

(22) (a) Nitta, Y.; Hiramatsu, Y.; Imanaka, T. *J. Catal.* **1990**, *126*, 235. (b) Nitta, Y.; Kato, T.; Imanaka, T. In *Heterogeneous Catalysis and Fine Chemicals III*; Guisnet, M., Barbier, J., Barrault, J., Bouchoule, C., Duprez, D., Pérot, G., Montassier, C., Eds.; Elsevier: Amsterdam, 1993; pp 83−90. (c) Jia, C. J.; Schwickardi, M.; Weidenthaler, C.; Schmidt, W.; Korhonen, S.; Weckhuysen, B. M.; Schüth, F. *J. Am. Chem. Soc.* **2011**, *133*, 11279. (d) Yang, J. H.; Gao, Y. J.; Zhang, W.; Tang, P.; Tan, J.; Lu, A. H.; Ma, D. *J. Phys. Chem. C* **2013**, *117*, 3785. (e) Wang, H.; Zhou, W.; Liu, J. X.; Si, R.; Sun, G.; Zhong, M. Q.; Su, H. Y.; Zhao, H. B.; Rodriguez, J. A.; Pennycook, S. J.; Idrobo, J. C.; Li, W. X.; Kou, Y.; Ma, D. *J. Am. Chem. Soc.* **2013**, *135*, 4149. (f) Wei, Z.; Wang, J.; Mao, S.; Su, D.; Jin, H.; Wang, Y.; Xu, F.; Li, H.; Wang, Y. *ACS Catal.* **2015**, *5*, 4783.

(23) (a) Westerhaus, F. A.; Jagadeesh, R. V.; Wienhöfer, G.; Pohl, M.-M.; Radnik, J.; Surkus, A.-E.; Rabeah, J.; Junge, K.; Junge, H.; Nielsen, M.; Brückner, A.; Beller, M. *Nat. Chem.* **2013**, *5*, 537. (b) Jagadeesh, R. V.; Junge, H.; Pohl, M.-M.; Radnik, J.; Brückner, A.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 10776. (c) Deng, J.; Song, H.-J.; Cui, M.-S.; Du, Y.-P.; Fu, Y. *ChemSusChem* **2014**, *7*, 3334. (d) Huang, D.; Luo, Y.; Li, S.; Zhang, B.; Shen, Y.; Wang, M. *Nano Res.* **2014**, *7*, 1054. (e) Stemmler, T.; Chen, F.; Pisiewicz, S.; Surkus, A.-E.; Pohl, M.-M.; Topf, C.; Beller, M. *J. Mater. Chem. A* **2015**, *3*, 17728. (f) Iosub, A. V.; Stahl, S. S. *Org. Lett.* **2015**, *17*, 4404. (g) Zhang, L.; Wang, A.; Wang, W.; Huang, Y.; Liu, X.; Miao, S.; Liu, J.; Zhang, T. *ACS Catal.* **2015**, *5*, 6563. (h) Zhong, W.; Liu, H.; Bai, C.; Liao, S.; Li, Y. *ACS Catal.* **2015**, *5*, 1850. (i) Bai, C.; Yao, X.; Li, Y. *ACS Catal.* **2015**, *5*, 884. (j) Zhou, Y.-X.; Chen, Y.-Z.; Cao, L.; Lu, J.; Jiang, H.-L. *Chem. Commun.* **2015**, *51*, 8292. (k) Fu, L.; Chen, Y.; Liu, Z. *J. Mol. Catal. A: Chem.* **2015**, *408*, 91. (l) Long, J.; Zhou, Y.; Li, Y. *Chem. Commun.* **2015**, *51*, 2331. (m) Chen, F.; Surkus, A.-E.; He, L.; Pohl, M.-M.; Radnik, J.; Topf, C.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2015**, *137*, 11718. (n) Yang, C.; Fu, L.; Zhu, R.; Liu, Z. *Phys. Chem. Chem. Phys.* **2016**, *18*, 4635.

(24) Kukula, P.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.* **2004**, *346*, 1487.

(25) Ombaka, L. M.; Ndungu, P. G.; Nyamori, V. O. *RSC Adv.* **2015**, *5*, 109.

(26) (a) Fujita, S.; Sano, Y.; Bhanage, B. M.; Arai, M. *J. Catal.* **2004**, *225*, 95. (b) Ghosh, A.; Kumar, R. *Microporous Mesoporous Mater.* **2005**, *87*, 33.

(27) See: http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.