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Selective one-pot synthesis of asymmetric secondary amines via N-alkylation of nitriles with alcohols

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ABSTRACT

The synthesis of asymmetric secondary amines (ASA) is commonly achieved by N-alkylation of primary amines with alcohols. Here, we investigated the ASA synthesis via the direct amination of alcohols with nitriles, which avoids the synthesis, separation and purification of the primary amines in a first step. Specifically, the ASA synthesis via N-alkylation of butyronitrile (BN) with primary (n-propanol, *iso*-butanol and n-octanol) and secondary (2-propanol, 2-butanol and 2-octanol) alcohols was studied on SiO_2-supported Co, Ni and Ru catalysts. Competitive BN hydrogenation-condensation reactions formed dibutylamine (the symmetric secondary amine) and tertiary amines as main secondary products. On Co/SiO_2, the ASA selectivities for BN/primary alcohol reactions were between 49 and 58% at complete BN conversion, forming dibutylamine and tertiary amines as byproducts. For BN/secondary alcohol reactions, Co/SiO_2 formed selectively (ASA + dibutylamine) mixtures containing 78–85% of ASA, thereby showing that the alcohol amination with nitriles is an attractive alternative route for the synthesis of valuable asymmetric secondary amines.

1. Introduction

Secondary amines are widely used by the fine chemical industry as they are important building blocks for the synthesis of agrochemicals, bioactive compounds, pharmaceuticals and dyestuffs [1,2]. Different routes have been reported for the selective synthesis of secondary amines from primary amines. For example, the N-alkylation of primary amines with alkyl halides is a straightforward synthesis route but poses serious environmental concerns because of the formation of large amounts of wasteful salts [1,3,4]. The reductive amination of aldehydes and ketones with primary amines is another well-known method to produce secondary amines [5,6,7]. Nevertheless, the reaction requires the presence of a strong hydride as reducing agent and is not always selective for monoalkylation of primary amines. The N-alkylation of primary amines with alcohols promoted by homogeneous metal complexes or transition metal-based solid catalysts is an efficient and environmentally benign method to produce secondary amines because it affords only water as by-product and may proceed without adding hydrogen [8,9,10]. On the other hand, secondary amines may be produced in high yields by selective hydrogenation of nitriles, which are inexpensive and commercially available compounds, using either homogeneous [11,12] or heterogeneous [13,14] catalysis. However, the nitrile hydrogenation process forms only symmetric secondary amines, and therefore the synthesis of asymmetric secondary amines has so far been achieved mainly via amination of alcohols, aldehydes or ketones with primary amines. As is well-known, primary amines are obtained at industrial level in high yields by selective hydrogenation of the corresponding nitriles [15,16,17]. Thus, it becomes attractive to develop a one-pot process to produce efficiently asymmetric secondary amines via the direct amination of alcohols with nitriles, which avoids the synthesis, separation and purification of the primary amines in a first step.

In this work, we investigate for the first time the selective one-pot synthesis of asymmetric secondary amines (ASA) via alcohol amination with nitriles by heterogeneous catalysis using metal-supported catalysts. In homogeneous catalysis, the synthesis of secondary and tertiary amines as a result of transfer hydrogenation of nitriles in alcohols has been reported using Ru(II) complexes [18,19]. The reaction pathways involved in the synthesis of ASA from amination of primary or secondary alcohols with saturated nitriles are presented in Scheme 1. Previous work on the hydrogenation of saturated nitriles to amines [20,21,22,23] has shown that nitrile R^1CN is initially hydrogenated to primary amine R^1CNH_2 via a highly reactive imine intermediate R^1CNH that may

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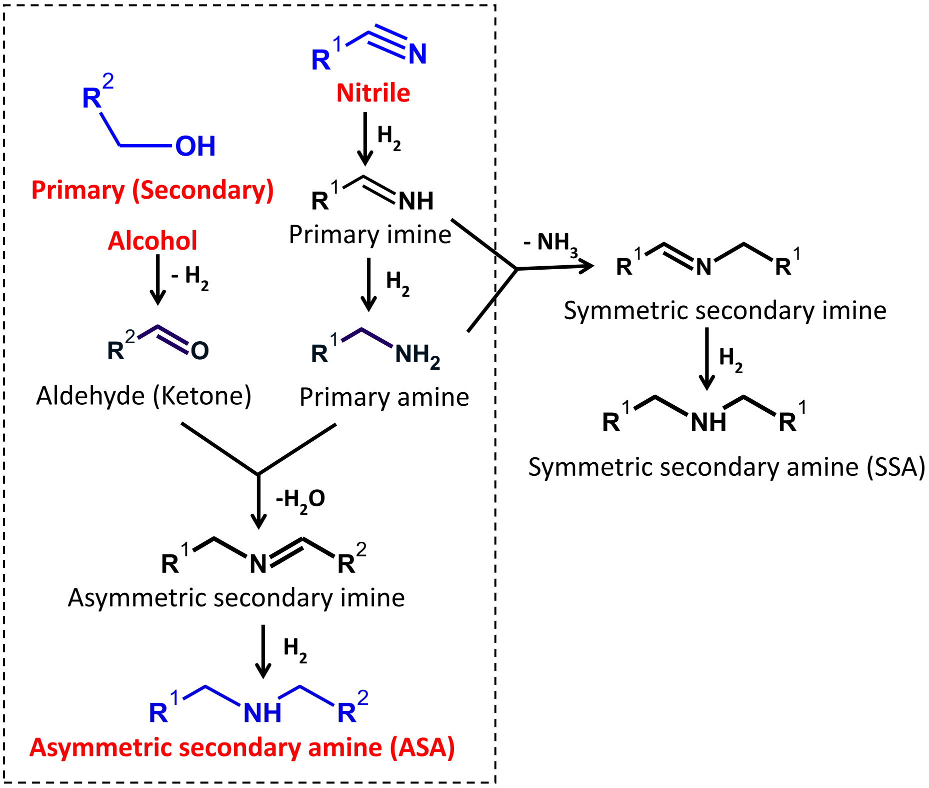

Scheme 1. Reaction network of the synthesis of asymmetric secondary amines via N-alkylation of nitriles with alcohols.

react with R^1CNH_2 to form by deamination a secondary imine which is further hydrogenated to the symmetric secondary amine (SSA). In the nitrile/alcohol reaction network of Scheme 1, the carbonyl compound formed by dehydrogenation of the primary or secondary alcohol reacts with primary amine R^1CNH_2 to yield an asymmetric secondary imine that is finally hydrogenated to the asymmetric secondary amine. The efficient synthesis of ASA from amination of alcohols with nitriles requires the development of active and selective metal-based catalysts that promote the reaction pathway leading from reactants to ASA avoiding the formation of byproducts via secondary reactions. Main secondary competitive reactions are the parallel formation of SSA from R^1CNH_2 as well as the consecutive reactions leading from SSA and ASA to tertiary amines.

In the present work we investigate the selective synthesis of ASA by N-alkylation of butyronitrile (BN) with primary (n-propanol, *iso*-butanol and n-octanol) and secondary (2-propanol, 2-butanol, 2-octanol) alcohols on silica-supported Co, Ni and Ru catalysts. In a previous work [17], we investigated the effect of the metal nature of metal/SiO_2 catalysts on the selective BN hydrogenation to butylamine and observed that Co, Ni and Ru exhibited higher catalytic performance than Cu, Pt and Pd. We selected therefore Co, Ni and Ru catalysts to study here the synthesis of ASA from the liquid-phase BN/alcohol reaction. Our results show that Co/SiO_2 efficiently catalyzes the synthesis of ASA via the amination of secondary alcohols with BN at high rates, producing selectively (ASA + dibutylamine) mixtures that contain 78–85% of ASA.

2. Experimental

2.1. Catalyst preparation

Co/SiO_2, Ni/SiO_2, and Ru/SiO_2 catalysts were obtained by supporting the metal on a commercial silica powder (Sigma-Aldrich G62, 60–200 mesh, 300 m^2/g) by incipient-wetness impregnation at 303 K. ($Co(NO_3)_2{\cdot}6H_2O$ (Aldrich 98%) and $Ni(NO_3)_2{\cdot}6H_2O$ (Fluka 98%) aqueous solutions were employed to impregnate Co and Ni, whereas Ru/SiO_2 was prepared using $RuCl_3{\cdot}H_2O$ (Aldrich 99.98%). The impregnated samples were dried overnight at 373 K and then calcined in air at 673 K for 2 h.

2.2. Catalyst characterization

Total surface areas (S_{BET}, m^2/g) were determined by N_2 physisorption at 77 K using the BET method in a Micromeritics ASAP 2100E sorptometer. Samples were previously outgassed at 523 K for 1 h. Metal loadings were measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES), using a Perkin-Elmer Optima 2100 unit. The solid structure and crystal size of calcined samples were analyzed by X-ray diffraction (XRD) in the range of $2\theta = 10–70°$ using a Shimadzu XD-D1 diffractometer and Ni-filtered Cu Kα radiation. Mean crystallite size were calculated using the Scherrer equation.

The metal dispersion (D_M, surface M atoms/total M atoms) of Ni/SiO_2, and Ru/SiO_2 catalysts was determined by hydrogen chemisorption. Volumetric adsorption experiments were performed at room temperature in a conventional vacuum unit. Samples were reduced in H_2 at 673 K for 2 h and then outgassed 2 h at 673 K prior to performing gas chemisorption experiments. Hydrogen uptakes were determined using the double isotherm method as detailed elsewhere [24]. A stoichiometric atomic ratio of H/$M_s = 1$, where M_s implies a metal atom on surface, were used to calculate D_M.

The temperature programmed reduction (TPR) experiments of calcined samples were carried out in a Micromeritics AutoChem II 2920, using 5% H_2/Ar gaseous mixture at 60 cm^3 STP /min. Samples (150 mg) were heated from 298 to 973 K at 10 K/min. Since water is formed during sample reduction, the gas exiting from the reactor was passed through a cold trap before entering the thermal conductivity detector.

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The carbon amount deposited on the catalysts during the catalytic tests were measured by temperature-programmed oxidation (TPO). Samples (22 mg) were heated in a 2% O_2/N_2 stream at 10 K/min from room temperature to 1073 K. The evolved CO_2 was converted to methane by means of a methanation catalyst (Ni/kieselghur) operating at 673 K and monitored using a flame ionization detector in an SRI 8610C gas chromatograph.

2.3. Catalytic activity

The liquid-phase reaction of butyronitrile (Aldrich, >99%) with primary [ethanol (Cicarelli, ACS), n-propanol (Cicarelli ACS), *iso*-butanol (Cicarelli ACS) or n-octanol (Merck)] and secondary [2-propanol (Cicarelli ACS), 2-butanol (Aldrich 99%) or 2-octanol (Aldrich 99%)] alcohols to produce ASA was carried out at 13 bar (H_2) in a Parr 4843 reactor at 383 K and 403 K. The reactor was loaded with 150 mL of BN/alcohol mixtures, 1.0 g of catalyst, and 1 mL of n-dodecane (Aldrich > 99%) as internal standard. Prior to catalytic tests, samples were reduced ex-situ in H_2 (60 mL/min) for 2 h at 673 K and loaded immediately to the reactor at room temperature under inert atmosphere. The reaction system was stirred at 800 rpm and heated to the reaction temperature at 2 K/min; the H_2 pressure was then rapidly increased to 13 bar to start the reaction.

The concentrations of BN and reaction products were determining during the reaction by ex-situ gas chromatography using a Agilent 6850 GC chromatograph equipped with flame ionization detector, temperature programmer and a 50 m HP-1 capillary column (50 m × 0.32 mm ID, 1.05 μm film). Product identification was previously achieved using a GC–MS Thermo Scientific unit (Trace GC 1300/ISQ Single quadrupole). Samples from the reaction system were taken by using a loop under pressure in order to avoid flashing. Data were collected every 15–40 min for 300–600 min. The batch reactor was assumed to be perfectly mixed. We verified that the catalytic activity results were obtained under kinetically controlled regime in the reaction conditions used in this work (stirring speeds of 700 rpm and particle diameters of commercial silica Sigma-Aldrich G62 between 74 and 150 μm). The quantitative criteria described by Ramachandran and Chaudhari [25] were used to analyze the significance of gas-liquid, liquid-solid and intraparticle mass transfer on the reaction kinetics. Selectivities (S_j, mol of product *j*/mol of butyronitrile reacted) were calculated as $S_j = C_j \nu_{BN} / \left(C^0_{BN} - C_{BN}\right) \nu_j$ where C_j and C_{BN} are the concentrations of product *j* and butyronitrile at time *t*, respectively, $C^0_{BN}$is the initial concentration of butyronitrile and ν_{BN} and ν_j are the stoichiometric coefficients of butyronitrile and product *j*, respectively. Yields (Y_j, mol of product *j*/mol of butyronitrile fed) were calculated as $Y_j = S_j X_{BN}$, where X_{BN} is the butyronitrile conversion.

3. Results and discussion

3.1. Catalyst characterization

The results of catalyst characterization by different techniques are given in Table 1. The metal content of Ni/SiO_2 and Co/SiO_2 was about 10 wt% while the Ru load in Ru/SiO_2 was 1.8 wt%. The surface area (300 m^2/g) of silica support did not change significantly after the metal impregnation and the consecutive oxidation/reduction steps used for obtaining metal/SiO_2 catalysts. The XRD diffractograms of calcined samples are shown in Fig. 1. Only polycristalline NiO (ASTM 4-835), Co_3O_4 (ASTM 9-418) and RuO_2 (ASTM 21-1172) were identified on Ni/SiO_2, Co/SiO_2 and Ru/SiO_2 catalysts, respectively. The oxide particle sizes determined using the Debye-Scherrer equation were about 12 nm for NiO and Co_3O_4; the RuO_2 XRD signal obtained on Ru/SiO_2 was too weak for measuring precisely the RuO_2 particle size.

Fig. 2 shows the TPR profiles of calcined samples. In the case of Ni/SiO_2 a broad asymmetric reduction band with a maximum at 643 K was observed. According to literature [26,27] this peak arises from the direct reduction to Ni^0 of large particles of bulk NiO interacting weakly with the silica support. No reduction peaks at higher temperatures that would reveal the presence of less reducible Ni phyllosilicate-type compounds [28,29] was observed. The Co/SiO_2 TPR curve showed two reduction peaks at 573 K and 623 K, respectively, which result from the reduction of Co_3O_4 following the sequence $Co^{3+} \rightarrow Co^{2+} \rightarrow Co^0$ [30]. The TPR profile of Ru/SiO_2 exhibited two superimposed H_2 consumption peaks at 461 K and 488 K, respectively, that probably reflect the existence of a bimodal distribution of particle sizes. Qualitatively, similar TPR profiles have been reported in literature for Ru-supported catalysts obtained by using $RuCl_3$ precursors [31]. On the basis of the temperature maxima determined from the TPR profiles of Fig. 2, we infer that the metal fraction of the catalysts used in this work was totally in the metallic state following the catalyst reduction procedure performed before the catalytic runs (treatment in pure H_2 at 673 K). The accessible metal fraction of reduced Ni/SiO_2 and Ru/SiO_2 was determined by selective H_2 chemisorption (Table 1). D_{Ni} on Ni/SiO_2 was only about 1%, which is consistent with the large NiO crystallite sizes determined from the XRD diffractograms in Fig. 1. The Ru dispersion determined on Ru/SiO_2 was also low, about 2%, and is consistent with previous work showing that preparation of silica-supported metal catalysts by incipient

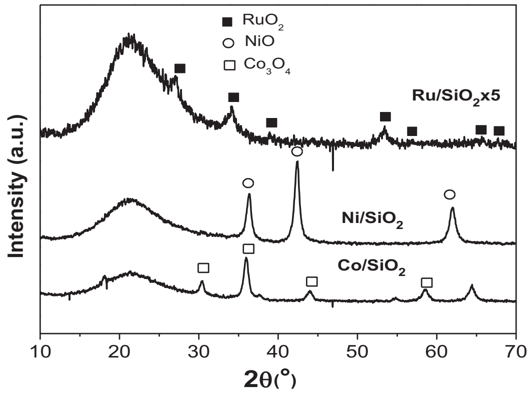

Fig. 1. X-ray diffractograms of Ni/SiO_2, Co/SiO_2 and Ru/SiO_2 samples.

Table 1
Catalyst characterization.

Catalyst	Metal loading[a] (wt%)	S_{BET} (m^2/g)	H_2 chemisorption (L STP/ mol metal)	Metal dispersion[b] D_M (%)	Oxide particle size[c] (nm)	Metal particle size[c] (nm)	TPR, T_{max} (K)
Ru/SiO_2	1.8	280	0.18	2	–	–	461, 488
Ni/SiO_2	10.5	290	0.14	1	12.1 (NiO)	13.7 (Ni^0)	643
Co/SiO_2	9.8	307	–	–	12.0 (Co_3O_4)	13.9 (Co^0)	573, 623

[a] Determined by ICP-AES.
[b] Determined from H_2 chemisorption.
[c] Determined by XRD.

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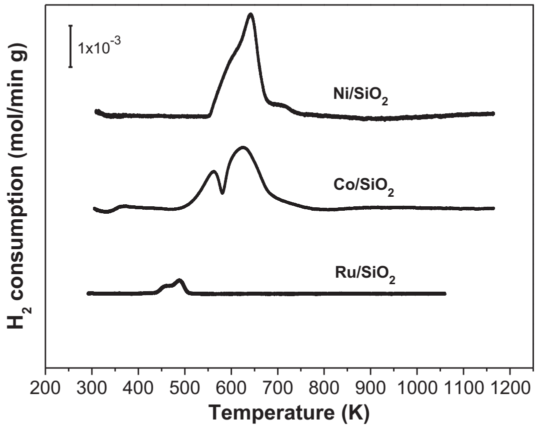

Fig. 2. TPR characterization of metal/SiO$_2$ catalysts. Heating rate: 10 K/min, W = 150 mg.

wetness impregnation leads to the formation of large metal crystallites [32,33].

3.2. Catalyst selection

In the reaction network of alcohol amination with BN (Scheme 1), BN is hydrogenated to butylamine (BA) via a butylimine intermediate that may interact with BA to give by deamination the secondary imine, butylidene-butylamine (BBA), which is further hydrogenated to dibutylamine (DBA), the symmetric secondary amine. The aldehyde or ketone formed by dehydrogenation of the corresponding primary or secondary alcohol, respectively, reacts with adsorbed BA species to yield by dehydration an asymmetric secondary imine that is consecutively hydrogenated to ASA.

The synthesis of ASA was initially studied on Co, Ni and Ru supported on SiO$_2$, using BN and ethanol as reactants. Results obtained at 383 K and 13 bar are presented in Fig. 3 that shows the evolution of BN conversion and yields with the progress of the reaction. Ru/SiO$_2$ converted completely BN after 400 min of reaction (Fig. 3A) and formed preponderantly butylamine at the end of the run ($Y_{BA} = 66\%$) together with significant amounts of dibutylamine ($Y_{DBA} = 25\%$). Butylidene-butylamine (BBA) was formed at the beginning of the reaction and then went through a maximum because was consecutively hydrogenated to DBA as depicted in Scheme 1. Ru/SiO$_2$ did not form the asymmetric secondary amine (N-ethylbutylamine), thereby showing that Ru does not promote the BN/ethanol reaction at 383 K. Ni/SiO$_2$ was more active than Ru/SiO$_2$ and converted completely BN after 100 min of reaction (Fig. 3B). Nevertheless, Ni/SiO$_2$ did not promote either the synthesis of any product coming from the reaction between BN and ethanol and thereby formed only BA, BBA and DBA via the BN hydrogenation-condensation pathways. In contrast, Fig. 3C shows that the Co/SiO$_2$ catalyst formed ASA from BA and ethanol producing a mixture of ASA ($Y_{ASA} = 30.5\%$), BA ($Y_{BA} = 42.3\%$) and DBA ($Y_{DBA} = 25.6\%$) at the end of the catalytic run. In an attempt to improve the ASA yield, an additional catalytic run was performed on Co/SiO$_2$ by increasing the temperature to 403 K (Fig. 3D). The results in Fig. 3D show that BA was rapidly formed from BN hydrogenation and then went through a maximum because was consecutively converted into ASA by reaction with ethanol. At the end of the 5-h run, BA was completely converted and the reaction mixture contained only ASA (64.0%) and DBA (31.3%).

The results in Fig. 3 show that at 383 K Co/SiO$_2$ promotes the formation of N-ethylbutylamine from ethanol amination with BN, while Ni/SiO$_2$ and Ru/SiO$_2$ are inactive to produce the asymmetric secondary amine. In a previous work [17], we studied the hydrogenation of BN in ethanol at$P_{H_2} = 13$ bar and 373 K on silica-supported Co, Ni and Ru catalysts and observed that Co/SiO$_2$ and Ni/SiO$_2$ formed efficiently BA at similar rates producing (BA + DBA) mixtures with about 85% BA at $X_{BN} = 100\%$; Ru/SiO$_2$ formed also preponderantly BA although was less active than Co and Ni catalysts. The selective formation of BA from BN hydrogenation on Co, Ni and Ru has been explained by considering that BN is adsorbed onto these metals via nitrene intermediates forming strong metal = N bonds that reduce the mobility of nitrene intermediates and stimulate fast hydrogenation of the carbon atom in the nitrile group, which prevents the surface condensation steps leading to secondary and tertiary amines [13,34,35]. These results show that the three metals can efficiently produce the adsorbed BA intermediate species required to react with surface ethanol-derived species and form N-ethylbutylamine. The superior catalytic performance exhibited by Co/SiO$_2$ as compared to Ni/SiO$_2$ or Ru/SiO$_2$ to produce ASA would not be related then with a different ability to promote the BN hydrogenation step towards BA, but with the reaction pathway involving the initial parallel alcohol dehydrogenation step to form a carbonyl adsorbed species which reacts consecutively with adsorbed BA to yield the asymmetric secondary imine (Scheme 1). In previous work, Co, Ni and Ru metals have been employed to promote the liquid-phase ethanol dehydrogenation to acetaldehyde [36,37]. In particular, Zaffran et al. [38] investigated the alcohol dehydrogenation mechanism on transition metals by DFT calculations and presented linear energy relations derived from the Brønsted-Evans-Polanyi principle for a series of CH and OH bond scissions in simple alcohol molecules on Co, Ni and Ru. DFT calculations predicted that the activation energy of the C-H bond dissociation on the metal surface with abstraction of an α-hydrogen is lower on Co than on Ru and Ni, which is consistent with the catalytic results presented here in Fig. 3.

In summary, results in Fig. 3D show that Co/SiO$_2$ is an efficient catalyst to produce selectively N-ethylbutylamine at 403 K from the one-step reaction between butyronitrile and ethanol. We decided therefore to employ Co/SiO$_2$ for investigating in detail the synthesis of ASA from BN and other primary and secondary alcohols.

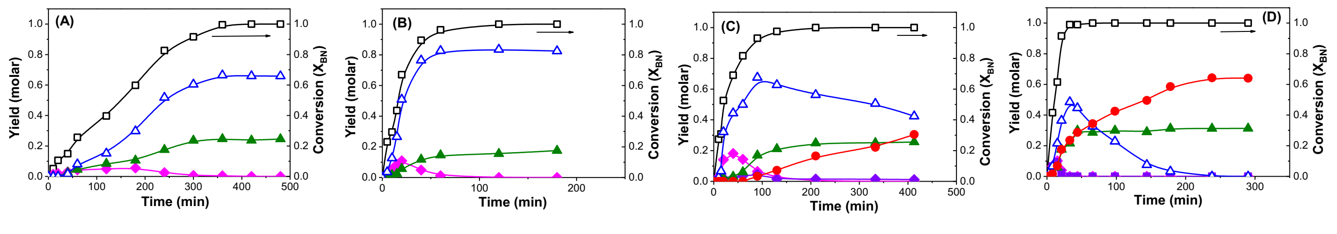

Fig. 3. Asymmetric secondary amine (ASA) synthesis from butyronitrile and ethanol on Ru/SiO$_2$ (A), Ni/SiO$_2$ (B), Co/SiO$_2$ (C) at 383 K, and on Co/SiO$_2$ at 403 K (D). Butyronitrile conversion (X_{BN}) and yields (Y_i): ● ASA, ▲ Dibutylamine (DBA), △ Butylamine (BA), ◆ Butylidene-butylamine (BBA) ■ Asymmetric secondary imine (ASI). [P_{H_2} = 13 bar, V = 150 mL, C^0_{BN} = 0.0767 mol/L, W_{cat} = 1 g].

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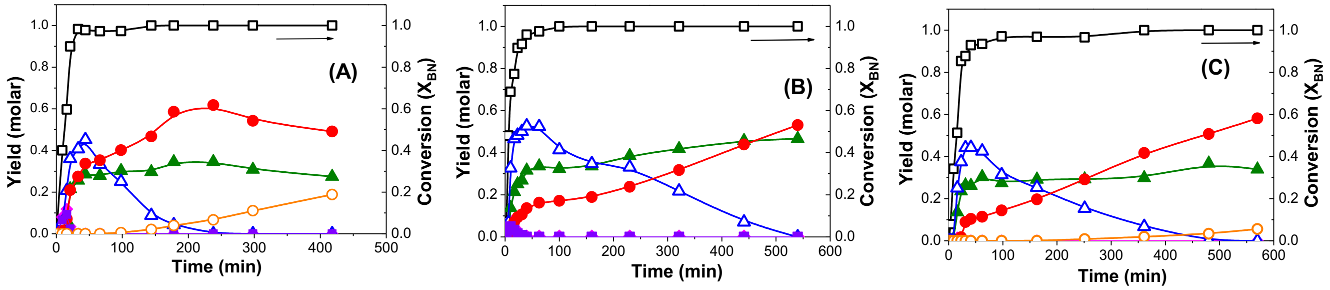

Fig. 4. Asymmetric secondary amines (ASA) synthesis from butyronitrile and primary alcohols: (A) n-propanol, (B) isobutanol, (C) n-octanol. Butyronitrile conversion (X_{BN}) and yields (Y_i): ● ASA, ▲ Dibutylamine (DBA), △ Butylamine (BA), ◆ Butylidene-butylamine (BBA), ■ Asymmetric secondary imine (ASI), ○ Asymmetric tertiary amines (ATA). [Catalyst: Co/SiO$_2$, T = 403 K, P_{H_2} = 13 bar, V = 150 mL, C^0_{BN} = 0.0767 mol/L, W_{cat} = 1 g.

3.3. ASA synthesis from BN and primary alcohols

The synthesis of ASA from BN and primary alcohols (n-propanol, *iso*-butanol and n-octanol) was studied at 403 K on Co/SiO$_2$; results are presented in Fig. 4. In order to quantitatively compare the catalyst activity and yields values of Fig. 4 we determined the initial BN conversion (r^0_{BN}, mmol/h g) and ASA formation (r^0_{ASA}) rates, and the values of X_{BN} and Y_j at the end of the runs; data are presented in Table 2. The r^0_{BN} and r^0_{ASA}values were determined from X_{BN} and Y_{ASA} curves of Fig. 4, respectively, by polynomial regression and numerical differentiation extrapolated to zero time according to:

$$r^0_{BN} = \frac{n^0_{BN}}{W_{cat}}\left[\frac{dX_{BN}}{dt}\right]_{t=0} \quad \text{and} \quad r^0_{ASA} = \frac{n^0_{BN}}{W_{cat}}\left[\frac{dY_{ASA}}{dt}\right]_{t=0}$$

where n^0_{BN} and W_{cat} are the initial moles of BN and the catalyst loading, respectively.

Let us first analyze the results obtained for BN/n-propanol reaction (Fig. 4A). BN was totally hydrogenated to BA in 30 min, probably via a highly reactive butylimine intermediate as shown in Scheme 1. Secondary imine BBA was formed from the condensation/deamination reaction between adsorbed butylimine and BA, and then was rapidly hydrogenated to DBA, the symmetric secondary amine. On the other hand, the N-alkylation of BA with adsorbed n-propanal species formed via dehydration the asymmetric secondary imine (ASI) that was rapidly hydrogenated to ASA (N-propylbutylamine). BA was completely converted after 250 min of reaction. ASA increased with the progress of the reaction reaching a maximum at about 250 min (Y_{ASA} = 62%) and then decreased because of its alkylation with n-propanol to yield N,N-dipropylbutylamine, the asymmetric tertiary amine (ATA). At the end of the 420-min run the reaction mixture contained ASA (49%), DBA (28%) and ATA (N,N-dipropylbutylamine 14%, N,N-dibutylpropylamine 5%).

Data in Table 2 show that the BN conversion rate (r^0_{BN} = 32.8 mmol/g h) was about six-times higher than the ASA formation rate (r^0_{ASA} = 5.5 mmol/g h), thereby revealing that the BN hydrogenation to BA was clearly faster than the BA alkylation with n-propanol.

The evolution of Y_i vs *t* curves for the reactions of BN with *iso*-butanol (Fig. 4B) and n-octanol (Fig. 4C) were qualitatively similar to those observed in Fig. 4A for BN/n-propanol reaction, indicating that DBA and ASA are obtained from BN and primary alcohols via the same reaction mechanism. Nevertheless, data in Table 2 show that reaction kinetics depended on the primary alcohol size; r^0_{ASA} followed, in fact, the order n-propanol > *iso*-butanol > n-octanol and longer reaction periods (about 500 min) were required to completely convert BA, the key intermediate molecule in the reaction network of Scheme 1, to ASA using *iso*-butanol and n-octanol as reactants. Furthermore, the r^0_{BN}/r^0_{ASA} ratio was 6.0 for n-propanol and augmented to 8.8 and 21.5 for *iso*-butanol and n-octanol, respectively (Table 2). At the end of the runs, Y_{ASA} was 53% (*iso*-butanol) and 58% (n-octanol), thereby confirming that ASA was the main product formed from the BN/primary alcohol reaction on Co/SiO$_2$ catalysts.

3.4. ASA synthesis from BN and secondary alcohols

The results obtained for the ASA synthesis from N-alkylation of BN with secondary alcohols are presented in Fig. 5 and Table 2. In the case of BN/2-propanol reaction (Fig. 5A), BN was completely converted after 60 min reaction and BA was detected at the beginning of the reaction in small amounts only because it was rapidly converted to DBA and ASI. ASI, the asymmetric secondary imine formed on the Co surface from reaction between adsorbed BA and 2-propanal species, went through a maximum as it was consecutively hydrogenated to ASA. The reaction was completed after 200 min giving a mixture of ASA (Y_{ASA} = 85%) and DBA (Y_{DBA} = 12%); the ASA yield was then clearly higher than that obtained in the BN/n-propanol reaction (Y_{ASA} = 49%). On the other hand, the initial ASA formation rate was r^0_{ASA} = 12.9 mmol/g h, significantly higher than that determined with n-propanol

Table 2
ASA synthesis by reaction of butyronitrile with primary and secondary alcohols.

Alcohol	r^0_{BN}(mmol/g h)	r^0_{ASA}(mmol/g h)	X_{BN}[a] (%)	Yield[a]				
				Y_{BA}	Y_{DBA}	Y_{ASA}	Y_{ATA}	Y_{Others}
n-Propanol	32.8 ± 0.3	5.5 ± 0.4	100	0	0.28	0.49	0.19	0.04
iso-Butanol	34.2 ± 0.4	3.9 ± 0.4	100	0	0.42	0.53	0	0.05
n-Octanol	25.8 ± 0.6	1.2 ± 0.2	100	0	0.34	0.58	0.05	0.03
2-Propanol	40.1 ± 0.3	12.9 ± 0.3	100	0	0.12	0.85	0	0.03
2-Butanol	42.7 ± 0.5	9.1 ± 0.3	100	0	0.14	0.85	0	0.01
2-Octanol	35.2 ± 0.6	5.9 ± 0.4	100	0	0.19	0.78	0	0.03

Catalyst: Co/SiO$_2$, T = 403 K, P = 13 bar, V = 150 mL, C^0_{BN} = 0.0767 mol/L, W_{cat} = 1 g.

[a] Results obtained at the end of the runs.

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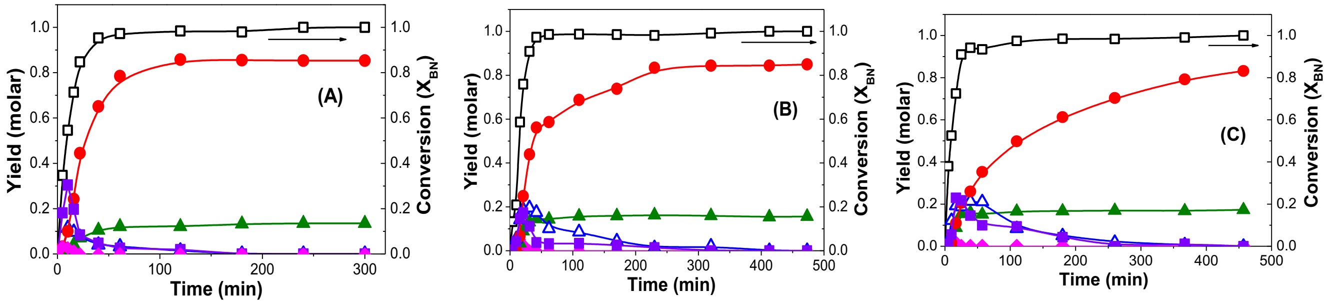

Fig. 5. Asymmetric secondary amines (ASA) synthesis from butyronitrile and secondary alcohols: (A) 2-propanol, (B) 2-butanol, (C) 2-octanol. Butyronitrile conversion (X_{BN}) and yields (Y_i): ● ASA, ▲ Dibutylamine (DBA), △ Butylamine (BA), ◆ Butylidene-butylamine (BBA), ■ Asymmetric secondary imine (ASI). Reaction conditions as in Fig. 4.

(r^0_{ASA} = 5.5 mmol/g h). The X_{BN} vs t and Y_i vs t curves obtained for BN/2-butanol (Fig. 5B) and BN/2-octanol (Fig. 5C) reactions were qualitatively similar to those observed for BN/2-propanol in Fig. 5A. The ASA yields obtained for BN/2-butanol (85%) and BN/2-octanol (78%) were comparable to that of BN/2-propanol (85%), but the ASA formation rate depended on the alcohol size, following r^0_{ASA} the order 2-propanol > 2-butanol > 2-octanol. Overall, the results of Fig. 4, Fig. 5 and Table 2 show that the synthesis of ASA is more selective and efficient when BN reacts with a secondary alcohol than with the primary alcohol of the same carbon atom number. Indeed, the ASA yields obtained here for BN/secondary alcohol reactions varied between 78% and 85% whereas those determined for BN/primary alcohols were in the 49–58% range. Furthermore, it is significant noting that the ASA formation rate was clearly higher when using secondary alcohols. In fact, from the values of Table 2, we observe that the r^0_{ASA} ratios for secondary/primary alcohols of the same carbon atom number, $(r^0_{ASA})^s/(r^0_{ASA})^p$, was 2.3 for 2-propanol/n-propanol and 2-butanol/*iso*-butanol, and 4.9 for 2-octanol/n-octanol. These latter results probably reflect the fact that aliphatic secondary alcohols are better hydrogen donors than the aliphatic primary alcohols with the same carbon atom number because dialkyl ketones have higher reduction potential than aldehydes [39,40]. Dehydrogenation of secondary alcohols on the metal surface of the catalyst forms adsorbed hydride and ketone-type species that react with adsorbed BA releasing a water molecule to give by condensation ASI which is finally hydrogenated to ASA by the surface hydride species. A higher coverage of the Co surface by ketone-type species than by aldehydic-type species would explain therefore the higher r^0_{ASA} values obtained in secondary alcohols as compared to primary alcohols. Consistently, the BA concentrations observed in BN/secondary alcohol reactions were clearly lower than those determined in the corresponding BN/primary alcohol reactions, which probably reflects that adsorbed BA species are more rapidly converted to the asymmetric secondary imine in secondary alcohols because of the higher concentration of surface carbonyl-type species formed from secondary alcohols. In summary, our results of Fig. 5 show that Co/SiO_2 promotes efficiently the synthesis of ASA by BN alkylation with secondary alcohols (2-propanol, 2-butanol and 2-octanol) yielding selectively (ASA + DBA) mixtures that contain 78–85% of ASA. It is important noting that the boiling point of DBA at 1.013 bar (432.6 K) is significantly higher than that of isopropylbutylamine (401.1 K), the ASA obtained in 2-propanol/BN reaction, and of N-*sec*-butyl-1butanamine (424.7 K) the ASA produced in 2-butanol/BN reaction, which allows to obtain pure ASA from the (DBA + ASA) mixtures by distillation.

The effect of BN concentration on the reaction kinetics and yields was investigated for 2-propanol and 2-butanol. The initial BN concentration was changed while maintaining unmodified the rest of the operating conditions. Results are presented in Table 3 and show that the Y_{ASA} value obtained at the end of the runs decreased when C^0_{BN} was increased for both alcohols. Regarding the reaction kinetics, it is observed in Table 3 that r^0_{BN} and r^0_{ASA} continuously decreased by increasing C^0_{BN}. In order to quantify the effect of BN concentration on the initial rates of BN conversion and ASA formation, the experimental data were interpreted by considering a power-law rate expression (Eq. (1))

$$r^0_i = k\left(C^0_{BN}\right)^{\alpha}\left(C^0_j\right)^{\beta} \tag{1}$$

where i is BN or ASA, and j is 2-propanol or 2-butanol. Reaction orders α were determined graphically from the r^0_i vs C^0_{BN} logarithmic plots that are given in Supporting Information (Fig. SI1) for both secondary alcohols. In all the cases, a negative order with respect to BN was determined. The values of α in 2-propanol were −0.10 and −0.23 for r^0_{BN} and r^0_{ASA}, respectively, whereas in 2-butanol the corresponding orders in BN were −0.15 and −0.66. These results show that the alkylation of BN with secondary alcohols on Co/SiO_2 is negative order in BN, which suggests that the strong adsorption of BN-derived nitrene intermediates on the metal would increasingly block the accessible surface sites for the alcohol adsorption as C^0_{BN} is augmented, thereby decreasing the ASA formation rate.

The apparent activation energies (E_a) of r^0_{BN} and r^0_{ASA} for BN/2-propanol reaction on Co/SiO_2 were obtained via an Arrhenius-type function, by plotting ln r^0_i as a function of 1/T (Fig. SI2 in Supporting Information). The experiments were carried out in the 383–413 K range. From the slopes of the resulting linear plots we determined E_a values of 26.1 kJ/mol and 30.6 kJ/mol for r^0_{BN} and r^0_{ASA}, respectively. The higher E_a value obtained for r^0_{ASA} is consistent with the results presented in Table 2 showing that, at a given C^0_{BN} value, r^0_{ASA} was significantly lower than r^0_{BN} for all the BN/alcohol reactions investigated in this work.

Finally, it is worth noting that the conventional synthesis of ASA by N-alkylation of primary amines with alcohols has been widely studied in absence of hydrogen via a borrowing-hydrogen or hydrogen-autotransfer strategy [9,41,42,43], in which the hydrogen required for the final reaction step (hydrogenation of ASI to ASA) is furnished by hydrogen transfer from the alcohol molecule. In order to compare the synthesis of ASA from N-alkylation of BN or BA with a secondary alcohol we carried out the BA/2-propanol reaction on Co/SiO_2 under the same conditions used for BN/2-propanol reaction in Fig. 5A, but in absence of hydrogen. In Fig. 6 we show the results obtained for the N-alkylation of BA with 2-propanol; the reaction was completed after 550 min and formed a product mixture containing 89% of ASA and 9% DBA. The ASA formation rate determined from the Y_{ASA} vs t curve of Fig. 6 was r^0_{ASA} = 2.4 mmol/g h, significantly lower than that obtained for BN/2-propanol reaction in Fig. 5A (12.9 mmol/g h). In summary,

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Table 3
N-alkylation of BN with 2-propanol and 2-butanol: Effect of BN concentration.

Alcohol	C^0_{BN} (mol/L)	r^0_{BN} (mmol/g h)	r^0_{ASA} (mmol/g h)	X_{BN}[a] (%)	Yield[a]			
					Y_{BA}	Y_{DBA}	Y_{ASA}	Y_{Others}
2-Propanol	0.077	40.1	12.9	100	0	0.12	0.85	0.03
2-Propanol	0.231	38.7	10.7	100	0	0.21	0.77	0.02
2-Propanol	0.385	33.6	8.8	100	0	0.24	0.73	0.03
2-Butanol	0.076	42.7	9.1	100	0	0.14	0.85	0.01
2-Butanol	0.224	38.2	5.1	100	0	0.21	0.78	0.01
2-Butanol	0.715	30.3	2.1	100	0.13	0.31	0.48	0.08

Catalyst: Co/SiO$_2$, T = 403 K, P = 13 bar, W_{cat} = 1 g; C^0_{IPA} = 12.99 mol/L, C^0_{2-but} = 10.87 mol/L.
[a] Results obtained at the end of the runs.

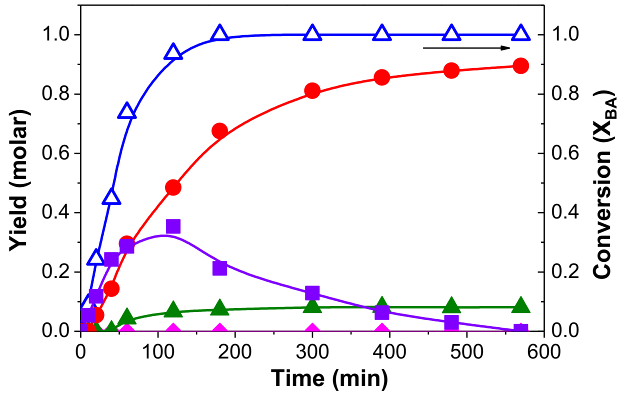

Fig. 6. ASA synthesis from butylamine and 2-propanol. Butylamine conversion (X_{BA}) and yields (Y_i): ● ASA, ▲ Dibutylamine (DBA), ◆ Butylidene-butylamine (BBA), ■ Asymmetric secondary imine (ASI). [Catalyst: Co/SiO$_2$, T = 403 K, P_{N_2} = 3 bar, V = 150 mL, C^0_{BA} = 0.0767 mol/L, W_{cat} = 1 g]

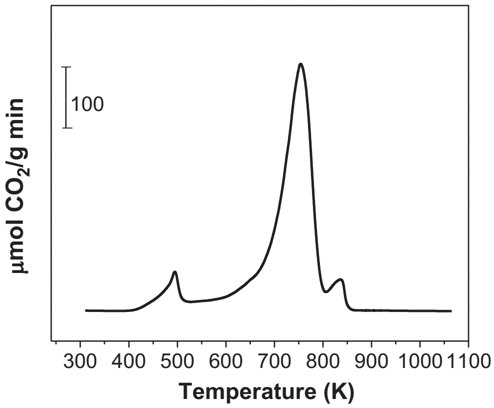

Fig. 8. TPO profile of Co/SiO$_2$ recovered after the first catalytic run showed in Fig. 7. Heating rate, 10 K/min.

the results of Fig. 5A and 6 show that ASA is formed on Co/SiO$_2$ from BN/2-propanol at similar yield but higher rate than from the conventional BA/2-propanol reaction in absence of hydrogen

3.5. Catalyst reuse

The possibility of reusing Co/SiO$_2$ for the synthesis of ASA from BN and 2-propanol was evaluated by performing three consecutive catalytic tests and regenerating the catalyst at the end of the runs; results are presented in Fig. 7. The following catalyst regeneration procedure was employed: i) the catalyst was recovered by filtration after the BN/2-propanol reaction, dried at 373 K for 12 h and calcined in air (60 cc/min) for 2 h at 773 K; ii) then the catalyst was reduced ex-situ in H$_2$ at 673 K for 1 h and loaded to the reactor under inert atmosphere to perform the next catalytic run. A small part (22 mg) of the Co/SiO$_2$ sample recovered after the first catalytic run was characterized by TPO technique to determine the carbon amount formed during the reaction. The obtained TPO profile is presented in Fig. 8 that shows that the coke burnt gave rise to a main asymmetric band with a maximum at 750 K and two small additional peaks at 495 K and 836 K, respectively. The amount of carbon determined from the area under the TPO curve in Fig. 8 was 3.5%. In basis of the TPO profile in Fig. 8, we inferred that the carbon deposits were completely oxidized and eliminated after the catalyst regeneration procedure employed in this work (catalyst calcination in air at 773 K for 2 h).

The results in Fig. 7 show that the X_{BN} vs *t* and Y_i vs *t* curves were qualitatively similar in the three consecutive catalytic runs, forming a mixture containing only ASA and DBA at the end of the runs. Quantitative data to compare the Co/SiO$_2$ activity and selectivity were obtained from Fig. 7 and are presented in Table 4. At the end of the three catalytic runs, X_{BN} was 100% and the values of Y_{ASA} and Y_{DBA} were about 83–85% and 14–17%, respectively, thereby showing that Co/SiO$_2$ may be regenerated and reused after reaction, maintaining its catalytic selectivity performance at full

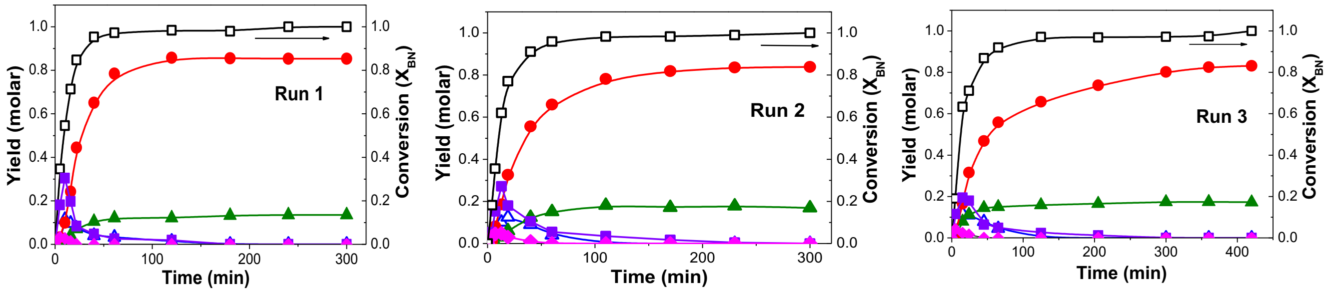

Fig. 7. Reuse of Co/SiO$_2$ in three consecutive catalytic tests for butyronitrile/2-propanol reaction. Butyronitrile conversion (X_{BN}) and yields (Y_i): ● Asymmetric secondary amine (ASA), ▲ Dibutylamine (DBA), △ Butylamine (BA), ◆ Butylidene-butylamine (BBA), ■ Asymmetric secondary imine (ASI). Reaction conditions as in Fig. 4.

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Table 4
Reuse of Co/SiO_2 for synthesis of ASA from BN and 2-propanol.

Catalytic Runs	r^0_{BN} (mmol/g h)	r^0_{ASA} (mmol/g h)	X_{BN}[a](%)	Yields[a]			
				Y_{BA}	Y_{DBA}	Y_{ASA}	Y_{Others}
Run 1	40.7	12.9	100	0	0.14	0.85	0.01
Run 2	34.2	10.8	100	0	0.16	0.83	0.01
Run 3	26.4	8.4	100	0	0.17	0.83	0

Catalyst: Co/SiO_2, T = 403 K, P = 13 bar, V = 150 mL, C^0_{BN} = 0.0767 mol/L, W_{cat} = 1 g.
[a] Results obtained at the end of the runs.

BN conversion. Nevertheless, the values of r^0_{BN} and r^0_{ASA} in Table 4 revealed that the catalyst activity decreased about 20% following every run/regeneration cycle. This activity drop was not caused by cobalt leaching during the catalytic runs as we verified by ICP analysis that the Co content of Co/SiO_2 sample recovered after Run 3 (Fig. 7) was practically the same than that of the fresh one. In Supporting Information, we compared the XRD diffractogram of fresh Co/SiO_2 with that of the catalyst recovered after Run 1 (Fig. SI3). Co_3O_4 was the only crystalline phase observed in both samples. No traces of the formation of cobalt carbide or nitride species were detected for spent Co/SiO_2 sample; in previous work [44] it has been reported that these species may be formed when contacting aliphatic amines with Ni or Co catalysts in absence of hydrogen, which provokes the in-situ catalyst deactivation for amine disproportionation reactions. From the diffractograms of Fig. SI3, we determined that the mean crystallite size of Co_3O_4 mixed oxide in spent Co/SiO_2 sample (13.2 Å) was greater than in fresh Co/SiO_2 (12.0 Å). Besides, in Fig. SI4 we show the XRD diffractograms of reduced fresh and spent Co/SiO_2 catalysts; the Co metal particle sizes were 13.7 Å (fresh) and 15.2 Å (spent), thereby suggesting that Co sintering took place during catalytic Run 1. From all these results, it is inferred that the catalytic activity loss observed in Table 4 when reusing the Co/SiO_2 catalyst probably reflects the loss of accessible Co surface active sites by coke deposition and sintering of the metallic phase.

4. Conclusions

The one-pot synthesis of asymmetric secondary amines (ASA) from N-alkylation of nitriles with alcohols is efficiently achieved on Co/SiO_2 catalysts. Here, we show that the alkylation of butyronitrile with secondary alcohols (2-propanol, 2-butanol and 2-octanol) on Co/SiO_2 yields selectively (ASA + dibutylamine) mixtures containing 78–85% of ASA. The butyronitrile alkylation with primary alcohols (n-propanol, *iso*-butanol, n-octanol) yields 49–58% of ASA at lower rates than with the secondary alcohol of the same carbon atom number. Co/SiO_2 is easily regenerated after the BN/alcohol reaction by carbon oxidation with air at mild temperatures and may be reused maintaining the selectivity to ASA at complete BN conversion.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.10.011.

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