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A kinetic investigation into the removal of carbobenzyloxy group from protected amines via hydrogenolysis reaction

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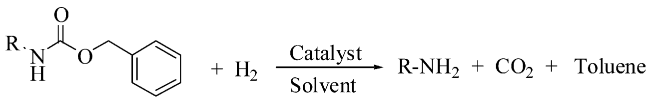
Abstract

Hydrogenolysis of a carbobenzyloxy group (CBz) was studied utilizing molecular hydrogen in the presence of carbon-supported palladium catalyst. It was demonstrated that the kinetics of the reaction are greatly influenced by the presence of the CO_2 by-product. It was found out that the presence of CO_2 determines whether the reaction is first or zero order since it causes deactivation of the catalyst via inhibition. The effect of potassium carbonate (K_2CO_3) and triethylamine (TEA) as additives was investigated. A considerable solvent effect was also observed that may be explained by the variation of dispersion of the catalyst from one solvent to another.

Keywords: CBz; K_2CO_3; TEA; Hydrogenolysis; Carbon dioxide

1. Introduction



Although deprotection of carbobenzyloxy groups (CBz) is a common and important reaction in organic synthesis [1,2], there are few published reports which provide understanding of the effects of reaction parameters ([2] and references therein [3–9]).

CBz deprotection reactions are typically conducted using supported palladium catalysts in the presence of molecular hydrogen. Other metals are not as effective as palladium. The preferred support is generally carbon, which provides higher activity than oxide supports [7].

It has been shown that additives have a significant impact on the reaction rate. Yamada et al. reported that the addition of water increases the reaction rate, as it refreshes the catalyst [5]. The addition of N-containing bases such as ethylenediamine and pyridine [8], ammonia, ammonium acetate, 2,2′-dipyridyl [3,10], or ethyelendiamine [9]; or modifying the palladium catalyst with hydroxyapatite [6] increase the reaction rate. The rate increase has been explained mainly as either resulting from a palladium-additive complex or from an increase in the basic character of the metal surface, thus making it more attractive for adsorption of acidic species such as protected amino acids [8].

In this study, the role of CO_2 was included into the kinetic discussion considering the headspace and concentration parameters. The effect of additives and solvents were also investigated.

2. Experimental

For all reactions 5% Pd/C, 50% wet catalyst was used (Escat 142, BASF Catalysts LLC). Surface area of the catalyst is 900 m^2/g. The palladium metal is pre-reduced and distributed on the edge of the pores of the support, i.e. edge distribution. This type of distribution minimizes the internal diffusion effects. Commercially available tetrahydrofuran (THF) or ethylacetate (EtOAc) solvents were used as received. An Endeavor Catalyst Screening System (Biotage) and RC1 (1 L, MP10) (Mettler-Toledo) were utilized for hydrogenolysis experiments. Hydrogen was maintained at a set pressure and hydrogen uptake was recorded. When the headspace is smaller than 40%, hydrogen uptake correlates well with the kinetics of

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the reaction which was also confirmed by calorimetry and FTIR. Headspace in the vessel was measured without agitation.

A React-IR 4000 (Mettler-Toledo) was used to monitor the reactions in an RC1 system. The peak at 2340 cm^{-1} was followed to determine the change of CO_2 in the liquid phase. The substrate and product peaks were also monitored.

The standard experimental condition is as follows; catalyst weight: 5 wt% of the substrate A (dry basis), concentration: 0.347 M, pressure of hydrogen: 20 psig and temperature: 25 °C. The standard reaction was performed under conditions where there is no external mass transfer effect. Prior to hydrogenation three nitrogen purges were followed by two hydrogen purges by increasing the pressure to 20 psig and venting down to 1 psig. Internal mass transfer effects were not fully investigated.

3. Effects of by-product CO_2 on to the kinetics of CBz deprotection reaction

Although the CBz deprotection of an amine is a widely known reaction, to our knowledge complications arising from the evolvement of CO_2 have not been investigated in detail. In the current study, presence of CO_2 was taken into account for the elucidation of effects of additives and change in reaction conditions.

3.1. Roles of headspace and concentration in relation to CO_2

During mechanistic investigation of the reaction, it became apparent that in addition to mass transfer and kinetic effects, the influence of the CO_2 for a given solvent and reactor fill level (headspace) should be carefully considered.

Experiments showed that external mass transfer coefficient above 0.07 s^{-1} resulted in the reaction being free of external mass transfer effects under standard conditions. Furthermore, it was established that neither the product nor the substrate causes any inhibition or catalyst poisoning. In order to examine this, first, a mixture of the product and catalyst in THF was stirred under nitrogen for 6 h prior to addition of the substrate which was then followed by hydrogenation. The reaction rate was the same as when the hydrogenolysis was conducted without pre-addition of the product. This suggests that product does not inhibit the reaction. Second, two reactions were conducted at two different substrate concentrations while the head space was kept significantly large in order to eliminate the effect of presence of carbon dioxide. The initial reaction rates were the same for both cases which also demonstrates that the reaction is in zero order in terms of substrate. Fig. 1 illustrates that as concentration of substrate changed from 0.11 M to 0.087 M, the initial reaction rate did not change. Furthermore, the residual palladium level in the solution after filtration was low (<5 ppm) suggesting that reaction is occurring on the catalyst surface rather than in the solution.

After investigating the effect of substrate and product on the reaction rate, the effect of the presence of carbon dioxide on the reaction rate was examined. It was found that the overall reaction rate is dependant on the concentration of the substrate, pressure, temperature, and the headspace of the reactor. Because all these parameters affect the concentration of the carbon dioxide in the liquid phase. Fig. 2 shows that the CO_2 % in the liquid phase changes as the headspace changes under the standard experimental conditions (20 psig of hydrogen and 25 °C) as calculated using VLE flash simulator. The figure emphasizes that the concentration of carbon dioxide in the reaction mixture increases as the head space volume decreases. Using calorimetry data and HPLC, the change in the reaction rate as a function of conversion at different reactor fill levels is demonstrated in Fig. 3a. From this data it is concluded that at the concentration of 0.347 M of substrate, the reaction is first order with 70% headspace, while at 25% headspace, it is zero order. A combination of zero and first orders is observed at 40% headspace. The highest reaction rate was observed at 70% headspace based on the calorimetry and HPLC data. Fig. 3a evidently shows that as the headspace changes without changing any other conditions, reaction rates and orders alter. Fig. 3b shows the corresponding hydrogen uptake at different fill levels. It should be noted that hydrogen uptake values are close to the theoretical uptake values for both 25% and 40% headspace, whereas the uptake is 25% less than that of the theoretical uptake for the 70% headspace. This further supports that as headspace increases, carbon dioxide % in the headspace increases, thus concentration of the carbon dioxide in the reaction mixture decreases. If the change in the reaction rates and orders were due to a change in the partial pressure of hydrogen, the same zero order behavior would be observed at

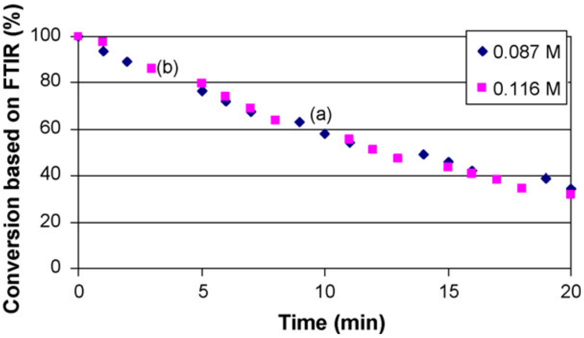

Fig. 1. Conversion as a function of time at 25 °C and 20 psig in THF solvent by monitoring SM by FTIR (a) 0.087 M substrate A concentration, 1 g cat./0.4 L and (b) 0.116 M substrate A concentration, 0.75 g cat./0.3 L.

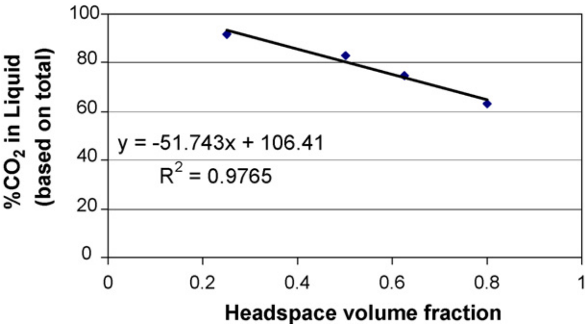

Fig. 2. % CO_2 in the liquid as a function of headspace in the absence of catalyst at 25 °C in THF.

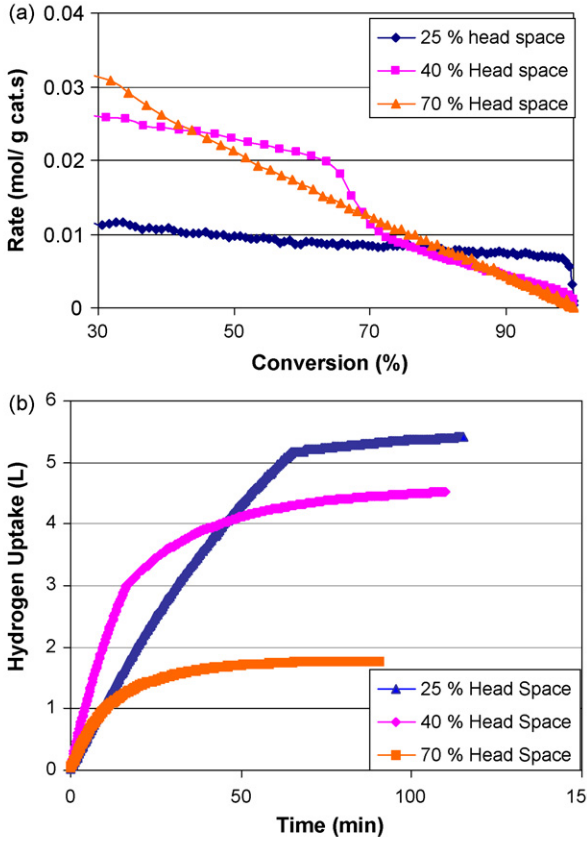

Fig. 3. (a) Change of rate as a function of conversion at different fill levels; (b) hydrogen uptakes as a function of time at different fill levels. Standard reaction conditions were applied for all the runs. 0.347 M of substrate A, 20 psig hydrogen and 25 °C and 5 wt% catalyst based on substrate.

the beginning of the reaction, when the concentration was decreased to half at 25% headspace. However, Fig. 4 shows that first order behavior was observed at 0.17 M concentration and at 25% headspace. In the light of Figs. 3b and 4, the zero order behavior for 25% and 40% headspace in Fig. 3a can be explained by the presence of a higher concentration of carbon dioxide in the liquid phase. It should be also noted that as concentration decreases in Fig. 4, reaction rate increases. This suggests the inhibition due to the presence of carbon dioxide, since the inhibition effects of substrate and product were eliminated, *vide ante*.

Once the inhibition effect in the presence of carbon dioxide was postulated, the possibility of deactivation of the catalyst by the inhibition was also investigated. It was shown in large-scale pilot plant runs that carbon dioxide (or species formed due to the presence of carbon dioxide) and hydrogen competitively adsorb on the catalyst surface at 0.347 M concentration, which may result in deactivation of the catalyst under certain conditions. Fig. 5a and b compares two reactions through FTIR profile for carbon dioxide and substrate over time using two different purging and hydrogen charging methods, which impacts the quantity of carbon dioxide in the liquid phase. In Fig. 5a, prior to hydrogenation, two-hydrogen purges were conducted at high agitation speed (tip speed: 4.4 m/s) and by feeding the hydrogen subsurface. The pressure of hydrogen was increased to 20 psig during each purge followed by venting to 1 psig. Since venting takes a long time in the plant, hydrogen concentration in the liquid phase is low as the purge cycles are conducted. On the other hand, reaction was already started since hydrogen was introduced subsurface and at high agitation

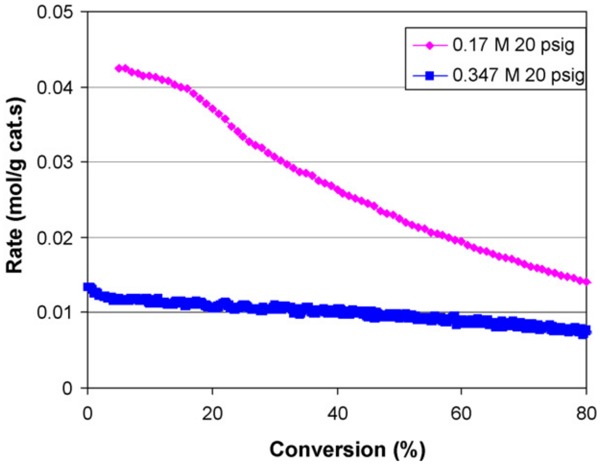

Fig. 4. Change of rate as a function of conversion at 25 °C and 25% head space at two different substrate A concentrations. Catalyst concentration: 3.75 g/ 750 mL.

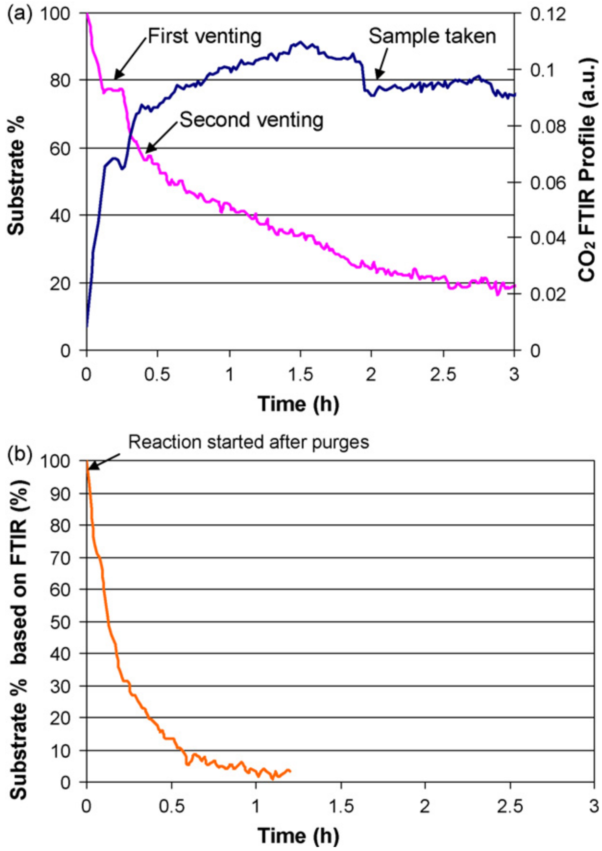

Fig. 5. Effect of purge protocol on the reaction rate (a) substrate % change by FTIR and FTIR profile for CO_2 as a function of time when two hydrogen purges were done at high agitation speed (tip speed: 4.4 m/s) and by feeding hydrogen subsurface; (b) substrate % change by FTIR as a function of time when hydrogen purges were conducted at low agitation speed (tip speed: 1.4 m/s) and by feeding hydrogen surface (reaction did not start during the purges).

speed and most of the formed carbon dioxide remained in the solution during the venting process. After introducing hydrogen at a pressure of 20 psig following these purges, the reaction rate was considerably slower than the reaction in Fig. 5b. After 2 h, the reaction stalled in Fig. 5a, whereas 100% conversion was achieved after 1 h in Fig. 5b. The experiment of Fig. 5a represents the ‘‘stressed’’ conditions of the typical conditions. Deactivation of the catalyst occurs due to the presence of carbon dioxide and the degree of the deactivation is determined by the concentration of hydrogen and substrate A (in other words carbon dioxide) in the solution.

It has been established up to now that the presence of carbon dioxide greatly affects the reaction rate. However, it is not known whether carbon dioxide or a species formed due to presence of carbon dioxide causes this behavior. Earlier reports suggest that carbon dioxide is not strongly adsorbed on the catalyst surface [12,13]. Therefore, catalyst deactivation via carbon monoxide inhibition can be prevented by oxidizing carbon monoxide to carbon dioxide. It may be considered that in the presence of hydrogen, it is possible to form carbon monoxide which causes deactivation for this CBz deprotection reaction. However, first, it should be pointed out that in the absence of hydrogen, more deactivation was observed. Second, the FTIR profile did not show any indication of presence of carbon monoxide during the reaction (Fig. 6). Furthermore, when THF was saturated with carbon dioxide in the presence of catalyst followed by introduction of hydrogen, no carbon monoxide was detected by FTIR. It may be argued that the level of the formed carbon monoxide is too low to be detected. However, it was also shown in Section 3.2 that when carbon dioxide is introduced to the reaction mixture prior to hydrogenation, reaction rate decreases considerably suggesting that deactivating species are formed in the absence of hydrogen. Further studies are in progress to elucidate whether carbon dioxide or a species derived from carbon dioxide is the deactivating species.

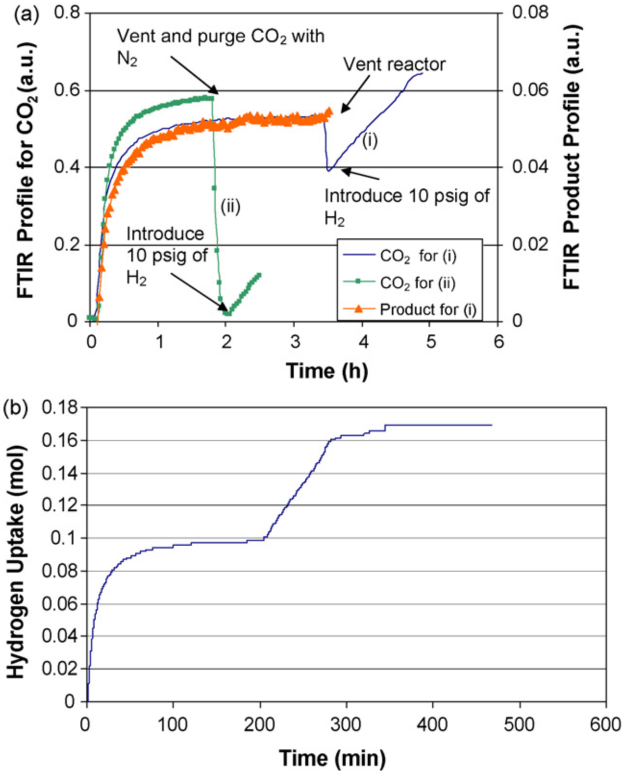

Fig. 7. (a) FTIR profiles for two different reactions under same conditions except once reaction slowed down (i) vented only, (ii) vented and purged with N_2 to remove CO_2; (b) hydrogen uptake for (a) (i). Reaction conditions: headspace: 40%, catalyst amount: 5 wt% of input; $T = 40\ ^{\circ}C$, $P = 10$ psig, concentration: 0.347 M.

In order to further insure that the presence of carbon dioxide causes catalyst deactivation and the change in rate is not caused by solvent saturation with carbon dioxide, two reactions were conducted at 40 °C and at a pressure of 10 psig (Fig. 7a). Under these conditions, more carbon dioxide would occupy the headspace and the concentration of the hydrogen would be lower in comparison with the standard experimental conditions due to higher temperature and lower hydrogen pressure, respectively. The reactions were followed by React-IR. FTIR profiles for product and dissolved CO_2 peaks were found to correlate suggesting that the kinetics can be followed by the change of the CO_2 intensity. In addition, the carbamic acid intermediate has not been observed by FTIR suggesting that

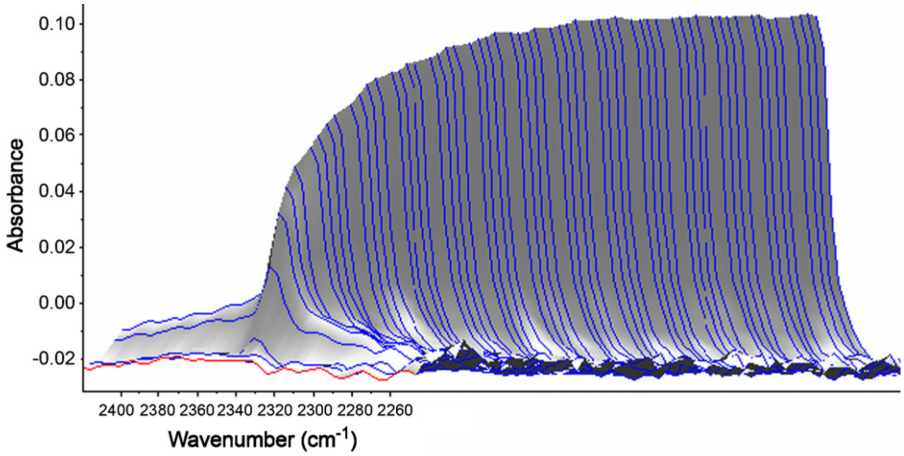

Fig. 6. 3D FTIR profile during the reaction.

formation of the product from this intermediate is the fast step. This also supports the mechanistic proposal of Humphries et al. that formation of the intermediate is slower than that of the product formation [7,8]. Both FTIR data and hydrogen uptake (Fig. 7a and b) indicate that after 35 min of reaction, the rate slowed down significantly. HPLC analysis indicated about 55% conversion after 100 min, corresponding to theoretical uptake of 2.6 L of hydrogen Actual hydrogen uptake was measured to be 2.1 L. This difference is due to the CO_2 vapor pressure in the headspace. In fact, Fig. 8 illustrates the predictions for CO_2 mole % in headspace and H_2 added during the reaction knowing the CO_2 solubility in THF and correlation for temperature dependency [14]. H_2 amount added (Fig. 8) and hydrogen uptake in Fig. 7b are in good agreement. Once CO_2 is removed completely from either the solvent and headspace or the headspace only, hydrogen is reintroduced. The reaction then becomes zero order and the rate is considerably lower than that of the initial rate for both cases suggesting that removing headspace and dissolved carbon dioxide did not make a difference in terms of reaction rate. Moreover, all these further support the idea that catalyst deactivation plays a role in the rate of reaction.

A Langmuir–Hinshelwood mechanism is proposed by taking into account that reaction is zero order in terms of substrate and catalyst is deactivated by the presence of CO_2:

$$\mathrm{A+S1} \underset{K_1}{\rightleftharpoons} \mathrm{AS1}$$

$$\mathrm{H_2+2S2} \underset{K_2}{\rightleftharpoons} \mathrm{2HS2}$$

$$\mathrm{AS1+HS2} \xrightarrow[k_3]{} \mathrm{AHS1+S2+Toluene}$$

$$\mathrm{AHS1+HS2} \underset{K_4}{\rightleftharpoons} \mathrm{PS1+S2+CO_2}$$

$$\mathrm{PS1} \underset{K_5}{\rightleftharpoons} \mathrm{P+S1}$$

$$\mathrm{XCO_2+S2} \underset{K_6}{\rightleftharpoons} \mathrm{XCO_2S2}$$

where S1 and S2 are two different sites on the catalyst, P is the product and AH is the carbamic acid intermediate and XCO_2 denotes species formed in the presence of carbon dioxide which deactivates the catalyst.

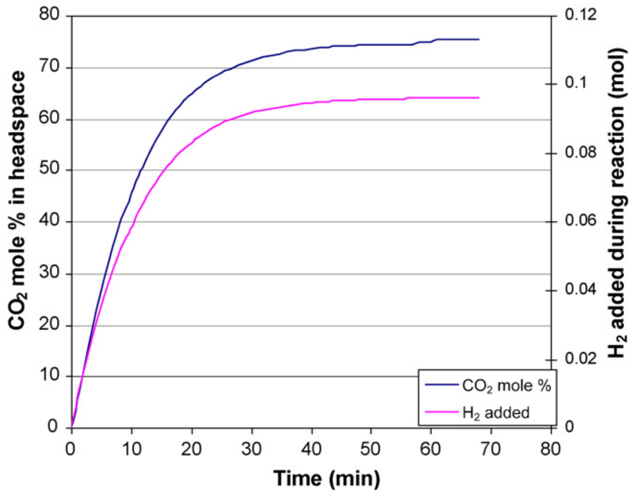

Fig. 8. Predictions for H_2 added and CO_2 mole % in the headspace during the reaction conducted at 40 °C.

Table 1
Comparison of rates in the presence of triethylamine (TEA) and acetic acid (AcOH)

TEA:AcOH ratio (mole equivalency)	Relative area % of input	Relative area % of product
2:0	4.4	95.6
2:1	7.0	93.0
2:2	15.6	84.4
1:1	14.4	85.6
0:2	37.6	62.4

T = 25 °C, P = 30 psig, concentration: 10 mL EtOAc/g of input, system: endeavor catalyst screening system for 0.5 g input. Reaction time: 30 min.

Assuming CO_2 and hydrogen are adsorbed on site S2 and A on site S1 is the mass and $K_1[\mathrm{A}] \gg 1$ the rate equation becomes:

$$r = \frac{k[\mathrm{H_2}]^{1/2}}{(1 + K_2[\mathrm{H_2}]^{1/2} + K_6[\mathrm{XCO_2}])}$$

where $k = L_1 L_2 k_3 K_2^{1/2}$.

3.2. Roles of additives in relation to CO_2

It has been reported that the CBz deprotection reaction can be performed under either acidic or basic conditions and selective CBz deprotection is possible in the presence of an acid additive [2,11]. On the other hand, bases such as ammonia, pyridine, ethylenediamine, or ammonium acetate can be added to selectively hydrogenolyze a CBz group in the presence of benzyl ether. In the current study, the reaction rate was considerably slower in the presence of an acidic additive but faster when a base was present and the solution was not buffered as tabulated in Table 1.

In order to better explain the effect of addition of a base, one should look into the possibility of a pH effect. It should be noted that the pH of the reaction mixture decreases during the reaction as CO_2 is evolved. In fact, the apparent pH was 5.5 after the

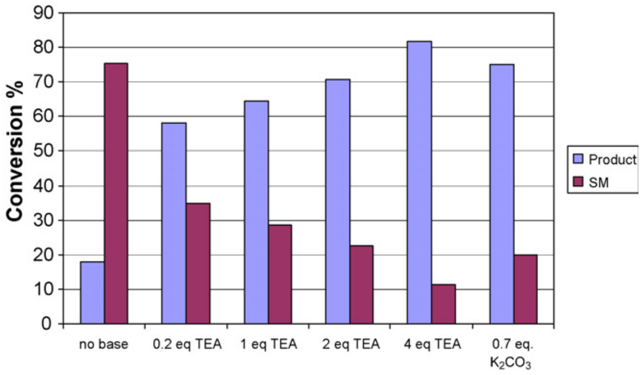

Fig. 9. The effect of addition of base on the reaction rate. Reaction time: 30 min. Different molar equivalencies of TEA and potassium carbonate (to input material) are added. T = 25 °C, P = 30 psig, 10 mL ethyl acetate/1.74 mmol input.

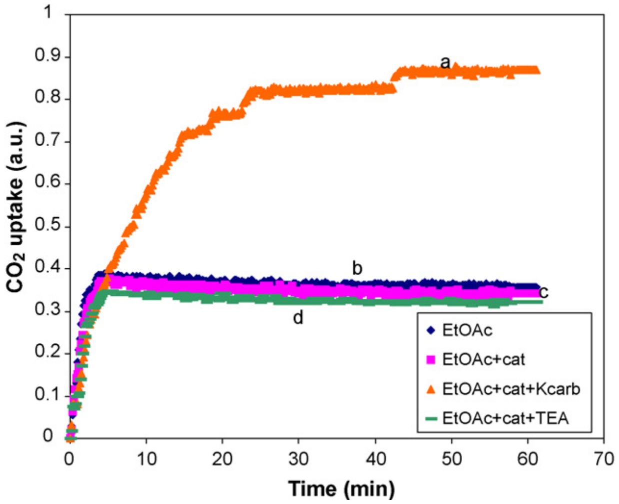

Fig. 10. CO_2 uptakes as a function of time in (a) EtOAc + catalyst + potassium carbonate; (b) EtOAc; (c) EtOAc + catalyst; (d) EtOAc + catalyst and TEA.

reaction completion and 6.5 after purging the CO_2 from the reaction stream. Fig. 9 illustrates that as the triethylamine (TEA) amount increases, the rate increases proportionally. The molar equivalencies (eq.) are based on the substrate A.

The ultimate selection of an additive would not only consider the reaction rate, but also the ease of removing this base post hydrogenolysis as well as the impact on product quality. Therefore, in addition to TEA, potassium carbonate was also considered as a basic additive. Since it is an inorganic base, it can be removed along with the spent catalyst by simple filtration. In addition, it is known that hot potassium carbonate solution is used in the ammonia industry to remove carbon dioxide [15–17]. When 0.7 eq. of potassium carbonate was added to the reaction mixture, the conversion was about 75% after 30 min while it was only 18% in the same time period when no base was applied (Fig. 9).

Since potassium carbonate is known as a CO_2 absorber [15–17], more insight into the effect of this base on the reaction rate was desired. The figure below demonstrates that potassium carbonate does indeed absorb CO_2 whereas this is not the case for TEA (Fig. 10). The partial absorption of CO_2 during the reaction may impact the pH as well as limit the possible poisoning of the catalyst. In order to gain insight on whether catalyst poisoning by CO_2 is a factor, substrate A was dissolved in THF and palladium/carbon catalyst was added. The mixture was then exposed to 10 psig of CO_2 pressure for 0, 2 or 4 h and then hydrogenolyzed under the standard conditions. For those reaction mixtures that were initially under CO_2 pressure, the gas was completely purged with nitrogen prior to the introduction of hydrogen. Fig. 11 illustrates the comparison of the rates for these three reactions, hydrogenolyzed directly or with prior exposure to CO_2. Since it was insured that all CO_2 was removed from the solvent, the slower reaction as reaction mixture was exposed to CO_2 for longer time can understandably be explained by the catalyst poisoning.

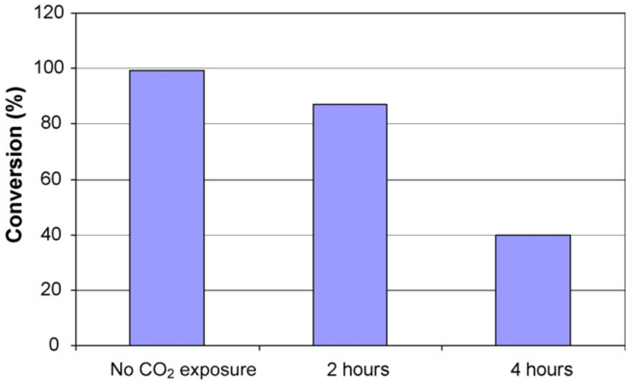

Fig. 11. Comparison of conversion after 30 min of reaction when the reaction mixture (input in THF with Pd/C catalyst) either directly hydrogenated or exposed to CO_2 first (2 h or 4 h under 10 psig of CO_2) and then hydrogenolyzed. $T = 25\ ^\circ C$, $P_{H_2} = 20$ psig, and concentration 5 mL/1.74 mmol input.

In order to differentiate the effect of the additives, two sets of experiments were performed. In the first set of experiments, TEA or potassium carbonate was added to the reaction mixture under standard conditions (Fig. 12a). The reaction rate was faster in the presence of TEA when compared directly with K_2CO_3 (Fig. 12a). In a second set of experiments, each reaction mixture with the basic additive present was exposed to 10 psig of CO_2 for 4 h, followed by intensive nitrogen purges prior to the introduction of hydrogen (Fig. 12b). It was found that the reaction rate is faster in the presence of potassium carbonate than that in the presence of TEA when the reaction mixtures are

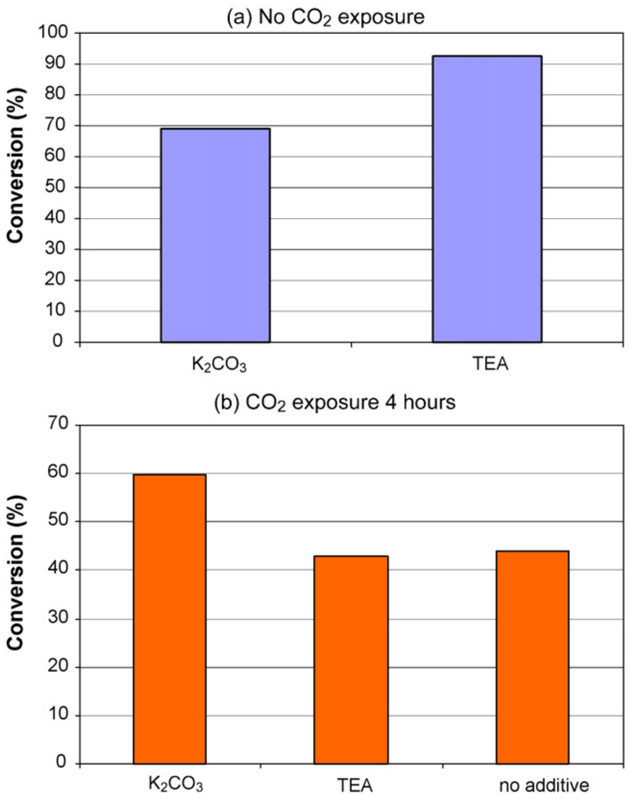

Fig. 12. Comparison of reaction rates (a) hydrogenolysis reaction in the presence of 0.7 eq. of K_2CO_3 and 2 eq. TEA in THF using Pd/C catalyst, $T = 25\ ^\circ C$, $P = 20$ psig, 5 mL/g input, and reaction time: 15 min; (b) the reaction mixtures in THF were first exposed to 10 psig of CO_2 for 4 h, followed by intensive nitrogen purges, and then hydrogenolysis as same conditions in (a), reaction time: 30 min.

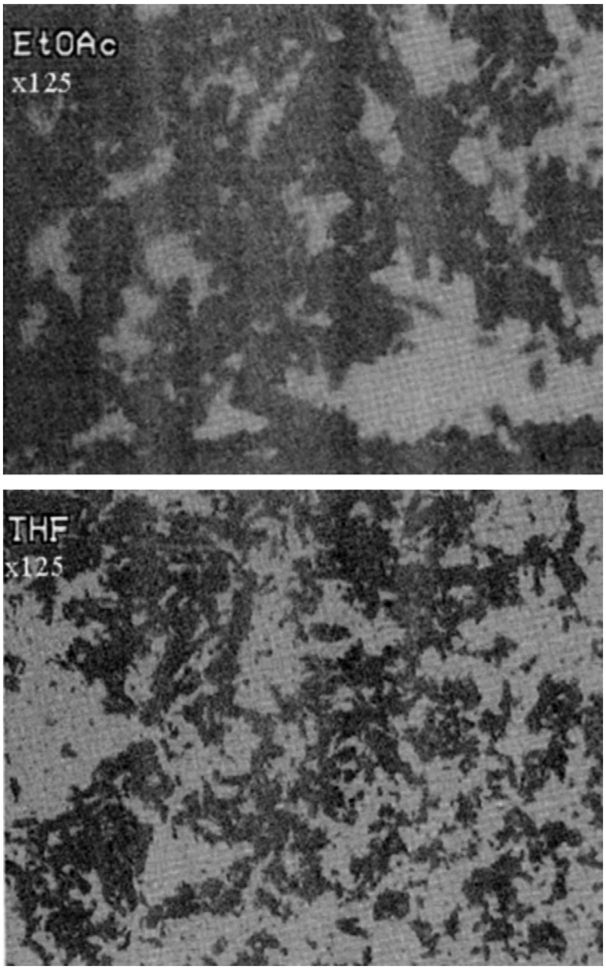

Fig. 13. Optical microscope picture of the catalyst (a) in THF and (b) in EtOAc.

Table 2
Properties of THF and EtOAc

Solvent	Apparent pH	Dielectric constant	Dipole moment
EtOAc	4.85	6.02	1.78
THF	5.05	7.52	1.63

pre-exposed to CO_2. These findings strongly suggest that potassium carbonate is playing a role as a CO_2 scavenger leading to an increase in the reaction rate by diminishing the poisoning of the catalyst, while TEA appears to enhance the reaction rate as a result of moderating the pH. It can be concluded that when CBz deprotection reactions are considered, both pH and catalyst poisoning factors should be taken into account.

4. Effect of solvent

For specific needs of the substrate, solvent choices were limited to ethereal solvents such as THF and alkyl acetates such as EtOAc. It was demonstrated that CBz deprotection is more rapid in THF than that in EtOAc. The table below shows the properties of each solvent which are similar (Table 2). Fig. 13 depicts a possible reason for the faster reaction rate in THF. It can be observed from the micrographs that catalyst particles are more dispersed in THF and agglomerated in EtOAc. In addition, the catalyst settles relatively quickly in EtOAc when mechanical agitation is stopped.

5. Conclusions

The CO_2 by-product plays a significant role in the reaction kinetics for CBz deprotection due to the fact that catalyst deactivation via inhibition occurs in the presence of carbon dioxide. In this reaction system, concentration, pressure, temperature and fill level of the reactor are important parameters since they affect the concentration of CO_2 in the liquid phase It was demonstrated that as the headspace decreases, reaction order changes at high substrate A concentrations. At high temperature (40 °C) and low pressure (10 psig), deactivation is more pronounced because of the low hydrogen concentration in the liquid phase. It was also shown that potassium carbonate decreases the possibility of the catalyst poisoning through absorption, while addition of triethylamine increases the reaction rate due to pH effects.

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