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Scalable Reactor Design for Pharmaceuticals and Fine Chemicals Production. 2: Evaluation of Potential Scale-up Obstacles for Asymmetric Transfer Hydrogenation

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Abstract:

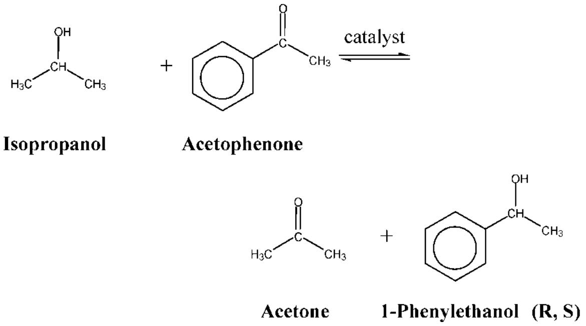
This paper is a continuation of our previous work, which reviewed the main factors that inhibit fine chemical and pharmaceutical reactor scalability. For scalable reactor design, it is suggested to first identify potential scale-up obstacles and then use shortcut calculations for their evaluation. This approach is demonstrated in this paper for the asymmetric transfer hydrogenation of acetophenone to its chiral alcohols, in the presence of the homogeneous catalyst, (1*R*,2*S*-amino-indanol/pentamethylcyclopentadienylrhodium) with isopropanol as hydrogen donor. The investigation reveals that removal of the by-product acetone from the reaction system shortens the required reaction time to achieve high conversion and reduces enantioselectivity erosion. A simple search algorithm is presented which can be used in principle for liquid reactions systems, where stripping of a reaction product or by-product is beneficial. The algorithm identified that the most influential factors that accelerate acetone removal are the acetone vapor–liquid equilibrium and the ratio of stripping gas flow rate per liquid volume. Because acetone removal efficiency is different in different batch reactor scales, this issue poses a scalability problem if optimal reaction performance is desired. Regardless of scale, the stirred vessel operated as a gas–liquid batch reactor has limitations with regards to allowable gas flow rate through the vessel due to impeller flooding. Therefore, reactor systems not constrained by limits in gas flow rate are advantageous.

1.Introduction

The whole workflow from a novel idea, which identifies a new chemical entity, to commercialisation and marketing of the corresponding product is a dynamic interaction of complex tasks that can be executed more or less in parallel.[2] The path from the laboratory flask to a functional plant involves identification of the required unit operations and the interactions among them. Selection of the best reactor design(s) at an early stage of process development, through a procedure that identifies potential scale-up obstacles, is of crucial importance in shortening the time required for the scale-up and/or providing an optimal process at launch. In our previous work,[1] we presented a broad review of potential scale-up obstacles for the pharmaceuticals and fine chemicals industry. Furthermore, a questionnaire was generated that can aid in collection of coarse-level information from different sources (laboratory data, literature, R&D groups). It is proposed that the collection of coarse-level information constitutes the first stage in reactor preselection. In a second stage, potential scale-up obstacles are identified and evaluated through shortcut calculations, leading to a scalability diagnosis. The evaluation process may require a reiteration at the level of coarse-level information collection to focus on process limitations. Because the batch reactor with all its permutations is the most widely employed in the pharmaceuticals and fine chemicals industry, we consider it as a benchmark for comparison to any other candidate reactor configurations. Such a comparison is made on the basis of performance indexes such as conversion, selectivity, and reaction time. The current work applies the above two-stage approach for reactor scalability assessment for the case of asymmetric transfer hydrogenation of acetophenone with a CATHy catalyst.

2. Asymmetric Hydrogenation of Acetophenone

Asymmetric transfer hydrogenation in the presence of a homogeneous catalyst is of significant importance in the synthesis of pharmaceutically relevant substances.[3] The use of hydrogen donor rather than molecular hydrogen avoids the risks and constraints associated with hydrogen handling and requirements for pressure vessels. In this study, asymmetric transfer hydrogenation of acetophenone, which is hydrogenated, to its chiral alcohol 1-phenylethanol is considered.



(1)

The catalyst used for the reaction is one from the CATHy family of catalysts. It is obtained by the chiral rhodium complex pentamethylcyclopentadienylrhodium chloride dimer combined with the ligand 1*R*,2*S*-aminoindanol. The resulting catalyst enables the rapid, high yielding asymmetric transfer hydrogenation of acetophenone with 2-propanol to produce (*R*)- and (*S*)-(1)-phenylethanol. After the catalyst solution is prepared, it is mixed with the reactant acetophenone. A small amount of sodium isopropoxide is added to the reaction mixture to bring

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10.1021/op700089q CCC: $37.00

the catalyst to its active state and thus to initiate the chemical reaction. The presence of atmospheric oxygen is detrimental to catalyst activity; therefore, the reaction mixture is held under nitrogen during operation. The reaction temperature considered is 30 °C as a reasonable compromise between catalyst activity and selectivity.

3. Coarse Level Information

Coarse level information for the reaction system was collected according to our proposed questionnaire[1] and is given in the Supporting Information. Physical and chemical properties of chemical species involved in the reaction system were identified. Experimental studies[4] were dedicated to obtain kinetic information. This is an essential step for identification of potential scale-up obstacles.

4. Identification and Evaluation of Potential Scale-up Obstacles

The reversibility of reactions hints that utilisation of reactant excess and/or product/by-product removal can affect reactor performance. Experimental studies[3] investigated the effect of acetone concentration on reaction conversion and selectivity by adding acetone into the reaction mixture before starting the reaction. The results showed that acetone presence inhibited the reaction but did not have a significant effect on enantioselectivity at low concentration (below ~0.1 M). However, at higher concentration (i.e., 0.5 M), a significant drop in conversion and erosion in enantioselectivity occurred. In the reaction system, isopropanol (both reactant and solvent) is used in excess. The vapour pressure properties indicate that it is possible to remove acetone, because it has a vapour pressure higher than all the other chemical species in the system. Acetone removal can be accomplished through stripping by using an inert gas or through distillation taking place simultaneously with the reaction. For distillation, a constraint that exists is that high temperature can lead to catalyst deactivation. Here we examine the former approach. The reaction system needs to be considered as a two-phase (gas–liquid) system. The additional phase increases the complexity of reactor design and identification of potential scale-up obstacles. Consequently, mass transfer between phases needs to be assessed.

4.1. Appraisal of Acetone Removal. Parametric studies were performed in order to investigate the effect of acetone removal from the liquid phase on conversion and enantioselectivity using a batch reactor model. In the first instance, the reactor was modelled as a single-phase system, where acetone removal from the liquid phase was accounted as a first-order irreversible reaction. The reactor model assumed perfect mixing and constant liquid phase volume and is given by the ordinary differential eq 2,

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = \sum_{j=1}^{N} \nu_{ij} r_j \qquad (2)$$

with initial conditions $t = 0$, $c_i = c_i^0$.

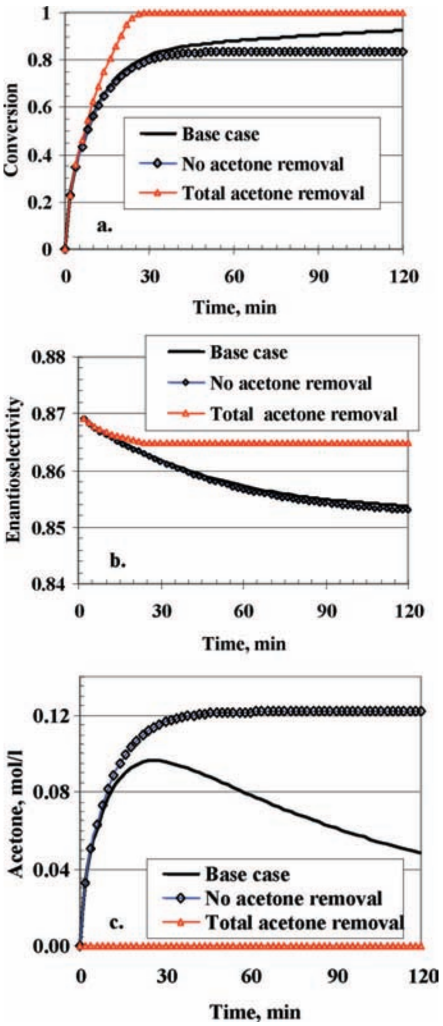

Figure 1. **Influence of acetone removal on (a) conversion, (b) enantioselectivity, and (c) acetone concentration, using a single-phase batch reactor model.**

The reaction rates r_j used are given in the Supporting Information. The base case experiment described by Sun et al.[3] used an initial liquid load of 250 mL, an initial acetophenone concentration of 0.144 M, and a ratio substrate:catalyst of 1000:1, while a constant nitrogen flow of 800 mL/min was bubbled through the liquid phase to remove acetone. The temperature was kept at 30 °C. For these conditions, the rate constant associated with the "acetone removal reaction" was estimated at 1×10^{-2} s^{-1}. To simulate total acetone removal, the rate constant was increased by two orders of magnitude, whilst for the situation when no acetone was removed from the liquid phase, the rate constant was set to zero. Figure 1 shows a comparison of these three cases in terms of conversion, enantioselectivity, and acetone concentration in the liquid phase. It can be seen that, if acetone were to be removed from the reaction mixture completely, 100 % conversion can be achieved in less than 30 min, with the highest enantioselectivity among the three cases. If no acetone removal takes place, the maximum conversion that can be achieved is 83 %, while erosion in enantioselectivity occurs.

4.2. Appraisal of Mass Transfer between Phases. Although the above model shows that acetone removal from the

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(4) Sun, X. Studies of Catalytic Asymmetric Transfer Hydrogenation in Batch and Continuous Reactors. PhD Thesis, University College London, 2007.

Table 1. **Mathematical model for stripping of a volatile component from a binary mixture**

liquid phase	$dc_i / dt = -k_l \cdot a \cdot (c_i - c_i^*)$; with initial condition $t = 0$, $c_i = c_i^0$
gas phase	$k_g \cdot a \cdot V_L (y_i^* - y_i) = Q_{gas} \cdot y_i$
interface	$k_g \cdot (y_i^* - y_i) = k_l (c_i - c_i^*)$
	$y_i^* = K_{eq} \cdot c_i^*$

Table 2. **Solutions for improvement of stripping of volatiles from a gas/liquid mixture**

case	actions that can improve stripping
A	• intensify mass transfer in the gas phase • increase interfacial area • decrease solubility (via pressure and temperature)
B	• decrease solubility • increase stripping agent flowrate
C	• intensify mass transfer in the liquid phase • increase interfacial area

reaction mixture leads to higher conversion in shorter reaction time and higher enantioselectivity, in real systems, its removal may be constrained by mass transfer resistances and acetone solubility in the reaction mixture. To identify the most influential factors for acetone stripping from the liquid phase, a shortcut model for acetone evaporation from a binary acetone–isopropanol mixture was formulated according to two-resistance film theory[5] with the following assumptions: gas and liquid phases are considered isothermal and perfectly mixed; liquid phase is in an unsteady state; there is no accumulation of the volatile component in the gas phase; and equilibrium composition is achieved at the gas–liquid interface instantaneously. The resulting model (given in Table 1) has the analytical solution

$$c_i(t) = c_i^0 \exp(-Mt) \tag{3}$$

where M depends on mass transfer coefficients in the gas and liquid phase, thermodynamic equilibrium, and the ratio of inert gas per volume of liquid phase utilized and is given by eq 4

$$M = \frac{k_l a}{1 + \frac{k_l}{k_g}\frac{1}{K_{eq}}\left(1 + \frac{k_g a V_L}{Q_{gas}}\right)} \tag{4}$$

The solution given by eq 3 shows that because of removal of component *i* from the liquid phase, its concentration in the liquid phase follows an exponential decrease, which depends on the value of M.

The expression of M, given by eq 4 suggests how stripping can be improved. The potential limiting factors can be high mass transfer resistance in the gas phase (low k_g); high mass transfer resistance in the liquid phase (low k_l); limitation due to thermodynamic equilibrium, low K_{eq} (high solubility); insufficient amount of inert gas used for stripping (low Q_g/V_L); insufficient interfacial area (low α). However, the complex expression of M indicates that intensifying any of these factors arbitrarily does not guarantee stripping improvement. A search algorithm presented in Figure 2 helps to identify the most influential parameters and where the bottleneck is located. For example if:

$$\frac{Q_{gas}}{aV_L} < k_g < \frac{k_l}{K_{eq}} \tag{5}$$

then

$$M \rightarrow K_{eq}\frac{Q_{gas}}{V_L} \tag{6}$$

This situation can occur when the mass transfer coefficient in the gas phase is high (minimal resistance in the gas phase) but the volatile component has high solubility in the mixture (low K_{eq}). In this case, if one wants to improve stripping by increasing interfacial area, no significant improvement will arise. The solutions that can lead to efficient stripping are either an increase in the stripping agent flow rate or manipulation of solubility by modifying the operating temperature, pressure, and composition. Figure 2 demonstrates that three cases can occur depending on the values of system parameters and Table 2 shows for each case what action can improve the efficiency of stripping. The values of the system parameters depend on scale, type of gas–liquid contactor, and operating conditions. They can be estimated on the basis of empirical correlations and thermodynamic data. Hence, potential bottlenecks can be different depending on the system chosen. The search algorithm is discussed below for stripping of acetone from acetone–isopropanol mixtures with an inert gas in stirred tank vessels.

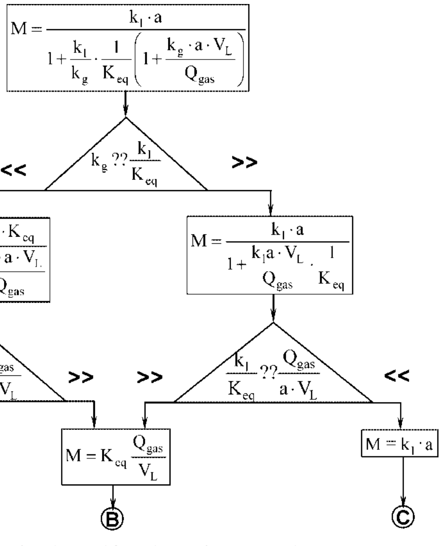

Figure 2. **Algorithm for identification of controlling parameters during stripping of volatile components.**

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[5] Geankoplis, C. J. *Transport Processes and Unit Operations*, 3rd ed.; Prentice Hall, Upper Saddle River,NJ, 1993.

4.2.1. Vapor–Liquid Equilibrium for Acetone–Isopropanol Mixture. Vapor–liquid equilibrium is achieved when the fugacities, which are a function of composition, pressure, and temperature, of the two phases are equal as given by eq 7

$$f^{L}(x_i, P, T) = f^{G}(y_i, P, T) \tag{7}$$

which can be expressed as

$$\gamma_i x_i P^{\mathrm{vap}} = \Phi_i y_i P_{\mathrm{tot}} \tag{8}$$

Because the total pressure is low, the fugacity coefficient Φ is close to unity.[6] Thus, at equilibrium, the relation between composition of the gas and liquid phase can be written as

$$y_i = \gamma_i \frac{P^{\mathrm{vap}}}{P_{\mathrm{tot}}} x_i \tag{9}$$

The equilibrium constant, based on mole fraction, can be expressed as

$$K'_{\mathrm{eq}} = \gamma_i \frac{P_i^{\mathrm{vap}}}{P_{\mathrm{tot}}} \tag{10}$$

It depends on composition by means of the activity coefficient γ_i , total pressure P_{tot}, and the vapour pressure of the volatile component, P^{vap} , which in turn is strongly dependent on temperature. In the calculations, it is assumed that the phase equilibrium between acetone and solvent isopropanol is not strongly affected by the presence of catalyst, substrate, and reaction products because of the dilute nature of the system. Vapor–liquid equilibrium data available in the literature for the binary mixture acetone–isopropanol[7] were correlated using a Redlich–Kister type correlation and Wilson equation[6] in order to obtain the activity coefficient of acetone in isopropanol. The average value of activity coefficient calculated by these methods as acetone concentration approaches zero was $\gamma_{\mathrm{acetone}} = 3$.

4.2.2. Mass Transfer Coefficient in the Gas Phase. Calderbank[8,9] underlined that small diffusion path in small bubbles and higher diffusion coefficients in the gas phase as compared to liquid phase, coupled with the effect of turbulence in the gas bubbles, results in negligible mass transfer resistance in a gas phase dispersed in a liquid phase. Assuming that the gas bubbles behave as rigid spheres without internal circulation, which are the conditions for minimum mass transfer rate, the mass transfer coefficient in the gas phase can be estimated as[10]

$$k_{\mathrm{g}} = \frac{2\pi^2}{3} \frac{D_{\mathrm{g}}}{d_{\mathrm{b}}} \tag{11}$$

At low gas flowrates, bubble size is a function of the orifice size through which the gas phase in introduced, d_{o}, liquid surface tension, and gas and liquid densities:[11]

$$d_{\mathrm{b}} = 1.817 \left[\frac{\sigma d_{\mathrm{o}}}{g(\rho_{\mathrm{l}} - \rho_{\mathrm{g}})} \right]^{1/3} \tag{12}$$

4.2.3. Mass Transfer Coefficient in the Liquid Phase. Mass transfer coefficient in the liquid side, k_{l}, can be estimated using the equations proposed by Calderbank and Moo-Young:[12]

$$k_{\mathrm{l}} = A \left(\frac{g\mu_{\mathrm{l}}}{\rho_{\mathrm{l}}} \right)^{1/3} \left(\frac{D_{\mathrm{l}}\rho_{\mathrm{l}}}{\mu_{\mathrm{l}}} \right)^{n} \tag{13}$$

where $A = 0.31$ and $n = 2/3$ for small bubbles, $d_{\mathrm{b}} < 2.5$ mm, and $A = 0.42$ and $n = 1/2$ for large bubbles, $d_{\mathrm{b}} > 2.5$ mm.

4.2.4. Interfacial Area. The interfacial area can be calculated from the gas hold-up

$$a = 6 \frac{\varepsilon}{d_{\mathrm{b}}} \tag{14}$$

Murugesan[13] presents an empirical correlation for the estimation of dispersed gas phase hold-up as

$$\varepsilon = C(u_{\mathrm{g}}^{*})^{0.5} \left(\frac{N^2 d_{\mathrm{R}}}{g} \right)^{0.45} \left(\frac{\mu_{\mathrm{l}}^{4} g}{\sigma^{3} \rho_{\mathrm{l}}} \right)^{0.08} \left(\frac{d_{\mathrm{w}}}{d_{\mathrm{T}}} \right)^{0.85} \left(\frac{d_{\mathrm{R}}}{d_{\mathrm{T}}} \right)^{0.65} \tag{15}$$

where

$$u_{\mathrm{g}}^{*} = \frac{u_{\mathrm{g}}}{\left(\frac{\sigma \Delta \rho g}{\rho_{\mathrm{l}}^{2}} \right)^{0.25}} \tag{16}$$

and the constant $C = 31.2$. For a laboratory flask with a volume of 500 mL, the values of the parameters used in eq 15 were flask diameter, $d_{\mathrm{T}} = 0.1$ m, stirrer diameter $d_{\mathrm{R}} = 0.05$ m, stirrer blade $d_{\mathrm{w}} = 0.01$ m, and stirrer speed $N = 12\ \mathrm{s}^{-1}$. For a gas flow rate of 800 mL/min and using the physical properties of isopropanol, eq 15 gives a gas hold-up $\varepsilon = 0.08$. The observed bubble diameters as well as the values according to eq 12 were in the range of 2.5 mm. Thus, the interfacial area given by eq 14 is about 192 m^{-1}. In addition, if the free surface of liquid is also considered, the interfacial area for the laboratory flask increases to about 215 m^{-1}.

4.2.5. Effect of Mass Transfer on Scalability. The search algorithm proposed earlier was applied to stirred vessels at three different scales: laboratory scale that contains a liquid volume of 250 mL (base case), pilot scale with a 46 L liquid volume, and plant scale with a 6 m^3 liquid volume. Visimix 2000

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(6) Prausnitz, J. M.; Lichtenthaler, R. N.; de Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*, 3rd ed.; Prentice-Hall, Upper Saddle River,NH, 1999.

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Table 3. **Physical and operational parameters of the different reactor scales**

Parameter	Laboratory scale	Pilot scale	Plant scale (1)	Plant scale (2)
liquid volume, V_L (m^3)	0.25×10^{-3}	0.046	6	6
gas flow rate, Q_{gas} (mol/s)	5.8×10^{-4}	0.24	6.8	6.8
interfacial area, α (m^{-1})	215	308	189	353
mass transfer coefficient in liquid phase, k_l (m/s)	1.48×10^{-4}	1.48×10^{-4}	1.48×10^{-4}	1.48×10^{-4}
mass transfer coefficient in gas phase, k_g (mol/(m^2 s))	1.5	0.694	0.516	0.6
gas hold-up, ε	0.05	0.22	0.184	0.296
bubble diameter (mm)	2	4.29	5.85	5.03
gas flow rate/liquid vol (s^{-1})	0.052	0.11	0.025	0.025
equilibrium constant, K_{eq} (m^3/mol)	7×10^{-5}			
k_l / K_{eq} (mol/(m^2 s))	2.1			
Q_{gas} / aV_L (mol/(m^2 s))	0.011	0.017	0.005	0.003
M	1.60×10^{-4}	3.54×10^{-4}	7.82×10^{-5}	7.88×10^{-5}

(www.visimix.com) was used to calculate the performance of the stirred vessels for pilot and plant scale, in terms of their hydrodynamics and gas–liquid mixing characteristics. VisiMix utilizes semiempirical mathematical models of phenomena taking place in mixing tanks. They are based on fundamental equations of turbulent transport of energy, momentum, and mass that have been simplified using appropriate experimental data. For the pilot scale, a disk turbine impeller with a rotation speed of 500 rpm and a motor power of 1.7 kW was used. For the plant scale, two impeller types were investigated. In plant scale (1), a disk turbine impeller with 1 stage, a rotation speed of 80 rpm, and a motor of 10 kW was used, whilst in plant scale (2), a turbine impeller with 2 stages, a rotation speed of 120 rpm, and a motor of 150 kW was considered. The values of mass transfer and other parameters involved in calculation of parameter M as given by eq 4 are presented in Table 3.

As discussed earlier, acetone removal is important for reduction of the reaction time and to avoid enantionselectivity erosion. The higher the value of M, the fastest acetone removal can be achieved (see equation 3). Table 3 shows that at large scale (6 m^3 for the liquid phase), parameter M is lower than at small scale, and hence, acetone removal is less efficient. Substituting the values of the mass transfer parameters in the search algorithm given in Figure 2, for operation at 30 °C and atmospheric pressure, we can identify that we operate in case B for all reactor scales. Therefore, acetone removal can be improved by decreasing acetone solubility and/or increasing the amount of inert gas per volume of the liquid phase. Because solvent will also be removed with acetone, solvent top-up may be required if the substrate concentration is not to increase.

Acetone solubility can be decreased by increasing the acetone vapour pressure (for example, by raising the temperature), or by decreasing total pressure (operation under a vacuum). However, operation at temperatures higher than 30 °C is limited by catalyst deactivation. Operating at low pressures is a feasible solution, which warrants further investigation. Increasing the ratio of gas flow rate per liquid volume would also be beneficial for acetone removal. It is interesting to note that the highest Q_{gas}/V_L is used in the pilot scale, which also gives the highest value of M. However, in the plant scale, Q_{gas}/V_L is lower because reactor operation is constrained by impeller flooding. The different values of M calculated in the various scales demonstrate that acetone removal poses a scalability problem. Obviously, one solution to ensure the same performance in scale-up in a batch reactor system would be to mimic in the laboratory scale the lower acetone efficiency of the large scale. However, even though this may minimise scale-up problems, it would be to the detriment of reaction performance. Regardless of scale, the stirred vessel operated as a gas–liquid batch reactor has limitations, mainly due to limitation in gas flow rate to avoid impeller flooding. Thus, to ensure satisfactory scalability and improve reaction performance, gas–liquid contactors with no limitations on gas flow rates such as rotating disk reactors[14] would be beneficial.

This work demonstrates that shortcut calculations are important in identification and evaluation of the correct potential scale-up obstacles. In the specific case study, hasty conclusions related to the controlling parameters that affect mass transfer may lead to inappropriate solutions for addressing scalability. For example, if it was assumed that acetone removal was limited by mass transfer resistances that could be alleviated by using a more efficient impeller, one would take the wrong track. This is illustrated in plant scale (1) and plant scale (2), in which intensification of mixing results in an almost double interfacial area (see Table 3). At the same time, the power consumption to drive the impeller increases from 6.7 to 150 kW, with a significant impact on operation cost. Still, the change in parameter M, which directly affects acetone removal and therefore reactor performance, is negligible.

5. Conclusions

Identification and evaluation of potential scale-up obstacles can benefit by shortcut calculations at the early stages of reactor selection. In this paper, this was demonstrated using as a case study the transfer hydrogenation of acetophenone to its chiral alcohols in the presence of a homogeneous catalyst with isopropanol as hydrogen donor. After a first stage of collection of coarse level information, a second stage of appraisal of potential scale-up obstacles identified that removal of the by-product (acetone) can benefit reaction performance. When acetone removal is accomplished by stripping with an inert gas, simplified calculations identified that (1) acetone removal can be a bottleneck for scale-up as well as optimal reaction performance, and (2) acetone removal efficiency by stripping depends on the scale of operation of stirred reactor vessels. The controlling parameters for improving reaction conversion and enantioselectivity were identified to be acetone vapor–liquid equilibrium and ratio of stripping gas flow rate to liquid volume.

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(14) Zanfir, M.; Sun, X.; Gavriilidis, A. *Chem. Eng. Sci.* **2007**, *62*, 741.

The vapor–liquid equilibrium can be favorably influenced by operating at low pressure, whereas the ratio of gas flow rate per liquid volume can be increased to improve the process performance. However, a stirred vessel operated as a gas–liquid batch reactor has limitations, mainly due to gas flow rate limitations posed by the need to avoid impeller flooding. To overcome such limitations, gas–liquid contactors that are not limited by gas flow rate would provide a better solution.

Acknowledgement

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NOTATION

A	constant in eq 13
c	concentration in liquid (mol/m^3)
C	constant in eq 15
d_b	gas bubble diameter (m)
d_o	inner diameter of gas feed tube (m)
d_R	impeller diameter (m)
d_T	vessel diameter (m)
d_w	width of impeller blade (m)
D	diffusion coefficient (m^2/s)
f	fugacity (N/m^2)
g	gravitational acceleration (m/s^2)
k_g	mass transfer coefficient in the gas phase (mol/(m^2 s))
K_{eq}	equilibrium constant based on concentration (m^3/mol)
K'_{eq}	equilibrium constant based on mole fraction
k_l	mass transfer coefficient in the liquid phase (m/s)
M	parameter defined in eq 4 (s^{-1})
N	impeller speed (s^{-1})
P	pressure (N/m^2)
P^{vap}	vapor pressure (N/m^2)
P_{tot}	total pressure (N/m^2)
Q_{gas}	molar flowrate of the gas phase (mol/s)
r	reaction rate (mol/(m^3 s))
T	temperature
t	time (s)
u_g	gas superficial velocity (m/s)
u_g^*	velocity defined by eq 16
V_L	volume of liquid phase in stirred vessel (m^3)
x	mole fraction in liquid phase
y	mole fraction in gas phase

GREEK SYMBOLS

α	interfacial area per unit liquid volume (m^{-1})
$\Delta\rho$	$\rho_l - \rho_g$
γ	activity coefficient
	gas holdup
μ	dynamic viscosity of the liquid (kg/(m s))
ν	stoichiometric coefficient
ρ	liquid density (kg/m^3)
σ	surface tension (N/m)
Φ	fugacity coefficient

SUBSCRIPTS

g	gas phase
i	chemical species
j	chemical reaction
l	liquid phase

SUPERSCRIPTS

0	initial values at time $t = 0$
*	gas–liquid interface

Supporting Information Available

Coarse level information (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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