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Intensified Azeotropic Distillation: A Strategy for Optimizing Direct Amidation

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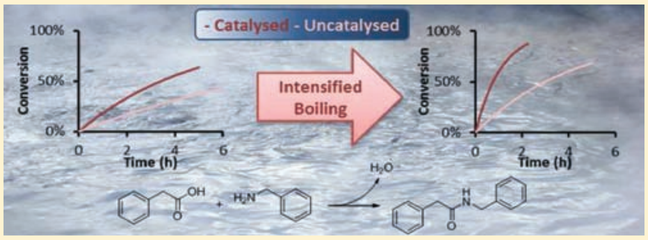
Supporting Information



ABSTRACT: The direct synthesis of amides from the corresponding carboxylic acids and amines is shown to operate under varying degrees of mixed kinetic and mass transfer rate control when water is removed by azeotropic distillation. Unless the volumetric heat input rate is reported, it is not possible to make a valid comparison between different catalysts, as the difference in Q_{boil} alone can be responsible for the apparent difference in observed rate. A systematic approach is developed to quantify the contribution of boil-up rate to conversion rate and so decouple the physical rates from the chemistry. Intensive boiling is used to improve the removal of water during azeotropic distillation and considerably enhance conversion. The results show that some acylations previously thought to be difficult or impossible can be achieved in the absence of coupling agents under green conditions. The use of a cascade of CSTR flow reactors operating under intensified conditions is assessed for scale up of direct amidation reactions and compared to a production scale batch reactor. The findings and conclusions of this work have general applicability to all condensation reactions.

1. INTRODUCTION

Direct Amidation. Amide synthesis is undoubtedly one of the most important bond forming reactions. A recent survey carried out by three leading pharmaceutical manufacturers reported that amide bond formation was utilized in the synthesis of 65% (84 of 128) of the drug candidates surveyed.[1] The most common synthetic strategies include activation of the carboxylic acid, either by forming the acyl chloride (44% of cases) or mixed anhydride or by using a coupling reagent.[2] Although these methods are very well-established in pharmaceutical manufacturing, they are disadvantaged by the need for additional process stages and poor atom economy reagents.[3] Indeed, a recent poll from the ACS Green Chemistry Institute Pharmaceutical Roundtable reported that amide formation avoiding poor atom economy reagents received the most number of votes. The poll surveyed and prioritized common reactions for which member companies felt better alternatives would bring significant environmental and economic benefits. These benefits arise mainly through reductions in waste produced, use of hazardous reagents, and number of process operations.[4]

Because it allows the synthesis of the amide bond in a single step without the need for any reagents, direct amide synthesis from the carboxylic acid and the amine is an attractive alternative. The condensation of carboxylic acids with amines at elevated temperatures is a known reaction[5] that is generally thought to be the result of "pyrolysis" of the ammonium carboxylate salt.[6] It is commonly assumed that the activation energy needed for the salt to be converted to the amide is too high to be achieved on most substrates without using forcing conditions, which makes this a method with little synthetic utility. Within the past decade, catalysts have been developed to lower this activation energy and enable condensation of the carboxylic acid with amines.[7] Arylboronic acids, in particular, proved efficient catalysts. Additionally, the use of boric acid as a cheap and effective alternative to more complex boron derivatives is growing in favor and has been applied successfully to the large-scale preparation of APIs.[8]

The mechanism by which the boron species promotes the formation of amides from carboxylic acids and amines is yet to be fully determined.[9,10] However, even under catalytic conditions, water removal is usually needed and the importance of removing water to ensure high conversion levels is regularly reported.[5b,11] Water removal is generally achieved using a combination of molecular sieves, Soxhlet extraction, and calcium hydride or using azeotropic distillation with toluene or xylenes as entrainers together with a Dean−Stark apparatus (or phase-splitter on plant) to effect separation of the biphasic mixture.[12] The latter is a form of ***reactive distillation***.

Azeotropic Reactive Distillation and Mixed-Rate Control Systems. Reactive distillation is a widely used technique to drive equilibrium-limited reactions such as condensations to high levels of conversion. Previous commercial work on a production-scale condensation identified a positive correlation between boil-up rate and reaction rate,

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which was exploited to bring about significant process improvements on plant. Yield was increased, and both impurity levels and batch times were reduced. In the case of condensation reactions generating water, the position of the equilibrium can be displaced by removing water to promote formation of the desired product (Figure 1).

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C + H_2O \xrightarrow[-H_2O]{k_{evap}} C$$

Figure 1. General mixed-rate controlled condensation.

The observed rate of product formation, r_{obs}, is a function of the parallel processes of chemical reaction (r_1, r_2) and water removal by evaporation (r_{evap}).

$$r_{obs} = f(\text{kinetic rate, mass transfer rate}) \tag{1}$$

Expressing reaction rates for the species as a power law function and the boil-up rate for water using Raoult's Law, eq 1 can be written in the form of a mass balance per unit volume.

$$\begin{aligned} r_{obs} &= \frac{-\mathrm{d}[A]}{\mathrm{d}t} \\ &= \frac{-\mathrm{d}[B]}{\mathrm{d}t} \\ &= \frac{\mathrm{d}[C]}{\mathrm{d}t} \\ &= \{k_1[A]^a[B]^b - k_2[C]^c[H_2O]^d\} \end{aligned} \tag{2}$$

$$\begin{aligned} \frac{\mathrm{d}[H_2O]}{\mathrm{d}t} &= \{k_1[A]^a[B]^b - k_2[C]^c[H_2O]^d\} \\ &\quad - \frac{Q_{boil}\gamma_{H_2O}\chi_{H_2O}\rho_{H_2O}}{\sum_1^n(\gamma_i\chi_i\rho_i)} \end{aligned} \tag{3}$$

where the term on the right-hand side of eq 3 is the rate of water evaporation from a mixture and Q_{boil} is the heat input per unit volume of the reaction mixture to provide boiling.

The observed rate of the reaction varies between the two extremes of kinetic control and mass transfer (evaporation rate) control. When the rate of water removal and the rate of the chemical reaction are of similar magnitude, both affect the overall observed rate of product formation, and the system is said to be under *mixed-rate control*. Typically, observed reaction times of between 0.5 and about 10 h fall into this class.

When water is removed via azeotropic distillation, physical factors affecting the system boil-up rate, such as Q_{boil}, will retard or accelerate the water evaporation rate. This has important implications when assessing system reactivity and when screening catalysts for mixed-rate control systems. If the effect of physical factors is not isolated and systematically quantified, their influence on observed rates may be wrongly attributed to chemical factors. By intensifying Q_{boil}, reactions will tend toward kinetic rate control.

The purpose of this paper is to demonstrate the benefits of applying a systematic approach to decoupling chemical reaction rates from the physical rate of evaporation. This is exemplified by the case of direct amidation reactions carried out under azeotropic removal of water.

2. RESULTS AND DISCUSSION

In the commercial process (*vide supra*), water was removed on plant using azeotropic distillation and a phase-splitter. The boil-up rate was controlled by varying the rate of heat transfer to the vessel $Q_{overall}$, which itself can be controlled by adjusting the temperature difference between the heating medium and the reaction temperature (ΔT). Variation of ΔT experimentally therefore provides a convenient means to assess the impact of heat transfer on the efficiency of water removal and hence conversion.

Volumetric Heat Input—Q_{boil}. The overall rate of heat transfer per unit volume of mixture, $Q_{overall}$, is a function of the overall heat transfer coefficient, U, the heat transfer area, A, and the temperature difference between the heating medium and the reaction temperature, ΔT.[13,14] Under steady state temperature (boiling conditions):

$$VQ_{overall} = UA\Delta T \tag{4}$$

In practice heat losses (Q_{loss}) occur through the top of the flask and connecting glassware causing vapors to condense on the walls before reaching the condenser. These losses may be considerable and vary from experiment to experiment without removing water from the system. Thus:

$$Q_{overall} = Q_{boil} + Q_{loss} \tag{5}$$

Combining eqs 4 and 5

$$Q_{boil} = UA\Delta T/V - Q_{loss} \tag{6}$$

It is possible to measure Q_{boil} as a function of ΔT[15] by monitoring the rate of condensation from a boiling solution. Experimental data for a range of entrainers were collected (Figures 2 and 3). The lowest values of Q_{boil} used were those corresponding to the lowest ΔT enabling both nucleate boiling as well as a constant vapor–liquid circuit inside the Dean–Stark system. The dependence of Q_{boil} on ΔT was found to be linear in the region under study (Table 1).

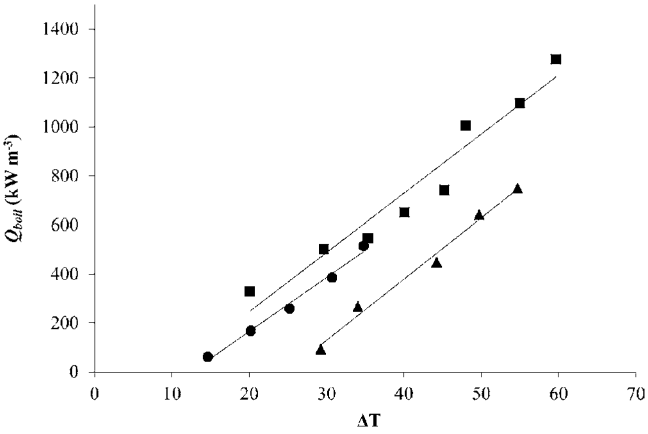


Figure 2. Dependence of the volumetric heat input, Q_{boil}, on ΔT: 100 mL flask; ■, water; ●, toluene; ▲, chlorobenzene.

The overall heat transfer coefficient, U, may be calculated from the slopes and Q_{loss} from the intercepts. In the case where different entrainers are compared (Figure 2), the same glass vessel was used; hence, the slopes (*i.e.* heat transfer coefficient) are the same but the losses are different due to the differing boiling points of the solvents. Figure 3 shows the effect of boiling water in two different sizes of vessel. The difference in

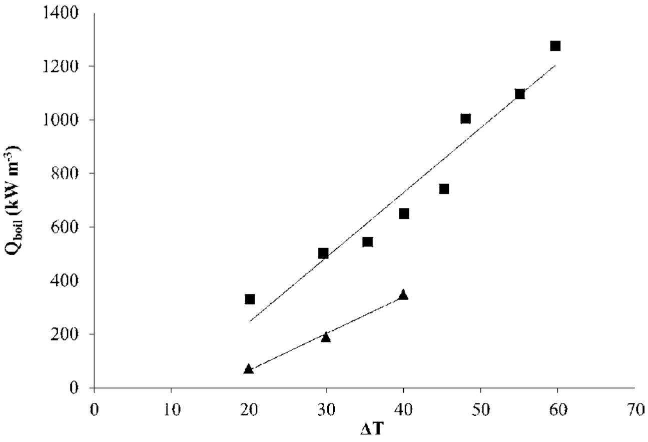


Figure 3. Dependence of the volumetric heat input, Q_{boil}, on ΔT: water; ■, 100 mL flask; ▲, 250 mL flask.

the slopes between the two reactors is due to the combination of the differences in surface/volume ratios and glass thicknesses.

In this case Q_{loss} does not vary significantly (±6%) with the flask size. This is indicative that most of the heat losses are caused by the Dean–Stark apparatus and its connection to the reaction vessel. Indeed, under the conventional design of the apparatus, the vapor phase is partially condensed by the cooler condensate phase returning to the vessel before reaching the condenser.

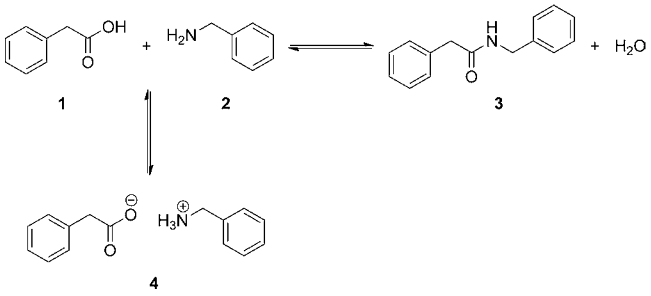
Effect of Q_{boil} on r_{obs} for Direct Amidation. The acylation of benzylamine (**2**) by phenylacetic acid (**1**) was chosen as a representative system for direct amidation run under azeotropic distillation conditions (Scheme 1).

When mixed, phenylacetic acid and benzylamine rapidly form the corresponding ammonium carboxylate salt, **4**, in an exothermic reaction. It is therefore important that the amine is slowly added to a cold solution of the acid. Alternatively, it was found that the salt could be isolated and used as starting material.

Experiments were carried out in toluene using the glassware equipment described above. The corresponding values for Q_{boil} at a particular ΔT were obtained from Table 1.

In the absence of catalyst, the increase in Q_{boil} from 40 to 482 kW m^{-3} causes the conversion rate to be doubled (Figure 4 (◆ vs ■) and Table 2). This is a significant finding and in accordance with the mixed-rate controlled nature of the system. When operating at a higher rate of water removal, the reaction tends to be limited by the forward rate for the acylation reaction. This in turn is limited by the association constant between the ammonium salt and the amine/carboxylic acid system. The results show that when operating at a low boil-up rate the direct acylation between phenylacetic acid and benzylamine could be regarded as a system of relatively low reactivity. Increasing Q_{boil} demonstrates that it is in fact not the case and that high conversion levels can be achieved under conditions where the reaction is not mass-transfer-limited. The approach presented here enables the determination of the optimal volumetric boil-up rate for direct amidation using a particular vessel and solvent system.

Scheme 1



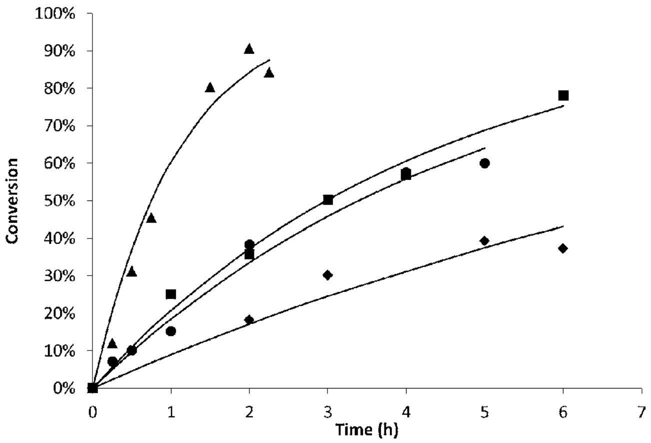


Figure 4. Conversion of **3** with time; ◆, ΔT = 14.3 °C; ■, ΔT = 34.3 °C; ●, 5 mol % $B(OH)_3$, ΔT = 14.3 °C; ▲, 5 mol % $B(OH)_3$, ΔT = 34.3 °C.

Table 2. Effects of Varying Q_{boil} on the Yield of the Direct Amidation of Phenylacetic Acid by Benzylamine

		yield[a]	
ΔT (°C)	Q_{boil} (kW m^{-3})	no catalyst[b]	$B(OH)_3$ (5 mol %)[c]
14.3	40	17%	34%
34.3	482	37%	84%

[a] GC yield. [b] Acid/amine, 1:1; toluene; 0.5 M; reflux; Dean–Stark; 2 h. [c] Acid/amine, 1:1; $B(OH)_3$ (5 mol %); toluene; 0.5 M; reflux; Dean–Stark; 2 h.

Addition of a catalyst further enhances the rate of conversion for both low and high Q_{boil} rates. Using a ΔT value of 34 °C (Q_{boil} = 482 kW m^{-3}) in the presence of boric acid achieves conversion levels of *ca* 85% in 2 h. This compares favorably with previously reported conversions under different sets of conditions (Table 3).

Table 1. Dependence of Q_{boil} on ΔT for Different Solvents

solvent	flask (mL)	bp (°C)	d (g cm^{-3})	ΔH_{vap}[16] (kJ mol^{-1})	linear dependence
water	100	100.0	1.00	45.8 at 373.75 K	$Q_{boil} = (24.2 \times \Delta T) - 238$
water	250	100.0	1.00	45.8 at 373.75 K	$Q_{boil} = (13.7 \times \Delta T) - 210$
toluene	100	110.6	0.867	33.3 at 383.8 K	$Q_{boil} = (22.1 \times \Delta T) - 276$
chlorobenzene	100	132.0	1.106	35.2 at 405.2 K	$Q_{boil} = (25.0 \times \Delta T) - 623$

Table 3. Yields for the Direct Acylation of Benzylamine by Phenylacetic Acid

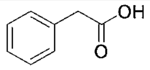
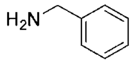
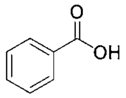
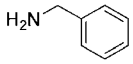
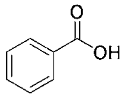
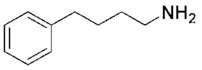
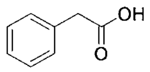
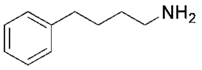
ref	solvent	temp (°C)	time (h)	water removal	catalyst/coupling agent	yield
17	neat	140	2	sieves	none	95%
18	*o*-xylene	reflux[a]	6	Dean−Stark	none	96%
19	THF	RT	14	N/A	$Sn[N(TMS)_2]_2$ (1 equiv)	82%
20	DCM	RT	0.5	N/A	2-pyridon-1-yl diphenyl phosphate (1 equiv)	85%
21	$CHCl_3$	reflux[a]	7	none	Fe^{3+}-K-10 montmorillonite	95%
22	DCM	RT	2	N/A	ODCT50 4/16/NMM(3 equiv)	94%
11c	DCM	RT	48	sieves	*o*-bromophenylboronic acid (cat.)	99%
23	MeCN	80	15	none	$B(OMe)_3$ (2 equiv)	92%
this work	toluene	reflux[b]	2	Dean−Stark	$B(OH)_3$ (cat.)	85%

[a] Q_{boil} unknown. [b] Q_{boil} = 482 kW m^{-3}.

It is particularly noteworthy from this work that, in the absence of catalyst, raising the volumetric heat input to 482 kW m^{-3} compared to the results obtained with a low rate of Q_{boil} has similar effects to the addition of 5 mol % boric acid. Thus, in the absence of a quantified and controlled rate of Q_{boil} or other means of water removal, the reported performance ascribed to a catalyst may be in serious error.

Three other sets of substrates were studied, and the catalytic effect of boric acid on the reactions was assessed under conditions where the system is not mass-transfer-limited (see Table 4), using a Q_{boil} of 482 kW m^{-3}.

Table 4. Conversions Recorded for Uncatalyzed and Boric Acid-Catalyzed Direct Amidations under Non-Mass-Transfer-Limited Conditions

Acid	Amine	Conversions[a] No Catalyst	Conversions[a] $B(OH)_3$ (5 mol%)
		69%	> 90%
		3%	20%
		2%	8%
		7%	32%

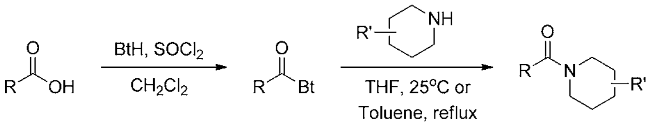
[a] GC yield; acid/amine, 1:1; toluene; 0.5 M; reflux; Dean−Stark; 482 kW m^{-3}; 5.5 h.

The low reactivity of the benzoic acid-based systems compared to other aromatic carboxylic acids had already been reported.[10f,11a,b] However, this is the first report of conversions recorded under conditions where boil-up is quantified and maintained constant. Hence, it is possible to confirm that benzoic acid is less reactive a carboxylic acid than phenylacetic acid independently of water removal efficiency. However, it is also apparent that 4-phenylbutylamine is less reactive than benzylamine. Consequently, in the cases where the heavier amine is used in the absence of a catalyst, the difference in reactivity between phenylacetic acid and benzoic acid (7% vs 2%, respectively) is significantly less than that observed in the case of benzylamine (69% vs 3%, respectively).

The enhancing effect of the catalyst can also be quantitatively assessed. In all cases, boric acid has increased the rate of conversion. The effect is more pronounced in systems where at least one of the reactants is of high or moderate reactivity. Hence, in the case of benzoic acid and 4-phenylbutylamine, only a marginal improvement in conversion is observed.

Acylation of secondary amines by carboxylic acids is often regarded as an even more unfavorable reaction than that of their primary counterparts. Direct synthesis of tertiary amides has scarcely been reported in spite of the range of applications. Useful targets include *N*-acylpiperidine mosquito repellent candidates.[24] The only reported synthetic procedure to date involves the intermediacy of the corresponding acylbenzotriazole via the acylchloride (Scheme 2).

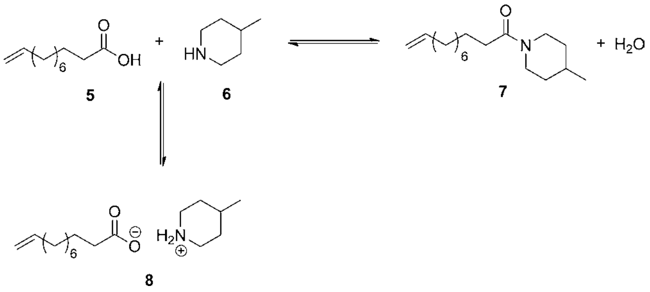
Scheme 2. General Procedure for the Preparation of *N*-Acylpiperidines for Use As Insect Repellents (Bt, Benzotriazolyl)



One of the most potent of the targets, when compared against DEET (*N*,*N*-diethyl-*m*-toluamide), was found to be 4-methyl-1-(1-oxo-10-undecylenyl)piperidine (**7**), for which a yield of 76% was obtained after 4 h under the general procedure in THF at room temperature.[25]

The direct acylation of 4-methylpiperidine (**6**) by undecylenic acid (**5**) in refluxing toluene is a heterogeneous reaction (Scheme 3). The reaction was initially trialled in the absence of a catalyst with the more elevated Q_{boil} of 482 kWm^{-3} (ΔT = 34.3 °C). Only 12% conversion was recorded after 8 h (Figure 5; ■). Comparatively, under the conditions used (Q_{boil} = 482 kW m^{-3} in a 100 mL flask) the conversion to **3** from **1** and **2** was not mass transfer-limited. Therefore, the results indicate that the undecelynic acid/piperidine system is of low reactivity.

Scheme 3



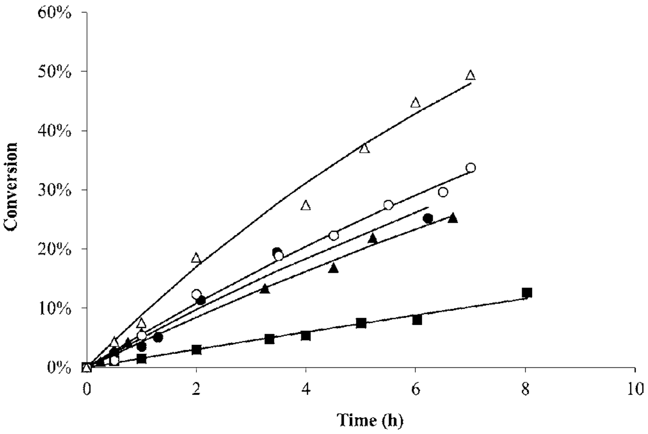


Figure 5. Conversion of **6** with time: ■, Δ*T* = 34.3 °C; ●, 5 mol % $B(OH)_3$, Δ*T* = 14.3 °C; ▲, 5 mol % $B(OH)_3$, Δ*T* = 34.3 °C; ○, 20 mol % $B(OH)_3$, Δ*T* = 14.3 °C; △, 20 mol % $B(OH)_3$, Δ*T* = 34.3 °C.

Higher conversions were attained by using 5 mol % boric acid; 25% of **7** after *ca.* 6.5 h (Figure 5; ● and ▲). However, no further improvement was gained by raising the amount of heat provided to the system; the reaction is kinetic rate-limited. By increasing the catalyst loading to 20 mol % boric acid, the system shifts toward mixed-rate control. At a Q_{boil} rate of 40 kW m^{-3} (ΔT = 14.3 °C), only a marginal improvement in conversion (30% in 6.5 h) was observed whereas when Q_{boil} is increased to 482 kW m^{-3}, conversion levels of 49% are achieved in 7 h (Figure 5; ○ and △).

Implications to Process Chemistry and Catalyst Screening. For both the secondary and tertiary amides studied in this work, the highest rate of conversion was achieved through a combination of catalyst and intensified boiling.

These observations have important consequences on the screening of catalysts for direct amidation using azeotropic distillation. Unless the volumetric heat input rate is reported, it is not possible to make a valid comparison between different catalysts, as the difference in Q_{boil} alone can be responsible for the apparent difference in observed rate. Reduction of the heat losses will also have beneficial effects. Any change in Q_{loss} (i.e., better or worse insulation) has to be taken into account when comparing results.

The underlying principles are not restricted, however, to direct amidation, but they have wider relevance to other mixed-rate control systems, which includes the large class of other condensation reactions. A systematic approach such as the one developed here could therefore be used to determine which of these systems would benefit from an optimized intensified boiling regime, as well as to determine the true efficiency of condensation catalysts and cocatalysts.

Scale-up Considerations. Although intensified boiling combined with an inexpensive catalyst can accelerate the rate of direct amidation to a level where it becomes an attractive method for production scale, the use of conventional glass-lined reactors is problematic. For example, a 5 m^3 Pfaudler reactor with U = 350 W m^{-2} K^{-1} and jacket heat transfer area of 13 m^2, heated by 2.5 bar steam would achieve Q_{boil} of only 15.5 kW m^{-3}. Using such equipment intensified boiling is not possible, and other reactor types must be considered. Flow reactors in the form of tubes would have a high heat transfer area to reactor volume ratio; however, they are not suitable for use with a reactive distillation system, as they do not provide a usable vapor space. Continuous stirred tank reactors (CSTR's) do provide a vapor space and are suitable for use with reactive distillation systems.

A train of CSTR flow reactors with very high volumetric heat transfer rates could be configured to provide intensified reactive distillation for condensation reactions. The system is outlined in Figure 6. The vapor from each vessel would be condensed using a single condenser and fed into a single phase separator. The outlet from the phase separator would feed into each reactor simultaneously.

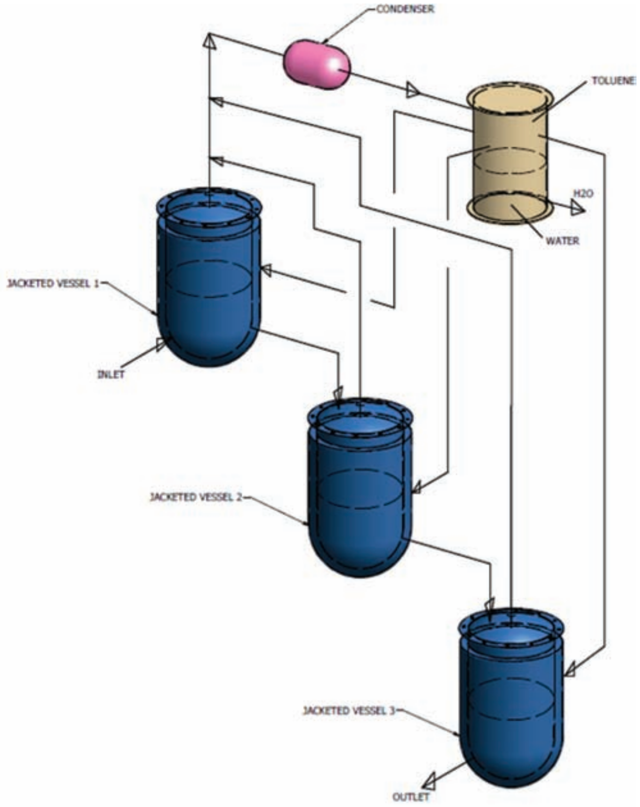


Figure 6. Schematic of a CSTR train for production.

The performance of the system may be calculated using conventional reaction engineering methods.[26] Phenylacetic acid–benzylamine was chosen as the reference system, and reaction rates from Figure 4 (▲, 5 mol % $B(OH)_3$, Q_{boil} = 482 kWm^{-3}) were used to calculate yields for each reactor in the train of CSTR's. Under the non-mass-transfer-limited conditions, the reaction is pseudo-first-order with a rate constant of 3.5×10^{-4} s^{-1}. The calculations assume a jacketed stainless steel cylindrical vessel (U = 700 W m^{-2} K^{-1}) fed with the reaction mixture in toluene. Each vessel is 5 L in volume, and the temperature differential between the jacket and reaction mixture is 20 °C (377 kW m^{-3}). The calculations suggest that 8–10 stages would be required to achieve >97% conversion with a production rate of 42 tonnes per annum.

The simulated performance of a 1 m^3 glass lined batch production reactor is also shown for comparison again using a 20 °C jacket/reactor temperature differential (Q_{boil} = 32 kW m^{-3}).[27] Batch times are based on the 36 h amidation reaction time plus 6 h to allow for the charging of the carboxylic acid and toluene, the highly exothermic addition of the amine to form the salt, and finally discharging the vessel. This vessel would also produce 42 tpa. However, the total volume of the flow reactor system in this calculation is 20 times smaller than the batch vessel, and rather surprisingly, the total energy used for boil up is only 55% that of the batch reactor.[27] Although the batch reactor operates at a low Q_{boil}, its size and long boil-up time result in this extra energy requirement. If the temperature differential were raised to 40 °C (Q_{boil} = 754 kW m^{-3}) in the CSTR's, only six stages would be required to achieve the same performance. Although at first sight a volumetric heat input rate of this order may seem high, it is still much less than the volumetric heat input rate of a domestic hot water kettle (>2000 kW m^{-3}) and far beyond the capability of a typical batch production vessel.

3. CONCLUSIONS

The direct synthesis of amides from the corresponding carboxylic acids and amines is shown to operate under varying degrees of mixed kinetic and mass transfer rate control when water is removed by azeotropic distillation. Unless the volumetric heat input rate is reported, it is not possible to make a valid comparison between different catalysts, as the difference in Q_{boil} alone can be responsible for the apparent difference in observed rate. By characterizing heat transfer and evaporation/boiling processes and relating these phenomena to conversion rates, a systematic screening method to reliably quantify the influence of intensified boiling in direct amidation reactions has been developed.

Intensified boiling during azeotropic reactive distillation combined with an inexpensive catalyst can accelerate the rate of direct amidation to a level where it becomes an attractive method for production scale. The use of a cascade of CSTR flow reactors operating under intensified conditions could provide the necessary high rates of heat transfer and so offer considerable advantage over a conventional batch reactor system.

4. EXPERIMENTAL SECTION

Materials and Equipment. The reactions were carried out in either a standard 3-neck 100 mL flask or a 3-neck 250 mL flask. The Dean–Stark apparatus was a commercially available piece of apparatus from Sigma-Aldrich.

All ^{1}H NMR spectra were recorded on either Varian Mercury-400 or Bruker Avance-400 spectrometers. ^{13}C NMR spectra were recorded on the Varian Mercury-400 and Bruker Avance-400 instruments at frequencies of 100 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS. Mass spectra for liquid chromatography–mass spectrometry (LCMS) were obtained using a Waters Ltd LCT Premier XE spectrometer running in EI mode with the positive electrospray method. GC-MS analysis was carried out on an Agilent 6890N GC equipped with a 5973N MSD Performance Turbo CI running in EI mode, and an Anatune Focus Autosampler/liquid handler. Melting points were recorded using a Stuart Scientific melting point apparatus, Analogue, SMP 11.

Chemical reagents and materials were purchased directly from Sigma-Aldrich and used without further purification, unless stated otherwise.

Direct Amidation: General Procedure. The oil bath temperature was set to 145 °C. In a 3-neck 100 mL round-bottom flask were placed toluene (50 mL), the acid (0.025 mol), the amine (0.025 mol), and boric acid (5 mol %, 77.3 mg). The flask was fitted with a Dean–Stark apparatus and placed in the oil bath. The mixture was stirred and samples taken at regular intervals. Samples were analyzed by GC-MS [injection temperature 250 °C; oven temperature; 50 °C for 0.5 min and then 50–80 at 5 °C min^{-1} and then 80–250 at 30 °C min^{-1} and then hold at 250 °C for 8 min].

Amides Isolation. Following on from the general procedure carried out under catalytic conditions:

The mixture was left to react for a further hour and was then cooled down and filtered. The salt was washed with toluene (2 × 25 mL) and the combined organic phases concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and then washed with 5% HCl (50 mL), brine (50 mL), 5% NaOH (50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*.

N-Benzylphenylacetamide. The general procedure for amide isolation was followed. Spectroscopic details were the same as those reported in the literature.[27]

N-Benzylbenzamide. The general procedure for amide isolation was followed. Spectroscopic details were the same as those reported in the literature.[27]

N-4-Phenylbutylbenzamide. The general procedure for amide isolation was followed. Spectroscopic details were the same as those reported in the literature.[9b]

N-4-Phenylbutylphenylacetamide. The title compound (3.26 g, 50% yield) was isolated as a white solid recrystallized from ethyl acetate/hexane. ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.43–1.47 (m, 2H), 1.53–1.58 (m, 2H), 2.58 (t, 2H, J = 7.7 Hz), 3.21–3.24 (m, 2H), 3.56 (s, 2H), 7.11–7.36 (m, 10H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 28.4, 29.0, 35.4, 39.4, 43.9, 125.8, 127.3, 128.3, 128.3, 129.0, 129.4, 135.0, 142.0, 170.8; HRMS (ES^+) [M^+] 268.1725 ($C_{18}H_{21}NO$ requires 268.1701); m/z (ES^+) 290 (M + Na, 100%), 268, 196; m/z (EI) 268, 267, 176, 91 (100%); elemental analysis (%): calcd for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24, found C 81.00, H 7.81, N 5.05; mp = 61 °C.

4-Methyl-1-(1-oxo-10-undecylenyl)piperidine. The general procedure for amide isolation was followed. Spectroscopic details were the same as those reported in the literature.[25]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

N-4-Phenylbutyl-phenylacetamide characterization data, including ^{1}H NMR spectrum, ^{13}C NMR spectrum, GC chromatogram, and electrospray MS results; and productivity calculations for a train of CSTR's and a batch reactor. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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$$Q_{boil} = \frac{(\Delta n_{ent} \Delta H_{vap_{ent}})}{V \Delta t}$$

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