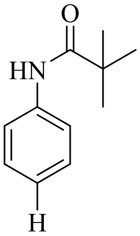
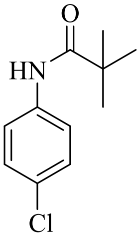
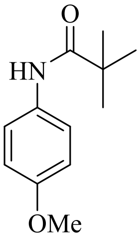
Supplemental Material

I. Solubility Estimates of Boc Derivatives

Experimentally, it would be difficult to accurately determine the solubilities of the Boc derivatives at elevated temperatures since hydrolysis would compete with the solubility measurements. In addition, accurate sampling of the water solutions at temperatures above 100°C would be experimentally problematic. As a consequence the solubilities were estimated using experiments coupled with theoretical calculations. The solubilities of analogous model "hydrolytically stable" amides (**Table A-1**) were determined at a series of temperatures below 100°C (**Figure A-1**).

Table A-1 Analogous substrates selected for solubility measurements

Structure	Name
	N-phenylpivalamide[1]
	N-(4-chlorophenyl)pivalamide[2]
	N-(4-methoxyphenyl)pivalamide[3]

Solubility data for N-phenylpivalamide, N-(4-methoxyphenyl) pivalamide and N-(4-chloro) pivalamide in water were determined by gravimetric analysis as a function of temperature from approximately 22°C up to 76°C. The data obtained are shown in **Figure A-1** were the solubility data (g of solute per L of water) are given. The numbers in **Figure A-1** are representative of experimental solubility of the analogue substrates determined by gravimetric analysis. The temperatures used for measuring the experimental solubility are at or below the melting point of the substrates. No evidence of degradation was observed as a result of the measurements. It should be emphasized that the solubility experiments were carried out by equilibrating the substrate-water system at temperature for 30 minutes with stirring. Homogeneous samples with known volume were then taken for gravimetric analysis. The water solvent of the different samples was removed under vacuum at 30°C and the mass of the solid left was quantified. In the absence of stirring, the experimentally determined solubilities were approximately 30% less. This is an important consideration since the kinetic experiments described in the main text were conducted without stirring. The experimental solubility of the substrates in **Figure A-1**, increases substantially at higher temperatures. The *p*-Cl substituted model had a considerably lower solubility than the models bearing the H or the *p*-OMe group.

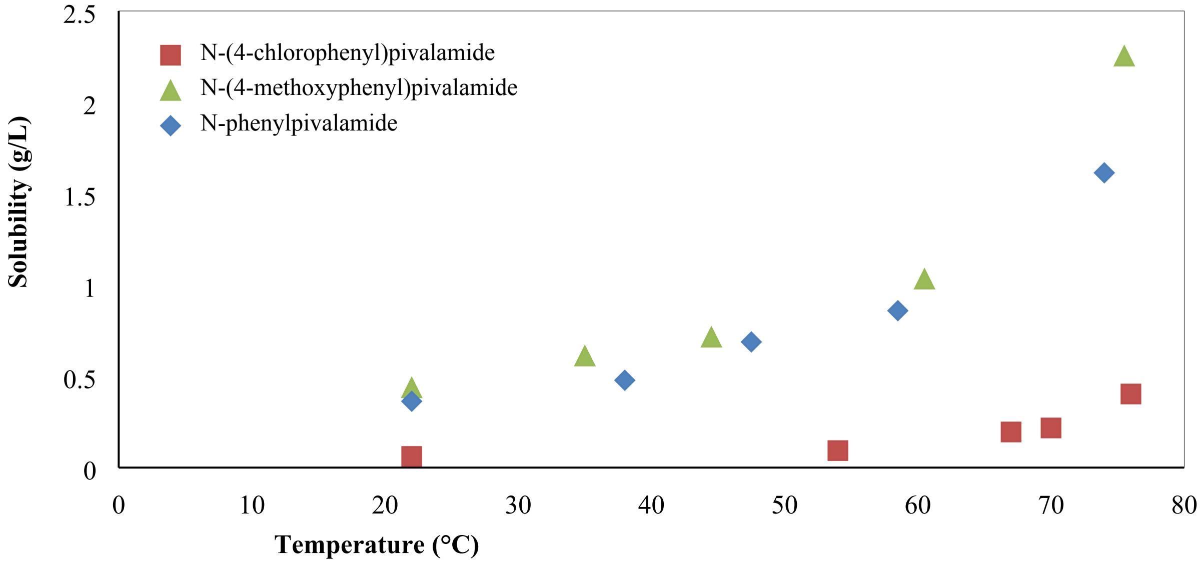


Figure A-1 Experimental solubility by gravimetric analysis

Using the experimental solubilities from **Figure A-1** and the non-ideal solubility equation[4] shown in **Equation A-1**, the solubility of these amide model substrates at 150°C was estimated. Using **Equation A-2**, an average of the activity coefficient was calculated for each substrate and then used to estimate the solubilities at 150°C using **Equation A-3**. A summary of the properties and calculated values are shown in **Table A-2**. The solubility values in water estimated at 150°C are 8.44 g/L for N-(4-methoxyphenyl) pivalamide, 5.84 g/L for N-phenylpivalamide and 1.70 g/L for N-(4-chlorophenyl) pivalamide. The calculated solubilities of the model amides at 150°C indicate that under the hydrolysis conditions presented here the N-phenylpivalamide and N-(4-methoxyphenyl)pivalamide would be completely soluble while the N-(4-chlorophenyl) pivalamide would only be partially soluble (approximately 25%).

$$ln\left(\frac{1}{x_2\gamma_2}\right) = \frac{\Delta H_{fus}}{R}\left[\frac{T_m - T}{T_m T}\right]$$ **Equation A-1**

$$\gamma_2 = \frac{1}{x_2.e^{\frac{\Delta H_{fus}}{R}\left[\frac{T_m - T}{T_m T}\right]}}$$ **Equation A-2**

$$x_2 = \frac{1}{\gamma_2.e^{\frac{\Delta H_{fus}}{R}\left[\frac{T_m - T}{T_m T}\right]}}$$ **Equation A-3**

Table A-2 Properties and Estimated Values for Model Amides

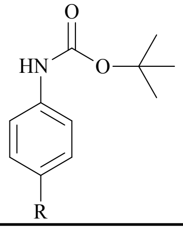
Entry	**Substrate**	**ΔH_{fus}[a] (J/g)**	**T_m[b] (K)**	**MW (g/mol)**	**γ_{avg}[c]**	**Estimated Solubility at 150°C (g/L)**
1	N-phenylpivalamide	131.40	407.14	177.24	2189	5.84
2	N-(4-methoxyphenyl)pivalamide	120.75	400.14	207.27	2053	8.44
3	N-(4-chlorophenyl)pivalamide	141.40	423.14	211.69	6934	1.70

[a, b] Measured using DSC

[c] Estimated from experimental data and correspond to the average from the different solubility measurements a s a function of temperature.

The solubilities of the Boc protected substrates were also calculated using COSMO-RS and data obtained from ACD Software at 25°C. The results are summarized in **Table A-3**. The solubility trend at 25°C follows the order: *tert*-butyl phenylcarbamate ≥ *tert*-butyl (4-methoxyphenyl) carbamate > *tert*-butyl (4-chlorophenyl) carbamate and *tert*-butyl (4-acetamidophenyl) carbamate > *tert*-butyl (4-pivalamidophenyl) carbamate. It is assumed that this same trend is followed at higher temperatures, although the solubilities of the substrates are enhanced as the temperature increases. As well, a lower solubility was predicted for the Cl substituted substrate using the two different software packages compared to H and OMe substituted substarte.

Table A-3 Predicted Solubilities at 25°C of the Boc Substrates

Substrate	Entry	R	Solubility Estimated by COSMO-RS (g/L)	Solubility Estimated by ACD Software (g/L)
	4	H	0.12	0.33
	5	OMe	0.12	0.31
	6	Cl	0.03	0.06
	7	N-Ac	0.87	---
	8	N-Piv	0.06	---

II. Kinetics of Boc Derivative Hydrolyses

The kinetics of the hydrolysis of the Boc derivatives of aniline, *p*-methoxyaniline and *p*-chloroaniline were analyzed using the integral method rate expressions for both first order and autocatalytic processes[5]. The expression for a first order reaction is shown in **Equation A-4** where C_{Ao} is the initial concentration of Boc protected aniline, C_A is the concentration of protected aniline at time t and k the apparent rate constant with units of min^{-1}. The expression for an autocatalytic reaction order is shown in **Equation A-5** where C_R and C_A are the concentration of unprotected and protected aniline at time t, C_{Ao} and C_{Ro} are the initial concentration of Boc protected aniline and unprotected aniline, Co is the sum of C_{Ao} and C_{Ro} and k is the apparent rate constant with units of $L.(mol.min)^{-1}$. The concentration after 5 minutes was used as the initial concentration for the analysis, since this is the time needed for the hydrolysis reaction to reach the desired temperature of 150°C. These integrated rate equations were used to fit the experimental data with a rate equation. Each of the substrates was analyzed using the integrated rate equations and their corresponding plots are displayed in **Figure A-2** to **Figure A-4**.

$$ln\left(\frac{C_{Ao}}{C_A}\right) = kt$$

Equation A-4

$$ln\left(\frac{C_R C_{Ao}}{C_A C_{Ro}}\right) = C_o k t$$

Equation A-5

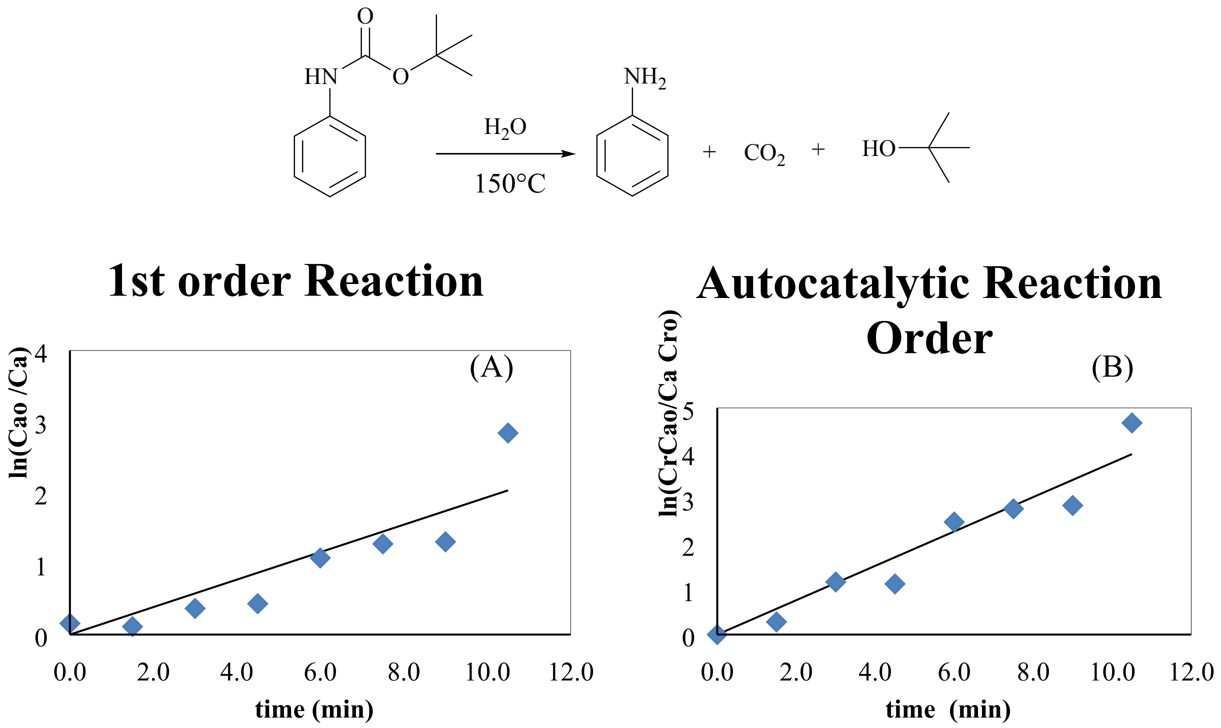


Figure A-2 Integral method analysis for the average data of Boc protected aniline substrate: (A) first order reaction analysis and (B) autocatalytic reaction order analysis

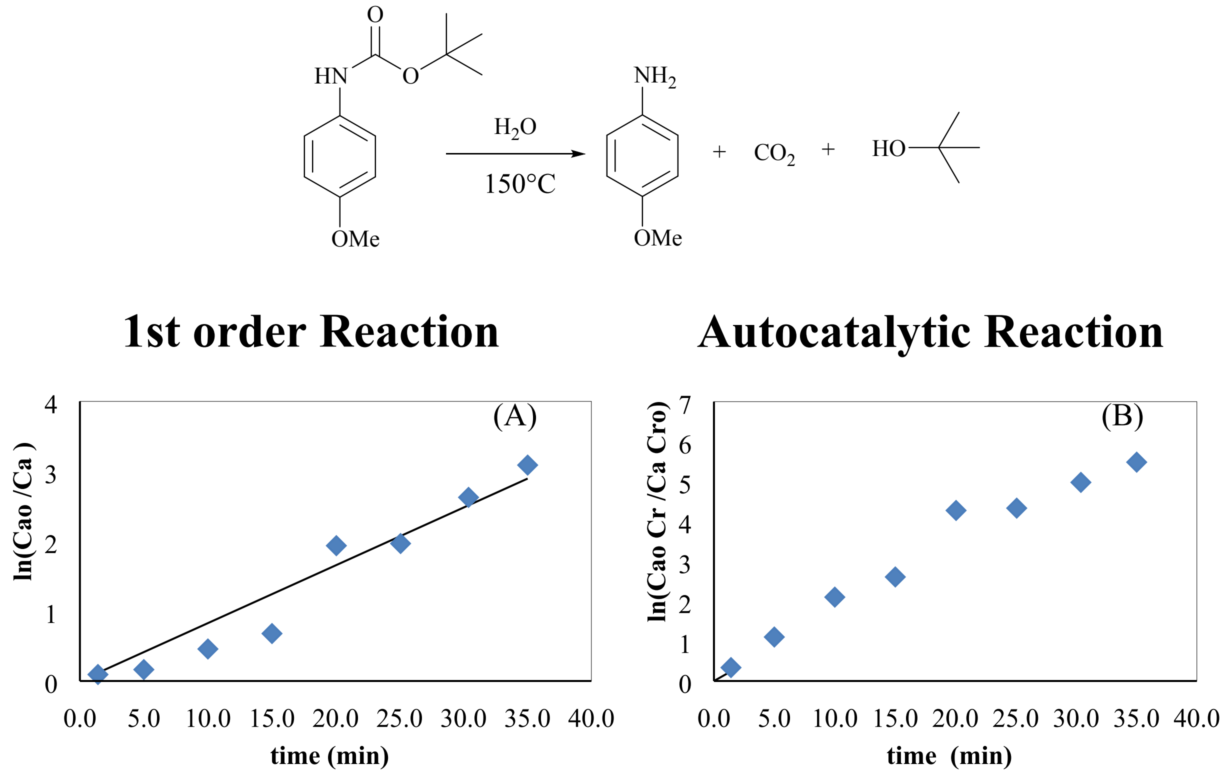


Figure A-3 Integral method analysis for the average data of Boc protected *p*-methoxyaniline substrate: (A) first order reaction analysis and (B) autocatalytic reaction order analysis

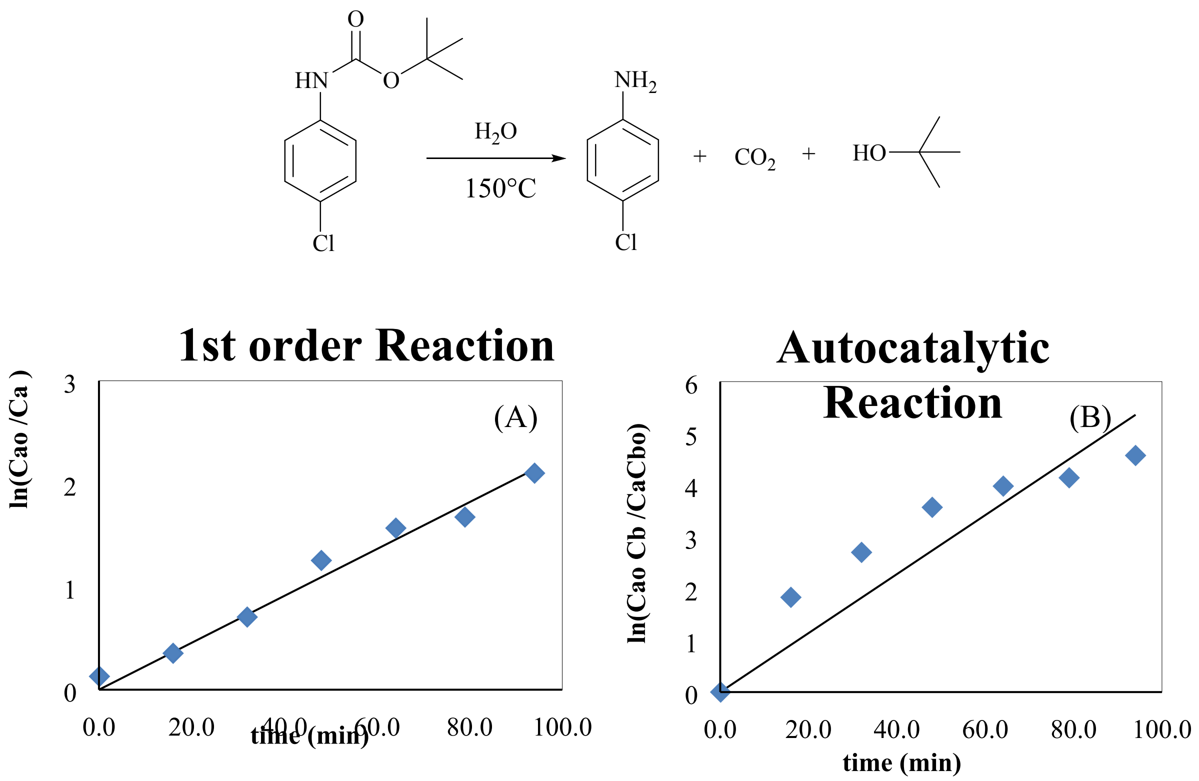


Figure A-4 Integral method analysis for the average data of Boc protected *p*-chloroaniline substrate: (A) first order reaction analysis and (B) autocatalytic reaction order analysis

References and Notes

1. To 1 mL (1.022 g, 0.011 mol) of aniline was added 25 mL anhydrous dichloromethane (DCM) under nitrogen with stirring in an ice water bath. 1.53 mL (1.113 g, 0.011 mol) of triethylamine was added dropwise to the cold solution. The reaction mixture was stirred for 10 min and 1.38 mL (1.35 g, 0.011 mol) of pivaloyl chloride was added dropwise (triethylammonium chloride solid precipitated). The reaction was allowed to reach room temperature and stirred overnight. The reaction was filtered and the residue washed with DCM. The filtrate was placed under reduced pressure to remove the organic solvent. The crude was purified on a silica column with ethyl acetate:hexane (10:90) as the eluent. 1.44 g (74%) of white solid was recovered. 1H NMR (400 MHz, CDCl3) δ 1.20 (s 9H), 7.04-7.08 (tt, 1H), 7.23-7.28 (tt, 2H), 7.51-7.54 (dt, 2H). 13C NMR (400 MHz, CDCl3) δ 27.33, 39.31, 120.15, 123.90, 128.55, 137.93, 176.64. HRMS (C11H15NO) Exact Mass Calculated: 177.1154 Found: 177.1158
2. From commercial source
3. To 1 g (0.00812 mol) of 4-methoxyaniline was added 25 mL anhydrous dichloromethane (DCM) under nitrogen with stirring in an ice water bath. 1.13 mL (.822 g, 0.00812 mol) of triethylamine was added dropwise to the cold solution. The reaction mixture was stirred for 10 min and 1 mL (0.98g, 0.00813 mol) of pivaloyl chloride was added dropwise (triethylammonium chloride solid precipitated). The reaction was allowed to reach room temperature and stirred overnight. The reaction was filtered and the residue washed with DCM. The filtrate was placed under reduced pressure to remove the organic solvent. The crude was purified on a silica column with ethyl acetate:hexane (10:90) as the eluent. 0.353 g (21%) of white solid was recovered. 1H NMR (400 MHz, CDCl3) δ 1.22 (s 9H), 3.69 (s, 1H), 6.72-6.77 (dd, 2H), 7.37-7.33 (dd, 2H). 13C NMR (400 MHz, CDCl3) δ 27.30, 39.06, 55.12, 113.63, 122.15, 131.03, 156.02, 176.57. HRMS (C12H17NO2) Exact Mass Calculated: 207.1259 Found: 207.1257
4. Prausnitz, J. M.; Lichtenthaler, R. N.; Gomes de Azevedo, E., *Molecular Thermodynamics of Fluid-Phase Equilibria*. 3rd Edition ed.; Prentice Hall: New Jersey, 1999.
5. Levenspiel, O., *Chemical Reaction Engineering*. 2nd Edition ed.; John Wiley & Sons, Inc.: New York, 1995.