

Amide Bond Formation via Reversible, Carboxylic Acid-Promoted Lactone Aminolysis

Megan A. Foley and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U.S.A.

Abstract:

A rapid carboxylic acid-promoted lactone aminolysis is reported. A number of carboxylic acids were found to promote this amide bond-forming transformation, with aliphatic acids being the most efficient. This reaction is an equilibrium process ($K_{\text{eq}} \approx 1.8$), and mechanistic investigations are consistent with mediation of a kinetically important proton-transfer step by the carboxylate, i.e., the conjugate base of the acid employed.

Introduction

Aliskiren (**1**) is the first orally available renin inhibitor approved by the FDA for the treatment of hypertension (Figure 1). Recently our laboratory has become interested in multistep, continuous flow chemical synthesis.¹ We selected **1** as a test case for the development of a robust continuous manufacturing process, beginning with an advanced intermediate and culminating in isolation of a pure drug substance. The near-term goal of the project is development of a synthetic route to **1** from lactone **2** (Scheme 1) with the long-term goal of implementing the reactions and purifications in a continuous system.

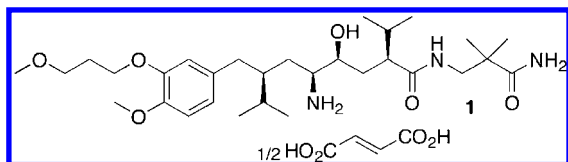
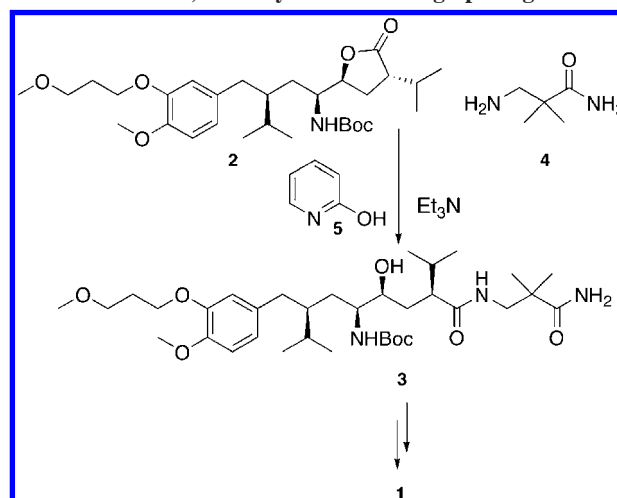


Figure 1. Aliskiren.

Aliskiren possesses a secondary amide moiety (**3**) that is commonly formed via ring-opening of the corresponding lactone (Scheme 1). Preparation of the amide from lactone **2** often involves a multistep sequence beginning with hydrolytic lactone opening to the corresponding acid, followed by protection of the liberated alcohol and amide bond formation, employing a peptide-coupling reagent.² Alternatively, direct lactone aminolysis procedures suffer from long reaction times or require harsh reaction conditions such as, AlMe_3 .³ With the ultimate goal of developing a continuous process, we set the following as criteria for conversion of **2** to **3**: (a) one chemical step, (b) a reaction time of less than one hour, (c) the use of only

inexpensive reagents and catalysts, (d) minimal solvent usage, and (e) a nonchromatographic purification. The closest precedent to this approach involves prolonged heating of the lactone **2** and amine **4** in the presence of 2-hydroxypyridine (**5**) and triethylamine, either neat⁴ or using *tert*-butylmethyl ether as a solvent (Scheme 1).⁵

Scheme 1. Direct, aminolytic lactone ring-opening



Results and Discussion

Optimization of the Lactone Aminolysis. We initially investigated several refinements of the literature process. For example, we screened several different catalysts⁶ and solvents and found that **5** was the most efficient and that the reaction was the fastest in the absence of solvent, but nevertheless required 6 h to reach 73% conversion at 90 °C. Increasing the reaction temperature to 120 °C and the stoichiometry of **4** from 3 to 5 equiv accelerated the reaction, resulting in 87% conversion after 90 min. While this finding was promising, 2-hydroxypyridine is of low water solubility, a trait that would complicate the purification step for a reaction in a continuous system.

In 2001, Novartis disclosed a general lactone-opening procedure employing a combination of sodium 2-ethylhexanoate (Na^+ salt of **6**) and an ammonium chloride salt as the catalytic system.⁷ These conditions seemed promising with regard to

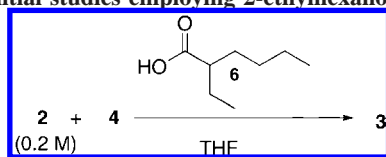
* Author to whom correspondence may be sent. E-mail: tfj@mit.edu.

- (1) Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 432.
- (2) (a) Kempf, D. J.; de Lara, E.; Stein, H. H.; Cohen, J.; Egan, D. A.; Plattner, J. J. *J. Med. Chem.* **1990**, *33*, 371. (b) Nadin, A.; López, J. M. S.; Neduveilil, J. G.; Thomas, S. R. *Tetrahedron* **2001**, *57*, 1861. (c) Yin, T. I.; Yang, G.; Tarassishin, L.; Li, Y.-M. *J. Org. Chem.* **2004**, *69*, 7344. (d) Maibaum, J.; Stutz, S.; Göschke, R.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Rahuel, J.; Baum, H.-P.; Cohen, N.-C.; Schnell, C. R.; Fuhrer, W.; Gruetter, M. G.; Schilling, W.; Wood, J. M. *J. Med. Chem.* **2007**, *50*, 4832.
- (3) Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 4766.

- (4) (a) Rüeger, H.; Stutz, S.; Göschke, R.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085. (b) Sandham, D. A.; Taylor, R. F.; Carey, S. J.; Fässler, A. *Tetrahedron Lett.* **2000**, *41*, 10091. (c) Dondoni, A.; De Lathauwer, G.; Perrone, D. *Tetrahedron Lett.* **2001**, *42*, 4819. (d) Herold, P.; Stutz, S.; Spindler, F. WO/02/02508, 2002. (e) Dong, H.; Zhang, Z.-L.; Huang, J.-H.; Ma, R.; Chen, S.-H.; Li, G. *Tetrahedron Lett.* **2005**, *46*, 6337. (f) Hanessian, S.; Guesné, S.; Chénard, E. *Org. Lett.* **2010**, *12*, 1816.
- (5) Sedelmeier, G.; Mickel, J. S.; Rüeger, H. WO/2006024501, 2006.
- (6) Nucleophilic catalysts examined include DMAP, DABCO, phenol, thiophenol, PPh_3 , and 4-pyrrolopyridine.

purification; the acid and the excess amine might be easily separated from the product using a simple continuous liquid–liquid extraction.⁸ However, use of this procedure for the opening of lactone **2** with amine **4** resulted in only a trace of **3** (Table 1, entry 1). Additionally, as it would likely clog a continuous flow reactor; NaCl, a byproduct generated from the ammonium chloride salt and sodium carboxylate, was a highly undesirable component. A modified procedure where free amine (**4**) in the presence of the carboxylic acid (**6**) was used, only afforded moderate improvement, with a the rate of product formation corresponding to a reaction time far longer than our target of one hour (Table 1, entries 3 and 4). Altering the stoichiometry of **4** with respect to acid **6** was beneficial, but the reaction outcome still fell short of our established criteria (Table 1, entry 5). Screening a number of solvents and mixtures of solvents capable of solubilizing both the lactone and the amine did not afford a significant improvement in either reaction rate or yield.

Table 1. Initial studies employing 2-ethylhexanoic acid



entry	promoter (equiv)	amine (equiv)	<i>T</i> (°C)	time (h)	conversion (%)
1	6 Na ⁺ (2.5)	4 HCl (1.5)	25	17	<5
2	6 Na ⁺ (2.5)	4 HCl (1.5)	70	6.5	15
3	6 (2.5)	4 (1.5)	70	50 min	5
4	6 (2.5)	4 (1.5)	70	6	23
5 ^a	6 (1)	4 (3)	70	6	67

^a [2]₀ = 1.0 M.

In an effort to maximize both rate and yield we turned to an examination of solvent-free⁴ or “melt” conditions. Both lactone **2** and amine **4** have relatively low melting points, and therefore, we chose 100 °C as the starting point of our investigations (Table 2, entry 1). Increasing the temperature to 120 °C provided 84% conversion in 50 min (Table 2, entry 3). The conversion did not change upon extended heating (Table 2, entry 4), and further experiments demonstrated that the reaction was in fact an *equilibrium process* with a *K*_{eq} of approximately 1.8 (see Supporting Information). Additional amine was only minimally effective in shifting the equilibrium toward product (see Supporting Information for complete table), and thus we carried out the remainder of our experiments using 5 equiv of **4**.

Table 2. Effects of temperature and amine stoichiometry^a

entry	<i>T</i> (°C)	equiv 4	time (min)	conversion (%) ^b
2	100	5	50	71
3	110	5	50	80
4	120	5	50	84
5	120	5	120	83 ^b
6	130	5	50	80 ^c
7	120	10	50	89
8	120	15	50	90
9	120	20	120	93
10	120	100	240	94

^a Reactions were run using 1 equivalent of **2** (250 mg, 0.47 mmol) and 1 equivalent of **6**. ^b Over 20 experiments were conducted using these conditions on scales from 200 mg to 25 g. The conversions ranged from 81–85%. ^c Byproduct formation was observed after 30 min. When the reaction was heated to 140 °C, the byproduct formation was significant. Several additional products were formed at higher temperatures (not isolated).

We also confirmed the necessity of the carboxylic acid as promoter; extremely low conversion was observed in its absence, even with extended reaction times (Table 3, entry 1). While 10% catalyst loading gave good conversion after 3 h (Table 3, entries 4–6), equilibrium could only be achieved in the targeted 1 h with use of a full equiv of **6**. Amounts of acid greater than 1 equiv did not significantly improve the rate.¹⁰ Thus, conditions shown in entry 2, Table 3 satisfied our criteria for reaction time, number of chemical steps (1), reagent and promoter costs, and solvent usage (none). There was some concern that in the absence of solvent the neat reaction mixture would be too viscous for conventional pumping mechanisms, thus hindering the development of a continuous system for this transformation. However, experimental data have indicated that the reaction mixture was flowable¹¹ at elevated temperature. Investigations directed toward realization of a continuous process for this reaction are ongoing.

Table 3. Effect of 2-ethylhexanoic acid on reaction rate

entry	equiv 6	time (min)	conversion (%)
1	0	50	3
2	1	50	84
3	1 (6 Na ⁺)	50	17
4	0.1	50	54
5	0.1	120	77
6	0.1	180	84
7	0.5	50	80
8	0.5	90	87

The general scope of the reaction was examined using a variety of alkyl amines. 2-Ethylhexanoic acid proved to be a versatile promoter of the lactone-opening reaction, as moderate to good yields were observed for each case (Table 4). Moreover, the remaining lactone could be recovered nearly quantitatively (Table 4, entry 1). We did not observe any conversion when *tert*-butyl amine was subjected to the reaction conditions at 46 °C (bp of amine). However, this observation was not surprising as we had established that the reaction proceeded best as a melt at elevated temperatures. Increasing the reaction temperature to 83 °C (mp of **2** and **4**) did not afford product; it is unclear if this is due to complete vaporization of *tert*-butyl amine or due to the steric nature of the amine. Closed continuous systems with no headspace can offer advantages over traditional batch reactors when volatile reagents are employed,¹ and thus this reaction could potentially proceed in a continuous flow reactor at elevated temperature.

Table 4. Amine scope^a

entry	amine	product	yield ^b (%)
1	4	3	83 (13% recovered 2) ^c
2	hexylamine	3a	82
3	benzylamine	3b	79
4	neopentyl amine ^d	3c	76
5	cyclohexyl amine	3d	60

^a We have not confirmed that entries 2–5 are an equilibrium process. ^b Isolated yields average of two runs. ^c This reaction was performed on scales up to 25 g of lactone **2**. The conversion and purity as determined by HPLC were in good agreement with the data for small reactions from which the isolated yield was determined. ^d Reactions run at 83 °C.

Although 2-ethylhexanoic acid seemed to be an effective promoter for lactone aminolysis we nonetheless explored other acids for this purpose. Given the pK_a differences between the amine and the acid, we expected that the predominant acidic species in the reaction would be the protonated amine. Thus, we prepared the 2-ethylhexanoate salt of **4** (**7**) and found that it performed as predicted: In a reaction of 1 equiv of **7** and 4 equiv of free amine **4**, 85% conversion was observed after 50 min. Surprisingly, the ammonium chloride salt of **4** (**8**) gave much poorer results under identical reaction conditions (40% conversion). We suspected that the hexanoate counterion was important for the solubility of the ammonium species, whereas the HCl salt was largely insoluble, resulting in a much slower reaction.

We screened several other carboxylic acids and found further support for the importance of reaction homogeneity. In cases where the reaction was homogeneous, the reactions proceeded with near identical conversion (Table 5; see Supporting Information for complete table), but reactions with visible precipitate were slower (Table 5; entries 1, 6–9), some to the point of being impractical (Table 5; entry 10).¹²

Table 5. Screen of aliphatic carboxylic acids^a

entry	acid	rxn appearance	conversion (%)
1	acetic	visible solid	75
2	propanoic	homogeneous	83
3	hexanoic	homogeneous	82
4	pivalic	homogeneous	85
5	cyclopentane	homogeneous	82
6	trichloroacetic	visible solid	51
7	perfluorooctanoic	visible solid	35
8	camphoric	visible solid	66
9	malic	visible solid	10
10	tartaric	visible solid	7

^a Lactone **2** (250 mg, 0.47 mmol) amine **4** (271 mg, 2.33 mmol), and one equivalent of the acid were heated to 120 °C for 50 min.

Table 6. Effect of benzoic acid substitution on reaction rate^a

entry	benzoic acid substituent	pK_a (in DMSO)	α	relative rate ^b ($rate_x/rate_H$)	conversion at 50 min (%)
1	3-(CH ₃) ₂ N ^c	5.1	-0.211	1.16 ^d	70 ^d
2	3-Me	4.24	-0.069	1.14 ^d	71 ^d
3	H	4.2	0	1	69 ^d
4	2-OMe	4.09		0.74	59 ^d
5	3-OMe	4.09	0.115	0.94 ^d	68 ^d
6	2-Me	3.91		1.12	72 ^d
7	3-I	3.86	0.352	0.69 ^d	53 ^d
8	3-Cl	3.83	0.373	0.65 ^d	55 ^d
9	3-Br	3.81	0.391	0.60 ^d	54 ^d
10	3-CF ₃	3.79	0.46	0.61 ^d	51 ^d
11	3-NO ₂	3.45	0.71	0.53 ^d	49 ^d
12	4-NO ₂	3.44	0.778	0.45	42 ^d
13	2-Cl	2.94		0.49	45
14	2-Br	2.85		0.51	42
15	2-I	2.85		0.47	44
16	nicotinic	2.84			46
17	picolinic	1.07		0.27	27

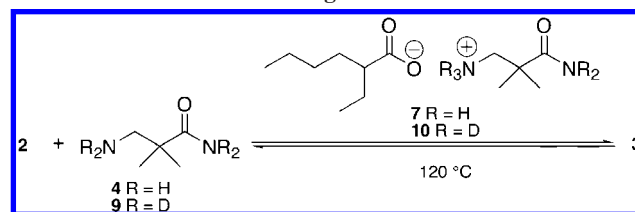
^a Lactone **2** (250 mg, 0.47 mmol) amine **4** (271 mg, 2.33 mmol) and one equivalent of the acid were heated to 120 °C for 50 min. ^b The overall order of the reaction and rate constants were not determined rate constants. The initial reaction rates used to calculate the relative rates in the table were determined by taking the slope of the line obtained by plotting conversion versus time for the first 10 minutes of the reaction. The scale of the reaction (0.46 mmol) and the size of the reaction vessel (5-mL microwave vial) were the same in all cases. ^c We have not ruled out the possibility that the aniline nitrogen participates in the reaction. ^d Average of two or more reactions (conversions were within 2–5% of one another).

Mechanistic Investigations. We extended our study to include benzoic acid derivatives with a range of pK_a values (Table 6).¹³ A surprising general trend emerged. A decrease in the acidity of the promoter employed gave an increase in reactivity; i. e., pK_a and rate are positively correlated. These results suggest that, in addition to solublizing the ammonium salt, the conjugate base of the acid catalyst may play an important role in, or prior to, the rate-determining step of the reaction.

A plot of $\log(rate_x/rate_H)$ versus the σ^{14} values for the meta- and para-substituted benzoic acids affords a line with a small negative slope ($\rho = -0.432$; $R^2 = 0.973$) (Chart 1).¹⁵ The small, negative value of ρ suggests that there is a small increase in positive charge¹⁶ on the carboxylate during the rate-determining step. In the absence of solvent, a kinetically important proton transfer facilitated by the carboxylate could account for these observations.

Deuterium-labeling experiments also support the hypothesis that proton transfer is kinetically important. A small but measurable normal isotope effect was found for the reaction shown in Scheme 2 ($rate_H/rate_D = 1.4$).¹⁷

Scheme 2. Deuterium-labeling studies



Deuterium-labeling experiments employing salts **11–14** and either amine **4** (salts **11** and **13**) or amine **9** (salts **12** and **14**) also exhibited a small normal isotope effect of 1.4 ($R^1 = H$) and 1.6 ($R^1 = NO_2$) (Scheme 3). The isotope effect for these substituents is similar in value to that observed for 2-ethylhexanoic acid, and we thus conclude that the reaction proceeds through a similar mechanism with all three catalysts.

Scheme 3. Deuterium-labeling studies

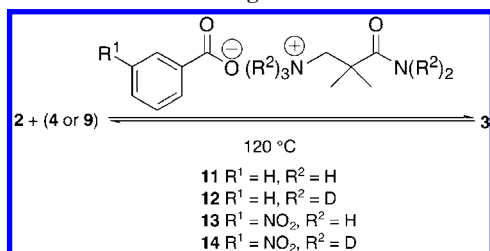
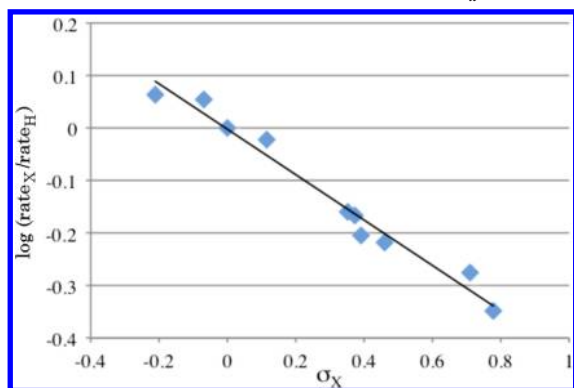


Chart 1. Plot of relative reaction rate versus σ_x



While this reaction is not directly analogous to aminolysis reactions carried out in water, we think comparison to these reactions is instructive. Jencks has demonstrated that aminolysis reactions involving poor leaving groups, such as alkyl alcohols, proceed through a water-mediated rate-determining proton-transfer step from nitrogen to oxygen.¹⁸ By analogy, in our system the carboxylate may play the role of water serving to transfer a proton in a kinetically important step. If this is the case we would expect to (and do) see a correlation between benzoic acid derivatives and reaction rate.

The deuterium-labeling studies and the linear correlation between reaction rate and the Hammett parameters for substituted benzoic acids present a strong argument for a kinetically important proton-transfer step involving the carboxylate. Two

pathways for the acid-catalyzed reaction are presented in Figure 2. Path A involves proton transfer to afford activated lactone **A**. Attack by amine **4** gives tetrahedral species **B**, which undergoes another proton transfer, giving neutral intermediate **C**. Protonation of the ether oxygen (**D**) generates a good leaving group, facilitating conversion to **3**. Alternatively, under the basic reaction conditions expulsion of an alkoxide followed by proton transfer to give **3** is also possible.

One can also arrive at intermediate **C** via attack on a neutral lactone by the amine to generate the charge-separated intermediate **G**. A carboxylate mediated proton transfer then affords **C** in either a stepwise (**H**) or concerted fashion. While we cannot distinguish between these two reaction paths, formation of intermediate **C** through Path B is consistent with our data and with the mechanism proposed by Jencks.¹⁹ While intermediate **C** can undergo ring-opening without protonation, the reaction is significantly faster when carboxylic acid, rather than sodium carboxylate, is employed (Table 3, entries 2 and 3), leading us to propose that lactone opening proceeds via intermediate **D**.

Conclusion

We have developed a rapid method for lactone aminolysis reactions that will be expected to be amenable for use in a continuous process. These conditions are particularly effective for certain hindered, electron-poor amines such as **4**. Aliphatic carboxylic acids were found to be the most effective promoters for this reaction, which we discovered to be an equilibrium process. While the reaction is acid-catalyzed, the conjugate base nonetheless plays a critical role in a kinetically important proton-transfer step. We found that the electronic properties of the carboxylate have a significant effect on the reaction rate, opening the possibility of developing an acid promoter or catalyst that will afford an even faster reaction.

Experimental Section

Materials and Methods. All solvents were either anhydrous, obtained from a commercially available purification system, or

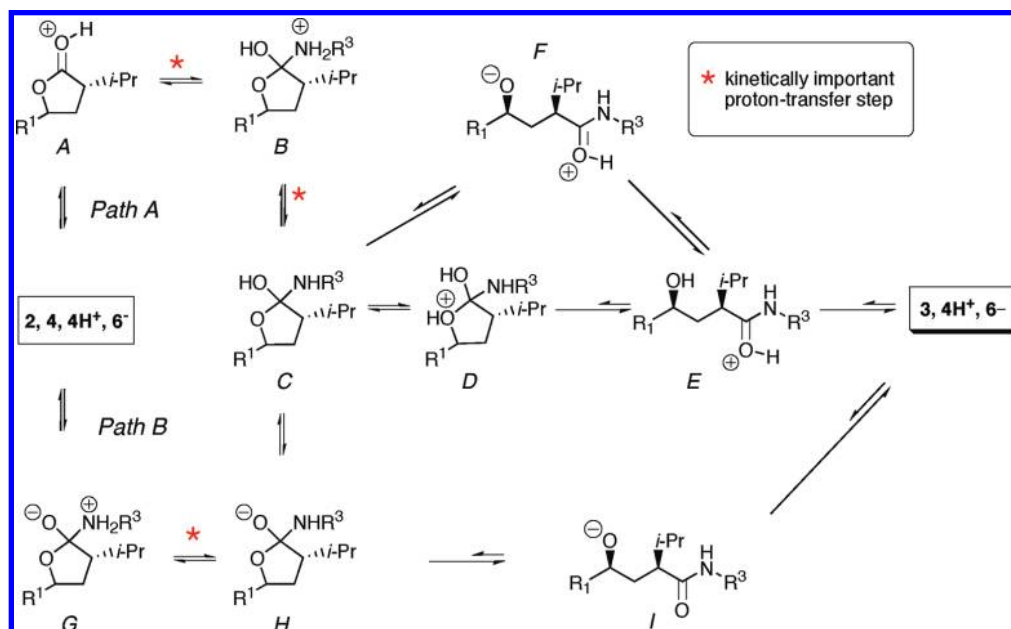


Figure 2. Possible reaction mechanisms.

ACS reagent grade. Reactions were carried out in oven-dried glassware. Oxygen was not removed from the reaction atmosphere unless specifically noted. Lactone **2** and amine **4** were obtained from Novartis and used without further purification. Benzylamine was distilled before use. Analysis was performed using reverse phase Agilent 1200 series LC/MS with a Zorbax SB-C18 column using an acetonitrile and an ion pairing reagent (1 L water, 5.65 g of hexanesulfonic acid sodium salt monohydrate, 2.75 g of sodium dihydrogen phosphate pH 2.3 adjusted with phosphoric acid) mobile phase (66:36 acetonitrile to ion pairing reagent). The product eluted in 3.7 min, and the starting lactone eluted in 14.2 min). The eluent was monitored at 254 and 280 nm. Preparative chromatographic separations were performed using Silicycle silica gel (230–400 mesh).

General Procedure for Lactone Opening. Lactone **2** (500 mg, 0.93 mmol) was placed in a 5-mL microwave vial (Biotage) equipped with a stir bar. Amine **4** (4.7 mmol) and 2-ethylhexanoic acid **6** were added and the vial was sealed. The vial was placed in an oil bath (120 °C except where noted) and heated for 50 min. The vial was then removed from the bath and unsealed. EtOAc (2 mL) and H₂O (2 mL) were added immediately, and the solution was allowed to stir and cool to

room temperature over 10 min. The mixture was poured into a separatory funnel, and the layers were separated. The aqueous phase was extracted twice with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The resulting oily solid was purified via column chromatography (2:1 hexanes/EtOAc to 1:1 hexanes/EtOAc).

General Procedure for Reaction Screening. A 5-mL microwave vial was charged with a stir bar. The lactone **2** (250 mg, 0.467 mmol), the amine **4** (271 mg, 2.33 mmol, unless otherwise indicated in Table 1), and the acid catalyst (1 equiv) were added, and the reaction was placed in a 120 °C oil bath. Samples were taken at the indicated time points by inserting a capillary pipet into the reaction vial and removing an aliquot of the viscous reaction mixture. In the absence of solvent, accurate addition of an internal or external standard on small scale was not reproducible. The reactions were very clean, showing only product and starting materials. The reaction progress was measured using the relative areas of the starting lactone and the amide product peaks on the LC/MS traces. Isolated yield and conversions were in good agreement.

Acknowledgment

This work was supported by the Novartis-MIT Center for Continuous Manufacturing. We thank the members of this team for advice, in particular Gerhard Penn, Berthold Schenkel, Oljan Repic, Thierry Schlama, Mike Girgis, Lukas Padeste, and Felix Kollmer. We thank Novartis for the generous donation of lactone **2** and amine **4**. We thank Dr. Randy Ewoldt (Hatsopoulos Microfluidics Laboratory at MIT) and Patrick Heider (Jensen Laboratory at MIT) for assistance with viscosity measurements. We also thank Professor Klavs F. Jensen, Professor Stephen L. Buchwald and their respective group members, Dr. Jeffery A. Byers and Dr. Matt Bedore (all MIT) for insightful discussions.

Supporting Information Available

Experimental procedures, complete tables, and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Received for review May 7, 2010.

OP1001269

- (7) Liu, W.; Xu, D. D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439.
- (8) Kralj, J. G.; Sahoo, H. R.; Jensen, K. F. *Lab Chip* **2007**, *7*, 256.
- (9) In reactions where **3** was isolated, conversion (LC/MS) and isolated yield were in good agreement (see Table 4, entry 1). The excess amine and acid could be recovered as a mixture from the aqueous phase in near quantitative yield (composition determined by ¹H NMR in D₂O).
- (10) Increasing the amount of **6** to either 1.5 or 2 equiv did not significantly improve the reaction rate. Employing an excess of **6** with respect to amine **4** led to byproduct formation.
- (11) The viscosity at 120 °C was determined to be 77 cP.
- (12) We screened several sulfonic acids and mineral acids and found that, even for the acids that afforded soluble ammonium salts, the reaction rates were much slower, (+)-CSA, (–)-CSA, and (±)-CSA gave the best results but only reached ~30% conversion after 2 h.
- (13) The pK_a values given in Table 6 are for the acids in DMSO. The pK_a values of the acids in the reaction medium are not known.
- (14) (a) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191. (b) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420.
- (15) The ammonium salts formed from 4-substituted benzoic acids (CF₃, OMe, Cl, and I) were not fully soluble in the reaction mixture, and the results are not included in Table 6.
- (16) The small, negative ρ value can also be thought of as a decrease in negative charge.
- (17) No equilibrium isotope effect was observed. The rates using **2** with ND-Boc were the same as when the proteo compound was used.
- (18) (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Barnett, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 4199.