FULL PAPER

Metal-Free Synthesis of N-Aryl Amides using Organocatalytic Ring-Opening Aminolysis of Lactones

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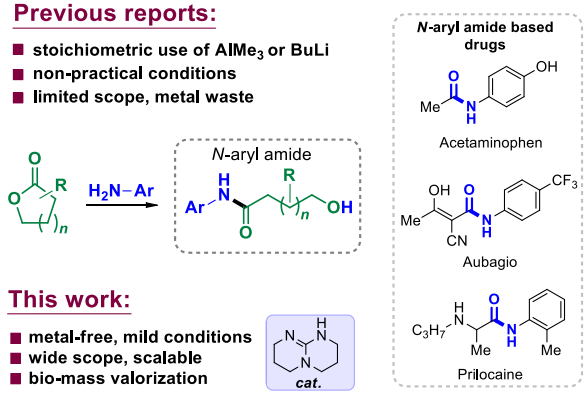
Abstract: Catalytic ring-opening of bio-sourced non-strained lactones with aromatic amines can offer a straightforward, 100% atom-economical and sustainable pathway towards relevant *N*-aryl amide scaffolds. We herein report the first general, metal-free and highly efficient *N*-aryl amide formation from poorly reactive aromatic amines and non-strained lactones under mild operating conditions using an organic bicyclic guanidine catalyst. This protocol has great application potential as exemplified by the formal syntheses of drug relevant molecules.

Introduction

Amide bonds are ubiquitous in nature and constitute key connecting linkages in peptides and proteins in living organisms. Moreover, it has been estimated that as many as 25% of all the current pharmaceuticals contain amide bonds, and three relevant examples (Acetaminophen, Aubagio and Prilocaine) are presented in Scheme 1.[1] Recently, amides also have found important applications in materials science, such as semiconductors and polymers as amide units combine properties including high stability and conformational diversity.[2] Although tremendous success in amide synthesis has been witnessed in the past decades,[3] the general concerns surrounding concomitant and significant waste production, cost-related features and the avoidance of metal residues ending up in commercial products have raised serious concerns regarding amide synthesis in the pharmaceutical industry and biological applications.[4] Consequently, the development of protocols with minimal waste generation under metal-free conditions is thus of great importance.[4,5]

Catalyst-free ring-opening aminolysis (ROA) of non-strained lactones using aryl amines has so far only been realized under ultrahigh pressure (9000 atm) with poor conversion and quite limited scope.[6] Alternatively, pre-activation of the aromatic amine with butyl lithium or addition of over-stoichiometric amounts of sensitive and flammable reagents such as $AlMe_3$ prior to ring-opening proved to be feasible approaches (Scheme 1) also in the context of total synthesis.[7] These harsh reaction conditions, however, may limit the functional group tolerance, scalability and practical application of these processes, and moreover a substantial amount of waste and metal residues are produced. As far as we know, the only known catalytic approach for the ROA of a non-strained lactone in the presence of an aromatic amine requires a tungstate based catalyst under microwave conditions at temperature beyond 100ºC with a fairly limited scope.[8] Therefore, the development of a general catalytic ROA strategy involving readily available lactones under metal-free and attractive mild conditions enabling the preparation of *N*-aryl amides has significant incentives. Such methodology with minimal waste release and scalability potential can rejuvenate *N*-aryl amide bond formation reactions addressing the ever increasing requirements for sustainable methods in modern organic synthesis.



Scheme 1. Organocatalytic approach (below) towards *N*-aryl amides using lactones and aromatic amines as reaction partners.

TBD proved to be an efficient catalyst in various transformations based on hydrogen bonding activation mode.[9] In particular, TBD has been used as catalyst for the ring-opening

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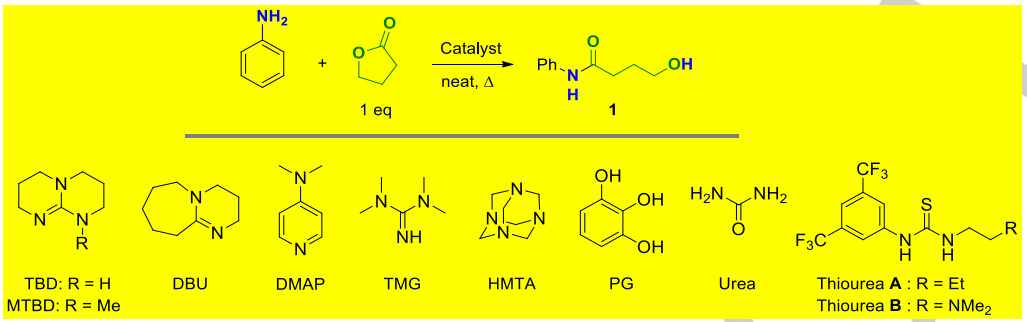
of lactones by alcohols and ring-opening polymerization of lactides[9d-e] and the formation of amides from γ-butyrolactone and benzylamine.[9f] In a wider context, the

Table 1. Screening of reaction conditions and organocatalysts for the synthesis of *N*-aryl amide **1** from aniline and γ-butyrolactone.[a]



Entry	Aniline [equiv]	Catalyst	Amount [mol%]	T [ºC]	Time [h]	Yield of **1** [%][b]
1	1.5	–	–	100	26	0
2	1.5	TBD	30	25	18	64
3	1.5	TBD	30	65	12	73
4	1.5	TBD	30	65	26	60
5	1.5	TBD	20	65	26	62
6	1.5	TBD	10	65	26	41
7	1.5	MTBD	30	65	26	0
8	1.5	DBU	30	65	26	8
9	1.5	DMAP	30	65	26	0
10	1.5	TMG	30	65	26	0
11	1.5	HMTA	30	65	26	0
12	1.5	PG	30	65	26	5
13	1.5	Urea	30	65	26	0
14	1.5	Thiourea **A**	30	65	26	0
15	1.5	Thiourea **B**	30	65	26	<2
16	1.5	TBD	30	40	12	73
17	1.2	TBD	30	40	12	70
18	1.2	TBD	30	40	24	82
19	1.2	TBD	40	40	24	80
20	0.8	TBD	30	40	24	72
21[c]	1.2	TBD	30	40	24	30
22[d]	1.2	TBD	30	40	24	38
23[e]	1.2	TBD	30	40	24	22

[a] 0.40 mmol of lactone, the indicated number of equivalents of aniline, and the catalyst were combined and reacted for the required time under neat conditions and open to air. [b] NMR yield using mesitylene as internal standard. [c] Using toluene as solvent (0.4 mL). [d] Using CH_3CN as solvent (0.4 mL). [e] Using DCM as solvent (0.4 mL).

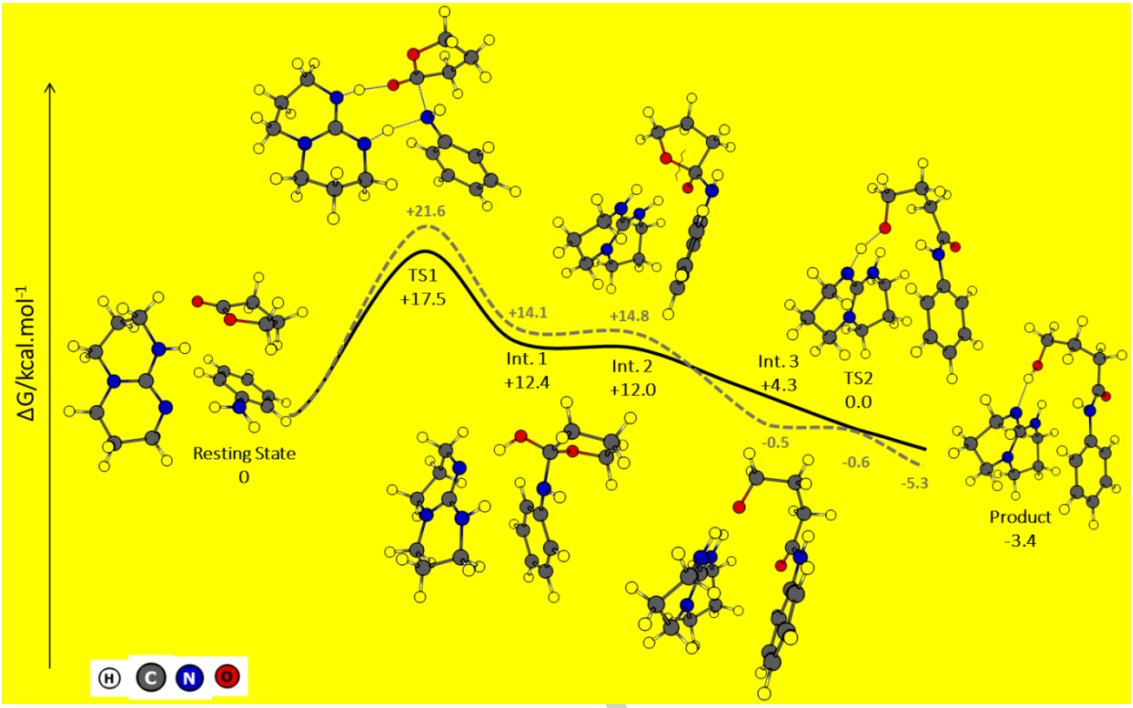


Figure 1: Free energies (kcal/mol) of the reaction pathway toward the formation of an *N*-aryl amide from aniline and γ-BL using TBD as catalyst (dark bold line), and from aniline and a seven-membered lactone (gray dashed line, smaller print) for comparison. The 3D molecular representations show the key interactions and intermediates in this proton relay mechanism.

catalytic amidation of acyclic esters by amines using TBD catalyst also has been reported.[9e,f] Inspired by the success of TBD-mediated hydrogen bonding activation, we envisioned that the use of TBD as a catalyst would trigger the reaction of lactones and unreactive aryl amines based on a "proton-relay" strategy.

Herein we report *N*-aryl amide formation using non-strained lactones and aromatic amines under mild, sustainable and metal-free conditions (Scheme 1). The process is broadly applicable to the conversion of a wide range of lactones with different ring sizes (up to 16) and substituted aromatic amines leading to the formation of *N*-aryl amides with synthetically useful hydroxy end-groups. The newly developed strategy has been applied in the preparation of pharmaceutically relevant amide compounds demonstrative of the synthetic potential of these hydroxyl-functionalized amide scaffolds.

Results and Discussion

Screening studies

We started our investigation by considering the reaction between aniline and γ-butyrolactone (γ-BL) as a model reaction (Table 1). As expected, the control reaction in the absence of any catalyst at 100°C did not result in any detectable conversion after 26 h in line with the challenging nature of this transformation (entry 1). To our delight, the use of TBD as catalyst (30 mol%) gave an appreciable NMR yield of the *N*-aryl amide product **1** (73%) after reaction at 65°C for 12 h (entry 3); prolonging the reaction time did not improve the yield of **1**. Decreasing the TBD loading to 10% still resulted in substantial product formation though more slowly (entry 6). *N*-methyl protected TBD (MTBD) did not show any reactivity (entry 7) highlighting the importance of the free N-H fragment in TBD to initiate a hydrogen-bond activation of both substrates. Other *N*-heterocyclic structures lacking proton-relay capability including DMAP, 1,1,3,3-tetramethylguanidine and hexamethylene-tetramine, and simple (thio)ureas did not show any reactivity under these conditions (entries 8-13). Known hydrogen-bond activators such as DBU (entry 8) and pyrogallol (entry 12) proved to be reactive under these conditions but gave a significantly poorer yield of <10% compared to the use of TBD. Finally the catalytic reaction using TBD (30 mol%, solvent-free) was optimized by lowering the temperature to 40°C and reducing the amount of aniline to 1.2 equiv giving *N*-aryl amide **1** in 82% yield (entry 18). The use of solvents (entries 21-23) gave slower catalysis illustrated by the lower yields of **1** (22-38%).

Mechanistic considerations

The overall (low) activation Gibbs free energy (17.5 kcal/mol) for the formation of *N*-aryl amide **1** derived from a five-membered lactone was determined by DFT analysis (Figure 1) reinforcing the experimental observation that the TBD-mediated conversion of γ-BL is feasible under mild operating conditions. The mechanistic steps mainly include proton storage and release processes, *i.e.* proton-relay. The TBD and reactant ensemble is taken as the energy reference. The rate limiting step is the concerted,

nucleophilic addition of the aniline and proton transfer to the catalyst, a process which requires 17.5 kcal/mol ($\Delta G^{\ddagger}$) to reach the transition state **TS1**. Equilibrium then occurs between species **Int. 1** and **Int. 2** which consists of a proton transfer between the oxygen atom in the newly formed adduct and TBD. This leads to the ring opening step whereby the C—O bond is broken restoring the sp^2 character of the attacked carbon centre (**Int. 3**). The final step is the proton transfer from TBD-H^+ to the alkoxide moiety.

Another exploratory avenue that was pursued was how the reaction kinetics changes upon expanding the lactone ring size. A seven-membered lactone was chosen as an additional substrate. Intuitively the aminolysis of a seven-membered lactone may seem more feasible since larger-size rings are thermodynamically less stable. However, the calculations suggested that the rate determining step (**TS1**) has a larger barrier height with respect to the amination of γ-BL (Figure 1). The origin of this increase is for a larger part due to enthalpy: $\Delta H^{\ddagger}$(**TS1**) = +22.9 kcal/mol for the amination of the seven-membered lactone whereas for the amination of γ-BL the enthalpy term $\Delta H^{\ddagger}$(**TS1**) is +18.4 kcal/mol. The **TS1** structures show clear differences as the seven-membered lactone exhibits longer bond distances between the implicated atoms holding together the trimolecular ensemble (see Supporting Information for more details).

In both cases the mechanistic steps that only involve proton exchange are barrier-less. The comparative data suggest that larger ring size lactones are probably more lethargic substrates and require thus activation at higher temperature: this is indeed what can be observed experimentally (*vide infra*).

Substrate scope studies

The substrate scope was then investigated under the optimized conditions using various amines and γ-BL as reaction partners (Figure 2, **a**). In general, good to excellent isolated yields of the amides **1**–**16** of up to 97% were obtained. A variety of functional groups are tolerated using this procedure including electron-donating (**2**, **3**, **7**, **11** and **12**) and remarkably also strongly electron-withdrawing groups (**8**–**10**) present in the *para* or *meta* position of the aniline scaffold. In these latter cases only modest product formation was achieved, and an increase in the reaction temperature or catalyst loading did not substantially improve the yield of amides **8**–**10** (Table S1-S4). Notably, when *p*-phenylenediamine was used as amine reagent, mono-amide **7** (85%) was produced selectively in excellent yield. The installation of an indole unit (**13**) having importance in drug development programs is also readily accomplished. The reactions of *ortho*-substituted and more sterically demanding secondary anilines/amines (such as *N*-methyl aniline) proved to be unproductive (see Tables S5-S8). This result may be expected since the formation of the required ternary transition state (Figure 1; **TS1**) depends on the steric requirements of both the lactone and amine substrate, with sterically more demanding secondary anilines/amines likely not being productive in this TBD-mediated process.

The presence of primary alkyl amines, being much more nucleophilic than aromatic ones, gave rise to excellent yields of the respective amides in quite short reaction times (88-97%, **15** and **16**). The same reactions proved, however, to be far more sluggish in the *absence* of TBD under similar conditions as observed in various total syntheses in which air-sensitive and stoichiometric $AlMe_3$ was required to promote the reactions.[7d,e] Importantly, comparing the protocol reported previously using sensitive metal reagents,[7] the present ROA of γ-BL using aniline can be easily performed at larger scale (40 mmol; upscale factor 100) open to air with an excellent isolated yield of amide **1** (R = H; 82%), and thus illustrates the practical aspect of this methodology.

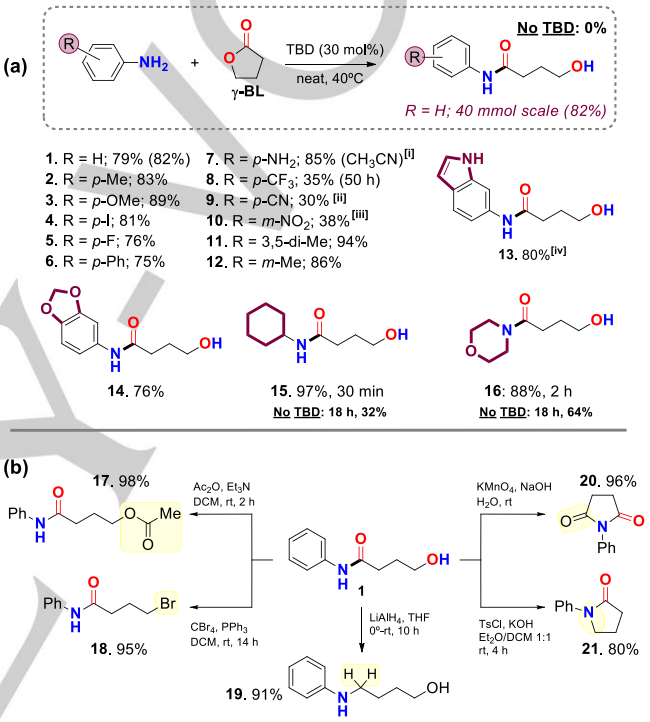


Figure 2. Scope in amine reaction partners (**a**) and post-modification of the *N*-aryl amide **1** derived from γ-BL (**b**). All reactions were performed with 0.40 mmol lactone, 1.2 eq. of aromatic amine, 40ºC, 24 h, open to air, all yields are of the isolated product. **[i]** 100 μL solvent, 16 h. **[ii]** lactone/amine = 4:1, 80ºC, 24 h. **[iii]** lactone/amine = 3:2, TBD (50 mol%), 80ºC, 100 h. **[iv]** 0.40 mmol of aromatic amine, 0.48 mmol of lactone, 4 h.

These *N*-aryl amides are useful intermediates and provide an easy entry to various other functional molecules (Figure 2, **b**). For example, treatment of *N*-aryl amide **1** with acetic anhydride at rt gave virtually quantitative yield of the ester **17**. The alkyl bromide derivative **18** (95%) could be easily prepared by an Appel-type reaction using CBr_4.[10] Reduction of amide **1** with $LiAlH_4$ afforded the primary *N*-aryl amino alcohol **19** (91%). Interestingly, oxidative conversion of amide **1** using $KMnO_4$ under basic conditions or utilizing tosyl chloride yielded the corresponding *N*-aryl succinimide **20** and *N*-phenyl γ-lactam **21**, respectively, instead of the corresponding acid and tosylated product. This illustrates the thermodynamically stable character of 5-membered ring systems and the tendency towards fast cyclization through an intramolecular nucleophilic attack of the amide group onto the γ-

carbon in compound **1**. It is worth noting that γ-lactams are important structural motifs of biologically active natural products and drug molecules.[11]

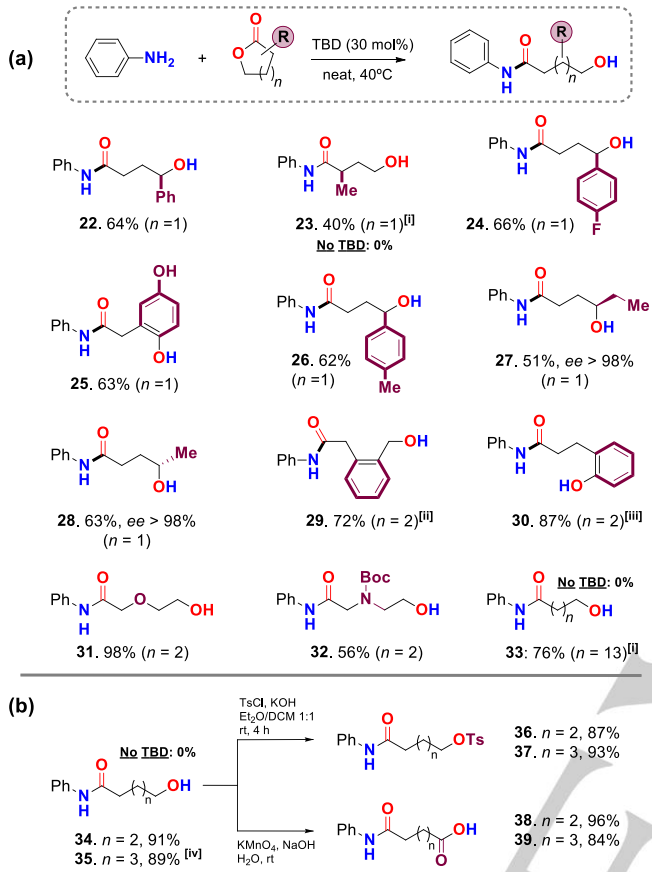


Figure 3. ROA of various lactones with different ring sizes (**a**) and end-group conversion of 6- and 7-membered lactones (**b**). All reactions performed with 0.40 mmol lactone, 1.2 eq. of amine, 40ºC, 24 h, open to air, all yields are of the isolated product. **[i]** 2.5 eq. aniline, 100ºC, 24 h. **[ii]** 2.2 eq. aniline, 70ºC, 19 h. **[iii]** 3 h, 40 μL CH_3CN used. **[iv]** 2.5 eq. aniline, 100ºC.

Further exploration of the product scope was carried out using various and functionalized 5 to 7-membered lactones as substrates (Figure 3). Gratifyingly, a variety of 5-membered lactones with α, β or γ-position substituted reacted well and afforded the corresponding *N*-phenyl amides **22**–**28** in moderate to good yields. The presence of both alkyl (**27** and **28**) and (substituted) aryl groups (**22** and **24**–**26**) in the γ-position of the 5-membered lactone substrate is endorsed. The conversion of α-methyl-γ-butyrolactone (*cf.*, synthesis of **23**; 40%) was found to be quite challenging even at elevated temperatures. Enantiopure amides **27** and **28** (*ee* > 98%) could be prepared from their enantio-enriched lactone precursors (*ee* > 95%, commercial substrates) and epimerization during the ROA process was not observed. Since the latter are reasonably cheap and commercially available, a direct enantiospecific entry towards amides is facilitated.

Heteroatoms (such as N and O) in the 6-membered lactones did not affect the efficiency of the ROA reaction (*cf.*, **31** and **32**). The conversion of a 7-membered lactone to produce amide **35** was sluggish at lower temperatures, but fortunately the reaction proceeded smoothly at 100ºC giving **35** in good yield (Figure 3, **b**: 89%) using an increased amount of aniline. Notably, at a higher temperature of 100ºC, the ROA also proved to be suitable for the preparation of the long hydroxy-alkyl *N*-aryl amide **33** (*n* = 13, 76%); compounds such as **33** having both hydrophilic and hydrophobic ends can find use as templates in the area of self-assembled materials.[12] The preparation of amides **33** and **35** typically requires higher reaction temperatures for efficient conversion as a result of a steric effect which is governed by the non-planar conformations of larger ring-size lactones, and consequently are more energy demanding with respect to the formation of the requisite key ternary transition state (**TS1** in Figure 1). The difference in reactivity between 5- and 7-membered lactones was also supported by DFT analysis, showing a larger energetic span for the 7-membered lactone conversion (Figure 1 and SI).

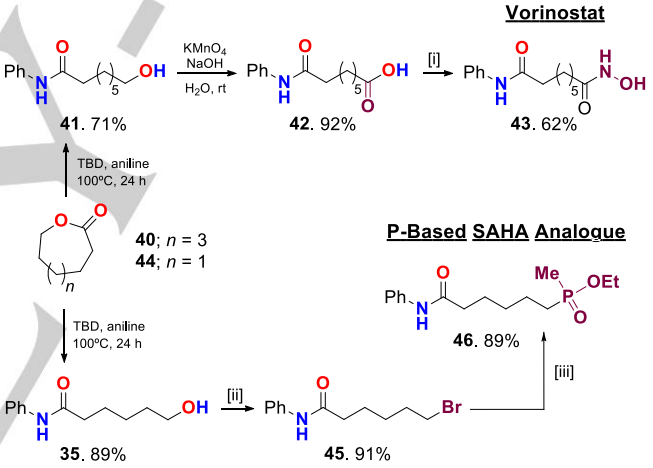


Figure 4. Preparation of pharmaceutically relevant compounds **43** and **46**. Conditions used: **[i]** ethyl chloroformate (1.3 eq.), anhydrous THF, NEt_3 (1.3 eq.), 0ºC, 30 min; then filtration, hydroxylamine (3 eq.), MeOH, rt, 1 h. **[ii]** CBr_4 (1.3 eq.), PPh_3 (1.3 eq.), CH_2Cl_2, rt, 14h. **[iii]** diethyl methylphosphonite (1.6 eq.), 120ºC, 10 h. All yields are of the isolated products.

Unlike the behaviour observed for *N*-aryl amide **1** derived from the 5-membered γ-BL, the tosylation and oxidation of *N*-aryl amides **34** and **35**, derived from 6- and 7-membered lactones respectively, led to the formation of the tosylates **36** and **37**, and carboxylic acids **38** and **39** under ambient conditions (Figure 3, **b**) and no cyclization was observed in these cases unlike in the case of 5-membered ring products **20** and **21** (Figure 2).[13]

Hydroxyl amides have found to be important building blocks and intermediates in synthetic chemistry and biology.[7d-e,14] The present developed organocatalytic protocol can be valorised as a key step for the preparation of pharmaceuticals (Figure 4). Vorinostat (**43**) could be prepared in three steps using the developed catalytic ROA process starting off with 9-membered lactone **40**. Vorinostat is known for the treatment of CTCL, a type

of cancer of the immune system and designated as a SAHA ("suberoyl-anilide-hydroxamic acid") type compound.[15] The developed ROA process was applied to lactone **40** using aniline and afforded *N*-aryl amide **41** in 71% yield. The *N*-aryl amide intermediate was then oxidized to the carboxylic acid compound **42** (92%) finally nucleophilic substitution in the activated acid species in the presence of hydroxyl amine furnished the targeted product **43** in 62% yield. As a Vorinostat analogue, the phosphorus-based *N*-aryl amide **46** was also found to be biologically active[16] and it could be easily prepared from the ROA of the 7-membered lactone **44** leading first to the *N*-aryl amide **35** (89%), which was converted to compound **45** (91%) by an Appel-type bromination, followed by a nucleophilic substitution of the bromide by phosphonite to furnish the phosphorus-based SAHA analogue **46** (89%). The easy access to compounds **43** and **46** suggests that this organocatalytic ROA process is suitable for the preparation of a wide array of SAHA analogues with different chain lengths.

Conclusions

In summary, the first general organocatalytic synthesis of valuable *N*-aryl amide scaffolds with wide functional diversity is presented through ROA of various ring-size lactones (featuring 5–7, 9, or 16 membered rings) by electron deficient aromatic amines. This method is based on the use of a readily available organocatalyst (TBD) enabling otherwise non-feasible catalytic ring-opening of the lactone partner under mostly highly mild and attractive reaction conditions (40ºC, neat, open to air). This new ROA process can be easily scaled up and tolerates various functional groups present either in the (aromatic) amine or lactone substrate. The developed catalytic approach enables the use of bio-based 5-, 6- and 7-membered lactones such as γ-butyrolactone, δ-valerolactone and ε-caprolactone[17] as platform molecules and their conversion into various valuable chemicals as demonstrated in the synthesis of Vorinostat and its phosphorus-based analogue. Hence, this metal-free and general route towards *N*-aryl amides with minimal waste release should provide a highly attractive alternative for amide synthesis in both academic laboratories and commercial settings.

Experimental Section

General considerations

Commercially available amines, solvents, lactones, other reagents and catalyst (TBD) were purchased from Aldrich or TCI and directly used without further purification. ^{1}H NMR, ^{13}C NMR and related 2D NMR spectra were recorded at room temperature on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to the residual deuterated solvent signals. All reported NMR values are given in parts per million (ppm). FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer. Mass spectrometric analyses were performed by the Research Support Group at ICIQ. The lactones used for the preparation of amides **24** and **26** were prepared according to a previously reported protocol.[18] The lactones used for the preparation of amides **31** and **32** were prepared as described previously.[19]

Typical procedure for the amide formation

A screw-capped vial was charged with the respective lactone (0.40 mmol, 1 eq.), amine (0.48 mmol, 1.2 eq.), TBD catalyst (30 mol%, 0.017 g). The reaction mixture was stirred at 40ºC for 24 h. Then, the product was purified by flash chromatography affording the corresponding product. All purified products were fully characterized by ^{1}H/^{13}C NMR spectra (^{19}F NMR spectra were acquired where necessary), IR and HRMS. Full details are provided in the Supporting Information.

DFT details

The Gaussian09 program (rev. D.01)[20] was used to calculate the reaction path. Truhlar's[21] hybrid Minnesota 06 (M06) exchange and correlation density functionals with def2-TZVPP basis sets,[22,23] were used for all the models using default integration grid settings. Geometry optimizations were computed in vacuo and additionally, potential energies and analytic Hessians were re-evaluated with a single point calculation using an ultrafine integration grid and the integral equation formalism of the polarizable continuum solvation model (IEFPCM) scheme, using the electronic density in accordance with Truhlar's scheme (SMD),[24,25] with the default settings for aniline. Molecular 3D renderings were made with the Chemcraft program.[26] Optimised structures are deposited at the iochem-BD repository (doi:10.19061/iochem-bd-1-21).[27]

Acknowledgements

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Keywords: aromatic amines • lactones • N-aryl amides • organocatalysis • ring-opening aminolysis

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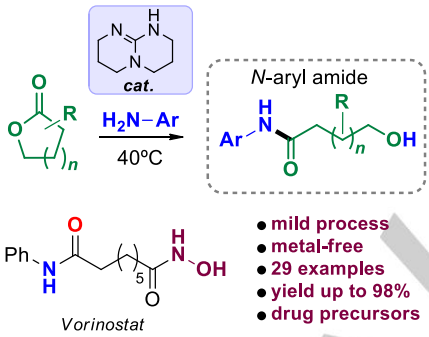
Entry for the Table of Contents:

FULL PAPER

Green Amides: A general, metal-free organocatalytic process for *N*-aryl amide synthesis has been developed using cheap and readily available lactones and aromatic amines. The formal ring-opening aminolysis (ROA) of the lactone partner takes place under mild reaction conditions and highlights the use of potentially bio-sourced lactones. The formal synthesis of pharma-relevant SAHA compounds is demonstrated using this new ROA methodology.



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Metal-Free Synthesis of N-Aryl Amides using Organocatalytic Ring-Opening Aminolysis of Lactones