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Intra- and Intermolecular Alkylation of *N,O*-Acetals and π-Activated Alcohols Catalyzed by in Situ Generated Acid

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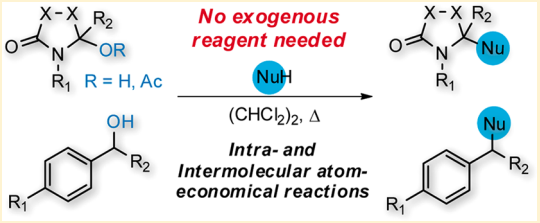
Supporting Information

ABSTRACT: Intramolecular and intermolecular alkylations of carbocation precursors of limited ionization ability, principally *N,O*-acetals, without the use of an exogenous reagent have been developed. The reactions are carried out in 1,1,2,2-tetrachloroethane (TCE) and take advantage of the ability of this solvent to continuously release small amounts of HCl by thermolytic elimination. A study of the reaction led to several improved protocols such as (1) preheated TCE, (2) microwave-assisted reactions, and (3) flow or sealed-tube conditions, which allow significant reaction rate enhancements and made possible some challenging reactions such as the α-amidoalkylation of ketones. Studies using flow chemistry confirmed not only that very low concentrations of HCl generated from the solvent were responsible for the reactivity but also that TCE had additional beneficial properties in comparison to other chlorinated solvents such as dichloroethane. The method can easily be extended to the alkylation using proelectrophiles such as π-activated alcohols, which are normally unreactive toward HCl catalysis. This work represents the first successful use of HCl, the simplest strong Brønsted acid, as an efficient alkylation catalyst.



INTRODUCTION

Carbocations are ubiquitous reactive intermediates in organic synthesis that readily participate in S_N1-type alkylation reactions.[1] One common method for the generation of carbocations is by loss of a leaving group attached to carbon, and this can be assisted by protonation or metalation as in the case of alcohols and their derivatives. Over the past decade, many different catalytic systems based on the use of Lewis and Brønsted acids for this activation mode have been reported, therefore considerably improving the value of cationic chemistry.[2,3] While highly stabilized carbenium ions[4] can be generated under extremely mild conditions, for example simply using hot water[5] or fluorinated alcohols as both solvents and promoters,[6,7] highly reactive carbocations[4] need to be generated from alcohol derivatives with markedly reduced polarizability, and therefore much stronger acidic promoters (and/or greater amounts of them) are required. This trend generally follows Mayr's scale: i.e., the strength and/or load of the catalyst grow as the *E* parameter of the cations increases. *N*-Acyliminium ions are prototypical examples of such highly reactive carbocations. Their C−C bond forming reactions with carbon nucleophiles upon acidic activation of *N,O*-acetals represent an important field of research in organic chemistry to provide useful α-functionalized amino compounds.[8] Despite their widespread use and many synthetic applications, it is remarkable to note that catalytic *N*-acyliminium ion chemistry has been rather neglected, and the use of stoichiometric or even an excess amount of an acidic reagent is routine. In this context, the best combination of promoter and solvent for a particular reaction often has to be screened in a time-consuming manner. As far as (super)stoichiometric amounts of strong Lewis acids (TMSOTf, $BF_3{\cdot}OEt_2$, $TiCl_4$, $SnCl_4$, ...) are concerned, the quality of these air- and moisture-sensitive reagents also becomes critical, and it is frequently required to distill them just prior to use. It is also worth noting that these methods generate a large aqueous waste stream during workup. Recently, we have reported that such reactions can nevertheless be achieved with very high catalytic and chemical efficiencies using superacidic reagents,[9−11] such as $Sn(NTf_2)_4$.[9d,12]

The aim of this study was to develop an experimentally simple and robust protocol for performing α-amidoalkylation of diverse carbon nucleophiles with the hope of extension to the

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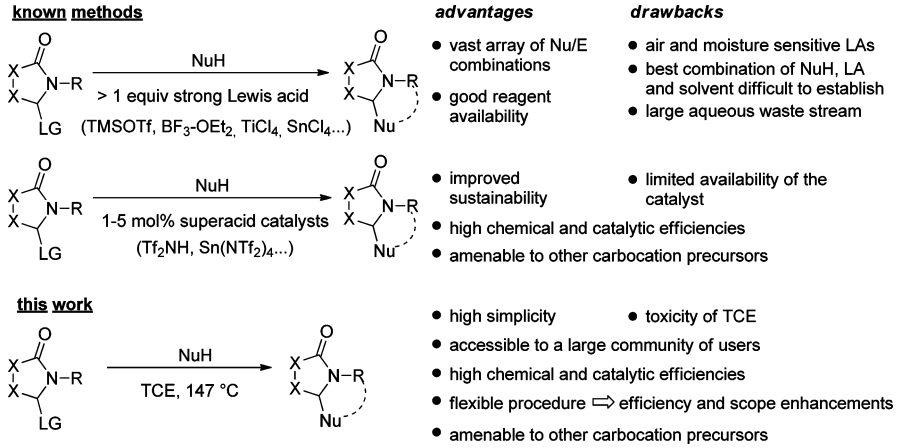
Scheme 1. Two Typical Approaches for the α-Amidoalkylation of Weak Carbon Nucleophiles and Our New Method



alkylation of related proelectrophiles such as, for example, π-activated alcohols.[2]

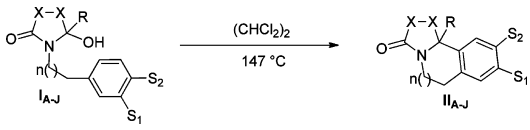
Our procedure is based on the use of 1,1,2,2-tetrachloroethane (TCE) as a solvent, which serves to generate trace amounts of HCl by thermolytic elimination. The mechanisms and kinetics of decomposition of TCE to generate HCl were investigated by Barton at temperatures above 263 °C.[13] We reasoned that release should still occur at significantly lower temperatures and provide very low levels of anhydrous HCl in the reaction solution. As opposed to the commercially available solutions of HCl which are supplied in hydrogen-bond acceptor solvents,[14] this in situ generated "free" HCl is expected to be significantly more active, while avoiding the need for dealing with gaseous HCl[15] and also preserving compatibility with the range of neutral carbon nucleophiles commonly used in alkylative chemistry.[2−11] If these assumptions were confirmed, efficient catalytic alkylation methods could be developed through successful use of one of the simplest acid catalysts, HCl. To the best of our knowledge, HCl has not been demonstrated as an efficient catalyst in S_N1-type alkylation involving *N*-acyliminium ions, while other common Brønsted acids such as PTSA and TFA are typically used in super-stoichiometric amounts for such reactions.

Herein we report the efficient S_N1 alkylation of *N*-acyliminium ions and other relatively electrophilic π-stabilized cations in TCE solvent in the absence of exogenous acidic activators. We acknowledge the toxicity associated with this solvent[16] but believe this can be compensated by the advantages of the method (Scheme 1).

RESULTS AND DISCUSSION

The intramolecular Friedel−Crafts type cyclization of *N*,*O*-acetals tethered to an arene nucleus is a major subtheme in *N*-acyliminium ion chemistry, and some efficient catalytic examples have been recently reported.[8a,b,9c,d,10d,e,11a,c] We therefore decided to focus our initial effort on this reaction type (Table 1). We were delighted that our working hypothesis was immediately rewarded with the observation of a fast and clean reaction of the model substrate $\mathbf{1_A}$ in refluxing TCE (entry 1). For comparison, thermal reactions in other high-boiling-point solvents such as xylene and dioxane, which are not able to generate HCl, expectedly gave much slower kinetics for substrate $\mathbf{1_A}$ (see footnote *a* in Table 1) and either decomposition or no conversion particularly when the less favorable cyclizations were attempted (viz. $\mathbf{1_C}$ and $\mathbf{1_H}$).

Table 1. Thermal Cyclization of *N*,*O*-Acetals Tethered to an Arene Nucleus in TCE



entry	substrate	time	product	yield (%)
1[a]	$\mathbf{I_A}$	1 h	$\mathbf{II_A}$	93
2	$\mathbf{I_B}$	4 h	$\mathbf{II_B}$	76[b]
3	$\mathbf{I_C}$	2 h	$\mathbf{II_C}$	84[b]
4	$\mathbf{I_D}$	1 h 45	$\mathbf{II_D}$	96
5	$\mathbf{I_E}$	1 h	$\mathbf{II_E}$	90[c]
6	$\mathbf{I_F}$	14 h	$\mathbf{II_F}$	85
7	$\mathbf{I_G}$	24 h	$\mathbf{II_G}$	86
8	$\mathbf{I_H}$	72 h	$\mathbf{II_H}$	65
9	$\mathbf{I_I}$	1 h	$\mathbf{II_I}$	99
10	$\mathbf{I_J}$	3 h 30	$\mathbf{II_J}$	92

[a]The cyclization of $\mathbf{I_A}$ was completed in 4 h and gave >95% yield when carried out in xylene at 138 °C. [b]No cyclization took place in boiling xylene. [c]A single stereoisomer was isolated.

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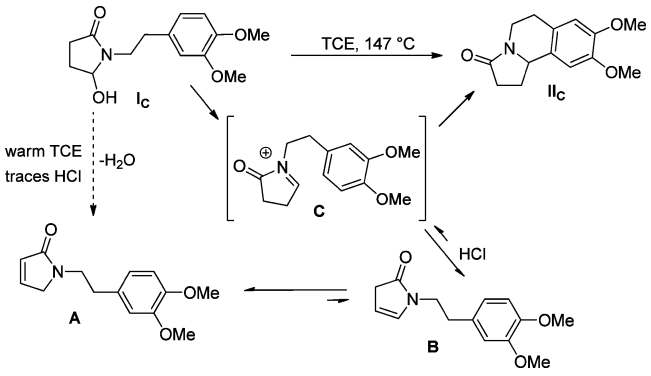
Delightfully, the less activated iminoacyl cation precursor hydroxy lactam $\mathbf{I_B}$ bearing only one methoxy substituent on the nucleophilic aryl group could also be converted to the product in good yield in refluxing TCE (entry 2). The facile cyclization of the less robust succinimide derivative $\mathbf{I_C}$ in comparison to phthalimide nicely exemplifies the synthetic applicability of the method (entry 3).

Careful monitoring of this reaction by ^{1}H NMR spectroscopy revealed that the transformation was a dehydrative process which produced the α,β-unsaturated pyrrolidinone **A** (Scheme 2) as the first detectable species, which presumably arises from

Scheme 2. Dehydrative Cyclization Pathway of Succinimide Hydroxy Lactam $\mathbf{I_C}$

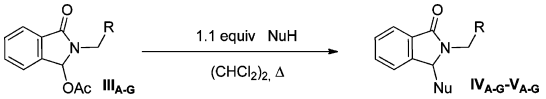


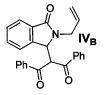
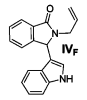
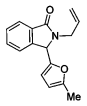
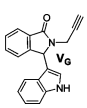
isomerization of enamide **B**, in turn generated by proton loss from the reactive *N*-acyliminium ion **C**.[17] Under our reaction conditions **A**−**C** are in equilibrium via an acid-catalyzed process, with **C** cyclizing to the product $\mathbf{II_C}$.[13,18]

The ability of the TCE method to further activate and alkylate the α,β-unsaturated pyrrolidone may offer a practical solution for certain amidoalkylation reactions which stop at the stage of the α,β-unsaturated pyrrolidinone under an ordinary catalytic regime.[10e] The homologous substrate $\mathbf{I_D}$ with a propyl linker performed nicely in this cyclization to give the desired seven-membered-ring tricyclic product $\mathbf{II_D}$ in high yield (Table 1, entry 4). These thermal conditions can also accommodate stereogenicity close to the reaction center, as exemplified by the successful amidoalkylation of $\mathbf{I_E}$, producing $\mathbf{II_E}$ in high yield and with complete stereocontrol (entry 5). The reaction scope of the method was further broadened with the cyclization of the tertiary hydroxyl lactams $\mathbf{I_F}$−$\mathbf{I_H}$ (entries 6−8). Cyclization of the methyl-substituted substrate $\mathbf{I_H}$ was shown to proceed by a dehydrative pathway similarly to the cyclization of **Ic** with, first, generation of a transient exocyclic enamide intermediate which then underwent acid-catalyzed cyclization. Furthermore, this cyclization protocol was also efficient for substrates $\mathbf{I_I}$ and $\mathbf{I_J}$ with a thiophene nucleophile (entries 9 and 10).

With these excellent preliminary results in hand, we next queried whether an effective intermolecular α-amidoalkylation variant could be implemented as well. As Table 2 shows (entries 1−7), using the optimized conditions allowed incorporation of a range of neutral nucleophiles NuH with the model *N*-allyl acetate $\mathbf{III_A}$. In this intermolecular variant, $\mathbf{III_A}$ was much more reactive than the parent hydroxy lactam, which reacted sluggishly with acetylacetone to give after 60 h in refluxing TCE compound $\mathbf{IV_A}$ with incomplete conversion and an isolated 77% yield (result not shown). Acetylacetone appeared to be more reactive than dibenzoylmethane under these thermal conditions (entry 1 vs 2), an observation which

Table 2. Thermal Intermolecular α-Amidoalkylation of Neutral C-Nucleophiles with 2-Acetoxy Lactams $\mathbf{III_A}$−$\mathbf{III_G}$



entry	R	NuH	product	time - yield (%)
1				7 h 30 - 100
2	"			14 h 30 - 77
3	"			8 h – 87[a]
4[b]	"			14 h – 65[c]
5[d]	"			2 h 30 - 79
6	"			2 h 30 - 81
7	"			14 h - 52
8				7 h 30 - 100
9		"		5 h - 99
10		"		7 h30 - 99
11		"		9 h - 96
12		"		7 h 30 - 100
13		"		7 h - 100
14	$\mathbf{III_B}$			2 h - 73

[a]Isolated as a 1:1 ratio of stereoisomers. [b]3 equiv of cyclohexanone was used. [c]Isolated as a 2:1 ratio of stereoisomers. [d]1.5 equiv of nucleophile was used.

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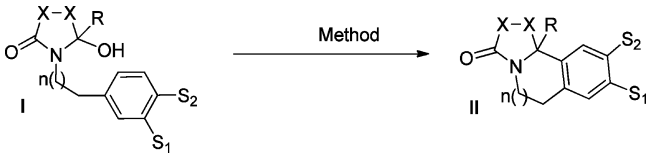
contrasts with the usual trend observed in acid-catalyzed alkylative chemistry.[19]

Successful creation of a quaternary center (Table 2, entry 3) and achievement of a challenging direct alkylation of cyclohexanone (entry 4) under these TCE conditions demonstrate the remarkable effectiveness of our method. Highly nucleophilic π-heteroaromatics gave products $\mathbf{IV_E}$ and $\mathbf{IV_F}$ rapidly in good yields (entries 5 and 6), while the rather sensitive 2-methylfuran gave $\mathbf{IV_G}$ in a moderate yield probably due to decomposition (entry 7). A variety of alkyl groups on the nitrogen, including unsaturated cases, were well tolerated in this new α-amidoalkylation protocol, producing the desired adducts $\mathbf{V_A}$–$\mathbf{V_G}$ in high yields (entries 8–14).

Given the hypothesis that HCl generated by the decomposition of the solvent was the active catalyst, we attempted the cyclization of $\mathbf{I_A}$ using preheated (overnight) TCE. Under those conditions, $\mathbf{II_A}$ was formed in about 5 min and isolated in 88% yield (Table 3, entry 2), while 1 h was originally required to reach full conversion (entry 1). With the aim of improving our original protocol, we have also developed conditions using microwave irradiation (entry 3), providing cyclized product $\mathbf{II_A}$ within 30 min in quantitative manner.

Table 3. Preheating of TCE and Microwave Irradiation as Tools for Efficient Intramolecular Alkylation[a]



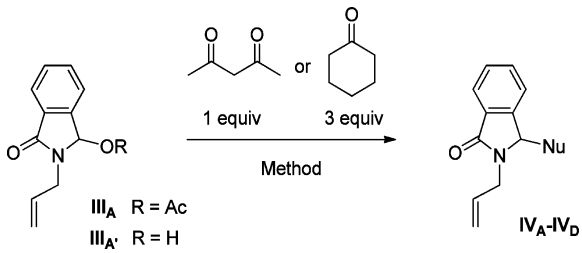
entry[b]	substrate	method	time	product	yield (%)[c]
1	$\mathbf{I_A}$	standard	1 h	$\mathbf{II_A}$	99
2		A	5 min		88
3		B	30 min		>99
4	$\mathbf{I_B}$	standard	4 h	$\mathbf{II_B}$	76
5		A	5 min		79
6		A[d]	14 h		90
7		B	55 min		>99
8	$\mathbf{I_H}$	standard	72 h	$\mathbf{II_H}$	65
9		A	2 h		>99
10	$\mathbf{I_C}$	standard	2 h	$\mathbf{II_C}$	84
11		B	40 min		>99
12	$\mathbf{I_D}$	standard	1 h 45 min	$\mathbf{II_D}$	96
13		A	25 min		96
14		B	1 h		97
15	$\mathbf{I_I}$	standard	1 h	$\mathbf{II_I}$	>99
16		B	35 min		>99
17	$\mathbf{I_E}$	standard	1 h	$\mathbf{II_E}$	90
18		B	35 min		>99

[a]Definitions of methods: standard, TCE, 147 °C; A, preheated TCE, 147 °C; B, TCE, 147 °C, microwave 300 W. [b]The structures of substrates $\mathbf{I_{A\text{-}E}}$ and products $\mathbf{II_{A\text{-}E}}$ can be seen in Table 1. [c]Isolated yield. [d]Reaction conducted at 80 °C.

Reduced reaction times were also observed for cyclization of the monomethoxy analogue $\mathbf{I_B}$ (Table 3, entries 4–7) using any of these improved procedures. Remarkably, it was also shown that successful cyclization of $\mathbf{I_B}$ could be performed at temperatures as low as 80 °C (entry 6).[20,21] A number of the cyclizations that proceeded with slow rates under the standard protocol were then repeated using these methods, and a significant and uniform diminution of the reaction times was obtained in every case (entries 8–18). Unfortunately, such an effect was not observed with lower boiling chlorinated solvents, since no conversion could be seen when $\mathbf{I_B}$ was exposed at 80 °C in preheated dichloroethane (DCE) and chloroform.

Similarly, the reactivity profile and reaction scope of the intermolecular couplings were significantly broadened, both in terms of reaction rate and yield, using both preheated TCE and microwave irradiation (Table 4), the latter method particularly giving spectacular improvements (entries 4 and 7). The reactions of $\mathbf{III_A}$ and its parent hydroxyl $\mathbf{III_{A'}}$ with cyclohexanone and acetylacetone are given here as representative examples. These outstanding effects exhibited by either method even enabled implementation of the more atom-economical yet challenging intermolecular α-amidoalkylation of hydroxy lactams,[22] which were beyond our reach with the initial protocol (Table 2). The yields of products for the couplings performed throughout this study are globally very high and, as far as we can compare, quite similar to those we previously obtained by using Brønsted and Lewis superacid catalysts,[9b,d] and this attests to the value of our TCE method.

Table 4. Preheating of TCE and Microwave Irradiation as Tools for Efficient Intermolecular Alkylation[b]



entry	NuH	substrate	method	time	product	yield(%)[a]
1		$\mathbf{III_A}$	**Standard**	14 h	$\mathbf{IV_D}$	65
2			**A**	2.5 h		100
3		$\mathbf{III_{A'}}$	**A**	14 h		74
4			**B**	1 h		>99
5		$\mathbf{III_{A'}}$	**Standard**	60 h	$\mathbf{IV_A}$	77
6			**A**	6 h		87
7			**B**	0.5 h		99

[a]Isolated yield. [b]Definition of methods: standard, TCE, 147 °C; A, preheated TCE, 147 °C; B, TCE, 147 °C, microwave 300 W.

A series of control experiments using optically pure substrates were run to demonstrate if a cationic (S_N1) type mechanism proceeding via generation of an *N*-acyliminium ion intermediate is involved as anticipated. In order to check this mechanistic hypothesis, we tested reactions using optically active hydroxy lactams (*S*)-$\mathbf{III_{A'}}$ and (*S*)-$\mathbf{I_A}$, which were obtained by chiral semipreparative HPLC.[23] When intra- and intermolecular reactions using these enantiopure hydroxy lactams (*S*)-$\mathbf{III_{A'}}$ and (*S*)-$\mathbf{I_A}$ were performed under the standard conditions (TCE, 147 °C), only racemic products were obtained, unambiguously supporting a S_N1-type mechanism for both intramolecular and intermolecular reactions (Scheme 3).

Flow chemistry represents a tremendous technological advancement in contemporary organic synthesis.[24] In particular, high temperatures and pressures are easily handled, and we surmised there could be some opportunities to extend this TCE chemistry by flow.[25] We have then briefly investigated the

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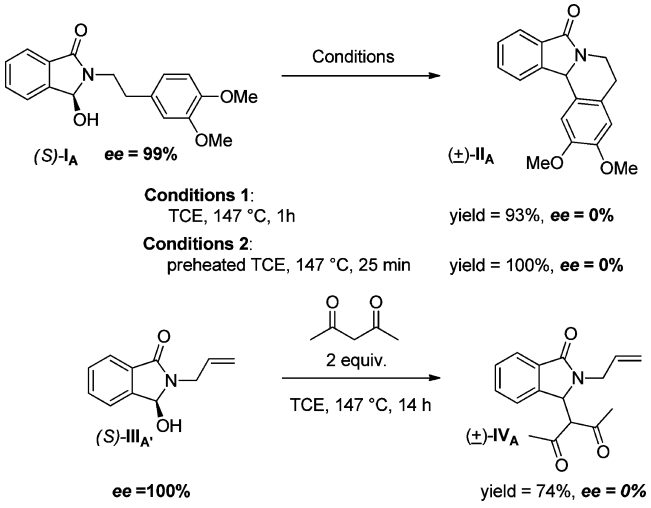
Scheme 3. Control Experiments using Optically Active Hydroxy Lactams (*S*)-III$_{A'}$ and (*S*)-I$_A$



thermal cyclization of $\mathbf{I}_A$ under flow chemistry conditions. We were delighted to observe clean and rapid formation of $\mathbf{II}_A$ at 160 °C with a 10 min reaction time, in a perfluoroalkyloxy polymer (PFA) column, as evidenced by inspection of the crude product mixtures by ^{1}H NMR spectroscopy and good isolated yield (94%) on a 0.1 g scale. Under flow conditions the reaction is significantly faster than the regular thermal reaction at the same temperature: for example, on occasion (see below) 90% conversion was reached at 120 °C after 30 min, whereas the regular thermal reaction gave little product. A similar effect was observed in the microwave experiments (see Tables 3 and 4). A reasonable explanation is that in our initial TCE reactions at reflux much of the HCl formed is likely to be driven out of the reaction mixture, whereas under flow and microwave conditions it is retained in the reaction vessel.[26]

Apart from its interest for implementing clean chemistry, flow chemistry also represents a practical means for optimizing reactions and performing kinetic studies. With a fixed reaction time of 20 min we measured conversions of $\mathbf{I}_A$ at various temperatures (Figure 1), which demonstrated a rapid increase in conversion with temperature. Preheating part of the solvent (170 °C, 40 min) before combining with the reaction solution dramatically increased the rate of reaction, e.g. complete conversion at 100 °C versus almost no conversion without (Figure 1), confirming the importance of catalyst generation from the solvent.

We next wished to quantify the amount of HCl generated. For this purpose, TCE was passed through a stainless steel column at various temperatures with a 10 min reaction time and then directly transferred into a solution of KCl in deionized water and the resulting decrease in pH was measured. The result allowed us to calculate the concentration of H^+ generated in the TCE at each temperature, and a plot of $-\log [H^+]$ vs temperature is given in Figure 2. It should be noted that at higher temperatures (>170 °C) there was evidence for attack on the stainless steel column—the emitted TCE was yellow, and significant amounts of a brown product were emitted from the column on subsequent aqueous washing. We repeated the runs up to 170 °C using a PFA reactor and obtained very

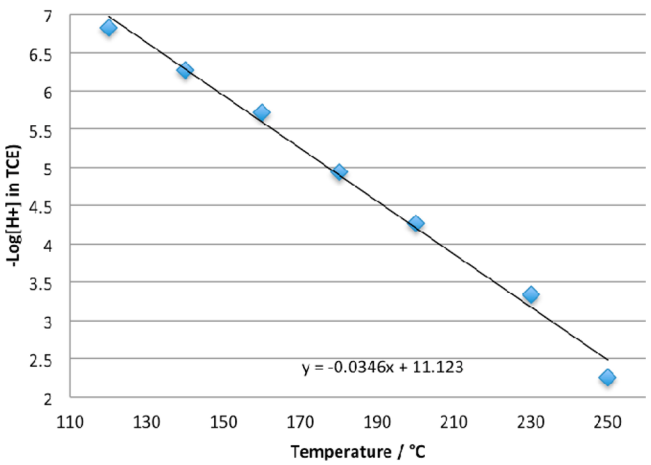


Figure 2. Concentration of HCl generated by heating TCE at various temperatures for 10 min under flow conditions.

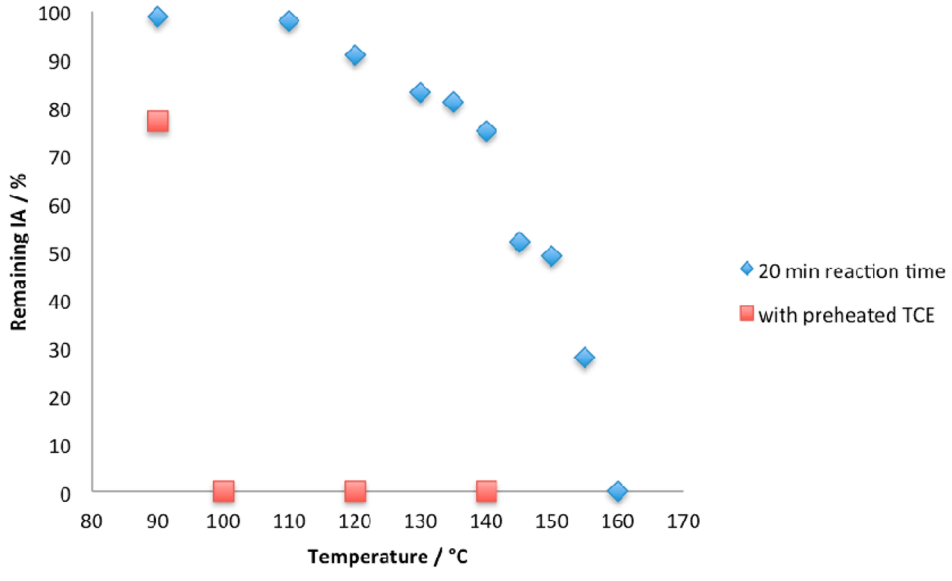


Figure 1. Conversion of $\mathbf{I}_A$ to $\mathbf{II}_A$ with and without preheating of solvent.

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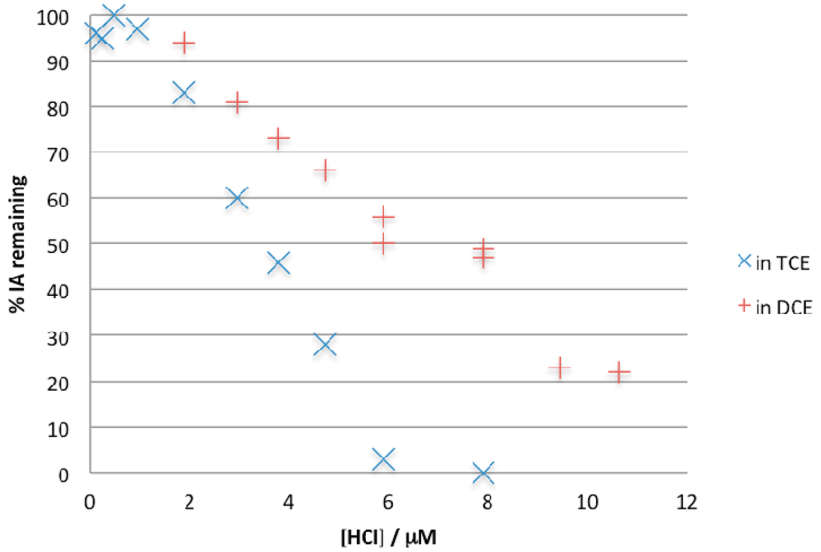
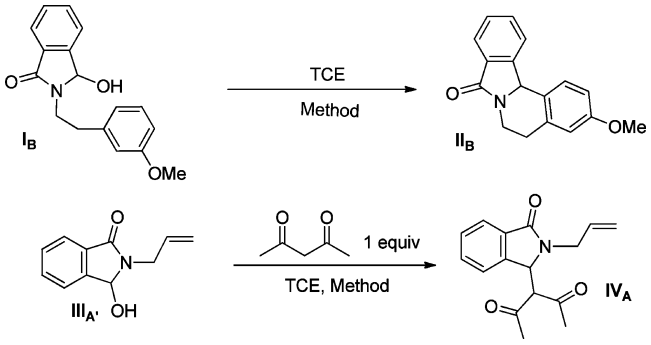


Figure 3. Catalysis of cyclization of $\mathbf{I_A}$ to $\mathbf{II_A}$ using added HCl in TCE and DCE at 100 °C for 20 min under flow conditions.

similar results, indicating that catalysis by iron salts is unimportant, at least up to this temperature. A notable feature of the HCl generation from TCE is the exponential increase in rate with temperature, as indicated by the approximately linear relationship between temperature and the logarithm of the amount of H^+ formed. In comparison, Barton observed first-order kinetics, after an induction period, in the temperature range 263−382 °C for this decomposition.[13] The extent of HCl formation we observe after 10 min at 250 °C is approximately half that expected from the kinetic data Barton reported at 263 °C, which is in reasonable agreement. The particular success of the microwave procedures may be related to the formation of locally superheated hot spots and hence rapid HCl generation. For reaction under flow at 160 °C with a 20 min reaction time (Figure 1), we can estimate the average concentration of HCl generated as 2.6×10^{-6} M, corresponding to approximately 0.023 mol %. For the reactions reported in Tables 1−3 (147 °C) we can estimate the [HCl] generated after 1 h to be 5.5×10^{-6} M, corresponding to about 0.005 mol %, if we assume that all remains in solution. For the "preheated" TCE experiments under flow conditions (Figure 1) we can estimate that the concentration of HCl generated is 11×10^{-6} M and corresponds to nearly 0.20 mol %, a sufficient level to enable complete conversion in 20 min at 100 °C (Figure 1). To confirm that the effect was due to HCl generation, we prepared solutions with known concentrations of HCl in TCE and 1,2-dichloroethane (DCE) and examined the effect on conversion of $\mathbf{I_A}$ to $\mathbf{II_A}$ at 100 °C (Figure 3). The results show that 6 μM HCl in TCE (corresponding to 0.05 mol % of HCl in these experiments) is sufficient to give complete conversion at 100 °C—a concentration similar to that which we calculated was generated by preheating the TCE above, supporting that HCl is the catalyst. At this juncture, it is worth pointing out that the catalytic efficiency of this TCE method is outstanding. HCl in DCE catalyzes the cyclization, but only 50% conversion is reached using a 6 μM concentration of HCl, in comparison to almost complete conversion in TCE, showing that DCE is a less efficient solvent than TCE when the concentrations of HCl are the same. Note that at 100 °C we would not expect significant HCl generation from TCE.

Next, a set of batch experiments was carried out to further characterize the method (Table 5). Carrying out the intra-

Table 5. Intra- and Intermolecular Alkylations of Hydroxy Lactams $\mathbf{I_B}$ and $\mathbf{III_{A'}}$ in Sealed Tubes



entry	substrate	method	product/substrate ratio[a]
1	$\mathbf{I_B}$	147 °C, 4 h, open air	$\mathbf{II_B}/\mathbf{I_B}$ > 99/1 (76)[b]
2		147 °C, 1 h, open air	$\mathbf{II_B}/\mathbf{I_B}$ 40/60
3		147 °C, 1 h, open air[c]	$\mathbf{II_B}/\mathbf{I_B}$ 40/60
4		147 °C, 1 h, sealed tube	$\mathbf{II_B}/\mathbf{I_B}$ > 99/1
5		147 °C, 1 h, sealed tube[c]	$\mathbf{II_B}/\mathbf{I_B}$ > 99/1
6		147 °C, 55 min, microwave	$\mathbf{II_B}/\mathbf{I_B}$ > 99/1
7	$\mathbf{III_{A'}}$	147 °C, 60 h, open air	$\mathbf{IV_A}/\mathbf{III_{A'}}$ 85/15 (77)[b]
8		147 °C, 6 h, sealed tube	$\mathbf{IV_A}/\mathbf{III_{A'}}$ 62/38
9		147 °C, 17 h, sealed tube	$\mathbf{IV_A}/\mathbf{III_{A'}}$ > 99/1
10		147 °C, 0.5 h, microwave	$\mathbf{IV_A}/\mathbf{III_{A'}}$ > 99/1

[a]The product/substrate ratio was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [b]Isolated yields are given in parentheses. [c]Reaction done in the presence of 1 equiv of water added on purpose.

molecular Friedel−Crafts reaction of $\mathbf{I_B}$ in sealed tubes[27] gave much faster reactions than their open-air variants (entry 4 vs 2), confirming that HCl escape from the latter conditions slows the reaction. The effect of using a sealed tube was also apparent in the intermolecular coupling affording $\mathbf{IV_A}$ (entry 7 vs 8), but in contrast to the cyclization of $\mathbf{I_B}$, the net result was inferior to the microwave experiment (entry 8 vs 10). However, prolonging the reaction as depicted in entry 9 allowed the

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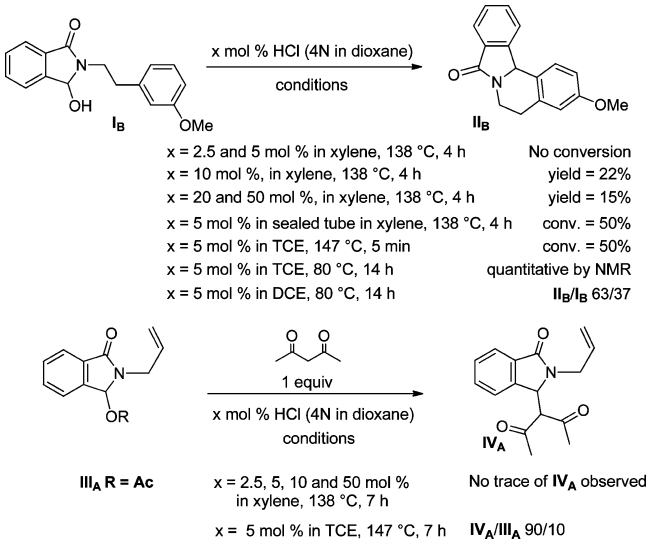
reaction to reach completion in a reasonable (nonoptimized) period of time. The sealed-tube conditions thus provide a convenient way to carry out the reactions (or to improve their performances) when microwave or flow equipment is not available. Water is continuously released in the medium as the reaction is progressing, and it was interesting to investigate its effect on the reaction outcome. Reactions started in the presence of 1 equiv of water led to results identical with those of anhydrous reactions in either open or sealed systems (Table 5, entries 3 and 5), demonstrating that water does not affect the cyclization.

Given that HCl is usually recognized as a poor alkylation catalyst in S_N1 reactions, the excellent catalytic performance systematically observed throughout this study is probably due to the constant in situ generation of anhydrous HCl together with the particular benefits of TCE as a medium for efficient electrophilic catalysis.[28] To gain a better understanding of the different roles played by TCE (and particularly as a reaction medium), use of a commercially available 4 N solution of dry HCl in dioxane to catalyze either cyclization of hydroxy lactam $\mathbf{I_B}$ or alkylation of acetoxy lactam $\mathbf{III_A}$ with acetylacetone in refluxing xylene and TCE was examined (Table 6).

Table 6. Use of Exogenous HCl



The intramolecular reaction in xylene gave poor yields after 4 h[29] (≤22% due to lack of conversion at catalyst loadings up to 5 mol % or extensive decomposition when 10−40 mol % of HCl was used).

Repeating the experiment at 5 mol % loading in a sealed tube proved beneficial, as already indicated (see Table 5), with about 50% conversion and little decomposition observed; however, the performance of this reaction remained far below that of the reaction in TCE (see results in Tables 1, 3, and 5 for comparison), although the latter contains a much smaller amount of HCl (see Figures 2 and 3 and comments thereof).

On simple replacement of xylene by TCE, the reaction proceeded cleanly and gave 50% conversion within 5 min at 147 °C and, as previously noted using preheated TCE, reached completion after 14 h at 80 °C (compare with entries 5 and 6 in Table 3, respectively). This set of comparative results demonstrates that 5 mol % exogenous HCl in solution is an acceptable mimic of preheated TCE but, more importantly, provides compelling evidence that TCE is more than a simple provider of dry HCl and has a very important impact on this alkylative method. The fact that a similar reaction executed in DCE (80 °C, 14 h) remained far from completion (63% conversion) is consistent with observations under flow conditions (Figure 3) and further reinforces the particular advantage of TCE.

Use of exogenous HCl also demonstrated limited efficacy in the intermolecular coupling of $\mathbf{III_A}$ with 2,4-pentanedione. The alkylation failed in boiling xylene whatever the amount of HCl used, and the parent phthalimide, presumably formed from $\mathbf{III_A}$ following a hydrolysis/dehydrogenation sequence, was returned as the major product. Repeating this reaction in refluxing TCE (5 mol % HCl) for 7 h also turned out to be beneficial and returned the desired product $\mathbf{IV_A}$ cleanly in excellent conversion (90%), again mimicking the conditions of the TCE method (but once more in a less efficient manner). In addition to lending additional credence to the benefits of TCE as a solvent, these results demonstrate that the combination of HCl in boiling xylene, but not the source of HCl employed herein, is responsible for the decomposition of $\mathbf{III_A}$ into phthalimide.

Overall, these comparative experiments exemplify that heating TCE is a useful way of continuously generating trace amounts of a "highly active" source of HCl. In addition, they show that the superiority of the TCE reactions also results from its particular features as a solvent. At this stage, the exact nature of such effects remained to be ascertained, but *N*-acyliminium stabilization by the inherent Lewis basicity of the solvent chlorine atoms could possibly be one explanation. Chloride abstraction, very well-known in cationic chemistry performed in chlorinated solvents, might even be involved.[30] This would lead to a transient α-chloro lactam which is known to be highly prone to ionization.[11a,b] In this context, the apparent superiority of TCE over DCE in reactions that were supposed to perform equally well in either solvent (see Figure 3 and Table 6) is noteworthy.

As many organic reactions are promoted by Brønsted acid catalysis, this method is expected to have utility in many more situations beyond the iminium ion chemistry reported here. As a preliminary effort into this direction, we questioned whether our methodology could also encompass π-activated alcohols.[2−4,6] We were delighted to observe that the alcohols $\mathbf{VI_A}$−$\mathbf{VI_D}$ reacted successfully with β-diketones in our thermal alkylative method, giving the desired alkylated products in excellent yields (Table 7).

To summarize, we have described a novel and highly efficient α-amidoalkylation catalyzed by very low levels of HCl generated in situ from the solvent 1,1,2,2-tetrachloroethane. Recognition of the importance of in situ generated acid led to markedly improved protocols, which allowed both considerable rate enhancements and higher applicability. The reaction works in both an intramolecular and intermolecular fashion with broad scope in terms of nucleophilic partners, and its mechanism has been demonstrated to be S_N1 under all circumstances. The known toxicity of TCE is a disadvantage we acknowledge, but its exquisite reactivity and simplicity of reaction procedure make its use worthwhile, particularly for small-scale reactions. This work represents the first successful use of HCl, the simplest strong Brønsted acid, as an alkylation catalyst and suggests an interesting new direction in cationic chemistry.[31] It can be applied to π-activated alcohol derivatives and might be easily extended to other robust N,O-acetal

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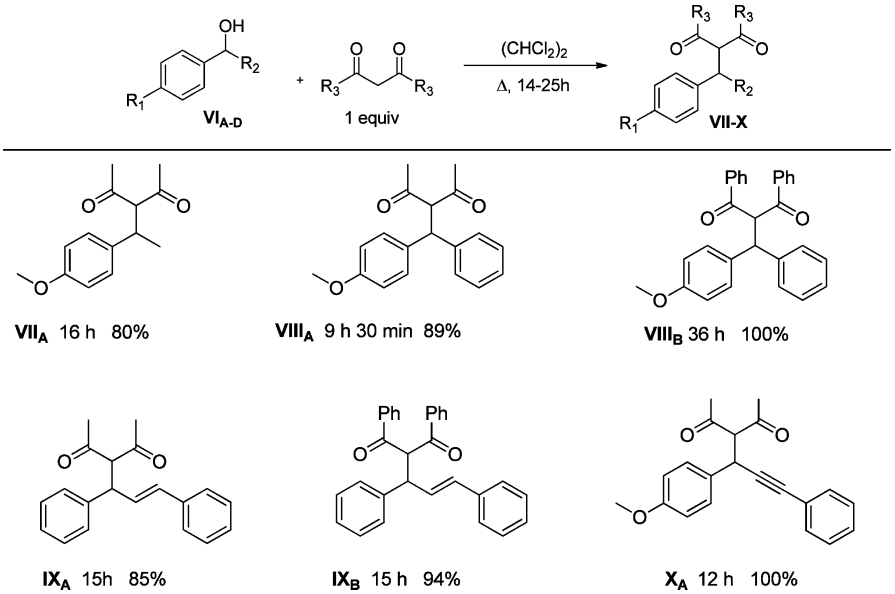
Table 7. Extension of the Thermal Alkylation Approach to the Alkylation of π Alcohols



systems and to any acid-catalyzed transformation beyond iminium ion chemistry.

EXPERIMENTAL SECTION

All reactions were carried out in an air atmosphere in oven-dried glassware with magnetic stirring except where stated. Xylene and toluene were distilled over CaH_2. Analytical grade 1,1,2,2-tetrachloroethane and dichloroethane were used without distillation in the flow experiments, and dichloroethane was distilled over CaH_2 prior to use in the batch reactions. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 with fluorescent indicator UV_{254} TLC plates. The spots were visualized with UV light (254 nm) and staining with a solution of *p*-anisaldehyde, followed by heat. Flash column chromatography was performed using silica gel 60 (particle size 0.040−0.063 mm). ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are reported in ppm using residual solvent peaks as reference ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintuplet; m, multiplet), coupling constant (J in Hz), and integration. ^{13}C NMR spectra were recorded at 75 MHz using broad-band proton decoupling, and chemical shifts are reported in ppm using residual solvent peaks as reference ($CHCl_3$: δ 77.20). Carbon multiplicities were assigned by DEPT techniques. High-resolution mass spectra were recorded on a Q-TOF instrument, which was operated under the following conditions: ion source ESI$^+$ or APCI, both in positive ionization mode. Melting points were measured using open capillary tubes and are uncorrected. GC-MS measurements were recorded on a mass spectrometer coupled with a gas chromatograph. Enantiomeric excesses were determined on an analytical HPLC using Daicel Chiralpak I_A, I_B, or I_C columns. Microwave reactions were performed using 10 mL reaction vessels, and the reaction mixture temperatures were measured with an external heating sensor. The reactions were carried out at a constant temperature of 147 °C, which was reached within 1 min. Flow chemistry was performed in a Vaportec R2/R4+ reaction system. All of the known products were confirmed by comparison of their ^{1}H NMR spectral data reported in the literature.

General Experimental Procedure for Thermal Intramolecular α-Amidoalkylation of Hydroxyl Lactams I_A−I_K. In a round-bottomed flask equipped with a reflux condenser and a magnetic stirrer were added one of the hydroxy lactams $\mathbf{I_A}$−$\mathbf{I_K}$ (83 μmol) and tetrachloroethane (750 μL). The reaction mixture was stirred at reflux (see reaction time specified for each compound), and complete conversion of the starting material was monitored by TLC and/or ^{1}H NMR. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding cyclized product.

2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (II_A). Prepared from hydroxy lactam $\mathbf{I_A}$ following the general procedure (reaction time 1 h). Purification by flash chromatography on silica gel (eluting with DCM/AcOEt 9/1) to give the title compound as a white solid (88% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.86 (d, J = 12.6 Hz, 1H), 7.83 (d, J = 12.6 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.11 (s, 1H), 6.65 (s, 1H), 5.62 (s, 1H), 4.52−4.44 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.46−3.37 (m, 1H), 3.05 (m, 1H), 2.84 (dt, J = 15.6 Hz, 3.9 Hz, 1H). Data are in accordance with previously reported results.[32]

3-Methoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (II_B). Prepared from hydroxy lactam $\mathbf{I_B}$ following the general procedure (reaction time 4 h). Purification by flash chromatography on silica gel (eluting with DCM/AcOEt 95/5) to give the title compound as a white solid (76% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.85 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.62−7.45 (m, 3H), 6.82 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 6.72 (d, J = 1.8 Hz, 1H), 5.61 (s, 1H), 4.40 (ddd, J = 12.6 Hz, 10.2 and 5.1 Hz, 1H), 3.75 (s, 3H), 3.46 (ddd, J = 13.5 Hz, 9.6 and 4.8 Hz, 1H), 3.03 (ddd, J = 15.3 Hz, 9.0 and 6.0 Hz, 1H), 2.84 (dt, J = 15.9 Hz, 4.5 Hz, 1H). Data are in accordance with previously reported results.[9d]

8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (II_C). Prepared from hydroxy lactam $\mathbf{I_C}$ following the general procedure (reaction time 2 h). Purification by flash chromatography on silica gel (eluting with AcOEt) to give the title compound as a white solid (89% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 6.62 (s, 1H), 6.57 (s, 1H), 4.73 (t, J = 7.5 Hz, 1H), 4.32 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.06−2.81 (m, 2H), 2.71−2.42 (m, 4H), 1.85 (m, 1H). Data are in accordance with previously reported results.[33]

2,3-Dimethoxy-6,7-dihydro-5H-benzo[3,4]azepino[2,1-a]-isoindol-9(13bH)-one (II_D). Prepared from hydroxy lactam $\mathbf{I_D}$ following the general procedure (reaction time 1 h 45 min). Purification by flash chromatography on silica gel (eluting with DCM/MeOH 98/2) to give the title compound as a yellow oil (96% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.90 (d, J = 7.6 Hz, 1H), 7.65−7.40 (m, 3H), 6.81 (s, 1H), 6.64 (s, 1H), 5.68 (s, 1H), 4.35 (ddd, J = 14.3 Hz, 6.7 and 1.9 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.36 (ddd, J = 14.3 Hz, 10.5 and 5.7 Hz, 1H), 2.67 (t, J = 6.2 Hz, 2H), 2.16 (m, 1H), 1.92 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 168.9, 148.4, 147.4, 144.2, 132.5, 132.3, 131.4, 128.4, 126.8, 123.9, 123.1, 113.9, 111.4, 65.5, 56.2, 55.9, 41.0, 31.1, 25.6. IR ($CHCl_3$): ν 2938, 2360, 2340, 1687, 1610 cm^{-1}. LRMS (ESI): m/z 310 [M + H]$^+$.

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HRMS (ESI): calcd for $C_{19}H_{19}NO_3$ [M + Na^+], 332.1263; found, 332.1268.

*2,3-Dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methanoisoindolo[1,2-a]isoquinolin-8(12bH)-one (**II$_E$**).* Prepared from hydroxy lactam **I$_E$** following the general procedure (reaction time 1 h 30 min). Purification by flash chromatography on silica gel (eluting with DCM/MeOH 98/2) to give the title compound as a white solid (90% yield as a single diastereoisomer). Mp: 127 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 6.66 (s, 1H), 6.56 (s, 1H), 6.33 (m, 1H), 6.25 (m, 1H), 4.23 (m, 1H), 4.05 (d, J = 1.9 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.30 (br s, 2H), 3.13 (dd, J = 9.5 Hz, 4.8 Hz, 1H), 2.98−2.77 (m, 3H), 2.54 (d, J = 12.4 Hz, 1H), 1.70 (d, J = 8.6 Hz, 1H), 1.49 (d, J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 173.6, 148.1, 147.9, 137.0, 134.3, 130.1, 125.6, 111.7, 107.7, 59.7, 56.2, 55.9, 51.4, 51.3, 46.5, 45.8, 44.6, 37.4, 27.8. IR ($CHCl_3$): ν 2963. 2360. 1669. 1516 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{21}NO_3$ [M + Na^+], 334.1414; found 334.1428.

*2,3-Dimethoxy-12b-phenyl-5,6-dihydroisoindolo[1,2-a]-isoquinolin-8(12bH)-one (**II$_F$**).* Prepared from hydroxy lactam **I$_F$** following the general procedure (reaction time 14 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound as a white solid (85% yield). Mp: 201 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.91 (d, J = 7.5 Hz, 1H), 7.57−5.70 (m, 3H), 7.25−7.23 (m, 3H), 7.11 (s, 1H), 6.98−6.96 (m, 2H), 6.70 (s, 1H), 4.25 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.27 (m, 1H), 3.02 (m, 1H), 2.67 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 167.8, 150.0, 148.6, 147.6, 141.9, 131.8, 129.9, 128.5, 128.4, 127.9, 127.8, 127.3, 124.0, 123.9, 111.9, 110.9, 69.8, 56.2, 55.9, 35.7, 28.2. IR ($CHCl_3$): ν 3054, 1686, 1265, 909, 736 cm^{-1}. LRMS (EI, 70 eV): m/z 355 ($M^{\bullet+}$ − CH_3, 9), 281 (23), 221 (57), 207 (41), 147 (61), 73 (100). HRMS (ESI): calcd for $C_{24}H_{21}NO_3$ [M + Na^+], 394.1414; found, 394.1409.

*2-Methoxy-12b-phenyl-5,6-dihydroisoindolo[1,2-a]isoquinolin-8-(12bH)-one (**II$_G$**).* Prepared from hydroxy lactam **I$_F$** following the general procedure (reaction time 24 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound as a white solid (86% yield). Mp: 169 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.92 (d, J = 7.3 Hz, 1H), 7.60−7.44 (m, 4H), 7.31−7.22 (m, 3H), 7.06−6.96 (m, 4H), 6.85−6.74 (m, 2H), 4.24 (dt, J = 13.1 and 6.6 Hz, 1H), 3.82 (s, 3H), 3.42 (dt, J = 13.2 and 6.6 Hz, 1H), 3.04 (dt, J = 16.0 and 7.0 Hz, 1H), 2.73 (dt, J = 15.9 and 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 167.0, 157.9, 148.8, 140.8, 135.8, 130.7, 130.5, 128.4, 128.1, 127.5, 127.3, 127.1, 126.8, 126.4, 125.9, 123.2, 122.8, 113.2, 110.8,68.9, 54.3, 35.0, 27.7. IR ($CHCl_3$): ν 3017, 1679, 1221, 1211 cm^{-1}. HRMS (ESI): calcd for $C_{23}H_{19}NO_2$ [M + H^+], 342.1489; found, 342.1491.

*2-Methoxy-12b-phenyl-5,6-dihydroisoindolo[1,2-a]isoquinolin-8-(12bH)-one (**II$_H$**).* Prepared from hydroxy lactam **I$_H$** following the general procedure (reaction time 72 h). Purification by flash chromatography on silica gel (eluting with DCM/AcOEt 90/10) to give the title compound as a beige solid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.87−7.83 (m, 2H), 7.64 (dt, J = 7.5 and 1.1 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.18 (s, 1H), 6.58 (s, 1H), 4.65 (ddd, J = 13.1 Hz, 6.5 and 1.2 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H), 3.39 (ddd, J = 13.1 Hz, 11.9 and 4.5 Hz, 1H), 3.04 (ddd, J = 16.0 Hz, 11.9 Hz and 6.5 HZ, 1H), 2.72 (m, 1H), 1.81 (s, 3H). Data are in accordance with previously reported results.[34]

*4,5-Dihydrothieno[3′,2′:3,4]pyrido[2,1-a]isoindol-7(11bH)-one (**II$_I$**).* Prepared from hydroxy lactam **I$_I$** following the general procedure (reaction time 1 h). Purification by flash chromatography on silica gel (eluting with DCM/MeOH 99/1) to give the title compound as a yellow solid (99% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.90 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.33−7.21 (m, 2H), 5.68 (s, 1H), 4.84 (dd, J = 12.9 Hz, 5.2 Hz, 1H), 3.39 (ddd, J = 13.4 Hz, 11.4 and 5.7 Hz, 1H), 3.13−2.84 (m, 2H). Data are in accordance with previously reported results.[35]

*4,5,9,9a-Tetrahydrothieno[2,3-g]indolizin-7(8H)-one (**II$_J$**).* Prepared from hydroxy lactam **I$_J$** following the general procedure (reaction time 3 h 30 min). Purification by flash chromatography on silica gel (eluting with dichloromethane/MeOH 98/2) to give the title compound as a brown solid (92% yield). Mp: 72−74 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.18 (d, J = 4.8 Hz, 1H), 6.81 (d, J = 4.8 Hz, 1H), 4.85−4.63 (m, 1H), 4.48 (dd, J = 13.4 Hz, 4.8 Hz, 1H), 3.09−2.75 (m, 3H), 2.67−2.34 (m, 3H), 1.79 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 173.6, 135.9, 133.0, 124.1, 123.4, 56.3, 37.2, 31.6, 26.7, 24.6. IR ($CHCl_3$): ν 3099, 2924, 2849, 1683 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{11}NOS$ [M + Na^+], 216.0459; found, 216.0459.

General Experimental Procedure for Thermal Intermolecular α-Amidoalkylation of Neutral C-Nucleophiles with Acetoxy Lactams III$_A$−III$_G$. In a round-bottomed flask equipped with a reflux condenser and a magnetic stirrer were added on eof the acetoxy lactams **III$_A$**−**III$_G$** (88.5 μmol), a C-nucleophile (1−3 equiv), and tetrachloroethane (500 μL). The reaction was stirred at reflux (see reaction time specified for each compound), and complete conversion of the starting material was monitored by TLC. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding alkylated product.

*3-(2-Allyl-3-oxoisoindolin-1-yl)pentane-2,4-dione (**IV$_A$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with acetylacetone (1 equiv) as nucleophile (reaction time 7 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (mixture ketone/enol form 1/19) as a colorless oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.90 (d, J = 7.5 Hz, 1H, enol form), 7.84 (d, J = 7.5 Hz, 1H, ketone form), 7.60 (t, J = 7.5 Hz, 2H, ketone and enol form), 7.51 (t, J = 7.5 Hz, 2H, ketone and enol form), 7.44 (d, J = 7.5 Hz, 1H, ketone form), 7.36 (d, J = 7.5 Hz, 1H, enol form), 5.68 (s, 1H, enol form), 5.46 (d, J = 3 Hz, 1H, ketone form), 5.16 (s, 1H, ketone form), 4.84 (dd, J = 17.7 Hz, 2.4 Hz, 1H, enol form), 4.69 (dd, J = 18.0 Hz, 2.4 Hz, 1H, ketone form), 4.46 (d, J = 3.3 Hz, 1H, ketone form), 4.17 (dd, J = 17.7 Hz, 2.4 Hz, 1H, ketone form), 3.80 (dd, J = 17.7 Hz, 2.4 Hz, 1H, enol form), 2.51 (s, 3H, enol form), 2.31 (t, J = 2.4 Hz, 1H, ketone form), 2.27 (t, J = 2.4 Hz, 1H, enol form), 2.18 (s, 3H, ketone form), 1.93 (s, 3H, ketone form), 1.36 (s, 3H, enol form). Data are in accordance with previously reported results.[9d]

*2-Allyl-3-(1-benzoyl-2-oxo-2-phenylethyl)-2,3-dihydroisoindol-1-one (**IV$_B$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with dibenzoylmethane (1 equiv) as nucleophile (reaction time 14 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound as a white solid (77% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.83 (d, J = 7.4 Hz, 1H), 7.65−7.45 (m, 5H), 7.43−7.30 (m, 7H), 5.88 (dddd, J = 16.7 Hz, 10 Hz, 6.6 and 5.2 Hz, 1H), 5.79 (d, J = 4.8 Hz, 1H), 5.73 (d, J = 4.8 Hz, 1H), 5.17 (dd, J = 10 Hz, 1.2 Hz, 1H), 5.17 (dd, J = 16.7 Hz, 1.2 Hz, 1H), 4.6 (dd, J = 15.8 Hz, 5.2 Hz, 1H), 3.75 (dd, J = 15.8 Hz, 6.6 Hz, 1H). Data are in accordance with previously reported results.[9d]

*2-Allyl-3-(1-acetyl-2-oxocyclopentanyl)-2,3-dihydroisoindol-1-one (**IV$_C$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with acetylcyclopentanone (1 equiv) as nucleophile (reaction time 8 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound (as a mixture of two diastereoisomers, ca. 1:1) as a colorless oil (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.95−7.87 (m, 2H), 7.58−7.48 (m, 4H), 7.31 (m, 1H), 7.05 (m, 1H), 5.88−5.70 (m, 2H), 5.61 (s, 1H), 5.56 (s, 1H), 5.28−5.19 (m, 3H), 5.05 (d, J = 17.3 Hz, 1H), 4.73−4.65 (m, 2H), 3.45 (dd, J = 15.7 Hz, 6.7 Hz, 1H), 3.32 (dd, J = 16.9 Hz, 6 Hz, 1H), 2.56 (s, 3H), 2.53 (s, 3H), 2.48−2.25 (m, 4H), 2.02−1.64 (m, 4H), 1.52−1.10 (m, 4H). Data are in accordance with previously reported results.[9d]

*2-Allyl-3-(2-oxocyclohexyl)isoindolin-1-one (**IV$_D$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with cyclohexanone (3 equiv) as nucleophile (reaction time 14 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (as a mixture of two diastereoisomers, ca. 2/1) as a white solid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.84−7.80 (m, 2H), 7.61−7.30 (m, 6H), 5.95−5.78 (m, 2H), 5.40 (s, 1H), 5.35−5.09 (m, 3H), 4.54 (dd, J =

15.7 Hz, 5.3 Hz, 1H), 4.43 (dd, J = 15.3 Hz, 6.4 Hz, 1H), 3.86−3.65 (m, 2H), 3.03−2.86 (m, 2H), 2.81 (dd, J = 11.6 Hz, 7.0 Hz, 1H), 2.61−2.52 (m, 2H), 2.44−2.29 (m, 2H), 2.08−2.02 (m, 2H), 1.83−1.23 (m, 10H). Data are in accordance with previously reported results.[9d]

*2-Allyl-3-(1H-pyrrol-2-yl)isoindolin-1-one (**IV$_E$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with pyrrole (1.5 equiv) as nucleophile (reaction time 2 h 30). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound as a white solid (79% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 8.57 (br s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.54−7.39 (m, 2H), 7.31 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 1.0 Hz, 1H), 6.40 (s, 1H), 6.19 (d, J = 2.7 Hz, 1H), 5.76 (m, 1H), 5.62 (s, 1H), 5.19−5.09 (m, 2H), 4.47 (dt, J = 15.4 Hz, 2.0 Hz, 1H), 3.41 (dd, J = 15.4 Hz, 7.5 Hz, 1H). Data are in accordance with previously reported results.[9b]

*2-Allyl-3-methylisoindolin-1-one (**IV$_F$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with indole (1.5 equiv) as nucleophile (reaction time 2 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound as a white solid (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 8.41 (br s, 1H), 7.98 (d, J = 6.9 Hz, 1H), 7.54−7.48 (m, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.30−7.27 (m, 2H), 7.18 (t, J = 8.0 Hz, 1H), 6.97−6.92 (m, 2H), 5.90−5.77 (m, 2H), 5.19−5.07 (m, 2H), 4.66 (dt, J = 15.6 Hz, 2.0 Hz, 1H), 3.44 (dd, J = 15.6 Hz, 7.4 Hz, 1H). Data are in accordance with previously reported results.[9b]

*2-Allyl-3-(1H-pyrrol-2-yl)isoindolin-1-one (**IV$_G$**).* Prepared from acetoxy lactam **III$_A$** following the general procedure with 2-methylfuran (1.5 equiv) as nucleophile (reaction time 14 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 75/25) to give the title compound as a colorless oil (52% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.88 (d, J = 7.1 Hz, 1H), 7.50 (q, J = 7.1 Hz, 2H), 7.33 (d, J = 6.9 Hz, 1H), 6.20 (d, J = 2.8 Hz, 1H), 5.93 (s, 1H), 5.82−5.70 (m, 1H), 5.52 (s, 1H), 5.17−5.10 (m, 2H), 4.58 (dd, J = 15.5 Hz, 4.3 Hz, 1H), 3.58 (dd, J = 15.5 Hz, 7.4 Hz, 1H) 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 168.0, 153.5, 147.3, 143.4, 133.0, 132.2, 131.8, 128.8, 123.9, 123.2, 117.9, 110.9, 106.5, 57.8, 43.2, 13.8. LRMS (EI, 70 eV): m/z 253 (100), 239 (6), 145 (23), 122 (18). IR ($CHCl_3$): ν 3017, 1686, 1217, 761 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{15}NO_2Na$ [M + Na$^+$], 276.0995; found, 276.1005.

*3-(3-Oxo-2-(prop-2-yn-1-yl)isoindolin-1-yl)pentane-2,4-dione (**V$_A$**).* Prepared from acetoxy lactam **III$_B$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 7 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound (mixture ketone/enol form 1/7) as a yellow oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.90 (d, J = 7.5 Hz, 1H, enol form), 7.84 (d, J = 7.5 Hz, 1H, ketone form), 7.60 (t, J = 7.5 Hz, 2H, ketone and enol form), 7.51 (t, J = 7.5 Hz, 2H, ketone and enol form), 7.44 (d, J = 7.5 Hz, 1H, ketone form), 7.36 (d, J = 7.5 Hz, 1H, enol form), 5.68 (s, 1H, enol form), 5.46 (d, J = 3 Hz, 1H, ketone form), 4.84 (dd, J = 17.7 Hz, 2.4 Hz, 1H, enol form), 4.69 (dd, J = 18.0 Hz, 2.4 Hz, 1H, ketone form), 4.46 (d, J = 3.3 Hz, 1H, ketone form), 4.17 (dd, J = 17.7 Hz, 2.4 Hz, 1H, ketone form), 3.80 (dd, J = 17.7 Hz, 2.4 Hz, 1H, enol form), 2.51 (s, 3H, enol form), 2.31 (t, J = 2.4 Hz, 1H, ketone form), 2.27 (t, J = 2.4 Hz, 1H, enol form), 2.18 (s, 3H, ketone form), 1.93 (s, 3H, ketone form), 1.36 (s, 3H, enol form). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 203.8, 202.1, 170.2, 147.3, 142.3, 133.8, 132.6, 129.5, 124.6, 124.3, 114.1, 77.6, 66.8, 48.0, 28.8, 28.4. IR (KBr/neat): ν 1686 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{15}NO_3$ [M + H$^+$], 270.1128; found, 270.1127.

*3-(2-(But-3-yn-1-yl)-3-oxoisoindolin-1-yl)pentane-2,4-dione (**V$_B$**).* Prepared from acetoxy lactam **III$_C$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 5 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound (mixture ketone/enol form 1/3.8) as a yellow oil (99% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.88 (d, J = 7.4 Hz, 1H, enol form), 7.84 (d, J = 7.7 Hz, 1H, ketone form), 7.60−7.44 (m, 5H, ketone and enol form), 7.32 (d, J = 7.4 Hz, 1H, enol form), 5.77 (s, 1H, enol form), 5.55 (s, 1H, ketone form), 4.38 (d, J = 1.9 Hz, 1H, ketone form), 4.30−4.21 (m, 1H, ketone form), 3.97−3.89 (m, 1H, enol form), 3.31−3.19 (m, 2H), 2.83−2.69 (m, 1H), 2.60 (t, J = 5.4 Hz, 1H, ketone form), 2.55−2.48 (m, 4H), 2.06 (s, 3H, ketone form), 1.93 (s, 3H, ketone form), 1.35 (s, 3H, enol form). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 202.7, 202.5, 198.3, 189.7, 168.8, 168.5, 145.4, 143.0, 132.5, 132.4, 132.2, 132.0, 129.2, 128.9, 124.1, 124.0, 123.9, 122.4, 105.4, 82.1, 81.6, 70.6, 70.5, 67.3, 59.8, 57.4, 39.5, 39.3, 31.1, 24.6, 23.1, 18.4, 18.3. IR (KBr/neat): ν 1686 cm^{-1}. LRMS (EI, 70 eV): m/z 240 (M$^{\bullet+}$ − CH_3CO, 18), 197 (M$^{\bullet+}$ − (2 × CH_3CO), 10), 188 (M$^{\bullet+}$ − Nu, 8), 173 (100), 77 (20). HRMS (ESI): calcd for $C_{17}H_{17}NO_3$ [M + H$^+$], 284.1281; found, 284.1289.

*3-(3-Oxo-2-phenethylisoindolin-1-yl)pentane-2,4-dione (**V$_C$**).* Prepared from acetoxy lactam **III$_D$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 7 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (mixture ketone/enol form 1/5.7) as a white solid (99% yield). Mp: 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.91 (d, J = 6.8 Hz, 1H, enol form), 7.85 (d, J = 7.2 Hz, 1H, ketone form), 7.52 (dq, J = 13.7 Hz, 6.9 Hz, 4H, ketone and enol form), 7.39 (d, J = 7.4 Hz, 1H, ketone form), 7.26−7.16 (m, 11H, ketone form), 5.26 (d, J = 2.5 Hz, 1H, ketone form), 5.17 (s, 1H, enol form), 4.34−4.25 (m, 1H, ketone form), 4.17−4.07 (m, 1H, enol form), 3.28−2.88 (m, 6H, ketone and enol form), 1.99 (s, 3H, enol form), 1.95 (d, J = 2.9 Hz, 1H, ketone form), 1.41 (s, 6H, ketone form), 1.31 (s, 3H, enol form). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 198.1, 189.5, 168.5, 145.2, 139.3, 132.5, 132.3, 129.1, 129.0, 128.9, 126.9, 124.0, 122.3, 105.3, 59.5, 42.3, 34.9, 24.4, 22.3. IR (KBr/neat): ν 1682 cm^{-1}. LRMS (EI, 70 eV): m/z 335 (M$^{\bullet+}$, 4), 244 (65), 235 (15), 215 (39), 202 (41), 173 (100), 155 (24), 131 (24). HRMS (ESI): calcd for $C_{21}H_{21}NO_3$ [M + H$^+$], 336.1594; found, 336.1593.

*3-(2-Benzyl-3-oxoisoindolin-1-yl)pentane-2,4-dione (**V$_D$**).* Prepared from acetoxy lactam **III$_E$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 9 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (mixture ketone/enol form 0/100) as a white solid (96% yield). Mp: 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.94 (d, J = 6.9 Hz, 1H), 7.58−7.49 (m, 2H), 7.34−7.21 (m, 6H), 5.44 (d, J = 15.0 Hz, 1H), 5.27 (s, 1H), 3.94 (d, J = 15.0 Hz, 1H), 1.79 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 197.5, 190.5, 168.3, 145.1, 137.0, 132.5, 132.1, 129.1, 128.9, 128.3, 128.0, 124.3, 122.3, 104.9, 57.7, 43.8, 24.2, 22.4. IR (KBr/neat): ν 1686 cm^{-1}. LRMS (EI, 70 eV): m/z 321 (M$^{\bullet+}$, 4), 236 (22), 230 (100), 221 (27), 188 (99), 170 (20), 131 (11), 91 (33). HRMS (ESI): calcd for $C_{20}H_{19}NO_3$ [M + H$^+$], 322.1438; found, 322.1446.

*3-(2-(3-Methylbut-2-en-1-yl)-3-oxoisoindolin-1-yl)pentane-2,4-dione (**V$_E$**).* Prepared from acetoxy lactam **III$_F$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 7 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (mixture ketone/enol form 1/8.3) as a yellow oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.87 (d, J = 7.3 Hz, 1H, enol form), 7.81 (d, J = 6.9 Hz, 1H, ketone form), 7.57−7.45 (m, 4H, ketone and enol forms), 7.39 (d, J = 7.4 Hz, 1H, ketone form), 7.30−7.26 (m, 1H, enol form), 5.47 (s, 1H, enol form), 5.28 (s, 1H, ketone form), 5.21−5.15 (m, 2H, ketone and enol forms), 4.63−4.50 (m, 2H, ketone and enol forms), 4.27 (d, J = 2.9 Hz, 1H, ketone form), 3.79 (dd, J = 15.4 Hz, 7.3 Hz, 1H, ketone form), 3.64 (dd, J = 14.9 Hz, 8.8 Hz, 1H, enol form), 2.34 (s, 3H, enol form), 2.15 (s, 3H, ketone form), 1.85 (s, 3H, ketone form), 1.74 (s, 3H, enol form), 1.71 (s, 3H, enol form), 1.65 (s, 3H, ketone form), 1.40 (s, 3H, ketone form), 1.38 (s, 3H, enol form). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 202.6, 202.3, 197.7, 189.9, 167.8, 145.1, 142.7, 137.2, 132.6, 132.2, 132.1, 129.1, 128.8, 124.4, 124.0, 123.9, 122.2, 119.9, 119.1, 105.5, 67.1, 58.1, 57.3, 38.8, 37.9, 31.4, 30.8, 27.1, 25.9, 24.3, 22.8, 18.2, 17.9. IR (neat): ν 1685 cm^{-1}. LRMS (EI, 70 eV): m/z 299 (M$^{\bullet+}$, 39), 256 (34), 231 (91), 200 (60),

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188 (100), 171 (41), 131 (35), 84 (31), 43 (72). HRMS (ESI): calcd for $C_{18}H_{21}NO_3$ [M + H$^+$], 300.1594; found, 300.1596.

*3-(2-(2-Methylallyl)-3-oxoisoindolin-1-yl)pentane-2,4-dione (**V$_F$**).* Prepared from acetoxy lactam **III$_G$** following the general procedure with acetylacetone (1.1 equiv) as nucleophile (reaction time 7 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 70/30) to give the title compound (mixture ketone/enol form 1/5.25) as a colorless oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.91 (d, J = 7.5 Hz, 1H, enol form), 7.86 (d, J = 10.8 Hz, 1H, ketone form), 7.60−7.42 (m, 5H), 7.33 (d, J = 7.5 Hz, 1H, enol form), 5.43 (s, 1H, enol form), 5.24 (d, J = 3.0 Hz, 1H, ketone form), 4.94 (s, 2H, ketone and enol form), 4.76 (s, 2H, ketone and enol form), 4.68 (d, J = 15.6 Hz, 2H, ketone and enol form), 4.27 (d, J = 3.3 Hz, 1H, ketone form), 3.65 (d, J = 15.9 Hz, 1H, ketone form), 3.39 (d, J = 15.3 Hz, 1H, enol form), 2.34 (s, 3H, enol form), 2.15 (s, 3H, ketone form), 1.88 (s, 3H, ketone form), 1.73 (s, 3H, enol form), 1.68 (s, 3H, ketone form), 1.37 (s, 3H, enol form). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ 201.3, 201.1, 196.4, 189.1, 167.6, 167.0, 144.0, 141.5, 140.2, 139.5, 131.2, 131.0, 128.0, 127.7, 123.1, 123.0, 121.2, 112.1, 112.0, 104.0, 65.9, 56.7, 56.0, 45.5, 44.3, 30.1, 29.7, 23.1, 21.8, 19.1, 19.0. IR (neat): ν 1684 cm^{-1}. LRMS (EI, 70 eV): m/z 242 ($M^{\bullet+}$ − CH_3CO, 56), 200 ($M^{\bullet+}$ − (2 × CH_3CO), 49), 188 (100), 186 ($M^{\bullet+}$ − $CH_3COCH_2COCH_3$, 60), 147 (58), 77 (40). HRMS (APCI): calcd for $C_{17}H_{19}NO_3$ [M + H$^+$], 286.1438; found, 285.1446.

*3-(1H-Indol-3-yl)-2-(prop-2-yn-1-yl)isoindolin-1-one (**V$_G$**).* Prepared from acetoxy lactam **III$_B$** following the general procedure with indole (1.1 equiv) as nucleophile (reaction time 2 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 60/40) to give the title compound as a white solid (73% yield). Mp: 111 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 8.29 (br s, 1H), 8.03−7.90 (m, 1H), 7.50 (q, J = 6.8 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.34−7.28 (m, 1H), 7.16 (t, J = 7.7 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.00 (s, 1H), 4.88 (dd, J = 17.5 Hz, 2.4 Hz, 1H), 3.50 (dd, J = 17.6 Hz, 2.2 Hz, 1H), 2.22 (t, J = 2.3 Hz, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$, 293 K): δ 167.6, 145.9, 136.8, 132.1, 131.5, 128.4, 125.3, 123.9, 123.7, 123.4, 122.7, 120.2, 119.1, 111.5, 110.2, 78.8, 71.8, 57.3, 29.4. IR (KBr/neat): ν 2254, 1682 cm^{-1}. LRMS (EI, 70 eV): m/z 286 ($M^{\bullet+}$, 40), 257 (15), 204 (56), 155 (100), 130 (20), 102 (23). HRMS (APCI): calcd for $C_{19}H_{14}N_2O$ [M + H$^+$], 287.1179; found, 287.1185.

General Procedure for Thermal Intermolecular Alkylation of Neutral C-Nucleophiles with π-Alcohols VI$_A$−VI$_D$. In a round-bottomed flask equipped with a reflux condenser and a magnetic stirrer were added one of the π-alcohols **VI$_A$**−**VI$_D$** (88.5 μmol), acetylacetone (1 equiv) or dibenzoylmethane (1 equiv), and tetrachloroethane (500 μL). The reaction mixture was stirred at reflux (see reaction time specified for each compound), and complete conversion of the starting material was monitored by TLC. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding alkylated product.

*3-(1-(4-Methoxyphenyl)ethyl)pentane-2,4-dione (**VII$_A$**).* Prepared from alcohol **VI$_A$** following the general procedure with acetylacetone as nucleophile (reaction time 16 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 90/10) to give the title compound as a white solid (80% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.18 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.99 (d, J = 11.4 Hz, 1H), 3.79 (s, 3H), 3.57 (m, 1H), 2.33 (s, 3H), 1.83 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H).

Data are in accordance with previously reported results.[36]

*3-((4-Methoxyphenyl)(phenyl)methyl)pentane-2,4-dione (**VIII$_A$**).* Prepared from alcohol **VI$_B$** following the general procedure with acetylacetone as nucleophile (reaction time 9 h 30 min). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 90/10) to give the title compound as a white solid (89% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.26−7.16 (m, 8H), 6.80 (d, J = 8.7 Hz, 2H), 4.76 (d, J = 12.3 Hz, 1H), 4.68 (d, J = 12.3 Hz, 1H,), 3.74 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). Data are in accordance with previously reported results.[36]

*2-((4-Methoxyphenyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (**VIII$_B$**).* Prepared from alcohol **VI$_B$** following the general procedure with dibenzoylmethane as nucleophile (reaction time 36 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 80/20) to give the title compound as a white solid (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.83 (d, J = 7.5 Hz, 4H), 7.51−7.31 (m, 8H), 7.31−6.92 (m, 5H), 6.78 (d, J = 9.9 Hz, 2H), 6.31 (d, J = 11.7 Hz, 1H), 5.28 (d, J = 11.7 Hz, 1H), 3.67 (s, 3H). Data are in accordance with previously reported results.[36]

*(E)-3-(1,3-Diphenylallyl)pentane-2,4-dione (**IX$_A$**).* Prepared from alcohol **VI$_C$** following the general procedure with acetylacetone as nucleophile (reaction time 15 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 80/20) to give the title compound as a white solid (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.34−7.20 (m, 10H), 6.43 (d, J = 15.8 Hz, 1H), 6.19 (ddd, J = 15.8 Hz, 5.1 and 2.7 Hz, 1H), 4.34 (m, 2H), 2.25 (s, 3H), 1.92 (s, 3H). Data are in accordance with previously reported results.[36]

*(E)-2-(1,3-Diphenylallyl)-1,3-diphenylpropane-1,3-dione (**IX$_B$**).* Prepared from alcohol **VI$_C$** following the general procedure with dibenzoylmethane as nucleophile (reaction time 15 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 90/10) to give the title compound as a white solid (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 8.04 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 7.3 Hz, 2H), 7.55−7.09 (m, 16H), 6.37−6.25 (m, 2H), 5.97 (d, J = 10.5 Hz, 1H), 4.80 (dd, J = 9.5 and 6.1 Hz, 1H). Data are in accordance with previously reported results.[37]

*3-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (**X$_A$**).* Prepared from alcohol **VI$_D$** following the general procedure with acetylacetone as nucleophile (reaction time 12 h). Purification by flash chromatography on silica gel (eluting with cyclohexane/AcOEt 85/15) to give the title compound as a white solid (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ 7.49−7.26 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 4.62 (d, J = 11.0 Hz, 1H), 4.19 (d, J = 11.0 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 1.94 (s, 3H). Data are in accordance with previously reported results.[38]

General Procedure for Thermal α-Amidoalkylation of Acetoxy or Hydroxy Lactams Using Preheated TCE. TCE was heated at reflux for 14 h under an inert atmosphere prior to use. After it was cooled to room temperature, TCE was used as such in general procedures for thermal intramolecular and intermolecular reactions.

General Procedure for Thermal α-Amidoalkylation of Hydroxy Lactams using Microwave Irradiation. In a microwave reaction vessel were added hydroxy lactam **VI$_A$** (20 mg, 105.7 μmol), a C-nucleophile (1−3 equiv in the case of intermolecular reactions), and tetrachloroethane (700 μL). The reaction mixture was stirred at reflux (300 W) (see reaction time specified for each compound), and complete conversion of the starting material was monitored by TLC and/or ^{1}H NMR. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding alkylated product.

General Procedure for Thermal Cyclization under Flow Conditions. 1,1,2,2-Tetrachloroethane (TCE), was stored over base (K_2CO_3) and filtered prior to the reaction.

A solution of 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one (0.007 g, 0.022 mmol) in TCE (2 mL) was inserted using an injection loop into a flow of TCE (0.5 mL/min) and passed through a 10 mL capacity PFA column (1 mm i.d., 20 min reaction time) heated to the required temperature and then through a back-pressure regulator (40 psi) and the appropriate fraction collected. This fraction was washed with an aqueous solution of $NaHCO_3$ (5%) to neutralize residual traces of HCl, the aqueous layer was extracted with one volume of dichloromethane, and the organic layer was dried over $MgSO_4$. Filtration and evaporation of the solvent (14 mbar, 60 °C) afforded the crude product, which was submitted for ^{1}H NMR analysis.

With Preheating of Solvent. A flow of TCE (0.25 mL/min) was passed through a 10 mL PFA reactor heated to 170 °C and then combined using a mixing T with a flow of TCE (0.25 mL/min) into which a solution of the substrate was inserted as above. The combined flow was passed through a 10 mL PFA column heated to the required temperature before being collected, worked up, and analyzed as above.

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Preparative-Scale Reactions. For preparative-scale reactions a solution of $\mathbf{I_A}$ (0.011 M) in TCE was pumped directly from a bottle through the pump and then the heated column, allowing potentially continuous production. The crude product was purified by chromatography on silica using 2% MeOH in DCM as eluent. For example, a 30 mL aliquot (0.33 mmol of $\mathbf{I_A}$) was pumped at 0.5 mL/min through a 10 mL PFA column held at 160 °C to give 0.092 g of pure $\mathbf{II_A}$ (94%).

Procedure for Monitoring HCl Formation from TCE under Flow Conditions. A plug of TCE (5 mL, stored over K_2CO_3) was inserted into a flow of toluene (1 mL/min) and pumped through a stainless steel reactor (10 mL, 1 mm i.d.) at various temperatures. For temperatures up to 170 °C a PFA column was also used. The reactor was connected to a cooling loop (100 cm, 1 mm i.d.), followed by a back-pressure regulator (250 psi). A sufficient plug of the output to ensure that all the TCE was included was collected in screw-capped polythene bottles (60 mL) containing aqueous KCl (30 mL of a 6.6 g/L solution in HPLC grade water). The bottles were capped and shaken, the contents were allowed to settle, and then the pH of the aqueous layer was measured. Remeasuring the pH after around 30 min was used to confirm the stability of the readings. We confirmed that a TCE/water mixture at room temperature did not form significant acid. The pH meter (Jenway 3071) with glass electrode (Hanna HI-1131) was freshly calibrated with pH 7.0 and pH 4.0 buffer solutions and kept in the KCl solution. Before and after each measurement the electrode was thoroughly rinsed (3×) with the KCl solution and the pH meter was periodically validated against buffer.

Procedure for Use of TCE and DCE Containing Known Amounts of Anhydrous HCl under Flow Conditions. HCl gas was generated as previously described[39] and absorbed into TCE or DCE. Aliquots of the solutions so formed were titrated against 0.01 N aqueous NaOH, giving HCl concentrations of 0.009 and 0.014 M in TCE and DCE, respectively. Additional solutions were prepared by a 10/1 dilution of the above. All HCl solutions were stored in sealed vessels to minimize loss of HCl. An appropriate volume of acid solution was added to ∼7.4 mg of $\mathbf{I_A}$ in a 2 mL volumetric vial, and further solvent was added to make up to the 2 mL mark. As soon as $\mathbf{I_A}$ had dissolved, the solution was loaded into a 10 mL injection loop and then passed through a 10 mL PFA (1 mm i.d.) column heated to 100 °C with a flow rate of 1 mL/min. In both cases the carrier solvent was DCE. For TCE, the reaction mixture plug was inserted between two 2 mL plugs of TCE. The reaction product was collected, worked up, and analyzed as above.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C spectra for all new compounds and text and a figure giving a description of results obtained from α-amidoalkylation reactions carried out in fluorinated alcohols as solvents. 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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(17) Indeed, after 1 h of reaction time, **Ic** has been completely converted, and the conjugated pyrrolidinone **A** was the major product detectable from the ^{1}H NMR spectrum along with minor amounts of the cyclized product **IIc**.
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(22) Hydroxy lactams derived from phthalimide are poorly reactive in room-temperature catalytic intermolecular amidoalkylations even using superacidic catalysts. For more details see ref 9b.
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