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In Situ-Generated Glycinyl Chloroaminals for a One-Pot Synthesis of Non-Proteinogenic α-Amino Esters

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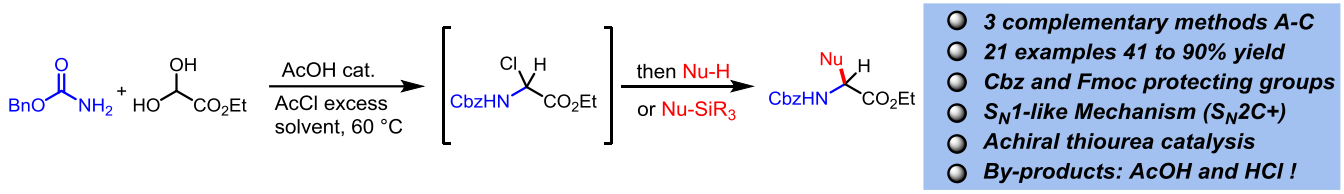
TOC/Abstract Graphic



ABSTRACT:

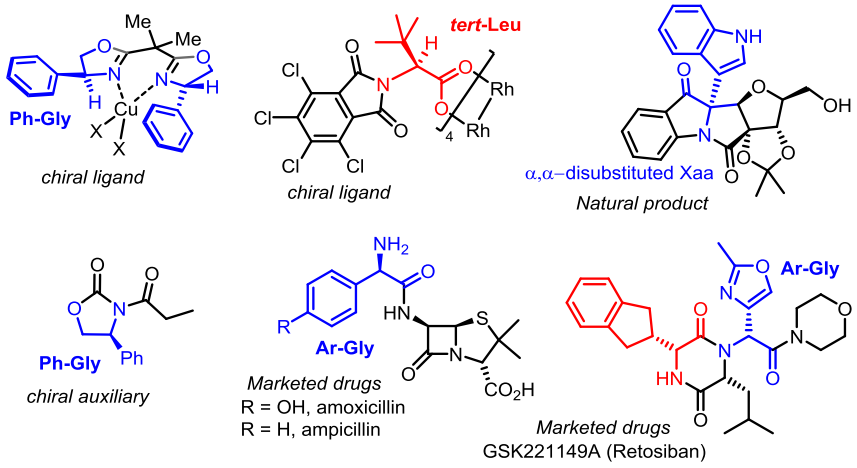
An acetyl chloride-mediated cascade transformation involving a primary carbamate, ethyl glyoxylate and various types of nucleophiles is reported for the synthesis of orthogonally protected α-amino esters. These reactions proceeded rapidly to afford the pivotal α-chloroglycine intermediate in excellent yields which can be directly functionalized *in situ* with various types of nucleophiles. A mild and unique AcOH(cat.)/AcCl system was found to promote an autocatalytic-like condensation and facilitate the multicomponent assembly of non-proteinogenic α-amino esters. To better understand this one pot transformation, and the orchestration of the components condensations, the investigation of a broader scope of nucleophiles and some kinetic studies are presented. Our findings suggest that halogenation step towards the formation of the α-chloroglycine is the rate determining step likely proceeding through the formation of an *N*-carbamoyl iminium. Also, the initial kinetic profiling for the nucleophilic substitution support an S_N1-like (S_N2C+) mechanism in which nucleophiles add to the iminium–chloride tight ionic pair. These results lead ultimately to the design of a new protocol in which an achiral hydrogen-bond donor thiourea catalyst was utilized to enhance the reaction scope and enable silylated nucleophile to be efficiently exploited to synthesize novel non-proteinogenic α-amino esters.

▪ INTRODUCTION:

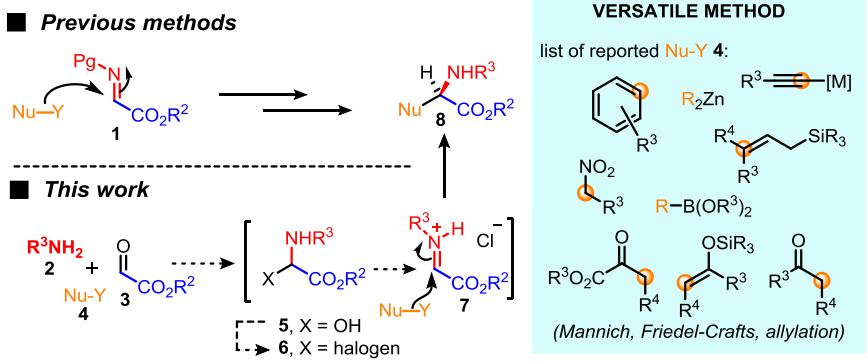
Non-proteinogenic α-amino acids (Xaas) represent an important class of organic compounds. They are prevalent foundational building blocks in many biologically active small-molecules, non-ribosomal peptides (NRPs) and pharmaceuticals (Figure 1).[1] For example, NRPS containing α-aryl glycine units prove to typically have important

antibacterial properties (*e.g.* amoxicillin, ampicillin, vancomycin, teicoplanin, ramoplanin) or anti-HIV properties (*e.g.* neuroprotectins A and B, feglymycin).[2] Due to their extraordinary diversity (structural and functional), non-proteinogenic Xaas are also widely used as chiral building blocks in the synthesis chiral auxiliaries, organocatalysts and ligand backbone for metal catalysis thus imparting them with a crucial role in modern organic synthesis. As a result, scalable and asymmetric synthesis of non-proteinogenic α-amino acids has attracted significant attention in the past decades.[3] For example, asymmetric alkylations of glycine-derived Schiff base[4] or azlactone[5] and NH-insertion[6] of α-diazo esters are well-documented and useful methods for the catalytic asymmetric synthesis of α-amino esters. Of importance, numerous asymmetric functionalizing methods of α-iminoglycinates **1** have also been reported (Strecker,[7] Mannich,[8] Petasis,[9] hydrogenation[10] or aza-Friedel−Crafts[11] reactions) demonstrating the prodigious versatility of this substrate for the synthesis of non-proteinogenic Xaas (Scheme 1). However, the instability of α-iminoglycinates **1**, which require cumbersome preparation and some typical protecting groups manipulations are an inherent limitation leading overall to multi-pot operations to produce marketable α-amino esters **8**.[12] To overcome some of these issues, α-haloglycine esters[13] **5** and α-amido sulfones[14] have been exploited as surrogates of α-iminoglycinates **1** (Scheme 1) in multi-pot operations. On the other hand, only sparse examples of cascade reactivity or multicomponent reactions (MCRs) to synthesize chiral α-amino esters in a single step have been reported.[15] The most practical asymmetric MCRs for the synthesis of non-proteinogenic Xaas are certainly the Strecker-3CR (requiring one hydrolysis extra-step) and

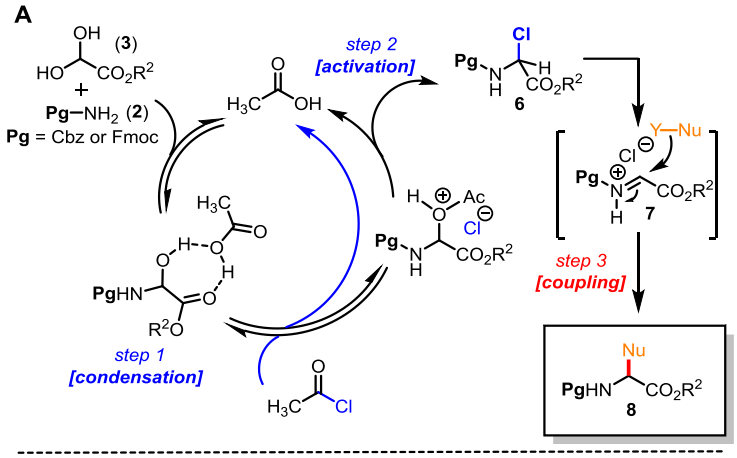
Figure 1. Chemicals derived from non-proteinogenic Xaa structural motifs

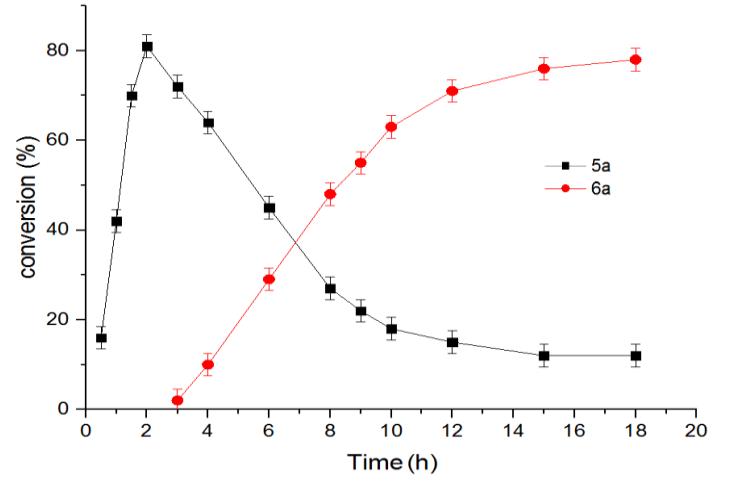


Scheme 1. Multicomponent assembly of non-proteinogenic α-amino esters **7**



Scheme 2. One-pot Synthesis of α-chloroglycine ester **6a** [a]





[a] Reaction mixture aliquots were taken during the course of the reaction and solvent was evaporated under vacuum. Mesitylene was added as an internal standard and conversions were calculated from ^{1}H NMR using a quantitative protocol with the appropriate acquisition parameters (see experimental section).

the Petasis-3CR which can accommodate several type of functionalizations. However, the vast majority of MCRs reported to date, using iminoglycinate **1** as pivotal intermediate are achiral and present a narrow scope of nucleophiles.[16] Thus we were drawn to establish a scalable and more versatile one-pot synthesis of α-amino esters which could also be amenable to enantioselective catalysis[17] to prepare Xaas bearing marketable carbamate protecting groups (*e.g.* *N*-protecting groups such as benzyloxycarbamate (Cbz) or fluorenylmethyloxycarbamate (Fmoc)[18]. We now wish to expand the scope of this work and fully exploit our recently reported autocatalytic-like synthesis of α-chloroglycinate **6a** to take advantages of the high reactivity of glycinate iminium **7** (Scheme 2). While α-halogenoglycine synthons have been extensively exploited in the 80's, no kinetic studies have been previously reported and the mode of reactivity was not well understood.[13,19] We hope to demonstrate that this novel method is truly amenable to the practical synthesis of numerous classes of α-amino esters and offers a great opportunity for some chiral variant to be developed.

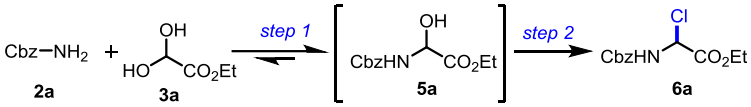
- **RESULTS AND DISCUSSION:**

Summary of Previous Results. Recently, our group established a suitable system for a practical racemic route to α-aryl α-amino esters bearing carbamate protecting groups.[18] We have previously shown that primary carbamates **2**, ethyl glyoxylate (hydrate) **3** and arene nucleophiles **4** have been condensed to achieve a stepwise 3-component synthesis of numerous α-aryl α-amino esters **8** in a single pot transformation (Scheme 2A). The reaction advances through a pathway involving three main steps: 1) the condensation between **2** and **3**, followed

by 2) the activation of the α-hydroxyglycine **5** to α-chloroglycine **6** and the final 3) nucleophile addition. As proposed in Scheme 2A, a system of AcOH(cat.)/AcCl was previously found to assist both steps (1 & 2) while enhancing the overall reaction' rate, leading us to propose a new mechanism for this transformation. We have previously suggested that the condensation between **2** and **3** catalyzed by acetic acid (10 mol%) afforded modest conversion to α-hydroxyglycine **5a** (72% conversion) due to the reversibility of the initial condensation step.[20] In the other end, catalyzed reaction with acid and excess of acetyl chloride proceeded more rapidly to a full conversion in **5a** and further afforded the desired α-chloroglycine **6a** in quantitative yields (Scheme 2B). To rationalize these results, we propose that catalytic amount of acid facilitates the condensation between benzyl carbamate **2a** and ethyl glyoxylate **3a** to rapidly form the first intermediate α-hydroxyglycine **5a** (less than 2 hours) which further irreversibly evolve by reaction with acetyl chloride (catalyzed by AcOH and/or HCl) to deliver α-chloroglycine ester **6a** in an autocatalytic-like manner.[21] The preliminary kinetic experiments support that the halogenation is the rate determining step (persistent hemiaminal **5a** >80% formation in 2 h) and that *acetyl chloride not only promotes the condensation step between* **2a** and **3a***, but also trap the water formed during the reaction, producing more acetic acid by-product which autocatalyzes and accelerates the overall cascade* (slope characteristic of a rate acceleration in α-chloroglycine **6a** formation; Scheme 2B).

Optimization of Reaction Conditions. From an extensive screening of hemiaminal **5a** activatation (previous publication[18]) to chloro-, bromo-, or acetoxy-aminals, acetyl chloride was found the most efficient reagent in the prospect of a tandem process. During the investigation, we faced the expected problem of full conversion to the desired α-chloroglycine **6a** and proposed that the modest yields observed for the condensation between carbamate **2a** and ethyl glyoxylate **3a**, 62% and 82% yield in chloroform and ethyl acetate respectively are due to the reversibility of the condensation (Table 1, entries 1 & 3).[20] Upon activation with acetyl chloride the reactions proceeded to full conversion and further afforded the desired α-chloroglycine **6a** with a

Table 1. Optimizations to synthesize the pivotal α-chloroglycin ester **6a**



entry	solvent, temp. [a]	activator	time (h)	conversion (%) [b]
1	$CHCl_3$, RT	-	12	**5a** (62) [c]
2	$CHCl_3$, RT	AcCl	18	**5a** (76); **6a** (4)
3	CH_3CO_2Et, RT	-	12	**5a** (82) [c]
4	CH_3CO_2Et, RT	AcCl	18	**5a** (59); **6a** (19)
5	CH_3CO_2Et, 60 °C	AcCl	9	**6a** (100)
6	$CHCl_3$, 60 °C	AcCl	12	**6a** (100)
7	THF, 60 °C	AcCl	12	**5a** (61); **6a** (25)[d]
8	Toluene, 60 °C	AcCl	12	**5a** (44); **6a** (56)
9	CH_3CN, 60 °C	AcCl	24	**6a** (100)

[a] Reactions were performed with **2a** (1.0 mmol), **3a** (1.3 mmol), acetyl chloride (2.5 mmol), and acetic acid (10 mol%); [b] Conversions are reported due to the innate instability of chloroaminal **6a**, using a quantitative ^{1}H NMR technique [ref 21] with mesitylene as internal standard; [c] Isolated yields of pure hemiaminal **5a** were 60% and 81% for entries 1 and 3 respectively; [d] Decomposition and possible polymerization were observed.

conversion of 4% and 19% respectively (Table 1, entries 2 & 4).[22] Under strict anhydrous conditions at 60 °C, α-chloroglycine **6a** was obtained in a quantitative manner in ethyl acetate and chloroform (Table 1, entries 5 & 6).[23] Several other solvents were tested (Table 1, entries 7-9), and α-chloroglycine **6a** was also synthesized quantitatively in CH_3CN in 24 hours. After optimizations, two sets of conditions in $CHCl_3$ and CH_3CN were established for the quantitative preparation of α-chloroglycine ester **6a** in a single step, which represents an advancement from the previous literature (2 steps).[24]

Scope and Limitation of the Methods A/B. We then turn our attention to the aza-Friedel−Crafts alkylation of the in situ generated α-chloroglycine ester **6a** with a series of arene nucleophiles (Table 2). Experiments were conducted with reduced amount of ethyl glyoxylate **3a** (1.05 equiv.) to avoid the formation of direct aza-Friedel−Crafts by-products.[25] According to the empirical nucleophilicity scale established by Mayr,[26] the reactivity of carbocations can be predicted using the correlation equation $\log k_{(20\ ^oC)} = s_N (E + N)$, in which the strength of the N-carbamoyliminium electrophile **9** would be characterized by the parameter E and the various π-nucleophile arenes tested would be characterized by two parameters N and s_N. For each substrate tested in the arylation (Table 2), both solvent conditions were compared $CHCl_3$ (**Method A**) and CH_3CN (**Method B**) and the reactivity parameters were used to rationalize the scope of the iminium arylations depending on solvent polarity. The experiments summarized in Table 2 revealed that the most reactive arenes (electron rich; N > 3.0) reacted in $CHCl_3$ at low temperatures (**Method A**) while less reactive arenes (electron poor; N < 1.5) reacted more cleanly in CH_3CN and at higher temperatures (**Method B**). Several phenolic derivatives were selected to compare their innate reactivity (electronic and steric factors) while heteroaromatic substrates also showed a broad scope of reactivity as demonstrated by the range of temperature utilized (entries 1-5). For example, anisole (N = -1.2, CH_2Cl_2)[27], furan (N = 1.4, CH_2Cl_2)[28], anthracene (N = 2.0, CH_2Cl_2)[29] as well as bromoresorcinol and a chalcone substrate shown very modest reactivity in $CHCl_3$ as anticipated from the corresponding nucleophilic factor (N), therefore these substrates were subjected to more efficient reaction conditions in CH_3CN (**Method B**). We then observe a complete switch of reactivity for the most electronically rich arenes, for which the mildest reaction conditions in $CHCl_3$ (**Method A**) afford the best results in terms of yield and regioselectivity (entries 6-12). Pyrrole (N = 4.6, CH_3CN), *N*-methylpyrrole (N = 5.8, CH_3CN)[30], indole (N = 5.6, CH_2Cl_2) and *N*-methylindole (N = 5.7, CH_2Cl_2)[31] are extremely powerful π-nucleophiles which facilitate the synthesis of the corresponding indolyl **8k-l** and pyrrolyl **8i**, **8m** α-amino esters in high yields (62-79% yields) as single regioisomers. Finally, several MCRs

were examined using dimethoxybenzene as nucleophile (N = 2.5, CH_2Cl_2)[32] (entry 6) in CH_3CN and $CHCl_3$ and it was found that particular carbamate protecting group also affect reactions' rate. While the Cbz-protected amino ester **8f** was obtained in 9 hours (82% yield) the corresponding Fmoc-protected product **8g** was produced more slowly over 36 hours in 61% yield. Some other limitation for both methods (A/B) are the over-reaction of electronically rich arenes (indole and pyrrole) which tend to competently polymerize while electron deficient heteroarenes (oxazole and thiazole) are unreactive even at elevated temperatures.

Mechanism Investigation. Taken altogether, the results shown above demonstrate that the empirical Mayr's scale of nucleophilicity seems extremely useful to predict the nucleophile reactivity with the *N*-carbamoyl iminium

Table 2. Scope for the synthesis of racemic α-aryl α-amino esters **8a-l** [a]

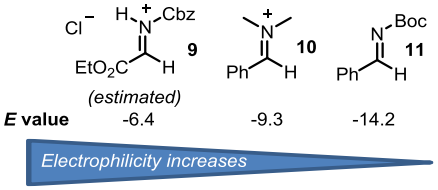
Entry	N factor[b]	Method A --- Step 3 --- Method B (Time, Temp, yield)	(Time, Temp, Yield)	Product
1	- 1.18	10 d, RT, <10%	24 h, 60 °C, **48%**[e] (6:1 *rr*)[c,d]	**8a**
2	1.36	14 d, RT, <10%	17 h, RT, **59%**[c,e]	**8b**
3	ND	2 d, 60 °C, 34% (2:1 *rr*)[d]	16 h, RT, **72%**[e]	**8c**
4	2.00	1.5 d, 60 °C, 74%	18 h, 60 °C, **82%**[e]	**8d**
5	ND	48 h, 40 °C, 10%	96 h, 0 °C, **41%**[e]	**8e**
6	2.48	9 h, 60 °C, **82%**[e] (5:1 *rr*)[d] 36 h, 60 °C, **61%** (10:1 *rr*)[d]	2 h, RT, 74% (5:1 *rr*)[d]	**8f** **8g**
7	ND	1.5 d, 60 °C, **71%**[e] (>20:1 *rr*)[d]	4 h, 60 °C, 74% (2:1 *rr*)[d]	**8h**
8	4.63	0.5 h, -60 °C, **67%**[e]	10 min, -40 °C, 45%	**8i**
9[f]	5.50	24 h, 40 °C, **46%**[e]	12 h, RT, 66%	**8j**
10	5.55	2 h, 0 °C, **64%**[e]	15 min, -40 °C, 42%	**8k**
11	5.75	3 h, -45 °C, **79%**[e]	30 min, -40 °C, 56%	**8l**
12	5.85	1.5 h, 0 °C, **62%**[e]	15 h, -40 °C, 58%	**8m**

8f, R^1 = Cbz
8g, R^1 = Fmoc

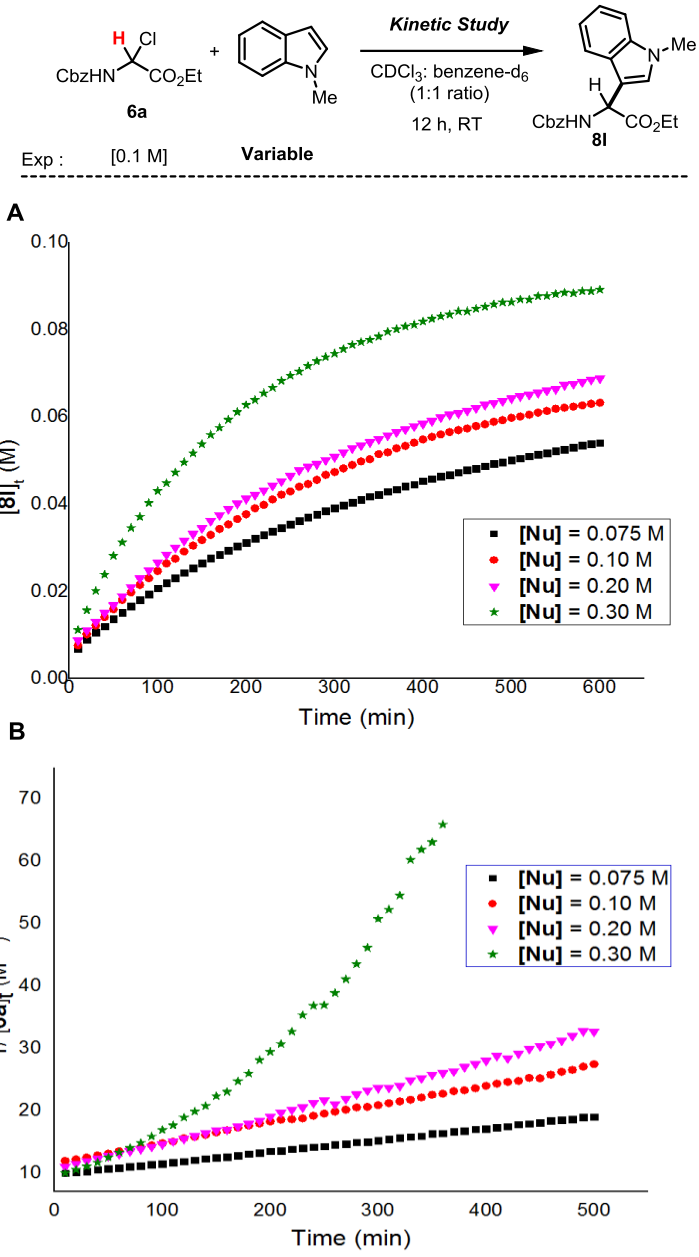
[a] **Method A**: reaction performed in $CHCl_3$, steps 1/2 for 12 h, **Method B**: reaction performed in CH_3CN, steps 1/2 for 24 h; both methods are followed by the addition of arenes (step 3) for the specified time and temperature; isolated yields are reported. [b] factors of nucleophilicity have been previously reported in CH_3CN or CH_2Cl_2. [c] Using excess of arenes (3.0 equiv.), the isolated yields for **8a** and **8b** are 60% and 71% respectively. [d] Ratio of regioisomers (*para/ortho*) are reported (*rr*) based on ^{1}H NMR integration values. [e] Synthesis of these compounds was previously reported, see ref. [18]. [f] Nucleophile employed is the aniline hydrochloric salt.

electrophile **9** (Table 2). Therefore, by using the approximate equation of reactivity that dictates the reaction advancement in which electrophiles and nucleophiles have to fulfil the conditions N + E ≥ -5, we were able to estimate the electrophilic parameter of iminium **9**. To this aim, several arene nucleophiles previously reported and characterized by Mayr were tested in the reaction with the *N*-Cbz α-chloroglycine ester **6a** (precursor of the proposed *N*-carbamoyl iminium electrophile **9**) at room temperature in CH_2Cl_2 for two days.[21,33] Reactions using anisole (N = -1.2, CH_2Cl_2) and thiofuran (N = -1.0, CH_2Cl_2) as nucleophiles only faintly proceeded while the reaction with a furan nucleophile (N = 1.4, CH_2Cl_2) delivered the corresponding α-amino esters under the same conditions (11% isolated yield).[21] Thus, it is reasonable to consider that an electrophilic value E can be estimated for the *N*-carbamoyl iminium electrophile **9**, in a tight ionic pair as E ≈ -5 -1.4 = -6.4 (Figure 2). In comparison, the most reactive iminium characterized by Mayr to date (*N,N*-dimethyl-substituted iminium **10**; E = -9.3) is likely in the range of 4 orders of magnitude less reactive than the present *N*-carbamoyl iminium **9**. Eventhough iminiums such as **9** have been previously proposed as the highly reactive intermediate for the formation of C-C bonds,[34] no concrete spectroscopic or kinetic evidence have been reported to support this hypothesis. Therefore we undertook a preliminary kinetic profiling of the aza-Friedel-Crafts reactions to assess the different mechanistic possibilities (Scheme 3). Observation of characteristic spectral features of both α-chloroglycine ester **6a**, *N*-methyl indole and product **8l** by *in situ* ^{1}H NMR spectroscopy enabled kinetic analysis of the

Figure 2. Comparison of iminium and imine electrophilic reactivities E



Scheme 3. Kinetic profiling to assess the Friedel-Crafts reaction mechanism



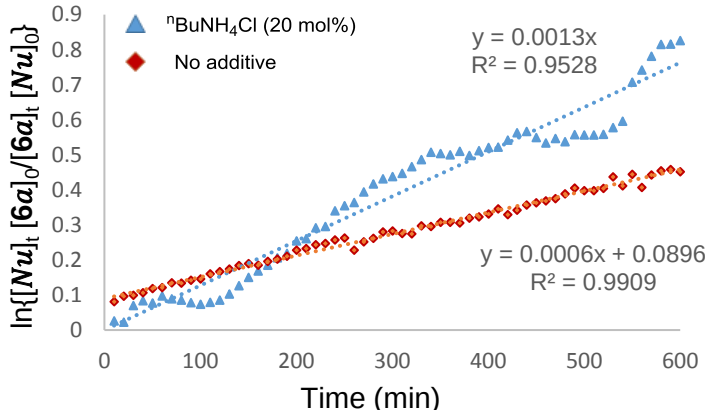
reaction progress under synthetically relevant conditions ($CDCl_3$–benzene-d_6 solvent mixture at room temperature). The kinetic order of each of the reagents was determined via "different-excess" experiments in which the initial concentration of *N*-methyl indole was varied while the concentration of **6a** was kept constant. Four distinct experiments were performed and plotted with the *N*-methyl indole concentration varying from [0.75 M] to [0.3 M] to measure the formation of product **8l** and determine the kinetic order in α-chloroglycine ester **6a** (overlay shown Scheme 3A). As shown in Scheme 3B, the plots of reciprocal concentration in [**6a**]$_t$ versus time exhibit slightly offset straight lines with different slopes which fit well with straight line regressions. This concludes that the kinetic order in α-chloroglycine **6a** for the reaction must be one while the reaction's kinetic follows a second-order rate law.[21] When a larger excess of *N*-methyl indole nucleophile was used (3 eq; green stars) while maintaining the concentration of α-chloroglycine [**6a**] at [0.1 M], the reaction appears to the reach a pseudo-first order condition as shown by the exponential plot of reciprocal concentration in [**6a**]$_t$ versus time (Scheme 3B). More surprisingly, the kinetic plots of reciprocal concentration in [**Nu**]$_t$ versus time also fit some straight line regressions that correlates to the same a kinetic order one in *N*-methyl indole (see supporting information Figures SI-3a, SI-7a, SI-10a, SI-14a). Taken together, these results support that the reaction displays first-order dependence on both concentrations of α-chloroglycine ester electrophile, [**6a**], and the *N*-methyl indole nucleophile [**Nu**]. The results are consistent with an S_N1-like mechanism (or S_N2C+ with a rate = *k* [**6a**] x [**Nu**]), which can be rationalized by suggesting that α-chloroglycine [**6a**] might undergo heterolysis to the corresponding iminium **9**, in a tight ionic-pair with the chloride anion which likely reduces the iminium reactivity, hence the increase of energy barrier for the nucleophilic attack to occur in the second step. In this scenario, the S_N1-like mechanism supports the fact that both steps of heterolysis and C–C bond formation are rate determining.[35] Furthermore the reaction with two equivalents of *N*-methyl indole nucleophile was reproduced with the addition of an external source of chloride anion to test for a possible ion return to the iminium **9** (tetrabutyl ammonium chloride: 20 mol%). This experiment shown in Figure 3 demonstrates that ion return might be evoked in this reaction while the overall rate acceleration of the reaction is likely due to a salt effect on the solvent ionic strength.[36] The plot of a general second-order expression $\ln\{[\boldsymbol{Nu}][\mathbf{6a}]_0/[\mathbf{6a}][\boldsymbol{Nu}]_0\}$ with time for the reaction without additive fits with the straight line, suggesting that the reaction follows a second-order kinetic (see Eq. 1).

A general second-order integrated rate law can be expressed as follows:

$$y = ln\frac{[\boldsymbol{Nu}][\boldsymbol{6a}]_0}{[\boldsymbol{6a}][\boldsymbol{Nu}]_0} = k_{obs}([\boldsymbol{Nu}]_0 - [\boldsymbol{6a}]_0)t \qquad \text{(Eq. 1)}$$

where $[\mathbf{6a}]_0 \neq [\mathbf{Nu}]_0$ and slope = K_{obs} * [xs]; where [xs] = ($[\mathbf{Nu}]_0$ –$[\mathbf{6a}]_0$)

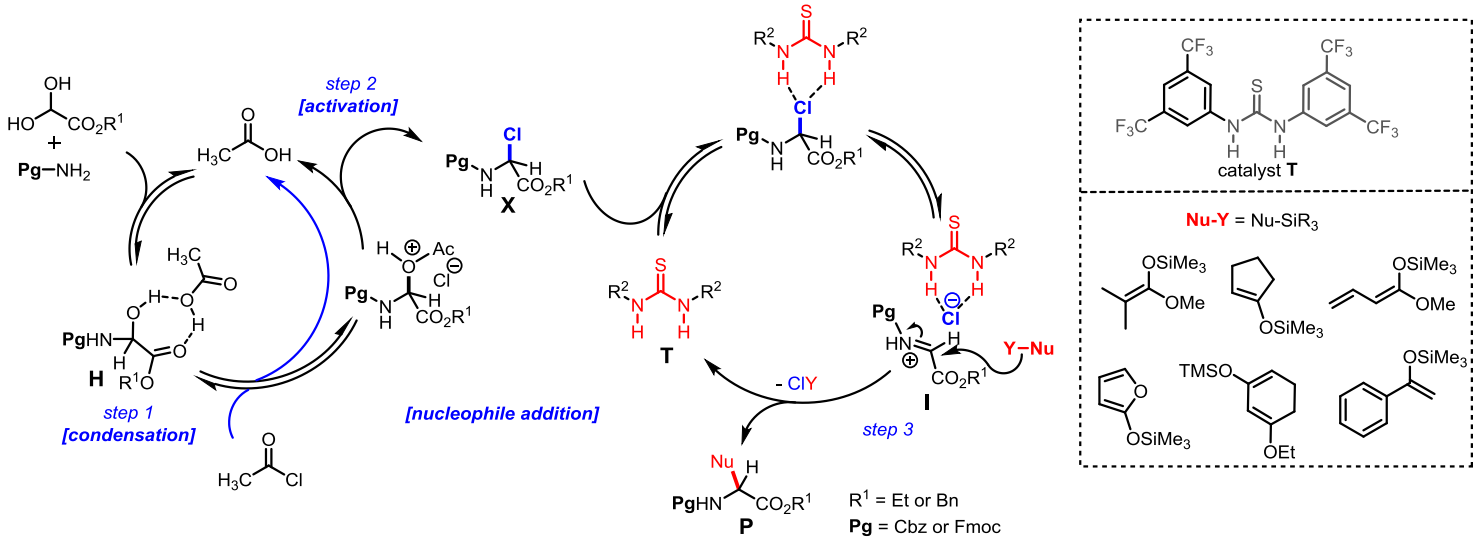
Figure 3. Salt effect on Friedel-Crafts reaction of α-chloroglycine and N-methyl Indole to prove the reaction mechanism



On the other hand, the presence of a chloride source provocked a significant deviation from the linear regression which could be attributed to a change in solvent polarity over time (ionic strength leading to increased rate), while a more pronounced equilibrium between the iminium ionic pair **9** and chloroaminal **6a** might simultaneously occurred (S_N2C+).

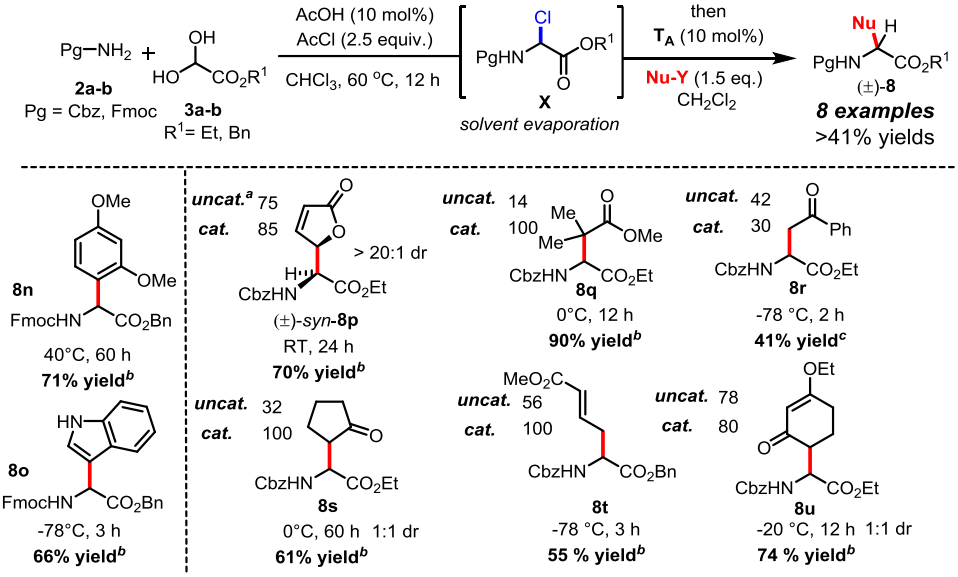
Complementary Method C: use of an H-bond donor catalyst. Both methods (A and B) employed for a stepwise multicomponent synthesis of α-aryl α-amino esters **8a-m**, were then expanded upon to other types of non-aromatic π-nucleophiles (silylenols and silyl ketene acetals). We rapidly faced the issues of silylated-nucleophile stability due to the enhanced acidity of the reaction media resulting from the stoichiometric amounts of HCl and AcOH generated overtime. A practical solution to this problem, arose from our abilities to generate the stable α-chloroaminal intermediate **9**, which can be stripped to dryness to remove traces of acids, therefore

Scheme 4. One-pot Synthesis of non-proteinogenic α-amino esters **P** using a tandem catalysis:



allowing for successive functionalization to occur in the same pot under neutral reaction conditions catalyzed by an hydrogen bond-donor catalysts (Scheme 4). By doing so, we postulated that addition of an achiral H-bond donor thiourea catalyst **T** could facilitate the chloroaminal **X** intermediate activation to generate *in situ* the reactive *N*-carbamoyl iminium (*e.g.* **9**) in a tight ionic pair specie **I**. The Schreiner's thiourea catalyst **T** was selected for its abilities of anion-binding to promote this complementary approach (**Method C**) which relies on the chloride leaving group activation by the catalyst to assist the functionalization stage and deliver the α-amino ester product **P**. This third method represents a merging of two successive catalysis in the same pot. To test this method, both arenes 1,3-dimethoxybenzene and indole nucleophiles have been tested and were successfully reacted to afford products **8n** and **8o** 71% and 66% yields respectively under the thiourea catalysis approach (Scheme 5). As mentioned above, the reactivity of *N*-Fmoc-protected chloroglycine is much less than its *N*-Cbz-protected counterpart (Table 2, entries 6 & 10) which demonstrates the strength of the achiral thiourea catalyst **T**. This expansion of the methodology also allowed us to prepare α-amino esters orthogonally protected (*N*-Fmoc and benzyl ester) and incorporate different acid-labile side chains nucleophiles that could not be installed otherwise. Thus seven novel products **8p**-**8v** have been synthesized with yields ranging from 41% to 90% and diastereoselectivity up to >20:1 (Scheme 5). Interestingly the γ-Butyrolactone-derived product **8p** was obtained in 70% yield as a single *syn*-diastereomer[37] while the other dimedone-derived product **8u** which could also be formed through a Diels–Alder-like transition state was obtained as a 1:1 mixture of diastereomers in 74% yield. Furthermore, silylenol ethers and silyl ketene acetals could be added smoothly to synthesize the α-amino ester products **8q**, **8r** and **8s** in 90%, 41% and 61% yields respectively. Noticeably, in each case, the reactions catalyzed by the achiral Schreiner's thiourea were much

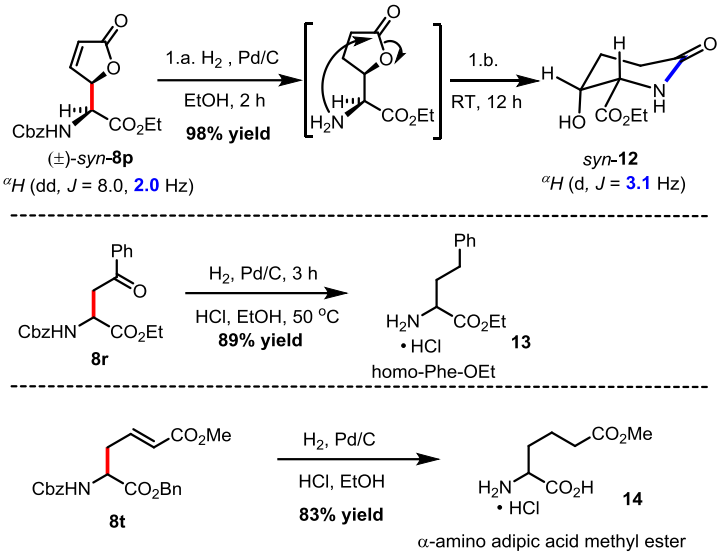
Scheme 5. Method C: One-pot synthesis of α-amino esters **8n-8u** catalyzed by thiourea [a-c]



[a] ^{1}H NMR yields of uncatalyzed versus catalyzed reactions were calculated from crude reaction mixtures using mesitylene as internal standard. [b] Isolated yields from catalyzed reactions. [c] Isolated yield from the uncatalyzed reaction.

more efficient and faster as shown by the synthesis of **8t** isolated in 55% yield as a single regioisomer (cat. 100% conv. versus uncat. 56% conv.). Finally, selected compounds were derivatized to show the applicability of our method in producing non-proteinogenic α-amino esters with site-specific designed protecting groups (Scheme 6). γ-Butyrolactone-derived α-amino ester **8p** was transformed to a rearranged product analogue to pipecolic ester **12** in one-pot and 98% yield.[37] Spectral analysis of the cyclic product **12** confirmed the relative *syn*-stereochemical assignment made for the γ-butyrolactone-derivative **8p**. *Homo*-Phe-OEt **13** was prepared from α-amino ester **8r** by a simple and efficient hydrogenation protocol. Also, the δ-monoprotected derivative of α-amino adipic acid **14** was prepared in 83% yield by hydrogenation of the synthetic α-amino ester **8t**.

Scheme 6. Direct derivatization of non-proteinogenic α-amino esters



In summary, we reported a general strategy for the one-pot synthesis of non-proteinogenic α-amino esters bearing orthogonal *N*-carbamoyl protecting groups (Cbz or Fmoc) from commercially inexpensive starting materials. Our results demonstrate that an autocatalytic-like approach for the synthesis of the pivotal α-chloroglycine ester intermediate was efficient and practical. This general strategy entails two distinct methods: i) a multicomponent-like process in which the three components are mixed in a temporally manner (Methods A/B: in CH_3CN or $CHCl_3$ respectively), and ii) a one-pot synthesis catalyzed through anion-abstraction by a hydrogen-bond donor thiourea catalyst (Method C: in CH_2Cl_2). These approaches are complementary and presumed to proceed via an activated iminium intermediate **9** that has been empirically characterized with an electrophilic value E = -6.4 (Mayr's scale). Our findings through the initial kinetic profiling support an S_N1-like mechanism (or S_N2C+) which is consistent with the effect of solvent on the reaction rates and the effect of the thiourea catalyst in facilitating the addition of weaker silylated nucleophiles. The discovery of the innate reactivity of α-chloroglycine esters via an S_N1-like mechanism and the corresponding *N*-carbamoyl iminium–chloride tight ionic pair supports that the scope of this reaction will not be only limited to relatively strong nucleophiles. Therefore,

the development of a reaction catalyzed by hydrogen-bond donors appears attractive to enable less reactive nucleophile to be incorporated (enantioselectively).[17] This one-pot synthesis of α-amino esters proved to be efficient and versatile as highlighted by the synthetic scope of α-aryl and α-alkyl amino esters **8a-g** prepared and the simplicity of functionalizations (*e.g.* **12-14**) due to the protecting groups' orthogonality. Ongoing studies are aimed at developing an asymmetric variant of this transformation and expanding the scope to additional classes of nucleophiles to prepare non-proteinogenic amino acids for non-ribosomal peptide synthesis.

EXPERIMENTAL SECTION:

Instrumentation and methods:

Infrared spectra were recorded on a Nicolet IS5 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm and CD_3CN at 1.94 ppm). Quantitative ^{1}H NMR spectra were performed using standard parameter (Pw = 90, at = 5, d1 = 15) and recorded on a Varian Mercury400; careful treatment of the NMR signal is required to proceed to quantification. Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on Varian Mercury400 (100 MHz) spectrometer. Chemical shifts are reported in ppm, with solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, CD_3CN at 1.9 ppm, 118.7 ppm and DMSO-d_6 at 39.5 ppm). Melting points were determined using an MPA 160 digital melting point apparatus. The low resolution ES-API mass spectra performed on FTICR mass spectrometer. Accurate mass (High resolution HRMS) was obtained from University of Florida using Agilent 6210 TOF instrument.

Reactions were performed in flame-dried glassware under a positive pressure of argon. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Analytical TLC was performed on 0.25 mm glass backed 60Å F-254 TLC plates. Flash chromatography was performed using 200-400 mesh silica gels (Silicycle, Inc.) or 60-325 mesh neutral alumina (Fisher, Inc.). Neutralized silica gel was prepared by adding 5 wt % of triethylamine in methylene chloride solution to normal-phase silica gel and mixed 30 mins at room temperature. The plates were visualized by exposure to UV light (254 nm) and developed by a solution of phosphomolybdic acid in ethanol, or vanillin/sulfuric acid in ethanol, or ninhydrin in ethanol, or potassium permanganate in water/potassium carbonate/sodium hydroxide or cerium-ammonium-molybdate in water/sulfuric acid and heat.

Reagents and solvents:

All reagents used in the present paper were acquired from Alfa Aesar or Sigma Aldrich. All bulk solvents were acquired from Fischer Scientific. Freshly distillated solvents were used in the reactions presented herein.

Chloroform was dried over $CaCl_2$ overnight prior to distillation (B.P. 61°C) and transferred under argon to a dark glass bottle with 3Å molecular sieves for storage. Tetrahydrofuran was purified by refluxing with and distilling from sodium with benzophenone and transferred under argon to a dark glass bottle for storage. Dichloromethane was dried over $CaCl_2$ overnight, prior to distillation (B.P. 40°C) and transferred under argon to a dark glass bottle with 3Å molecular sieves for storage. Toluene was dried over CaH_2 and molecular sieves and transferred under argon to a dark glass bottle for storage. Full procedures can be found in Purification of Laboratory Chemicals by Armarego, W. L.F.; and Chai C. L. L., Elsevier (Sixth Edition).

General procedures A/B for the one-pot preparation of α-Amino Ester (Methods A/B):

In a flame dried round bottom flask under argon, a mixture of benzyl carbamate **2a** (76 mg, 0.50 mmol, 1.0 equiv.), ethyl glyoxylate **3a** (108 µL**,** 0.05 mmol, and 1.05 equiv.), acetyl chloride (95 µL, 1.25 mmol, and 2.5 equiv.), and acetic acid (3 µL, 10 mol %, 0.1 equiv.), in $CHCl_3$ **(Method A)** or CH_3CN **(Method B)** solvent (5.0 mL; [0.1 M]) were stirred for 24 h or 12 h respectively (steps 1/2) at 60 °C. After that point, the reaction mixture was cooled down to RT then the arene nucleophile (1.5 equiv.) was added to the reaction mixture (step 3) and stirred at the indicated temperature for the appropriate time (x h). After full consumption of chloroaminal intermediate **5** (observed by TLC *caution*: same R_f value as the hydroxyaminal **3**), the reaction mixture was quenched with a saturated solution of sodium bicarbonate (20.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated under vacuum to afford the crude reaction mixture. The crude mixture was then purified by flash chromatography using an appropriate elution.

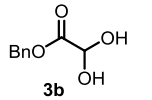
General procedure C (Method C): One-pot synthesis of α-amino esters 8n-8u catalyzed by the Schreiner's thiourea:

In a flame dried round bottom flask under argon, a mixture of primary carbamate **2** (0.50 mmol, 1.0 equiv.), glyoxylate **3** (0.05 mmol, and 1.05 equiv.), acetyl chloride (95 µL, 1.25 mmol, and 2.5 equiv.), and acetic acid (3 µL, 10 mol %, 0.1 equiv.), were stirred in $CHCl_3$ solvent (5.0 mL; [0.1 M]) for the appropriate time (x h: steps 1/2) at 60 °C. The reaction mixture was then cooled down to RT and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in appropriate solvent (5.0 mL; [0.1 M]) and Schreiner's thiourea catalyst (10 mol %) was added consecutively with nucleophile (1.5 equiv.) (step 3) in the reaction mixture and stirred at the indicated temperature for the appropriate time (x h). After full consumption of chloroaminal intermediate **6** (observed by TLC *caution*: same R_f value as the hydroxyaminal **5**), the reaction mixture was quenched with a saturated solution of sodium bicarbonate (20.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated under vacuum to afford the crude reaction mixture. The crude mixture was then purified by flash chromatography using an appropriate elution.

A. Compounds Characterization

The synthesis and characterization of compounds **8a-8m** (except **8g**) was previously reported by our group.[18]

Benzyl glyoxylate 3b:



3b

$C_9H_{10}O_4$

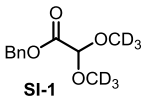
MW= 182.2 g.mol^{-1}

Dibenzyl 2,3-dihydroxysuccinate (330 mg, 1.0 mmol, 1.0 equiv.) was dissolve in methanol (6.0 ml) and a solution of $NaIO_4$ (321 mg, 1.5 mmol, 1.5 equiv.) in H_2O (3.0 ml) was added. The reaction was stirred for 6 h at 0 °C until the full consumption of the starting material. After that point, the reaction was partitioned between H_2O and diethyl ether. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give mixture of benzyl glyoxylate hydrate **3b** and aldehyde **SI-1** (13:1) as a colorless liquid. The product was used without further purification in the synthesis for the next step.

R_f = 0.35 (hexanes/ethyl acetate 70:30; UV Active. **IR** (Neat) ν_{max} = 696, 737, 847, 908, 967, 1078, 1212, 1278, 1356, 1455, 1498, 1744, 3438 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) δ 7.53 – 7.32 (m, 5H), 5.25 (q, J = 12.1 Hz, 2H), 4.90 (d, J = 11.1 Hz, 1H), 3.78 (bs, 1H). (Note: Integration value does not match exactly due to the exchangeable –OH group.). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 183.7, 170.5, 168.8, 168.8, 134.8, 134.7,

134.7, 128.6, 128.6, 128.5, 128.4, 128.39, 90.9, 88.7, 87.1, 67.9, 67.9, 67.6. **HRMS** (DART) m/z: $[M + NH_4]^+$ Calcd for C9H14NO4 200.0917; Found 200.0913 (-2.0 ppm).

Compound SI-1: Prepared by adding CD_3OD to the crude reaction mixture of benzyl glyoxylate hydrate **3b**. **^{1}H NMR** (400 MHz, CD_3OD): δ (ppm) 7.47 – 7.25 (m, 5H), 5.20 (s, 2H), 4.92 (s, 1H).

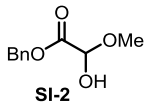


SI-1

$C_{11}H_8D_6O_4$

MW = 216.3 g. mol^{-1}

Compound SI-2: Prepared by adding methanol (1.0 equiv.) in the $CDCl_3$ solution of the crude reaction mixture of benzyl glyoxylate hydrate **3b**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.44 – 7.30 (m, 5H), 5.34 – 5.15 (m, 2H), 4.90 (d, *J* = 11.3 Hz, 1H), 3.80 (d, *J* = 11.2 Hz, 1H), 3.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 169.2, 134.8, 128.7, 128.6, 93.4, 67.8, 55.4. **HRMS** (DART) m/z: $[M + NH_4]^+$ Calcd for C10H16NO4 214.1074, Found 214.1072 (-0.9 ppm). **SMILES:** OC(O)C(OCC1=CC=CC=C1)=O

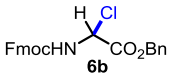


SI-2

$C_{10}H_{12}O_4$

Mw = 196.2 g.mol^{-1}

N-Fmoc-Gly(α-Cl)-OBn 6b: Protected α-chloroglycine benzyl ester **6b** was synthesized using following procedure: In a flame dried scintillation vial, a mixture of 9-Fluorenylmethyl carbamate **2b** (120 mg, 0.50 mmol, 1.0 equiv.), benzyl glyoxylate hydrate **3b (**109 mg**,** 0.60 mmol, 1.2 equiv), acetyl chloride **(**107 µL**,** 1.50 mmol, 3.0 equiv.) and acetic acid (3 µL, 0.05 mmol, 10 mol%) were stirred under argon in anhydrous chloroform (5.0 mL) for 24 hours at 60 °C. The reaction mixture was cooled down to RT and directly evaporated under vacuum to obtain the desired product **6b** as a white solid (211 mg, 0.50 mmol, quant. yield). Compound **6b** can be stored in an amber glass container at RT for 7 days in a desiccator without major decomposition <5-10%). **R_f** = 0.30 (EtOAc/hexanes 30:70; UV active, stains green-yellow with vanillin) ***Caution!!*** Compound **6b** is not stable on silica gel; it hydrolyses back to the corresponding hemiaminal which can be observed by TLC at the R_f mentioned above. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.78 (d, J = 7.6 Hz, 2H), 7.57 (s, 2H), 7.45 – 7.30 (m, 10H), 6.22 (s, 1H), 5.30 (s, 2H), 4.48 (d, J = 6.4 Hz, 2H), 4.24 (t, J = 6.4 Hz, 1H).



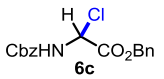
6b

$C_{24}H_{20}ClNO_4$

MW = 421.1 g.mol^{-1}

SMILES:[H][C@](Cl)(C(OCC1=CC=CC=C1)=O)NC(OCC2C(C=CC=C3)=C3C4=C2C=CC=C4)=O

N-Cbz(α -Cl)-OBn 6c: Protected α-chloroglycine benzyl ester **6c** was synthesized using following procedure: In a flame dried scintillation vial, a mixture of benzyl carbamate **2a** (76 mg, 0.50 mmol, 1.0 equiv.), benzyl glyoxylate hydrate **3b (**109 mg**,** 0.60 mmol, 1.2 equiv), acetyl chloride **(**107 µL**,** 1.50 mmol, 3.0 equiv.) and acetic acid (3 µL, 0.05 mmol, 10 mol%) were stirred under argon in anhydrous chloroform (5.0 mL) for 16 hours at 60 °C. The reaction mixture was cooled down to RT and directly evaporated under vacuum to obtain the desired product **6c** as a white solid (167 mg, 0.50 mmol, quant. yield). Compound **6c** can be stored in an amber glass container at RT for 7 days in a desiccator without major decomposition <5-10%). **R_f** = 0.25 (EtOAc/hexanes 30:70; UV active, stains green-yellow with vanillin) ***Caution!!*** Compound **6c** is not stable on silica gel; it hydrolyses back to the corresponding hemiaminal which can be observed by TLC at the R_f mentioned above. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) 7.48 – 7.26 (m, 10H), 7.05 (bs, 1H), 6.25 (d, J = 10.4 Hz, 1H), 5.25 (dd, J = 12.3 Hz, 2H), 5.15 (s, 2H). **^{13}C NMR** (100 MHz, $CD3Cl_3$): δ (ppm) 165.8, 153.9, 135.3, 134.3, 128.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 128.4, 68.7, 68.1, 63.4.



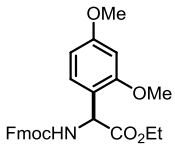
6c

$C_{17}H_{16}ClNO_4$

MW = 333.8 g.mol^{-1}

SMILES: [H][C@](Cl)(C(OCC)=O)NC(OCC1C(C=CC=C2)=C2C3=C1C=CC=C3)=O

Ethyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(2,4-dimethoxyphenyl)acetate 8g:

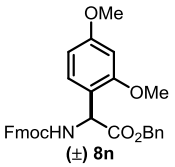


(±) **8g**

$C_{27}H_{27}NO_6$
MW: 461.5 g.mol^{-1}

Product **8g** was synthesized following the ***general procedure A.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: 1, 3-dimethoxy benzene (52 mg**,** 0.37 mmol, 1.5 equiv.) as nucleophile at 60 °C for 36 h. The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (15:85) to deliver the desired product **8g** (10:1 rr) as a white solid (141 mg, 0.31 mmol, 61% yield). $\mathbf{R_f}$ = 0.25 (Ethyl acetate/Hexanes 75:25; UV Active, stains pink red in vanillin). **Mp** = 82-85 °C, **IR** (Neat) ν_{max} = 659, 694, 728, 740, 758, 789, 828, 884, 935, 985, 1020, 1043, 1086, 1103, 1120, 1160, 1181, 1207, 1242, 1260, 1296, 1320, 1446, 1507, 1533, 1589, 1614, 1685, 1732, 3320 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) 7.85 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 5.38 (d, *J* = 8.4 Hz, 1H), 4.40 – 4.28 (m, 2H), 4.25 (t, *J* = 6.6 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 6H), 1.16 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3CN): δ (ppm) 171.4, 161.5, 158.4, 156.1, 144.4, 144.3, 141.4, 130.5, 127.9, 127.4, 125.4, 120.2, 118.0, 104.8, 98.9, 66.6, 61.4, 55.6, 55.3, 54.0, 47.2, 13.7. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C27H27NO6Na 484.1731, Found 484.1723 (-1.6 ppm).
SMILES: O=C(OCC1C2=C(C=CC=C2)C3=C1C=CC=C3)N[C@H](C(OCC)=O)C4=C(OC)C=C(OC)C=C4

Benzyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(2,4-dimethoxyphenyl)acetate 8n:

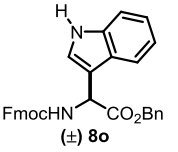


(±) **8n**

$C_{32}H_{29}NO_6$
MW: 523.6 g.mol^{-1}

Product **8n** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (2.5 mL) at 60 °C for 24 h.
Step 3: Dimethoxy benzene (52 mg**,** 0.37 mmol, 1.5 equiv.) as nucleophile at 40 °C for 60 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (15:85) to deliver the desired product **8n** (14:1 rr) as a white solid (92 mg, 0.18 mmol, 71% yield). $\mathbf{R_f}$ = 0.30 (EtOAc/hexanes 30:70; UV Active, stains pink red in vanillin). **Mp** = 75-78 °C, **IR** (Neat) ν_{max} = 659, 694, 727, 739, 757, 790, 985, 1007, 1031, 1043, 1085, 1108, 1120, 1145, 1160, 1180, 1208, 1231, 1260, 1276, 1320, 1450, 1475, 1508, 1533, 1685, 1709, 1732, 2852, 2922 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.75 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.18 (m, 8H), 6.47 – 6.42 (m, 1H), 6.42 (s, 1H), 5.92 (d, *J* = 8.7 Hz, 1H), 5.52 (d, *J* = 8.7 Hz, 1H), 5.22 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.48 – 4.35 (m, 1H), 4.34 – 4.26 (m, 1H), 4.22 (t, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 171.4, 161.4, 158.2, 156.1, 144.2, 144.1, 141.5, 131.3, 128.6, 128.4, 128.2, 127.9, 127.3, 125.4, 125.4, 118.3, 104.5, 99.2, 67.4, 67.2, 55.7, 55.5, 55.2, 47.4, 30.0. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd. for C32H29NO$_6$Na 546.1887, Found 546.1879 (-1.5 ppm).
SMILES:O=C(N[C@H](C(OCC1=CC=CC=C1)=O)C2=C(OC)C=C(OC)C=C2)OCC3C(C=CC=C4)=C4C5=C3C=CC=C5

Benzyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(2,4-dimethoxyphenyl)acetate 8o:



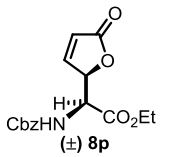
(±) **8o**

$C_{32}H_{26}N_2O_4$
MW: 502.6 g.mol^{-1}

Product **8o** was synthesized following the ***general procedure C.***
Step 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 24h.
Step 3: Indole (84 mg**,** 0.37 mmol, 1.5 equiv.) as nucleophile at -78°C for 0.5 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (15:85). Another purification performed by flash chromatography using solvent system of ether and dichloromethane (2:98) to obtain the pure desired products **8o** as a white solid (84 mg, 0.13 mmol, 66% yield). $\mathbf{R_f}$ = 0.36 (Ethyl Acetate/hexanes 30:70; UV Active, stains green in vanillin). **Mp** = 139-142 °C, **IR** (Neat) ν_{max} = 697, 739, 1010, 1045, 1103, 1182, 1216, 1277, 1324, 1450, 1498, 1704, 3400 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) ^{1}H NMR 8.20 (s, 1H), 7.73 (dd, *J* = 17.2, 7.8 Hz, 3H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.39 (dd, *J* = 7.4, 6.8 Hz, 3H), 7.29 (s, 8H), 7.14 (dd, *J* = 15.5, 8.1 Hz, 3H), 5.74 (s, 1H), 5.28 – 5.10 (m, 2H), 4.50 – 4.31 (m, 2H), 4.22 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (100 MHz, CD_3CN): δ (ppm) 171.4, 155.8, 143.8, 141.4, 141.3, 136.4, 135.3, 128.6, 128.4, 128.2, 127.8, 127.2, 125.4, 125.2, 125.2, 123.6, 122.9, 120.5, 120.1, 119.3, 111.6, 110.9, 67.5, 67.3, 51.6, 47.2. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C32H26N2O4Na 525.1785; Found 525.1779 (+1.1 ppm).

SMILES:[H]N1C2C(C=CC=C2)C([C@@H](C(OCC3=CC=CC=C3)=O)NC(OCC4C(C=CC=C5)=C5C6=C4C=CC=C6)=O)=C1

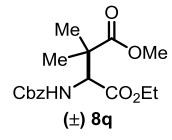
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(5-oxo-2,5-dihydrofuran-2-yl)acetate 8p:



(±) **8p**
$C_{16}H_{17}NO_6$
MW: 319.3 g.mol^{-1}

Product **8p** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h
Step 3: 2-(Trimethylsiloxy)furan (117 mg**,** 0.75 mmol, 1. 5 equiv.) as nucleophile at 0 °C for 24 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of CH_2Cl_2/ether (95:5) to deliver the desired product **8p** as a colorless liquid (112 mg, 0.35 mmol, 70% yield). $\mathbf{R_f}$ = 0.25 (CH_2Cl_2/ether 95:5; UV Active, stains pink red in vanillin). **IR** (Neat) ν_{max} = 697, 733, 775, 800, 829, 875, 918, 982, 1026, 1044, 1062, 1100, 1156, 1205, 1248, 1323, 1370, 1455, 1530, 1603, 1699, 1746, 2936, 3311 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.49 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.37 – 7.28 (m, 5H), 6.13 – 6.01 (m, 1H), 5.57 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.48 (bs, 1H), 5.06 (s, 2H), 4.77 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.32 (t, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 172.3, 167.9, 156.1, 152.9, 135.9, 128.6, 128.4, 128.1, 122.9, 82.9, 67.4, 62.9, 54.6, 14.2. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for C16H17NO6Na 342.0948, Found 342.0951(+0.9 ppm).
SMILES: O=C(C=C1)O[C@@H]1[C@@H](C(OCC)=O)NC(OCC2=CC=CC=C2)=O

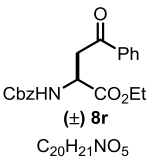
4-ethyl 1-methyl 3-(((benzyloxy)carbonyl)amino)-2,2-dimethylsuccinate 8q:



(±) **8q**
$C_{17}H_{23}NO_6$
MW: 337.4 g.mol^{-1}

Product **8q** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h
Step 3: trimethyl((3-methylbut-2-en-2-yl)oxy)silane (119 mg**,** 0.75 mmol, 1.5 equiv.) as nucleophile at 0 °C for 12 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of hexanes/ethylacetate (70:30) to deliver the desired product **8q** as a colorless liquid (152 mg, 0.45 mmol, 90% yield). $\mathbf{R_f}$ = 0.30 (hexanes/ethylacetate 70:30; UV Active). **IR** (Neat) ν_{max} = 683, 702, 729, 757, 787, 824, 848, 875, 919, 983, 1003, 1025, 1046, 1135, 1171, 1207, 1242, 1278, 1332, 1371, 1392, 1455, 1469,1526, 1713, 2982, 3363 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.27 (m, 5H), 5.62 (d, *J* = 9.5 Hz, 1H), 5.12 (s, 2H), 4.66 (d, *J* = 9.7 Hz, 1H), 4.16 (ddd, *J* = 14.2, 7.1, 2.7 Hz, 2H), 3.70 (s, 3H), 1.29 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 176.0, 170.6, 156.6, 136.4, 128.8, 128.5, 128.4, 67.5, 61.9, 60.0, 52.4, 45.9, 23.3, 21.6, 14.26. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for C17H23NO6Na 360.1418; Found 360.1422 (+1.1 ppm).
SMILES: O=C(OC)C(C)(C)[C@@H](C(OCC)=O)NC(OCC1=CC=CC=C1)=O

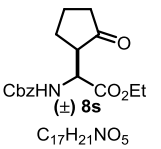
Ethyl 2-(((benzyloxy)carbonyl)amino)-4-oxo-4-phenylbutanoate 8r:



(±) **8r**
$C_{20}H_{21}NO_5$
MW: 355.4 g.mol^{-1}

Product **8r** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: 1-Phenyl-1-trimethylsiloxyethylene (144 mg**,** 0.75 mmol, and 1.5 equiv.) as nucleophile at -78 °C for 3 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of hexanes/ethylacetate (85:15) to deliver the desired product **8r** as a colorless liquid (81 mg, 0.23 mmol, 46% yield). $\mathbf{R_f}$ = 0.25 (hexanes/ethylacetate 70:30; UV Active). **IR** (Neat) ν_{max} = 690, 879, 1045, 1086, 1217, 1272, 1378, 1450, 1709, 2889, 2973, 3342 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 7.8 Hz, 2H), 7.63 – 7.56 (m, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.38 – 7.29 (m, 5H), 5.89 (d, J = 8.0 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.78 – 4.70 (m, 1H), 4.21 (q, J = 7.0 Hz, 2H), 3.67 (ddd, J = 83.7, 18.2, 4.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for C20H22NO5 356.1492; Found 356.1496 (+1.1 ppm).
SMILES: O=C(C1=CC=CC=C1)C[C@@H](C(OCC)=O)NC(OCC2=CC=CC=C2)=O
The spectral data is consistent with the reported compound in the literature.[38]

Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(-2-oxocyclopentyl)acetate 8s:

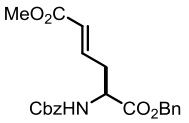


(±) **8s**
$C_{17}H_{21}NO_5$
MW: 319.1 g.mol^{-1}

Product **8s** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: (cyclopent-1-en-1-yloxy)trimethylsilane (117 mg**,** 0.75 mmol, and 1.5 equiv.) as nucleophile at 0 °C for 60 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of hexanes/ethylacetate (80:20) to deliver the desired product in mixture of diastereomers (42:58)

8s as a colorless liquid (97 mg, 0.30 mmol, 61% yield). R_f = 0.20 (hexanes/ethylacetate 70:30; UV Active). **IR** (Neat) ν_{max} = 1322, 1370, 1401, 1454, 1520, 1721, 2965, 3340 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN): diastereomers (42:58) δ (ppm) 7.46 – 7.21 (m, 5H), 6.08 – 5.83 (m, 1H), 5.08 (dd, J = 8.4, 2.1 Hz, 2H), 4.65 – 4.47 (m, 1H), 4.23 – 4.08 (m, 2H), 2.75 – 2.58 (m, 1H), 2.31 – 2.18 (m, 1H), 2.11 – 1.98 (m, 2H), 1.85 – 1.70 (m, 2H), 1.62 (ddd, J = 23.4, 11.6, 6.7 Hz, 1H), 1.20 (t, J = 9.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): diastereomers (42:58) δ (ppm) 217.7, 217.3, 170.9, 170.5, 156.4, 155.8, 136.2, 136.1, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 66.9, 66.9, 61.7, 61.6, 61.6, 53.2, 53.0, 51.6, 50.8, 37.9, 37.7, 25.9, 25.6, 20.5, 20.3, 14.0. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for C17H21NO5Na 342.1312; Found 342.1318 (+1.8 ppm).
SMILES: O=C(CCC1)[C@H]1[C@@H](C(OCC)=O)NC(OCC2=CC=CC=C2)=O

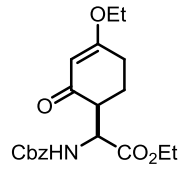
6-benzyl 1-methyl-5-(((benzyloxy)carbonyl)amino) (E)hex-2-enedioate 8t:



(±) **8t**
$C_{22}H_{23}NO_6$
MW: 397.4 g.mol^{-1}

Product **8t** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: (E)-((1-methoxybuta-1,3-dien-1-yl)oxy)trimethylsilane[39] (129 mg**,** 0.75 mmol, 1.5 equiv.) as nucleophile at -78 °C for 3 h.
The crude reaction mixture showing one regioisomer was purified by flash chromatography using an isocratic solvent system of hexanes/ethylacetate (80:20) to deliver the desired product **8t** as a colorless liquid (109 mg, 0.27 mmol, 55% yield). R_f = 0.30 (hexanes/ethylacetate 70:30; UV Active). **IR** (Neat) ν_{max} = 696, 737, 775, 844, 910, 977, 1044, 1082, 1173, 1265, 1340, 1386, 1435, 1455, 1523, 1660, 1715, 2951, 3344 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.42 – 7.28 (m, 10H), 6.92 – 6.68 (m, 1H), 5.83 (dd, J = 15.6, 0.9 Hz, 1H), 5.69 (d, J = 7.9 Hz, 1H), 5.17 (dd, J = 23.7, 12.2 Hz, 2H), 5.10 (s, 2H), 4.57 (dd, J = 13.2, 6.4 Hz, 1H), 3.69 (d, J = 0.9 Hz, 3H), 2.75 (dt, J = 12.6, 6.1 Hz, 1H), 2.68 – 2.58 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 170.9, 166.1, 155.7, 142.2, 136.1, 134.9, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 124.6, 67.5, 67.0, 52.9, 51.5, 34.8. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for C22H23NO6Na 420.1418; Found 420.1418 (0 ppm).
SMILES: O=C(N[C@H](C(OCC1=CC=CC=C1)=O)C/C=C/C(OC)=O)OCC2=CC=CC=C2

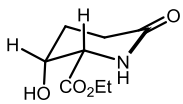
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate 8u:



(±) **8u**
$C_{20}H_{25}NO_6$
MW: 375.4 g.mol^{-1}

Product **8u** was synthesized following the ***general procedure C.***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: ((5-ethoxycyclohexa-1,5-dien-1-yl)oxy)trimethylsilane[40] (159 mg, 0.75 mmol, 1.5 equiv.) as nucleophile at -20 °C for 12 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of hexanes/ethylacetate (70:30) to deliver the mixture of two diastereomer (1:1) of 8u as a colorless liquid (129 mg, 0.37 mmol, 74% yield). Two diasteromers were separated on preparative TLC (same plate were run 3 times) using solvent system of hexanes and ethyacetate (80:20) to obtain the pure two diasteromers in 1:1 ratio. R_f = 0.20 (hexanes/ethylacetate 70:30; UV Active). **IR** (Neat) ν_{max} = 697, 738, 776, 819, 851, 892, 1026, 1051, 1191, 1328, 1379, 1454, 1499, 1600, 1645, 1716, 2938, 3348 cm^{-1}. ***syn*-diastereomer :^{1}H NMR** (400 MHz, CD_3CN): δ ppm 7.55 – 7.22 (m, 5H), 5.62 (d, J = 9.4 Hz, 1H), 5.27 (s, 1H), 5.20 – 5.00 (m, 2H), 4.44 (dd, J = 9.6, 3.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.98 – 3.81 (m, 2H), 3.20 – 3.03 (m, 1H), 2.63 (ddd, J = 17.5, 12.6, 4.7 Hz, 1H), 2.37 (ddd, J = 17.7, 4.9, 2.2 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.83 (ddd, J = 25.9, 12.9, 5.0 Hz, 1H), 1.30 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3CN): δ ppm 198.5, 179.2, 172.1, 157.7, 138.1, 129.4, 128.9, 128.6, 102.7, 67.3, 65.7, 62.0, 55.2, 49.2, 29.6, 25.4, 14.4, 14.4. ***anti*-diastereomer : ^{1}H NMR** (400 MHz, CD_3CN): δ ppm 7.48 – 7.22 (m, 5H), 5.98 (d, J = 7.7 Hz, 1H), 5.29 (d, J = 1.2 Hz, 1H), 5.19 – 5.00 (m, 2H), 4.60 (dd, J = 9.3, 4.2 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.02 – 3.85 (m, 2H), 2.76 (dt, J = 12.2, 4.8 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.41 – 2.32 (m, 1H), 2.08 – 1.97 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3CN): δ ppm 197.9, 178.9, 172.5, 157.1, 138.1, 129.4, 128.9, 128.7, 102.7, 67.2, 65.6, 62.0, 54.9, 48.9, 29.5, 24.7, 14.4. **HRMS** (ESI-TOF) m/z: $[M - H]^-$ Calcd for C20H25NO6 374.1609; Found 374.1608 (-0.3 ppm).
SMILES: O=C(C=C1O)CC[C@H]1[C@@H](C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl 3-hydroxy-6-oxopiperidine-2-carboxylate 12:



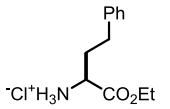
(±) **12**

$C_8H_{13}NO_4$

MW: 187.2 g.mol^{-1}

To a solution of **8p** (96 mg**,** 0.3 mmol, 1.0 equiv.) in ethanol (10.0 mL), 10% Pd/C (30 mg, 0.03 mmol, 0.1 equiv.) was added. The reaction mixture was hydrogenated at RT under hydrogen pressure (balloon: 1.0 atm). The starting material **8p** was consumed after 3 h, as indicated by TLC. The hydrogen balloon was removed and the reaction mixture was stirred another 12 h at RT until full consumption of the intermediate ($\mathbf{R_f}$ = 0.1 in ethylacetate/methanol 90:10; stains yellow in ninhydrin). The reaction mixture was then filtered through celite and washed with ethanol (5.0 mL). The filtrate was evaporated under vacuum to obtain **12** in a pure form (55 mg, 0.29 mmol, 98% yield) as pale yellow liquid. $\mathbf{R_f}$ = 0.2 (methanol/dichloromethane 5:95; not UV active, stains yellow brown in ninhydrin solution). **IR** (Neat) ν_{max} = 860, 881, 939, 968, 1024, 1072, 1177, 1445, 1574, 1650, 1731, 1773, 2981, 3368 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 4.94 (td, J = 7.2, 3.1 Hz, 1H), 4.23 (qd, J = 7.1, 1.5 Hz, 2H), 3.47 (d, J = 3.1 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.53 (ddd, J = 17.9, 10.3, 7.9 Hz, 1H), 2.40 – 2.27 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 177.1, 172.5, 80.8, 61.8, 57.6, 28.6, 24.2, 14.2. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H14NO4 188.0917; Found 188.0919 (+1.1 ppm).
SMILES: O=C1N[C@](H])(C(OCC)=O)[C@@](O)([H])CC1

Ethyl 2-amino-4-phenylbutanoate 13:



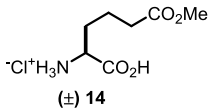
(±) **13**

$C_{12}H_{18}ClNO_2$

MW: 243.7 g.mol^{-1}

To a solution of **8r** (71 mg**,** 0.2 mmol, 1.0 equiv.) in ethanol (5.0 mL), 1 N HCl (200 µL) was added followed by 10% Pd/C (20 mg, 0.02 mmol, 0.1 equiv.). The mixture was hydrogenated at 55°C under hydrogen pressure (balloon: 1.0 atm). The reaction was completed after 3 h as determined by TLC, the mixture was then filtered through celite and washed with ethanol (5.0 mL). The filtrate was evaporated under vacuum to obtain the crude reaction mixture as a solid. The solid was suspended in diethyl ether (3.0 mL) and sonicated for 5 minutes and finally filtered to obtain **13** (41 mg, 0.17 mmol, 89% yield) as a white solid. $\mathbf{R_f}$ = 0.1 (ethylacetate/methanol 90:10; UV Active, stains yellow in ninhydrin). **IR** (Neat) ν_{max} = 672, 702, 737, 759, 981, 1019, 1033, 1062, 1084, 1104, 1156, 1199, 1238, 1266, 1377, 1454, 1497, 1752, 2843, 2866, 2973 cm^{-1}. **^{1}H NMR** (400 MHz, D_2O): δ (ppm) 7.33 – 7.23 (m, 2H), 7.19 (d, J = 7.5 Hz, 3H), 4.16 – 4.06 (m, 2H), 3.99 (t, J = 6.3 Hz, 1H), 2.76 – 2.54 (m, 2H), 2.27 – 2.03 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, D_2O): δ (ppm) 170.1, 139.8, 128.8, 128.4, 126.6, 63.5, 52.3, 31.3, 30.2, 13.1. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for C12H18NO2 208.1332; Found 208.1331 (-0.5 ppm). **SMILES:** [NH3+]C(C(OCC)=O)CCC1=CC=CC=C1.[Cl-]

2-amino-6-ethoxy-6-oxohexanoic acid 14:



(±) **14**

$C_7H_{14}ClNO_4$

MW: 211.6 g.mol^{-1}

To a solution of **8t** (80 mg**,** 0.2 mmol, 1.0 equiv.) in ethanol (5.0 mL), HCl ([1 N], 200 µL) was added followed by 10% Pd/C (20 mg, 0.02 mmol, 0.1 equiv). The mixture was hydrogenated at RT under hydrogen pressure (balloon: 1.0 atm). When the reaction was completed as determined by TLC, the mixture was filtered through Celite and washed with ethanol (5.0 mL). The filtrate was evaporated under vacuum to obtain the crude reaction mixture. The solid was suspended in diethyl ether (3.0 mL) and sonicated for 5.0 minutes and finally filtered to obtain **14** in a pure form (36 mg, 0.17 mmol, 83% yield) as white solid. $\mathbf{R_f}$ = 0.35 (n-butanol: acetic acid: water 3: 1: 1(by volume); stains yellow brown in ninhydrin). **IR** (Neat) ν_{max} = 739, 804, 827, 888, 943, 985, 1093, 1141, 1183, 1203, 1220, 1260, 1352, 1437, 1481, 1602, 1727, 2982 cm^{-1}. **^{1}H NMR** (400 MHz, D_2O): δ (ppm) 3.95 (t, J = 6.2 Hz, 1H), 3.71 (s, 3H), 2.49 (t, J = 7.2 Hz, 2H), 2.04 – 1.85 (m, 2H), 1.83 – 1.64 (m, 2H). **^{13}C NMR** (100 MHz, D_2O): δ (ppm) 176.2, 172.0, 52.6, 52.2, 32.7, 29.0, 19.7. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C7H14NO_4$ 176.0917; Found 176.0918 (+0.6 ppm).
SMILES: [NH3+]C(C(O)=O)CCCC(OC)=O.[Cl-]

▪ ASSOCIATED CONTENT

*** Supporting Information**

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. 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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