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Autocatalytic one pot orchestration for the synthesis of α-arylated, α-amino esters†

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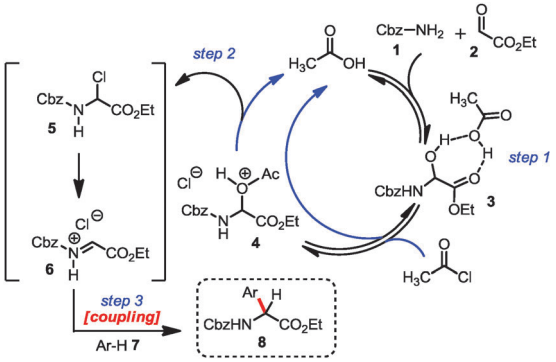
A novel acetyl chloride-mediated cascade transformation involving three components (benzyl carbamate, ethyl glyoxylate and arene nucleophiles) is reported. Aryl orthogonally protected α-amino acids are obtained in a one pot cascade, using a mild AcOH–AcCl system, *via* a critical autocatalytic dehydration-activation step ensuring an original and efficient Friedel–Crafts orchestration.

Facile and scalable synthesis of α-amino acids has attracted significant attention in the past decades. Several synthetic methods of functionalizing α-iminoglycinates **6** to access α-amino acids or esters have been reported (Strecker,[1] Mannich[2] or Friedel–Crafts[3] reactions). While these methods have proven to be applicable for the enantioselective synthesis of α-amino esters, both access to the starting α-iminiumglycinates **6** (1 to 3 steps) and late stage protecting group manipulations required several synthetic steps to produce marketable α-amino acids or esters, leading to a lengthy overall sequence.[1–3] On the other hand, α-hydroxy **3**,[4] α-alkoxy,[5] α-acetoxy,[6] and α-halogeno[7] **5** glycinate esters, which are valuable *in situ* precursors of α-iminiumglycinates **6**, have been less studied for functionalizing the glycine α-stereocenter. Thus, only sparse examples of cascade reactivity (so called multicomponent reactions) to synthesize α-amino esters in a single step have been reported.[8]

We decided to develop a suitable system for a novel and versatile one pot synthesis of α-amino esters bearing marketable carbamate protecting groups.[9] In this communication, a reliable synthesis of racemic arylglycine derivatives **8** is described, taking advantage of an unprecedented autocatalytic process and the high reactivity of chloroaminal intermediate **5** to initiate the desired Friedel–Crafts arylation (Scheme 1). To this end, a single pot transformation of primary carbamate **1** with ethyl glyoxylate **2** and arene nucleophiles **7** was envisioned. If the reaction would advance in an orderly fashion, the desired α-amino esters **8** could arise through a pathway involving three main steps: (1) condensation, (2) activation and (3) arylation. To be successful, these three steps would need to be perfectly orchestrated to direct the desired arylation of advanced intermediates **5** or **6** with arene **7** and circumvent the direct condensation with ethyl glyoxylate **2**. Supporting this idea, the work by Fessner established a rare example of a one pot multicomponent Friedel–Crafts reaction using acetic acid and excess of hydrochloric acid gas to form racemic α-arylated amino acids.[8j] Inspired by this appreciable precedent, we envisioned that the highly regioselective Friedel–Crafts reaction could be redesigned to become more effective and suitable for asymmetric catalysis applications.

A proposed concept, rationalizing a possible orchestration between three components **1**, **2** and **7** is outlined in Scheme 1. A catalytic amount of acid would facilitate the condensation between benzyl carbamate **1** and ethyl glyoxylate **2** to form hemiaminal **3**. Next, acetyl chloride would simultaneously activate hemiaminal **3** to deliver chloroaminal **5** while trapping water thereof, generating acetic acid and rending the process autocatalytic in acid.

During the chlorination step, a putative onium **4** would be formed which would likely undergo nucleophilic displacement



Scheme 1 Concept of autocatalysis in AcOH promoting simultaneously both condensation and activation steps (steps 1/2) to chloroaminal **5**.

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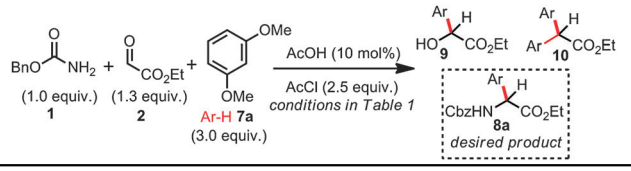
Table 1 Attempts of a one pot synthesis of α-amino esters **8a**



Entry	Solvent, temperature	Time (h)	Yield (%)
1	$CHCl_3$, RT	18	**9** (57%) **10** (22%)
2	Ethyl acetate, RT	18	**8a** (28%) **10** (17%)[a]

[a] Hemiaminal **3** was isolated in 13% yield.

to *in situ* deliver the activated chloroaminal **5**. Finally, the arylation will likely proceed *via* an S_N1 mechanism through iminium **6** to ultimately provide the desired α-amino ester **8**.

In our initial studies for the synthesis of activated aminals (such as chloro, bromo, or acetoxy from hemiaminal **3** (step 2)),[5–7] acetyl chloride was found to be the most efficient and milder reagent in the prospect of a tandem process. Our first attempts at a one pot reaction between benzyl carbamate **1**, ethyl glyoxylate **2** and 1,3 dimethoxybenzene **7a**, with catalytic amounts of acetic acid and excess of acetyl chloride confirmed the anticipated nucleophilic chemoselectivity issues leading to multiple uncontrolled arylations (Table 1). In chloroform and ethyl acetate (entries 1 and 2), reaction profiles differ but both by-products **9** or **10** from direct glyoxylate **2** arylations were isolated. To our delight, the reaction in ethyl acetate yielded the desired α-amino ester **8a** in 28% in the first attempt.

To gain more insight into the proposed concept of autocatalysis and the reaction mechanism, control experiments starting from hemiaminal **3** and other plausible reaction intermediates acetoxy- and chloroaminal **5** were investigated.[10] Interestingly, addition of arene **7a** to hemiaminal **3** (or acetoxy-derivative) afforded the bis-arylated product **10** along with the desired α-amino ester **8a** in 35% and 16% yields respectively.[10] This result supports that hemiaminal **3** has a high tendency to fragment (retro-condensation) before undergoing successive arylations leading to **10**.[11]

Also, treatment of chloroaminal **5** with D_2O regenerates the deuterated-hemiaminal **3** demonstrating that water should be entirely excluded from the reaction media to achieve full conversion to α-chloroglycinate **5** and enable the cascade reaction.

Due to the lack of controlled reactivity in one pot (Table 1), we then examined the condensation and activation steps in more detail. Xu[7e] and others[12] demonstrated that both acidity and the amount of Brønsted acid used to catalyze the condensation between carboxamides and alkyl glyoxylates are important to efficiently produce hemiaminals. As shown by the slow rate of the acid catalysis (10 mol%) (Fig. 1; catalysis A), the modest conversions[13] to hemiaminal **3** may result from the reversibility of the condensation.[10,11] Upon addition of acetyl chloride, the reaction proceeded more quickly to full conversion in hemiaminal **3** and further afforded the desired chloroaminal **5** in good yield (Fig. 1; autocatalysis B). These kinetic experiments support that acetyl chloride displaces the reaction equilibrium towards hemiaminal **3** and chloroaminal **5**.[10]

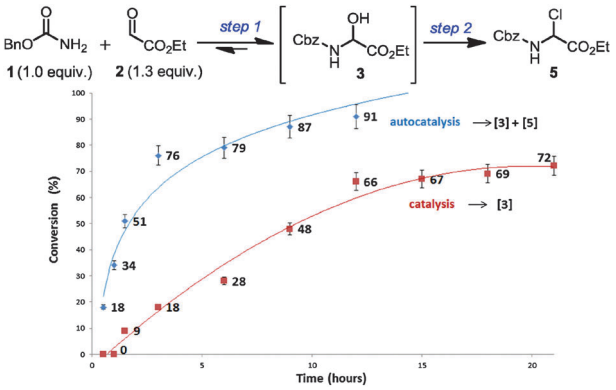


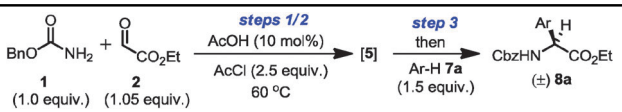
Fig. 1 Experimental kinetic evidence showing high performance autocatalysis. Reactions were performed with: *catalysis A*: **1** (1.0 mmol), **2** (1.3 mmol), acetic acid (10 mol%) at RT, in chloroform; *autocatalysis B*: similar reaction condition to A with acetyl chloride (2.5 mmol); conversions are reported using a quantitative ^{1}H NMR technique [ref. 13] with mesitylene as the internal standard.

Thus, acetyl chloride was found to not only activate hemiaminal **3**, *but also trap the water formed during the reaction, producing acetic acid which autocatalyzes and accelerates the first step of the cascade* (Scheme 1).[14] It is important to notice that acetic and hydrochloric acids are the main reaction by-products and that the reaction was not compatible with the use of molecular sieves.[10] Several solvents were also tested in the reaction (toluene, THF, ethyl acetate, chloroform and acetonitrile), and full conversion in chloroaminal **5** was established either in acetonitrile or chloroform at 60 °C.[10]

We then examined the tandem cascade reaction in the preselected solvents (Table 2). Experiments were conducted with a reduced amount of ethyl glyoxylate (1.05 equiv.) to avoid any formation of arylated by-products **9–10**. In ethyl acetate, the cascade reaction was messy (Table 2, entry 1) leading to a difficult isolation of the desired product **8a** in a modest 9% yield. After optimization, both reactions in $CHCl_3$ and CH_3CN effectively delivered the α-amino ester **8a** at a variable temperature (Table 2, entries 2–4). The best result was obtained in chloroform at 60 °C leading to the isolation of α-amino ester **8a** in 82% yield (Table 2, entry 3).

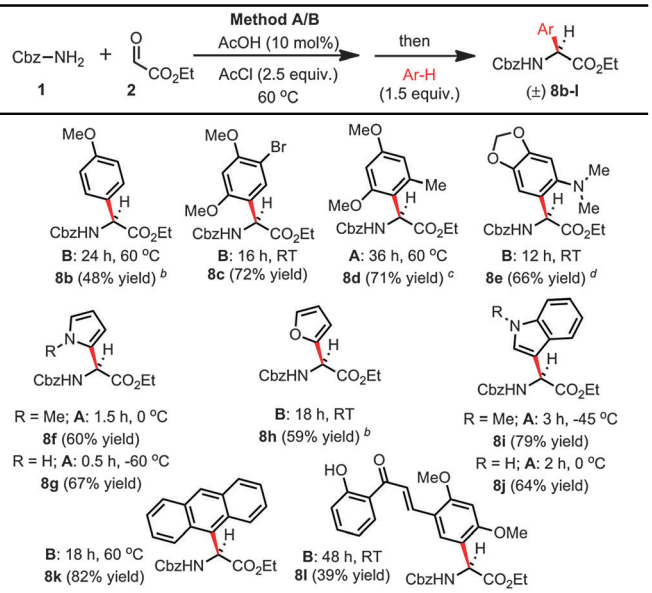
Having established two sets of conditions in $CHCl_3$ and CH_3CN for Friedel–Crafts reaction, we turned our attention to

Table 2 Optimization for a one pot synthesis of racemic α-amino esters **8a**



		Step 1/2	Step 3		
Entry	Solvent	Time (h)	Time (h)	Temp.	Yield (%)
1	CH_3CO_2Et	9	24	RT	9
2	$CHCl_3$	12	36	RT	65
3	**$CHCl_3$**	**12**	**9**	**60 °C**	**82**
4	CH_3CN	24	2	RT	74
5	CH_3CN	24	0.5	60 °C	69

Table 3 Scope for the synthesis of racemic α-amino esters **8b–l**[a]



[a] Method A: reaction performed in $CHCl_3$, steps 1/2 for 12 h, method B: reaction performed in CH_3CN, step 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] Using excess arenes (3.0 equiv.), the isolated yields for **8b** and **8h** are 60% and 61% respectively. [c] Using method B at 60 °C for 4 h, **8d** was isolated in 74% yield (2 : 1 mixture of regioisomers). [d] Nucleophile employed is the aniline hydrochloric salt.

the scope of the cascade reaction with a series of challenging arene nucleophiles (Table 3). According to the empirical nucleophilicity scale from Mayr,[15] we discovered that the most reactive arenes (*N* factor > 3.0) reacted regioselectively in $CHCl_3$ at low temperatures (Method A) while less reactive arenes (*N* factor < 1.5) reacted more cleanly in CH_3CN and at higher temperatures (Method B). Several phenolic and aniline derivatives **8a–e** 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 for the synthesis of **8f–j**. Pyrrolyl **8f–g**, furanyl **8h** and indolyl **8i–j** aminoester derivatives were prepared in high yields as single regioisomers. Finally, anthracenyl product **8k** was obtained easily in 82% yield, while the more unusual and complex chalcone α-amino ester derivative **8l** was isolated in a reasonable 39% yield.

In summary, we reported a one pot synthesis of aryl α-amino acid bearing orthogonal protecting groups *via* Friedel–Crafts reaction employing activated iminiums generated from inexpensive, commercially available starting materials. Our results show this cascade to be autocatalytic in acetic acid and mediated by acetyl chloride to shuttle water out of the system. This novel one pot synthesis is efficient and versatile as highlighted by the synthetic scope of arylated α-amino esters **8a–l** prepared. Ongoing studies are aimed at developing an asymmetric variant of this transformation and expanding the scope to additional classes of nucleophiles.

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