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Aldehyde-induced metal-free decarboxylation of α-amino acids to synthesize *N*-alkyl-β-alkenyl cyclic amines with high stereoselectivity

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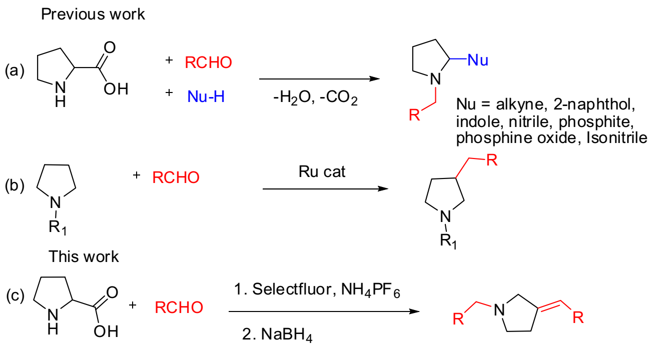
ABSTRACT

In contrast to the continuously growing number of methods that allow for the efficient α-functionalization of α-amino acids, few strategies exist that enable the direct functionalization of α-amino acids in the β-position. A one-pot difunctionalizative reaction has been developed for the aldehyde-induced metal-free decarboxylation of α-amino acids to synthesize *N*-alkyl-β-alkenyl cyclic amines with high stereoselectivity.

Introduction

There has recently been a considerable increase in the development of new reactions for the preparation of cyclic amines and related alkaloids because of their potential pharmaceutical value and synthetic applications.[1] The direct α–C(sp^3)–H bond functionalization of amines has emerged as one of the most important tools for the construction of bioactive nitrogen containing complex molecules.[2] Recent work of Li's,[3] Seidel's,[4] Wang's[5] and Batra's[6] groups have demonstrated the utility of α-amino acid derived azomethine ylides for the synthesis of a variety of α-functionalized saturated cyclic amines (Scheme 1a). Pan[7a] reported the synthesis of *N*-alkylindoles from aldehydes with 2-carboxyindoline by decarboxylative redox amination.

In stark contrast to amine α-functionalization methods, due to the β–C(sp^3)–H bonds of cyclic amines are inert, the preparation of β-functionalized cyclic amines always require a multistep process, and the direct functionalization of amines at the β-position remains rare. For example, Bruneau[8] reported a Ru(II)-catalyzed sequential dehydrogenation process to realize the β-alkylation of amines that proceeds via an azomethine ylide intermediate (Scheme 1b). Seidel[9] and Sartillo-Piscil[10] reported the α,β-difunctionalization cascade reaction of simple cyclic amines. To the best of our knowledge, however, there have been no reports on the N—H/β—C(sp^3)—H difunctionalization of α-amino acids under metal-free condition. In traditional methods, β-alkenylative cyclic amines were synthesized by radical cyclization[11] or Horner–Wadsworth–Emmons reaction[12] without *Z*/*E* selectivity. These procedures generally need harsh reaction conditions and complex starting materials. Here we reported the one-pot aldehyde-induced metal-free decarboxylation of α-amino acids to synthesize *N*-alkyl-β-alkenyl cyclic amines with high stereoselectivity (Scheme 1c).



Scheme 1. Models of functionalization of cyclic amines.

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Results and discussion

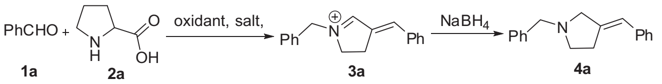
Our study began with the reaction of 1.0 mmol of benzaldehyde, 0.75 mmol of l-proline and 1.0 mmol of NH_4PF_6 in toluene at 110 °C for 12 h. After cooling, the iminium salt formed was converted to corresponding amine by $NaBH_4$, and the desired product **4a** was obtained in 10% yield (Table 1, entry 1). Then, different salts were examined, NH_4PF_6 gave the best yield (entries 2–4). No product was obtained without the salt, the salt not only promoted the condensation of the aldehyde with enamine **5** but also stabilized the unsaturated iminium **3** (Table 1, entry 5). To further improve the yield, a series of oxidants were screened to promote the decarboxylation, Selectfluor gave the highest yield (Table 1, entries 6–12). To our surprise, when only Selectfluor was used, 25% yield of the product was obtained. The Selectfluor acted as not only the oxidant but also the salt (Table 1, entry 13). Screening of solvents indicated that toluene was still the best solvent for this reaction (Table 1, entries 14–17). When the reaction was performed at 130 °C for 24 h, an excellent yield was obtained (Table 1, entry 18). When the amount of Selectfluor and NH_4PF_6 was added by double or 4Å MS (40 mg) was added, the yield was not improved obviously (Table 1, entries 19 and 20). In addition, different acids, bases, and metal catalysts were also evaluated as additives for the reaction, the conversion was not enhanced (see supplementary data). Therefore, the optimized conditions were benzaldehyde (1.0 mmol), L-proline (0.75 mmol), Selectfluor (1.0 mmol), NH_4PF_6 (1.0 mmol) in toluene at 130 °C for 24 h.

With the optimal conditions established above, we then examined the scope of the substrates **1** and **2**, and the results are summarized in Table 2. A variety of aromatic aldehydes bearing various types of substituents were employed in the reaction to give the corresponding products with moderate yields, along with alcohols reduced from the corresponding starting aldehydes and some unidentified acids. In most cases, good stereoselectivity were observed, and the *E*/*Z* ratio of all products was determined by ^1H NMR, for which the stereochemistry was revealed by NOESY experiments (Table 2, entries 1–13). This reaction was conducted at 130 °C, we thought it tends to generate the product of thermodynamic stability. In most conditions, the *E* unsaturated iminium **3** was more stable than *Z* isomer. Moreover, we focused on the reaction of 2-naphthaldehyde, 2-furaldehyde and 2-thiophenecarboxaldehyde, 35%, 38% and 44% yield of corresponding products were obtained, respectively (Table 2, entries 14–16). While aliphatic aldehydes were employed, no desired product was observed. After expanding the scope of aldehydes, we focused on the use of different amino acids. D-Pipecolic acid **2b** was also viable substrates in this reaction, and good stereoselectivity was observed (Table 2, entry 17). However, 2-carboxyindoline **2c** reacted with benzaldehyde gave a complex reaction mixture (Table 2, entry 18).

Notably, trace amount of intermediates **5a** was detected by GC–MS analysis when the reaction time was shorten to 1 h. We failed to isolate **5a**, due to it could react with aldehyde fastly (Scheme 2a). Using 1-benzylindole **9** to react with benzaldehyde **1a** mediated by NH_4PF_6, compound **10** was the major product (Scheme 2b).

According to the reaction results and previous researches, we proposed a mechanism based on the formation of azomethine ylide (Scheme 3). In the first step, α-amino acid is condensed with the aldehyde resulting in imine **6** with the loss of water molecule. This is followed by decarboxylation to form the azomethine ylide **7**, which is a zwitterionic species.[3–6] This species undergoes intramolecular proton transfer to furnish the enamine **5**.[7,8a,13b] Further condensation of the aldehyde and dehydration would afford the unsaturated iminium **3**,[8a,13] which could be readily reduced by $NaBH_4$.

Table 1
Optimization of the reaction conditions.[a]



Entry	Oxidant	Salt	Temp. (°C)	Solvent	Yield (%)[b]
1		NH_4PF_6	110	$PhCH_3$	10
2		KPF_6	110	$PhCH_3$	Trace
3		NH_4BF_4	110	$PhCH_3$	8
4		$NaBF_4$	110	$PhCH_3$	Trace
5			110	$PhCH_3$	0
6	$K_2S_2O_8$	NH_4PF_6	110	$PhCH_3$	40
7	$Na_2S_2O_8$	NH_4PF_6	110	$PhCH_3$	25
8	$NH_4S_2O_8$	NH_4PF_6	110	$PhCH_3$	29
9	DTBP	NH_4PF_6	110	$PhCH_3$	Mixture
10	NFSI	NH_4PF_6	110	$PhCH_3$	35
11	$NaIO_4$	NH_4PF_6	110	$PhCH_3$	Trace
12	Selectfluor	NH_4PF_6	110	$PhCH_3$	50
13	Selectfluor		110	$PhCH_3$	25
14	Selectfluor	NH_4PF_6	110	*n*-BuOH	Mixture
15	Selectfluor	NH_4PF_6	110	1,4-Dioxane	45
16	Selectfluor	NH_4PF_6	110	DMF	Mixture
17	Selectfluor	NH_4PF_6	110	CH_3NO_2	Trace
18[c]	Selectfluor	NH_4PF_6	130	$PhCH_3$	60
19[d]	Selectfluor	NH_4PF_6	130	$PhCH_3$	61
20[e]	Selectfluor	NH_4PF_6	130	$PhCH_3$	62

[a] Reaction conditions: benzaldehyde (1.0 mmol), L-proline (0.75 mmol), oxidant (1.0 mmol), salt (1.0 mmol), solvent (5.0 mL), 12 h, after cooling, $NaBH_4$ (5.0 mmol) at 0 °C for 1 h, unless otherwise noted.

[b] NMR yield.

[c] Reaction time was extended to 24 h.

[d] Selectfluor (2.0 mmol), NH_4PF_6 (2.0 mmol) was used, 24 h.

[e] 4ÅMS (40 mg) was added, 24 h.