Preparation of $\alpha$-amino acids via Ni-catalyzed reductive vinylation and arylation of $\alpha$-pivaloyloxy glycine†

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This work emphasizes easy access to $\alpha$-vinylic and aryl amino acids via Ni-catalyzed cross-electrophile coupling of bench-stable $N$-carbonyl-protected $\alpha$-pivaloyloxy glycine with vinyl/aryl halides and triflates. The protocol permits the synthesis of $\alpha$-amino acids bearing hindered branched vinyl groups, which remains a challenge using the current methods. On the basis of experimental and DFT studies, simultaneous addition of glycine $\alpha$-carbon (Gly) radicals to Ni(0) and Ar–Ni(i) may occur, with the former being more favored where oxidative addition of a C(sp$^2$) electrophile to the resultant Gly–Ni(i) intermediate gives a key Gly–Ni(ii)–Ar intermediate. The auxiliary chelation of the $N$-carbonyl oxygen to the Ni center appears to be crucial to stabilize the Gly–Ni(i) intermediate.

Introduction

Ni-catalyzed cross-electrophile coupling has emerged as a powerful tool for expedient creation of C(sp$^3$)–C bonds, in which alkyl radical intermediates are generally involved. However, to the best of our knowledge, application of this strategy to the reductive coupling of $\alpha$-glycinyl electrophiles, which enables direct decoration of the $\alpha$-carbon of glycine derivatives, remains unexplored. A prominent obstacle may be the rapid conversion of $\alpha$-glycinyl electrophiles to imino or iminium esters that are well-established for addition reactions. Reduction of an $\alpha$-glycinyl electrophile to generate a glycinyl $\alpha$-$C$(sp$^3$)–radical was hitherto unknown. Realization of such a radical forming process may invoke a reductive coupling protocol for facile structural enrichment of $\alpha$-amino acids.

Unusual and unnatural $\alpha$-vinyl and $\alpha$-aryl amino acids have seen a broad range of applications in drug discovery, biomaterials, and protein engineering. † Selected examples include amoxicillin, forphenicine, the trypsin inhibitor radiosumin, the phytotoxin rhizobitoxine, butadienylglycine (found in the defensive secretion of beetles), and 2-amino-3-(3,4-dihydroxyphenyl)but-3-en-1-ol, an antidepressant (Scheme 1a). Numerous synthetic methods have been developed to access $\alpha$-aryl and $\alpha$-vinylic amino acids based on two-electron addition (e.g., R-Li, -Zn and -B and electron-rich arenes) to glycine cation equivalents such as iminoesters (Scheme 1b). Nevertheless, decoration of glycine $\alpha$-carbons with branched vinyl groups bearing multiple substituents remains a challenge.

Herein, we describe the Ni-catalyzed reductive coupling of N-carbonyl-protected $\alpha$-pivaloyloxy glycine derivatives with aryl and vinyl halides/triflates to afford unusual $\alpha$-aryl/vinyl amino acids. The use of $\alpha$-pivaloyloxy glycine proved crucial for the coupling reaction probably because it converts in situ into the active $\alpha$-iodoglycine or iminium ester at low concentrations. Upon SET reduction or halide abstraction, a glycinyl (Gly) radical intermediate was produced. DFT studies suggest that the Gly radical may simultaneously add to Ni(0) and Ar–Ni(i), but with the former being more favored to give a highly stable Gly–Ni(i) chelate wherein the auxiliary chelation of the $N$-carbonyl oxygen to the Ni center appears to be pivotal. Oxidative addition of an aryl halide to the Ni(ii) species forms a key Gly–Ni(III)–Ar intermediate (Scheme 1c). The necessity of the $N$-carbonyl protecting groups may provide useful information about coupling reactions of functionalized alkyl precursors which are currently essential for Ni-catalyzed stereoselective synthesis of C–C bonds.

Results and discussion

Optimization of the reaction conditions

We began our studies by investigating the coupling of benzoyl protected $\alpha$-pivaloyloxy glycine ethyl ester 1a and (2-bromovinyl) benzene 2 ($E/Z = 5:1$). An extensive survey of experimental parameters led us to identify the optimal reaction conditions at
hydro-reduction product 1a-H donating and -withdrawing groups as evidenced by 1H NMR spectra (Fig. 1). The substituents 2,2-disubstituted vinyl bromides appeared to be slightly more effective than that observed for the mono-substituted ones (Table 1). An outstanding feature of this vinylation protocol was its competency in the conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the cases of 3-vinyl bromide substrates, which produced the phenyl, alkyl, and silyl-substituted vinyl glycines were compatible with the coupling conditions, the trimethylsilyl-substituted vinyl glycines were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e., 11–15). An outstanding feature of this vinylation protocol was its competency in the 3d, 20% of the enamine tautomer was also detected. The naphthyl, anthranyl, furyl, and thiyl-conjugated vinyl bromides all delivered the corresponding vinyl glycines (4–7) in good to excellent yields. The dienyl glycine 8 was obtained in 75% yield, which can be used for further transformations (e.g., Diels–Alder reactions). The alkyl-substituted 1-vinyl bromides (E and Z mixtures) en route to 9 and 10 were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the 3d, 20% of the enamine tautomer was also detected. The naphthyl, anthranyl, furyl, and thiyl-conjugated vinyl bromides all delivered the corresponding vinyl glycines (4–7) in good to excellent yields. The dienyl glycine 8 was obtained in 75% yield, which can be used for further transformations (e.g., Diels–Alder reactions). The alkyl-substituted 1-vinyl bromides (E and Z mixtures) en route to 9 and 10 were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the 3d, 20% of the enamine tautomer was also detected. The naphthyl, anthranyl, furyl, and thiyl-conjugated vinyl bromides all delivered the corresponding vinyl glycines (4–7) in good to excellent yields. The dienyl glycine 8 was obtained in 75% yield, which can be used for further transformations (e.g., Diels–Alder reactions). The alkyl-substituted 1-vinyl bromides (E and Z mixtures) en route to 9 and 10 were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the 3d, 20% of the enamine tautomer was also detected. The naphthyl, anthranyl, furyl, and thiyl-conjugated vinyl bromides all delivered the corresponding vinyl glycines (4–7) in good to excellent yields. The dienyl glycine 8 was obtained in 75% yield, which can be used for further transformations (e.g., Diels–Alder reactions). The alkyl-substituted 1-vinyl bromides (E and Z mixtures) en route to 9 and 10 were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the 3d, 20% of the enamine tautomer was also detected. The naphthyl, anthranyl, furyl, and thiyl-conjugated vinyl bromides all delivered the corresponding vinyl glycines (4–7) in good to excellent yields. The dienyl glycine 8 was obtained in 75% yield, which can be used for further transformations (e.g., Diels–Alder reactions). The alkyl-substituted 1-vinyl bromides (E and Z mixtures) en route to 9 and 10 were also viable, wherein conversion of the Z-vinyl bromides to the E-products was much less effective than that observed for 2 (Table 1). The 2,2-disubstituted vinyl bromides appeared to be slightly more effective than the mono-substituted ones (e.g., 11–15). An outstanding feature of this vinylation protocol was its competency in the

### Substrate scope

The established vinylation conditions (Table 1, entry 1) proved to be general for various vinyl halides (Fig. 1). The substituents on the phenyl rings of styrenyl bromides include both electron-donating and -withdrawing groups as evidenced by 3b–3f. For

### Table 1 Optimization for the reaction of 1a with 2

| Entry | Variation from the standard conditions | Yield%<sup>a</sup> |
|-------|----------------------------------------|------------------|
| 1     | No changes                             | 65 (75)<sup>b</sup> |
| 2     | w/o Ni                                 | Trace            |
| 3     | w/o Zn                                 | Not detected     |
| 4     | w/o TBAI                               | Trace            |
| 5     | w/o MgCl<sub>2</sub>                   | Trace            |
| 6     | NiCl<sub>2</sub>                       | 10               |
| 7     | L2 instead of L1                       | Trace            |
| 8     | L3 instead of L1                       | 62               |
| 9     | L4 instead of L1                       | 18               |
| 10    | L5 instead of L1                       | Not detected     |
| 11    | 1a (8 mmol)                            | 63<sup>c</sup>   |

<sup>a</sup> NMR yield using 2,5-dimethylfuran as the internal standard.<br><sup>b</sup> Isolated yield.<br><sup>c</sup> The reaction was run on a gram scale.
The vinylation method was also extended to the generation of arylated glycines (Fig. 1). The reactions exhibited excellent functional group compatibility, retaining such functionalities as aldehyde in 35c and vinyl in 35f and 35g. The naphthyl and anthrenyl bromides afforded 36 and 37 in high yields. Electron-rich heteroaromatics such as 3-bromofuran and thiophene gave 38 and 39 in low yields. This problem could be solved using the iodo analogs, as exemplified by 40 and 35j.

The N-carbonyl protecting groups ranging from benzoyl groups decorated with electron-donating and -withdrawing substituents, to thiophenyl, Cbz, and Boc were suitable as evidenced in 41–45 (Fig. 2). In the case of arylation, Fmoc was more effective than Boc and Cbz groups (see 46–48). In contrast, N-tert-butylsulfinyl was ineffective. Moreover, hydrolysis of 26 and 35k with hydrochloric acid afforded the amino acid salts 50 and 51 in good yields (eqn (1)).

\[
\begin{align*}
26 & \xrightarrow{\text{a}} 50 \\
35k & \xrightarrow{\text{aq. HCl}} 51
\end{align*}
\]

Mechanistic and computational studies

1. Possible in situ formation of an α-haloglycine or iminium salt. The use of pivaloyloxy glycine is crucial for this coupling event. Reaction of bromobenzene with unstable iminoester 52 (with or without 1 equiv. of PivOH) or unstable α-bromo glycine 53 only resulted in a trace amount of 35a (eqn (3)). The formation of hydro-deoxygenative glycine 1a-H as the major product (eqn (2)) implied that pre-formed iminoester or α-halogeniclycine was not suitable for this coupling event.
Exposure of 1a to TBAI and/or MgCl₂ resulted in nearly full recovery of 1a even after 48 h, indicating that halide substitution was unable to effectively cleave the C-O bond in 1a (eqn (3)). However, in the presence of Zn and TBAI, 1a was consumed and majorly reduced to 1a-H within ~1 hour, while the use of Zn and MgCl₂ was ineffective. It was noted that in the standard catalytic coupling reaction, 1a went to completion within ~1 h (Fig. S1†). We reason that TBAI triggers the conversion of 1a to an imino/iminium ester or α-iodoglycine which acts as the actual coupling partner. This process could be equilibrated or slow so that low concentrations of the active species were maintained. When Zn was present, fast reduction of the in situ generated active species facilitated the consumption of 1a and ensured a matched coupling reactivity with the C(sp²)-partners (eqn (4)). No deuterium incorporation into 1a-H was detected when D₂O was added to eqn (3), implying that a radical process may take place in the reduction.

**Figure 3** The reaction profile for the formation of 35l and 35b in eqn (8) in the presence of Zn. Yield based on 1 equiv. of 1a.

**Table 1**

| TBAI | MgCl₂ | Zn | time | recovered 1a | 1a-H |
|------|-------|----|------|-------------|------|
| 100% | 0%    | 0% | 48 h | major       | not applicable |
| 100% | 150%  | 0% | 48 h | major       | not applicable |
| 0%   | 150%  | 200% | 1 h | major       | trace    |
| 0%   | 150%  | 200% | 1 h | trace       | major |

**Scheme 1**

(2) Formation of an α-glycyl carbon radical intermediate. More importantly, α-cyclopropyl imine 54 resulted in the radical ring-opening product 55 under Zn/MgCl₂/TBAI conditions (eqn (5)). The catalytic reaction as in Table 1, entry 1 was completely inhibited upon introduction of 2 equiv. of TEMPO. These results suggest that the catalytic reaction involves generation of a glycine α-carbon radical via single-electron reduction/halide abstraction of the in situ-formed iminium intermediate or α-iodoglycine by MgCl₂-activated Zn, or L₅-Ni²⁺ (eqn (6)). The L₅-Ni²⁺ species can be generated from reduction of L₅-Ni¹⁺ by Zn or from the reductive elimination of a Gly−[L₅]Ni¹⁺−Ar intermediate (Scheme 1c).
The seemingly unusual observation in eqn (8) led us to consider the viability of addition of a Gly radical to Ni(0), which would generate a Gly–Ni(i) species. Subsequent oxidative addition of an aryl halide to Gly–Ni(i) would give the key Gly–Ni(III)–Ar intermediate (Scheme 1). DFT computations provide support for this mechanistic proposal (Scheme 1 and Fig. S4†). There is a large decrease of free energy of 66 kcal mol⁻¹ as the Ni(0) catalyst binds the Gly radical carbon, forming the highly stable Gly–Ni(I)–Ln intermediate IM1 wherein the chelation of benzoyl oxygen to the Ni(i) center is prominent. Oxidative addition of bromobenzene to IM1 requires overcoming an energy barrier of 16.9 kcal mol⁻¹ to give the Ni(III) intermediate IM2. The subsequent reductive elimination proved to be rate-determining with an activation energy of 17.3 kcal mol⁻¹. In comparison, DFT studies indicate that the radical-chain mechanism as in Scheme S4† was disfavored, because the precursor complex I5 to the oxidative addition of bromobenzene to Ln–Ni(0) would be much less stable than complex IM1 (Fig. 4). The Ni(0) catalyst would proceed to IM1, which is completely irreversible.

**Conclusions**

In summary, we have demonstrated that α-pivaloyloxy glycine effectively coupled with vinyl and aryl halides/triflates to afford C(sp³)-functionalized α-amino acids under Ni-catalyzed reductive conditions. This method displays unique competency for incorporating hindered α- and tri-substituted vinyl moieties into the α-position of glycine, which is unattainable by previous methods. Mechanistically, a glycine α-carbon radical is thought to arise from the reduction of an in situ generated iminium or α-iodoglycine by Zn or a Ni(i) species, which then participates in the coupling process by addition to Ni(0) and Ar–Ni(i). DFT calculations showed that addition of the glycine carbon radical to Ln–Ni0 to give Ln–Ni3–Gly followed by oxidative addition to ArX is possibly a more favored process. The auxiliary chelation of N-carbonyl to the Ni center appears to play a profound role in stabilizing the Ni intermediate, which may become crucial in developing an asymmetric version of this amino-acid forming event, which is ongoing in our laboratory and will be reported in due course.

**Conflicts of interest**

There are no conflicts to declare.

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