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Preparation of α-amino acids *via* Ni-catalyzed reductive vinylation and arylation of α-pivaloyloxy glycine†

Xianghua Tao,[a] Yanchi Chen,[a] Jiandong Guo,[b] Xiaotai Wang *[bc] and Hegui Gong *[a]

This work emphasizes easy access to α-vinyl and aryl amino acids *via* Ni-catalyzed cross-electrophile coupling of bench-stable *N*-carbonyl-protected α-pivaloyloxy glycine with vinyl/aryl halides and triflates. The protocol permits the synthesis of α-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 α-carbon (Gly) radicals to Ni(0) and Ar–Ni(II) 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(III)–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 expeditious creation of C(sp^3)–C bonds,[1] in which alkyl radical intermediates are generally involved. However, to the best of our knowledge, application of this strategy to the reductive coupling of α-glycinyl electrophiles, which enables direct decoration of the α-carbon of glycine derivatives, remains unexplored.[2] A prominent obstacle may be the rapid conversion of α-glycinyl electrophiles to imino or iminium esters that are well-established for addition reactions.[3,4] Reduction of an α-glycinyl electrophile to generate a glycinyl α-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 α-amino acids.[2]

Unusual and unnatural α-vinyl and -aryl amino acids have seen a broad range of applications in drug discovery, biomaterials, and protein engineering.[5–7] Selected examples include amoxicillin,[8] forphenicine,[9] the trypsin inhibitor radiosumin,[10] the phytotoxin rhizobitoxine,[11] butadienylglycine (found in the defensive secretion of beetles),[12] and 2-amino-3-(3,4-dihydroxyphenyl)but-3-enoic acid as an antidepressant (Scheme 1a).[13] Numerous synthetic methods have been developed to access α-aryl and -vinyl 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).[14–16] Nevertheless, decoration of glycine α-carbons with branched vinyl groups bearing multiple substituents remains a challenge.[17]

Herein, we describe the Ni-catalyzed reductive coupling of *N*-carbonyl-protected α-pivaloyloxy glycine derivatives with aryl and vinyl halides/triflates to afford unusual α-aryl/vinyl amino acids. The use of α-pivaloyloxy glycine proved crucial for the coupling reaction probably because it converts *in situ* into the active α-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(II), 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(I) 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.[18]

Results and discussion

Optimization of the reaction conditions

We began our studies by investigating the coupling of benzoyl protected α-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

[a]*College of Materials Science and Engineering, Center for Supramolecular Materials and Catalysis, Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China. E-mail: hegui_gong@shu.edu.cn*

[b]*Hoffmann Institute of Advanced Materials, Shenzhen Polytechnic, 7098 Liuxian Boulevard, Nanshan District, Shenzhen 518055, P. R. China*

[c]*Department of Chemistry, University of Colorado Denver, Campus Box 194, P. O. Box 173364, Denver, Colorado 80217-3364, USA. E-mail: xiaotai.wang@ucdenver.edu*

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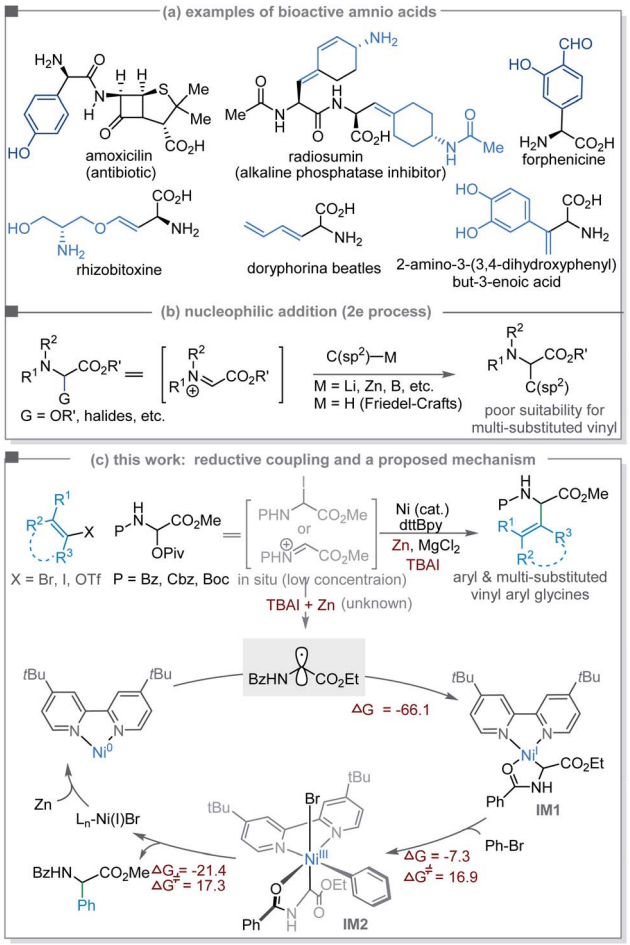


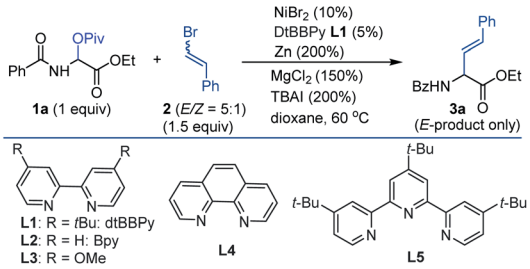
Scheme 1 (a) Examples of bioactive compounds consisting of unusual amino acids. (b) C(sp^2)-functionalization of glycine cation equivalents using 2e addition strategies. (c) Ni-catalyzed reductive coupling strategy for the preparation of unusual α-amino acids.

60 °C comprising $NiBr_2$/dtBBpy in combination with the reductant Zn, the additives $MgCl_2$ and TBAI, and the solvent 1,4-dioxane.[19] The vinyl glycine product **3a** was isolated in 75% yield consisting only of the *E*-isomer (Table 1, entry 1).[20] Control experiments indicated that $NiBr_2$, Zn, $MgCl_2$, and TBAI all were essential reagents (entries 2–5). Other nickel sources, ligands or temperatures gave inferior results (entries 6–10 in Table 1). The reaction could be performed on a gram scale with slightly diminished efficiency (entry 11). The need for 5 mol% ligand (**L1**) was tentatively explained by the inhibited formation of hydro-reduction product **1a-H**. The remaining non-ligand chelated 5 mol% Ni may be stabilized by weak coordination with **1a**, which could ensure the formation of a decent amount of Ni–**L1** complex for efficient catalysis, provided formation of inactive Ni species is possible over the course of the reaction.

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%[a]
1	No changes	65 (75)[b]
2	w/o Ni	Trace
3	w/o Zn	Not detected
4	w/o TBAI	Trace
5	w/o $MgCl_2$	Trace
6	$NiCl_2$	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[c]

[a] NMR yield using 2,5-dimethylfuran as the internal standard. [b] Isolated yield. [c] The reaction was run on a gram scale.

3d, 20% of the enamine tautomer was also detected.[19] 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 cases of α-vinyl bromide substrates, which produced the phenyl, alkyl, and silyl-substituted vinyl glycines **16–20** in moderate to good yields. The low yield for **18** was due to homocoupling of the α-vinyl bromide. The 1,2-disubstituted *Z*-alkenyl bromides were compatible with the coupling conditions, affording **21–24** in moderate to good yields. To our delight, the trimethyl substituted vinyl bromide delivered **25** in 44% yield, which is difficult to access with concurrent methods.

Vinyl triflates that could be readily obtained from ketones or alkynes were viable (Fig. 1). By replacing $NiBr_2$ with $NiCl_2(Py)_4$, coupling of **1a** with cyclohexenyl triflate produced **26** in 80% yield. Products **27** and **28** bearing cycloheptenyl and cyclooctenyl groups were obtained in moderate yields, while the formation of cyclododecenyl amino acid **29** was of lower yield. The conjugated 3,3,5-trimethyl-4-oxocyclohexa-1,5-dien-1-yl, sterically hindered 2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoindenyl and phenyl-conjugated vinyl triflates within a cycloheptene ring resulted in **30–32** in moderate yields. While 2-hexenyl glycine **33** was obtained in 62% yield, the more hindered heptenyl glycine **34** was produced in 20% yield.

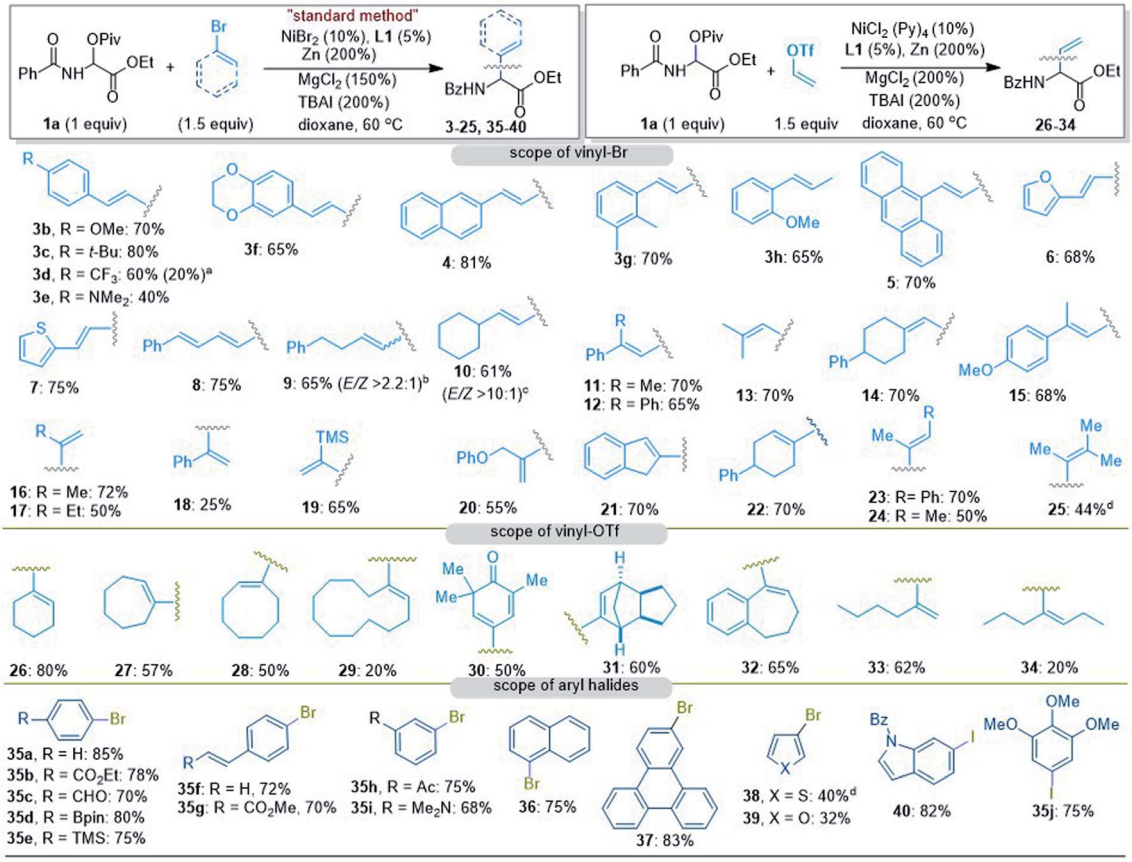
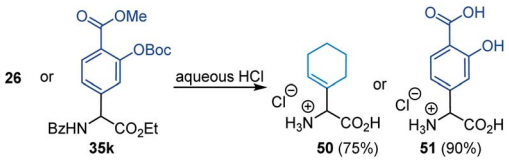


Fig. 1 Coupling of **1a** with vinyl bromides and triflates, and aryl halides using the conditions in Table 1, entry 1 with isolated yields. [a]Yield of isomerization to α-enamine determined by ^{1}H NMR analysis after purification. [b]A mixture of *E*/*Z* vinyl–Br in a ratio of 1.8 : 1 was used. [c]A mixture of *E*/*Z* vinyl–Br in a ratio of 10 : 1 was used. [d]$NiCl_2$(DME).

The vinylation method was also extended to the generation of arylated glycines **35–40** (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)).



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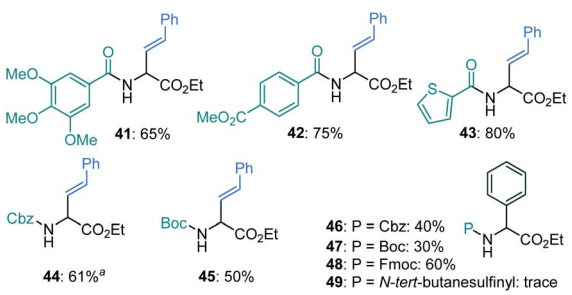
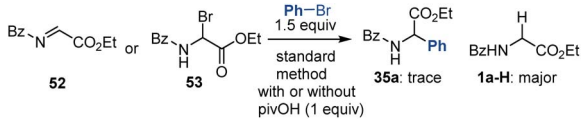


Fig. 2 Variation of amine-protecting groups. [a]$NiCl_2$ was used in place of $NiBr_2$.

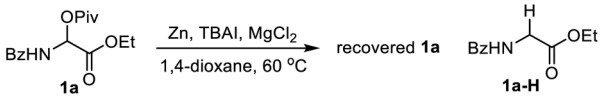
Mechanistic and computational studies

(1) Possible *in situ* formation of an α-haloglycine or iminium salt. The use of pivaloyloxy glycine is crucial for this coupling event.[21] 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-halo glycine was not suitable for this coupling event.[19]



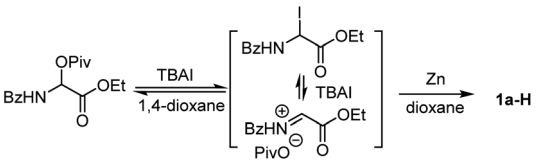
(2)

Exposure of **1a** to TABI and/or $MgCl_2$ 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 $MgCl_2$ was ineffective. It was noted that in the standard catalytic coupling reaction, **1a** went to completion within ~1 h (Fig. S1†).[19] 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(sp^2)-partners (eqn (4)). No deuterium incorporation into **1a-H** was detected when D_2O was added to eqn (3), implying that a radical process may take place in the reduction.



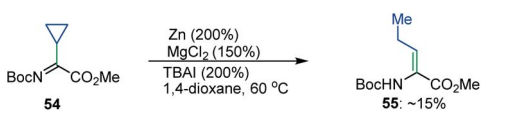
TBAI	$MgCl_2$	Zn	time	recovered **1a**	**1a-H**
100%	0%	0%	48 h	major	not applicable
100%	150%	0%	48 h	major	not applicable
0%	150%	200%	1 h	major	trace
100%	0%	200%	1 h	trace	major

(3)



(4)

(2) Formation of an α-glycinyl carbon radical intermediate. More importantly, α-cylcopropyl imine **54** resulted in the radical ring-opening product **55** under Zn/$MgCl_2$/TBAI conditions (eqn (5)). The catalytic reaction as in Table 1, entry 1 was completely inhibited upon introduction of 2 equiv. of TEMPO.[19] 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 $MgCl_2$-activated Zn, or L_n–Ni^I (eqn (6)).[22–24] The L_n–Ni^I species can be generated from reduction of L_n–Ni^{II} by Zn or from the reductive elimination of a Gly–(L_n)Ni^{III}–Ar intermediate (Scheme 1c).



(5)

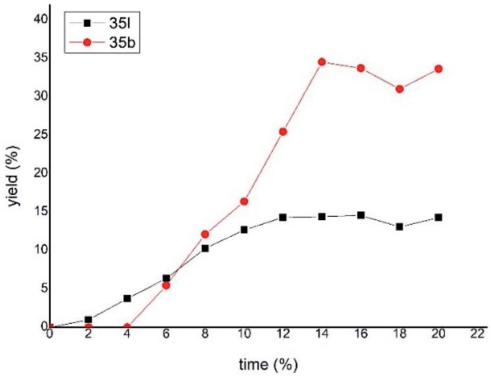
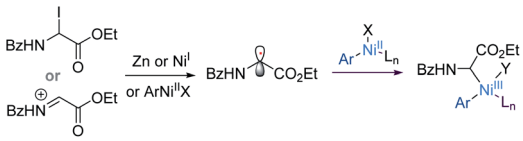
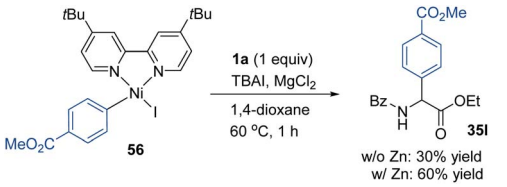


Fig. 3 The reaction profile for the formation of **35l** and **35b** in eqn (8) in the presence of Zn. Yield based on 1 equiv. of **1a**.

(3) Addition of the α-glycinyl carbon radical to ArNi(0) *vs.* ArNi(II). According to a well-established radical-chain mechanism, the putative Gly radical could be trapped by an Ar–Ni(II) species (eqn (6) and Scheme S4†).[24] Thus, we performed stoichiometric reactions of the Ar^1–Ni^{II} complex **56** with **1a** with and without Zn (eqn (7)).[19,25] The reactions resulted in **35l** in 30% and 60% yields, respectively, suggesting that C(sp^2)–Ni^{II} complexes might engage in the coupling event.[24] However, in a deliberately designed competition reaction of **1a** with an equimolar mixture of **55** and ethyl bromobenzoate (Ar^2Br), **35b** was formed in preference to **35l** (2.3 : 1) (eqn (8)). Without Ni/**L1**, **35b** remained the dominant product when Zn was used. The preferential formation of **35b** should not be directed by addition of a Gly radical to the *in situ* formed Ar^2–Ni(II), which would instead give **35I** as the major product. Thus, a competing process that bypasses the aryl–Ni^{II} species may occur and be more favored. This idea was further confirmed by the reaction profiles shown in Fig. 3. The formation of **35b** becomes much faster than that of **35l** after an induction period, during which Ni(0) species is presumably generated.[26] Likewise, the reaction cannot be dictated by Ar–Ni(I) that is most likely generated from single electron reduction of Ar–Ni(II).[27,28] This would again warrant **35I** as the major product, which opposes the observation in eqn (8).



(6)



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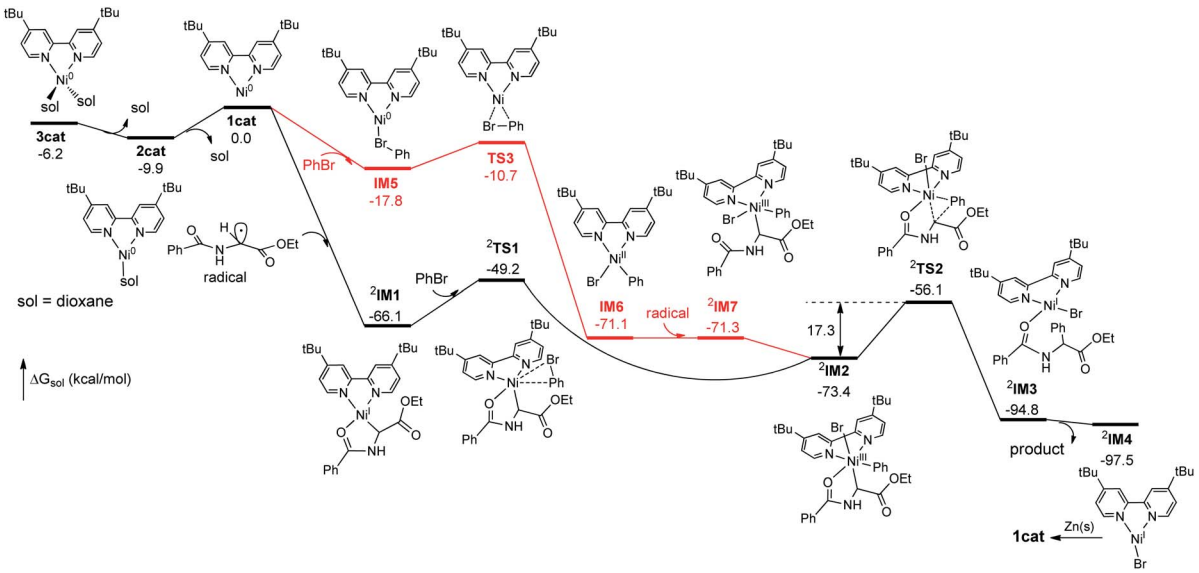
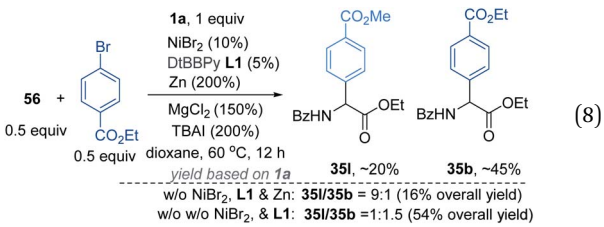


Fig. 4 Free energy profile comparing the favored $Ni^0 \rightarrow Ni^I \rightarrow Ni^{III} \rightarrow Ni^I$ pathway (black) and the $Ni^0 \rightarrow Ni^{II} \rightarrow Ni^{III} \rightarrow Ni^I$ pathway (red) with upper left superscripts indicating the spin states of open-shell, paramagnetic species.



(8)

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.[29] 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†).[19] 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)–L_n 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 L_n–Ni(0) would be much less stable than complex **IM1** (Fig. 4).[19] 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(sp^2)-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(II). DFT calculations showed that addition of the glycinyl carbon radical to L_n–Ni^0 to give L_n–Ni^I–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.

Acknowledgements

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Notes and references

1 For reviews on cross-electrophile couplings, see: (*a*) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini and A. J. Wangelin, *Chem.–Eur. J.*, 2014, **20**, 6828–6842; (*b*) T. Moragas, A. Correa and R. Martin, *Chem.–Eur. J.*, 2014, **20**, 8242–8252; (*c*) D. J. Weix, *Acc.*

Chem. Res., 2015, **48**, 1767–1775; 43–72; (*d*) J. Gu, X. Wang, W. Xue and H. Gong, *Org. Chem. Front.*, 2015, **3**, 1411–1421; (*e*) J. Liu, Y. Ye, J. L. Sessler and H. Gong, *Acc. Chem. Res.*, 2020, **53**, 1833–1845.

2 The involvement of glycine α-carbon radicals has also been proposed in the recent photo-induced or oxidative C–H bond radical fragmentation of glycine derivatives, wherein electron-rich substituents on the amino moieties are curial, see: comment: The generation and utility of glycine α-carbon radicals have also been proposed in the recent photo-induced or oxidative dehydride of the C–H bonds of glycine derivatives, wherein electron-rich substituents on the amine are crucial, see: (*a*) C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 15841–15846; (*b*) Y. Matsumoto, J. Sawamura, Y. Murata, T. Nishikata, R. Yazaki and T. Ohshima, *J. Am. Chem. Soc.*, 2020, **142**, 8498–8505.

3 For a Petasis borono–Mannich reaction, see: (*a*) Z. He and A. K. Yudin, *J. Am. Chem. Soc.*, 2011, **133**, 13770–13773; for a Rh-catalyzed hydrogen-mediated reductive coupling of conjugated alkynes with ethyl (*N*-sulfinyl)iminoacetates, see: (*b*) J.-R. Kong, C.-W. Cho and M. J. Krische, *J. Am. Chem. Soc.*, 2005, **127**, 11269–11276.

4 For an example of addition of alkyl radicals to sulfinyl iminoesters, see: (*a*) S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K.-S. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin and P. S. Baran, *Angew. Chem., Int. Ed.*, 2018, **57**, 14560–14565; for an example of addition of alkyl radicals to imines, see: (*b*) J. Yi, S. O. Badir, R. Alam and G. A. Molander, *Org. Lett.*, 2019, **21**, 4853–4858.

5 For a selected review on protein engineering, see: K. Lang and J. W. Chin, *Chem. Rev.*, 2014, **114**, 4764–4806.

6 R. Liu and G. A. Hudalla, *Molecules*, 2019, **24**, 1450.

7 (*a*) Y. Mehellou, H. S. Rattan and J. Balzarini, *J. Med. Chem.*, 2018, **61**, 2211–2226; (*b*) A. A. Vinogradov, Y. Yin and H. Suga, *J. Am. Chem. Soc.*, 2019, **141**, 4167–4181.

8 F. Mori, A. Cianferoni, S. Barni, N. Pucci, M. E. Rossi and E. Novembre, *J. Allergy Clin. Immunol.*, 2015, **3**, 375–380.

9 H. Morishima, J. Yoshizawa, R. Ushijima, T. Takeuchi and H. Umezawa, *J. Antibiot.*, 1982, **35**, 1500–1506.

10 Radiosumin: H. Noguchi, T. Aoyama and T. Shioiri, *Tetrahedron Lett.*, 1997, **38**, 2883–2886.

11 U. Sahm, G. Knobloch and F. Wagner, *J. Antibiot.*, 1973, **26**, 389–390.

12 M. Timmermans, T. Randoux, D. Daloze, J. C. Braekman, J. M. Pasteels and L. Lesage, *Biochem. Syst. Ecol.*, 1992, **20**, 343–349.

13 For bioactive alpha-styryl aminoacids, see: S. J. Friedman, D. E. Frankhouser, R. A. MacDonald and G. D. Street, *US Pat.*, 4346110, 1982.

14 (*a*) N. Sakai, H. Hori, Y. Yoshida, T. Konakahara and Y. Ogiwara, *Tetrahedron*, 2015, **71**, 4722–4729; (*b*) N. Sakai, J. Asano, Y. Kawada and T. Konakahara, *Eur. J. Org. Chem.*, 2009, 917–922; (*c*) R. Frauenlob, C. García, G. A. Bradshaw, H. M. Burke and E. Bergin, *J. Org. Chem.*, 2012, **77**, 4445–4449; (*d*) M. A. Beenen, D. J. Weix and J. A. Ellman, *J. Am. Chem. Soc.*, 2006, **128**, 6304–6305; (*e*) C. Haurena, E. Le Gall, S. Sengmany, T. Martens and M. Troupel, *J. Org. Chem.*, 2010, **75**, 2645–2650.

15 Friedel–Crafts: (*a*) C. F. Bigge, J. T. Drummond, G. Johnson, T. Malone, A. W. Probert Jr, F. W. Marcoux, L. L. Coughenour and L. J. Brahce, *J. Med. Chem.*, 1989, **32**, 1580–1590; (*b*) J. Halli and G. Manolikakes, *Eur. J. Org. Chem.*, 2013, 7471–7475.

16 (*a*) G. Dyker, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1700–1702; Petasis borono–Mannich reactions are known as three-component reactions of amine, glyoxylic acid and organoboron reagents wherein coordination of the carboxylate group and boron is key: (*b*) N. R. Candeias, F. Montalbano, P. M. S. D. Cal and P. M. P. Gois, *Chem. Rev.*, 2010, **110**, 6169–6193.

17 (*a*) Z. He and A. K. Yudin, *J. Am. Chem. Soc.*, 2011, **133**, 13770–13773; (*b*) J.-R. Kong, C.-W. Cho and M. J. Krische, *J. Am. Chem. Soc.*, 2005, **127**, 11269–11276.

18 (*a*) H. Huo, B. J. Gorsline and G. C. Fu, *Science*, 2020, **367**, 559–564; (*b*) X. Wei, W. Shu, A. García-Domínguez, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2020, **142**, 13515–13522.

19 See the ESI for details.†

20 The coupling of pure (*Z*)-**2a** with **1a** under the standard reaction conditions led to a trace amount of **3a** along with dimerization and a substantial amount of unknown products that may arise from oligomerization of styrene *via* hydrodebromination of (*Z*)-**2a**, suggesting that (*Z*)-vinyl bromides are not suitable for the coupling event.

21 For examples of coupling of activated benzyl C–OPiv *via* oxidative addition to Ni(0), see: (*a*) Q. Zhou, H. D. Srinivas, S. Dasgupta and M. P. Watson, *J. Am. Chem. Soc.*, 2013, **135**, 3307–3310; (*b*) E. J. Tollefson, L. E. Hanna and E. R. Jarvo, *Acc. Chem. Res.*, 2015, **48**, 2344–2353.

22 Our previous studies indicate that the necessity of $MgCl_2$ in the catalytic process was attributed to activating Zn and generating a more stable Ni–Cl bond by halide exchange.

23 The redox potentials of the 2,2′:6′,2″-terpyridine–Ni(I)–Me complex (−1.32 V) and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine–Ni(I)–Me (−1.44 V) have been reported (both *vs*. Ag/Ag^+ in THF solution): (*a*) G. D. Jones, C. McFarland, T. J. Anderson and D. A. Vicic, *Chem. Commun.*, 2005, 4211–4213; for additional discussion of a discrete **L1**–Ni(I) complex that can react with Ph_3CCl *via* an outer-sphere halide abstraction process to afford Ph_3C radical, see: (*b*) M. M. Beromi, G. W. Brudvig, N. Hazari, H. M. C. Lant and B. Q. Mercado, *Angew. Chem., Int. Ed.*, 2019, **58**, 6094–6098.

24 Other than by Ni(I), abstraction of halides by ArNi(II)X to generate an alkyl radical is possible. S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, 2013, **135**, 16192–16197.

25 For details of the reaction profile including formation of Ar^1I in the presence of Zn, see Schemes S1 and S2 and the discussions in the ESI.†

26 Reduction of Ni(II) to L_n–Ni(0) by Zn can be significantly accelerated by $MgCl_2$: (*a*) S. Ni, N. M. Padial, C. Kingston,

J. C. Vantourout, P. S. Baran, *et al.*, *J. Am. Chem. Soc.*, 2019, **141**, 6726–6739; (*b*) C. Zhao, X. Jiao, X. Wang and H. Gong, *J. Am. Chem. Soc.*, 2014, **136**, 17645–17651.

27 In the Ni-catalyzed reductive coupling of aryl halides with imines, addition of aryl–Ni^{I} to an imine was proposed by Doyle. The radical nature of the alkyl group also led us to conclude that such a mechanism may not operate in the present amino acid forming process. C. Heinz, J. P. Lutz, E. M. Simmons, M. M. Miller, W. R. Ewing and A. G. Doyle, *J. Am. Chem. Soc.*, 2018, **140**, 2292–2300.

28 Generation of Ar–Ni(I) by single electron reduction of Ar–Ni(II) has been reported, see: Q. Lin and T. Diao, Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes, *J. Am. Chem. Soc.*, 2019, **141**, 17937–17948.

29 O. Gutierrez, C. Tellis, J. D. N. Primer, G. A. Molander and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2015, **137**, 4896–4899.