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Taming the captodative glycyl radical for nickel-photocatalytic cross-coupling with alkyl chlorides

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The captodatively stabilized glycyl radical was engaged in nickel photocatalysed C(sp^3)–C(sp^3) cross-coupling to obtain non-canonical amino acids. DFT-guided optimization of the amine protecting groups allowed for radical destabilization and tuning of its SOMO–LUMO gap. Optimization and control experiments highlight a radical cross-coupling mechanism.

The glycyl radical is an important motif as the smallest fragment of amino acids and is frequently found in nature in glycyl radical enzymes.[1,2] Utilizing this small radical building block allows for the straightforward synthesis of non-canonical amino acids for various medicinal applications (Fig. 1A).[3–9]

Synthetically, common strategies use NHPh or NHPMP (*para*-methoxyphenyl) substitution at the N-terminus to generate the glycyl radical (Fig. 1B). Subsequently, the stable radical was applied in cycloaddition reactions with alkenes,[10–15] in dehydrogenative coupling reactions with *N*-alkyl amides,[16,17] in (intercepted) conjugate addition reactions,[18,19] in arylation with aryl nitriles followed by cyanide elimination,[20] in coupling reactions of imines (Schiff bases with benzophenone imine as the activating group),[21,22] or in alkylation reactions often in conjunction with peroxides.[23] To the best of our knowledge, only one example used an *N*-amide to convert the glycyl radical in the presence of iron(III) chloride as a catalyst and di-*tert*-butyl peroxide (DTBP) as an oxidant.[24] Simultaneously, so far, metal-catalysed cross-coupling reactions with glycyl radicals remain underdeveloped. We were wondering whether a designed glycyl radical would enable efficient cross-coupling reactions.

The challenge in glycyl radical formation and synthetic use lies in its captodative stabilization with adjacent electron-donating (blue, amine) and electron-withdrawing (red, acid) groups. For such captodative radicals, the electrophilicity (ω) of these radicals increases (*e.g.*, 1.47), making them ambiphilic, compared to common nucleophilic carbon-centred radicals (0.93, Fig. 1C).[25] The captodative effect is quantified by the degree of radical stability and its radical stabilization energy (RSE, ΔE).[26,27,45] Leroy[28] and Pasto[29,30] theoretically described the stabilization of disubstituted methyl radicals of CHXY-type, which was updated at a higher level of theory lately.[31] While the bond-dissociation energy (BDE) decreases for the captodatively stabilized glycine C–H bond, the respective RSE of the glycyl radical reaches theoretical values of up to 20 kcal mol^{-1}.

Using quantum mechanics, the perturbation energy (ΔE), gained or lost upon orbital overlap during a reaction, can

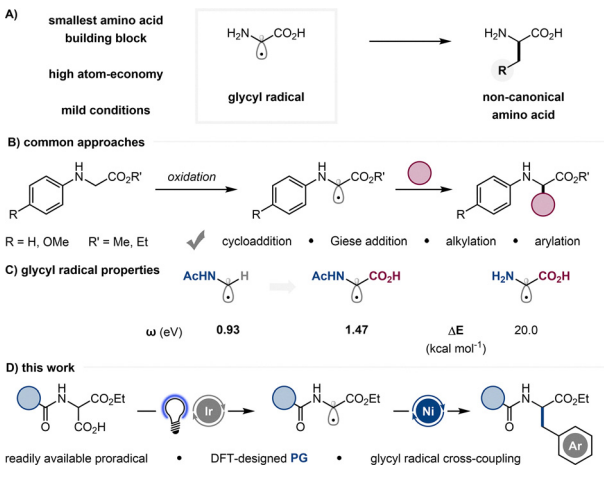

Fig. 1 The glycyl radical is an important motif to obtain non-canonical amino acids (A). Commonly, *N*-aryl derivatives are used (B) to overcome captodative stabilization (C), whereas we designed an *N*-amide for nickel photocatalytic cross-coupling (D).

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be determined using the Fukui–Klopman–Salem (FKS)[32–34] equation:

$$\Delta E = \left(-\sum_{a,b}(q_a + q_b)\beta_{ab}S_{ab}\right) + \left(\sum_{k<l}\frac{Q_k Q_l}{\varepsilon R_{kl}}\right) + \left(\sum_{r}^{\text{occ}}\sum_{s}^{\text{unocc}} - \sum_{s}^{\text{occ}}\sum_{r}^{\text{unocc}}\frac{2(\Sigma_{ab}c_{ra}c_{sb}\beta_{ab})^2}{E_r - E_s}\right),$$

consisting of an electronic term (first), a solvation term (middle), and a frontier orbital overlap or energy gap term (last). The application of the FKS equation to a radical process is mainly controlled by frontier orbital interactions and the charge term takes a secondary role. Therefore, the equation can be simplified by grouping the first endoergic term and the second Coulombic term (ΔE_a). The required frontier orbitals (FOs) determining the reactivity with transition metals are the HOMO, the LUMO and the SOMO of the radical. The value of the energy gap between both frontier orbital processes (SOMO–LUMO or SOMO–HOMO) will determine which of them is the most important and determines the reaction pathway (*vide infra*). As an approximation, the Fukui–Klopman–Salem equation can be simplified as:

$$\Delta E = \Delta E_a + \Delta E_{\text{SOMO-FO}},$$

with a major contribution arising from the frontier orbital gap of the glycyl radical and the respective metal catalyst ($\Delta E_{\text{SOMO-FO}}$). In this study, we hypothesize that this energy gap can serve as a predictive tool to estimate the reactivity of (i) glycyl radicals themselves and their electrophilicity[25] and (ii) in catalytic transformations toward radical cross-coupling reactions.

Given our recent interest in the synthesis of non-canonical amino acids,[35] we became curious whether the stable glycyl radical can be applied in nickel photoredox catalysis to obtain such amino acids (Fig. 1D). While nickel complexes are known to engage with alkyl halides in an outer-sphere reaction,[36,37] we indeed observed catalytic behaviour by cyclic voltammetry (CV, see Section S7, SI). No cross-coupling with photochemically generated glycyl radical **1a** was observed. Drawing inspiration from photochemical nickel-catalysed cross-coupling,[38,39] we hypothesized that *N*-Boc amino malonate mono-ethyl ester (**2a**), as a proradical, can be oxidized using an excited state iridium(III) photocatalyst, reducing the photocatalyst and upon liberation of CO_2 yielding the stable glycyl radical **1a**, which may be stabilized by charge disproportionation to **1a′** (Fig. 2A). In the presence of a base, an H-shift is plausible yet yielding the decarboxylated glycine **3a** as a byproduct. Since intermediate **1a′** is proposed to be stabilized by polar solvents, we screened various solvents and bases and saw significant amounts of glycine **3a** (see Section S2, SI). Ultimately, acetonitrile and sodium carbonate appeared to be the most suitable combination, despite the fact that such a polar solvent may interfere with the undesired pathway. Next, an *in situ* generated low-valent nickel(0) catalyst can undergo oxidative addition with various electrophiles **4**. Subsequently, the stable glycyl radical **1a** adds to Ni(II), generating a high-valent Ni(III) prone to reductive elimination to generate the non-canonical amino acid cross-coupling product **5**. We observed that weak electrophiles like aryl or benzyl bromides ($\mathbf{4_{PhBr}}$ and $\mathbf{4_{BnBr}}$) give the desired product only in traces (Fig. 2A, box). Gratifyingly, benzyl chlorides $\mathbf{4_{BnCl}}$ gave the desired C(sp^3)–C(sp^3) coupled product in 13% yield. However, benzyl mesylates $\mathbf{4_{BnOMs}}$, which are often similar in reactivity, gave no product. Therefore, we chose to investigate the cross-coupling reaction with benzyl chlorides. The two catalytic cycles are turned over by simultaneous reduction of Ni(I) and oxidation of Ir(II). Such C(sp^3)–C(sp^3) cross-coupling reactions are scarce and were only realized in the last decade.[40] Based on the intrinsic radical stabilization of the glycyl radical, we hypothesized that variations of the amine protecting group will adjust the desired reactivity by lowering its LUMO energy. A lower SOMO–LUMO gap of the glycyl radical should allow for higher reactivity and better orbital overlap in the later Ni(III) complex formed after radical addition. We screened variations at both the C- and

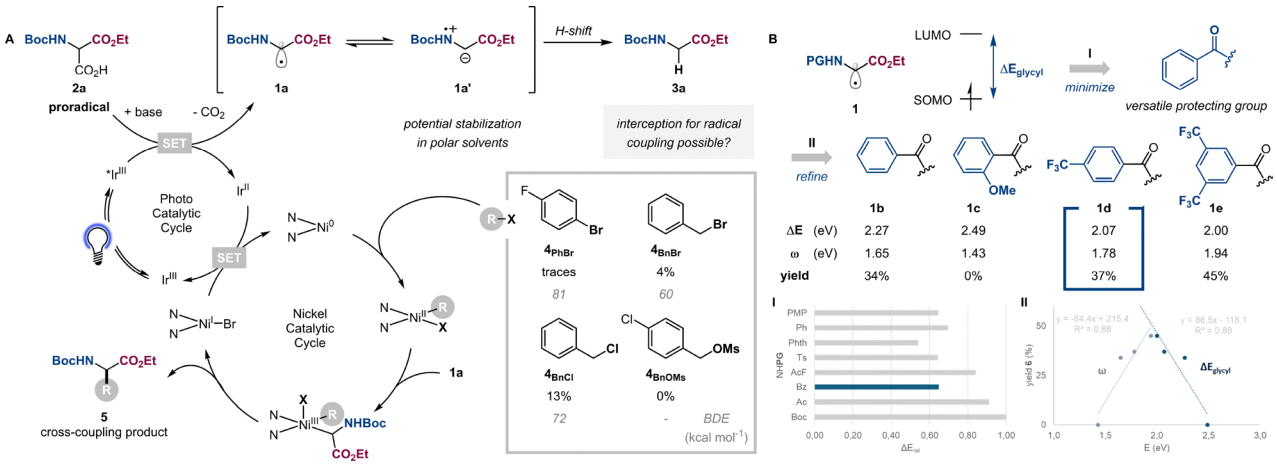


Fig. 2 Captodative stabilization can lead to an H-shift and limit cross-coupling efficiency of proradical substrates (**2**) in nickel photocatalytic reactions (A). Benzyl chlorides proved compatible in cross-coupling. Density-functional theory (DFT) calculations (BP86 D3 def2-TZVP level of theory) guided the way for benzoate (Bz) protecting groups for efficient cross-coupling (B). The type (I) and the substitution pattern of the protecting group were assessed (II).

N-terminus of the glycyl radical by DFT calculations (see Section S3, SI). Hence, only *N*-phenyl benzamide at the C-terminus proved effective in significantly lowering the SOMO–LUMO gap, which was observed recently.[41] Likewise, we investigated common amide and carbamate protecting groups by DFT calculations and observed that the Boc group exhibits the largest SOMO–LUMO gap (ΔE_{glycyl}), hence is likely the most stable and least reactive radical. Upon lowering the energy gap, benzoyl and phthalimide proved most effective, similar to tosylates, while *N*-phenyl and trifluoroacetates gave large energy gaps (Fig. 2B-I). Moving forward, we decided to use benzoates (Bz) to destabilize the glycyl radical and decrease its SOMO–LUMO gap, since variations will be synthetically easy, based on the broad commercial availability of benzoic acids. In another round of DFT optimization, we investigated the effect of electronic and steric properties of various benzoyl amides on the SOMO–LUMO gap (Fig. 2B–II and Section S3, SI). Electron-deficient benzamides were more effective in lowering the energy gap, while simultaneously giving more electrophilic radicals. Unfortunately, some of the promising benzamide derivatives turned out to be synthetically inaccessible (see the SI). We were pleased to see an inverse linear correlation between the yield of product **6** and ΔE_{glycyl} and ω (Fig. 2B–II, bottom right). The cross-coupling efficiency increases with a higher electrophilicity ω and decreases with a lower SOMO–LUMO gap (*vide infra*). Finally, we chose 4-trifluoromethyl benzoate ($BzCF_3$) as an ideal compromise between electronic effects, synthetic feasibility, and molecular weight to generate destabilized glycyl radical **1d**.

With these insights in hand, we aimed to investigate the reactivity of such electrophilic radicals with nickel intermediates. To validate our initial assumption that changes in radical polarity effect the frontier orbital interactions between the glycyl radical and nickel(II) intermediates, we calculated the SOMO energies for **1a** (Boc) and **1d** ($BzCF_3$) and compared them with the HOMO and LUMO energies of the respective nickel(II) oxidative addition complexes as well as the final nickel(III) intermediates (see Section S3, SI). Besides the mentioned smaller ΔE_{glycyl} for **1d**, the major observation is the lowering of the SOMO level of the nickel(III) intermediate (Fig. 3A, arrow).[42,43] Following the possible orbital interactions between **1** and Ni(II), we determined the possible scenarios of $\Delta E_{SOMO-LUMO}$ or $\Delta E_{SOMO-HOMO}$ based on the FKS equation (for details, see Section S3, SI).[44]

Generally, lower values were obtained for $\Delta E_{SOMO-LUMO}$ interactions, suggesting them as the major frontier orbital interactions. For **1a** and **1d**, the $\Delta E_{SOMO-LUMO}$ energy gap decreased from 12.6 to 5.2 kcal mol^{-1} (Fig. 3B). Similarly, benzyl bromides give significantly lower yields and the $\Delta E_{SOMO-LUMO}$ energy gap increases from 2.9 to 5.1 kcal mol^{-1}. Although the origin of this discrepancy remains unclear, a SOMO–LUMO gap in the range of 5 kcal mol^{-1} seems to provide effective cross-coupling reactivity. In the future, more in-depth investigations will show whether such a model allows for a better and more general prediction of the reactivity of captodatively stabilized radicals in metal-catalysed reactions.

Finally, with DFT-guided radical reactivity in hand, we aimed to develop a synthetic method harnessing the intrinsically stable glycyl radical in the $C(sp^3)$–$C(sp^3)$ cross-coupling

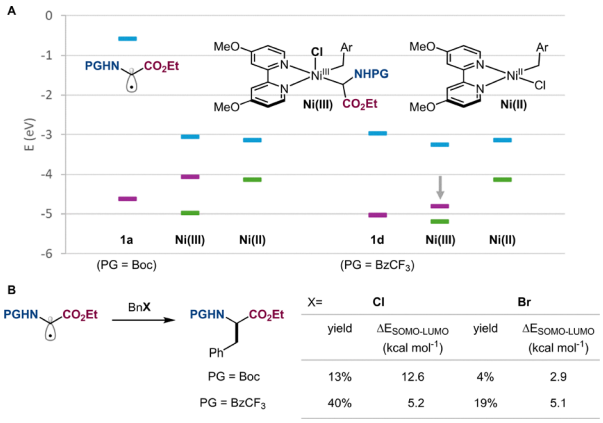
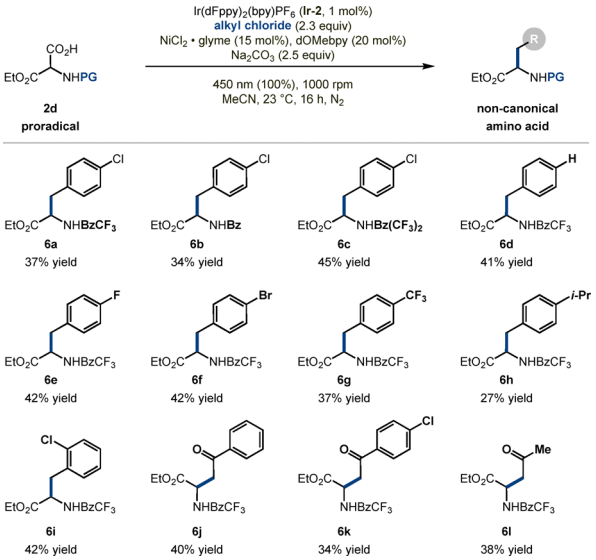


Fig. 3 Comparison of the HOMO (green), SOMO (purple), and LUMO (blue) energies for **1a** and **1d**, the oxidative addition complex (dOMebpy)-Ni(Cl)(4-Cl-Bn) (Ni(II)), and their respective Ni(III) intermediates after radical trapping (A). Energies obtained from DFT calculations (UKS BP86 D3 def2-TZVP level of theory). Correlation between benzyl halide and the amine protecting group with regard to the yield of the cross-coupling product and the SOMO–LUMO energy gap as obtained from the FKS equation ($\Delta E_{SOMO-LUMO}$, B).

reaction with nickel photoredox catalysis. With *N*-$BzCF_3$-protected amino malonate mono-ethyl ester (**2d**), which was obtained in two steps from commercial diethyl amino malonate hydrochloride, and 4-chloro benzyl chloride (**4a**), we optimized the reaction procedure to obtain the phenylalanine derivative **6a** (see Section S2, SI). Again, MeCN and Na_2CO_3 turned out to be superior as a solvent and a base compared to DMF and THF, as well as NaOH or K_2CO_3, resulting in 45% ^{1}H NMR yield against the internal standard. When the common photocatalyst $Ir(dF(CF_3)ppy)_2$-(dtbbpy)PF_6 was exchanged for 4CzIPN or $Ir(dFppy)_2(bpy)PF_6$, the latter gave another boost in reactivity (see the SI for other PC). 4,4′-Dimethoxy 2,2′-bipyridine (dOMebpy) gave higher yields than regular bpy and among the organic bases tested, only 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (DTP) gave reasonable conversion (see the SI for more ligands and bases). With optimized conditions, the overall performance of the reaction could be increased fourfold from the initial 14% to more than 58% yield. Furthermore, we questioned whether tertiary radicals would engage in the cross-coupling reaction. With differently protected 2-methyl amino malonates in hand, we applied the optimized conditions, but only obtained low yields <10% (see Section S4, SI). In order to verify the involved glycyl radical under optimized conditions, we performed control experiments and the reaction only operates when all components, like light, photocatalyst, nickel catalyst, and base, are present (see Section S6, SI). Radical trapping experiments with TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl), electron-rich and -deficient olefins, and electrophiles confirmed that productive radical cross-coupling is diminished or inhibited. A nucleophilic substitution of carbanions of **1a**′-type intermediates with benzyl chlorides or electrophiles cannot be ruled out at this point, but is unlikely to be the predominant reaction pathway.

With the optimized conditions in hand, we investigated the scope of suitable benzyl chlorides under optimized conditions.



Scheme 1 Scope of products obtained from the cross-coupling of the glycyl radical and activated chlorides. Isolated yields are shown.

Benzoyl (**6b**) and *meta*,*meta*-bis-CF_3 benzoyl protected amino malonate (**6c**) gave the cross-coupling product in similar yields compared to the optimized product **6a** (Scheme 1). Benzyl chloride (**6d**) and *para*-substituted benzyl chlorides were compatible under these conditions. 4-Fluoro (**6e**), 4-bromo (**6f**), 4-trifluoromethyl (**6g**), and 4-iso-propyl (**6h**) phenylalanines were obtained in good yields of up to 42%, given the overall challenging reaction. 2-Chlorobenzyl chloride gave product **6i** in 42% isolated yield. To our surprise, the reaction was very sensitive to benzyl chlorides with different electronic or steric demands (see Section S5, SI). Unfortunately, both electron-rich (*e.g.*, naphthyl, *para*- or *ortho*-methoxyphenyl) and electron-poor benzyl chlorides (*e.g.*, *para*-nitrophenyl, pyridyl) proved incompatible. As expected, benzyl bromides and aliphatic chlorides were not suitable or gave low yields according to ^{1}H NMR spectroscopic and LCMS analyses, respectively. Gratifyingly, α-chloro carbonyl compounds gave synthetically useful yields. While α-chloro esters or nitriles gave low yields, α-chloro ketones could be coupled and γ-oxo homophenylalanine **6j** and **6k** were obtained in 40% and 34% yields, respectively. Finally, amino acid **6l** was isolated in 38% yield from α-chloro acetone.

In conclusion, we have developed a new benzamide protecting group strategy, which allows us to tune the SOMO–LUMO gap, destabilize the radical, increase the electrophilicity, and thus engage captodative glycyl radicals in nickel photoredox cross-coupling reactions. Aminomalonate monoesters are readily available starting materials but suffer from background proto-decarboxylation. Nonetheless, we could develop reaction conditions that can outperform the deleterious reactivity and allow effective C(sp^3)–C(sp^3) cross-coupling reactions toward non-canonical amino acids in moderate isolated yields. This development will further spark our efforts in developing strategies to obtain non-canonical amino acids and will assist the community in establishing new radical reactivity concepts, starting from affecting intrinsic stabilization.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data for this article, including CV data and DFT (ORCA) input and output files, as well as NMR spectra and HRMS data, are available at Edmond at https://doi.org/10.17617/3.DPOBYI.

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6cc02549h.

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