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RESEARCH ARTICLE

Selective 1,2-Aryl-aminoalkylation of Alkenes Enabled by Metallaphotoredox Catalysis

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Abstract: A highly chemo- and regioselective intermolecular 1,2-aryl-aminoalkylation of alkenes by photoredox/nickel dual catalysis is described here. This three-component conjunctive cross-coupling is highlighted by its first application of primary alkyl radicals, which are not compatible in previous reports. The readily prepared *α*-silyl amines could be transferred to *α*-amino radicals by photo-induced single electron transfer step. The radical addition/cross-coupling cascade reaction proceeds under mild, base-free and redox-neutral conditions with good functional group tolerance, and importantly, provides an efficient and concise method for the synthesis of structurally valuable *α*-aryl substituted *γ*-amino acid derivatives motifs.

Introduction

α-Aryl substituted *γ*-amino acid derivatives are unique structural motifs with important biologically actives in antagonists and pharmaceutical compounds, such as neurokinin 3 receptor (NK3) antagonist **I**, HIV-1 therapeutic agent chemokine receptor CCR5 antagonist **II**, antihyperalgesic agent mu receptor agonist Loperamide **III** as well as antiarrhythmic agent Disobutamide **IV**, and so on (**Figure 1**).[1] The traditional synthetic procedures [1c, 1d, 2] for *α*-aryl substituted *γ*-amino acid derivatives relied on multiple synthetic steps and the usage of either strong oxidants or reductants or highly reactive organometallic reagents, which suffered from relatively narrow functional group compatibility and low atom and step economy. Thus, developing more efficient and concise protocols towards to them are of high interest.

From readily simple feedstock chemicals to rapidly buildup structurally complex and valuable molecules with high atom-, step- and redox-economy is a longstanding topic in organic synthesis. Among which, three-component conjunctive cross-coupling of olefins provides a straightforward way to achieve this goal by simultaneous formation of two C–C bonds in a single step from easily accessible olefins. [3] Classically, transition metal catalysis especially with palladium or nickel-catalyzed conjunctive cross-coupling of alkenes with a C-nucleophilie and a C-electrophilie via either two-electron [4] or single-electron [5] transfer displays a powerful strategy in this context (**Scheme 1-a**). Nevertheless, these protocols rely heavily on the use of stoichiometric organometallic reagents, resulting sore for a variety of functional groups. Recently, reductive conjunctive cross-coupling [6] involving two C-electrophilies has been developed as an alternative method, which did not require any additional pre-

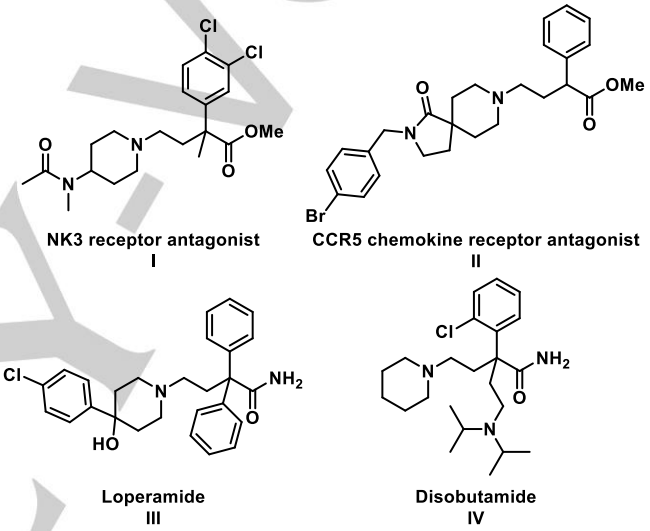

Figure 1. Representative biologically active compounds containing *α*-aryl substituted *γ*-amino acid derivative motifs.

functionalization of the substrates, thus, avoiding the use of organometallic reagents. However, these catalytic processes have to use stoichiometric amount of reductants such as Zn/Mn powder or organic amines to sustain the catalytic cycles. Therefore, further developing redox-neutral conjunctive cross-coupling of alkenes dealing with more general and mild C-nucleophilies, to broaden the substrate scope and enrich the structural diversity of the synthetic target molecules are highly valuable.

The merger of nickel and visible light photoredox catalysis [7] could enable common sp^3-hybridized C-nucleophilies instead of highly reactive organometallic reagents to participate the unprecedented C–C bond formations. [8] The excited state of visible light photocatalysts are potent single-electron oxidants, which can readily undergo reductive quenching via single-electron-transfer (SET) oxidation of various Csp^3-nucleophilies to the corresponding alkyl radicals. This novel synergistic catalytic strategy provides a powerful potential to explore three-component conjunctive cross-coupling of π-bond systems with sp^3-hybridized C-nucleophilies. In this aspect, Chu[9a], Nevado[9b], Molander[9c] and Aggarwal group[9d] have recently reported elegant examples of three-component conjunctive cross-coupling of alkenes with

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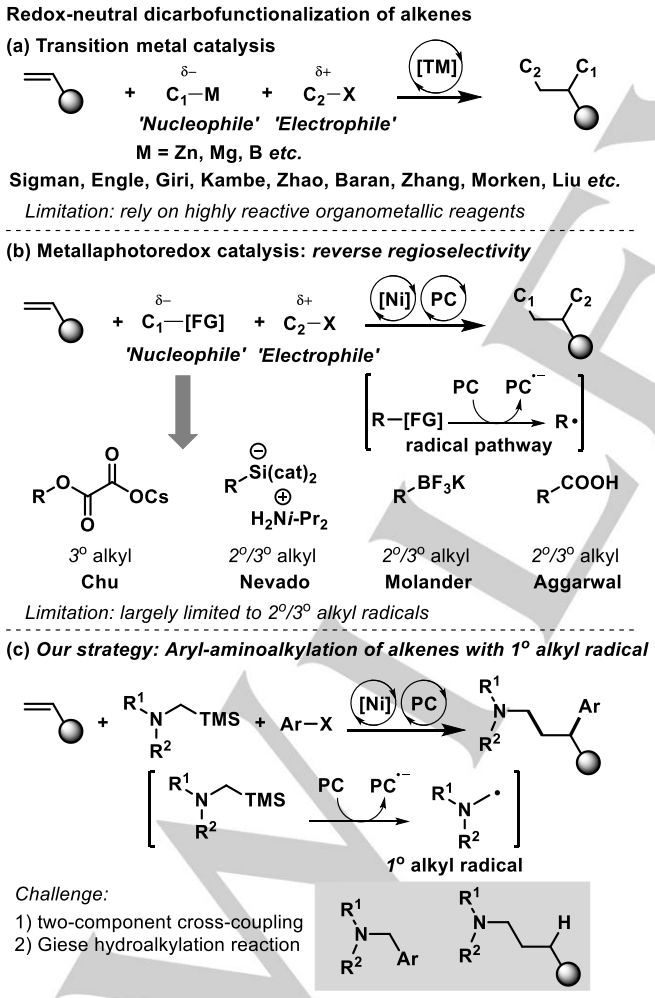
aryl halides and alkyl radical precursors, namely alkyl oxalate esters, silicates, trifluoroborates and carboxylic acids, respectively (**Scheme 1-b**). One distinct feature of this dual catalytic system is that the regioselectivity is completely reversed due to the initial step arising from radical addition of C-nucleophilie site, which is complementary to single metal catalyzed processes.[4h,5e] Disappointingly, the aforementioned catalytic systems are restricted to secondary and tertiary alkyl radicals, while primary alkyl radicals are not compatible due to the overwhelmingly competitive two-component cross-coupling.[8a-b,10] So far, the sole example with applying primary alkyl radical in conjunctive cross-coupling was reported recently by Aggarwal *et. al*, however, the yield was pretty low (11%). [9d] Thus, further endeavors to develop conjunctive cross-coupling reactions with new varieties of Csp^3-nucleophilies as alkyl radical precursors, especially primary alkyl radicals containing synthetic valuable functionalities will be highly desired. Herein, we described a practical three-component conjunctive cross-coupling of alkenes with primary alkyl radicals derived from *α*-silyl amines (**Scheme 1-c**). Indeed, this highly valuable *α*-amino radical[11] triggered cascade process paves a facile synthetic way for rapid constructing a fruitful library of *α*-aryl substituted *γ*-amino acid derivatives, which are highly important skeletons in pharmaceutically active molecules.

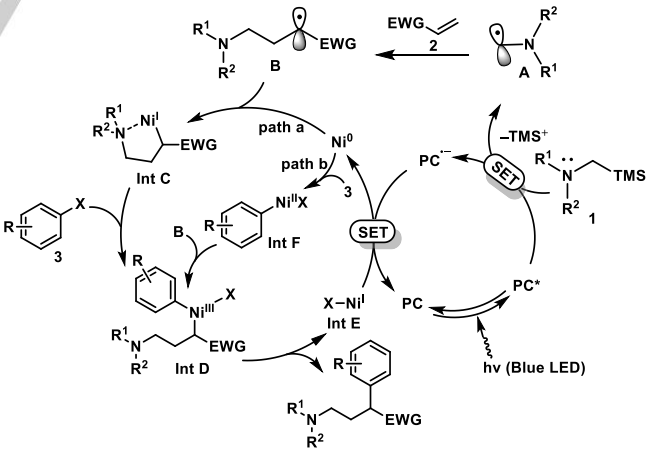


Scheme 1. State-of-the-art of redox-neutral difunctionalization of alkenes and our proposal for primary alkyl radical triggered three-component conjunctive cross-coupling with alkenes by metallaphotoredox catalysis.

A proposed catalytic cycle is depicted in **Scheme 2**. Since *α*-silyl amines have relatively low oxidative potentials (~0.4–0.8 V vs SCE in MeCN),[12] which would be facile oxidized by the excited state photocatalysts (PC*) to give primary *α*-amino radical **A**, radical **A** rapidly undergo Giese-type addition to generate radical **B**, which sequentially intercepted by Ni(0) to form alkyl-Ni(I) **Int C**, then go through oxidative addition with Ar–X to produce the key Ni(III) **Int D** (path a), followed by facile reductive elimination to get the conjunctive cross-coupled product and Ni(I) **int E**, Final SET between the reduced state of $PC^{\bullet-}$ and Ni(I) **int E** regenerates the ground-state PC as well as Ni(0) to complete both catalytic cycles. Alternatively, the Ni(III) **Int D** could also be formed by the recombination of radical **B** to Ni(II) **Int F** arising from the oxidative addition of Ar–X with Ni(0) (path b).[13]

This process has two major challenges: 1) compared with secondary or tertiary alkyl radicals, primary alkyl radicals are much less congested and thus, more reactive to participate the competitive two-component cross-coupling to delivery undesired byproduct **5**;[14] 2) the thermodynamically favorable SET between alkyl radical **B** ($E_{1/2}^{R\bullet/R^-} \approx -0.6$ V vs SCE in CH_3CN)[15] and the reduced state of $PC^{\bullet-}$ (the oxidative potential for commonly used $PC^{\bullet-}$ ranges from –0.8 to –2.2 V vs SCE in CH_3CN)[7a] facilitates undesired Giese-type hydroalkylation byproduct **6**.[16] Besides, protodehalogenation of aryl halide under metallaphotoredox conditions is another obstacle, [9d] which could not be neglected.

We envisioned that our proposed primary *α*-amino radical triggered conjunctive cross-coupling of alkenes has a high possibility to succeed based on the following hypotheses: 1) due to the perfect polarity-matching-effect, the rate of addition of the strong nucleophilic *α*-amino radical **A** to electron deficient alkene could be faster than addition of **A** to Ni-center, this is the key to avoid formation of the two-component cross-coupling byproduct **5**; 2) due to the highly electron-deficient property of radical **B**, the rate of addition of **B** to Ni-center could be faster than single electron reduction of **B** by the reduced state photocatalyst ($PC^{\bullet-}$) to suppress the competitive Giese-type reaction.



Scheme 2. Plausible mechanism.

Results and Discussion

Due to the advantages of low oxidative potentials, simple synthetic procedure [14] (by a single S_N2 reaction between amines and (chloromethyl)trimethylsilane) as well as tolerating a base-free condition with *α*-silyl amines, we chose 1-((trimethylsilyl)methyl)piperidine **1a** ($E_{1/2}$(**1a**$^{\bullet+}$/**1a**) = +0.71 V vs

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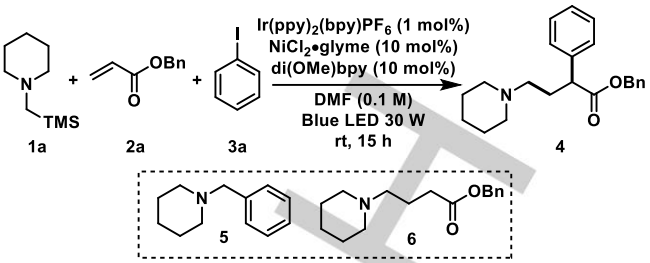
SCE in CH_3CN),[14] as the representative *α*-amino radical precursor, and commenced our study with the reaction of benzyl acrylate **2a** and iodobenzene **3a** (**Table 1**). After extensive optimizations,[17] we were pleased to find that using $Ir(ppy)_2bpyPF_6$ ($E_{1/2}^{*Ir(III)/Ir(II)}$ = +0.91 V vs SCE in CH_3CN) [18] as photocatalyst, $NiCl_2$•glyme combined with di(OMe)bpy as transition metal catalyst, the three-component reaction was conducted smoothly in DMF to get the desired product **4** with the best yield of 79% (entry 1), the byproducts **5** and **6** were detected as result of the competitive two-component cross-coupling and Giese hydroalkylation, respectively. Ligand screening shown that dtbbpy resulted in a comparable yield of **4**, whereas electron-deficient di(COOMe)bpy completely retarded the desired reaction (entries 2-3). To our delight, organo photocatalyst 4CzIPN could also be employed in lieu of Ir-complex and give a wider choice of photocatalysts selection (entry 4). The molar ratio between the three reaction components has a big effect on the outcomes: reducing the molar ratio of **1a** and **2a** to 1.5 equivalent lead a significantly decreased yield of **4**, and excess amount of **2a** and **3a** disfavored the conjunctive cross-coupling as well (entries 5-6). Decreasing the catalyst loading to 0.5 mol% could also get an acceptable yield (entry 7). Surprisingly, water was found to be well tolerated in such catalytic process, even with 0.5 mL of H_2O (v/v = 1/1) could still get 20% yield (see SI), this result provides a possibility to develop biomolecule-compatible neutral aqueous conditions for future biological applications (entry 8). Finally, a series of control experiments displayed that photocatalyst, nickel, ligand and light are all indispensable (entries 9-11).

Table 1. Selected optimization of the reaction conditions. [a]



Entry	Deviation from standard conditions	NMR yield (%)[b] 4	5	6
1	none	79	13	16
2	dtbbpy (10 mol%)	72	21	15
3	di(COOMe)bpy (10 mol%)	0	10	43
4	4CzIPN (2 mol%)	67	18	21
5	1a : 2a : 3a = 1.5 : 1.5 : 1	50	34	11
6	1a : 2a : 3a = 1 : 2 : 2	32	10	15
7	$Ir(ppy)_2(bpy)PF_6$ (0.5 mol%)	61	18	10
8	5.0 equiv H_2O was added	72	11	13
9	no Ni, no ligand	0	0	53
10	no photocatalyst	0	0	0
11	no light	0	0	0

[a] All reactions were carried out on 0.1 mmol scale, and the optimal ratio of **1a**:**2a**:**3a** = 2:2:1. [b] The yields were determined by crude ^{1}H NMR spectrum with 1,3,5-trimethylbenzene as an internal standard.

With a set of optimized conditions in hand, we started to evaluate the generality of this dual catalytic three-component reaction (**Table 2**). Both cyclic and acyclic *α*-silyl amines worked well to deliver the corresponding *α*-aryl substituted *γ*-amino acid esters in moderate to excellent yields. Especially, the substrates containing pharmaceutically relevant moieties such as piperidine, pyrrolidine, morpholine and piperazine, which are among the most frequent *N*-heterocyclic functions employed in drugs, were incorporated smoothly with decent yields (**4**, **7-10**). The reaction was not only limited to aliphatic *α*-silyl amines, but also be suitable for aromatic amines (**13-14**). *α*-Silyl secondary amine with a free NH group was not compatible (**15**), which made the reaction quite messy and only a little of radical precursor recovered (18% from crude ^{1}H NMR spectrum). Besides, less than 10% NMR yield of Michael addition product detected. We suggested that secondary amine might be able to form nitrogen radical intermediate via deprotonation instead of desilylation. [19] We were curious about the reactivity of *α*-amino radicals derived from amides as they are less nucleophilic, for this purpose, Boc-protected amine substrate was prepared and subjected to the reaction system, to our surprise, no reaction occurred and almost quantitative starting material recovered afterward (**16**). A rational explanation for this could be that the oxidative potential of carbamate (≈ +1.69 V) was outside of the reductive potential range of the excited-state of $Ir(ppy)_2(bpy)PF_6$ (+ 0.91 V), leading a failure in SET process to form *α*-amino radical properly. This might be the same reason why the products (the average oxidation potential was ~0.3 V higher than their *α*-silyl amine ancestors) were not further oxidized by the photocatalyst.

Subsequently, we began to explore the applicability of alkenes (**Table 2**, middle). Acrylates with different substituents were investigated and the results shown that the yield linearly decreased with the increasing of the steric hindrance of the ester group (**17-19**) (e.g. methyl, ethyl, *tert*-butyl). Prolonged reaction time did not promote the yield for sterically demanding substrate (e.g. **19**). There was no intramolecular cyclization product formed when using allyl acrylate as substrate (**20**), indicating that the rate of combination of electrophilic *α*-carbonyl radical with nickel species is much faster than the intramolecular radical addition cyclization. Acrylate with a distal *N*-hydroxyphthalimidyl group also proceeded smoothly to give **22** with highly enriched functionality. Those complex acrylates derived from natural product such as estrone and cholesterol (**23-24**) were well tolerated in the three-component conjunctive cross-coupling. It is noteworthy to mention that among these three examples, alkene was chosen as the limiting reagent (1.0 equiv.) to further demonstrate the potential of this methodology in late-stage modifications. Internal alkene reacted with significantly low yield, probably due to the steric hindrance effect, but in excellent diastereoselectivity (**21**). Besides of acrylates, acrylonitrile was an alternative good Giese acceptor, some representative *α*-silyl amines and aryl iodides were reacted with acrylonitrile smoothly, delivering the corresponding products (**25**–**30**) in good yields. The outcomes *α*-aryl-*γ*-amino substituted nitriles could be readily transferred to the highly valuable 1,4-diamines, which are ubiquitous moieties in important biologically active molecules. [20] To our delight, we further found that the more challenging *α*, *β*-unsaturated ketone and acrylamide substrate could also be compatible with this dual catalytic conjunctive cross-coupling. For instance, the reaction of pent-1-en-3-one was carried out smoothly to obtain **31** in moderate yield. The less electron-deficient acrylamide delivered the corresponding *γ*-amino amide product **32** in 26% yield, and the competitive two-component cross-coupling byproduct was obtained in 56% yield. However, vinyl sulfone could not delivery any desired product, instead, a huge amount of two-component cross-coupling byproduct obtained (67% NMR yield) and a trace amount of desulfonation

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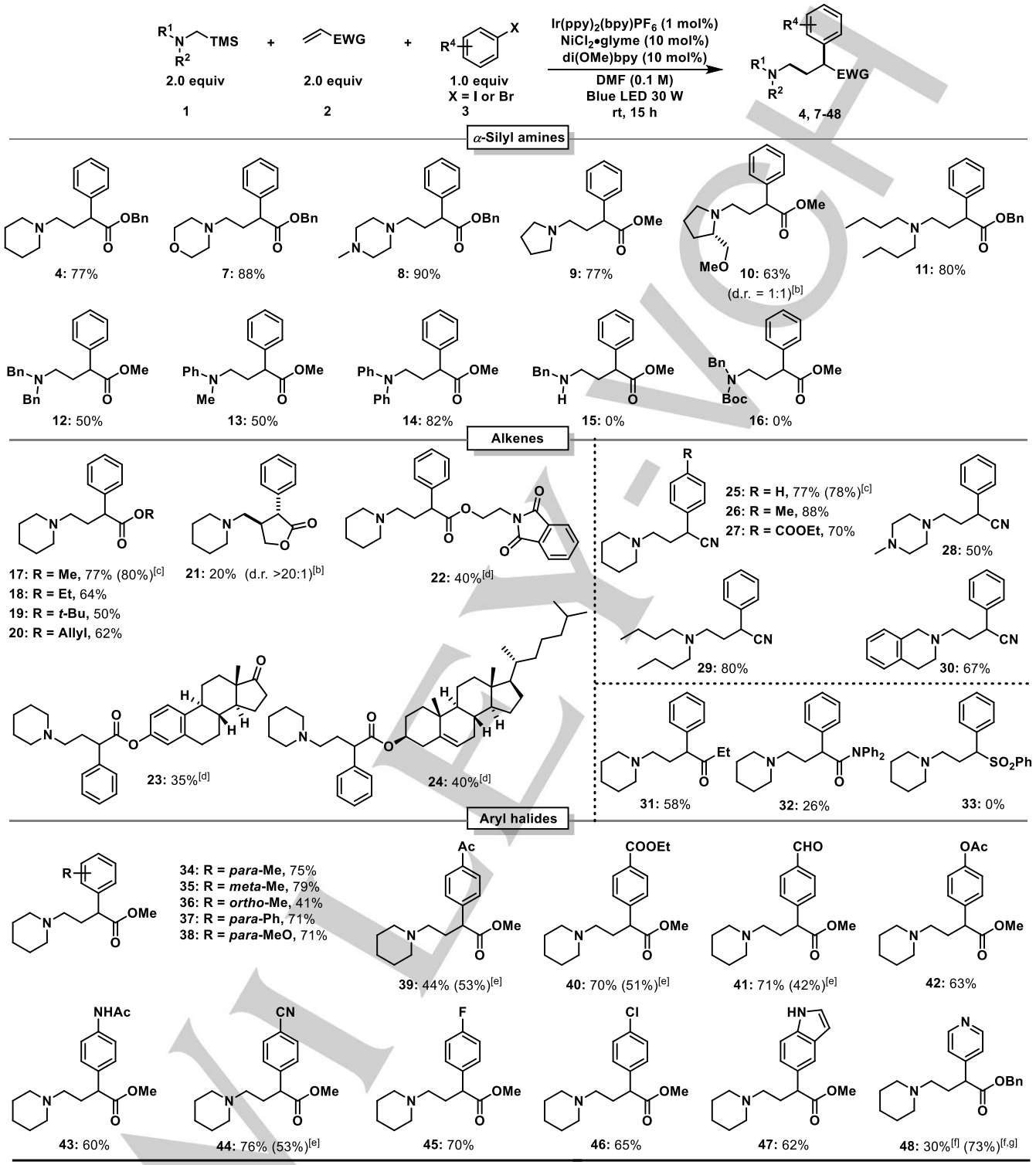
Table 2. Substrate scope of the dual photoredox/nickel-catalyzed three-component conjunctive cross-coupling reaction. [a]



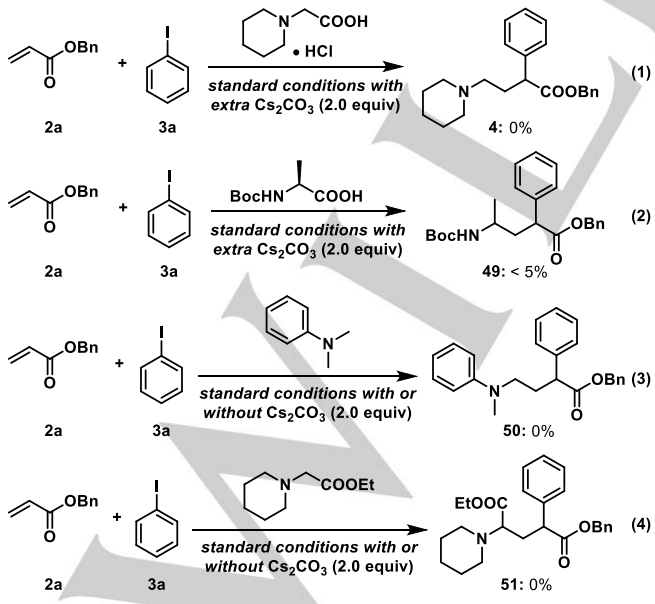
[a] Unless otherwise stated, all reactions were performed on a 0.3 mmol scale and the yields are isolated yields by column chromatography on silica gel. [b] The d.r. value was determined by the crude ^{1}H NMR spectrum analysis. [c] The reaction was scaled up to 5.0 mmol scale. [d] The condition of acrylate (0.3 mmol, 1.0 equiv), PhI (0.6 mmol, 2.0 equiv) and 1-((trimethylsilyl)methyl)piperidine (0.6 mmol, 2.0 equiv) was used. [e] Aryl bromide (1.0 equiv) was used. [f] ^{1}H NMR yield as **48** could not be isolated as its pure form. [g] 20 mol% of $NiCl_2$·glyme/diOMebpy was added.

allylic amine observed (less than 5%) (**33**). Further Attempts to utilize styrene, vinyl boronic ester as well as vinyl phosphate were failed (for more details, see SI). To further demonstrate the synthetic potential, the three-component reaction was scaled up to a gram scale (5.0 mmol), affording products **17** and **25** without diminished yield.

Finally, we turned our attentions to exploring the scope with respect to aryl iodides (**Table 2**, below). A wide range of both

electron-rich and electron-deficient substituted aryl iodides could be efficiently coupled to deliver the desired products in moderate to good yields. The reaction is sensitive to steric hindrance as *ortho*-methyl substituted iodobenzene resulted in a consistent decrease in yield (**34-36**). Aryl iodides incorporated with a variety of functional groups, including ketone, ester, aldehyde, acetyl protected hydroxyl and amino, nitrile, fluoride and chloride, were viable coupling partners under the standard conditions (**39-46**). In particular, heterocyclic iodides including unprotected indole and pyridine did also participate successfully in the three-component reaction (**47-48**). When using 4-iodopyridine as the substrate, 20 mol% of catalyst loading was necessary to ease the pyridine coordination possibility to nickel center. Furthermore, apart from aryl iodide, aryl bromide could also be suitable to perform the reaction, albeit with a relatively lower efficiency (**39-41, 44**). It should be noted that only a trace amount of protodehalogenation byproduct was detected in some individual cases (< 5%).

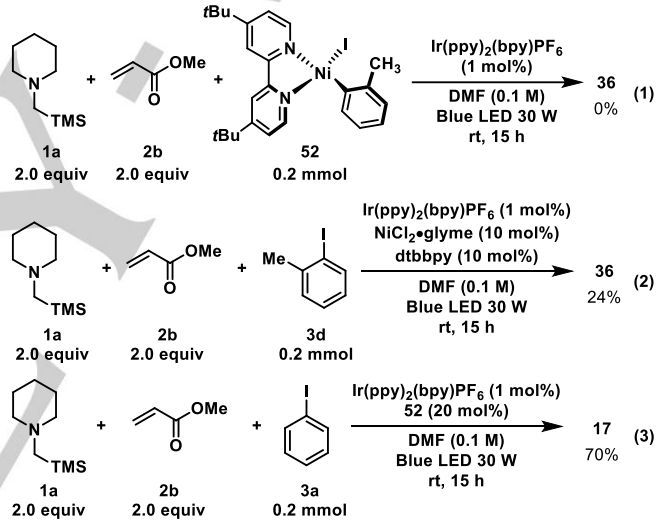
To demonstrate the unique effect of *α*-silyl amines in this three-component conjunctive cross-coupling, we further examined the reactivity of *α*-amino acid, tertiary amine and *α*-amino acid ester, which are commonly used as *α*-amino radical precursors. To our surprise, the reaction involving the exact same *α*-amino radical intermediate derived from 2-(piperidin-1-yl) acetic acid hydrochloride could not work at all, and the amino acid starting material was decomposed completely afterward. Furthermore, *N*-(*tert*-butoxycarbonyl)-L-alanine under the standard conditions could only afford a trace amount of the desired product **49** (less than 5% ^{1}H NMR yield), conversely, 40% yield of two-component coupling product and 35% yield of Giese hydroalkylation product were detected by the analysis of the crude ^{1}H NMR spectrum. This result is consistent with the finding reported by Aggarwal *et al*.[9d] On the other hand, *N*, *N*-dimethylaniline and *α*-amino acid ester could not give any desired product **50** or **51**, in both cases, most amine starting material recovered, and only 15% ^{1}H NMR yield of the Giese hydroalkylation product was detected with *N*, *N*-dimethylaniline as radical precursor (**Scheme 3**). The inert reactivity of less



Scheme 3. Control experiments of other *α*-amino radical precursors for this three-component conjunctive cross-coupling.

nucleophilic *α*-amino radical was further confirmed by the reaction of carbamate and ester substrate in Scheme 3-2 and 3-4 (compared with **16** in Table 2). Those control experiments demonstrated that the subtle characters of *α*-silyl amines as *α*-amino radical precursors for this three-component conjunctive cross-coupling.

To gain more insight into the mechanism, we synthesized the ligated Ar–Ni^{II}–I complex **52**[21] and found that the stoichiometric reaction of the (*o*-tolyl)-Ni(II) complex **52** with **1a** and methyl acrylate **2b** failed to yield the desired product **36** (**Scheme 4-1**). Considering that dtbbpy was not the optimal ligand for this process, we performed a control experiment with catalytic $NiCl_2$•glyme and dtbbpy as ligand and isolated 24% yield of **36** expectedly (**Scheme 4-2**). Moreover, to exclude the possibility of decomposition of (*o*-tolyl)-Ni(II) complex, the catalytic efficiency of (*o*-tolyl)-Ni(II) complex **52** was further examined by adding another different aryl iodide and the result shown a good reactivity (**Scheme 4-3**). All the above-performed reactions suggested that Ar–Ni(II) might not be a reactive intermediate for the described catalytic cycle, in other words, Ni^0/Ni^{II}/Ni^{III} pathway (path b in Scheme 2) is rather unlikely. [9a, 21]



Scheme 4. Preliminary experiments on mechanistic study.

Conclusion

In summary, a dual photoredox/nickel-catalyzed conjunctive cross-coupling of electron-deficient alkenes with *α*-silyl amines and aryl halides has been developed. This three-component reaction displayed very broad substrate scope and good functional group compatibility. Acrylates, acrylonitrile as well as *α*, *β*-unsaturated ketone and acrylamide were readily incorporated in this three-component conjunctive cross-coupling. Additionally, aryl halides including both iodides and bromides were compatible. This protocol benefits from its good selectivity, mild, base-free and redox-neutral conditions, and it is further characterized by the unprecedented tolerance of primary alkyl radicals, which were reluctant to cooperate in previous reports. The developed dicarbofunctionalization (DCF) process allows a rapid buildup of molecular complexity, especially provides an efficient and concise synthetic way for *α*-aryl substituted *γ*-amino acid derivatives. Further mechanistic studies on explanation of the high reactivity and selectivity and asymmetric version are currently ongoing in our laboratory.

Acknowledgements

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Keywords: metallaphotoredox catalysis • three-component reactions • 1,2-dicarbofunctionalization • alkenes • conjunctive cross-coupling

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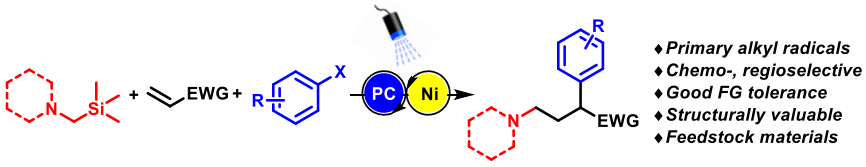

A photoredox/nickel dual catalyzed three-component conjunctive cross-coupling of alkenes with *α*-silyl amines and aryl halides is reported here. This catalytic process allows for applying primary alkyl radicals in three-component dicarbofunctionalization (DCF) of π-bond system, and characterized by the mild, base-free and redox-neutral conditions, as well as broad substrate scope and functional group compatibility. Our developed method provides a fast and efficient way to synthesize structurally valuable *α*-aryl substituted *γ*-amino acid moieties.