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Copper-catalyzed aerobic decarboxylative coupling between cyclic α -amino acids and diverse C–H nucleophiles with low catalyst loading†

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An aerobic decarboxylative cross-coupling of α -amino acids with diverse C–H nucleophiles has been realized using $\text{Cu}_2(\text{OH})_2\text{CO}_3$ (1 mol%) as the catalyst under air. This protocol enables highly efficient formation of various $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$, $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)\text{--C}(\text{sp})$ bonds under simple conditions without the use of any ligand or extra oxidant, providing a practical approach to numerous nitrogen-containing compounds in good to excellent yields. The efficiency and practicability were also demonstrated by the gram-scale experiment and three-step synthesis of a Rad51 inhibitor.

Introduction

Decarboxylative coupling has recently emerged as a powerful method for the construction of C–C and C–heteroatom bonds in organic synthesis.^{1,2} In contrast to conventional coupling reactions where expensive and sensitive organometallic reagents are usually required, decarboxylative coupling utilizes carboxylic acids that are readily available, bench-stable and simple to handle. Moreover, these reactions generate active carbon species *in situ* along with nontoxic carbon dioxide, which enables highly chemo- and regioselective cross-couplings with various coupling partners.

Pyrrolidines are privileged structural motifs in a wide variety of natural and unnatural products.³ The highly pronounced biological activities of pyrrolidine-containing compounds have made them attractive synthetic targets in medicinal chemistry. In the past decade, redox-neutral C–H functionalization affords a useful and economically efficient synthetic approach to these active molecules.⁴ On the other hand, proline is among the most abundant biomass feedstock in nature. As such, site-specific decarboxylative functionalization of proline has received particular attention, since this approach provides a facile and versatile synthesis of pyrrolidine derivatives. Recently, several research groups have developed useful synthetic methods for these nitrogen heterocycles through decarboxylative coupling between proline and diverse C–H nucleophiles. Li and Liang⁵ cooperatively developed a copper-catalyzed oxidative decarboxylative C–C coupling of *N*-benzyl-proline with alkynes, indoles

and nitromethane in the presence of peroxide and ligand (Fig. 1a). Later they expanded the substrate scope of C–H nucleophiles to naphthols *via* iron catalysis (Fig. 1b).⁶ Subsequently, Seidel's and other groups independently realized copper-catalyzed α -functionalization of proline under neutral conditions, which involved the aldehyde- and ketone-induced formation of the azomethine ylide as the key step (Fig. 1c–d).⁷ Chien and co-workers recently reported an intermolecular decarbonylative Mannich reaction of *N*-benzyl-proline with methyl ketones in the presence of oxalyl chloride (Fig. 1e).⁸ In addition, significant progress has been achieved in visible-light-induced radical decarboxylative functionalization of α -amino acids including proline derivatives (Fig. 1f).⁹ However, most of the above methods suffer from one or more drawbacks, such as the requirement of peroxide, organic ligand or transition metal catalyst with high loading, and harsh reaction conditions. From the viewpoint of sustainable chemistry, it is still highly desirable to develop simple and practical methods for decarboxylative functionalization of proline and its derivatives. Herein we wish to report a copper-catalyzed aerobic decarboxylative coupling between cyclic α -amino acids and diverse C–H nucleophiles (Fig. 1g). The major advantage of our findings including: (1) the use of earth-abundant copper catalyst with 1 mol% loading; (2) ligand peroxide-free conditions; (3) efficient construction of various $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$, $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)\text{--C}(\text{sp})$ bonds (more than 40 examples, 54–92% yields); (4) gram-scale synthesis; (5) application in facile synthesis of a Rad51 inhibitor.

Results and discussion

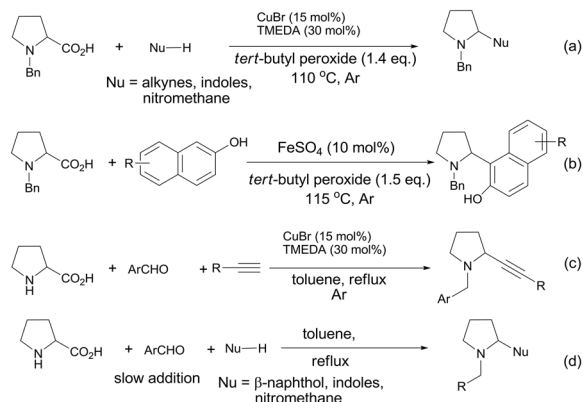
We chose *N*-benzyl proline (**1a**) and indole (**2a**) as model reaction substrates. In the presence of CuBr_2 (10 mol%) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the desired tertiary

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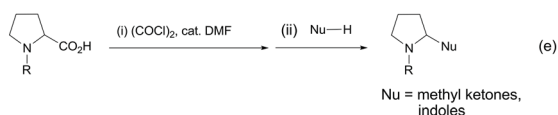
† Electronic supplementary information (ESI) available: Copies of ^1H , ^{13}C NMR spectra. See DOI: 10.1039/c8ra02340a



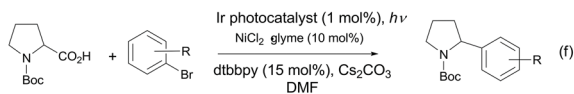
Transition-metal catalyzed decarboxylative coupling



Decarboxylative Mannich reaction



Photoredox-metal catalyzed decarboxylative arylation



This work

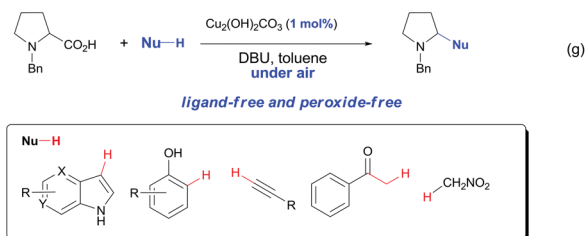


Fig. 1 Decarboxylative functionalization of cyclic α-amino acids.

amino-indole product **3a** was obtained in 48% isolated yield after 24 h (Table 1, entry 1). In order to improve the yield, a series of Cu(I), Cu(II), Fe(II) and Fe(III) salts were examined and $\text{Cu}_2(\text{OH})_2\text{CO}_3$ gave the best yield (entries 2–13). Comparing with Cu(I) catalyst, Cu(II) catalyst resulted in higher yield. Changing Cu catalyst to Fe catalyst could also generate the desired product, and FeCl_3 afforded comparable yield with $\text{Cu}_2(\text{OH})_2\text{CO}_3$ (64% vs. 65%). In view of the lower price of $\text{Cu}_2(\text{OH})_2\text{CO}_3$, we chose $\text{Cu}_2(\text{OH})_2\text{CO}_3$ as optimal catalyst. Subsequently, different solvents, including *N,N*-dimethylformamide (DMF), chlorobenzene, dimethyl sulfoxide (DMSO) and mesitylene were screened with $\text{Cu}_2(\text{OH})_2\text{CO}_3$ as catalyst (entries 14–17). It was found that toluene was the optimal choice for this transformation (entry 7). The attempts using other bases such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA), triethylamine, Ag_2CO_3 and Cs_2CO_3 were also investigated, but all resulted in lower yields than DBU (entries 18–21). The amount of base showed obvious effect on the reaction, the use of 3 equiv. of DBU resulted in the highest yield (entries 23–24). To clarify whether DBU plays as a ligand or a base in this reaction,

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Base	Yield ^b (%)
1	CuBr_2	Toluene	DBU	48
2	$\text{Cu}(\text{OAc})_2$	Toluene	DBU	48
3	$\text{Cu}(\text{OTf})_2$	Toluene	DBU	36
4	CuCl_2	Toluene	DBU	32
5	CuO	Toluene	DBU	15
6	$\text{Cu}(\text{OH})_2$	Toluene	DBU	10
7	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	65
8	CuI	Toluene	DBU	35
9	CuCl	Toluene	DBU	27
10	CuBr	Toluene	DBU	34
11	FeCl_3	Toluene	DBU	64
12	FeSO_4	Toluene	DBU	44
13	$\text{Fe}(\text{OAc})_3$	Toluene	DBU	42
14	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	DMF	DBU	43
15	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	PhCl	DBU	42
16	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Mesitylene	DBU	37
17	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	DMSO	DBU	32
18	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	TMEDA	35
19	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	Et_3N	35
20	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	Ag_2CO_3	25
21	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	Cs_2CO_3	38
22 ⁱ	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	KOH	20
23 ^c	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	68
24 ^d	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	45
25 ^{c,e}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	64
26 ^{c,f}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	65
27 ^c	—	Toluene	DBU	0
28 ^{c,f,g}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	5
29 ^{c,f,h}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	35
30 ^{c,f,j}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	25
31 ^{c,f,k}	$\text{Cu}_2(\text{OH})_2\text{CO}_3$	Toluene	DBU	5

^a Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (10 mol%), base (4 equiv.), solvent (2 mL), 110 °C, under air for 24 h. ^b Isolated yield. ^c DBU (3 equiv.). ^d DBU (2 equiv.). ^e $\text{Cu}_2(\text{OH})_2\text{CO}_3$ (5 mol%). ^f $\text{Cu}_2(\text{OH})_2\text{CO}_3$ (1 mol%). ^g Under N_2 . ^h Under O_2 . ⁱ Using 20 mol% DBU as ligand and KOH (3 equiv.) as base. ^j Under 80 °C. ^k Under 60 °C.

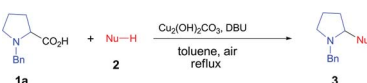
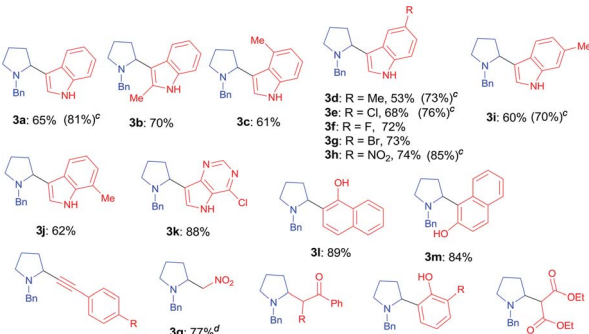
we have also carried out a control experiment with catalytic amount of DBU (20 mol%) and 3.0 equiv. of KOH, and obtained low yield (20%, entry 22 in Table 1). In view of the comparable basicity of DBU and KOH, we assumed that DBU might not be a ligand but mainly act as a base. To our delight, 1 mol% of $\text{Cu}_2(\text{OH})_2\text{CO}_3$ is sufficient to provide the desired product **3a** in 65% yield within 24 h (entries 25–26). This cross-coupling did not occur in the absence of $\text{Cu}_2(\text{OH})_2\text{CO}_3$ catalyst (entry 27). We have also performed the reaction under N_2 and O_2 atmosphere respectively, and the yields were 5% and 35% (entries 28–29 in Table 1), which implied that O_2 was essential for this transformation. Lower temperatures as 80 °C and 60 °C caused poor yields (<25%, entries 30–31), which indicated that high temperature was necessary for the conversion.

With the optimal reaction condition in hand (entry 26 in Table 1), we next set out to examine the scope of the new



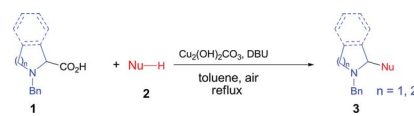
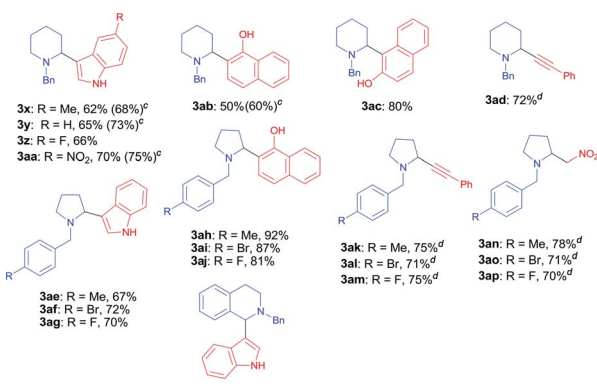
protocol with different C–H nucleophiles and the results were shown in Table 2. To our delight, this reaction exhibited broad substrate scope with respect to a wide range of sp^2 , sp^3 and sp C–H nucleophiles. Indoles with either electron-withdrawing groups (5-F, 5-Cl, 5-Br, 5- NO_2) or electron-donating groups (4-Me, 5-Me, 6-Me and 7-Me) reacted smoothly with *N*-benzyl proline **1a** and afforded the corresponding C(sp^2)-C(sp^3) coupling products **3a–3j** in moderate to good yields (52–74%), albeit indoles bearing electron-withdrawing substituents (**3f**, **3g**, **3h**) provided slightly higher yields than that with electron-donating groups. It should be noted that increasing the catalyst loading to 10 mol% could further improve the yields to 73–81% (see the yields in parentheses). The coupling of **1a** with 4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidine also proceeded smoothly, affording **3k** in 88% yield. Moreover, α - and β -naphthols were suitable coupling partners, the corresponding C(sp^2)-C(sp^3) coupling products **3l** and **3m** can be obtained in 89% and 84% yields, respectively. In addition, C(sp)-C(sp^3) bond could also be constructed *via* the reaction of various aromatic alkynes with *N*-benzyl proline, affording the related coupling products **3n–3p** in good yields (70–75%). Furthermore, this method was also suitable for the decarboxylative coupling of C(sp^3)-C(sp^3) bonds, and the reactions proceeded smoothly for nitromethane and acetophenone nucleophiles. Among them, products **3q** and **3r** are synthetic precursors for some bioactive natural products.¹⁰ The hindered C–H nucleophiles including propiophenone, 1,2-diphenylethan-1-one and diethyl malonate were also tested in this reaction with *N*-benzyl proline **1a** under standard conditions. Unfortunately, these nucleophiles were found to be incompatible with the developed protocol, and gave complex mixture with only trace products (detected by mass spectroscopy). Furthermore, *o*-cresol and phenol were also tested, but only trace products were obtained (detected by mass spectroscopy).

Table 2 Scope of C–H nucleophiles^{a,b}

	
	<p>3a: 65% (81%)^c 3b: 70% 3c: 61% 3d: R = Me, 53% (73%)^c 3e: R = Cl, 68% (76%)^c 3f: R = F, 72% 3g: R = Br, 73% 3h: R = NO_2, 74% (85%)^c 3i: 60% (70%)^c 3j: 62% 3k: 88% 3l: 89% 3m: 84% 3n: R = H, 71%^d 3o: R = Me, 70%^d 3p: R = F, 75%^d 3q: 77%^d 3r: R = H, 54% 3s: R = Me, trace 3t: R = Ph, trace 3u: R = H, trace 3v: R = Me, trace 3w: trace</p>

^a Reaction conditions: **1a** (0.4 mmol), nucleophile (0.2 mmol), $Cu_2(OH)_2CO_3$ (1 mol%), DBU (3 equiv.), toluene (2 mL), under air for 24 h at 110 °C. ^b Isolated yields. ^c 10 mol% $Cu_2(OH)_2CO_3$, 130 °C, 48 h. ^d Using 3 equiv. of nucleophile.

Table 3 Scope of cyclic α -amino acids^{a,b}

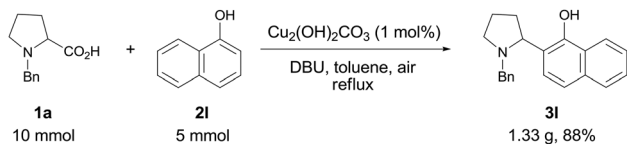
	
	<p>3a: 62% (68%)^c 3b: 50% (60%)^c 3c: 80% 3d: 72%^d 3e: R = Me, 62% 3f: R = H, 65% (73%)^c 3g: R = F, 66% 3h: R = NO_2, 70% (75%)^c 3i: R = Me, 92% 3j: R = Br, 87% 3k: R = F, 81% 3l: R = Me, 67% 3m: R = Br, 72% 3n: R = F, 70% 3o: R = Me, 75%^d 3p: R = Br, 71%^d 3q: R = F, 75%^d 3r: R = Me, 78%^d 3s: R = Br, 71%^d 3t: R = F, 70%^d 3u: 82%</p>

^a Reaction conditions: **1a** (0.4 mmol), nucleophile (0.2 mmol), $Cu_2(OH)_2CO_3$ (1 mol%), DBU (3 equiv.), toluene (2 mL), under air for 24 h at 110 °C. ^b Isolated yields. ^c 10 mol% $Cu_2(OH)_2CO_3$, 130 °C, 48 h. ^d Using 3 equiv. of nucleophile.

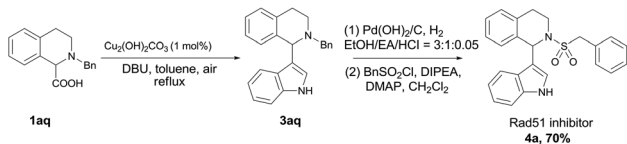
We next explored the scope of cyclic α -amino acids and the results were summarized in Table 3. Besides pyrrolidine, piperidine is also common heterocyclic skeleton existing in numerous natural products¹¹ albeit the decarboxylative coupling of piperidine carboxylic acid has less been explored.^{5,6,7a} We examined the decarboxylative coupling of *N*-benzyl piperidine carboxylic acid with diverse C–H nucleophiles including indoles, naphthols and alkynes. A range of indoles bearing electron-donating groups (–Me) or electron-withdrawing groups (–F and – NO_2) at the C5 position reacted smoothly with *N*-benzyl piperidine-2-carboxylic acid, affording the coupling products **3x–3aa** with moderate to good yields (62–70%). Increasing the amount of copper catalyst to 10 mol% resulted in higher yields (68–75%). This coupling reaction also proceeded successfully with α -naphthol and β -naphthol, leading to **3ab** and **3ac** in 50% and 80% yields, respectively. Moreover, phenylacetylene readily underwent the coupling to afford the corresponding piperidine-alkyne product **3ad** with good yield. A range of *N*-benzyl prolines bearing different substituents (F-, Br- and Me-) at the *para*-position of the phenyl ring were also investigated, giving various products including indolyl pyrrolidines **3aq–3as**, tertiary aminonaphthols **3ah–3aj**, propargylamines **3ak–3am** and β -nitroamines **3an–3ap** in moderate to high yields (67–92%). In particular, tetrahydroisoquinoline acid, an important moiety in many pharmaceuticals and natural products, was also found to be competent substrate under the standard decarboxylative coupling conditions (**3aq**, 82%). Moreover, when *N*-benzyl L-proline was used in this reaction, only racemic product **3a** was obtained, which was in agreement with the oxidative decarboxylation of L-proline and subsequent racemization of product.



Paper



Scheme 1 Gram-scale preparation of 3l.

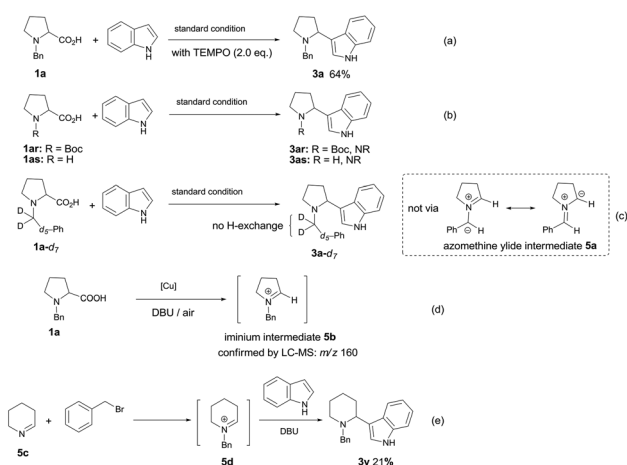


Scheme 2 New synthetic route of Rad51 inhibitor.

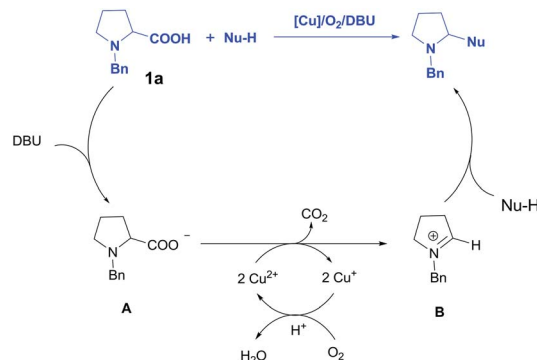
To explore the practical utility of this method, a gram-scale experiment was performed with *N*-benzyl proline **1a** and α -naphthol **2l** (Scheme 1). The coupling product **3l** could be obtained in 88% yield with only 1 mol% of copper catalyst, which demonstrated that this protocol was scalable and practical.

The efficiency and convenience of this copper-catalyzed decarboxylative coupling reaction was further demonstrated in the facile synthesis of IBR2 analogue **4a**, which is a Rad51 inhibitor for the treatment of triple-negative human breast cancer (Scheme 2).^{12,13} The decarboxylative coupling of tetrahydroisoquinoline acid with indole was employed as the key step to afford intermediate **3aq**, subsequent *N*-deprotection and *N*-sulfonylation led to the IBR2 analogue **4a** (70% yield, 3 steps). This new synthetic route is a significant simplification when comparing with the previous eight to thirteen steps using conventional synthetic approaches.^{12,13a}

In order to gain mechanistic insight into this transformation, some control experiments were performed. The reaction proceeded well in the presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinoxy), affording the desired product **3a** in 64% yield (Scheme 3a), which ruled out the involvement of a radical coupling pathway. The function of *N*-protective group was also explored. When *N*-Boc-proline or *N*-H free proline was



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism for the copper-catalyzed decarboxylative C–H cross-coupling.

employed under the standard conditions with indole, no desired product was observed (Scheme 3b), which implied the necessity of benzyl group for the formation of azomethine ylide intermediate.^{5,6,7a} To test whether the azomethine ylide intermediate **5a** was involved in this reaction, we have prepared the deuterium-labeled *N*-benzylproline (**1a-d₇**) and subjected it to the reaction with indole under our optimized conditions. The ¹H NMR spectrum of **3a-d₇** indicated that all deuterium atoms were retained, no deuterium–hydrogen exchange occurred at the benzylic position, which excluded the possibility of azomethine ylide intermediate **5a** (Scheme 3c). To our delight, *N*-benzyl iminium intermediate **5b** (*m/z* = 160) could be detected by ESI-MS from the reaction mixture, which demonstrated that *N*-alkyl iminium might be the reactive intermediate (Scheme 3d). We also tried to prepare the possible *N*-benzyliminium intermediate **5d** *in situ* from **5c**, then carried out the subsequently Mannich reaction with indole in the presence of DBU. The desired product **3y** can be isolated in 21% yield (Scheme 3e).

On the basis of literatures^{5,6} and our experimental observations, a tentative mechanism has been depicted in Scheme 4. Initially, the deprotonation of *N*-Bn-proline **1a** by DBU generated intermediate **A**, then the oxidative decarboxylation of **A** catalyzed by Cu₂(OH)₂CO₃ afforded *N*-benzyl iminium intermediate **B**, which underwent a Mannich reaction with carbon nucleophile to deliver the desired product. The regeneration of the Cu catalyst was realized *via* the oxidation of O₂ in air. It should be mentioned that this mechanism is different from Li's work, where an azomethine ylide was proposed as reactive intermediate.⁵

Conclusions

In summary, we have developed a ligand-free, copper-catalyzed aerobic decarboxylative coupling of cyclic α -amino acids and diverse C–H nucleophiles (indoles, naphthols, alkynes, ketones and nitroalkanes) with extremely low catalyst loading (1 mol%). This simple catalytic system enabled the direct construction of various C(sp³)–C(sp³), C(sp³)–C(sp²) and C(sp³)–C(sp) bonds in numerous nitrogen-containing heterocycles. The efficiency and practicability of this protocol was also demonstrated by gram-scale preparation and three-step synthesis of a Rad51 inhibitor.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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