C–C Coupling

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The Copper-Catalyzed Decarboxylative Coupling of the sp^3-Hybridized Carbon Atoms of α-Amino Acids**

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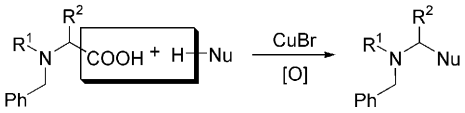
Carbon–carbon bond formation by transition-metal-catalyzed decarboxylative couplings has proven to be an important synthetic method because of its efficiency, selectivity, as well as convenience.[1,2] For example, Gooßen and co-workers and Myers and co-workers have reported palladium-catalyzed decarboxylative coupling of sp^2-hybridized carbon centers. A large number of useful building blocks, such as biaryls, aryl ketones, and vinyl arenes were obtained.[3,4] Tunge and co-workers reported the intramolecular decarboxylative coupling reaction of sp^3- and sp-hybridized carbon atoms, a powerful strategy for the formation of a C–C bond through decarboxylation of ester derivatives.[5] In contrast to the above-mentioned decarboxylative coupling reactions, intermolecular decarboxylative coupling of sp^3-hybridized carbon atoms with other nucleophiles remains a significant challenge.

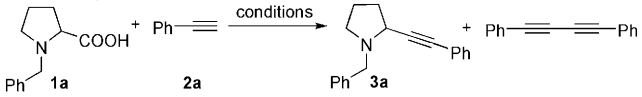
Compounds containing heteroatoms such as nitrogen atoms exist widely in nature.[6] The synthesis of these compounds has attracted much attention in both industrial and academic research because of their biological and pharmaceutical properties.[7] α-Amino acids are often more readily available than other compounds in nature and are among the most attractive nitrogen-containing motifs. Therefore, site-specific functionalization of α-amino acid skeletons using various nucleophiles would provide a useful and economically efficient synthetic approach to active molecules. Furthermore, the functionalization of sp^3-hybridized C–H bonds adjacent to nitrogen atoms is of great interest in the synthesis of heterocycles.[8] The carboxylic group adjacent to the nitrogen atom in α-amino acids provides the possibility for selective functionalization by using decarboxylative coupling reactions. Herein we report a novel intermolecular decarboxylative coupling of α-amino acids catalyzed by CuBr. This methodology was applied to C_{sp^3}–C_{sp}, C_{sp^3}–C_{sp^2}, and C_{sp^3}–C_{sp^3} bond formations, and various products having the functional groups adjacent to the nitrogen center were obtained (Scheme 1).

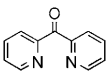


Scheme 1. Copper-catalyzed decarboxylative coupling of α-amino acids.

Our study began with the reaction of *N*-benzyl-proline **1a**, 1.5 equivalents of phenylacetylene (**2a**), 1.4 equivalents of *tert*-butyl hydroperoxide (TBHP), and 15 mol% of CuBr as the catalyst stirred in toluene under an argon atmosphere at 110 °C overnight. The desired product **3a** was obtained in 42% yield (Table 1, entry 1). To improve the yields, various oxidants were examined (Table 1, entries 2–5). We later found

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	Ligand	NMR yield [%][b]	Dimer yield [%][c]
1	CuBr	HO-O-tBu	–	42	8
2	CuBr	Ph-O-O-tBu	–	31	trace
3	CuBr	Ph-O-O-Ph	–	45	trace
4	CuBr	Ph(C=O)O-O-tBu	–	trace	6
5	CuBr	tBu-O-O-tBu (**4a**)	–	81	7
6	CuI	**4a**	–	65	11
7	CuOTf	**4a**	–	36	trace
8	CuCl	**4a**	–	54	trace
9	CuBr	**4a**	NEt_3	82	trace
10	CuBr	**4a**	**5a**	90	trace
11	CuBr	**4a**		73	trace

[a] Reactions were carried out on a 0.3 mmol scale in toluene (1.5 mL) under argon at 110 °C, overnight with **1a** (1.0 equiv), **2a** (1.5 equiv), oxidant (1.4 equiv), catalyst (0.15 equiv), and ligand (0.30 equiv). [b] Reported yields were based on **1a** and determined by NMR methods using an internal standard. [c] Yield of isolated product.

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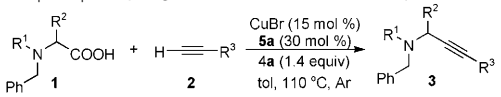
that *tert*-butyl peroxide (**4a**) was the oxidant of choice for this reaction, giving higher yields than other oxidants. Among the copper catalysts examined, CuBr was the most effective catalyst for this reaction compared to CuI, CuOTf, and CuCl (Table 1, entries 6–8). In addition, different nitrogens were examined (Table 1, entries 9–11). After additional screening, 30 mol% of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) gave the best results, leading to the product in 90% yield. Notably, only a small amount of phenylacetylene dimerized under all the oxidative reaction conditions examined (Table 1). The optimized reaction conditions employ 1.0 equivalents of α-amino acid **1**, 1.5 equivalents of alkyne **2**, 1.4 equivalents of *tert*-butyl proxide (**4a**), 15 mol% of CuBr, and 30 mol% ligand **5a**, in toluene at 110°C under argon.

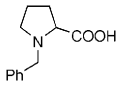
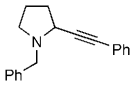
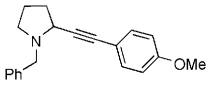
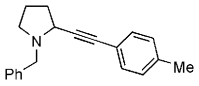
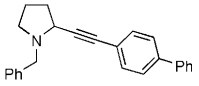
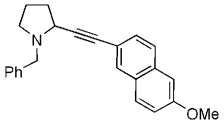
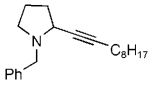
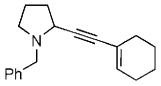
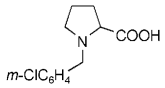
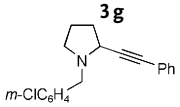
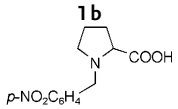
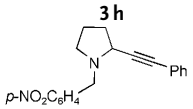
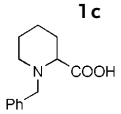
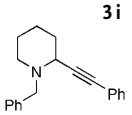
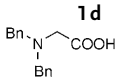
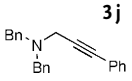
To examine the scope of this decarboxylative coupling reaction, various alkynes were reacted under the optimized reaction conditions, and the results are summarized in Table 2. In most cases, aromatic alkynes afforded the corresponding products in good yields (Table 2, entries 1–5), and alkynes containing an aliphatic group or a 1-cyclohexenyl group were also applicable (Table 2, entries 6 and 7). Meanwhile, the use of *N*-benzyl-proline bearing different substituents at the *meta*- and *para*-positions of the phenyl ring gave the corresponding products in moderate to good yields (Table 2, entries 8 and 9). When *N*-benzyl-pipecolic acid (**1d**) was used in this reaction, *N*-benzyl-piperidine derivative **3j** was obtained in 81% yield (Table 2, entry 10). For catenarian amino acid **1e**, which is noncyclic and does not have an α-substituent, the corresponding product **3k** was also formed albeit in lower yield (Table 2, entry 11).

Encouraged by these results of this decarboxylative C_{sp^3}–C_{sp} coupling, we envisaged the trapping of the cationic intermediate by other nucleophiles (pronucleophiles). We tested this method on the decarboxylative C_{sp^3}–C_{sp^2} coupling of α-amino acids with indoles. To our delight, the reaction proceeded under the same conditions to afford the indole coupling products having an unprotected NH group. 2-Methylindole (**6a**) and 5-bromoindole (**6b**) each reacted smoothly with *N*-benzyl-proline **1a** to give the desired products (Table 3, entries 1 and 2). Various α-amino acid derivatives were subjected to the decarboxylative coupling reaction and moderate to good yields of the products were obtained (Table 3, entries 3–5). Notably, the reactions occurred selectively at the C3-position of the indoles when this position was not substituted. When the

Table 2: Decarboxylative C_{sp^3}–C_{sp} coupling of α-amino acids with alkynes.[a]

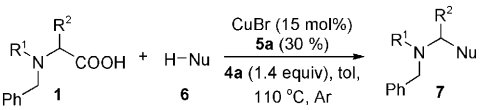


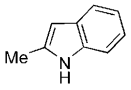
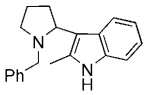
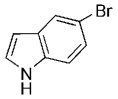
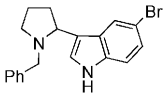
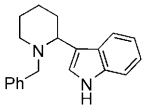
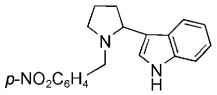
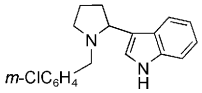
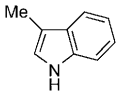
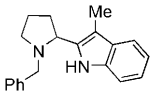
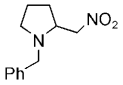
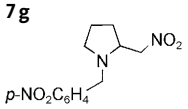
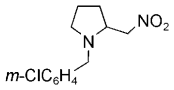
1 2 3

Entry	1	R^3	Product	Yield [%][b]
1		Ph		
	1a	**2a**	**3a**	90(80)
2		4-$MeOC_6H_4$		
	1a	**2b**	**3b**	86(70)
3		4-MeC_6H_4		
	1a	**2c**	**3c**	89(73)
4		4-PhC_6H_4		
	1a	**2d**	**3d**	95(80)
5		6-methoxynaphthalenyl		
	1a	**2e**	**3e**	74(56)
6		C_8H_{17}		
	1a	**2f**	**3f**	83(65)
7		1-cyclohexenyl		
	1a	**2g**	**3g**	76(56)
8				
	1b	**2a**	**3h**	86(77)
9				
	1c	**2a**	**3i**	58(41)
10				
	1d	**2a**	**3j**	81(74)
11				
	1e	**2a**	**3k**	39(20)

[a] α-Amino acid (1.0 equiv), alkyne (1.5 equiv), **4a** (1.4 equiv), **5a** (30 mol%), and CuBr (15 mol%) in toluene (1.5 mL). [b] NMR yields are based on α-amino acid and determined by NMR methods using an internal standard; yield of isolated product is given in parentheses.

Table 3: Decarboxylative C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp} coupling of α-amino acids.[a]

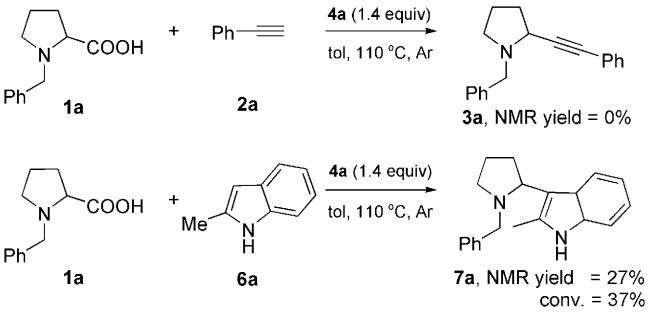


Entry	1	6	Product	Yield [%][b]
1	1a	 6a	 7a	87(74)
2	1a	 6b	 7b	87(74)
3	1d	 6c	 7c	78(63)
4	1c	6c	 7d	57(50)
5	1b	6c	 7e	82(69)
6	1a	 6d	 7f	0
7	1a	CH_3NO_2 6e	 7g	89(86)[c]
8	1c	6e	 7h	73(58)[c]
9	1b	6e	 7i	77(67)[c]

[a] α-Amino acid (1.0 equiv), nucleophile (1.5 equiv), **4a** (1.4 equiv), **5a** (30 mol%), and CuBr (15 mol%) in toluene (1.5 mL). [b] NMR yields are based on α-amino acid and determined by NMR methods using an internal standard; yield of isolated product is given in parentheses. [c] Used 3 equivalents of the nucleophile.

C3-position of the indole was substituted, the C2-products are not obtained (compare entries 1 and 6 in Table 3). This methodology provides the simplest way to construct indolyl pyrrolidines and piperidines, and also opens a new avenue to constructing and studying more complex alkaloids. Excitingly, this method was also applied to the decarboxylative coupling of C_{sp^3}–C_{sp^3} centers and the reaction proceeded readily for various α-amino acids and nitromethane (Table 3, entries 7–9). The further reaction products, vicinal diamines, are important structural motifs in biologically active natural products and are used as core units for chiral auxiliaries and chiral ligands in asymmetric catalysis.[9]

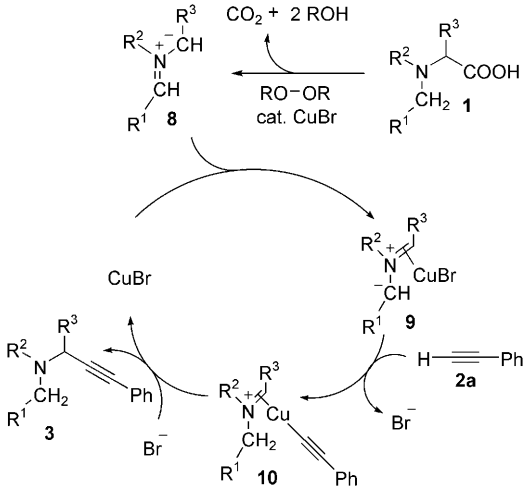
The effect of copper in the decarboxylation process was also examined. Not surprisingly, the direct coupling product **3a** was not observed in the reaction of **1a** and **2a** without the CuBr catalyst. On the contrary, the decarboxylative coupling reaction between **1a** and **6a** afforded the desired coupling product in a diminished yield and conversion (Scheme 2). These results confirmed that CuBr facilitates the decarboxylation process and catalyzes the C–C bond formation.



Scheme 2. Decarboxylative coupling reaction without CuBr.

A proposed mechanism based on the experimental data is shown in Scheme 3. The oxidative decarboxylation of α-amino acid **1** is catalyzed by CuBr to gave imine-type intermediate **8.**[10–12] The organocopper intermediate **8** then tautomerizes to give intermediate **9**. Finally, the coupling of **9** with **2a** results in the desired products **3**,[13] and regenerates the copper catalyst for additional reaction.

In summary, we have developed a novel CuBr-catalyzed intermolecular decarboxylative C_{sp^3}–C_{sp^3}, C_{sp^3}–C_{sp^2}, and C_{sp^3}–C_{sp} coupling reaction using α-amino acids as starting materials under neutral conditions. In this process, propargylamines, indolyl pyrrolidines and piperidines, and β-nitroamines were obtained, all of which are important structural



Scheme 3. Proposed mechanism for the copper-catalyzed decarboxylative coupling between an α-amino acid and phenylacetylene.

features of natural products and pharmaceuticals. This catalytic reaction is an efficient method for the synthesis of various nitrogen-containing compounds. The scope, mechanism, and synthetic applications of this reaction are under investigation.

Experimental Section

General procedure (Table 2, entry 1): CuBr (0.045 mmol, 15 mol%) was added to a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**5a**; 0.09 mmol, 30 mol%) in toluene (1.5 mL). The mixture was stirred for 10 min under argon. *N*-Benzyl-proline **1a** (0.30 mmol), alkyne **2a** (0.45 mmol), and *tert*-butyl peroxide (**4a**; 0.42 mmol) were then added to the reaction mixture. The reaction was heated to 110 °C as soon as possible, stirred overnight, and then cooled to room temperature. The resulting suspension was diluted with ethyl acetate and filtered through a short column of Fluorisil using ethyl acetate. The solvent was evaporated and the residue was purified on silica gel (hexanes/diethyl ether 15:1→10:1) to afford propargylamine derivatives **3a** in 80% yield upon isolation as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.48$–7.23 (m, 10H), 4.07 (d, $J = 12.9$ Hz, 1H), 3.64–3.58 (m, 2H), 2.83–2.76 (m, 1H), 2.59–2.52 (m, 1H), 2.22–1.76 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 138.7, 131.7, 129.2, 128.2, 128.2, 127.9, 126.9, 123.4, 88.7, 84.9, 57.2, 54.4, 51.5, 31.6, 22.0$ ppm; HRMS calcd for $C_{19}H_{19}N$: 261.1518; found: 261.1505.

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