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Aldehyde- and Ketone-Induced Tandem Decarboxylation-Coupling (Csp^3−Csp) of Natural α-Amino Acids and Alkynes

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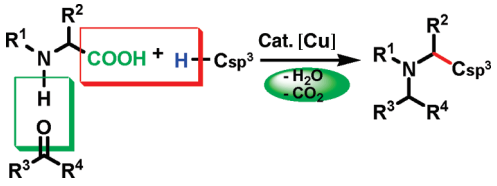

An interesting aldehyde- and ketone-induced intermolecular tandem decarboxylation-coupling (Csp^3−Csp) catalyzed by copper with use of natural α-amino acids as starting materials is developed under neutral conditions with the production of CO_2 and H_2O as the only byproducts. Various functionalized nitrogen-containing compounds were obtained by this method. In these processes, interesting regioselectivites of the alkylation were observed, which has been rationalized by the relative stability of proposed resonance structures based on computation methods.

Introduction

The transition metal-catalyzed cross-coupling reactions (e.g., Negishi,[1] Stille,[2] Suzuki−Miyaura,[3] Sonogashira,[4] and Kumada[5] couplings) have been established as convenient, practical, and effective methods for constructing C−C bonds in modern organic synthesis.[6] Although they have been employed in a broad range of applications,[7] there are still disadvantages such as the requirement of usually expensive transition metal catalysts and producing stoichiometric quantities of unwanted metal/metalloid byproducts in the transmetalation steps. Recently, interest in the area of decarboxylative coupling has increased rapidly due to the fact that these reactions occur under relatively neutral conditions, avoiding the use of preformed "organometallic reagents" that are typically necessary for transmetalation and eliminating the stoichiometric quantities of unwanted metal/metalloid byproducts.[8,9]

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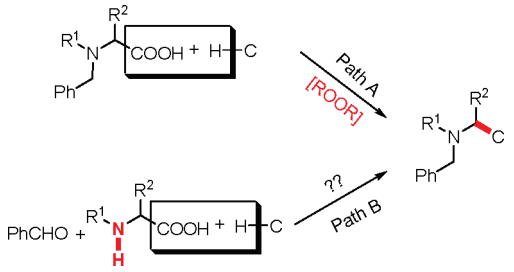
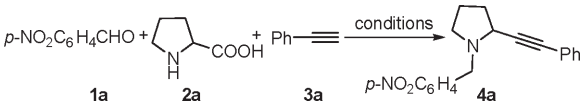
SCHEME 1. Copper-Catalyzed Oxidative Decarboxylative Coupling of Tertiary α-Amino Acids (Path A) and Aldehyde-Induced Decarboxylation-Coupling of Secondary α-Amino Acids (Path B)



To date, while seeking selective methods to functionalize the α Csp^3−H bond of nitrogen-containing compounds,[10] we have developed various Cross-Dehydrogenative-Coupling (CDC) by directly utilizing two different C−H bonds.[11] While these reactions provided the simplest and most direct approach to generate such compounds, the scope of the reactions and the regioselectivity of the C−C bond to be formed are still relatively limited. Alternatively, the carboxylic group of α-amino acids provides the possibility for site-specific functionalization of α-amino acids skeletons, using decarboxylative coupling reactions to generate amine derivatives. In the meantime, α-amino acids are often more readily accessible than other compounds in nature and are among the most attractive synthons for cross-coupling.[12] With this notion in mind, very recently, we have developed a C−C bond-forming reaction based on a copper- and iron-catalyzed oxidative decarboxylative coupling of sp^3-hybridized carbons of α-amino acids (Scheme 1, path A).[13] Although these results provide new and alternative ways to construct different Csp^3−Csp, Csp^3−Csp^2, and Csp^3−Csp^3 bonds, there are still several limitations for these methods. First, a stoichiometric quantity of peroxide was used. Avoiding the use of peroxide would offer a more atom-economical and much safer process.[14] Second, the tertiary α-amino acids described by Path A (protected by benzyl groups) require preparation in separate steps in advance, which also generates waste. Finally, the oxidative coupling methods are not applicable to secondary α-amino acids, which are more prevalent in nature. Thus, the direct α-functionalization of existing secondary α-amino acids is highly desirable and synthetically useful. To address these challenges, herein we report an interesting aldehyde- and ketone-induced intermolecular tandem decarboxylation-coupling of secondary α-amino acids with alkynes catalyzed by copper to afford propargylic amine derivatives,[11,15] releasing H_2O and CO_2 as the only byproducts (Scheme 1, path B).

TABLE 1. Optimization of Reaction Conditions[a]



entry	catalyst	temp (°C)	NMR yield[b] (%)
1	$Au(PPh_3)Cl$	100	<5[c]
2	$AuCl_3$	100	28[c]
3	$Ag(PPh_3)F$	100	32
4	CuOTf	100	33
5	$Cu(OTf)_2$	100	28
6	$CuBr_2$	100	32
7	CuBr	100	44
8	CuI	100	45
9	CuI	130	90
10	CuI	130	95[d]

[a]Reactions were carried out on a 0.3 mmol scale in 1.5 mL of toluene under argon overnight with 1.0 equiv of **1a**, 1.5 equiv of **2a**, 1.4 equiv of **3a**, and 0.15 equiv of catalyst. [b]Reported yields were based on **1a** and determined by NMR with use of an internal standard. [c]0.05 equiv of catalyst was used. [d]1.4 equiv of **1a**, 1.5 equiv of **2a**, and 1.0 equiv of **3a** were used and the reported yield was based on **3a**.

Results and Discussion

Our study began with the reaction of 1.0 equiv of 4-nitrobenzaldehyde **1a**, 1.5 equiv of proline **2a**, 1.4 equiv of phenylacetylene **3a**, and 5 mol % of $AuCl(PPh_3)$ as the catalyst in toluene at 100 °C under argon overnight. A trace amount of the desired pyrrolidine heterocycle **4a** was obtained (Table 1, entry 1). To improve the yields, various catalysts such as $AuCl_3$, $Ag(PPh_3)F$, and various copper salts were examined (entries 2−8), which were shown to be effective for similar reactions.[15] Among them, CuI provided the highest yield. Different temperatures were also tested. When the reaction was performed at 130 °C, an excellent yield was obtained (entry 9). Later, we found that the use of 1.4 equiv of **1a**, 1.5 equiv of **2a**, and 1.0 equiv of **3a** gave the best yield (entry 10). The optimum reaction conditions thus far developed employ 1.4 equiv of aldehyde **1**, 1.5 equiv of amino acid **2**, 1.0 equiv of alkyne **3**, and 15 mol % of CuI, in toluene at 130 °C under argon.

To examine the scope of this aldehyde-assisted decarboxylation-coupling reaction, various alkynes were examined under the above optimized conditions, and the results are summarized in Table 2. For aromatic alkynes, the reaction often afforded the corresponding products in moderate to good yields (Table 2, entries 1−5). In addition, alkynes containing an aliphatic group or a 1-cyclohexenyl group were also applicable in this transformation (entries 6 and 7). Meanwhile, the use of benzaldehyde bearing an electron-withdrawing group at different positions gave the corresponding products **4h**, **4i**, and **4j**, respectively (entries 8−10). However, benzaldehyde bearing an electron-donating group gave a lower yield (entry 11).[16] When 4-methoxybenzaldehyde **1f** was used, two types of C−C bond

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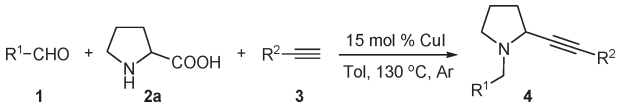
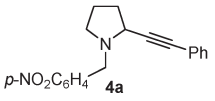
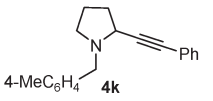
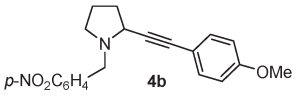
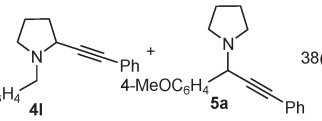
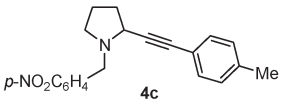
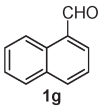
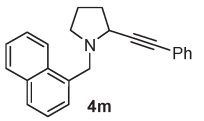
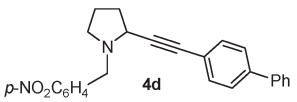
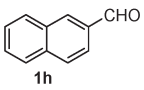
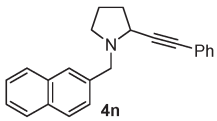
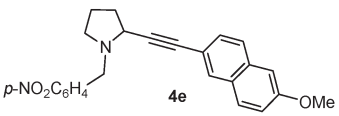
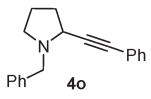
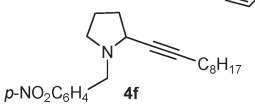
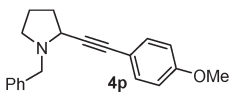
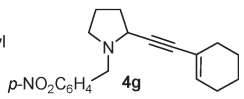
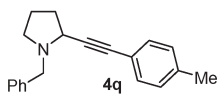
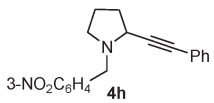
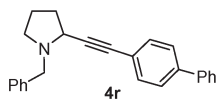
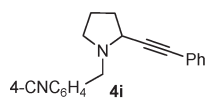
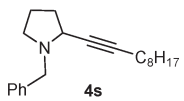
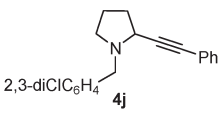
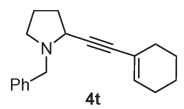
TABLE 2. Tandem Decarboxylation-Coupling of Secondary α-Amino Acids and Alkynes[a]



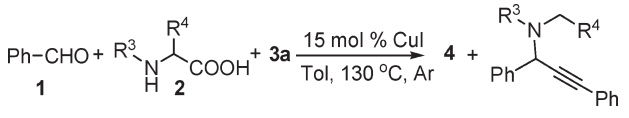
entry	R^1	R^2	product	yield (%)	entry	R^1	R^2	product	yield (%)
1	4-$NO_2C_6H_4$ **1a**	Ph **3a**	 **4a**	81	11	4-MeC_6H_4 **1e**	**3a**	 **4k**	61
2	**1a**	4-$MeOC_6H_4$ **3b**	 **4b**	74	12	4-$MeOC_6H_4$ **1f**	**3a**	 **4l** **5a**	38(18)[b]
3	**1a**	4-MeC_6H_4 **3c**	 **4c**	72	13	 **1g**	**3a**	 **4m**	71
4	**1a**	4-PhC_6H_4 **3d**	 **4d**	73	14	 **1h**	**3a**	 **4n**	65
5	**1a**	**3e**	 **4e**	65	15	Ph **1i**	**3a**	 **4o**	60
6	**1a**	C_8H_{17} **3f**	 **4f**	58	16	**1i**	**3b**	 **4p**	53
7	**1a**	1-cyclohexenyl **3g**	 **4g**	66	17	**1i**	**3c**	 **4q**	47
8	3-$NO_2C_6H_4$ **1b**	**3a**	 **4h**	72	18	**1i**	**3d**	 **4r**	51
9	4-CNC_6H_4 **1c**	**3a**	 **4i**	76	19	**1i**	**3f**	 **4s**	37
10	2,3-diClC_6H_4 **1d**	**3a**	 **4j**	46	20	**1i**	**3g**	 **4t**	42

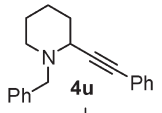
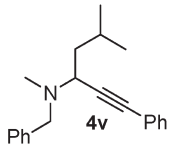
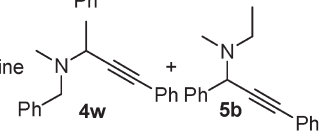
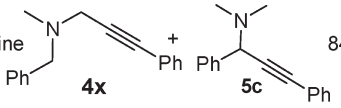
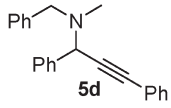
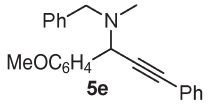
[a]Aldehyde (1.4 equiv), amino acid (1.5 equiv), alkyne (1.0 equiv), and CuI (15 mol %) in toluene (1.5 mL). [b]Isolated yield of **5a** is given in parentheses.

formation products ***4l*** and **5a** were obtained (entry 12). Furthermore, the use of α-naphthaldehyde and *β*-naphthaldehyde gave the corresponding coupling products in good yields (entries 13 and 14). The reactions of benzaldehyde with different alkynes were also examined; the corresponding coupling products were obtained in moderate yields (entries 15−20). In these reactions, only trace amounts of regioisomers resulting from the coupling at the benzylic carbon were observed by ^{1}H NMR or GC-MS of the crude reaction mixture. We were unable to isolate and purify these trace amounts of regioisomers.

Subsequently, our investigations were focused on the use of various amino acids. When cyclic amino acid pipecolic acid **2b** was used, *N*-benzylpiperidine derivative **4u** was obtained in a moderate yield (Table 3, entry 1). For catenarian amino acid *N*-methylleucine **2c**, the corresponding product **4v** was formed (entry 2). Similarly, *N*-methylalanine was also applicable, however, affording a mixture of two regioisomers (entry 3). To our surprise, when amino acid **2e** without an α-substituent was used, the reaction gave almost exclusively the isomeric benzylic alkynylation product; only a very small amount of the "ipso"- coupling product was observed (entry 4). The reactions of amino acid **2f** with different aldehydes also gave the regioisomers **5d**, **5e** and trace amounts of the "ipso"-coupling products (entries 5 and 6).

TABLE 3. Tandem Decarboxylation-Coupling of Different α-Amino Acids[a]



entry	1	2	product	yield (%)
1	1i	Pipecolic acid **2b**	 **4u**	38
2	1i	*N*-Methyl-leucine **2c**	 **4v**	52[c]
3	1i	*N*-Methy-alanine **2d**	 **4w** + **5b**	32[b,c]
4	1i	*N*-Methyl-glycine **2e**	 **4x** + **5c**	84(<5)[d]
5	1i	*N*-Benzyl-glycine **2f**	 **5d**	78[c]
6	1f	2f	 **5e**	85[c]

[a]Aldehyde (1.4 equiv), amino acid (1.5 equiv), alkyne (1.0 equiv), and CuI (15 mol %) in toluene (1.5 mL). [b]**4w**:**5b** = 3:1. [c]Aldehyde (1.0 equiv), amino acid (1.5 equiv), and alkyne (1.4 equiv) were used. [d]NMR yield of **4x** is given in parentheses.

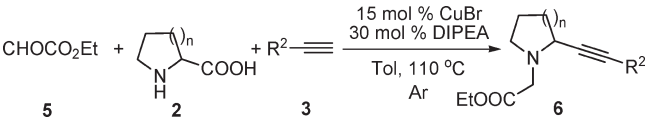
Interestingly, ethyl glyoxalate[17] can also be used in this reaction readily when using CuBr and *N*,*N*-diisopropylethylamine (DIPEA) as the catalytic system at 110 °C. Alkynes containing an aromatic, 1-cyclohexenyl, or aliphatic group were subjected to the tandem decarboxylation-coupling reactions and moderate to good yields were obtained (Table 4, entries 1−8). Six-member-ring amino acid **2b** can also be used to give a new amino acid derivative **6i** in 38% yield (entry 9). The use of CuI as catalyst gave a lower yield of the corresponding decarboxylation-coupling product.

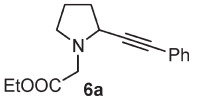
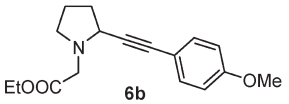
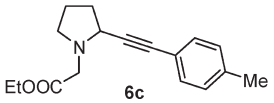
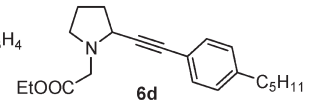
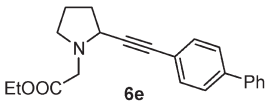
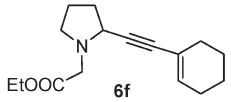
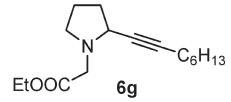
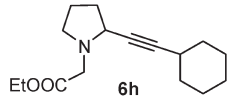
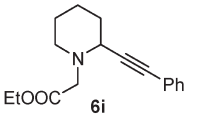
Encouraged by these results of this aldehyde-induced tandem decarboxylation-coupling reaction, we then tried to incorporate ketone as the substrate in this coupling process. Subsequently, We were pleased to find that ethyl pyruvate **7** led to the formation of coupling products smoothly using CuBr and $N(Et)_3$ as the catalytic system at 110 °C. The results were summarized in Table 5. However, attempts to use other ketones such as acetophenone and ethyl 3,3,3-trifluoro-2-oxopropanoate were not successful.

To further understand the role of aldehyde and copper in this process, we examined the reaction of proline **2a** with

(17) Ethyl glyoxalate is in toluene (50 wt % in toluene).

TABLE 4. Decarboxylation-Coupling for the Synthesis of Amino Acids Derivatives[a]



entry	2	3	product	yield (%)
1	2a	3a	 **6a**	67
2	2a	3b	 **6b**	74
3	2a	3c	 **6c**	49
4	2a	$R^2 = C_5H_{11}C_6H_4$ **3h**	 **6d**	62
5	2a	3d	 **6e**	64
6	2a	3g	 **6f**	49
7	2a	$R^2 = C_6H_{13}$ **3i**	 **6g**	41
8	2a	$R^2 = C_6H_{11}$ **3j**	 **6h**	36
9	2b	3a	 **6i**	38

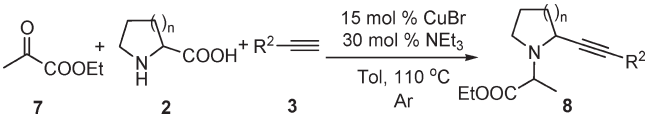
[a]Ethyl glyoxalate (1.4 equiv), amino acid (1.5 equiv), alkyne (1.0 equiv), CuBr (15 mol %), and DIPEA (30 mol %) in toluene (1.5 mL).

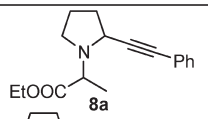
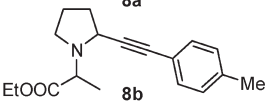
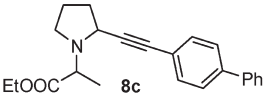
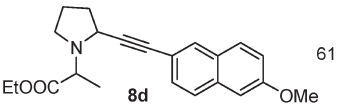
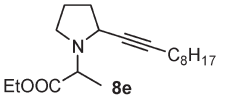
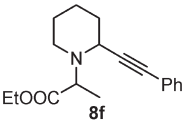
alkyne **3a** under the optimized reaction conditions above. No direct coupling product **9** was obtained. However, when no copper catalyst is used, only a trace amount of the coupling product **4o** was observed with GC-MS analysis (Scheme 2). These results confirmed that aldehyde is essential to induce decarboxylation[16,18] and CuI catalyst is important in the C−C bond formation step.

A tentative mechanism was proposed in Scheme 3. The first step is most likely the formation of an imine-type intermediate **10**, which then undergoes decarboxylation[16,19] to form intermediate **B**. The intermediate will be in equilibrium

(18) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519–541.
(19) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517.

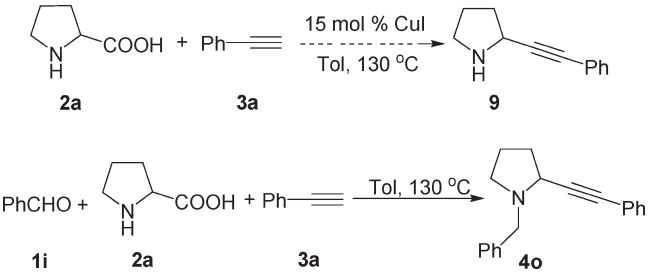
TABLE 5. Decarboxylation-Coupling of Ketones[a]



entry	2	3	product	yield (%)	dr[b]
1	2a	3a	 8a	64	1.5:1
2	2a	3c	 8b	65	1.5:1
3	2a	3d	 8c	60	1.5:1
4	2a	3e	 8d	61	1.6:1
5	2a	3f	 8e	53	1.5:1
6	2b	3a	 8f	51	1.6:1

[a]Ethyl pyruvate (1.4 equiv), amino acid (1.5 equiv), alkyne (1.0 equiv), CuBr (15 mol %), and NEt_3 (30 mol %) in toluene (1.5 mL). [b]Detected by NMR.

SCHEME 2. The Effect of Aldehyde and Copper

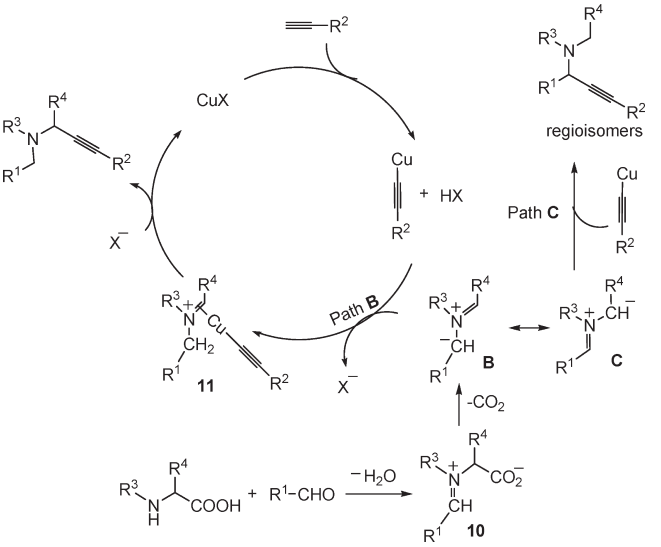


with intermediate **C**. Reaction of **B** or **C** with acetylide intermediate resulted in the generation of an organocopper intermediate, which undergoes intramolecular nucleophilic addition to give the desired products and regenerates the copper catalyst for further reactions.[11,13,15]

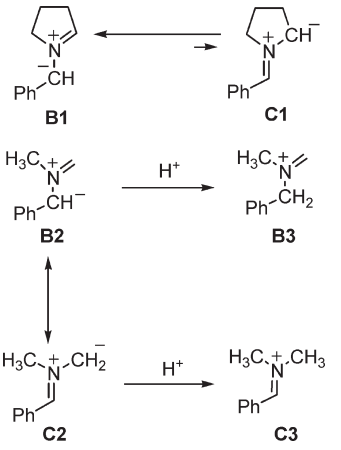
Theoretical Basis of the Regioselectivity

To have a better understanding of factors controlling the coupling regioselectivity of the reaction and thus provide a predictable and synthetically useful tool, we decided to look at the relative stability as well as the effect of substituents on resonance structures **B** and **C**. We reasoned that the regioselecivity could be due to the relative stability of these two resonance structures when bearing different substituents. To validate this hypothesis, the relative energies of resonance

SCHEME 3. Proposed Mechanism of the Aldehyde-Induced Decarboxylation-Coupling



SCHEME 4. Explanation of Regioselectivity



structures **B** and **C** were calculated with use of Gaussian98 programs.[20] The calculation shows that the energy of **B1** is ca. 15.28 kJ/mol lower than that of **C1**, and thus the regioselecitivty of this reaction is likely determined by resonance structure **B1** (Path B). If there is no α-substituent, the energies of **B2** and **C2** are nearly the same. Therefore, there is the same possibility to form either structure **B3** or **C3**. However, the energy of **B3** is ca. 48.07 kJ/mol higher than **C3**. Thus, path C is more favorable in this case (Scheme 4 and Figure 1).

(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

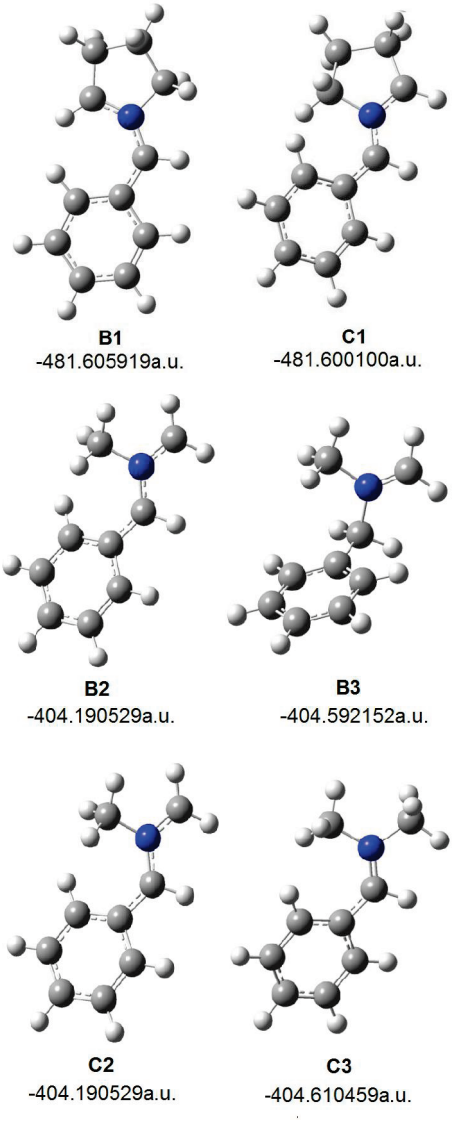


FIGURE 1. Calculation of the relative energies of resonance structures by Gaussian98.

Conclusion

In summary, we have developed an interesting aldehyde- and ketone-induced tandem decarboxylation-coupling (Csp^3-Csp) reaction catalyzed by copper using secondary α-amino acids as starting materials under neutral conditions providing CO_2 and H_2O as the only byproducts. In these processes, an interesting regioselectivity was observed. Such regioselectivities were explained by using computation methods.

Experimental Section

General Procedure. Table 2, entry 1: To a solution of proline **2a** (51.8 mg, 0.45 mmol) in toluene (1.5 mL) was added CuI (8.6 mg, 0.045 mmol, 15 mol %). The mixture was stirred for 10 min under argon. Aldehyde **1a** (63.4 mg, 0.42 mmol) and alkyne **3a** (30.6 mg, 0.30 mmol) were added. The reaction temperature was raised to 130 °C as soon as possible. The resulting mixture was stirred at the same temperature overnight, and then cooled to room temperature. The resulting suspension was diluted with ethyl acetate (2.0 mL) and filtered through a short fluorisil column eluting with ethyl acetate (15 mL). Solvent was evaporated and the residue was purified by column chromatography (hexanes/diethyl ether = 15:1−4:1) on silica gel to afford propargylamine derivatives **4a** in 81% (74.4 mg) isolated yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.19−8.15 (m, 2H), 7.58−7.54 (m, 2H), 7.46−7.40 (m, 2H), 7.33−7.29 (m, 3H), 4.11 (d, J = 13.8 Hz, 1H), 3.72 (d, J = 13.8 Hz, 1H), 3.66−3.61 (m, 1H), 2.81−2.74 (m, 1H), 2.61−2.53 (m, 1H), 2.26−1.80 (m, 4H).

Table 4, entry 1: To a solution of *N*,*N*-diisopropylethylamine (11.6 mg, 0.09 mmol) in toluene (1.5 mL) was added CuBr (6.4 mg, 0.045 mmol, 15 mol %). The mixture was stirred for 10 min under argon. Aldehyde **5** (83.2 μl, 0.42 mmol), amino acids **2a** (51.8 mg, 0.45 mmol), and alkyne **3a** (30.6 mg, 0.30 mmol) were added. The reaction temperature was raised to 110 °C as soon as possible. The resulting mixture was stirred at the same temperature overnight, and then was cooled to room temperature. The resulting suspension was diluted with ethyl acetate and filtered through a short fluorisil column eluting with ethyl acetate. Solvent was evaporated and the residue was purified by column chromatography (hexane/diethyl ether = 10:1−4:1) on silica gel to afford the coupling products **6a** in 67% (51.7 mg) isolated yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43−7.39 (m, 2H), 7.30−7.26 (m, 3H), 4.23−4.16 (m, 2H), 3.95−3.91 (m, 1H), 3.67−3.44 (m, 2H), 2.96−2.88 (m, 1H), 2.83−2.76 (m, 1H), 2.27−2.20 (m, 1H), 2.09−1.85 (m, 3H), 1.30−1.25 (m, 3H); ^{13}C NMR (ppm) δ 170.8, 131.7, 128.2, 128.0, 123.0, 87.8, 85.0, 60.6, 54.4, 53.7, 51.7, 31.8, 22.3, 14.2; HRMS calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1488.

Table 5, entry 1: To a solution of NEt_3 (9.1 mg, 0.09 mmol) in toluene (1.5 mL) was added CuBr (6.4 mg, 0.045 mmol, 15 mol %). The mixture was stirred for 10 min under argon. Ketone **7** (48.7 mg, 0.42 mmol), amino acids **2a** (51.8 mg, 0.45 mmol), and alkyne **3a** (30.6 mg, 0.30 mmol) were added. The reaction temperature was raised to 110 °C as soon as possible. The resulting mixture was stirred at the same temperature overnight, and then was cooled to room temperature. The resulting suspension was diluted with ethyl acetate and filtered through a short fluorisil column eluting with ethyl acetate. Solvent was evaporated and the residue was purified by column chromatography (hexane/diethyl ether = 15:1−5:1) on silica gel to afford the coupling products **8a** in 64% (52.0 mg) isolated yield as a yellow oil. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43−7.39 (m, 2H), 7.29−7.26 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.06−4.02 (m, 1H), 3.77 (q, J = 6.9 Hz, 1H), 3.00−2.93 (m, 1H), 2.87−2.79 (m, 1H), 2.28−2.19 (m, 1H), 2.06−1.81 (m, 3H), 1.43 (d, J = 7.2 Hz, 3H), 1.35−1.22 (m, 3H); ^{13}C NMR (ppm) δ 173.5, 131.7, 128.1, 127.9, 123.2, 88.6, 84.7, 60.3, 57.6, 52.7, 46.9, 32.1, 22.2, 17.8, 14.3; HRMS calcd for $C_{17}H_{21}O_2N$ 271.1572, found 271.1567. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43−7.38 (m, 2H), 7.30−7.25 (m, 3H), 4.23−4.10 (m, 3H), 3.46 (q, J = 6.9 Hz, 1H), 2.96−2.89 (m, 1H), 2.71−2.63 (m, 1H), 2.28−2.17 (m, 1H), 2.08−1.83 (m, 3H), 1.45 (d, J = 6.9 Hz, 3H), 1.35−1.25 (m, 3H); ^{13}C NMR (ppm) δ 174.2, 131.7, 128.2, 128.0, 123.1, 87.6, 85.0, 60.6, 59.9, 51.5, 49.6, 31.6, 22.3, 17.1, 14.2; HRMS calcd for $C_{17}H_{21}O_2N$ 271.1572, found 271.1566.

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Supporting Information Available: Typical experimental procedure, characterization data, NMR spectra, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.