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Copper-Catalyzed Aerobic Enantioselective Cross-Dehydrogenative Coupling of *N*-Aryl Glycine Esters with Terminal Alkynes

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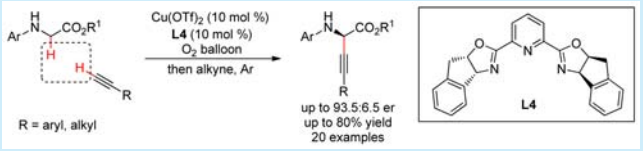
Supporting Information

ABSTRACT: A copper-catalyzed enantioselective cross-coupling of a C_{sp3}−H moiety (*N*-aryl glycine ester) with a C_{sp}−H component (terminal alkyne) using molecular oxygen as the terminal oxidant is described for the first time. The sustainable method provides an efficient and environmentally friendly approach to rapidly prepare a diverse array of optically active non-natural α-amino acids.



The construction of C−C bonds through cross-dehydrogenative coupling (CDC) of two easily accessible C−H components under oxidative condition has emerged as one of the most straightforward and economical approaches for increasing molecular complexity and functional group content with minimal waste generation.[1,2] Despite significant progress, existing CDC reactions typically require the use of a stoichiometric oxidant such as DDQ, TBHP, and IBX, which generate undesired waste. More ideal molecular oxygen as the oxidant in view of economical and ecological aspects with H_2O as the only byproduct has not been well adopted for the process.[3] On the other hand, the development of the catalytic enantioselective CDC variant remains a formidable challenge.[4,5] Consequently, only few examples of aerobic enantioselective CDC have been established to date.[6] Cui and Jiao reported an organocatalytic enantioselective α-alkylation of aldehydes with xantheses.[6a] Xu disclosed an enantioselective β-alkylation of aldehydes with dialkyl malonates by merging oxidative enamine and palladium catalysis.[6b] Gong and Meggers documented a rhodium-catalyzed enantioselective CDC of amines with ketones.[6d] All these transformations involve the oxidative coupling of a C_{sp3}−H component with the other reactive C_{sp3}−H bond adjacent to the carbonyl moiety. Wang reported an enantioselective olefination of *N*-arylated tetrahydroisoquinolines with α,β-unsaturated carbonyls, involving the aerobic oxidative coupling of the C_{sp3}−H bond adjacent to amines with the C_{sp2}−H bond adjacent to the carbonyl group.[6e] To the best of our knowledge, no example of aerobic, catalytic enantioselective CDC reaction involving a C_{sp}−H component like the terminal alkyne has been established.

Optically active α-amino acids are fundamental subunits spread across numerous pharmaceutical agents and have been widely utilized as chiral auxiliaries and catalysts in organic synthesis.[7] More importantly, integrating non-natural (synthetic) amino acids into existing bioactive peptides has been identified as an effective optimizing strategy in proteomics as well as drug discovery projects. Thus, general methods to prepare chiral non-natural α-amino acids by direct modifying natural moieties are highly desirable.[8] Glycine is the simplest and cheapest natural amino acid. Therefore, the catalytic enantioselective CDC of glycine derivatives with a variety of commercially available C−H components would provide a straightforward and rapid access to a high-quality collection of chiral non-natural α-amino acids bearing diverse substituents at the α-position for subsequent manipulation and application.[9] The Wang group established the first catalytic enantioselective CDC of *N*-aryl glycine esters with β-ketoesters mediated by DDQ, generating a series of chiral α-alkylated glycine derivatives.[5e] Despite great innovation, two aspects merit further comment. First, DDQ is moderately expensive and poses modest toxicity concerns (LD_{50} = 82 mg/kg), the potential for HCN liberation upon exposure to H_2O, and the purification difficulties. The employment of molecular oxygen as the terminal oxidant would be highly desirable based on economical and environmental factors. Second, the ability of the ketoester moieties to engage in the subsequent manipulation was relatively limited. In contrast, alkynes are outstanding precursors for functionally diverse structures due to the ability to participate in numerous transformations. The Li group reported a nonenantioselective TBHP-mediated CDC of glycine amides with arylacetylenes.[10] However, no reactivities were observed for simple alkyl acetylenes with broader synthetic utilities as well as the corresponding glycine esters. To the best of our knowledge, a catalytic enantioselective CDC of glycine derivatives with terminal alkynes has not been disclosed to date. Herein, we report the first aerobic catalytic enantioselective CDC of C_{sp3}−H moieties with C_{sp}−H components.

Initially, the CDC of *N*-aryl glycine ester **1a** with arylacetylene **2a** using molecular oxygen as the oxidant was selected as the

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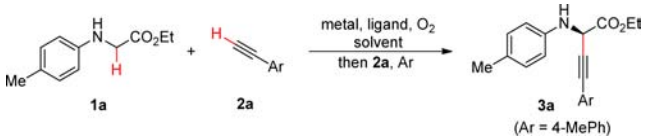
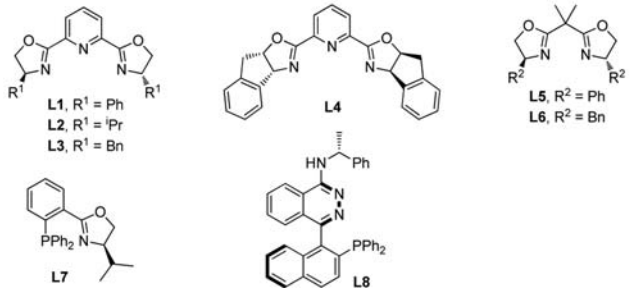
model reaction for optimization (Table 1). No reaction took place in the absence of any metal additive (Table 1, entry 1).

Table 1. Reaction Condition Optimization[a]



entry	L	metal	solvent	yield (%)[b]	er[c]
1	–	–	CH_2Cl_2	< 5	n.d.
2	–	$Cu(OTf)_2$	CH_2Cl_2	67	n.d.
3	**L1**	$Cu(OTf)_2$	CH_2Cl_2	40	83.5:16.5
4	**L2**	$Cu(OTf)_2$	CH_2Cl_2	45	71:29
5	**L3**	$Cu(OTf)_2$	CH_2Cl_2	32	76:24
6	**L4**	$Cu(OTf)_2$	CH_2Cl_2	54	86:14
7	**L5**	$Cu(OTf)_2$	CH_2Cl_2	< 5	n.d.
8	**L6**	$Cu(OTf)_2$	CH_2Cl_2	13	56:44
9	**L7**	$Cu(OTf)_2$	CH_2Cl_2	56	51:49
10	**L8**	$Cu(OTf)_2$	CH_2Cl_2	24	70:30
11	**L4**	CuOTf	CH_2Cl_2	27	78:22
12	**L4**	CuBr	CH_2Cl_2	20	66:34
13	**L4**	CuCl	CH_2Cl_2	< 5	n.d.
14	**L4**	$Cu(OTf)_2$	CH_3CN	49	71.5:28.5
15	**L4**	$Cu(OTf)_2$	Et_2O	29	81:19
16	**L4**	$Cu(OTf)_2$	toluene	78	90:10
17	**L4**	$Cu(OTf)_2$	$CF_3C_6H_5$	58	89:11
18[d]	**L4**	$Cu(OTf)_2$	toluene	26	85:15

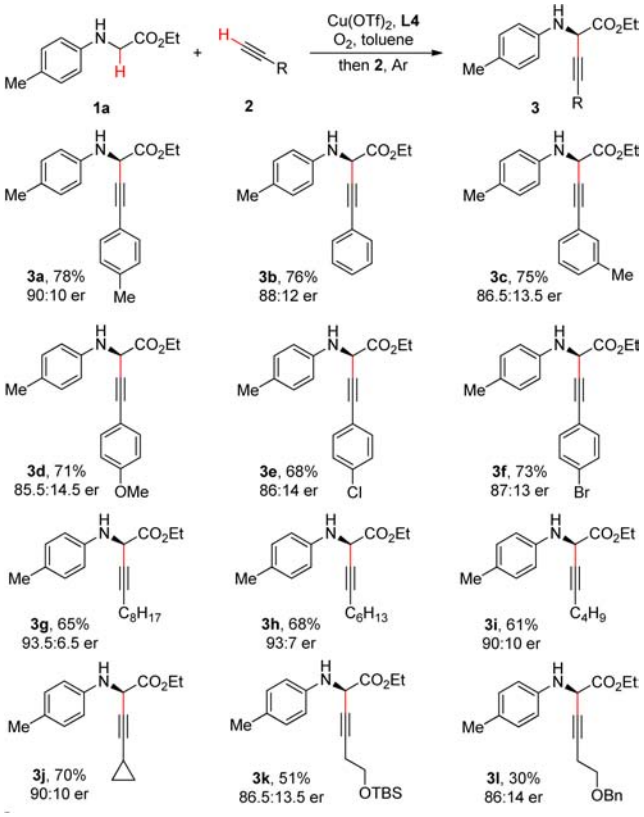


[a]Reaction condition: **1a** (0.1 mmol), ligand (0.01 mmol), and $Cu(OTf)_2$ (0.01 mmol) in toluene (1.0 mL) under 1 atm molecular oxygen at 40 °C for 2 h, followed by the addition of **2a** (0.2 mmol) under N_2 atmosphere overnight. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Air instead of oxygen. n.d. = not determined.

$Cu(OTf)_2$ proved to be able to catalyze the CDC reaction (entry 2). A systematic exploration of chiral ligands **L1**–**L8** and metal sources revealed that pybox **L4** with $Cu(OTf)_2$ should be the ideal combination in terms of the enantiomeric ratio and the yield (entries 3–13). The further study on the solvent effect identified toluene to be optimal (entries 14–17). Replacing molecular oxygen with air gave an inferior result (entry 18).

The scope of the aerobic catalytic enantioselective CDC of *N*-aryl glycine ester **1a** with a variety of terminal acetylenes was explored (Scheme 1). A variety of the electronically varied aryl acetylenes with different substituent patterns were well

Scheme 1. Scope of the Terminal Alkynes[a]



[a]Reaction condition: **1a** (0.1 mmol), **L4** (0.01 mmol), and $Cu(OTf)_2$ (0.01 mmol) in toluene (1.0 mL) under 1 atm molecular oxygen at 40 °C for 2 h, followed by the addition of **2** (0.2 mmol) under N_2 atmosphere overnight.

compatible with the system, providing expected α-alkynylated glycine esters **3a**–**3f** in good er value and yields. Classically, the efficient synthesis of glycine derivatives bearing alkyl acetylenes at the α-position has proved to be challenging probably due to the reduced reactivity of alkyl acetylenes.[10,11] Excitedly, such components like **2g**–**2i** participated in the aerobic catalytic enantioselective CDC process smoothly with even better enantiomeric ratio (up to 93.5:6.5 er) than aryl acetylenes. Additionally, alkyl acetylenes with commonly encountered functional group such as cyclopropyl (**2j**), silyl ether (**2k**), and benzyl ether (**2l**) were also well tolerated. Given that alkyl acetylenes are excellent precursors for functionally diverse structures due to the ability to engage in numerous transformations, the method displays the capability in creating diversely functionalized chiral non-natural α-amino acid derivatives in high efficiency.

The scope of glycine derivatives **1** was next explored (Scheme 2). The electronic substituent effect on the aniline moiety was first studied. Monomethyl substituted aniline **1a** in Scheme 1 proved to be the best substrate in terms of the enantiomeric ratio and yields. Replacing the methyl substituted aniline with either more electron-rich **4b** and **4c** or -deficient **4d** and **4e** led to a drop in both efficiency and er value. The steric substituent effect of ester moieties was then investigated. Isopropyl ester **4f** provided better er value than those of ethyl (**3b**) and isobutyl (**4g** and **4h**)

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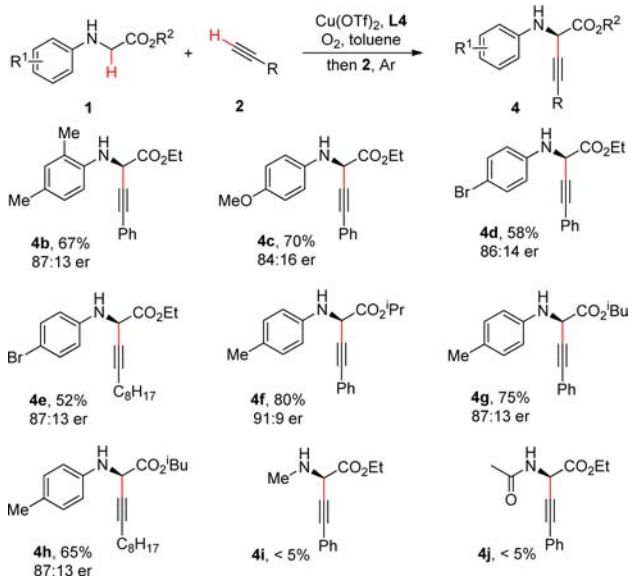
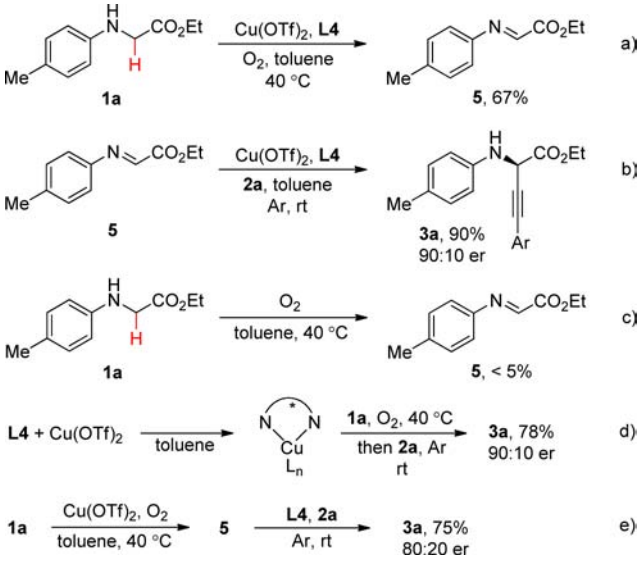
Scheme 2. Scope of the Glycine Esters



ones. The aryl group linked to the nitrogen was crucial to the reaction, and no reactivity was observed for *N*-alkyl glycine ester **4i** or *N*-acyl **4j**.

In the presence of pybox **L4** and $Cu(OTf)_2$ under molecular oxygen atmosphere, *N*-aryl glycine ester **1a** was converted to an intermediate detected by TLC analysis, which was identified as the α-imino ester **5** (Scheme 3a). Subjecting **5** to the catalytic

Scheme 3. Control Experiments for Mechanistic Studies



enantioselective alkynylation conditions providing expected **3a** in comparable er value to that of the CDC starting from *N*-aryl glycine ester **1a** (Scheme 3b), suggesting that **5** should be an intermediate for the process. Recently, α-imino esters were disclosed to be prepared through the autoxidation of *N*-aryl glycine ester precursors.[6d,9f] Therefore, the role of $Cu(OTf)_2$ was next examined. No expected **5** was observed in the absence of $Cu(OTf)_2$ under molecular oxygen atmosphere, indicating the involvement of $Cu(OTf)_2$ in the oxidation process (Scheme 3c). The addition sequence of reaction components proved to be crucial to the enantioselectivity. The standard procedure involving the premixing of **L4** and $Cu(OTf)_2$ followed by the addition of **1a** and **2a** proved to be the best sequence (Scheme 3d), whereas performing the oxidation of **1a** with $Cu(OTf)_2$ and molecular oxygen followed by the introduction of **L4** and **2a** afforded an inferior er value (Scheme 3e).

The control experiments together with the absolute configuration of the outcome suggested a preliminary model for enantioinduction (Scheme 4).[11] It was proposed that by

Scheme 4. Proposed Stereochemical Model

coordination of the imino ester to the copper center in a bidentate fashion, the imino ester is activated for addition through **6b**, providing the expected (*R*)-**3a**.[12] Significant steric hindrance between the aryl substituent of the imino ester and the R^1 group of the ligand destabilizes the transition state **6a** that would lead to the opposite enantiomer of the product.

In conclusion, the first catalytic enantioselective cross-coupling of a C_{sp3}–H component with C_{sp}–H moiety using molecular oxygen as the terminal oxidant has been described. The $Cu(OTf)_2$-catalyzed CDC of *N*-aryl glycine esters with a wide variety of alkyl as well as aryl acetylenes bearing common functional groups proceeded smoothly, rapidly providing a large array of diverse chiral non-natural α-amino acid derivatives in good efficiency and enantiomeric ratio. We envision that the sustainable method outlined herein will have potential applications in increasingly significant proteomics and peptide-based drug discovery research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01328.

Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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