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Dehydrogenative Cross-Coupling Reaction between *N*-Aryl α-Amino Acid Esters and Phenols or Phenol Derivative for Synthesis of α-Aryl α-Amino Acid Esters

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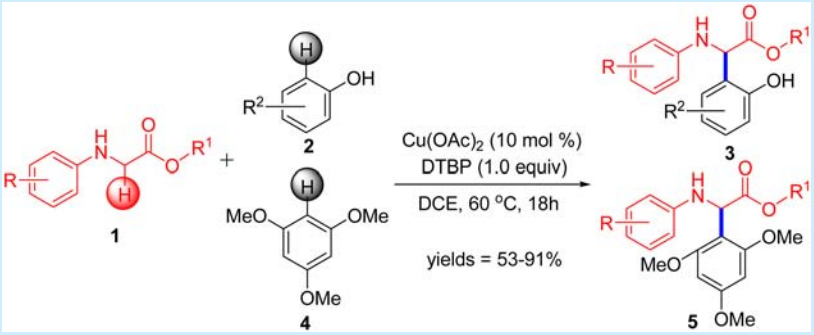
Supporting Information



ABSTRACT: A novel dehydrogenative cross-coupling (DCC) reaction between *N*-arylglycine esters and phenols or 1,3,5-trimethoxybenzene was developed by copper catalysis using di-*tert*-butyl peroxide (DTBP) as an oxidant. Under optimized conditions, a range of *N*-arylglycine esters **1** underwent the DCC reaction smoothly with various phenols **2** or 1,3,5-trimethoxybenzene **4** to give desired α-aryl α -amino acid esters **3** or **5**, respectively, with high *ortho* regioselectivities in a moderate to excellent yield. A possible mechanism involving aromatic electrophilic substitution is proposed.

Currently, the use of only C−H bonds to undergo dehydrogenative cross-coupling (DCC) reactions is thought of as a new generation of C−C bond formations because DCC reactions avoid prefunctionalization of substrates and are more atom economic and environmentally friendly.[1] Among the DCC reactions, much attention has been paid to the direct coupling of α-C(sp^3)−H bonds of α-amino acid derivatives with the C−H bonds of various nucleophiles for the synthesis of various α-substituted α-amino acid derivatives.[2−4] For example, in 2008, Li and co-workers found the first example of DCC reaction between *N*-substituted glycine derivatives and malonates by the catalysis of a copper complex.[2a] In 2010, our group revealed a DCC reaction between *N*-arylglycine esters and ketones under the cooperative catalysis of copper salt and secondary amine.[2b] In 2011, Wang et al. disclosed an asymmetric DCC reaction of *N*-arylglycine esters with α-substituted β-ketoesters by a chiral copper catalyst.[2c] In 2012, Bao and co-workers developed an oxidative coupling reaction of *N*,*N*-disubstituted glycine esters with naphthols to give the desired α-naphthylated α-amino acid esters.[3b] Although some phenols bearing electron-donating groups on benzene rings also performed the DCC readily, 4-bromophenol as a sole example of a phenol bearing an electron-withdrawing group on the benzene ring could not lead to the desired coupling product. Herein, we present our recent work on the DCC reaction of *N*-monosubstituted α-amino acid esters with phenols bearing electron-withdrawing groups as well as electron-donating groups on benzene rings or trimethoxybezene for the synthesis of α-aryl α-amino acid esters.

Initially, we chose *N*-arylglycine ester **1a** and phenol **2a** as a model reaction to explore and to optimize the DCC reaction between them. When the reaction of *N*-arylglycine ester **1a** with phenol **2a** was performed under the catalysis of 10 mol % of CuBr using O_2 as an oxidant in toluene at 60 °C, we were pleased to find that the desired α-aryl α-amino acid ester **3aa** was formed, albeit in 26% yield (entry 1, Table 1). Then, other transition-metal catalysts were probed, and $Cu(OAc)_2$ proved to be best with 45% yield for coupling product **3aa** (compare entries 1−4 with entry 3, Table 1; also see the Supporting Information). A series of oxidants such as *tert*-butyl hydroperoxide (TBHP), dicumyl peroxide (DCP), *tert*-butyl perbenzoate (TBPB), and di-*tert*-butyl peroxide (DTBP) were examined, and DTBP showed the best efficiency with regard to the yield of **3aa** (compare entries 6 and 7 with entry 8, Table 1; also see the SI). Among various solvents screened, dichloroethane (DCE) led to the best yield of **3aa** (compare entries 8 and 9 with entry 10, Table 1; also see SI). In the absence of $Cu(OAc)_2$, **3aa** was isolated in only 7% yield (entry 11, Table 1). Increasing the amount of $Cu(OAc)_2$ led to a reduction in

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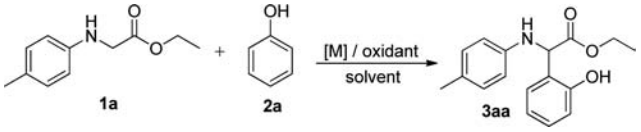
Table 1. Optimization of the DCC Reaction between *N*-Arylglycine Ester 1a and Phenol 2a[a]



entry	[M] (10 mol %)	oxidant	solvent	yield[b] (%)
1	CuBr	O_2	toluene	26
2	Cu_2O	O_2	toluene	34
3	$Cu(OAc)_2$	O_2	toluene	45
4	$FeCl_3$	O_2	toluene	NP
5	$Cu(OAc)_2$	–	toluene	12
6	$Cu(OAc)_2$	DCP	toluene	15
7	$Cu(OAc)_2$	TBPB	toluene	40
8	$Cu(OAc)_2$	DTBP	toluene	49
9	$Cu(OAc)_2$	DTBP	xylene	25
10	$Cu(OAc)_2$	DTBP	DCE	56
11	–	DTBP	DCE	7
12[c]	$Cu(OAc)_2$	DTBP	DCE	31
13[d]	$Cu(OAc)_2$	DTBP	DCE	28
14[e]	$Cu(OAc)_2$	DTBP	DCE	39
15[f]	$Cu(OAc)_2$	DTBP	DCE	64

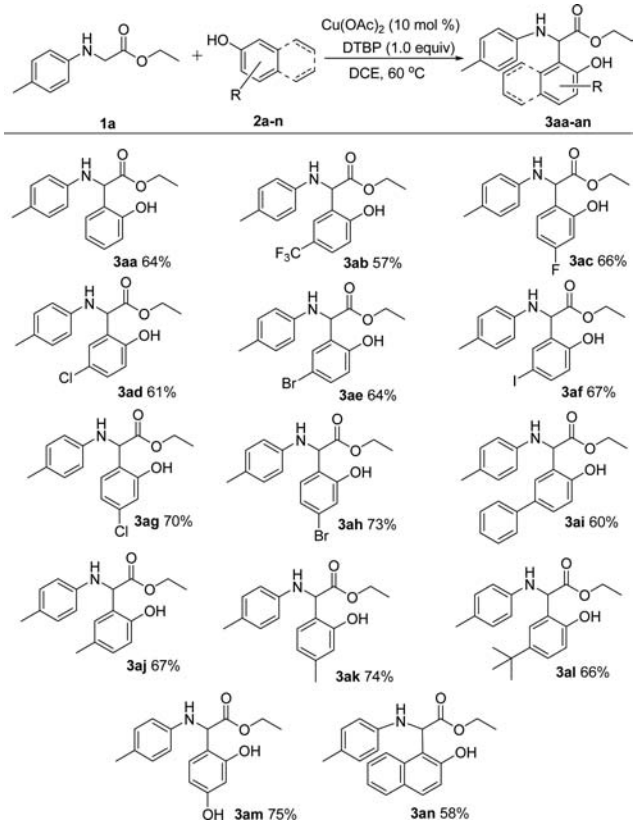
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst (10 mol %), and solvent (2.0 mL) at 60 °C; under O_2 (1 atm) or using oxidant (1.0 equiv) for 24 h. [b]Isolated yields. [c]At 15 mol % $Cu(OAc)_2$ [d]At 80 °C. [e]At 40 °C. [f]18 h.

the yield of **3aa** (entry 12, Table 1). The optimization experiment also indicated that raising the temperature to 80 °C or lowering the temperature to 40 °C was not beneficial to the DCC reaction (compare entries 13 and 14 with entry 11, Table 1).

On the basis of the screening of the reaction conditions, it can be concluded that the optimized reaction should be performed under catalysis of $Cu(OAc)_2$ (10 mol %) using DTBP (1.0 equiv) as an oxidant in DCE at 60 °C. Under the optimized reaction conditions, we investigated the scope of phenols in the DCC reaction with *N*-arylglycine ester **1a**. It was found that various phenols (**2a**–**m**) were able to undergo the DCC reaction with *N*-arylglycine ester **1a**, affording α-aryl α-amino acid esters **3aa**–**am** in 57–75% yields (Scheme 1). Different from reported protocol,[3b] in the presented DCC reaction, the phenols **2b**–**h** bearing electron-withdrawing groups also led to α-aryl α-amino acid esters **3ab**–**ah** expediently besides those **2i**–**m** bearing electron-donating groups. Under the optimized conditions, benzene did not perform the DCC reaction with *N*-arylglycine ester **1a**.

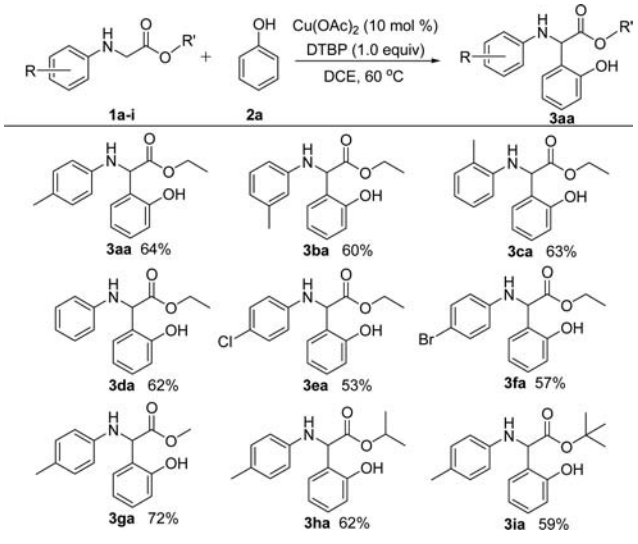
After the scope of phenols was examined, a series of *N*-arylglycine esters **1a**–**i** were investigated in the DCC reaction with phenol **2a**. It was found that under the optimized conditions the DCC reaction proceeded smoothly to give α-aryl α-amino acid esters **3aa**–**ia** in 53–72% yields (Scheme 2). The experimental results indicated that the DCC reaction has high regioselectivities with *ortho*-coupling products **3aa**–**ia**. No *para*-coupling counterpart was isolated in the DCC reaction. A range of *N*-arylglycine esters **1a**–**c** bearing both electron-donating groups and those **1e**–**f** bearing electron-withdrawing groups led to the desired coupling product **3aa**–**fa** readily in satisfactory yields. The experimental results also demonstrated that methyl, isopropyl, and *tert*-butyl glycine esters **1g**–**i** as well as ethyl glycine ester **1a** were able to perform the DCC reaction

Scheme 1. DCC Reaction between *N*-Arylglycine Ester 1a and Phenol Derivatives 2a–n by Copper Catalysis



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), and solvent (2 mL), at 60 °C; under oxidant for 18 h. [b]Isolated yields.

Scheme 2. DCC Reaction between *N*-Arylglycine Esters 1a–i and Phenol 2a by Copper Catalysis



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), and solvent (2 mL), at 60 °C; under oxidant for 18 h. [b]Isolated yields.

with phenol **2a** to give the desired coupling product **3ga**–**ia** in 59–72% yields.

Moreover, 1,3,5-trimethoxybenzene **4** as an electron-rich aromatic nucleophile performed the DCC reaction smoothly with a variety of *N*-arylglycine esters **1a**–**i** under the optimized

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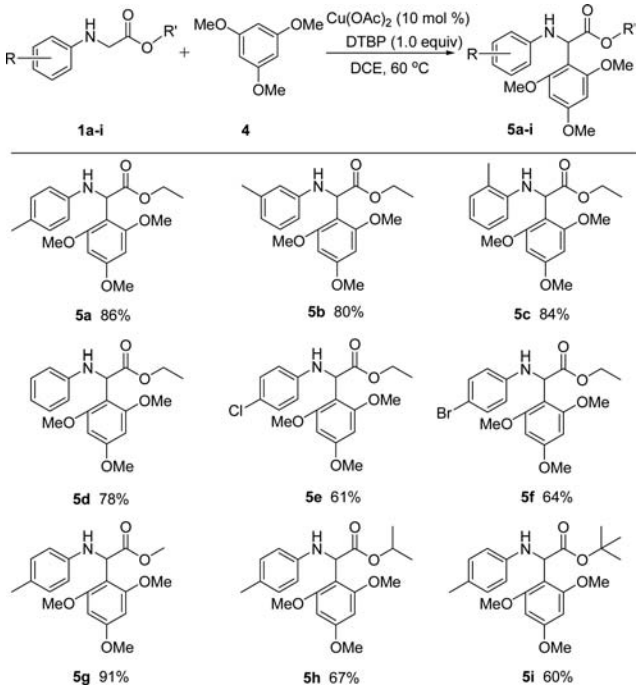
conditions (Scheme 3). Moderate to excellent yields of desired α-aryl α-amino acid esters **5a–i** were achieved. When anisole was employed to perform the DCC reaction with glycine ester **1a**, no desired coupling product was observed under the optimized conditions.

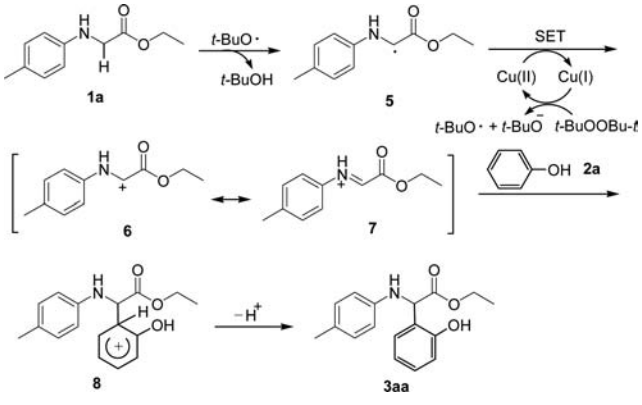
Scheme 3. DCC Reaction between *N*-Arylglycine Esters 1a–i and 1,3,5-Trimethoxybenzene 4 by Copper Catalysis



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), and solvent (2 mL), at 60 °C; under oxidant for 18 h. [b]Isolated yields.

When 2,6-di-*tert*-butyl-4-methylphenol (BHT), a radical scavenger, was added into the reaction system of 4-methyl *N*-arylglycine ester **1a** with phenol **2a** under optimized conditions, the yield of coupling product **3aa** was dramatically decreased to 18%. This result suggests that the reaction may undergo a radical mechanism. A plausible mechanism of the reaction may proceed as follows (Scheme 4). Initially, a *tert*-butoxyl radical generated by the dissociation of DTBP may abstract α-hydrogen of glycine ester **1a** to form radical **5**.[2d] A single-electron transfer (SET) from **5** to copper(II) leads to cation **6** and copper(I), which can be oxidized to copper(II) for catalytic recycle by DTBP.[5] Immediately, cation **6** can tautomerize to iminium ion **7**.[2b] Then, phenol **2a** undergoes electrophilic addition with iminium ion **7** to generate σ-complex **8**, followed by loss of a proton to give the desired α-aryl α-amino acid ester **3aa**.

Scheme 4. Plausible Mechanism for the DCC Reaction



In conclusion, we have developed a novel DCC reaction between *N*-arylglycine esters **1** and phenols **2** by copper catalysis using DTBP as an oxidant. A range of *N*-arylglycine esters **1** undergo the DCC reaction with various phenols **2** bearing electron-withdrawing groups as well as electron-donating groups on benzene rings, smoothly affording desired α-aryl α-amino acid esters **3** with high *ortho*-regioselectivities in 53–75% yields. The optimized reaction conditions are also suitable for 1,3,5-trimethoxybenzene to perform the DCC reaction with a variety of *N*-arylglycine esters **1** to give α-aryl α-amino acid esters **5** in moderate to excellent yields. A possible mechanism involving aromatic electrophilic substitution is also proposed. Further studies on the DCC reactions between other α-amino acid derivatives and aromatic compounds and related mechanisms are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00162.

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR, and HRMS spectra for the DCC products (PDF)

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Notes

The authors declare no competing financial interest.

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