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Dehydrogenative Cross-Coupling Reaction by Cooperative Transition-Metal and Brønsted Acid Catalysis for the Synthesis of β-Quinolinyl α-Amino Acid Esters

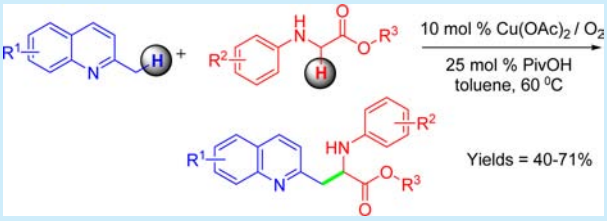
Zhi-Qiang Zhu,[†] Peng Bai,[†] and Zhi-Zhen Huang*[,†,‡]

[†]Department of Chemistry, Zhejiang University, Hangzhou, 310028, P. R. China

[‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, P. R. China

Supporting Information

ABSTRACT: A novel dehydrogenative cross-coupling (DCC) reaction between methylquinoline derivatives and *N*-aryl glycine esters was developed by a cooperative catalysis of copper salt and Brønsted acid, affording an efficient synthesis of β-quinolinyl α-amino acid esters. A plausible mechanism using a proton to activate the methylquinoline derivative and copper(II) to activate *N*-aryl glycine ester has been proposed.



At present, the use of only C−H bonds to undergo dehydrogenative cross-coupling (DCC) reactions is considered 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, the direct coupling of α-C(sp^3)−H bonds of α-amino acid derivatives with the C−H bonds of various nucleophiles demonstrated considerable importance for the synthesis of versatile α-substituted α-amino acid derivatives.[2] For example, in 2008, Li et al. found the first example of a DCC reaction between α-amino acid derivatives and malonates by the catalysis of a copper complex.[2a] In 2010, our group developed a DCC reaction between α-amino acid derivatives and ketones under the cooperative catalysis of copper salt and secondary amine.[2b] In 2011, Wang and coworkers reported an asymmetric DCC reaction of *N*-substituted glycine esters with α-substituted β-ketoesters by a chiral copper catalyst.[2c] In 2014, Huo's group developed a copper-catalyzed DCC reaction of α-amino acid derivatives with indoles to give desired arylated products.[2j]

Quinolines are biologically important compounds that widely occur in nature and are useful as drugs or drug candidates in medicinal chemistry.[3,4] Many investigations have been conducted to introduce quinoline moieties into organic molecules by C−H bond functionalizations of quinoline derivatives. Recently, 2-alkylquinolines activated by Lewis acid or transition-metal catalysts were found to be elegant nucleophiles to perform their C−H bond functionalizations with various electrophiles.[5] Furthermore, some efforts have been focused on the reactions of 2-alkylquinolines with electrophiles by the catalysis of Brønsted acids[6] or in the absence of catalysts.[7] For example, in 2012 Yang et al. successfully developed a Brønsted acid promoted nucleophilic addition of 2-alkylquinolines to aldehydes.[6a] Tian's group reported that methylquinolines were able to perform a nucleophilic reaction smoothly with *N*-alkyl anilines to give polysubstituted alkenes in moderate to excellent yields with excellent *E*-selectivities.[7a] In 2014, a novel DCC reaction of 2-methylquinolines with *N*-aryl tetrahydroisoquinolines under the dual catalysis of a copper salt and Brønsted acid was disclosed.[6b] However, to the best of our knowledge, the DCC reaction of alkylquinolines or alkylpyridines with α-amino acid derivatives as electrophiles has remained unknown. Owing to the biological importance of quinoline and α-amino acid derivatives, and as the continuation of our studies on DCC reactions,[2b,8] we carried out the investigation on the DCC reaction of methylquinolines with α-amino acid esters for the synthesis of β-quinolinyl α-amino acid esters by a cooperative transition-metal and Brønsted acid catalysis.

Initially, 2-methylquinoline **1a** and *N*-4-methylphenyl glycine ester **2a** were chosen as model substrates to explore and optimize their coupling reaction. When the reaction performed in the presence of 10 mol % CuCl and 25 mol % pivalic acid (PivOH) under an oxygen atomsphere at 60 °C, we were pleased to find that the desired β-quinolinyl α-amino acid esters **3aa** was formed in 35% yield (entry 1, Table 1). Then, other transition-metal catalysts were examined in the reaction. The experiment indicated that among these transition-metal salts, $Cu(OAc)_2$ is most efficient for the yield (compare entries 1−4 with entry 5, Table 1; also see Supporting Information (SI)). No desired product **3aa** was observed in the absence of a copper catalyst (entry 6, Table 1). When other oxidants rather than oxygen were employed, lower or no yields of **3aa** were obtained (compare entries 7−8 with entry 5, Table 1; also see SI). For the screening of a Brønsted acid, it was found that 25 mmol % PivOH was best to afford the desired product **3aa** in 60% yield (compare entries 9−11 with entry 5, Table 1). The

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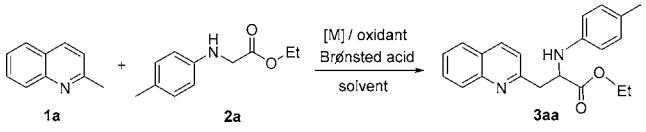
Table 1. Optimization of DCC Reaction between 2-Methylquinoline 1a and *N*-4-Methylphenylglycine Ester 2a[a]



entry	[Cu]	oxidant	BA	solvent	yield (%)[b]
1	CuCl	O_2	PivOH	DCE	35
2	CuBr	O_2	PivOH	DCE	20
3	$CuBr_2$	O_2	PivOH	DCE	18
4	$Cu(OTf)_2$	O_2	PivOH	DCE	36
5	$Cu(OAc)_2$	O_2	PivOH	DCE	60
6	–	O_2	PivOH	DCE	–
7	$Cu(OAc)_2$	DTBP	PivOH	DCE	45
8	$Cu(OAc)_2$	$K_2S_2O_8$	PivOH	DCE	37
9	$Cu(OAc)_2$	O_2	AcOH	DCE	46
10	$Cu(OAc)_2$	O_2	PhCOOH	DCE	45
11	$Cu(OAc)_2$	O_2	*p*-TSA	DCE	30
12	$Cu(OAc)_2$	O_2	PivOH	THF	62
13	$Cu(OAc)_2$	O_2	PivOH	toluene	70 (67)[c]
14[d]	$Cu(OAc)_2$	O_2	PivOH	toluene	66
15	$Cu(OAc)_2$	O_2	–	toluene	36

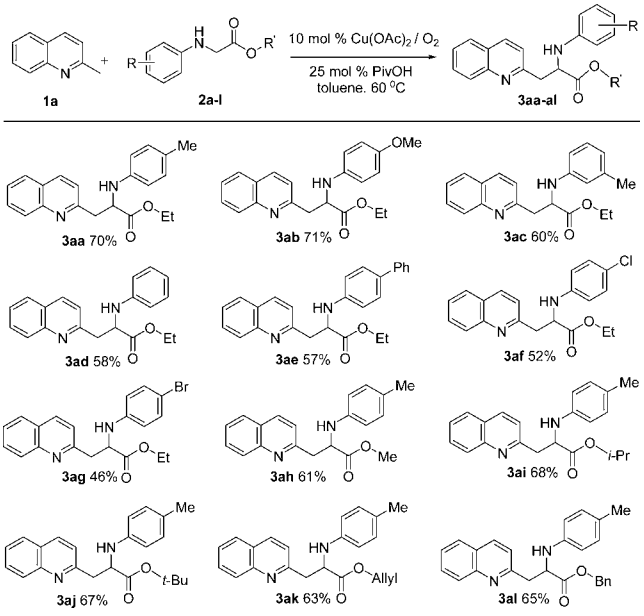
[a]The mixture of **1a** (0.4 mmol), **2** (0.2 mmol), catalyst (10 mol %), and Brønsted acid (25 mol %) was stirred in solvent (2 mL) at 60 °C; under O_2 (1 atm) for 24 h. [b]Isolated yields. [c]At 80 °C. [d]10 mol % pivalic acid

effect of solvent on this reaction was also investigated. Toluene was proved to be best in the yield of **3aa** as compared to DCE, THF, MeCN, EtOH, and CH_3Cl (compare entries 5, 12 with entry 13, Table 1; also see SI). Decreasing the loading of PivOH from 25 to 10 mol % led to a reduction in the yield of **3aa** (compare entry 14 with entry 13, Table 1). In the absence of PivOH, the yield of **3aa** was decreased remarkably (entry 15, Table 1).

After the reaction conditions were screened, it can be concluded that the optimized reaction should be performed under the catalysis of 10 mol % $Cu(OAc)_2$ and 25 mol % PivOH at 60 °C in toluene using oxygen as an oxidant. Under the optimized conditions, we found that various *N*-aryl glycine esters **2a–l** were able to undergo the DCC reaction smoothly with 2-methylquinoline **1a** to give desired coupling products **3aa–al** in the yields of 46–71% (Scheme 1). The experimental results also indicated that this DCC reaction is not very sensitive to the groups connected with carbonyl groups, such as ethyl, methyl, isopropyl, *tert*-butyl, allyl, and benzyl ester **2**. The electron-donating groups on *N*-benzene rings of glycine esters **2a–c** seem to be more beneficial to the DCC reaction as compared to the electron-withdrawing groups on *N*-benzene rings of glycine esters **2f–g**.

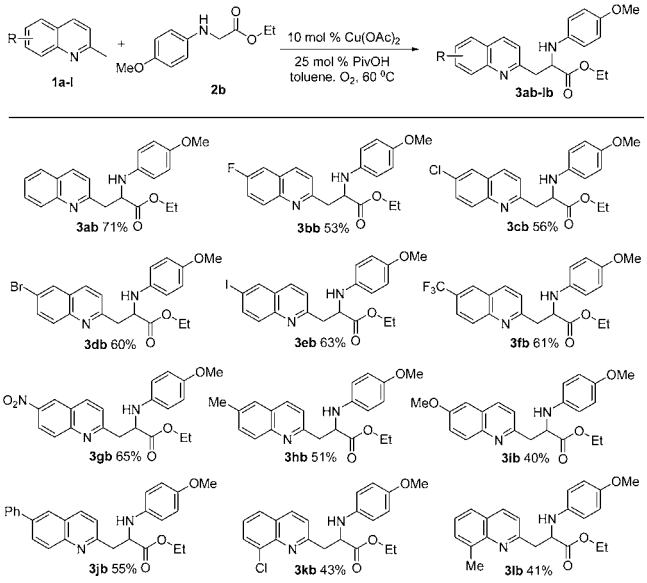
Then, various 2-methylquinolines **1** were examined in the DCC reaction with *N*-aryl glycine esters **2b**. The experiment demonstrated that the 2-methylquinolines **1a–l** bearing either electron-donating or -withdrawing groups on the 6-position of quinoline rings underwent the DCC reaction expediently with *N*-aryl glycine esters **2b** to give desired coupling products **3ab–lb** in satisfactory yields (Scheme 2). The 2-methylquinolines **1b–g** bearing electron-withdrawing groups on the 6-position quinoline rings resulted in better yields of coupling products **3bb–gb** than 2-methylquinolines **1h–i** bearing electron-donating groups. The 2-methylquinolines **1k–l** bearing a chloro group as an electron-withdrawing group or methyl

Scheme 1. DCC Reaction between 2-Methylquinoline 1a and *N*-Aryl Glycine Esters 2a–l under the Cooperative Catalysis of $Cu(OAc)_2$ and PivOH[a,b]



[a]The mixture of **1a** (0.4 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (10 mol %) and pivalic acid (25 mol %) was stirred in toluene (2 mL) at 60 °C under O_2 (1 atm) for 24 h. [b] Isolated yields.

Scheme 2. DCC Reaction between 2-Methylquinoline Derivatives 1a–l and *N*-Aryl Glycine Ester 2b under the Cooperative Catalysis of $Cu(OAc)_2$ and PivOH[a,b]



[a]The mixture of **1** (0.4 mmol), **2b** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), and pivalic acid (25 mol %) was stirred in toluene (2 mL) at 60 °C; under O_2 (1 atm) for 24 h. [b] Isolated yields.

group as an electron-donating group on the 8-position of quinoline rings could also undergo the DCC reaction smoothly with *N*-aryl glycine esters **2b** to give desired coupling products **3kb–lb**. When 2-methylpyridine was employed instead of 2-methylquinolines, no expected coupling product was observed.

Based on the literature,[6,9] a plausible mechanism for the DCC reaction is depicted in Scheme 3. Initially, 2-methylquino-

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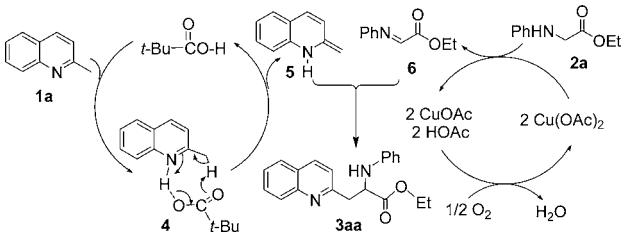
Scheme 3. Plausible Mechanism



line **1a** is tautomerized into enamine intermediate **5** under the catalysis of PivOH as a Brønsted acid.[6] The more reactive enamine **5** then nucleophilically attacks imine intermediate **6**, which is resulted from the oxidation of glycine ester **2a** by two molecules of $Cu(OAc)_2$,[2b] giving the desired coupling product **3aa**. Finally, the oxidation of CuOAc by oxygen regenerates $Cu(OAc)_2$ as a transition-metal catalyst.

In conclusion, we have developed a novel DCC reaction of methylquinoline derivatives **1** with *N*-aryl glycine esters **2** under the cooperative catalysis of copper salt and Brønsted acid. The new protocol tolerates various functional groups, such as nitro, fluoro, chloro, bromo, iodo, trifluoromethyl, methoxy, allyl, and phenyl groups, affording an efficient synthesis of β-quinolinyl α-amino acid esters **3**. A plausible mechanism using a proton to activate methylquinoline derivative **1** and copper(II) to activate *N*-aryl glycine ester **2** has also been proposed. Further studies on the C−C bond formations between $C(sp^3)$−H bonds of alkylazaarenes and $C(sp^3)$−H bonds of other substrates and related mechanisms are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra of ^{1}H NMR, ^{13}C NMR, and HRMS for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: huangzhizhen@zju.edu.cn.

Notes

The authors declare no competing financial interest.

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