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A General and Practical Access to Chiral Quinoxalinones with Low Copper-Catalyst Loading

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Abstract: A general, straightforward, and practical access to multi-substituted chiral quinoxalin-2-ones has been achieved based on the copper(I) chloride-dimethylethylenediamine (DMEDA) catalyst system. With the use of 1 mol% copper(I) chloride, structurally diverse quinoxalin-2-ones were generated with high optical purity from readily available starting materials, 2-haloanilines and α-amino acids, in a one-pot manner.

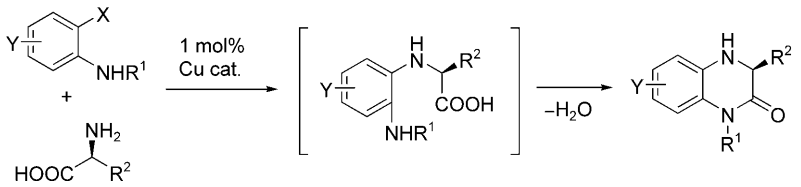
Keywords: copper catalyst; coupling reactions; low catalyst loading; quinoxalinones; Ullmann reaction

Introduction

Recently, Ullmann-type coupling reactions[1] using copper as catalyst introduced by Ullmann,[2] Goldberg,[3] Buchwald,[4] Ma[5] and Taillefer[6] are attracting much attention, because of the experimental simplicity, economic points of view, as well as low toxicity and stability of the catalyst. Therefore, various efficient and useful carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur bond forming reactions were developed in recent years.[1]

The domino-type reaction which forms two or more carbon-carbon and carbon-heteroatom bonds within a one-pot process is of particular interest because the core structures (pharmaceutical fragments[7]) such as the heterocyclic compounds found in many pharmaceuticals, agrochemicals and natural products can be constructed efficiently in a single operation.[8] There are a lot of examples that use the palladium catalysts so far.[9] Some examples that use a copper catalyst in domino reactions have appeared in recent years.[1] However, the amounts of copper catalyst used are larger (usually 5 to 10 mol%) than those of palladium, rhodium and iridium catalysts and a decrease is highly desirable from economical and environmental viewpoints.[10]

Herein, we report the unprecedented example for a low catalyst-loading domino-type reaction to form the multi-substituted quinoxalinones as their chiral forms from readily available starting materials (Scheme 1). Quinoxaline and derivatives are an important structural motif frequently found in pharmaceutical drugs[11] and agrochemicals.[12] Representative syntheses of quinoxalinones include the microwave assisted condensation of 1,2-phenylenediamine with citric acid,[11a] nucleophilic substitution of 2-fluoronitrobenzene with methyl pyrrole-2-carboxylate[13] and/or an α-amino acid[11b] followed by reductive cyclization, organocatalytic hetero-Diels–Alder reaction of aldehydes with *o*-benzoquinone diimide followed by oxidation,[14] the addition of *o*-phenylenediamine to dialkyl acetylenedicarboxylates followed by reaction



Scheme 1. Copper-mediated one-pot formation of quinoxalinones.

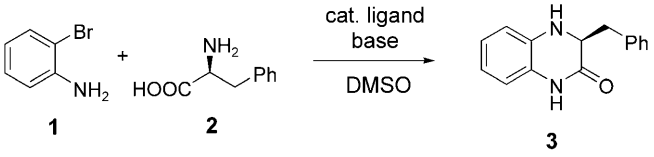
with arylsulfonyl isocyanates.[15] However, these methods might suffer from the limited availability of the starting materials, harsh conditions, poor yield, narrow scope, and/or expensive catalysts. Therefore, more efficient and facile routes to these useful molecules under mild onditions are needed.

Results and Discussion

Optimization of Conditions for the Reaction of 2-Bromoaniline and L-Phenylalanine

In our previous paper, we reported the synthesis of quinoxalinones from 2-haloanilines and amino acids by the use of traditional higher loading catalytic conditions (10 mol% copper(I) iodide using cesium carbonate as base in DMSO at 125 °C for 5 h under a nitrogen ballon).[16] Unfortunately, we did not make a further effort to improve the conditions. For this purpose, copper(I) chloride and potassium phosphate were newly selected as catalyst and base after the preliminary survey.[17] Both of them are easy to handle, less expensive and less toxic. 2-Bromoaniline **1** and L-phenylalanine **2** were employed as standard substrates to seek the optimal reaction conditions. Reaction of **1** with **2** (2 equiv.)[16,18] in the presence of 10 mol% copper(I) chloride and potassium phosphate (2 equiv.) in DMSO at 120 °C for 12 h under a nitrogen balloon gave the target quinoxalinone **3** in 85% yield (Table 1, entry1). On decreasing the catalyst to 1 mol%, **3** was obtained in 66% yield (entry 2). To our delight, satisfactory results (91%) were realized in the sealed tube (entry 3).[19] We next investigated the effect of ligand. TMEDA and EDA did not exert a notable effect, although DMEDA[10b] gave a slight better yield (entries 4, 5, and 6). On further decreasing the catalyst to 0.5 and 0.1 mol%, the reactions afforded unsatisfactory results (entries 7 and 8). The excellent conversion was realized with 1 mol% copper(I) chloride and 20 mol% DMEDA to produce quinoxalinone **3** in 99% yield after 24 h (not shown) and the efficiency was retained even at 110 °C (entry 9). On lowering the temperature to 100 °C, the yield decreased to 44% (not shown). When the amount of DMEDA was diminished to 1 mol%, 5 mol%, and 10 mol%, the yields of **3** were 94%, 95%, and 97%, respectively (not shown). In a blank experiment, the reaction did not proceed in the absence of copper catalyst. The presence of base was also essential. The reaction without base gave only 1% yield of compound **3** (not shown). Iron(III) chloride was a less effective catalyst in the present system (entry 10). The use of the organic base DBU also afforded the desired product **3** in high yield, although a prolonged reaction time (48 h) was needed (entry 11). The use of an organic base would be advantageous from the practical point of view to avoid the waste of inorganic salt.[20] Most of the cases with copper-catalyzed reaction, except for Sonogashira coupling,[21] use inorganic bases such as cesium carbonate, potassium phosphate, potassium carbonate, sodium hydroxide,[1] the use of organic base is, to the best of our knowledge, unprecedented. We are now seeking new reaction conditions based on the use of an organic base in the copper-catalyzed reaction. Consequently, three options for the conditions have been discovered: (i) ligand-free conditions (entry 3), (ii) conditions with high conversion at relatively low temperatures (entry 9), and (iii) conditions without the use of an inorganic salt (entry 11).

Table 1. Optimization of reaction conditions for the reaction with 2-bromoaniline **1** and L-phenylalanine **2**.[a]



1 2 3

Entry	Cat. [mol%]	Base	T [°C]	t [h]	L	Yield [%][b]
1[c]	CuCl [10]	K_3PO_4	120	12	None	85
2[c]	CuCl [1]	K_3PO_4	120	12	None	66
3	CuCl [1]	K_3PO_4	120	12	None	91
4	CuCl [1]	K_3PO_4	120	12	EDA	86
5	CuCl [1]	K_3PO_4	120	12	TMEDA	81
6	CuCl [1]	K_3PO_4	120	12	DMEDA	93
7	CuCl [0.5]	K_3PO_4	120	48	DMEDA	71
8	CuCl [0.1]	K_3PO_4	120	48	DMEDA	19
9	CuCl [1]	K_3PO_4	110	24	DMEDA	99
10	$FeCl_3$ [10]	K_3PO_4	130	24	DMEDA	2
11	CuCl [1]	DBU	110	48	DMEDA	96

[a] Unless otherwise stated, reactions were carried out with **1** (1.97 mmol), **2** (3.94 mmol, 2 equiv), catalyst (1 mol%), ligand (20 mol%), and base (3.94 mmol, 2 equiv.) in DMSO (7 mL) under a nitrogen atmosphere in the sealed tube.

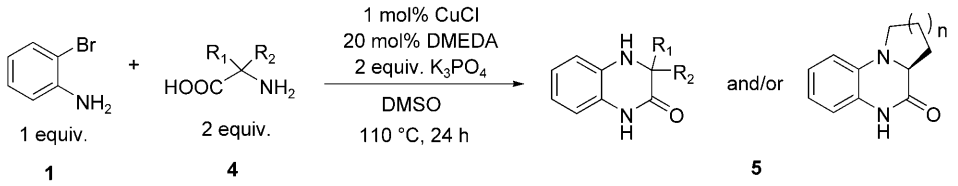
[b] Isolated yield.

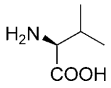
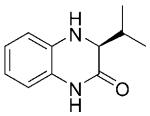
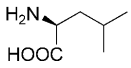
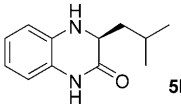
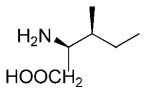
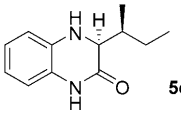
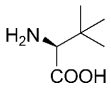
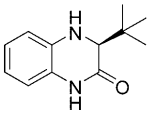
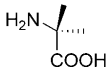
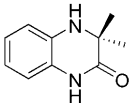
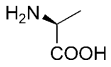
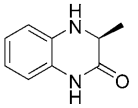
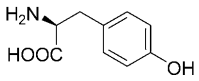
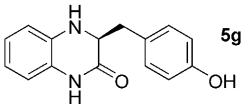
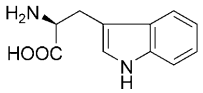
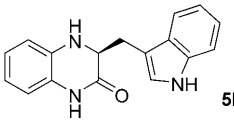
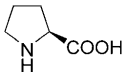
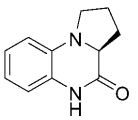
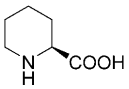
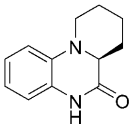
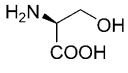
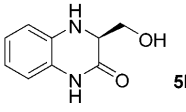
[c] Reaction under nitrogen baloon. DMEDA = dimethylethylenediamine, EDA = ethylenediamine, TMEDA = tetramethylethylenediamine, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Copper-Catalyzed Synthesis of Substituted Quinoxaline-2-ones *via* Coupling of 2-Bromoaniline with Diverse α-Amino Acids

Next, we examined the scope and limitation of the α-amino acids for this transformation with the optimized conditions (Table 1, entry 9) and the results are summarized in Table 2. A variety of α-amino acids was feasible to this protocol. It was noted that the

Table 2. Copper-catalyzed synthesis of substituted quinoxalin-2-ones **5** *via* coupling of 2-bromoaniline **1** with diverse α-amino acids **4**.[a]



Entry	**4**	**5**	Yield [%][b]
1		 **5a**	86
2		 **5b**	92
3		 **5c**	77
4		 **5d**	59; 62[c]
5		 **5e**	65
6		 **5f**	74
7		 **5g**	75
8		 **5h**	92
9		 **5i**	59; 58[c]
10		 **5j**	81
11		 **5k**	74

[a] *Reaction conditions:* 2-bromoaniline (1.97 mmol), amino acid (3.94 mmol, 2 equiv.), CuCl (1 mol%), DMEDA (20 mol%), and K_3PO_4 (3.94 mmol, 2 equiv.) in DMSO (7 mL) at 110 °C under a nitrogen atmosphere in the sealed tube.
[b] Isolated yield.
[c] Reactions with DBU (2 equiv.) as base instead of K_3PO_4 for 48 h.

product **5c** derived from L-isoleucine with 2-bromoaniline was a single stereoisomer by NMR analysis which showed that the possible epimerization of the chiral center at C-3 position did not take place throughout the reaction and work-up process (entry 3). A high tolerance towards functional groups in the amino acids was observed when tyrosine, tryptophan and serine were employed as coupling partner without protecting hydroxy and amino groups to afford the corresponding quinoxalinones **5g**, **5h** and **5k** in good yields (entries 7, 8, and 11). The α,α′-substituted amino acid, 2-aminoisobutyric acid, was also tolerated for this cyclization with an acceptable yield (entry 5). Amino acids with a secondary amine function also worked well to give tricyclic quinoxalinones **5i** and **5j** in good yields (entries 9 and 10). The reaction of the simplest amino acid, glycine, with 2-bromoaniline gave only a 9% yield of 3,4-dihydro-1*H*-quinoxalin-2-one because of its high polarity which prevented an efficient isolation (not shown). No reaction was observed when cysteine was employed as a coupling partner. In this case, the starting material was recovered quantitatively. Probably, cysteine might work as a catalyst poison.

Copper-Catalyzed Synthesis of Multiply Substituted Quinoxalin-2-ones *via* Coupling of Substituted 2-Bromoanilines with α-Amino Acids

Table 3 shows the results by employing various 2-bromoanilines as coupling partner in this transformation. 4-Methyl-, 4-chloro-, 2-trifluoromethoxy-, pyridyl-, and *N*-alkylanilines were investigated. As a result, these substituted anilines reacted with several α-amino acids to generate the corresponding diverse multiply substituted quinoxalinones **7a** to **7h** without a significant loss of reactivity.

Assumption of Optical Purity

As quinoxalinones are known to be useful templates for drug development, it is highly desirable to develop a general and practical method for the synthesis of chiral quinoxalinones.[11c,22] To date, limited methods have appeared for the synthesis of optically active quinoxalinones,[11c,23] which include liquid-phase synthesis under microwave irradiation,[23a] organocatalytic hetero-Diels–Alder reactions,[14,23b] enantioselective reduction of quinoxalines and quinoxalinones.[23d] However, they all requre multiple reaction steps.

As mentioned above, the loss of chirality of quinoxalinone **5c** derived from L-isoleucine has not been observed throughout the reaction process (Table 1, entry 3). To confirm the optical purity of another product, quinoxalinones **3** and **5a** were selected and transformed into diastereomers **9** and **10** by the reaction of L-menthyl chloroformate **8**, respectively, as shown in Scheme 2. None of peaks corresponding to the possible diastereomer have been observed based on NMR analysis compared to authentic samples derived from racemic **3** and **5a** so that we concluded tentatively that the possible epimerization at the C-3 position has not occured to produce final products with high optical purity. This underlines the mildness of the reaction conditions.

Assumption of the Reaction Path

It was assumed that this annulation reaction would take place *via* the first C–N coupling followed by intramolecular dehydrative amide bond formation. Control experiments with the use of aniline and amino acid under our conditions did not give any reaction products (Scheme 3). On the other hand, the reaction of 2-bromoaniline with an amino acid afforded the coupling product **11** in 66% yield. These results suggested the possible reaction course stated above.

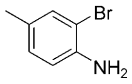
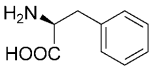
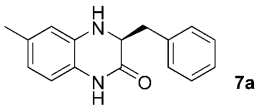
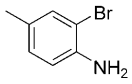
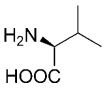
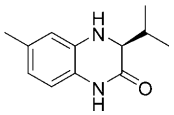
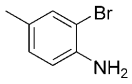
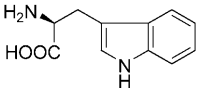
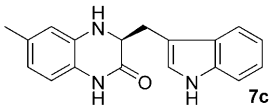
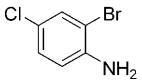
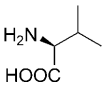
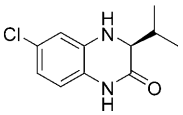
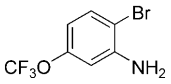
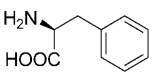
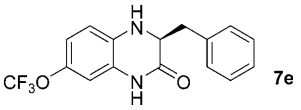
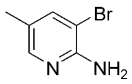
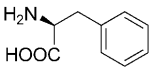
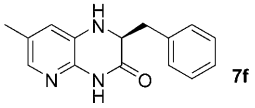
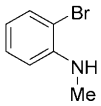
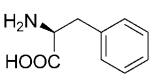
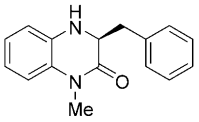
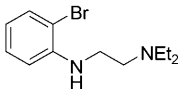
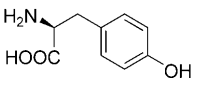
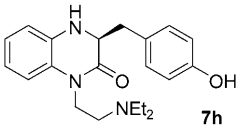
Convenient Synthesis of GW420867X

Finally, we wanted to demonstrate the utility of this method through the synthesis of GW420867X **14**,[24] a non-nucleoside reverse transcriptase inhibitor (Scheme 4). 2-Bromo-4-fluoroaniline **12** was reacted with (*S*)-(+)-2-aminobutyric acid under the conditions to give a 97% yield of quinoxalinone **13**, which was transformed into GW420867X **14** in 88% yield by standard methods.

Conclusions

In conclution, we have found an efficient, low catalyst loading protocol to synthesize optically pure quinoxalinones in a one-pot process without the use of protecting groups from readily accessible and inexpensive raw materials (both coupling partners, catalyst, ligand, and base). The efficiency was even better than that of our previous report[16] in which 10 mol% of catalyst was used. This method tolerates a variety of functional groups on both coupling partners (Table 2 and Table 3). Ligand-free conditions also exhibit the excellent efficiency (Table 1, entry 3).[25] The conditions employing an organic base instead of potassium phosphate also gave good yields of products which avoided the inorganic waste (Table 1, entry 11). Structurally diverse multiply substituted quinoxalinons have been synthesized efficiently with the optimized conditions as need for a chemical library (Table 2 and Table 3). The optical purity of the products was tentatively as-

Table 3. Copper-catalyzed synthesis of multi-substituted quinoxalin-2-ones **7** *via* coupling of substituted 2-bromoanilines **6** with α-amino acids **4**.[a]

Entry	6	4	7	Yield [%][b]
1			 **7a**	83
2			 **7b**	81
3			 **7c**	99
4			 **7d**	74; 82[c]
5			 **7e**	81
6			 **7f**	74
7			 **7g**	93
8			 **7h**	74

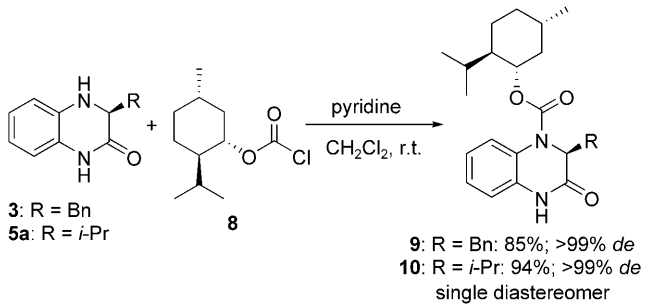
[a] *Reaction conditions:* 2-bromoaniline (1.97 mmol), amino acid (3.94 mmol, 2 equiv.), CuCl (1 mol%), DMEDA (20 mol%), and K_3PO_4 (3.94 mmol, 2 equiv.) in DMSO (7 mL) at 110 °C under a nitrogen atmosphere in the sealed tube.
[b] Isolated yield.
[c] Reaction with DBU as base (2 equiv.) instead of K_3PO_4 for 48 h.

signed by their derivatizaion to diastereomers and NMR analysis. The present method was successively applied to a concise synthesis of the chiral drug GW420867X and therefore may find more applications in organic synthesis and pharmaceutical development.[11,12,22] Studies on further applications of this strategy are underway and will be disclosed in due course.

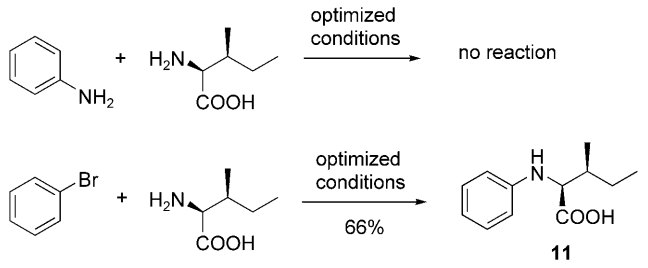
Experimental Section

General Procedure for Copper-Catalyzed Coupling Reaction of 2-Bromoanilines with α-Amino Acids to form Quinoxalin-2-ones (2-mmol Scale)

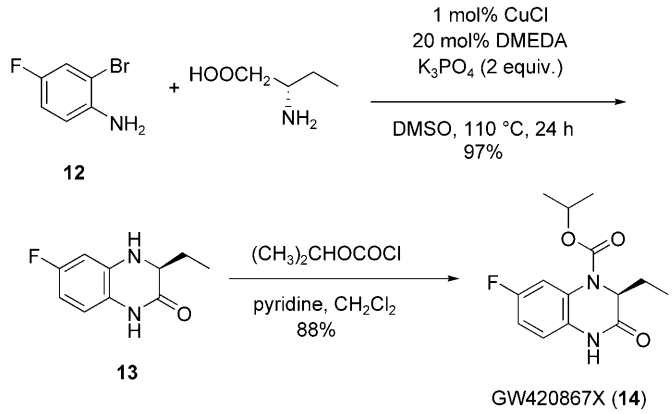
After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried sealed tube equipped with



Scheme 2. Derivatization of quinoxalin-2-ones **3** and **5a** to diastereomers **9** and **10**.



Scheme 3. Reaction of aniline and bromobenzene with L-isoleucine under the optimized conditions.



Scheme 4. Synthesis of GW420867X **14**.

a magnetic stirring bar was charged with CuCl (2.0 mg, 0.02 mmol), DMEDA (34.0 mg, 0.40 mmol), the amino acid (3.94 mmol), K_3PO_4 (0.84 g, 3.94 mmol), and the aryl bromide (1.97 mmol), if a solid. The tube was evacuated, backfilled with nitrogen. If a liquid, the aryl bromide was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMSO (7 mL). The tube was sealed under a positive pressure of nitrogen, stirred and heated to 110 °C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (~20 mL) and filtered through a plug of celite®, the filter cake being further washed with ethyl acetate (~5 mL). The filtrate was washed twice with water (~10 mL × 2). The collected aqueous phases were twice extracted with chloroform (~10 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated under vacuum to yield the crude product which was purified by silica gel chromatography with an eluent of hexane and ethyl acetate. The products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectra.

Acknowledgements

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[17] See Supporting Information.

[18] When 1.0 and 1.5 equiv. of L-phenylalanine were employed, the yields were decreased to 17% and 50%, respectively, under the optimized conditions.

[19] It is assumed that the nitrogen-oxygen interchange through the rubber of the balloon could occur to prevent the catalytic activity.

[20] Although it is easy to remove the inorganic base from the reaction mixture by aqueous work-up, a large amount of aqueous waste containing inorganic salts is produced and it is costly for disposal. Another advantage with the use of DBU was the ease of the purification process, which avoided the elaboration of unsoluble materials frequently observed when inorganic salts were employed as base to prevent the easy isolation of product.

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[25] It was assumed that the amino acid itself would work as a ligand, see: ref.[1c]

