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Efficient synthesis of useful heterocycles via transition metal-catalyzed cascade processes

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Abstract This paper reports our recent results from synthesis of some useful heterocycles, for example oxazolidinones, indoles, and quinoxalinones, by transition metal-catalyzed cascade processes. The scope and limitations of these procedures and the reaction mechanism for formation of the heterocycles are also discussed.

Keywords Palladium catalyst · Oxazolidone · Indoles · Copper catalyst · One-pot synthesis · Quinoxalinones

Introduction

Nitrogen-containing heterocyclic compounds are useful building blocks for development of pharmaceuticals, agrochemicals, functional materials, and dyes [1]. A huge number of methods have been reported for construction of heterocyclic structures [2]. Transition metal-catalyzed cascade processes are attractive methods for preparation of heterocycles [3]. Because of the mild reaction conditions, broad functional group tolerance, simple reaction manipulations, short reaction steps, and cost effectiveness, the methods are practical and green processes for efficient synthesis of heterocyclic compounds [4]. In this paper we describe the facile synthesis of oxazolidinones [5], indoles [6], and quinoxalinones [7] by palladium and copper-catalyzed cascade processes.

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Palladium-catalyzed synthesis of oxazolidinones

Oxazolidinone **1** (Fig. 1) is a five-membered heterocycle containing nitrogen and oxygen atoms. Oxazolidinone derivatives have a wide variety of biological activity. For example, antifungal drug linezolid **2** has been used for treatment of vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).

Initially, we expected that reaction of amines with a symmetrical dicarbonate **3**, with two leaving groups, as starting materials, under palladium-catalyzed conditions, would furnish oxazolidinones **4** via, first, intermolecular allylic amination, followed by intramolecular nucleophilic attack (Fig. 2).

To test the hypothesis, we investigated reaction of dicarbonate **3** with benzylamine as model substrates in the presence of $[Pd(\eta^3\text{–}C_3H_5)Cl]_2$ (0.062 mol%) and 1,1-bis(diphenylphosphino)ferrocene (dppf) (1.6 mol%) in dichloromethane at room temperature. This gave oxazolidone **4a** in moderate yield (58 %) (Fig. 3) [5].

We next investigated the generality, scope, and limitations of this oxazolidinone-forming reaction. A wide range of amines with benzyl, cyclic, unsaturated, free

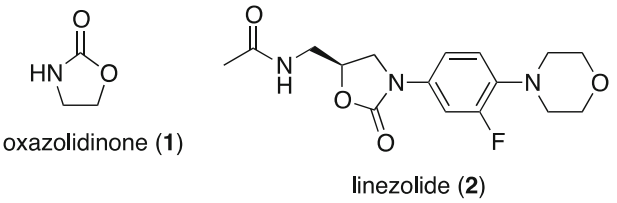


Fig. 1 Structures of oxazolidinone (**1**) and linezolid (**2**)

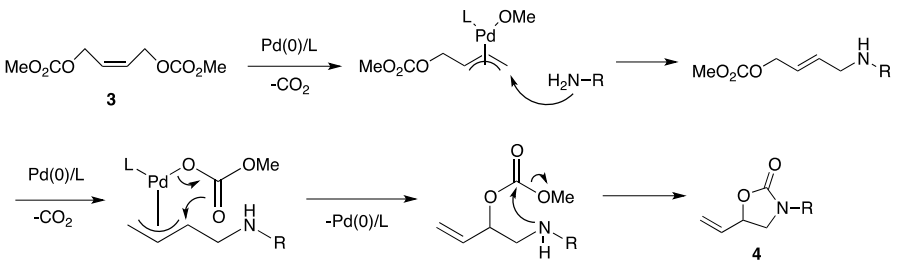


Fig. 2 Reaction pathway proposed for formation of oxazolidinone

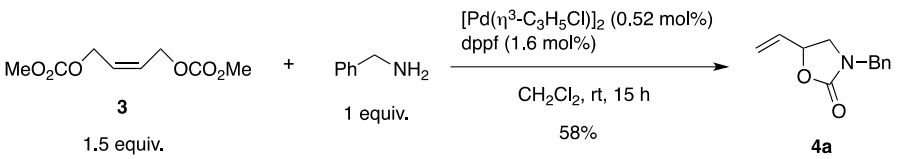
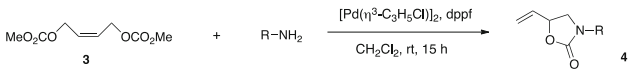
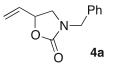
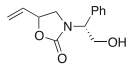
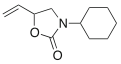
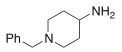
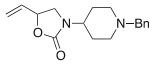
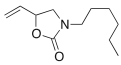
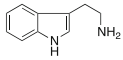
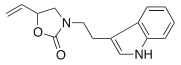
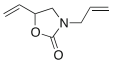
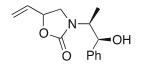
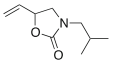
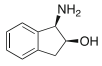
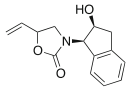
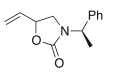
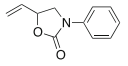


Fig. 3 Reaction of dicarbonate **3** with benzylamine

Table 1 Synthesis of oxazolidinone derivatives



Entry	Amine	Product	Yield (%)[a]	Entry	Amine	Product	Yield (%)[a]
1		 4a	58	7			56[b]
2			67	8			61
3			67	9			74
4			70	10			57[b]
5			55	11			41[c]
6			62[b]	12			0

hydroxyl, and amino groups afforded corresponding oxazolidinones with moderate to excellent yields except for aniline derivatives (Table 1).

Copper-catalyzed synthesis of 2,3-disubstituted indoles

The indole skeleton is well known as a structure frequently found in natural products and drugs (Fig. 4). Traditional methods for synthesis of indoles, for example the Fischer indole synthesis, have problems with regioselectivity at the cyclization positions when unsymmetrical substrates are used. Accordingly, development of a selective method for synthesis of substituted indoles is still an important task in organic synthesis.

We expected that reaction of 2-haloanilines and β-keto esters would afford 2-alkyl or aryl-3-indole carboxylic acid esters via two possible routes (Fig. 5). Path A includes, first, enamine formation, followed by intramolecular Heck-type coupling. Path B consists of, first, C–C bond formation, then subsequent C–N bond-forming cyclization to afford the indole.

Results from optimization of indole synthesis by reaction of 2-iodoaniline **5** with methyl acetoacetate **6** as model substrates are listed in Table 2. In the presence of copper iodide the desired indole **7** was formed in 35 % yield [6]. Several additives, bases, and solvents were tried, as shown in entries 2–7. It was found the best conditions were use of BINOL as additive in the presence of cesium carbonate as base in DMSO at 50 °C for 4 h (Table 2, entry 7).

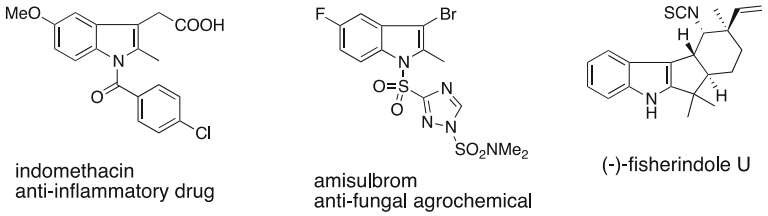


Fig. 4 Biologically active indoles

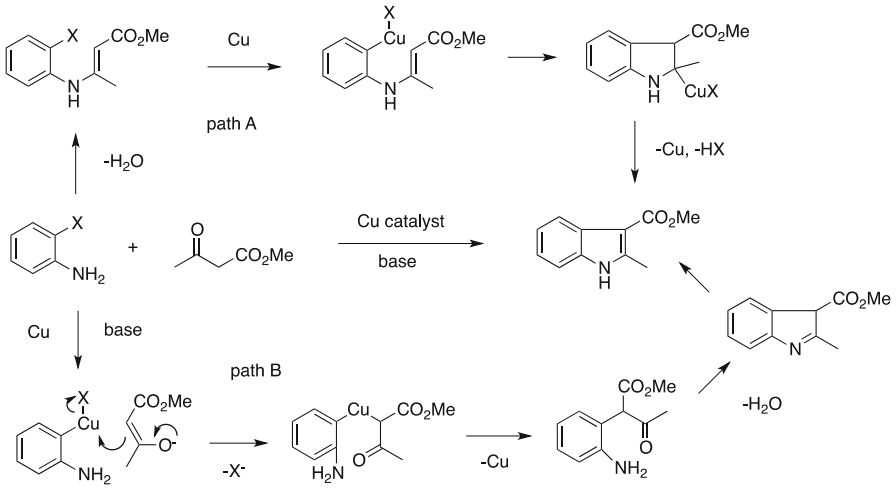
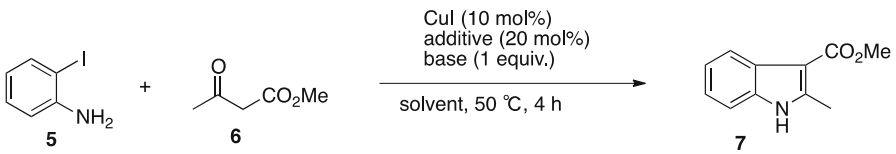


Fig. 5 Plausible pathways for formation of the indole structure

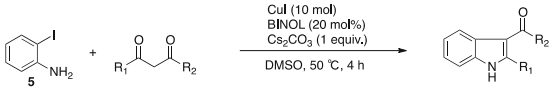
Table 2 Results from studies conducted to optimize indole formation

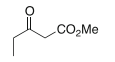
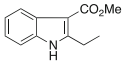
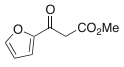
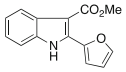
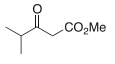
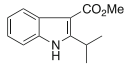
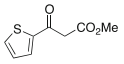
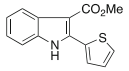
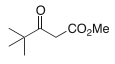
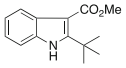
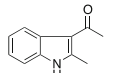
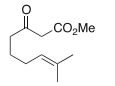
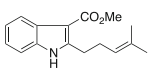
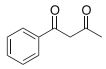
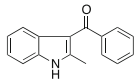
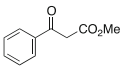
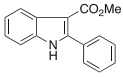
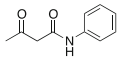
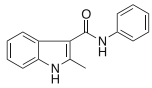
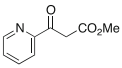
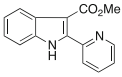


Entry	Additive	Base	Solvent	Yield (%)[a]
1	None	K_2CO_3	DMSO	35
2	L-Proline	K_2CO_3	DMSO	26
3	Ethylenediamine	K_2CO_3	DMSO	36
4	$MeNHCH_2CO_2H$	K_2CO_3	DMF	26
5	BINOL	K_2CO_3	DMSO	61
6	BINOL	K_3PO_4	DMSO	48
7	BINOL	Cs_2CO_3	DMSO	79

[a] Isolated yield after silica get chromatography

Table 3 Synthesis of substituted indoles



Entry	Carbonyl compound	Product	Yield (%)[a]	Entry	Carbonyl compound	Product	Yield (%)[a]
1			60	7			95
2			62	8			46
3			68	9			57
4			72	10			59
5			55	11			90[b]
6			59				

Under the optimized conditions, a series of β-keto esters, 1,3-diketones, and a β-keto amide was used in this transformation. As shown in Table 3, bulky, unsaturated, aromatic, and heteroaromatic β-keto esters produced the corresponding indoles in moderate to excellent yields. 1,3-Diketones (Table 3 entries 9 and 10) and a β-keto amide also afforded indoles in good yields.

General and practical access to chiral quinoxalinones, with low copper-catalyst loading

Quinoxaline and quinoxalinone are also important substructures for development of pharmaceuticals, agrochemicals, and functional materials. Some known bioactive quinoxalinones have a chiral center at the C3 position (Fig. 6). We therefore wished to develop a general and practical method for synthesis of chiral quinoxalinones.

It was expected that, as shown in Fig. 7, reaction of 2-haloanilines with amino acids in the presence of copper catalyst would directly enable one-pot synthesis of chiral quinoxalinones by sequential Buchwald–Hartwig type C–N bond formation and amide bond formation.

To our delight, reaction of 2-bromoaniline **8** with phenylalanine **9** in the presence of 1 mol% cuprous chloride provided the desired chiral quinoxalinones **10** in excellent yield (Table 4, entry 1) [7]. The effect of additives was next investigated. As shown by entries 2 and 3, EDA and TMEDA were less effective in the transformations. Slightly better conversion was realized by use of DMEDA (entry 4)

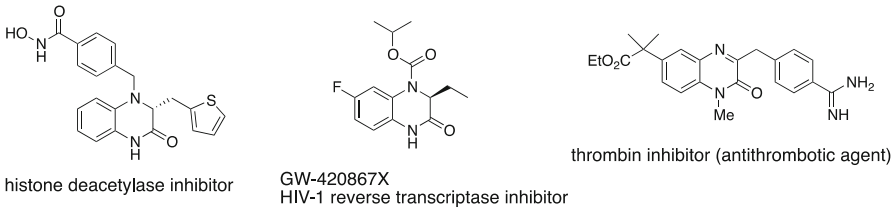


Fig. 6 Biologically active quinoxalinones

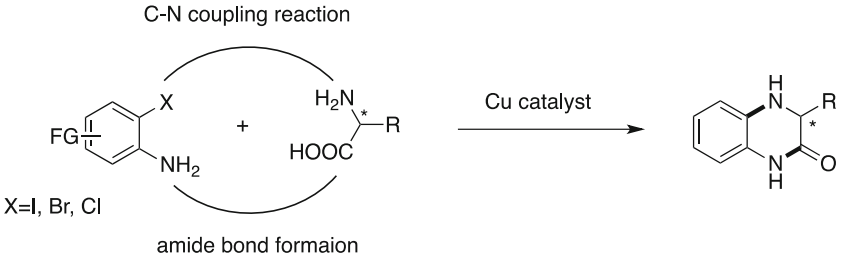
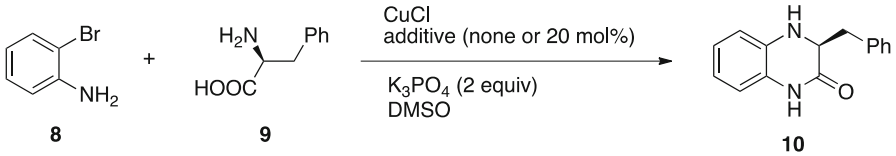


Fig. 7 Working hypothesis for formation of chiral quinoxalinone

Table 4 Optimization of the reaction conditions



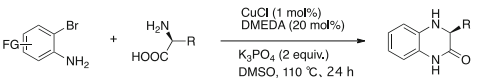
Entry	CuCl (mol%)	Temp. (°CC)	Time (h)	Additive	Yield (%)[a]
1	1	120	12	None	91
2	1	120	12	EDA	86
3	1	120	12	TMEDA	81
4	1	120	12	DMEDA	93
5	**1**	**110**	**24**	**DMEDA**	**99**
6	0.5	120	48	DMEDA	71

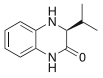
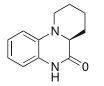
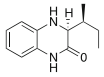
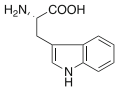
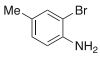
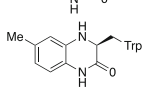
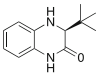
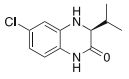
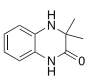
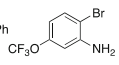
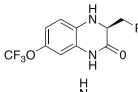
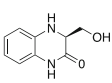
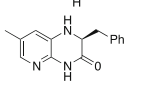
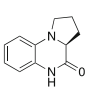
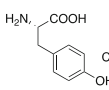
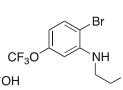
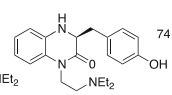
[a] Isolated yield

and, finally, entry 5 at lower temperature was selected as the optimum conditions. Reduction of the amount of catalyst to 0.5 mol% resulted in poor conversion, even the reaction time was increased (entry 6).

Under these optimized conditions, a variety of amino acids, including branched, bulky, disubstituted, free hydroxyl, cyclic, tryptophan, those with electron-donating and withdrawing groups on aromatic ring, pyridine, and N-substituted aniline, tolerated the reaction, providing a series of chiral quinoxalinones in good yield without the need for protection of amino and carboxyl groups (Table 5)

Table 5 Synthesis of quinoxalinones



Entry	Amino Acid	Aniline	Quinoxalinone	Yield (%)[a]	Entry	Amino Acid	Anilime	Quinoxalinone	Yield (%)[a]
1				86	7				81
2				77	8				99
3				59	9				74
4				65	10				81
5				74	11				74
6				59	12				74

[a]Isolated yields.

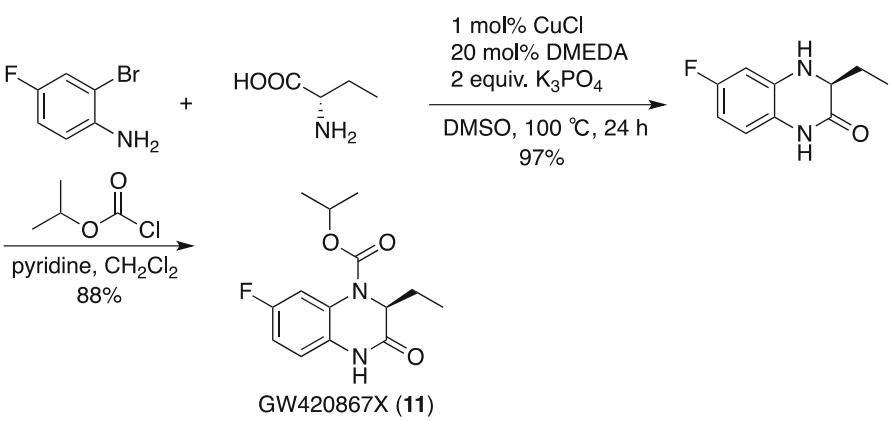


Fig. 8 Synthesis of GW420867X (**11**)

To demonstrate the utility of the transformation, the anti-HIV agent GW420867X (**11**) was synthesized from commercially available reagents in two steps in high yield (Fig. 8).

Conclusions

In this paper we report our efforts to synthesize useful heterocyclic structures by means of transition metal-catalyzed cascade processes. As series of oxazolidinones, indoles, and quinoxalinones with diverse structures was synthesized efficiently by use of simple experimental procedures under relatively mild conditions. These methods could therefore serve as powerful tools enabling facile access to heterocyclic building blocks for discovery of new drugs and functional materials.

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