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Highly diastereoselective synthesis of 3-indolylglycines *via* an asymmetric oxidative heterocoupling reaction of a chiral nickel(II) complex and indoles†

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Daizong Lin,[a] Jiang Wang,[a] Xu Zhang,[ab] Shengbin Zhou,[a] Jie Lian,[ab] Hualiang Jiang[a] and Hong Liu*[ab]

The asymmetric synthesis of 3-indolylglycine derivatives was achieved by an oxidative heterocoupling reaction. This method for the selective C-3 functionalization of unprotected indoles with the chiral equivalent of a nucleophilic glycine nickel(II) complex afforded adducts with high diastereoselectivities. The decomposition of adducts readily afforded 3-indolylglycine derivatives in high yields.

Optically active non-proteinogenic amino acids are versatile motifs in natural products, asymmetric chemical investigations as well as medicinal and peptide/peptidomimetic chemistry.[1] Among non-proteinogenic amino acids, 3-indolylglycine and its derivatives have attracted appreciable attention due to their wide application in organic synthesis and drug discovery.[2] Accordingly, the development of efficient methods in their preparation is of considerable interest in academia and industry. Symmetric syntheses and resolution are achieved initially.[3] O'Donnell *et al.* demonstrated that a nucleophilic reaction of an indole and an equivalent of glycine with a leaving group affords 3-indolylglycinamide as racemic mixtures.[3a] Janczuk *et al.* also reported an achiral electrophilic substitution of indole and imide, and described an enzymatic resolution.[3b] However, compared with symmetric preparation, the asymmetric synthesis represents the most direct approach. Several enantioselective syntheses of 3-indolylglycine have been described;[4] Wanner *et al.* reported a chiral phosphoric acid-catalyzed Friedel–Crafts reaction of substituted glyoxyl imines with indoles;[4a] Ji *et al.* also described a diastereoselective Friedel–Crafts alkylation of indoles and a chiral imine.[4b] Nevertheless, most of those methods are Friedel–Crafts reactions using chiral Lewis acid catalysts or involving chiral amine auxiliaries. Hence, existing problems (*e.g.*, control of reaction stereoselectivity or removal of the chiral ligands) may limit their applications. In spite of the fact that the approaches of enzymatic resolution and asymmetric synthesis have been described, developing highly enantioenriched synthetic methods of 3-indolylglycines is of urgent need.

The oxidative heterocoupling reaction, considered to be one type of C–H functionalization, has been developed in recent decades.[5] Importantly, a new C–C bond is formed by direct oxidative coupling of two electron-rich carbons (the indole C-3 and the α carbon of the carbonyl group), thereby avoiding the prefunctionalization or protection of the substrates. This reaction has many merits: excellent tolerability of functional groups; high levels of regioselectivity (exclusively coupling at the indole 3-position); and the potential to scale-up production. On the other hand, chiral nickel(II) complexes of the Schiff base of glycine have been widely used to synthesize optically active non-proteinogenic amino acids *via* aldol,[6] Michael addition,[7] Mannich,[8] and *C*-alkylation[9] reactions. Given our recent involvement in the asymmetric synthesis of optically active amino acids *via* nucleophilic reactions of the nickel(II) complex and electron-deficient substrates,[10] we sought to further extend the scope of substrates to electron-rich indoles and aimed to develop a new synthetic protocol of 3-indolylglycines *via* the oxidative heterocoupling reaction of a nickel(II) complex (Scheme 1). This method exhibits the following advantages: (i) predictable stereochemical outcome; (ii) high diastereoselectivity; (iii) operationally convenient reaction procedures; (iv) low-cost material; (v) easy and virtually complete recovery of ligands (*S*)-BPB. Herein, we present an asymmetric oxidative coupling reaction of the chiral nickel(II) complex and unprotected indoles, as a general method leading to optically active 3-indolylglycine.

Initially, using a simple indole and chiral nickel(II) complex (*S*)-**1**, we isolated 20% of the desired oxidative coupling product **3a** with 71% de at ambient temperature with lithium hexamethyldisilazide (LiHMDS) as the base and copper(II) acetylacetonate ($Cu(acac)_2$) as the oxidant (Table 1, entry 1), based on the conditions reported in the literature.[11] According to this result, we chose to study (*S*)-**1** and indole **2a** as a model substrate for optimizing reaction conditions (Table 1). To improve the diastereoselectivity of the target complex, we reduced the temperature to −40 °C.

[a] *State Key Laboratory of Drug Research, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China. E-mail: hliu@mail.shcnc.ac.cn*
[b] *Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing, 210009, P. R. China*

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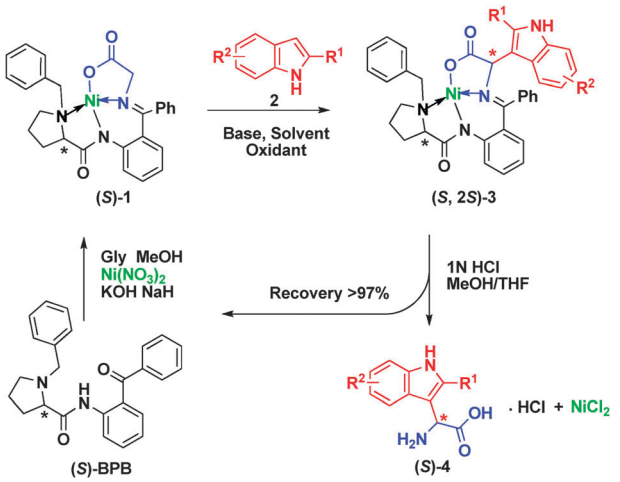
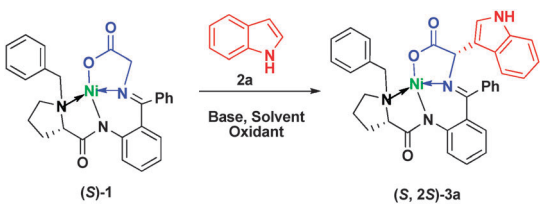


Scheme 1 Asymmetric synthesis of 3-indolylglycines *via* oxidative heterocoupling reaction of nickel(II) complex and indoles.

Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solution	Oxidant	Temp/°C	Yield (%)	de[b] (%)
1	LiHMDS	THF	$Cu(acac)_2$	rt	20	71
2	LiHMDS	THF	$Cu(acac)_2$	−40	35	92
3	NaHMDS	THF	$Cu(acac)_2$	−40	22	97
4	NaH	THF	$Cu(acac)_2$	−40	5	ND[c]
5	LDA	THF	$Cu(acac)_2$	−40	59	>99
6	LDA	THF	$Cu(OAc)_2$	−40	42	98
7	LDA	THF	Iodine	−40	0	ND
8	LDA	THF	DDQ	−40	0	ND
9	LDA	THF	$Fe(acac)_3$	−40	Trace	ND
10	LDA	CH_2Cl_2	$Cu(acac)_2$	−40	0	ND
11	LDA	DME	$Cu(acac)_2$	−40	0	ND
12	LDA	Et_2O	$Cu(acac)_2$	−40	23	89
13	LDA	THF	$Cu(acac)_2$	rt	34	97
14	LDA	THF	$Cu(acac)_2$	0	42	98
15	LDA	THF	$Cu(acac)_2$	−20	47	>99
16	LDA	THF	$Cu(acac)_2$	−60	22	>99
17[d]	LDA	THF	$Cu(acac)_2$	−40 to rt	63	>99

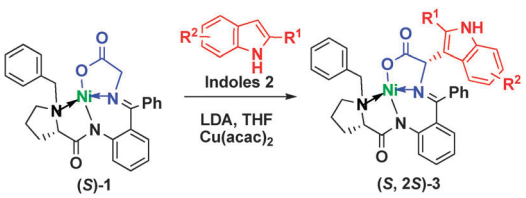
[a] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.80 mmol of **2a** in 10 mL of solvent with 0.66 mmol of base for 0.5 h, then 0.3 mmol of oxidant was added over 1 h. [b] Determined by chiral HPLC analysis (see the ESI for details). [c] ND not detected. [d] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.80 mmol of **2a** in 10 mL of THF with 0.66 mmol of LDA for 0.5 h at −40 °C, then 0.3 mmol of $Cu(acac)_2$ was added, and raised to room temperature naturally over 1 h. (The optimization of the equivalents of the base, oxidants and indole, see the ESI for details).

This condition afforded the adduct (*S*, 2*S*)-**3a** with high diastereoselectivity (92% de, entry 2). Various alternative bases were then screened. A higher yield and diastereoselectivity was observed with lithium diisopropylamide (LDA) as the base than with LiHMDS, sodium hexamethyldisilazide (NaHMDS) and sodium hydride (NaH) (entries 2–5). $Cu(acac)_2$ demonstrated the best performance among the screened oxidants such as copper(II) acetate ($Cu(OAc)_2$), ferric acetylacetonate ($Fe(acac)_3$), iodine, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (entries 6–9) (see the ESI† for the optimization of copper(II) oxidants). The ideal solvent for the oxidant reaction was tetrahydrofuran (THF) (entries 10–12). The effect of temperature was then investigated.

The adduct **3a** was formed in higher yield at −40 °C than at other temperatures (entries 13–16). Furthermore, adding the oxidant at −40 °C and then allowing the reaction to warm to room temperature before quenching afforded a slightly higher yield (63%, entry 17) than that of the corresponding reaction at −40 °C (entry 5). From this viewpoint, we chose LDA as the base, $Cu(acac)_2$ as the oxidant, THF as the solvent, and a temperature range from −40 °C to ambient temperature to probe the generality of this asymmetric reaction (entry 17). To confirm the stereochemical generation of the reaction, we crystallized the optically pure product **3a**. The absolute configuration of **3a** was determined to be (*S*, 2*S*) by X-ray crystallography[12] (Fig. S1 in the ESI†). Then, a radical mechanism of this reaction was proposed in the ESI† (Scheme S1).

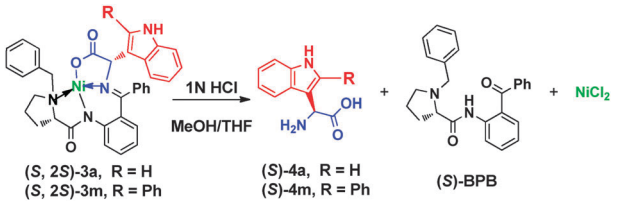
With the optimal reaction conditions identified, we next explored the generality of the substrate. Various indoles were investigated, and most of them afforded the products **3** in moderate yields with high diastereoselectivities. The results are summarized in Table 2. Investigation of the electronic effect showed that the indole with an electron-donating group or halogen substituted at the 5-position of the indole was well tolerated in this reaction (entries 1–5). However, the yield decreased rapidly if an indole with an electron-withdrawing group at the 5-position was adopted. This was due to a reduction in the electron density at the carbon atom at the 3-position of the indole by an electron-withdrawing group at the 5-position of the

Table 2 Oxidative coupling reaction of nickel(II) complex (*S*)-**1** with indoles **2**[a]



Entry	3	R^1	R^2	Yield (%)	de[b] (%)
1	**3a**	H	H	63	>99
2	**3b**	H	5-OMe	60	>99
3	**3c**	H	5-F	40	>99
4	**3d**	H	5-Cl	35	>99
5	**3e**	H	5-Br	33	>99
6	**3f**	H	5-NO_2	Trace	ND[c]
7	**3g**	H	4-Me	62	>99
8	**3h**	H	5-Me	56	99
9	**3i**	H	6-Me	60	>99
10	**3j**	H	7-Me	54	98
11	**3k**	Me	H	65	98
12	**3l**	COOEt	H	55	96
13	**3m**	Ph	H	74	97
14	**3n**	Me	OMe	60	97

[a] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.80 mmol of **2** in 10 mL of THF with 0.66 mmol of LDA for 0.5 h at −40 °C, then 0.3 mmol of $Cu(acac)_2$ was added, and raised to room temperature naturally over 1 h. [b] Determined by chiral HPLC analysis (see the ESI for details). [c] ND: not detected.



Scheme 2 Decomposition of nickel(II) complex **3** to release 3-indolylglycine derivatives **4**.

indole (entry 6). Then, our focus was turned to evaluation of the steric effects. Indoles bearing a methyl substituent at the 4-, 5-, 6- or 7-position of the indole ring were suitable substrates and afforded the corresponding products with excellent diastereoselectivity (98–99% de) (entries 7–10). Nevertheless, a 3-methyl indole did not afford the desired products under this condition, which confirmed that the reaction occurred selectively at the 3-position of the indole. It is noticeable that the diastereoselectivities and chemical yields were not decreased by substitution at the indole 2-position next to the reaction site, regardless of the steric and electronic effect of the substituted group (entries 11–13). Furthermore, the disubstitution at the indole 2- and 5-positions did not affect the diastereoselectivity (97% de) (entry 14).

Disassembly of the diastereomerically pure complex (*S*, 2*S*)-**3** under an acidic condition (THF/methanol/HCl) afforded the target amino acid (*S*)-3-indolylglycine derivatives **4** in good ee values (97–98% ee) and yields (85–93%) at room temperature (Scheme 2). The chiral ligand (*S*)-**BPB** was recovered readily in quantitative yield and could be reused *via* a simple procedure. The specific rotation of the recovered (*S*)-**BPB** is the same as that of the fresh-prepared (*S*)-**BPB**.

In conclusion, we successfully developed a practical and highly efficient diastereoselective route to synthesize 3-indolylglycine derivatives *via* the oxidative heterocoupling reaction of unprotected indoles and chiral equivalent of nucleophilic glycine. A broad range of indoles could be employed under an operationally simple condition. The resulting adducts were converted into the target amino acids in high yields. Moreover, the method provided opportunities for the reaction of extensive nucleophilic carbons and chiral nickel(II) complexes for the synthesis of various chiral non-proteinogenic amino acids.

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12 CCDC 909566 contains the supplementary crystallographic data for this paper.