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Organocatalytic Asymmetric Michael Addition of Oxazolones to Arylsulfonyl Indoles: Facile Access to *syn*-Configured α,β-Disubstituted Tryptophan Derivatives

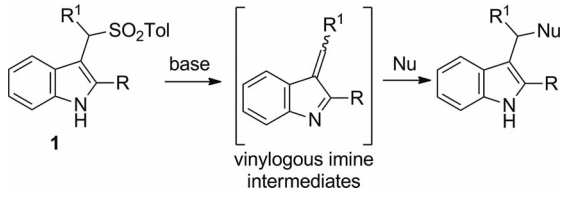
Chang-Wu Cai,[a] Xing-Li Zhu,[a] Song Wu,[a] Zong-Le Zuo,[a] Liang-Liang Yu,[a] Da-Bin Qin,[a] Quan-Zhong Liu,[a] and Lin-Hai Jing*[a]

Keywords: Organocatalysis / Asymmetric synthesis / Heterocycles / Michael addition / Enantioselectivity

Enantioselective Michael addition of oxazolones to in situ generated vinylogous imine intermediates is reported. A series of optically active 3-alkylindole derivatives with adjacent quaternary and tertiary stereocenters was obtained. The resulting adducts can readily be converted into *syn*-configured α,β-disubstituted tryptophan derivatives without compromising the stereoselectivities.

Introduction

Tryptophan, an essential amino acid for many organisms, is an important structural unit and synthetic intermediate of various bioactive compounds and natural products.[1] Likewise, α,β-disubstituted tryptophan structural motifs are widely found in biologically active molecules and naturally occurring compounds such as stephacidins,[2a–2d] cycloaplysinopsins,[2e,2f] tubastrindoles,[2g] dictazolines,[2g–2i] dictazoles,[2i] and waikialoid.[2j] Although this structural scaffold is very important, to the best of our knowledge, only one asymmetric catalytic version has been reported for the synthesis of α,β-disubstituted tryptophan derivatives with methyl or ethyl groups at the β-position.[3] Furthermore, enantioselective routes to these compounds have been less explored.[4] Therefore, to explore an efficient approach for the synthesis of α,β-disubstituted tryptophan derivatives with various substituents at the α- and β-positions is still highly desired. In 2006, an innovative solution to the indole skeleton by using arylsulfonyl indole **1** was developed by the Petrini group.[5] In that work, compound **1**[6] was used to generate highly active vinylogous imine intermediates in situ under basic conditions, and these species were then treated with nucleophiles to afford 3-substituted indole derivatives (Scheme 1).[7,8] Inspired by these elegant studies, and considering that oxazolone[9] is an excellent masked amino acid fragment,[3,10] herein we wish to describe the first stereoselective Michael addition of oxazolones to vinylogous imine intermediates generated in situ from arylsulfonyl-substituted indoles under simple chiral organocatalysis. The resulting adducts can be further conveniently converted into *syn*-configured α,β-disubstituted tryptophan derivatives with various substituents at the α- and β-positions without compromising the stereoselectivities.



Scheme 1. Nucleophilic Michael addition to vinylogous imine intermediates generated in situ from arylsulfonyl indoles **1**.

Results and Discussion

At the outset of our studies, arylsulfonyl indole **1a** and oxazolone **2a** were chosen as model substrates to optimize the reaction conditions, and the results are listed in Table 1. The natural cinchona alkaloids quinine (**3a**), cinchonidine (**3b**), and cinchonine (**3c**) only gave poor yields and enantioselectivities and various levels of diastereoselectivities (Table 1, entries 1–3). Cinchona alkaloid derived Hatakeyama catalyst **3d** showed unsuccessful results under the reaction conditions (Table 1, entry 4).[11] Subsequently, our attention turned to bifunctional thiourea catalysts.[12] Takemoto catalyst **3e** provided an excellent *ee* value, although with poor diastereoselectivity (Table 1, entry 5).[13] No satisfying result was achieved when thiourea catalyst **3f** bearing a chiral diaminocyclohexane skeleton was used (Table 1, entry 6).[13c] Then, we began to investigate cinchona alkaloid derived thiourea catalysts **3g**–**j**.[14] To our delight, catalyst **3j** gave the best *dr* and *ee* value (Table 1, entry 10).[14e] To improve the yield, the reaction concentration was increased

[a] Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, China West Normal University,
1 Shi Da Road, Nanchong 637002, P. R. China
E-mail: cwnujlh@yahoo.com.cn

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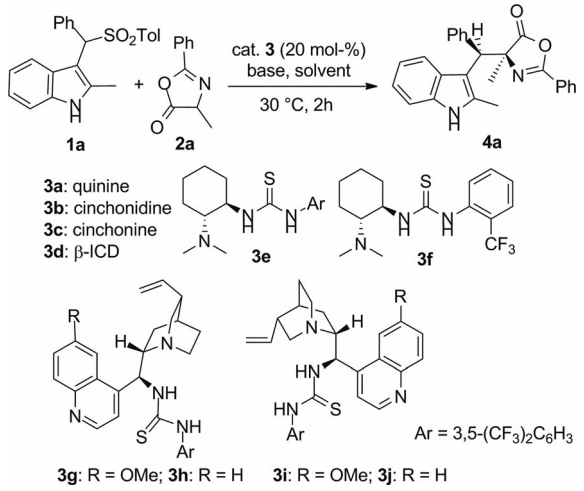
Table 1. Optimization of the reaction conditions.[a]



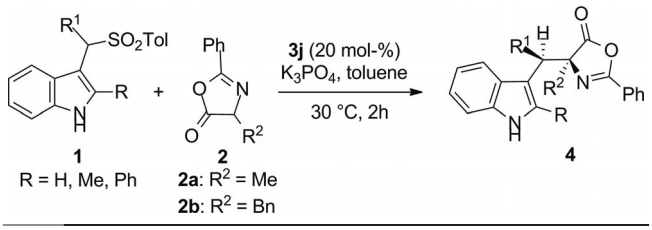
Entry	Cat.	Base	Solvent	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1[e,f]	**3a**	K_3PO_4	toluene	30	63:37	43
2[e,f]	**3b**	K_3PO_4	toluene	35	71:29	36
3[e,f]	**3c**	K_3PO_4	toluene	40	50:50	–19
4[e,f]	**3d**	K_3PO_4	toluene	29	71:29	< –5
5[e,f]	**3e**	K_3PO_4	toluene	58	57:43	94
6[e,f]	**3f**	K_3PO_4	toluene	50	62:38	89
7[e,f]	**3g**	K_3PO_4	toluene	64	57:43	–87
8[e,f]	**3h**	K_3PO_4	toluene	44	77:23	–94
9[e,f]	**3i**	K_3PO_4	toluene	60	69:31	95
10[e,f]	**3j**	K_3PO_4	toluene	52	79:21	97
11[f]	**3j**	K_3PO_4	toluene	62	79:21	96
12	**3j**	K_3PO_4	toluene	63	82:18	97
13	**3j**	Na_2CO_3	toluene	45	78:22	91
14	**3j**	K_2CO_3	toluene	56	78:22	95
15	**3j**	KF	toluene	30	70:30	81
16	**3j**	KF/Al_2O_3	toluene	45	76:24	90
17	**3j**	NaOH	toluene	50	71:29	91
18	**3j**	KOH	toluene	72	70:30	92
19	**3j**	Et_3N	toluene	31	62:38	49
20	**3j**	K_3PO_4	benzene	60	82:18	97
21	**3j**	K_3PO_4	*p*-xylene	53	73:27	98
22	**3j**	K_3PO_4	mesitylene	50	71:29	96
23	**3j**	K_3PO_4	chlorobenzene	55	72:28	97
24	**3j**	K_3PO_4	chloroform	40	73:27	80
25	**3j**	K_3PO_4	DCM	40	80:20	95
26	**3j**	K_3PO_4	DCE	41	77:23	94

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.11 mmol), **2a** (0.1 mmol), catalyst (0.02 mmol), and base (0.11 mmol) in solvent (1.0 mL) at 30 °C for 2 h. [b] Isolated yield. [c] Determined by analysis of the crude mixture by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] Solvent: 2 mL. [f] Reaction time: 5 h.

onefold by reducing the volume of solvent, and the product was obtained in 62% yield (Table 1, entry 11). Further study showed that the yield did not decrease upon shortening the reaction time from 5 to 2 h (Table 1, entry 12). To further optimize the reaction, other parameters such the base and solvent were examined. Nevertheless, better results in terms of yield, diastereoselectivity, and enantioselectivity (Table 1, entries 13–26) were not obtained relative to the results obtained with K_3PO_4 and toluene.[8d]

With the optimized reaction conditions in hand, we then screened a series of arylsulfonyl indoles **1** and oxazolones **2** to establish the general utility of this asymmetric transformation. As summarized in Table 2, most arylsulfonyl indoles and oxazolones underwent the reaction smoothly to afford *syn*-selective addition products with good results. Substrates with a substituent in the *para* position of the phenyl ring of R^1 gave a slightly higher yield and enantioselectivity than did substrates with a substituent in the *meta* position. For example, 4-F-substituted **1b** gave the product in 69% yield with 90% *ee*, whereas 3-F-substituted **1e** gave the product in only 64% yield with 88% *ee* (Table 2, entry 2 vs. 5). A similar phenomenon was also observed in the reaction of **1c** compared with that of **1f** (Table 2, entry 3 vs. 6). However, an even greater difference was achieved when *ortho*-substituted **1q** was used (Table 2, entry 17 vs. 19). It is noteworthy that when **1m** was treated with **2a** under the optimized reaction conditions, only 50% *ee* could be obtained (Table 2, entry 13). This seems to imply that sterics at the 2-position of the indole core play an important role in the enantioselectivity of the reaction, which is in line with previous reports.[8a,8c,8d,8h] Nevertheless, if the R group was changed from methyl to phenyl, relatively low stereoselecti-

Table 2. Asymmetric Michael addition of oxazolones to arylsulfonyl indoles.[a]



Entry	**1**: R, R^1	**2**	**4**	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**1a**: Me, Ph	**2a**	**4a**	63	82:18	97
2	**1b** Me, 4-FC_6H_4	**2a**	**4b**	69	81:19	90
3	**1c**: Me, 4-ClC_6H_4	**2a**	**4c**	65	83:17	97
4	**1d**: Me, 4-BrC_6H_4	**2a**	**4d**	70	82:18	96
5	**1e**: Me, 3-FC_6H_4	**2a**	**4e**	64	79:21	88
6	**1f** Me, 3-ClC_6H_4	**2a**	**4f**	52	79:21	91
7	**1g**: Me, 4-MeC_6H_4	**2a**	**4g**	81	82:18	84
8	**1h**: Me, 4-$OMeC_6H_4$	**2a**	**4h**	77	82:18	91
9	**1i**: Me, 3,4-$(OMe)_2C_6H_4$	**2a**	**4i**	50	90:10	97
10	**1j**: Me, 3-$CF_3C_6H_4$	**2a**	**4j**	65	77:23	89
11	**1k**: Ph, 4-BrC_6H_4	**2a**	**4k**	55	67:33	90
12	**1l**: Ph, 2-$OMeC_6H_4$	**2a**	**4l**	40	87:13	93
13	**1m**: H, Ph	**2a**	**4m**	60	75:25	50
14[e]	**1n**: Me, 3,4-$Cl_2C_6H_4$	**2b**	**4n**	88	58:42	95
15[e]	**1o**: Me, 1-naphthyl	**2b**	**4o**	74	87:13	80
16[e]	**1p**: Me, 3-MeC_6H_4	**2b**	**4p**	51	58:42	91
17[e]	**1q**: Me, 2-$OMeC_6H_4$	**2b**	**4q**	45	87:13	81
18[e]	**1c**: Me, 4-ClC_6H_4	**2b**	**4r**	62	69:31	95
19[e]	**1h**: Me, 4-$OMeC_6H_4$	**2b**	**4s**	71	75:25	86

[a] Unless otherwise noted, all reactions were carried out with **1** (0.11 mmol), **2** (0.1 mmol), **3j** (0.02 mmol), and K_3PO_4 (0.11 mmol) in toluene (1.0 mL) at 30 °C for 2 h. [b] Isolated yield. [c] Determined by analysis of the crude mixture by ^{1}H NMR spectroscopy. [d] Measured by using chiral stationary phase HPLC. [e] Reaction time: 4 h.

vity was observed (Table 2, entry 4 vs. 11), likely because larger steric hindrance weakens the positive π–π interaction of the "closed" conformation of the transition state (see the Supporting Information).[15] As described in the literature,[16] benzyl-substituted oxazolone **2b** gave slightly inferior results compared with methyl-substituted **2a** (Table 2, entry 3 vs. 18 and entry 8 vs. 19).

The absolute configuration of the two contiguous stereocenters of Michael addition product **4a** was unambiguously assigned as (10*R*,11*S*) by X-ray diffraction analysis (Figure 1).[17] The absolute configurations of the other products were assigned by analogy.

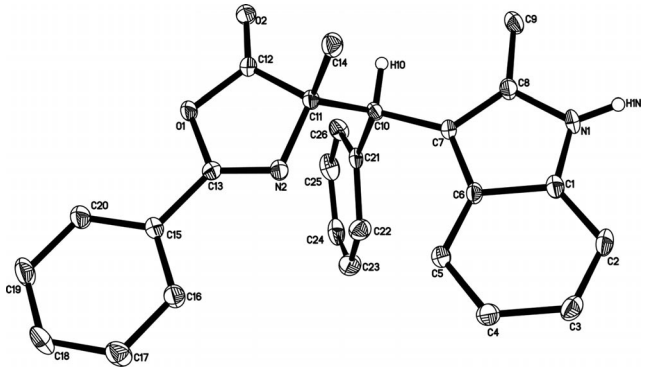
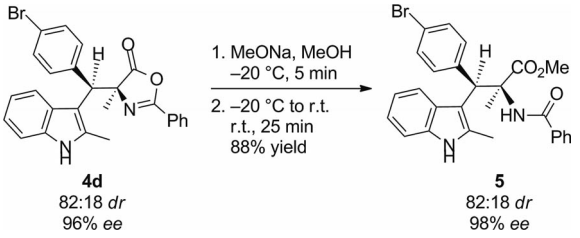


Figure 1. X-ray crystal structure of compound **4a**.

The synthetic versatility of the adducts was illustrated by a further transformation. Adduct **4d** was readily converted into *syn*-selective α,β-disubstituted tryptophan derivative **5** in 88% yield by ring opening of the oxazolone subunit with sodium methoxide[3,10h] without a decrease in the diastereoselectivity and enantioselectivity (Scheme 2).



Scheme 2. Transformation of adduct **4d** into **5**.

Conclusions

In conclusion, we have developed the first highly stereoselective Michael addition reaction of oxazolones to vinylogous imine intermediates generated in situ from arylsulfonyl indoles under chiral thiourea catalysis. A series of optically active C-3 alkyl-substituted indole derivatives with adjacent quaternary and tertiary stereocenters was obtained, and the resulting adducts could be readily converted into *syn*-configured α,β-disubstituted tryptophan derivatives with various substituents at the α- and β-positions without a decrease in the diastereoselectivities and enantioselectivities. Further investigations to broaden the scope of this type of transformation are currently underway.

Experimental Section

General Procedure: An ordinary test tube equipped with a magnetic stirring bar was charged with catalyst **3j** (0.02 mmol), arylsulfonyl indole **1** (0.11 mmol), oxazolone **2** (0.1 mmol), K_3PO_4 (0.11 mmol), and toluene (1 mL) and then sealed in air. After stirred at 30 °C for 2 h, the reaction mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:5–1:20) to afford product **4**. The product was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. The diastereomeric ratio was determined by analysis of the crude material by NMR spectroscopy, and the enantiomeric excess was determined by chiral-phase HPLC analysis.

Supporting Information (see footnote on the first page of this article): Analytical data for all prepared compounds with copies of the ^{1}H NMR and ^{13}C NMR spectra and HPLC chromatographs.

Acknowledgments

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[17] CCDC-896163 (for **4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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