ORGANIC LETTERS

2010
Vol. 12, No. 8
1688−1691

Ag-Catalyzed Diastereo- and Enantioselective Synthesis of β-Substituted Tryptophans from Sulfonylindoles

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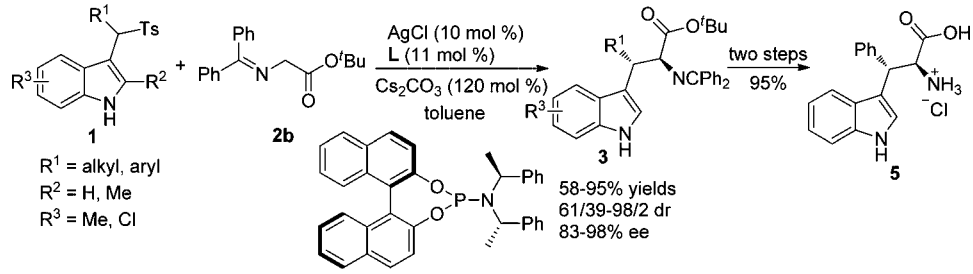
Received January 22, 2010

ABSTRACT



The asymmetric catalytic synthesis of β-substituted tryptophan derivatives was realized in high diastereo- and enantioselectivity by the reaction of glycine derivatives with sulfonylindoles in the presence of catalyst derived from AgCl and a commercially available chiral monodentate phosphoramidite ligand. The resulting adduct was readily converted to β-substituted tryptophan in 95% overall yield for two steps, which presented a highly efficient route to chiral β-substituted tryptophan.

Tryptophan as an essential amino acid is an important structural unit and synthetic intermediate of various natural products.[1] Among them, β-substituted tryptophans as a useful class of compounds are found in biologically active molecules and natural products such as telomycine,[2a] streptonigrine,[2b] lavendamycine,[2c] fumitremorgin,[2d] and cyclomarines.[2e] The β-substituted tryptophans have also been used in the research of peptide−receptor relationships by means of replacing natural amino acids.[3] Although this structural scaffold is important in organic synthesis, only one asymmetric catalytic version appeared for the synthesis of β-substituted tryptophans with low diastereoselectivity.[4] Furthermore, the reports for the enantioselective route to these compounds have been limited.[5] β-Substituted tryptophans are composed of two parts, an α-amino acid moiety and an indole core. Glycine derivatives have served as precursors in the synthesis of α-amino acids for a long

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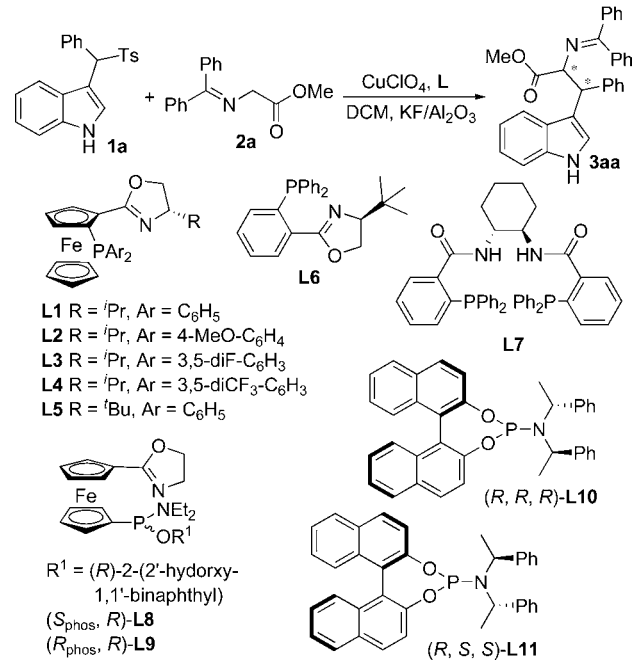
10.1021/ol100161n
Published on Web 03/24/2010

time.[6] On the other hand, sulfonylindoles have been reported to produce vinylogous imines in situ in the presence of base,[7] which react with various nucleophiles, such as Grignard reagents,[7a] Reformatsky reagents,[7b] nitroalkanes,[7c] aldehydes,[7d,8a] and enamide.[8b] Recently, we have focused on the applications of glycine derivatives in asymmetric catalysis;[9] herein we communicate an unprecedented Ag-catalyzed asymmetric reaction of glycine derivatives with sulfonylindoles, which offers a general procedure leading to chiral β-substituted tryptophans.

We commenced our study by exposure of sulfonylindole **1a** with glycine imine **2a** using a catalyst derived from $CuClO_4$ and various readily available chiral ligands (Table 1). The results revealed that the ligand with different coordination atom had a great impact on the enantio- and diastereoselectivity of the reaction. The use of FcPHOX **L1**−**L5**[10] afforded the corresponding adduct **3aa** in high enantioselectivity (81−90%) and chemical yield but in low diastereoselectivity (1/1−2/1). The change of electronic factor of ligands exerted limited effect on both enantio- and diastereoselectivities, which differs from our early observation (entries 1−5).[9a,b] PHOX **L6**[11] and Trost's ligand **L7**[12] demonstrated low stereocontrol in the present reaction, obtaining nearly racemic product (entries 6 and 7). SiocPhox **L8** and **L9**[13] developed in our group were also proved to be unsuitable for the reaction (entries 8 and 9). Finally, we were pleased to find that diastereoselectivity of the adduct **3aa** was improved greatly by employing commercially available

Table 1. Screening of the Chiral Ligand for $CuClO_4$-Catalyzed Reaction of Sulfonylindole **1a** with Glycine Ester **2a**[a]



entry	ligand	yield[b] (%)	*anti*/*syn*[c]	ee of *anti*/*syn*[d] (%)
1	**L1**	84	57/43	83/83
2	**L2**	86	64/36	80/73
3	**L3**	98	71/29	90/88
4	**L4**	82	64/36	81/−
5	**L5**	88	36/64	80/97
6	**L6**	87	60/40	18/43
7	**L7**	83	53/47	2/14
8	**L8**	81	62/38	35/23
9	**L9**	78	57/48	37/31
10	**L10**	59	71/29	86/35
11	**L11**	85	83/17	86/−

[a] Molar ratio of **1a**/**2a**/$CuClO_4$/**L** = 100/110/10/11, 80 mg of 40 wt % KF on basic alumina was used as base. [b] Determined by ^{1}H NMR with CH_3NO_2 as the internal standard. [c] The ratio was determined by ^{1}H NMR. [d] Determined by chiral HPLC.

monodentate phosphoramidite ligands **L10** and **L11**;[14] the latter was better in terms of both selectivity and yield (entry 10 vs entry 11).

With ligand **L11**, we set out to optimize reaction conditions, and the results are summarized in Table 2. Examination of glycine imines **2** led to the bulky *tert*-butyl esters **2b** as optimal substrates, affording the adduct **3ab** in 80% yield with 85/15 dr, 96% ee (entry 1, Table 2, vs entry 11, Table 1). With *tert*-butyl esters **2b**, the effect of solvent was evaluated, which revealed that the enantio- and diastereoselectivities decreased in THF relative to that in CH_2Cl_2 (entry 2 vs entry 1). The diastereoselectivity was maintained in DME, while the enantioselectivity was lower (entry 3). The yield in toluene increased from 80% to 88% while the

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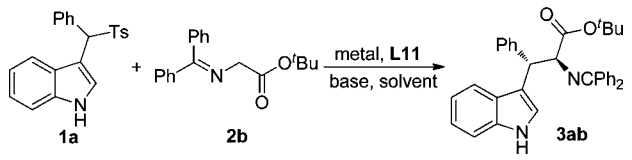
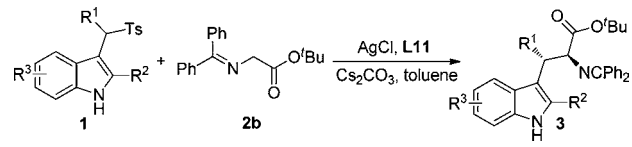
Table 2. Optimization of Reaction Conditions for Reaction of Sulfonylindole **1a** with Glycine Ester **2b**[a]



entry	metal	solvent	base	yield[b] (%)	*anti*/*syn*[c]	ee of *anti*[d] (%)
1	$CuClO_4$	DCM	KF/Al_2O_3	80	85/15	96
2	$CuClO_4$	THF	KF/Al_2O_3	90	78/22	93
3	$CuClO_4$	DME	KF/Al_2O_3	90	85/15	86
4	$CuClO_4$	toluene	KF/Al_2O_3	88	87/13	96
5	AgOAc	toluene	KF/Al_2O_3	72	87/13	87
6	AgOTf	toluene	KF/Al_2O_3	70	81/19	92
7	AgCl	toluene	KF/Al_2O_3	64	91/9	86
8	AgCl	toluene	Et_3N	NR	−/−	
9	AgCl	toluene	KO^{t}Bu	50	45/55	
10	AgCl	toluene	Cs_2CO_3	87	97/3	92
11	AgCl	toluene	K_2CO_3	9	97/3	
12[e]	AgCl	toluene	Cs_2CO_3	52	96/4	93
13[f]	AgCl	toluene	Cs_2CO_3	9	98/2	
14[g]	AgCl	toluene	Cs_2CO_3	80	96/4	95

[a] Molar ratio of **1a**/**2b**/metal/**L11**/base = 100/110/10/11/120. 80 mg of 40 wt % KF on basic alumina was used as base. [b] Determined by ^{1}H NMR with CH_3NO_2 as the internal standard. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] 60 mol % Cs_2CO_3. [f] 12 mol % Cs_2CO_3. [g] Ts in **1a** was replaced by SO_2Ph.

Table 3. Substrate Scope for AgCl-Catalyzed Reaction of Sulfonylindoles **1** with Glycine Ester **2b**[a]



entry	**1**, R^1, R^2, R^3	yield[b] (%)	*anti*/*syn*[c]	ee of *anti*/*syn*[d] (%)
1	**1a**, Ph, H	87	97/3	92/−
2	**1b**, 4-MeO-C_6H_4, H, H	71	96/4	88/−
3	**1c**, 4−Cl-C_6H_4, H, H	95	98/2	97/−
4	**1d**, 4−Br-C_6H_4, H, H	80	98/2	91/−
5	**1e**, 4-NO_2−C_6H_4, H, H	93	95/5	96/−
6	**1f**, Me, H, H	58	73/27	84/70
7	**1g**, ^{i}Pr, H, H	88	96/4	89/−
8[e]	**1h**, ^{n}Pr, H, H	86	61/39	91/96
9[e]	**1i**, 2-fural, H, H	75	62/38	96/−
10	**1j**, Ph, Me, H	90	95/5	86/−
11	**1k**, Ph, H, 5-Me	93	88/12	89/−
12	**1l**, Ph, H, 5-Cl	93	84/16	83/−
13[f]	**1m**, Ph, H, 4-Me	91	90/10	98/−

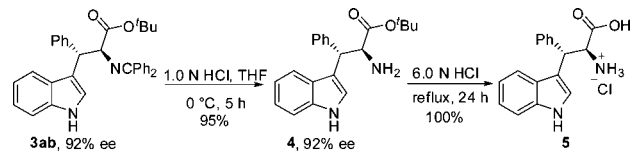
[a] The reaction was carried out with **1** (0.2 mmol), **2b** (0.22 mmol), AgCl (0.02 mmol), **L11** (0.022 mmol), and Cs_2CO_3 (0.24 mmol) in toluene (2 mL) at rt. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] **L1** as ligand. [f] Ts was replaced by SO_2Ph.

selectivity was the same as that in CH_2Cl_2 (entry 4 vs entry 1). The screening of Lewis acid showed that silver salts such as AgOAc and AgOTf were also able to smoothly catalyze the Michael reaction albeit with lower enantioselectivity (entries 5 and 6), while AgCl enhanced the diastereoselectivity but lowered the enantioselectivity (entry 7 vs entry 1). To improve the selectivity further, we studied the impact of base and identified Cs_2CO_3 as the best one with dr 97/3 and ee being 92% among the bases we tested (entry 10 vs entries 8, 9, and 11). The reaction occurred sluggishly in the presence of weak base such as Et_3N and K_2CO_3 (entries 8 and 11). Much lower diastereoselectivity was provided in the case of KO^{t}Bu as base (entry 9). The chemical yields of the reaction decreased sharply using substoichiometric or catalytic amount of base, although the diastereoselectivity and enantioselectivity were maintained (entries 12 and 13 vs entry 10). The replacement of *p*-toluenesulfonyl of sufonylindole **1a** by benzenesulfonyl resulted in the slight decrease of the yield (entry 14 vs entry 10).

The substrate scope was investigated under the optimized conditions, and the results are compiled in Table 3. A wide variety of sulfonylindoles were suitable substrates to provide the adducts **3** with *anti*-selectivity in 58−95% yields and high enantioselectivity. Both electron-withdrawing and donating groups at the *para*-position of the phenyl ring were tolerated in sulfonylindoles **1** (entries 2−5). The electron-deficient substrate **1c** gave the best result, affording adduct **3cb** in 95% yield with 98:2 dr and 97% ee (entry 3). Although the diastereo- and enantioselectivities were lower for sulfonylindoles **1f** with methyl substitutent (entry 6), excellent diastereo- and enantioselectivities were achieved for the isopropyl derivative **1g** (entry 7). These results suggested the importance of steric hindrance in the stereocontrol of the reaction. In the case of sulfonylindole **1h** with linear propyl substituent and **1i** bearing a fural substituent, selectivity was poor under standard conditions, while 91% ee for **1h** and 96% ee for **1i** were achieved for *anti* isomer albeit with low diastereoselectivity by using **L1** as ligand (entries 8 and 9). The sulfonylindoles with Me or Cl as substituent at the 2 and 5 positions of indole ring were also suitable substrates to provide corresponding products, although the stereoselectivities were a bit lower (entries 10−12), while sulfonylindole **1m** with Me as substituent at 4 position gave excellent enantioselectivity (entry 13).

The absolute configuration of the adduct **3db** was determined unambiguously as (2*S*,3*S*) by X-ray diffraction analysis of *anti*-**3db**. The adduct **3ab** was readily converted to β-phenyl tryptophan **5** by conventional sequences in 95% overall yield in two steps, which presented a straightforward route to β-substituted tryptophans (Scheme 1).

Scheme 1. Transformation of Adduct **3ab** to β-Phenyl Tryptophan



In conclusion, we presented a straightforward route to β-substituted tryptophans via the asymmetric catalytic reaction of glycine derivatives with sulfonylindoles using a catalyst derived from AgCl and a commercially available chiral monodentate phosphoramidite ligand. The investigations on the reaction mechanism, the extension of substrates, as well as the applications of the methodology in organic synthesis are underway.

Acknowledgment. Financially supported by the Major Basic Research Development Program (2010CB833300), NSFC (20872161, 20821002, 20932008), Chinese Academy of Sciences, and Science and Technology Commission of Shanghai Municipality (10ZR1436800). This paper is dedicated to Professor A. S. C. Chan on the occasion of his 60th birthday.

Supporting Information Available: General experimental procedure, spectral data for **3ab**−**mb**, and X-ray analysis data of **3db** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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