Organocatalysis

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Chiral Brønsted Acid Catalyzed Stereoselective Addition of Azlactones to 3-Vinylindoles for Facile Access to Enantioenriched Tryptophan Derivatives**

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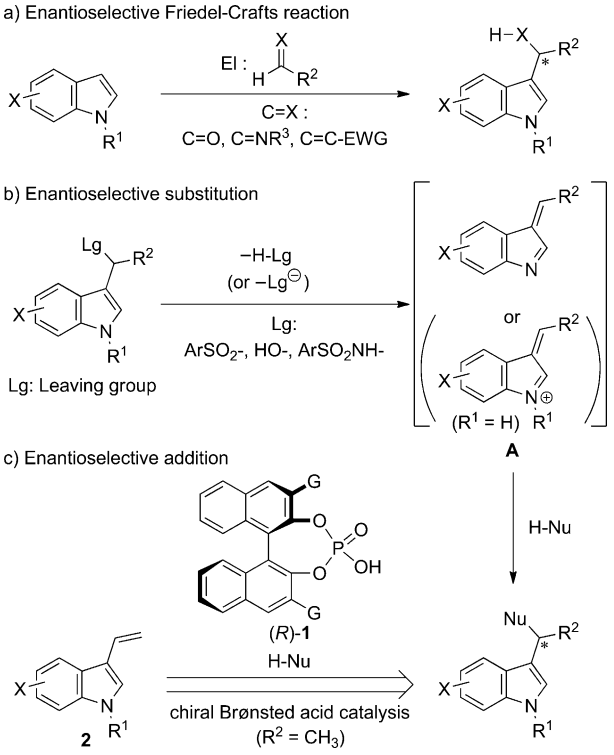
3-Substituted indoles are common structural motifs in a number of synthetic and naturally occurring compounds. The broad spectrum of their biological activity has stimulated intensive interest in their asymmetric synthesis. A number of excellent approaches for the preparation of optically active 3-substituted indoles have been reported to date (Scheme 1).[1] The most common strategy is through an enantioselective Friedel–Crafts reaction with electrophiles (El) at the 3-position (Scheme 1 a).[2] In recent years, nucleophilic substitution of a leaving group (Lg) at the "benzylic" 1′-position[3] has emerged as an alternative approach for introducing a chiral side chain at the 3-position of indoles (Scheme 1 b).[4–7] Enantioselective catalysis with organocatalysts[4–6] or chiral metal complexes[7] accelerates this substitution reaction through the formation of vinylimine (or iminium) intermediates **A** (Scheme 1 b), with the concomitant loss of a leaving group, such as an arylsulfonyl,[4a,6,7] hydroxy,[4b,c,5a–d] or sulfonamido[5e] group. Binaphthol-derived phosphoric acids **1** (Scheme 1) are one class of efficient organocatalysts for these substitution reactions.[5]

Chiral phosphoric acids **1** were developed independently by Akiyama et al. and by our group.[8] These compounds have become some of the most versatile chiral Brønsted acid catalysts,[9] and have been applied to a broad range of enantioselective transformations.[10,11] As part of our continuing efforts to broaden the scope of enantioselective catalysis with **1**,[11] we envisioned the enantioselective addition of a nucleophile (H-Nu) to the double bond of 3-vinylindoles **2** catalyzed by (*R*)-**1** (Scheme 1 c). 3-Vinylindoles have been employed as the diene component in enantioselective (hetero) Diels–Alder reactions, which give rise to enantioenriched polycyclic indoles.[12,13] However, to our knowledge, they have never been utilized in enantioselective addition reactions. Our method provides an alternative approach to enantioenriched indoles with a chiral side-chain at the 3-position.



Scheme 1. Methods for the asymmetric synthesis of 3-substituted indole derivatives.

To validate the proposed transformation, we aimed to develop the enantioselective addition reaction of azlactones **3** to 3-vinylindoles **2** catalyzed by (*R*)-**1** to yield the addition products **4** (Scheme 2). The substituted indoles **4** can be readily converted into β-substituted tryptophan derivatives **5**, which have quaternary stereogenic centers at the α-position,[14,15] through ring opening of the azlactone subunit. Tryptophan plays a key role in protein stability and recognition, despite its scarcity in known proteins.[16] The substitution of non-natural α-amino acids for natural amino acids in nonproteinogenic analogues of conformationally restricted peptides is increasingly important. Therefore, the asymmetric

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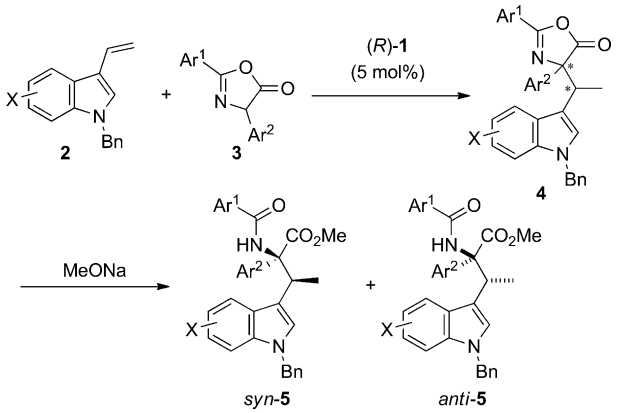
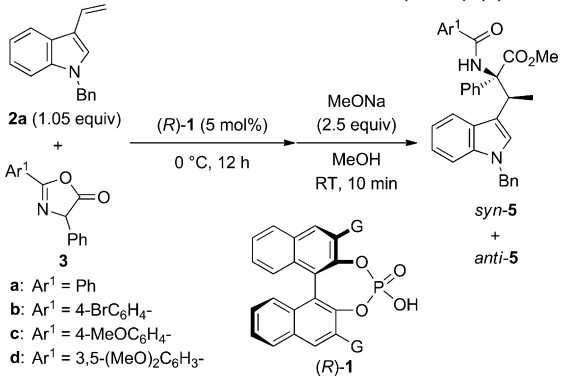


Scheme 2. Diastereo- and enantioselective synthesis of **5** through the addition of **3** to **2**, catalyzed by (*R*)-**1**.

synthesis of non-natural α-amino acids has received much attention.[17] In this context, stereoregulated tryptophan analogues, in particular multi-substituted derivatives, are attractive targets in peptide design. However, methods for the stereoselective synthesis of these compounds have achieved limited success.[7,18] Herein, we report the enantioselective addition reaction of azlactones **3** to 3-vinylindoles **2**, catalyzed by chiral phosphoric acids (*R*)-**1**. The present method provides a highly stereoselective and facile route to tryptophan derivatives **5**, which have adjacent quaternary and tertiary stereogenic centers.

At the outset of our studies, we tested a range of chiral phosphoric acid catalysts (*R*)-**1** with different G groups,[19] and several azlactones **3** with various Ar^1 substituents. The initial screening was performed with *N*-benzyl-protected 3-vinylindole **2a**,[20] **3**(Ar^2=Ph), and (*R*)-**1** (5 mol%) at 0°C in toluene. The diastereo- and enantioselectivity of the reaction was determined after ring opening of the azlactone subunit of **4** with sodium methoxide to prepare **5**. As shown in Table 1, the addition reaction of **3** to **2a** and subsequent ring opening afforded **5** in moderate to good yields. A marked effect of the substituent G on the diastereoselectivity was noted (Table 1, entries 1–3). Although catalysts (*R*)-**1a** (G = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$-)[15f] and (*R*)-**1b** (G = 9-anthryl) provided low to moderate *syn* diastereoselectivity (Table 1, entries 1 and 2), (*R*)-**1c** (G = 4-biphenyl) afforded *syn*-**5aa** in good diastereoselectivity, but modest enantioselectivity (Table 1, entry 3). Subsequent manipulation of the Ar^1 substituent of **3** had a significant impact on the reactivity, as well as the diastereo- and enantioselectivity (Table 1, entries 4–6). The introduction of either 4-bromophenyl (**3b**) or 3,5-dimethoxyphenyl substituents (**3d**)[15f,21] as the Ar^1 group resulted in a considerable decrease in the enantioselectivity (Table 1, entries 4 and 6). In contrast, when Ar^1 was changed to a 4-methoxyphenyl group (PMP, **3c**), the yield and the stereoselectivity both increased (Table 1, entry 5). The effects of different solvents on the reaction of **2a** with **3c** were also investigated. All our attempts to change the solvent were unsuccessful in improving the yield, or the stereochemical outcome (Table 1, entries 7–9). As expected, when the reaction temperature was reduced to −20°C, the diastereo- and enantioselectivity increased to

Table 1: Enantioselective addition of **3** to **2a** catalyzed by (*R*)-**1**.[a]



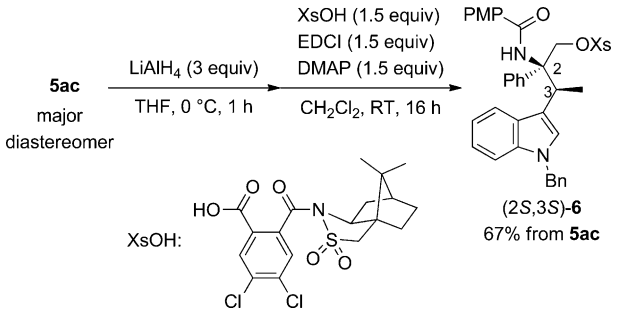
Entry	Cat.	3	Product	Solvent	Yield [%][b]	*syn*-**5**/ *anti*-**5**[c]	*ee* [%] for *syn*-**5**[d]
1	**1a**	**3a**	**5aa**	toluene	47	70:30	39
2	**1b**	**3a**	**5aa**	toluene	62	56:44	13
3	**1c**	**3a**	**5aa**	toluene	59	87:13	40
4	**1c**	**3b**	**5ab**	toluene	62	93:7	21
5	**1c**	**3c**	**5ac**	toluene	75	93:7	78
6	**1c**	**3d**	**5ad**	toluene	49	76:24	19
7	**1c**	**3c**	**5ac**	CH_3CN	88	58:42	10
8	**1c**	**3c**	**5ac**	CH_2Cl_2	57	75:25	25
9	**1c**	**3c**	**5ac**	Et_2O	28	92:8	71
10[e]	**1c**	**3c**	**5ac**	toluene	70	97:3	85
11[e,f]	**1c**	**3c**	**5ac**	toluene	85	98:2	93
12[e,g]	**1c**	**3c**	**5ac**	toluene	75	98:2	94
13[e,h]	**1c**	**3c**	**5ac**	toluene	82	98:2	93
14[e,i]	**1c**	**3c**	**5ac**	toluene	85	98:2	94[j]

[a] Unless otherwise noted, all reactions were carried out with (*R*)-**1** (0.01 mmol, 5 mol%), **2a** (0.21 mmol, 1.05 equiv), and **3** (0.20 mmol) in toluene (1.0 mL) at 0°C. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] At −20°C for 24 h. [f] Molecular sieves (3 Å, 100 mg) were added. [g] Molecular sieves (4 Å, 100 mg) were added. [h] Molecular sieves (5 Å, 100 mg) were added. [i] 1.2 equiv of **2a** (0.24 mmol) and molecular sieves (4 Å, 100 mg) were used. [j] The *ee* value was 17% for *anti*-**5ac**.

97% *syn* and 85% *ee*, respectively (Table 1, entry 10). Further improvement of the stereoselectivity was achieved by adding molecular sieves (3 Å, 4 Å, and 5 Å; Table 1, entries 11–14).[13b,22] The reaction gave rise to **5ac** with an excellent *syn* diastereoselectivity (98%), and the enantioselectivity for *syn*-**5ac** reached 94% *ee* when 4 Å molecular sieves were used (Table 1, entry 12). The yield was improved by increasing the amount of **2a** to 1.2 equivalents (Table 1, entry 12 versus entry 14).

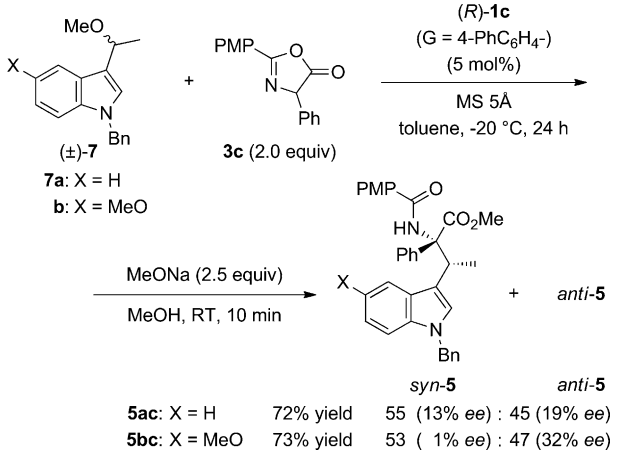
The relative and absolute stereochemistry of the major isomer **5ac** was unambiguously determined to be 2*S*,3*S* by X-ray crystallographic analysis of **6**.[23] Compound **6** was obtained by reducing the methyl ester **5ac** to an alcohol, then transforming the alcohol into ester **6,** by treatment with camphorsultam of known configuration (XsOH; Scheme 3).

As an alternative to the addition reaction (Scheme 1c), product **5** can also be synthesized by a substitution reaction (Scheme 1b). Hence, we conducted this substitution reaction



Scheme 3. Derivatization of the major diastereomer **5ac** (Table 1, entry 14) to **6**. DMAP = 4-dimethylaminopyridine; EDCI = ethyldimethylaminopropylcarbodiimide hydrochloride.

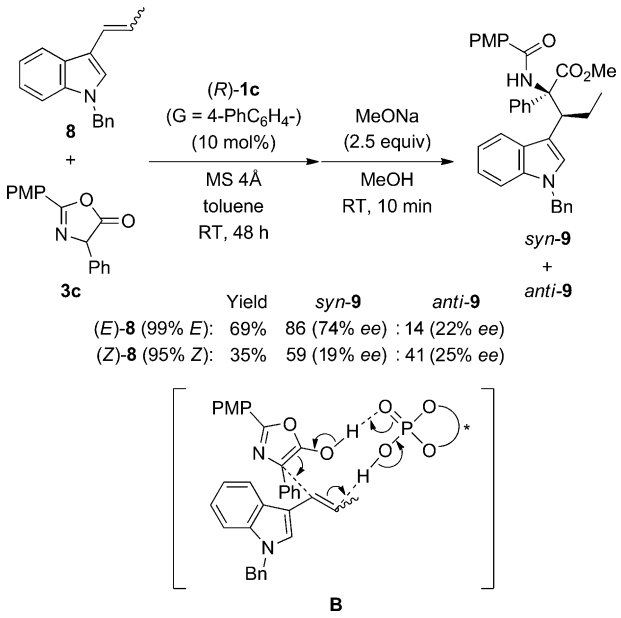
with 3-substituted indoles **7**, of which the leaving group at the 1′ position was a methoxy moiety,[24] under conditions similar to the optimized addition reaction. The stereochemical outcomes of the addition and substitution methods were then compared (addition reaction: Table 1, entry 13).[25] Despite the striking resemblance of the plausible reactive intermediate **A** (Scheme 1) which is generated during the course of the substitution reaction of **7** and the addition reaction with **2a**, the substitution reaction of **7a** afforded **5ac** with almost no stereoselectivity (Scheme 4). Interestingly, *syn*-**5ac** had the opposite absolute configuration, albeit with a



Scheme 4. Substitution reaction of **7** with **3c** catalyzed by (*R*)-**1c**. MS = molecular sieves; PMP = 4-methoxyphenyl.

low enantioselectivity, even when the same (*R*)-**1c** was employed in the substitution reaction. In addition, the substitution reaction of 5-methoxyindole derivative **7b** also produced quite low stereoselectivity. These results clearly indicate that the mechanisms of the substitution and addition reactions are entirely different, and that the addition method is essential for achieving high stereoselectivity in the present reaction system.

To gain further insight into the mechanism of the addition reaction, we attempted the reaction of **3c** with (*E*)- and (*Z*)-3-(prop-1-enyl)indoles **8**. As shown in Scheme 5, there were marked differences in the reactivity of (*E*)-**8** and (*Z*)-**8**.



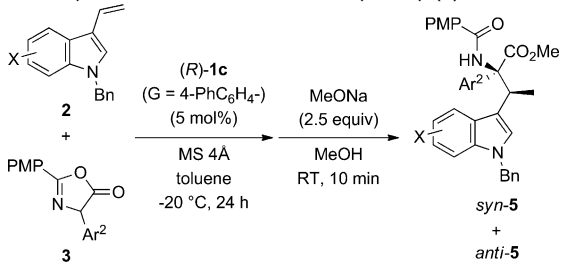
Scheme 5. Addition reaction of **3c** to (*E*)- and (*Z*)-**8** catalyzed by (*R*)-**1c**. MS = molecular sieves; PMP = 4-methoxyphenyl.

Notably, the stereochemical outcome of the reaction was highly dependent on the geometry of **8**.[26] These results imply that the common intermediate **A** (Scheme 1) is unlikely to be involved in these reactions.[27] Although the precise mechanism has not yet been determined, it seems likely that the addition reaction proceeds through an ene reaction, such as ternary system **B** (Scheme 5).[28]

Having identified a promising method for the stereoselective transformation of **2**, we explored the scope of the addition reaction with different substrates (Table 2).[29] Excellent *syn* diastereo- and enantioselectivity were maintained with C5-substituted indoles, irrespective of the electronic properties of the substituent X (Table 2, entries 1–3). However, the introduction of an electron-withdrawing group at the 6 position led to a considerable reduction in the yield and the enantioselectivity, although a high level of *syn* diastereoselectivity was retained (Table 2, entry 4). Further investigation into the scope of the reaction revealed that the introduction of substituents to the Ar^2 group of **3** significantly affected the outcome of the reaction (Table 2, entries 5–10). *Ortho* substitution of the Ar^2 group prevented the formation of **5ae**. (Table 2, entry 5). In contrast, azlactones with *meta*- or *para*-substituted Ar^2 groups underwent the addition reaction to afford the corresponding products **5**, with high *syn* diastereo- and enantioselectivity (Table 2, entries 6–10). In these cases, the yields were dependent on the electronic properties of the substituents. Electron-donating substituents furnished higher yields than those obtained with electron-withdrawing substituents (Table 2, entries 6–8 versus entries 9 and 10).

In conclusion, we have demonstrated a highly *syn* diastereo- and enantioselective addition of azlactones to 3-vinylindoles catalyzed by a chiral phosphoric acid. The present method enables facile access to tryptophan derivatives with adjacent quaternary and tertiary stereogenic

Table 2: Scope of the addition reaction catalyzed by (*R*)-**1c**.[a]



e: Ar^2 = 2-$MeOC_6H_4$- **h**: Ar^2 = 4-MeC_6H_4-
f: Ar^2 = 3-$MeOC_6H_4$- **i**: Ar^2 = 4-ClC_6H_4-
g: Ar^2 = 4-$MeOC_6H_4$- **j**: Ar^2 = 4-BrC_6H_4-

Entry	2	3	5	Yield [%][b]	*syn*-5/ *anti*-5[c]	*ee* [%] for *syn*-5[d]
1	**2b**: 5-MeO	**3c**	**5bc**	76	96:4	91
2[e]	**2c**: 5-MeO_2C	**3c**	**5cc**	73	98:2	94
3	**2d**: 5-Br	**3c**	**5dc**	63	98:2	95
4	**2e**: 6-Br	**3c**	**5ec**	41	96:4	75
5	**2a**	**3e**	**5ae**	trace	–	–
6	**2a**	**3f**	**5af**	82	93:7	89
7	**2a**	**3g**	**5ag**	87	98:2	90
8	**2a**	**3h**	**5ah**	71	98:2	89
9	**2a**	**3i**	**5ai**	58	91:9	83
10	**2a**	**3j**	**5aj**	35	93:7	90

Unless otherwise noted, all reactions were carried out with (*R*)-**1c** (0.01 mmol, 5 mol%), **2** (0.24 mmol, 1.2 equiv), **3** (0.20 mmol), and molecular sieves (4 Å, 100 mg) in toluene (1.0 mL) at −20 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] 2.0 equiv of **2c** (0.4 mmol) was used.

centers. Such derivatives are potentially useful for the preparation of conformationally restricted peptides and biologically active non-proteinogenic analogues. Furthermore, the highly stereoselective transformation could not be achieved by a substitution reaction, which is as another common approach to the modification of 3-substituted indoles. Further studies to elucidate the mechanism and the origin of the stereochemical outcome of the addition reaction are underway.

Experimental Section

Representative procedure: Vinylindole **2a** (56.0 mg, 0.24 mmol), azlactone **3c** (53.5 mg, 0.20 mmol), and molecular sieves (4 Å, 100 mg) were added to a dried test tube, under nitrogen. After cooling to −20 °C, toluene (1.0 mL) and then (*R*)-**1c** (5 mol%, 6.5 mg, 0.01 mmol) were added. The mixture was stirred for 24 h, then NaOMe (1.0 mL, 0.5 M in MeOH) was added. The mixture was allowed to warm to room temperature and stirred for 10 min. After cooling to 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient elution with hexane/EtOAc from 4:1 to 2:1) and gel permeation chromatography to give the product **5ac** as a white solid in 85% yield. The diastereomeric ratio and enantiomeric excess were determined by HPLC analysis on a chiral stationary phase (*syn*/*anti* = 98:2, 94% *ee* for *syn*-**5ac**).

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[20] The addition reaction of N-H vinylindole, instead of **2a**, with **3a** catalyzed by (*R*)-**1c** (5 mol%) afforded the corresponding product in low yield (20%) and a nearly racemic form.

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[23] CCDC 815051 (**6**) 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.

[24] We employed methyl ether **7** instead of the indole derivative bearing a hydroxy group at the 1′-position to avoid the formation of the homodimmeric ether of the indole substrate.

[25] Molecular sieves (5 Å) were employed as a scavenger for the methanol generated during the reaction.

[26] We reported highly diastereo- and enantioselective direct aldol-type reactions of azlactones with vinyl ethers catalyzed by chiral phosphoric acid (*R*)-**1a** (see Ref. 15f). The aldol-type reaction of both (*E*)- and (*Z*)-vinyl ethers resulted in exactly identical stereochemical outcomes. Hence, we proposed that the common intermediate, an oxocarbenium ion generated by protonation of vinyl ethers, was involved in the aldol-type reaction.

[27] On the basis of this mechanistic consideration, the substitution reaction shown in Scheme 4 might proceed through a vinyliminium intermediate (as previously postulated by several research groups; see Refs. [4–7]), or, given the minimal stereoselectivity, through an S_N2-type pathway. In an S_N2-type process, the stereochemical outcome would substantially reflect the stereochemistry of the 1′-position of **7**, thus, racemic mixtures would be expected.

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