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Communication

Asymmetric synthesis of pyrrolo[1,2-*a*]indoles *via* organocatalytic [3 + 2] annulation of substituted 2-vinylindoles with azlactones

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ABSTRACT

The chiral phosphoric acid catalyzed asymmetric [3 + 2] annulation of substituted 2-vinylindoles with azlactones has been established. This reaction represented a practical approach for the synthesis of structurally diverse pyrrolo[1,2-*a*]indoles with two vicinal stereocenters including one tetrasubstituted stereocenter in good yields and good stereoselectivities under mild conditions.

Chiral polycyclic indoles are privileged structures found in a great many of natural bioactive products and drug molecules [1]. Among them, chiral pyrrolo[1,2-*a*]indole scaffold has received much attentions owing to the remarkable biological activities [2], and development of the straightforward approaches to such structures has been an important task [3–6]. Among the known strategies, catalytic asymmetric [3 + 2] annulations were considered to be the most efficient and economical approach [6]. In 2013, Enders and coworkers reported an elegant *N*-heterocyclic carbene catalyzed asymmetric [3 + 2] annulation of 2-nitrovinylindoles with α-chloroaldehydes (Scheme 1, Eq. 1) [6a]. Recently, α-ketoesters and hemiacetals were successfully applied in the catalytic asymmetric [3 + 2] annulations with 2-nitrovinylindoles by our (Scheme 1, Eq. 2) [6b] and Liu's group (Scheme 1, Eq. 3) [6c]. Besides, the research group of Schneider [6d-e], Rodríguez [6f], and Shi [6g] independently developed the Brønsted acid catalyzed asymmetric [3 + 2] annulations of 2-indolyl compounds with electron-rich alkenes for the direct synthesis of structurally diverse pyrrolo[1,2-*a*]indoles. Despite these remarkable advances, the construction of chiral pyrrolo[1,2-*a*]indoles bearing a quaternary stereocenter at C2 position still challenging and highly desirable remains (Scheme 2).

Azlactones appear as a class of useful reactants in organic synthesis because they are readily available and versatile reactive character [7]. In particular, the catalytic asymmetric [3 + 2] [8] and [4 + 2] [9] annulations with azlactones have been well-documented for the synthesis of diverse cyclic structures. In conjunction with our continuing efforts in the diversity-oriented synthesis of chiral polycyclic indoles [6b,10], we envisaged that azlactones could serve as a two-atom building block, engage electron-withdrawing group substituted 2-vinylindoles *via* a tandem Michael/ring open process, thus delivering chiral pyrrolo[1,2-*a*] indoles with an aza-quaternary stereocenter at C2 position by formal [3 + 2] annulation. To achieve this goal, we reported herein chiral phosphoric acid catalyzed asymmetric [3 + 2] annulation of 2-acylvinylindoles with azlactones, providing a straightforward approach to structurally diverse pyrrolo[1,2-*a*]indoles in good to high diastereo- and enantioselectivities (Scheme 1, Eq. 4).

Initially, β-(indol-2-yl)-α,β-unsaturated ketone **1a** and azlactone **2a** were chosen as model substrates to test the feasibility of this [3 + 2] annulation by employing chiral phosphoric acid [11] as catalyst (Table 1). A series of BINOL-derived chiral phosphoric acids **4** were evaluated for this [3 + 2] annulation in toluene at 50 °C (entries 1–9), and the desired [3 + 2] annulation proceeded smoothly. Cycloadduct **3a** was generated in 55% yield, 33% *ee* and 90:10 dr when using chiral phosphoric acid **4f** as catalyst (entry 6). Subsequently, the backbone of **4f** was changed from BINOL to H_8-BINOL to improve the stereoselectivity (entry 10). Unfortunately, only racemic product was observed with chiral

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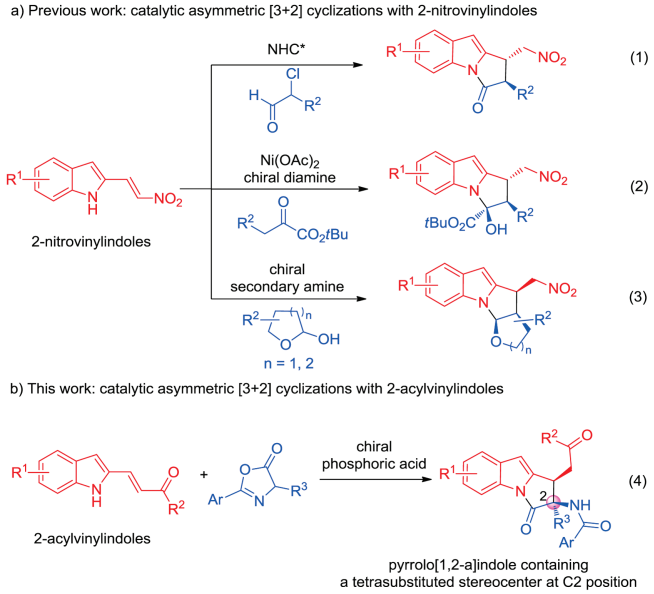
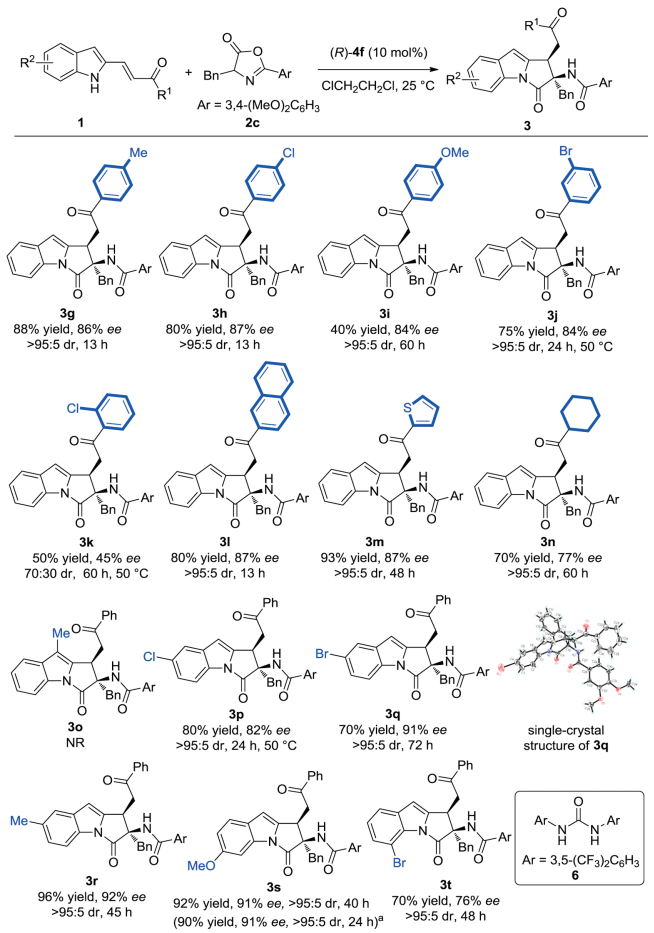
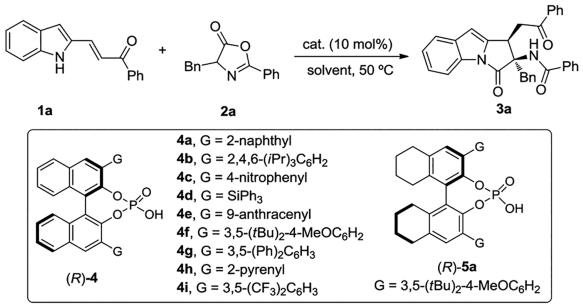


Scheme 1. Catalytic asymmetric [3 + 2] annulations with 2-nitrovinylindoles and 2-acylvinylindoles.



Scheme 2. Substrate scope of 2-acylvinylindoles **1**. Reactions were performed with **1** (0.1 mmol), **2c** (0.15 mmol) in 1.0 mL 1,2-dichloroethane at 25 °C. Isolated yields of two diastereomers; dr values were determined by ^{1}H NMR spectroscopy; *ee* values were determined by chiral HPLC analysis. [a] The gram-scale reaction was performed, affording product **3s** with 1.06 g.

Table 1
Optimization of reaction conditions.[a]



Entry	Cat.	Solvent	Yield (%)[b]	*ee* (%)[c]	dr[d]
1	**4a**	Toluene	47	9	74:26
2	**4b**	Toluene	48	9	71:29
3	**4c**	Toluene	45	6	75:25
4	**4d**	Toluene	45	6	75:25
5	**4e**	Toluene	70	24	85:15
6	**4f**	Toluene	55	33	90:10
7	**4g**	Toluene	51	6	80:20
8	**4h**	Toluene	45	4	75:25
9	**4i**	Toluene	59	13	75:25
10	**5a**	Toluene	45	0	83:17
11	**4f**	$CHCl_3$	70	52	92:8
12	**4f**	$ClCH_2CH_2Cl$	70	56	92:8
13	**4f**	CCl_4	67	46	90:10
14	**4f**	THF	22	10	80:20
15	**4f**	Xylene	50	25	87:13
16	**4f**	CH_3CN	35	13	80:20
17	**4f**	$C_6H_5CF_3$	60	38	90:10
18	**4f**	EtOAc	35	33	88:12

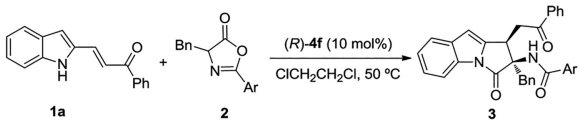
[a] Unless others stated, reactions were performed with **1a** (0.1 mmol), **2a** (0.15 mmol) in 1.0 mL solvent at 50 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR spectroscopy.

phosphoric acid **5a**. To further improve the enantioselectivity, the solvent effect in this reaction was investigated (entries 11–18), and the chlorinated solvents proffer better results (entries 11–13), with 1,2-dichloroethane as the best choice (entry 12, 70% yield, 56% *ee*, 92:8 dr).

Having established the optimal catalyst and solvent, we next turned our attention to improve the enantioselectivity by modifying the substituent Ar on azlactone **2** (Table 2). Pleasingly, when the electron-donating group OMe was introduced on the benzene ring, an obvious improved diastereo- and enantioselectivity was detected (entries 1–3). In particular, the azlactone **2c** with 3,4-dimethoxyphenyl group provided the corresponding pyrrolo[1,2-*a*]indole **3c** in 96% yield with 83% *ee* and >95:5 dr (entry 2). Next, the other electron-donating group was studied, such as piperonyl and 4-dimethylaminophenyl, unfortunately, no better result was gained (entries 4, 5). Subsequently, the reaction temperature was cooled to room temperature to increase the enantioselectivity, and the *ee* value of product **3c** was raised to 89% (entry 6).

After identifying the optimal reaction conditions and the suitable substituent on the azlactone, the substrate scope of 2-acylvinylindoles **1** was evaluated. A wide range of *β*-(indol-2-yl)-*α*,*β*-unsaturated ketone **1** bearing electron-deficient groups and electron-rich groups on the benzene ring proceeded smoothly, affording corresponding [3 + 2] cycloadducts **3g–j** in good yield with high diastereoselectivities (>95:5 dr) and good enantioselectivities (84%–87% *ee*), except the *ortho*-substituent on the phenyl ring, which provided diminished stereoselectivity (70:30

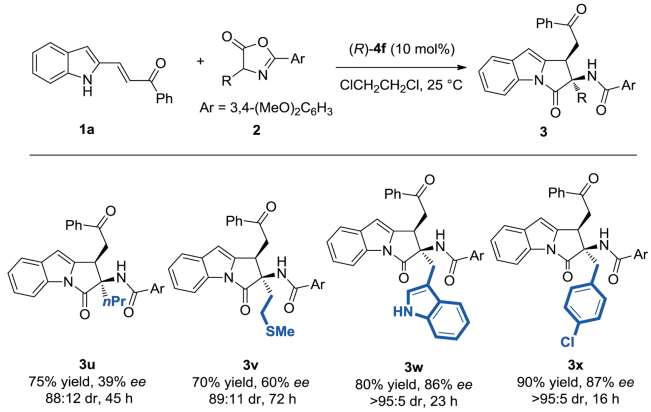
Table 2
Evaluation of the substituent Ar on azlactone.[a]



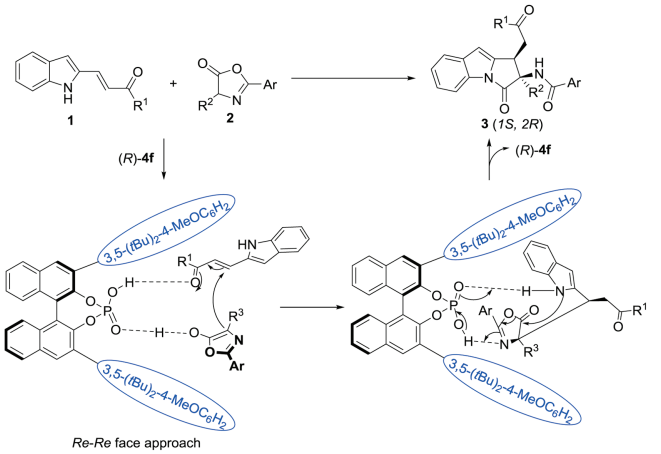
Entry	Ar (**2**)	**3**	Yield (%)[b]	*ee* (%)[c]	dr[d]
1	4-MeOC$_6$H$_4$ (**2b**)	**3b**	90	70	95:5
2	3,4-(MeO)$_2$C$_6$H$_3$ (**2c**)	**3c**	96	83	>95:5
3	3,4,5-(MeO)$_3$C$_6$H$_2$ (**2d**)	**3d**	85	79	>95:5
4	Piperonyl (**2e**)	**3e**	75	63	>95:5
5	4-Me$_2$NC$_6$H$_4$ (**2f**)	**3f**	78	76	>95:5
6[e]	3,4-(MeO)$_2$C$_6$H$_3$ (**2c**)	**3c**	90	89	>95:5

[a] Unless others stated, reactions were performed with **1a** (0.1 mmol), **2b–f** (0.15 mmol) in 1.0 mL 1,2-dichloroethane at 50 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR spectroscopy.
[e] Reaction at 25 °C.

dr, 45% *ee*). Additionally, 2-naphthyl and 2-thienyl substituted 2-indolylpropenone were also tolerated in this reaction and delivered the corresponding products **3l** and **3m** with excellent diastereoselectivities (>95:5 dr) and good enantioselectivities (87% *ee*). The reaction with alkyl-substituted *β*-(indol-2-yl)-*α*,*β*-unsaturated ketone still proceeded smoothly, however, lower enantioselectivity was observed (77% *ee*). Subsequently, the substituent on indole ring was studied. The reaction was dull when the methyl group was introduced on the C3 position of indole. *β*-(Indol-2-yl)-*α*,*β*-unsaturated ketone bearing various substituents on C5 – C6 positions of indole were successfully applied in the reaction, and pyrrolo[1,2-*a*]indoles **3p**–**3s** were generated in high yields (70%–96%) with good enantioselectivities (82%–92% *ee*). Notably, *β*-(Indol-2-yl)-*α*,*β*-unsaturated ketone with Br atom at C7 position only provided the Michael adduct under the standard conditions. Inspired by Scheidt's report [12], cooperative catalyst urea **6** (10 mol%) was added to promote the annulation process, pleasingly, the cycloadduct **3t** was gained in 70% yield, albeit with a decreased enantioselectivity (76% *ee*). In addition, the relative and absolute configurations of product **3q** were unambiguously confirmed by single-crystal X-ray analysis (crystallographic data with CCDC No. 1950068 is deposited in Cambridge Centre.



Scheme 3. Substrate scope of azlactones **2**. Reactions were performed with **1a** (0.1 mmol), **2** (0.15 mmol) in 1.0 mL 1,2-dichloroethane at 25 °C. Isolated yields of two diastereomers; dr values were determined by ^{1}H NMR spectroscopy; *ee* values were determined by chiral HPLC analysis.



Scheme 4. Proposed transition states.

Moreover, a gram-scale experiment was conducted, affording product **3s** (1.06 g) in 90% yield, 91% *ee*, and >95:5 dr.

Next we evaluated the substrate scope of azlactone **2** (Scheme 3). The benzyl group was crucial for the enantioselectivity controlling. Azlactones derived from norvaline and methionine provided the corresponding products **3u** and **3v** in good yields (70%–75%) with a decreased diastereo- and enantioselectivities (39%–60% *ee*, 88:12–89:11 dr). Azlactones bearing 3-indolyl and 4-chlorophenyl were also amenable to this transformation, furnishing products **3w** and **3x** in good yields (80%–90%) and good enantioselectivities (86%–87% *ee*).

We proposed a stereocontrolled model to explicate the observed stereochemical preference. As illustrated in Scheme 4, chiral phosphoric acid (*R*)-**4f** simultaneously activated the two substrates by hydrogen-bonding interactions, and the *Re* face of alkene was attacked by the *Re* face of the enolate of azlactone. Subsequently, the NH on indole ring and the imine of azlactone were activated *via* the hydrogen-bonding interactions with (*R*)-**4f** respectively, which facilitated the intramolecular aminolysis, and afforded the product (1*S*,2*R*)-**3**.

In conclusion, we have developed a practical synthetic route to polysubstituted pyrrolo[1,2-*a*]indoles *via* organocatalytic asymmetric [3 + 2] annulation of substituted 2-vinylindoles with azlactones. By using BINOL-derived chiral phosphoric acid (*R*)-4f as a catalyst under mild conditions, a series of pyrrolo[1,2-*a*] indoles bearing a tetrasubstituted stereocenter at C2 position were obtained in good yields and good diastereo- and enantioselectivities. Further studies about the annulation of 2-vinylindoles for the synthesis of polycyclic indoles are currently underway.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.008.

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