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Chiral phosphoric acid-catalyzed regioselective synthesis of spiro aminals with quaternary stereocenters

Xin-Wei Wang [a,b], Mu-Wang Chen [b], Bo Wu [b], Baomin Wang [a], Boshun Wan [b], Yong-Gui Zhou [a,b]

[a] Zhang Dayu School of Chemistry, Dalian University of Technology, Dalian 116024, PR China
[b] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, PR China

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ABSTRACT

A chiral phosphoric acid-catalyzed enantioselective synthesis of spiro[indoline-3,6′-indolo[1,2-*c*]quinazolin]-2-ones has been developed by condensation/*N*-alkylation cascade from 2-(1*H*-indolyl)anilines and isatins, affording the spiro aminals with quaternary stereogenic centers with up to 93% ee. The protocol could be expanded to 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)aniline and a variety of pyrrole-derived spiro chiral aminals were also obtained in good yields (71–91%) with excellent enantioselectivities (89%-94% ee).

Enantiomerically enriched aminal moieties are ubiquitous in biologically active natural products, pharmacologically relevant compounds and man-made chiral catalysts [1]. Among them, the optically active aminals containing indole skeleton occur in natural alkaloids and biologically active molecules [2]. For example, chiral (-)-goniomitine is a natural product isolated from the Gonioma Malagasy [2a]. The original semi-synthetic bisindole alkaloid **A** displayed a moderate cytotoxicity on L1210 leukemia cells (Fig. 1) [2b].

In recent years, a series of methods have been developed to access the optically active aminals containing indole skeleton. However, controlling regioselectivity in *N*-alkylation reactions remains a challenge because C3 of indole is much more nucleophilic than the nitrogen atom. Consequently, indoles with substituents blocking the C3 position were used to achieve *N*-alkylated aminals *via* chiral phosphoric acid-catalyzed (CPA-catalyzed) [3 + 3] cycloaddition [3], *N*-alkylation reaction of indoles with *in situ* generated cyclic *N*-acyl ketimines [4] and dearomatization reaction of isoquinolines with indole derivatives [5]. Another way to circumvent this problem was to employ chiral catalysts or bases to interact with the acidic proton on the *N* atom of indoles in order to promote the *N*-alkylation [6–8]. An efficient chiral Brønsted acid-catalyzed enantioselective *N*-alkylation of indoles and α,β-unsaturated γ-lactams was reported by Huang (Scheme 1a) [6]. Smith and coworkers demonstrated a chiral cation-directed enantioselective *N*-functionalization of indoles by phase-transfer catalysis (PTC) under basic conditions (Scheme 1b) [7]. Trost and co-workers developed the regioselective and enantioselective *N*-alkylation of indole with *N*-alkoxyacylimines catalyzed by a chiral zinc-ProPhenol dinuclear complex (Scheme 1c) [8]. In addition, a novel method to chiral aminals *via* palladium-catalyzed C — N coupling using chiral bisphosphine mono-oxides was described by Li and co-workers (Scheme 1d) [9].

Despite considerable efforts have been devoted to enantioenriched indoles *N*-alkylated aminals, the asymmetric synthesis of these compounds bearing quaternary stereocenters were limited to 3-substituted indoles. The preparation of aminals containing quaternary stereocenters using simple indoles without substituted group in C3 position encounters challenges. These difficulties can be ascribed to the following factors: 1) the C3-alkylation occurs more easily because C3 position of indoles is more nucleophilic than the nitrogen atom; 2) when ketones or ketimines with low activity were employed in such reactions, relatively stricter reaction conditions are required, which may convert sensitive aminals into stable C3-alkylation products.

In 2005, Antilla's group reported amidation of imines for the synthesis of the chiral aminals catalyzed by vaulted biphenanthrol (VAPOL) derived phosphoric acid with excellent enantioselectivity [10]. Since then, various chiral aminals have been prepared using phosphoric acids as the catalysts [3–6,11,12]. Recently, we reported chiral phosphoric acid-catalyzed synthesis of fluorinated 5,6-dihydroindolo-[1,2-*c*]-quinazolines with quaternary stereocenters from 3-substituted indoles and fluorinated ketones [13].

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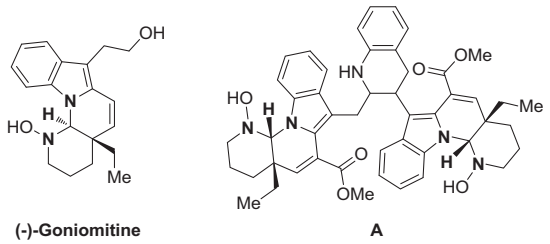
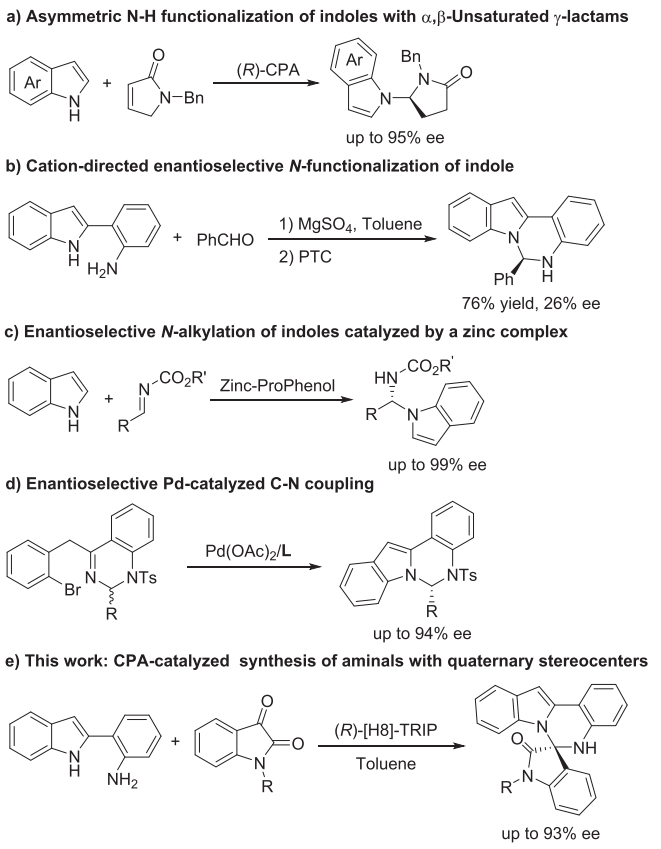


Fig. 1. The selected bioactive molecules containing 5,6-dihydroindolo[1,2-*c*]quinazoline motif.



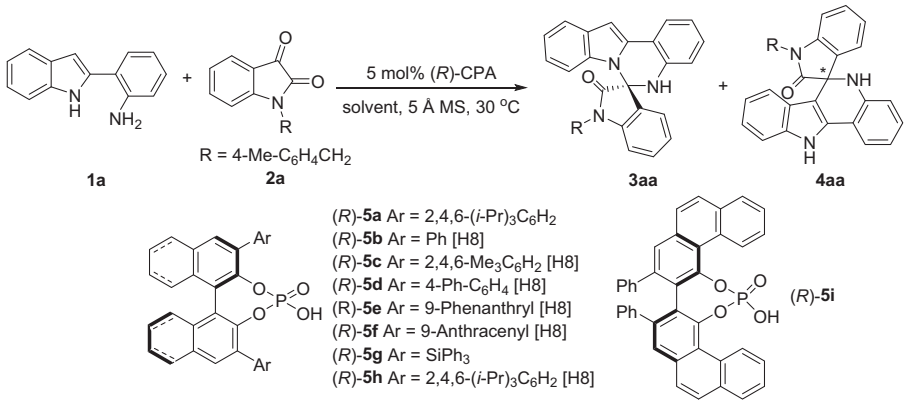
Scheme 1. Synthesis of indole *N*-alkylated chiral aminals without substituents blocking C3 position.

In previous research, we found 2-(1*H*-indolyl)aniline without substituent in 3-position reacted with trifluoromethyl aryl ketones to afford the chiral *N*-functionalization products as predominant product and C3-alkylation as side-product. Inspired by the recent progress on chiral phosphoric acid-catalyzed synthesis of chiral aminals, we have interest in exploring the reactions of 2-(1*H*-indolyl)anilines and cyclic isatins. Herein, we reported chiral phosphoric acid-catalyzed regioselective and enantioselective reactions of 2-(1*H*-indolyl)anilines and isatins to afford spiro aminals bearing quaternary stereogenic centers by condensation/*N*-alkylation cascade with up to 93% ee (Scheme 1e).

We began our studies with 2-(1*H*-indolyl)aniline **1a** and isatin **2a** as the model substrates using our previous optimal catalyst (*R*)-3,3-bis(2,4,6-triisopropylphenyl)-1,1-binaphthyl-2,2-diyl hy-drogenphosphate (TRIP, **5a**) in synthesis of fluorinated 5,6-dihydroindolo [1,2-*c*]-quinazolines [12]. To our surprise, 2-(1*H*-indolyl)aniline **1a** reacted with isatin **2a** in toluene in the presence of 50 mg of 5 Å MS as the dehydrating agent, affording *N*-alkylation product **3aa** in 83% yield with 89% ee, while the C3-alkylation product was obtained in 13% yield with 29% ee (Table 1, entry 1). In order to achieve better regioselectivity and enantioselectivity, different chiral phosphoric acids were tested. Most of catalysts furnished the reactions with poor regioselectivity (Table 1, entries 2–6 and 9). With steric hindrance of the substituted groups at the 3,3′-positions of chiral phosphoric acids used, the reaction had higher activity and gave **3aa** with better enantioselectivities (Table 1, entries 1–6). However, when sterically congested catalyst (*R*)-**5g** was examined, C3-alkylation product **4aa** was predominant with 1:18.2 r.r. (regioselectivity ratio) and poor enantioselectivity (Table 1, entry 7). Employing chiral catalyst (*R*)-**5h**, best regioselectivity and enantioselectivity was obtained (Table 1, entry 8). VAPOL-derived chiral phosphoric acid (*R*)-**5i**, which was utilized as best catalyst to catalyze intermolecular imine amidation reaction reported by Antilla [10,11a], giving 1:1.3 r.r. with opposite configuration of **3aa** (Table 1, entry 9). Therefore, (*R*)-**5g** was identified as the optimal catalyst for screening of reaction solvents (Table 1, entries 10–18). When tetrahydrofuran and acetonitrile were used as reaction media, **4aa** was afforded as major product in high yields albeit with low ee (Table 1, entries 12 and 14). Compared to other solvents, such as ether and ethyl acetate, toluene and dichloromethane gave better results in terms of yields and enantioselectivities. The solvents including *p*-xylene, 1,2-dicloroethane, trifluorotoluene and benzene were further tested, toluene was superior than others. Other reaction conditions such as temperature, the ratio of **1a** to **2a** and concentration were also investigated in efforts to improve the enantioselectivity and regioselectivity, but no better results were gained (Table 1, entries 19–24). Finally, the conditions of entry 8 were chosen as the optimal reaction conditions using 5 mol % (*R*)-**5h** as the catalyst and 1.1 equivalent of **2a** to **1a** in toluene (0.1 M) in the presence of 50 mg of 5 Å MS.

With the optimized conditions in hand, various substrates were examined to explore the generality and limitations of this methodology. Under standard conditions, the *N*-alkylation product **3aa** could be isolated in 81% yield with 90% ee (Scheme 2, **3aa**). The influence of *N*-substituted isatins **2a**-**2f** was examined first. The steric hindrance of *N*-substituted groups in isatins played a crucial role in controlling regioselectivity, but slightly affected the enantioselectivity. Different aryl methyl substituted isatins **2a** and **2c**-**2e** delivered the corresponding products containing spiro quaternary stereocenters in excellent enantioselectivities and good yields. When *N*-methyl isatin **2b** was employed, the regioselectivity was dramatically reduced to 1.9:1 r.r.. Protecting isatin with 1-naphthalenyl methyl did not increase the reaction selectivity (Scheme 2, **3ae** vs **3aa**). Sterically hindered benzhydryl protected isatin **2f** furnished the reaction in higher 12.5:1 r.r., but the ee value of **3af** was dropped to 86%. The *p*-methoxybenzyl (PMB) substituent was selected as the optimal protecting group in terms of regioselectivities and enantioselectivities for following exploration. Next, the reaction of various 2-(1*H*-indolyl)anilines **1** and isatin **2d** were studied (Scheme 2, **3bd-3fd**). 2-(5-Methyl-1*H*-indol-2-yl)aniline **1b** underwent the reaction smoothly and afforded **3bd** in 85% isolated yield and 91% ee (Scheme 2, **3bd**). 2-(1*H*-indolyl)-anilines **1c** bearing an electron-withdrawing group in 5-position of indole gave corresponding product **3 cd** with excellent enantioselectivity, while, the regioselectivity was moderate, which might be attributed to the decreased nucleophilicity of *N* atom (Scheme 2, **3cd**). 2-(1*H*-indolyl)aniline **1d** with a methyl group in 3-position of indole provided **3dd** in quantitative yield but remarkable decrease of enantioselectivity (Scheme 2, **3bd**). The substituted groups at *para*-position of aniline moiety did not affect the enantioselectivities (Scheme 2, **3ed** and **3fd**). Excellent regioselectivity was gained with *p*-methyl substituted anline **1f** (Scheme 2, **3fd**). A series of *N*-PMP protected isatins bearing different groups ranging from the 5-position to 7-position were also

Table 1
Optimization of reaction parameters.[a]



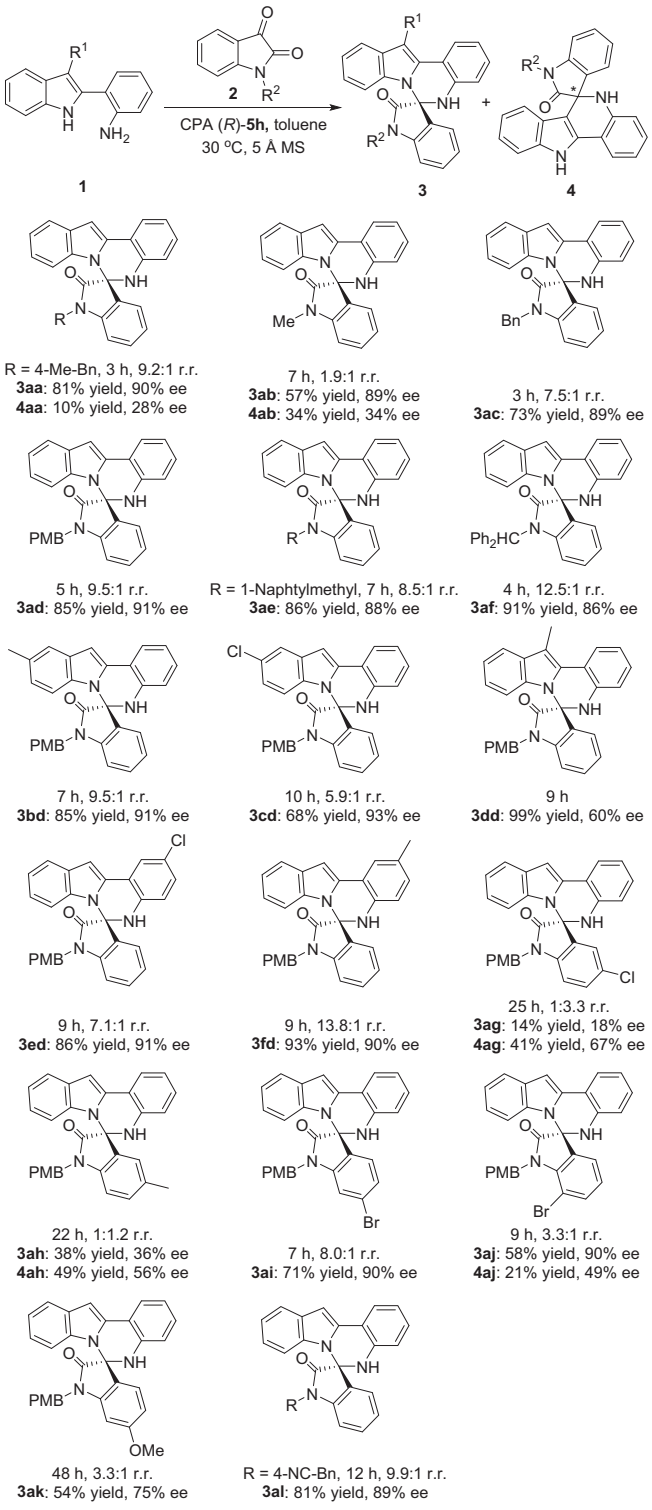
Entry	CPA	Solvents	t (h)	*N*-alk. Yield (%)[b]	*N*-alk. Ee (%)[c]	C3-alk. Yield (%)[b]	C3-alk. Ee (%)[c]	**3aa**:**4aa**[b]
1	(*R*)-**5a**	toluene	3	83	89	13	29	6.3:1
2	(*R*)-**5b**	toluene	24	40	−2	54	1	1:1.3
3	(*R*)-**5c**	toluene	8	41	70	57	55	1:1.4
4	(*R*)-**5d**	toluene	42	32	35	67	6	1:2.2
5	(*R*)-**5e**	toluene	5	44	79	42	25	1.0:1
6	(*R*)-**5f**	toluene	4	19	86	65	41	1:3.7
7	(*R*)-**5g**	toluene	48	<5	–	87	3	1:18.2
8	(*R*)-**5h**	toluene	**3**	**89**	**90**	**9**	**28**	**10.2:1**
9	(*R*)-**5i**	toluene	11	43	−68	54	5	1:1.3
10	(*R*)-**5h**	DCM	12	89	88	11	−3	7.8:1
11	(*R*)-**5h**	Et_2O	21	69	92	31	52	2.2:1
12	(*R*)-**5h**	THF	24	<5	–	88	5	1:19.7
13	(*R*)-**5h**	EtOAc	22	60	92	36	36	1.7:1
14	(*R*)-**5h**	MeCN	48	15	82	79	7	1:5.3
15	(*R*)-**5h**	DCE	10	77	83	20	−13	3.8:1
16	(*R*)-**5h**	*p*-xylene	3	89	90	10	30	8.8:1
17	(*R*)-**5h**	$PhCF_3$	4	80	86	17	17	4.8:1
18	(*R*)-**5h**	benzene	22	83	90	15	31	5.7:1
19[d]	(*R*)-**5h**	toluene	41	82	91	9	6	8.7:1
20[e]	(*R*)-**5h**	toluene	2.5	90	89	9	34	9.7:1
21[f]	(*R*)-**5h**	toluene	3	84	90	10	34	8.4:1
22[g]	(*R*)-**5h**	toluene	2	89	90	9	28	9.9:1
23[h]	(*R*)-**5h**	toluene	2	88	90	12	22	7.3:1
24[i]	(*R*)-**5h**	toluene	6	88	90	9	29	10.2:1

[a] Reactions were performed with **1a** (0.10 mmol) and **2a** (0.11 mmol) in toluene (1.0 mL) using 5 mol% (*R*)-**5** as catalyst at 30 °C.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.
[d] At 0 °C.
[e] At 50 °C.
[f] **1a** (0.11 mmol) and **2a** (0.10 mmol) were used.
[g] **1a** (0.10 mmol) and **2a** (0.13 mmol) were used.
[h] 0.5 mL toluene was used.
[i] 2.0 mL toluene was used.

explored (Scheme 2, **2g-2j**). The 7-bromo substituted isatin **2i** was very compatible to produce the corresponding aminal **3ai** in 71% yield with 90% ee (Scheme 2, **3ai**). With substituents in 5-position of isatins, both 5-chloro and 5-methyl isatins led to poor regisoselectivities, and C3 alkylation adducts were isolated as major products with moderate enantioselectivities, probably due to the steric effect (Scheme 2, **4ag, 4ah**). The 7-bromo substituted isatin **2j** was also reactive to afford **3aj** in 58% yield and 90% ee albeit with poor regioselectivity (Scheme 2, **3aj**). For *N*-substituted isatin **2 k** with a methoxy group at the benzene ring, the desired product **3ak** was obtained with moderate regioselectivitity and enantioselectivity when reaction time was prolonged (Scheme 2, **3ak**). 4-Cyanobenzyl protected isatin **2 l** also was suitable reaction partners for this cascade reaction, giving the spiro aminal **3al** with good regisoselectivitity and enantioselectivity (Scheme 2, **3al**). The absolute configuration of product **3aa** was assigned as *S* based on the X-ray diffraction analysis after recrystallization from the mixed solvents (ethyl acetate/dicloromethane/hexanes) to upgrade ee to > 99%.

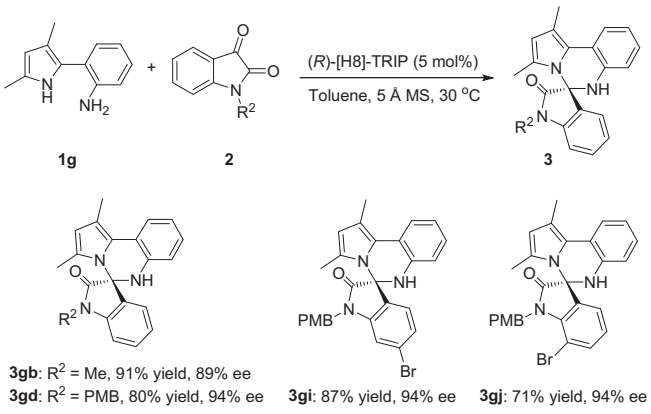
In order to further evaluate generality of this strategy, pyrrole derived 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)aniline **1 g** was examined under the above standard conditions for the synthesis of spiro chiral aminals. The *N*-PMB substituted isatin **2d** reacted with 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)aniline **1 g**, affording the desired spiro aminal **3gd** with higher 94% ee than that of *N*-methyl isatin **2b** (Scheme 3, **3**gb vs **3gd**). The *N*-PMB protected isatins **2i** and **2j** were amenable to give the corresponding chiral spiro aminal products in good yields and 94% ee (Scheme 3, **3gi** and **3gj**).

In conclusion, we have demonstrated a chiral phosphoric acid-catalyzed condensation/*N*-alkylation cascade for regioselective and enantioselective synthesis of spiro[indoline-3,6′-indolo-[1,2-*c*]quinazolin]-2-ones bearing spiro quaternary stereocenters from 2-(1*H*-indolyl)anilines and isatins. This methodology provides a



Scheme 2. Substrate scope. Conditions: **1** (0.20 mmol) and **2** (0.22 mmol) in toluene (2.0 mL) using 5 mol% (*R*)-**5h** as catalyst in the presence of 100 mg 5 Å MS at 30 °C.

straight and facile access to aminals which are prevalent in natural products and pharmaceutical chemistry with good yields and up to 93% ee. The substrate scope could be extended to 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)aniline for synthesis of pyrrole derived spiro chiral aminals. Detailed mechanistic investigations of the origin of unique regioselectivity and enantioselectivity and highly



Scheme 3. Substrate scope: 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)aniline. Condition: **1 g** (0.20 mmol) and **2** (0.22 mmol) in toluene (2.0 mL) using 5 mol% (*R*)-**5h** as catalyst in the presence of 100 mg 5 Å MS at 30 °C.

enantioselective synthesis of C3 alkylation products are now in progress in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152793.

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