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An enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived *N*-Boc ketimines†

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By employing a chiral phosphoric acid as a catalyst, an enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived *N*-Boc ketimines was realized. The reaction provided a wide variety of novel 3-isoxazole 3-amino-oxindoles with good yields (up to 99%) and moderate to good enantioselectivities (up to 99%). The absolute configuration of one product was assigned by X-ray crystal structural analysis and a plausible reaction mechanism was proposed. In addition, a scale-up reaction was performed successfully. Finally, one product was subjected to Suzuki–Miyaura coupling with phenylboronic acid to afford the product in a moderate yield without erosion of the enantioselectivity.

Introduction

Chiral 3,3-disubstituted oxindoles are important structural motifs in a large number of natural products and pharmaceuticals. Among them, chiral 3-substituted 3-amino-oxindoles represent pharmaceutically interesting molecules.[1] Consequently, the asymmetric synthesis of chiral 3-substituted 3-amino-oxindoles has attracted much attention and many efficient strategies for the construction of novel chiral 3-substituted 3-amino-oxindoles have been established.[2] Among these strategies, asymmetric reactions of isatin-derived ketimines are highly efficient and straightforward in the preparation of diverse chiral 3-substituted 3-amino-oxindoles.[3–5] In particular, the asymmetric aza-Friedel–Crafts reaction of isatin-derived ketimines with electron-rich arenes[4] and asymmetric addition of arylboronic acids or arylboroxines to isatin-derived ketimines[5] have been well developed to deliver various highly enantio-enriched 3-aryl 3-amino-oxindoles.

Isoxazole derivatives exhibit numerous biological activities, including insecticidal, antibacterial, antibiotic, antiviral, antitumour, antifungal, *etc*.[6] Owing to the significance of isoxazoles in drug discovery, the construction of novel isoxazole derivatives is of great importance.

Recently, we disclosed a highly enantioselective dearomative [3 + 2] annulation of 5-aminoisoxazoles with quinone monoimines.[7] Owing to the good nucleophilicity of 5-aminoisoxazoles, we envisioned that they can also be used in asymmetric Friedel–Crafts reactions.[8] In continuation of the research on asymmetric transformations of 5-aminoisoxazoles, herein we present the enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived ketimines. In the presence of a chiral phosphoric acid catalyst, the reactions proceeded smoothly to generate a wide range of novel 3-isoxazole-3-amino-oxindoles with good yields (up to 99%) and moderate to good enantioselectivities (up to 99%). The absolute configuration of one product was determined by X-ray crystal structural analysis. Accordingly, a plausible reaction mechanism was proposed. In addition, a scale-up reaction was performed using only 0.5 mol% of the catalyst and a good result was achieved. Furthermore, one product was used in Suzuki–Miyaura coupling with phenylboronic acid to afford the product in a moderate yield with excellent enantioselectivity.

Results and discussion

First, various chiral phosphoric acids were evaluated in the Friedel–Crafts reaction of *N*-ethyl-3-phenylisoxazol-5-amine **1a** with isatin-derived *tert*-butyl(1-ethyl-2-oxoindolin-3-ylidene)carbamate **2a** in dichloromethane at 0 °C for 2 hours. As can be seen in Scheme 1, all of the chiral phosphoric acids promoted the reaction smoothly to provide 3-isoxazole-3-amino-oxindole **3aa** in quantitative yields and **PA4**, which bears a 2-naphthyl group in the 3,3′ position of BINOL, gave the product **3aa** with

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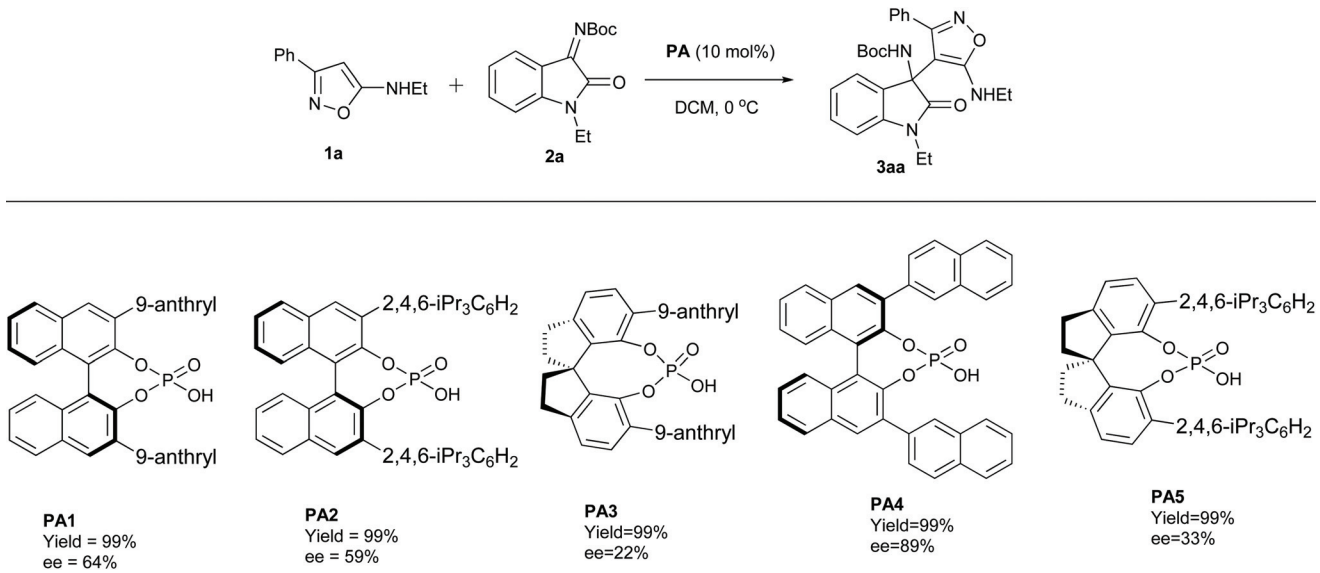
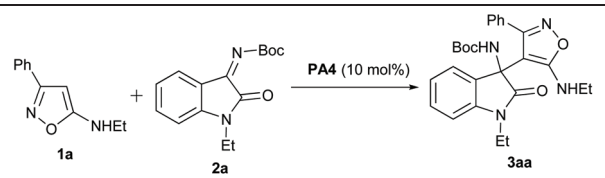


Scheme 1 Evaluation of chiral phosphoric acids. Unless otherwise specified, the reactions were carried out with 0.10 mmol of **1a**, 0.15 mmol of **2a** and 10 mol% of **PA** in 1 mL of dichloromethane at 0 °C for 2 hours. Yields refer to isolated product based on **1a**. Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

the highest ee value of 89%. Thus **PA4** was determined as the optimal catalyst and used in the following investigations.

Subsequently, the other conditions were optimized. The results are presented in Table 1. First, various solvents were evaluated. Similar outcomes were observed in reactions in dichloromethane, chloroform and toluene (Table 1, entries 1–3). To our delight, MTBE and THF exhibited quantitative yields as well as excellent enantioselectivities (Table 1, entries 4 and 5).

Table 1 Optimization of the conditions[a]



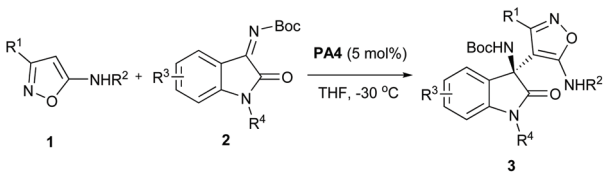
Entry	Solvent	T (°C)	t (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	0	2	99	89
2	$CHCl_3$	0	2	99	89
3	Toluene	0	6	99	88
4	MTBE	0	6	99	96
5	THF	0	6	99	96
6	CH_3CN	0	6	99	50
7[d]	THF	0	12	93	96
8[e]	THF	0	12	93	94
9[d]	THF	−10	12	95	97
10[d]	THF	−30	12	99	98

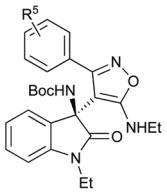
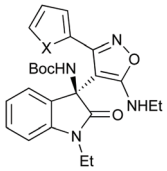
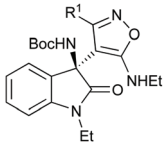
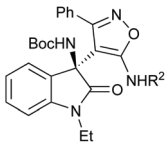
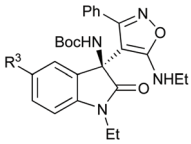
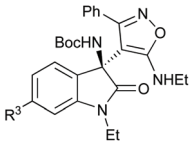
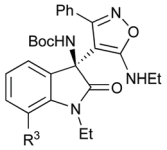
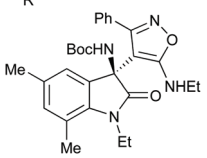
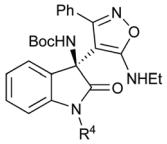
[a] Unless otherwise specified, the reactions were carried out with 0.10 mmol of **1a**, 0.15 mmol of **2a** and 10 mol% of **PA4** in 1 mL of the solvent. [b] Yield of the isolated product based on **1a**. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] 5 mol% of **PA4** was used. [e] 2 mol% of **PA4** was used.

The reaction in acetonitrile delivered a much lower ee value (Table 1, entry 6). Therefore THF was determined as the most favourable solvent for the reaction. When we tried to lower the catalyst loading to 5 mol%, the enantioselectivity remained the same (Table 1, entry 7). Further lowering the catalyst loading to 2 mol% led to a little decrease in the ee value (Table 1, entry 8). When the reaction was conducted at −10 °C for 12 hours, a little increase in enantioselectivity was observed (Table 1, entry 9). Further lowering the temperature to −30 °C led to an excellent ee value without a decrease in the yield (Table 1, entry 10).

Having established the optimal conditions, the scope of the enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived *N*-Boc ketimines was investigated. The results are presented in Table 2. First, various 5-aminoisoxazoles were tested in the reaction with isatin-derived *N*-Boc ketimine **2a**. Generally, 5-aminoisoxazoles with different 3-aryl substituents were tolerable in the reaction to afford the corresponding 3-isoxazole-3-amino-oxindoles in quantitative yields with high ee values (Table 2, entries 1–8). However, only moderate enantioselectivities were observed with two 3-alkyl-5-aminoisoxazoles (Table 2, entries 9 and 10). Some 3-phenylisoxazol-5-amines with different *N*-substituents underwent the reaction with **2a** to give the products with quantitative yields and good enantioselectivities (Table 2, entries 11–13), in which *N*-benzyl substrate **1l** exhibited lower enantioselectivity (Table 2, entry 12). Afterwards, various isatin-derived *N*-Boc ketimines were also subjected to the reaction with *N*-ethyl-3-phenylisoxazol-5-amine **1a**. Ketimines with various electron-donating and electron-withdrawing groups on the benzene part were generally tolerated in the reaction and afforded the corresponding 3-isoxazole 3-amino-oxindoles in quantitative yields with good ee values (Table 2, entries 14–26).

Table 2 Substrate scope of the enantioselective aza-F–C reaction of 5-aminoisoxazoles **1** with isatin-derived *N*-Boc ketimines **2**[a]



Entry	3		t (h)	Yield[b] (%)	ee[c,d] (%)
1		**3aa** (R^5 = H)	12	99	98
2		**3ba** (R^5 = 4-F)	12	98	96
3		**3ca** (R^5 = 4-Cl)	12	99	98
4		**3da** (R^5 = 3-Cl)	12	97	99
5		**3ea** (R^5 = 4-Br)	12	95	97
6		**3fa** (R^5 = 4-OMe)	12	99	91
7		**3ga** (X = O)	12	99	95
8		**3ha** (X = S)	12	99	96
9		**3ia** (R^1 = i-Pr)	60	99	53
10		**3ja** (R^1 = Me)	12	99	69
11		**3ka** (R^2 = Me)	12	99	98
12		**3la** (R^2 = Bn)	12	99	88
13		**3ma** (R^2 = allyl)	12	99	96
14		**3ab** (R^3 = Cl)	24	92	95
15		**3ac** (R^3 = Br)	12	99	97
16		**3ad** (R^3 = Me)	12	88	98
17		**3ae** (R^3 = OMe)	12	99	96
18		**3af** (R^3 = NO_2)	12	94	92
19		**3ag** (R^3 = F)	12	98	98
20		**3ah** (R^3 = Cl)	12	99	94
21		**3ai** (R^3 = Br)	12	99	96
22		**3aj** (R^3 = Cl)	12	99	92
23		**3ak** (R^3 = Br)	12	99	97
24		**3al** (R^3 = Me)	12	95	98
25		**3am** (R^3 = CF_3)	12	98	88
26		**3an**	12	99	96
27		**3ao** (R^4 = Me)	12	99	96
28		**3ap** (R^4 = Bn)	12	99	98
29		**3aq** (R^4 = Boc)	40	94	92
30		**3ar** (R^4 = H)	24	84	83

[a] Unless otherwise specified, the reactions were carried out with 0.10 mmol of **1**, 0.15 mmol of **2**, and 5 mol% of **PA4** in 1 mL of THF at −30 °C. [b] Yield of the isolated product based on **1**. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of **3ca** was determined by X-ray analysis and the absolute configurations of the other products were assigned by analogy.

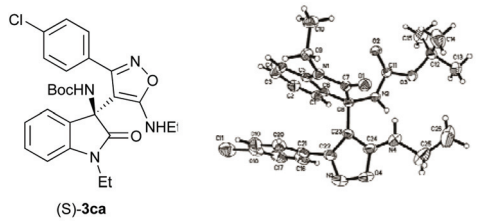


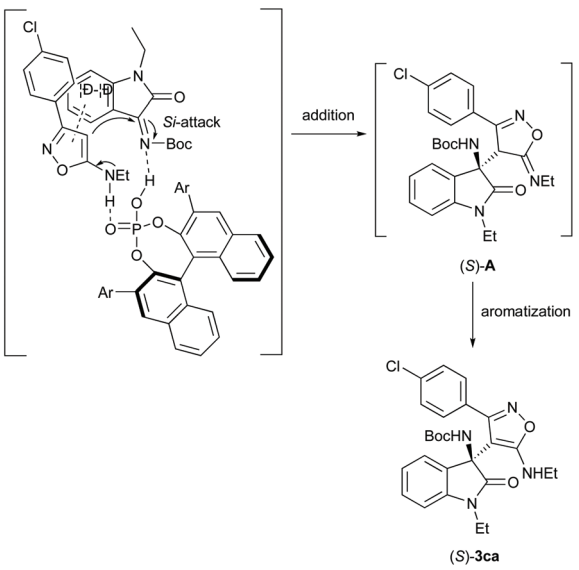
Fig. 1 X-ray crystal structure of (*S*)-**3ca**.

Furthermore, some ketimines with different 1-substituents were also used in the reaction with **1a**. Good results were obtained with 1-methyl, 1-benzyl and *N*-Boc ketimines (Table 2, entries 27–29). However, the reaction of N–H ketimine **2r** with **1a** delivered an obviously lower yield and lower enantioselectivity (Table 2, entry 30).

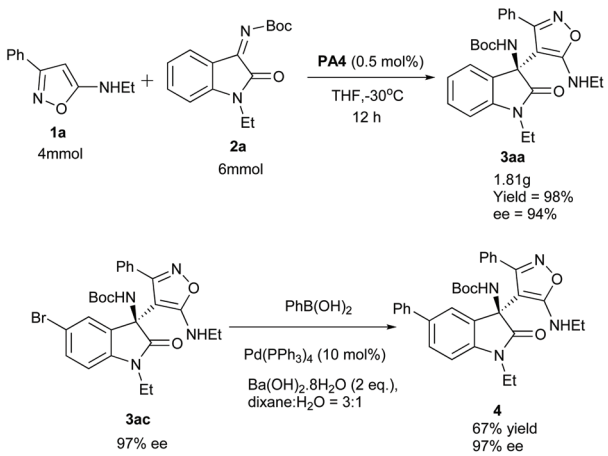
The absolute configuration of **3ca** was determined as (*S*) by X-ray crystal structural analysis[9] (Fig. 1). Consequently, the other products can be assigned absolute configurations by analogy.

Based on the absolute configuration of product **3ca**, a plausible reaction mechanism was proposed. As outlined in Scheme 2, first, bifunctional phosphoric acid activated both isoxazole **1c** and isatin-derived *N*-Boc ketimine **2a**. In addition, maybe the arene–arene interaction between the aromatic systems of the two substrates could stabilize the transition state. Thus isoxazole **1c** attacked ketimine **2a** from the *Si*-face to generate the intermediate (*S*)-**A** which underwent aromatization immediately to give 3-isoxazole 3-amino-oxindole (*S*)-**3ca**.

To illustrate the synthetic utility of this methodology, in the presence of 0.5 mol% of **PA4**, a scale-up enantioselective F–C reaction of **1a** with **2a** was performed. The reaction provided (*S*)-**3aa** with an excellent yield and enantioselectivity. Moreover, product **3ac** was subjected to Suzuki–Miyaura cross coupling with phenylboronic acid to afford compound **4** in a moderate yield without erosion of the ee value (Scheme 3).



Scheme 2 Plausible reaction mechanism.



Scheme 3 Scale-up synthesis of **3aa** and Suzuki–Miyaura cross coupling of **3ac** with phenylboronic acid.

Conclusions

In conclusion, we have developed an efficient enantioselective Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived *N*-Boc ketimines catalyzed by a chiral phosphoric acid. The reactions provided novel 3-isoxazole 3-amino-oxindoles with good yields (up to 99%) and moderate to good enantioselectivities (up to 99%). This transformation has a broad substrate scope and the reaction could be scaled up successfully. The absolute configuration of one product was determined as *S* by X-ray crystal structural analysis and a plausible reaction mechanism was proposed. Moreover, Suzuki–Miyaura coupling of one product with phenylboronic acid was performed and the phenylated product was obtained in a moderate yield without loss of the enantioselectivity.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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