Chiral phosphoric acid-catalyzed Friedel-Crafts reaction of 2,5-disubstituted and 2-monosubstituted pyrroles with isoindolinone-derived ketimines

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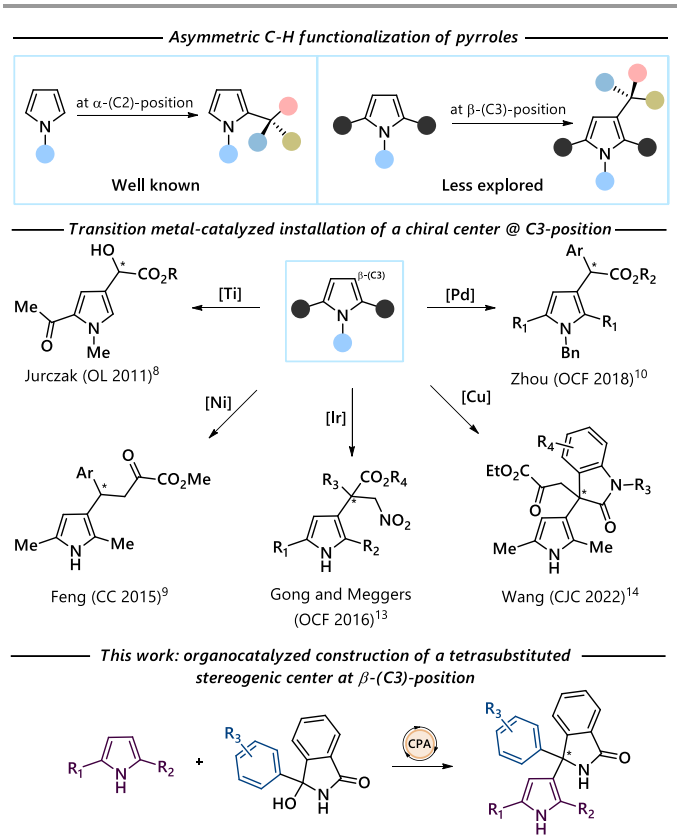
Enantioselective reaction between 2,5-disubstituted pyrroles and diaryl-ketimines, generated *in situ* from isoindolinone-derived alcohols, is described. Pyrrole derivatives possessing congested tetrasubstituted stereogenic center in β-(C3) position are generally obtained in high yields and enantioselectivities. The transformation can be extended to 2-monosubstituted pyrroles, generating chiral α-(C5) functionalized pyrrole products. Control experiments were conducted In order to elucidate origins of low enantioselectivities observed in some of the products.

Introduction

The direct asymmetric C–H functionalization of pyrroles serves as the most straightforward approach for the synthesis of enantioenriched pyrrole derivatives.[1] However, compared to indoles, the functionalization of pyrroles is much more challenging. Because of their inherent small molecular size, the coordination of pyrroles with chiral catalysts results in weak steric interactions, which leads to difficulties in controlling the enantioselectivity. Reactions on pyrroles predominantly occur at its more nucleophilic α-(C2)-position.[2] The first enantioselective Friedel–Crafts reaction of pyrrole with α,β-unsaturated aldehydes was reported in 2001 by MacMillan.[3] Following this seminal report, numerous asymmetric transformations of pyrroles at α-(C2)-position with various electrophilic partners under transition-metal and organocatalytic conditions started to continuously appear in the literature.[4]

On the other hand, asymmetric functionalization of β-(C3)-position on pyrroles is often challenging to realize. β-Functionalized pyrroles serve as precursors for the synthesis of other bioactive compounds,[5] and are structural cores of natural products[6] and functional materials.[7] However, only few reports tackle the asymmetric functionalizations at this position (Scheme 1). In 2011, Jurczak et al reported a highly enantioselective and β-(C3)-selective reaction between pyrroles and glyoxylates catalyzed by chiral Ti(IV) complex.[8] By employing chiral Ni-complex catalyst, Feng et al performed an enantioselective β-(C3)-alkylation of 2,5-dimethylpyrrole.[9] In a Pd-catalyzed Friedel-Crafts reaction, Zhou et al efficiently constructed a stereogenic center at β-(C3) position of symmetrically 2,5-disubstituted pyrroles.[10] Within general studies on the asymmetric C-H functionalization of indoles[11] and pyrroles at their α-(C2)-position,[12] the authors demonstrated that developed methodologies can also be applied for the asymmetric β-(C3)-alkylation of 2,5-dimethyl pyrrole. It is worth noting that all of these reports yield products with tertiary stereogenic centers.



Scheme 1. Enantioselective β-(C3)-functionalizations of pyrroles.

To the best of our knowledge, only three systematic studies are reported for the construction of a tetrasubstituted stereogenic center in the pyrrole β-(C3) position. Gong and Meggers successfully β-(C3)-alkylated unsymmetrical 2,5-disubstituted pyrroles in a highly regioselective fashion utilizing a chiral Ir-complex.[13] In 2022, Wang et al reported a Cu-catalyzed addition of 2,5-dimethylpyrrole to isatin derived β,γ-unsaturated α-ketoesters.[14] Although not employing Friedel-Crafts alkylation strategy, Kumar et al successfully installed quaternary stereogenic center at β-(C3)-position of pyrroles by developing one-pot chiral amine-catalyzed aldol reaction between succinaldehyde and ketones, followed by the Paal-Knorr reaction with a primary amine.[15]

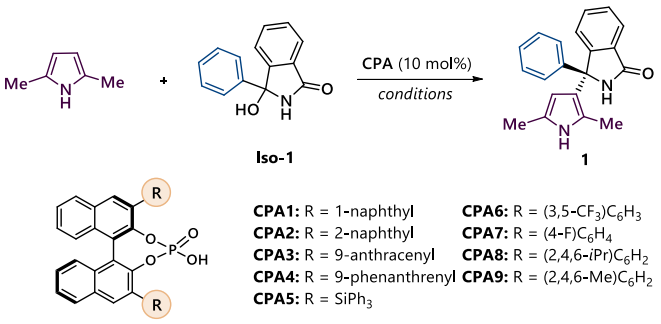
We envisaged to build on these elegant examples, and develop asymmetric organocatalytic methodology for the installation of a congested tetrasubstituted stereogenic center in pyrrole β-(C3) position. Following our recent reports on arylations of isoindolinone-derived ketimines,[16] herein we present a chiral phosphoric acid-catalyzed reaction between pyrroles and ketimines generated *in situ* from 3-hydroxyisoindolinones.[17]

Results and Discussion

We started our investigations by combining 2,5-dimethylpyrrole with 3-phenyl 3-hydroxyisoindolinone **Iso-1** in the presence of various chiral phosphoric acids **CPA*** in toluene (0.1M solution) at room temperature (Table 1). Our initial attempt with 1-naphthyl-substituted chiral phosphoric acid **CPA1** in toluene at room temperature led to the complete conversion to target product **1** within 1 hour, and with moderate enantioselectivity (entry 1). The reaction rate decreased when 2-naphthyl substituent was placed on the flanking rings of the chiral catalyst (**CPA2**), accompanied by virtually no stereochemical induction in the product (entry 2). The introduction of 9-anthracenyl group on the 3,3' positions of the catalyst (**CPA3**) did not improve reaction parameters (entry 3), however placing 9-phenanthrenyl substituent in these positions (**CPA4**) resulted in the highest enantioselectivity thus far, albeit with a substantially prolonged reaction time (entry 4). The enanatioselectivity was further improved when -$SiPh_3$ substituent was placed on the catalyst backbone (**CPA5**, entry 5). 3,5-difluoro- (**CPA6**) and 4-fluoro-substituted (**CAP7**) phenyl rings on the catalyst improved the reaction rate, but with a drop in the enantioselectivity (entries 6 and 7). Results up to this point indicated that bulkier substituents on the chiral phosphoric acid provide best outcome for this transformation. Hence, **CPA8** and **CPA9** were employed as catalysts (entries 8 and 9), and the best result was obtained with (*R*)-TRIP, generating product after 8 hours in almost quantitative yield and 90:10 e.r.

By identifying the optimal catalyst, the influence of temperature, solvent, additives, and catalyst loading was investigated. Interestingly, performing the reaction at lower temperatures resulted in a significant drop in the enantioselectivity (entries 10 and 11). Although this phenomenon is generally unusual, there are several reports describing proportional relationship between the increment in the temperature with an increase of the enantioselectivity.[18] The yield and the enantiomeric ratio in product remained the same when the reaction temperature was increased to 40 °C, but the reaction was completed within 1 hour (entry 12).

Table 1. Optimization of reaction conditions.[a]



CPA1: R = 1-naphthyl **CPA6:** R = (3,5-CF_3)C_6H_3
CPA2: R = 2-naphthyl **CPA7:** R = (4-F)C_6H_4
CPA3: R = 9-anthracenyl **CPA8:** R = (2,4,6-*i*Pr)C_6H_2
CPA4: R = 9-phenanthrenyl **CPA9:** R = (2,4,6-Me)C_6H_2
CPA5: R = $SiPh_3$

Entry	Cat.	Solvent	Temp(°C)	Time(h)	Yield(%)	e.r.
1	**CPA1**	Toluene	rt	1	>96	77:23
2	**CPA2**	Toluene	rt	3	>96	57:43
3	**CPA3**	Toluene	rt	8	>96	68:32
4	**CPA4**	Toluene	rt	24	>96	82:18
5	**CPA5**	Toluene	rt	24	>96	85:15
6	**CPA6**	Toluene	rt	3	>96	78:22
7	**CPA7**	Toluene	rt	2	>96	69:31
8	**CPA8**	Toluene	rt	8	>96	90:10
9	**CPA9**	Toluene	rt	8	>96	85:15
10	**CPA8**	Toluene	0	48	91	70:30
11	**CPA8**	Toluene	−10	72	89	68:32
12	**CPA8**	Toluene	40	1	>96	90:10
13	**CPA8**	Chloroform	40	1	>96	90:10
14	**CPA8**	DCM	40	1	>96	89:11
15	**CPA8**	MeCN	40	1	>96	87:13
16	**CPA8**	Nitromethane	40	6	>96	88:12
17	**CPA8**	Cyclohexane	40	24	70	89:11
18	**CPA8**	THF	40	24	n.r.	–
19	**CPA8**	*p*-Xylene	40	3	>96	90:10
20[b]	**CPA8**	Toluene	40	8	>96	90:10
21	**CPA8**	Toluene	60	0.5	>96	92:8
22	**CPA8**	Toluene	80	<0.25	>96	92:8
23[c]	**CPA8**	**Toluene**	**80**	**0.25**	**>96**	**92:8**
24[d]	**CPA8**	Toluene	80	48	traces	–

[a]Reaction conditions: 2,5-dimethylpyrrole (0.11 mmol), 3-phenyl 3-hydroxy isoindolinone **Iso-1** (0.1 mmol), **CPA*** (10 mol%), toluene (0.1M solution). Yield calculated with respect to **Iso-1**. [b]3Å molecular sieves (1 g/mmol). [c]**CPA8** (5 mol%). [d]**CPA8** (1 mol%).

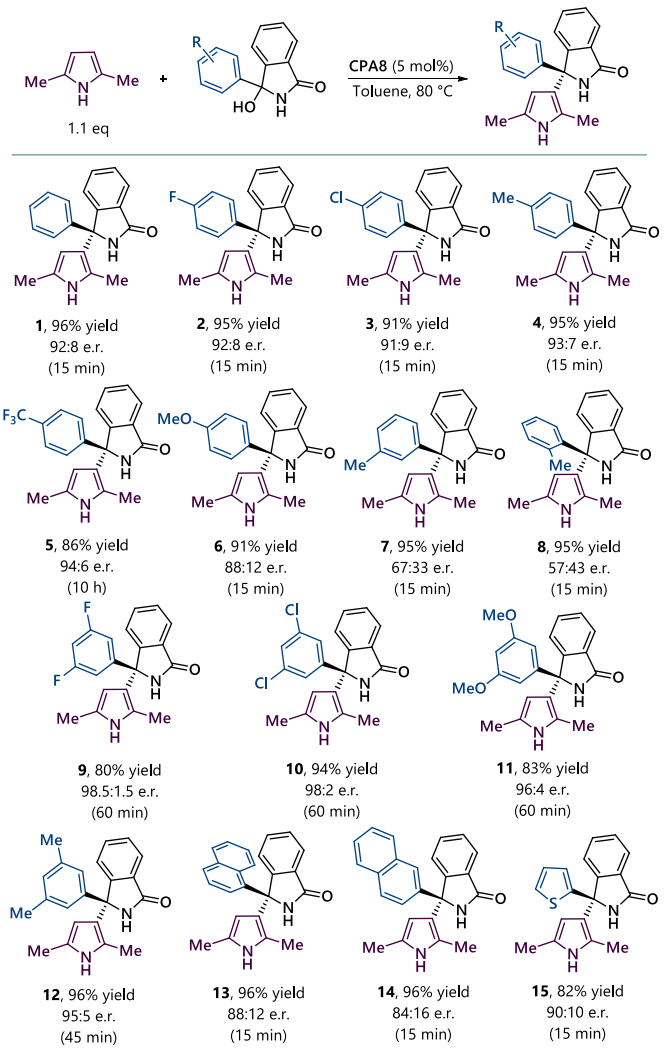
Next, the reaction was performed in other commonly used solvents. The transformation maintained its

effectiveness when it was conducted in halogenated solvents (entries 13 and 14) and acetonitrile (entry 15). The reaction yield and enantioselectivity remained the same when nitromethane and cyclohexane were used as solvents, though with substantially prolonged reaction times (entries 16 and 17). On the other hand, the reaction resulted in an unseparable mixture of products when it was conducted in tetrahydrofuran (entry 18). Performing the transformation in *p*-xylene did not improve the reaction outcome (entry 19). Hence, further optimizations were carried out in toluene.

Employing drying agent as an additive did not influence reaction yield or enantioselectivity, however, it significantly prolonged the reaction time (entry 20). Increasing of the reaction temperature significantly improved the reaction rate without disrupting the reaction parameters (entries 21 and 22). Finally, the reaction maintained its effectiveness when the catalyst loading was lowered to 5 mol% (entry 23), while only traces of product were observed when it was further lowered to 1 mol% (entry 24). Hence, the chosen reaction conditions included isoindolinone ketimine precursor (1.0 eq), pyrrole derivative (1.1 eq), and catalyst **CPA8** (5 mol%) in toluene at 80 °C (entry 23).

With the optimized conditions in hand, we turned our attention to investigate substrate scope and reaction limitations with various 3-aryl 3-hydroxyisoindolinones (Table 2). 2,5-Dimethylpyrrole reacted efficiently with a range of isoindolinone alcohols. When alkyl groups and halogen atoms were placed in the *para* position of the 3-aryl substituent on the isoindolinone core, products **2–4** were obtained in high yields and enantioselectivities. The substrate bearing *p*-trifluoromethyl as substituent was also well tolerated, though the reaction time was prolonged to 10 hours (**5**). Placing electron-donating methoxy group on this position resulted in a slight drop in the enantioselectivity (**6**). However, when substituent in *meta* position on the 3-aryl ring was introduced, the corresponding product **7** was isolated in poor enantiomeric ratio. Furthermore, placing the substituent in its *ortho* position yielded target product practically as a racemate (**8**). Although the increased steric hindrance around the reactive center of the nucleophile does not influence reaction rate, it seems that it plays a major role in favorable arrangement of the transition state. On the other hand, placing substituents in both *meta* positions resulted in products with excellent enantioselectivities, albeit with rather longer reaction times (**9–12**). Introduction of 1-naphthyl and 2-naphthyl groups on the isoindolinone ring resulted in moderate enantioselectivity in products (**13** and **14**). The transformation was also tolerant when heterocyclic ring was employed as 3-aryl substituent (**15**).

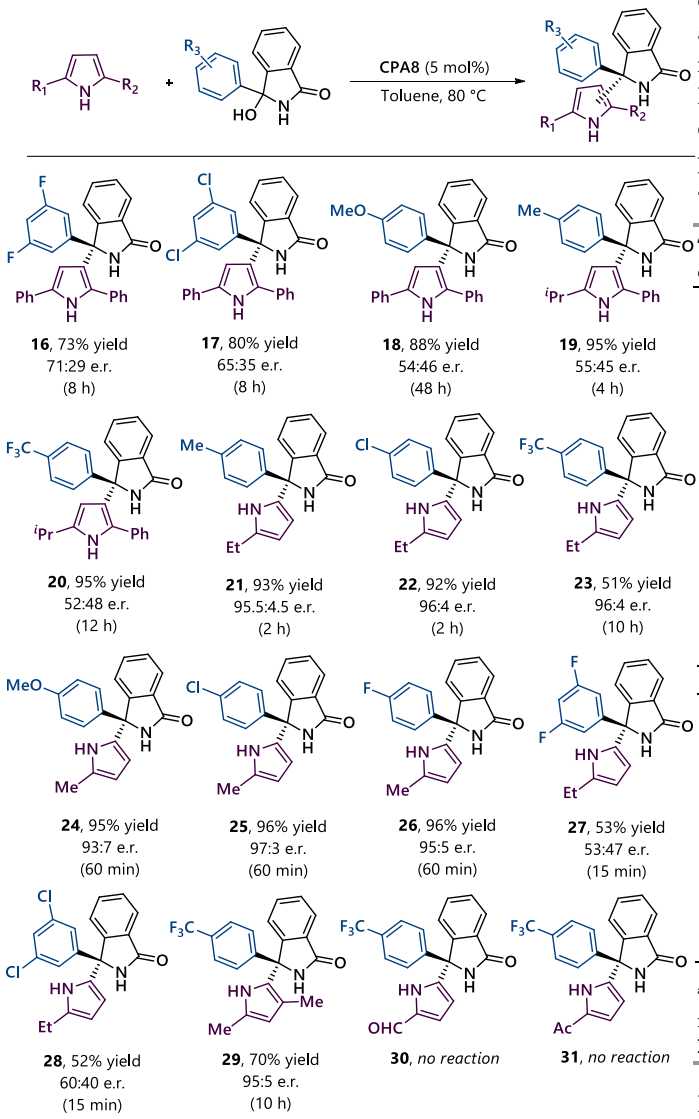
Table 2. Substrate scope I: Isoindolinones.[a]



[a]Reaction conditions: Isoindolinone alcohol (0.1 mmol), 2,5-dimethylpyrrole (0.11 mmol), **CPA8** (5 mol%), 80 °C, toluene. Yield calculated with respect to isoindolinone alcohol.

Next, we turned our attention to investigating substrate scope and reaction limitations with various pyrroles (Table 3). Employing 2,5-diphenylpyrrole as a nucleophile yielded products either in moderate enantioselectivity (**16** and **17**) or virtually without any chiral induction (**18**), regardless of the nature of isoindolinone alcohol used. Unsymmetrical pyrroles provided products regioselectively in high yields, but practically as racemates (**19** and **20**). It should be noted that almost all of these reactions were significantly slower when compared to the reactions performed with 2,5-dimethylpyrrole.

Table 3. Substrate scope II: Pyrroles.[a]



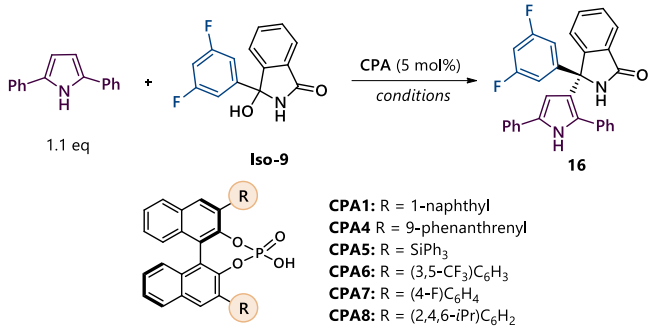
[a]Isoindolinone alcohol (0.1 mmol), pyrrole derivative (0.11 mmol), **CPA8** (5 mol%), 80 °C, toluene. Yield calculated with respect to isoindolinone alcohol.

2-Monosubstituted pyrroles reacted as expected through their α-(C5)-positions with a range of isondolinones bearing *para* substituted 3-aryl rings to generate products **21–26** in high yields and enantioselectivities. Interestingly, when 3,5-difluoro- and 3,5-dichloro-3-phenyl-substituted isoindolinone alcohols were employed as electrophiles, corresponding products were obtained in poor enantioselectivities (**27** and **28**). 2,4-dimethyl pyrrole also provided α-(C5)-alkylated product, in good yield and high enantioselectivity (**29**). Finally, only starting materials were retrieved from the reaction mixture when the reaction was performed with 2-formyl- and 2-acetylpyrrole (**30** and **31**).

We rationalized that there are two possible reasons why poor enantioselectivities were observed in some of the products: (i) chosen optimized reaction conditions are not suitable for these nucleophiles, and (ii) a partial racemization occurs, in which case reversibility issues are possibly at play.

In order to investigate the first assumption, optimization of the reaction conditions was performed for the preparation of product **16** (Table 4).

Table 4. Optimization of reaction conditions with 2,5-diphenylpyrrole.[a]



Entry	Cat.	Solvent	Temp(°C)	Time(h)	Yield(%)	e.r.
1	**CPA1**	Toluene	80	2	95	50:50
2	**CPA4**	Toluene	80	0.5	91	60:40
3	**CPA5**	Toluene	80	12	86	51:49
4	**CPA6**	Toluene	80	3	79	52:48
5	**CPA7**	Toluene	80	1.5	88	53:47
6	**CPA8**	Toluene	40	72	75	73:23
7	**CPA8**	*p*-Xylene	40	72	25	72:28
8	**CPA8**	Chloroform	40	72	96	53:47
9	**CPA8**	Acetonitrile	40	72	80	54:46
10	**CPA8**	Cyclohexane	40	72	10	85:15

[a]Reaction conditions: **Iso-9** (0.1 mmol), 2,5-diphenylpyrrole (0.11 mmol), **CPA*** (10 mol%), *conditions*. Yield calculated with respect to **Iso-9**.

By employing various **CPA*** catalysts, the reaction rates (except in the case of **CPA5**) and reaction yields were significantly increased. However, in all cases products were isolated practically as racemates or with poor enantioselectivity (entries 1–5). Next, the influence of the temperature and solvents was investigated. When the reaction was performed in toluene at 40 °C with (*R*)-TRIP **CPA8** as catalyst, yield and enantioselectivity remained the same, though the reaction was prolonged to 72 hours (entry 6). The reaction in *p*-xylene was stopped after 72 hours, and product **16** was isolated in 25% yield without any change in the enantioselectivity (entry 7). Conducting the reactions in chloroform and acetonitrile resulted in high yields, but almost racemic products (entries 8 and 9). The best enantioselectivity was observed when the transformation was conducted in cyclohexane, however, after 72 hours the product was isolated in only 10% yield (entry 10).

Next, possible partial racemization because of the reversibility of the process was investigated, and the results are presented in Figure 1 (see Supporting Information for details).

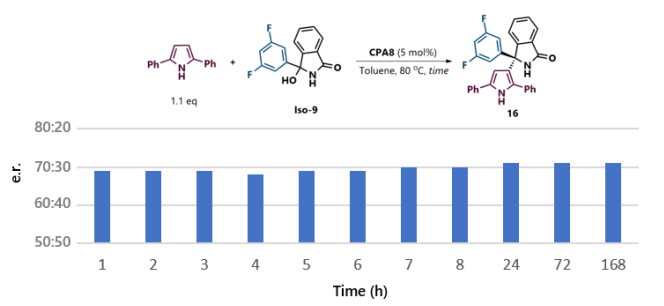
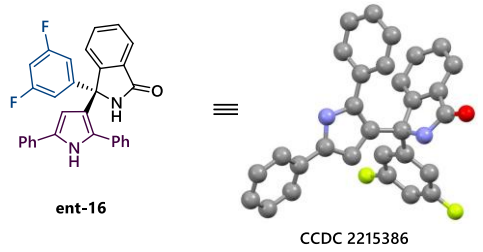


Figure 1. Enantioselectivity in **16** over time. The product was first detected in the reaction mixture after 1 hour, and the starting material was completely consumed after 8 hours.

The enantiomeric ratio in the product did not change during the course of the reaction. After the reaction was completed (after 8 hours), and even after leaving the reaction mixture for additional 6 days, no sign of racemization was detected. This result does not rule out reversibility of the process, however, it shows that even if the reversibility does take place, it does not influence the enantiomeric ratio in the product.

Both of these experiments indicate that conditions determined in Table 1 strike a fine balance between the reactivity and enantioselectivity when more sterically hindred 2,5-disubstituted pyrroles are employed. By tweeking the reaction conditions, the enantioselectivity can be increased at the expense of the reaction rate, and *vice versa*.

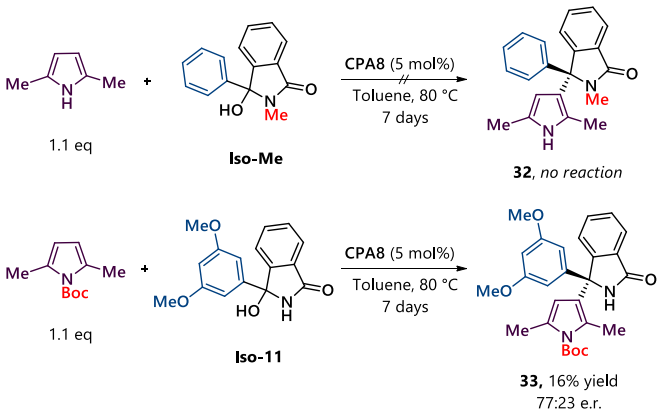
The absolute configuration of **16** was unambiguously assigned to be (*S*) by the X-ray structure analysis of its opposite enantiomer **ent-16** (Scheme 2). This suggests that the nucleophilic attack comes from the *re* face of the planar ketimine, and the absolute configurations of major enantiomers of the remaining products were assigned by analogy.



Pure enantiomer obtained by chiral resolution on HPLC.

Scheme 2. X-Ray structure of the product **ent-16.**

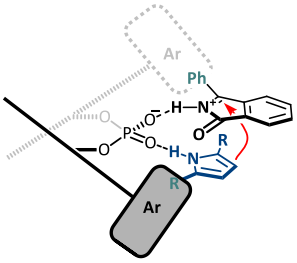
In order to elucidate the role of non-bonding interactions between the catalyst and the reaction partners, control experiments with *N*-protected pyrrole and *N*-protected isoindolinone derivatives were performed (Scheme 3).



Scheme 3. Control experiments.

In the reaction between 2,5-dimethylpyrrole and *N*-methylated 3-phenyl 3-hydroxyisoindolinone **Iso-Me**, only starting materials were detected in the reaction mixture after 7 days under optimized conditions. It is worth noting that the same reaction catalyzed by *p*-toluenesulfonic acid yielded product **rac-32** in 85% yield after 2 hours. This observation indicates that the activation of *N*-protected isoindolinone alcohols is highly dependant on the acidity of the catalyst. The reaction between **Iso-11** and Boc-protected 2,5-dimethylpyrrole was also performed. Under the standard reaction conditions, the reaction was stopped after 7 days, and product **33** was isolated in low yield and moderate enantioselectivity, indicating that N*H* plays a significant role in the nucleophilicity of investigated pyrroles.

Based on the absolute configurations of major enantiomers and conducted control experiments, we propose the following stereochemical model of asymmetric induction (Scheme 4).

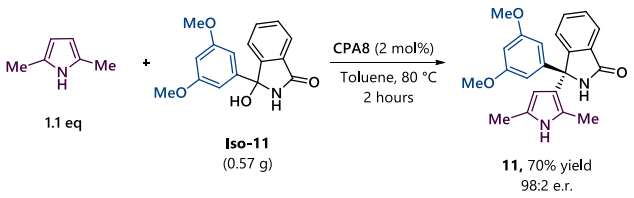


Scheme 4. Proposed mechanism of stereochemical induction.

Following the protonation of isoindolinone alcohol, water is eliminated to generate a reactive ketiminium species. The formed cation forms an ion pair with the anionic phosphate catalyst, and blocks the *si* face of the substrate. The approaching pyrrole derivative preferably attacks the planar ketimine from the opposite side to yield major enantiomers with (*S*)

configuration. Probable hydrogen bonding between pyrrole and the catalyst most likely plays a role in the stereochemical outcome.

Finally, we explored the possibility of conducting the transformation on a larger scale (Scheme 5). Although optimization of reaction conditions revealed that the transformation does not proceed with 1 mol% of the catalyst loading, the scale-up reaction was successfully performed with 2 mol% of **CPA8** without the erosion of enantiomeric purity in the product.



Scheme 5. The scale-up reaction.

Conclusions

In conclusion, we have developed a chiral phosphoric acid-catalyzed Friedel-Crafts alkylation of C2/C5-disubstituted pyrroles at β-(C3) position, with a range of isoindolinone-derived ketimines. The transformation is also tolerant of 2-monosubstituted pyrroles, and results in α-(C5) functionalized pyrroles. Control experiments indicate that non-bonding interactions between substrates and the catalyst are important for the successful outcome of the transformation. Although the reaction is highly dependant on the structure of the pyrrole derivative employed, we hope that the presented study can provide useful knowledge in the development of new methodologies towards construction congested stereogenic centers at pyrrole β-(C3) position.

Experimental Section

General procedure

Chiral phosphoric acid **CPA8** (0.005 mmol) was added to a suspension of isoindolinone alcohol (0.10 mmol) in toluene (2 mL) at room temperature. After stirring for 5 min, pyrrole derivative (0.11 mmol) was added, and the resulting reaction mixture was stirred in an oil bath at 80 °C until full consumption of the starting material (monitored by TLC). The reaction mixture was cooled to room temperature and directly purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether as an eluent system. The solvent was evaporated, and the residue triturated with hexane to afford the corresponding product.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ CCDC 2215386 contains the supplementary crystallographic data for this paper.

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