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

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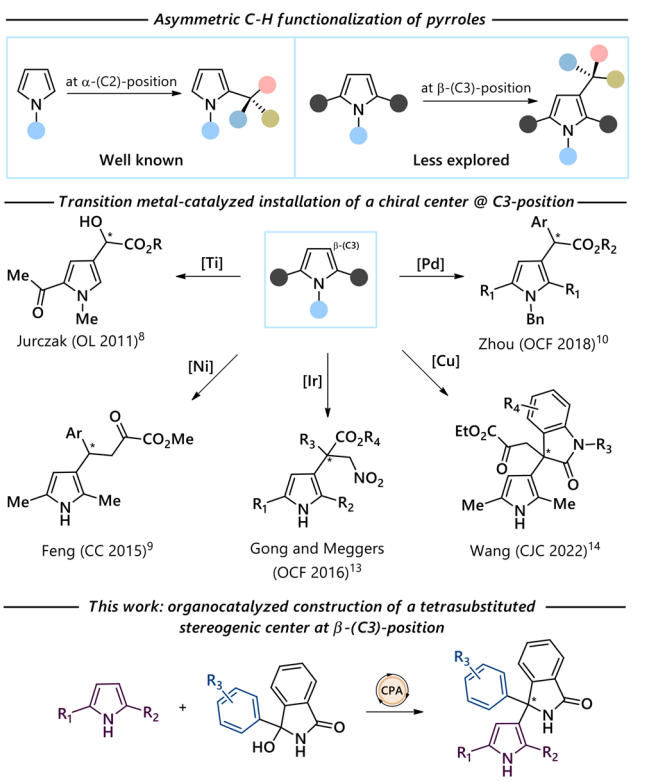
The enantioselective reaction between 2,5-disubstituted pyrroles and diaryl-ketimines, generated *in situ* from isoindolinone-derived alcohols, is described. Pyrrole derivatives possessing a congested tetrasubstituted stereogenic center at the β-(C3) position are generally obtained in high yields and 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 the origin of the 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 their more nucleophilic α-(C2)-position.[2] The first enantioselective Friedel–Crafts reaction of pyrroles with α,β-unsaturated aldehydes was reported in 2001 by MacMillan.[3] Following this seminal report, numerous asymmetric transformations of pyrroles at the 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 at the β-(C3)-position of pyrroles is often challenging to realize. β-Functionalized pyrroles serve as precursors for the synthesis of other bioactive compounds[5] and they are the structural cores of natural products[6] and functional materials.[7] However, only a few reports address the asymmetric functionalization 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 a chiral Ti(IV) complex.[8] By employing a chiral Ni-complex catalyst, Feng *et al.* performed an enantioselective β-(C3)-alkylation of 2,5-dimethylpyrrole.[9] Through a Pd-catalyzed Friedel–Crafts reaction, Zhou



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

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et al. efficiently constructed a stereogenic center at the β-(C3) position of symmetrically 2,5-disubstituted pyrroles.[10] In general studies on the asymmetric C–H functionalization of indoles[11] and pyrroles at their α-(C2)-position,[12] the authors demonstrated that the developed methodologies can also be applied for the asymmetric β-(C3)-alkylation of 2,5-dimethyl pyrroles. It is worth noting that all of these studies reported products with tertiary stereogenic centers.

To the best of our knowledge, only three systematic studies have reported the construction of a tetrasubstituted stereogenic center at the β-(C3) position of pyrroles. Gong and Meggers successfully β-(C3)-alkylated unsymmetric 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 the Friedel–Crafts alkylation strategy, Kumar *et al*. successfully installed a quaternary stereogenic center at the β-(C3)-position of pyrroles by developing a 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 an asymmetric organocatalytic methodology for the installation of a congested tetrasubstituted stereogenic center at the β-(C3) position of pyrroles. 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]

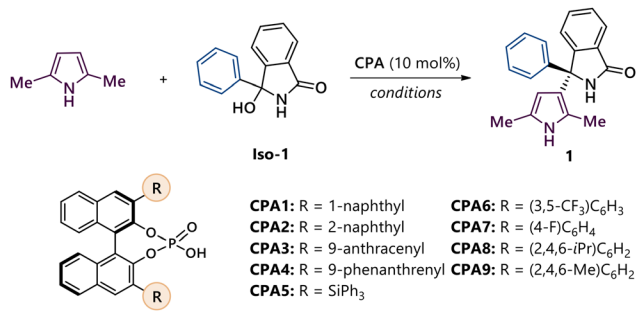
Results and discussion

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 (0.1 M solution) at room temperature (Table 1). Our initial attempts with 1-naphthyl-substituted chiral phosphoric acid **CPA1** in toluene at room temperature led to complete conversion to the target product **1** within 1 hour and with moderate enantioselectivity (entry 1). The reaction rate decreased when the 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 the 9-anthracenyl group at the 3 and 3′ positions of the catalyst (**CPA3**) did not improve the reaction parameters (entry 3); however, placing the 9-phenanthrenyl substituent in these positions (**CPA4**) resulted in the highest enantioselectivity obtained thus far, albeit with a substantially prolonged reaction time (entry 4). The enantioselectivity was further improved when the –$SiPh_3$ 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 reduction in the enantioselectivity (entries 6 and 7). The results obtained up to this point indicated that bulkier substituents on the chiral phosphoric acid provide the 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 the product after 8 hours in an almost quantitative yield and with 90 : 10 e.r.

After 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 the proportional relationship between the increment in temperature and an increase in the enantioselectivity.[18] The yield and the enantiomeric ratio of the product remained the same when the reaction temperature was increased to 40 °C, but the reaction was completed within 1 hour (entry 12).

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

Table 1 Optimization of reaction conditions[a]



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] 3 Å molecular sieves (1 g $mmol^{-1}$). [c] **CPA8** (5 mol%). [d] **CPA8** (1 mol%).

14) and acetonitrile (entry 15). The reaction yield and enantioselectivity remained the same when nitromethane and cyclohexane were used as solvents, although with substantially prolonged reaction times (entries 16 and 17). On the other hand, the reaction resulted in an inseparable 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 a drying agent as an additive did not influence the reaction yield or enantioselectivity; however, it significantly prolonged the reaction time (entry 20). Increasing 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 trace amounts of the product were observed when it was further lowered to 1 mol% (entry 24). Hence, the chosen reaction conditions included the isoindolinone ketimine precursor (1.0 eq.), pyrrole derivative (1.1 eq.), and catalyst **CPA8** (5 mol%) in toluene at 80 °C (entry 23).

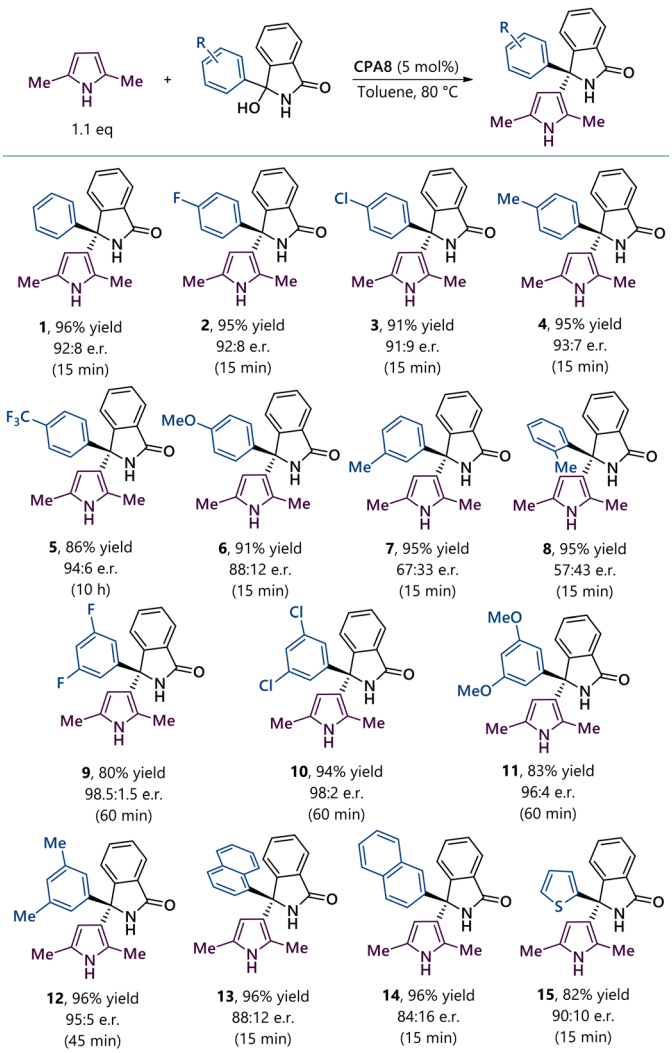
With the optimized conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations with various 3-aryl 3-hydroxyisoindolinones (Table 2).

2,5-Dimethylpyrrole reacted efficiently with a range of isoindolinone alcohols. When alkyl groups and halogen atoms were placed at 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 the substituent was also well tolerated, although the reaction time was prolonged to 10 hours (**5**). Placing the electron-donating methoxy group at this position resulted in a slight drop in the enantioselectivity (**6**). However, when a substituent at the *meta* position on the 3-aryl ring was introduced, the corresponding product **7** was isolated in a poor enantiomeric ratio. Furthermore, placing the substituent at its *ortho* position yielded the target product practically as a racemate (**8**). Although the increased steric hindrance around the reactive center of the nucleophile does not influence the reaction rate, it seems to play a major role in the favorable arrangement of the transition state. On the other hand, placing substituents at 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 a heterocyclic ring was employed as the 3-aryl substituent (**15**).

Next, we turned our attention to investigating the substrate scope and reaction limitations with various pyrroles (Table 3).

Employing 2,5-diphenylpyrrole as a nucleophile yielded products either with moderate enantioselectivity (**16** and **17**) or virtually without any chiral induction (**18**), regardless of the nature of the isoindolinone alcohol used. Unsymmetric pyrroles provided products regioselectively in high yields, but practically as racemates (**19** and **20**). It should be noted that

Table 2 Substrate scope I: isoindolinones[a]



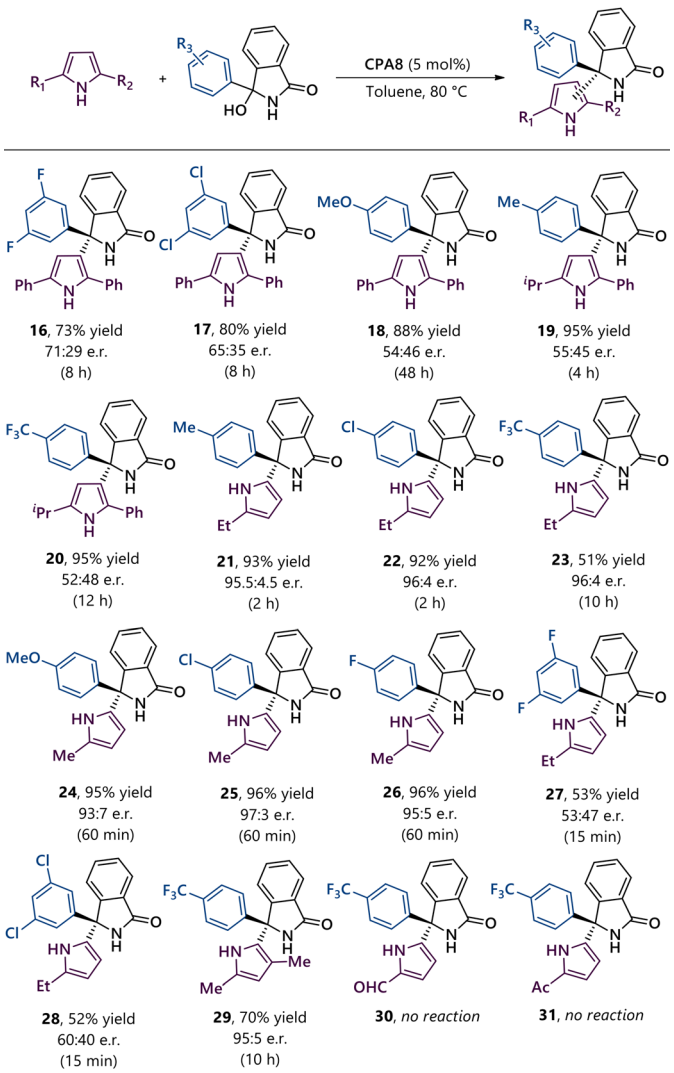
[a] Reaction conditions: isoindolinone alcohol (0.1 mmol), 2,5-dimethylpyrrole (0.11 mmol), **CPA8** (5 mol%), 80 °C, toluene. Yield calculated with respect to isoindolinone alcohol.

almost all of these reactions were significantly slower than the reactions performed with 2,5-dimethylpyrrole.

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, the corresponding products were obtained in poor enantioselectivities (**27** and **28**). 2,4-Dimethyl pyrrole also provided the α-(C5)-alkylated product in good yield and high enantioselectivity (**29**). Finally, only the starting materials were retrieved from the reaction mixture when the reaction was performed with 2-formyl- and 2-acetylpyrrole (**30** and **31**).

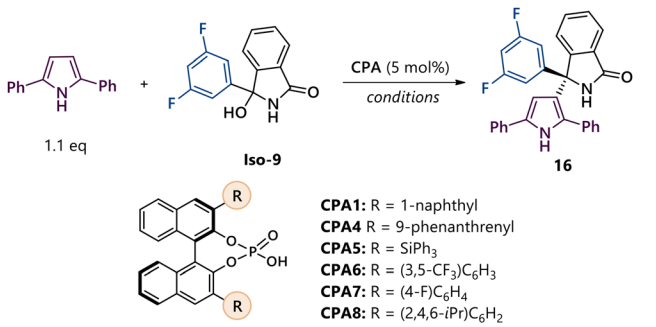
We rationalized that there are two possible reasons why poor enantioselectivities were observed in some of the products: (i) the chosen optimized reaction conditions are not

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.

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%). Yield calculated with respect to **Iso-9**.

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).

By employing various **CPA*** catalysts, the reaction rates (except in the case of **CPA5**) and reaction yields were significantly increased. However, in all cases, the products were isolated practically as racemates or with poor enantioselectivity (entries 1–5). Next, the influence of temperature and solvents was investigated. When the reaction was performed in toluene at 40 °C with (*R*)-TRIP **CPA8** as the catalyst, the yield and enantioselectivity remained the same, although 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 were obtained (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 shown in Fig. 1 (see the ESI† for details).

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 an additional 6 days, no sign of racemization was detected. This result does not rule out the reversibility of the

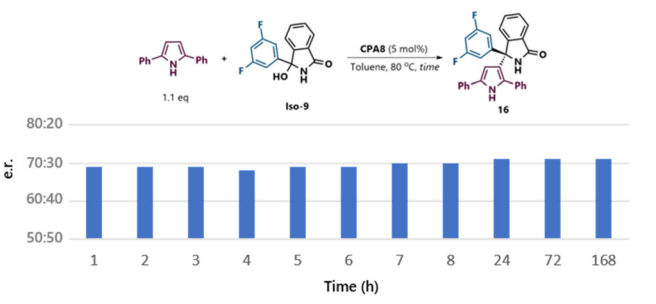


Fig. 1 Enantioselectivity in **16** over time. The product was first detected in the reaction mixture after 1 hour, and the starting material was completely consumed after 8 hours.

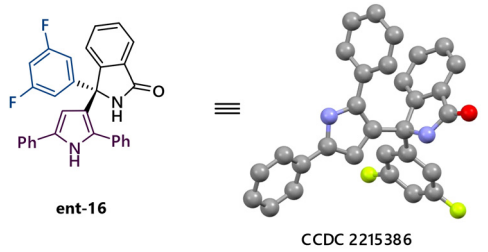
process; however, it shows that even if reversibility does take place, it does not influence the enantiomeric ratio of the product.

Both of these experiments indicate that the conditions shown in Table 1 strike a fine balance between reactivity and enantioselectivity when more sterically hindered 2,5-disubstituted pyrroles are employed. By tweaking 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 as (*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 the major enantiomers of the remaining products were assigned by analogy.

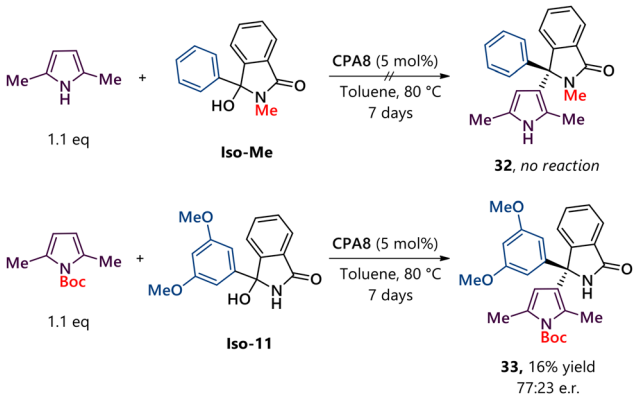
In order to elucidate the role of non-bonding interactions between the catalyst and the reaction partners, control experiments with *N*-protected pyrrole and *N*-protected isoindolinone derivatives were performed (Scheme 3).

In the reaction between 2,5-dimethylpyrrole and *N*-methylated 3-phenyl 3-hydroxyisoindolinone **Iso-Me**, only the starting materials were detected in the reaction mixture after 7 days under the optimized conditions. It is worth noting that the same reaction catalyzed by *p*-toluenesulfonic acid yielded the product **rac-32** in 85% yield after 2 hours. This observation indicates that the activation of *N*-protected isoindolinone alcohols is highly dependent on the acidity of the

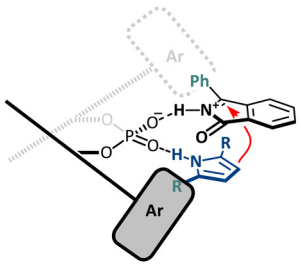


Pure enantiomer obtained by chiral resolution on HPLC.

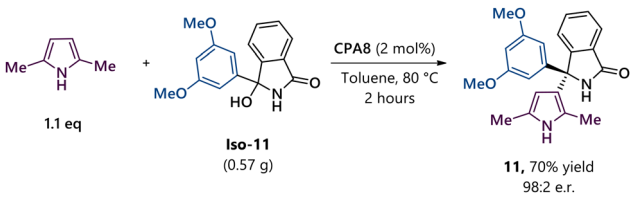
Scheme 2 X-Ray structure of the product ***ent*-16**.



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism of stereochemical induction.



Scheme 5 The scale-up reaction.

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 with moderate enantioselectivity, indicating that N*H* plays a significant role in the nucleophilicity of the investigated pyrroles.

Based on the absolute configurations of the major enantiomers and the conducted control experiments, we propose the following stereochemical model of asymmetric induction (Scheme 4). 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 the (*S*) configuration. Probable hydrogen bonding between the 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 the reaction conditions revealed that the transformation does not proceed with 1 mol% catalyst loading, the scale-up reaction was successfully performed with 2 mol% of **CPA8** without the erosion of the enantiomeric purity of the product.

Conclusions

In conclusion, we have developed a chiral phosphoric acid-catalyzed Friedel–Crafts alkylation of C2/C5-disubstituted pyrroles at the 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 dependent on the structure of the pyrrole derivative employed, we hope that the presented study can provide useful knowledge for the development of new methodologies towards the construction of congested stereogenic centers at the β-(C3) position of pyrroles.

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, the 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 the eluent system. The solvent was evaporated, and the residue was triturated with hexane to afford the corresponding product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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