Received 00th January 20xx,

1. Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička c. 54, 10000 Zagreb, Croatia. E-mail: [matija.gredicak@irb.hr](mailto:matija.gredicak@irb.hr)
2. State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: [slyou@sioc.ac.cn](mailto:slyou@sioc.ac.cn)

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Enantioselective construction of a congested quaternary stereogenic center in isoindolinones bearing three aryl groups *via* an organocatalytic formal Betti reaction

Arben Beriša,a Danijel Glavač,a Chao Zheng,b Shu-Li Youb\* and Matija Gredičaka\*

An efficient enantioselective formal Betti reaction between phenols and diaryl ketimines generated *in situ* from isoindolinone alcohols is described. In a reaction catalyzed by a chiral phosphoric acid, a broad range of ketimines and phenols afforded isoindolinone derivatives comprising a congested quaternary stereogenic center bearing three aryl groups in high yields, and high regioselectivities and enantioselectivities.

Introduction

Arylation of benzophenone-derived ketimines is the most effective and straightforward route towards the construction of a quaternary stereogenic center bearing three phenyl rings. The scarcity of reported methodologies stems from the remarkably low reactivity of bis-aromatic ketimines, and from the inherent difficulty for the catalyst to control the enantioselectivity due to the lack of sufficient steric difference between two phenyl rings. Hence, only few notable examples of asymmetric arylations of diaryl ketimines have been reported to date.

In 2012, Hayashi and Nishimura developed an enantioselective arylation of saccharin-derived cyclic ketimines with arylboroxines in the presence of a chiral rhodium complex.1 Following this seminal work, several rhodium2 and palladium3 catalyzed asymmetric arylations of cyclic *N*-sulfonyl diaryl ketimines have been reported in the literature. In contrast to these elegant examples on transition-metal catalysis, their organocatalytic counterparts are virtually non-existent in the literature. Although asymmetric organocatalytic additions of phenyl-derived nucleophiles to aldimines are well known,4 reports on their additions to ketimines are rather scarce in the literature.5 Reported strategies usually employ naphthol derivatives as nucleophiles, and isatine-derived ketimines as electrophiles (Scheme 1).6

In this context, seminal report by Pedro describes quinine-thiourea catalyzed addition of naphthols and electron-rich phenols to isatin derived ketimines.6a The same type of nucleophile was utilized in the quinine-squaramide catalyzed addition to quinazoline-type cyclic trifluoromethyl ketimines reported by Wang and Xie.6d In 2020, Li developed regio- and enantioselective addition of electron-rich phenols to isatin-derived ketimines.7 However, to the best of our knowledge, there are no reports on the asymmetric organocatalytic methodologies for the construction of quaternary centers of chirality bearing three phenyl rings.



**Scheme 1.** Enantioselective organocatalytic additions of phenol derivatives to ketimines for the generation of tetrasubstituted stereogenic centers.

On the other hand, 3,3-disubstituted isoindolinones are core structural skeletons embedded in many natural products and biologically active compounds (Scheme 2).8 Their biological activities are greatly influenced by the type of substituents and absolute configuration on this position. Hence, it is not surprising that the stereoselective synthesis of chiral isoindolinone derivatives – particularly the ones possessing quaternary stereogenic center – has received a lot of attention in the past decade.



Scheme 2. Examples of biologically active 3,3-disubstituted isoindolinones.

Developed methodologies for the synthesis of such derivatives include asymmetric aza-Friedel-Crafts reactions,9 and additions of heteroatoms10 and non-aromatic carbon nucleophiles.11 However, there are still no reports on organocatalytic protocols for the installation of the third phenyl ring on the isoindolinone C3 position in an enantioselective fashion. The development of such protocols would expand the chemical space of isoindolinone derivatives comprising quaternary stereogenic centers, and add a new dimension to the existing methods.

Results and discussion

Herein, we report a chiral phosphoric acid-catalyzed formal Betti reaction between phenols and *N*-acyl diaryl ketimines generated *in situ* from 3-hydroxyisoindolinones.

We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone **Is-1** with 2,6-dimethylphenol in the presence of various chiral phosphoric acids in chloroform (0.1M solution) at 40 °C (Table 1). Our initial attempt with 9-phenanthrenyl-substituted chiral phosphoric acid **BA1** led to the complete conversion to the desired product **1** after 14 days, with promising levels of enantioselectivity of 85:15 e.r. (entry 1). When 9-anthracenyl was placed on the phenyl ring of the acid (**BA2**), the reaction maintained its effectiveness with increased enantiomeric purity (entry 2). The introduction of bulkier substituents on the catalyst resulted in substantially lower enantiomeric ratios (entries 3 and 4). By positioning triphenylsilyl group as a flanking substituent of the chiral phosphoric acid, the product was isolated in a low yield and virtually as a racemate (entry 5). The efficiency of the SPINOL-derived catalysts was also explored. Placing *p*-methoxyphenyl and trimethylsilyl substituents on the SPINOL backbone resulted in moderate yields with no induction of enantiomeric purity in the products (entries 6 and 7).

After identifying **BA2** as the optimal catalyst for the transformation, the influence of solvent, temperature, additives, and concentration was investigated. By conducting the reaction in other commonly used solvents, the reaction time was shortened to 10 days (entries 8–10). Performing the reaction at 50 °C demonstrated an improved reaction rate, but at the expense of enantioselectivity (entry 11). Similar results were observed when a drying agent was added to the reaction mixture (entry 12). Next, we investigated the influence of the reaction concentration, and discovered that the reaction time was shortened to 48 hours when the concentration was doubled, accompanied by substantially higher enantiomeric ratio in the product (entry 13).12 Conducting the reaction at room temperature, as well as lowering the amount of phenol did not further improve reaction outcomes (entries 14 and 15).

Hence, the chosen reaction conditions included diaryl ketimine precursor (1.0 eq), phenol (5.0 eq), and catalyst **BA2** (10 mol%) in toluene (0.2M suspension) at 40 °C (entry 13).

**Table 1.** Enantioselective reaction optimization.



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **entry** | **cat.** | **solvent** | **time (d)** | **yield** | **e.r.** |
| 1 | **BA1** | chloroform | 14 | 96 | 85:15 |
| 2 | **BA2** | chloroform | 14 | 96 | 90:10 |
| 3 | **BA3** | chloroform | 14 | 96 | 72:28 |
| 4 | **BA4** | chloroform | 14 | 96 | 73:27 |
| 5 | **BA5** | chloroform | 14 | 29 | 55:45 |
| 6 | **BA6** | chloroform | 14 | 48 | 46:54 |
| 7 | **BA7** | chloroform | 14 | 71 | 57:43 |
| 8 | **BA2** | dichloromethane | 10 | 96 | 76:24 |
| 9 | **BA2** | toluene | 10 | 96 | 90:10 |
| 10 | **BA2** | benzene | 10 | 96 | 89:11 |
| 11 | **BA2** | toluene | 1 | 83 | 86:14b |
| 12 | **BA2** | toluene | 0.5 | 96 | 79:21c |
| **13** | **BA2** | **toluene** | **2** | **96** | **96.5:4.5d** |
| 14 | **BA2** | toluene | 12 | 91 | 92:8d,e |
| 15 | **BA2** | toluene | 5 | 96 | 88:12d,f |
| 16 | **BA2** | toluene | 8 | 45 | 86:14d,g |

aReactions conditions: isoindolinone alcohol (0.1 mmol), 2,6-dimethylphenol (0.5 mmol), **BA\*** (0.01 mmol), solvent (1.0 mL). e.r. determined by HPLC with a chiral stationary phase. b50 °C. c3Å molecular sieves (1g/mmol). dToluene (0.5 mL). eRoom temperature. f2,6-dimethylphenol (3.0 eq, 0.3 mmol). g**BA2** (5 mol%).

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

**Table 2.** Substrate scope I: Diaryl ketimines.a



aReactions conditions: isoindolinone alcohol (0.1 mmol), 2,6-dimethylphenol (0.5 mmol), **BA2** (0.01 mmol), toluene (0.5 mL). e.r. determined by HPLC with a chiral stationary phase. bIncomplete conversion.

2,6-Dimethyl phenol reacted efficiently with a range of different diaryl ketimines providing high yields and enantioselectivities. When *para* substituted 3-aryl groups were placed on the isoindolinone core, the reaction maintained its high efficiency and generally furnished products in excellent yields and enantioselectivities (**2–4**). The substrate bearing *p*-chlorine as substituent was also well tolerated, though the conversion was moderate (**5**, 35% yield, 91:9 e.r.). Introduction of the electron donating methoxy group in the same position resulted in significant drop in the enantioselectivity (**6**, 96% yield, 84:16 e.r.). On the other hand, when *ortho* substituent was introduced on the 3-aryl ring, the conversion was significantly suppressed, and the product was isolated in poor enantiomeric ratio (**7**, 23% yield, 66:34 e.r.). The most probable rationalization for this observation is that the increased steric hindrance around the reaction center hampers the reactivity, and overrides the steric influence of the chiral phosphoric acid catalyst.

Placing methyl substituents in both *meta* positions on the 3-aryl ring resulted in lower enantiomeric ratio in the product **8**, however, placing chlorine and trifluoromethyl groups in the same positions, respectively, resulted in very high enantioselectivities (**9**, 84% yield, 97:3 e.r. and **10**, 75% yield, 98:2 e.r.). Substituents placed on the isoindolinone ring were also well tolerated (**11** and **12**). It should be noted that some examples required slightly elevated reaction temperature for the transformation to occur.

Furthermore, we turned out attention to investigating substrate scope and limitations of the reaction with various phenols (Table 3).

**Table 3.** Substrate scope II: Phenols.a

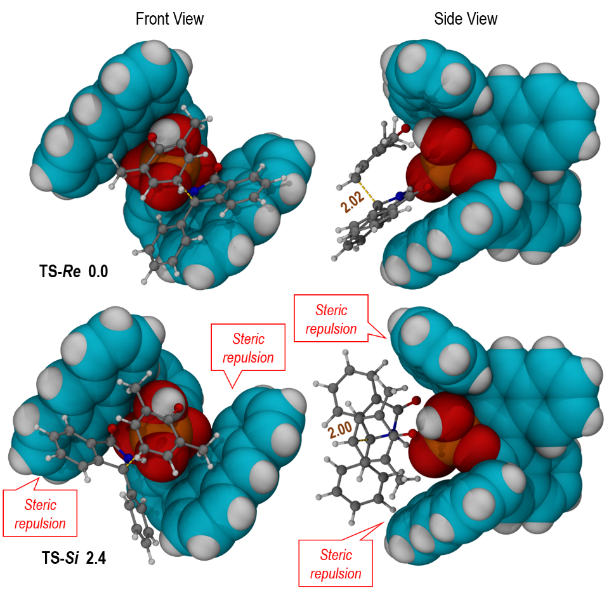


aReactions conditions: isoindolinone alcohol (0.1 mmol), phenol derivative (0.5 mmol), **BA2** (0.01 mmol), toluene (0.5 mL) e.r. determined by chiral stationary HPLC. bIncomplete conversion.

The introduction of alkyl groups in both *ortho* positions on phenol resulted in high yields and enantiomeric ratios (**13–15**). The reaction also proceeded when reaction center-deactivating methoxy groups were placed in these positions, albeit in slightly lower enantioselectivity (**16**). It is worth noting that the other regioisomer (addition through *meta* position with respect to hydroxy group) was not detected in the reaction mixture.

Next, we investigated the reaction outcomes with mono-substituted phenols, where the regioselectivity of the reaction also comes into play. The transformation did not lose its effectiveness, and all employed phenols yielded only one regioisomer (**17–22**). In several examples the conversion dropped, and slight decreases in enantioselectivities were observed. However, when 2,5-disubstituted phenol was used as a nucleophile, product **23** was isolated in high yield and as a single regioisomer, but practically as a racemate. Most likely the steric hindrance around the reaction center overrides the steric influence of the catalyst, similar as in the case of product **7**. The reaction with phenol yielded product **24** in 49% yield and 94:6 e.r. We concluded the substrate scope by performing mix-and-match reactions comprising various diaryl ketimines and phenols, and all products were obtained in high enantioselectivities, ranging from 97:3 e.r. to >99:1 e.r. (**25–31**).

The absolute configuration of **25** was unambiguously assigned to be (*R*) by the X-ray structure analysis of its opposite enantiomer **ent-25**.13 In order to shed light on the origin of the stereochemical induction, density functional theory (DFT) calculations have been performed using the reaction yielding **1** with chiral phosphoric acid **BA2** as the model. The optimized structures of the key stereochemically-discriminating transition states are shown in Figure 1. The transition state where the *Re* face of the ketimine receives the nucleophilic attack of 2,6-dimethylphenol (**TS-*Re***) is more favorable compared with that of the corresponding *Si* face (**TS-*Si***) by 2.4 kcal/mol. This result in qualitative agreement with the dominant formation of (*R*)-**1** in experiments. Strong steric repulsion between both substrates with the anthracenyl groups of the chiral catalyst can be found in **TS-*Si***, which is believed as the key reason behind the observed enantioselectivity.



**Figure 1**. B3LYP-D3(BJ)/def2-TZVPP (SMD, toluene)//B3LYP-D3(BJ)/def2-SVP (gas phase) level of theory. The chiral phosphoric acid is presented with VDW model and the substrates are presented in ball-and-stick model. The forming C–C bonds are highlighted using yellow dash lines. The figures in bold are the relative Gibbs free energies (in kcal/mol), and the figures in brown are the bond distances of the forming C–C bonds (in Å).

In order to further elucidate stereochemical induction of the reaction, experiments with *N*-protected isoindolinone alcohol and *O*-protected phenol were performed (Scheme 3).



**Scheme 3.** Control experiments and a postmodification reaction.

In the reaction between *N*-isopropyl hydroxyisoindolinone **Is-2** and 2,6-dimethylphenol, only starting materials were detected in the reaction mixture after 7 days, even after elevating the reaction temperature. On the other hand, the same reaction catalyzed by *p*-toluenesulfonic acid yielded racemic product **rac-32** in 90% yield (see SI for data). These results indicate that the acidity of the catalyst plays a significant role in the activation of *N*-protected isoindolinone derivatives. We also performed the reaction between **Is-1** and 2,6-dimethyl anisole. Under the standard reaction conditions, only starting materials were isolated from the reaction mixture. Employing more acidic catalysts and more elevated reaction temperature did not change the outcomes, indicating that O*H* is crucial for the nucleophilicity of investigated phenols. Since one of the control experiments showed that the transformation does not proceed with anisole derivatives as nucleophiles, access to these compounds was demonstrated by employing standard *O*- alkylation (**34**, 63% yield, 98:2 e.r.).

Conclusions

In conclusion, we have developed a chiral phosphoric acid-catalyzed formal Betti reaction between phenols and *in situ* generated *N*-acyl diaryl ketimines. The transformation proceeds smoothly with a broad range of phenols and ketimines to afford isoindolinone derivatives comprising quaternary center of chirality bearing three phenyl rings in high yields, and high enantioselectivities and regioselectivities. The origin of the stereochemistry was supported by DFT calculations. We anticipate that the utility of the developed transformation will be further explored in the construction of more complex structures.

Experimental section

General procedure

A chiral catalyst (0.01 mmol) was added to a suspension of a isoindolinone alcohol (0.1 mmol) in toluene (0.5 mL) at room temperature. Selected phenol derivative (0.5 mmol) was added, and the resulting reaction mixture was stirred at 40 °C until complete consumption of starting material monitored by TLC. The solvent was evaporated, and the residue was directly purified by column chromatography on silica gel.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support was provided by the Croatian Science Foundation (grant no. IP-2018-01-4053) and Science and Technology Commission of Shanghai Municipality (grant no. 19590750400).

Notes and references

1. T. Nishimura, A. Noishiki, G. Chit Tsui and T. Hayashi, Asymmetric synthesis of (Triaryl)methylamines by rhodium-catalyzed addition of arylboroxines to cyclic *N*-sulfonyl ketimines, *J. Am. Chem. Soc.*, 2012, **134**, 5056–5059.
2. (a) T. Nishimura, A. Noishiki, Y. Ebe and T. Hayashi, Hydroxorhodium/chiral diene complexes as effective catalysts for the asymmetric arylation of 3-aryl-3-hydroxyisoindolin-1-ones, *Angew. Chem. Int. Ed.*, 2013, **52**, 1777–1780. (b) H. Wang, T. Jiang and M. H. Xu, Simple branched sulfur-olefins as chiral ligands for Rh-catalyzed asymmetric arylation of cyclic ketimines: Highly enantioselective construction of tetrasubstituted carbon stereocenters, *J. Am. Chem. Soc.*, 2013, **135**, 971–974.
3. (a) G. Yang and W. Zhang, A palladium-catalyzed enantioselective addition of arylboronic acids to cyclic ketimines, *Angew. Chem. Int. Ed.*, 2013, **52**, 7540–7544. (b) Y. Álvarez-Casao, D. Monge, E. Álvarez, R. Fernández and J. M. Lassaletta, Pyridine-hydrazones as N,N′-Ligands in Asymmetric Catalysis: Pd(II)-Catalyzed Addition of Boronic Acids to Cyclic Sulfonylketimines, *Org. Lett.*, 2015, **17**, 5104–5107. (c) B. Zhou, K. Li, C. Jiang, Y. Lu and T. Hayashi, Modified Amino Acid-Derived Phosphine-Imine Ligands for Palladium-Catalyzed Asymmetric Arylation of Cyclic N-Sulfonyl Imines, *Adv. Synth. Catal.*, 2017, **359**, 1969–1975. (d) C. Jiang, Y. Lu and T. Hayashi, High performance of a palladium phosphinooxazoline catalyst in the asymmetric arylation of cyclic N-sulfonyl ketimines, *Angew. Chem. Int. Ed.*, 2014, **53**, 9936–9939. (e) C. Schrapel and R. Peters, Exogenous-Base-Free Palladacycle-Catalyzed Highly Enantioselective Arylation of Imines with Arylboroxines, *Angew. Chem. Int. Ed.*, 2015, **54**, 10289–10293. (f) C. Schrapel, W. Frey, D. Garnier and R. Peters, Highly Enantioselective Ferrocenyl Palladacycle-Acetate Catalysed Arylation of Aldimines and Ketimines with Arylboroxines, *Chem. Eur. J.*, 2017, **23**, 2448–2460. (g) Z. Qiu, Y. Li, Z. Zhang and D. Teng, Spiro indane-based phosphine–oxazoline ligands for palladium-catalyzed asymmetric arylation of cyclic *N*-sulfonyl imines, *Transit. Met. Chem.*, 2019, **44**, 649–654. (h) M. F. Li, A. Q. Miao, H. Y. Zhu, R. Wang, W. J. Hao, S. J. Tu and B. Jiang, Palladium/ N, N′-Disulfonyl Bisimidazoline-Catalyzed Enantioselective Addition of Arylboronic Acids to Cyclic N-Sulfonyl Ketimines, *J. Org. Chem.*, 2020, **85**, 13602–13609.
4. (a) G. Liu, S. Zhang, H. Li, T. Zhang and W. Wang, Organocatalytic enantioselective Friedel-Crafts reactions of 1-naphthols with aldimines, *Org. Lett.*, 2011, **13**, 828–831. (b) P. Chauhan and S. S. Chimni, Asymmetric organocatalytic aza-Friedel-Crafts reaction of naphthols with N-sulfonyl imines, *Eur. J. Org. Chem.*, 2011, 1636–1640. (c) G. X. Li and J. Qu, Enantioselective Friedel-Crafts reactions between phenols and *N*-tosylaldimines catalyzed by a leucine-derived bifunctional catalyst, *Chem. Commun.*, 2012, **48**, 5518–5520. (d) P. Chauhan and S. S. Chimni, Organocatalytic enantioselective aza-Friedel-Crafts reaction of sesamols with N-sulfonylimines catalyzed by 6′-OH Cinchona alkaloids, *Tetrahedron Lett.*, 2013, **54**, 4613–4616. (e) S. Takizawa, S. Hirata, K. Murai, H. Fujioka and H. Sasai, C3-Symmetric chiral trisimidazoline-catalyzed Friedel-Crafts (FC)-type reaction, *Org. Biomol. Chem.*, 2014, **12**, 5827–5830. (f) M. Montesinos-Magraner, R. Cantón, C. Vila, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, Organocatalytic enantioselective aza-Friedel-Crafts reaction of 2-naphthols with benzoxathiazine 2,2-dioxides, *RSC Adv.*, 2015, **5**, 60101–60105. (g) Y. W. Li, L. M. Wang, Y. Jin and S. Chang, Cinchona alkaloid derivatives catalyzed asymmetric aza-Friedel–crafts reaction of α-naphthols with aryl aldimines, *Chirality*, 2017, **29**, 458–463. (h) S. Takizawa, M. Sako, M. A. Abozeid, K. Kishi, H. D. P. Wathsala, S. Hirata, K. Murai, H. Fujioka and H. Sasai, Enantio- and diastereoselective Betti/aza-michael sequence: Single operated preparation of chiral 1,3-disubstituted isoindolines, *Org. Lett.*, 2017, **19**, 5426–5429. (i) Y. Wang, L. Jiang, L. Li, J. Dai, D. Xiong and Z. Shao, An Arylation Strategy to Propargylamines: Catalytic Asymmetric Friedel–Crafts-type Arylation Reactions of C-Alkynyl Imines, *Angew. Chem. Int. Ed.*, 2016, **55**, 15142–15146. (j) Z. B. Zhao, L. Shi, Y. Li, F. J. Meng and Y. G. Zhou, Facile synthesis of chiral ϵ-sultams: Via an organocatalytic aza-Friedel-Crafts reaction, *Org. Biomol. Chem.*, 2019, **17**, 6364–6368. (k) H. Okamoto, K. Toh, T. Mochizuki, H. Nakatsuji, A. Sakakura, M. Hatano and K. Ishihara, Chiral pyrophosphoric acid catalysts for the para-selective and enantioselective aza-friedel-crafts reaction of phenols, *Synthesis*, 2018, **50**, 4577–4590.

*For recent review, see:* (l) I. N. Egorov, S. Santra, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. Majee, B. C. Ranu, V. L. Rusinov and O. N. Chupakhin, Direct Asymmetric Arylation of Imines, *Adv. Synth. Catal.*, 2020, **362**, 4293–4324. *and references cited therein.*

1. *For some other representative types of asymmetric organocatalytic arylations employing phenol derivatives as nucleophiles, see:* (a) J. Le Wu, J. Y. Wang, P. Wu, J. R. Wang, G. J. Mei and F. Shi, Diastereo- and enantioselective construction of chiral cyclopenta[: B] indole framework via a catalytic asymmetric tandem cyclization of 2-indolymethanols with 2-naphthols, *Org. Chem. Front.*, 2018, **5**, 1436–1445. (b) C. Vila, L. Quintero, G. Blay, M. C. Muñoz and J. R. Pedro, Organocatalytic Enantioselective Synthesis of α-Hydroxyketones through a Friedel-Crafts Reaction of Naphthols and Activated Phenols with Aryl- and Alkylglyoxal Hydrates, *Org. Lett.*, 2016, **18**, 5652–5655. (c) H. H. Zhang, C. S. Wang, C. Li, G. J. Mei, Y. Li and F. Shi, Design and Enantioselective Construction of Axially Chiral Naphthyl-Indole Skeletons, *Angew. Chem. Int. Ed.*, 2017, **56**, 116–121. (d) T. Y. Lin, H. H. Wu, J. J. Feng and J. Zhang, Transfer of Chirality in the Rhodium-Catalyzed Chemoselective and Regioselective Allylic Alkylation of Hydroxyarenes with Vinyl Aziridines, *Org. Lett.*, 2017, **19**, 2897–2900. (e) D. Wu, X. Zhang, Y. Xu, Y. Xue, J. Li, W. Wang and J. Zhu, Organocatalytic enantioselective friedel-crafts reaction of 1-naphthols with isatins and an unexpected spontaneous dehydration process, *Asian J. Org. Chem.*, 2014, **3**, 480–486. (f) C. S. Wang, T. Z. Li, S. J. Liu, Y. C. Zhang, S. Deng, Y. Jiao and F. Shi, Axially Chiral Aryl-Alkene-Indole Framework: A Nascent Member of the Atropisomeric Family and Its Catalytic Asymmetric Construction, *Chin. J. Chem.*, 2020, **38**, 543–552. (g) M. Montesinos-Magraner, C. Vila, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, Organocatalytic Enantioselective Friedel-Crafts Alkylation of 1-Naphthol Derivatives and Activated Phenols with Ethyl Trifluoropyruvate, *Adv. Synth. Catal.*, 2015, **357**, 3047–3051. (h) C. Zhang, Y. Cheng, F. Li, Y. Luan, P. Li and W. Li, Organocatalytic Enantioselective Regiodivergent C−H Bond Functionalization of 1-Naphthols with 1-Azadienes, *Adv. Synth. Catal.*, 2020, **362**, 1286–1291. (i) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi and K. Nagasawa, Entropy-controlled catalytic asymmetric 1,4-type Friedel-crafts reaction of phenols using conformationally flexible guanidine/bisthiourea organocatalyst, *Angew. Chem. Int. Ed.*, 2010, **49**, 7299–7303. (j) S. Saha, S. K. Alamsetti and C. Schneider, Chiral Brønsted acid-catalyzed Friedel-Crafts alkylation of electron-rich arenes with in situ-generated ortho-quinone methides: highly enantioselective synthesis of diarylindolylmethanes and triarylmethanes, *Chem. Commun.*, 2015, **51**, 1461–1464. (k) Y. H. Chen, D. J. Cheng, J. Zhang, Y. Wang, X. Y. Liu and B. Tan, Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols, *J. Am. Chem. Soc.*, 2015, **137**, 15062–15065. (l) J. Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti and Q. L. Xu, Symmetry in Cascade Chirality-Transfer Processes: A Catalytic Atroposelective Direct Arylation Approach to BINOL Derivatives, *J. Am. Chem. Soc.*, 2016, **138**, 5202–5205. (m) M. Montesinos-Magraner, C. Vila, G. Blay and J. R. Pedro, Catalytic Enantioselective Friedel-Crafts Reactions of Naphthols and Electron-Rich Phenols, *Synthesis*, 2016, **48**, 2151–2164. *and references cited therein.* (n) J. Kaur, A. Kumar and S. S. Chimni, Cinchonidine thiourea catalyzed asymmetric addition of phenols to oxindole derivatives, *RSC Adv.*, 2014, **4**, 62367–62374. (o) A. Kumar, J. Kaur, P. Chauhan and S. S. Chimni, Organocatalytic asymmetric Friedel-crafts reaction of sesamol with isatins: Access to biologically relevant 3-aryl-3-hydroxy-2-oxindoles, *Chem. Asian J.*, 2014, **9**, 1305–1310. (p) E. Paradisi, P. Righi, A. Mazzanti, S. Ranieri and G. Bencivenni, Iminium ion catalysis: The enantioselective Friedel–Crafts alkylation–acetalization cascade of naphthols with α,β-unsaturated cyclic ketones, *Chem. Commun.*, 2012, **48**, 11178–11180. (r) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, Enantioselective synthesis of multisubstituted biaryl skeleton by chiral phosphoric acid catalyzed desymmetrization/kinetic resolution sequence, 2013, **135**, 3964–3970.
2. (a) M. Montesinos-Magraner, C. Vila, R. Cantõn, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, Organocatalytic asymmetric addition of naphthols and electron-rich phenols to isatin-derived ketimines: Highly enantioselective construction of tetrasubstituted stereocenters, *Angew. Chem. Int. Ed.*, 2015, **54**, 6320–6324. (b) P. Kumari, S. Barik, N. H. Khan, B. Ganguly, R. I. Kureshy, S. H. R. Abdi and H. C. Bajaj, The origin for highly enantioselective induction of 1-naphthol to isatin-derived N-Boc ketimines catalyzed by quinine thiourea catalyst: An experimental and computational study, *RSC Adv.*, 2015, **5**, 69493–69501. (c) S. Karahan and C. Tanyeli, Organocatalytic enantioselective construction of isatin-derived: N -alkoxycarbonyl 1,3-aminonaphthols via sterically encumbered hydrocarbon-substituted quinine-based squaramide, *New J. Chem.*, 2017, **41**, 9192–9202. (d) D. Zhou, Z. Huang, X. Yu, Y. Wang, J. Li, W. Wang and H. Xie, A Quinine-Squaramide Catalyzed Enantioselective Aza-Friedel-Crafts Reaction of Cyclic Trifluoromethyl Ketimines with Naphthols and Electron-Rich Phenols, *Org. Lett.*, 2015, **17**, 5554–5557. (e) Z. Chen, T. Zhang, Y. Sun, L. Wang and Y. Jin, Organocatalytic enantioselectiveaza-Friedel-Crafts alkylation of β-naphthols and isatin-derived ketiminesviaa Takemoto-type catalyst, *New J. Chem.*, 2021, **45**, 10481–10487. (f) C. H. Chang, N. Sathishkumar, Solvent-Dependent Enantiodivergent Friedel-Crafts Reaction of Arylsulfonyl Indoles with 1-Naphthols, Y. T. Liao, H. T. Chen and J. L. Han, *Adv. Synth. Catal.*, 2020, **362**, 903–912. (g) M. Rodríguez-Rodríguez, A. Maestro, J. M. Andrés and R. Pedrosa, Supported Bifunctional Chiral Thioureas as Catalysts in the Synthesis of 3-Amino-2-Oxindoles through Enantioselective aza-Friedel-Crafts Reaction: Application in Continuous Flow Processes, *Adv. Synth. Catal.*, 2020, **362**, 2744–2754. (h) J. L. Han, Y. T. Liao and C. H. Chang, Asymmetric Organocatalytic Conjugate Addition of Electron-Rich Phenols and 1,3-Dicarbonyls to Arylsulfonyl Indoles in an Oil-Water Biphasic System, *Eur. J. Org. Chem.*, 2019, 5815–5823. (i) C. Vila, A. Rendón-Patiño, M. Montesinos-Magraner, G. Blay, M. C. Muñoz and J. R. Pedro, Organocatalytic Enantioselective Functionalization of Hydroxyquinolines through an Aza-Friedel-Crafts Alkylation with Isatin-derived Ketimines, *Adv. Synth. Catal.*, 2018, **360**, 859–864. (j) M. Montesinos-Magraner, C. Vila, A. Rendón-Patiño, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, Organocatalytic Enantioselective Friedel-Crafts Aminoalkylation of Indoles in the Carbocyclic Ring, *ACS Catal.*, 2016, **6**, 2689–2693.

*For non-isatine derived ketimines as electrophiles, see:* (k) Z. T. Yang, W. L. Yang, L. Chen, H. Sun and W. P. Deng, Organocatalytic Enantioselective aza-Friedel-Crafts Reactions of Pyrazolinone Ketimines with Hydroxyindoles and Electron-Rich Phenols, *Adv. Synth. Catal.*, 2018, **360**, 2049–2054. (l) U. Kaya, P. Chauhan, S. Mahajan, K. Deckers, A. Valkonen, K. Rissanen and D. Enders, Squaramide-Catalyzed Asymmetric aza-Friedel–Crafts/N,O-Acetalization Domino Reactions Between 2-Naphthols and Pyrazolinone Ketimines, *Angew. Chem. Int. Ed.*, 2017, **56**, 15358–15362. (m) K.-F. Zhang, J. Nie, R. Guo, Y. Zheng, J.-A. Ma, Chiral Phosphoric Acid-Catalyzed Asymmetric Aza-Friedel–Crafts Reaction of Indoles with Cyclic *N*-Acylketimines: Enantioselective Synthesis of Trifluoromethyldihydroquinazolines,*Adv. Synth. Catal.*, 2013, **355**, 3497–3502.

1. L. Cai, X. Liu, J. Wang, L. Chen, X. Li and J. P. Cheng, Enantioselective and regioselective aza-Friedel-Crafts reaction of electron-rich phenols with isatin-derived ketimines, *Chem. Commun.*, 2020, **56**, 10361–10364.
2. (a) A. Mertens, H. Zilch, B. König, W. Schäfer, T. Poll, W. Kampe, H. Seidel, U. Leser and H. Leinert, Selective Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors. New 2,3-Dihydrothiazolo[2,3-a]isoindol-5(9bH)-ones and Related Compounds with Anti-HIV-1 Activity, *J. Med. Chem.*, 1993, **36**, 2526–2535. (b) P. R. Gentry, M. Kokubo, T. M. Bridges, N. R. Kett, J. M. Harp, H. P. Cho, E. Smith, P. Chase, P. S. Hodder, C. M. Niswender, J. S. Daniels, P. Je, M. R. Wood and C. W. Lindsley, Discovery of the First M5‑Selective and CNS Penetrant Negative Allosteric Modulator (NAM) of a Muscarinic Acetylcholine Receptor: (S)‑9b-(4-Chlorophenyl)-1-(3,4-difluorobenzoyl)-2,3-dihydro‑1H‑imidazo[2,1‑a] isoindol-5(9bH)‑one (ML375), *J. Med. Chem.*, 2013, **56**, 9351–9355. (c) J. J. Baldwin et al, Preparation of phenyloxooxatriazatridecanylcarbamate derivatives and analogs as renin inhibitors, WO2008156816, 2008. (d) N. A. L. Pereira, Â. Monteiro, M. Machado, J. Gut, E. Molins, M. J. Perry, J. Dourado, R. Moreira, P. J. Rosenthal, M. Prudêncio and M. M. M. Santos, Enantiopure Indolizinoindolones with in vitro Activity against Blood- and Liver-Stage Malaria Parasites, *ChemMedChem*, 2015, **10**, 2080–2089. (e) I. R. Hardcastle, J. Liu, E. Valeur, A. Watson, U. Ahmed, T. J. Blackburn, K. Bennaceur, W. Clegg, C. Drummond, J. A. Endicott, B. T. Golding, R. J. Gri, J. Gruber, K. Haggerty, R. W. Harrington, C. Hutton, S. Kemp, X. Lu, J. M. Mcdonnell, D. R. Newell, M. E. M. Noble, S. L. Payne, C. H. Revill, C. Riedinger, Q. Xu and J. Lunec, Isoindolinone Inhibitors of the Murine Double Minute 2 (MDM2)-p53 Protein-Protein Interaction: Structure-Activity Studies Leading to Improved Potency, *J. Med. Chem.*, 2011, **2**, 1233–1243. (f) R. D. Daily and T. A. Woods, Preparation of isoindolinone compounds as CDC7 inhibitors in treating cancer, WO2014143601, 2014.
3. (a) D. Glavač, C. Zheng, I. Dokli, S.-L. You and M. Gredičak, Chiral Brønsted Acid Catalyzed Enantioselective aza-Friedel-Crafts Reaction of Cyclic α-Diaryl *N*-Acyl Imines with Indoles, *J. Org. Chem.*, 2017, **82**, 8752–8760. (b) X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, Organocatalyzed Enantioselective Synthesis of Quaternary Carbon-Containing Isoindolin-1-ones, *Eur. J. Org. Chem.*, 2011, 3060–3066.
4. (a) J. Suć, I. Dokli and M. Gredičak, Chiral Brønsted acid-catalysed enantioselective synthesis of isoindolinone-derived *N*(acyl),*S*-acetals, *Chem. Commun.*, 2016, **52**, 2071–2074. (b) R. A. Unhale, N. Molleti, N. K. Rana, S. Dhanasekaran, S. Bhandary and V. K. Singh, Chiral phosphoric acid catalyzed enantioselective addition of thiols to in situ generated ketimines: synthesis of *N,S*-ketals, *Tetrahedron Lett.*, 2017, **58**, 145–151. (c) A. Suneja, R. A. Unhale and V. K. Singh, Enantioselective Hydrophosphonylation of in Situ Generated *N*-Acyl Ketimines Catalyzed by BINOL-Derived Phosphoric Acid, *Org. Lett.*, 2017, **19**, 476–479. (d) L. Zhang, B. Wu, Z. Chen, J. Hu and X. Zeng, Chiral phosphoric acid catalyzed enantioselective N -alkylation of indoles with in situ generated cyclic N-acyl ketimines, *Chem. Commun.*, 2018, **54**, 9230–9233.
5. (a) M.-Y. Rong, J.-S. Li, Y. Zhou, F.-G. Zhang and J.-A. Ma, *Org. Lett.*, Catalytic Enantioselective Synthesis of Difluoromethylated Tetrasubstituted Stereocenters in Isoindolones Enabled by a Multiple-Fluorine System, 2020, **22**, 9010–9015. (b) L. Wang, J. Zhong and X. Lin, Enantioselective Synthesis of Difluoroalkylated Isoindolinones via Chiral Spirocyclic Phosphoric Acid-Catalyzed Mannich-type Reaction, *Synlett*, 2021, **32**, 417–422. (c) R. A. Unhale, M. M. Sadhu, S. K. Ray, R. G. Biswas and V. K. Singh, A chiral Brønsted acid-catalyzed highly enantioselective Mannich-type reaction of α-diazo esters with in situ generated N-acyl ketimines, *Chem. Commun.*, 2018, **54**, 3516–3519. (d) K. N. Reddy, M. V. K. Rao, B. Sridhar and B. V. Subba Reddy, BINOL Phosphoric Acid-Catalyzed Asymmetric Mannich Reaction of Cyclic N-Acyl Ketimines with Cyclic Enones, *Chem. Asian J.*, 2019, **14**, 2958–2965. (e) F. F. Feng, J. S. Li, S. Li and J. A. Ma, Enantioselective Addition of Enamides to Cyclic Ketimines: Access to Chiral 3,3-Disubstituted Isoindolin-1-Ones, *Adv. Synth. Catal.*, 2019, **361**, 4222–4226. (f) Z. Kang, D. Zhang, J. Shou and W. Hu, Enantioselective Trapping of Oxonium Ylides by 3-Hydroxyisoindolinones via a Formal SN1 Pathway for Construction of Contiguous Quaternary Stereocenters, *Org. Lett.* 2018, **20**, 983–986.
6. Conducting the reaction in 0.25 mL of toluene (potentially 0.4M suspension) was not possible, since the starting materials adsorbed solvent, and the mixture remained a solid, rather than becoming a suspension.
7. CCDC 2073369 contains the supplementary crystallographic data for this paper.