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Construction of chiral Betti base precursors containing congested quaternary stereogenic center *via* chiral phosphoric acid-catalyzed arylation of isoindolinone-derived ketimines

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Synthesis of enantioenriched Betti base precursors containing congested quaternary stereocenter is described. In a chiral phosphoric acid-catalyzed reaction, a series of *in situ* generated isoindolinone-derived ketimines and phenol derivatives yield products in good to excellent yields, and moderate enantioselectivities. Conversion of obtained products into chiral Betti bases with the retention of optical purity is demonstrated.

Introduction

The Betti reaction is a multicomponent Mannich-type reaction between amines (or ammonia), aryl aldehydes, and naphthols for the synthesis of aminobenzylnaphthols, so-called Betti bases.1 Chiral Betti bases are often employed as ligands in asymmetric transition metal-catalyzed transformations,2 and are useful building blocks in the synthesis of compounds with various biological activities.3 Up to early 2000s, optically pure Betti bases were obtained either by enantioseparation of racemic compounds,4 or by employing chiral amines as substrates.5 The emergence of asymmetric catalysis has governed research towards the development of elegant and practical methodologies for their synthesis, and they mostly include enantioselective additions of electron-rich phenol derivatives to aldimines.6 On the other hand, strategies for the generation of chiral Betti bases containing quaternary stereogenic center on their benzyl carbon are still underexplored.

In this regard, seminal developments were made in 2015, when Pedro7 and Khan and Ganguly8 independently reported a quinine-thiourea catalyzed addition of 1-naphthols and electron-rich phenols to isatin-derived ketimines (Scheme 1A), and the following years have seen the development of effective methodologies for the preparation of these derivatives.9 In the same year, Wang and Xie reported quinine-squaramide catalyzed addition of electron-rich phenol derivatives to quinazoline-type cyclic trifluoromethyl ketimines.10 In 2017, Chauhan and Enders developed enantioselective reaction between 1-naphthols and pyrazolinone-derived ketimines utilizing the same type of catalyst.11 Within their study on asymmetric addition of electron-rich phenols through their *para* position on isatin-derived ketimines, Li et al obtained chiral Betti bases as side products of the reaction.12



**Scheme 1.** Catalytic methodologies towards chiral Betti bases and their precursors containing quaternary stereogenic center on benzyl carbon.

However, to the best of our knowledge, there are still no reports on the asymmetric methodologies for the construction of Betti bases with more congested stereogenic centers, such as triaryl-substituted centers of chirality. Although these stereocenters can be obtained by transition metal-catalyzed arylations of diaryl ketimines,13 these protocols are not tolerant on substrates comprising hydroxy group, and hence cannot generate Betti bases. On the other hand, their organocatalytic counterparts do not yield products with required aminobenzylphenol structural motif, since hydroxy group is usually placed in *para* position with respect to benzyl carbon.12,14

Following our recent report on non-chiral formal Betti reaction between phenols and diarylketimines,15 herein we present a chiral phosphoric acid-catalyzed arylation of ketimines, generated *in situ* from 3-hydroxyisoindolinones, for the preparation of Betti base precursors containing congested, triaryl-substituted quaternary stereogenic center (Scheme 1B).

Results and Discussion

We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone **IS-1** with *p*-chlorophenol in the presence of various chiral phosphoric acids (Table 1).

**Table 1.** Screening of reaction conditions.a



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Entry** | **Cat.** | **Solvent** | **Temp. (°C)** | **Time (h)** | **Yield (%)** | **e.r.** |
| 1 | **CPA1** | Toluene | 80 | 36 | 91 | 50:50 |
| 2 | **CPA2** | Toluene | 80 | 72 | 88 | 46:54 |
| 3 | **CPA3** | Toluene | 80 | 48 | 87 | 44:56 |
| 4 | **CPA4** | Toluene | 80 | 24 | 92 | 45:55 |
| 5 | **CPA5** | Toluene | 80 | 48 | 87 | 64:36 |
| 6 | **CPA6** | Toluene | 80 | 48 | 91 | 69:31 |
| 7 | **CPA7** | Toluene | 80 | 72 | 82 | 48:52 |
| 8 | **CPA6** | Acetonitrile | 80 | 48 | traces | – |
| 9 | **CPA6** | Nitrobenzene | 80 | 48 | 47 | 71:29 |
| 10 | **CPA6** | Nitromethane | 80 | 48 | 33 | 80:20 |
| 11 | **CPA6** | Chloroform | 60 | 72 | 85 | 76:26 |
| **12** | **CPA6** | **Chloroform** | **40** | **144** | **89** | **86:14** |
| 13 | **CPA6** | Dichloromethane | 40 | 144 | 76 | 82:18 |
| 14 | **CPA6** | Chloroform | 40 | 168 | 84 | 70:30c |
| 15 | **CPA6** | Chloroform | 40 | 168 | 91 | 77:23d |
| 16 | **CPA6** | Chloroform | 40 | 168 | 54 | 78:22e |
| 17 | **CPA6** | Chloroform | 40 | 168 | 90 | 72:28f |
| 18 | **CPA6** | Chloroform | 40 | 168 | 88 | 81:19g |
| 19 | **CPA6** | Chloroform | 40 | 168 | 40 | 82:18h |

aReaction conditions: **IS-1** (0.13 mmol), *p*-chlorophenol (0.65 mmol), **CPA\*** (0.013 mmol), solvent (3.0 mL), 80 °C. e.r. determined by HPLC with a chiral stationary phase. cMgSO4 (100 mg). d*p-*Chlorophenol (10.0 eq). e*p-*Chlorophenol (3.0 eq) fChloroform (1.3 mL). gChloroform (6.0 mL). h**CPA6** (5 mol%).

Our initial attempt with (triphenyl)silyl-substituted chiral phosphoric acid **CPA1** in toluene led to complete conversion to the desired product **1** within 36 hours at 80 °C, however, without any induction of enantioselectivity (entry 1). Introduction of the pentafluorophenyl group on the BINOL backbone (**CPA2**) led to the increased reaction time, and with negligible increase in the optical purity (entry 2). With the introduction of the *tert*-butyl group (**CPA3**) and chlorine (**CPA4**) on the phenyl ring of the acid, the reaction maintained its poor level of enantioselectivity (entries 3 and 4). The employment of *R*-TRIP catalyst **CPA5** yielded product **1** after 48 hours in 87% yield and 64:36 e.r. (entry 5). Similar result was obtained when 9-phenanthrenyl substitutent was placed on the BINOL core (**CPA6**, entry 6). Chiral phosphoric acid bearing 1-naphthyl group (**CPA7**) slowed down the reaction, and afforded **1** without any significant asymmetric induction (entry 7).

After identifying catalyst **CPA6** as the catalyst of choice, the influence of solvent, temperature, drying agent, and reagent loading was investigated. By conducting the reaction in acetonitrile, only starting materials were detected in the reaction mixture after 48 hours (entry 8). When nitrobenzene was used as solvent, product **1** was isolated in lower yield, and virtually the same enantioselectivity as in toluene (entry 9). The reaction performed in nitromethane afforded product in even lower yield, but substantially higher enantiomeric ratio (entry 10). On the other hand, conducting the reaction in chloroform at 60 °C yielded product in high yield and moderate enantioselectivity (entry 11). The enantioselectivity of the reaction increased when temperature was lowered to 40 °C, though the reaction time was also prolonged (89% yield, 86:14 e.r., entry 12). Performing the reaction in dichloromethane did not further improve reaction outcome (entry 13). When drying agent was used as an additive, the conversion rate remained the same, but the enantiomeric ratio in the product significantly dropped (entry 14). The reaction was not improved when the amount of *p*-chlorophenol was increased (entry 15) or decreased (entry 16), nor when the reaction concentration was changed (entries 17 and 18). Finally, lowering the catalyst loading did not enhance the reaction outcome (entry 19).

Hence, chosen reaction conditions include isoindolinone alcohol (1.0 eq), phenol (5.0 eq), and **CPA6** (10 mol%) in chloroform at 40 °C.

With the optimized reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations. Initially, we examined formation of products with various 3-aryl 3-hydroxyisoindolinones (Table 2). *p*­-Chlorophenol reacted readily with several different 3-aryl 3-hydroxyisoindolinones, although the reaction times were significantly prolonged compared to the model reaction. When alkyl substituents were placed around the 3-aryl ring, a small drop in yield and enantioselectivity was observed (**2** and **3**). By introducing electron-donating groups on *meta* positions of the 3-aryl substituent, no significant change in enantiomeric ratios was observed (**4** and **5**). On the other hand, when methoxy group was placed in *para* position, product **6** was obtained in excellent yield, but in slightly lower enantioselectivity. Introduction of trifluoromethyl, halogen, and 3-naphthyl substituents on the C3 position of isoindolinone ring did not change the efficiency of the reaction (**7**–**10**). The transformation proceeded uneventfully when substitution on phthalimide aromatic ring was introduced (**11** and **12**).

Interestingly, the transformation did not proceed with *ortho* substituted 3-aryl substituents on the imine precursor; only starting materials were retrieved when substrates with *o*-methylphenyl and *o*-methoxyphenyl groups were submitted to chosen reaction conditions. Based on these experiments, this limitation most likely stems from the increased steric hindrance around the reaction center, rather than from the electronic effects.

**Table 2.** Substrate scope I: isoindolinone alcohols.a



aReaction conditions: isoindolinone alcohol (0.13 mmol), *p*-chlorophenol (0.65 mmol), **CPA6** (0.013 mmol), chloroform (3.0 mL), 40 °C. e.r. determined by HPLC with a chiral stationary phase. bScale-up reaction (1.0 mmol): 60% yield, 74:26 e.r., 14 days.

Next, we turned our attention to investigating the scope and limitations of the reaction with various phenols (Table 3). Initially, we chose isoindolinone **IS-1** as a model alcohol for the investigation of the influence of phenol derivatives on the reaction outcome. In general, the reaction maintained its effectiveness regardless of the nature of the *para* substituent on phenol. By switching chlorine with bromine, both yield and enantioselectivity of the reaction dropped (**13**). Excellent yields were obtained with alkyl substituents in *para* position on phenol, without significant change in the enantioselectivities (**14–16**). When trifluoromethyl group was placed on phenol, the reaction time was prolonged, and the product **17** was isolated in lower yield. By placing electron-donating groups in phenol, the transformation maintained its effectiveness, both in terms of yield and enantioselectivity (**18**–**20**). On the other hand, product yields and enantiomeric ratios slightly dropped when 3-aryl substituted 3-hydroxyisoindolinones were reacted with various phenols (**21–24**).

We also investigated reaction efficiency with more nucleophilic phenol derivatives, 1-naphthol and sesamol. When submitted to standard reaction conditions, reaction time was shortened to 16 hours, and products were isolated in excellent yield, but poor enantioselectivity (**25** and **26**). Lowering the reaction temperature to 0 °C did not improve optical purity in the products. Finally, we investigated the influence of 2,4-disubstituted phenol on the reaction outcome, and product **27** was isolated in moderate yield and poor enantioselectivity.

**Table 3.** Subsrate scope II: phenols.a



aReaction conditions: isoindolinone alcohol (0.13 mmol), phenol (0.65 mmol), **CPA6** (0.013 mmol), chloroform (3.0 mL), 40 °C. e.r. determined by HPLC with a chiral stationary phase. bStarting material retrieved.

The absolute configuration of the major enantiomer of the product **23** was unambiguously assigned to be (*S*) by X-ray structure analysis. This result indicates nucleophilic attack from *re* face of the planar ketimine, and the absolute configurations of major enantiomers of the remaining products were assigned by analogy.

In order to elucidate the role of non-bonding interactions, experiments with *N*-protected isoindolinone alcohol and *O*-protected phenol were performed (Scheme 2). When *N*-methyl 3-hydroxyisoindolinone **IS-2** and *p*-chlorophenol were submitted to standard reaction conditions, product **28** was not observed. Likewise, in a reaction between isoindolinone **IS-1** and *p*-bromoanisole only starting materials were isolated from the reaction mixture. These experiments indicate that N*H* is required for the generation of reactive ketiminium species, and that O*H* plays an important role in the nucleophilicity of the phenyl ring.



**Scheme 2.** Control experiments.

Based on the absolute configurations of major enantiomers and conducted control experiments, we propose the following stereochemical model of asymmetric induction, based on reports by Simόn and Goodman (Scheme 3).16 Following the protonation of isoindolinone alcohol, water is eliminated to generate a reactive ketiminium species. Formed cation forms an ion pair with the anionic phosphate catalyst, and blocks the *si* face of the substrate. The approaching phenol preferably attacks the planar ketimine from the opposite side to yield major enantiomers with (*S*) configuration. Although it remains unclear at this point, probable hydrogen bonding between phenol and the catalyst17 most likely plays a role in the stereochemical outcome.



**Scheme 3.** Proposed mechanism of stereochemical induction

Finally, in addition to the scale-up reaction (Table 2, **1**), we demonstrated the conversion of obtained precursors into Betti bases (Scheme 4). The reduction of amide group in product **3** was successfully performed with borane dimethylsulfide complex, yielding chiral Betti base **30** with the retention of optical purity.



**Scheme 4.** Access to chiral Betti bases from obtained precursors.

Conclusions

In conclusion, we have developed a chiral phosphoric acid-catalyzed reaction for the construction of chiral Betti base precursors containing congested, triaryl-substituted stereogenic center. The transformation proceeds smoothly with a broad range of phenols and ketimines to afford products in good to excellent yields, and moderate enantioselectivities. Access to Betti bases from obtained products was also demonstrated. Although with limitations, we hope that presented study can provide useful knowledge in the development of new methodologies toward Betti bases with congested stereocenters.

Experimental Section

General procedure. To a flame-dried Schlenk tube containing a suspension of isoindolinone alcohol18 (0.13 mmol) in chloroform (3.0 mL), phenol derivative (0.65 mmol) and **BA6** (0.013 mmol) were added, and the resulting 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.

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