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Enantioselective Construction of Tetrasubstituted Stereocenter in Isoindolinones *via* Organocatalyzed Reaction Between Ketones and 3-Hydroxyisoindolinones

An efficient enantioselective reaction between ketones and 3-hydroxyisoindolinones is described. In a reaction catalyzed by a chiral phosphoric acid, a broad range of ketones and *in situ* generated ketimines afforded isoindolinone derivatives comprising tetrasubstituted stereocenter in high yields and enantioselectivities. Developed methodology is also suitable for the construction of compounds with vicinal stereogenic centers**.**

Recent years have seen the emergence of catalytic stereoselective approaches towards non-racemic construction of 3-alkyl isoindolinones.1 These heterocyclic cores are found in a broad array of bioactive molecules (Scheme 1),2 and in most cases only a single enantiomer is effective, or has a better activity profile than the other.



Scheme 1. Representative bioactive 3-alkyl isoindolinones.

However, the construction of isoindolinone derivatives with tetrasubstituted 3-alkyl stereogenic center is not trivial. Although the most efficient strategy seems to be the addition of nucleophiles to 3-alkyl isoindolinone-derived ketimines, this approach is not without drawbacks. During the addition of an external nucleophile, a competitive *β*-hydrogen elimination on the alkyl chain leads to the irreversible formation of enamide derivatives, which either diminishes the reaction yield or completely suppresses targeted transformation.3 Hence, strategies for the construction of such stereogenic center in isoindolinones rely on stereoselective employment of non-aromatic carbon nucleophiles in Mannich-type reactions (Scheme 2).



Scheme 2. Strategies employing non-aromatic carbon nucleophiles.

In 2018, the Singh group developed highly enantioselective addition of α-azoesters to *in situ* formed isoindolinone-derived ketimines.4 Reddy et al developed enantioselective organocatalytic Mannich reaction between 3-hydroxyisoindolinones and cyclic enones, however, the reaction was not tolerant on acyclic ketones.5 Li and Ma reported synthesis of chiral 3-aryl-alkyl isoindolinones by employing asymmetric addition of *N*-acetyl enamides to isoindolinone alcohols.6 In 2020, Zhang and Ma7 and Lin8 independently developed a chiral phosphoric acid-catalyzed Mukaiyama-Mannich reaction of difluoroenoxysilanes with isoindolinone-iminium ions to construct difluoromethylated derivatives.

Although elegant examples for the synthesis of isoindolinone derivatives with 3-alkyl tetrasubstituted stereocenter, carbon nucleophiles employed in these methodologies have inherent inability to generate vicinal stereogenic centers. To the best of our knowledge, the only example for the construction of vicinal stereogenic centers in these derivatives was reported by Hu.9 In a three-component relay reaction mediated by Rh(ii)/chiral phosphoric acid catalysts, trapping of oxonium ylides by isoindolinones afforded products in high enantioselectivities, though as separable mixtures of diastereomers.

Herein, we report a chiral phosphoric acid catalyzed reaction between ketones and *in situ* generated ketimines for the construction of 3-alkyl tetrasubstituted stereocenter in isoindolinones, also suitable for the generation of vicinal stereogenic centers.

We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone **SI-1** with acetophenone at 60 °C in carbon tetrachloride in the presence of various chiral phosphoric acids (Table 1). **BA1** successfully catalyzed this transformation, and product **1** was isolated in 90% yield and 73:27 e.r. (entry 1). Catalyst **BA2** demonstrated an improved reaction rate, but at the expense of enantioselectivity (entry 2). By employing (*R*)-TRIP as catalyst, the complete conversion was observed after 3 days, and the product was isolated in 88:12 e.r. (entry 3). On the other hand, the reaction catalyzed by **BA4** was stopped after 7 days, with the product being isolated in a moderate yield and enantioselectivity (entry 4). A similar trend was also observed with catalysts **BA5** and **BA6** (entries 5 and 6), while the reaction mediated by **BA7** demonstrated shorter reaction time (entry 7). Introduction of 9-anthracenyl substituent on the flanking aromatic rings of the catalyst resulted in the high yield, but moderate enantiomeric ratio in the product (entry 8).

After identifying (*R*)-TRIP as the catalyst of choice, the influence of solvent, temperature, additives, and reagent loading was investigated. Enantiomeric purity in the product slightly increased when the reaction was performed in hydrocarbon solvents (entries 9–11) and nitromethane (entry 12). By conducting the reaction in toluene and dichloromethane, the reaction times were significantly prolonged, and product was obtained in moderate enantioselectivities (entries 13 and 14). The best result in terms of optical purity was obtained in acetonitrile, however, at the expense of isolated yield (entry 15). By increasing the reaction temperature, the conversion rate was significantly improved without the loss of enantioselectivity in the product (entry 16).

Table 1. Enantioselective reaction optimization.a



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| entry | cat. | solvent | temp. (°C) | time (h) | yield (%) | e.r. |
| 1 | **BA1** | CCl4 | 60 | 120 | 90 | 73:27 |
| 2 | **BA2** | CCl4 | 60 | 24 | 87 | 53:47 |
| 3 | **BA3** | CCl4 | 60 | 72 | 79 | 88:12 |
| 4 | **BA4** | CCl4 | 60 | 168 | 43 | 64:36 |
| 5 | **BA5** | CCl4 | 60 | 168 | 56 | 67:33 |
| 6 | **BA6** | CCl4 | 60 | 168 | 79 | 66:34 |
| 7 | **BA7** | CCl4 | 60 | 48 | 74 | 61:39 |
| 8 | **BA8** | CCl4 | 60 | 72 | 93 | 81:19 |
| 9 | **BA3** | hexane | 60 | 72 | 77 | 90:10 |
| 10 | **BA3** | cyclohexane | 60 | 168 | 82 | 90:10 |
| 11 | **BA3** | heptane | 60 | 168 | 45 | 91:9 |
| 12 | **BA3** | nitromethane | 60 | 168 | 41 | 90:10 |
| 13 | **BA3** | toluene | 60 | 312 | 85 | 86:14 |
| 14 | **BA3** | DCM | 40 | 480 | 58 | 74:26 |
| 15 | **BA3** | acetonitrile | 60 | 144 | 45 | 95:5 |
| 16 | **BA3** | acetonitrile | 80 | 72 | 89 | 94:6 |
| 17 | **BA3** | acetonitrile | 80 | 72 | 57 | 93:7b |
| **18** | **BA3** | **acetonitrile** | **80** | **48** | **95** | **95:5c** |
| 19 | **BA3** | acetonitrile | 80 | 168 | 98 | 92:8d |

*a*Reactions performed on a 0.10 mmol scale. e.r. determined by the chiral HPLC. *b*Additive: 3Å molecular sieves (1g/mmol). *c*Acetophenone (5.0 equiv). *d*Acetophenone (20.0 equiv).

The addition of a drying agent did not improve the reaction outcome (entry 17). The reaction rate was further improved when 5.0 equiv. of acetophenone was used (entry 18), however, employment of 20.0 equiv. of ketone had the opposite effect (entry 19).

Hence, the chosen reaction conditions for the enantioselective reaction between ketones and isoindolinone-derived ketimines include isoindolinone alcohol (1.0 equiv), ketone (5.0 equiv), and **BA3** catalyst (10 mol%) in acetonitrile at 80 °C.

With the optimized reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations. Initially, we examined reactions between acetophenone and various isoindolinone alcohols (Table 2). Acetophenone reacted efficiently with a range of ketimines providing products in high yields and enantioselectivities. When *para* substituted 3-aryl rings were placed on the isoindolinone core, the reaction maintained its efficiency regardless of the nature of the substitutent and furnished products **2–6**. Interestingly, the reaction with 3-(4-trifluoromethyl)-phenyl 3-hydroxyisoindolinone required 8 days for completion. *Meta* and *ortho* substituents on the 3-aryl ring were also well tolerated (**7–9**). Introduction of di-*meta* substituted 3-aryl rings did not change the reaction outcome, however, in some cases reaction times were substantially prolonged (**10**–**12**). The reaction was also tolerant on substituents placed on the isoindolinone aromatic ring (**13**).

Table 2. Substrate scope I: Isoindolinones.a



*a*Reactions performed on a 0.10 mmol scale. e.r. determined by the chiral HPLC. *b*Reaction stopped, starting material retrieved.

Furthermore, we turned our attention to investigating the scope and limitations of the reaction with various ketones (Table 3). Under the standard reaction conditions, reactions with 4'-fluoro- and 4'-methylacetophenone afforded products **14** and **15** in high yields and enantioselectivites. Placing the electron-donating group at each position around the aromatic ring of ketone did not have any significant impact on the reaction outcome (**16–18**), and the reaction was also tolerant of acyclic enone (**19**, 68% yield, 96:4 e.r.).

Next, we explored the possibility of accessing products with vicinal stereogenic centers by submitting α-substituted ketones to standard reaction conditions. When propiophenone was employed, diastereomers **20** and **20'** were isolated in high overall yield, but low enantioselectivities.10 Increasing of the α-chain on ketone did not have a positive effect on the reaction outcome (**21**/**21'**). Although the reaction with cyclohexanone showed more preference for one diastereomer (**22**/**22'**), both of them were isolated in low optical purities. On the other hand, when phenyl substituent was placed on the α-position of ketone, product **23** was obtained in high diastereoselectivity and enantioselectivity (69% yield, >20:1 d.r., 95:5 e.r.). The reaction maintained its effectiveness when 2-phenylacetophenone was employed with a series of isoindolinone derivatives (**24–32**). These results indicate that the favourable interaction with the catalyst during the stereochemical induction step (in terms of diastereomeric and enantiomeric reaction outcome) is proportional to the size of the α-substituent on ketone, and does not significantly depend on the substituents on ketimine.

Table 3. Substrate scope II: ketones.a



*a*Reactions performed on a 0.10 mmol scale. d.r. determined by the 1H NMR of the crude reaction mixture. e.r. determined by the chiral HPLC. *b*Starting material retrieved.

Isoindolinone alcohol possessing substituent in *ortho* position of the 3-aryl ring had negative effect on the reaction outcome; the reaction was stopped after 7 days, and although it proceeded in high diastereoselectivity, product **33** was isolated in poor enenatioselectivity (39% yield, >20:1 e.r., 59:41 e.r.).

The absolute configuration of **1** was assigned to be (*R*) by comparing its HPLC traces with a known compound,6 while the absolute configuration of **24** was unambiguously assigned to be (*R,S*) by X-ray structure analysis.11 The absolute configurations of the remaining products were assigned by analogy. Based on the absolute configurations of both products, we propose the following stereochemical model of asymmetric induction, based on reports by Simόn and Goodman (Scheme 3).12



Scheme 3. Proposed mechanism of stereochemical induction.

Following the protonation of 3-hydroxy isoindolinone, water is eliminated to generate a reactive ketiminium cation, which forms an ion pair with the anionic phosphate catalyst. The *re* face of the substrate is blocked, and the approaching enol attacks the planar ketimine from the opposite side to yield products with a (*R*) configuration. Although it remains unclear at this point, probable hydrogen bonding between enol and the catalyst13 most likely influences the stereochemical outcome.

Finally, in addition to the successful scale-up reaction (**24**, Table 3), we explored possibilities for the utilization of obtained products in further transformations (Scheme 4).



Scheme 4. Postmodification reactions.

Compound **19** underwent 6-*endo-trig* cyclization (intramolecular Michael addition) mediated by *p*-toluenesulfonic acid, providing access to both diastereomers **34** (10% yield, 95:5 e.r.) and **34'** (44% yield, 95:5 e.r.). The reduction of carbonyl group in product **6** was successfully performed with sodium borohydride, yielding both diastereomers **35** and **35'** in high overall yield and without the loss of optical purity. Since a considerable number of examples possess methoxy group, its cleavage and access to corresponding phenol derivatives was demonstrated by treating **15** with boron tribromide (**36**, 97% yield, optical purity retained).

In conclusion, we have developed a chiral phosphoric acid-catalyzed reaction between isoindolinone-derived ketimines and ketones for the construction of tetrasubstituted 3-alkyl-aryl stereocenter in isoindolinones. Developed methodology is successfully applied for the generation of compounds with vicinal stereogenic centers. This transformation offers a stereoselective approach to a new class of isoindolinone derivatives that may find application as natural product analogues and frameworks for the discovery of bioactive compounds.

There are no conflicts to declare.

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