Enantioselective Organocatalyzed aza-Michael Addition Reaction of 2-Hydroxybenzophenone Imines to Nitroolefins under Batch and Flow Conditions

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Abstract: Herein, an asymmetric organocatalytic aza-Michael addition reaction of ketimines to nitroolefins is presented. The use of 2-hydroxybenzophenone imine improves the enantioselective addition of N-centered nucleophiles to nitroalkenes by means of intramolecular hydrogen bond formation at the imine moiety. Moreover, the versatility of the process is demonstrated under both batch and flow conditions, showing the synthesis of a large variety of nitroamine derivatives with excellent yields and enantioselectivities. In addition, we applied this methodology to the formal synthesis of VNI, a drug-like scaffold for the treatment of Chagas disease.

Keywords: Enantioselective; Organocatalysis; aza-Michael; 2-Hydroxybenzophenone; Flow system

Introduction

Operational simplicity remains fundamental in basic research since some of the chemical transformations can afterwards be driven at the industry level. Setting the focus on enantioselective procedures, asymmetric organocatalysis fulfills this requirement, gaining importance throughout the years. Especially, for the construction of C–N bonds, organocatalysis has contributed with the aza-Michael addition reaction thanks to the great variety of activation modes that it offers for different substrates. Thus, α,β-unsaturated carbonyl compounds stand out as the most employed Michael acceptors dealing with enals and enones, and more recently also conjugated acids and esters.

More specifically, the employment of nitroolefins as the electrophilic counterpart has attracted the attention of the organic community since they provide access to remarkable scaffolds in chemistry, such as 1,2-diamines, once the conjugate addition is performed (Scheme 1, equation A). Such nitrogen atom-centered nucleophiles that enable their transformation into amine moieties comprise azides, carbamates or even anilines, but harsh reaction conditions must be handled to obtain the free nitrogen atom. In addition, other nucleophilic aminating reagents, such as benzotriazoles, hydrazines, or phthalimide derivatives cannot be easily transformed into free amines. The use of imines has also been described for the preparation of chiral 1,2-diamines via N-functionalization of nitroalkenes but with moderate enantioselectivities. Therefore, an easy and straightforward methodology for the highly enantioselective synthesis of 1,2-diamine scaffolds, using N-centered nucleophiles, remains elusive. Moreover, as far as we...
know, the organocatalytic synthesis of these diamine derivatives using flow conditions has not been reported to date.

Inspired by the limitation of achieving highly enantiopure precursors of β-amino-nitro compounds, we wondered if a ketimine with an ortho hydroxyl group could improve the asymmetric organocatalytic aza-Michael addition to nitroalkenes (Scheme 1, equation B). Furthermore, the easy C=N hydrolysis of the ketimine and reduction of the NO₂ group would give access to 1,2-diamines and enable the synthesis of a bioactive precursor product. Moreover, the development of this process under flow conditions could allow the synthesis of aza-Michael compounds and facilitate the scale-up of the reaction, keeping excellent enantioselectivities overall.

**Results and Discussion**

Initially, we started with a proof of concept to confirm the role of the OH group at ketimine 1 in the reactivity and selectivity of the process (Scheme 2). Under standard reaction conditions, using commercially available Takamoto’s thiourea catalyst 3a, benzophenone imine 1a reacted with trans-β-nitrostyrene 2a, obtaining the aza-Michael adduct 4a in full conversion but as a racemic mixture. Gladly, 2-hydroxybenzophenone imine 1b led to the corresponding N-functionalized derivative 5a in very high yield and enantioselectivity (98% ee). By contrast, the use of methanol as solvent provoked a dramatic change in the reactivity, giving 5a in low yield and enantioselectivity (15% ee). This fact confirmed the importance of the OH group at the imine for the asymmetric aza-Michael addition.

Having established that the presence of the OH group is essential for the aza-Michael addition of ketimine 1b to β-nitrostyrene 2a, we next screened the reaction conditions, testing different organocatalysts beyond Takamoto’s thiourea (Table 1). Cinchona alkaloid catalysts derived of thiourea (entries 2, 4 and 5) and squaramide (entry 3) were analyzed, finding 3e (entry 5) as the best bifunctional catalyst. Solvents were examined (entries 6–7 and table S1 in ESI for complete screening of the reaction conditions), obtaining the highest enantioselectivity values using CH₂Cl₂ (entry 5). Then, we studied the catalyst loading of the reaction (entries 8–10), attaining the aza-Michael product 5a in excellent yield and enantioselectivity in only 3 hours and using a 10 mol% of organocatalyst 3e (entry 9) as the optimal reaction conditions. With the optimized conditions in hand (Table 1, entry 9), we evaluated the scope of the reaction (Table 2).

Therefore, a large assortment of nitroolefins covering diverse aromatic rings from naphthyl 5b to different electronic nature such as electron-donating (5c and 5d) and electron-withdrawing groups (5e) were successfully tolerated. The reaction worked with halogens in ortho- and para-positions (5f–5l), obtaining good yields (75–98%) and excellent enantioselectivities (99–>99% ee). Moreover, furane, thiophene, and pyridine nitroalkene derivatives led to the corresponding final adducts in very good results (5j–5l).
Table 1. Screening of the reaction conditions for the addition of 1b to 2a.\(^{[a]}\)

| Entry | Catalyst (mol%) | Solvent | Time (h) | Conv.\(^{[b]}\) (%) | ee\(^{[c]}\) (%)\(^{[d]}\) |
|-------|-----------------|---------|---------|----------------------|-----------------------|
| 1     | 3a (20)         | CHCl\(_3\) | 22      | 100(88)\(^{[e]}\)   | 98                    |
| 2     | 3b (20)         | CHCl\(_3\) | 22      | 100 – 98             |                       |
| 3     | 3c (20)         | CHCl\(_3\) | 22      | 100 – 95             |                       |
| 4     | 3d (20)         | CHCl\(_3\) | 22      | 100 – 97             |                       |
| 5     | 3e (20)         | CHCl\(_3\) | 22      | 100 – 99             |                       |
| 6     | 3e (20)         | Acetone  | 22      | 66 – 95              |                       |
| 7     | 3e (20)         | Toluene  | 22      | 98 – 66              |                       |
| 8     | 3e (20)         | CHCl\(_3\) | 3       | 100 – 99             |                       |
| 9     | 3e (10)         | CHCl\(_3\) | 22      | 100(98)\(^{[f]}\)   | 99                    |
| 10    | 3e (5)          | CHCl\(_3\) | 3       | 100 – 98             |                       |

\(^{[a]}\) Conditions: 1b (0.06 mmol), 2a (0.05 mmol) and organocatalyst 3 in 0.3 mL of the corresponding solvent at room temperature for the time indicated each case.

\(^{[b]}\) Determined by \(^1\)H NMR.

\(^{[c]}\) Isolated yield after flash chromatography.

\(^{[d]}\) Determined by chiral SFC.

94–99\% ee). The reaction also worked well with nitroalkenes bearing primary (5m), secondary (5n) and tertiary (5o) alkyl chain residues, achieving the final products (5m-5o) in >99\% ee’s, regardless of the steric hindrance. Finally, the 1-nitro-1-cyclohexene yielded the α-substituted-β-aminated product 5p with excellent enantioselectivity (>99\% ee) and diastereoselectivity (d.r. = 5:1).

Encouraged by these findings, we assessed the scope regarding the ketimine scaffold bearing other functionalities. We were pleased to observe that the reaction was also working with different substitution patterns in the aryl ring, affording the desired β-aminated nitro derivatives 5q–5s in remarkable enantioselective ranges (98–99\% ee). Absolute con-

**Text**

... enantioselective outcome...
Table 2. Substrate scope for 2-hydroxybenzophenones 1 and nitroolefins 2.[a]

| 1  | 2  | 3e (10 mol%) | CH₂Cl₂, rt, 3-22 h |
|----|----|-------------|--------------------|
| ![Aromatic substitution](image1) | ![Aromatic substitution](image2) | ![Aromatic substitution](image3) | ![Aromatic substitution](image4) |
| 5a | 98% yield | 99% ee |
| 5b | 95% yield | >99% ee |
| 5c | 97% yield | 99% ee |
| 5d | 90% yield | 99% ee |
| 5e | 97% yield | 99% ee |
| ![Heterocycles](image5) | ![Heterocycles](image6) | ![Heterocycles](image7) | ![Heterocycles](image8) |
| 5f | 98% yield | 99% ee |
| 5g | 94% yield | 99% ee |
| 5h | 82% yield | >99% ee |
| 5i | 75% yield | >99% ee |
| ![Aliphatic substitution](image9) | ![Aliphatic substitution](image10) | ![Aliphatic substitution](image11) | ![Aliphatic substitution](image12) |
| 5j | 80% yield | 94% ee |
| 5k | 65% yield | >99% ee |
| 5l | 95% yield | 98% ee |
| 5m | 94% yield | >99% ee |
| 5n | 96% yield | >99% ee |
| ![Ketimine substitution](image13) | ![Ketimine substitution](image14) | ![Ketimine substitution](image15) | ![Ketimine substitution](image16) |
| 5q | 97% yield | >99% ee |
| 5r | 75% yield | 98% ee |
| 5s | 98% yield | 98% ee |
| 5o | 90% yield | >99% ee |
| 5p | 92% yield | 5:1 d.r.: >99% ee |

[a] All the reactions were performed using 0.06 or 0.1 mmol of 1, 0.05 mmol of 2 and 10 mol% of organocatalyst 3e in CH₂Cl₂ (0.3 mL). ee (enantiomeric excess) and d.r. (diastereomeric ratio) were determined by chiral SFC and ¹H NMR, respectively. Isolated yield after flash chromatography.

[b] Reaction time 40 hours.
was preserved during the derivatization steps (see ESI).

**Conclusion**

In summary, we report that it is possible to \( N \)-functionalize a wide range of nitroolefins in an asymmetric fashion (up to >99% ee) thanks to the use of 2-hydroxybenzophenone imine as aminating reagent. Furthermore, this organocatalytic approach can be driven under flow conditions using acetone as solvent. Finally, we have shown that this methodology can be used for the formal synthesis of VNI, a

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**Scheme 3.** Batch (left) and flow (right) reaction setups for the addition of ketimine 1b to nitroalkenes 2.

**Scheme 4.** Formal synthesis of VNI and catalyst and chemical auxiliary recovery.
bioactive molecule, with excellent yield and enantioselectivity.

Experimental Section

General Procedure for the Synthesis of Products 5 under Batch Conditions

A dry vial equipped with a magnetic stirring bar was charged with organocatalyst 3e (10 mol%), the corresponding nitroolefin 2 (0.05 mmol, 1.0 equiv.), ketimine 1b (0.1 mmol, 2.0 equiv.) and organocatalyst 3e (10 mol%) were dissolved in acetonitrile (0.5 mL). The mixture was stirred at room temperature for the time indicated in each case (reaction was monitored by 1H NMR). Upon completion, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography to give product 5.

General Procedure for the Synthesis of Products 5 under Flow Conditions

The corresponding nitroalkene 2 (0.05 mmol, 1.0 equiv.), ketimine 1b (0.1 mmol, 2.0 equiv.) and organocatalyst 3e (10 mol%) were dissolved in acetonitrile (0.5 mL). The mixture was flowed through the coil reactor by pumping acetonitrile at 0.6 mL/min. The outcome was collected in a test tube, solvent was removed under reduced pressure and the crude was analyzed by 1H NMR. The residue was purified by flash column chromatography to give product 5.

For complete optimization studies, detailed experimental procedures for **aza-Michael adducts and formal synthesis**, along with characterization data of compounds, see Supporting Information.

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