

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.

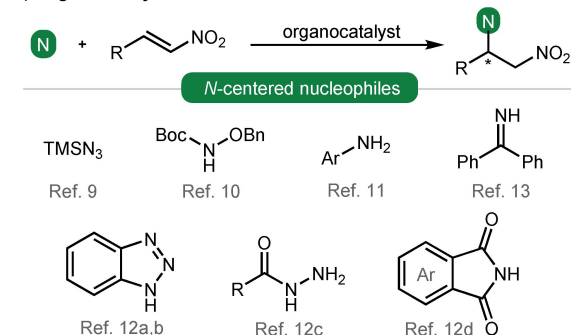
Keywords: Enantioselective; Organocatalysis; *aza*-Michael; 2-Hydroxybenzophenone; Flow system

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^[1] this requirement, gaining importance throughout the years.^[2] Especially, for the construction of C–N bonds,^[3] 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^[4–6] stand out as the most employed Michael acceptors dealing with enals and enones, and more recently also conjugated acids^[7] and esters.^[8]

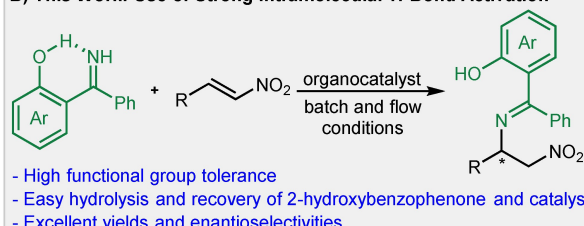
More specifically, the employment of nitroolefins as the electrophilic counterpart has attracted the

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,^[9] carbamates^[10] or even anilines,^[11] but harsh reaction conditions must be handled to obtain the free nitrogen atom. In addition, other nucleophilic aminating reagents, such as benzotriazoles,^[12a–b] hydrazines,^[12c] or phthalimide^[12d] 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.^[13] 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

A) Organocatalytic Enantioselective *aza*-Michael Addition to Nitroolefins

- Difficult transformation into free amine derivatives
- From moderate to good enantioselectivities
- Only batch conditions described

B) This Work: Use of Strong Intramolecular H-Bond Activation



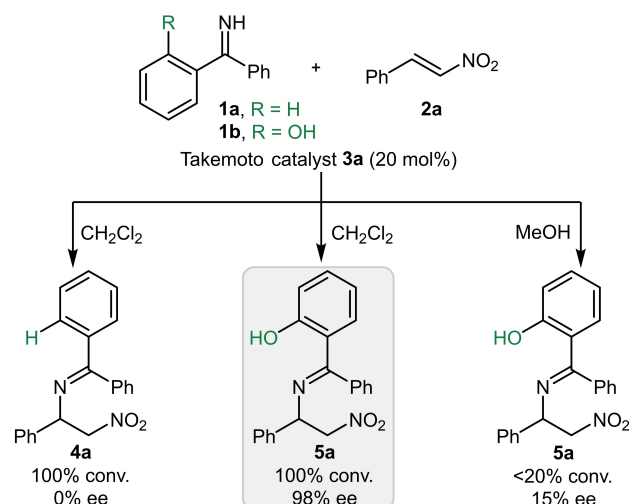
Scheme 1. General view of aminating reagents for enantioselective organocatalytic *aza*-Michael addition to nitroolefins and present work.

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^[14] 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 in the reactivity and selectivity of the process (Scheme 2). Under standard reaction conditions, using commercially available Takemoto'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



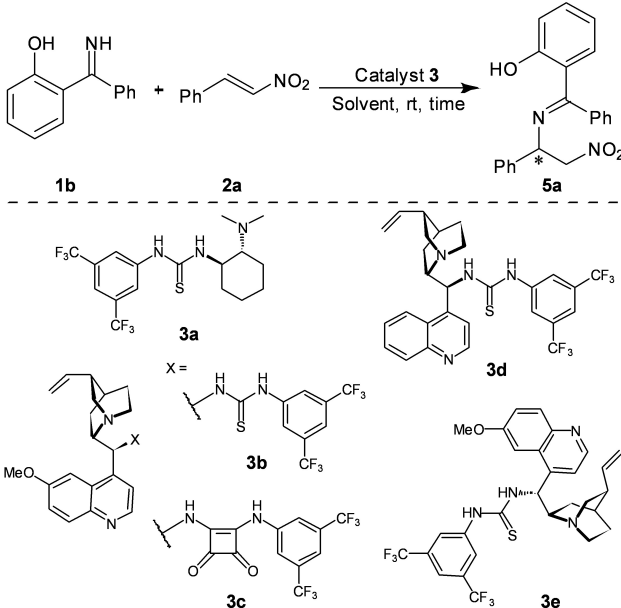
Scheme 2. Proof of concept for evaluating the role of the OH group at ketimine **1**. Conversions and enantiomeric excesses were determined by ¹H NMR spectroscopy and chiral Super-critical Fluid Chromatography (SFC), respectively.

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 Takemoto'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–5i**), 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 (%) ^[d]
1	3a (20)	CH ₂ Cl ₂	22	100(88) ^[c]	98
2	3b (20)	CH ₂ Cl ₂	22	100	−98
3	3c (20)	CH ₂ Cl ₂	22	100	95
4	3d (20)	CH ₂ Cl ₂	22	100	−97
5	3e (20)	CH ₂ Cl ₂	22	100	99
6	3e (20)	Acetone	22	66	95
7	3e (20)	Toluene	22	98	66
8	3e (20)	CH ₂ Cl ₂	3	100	99
9	3e (10)	CH ₂ Cl ₂	3	100(98) ^[c]	99
10	3e (5)	CH ₂ Cl ₂	3	100	98

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

^[b] Determined by ¹H 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).

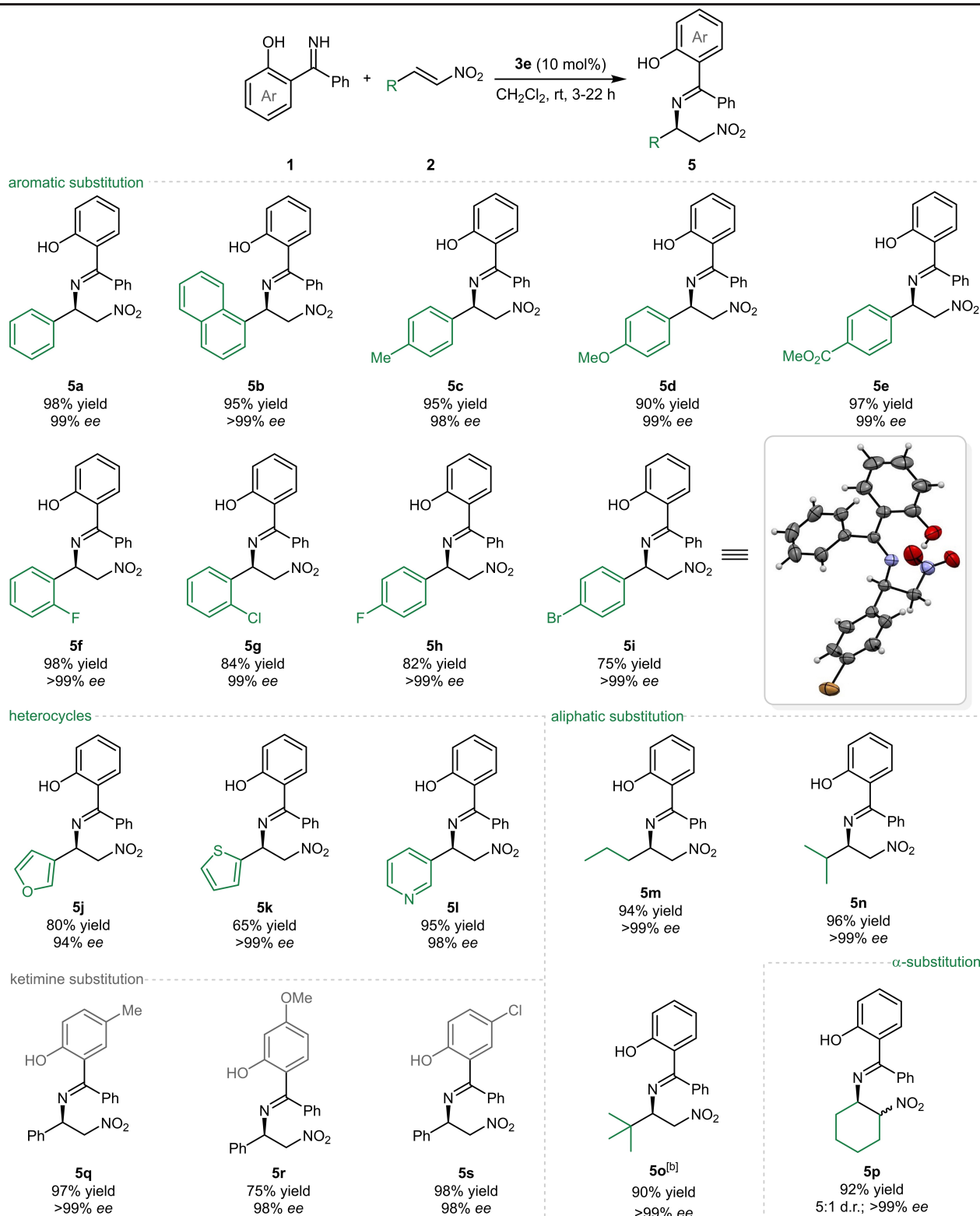
Encouraged by these findings, we assessed the scope regarding the ketimine scaffold bearing other functionalities. We were pleased to observe that the reaction was also working with different substitution patterns in the aryl ring, affording the desired β -aminated nitro derivatives **5q–5s** in remarkable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

figuration of **5i** was determined as the (*R*) enantiomer by X-ray diffraction analysis.^[15] We assumed the same stereochemical outcome for all the *aza*-Michael adducts.

Given the good results reached with this asymmetric methodology and the potential that it offers for organic synthesis, we next decided to drive the enantioselective *aza*-Michael addition using a more sustainable solvent. Thus, we tested the reaction with four representative nitroolefins in batch conditions using acetone (Scheme 3, left). In all cases, adducts **5a**, **5d**, **5h** and **5m** were achieved in moderate to good yields (57–96%) and high enantiomeric excesses (88–96% *ee*) after 20 hours. Considering the moderate yields obtained for some substrates (57–77%) in batch conditions, and the possibility of gaining about the use of a flow system.^[16] Therefore, a coil reactor (V = 18 mL) made of perfluoroalkoxy (PFA) capillary tube (1/8" OD; 1.60 mm ID, 9 m length) submerged in water (15 °C approximately for temperature control) was selected as flow setup. Screening of the reaction conditions (see table S2 in ESI for details) gave rise to **5a** in 100% conversion in just 30 minutes (92% yield and 93% *ee*). The robustness of the present C–N bond formation reaction was proved since compounds **5d**, **5h** and **5m** were sequentially obtained in short residence times (30 min–2 h) with full conversion and excellent results using this technique.

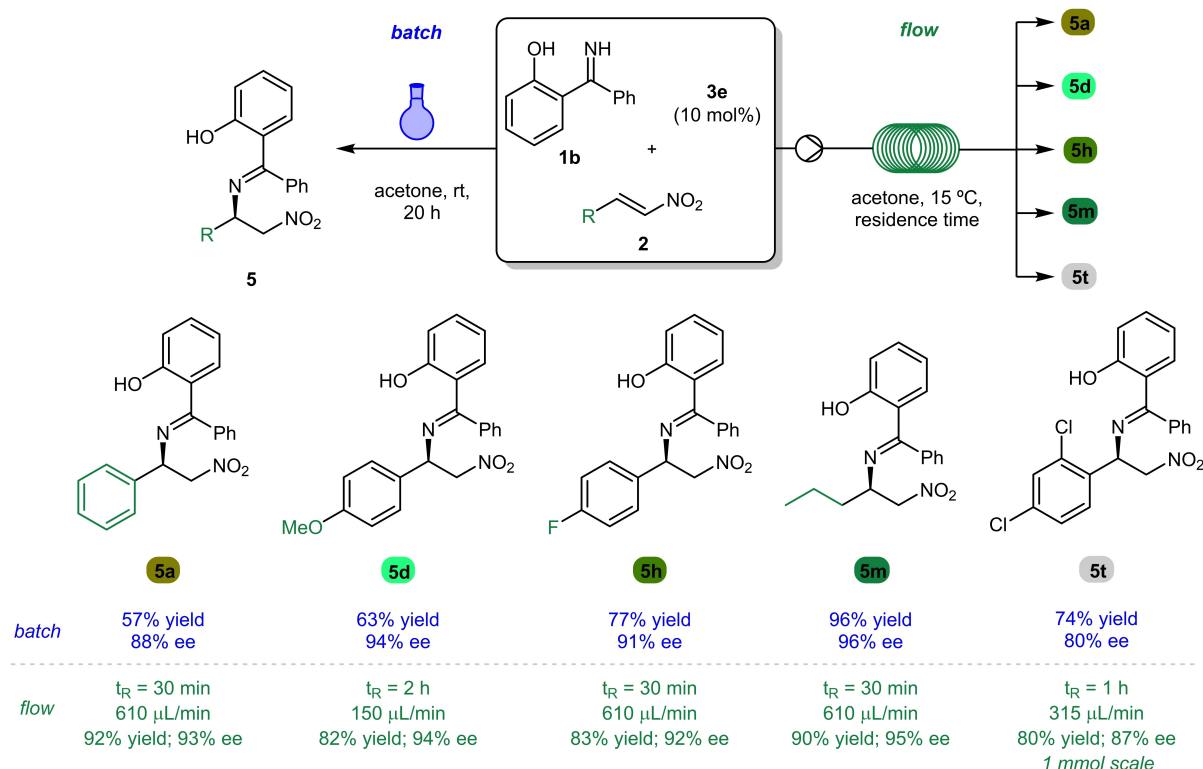
Lastly, in order to emphasize the fruitfulness of this methodology, we envisioned the formal synthesis of VNI, an equivalent to Posaconazole, a drug-like for the treatment of Chagas disease (Scheme 4).^[17]

First, to check the reactivity of the commercially available *trans*-2,4-dichloro- β -nitrostyrene (**2t**) under this organocatalytic approach, we carried out the reaction in batch using CH₂Cl₂ as solvent, achieving compound **5t** in 89% yield and 98% *ee*. Then, in order to increase the reaction scale and the use of a greener solvent (acetone), we performed the addition reaction in flow, affording **5t** in 80% yield and 87% *ee* after 1 hour residence time. In addition, we were also able to recover the catalyst **3e** in 85% yield after a percolate of the reaction crude. Then, adduct **5t** was subjected to hydrolysis conditions by treatment with aqueous HCl, affording the corresponding amine hydrochloride, which was directly protected as a Boc carbamate **6**. It should be noted that during the work-up of the hydrolysis reaction it was possible to recover a 90% of the 2-hydroxybenzophenone (**8**), the precursor of ketimine **1b**. The subsequent reduction of the nitro group under ordinary hydrogenation conditions using Ni₂B, generated *in situ* from NiCl₂ and NaBH₄, led to the amine **7**, which is the described intermediate in the literature for the synthesis of VNI. The *ee* values obtained indicate that the enantioselective outcome

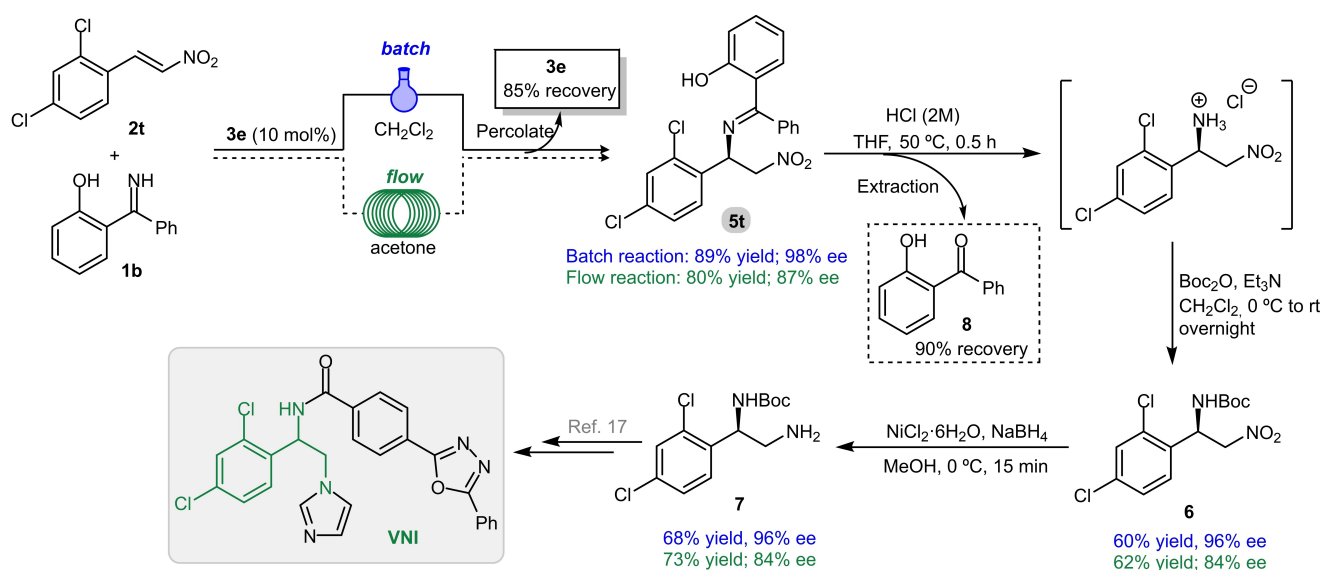
Table 2. Substrate scope for 2-hydroxybenzophenones **1** and nitroolefins **2**.^[a]

^[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.



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.

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

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 **1** (1.2 or 2.0 equiv., indicated in each case) and 0.3 mL of CH₂Cl₂. The resulting 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 residue 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 acetone (0.5 mL). The mixture was flowed through the coil reactor by pumping acetone 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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