Asymmetric Dearomative (3+2)-Cycloaddition Involving Nitro-Substituted Benzoheteroarenes under H-Bonding Catalysis †

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† Dedicated to Professor Janusz Jurczak on the occasion of his 80th birthday.
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Abstract: In our studies, the organocatalytic 1,3-dipolar cycloaddition between 2-nitrobenzofurans or 2-nitrobenzothiophene and N-2,2,2-trifluoroethyl-substituted isatin imines has been developed. The reaction has been realized by employing bifunctional organocatalysis, with the use of squaramide derivative being crucial for the stereochemical efficiency of the process. The usefulness of the cycloadducts obtained has been confirmed in selected transformations, including aromative and non-aromatic removal of the nitro group.

Keywords: organocatalysis; CADA reactions; dearomative (3+2)-cycloaddition; 2-nitrobenzofurans; azomethine ylides

1. Introduction

Catalytic asymmetric dearomatization (CADA) reactions constitute popular strategies for the synthesis of complex natural products, biologically active compounds, and pharmaceuticals from readily available aromatic molecules [1–10]. Despite their high synthetic potential, challenges related to the control of the regio- and stereo-selectivity of these processes, while overcoming the loss of aromaticity, still constitute an important issue.

CADA reactions are primarily focused on transformations involving structurally simple electron-rich arenes and heteroarenes, such as naphthols [11–18], phenols [19,20], indoles [21–24], and pyroles [25–28]. The application of (hetero)aromatic reactants as electrophilic counterparts in such strategies is much less common. Recently, a novel approach based on the application of (hetero)aromatic derivatives bearing a suitable electron-withdrawing substituent in their structure emerged as a useful strategy to reverse reactivity of these systems, thus expanding the synthetic potential of CADA transformations.

CADA reactions involving electron-deficient nitro(hetero)arenes, such as 2- or 3-nitroindoles [29–38], 2-nitrobenzofurans [37,39–44], and 2- or 3-nitrobenzothiophenes [39,40,43,45,46], have recently provided a direct route to highly substituted polycyclic compounds with multiple stereogenic centers. Due to the immense biological importance of benzo-fused units, the development of new approaches for the synthesis of these compounds is highly desirable. In this context, enantioselective dearomative annihilations involving nitro(hetero)arenes leading to nitrogen-containing heterocyclic compounds are in great demand. However, to the best of our knowledge, few literature reports describing the asymmetric dearomative (3+2)-cycloaddition of 2-nitrobenzofurans with azomethine ylides are available (Scheme 1). In 2019, Wang, Guo, and co-workers discovered the Cu(I)-catalyzed dearomative 1,3-dipolar cycloaddition for the construction of chiral tricyclic hydrobenzofurans for the first time (Scheme 1, eq. 1) [47]. Later, the same group developed...
a method for the preparation of chiral tropane derivatives via copper-catalyzed dearomative (3+2)-cycloaddition of 2-nitrobenzofurans and cyclic azomethine ylides (Scheme 1, eq. 2) [48]. Very recently, Wang et al. reported the dearomative cycloaddition for the stereoselective preparation of polycyclic benzofused tropane derivatives by employing bifunctional phosphonium salts as phase-transfer catalysts (Scheme 1, eq. 3) [49].

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\text{Gao: Cu(I)-catalyzed dearomative 1,3-dipolar cycloaddition}
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\text{Wang & Gao: dearomative (3 + 2)-cycloaddition catalyzed by a copper complex}
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\text{Wang: dearomative (3 + 2)-cycloaddition realized using PTC catalysis}
\]

\[
\text{This work:}
\]

Combining three structural motifs
One spiro-quaternary stereocenter
Three contiguous stereocenters

Excellent stereoselectivities
High efficiency
Broad substrate scope

Scheme 1. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2.

In continuation of our efforts on the development of asymmetric dearomative transformations [50–55], we became interested in CADA reactions involving electron-deficient heteroaromatic systems. Herein, we report the organocatalytic dearomative 1,3-dipolar cycloaddition between nitro-substituted benzoheteroarenes with azomethine ylides, as realized under bifunctional catalysis, yielding optically active pyrrolidine-fused spirocyclic dihydrobenzofuran and dihydrobenzothiophene derivatives bearing four contiguous stereocenters. In the context of our studies, it should be noted that a complementary approach involving bifunctional phase-transfer catalysis (PTC) was recently developed by Ren and Wang et al. [56].

2. Results and Discussion

2.1. Optimization Studies

Optimization studies were performed using 2-nitrobenzofuran 1a and N-2,2,2-trifluoroethyl-substituted isatin imine 2a as model reactants. Initially, quinine 4a was employed as a catalyst and the reaction was run in CDCl₃ for the ease of data processing (Table 1, entry 1). Pleasingly, the formation of desired 1,3-dipolar cycloadduct 3a was observed; however, low yield and diastereoselectivity were observed. Furthermore, chiral UPC² analysis of isolated product 3a showed that the reaction proceeded without induction of asymmetry. Therefore, various Brønsted base-type catalysts were evaluated to improve effectiveness and stereoselectivity of the process. Interestingly, the use of commercially available dimeric catalysts 4b or 4c provided a significant increase in conversion and diastereoselectivity (Table 1, entries 2–3). Moreover, when catalyst 4c was used, 3a was obtained with satisfactory enantioselectivity (Table 1, entry 3). Subsequently, the influence of bifunctional catalysts 4d–h on the studied transformation was examined.
and conversion and diastereoselectivity (Table 1, entries 2–3). Moreover, when catalyst used, the influence of bifunctional catalysts (Table 1, entries 5–8). Finally, catalyst used, (Table 1, entries 4–8). Performed experiments revealed that squaramide-based catalysts problem was eventually solved by the use of 1.5-fold excess of imine transformation, but a longer reaction time was required (Table 1, entry 16). However, imine mixture did not bring improvement in terms of yield or stereoselectivity of the formation of 2-nitrobenzofurane (Table 1, entry 8). Subsequently, screening of solvents was initiated (Table 1, entries 9–15). Unfortunately, the decrease in reactivity caused by poor substrate solubility or diminished stability was observed. Decrease in concentration of the reaction mixture did not bring improvement in terms of yield or stereoselectivity of the transformation, but a longer reaction time was required (Table 1, entry 16). However, imine degradation was observed as the consequence of prolonged reaction time. This problem was eventually solved by the use of 1.5-fold excess of 2a. This change resulted in almost full conversion of 2-nitrobenzofurane 1a, and 3a was obtained with excellent yield and stereoselectivity (Table 1, entry 17). In the hope of improving enantioselectivity, the reaction was performed at lower temperature but, disappointingly, without any enhancement of cycloadduct 3a enantiomeric ratio (Table 1, entry 18). Moreover, 20 mol% loading of the catalyst turned out to be crucial for completion of the reaction, as its lowering led to an inhibition of the process (Table 1, entry 19). Finally, it was found that the reaction proceeded with comparable results in freshly distilled chloroform (Table 1, entry 20). It is worth noting that the presented reaction was readily scalable to one-mmol scale, affording product 3a with a good outcome (Table 1, entry 21).

Table 1. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2—optimization studies [a].

| Cat. | Solvent | Conv. (Yield) [%] | dr | er |
|------|---------|------------------|----|----|
| 1    | 4a      | CDCl₃ 41 (39)    | 4:1 | 50:50 |
| 2    | 4b      | CDCl₃ 92 (88)    | >20:1 | 43:57 |
| 3    | 4c      | CDCl₃ >95 (90)   | >20:1 | 10:90 |
| 4    | 4d      | CDCl₃ >95 (88)   | >20:1 | 52:48 |
| 5    | 4e      | CDCl₃ 65 (58)    | >20:1 | 95:5  |
| 6    | 4f      | CDCl₃ 75 (69)    | >20:1 | 95:5  |
| 7    | 4g      | CDCl₃ 72 (68)    | >20:1 | 90:10 |
| 8    | 4h      | CDCl₃ 85 (78)    | >20:1 | 96:4  |
| 9    | 4h      | CH₂Cl₂ 76 (73)   | >20:1 | 93:7  |
Table 1. Cont.

| Cat. | Solvent | Conv. (Yield) [%] [b,c] | dr [b] | er [d] |
|------|---------|-------------------------|--------|--------|
| 10   | 4h      | DCE 52                  | >20:1  | n.d.   |
| 11   | 4h      | AcOEt 51                | >20:1  | n.d.   |
| 12   | 4h      | CH$_3$CN 25             | 5:1    | n.d.   |
| 13   | 4h      | Et$_2$O 49              | >20:1  | n.d.   |
| 14   | 4h      | THF 34                  | >20:1  | n.d.   |
| 15   | 4h      | PhCH$_3$ 70             | >20:1  | n.d.   |
| 16   | 4h      | CDCl$_3$ 73 (68)        | >20:1  | 93:7   |
| 17   | 4h      | CDCl$_3$ >95 (89)       | >20:1  | 96:4   |
| 18   | 4h [f,g]| CDCl$_3$ 85 (79)        | >20:1  | 95:5   |
| 19   | 4h [f,h]| CDCl$_3$ <10           | n.d.   | n.d.   |
| 20   | 4h [f,i]| CHCl$_3$ >95 (88)       | >20:1  | 95.5:4.5 |
| 21   | 4h [f,j]| CHCl$_3$ >95 (77)       | >20:1  | 95:5   |

[a] Reactions performed on a 0.05 mmol scale using 1a (1.0 equiv.), 2a (1.2 equiv.), and the catalyst 4 (20 mol%) in the corresponding solvent (0.1 mL) for 48 h at rt. [b] Determined by $^1$H NMR of a crude reaction mixture. [c] In parenthesis, isolated yields are given. [d] Determined by chiral UPC$^2$ analysis. [e] Reaction performed in 0.2 mL of the solvent for 96 h. [f] Imine 2a (1.5 equiv.) was used. [g] Reaction performed at 5°C for 96 h. [h] Catalyst (5 mol%) was used. [i] Freshly distilled over P$_2$O$_5$ chloroform was used as a solvent. [j] Reaction performed on 1 mmol scale. DCE—1,2-dichloroethane.

### 2.2. Scope Studies

With the optimized reaction conditions in hand, the scope of the reaction was evaluated. In the first step, structurally diversified dipole precursors 2a–k were tested in an organocatalytic process (Scheme 2). Imines 2a–c with different protecting groups at the nitrogen atom were well tolerated in the developed (3+2)-cycloaddition, providing products 3a–c in good yields and with excellent stereocontrol. Moreover, non-protected isatin-derived imine 2d worked well, giving access to 3d with similar results. It is worth noting that the developed reaction was unbiased towards the electronic properties of substituents in dipole precursors 2, as products with both electron-donating (2e, f) and electron-withdrawing groups (2g–j) were efficiently obtained in a highly stereoselective manner. Moreover, imine 2k with a double substitution pattern gave access to product 3k as a single diastereoisomer, in high yield but with diminished enantiocontrol.

In the next step, the scope of dipolarophiles 1 was examined (Scheme 3). 2-Nitrobenzofuranes 1b–f substituted in the 5-position with groups of different electron properties reacted smoothly in the developed cycloaddition, providing products 3l–p in high yields and with excellent stereoselection. Notably, the bulky tert-butyl group in 1d and the strongly electron-withdrawing nitro substituent in 1f were well tolerated, as demonstrated in the synthesis of 3n and 3p, where the desired reaction proceeded without any loss in enantioselectivity. Notably, cycloadduct 3q with the benzofuran ring functionalized in the 6-position was efficiently obtained following the developed method. Moreover, the substrate scope was further expanded by the use of 2-nitrobenzothiophene 1h. Surprisingly, the developed cycloaddition provided 3r in high yield but with poor enantiocontrol under standard conditions. Thankfully, short re-optimization studies revealed that thiourea catalyst 4d significantly enhanced the stereocontrol affording 3r with good enantioselectivity.
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Scheme 2. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2—scope studies.

Scheme 3. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2—scope studies.

2.3. Synthetic Utility of Products 3

With the scope studies accomplished, the usefulness of obtained products 3 was demonstrated in selected transformations (Scheme 4). Base-promoted nitro group removal gave access to spirocyclic compound 5 with aromatic benzofuran moiety. Furthermore, the reductive denitration of the starting material 3a was easily performed by utilization of tributyltin hydride and AIBN, providing dihydrobenzofuran 6 in high yield. Notably, the stereochemical composition of the starting material 3a was fully preserved in both cases, as products 5 and 6 were obtained as single diastereoisomers.
Scheme 4. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2—transformations.

2.4. Absolute Configuration Assignment and Mechanistic Considerations

The absolute configuration of product 3a was assigned by X-ray analysis (Scheme 5, top) [57]. The stereochemistry of products 3b–r was determined by analogy. The absolute stereochemistry allowed us to propose a plausible stereochemical model of the cycloaddition (Scheme 5, bottom). The reaction is initiated by two independent processes. The substrate 1 is activated and oriented by the hydrogen bonds of squaramide moiety of the catalyst 4h. Simultaneously, the quinuclidine moiety of the alkaloid catalyst deprotonates the N-2,2,2-trifluoroethyl-substituted isatin imine 2, leading to the formation of azomethine ylide 7. According to the proposed dual-activation model (3+2)-cycloaddition between 1 and 7 takes place providing 3 in a stereoselective manner.

Scheme 5. Asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2—mechanistic considerations.

3. Materials and Methods

3.1. General

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for $^1$H and 176 MHz for $^{13}$C, respectively. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals (CDCl$_3$: 7.26 ppm for $^1$H NMR, 77.16 ppm for $^{13}$C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization referenced to the mass of the charged species. Optical rotations were measured on a PerkinElmer 241 polarimeter and [a]$_D$ values are given in deg·cm$^{-1}$·g$^{-1}$·dm$^{-1}$, concentration c is listed in g·(100 mL)$^{-1}$. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or Hanessian’s stain. The enantiomeric ratio (er) of the products was determined by chiral stationary phase UPC$^5$ (Daicel Chiralpak IA column). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC), silica gel (60, 35–70 µm,
Merck KGaA, Darmstadt, Germany), 2-Nitrobenzofurans 1, 2-nitro-benzo[b]thiophene 1r, and imines 2 were obtained using literature procedures [58–60].

3.2. General Procedure for the Enantioselective Synthesis of 3

In an ordinary 4 mL glass vial equipped with a Teflon-coated magnetic stirring bar and screw cap, nitro-substituted benzoheteroarene 1 (1.0 equiv., 0.05 mmol), catalyst 4h (0.2 equiv., 0.01 mmol, 6.3 mg), and the corresponding imine 2 (1.5 equiv., 0.075 mmol) were dissolved in freshly distilled CHCl₃ (0.1 mL). The reaction mixture was stirred for the indicated time at ambient temperature. After full conversion of the starting material 1 (as confirmed by ¹H NMR of a crude reaction mixture), the reaction mixture was directly subjected to flash chromatography on silica gel to obtain pure products 3. The standard samples of products 3 for chiral UPC² separation studies were prepared using equimolar mixture of quinine and quinidine as catalyst (See Supplementary Materials).

3.3. Procedure for the Enantioselective Synthesis of 3a on a 1 mmol Scale

In an ordinary 12 mL glass vial equipped with a Teflon-coated magnetic stirring bar and screw cap, 2-nitrobenzofuran 1a (1.0 equiv., 1.0 mmol, 163 mg), catalyst 4h (0.2 equiv., 0.2 mmol, 126 mg), and corresponding imine 2a (1.5 equiv., 0.15 mmol, 363 mg) were dissolved in freshly distilled CHCl₃ (2 mL). The reaction mixture was stirred for 48 h at ambient temperature and was directly subjected to flash chromatography on silica gel (eluent: from hexanes/dichloromethane 1:1 to 100% dichloromethane) to obtain product 3a as a single diastereoisomer (>20:1, 95:5 er) in 77% yield (312.1 mg).

3.4. Procedure for the Diastereoselective Synthesis of 5

To a stirred solution of 3a (1.0 equiv., 0.128 mmol, 51 mg) in MeCN (1.5 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.0 equiv., 0.256 mmol, 39 mg) was added. The reaction mixture was stirred for 72 h at room temperature and subsequently purified by flash chromatography on silica gel (eluent hexanes/ethyl acetate 4:1) to obtain product 5 as single diastereoisomer (>20:1) in 75% yield (34.4 mg).

3.5. Procedure for the Diastereoselective Synthesis of 6

To a stirred solution of 3a (1.0 equiv., 0.05 mmol, 20.3 mg) in dry toluene (0.5 mL), tributyltin hydride (4.0 equiv., 0.2 mmol, 58 mg) and AIBN (2.0 equiv., 0.1 mmol, 16.4 mg) were added at room temperature. The reaction mixture was stirred for 3 h at 80 °C, cooled to room temperature, and CCl₄ (0.15 mL) was added dropwise. After stirring for 5 min, saturated KF aq. solution (10 mL) was added and resulting mixture was extracted with AcOEt (3 × 10 mL). Combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to obtain crude product, which was purified by flash chromatography on silica gel (eluent: hexanes/dichloromethane 1:1 to dichloromethane 100%) to obtain product 6 as single diastereoisomer (>20:1) in 68% yield (12.3 mg).

4. Conclusions

In conclusion, asymmetric dearomative (3+2)-cycloaddition between nitro-substituted benzoheteroarenes 1 and N-2,2,2-trifluoroethyl-substituted isatin imines 2 was developed. A squaramide-based cinchona alkaloid derivative efficiently promoted the reaction, ensuring high stereoselectivity of the process. Substrate specificity of the catalysts with regard to heteroaromatic framework was observed. Enantiomerically enriched products underwent chemoselective transformations that involved removal of the nitro group proceeding either with the concomitant aromatization of the heteroarene framework or in a non-aromatic manner.

Supplementary Materials: The following are available online. Characterization data for obtained products, X-ray data for product 3a, copies of ¹H and ¹³C NMR spectra, UPC² plots for the cycloaddition products 3.
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