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Bifunctional Organocatalysts and Brønsted Bases in Cooperative Catalysis for the Asymmetric [4 + 2] Cycloaddition of In Situ-Generated Dienes from Isochromane-3,4-Diones with Nitroalkenes

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Abstract: Herein, the first asymmetric Diels–Alder reaction involving in situ-generated dienes from readily available isochromane-3,4-diones is reported, using nitroalkenes as dienophilic counterparts. The reaction is catalyzed by a bifunctional thiourea-*epi*-quinine organocatalyst, cooperatively assisted by readily available Brønsted base cocatalysts. This strategy enables highly enantio- and exo-diastereo-selective [4 + 2] cycloaddition with a wide range of nitroalkenes, leading to the formation of valuable bridged lactones, a motif found in many natural products. The method applies not only to *β*-nitrostyrenes, but also to aliphatic nitroalkenes such as (nitromethylene) cyclohexane, leading to an unusual bridged spiro lactone. The reaction proceeds with complete regioselectivity, furnishing the products in high yields and achieving enantiomeric ratios (e.r.) ranging from 90:10 to 98:2. The use of Brønsted base as a cocatalyst not only enhances the turnover and promotes diene formation by vinylogous dienolization, leading to a higher yield in shorter reaction times, but also improves the enantioselectivity. In addition, follow-up reactivity is investigated, furnishing interesting novel bridged amino ester and tetraline motifs.

Keywords: asymmetric Diels–Alder, bridged compounds, heterocycles, lactones, organocatalysis

1. Introduction

The Diels–Alder (DA) reaction is one of the most versatile transformations in organic synthesis, owing to its broad applications to diverse dienes and dienophiles.[1] The enantioselective DA reaction is a well-established method for the asymmetric construction of multiple stereogenic carbon centers,[2] enabling the highly diastereo- and enantio-selective synthesis of a great number of complex cyclic molecules.[3] Consequently, the continued development of practical asymmetric DA reactions using readily available and valuable dienes and dienophiles remains essential for expanding their utility. Within our research interest in developing new synthetic methodologies,[4–7] in recent years, we have explored the reactivity of a rather overlooked lactone, 3-isochromanone, and its derivatives.[5–7] Our studies have determined the nucleophilicity of the generated carboanions in collaboration with Ofial's group[5] and have highlighted its easy functionalization and applicability under mild conditions in Michael reactions,[5] in [3 + 3] spiro-cyclization[6] and in [4 + 2] cycloadditions.[7] In particular, we reported for the first time a [4 + 2] cycloaddition involving an in situ-generated diene **2** promoted by Hunig's base from isochromane-3,4-dione **1**, in the presence of a wide range of electron-deficient dienophiles.[7] The broad scope, along with the mild basic conditions under which the transformation proceeds, suggests that this novel DA reaction holds significant potential for developing unprecedented asymmetric variants. Even though a few DA reactions of a different

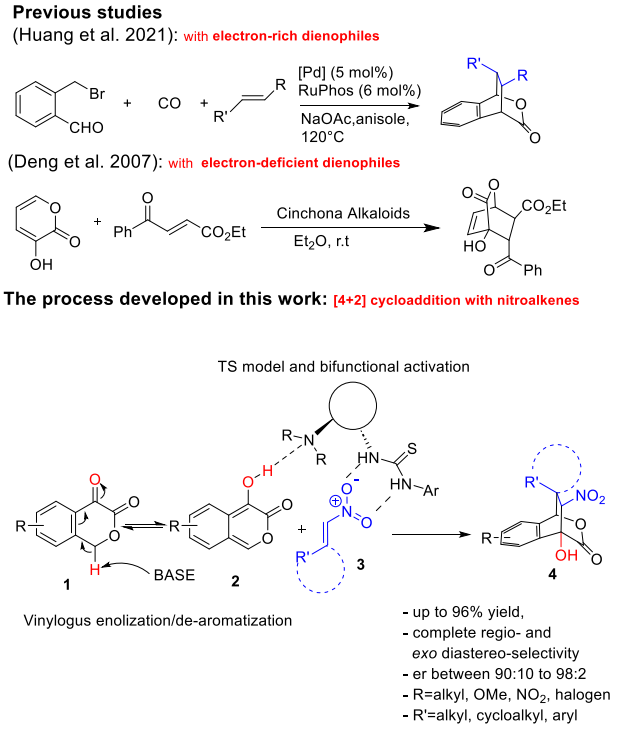
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isochromanone-derived diene have been reported (**Scheme 1**),[8] the harsh conditions required for in situ generation of the dienes prevented the development of asymmetric versions. Consequently, an enantioselective approach to these interesting polycyclic lactones, a motif found in several structurally complex natural products,[9] remains unexplored.

Over the past several years, pyrone-based DA reactions have been an invaluable tool to generate diverse heterocyclic compounds (Scheme 1), including structurally complex natural products (Scheme 1).[10,11] Even though 3-hydroxy-2-pyrones are already in diene form, they exhibit aromatic character according to Huckel's rule. The use of a base is essential to activate 3-hydroxy-2-pyrones, facilitating the DA reaction at an appropriate rate and preventing CO_2 elimination via the retro-DA reaction.[10b,h] On the other hand, vinylogous enolization of *ortho*-alkyl-substituted aromatic carbaldehydes is a challenging process because of the unfavorable loss of aromaticity.[12] Only a limited number of asymmetric methodologies are capable of generating highly reactive *ortho*-quinodimethane intermediates, which can be exploited in organocatalytic asymmetric transformations.[12]

In our study, the use of a base is crucial for dienol **2** formation by dearomatization of dione **1**,[7] and the DA is favored due to the reformation of the aromatic ring upon trapping with a dienophile. However, it remains unexplored whether the in situ-formed diene undergoes activation by chiral base to promote asymmetric DA reaction. Asymmetric DA reaction of **1** could be promoted by suitable chiral organocatalysts, according to the TS proposed in Scheme 1.[12–15] The formation of a dienol intermediate **2** suggests that a catalytic entity possessing both hydrogen-bond donors' and acceptors' groups could activate and enantioselectively orient the diene and the dienophile through multiple hydrogen bonding interactions. In the present study, we focused on nitroalkenes **3** as the dienophilic counterpart, since they can be engaged in strong hydrogen-bond interactions with organocatalysts,[12–15] as indicated in Scheme 1.

Based on these hypotheses, we wish to describe, for the first time, the development of an efficient asymmetric DA reaction, involving in situ-generated dienes **2** derived from readily available isochromane-3,4-dione **1** and nitroalkenes **3** as dienophiles, cooperatively catalyzed by cinchona alkaloid-derived bifunctional organocatalysts and Hunig's base.

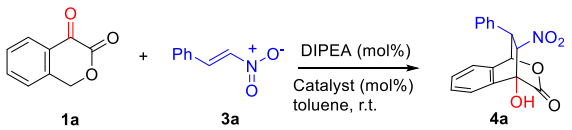


Scheme 1. Transition state (TS) model for asymmetric activation of DA reaction of **1** and previous studies.

2. Results and Discussion

Starting from the proposed TS hypothesis (Scheme 1), we investigated the reaction of the dione **1a** and *β*-nitrostyrene **3a** in the presence of different bifunctional organocatalysts (**Table 1** and **Figure 1**). Our initial

Table 1. Reaction analysis with different organocatalysts and conditions.



Entry[a]	Catalyst [mol%]	DIPEA [mol%]	Time [h or d]	Yield [%][b]	e.r.[c]
1	I (20)	–	82 h	62	91/9
2	I (20)	(20)	68 h	88	93/7
3	–	(20)	68 h	58	–
4	II (20)	(20)	60 h	76	53/47
5	III (20)	(20)	40 h	68	16/84
6	IV (20)	(20)	74 h	84	9/91
7	I (10)	(20)	72 h	84	93/7
8	I (5)	(20)	5 d	81	92/8
9	I (20)	(10)	69 h	78	92/8
10	I (10)	(10)	72 h	74	93/7
11[d]	I (10)	(20)	72 h	76	93/7
12[e]	I (10)	(20)	72 h	82	93/7
13[e]	IV (10)	(20)	96 h	71	9/91

[a] All the reactions were performed at [3a] = 0.25M.
[b] Isolated yield.
[c] Determined by HPLC on chiral stationary phase.
[d] 1.5 equiv. of dione used.
[e] Reaction performed on 1 mmol scale of 3a.

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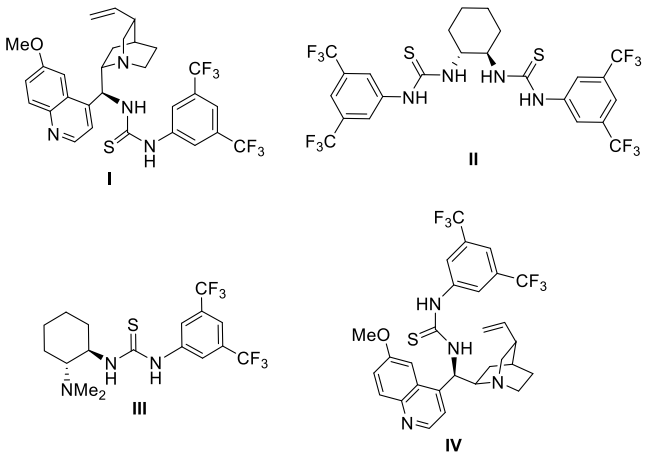


Figure 1. Some of the organocatalysts investigated in this work.

experiments focused on the use of 20 mol% of the readily available chiral bifunctional organocatalyst **I**,[13,14a–c] derived from quinine (Figure 1), using toluene as solvent (Table 1, entry 1). Encouragingly, the target product **4a** was obtained with complete regio- and diastereoselectivity and with a high enantiomeric ratio of 91:9. However, despite the relatively long reaction time, the yield remained moderate. Since we did not observe full conversion of the starting materials, we decided to evaluate the effect of a catalytic amount of Hunig's base (20 mol%) in combination with **I** to improve the turnover and favor the γ-deprotonation. Despite the possibility to promote an uncatalyzed achiral background reaction, under these new conditions, we observed a nearly complete conversion, along with an increase of both the enantioselectivity (93:7 e.r.) and the isolated yield (88%), in a shorter reaction time (Entry 2). The use of 20 mol% of Hunig's base only, under identical conditions, led to the product in a surprisingly good yield of 58% (Entry 3). This control experiment clearly indicates that the two catalysts cooperate rather than compete. In another control experiment, we used a chiral bis-thiourea **II**, derived from (*1R*,*2R*)-diaminocyclohexane and 20 mol% of the Hunig's base (Entry 4). Under these conditions, we observed the formation of the polycyclic product; however, enantioselectivity was nearly absent. This result highlights that a molecule with the attitude of forming only hydrogen-bond donor networks is not capable of the enantioselective orientation of the diene and the dienophile, even though the lactone's carbonyl group could serve as a hydrogen-bond acceptor. In contrast, Takemoto's catalyst **III**,[14d] which has the same chiral scaffold as **II**, led to the desired product with moderate yield and enantioselectivity (Entry 5). These findings clearly indicate that a bifunctional organocatalyst is essential for enantiofacial control of the reaction, as it coordinates both diene and dienophile in the TS. Hunig's base (DIPEA) influences both catalytic turnover and enantioselectivity, likely facilitating the deprotonation of compound **1**, thereby making the organocatalyst fully available for asymmetric induction in the transition state.[1]H NMR experiments in DMSO d_6, using equimolar amounts of **1** and DIPEA, revealed the appearance of additional peak at 6.20 ppm after 20 min (see Supporting Information for details). This signal closely matches that of 3-hydroxy-2-pyrone in its ^{1}H NMR spectrum.[11j] Based on these observations, we propose that the transformation proceeds via a concerted mechanism, analogous to the base-promoted DA reaction of 3-hydroxy-2-pyrones.[10h] This is consistent with the observed high exo-diastereo-selectivity and with the fact that no Michael-type intermediates were detected. Moreover, the reactions involving dimethyl maleate or fumarate in the presence of DIPEA,[7] which also proceed with complete diastereo-selectivity, further support a concerted pathway. Further studies are currently underway to elucidate the mechanistic details of this transformation.

Continuing the catalyst screening, the pseudo-enantiomer of **I**, the thiourea-*epi*-quinidine **IV**, provided the enantiomeric product *ent*-**4a** with a comparable level of enantioselectivity (Entry 6). Although the enantioselectivity has already reached a high level, we further explored different organocatalysts to investigate structure–activity relationships. All the data are reported for brevity in Table S1 and Figure S1 of the Supporting Information. Regarding the effect of the hydrogen-bond donor group, quinine **V** was not able to furnish high enantioselectivity (Entry S1), while squaramide-*epi*-quinine **VI** afforded the product in a slightly lower e.r. than **I** (Entry S2). Additionally, urea-*epi*-quinine catalyst **VII**, bearing a weaker hydrogen-bond donor group, resulted in a significantly lower enantioselectivity (Entry S3). Other Cinchona-derived organocatalysts, such as the thiourea-*epi*-hydroquinine **VIII** (Entry S4), provided lower enantioselectivity than **I**, highlighting that even a remote structural modification (ethyl vs. vinyl) can affect the catalyst performance, likely due to differences in solubility or conformational effects. A similar detrimental impact was observed by thiourea-*epi*-cinchonine **IX** (Entry S5), lacking a methoxy group on the quinoline compared to **IV**. Catalyst **X,** having the same chiral scaffold as Takamoto's, exhibited rather low enantioselectivity (Entry S6), while the camphor-derived squaramide **XI**[15c,d] led to moderate enantioselection and good yield (Entry S7).

We continued our analysis of the reaction conditions, evaluating the impact of the reaction temperature, medium concentration, use of different solvents, and Brønsted bases as cocatalysts, as well as varying catalysts and reagent amounts (Table 1 and Table S2 of the Supporting Information). Lowering the reaction temperature to 4 °C did not significantly affect the enantioselectivity, but reduced the yield (Table S2, Entry S1). Performing the reaction under more diluted or concentrated conditions led to slightly lower enantioselectivity

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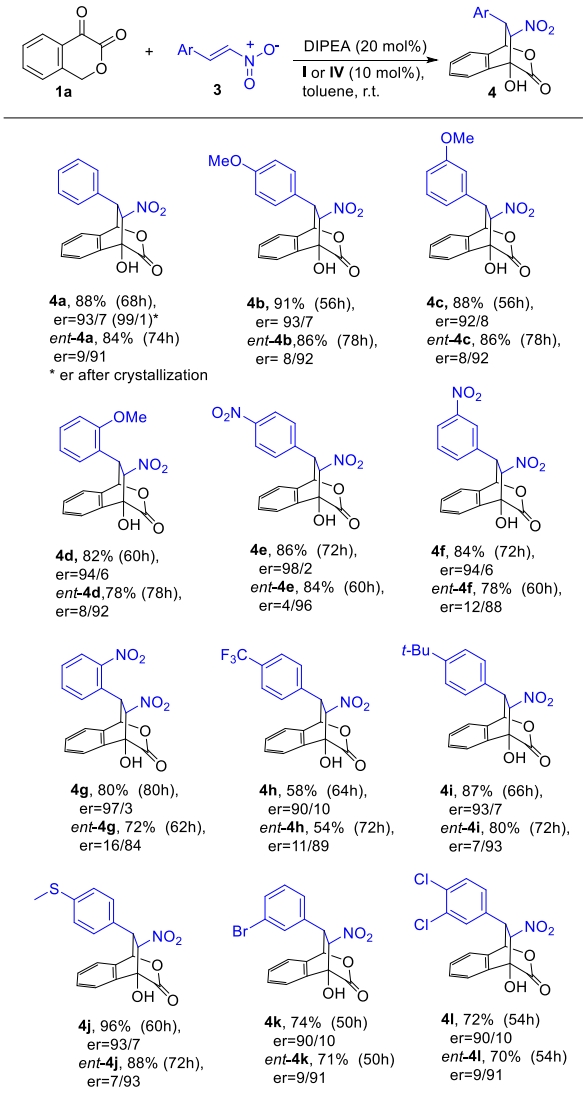
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(Entries S2 and S3). Solvent screening revealed that xylene and trifluorotoluene provided results comparable to toluene (Entries S4 and S5), while DCM and MTBE led to significantly lower enantiomeric ratios (Entries S6 and S7). Alternative bases were also tested, yielding the adduct with slightly lower enantioselectivity (Entries S8–10). Methyldicyclohexylamine and DABCO promoted the reaction in a shorter time, while NaOAc showed lower reactivity (Entry S10). The investigation of catalyst loading was more useful (Table 1). Reducing **I** from 20 to 10 mol% produced no significant difference (Entry 7), but a further decrease to 5 mol% led to an increase in the reaction time to achieve comparable conversion (Entry 8). The reaction was not affected by decreasing the amount of Hunig's base to 10 mol%, yielding similar outcomes with both using 20 and 10 mol% of **I** (Entries 9 and 10). It was possible to decrease the amount of the dione to 1.5 equiv. in the presence of 10 mol% of **I** (Entry 11), although a longer reaction time was required.

Under the best conditions, the reactions with both **I** and **IV** were scaled up to 1 mmol scale, leading to the same enantioselectivity and slightly lower yields (Entries 12 and 13). The used catalyst **I** was easily recovered by column chromatography in high yield and reused without a decrease in efficiency in terms of yield and enantioselectivity (see Supporting Information for further details). Notably, the enantiopurity of the adduct **4a** was further increased by a heterochiral crystallization process, during which the racemate selectively crystallized, allowing the enantioenriched product to be recovered from the solution with an excellent enantiomeric ratio of 99:1.

To explore the reaction scope (**Table 2–4**), different nitroalkenes and isochromane-3,4-diones with additional substituents on the aromatic rings were prepared and tested under the conditions of Entry 7 of Table 1. We opted to use 10 mol% of **I** and 20 mol% of the Hunig's base, as decreasing the catalyst's amount did not result in significant changes in reaction outcome. Instead of synthesizing racemates to obtain analytical standards of the adducts for HPLC analysis, we performed two parallel experiments using **I** and **IV**. This approach also enables us to systematically investigate if both enantiomers of the adducts can be obtained with comparable selectivity when using pseudo-enantiomeric catalysts, as observed with β-nitrostyrene. All the reactions were monitored by thin layer chromatography (TLC). We started to evaluate the effect of strong electron-withdrawing groups (EWG) and electron-donating groups (EDG) at various positions of the aromatic ring of the β-nitrostyrene, obtaining very high yields in all the cases (Table 2). We observed high enantioselectivity, comparable to that of β-nitrostyrene itself, when a methoxy group was present, regardless of its position on the aromatic ring (**4b–4d**). Both organocatalysts showed comparable efficiency. In the presence of a

Table 2. Analysis of the scope using nitrostyrenes.



nitro group, the enantioselectivity reached excellent values of 98:2 e.r. for *p*-nitro (**4e**), 94:6 for *m*-nitro (**4f**), and 97:3 for *o*-nitro derivative (**4g**) when **I** was used. In contrast, **IV** afforded the enantiomeric product in an almost comparable reverse ratio of 4:96 for *p*-nitro, but significantly lower values for *o*-nitro and *m*-nitro (16:84 and 12:88, respectively). Such differences between the catalysts have never been observed with any other substrates. In fact, the presence of an EWG like *p*-CF_3 (**4h**) as well as EDGs such as *p*-*t*Bu (**4i**) and *p*-SMe (**4j**) led to comparable high enantioselectivity. Similar levels of enantioselection were observed with the halogenated nitrostyrenes, yielding **4k** and **4l**.

Nitroalkenes bearing different substituents were also prepared and tested (Table 3). In all the cases, comparable high enantioselectivity with very good yields were achieved, as for **4m**, a substrate bearing a 2-furan ring or additional unsaturation derived from the condensation

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Table 3. Analysis of the scope using diverse nitroalkenes.

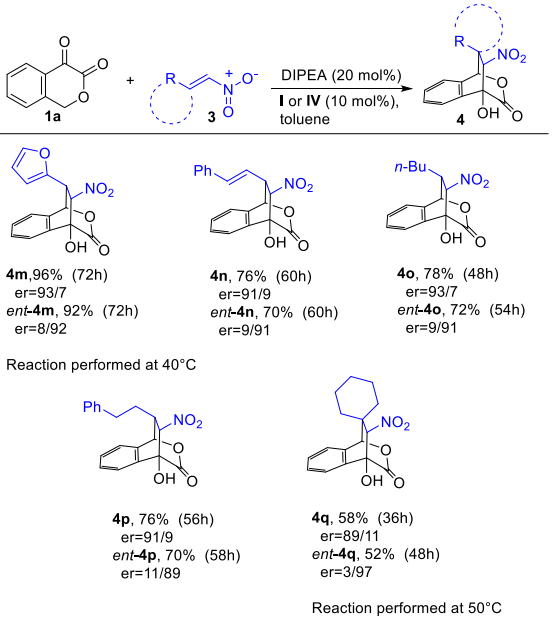
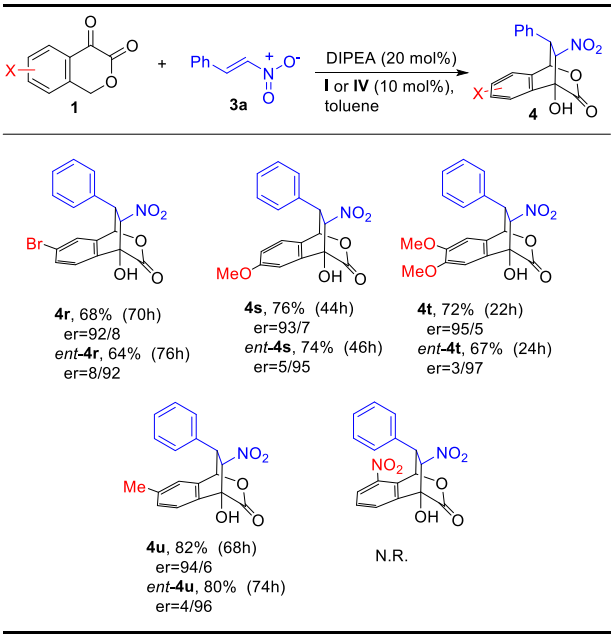


Table 4. Analysis of the scope using differently substituted diones.



of cinnamaldehyde with nitromethane (**4n**). Nitroalkenes with aliphatic substituents were also successfully reacted with a *n*-butyl chain (**4o**), or when an additional aromatic ring was not directly conjugated to the double bond (**4p**). Interestingly, sterically hindered trisubstituted alkene (nitromethylene)cyclohexene was also reacted, yielding an uncommon spiro-bridged lactone **4q** bearing two quaternary and tertiary stereocenters. To our knowledge, this type of alkenes has never been used in [4 + 2] cycloaddition, but only in Michael reactions.[16] To achieve satisfactory reactivity, the reactions for **4m** and **4q** were performed at 40 and 50 °C, respectively, without affecting the enantioselectivity in comparison to the observed trend.

Isochromane-3,4-diones further substituted at different positions on the aromatic ring, with derivatives bearing a 7-Br (**4r**) and a 6-OMe (**4s**), were also prepared and tested, leading to high enantiomeric ratios as well (Table 4). Notably, the 6,7-dimethoxy derivative (**4t**) exhibited excellent enantioselectivities with both **I** and **IV** (95:5 and 3:97 e.r., respectively). Also, the synthetically challenging dione bearing a 7-Me substituent was prepared (see Supporting Information for further details) and reacted, affording both **4u** and *ent*-**4u** in high yields and very high e.r. However, in the presence of a 5-NO_2 group we did not observe any reaction even in the high temperature probably because the HOMO lowering of the nitro group leads to inhibition of the reactivity of diene formed.

X-ray diffraction analysis on single crystals of **4g** confirmed the exo-selectivity and allowed to determine the absolute configuration (*1R,2S,3S,4S*), which was extended to all the other derivatives by analogy (**Figure 2**).

The availability of a high amount of the enantioenriched product **4a** (see Table 1, entry 12) gave the opportunity to investigate follow-up reactivity. Selective reduction of the nitro group was carried out in the presence of zinc and HCl,[17] affording the bridged amino lactone **5a** (**Scheme 2**). Analysis of the crude reaction mixture by ^{1}H NMR indicated the formation of a single major product along with some decomposition. We were able to fully characterize this compound, but it proved to be rather unstable. Therefore, we decided to protect the amine as *tert*-butoxycarbonyl (Boc) derivative, leading

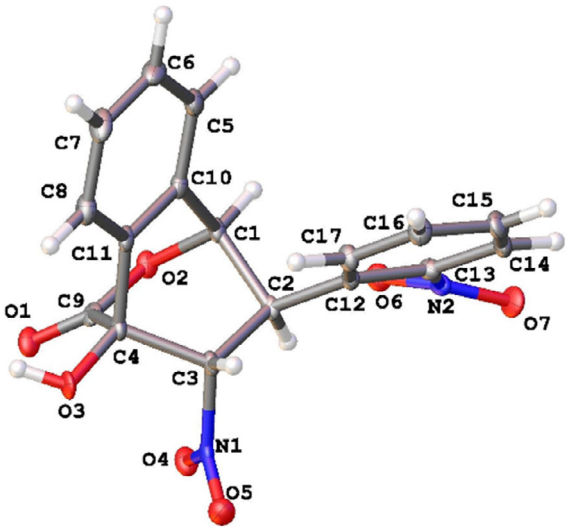
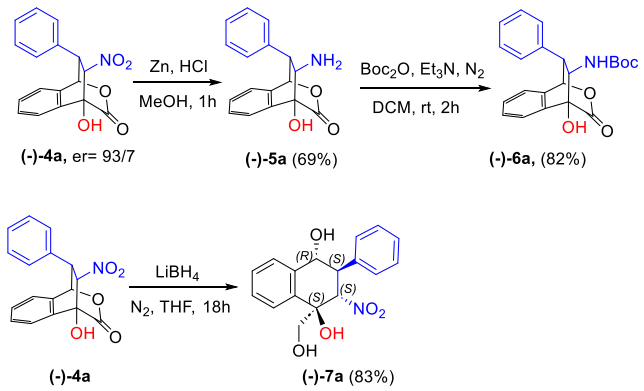


Figure 2. ORTEP diagram of (–)–**4g**. Crystals of (–)–**4g** were obtained by slow evaporation of a solution of **4g** (10 mg) in a diethyl ether/isopropanol mixture (1 mL, v/v = 1:4).

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Scheme 2. Follow-up reactivity investigation.

to **6a** in high yield. The sequence was also successfully applied for the synthesis of *ent*-**6a**, highlighting the reproducibility of the transformations (see Supporting Information for further details). Reductive ring opening of **4a** and *ent*-**4a** was then carried out in the presence of lithium borohydride ($LiBH_4$), furnishing the enantiomeric triol nitro-tetrahydronaphthols **7a** and *ent*-**7a**, showing a tetraline motif found in many bioactive and pharmaceutical compounds.[18] Also in this case, ^1H NMR analysis of the crudes suggested that no epimerization occurred. However, no further transformations were carried out. Based on these outcomes, we confidently assigned the absolute configurations as described in Scheme 2.

3. Conclusions

In conclusion, we have developed the first asymmetric DA reaction of in situ-generated dienes by vinylogous dienolization of readily available isochromane-3,4-diones, using nitroalkenes as dienophiles. The reaction is catalyzed by bifunctional thiourea-epi-quinine organocatalyst, cooperatively assisted by Hunig's base as a cocatalyst. This strategy enables highly enantio- and exo-diastereo-selective [4 + 2] cycloaddition with a wide range of nitroalkenes including not only *β*-nitrostyrenes, but also aliphatic nitroalkenes such as (nitromethylene) cyclohexane leading to an unprecedented bridged spiro lactone, achieving very high enantiomeric ratios (e.r.) in all the cases ranging from 90:10 to 98:2. The reaction proceeds with good to excellent yields and complete regioselectivity. Additionally, follow-up reactivity studies were conducted, highlighting the versatility of the obtained products.

4. Experimental Section

General Procedure for Asymmetric [4 + 2] Cycloaddition. Synthesis of (–)–4a: In a round-bottom flask equipped with a magnetic steer bar, isochromane-3,4-dione (**1a**) (32 mg, 0.2 mmol, 2 equiv.), the *trans*-β-nitrostyrene (**3a**) (15 mg, 0.1 mmol, 1 equiv.), and catalyst **I** (6 mg, 0.01 mmol, 0.1 equiv.) were dissolved in toluene (0.4 mL) at room temperature. DIPEA (3.48 µL, 0.02 mmol, 0.2 equiv.) was then added, and the resulting reaction was stirred at room temperature and monitored by TLC. After 72 h, the heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) to afford (–)–**4a** (27 mg, 88% yield, e.r. 93:7) as a white solid. $[\alpha]_D^{21} = -70.4$ ($c = 0.20$, $CHCl_3$).

Recrystallization of (–)–4a: Compound (–)–**4a** (7 mg, 0.075 mmol, e.r. 93:7) was dissolved in *n*-hexane (0.6 mL) and CH_2Cl_2 (0.2 mL) under reflux until full dissolution. The resulting solution was subjected to crystallization over a period of 24 h at –18 °C. The filtrate was evaporated under reduced pressure to afford enantiopure (–)–**4a** (4.3 mg, 62% yield, e.r. = 99:1) as an amorphous solid. $[\alpha]_D^{21} = -73.3$ ($c = 0.15$, $CHCl_3$).

Synthesis of (–)–5a (Scheme 2): To a solution of compound (–)–**4a** (31 mg, 1 equiv., 0.1 mmol) in methanol (500 µL) in a round-bottom flask were added zinc dust (32 mg, 4 equiv., 0.4 mmol) and 6M HCl (150 µL) at 0 °C. The mixture was stirred at room temperature for 40–45 min. Then, the mixture was treated with 1M NaOH until the pH reached 7 and extracted twice with ethyl acetate. Combined organic layers were then dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography on silica gel (chloroform/methanol 99:1 to chloroform/methanol 95:5) gave the product yield: 19 mg, 69% (an amorphous solid). $[\alpha]_D^{22} = -58.8$ ($c = 0.60$, $CHCl_3$).

Synthesis of (–)–6a: To a solution of compound (–)–**5a** (28 mg, 1 equiv., 0.1 mmol) and di-*tert*-butyl dicarbonate (24 mg, 1.1 equiv., 0.11 mmol) in dry DCM (500 µL) in a round-bottom flask which was stirred under a nitrogen atmosphere was added triethylamine (16 µL, 1.1 equiv., 0.11 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) to afford (–)–**6a** (31 mg, 82% yield) as a white solid. $[\alpha]_D^{21} = -77.0$ ($c = 0.20$, $CHCl_3$).

Synthesis of (–)–7a: $LiBH_4$ (0.3 mmol, 160 µL of 2M solution in THF, 3 equiv.) was added dropwise to a solution of (–)–**4a** (0.1 mmol, 31 mg, 1 equiv.) in the anhydrous THF (0.5 mL) under a nitrogen atmosphere at 0 °C for 1 h, and the reaction mixture was allowed to stir at room temperature overnight. Then, the mixture was diluted with water (100 µL) and 1 mL of MeOH and allowed to stir for 30 min. After evaporation of the solvent, the crude was directly purified by chromatography on silica gel (chloroform/methanol, 95:5 to chloroform/methanol, 90:10), affording a white solid. Overall yield = 83%, 26 mg, $[\alpha]_D^{21} = -60.3$ ($c = 0.45$, $CHCl_3$).

Deposition Numbers https://www.ccdc.cam.ac.UK/services/structures?id=doi:10.1002/cctc.2450095 for (–)–**4g**, 2450094 for *rac*-**4a**, contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe http://www.ccdc.cam.ac.UK/structures Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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