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Regioselective Asymmetric Formal (3+2) Cycloadditions of Nitrone Ylides from Isatins and Enals

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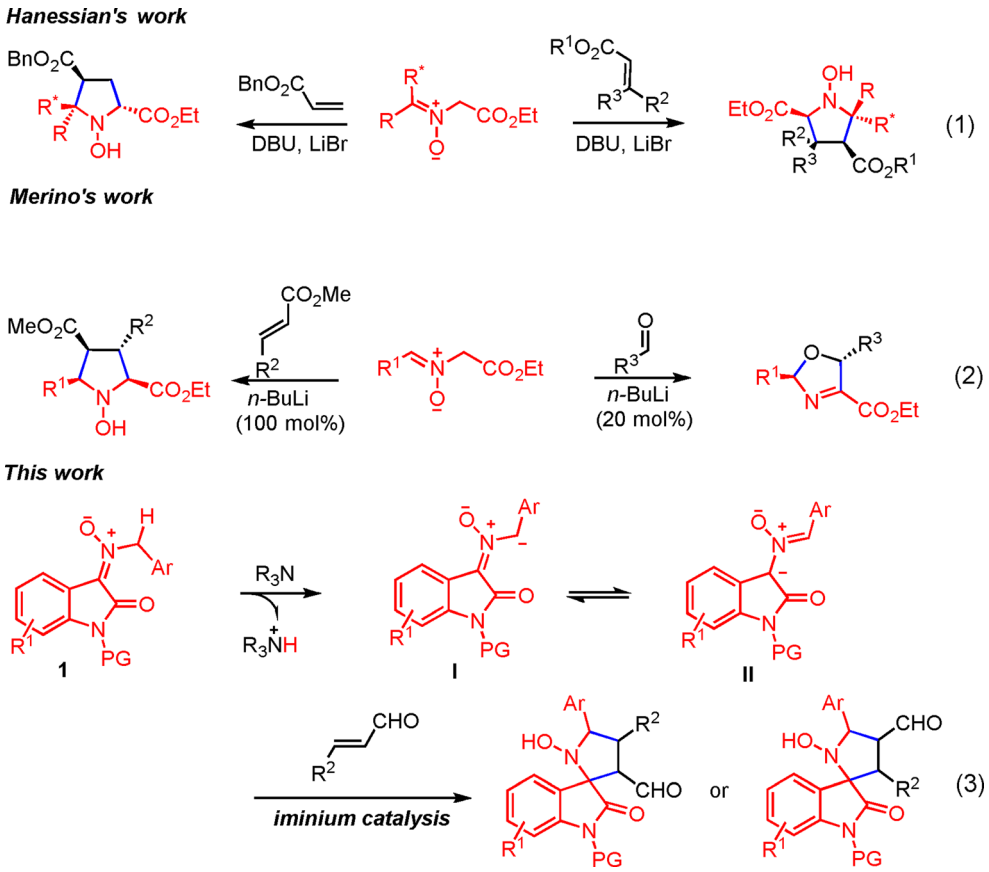
Abstract: A highly regio-, diastereo- and enantioselective formal (3+2) cycloaddition reaction of nitrone ylides from isatins and α,β-unsaturated aldehydes was developed *via* iminium catalysis in the presence of an additional base, furnishing a spectrum of 1′-hydroxy-3,2′-pyrrolidinylspirooxindole frameworks. Interestingly, the regioselectivity could be finely switched in the reactions between nitrone ylides and crotonaldehyde by adding catalytic amounts of lithium perchlorate and copper(II) bromide.

Keywords: cycloaddition reaction; iminium catalysis; nitrone ylides; regioselectivity; α,β-unsaturated aldehydes

Nitrone reagents are widely applied as 1,3-dipoles in concerted (3+2) dipolar cycloaddition reactions, given their ease of handling and the usefulness of the isoxazolidine products.[1] In addition, the C=N double bond in nitrones is a fundamentally electrophilic group in organic chemistry, which could be attacked by diverse nucleophiles, furnishing valuable N-hydroxy substances.[2] On the other hand, nitrones bearing a CH group adjacent to the N-atom can potentially be deprotonated owing to the electron-withdrawing effect of nitrone functionality, giving new different dipoles, nitrone ylides, which also can undergo (3+2) cycloadditions with electron-poor alkenes like those of the analogous azomethine ylides,[3] whereby polysubstituted 1-hydroxypyrrolidines will be produced. Nevertheless, this kind of transformation is much less exploited in spite of its potential synthetic utility. In 2002, the Hanessian group successively reported the (3+2) cycloadditions of nitrone ylides derived from ethyl *N*-hydroxyglycinate with electron-deficient alkenes in the presence of LiBr and DBU [Scheme 1, Eq. (1)].[4] Almost a decade later, the Merino group presented a complete study on the reaction of similar nitrone ylides with diverse activated alkenes, and a full theoretical investigation of the reaction mechanism favored a stepwise process.[5] Furthermore, aldehydes were applied to give 3-oxazolines in the presence of catalytic amounts of *n*-butyllithium [Scheme 1, Eq. (2)].[6] As a matter of fact, the current applicable nitrone ylides are limited to derivatives from *N*-hydroxyglycinates. Moreover, to the best of our knowledge, (3+2) cycloadditions with nitrone ylides in a catalytic asymmetric manner has rarely been explored.[7]

The oxindole skeleton is extensively witnessed in natural products and synthetic bioactive materials, and the reagents containing an oxindole motif also provoke continuing attention in organic synthesis.[8] We are interested in a readily available type of nitrone substances **1** between isatins and *N*-benzylhydroxylamines.[9] We envisaged that the acidity of the benzyl CH group would be significantly enhanced owing to the strong electron-withdrawing capacity of oxindole motif,[10] thus allowing the facile generation of nitrone ylide species **I** only under mild basic conditions. In addition, it is feasible that the umpolung nitrone ylide intermediates **II** would be formed through simple isomerization [Scheme 1, Eq. (3)].[11,12] As a result, switchable regioselective (3+2) cycloadditions with α,β-unsaturated aldehydes might be accomplished through the well-established chiral iminium catalysis.[13]

Consequently, we initially investigated the reaction between nitrone **1a** and cinnamaldehyde **2a** in toluene, by employing chiral amine[13c] **C1** and benzoic acid. However, no reaction occurred after 24 h at 40 °C (Table 1, entry 1). Gratifyingly, by replacing the acid with catalytic amounts of triethylamine, the desired (3+2) cycloaddition reaction proceeded smoothly without the aid of a Lewis acid,[4,5] giving two regioselective products **3a** and **4a** in a low ratio

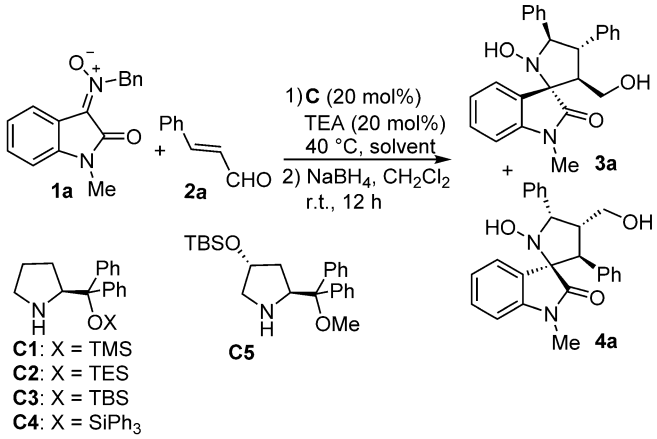


Scheme 1. Formal (3+2) cycloadditions of nitrone ylides.

after reduction with $NaBH_4$,[14] but with excellent diastereo- and enantioselectivity (major product **3a**, Table 1, entry 2). It should be noted that the direct (3+2) dipolar cycloaddition product of nitrone **1a** and enal **2a** has not been detected.[15] Moreover, the Michael addition adduct from nitrone ylide **I** and **2a** could be detected in the reaction, indicating that the current (3+2) cycloaddition also proceeded in a stepwise manner.[5,16] Subsequently, the solvent was found to have dramatic effect on the regioselectivity (Table 1, entries 3–6), and the product **3a** was produced exclusively in CH_3CN in high efficiency (Table 1, entry 6). On decreasing the catalyst loadings a longer time was required to achieve high conversion but with the retained selectivity (Table 1, entry 7). In addition, similar data were afforded by conducting the reaction at ambient temperature (Table 1, entry 8). A few chiral amine catalysts with bulkier groups were tested, whereby slightly inferior results were generally obtained (Table 1, entry 9–12).

With the optimized catalytic conditions in hand, we then investigated a variety of nitrone substrates from isatins and α,β-unsaturated aldehydes under the catalysis of amine **C1** (20 mol%) and TEA (20 mol%) in CH_3CN at 40 °C. The results are summarized in Table 2. In general, good to excellent regioselectivity was observed for the tested reactions, and the corresponding spirooxindoles could be directly isolated as pure isomers after reduction. At first, a spectrum of nitrones derived from isatins and diverse *N*-arylmethyl- or heteroarylmethyl-hydroxylamines was explored in the reactions with cinnamaldehyde **2a**, and products **3a–3j** were obtained in moderate to high yields with outstanding enantioselectivity (Table 2, entries 1–10). Unfortunately, nitrones with simple *N*-alkyl or *N*-allyl groups exhibited no reactivity.[18] Similar good results were afforded by nitrones from variously substituted isatins and *N*-benzylhydroxylamine (Table 2, entries 11–14). In addition, α,β-unsaturated aldehydes bearing diverse β-aryl or β-heteroaryl groups could be well tolerated in the reactions with nitrone **1a** (Table 2, entries 15–19). Both 2-pentenal and 4-methyl-2-pentenal could deliver the corresponding products in excellent regioselectivity (Table 2, entries 20 and 21); nevertheless, poor regioselectivity was observed for the reactions with crotonaldehyde and 2-hexenal, while excellent enantioselectivity was obtained for both regioisomers (Table 2, entries 22 and 23). An *N*-MOM-protected nitrone substrate also gave the product **3x** in good results (Table 2, entry 24). A nitrone derived from isatins and *N*-hydroxyglycinates was also explored, smoothly

Table 1. Screening studies on the formal (3+2) cycloaddition of nitrone **1a** and cinnamaldehyde **2a**.[a]



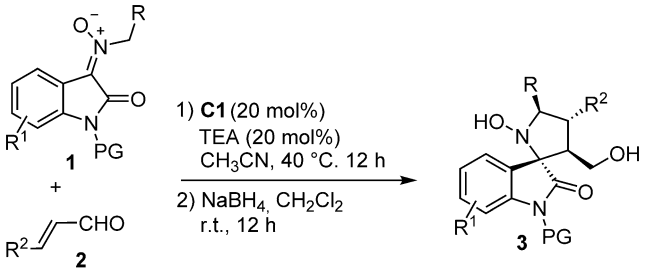
Entry	Cat.	Solvent	*t* [h]	Yield[b] [%]	**3a**/**4a**[c]	*ee*[d] [%]
1	**C1**	toluene	24	–	–	–
2	**C1**	toluene	24	80	3:1	95
3	**C1**	CH_2Cl_2	24	72	5:1	95
4	**C1**	$CHCl_3$	24	77	6:1	94
5	**C1**	THF	24	91	9:1	98
6	**C1**	**CH_3CN**	**4**	**87**	**>19:1**	**98**
7[e]	**C1**	CH_3CN	13	85	>19:1	96
8[f]	**C1**	CH_3CN	13	88	>19:1	97
9	**C2**	CH_3CN	6	85	>19:1	98
10	**C3**	CH_3CN	10	80	>19:1	97
11	**C4**	CH_3CN	12	84	>19:1	94
12	**C5**	CH_3CN	10	70	>19:1	95

[a] *Reaction conditions:* **1a** (0.05 mmol), **2a** (0.06 mmol), catalyst (20 mol%), and TEA (20 mol%) in solvent (0.5 mL) at 40 °C. Then the products were reduced with $NaBH_4$.
[b] Combined yield of isolated isomers for two steps.
[c] Determined by ^1H NMR analysis of crude mixture.
[d] Determined by HPLC analysis on a chiral stationary phase for **3a**.
[e] With 10 mol% of **C1**.
[f] At room temperature.

giving the corresponding product **3y** in good outcome (Table 2, entry 25). Finally, the reaction of **1a** and **2a** was tested at a gram scale, and a moderate yield with retained stereocontrol was observed after 24 h (Table 2, entry 26). It should be noted that poor reactivity was observed for the nitrone used by the Merino group.[18]

Subsequently, we turned our attention to the potentially switchable formal cycloaddition reaction *via* nitrone ylide **II**.[19] While all attempts were unsatisfactory for the reaction of nitrone **1a** and cinnamaldehyde **2a**,[18] we selected crotonaldehyde **2b** as the electrophile since regioisomer **4v** was apparently generated under the previously used conditions. We screened an array of Lewis acids (Table 3, entries 1–5), and found that the combination of $LiClO_4$ (20 mol%) and small

Table 2. Substrate scope and limitations.[a]

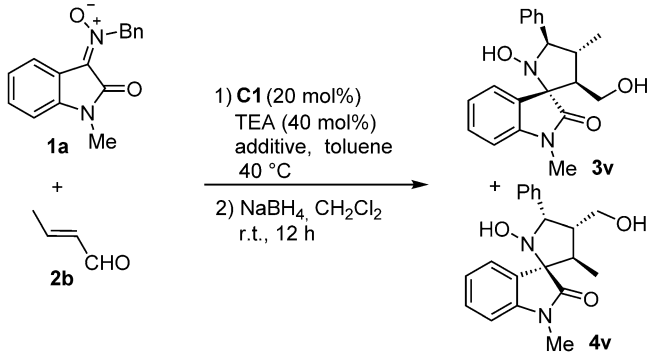


Entry	R, R^1	R^2	Yield[b] [%]	*ee*[c] [%]
1	Ph, H	Ph	**3a**, 90	98[d]
2	4-MeC_6H_4, H	Ph	**3b**, 85	98
3	4-$MeOC_6H_4$, H	Ph	**3c**, 80	97
4	4-ClC_6H_4, H	Ph	**3d**, 81	95
5	2-BrC_6H_4, H	Ph	**3e**, 82	96
6	3-BrC_6H_4, H	Ph	**3f**, 85	92
7	4-$CF_3C_6H_4$, H	Ph	**3g**, 73	97
8	1-naphthyl, H	Ph	**3h**, 71	92
9	3-furyl, H	Ph	**3i**, 71	89
10	2-thienyl, H	Ph	**3j**, 87	90
11	Ph, 5-Cl	Ph	**3k**, 80	97
12	Ph, 5-Br	Ph	**3l**, 69	95
13	Ph, 6-Br	Ph	**3m**, 72	92
14	Ph, 5-MeO	Ph	**3n**, 68	97
15	Ph, H	3-ClC_6H_4	**3o**, 80	94
16	Ph, H	4-BrC_6H_4	**3p**, 75	93
17	Ph, H	3-MeC_6H_4	**3q**, 75	96
18	Ph, H	3-$MeOC_6H_4$	**3r**, 81	96
19	Ph, H	2-furyl	**3s**, 83	96
20	Ph, H	Et	**3t**, 87	99
21	Ph, H	*i*-Pr	**3u**, 83	98
22[e]	Ph, H	Me	**3v**, 55 (27)	98 (98)
23[e]	Ph, H	*n*-Pr	**3w**, 45 (38)	98 (98)[d]
24[f]	Ph, H	Ph	**3x**, 76	97
25	CO_2Et, H	Ph	**3y**, 75	93
26[g]	Ph, H	Ph	**3a**, 69	97

[a] *Reaction conditions:* **1** (0.15 mmol, PG = Me), **2** (0.18 mmol), amine **C1** (20 mol%) and TEA (20 mol%) in CH_3CN (1.5 mL) at 40 °C. Then the products were reduced with $NaBH_4$.
[b] Isolated yield of **3** for two steps.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] The absolute configuration of **3a** and **4w** was determined by X-ray analysis.[17] The other products were assigned by analogy.
[e] Data in parentheses referred to the isolated regioisomers **4**.
[f] PG = MOM.
[g] With 3.76 mmol (1.0 g) of **1a**, for 24 h.

amounts of $CuBr_2$ (0.3 mol%) could dramatically switch the regioselectivity, delivering the desired product **4v** in high regio- and enantioselectivity (Table 3, entry 5). It should be noted that the amount of $CuBr_2$ was crucial for the reaction, as the inferior results were observed with lower or higher loadings

Table 3. Screening studies on switchable formal (3+2) cycloaddition of nitrone **1a** and crotonaldehyde **2b**.[a]



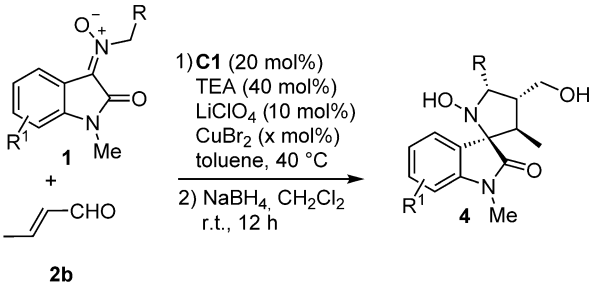
Entry	Additive (mol%)	*t* [h]	Yield[b] [%]	**3v**/**4v**[c]	*ee*[d] [%]
1	$LiClO_4$ (20)	30	73	1:1.6	ND[e]
2	$LiBF_4$ (20)	36	69	1:1.4	ND
3	LiBr (20)	72	ND	ND	ND
4	$CuBr_2$ (20)	72	ND	ND	ND
5	$LiClO_4$ (20) $CuBr_2$ (0.3)	32	71	1:11	92
6	$LiClO_4$ (20) $CuBr_2$ (0.1)	48	73	1:2	ND
7	$LiClO_4$ (20) $CuBr_2$ (0.5)	34	68	1:8	92
8	$LiClO_4$ (20) $CuCl_2$ (0.3)	60	63	1:3	95
9	$LiClO_4$ (20) $Cu(OAc)_2$ (0.3)	28	74	1:9	94
10	$LiClO_4$ (20) $Zn(OAc)_2$ (0.3)	26	72	1:2	97
11	**$LiClO_4$ (10) $CuBr_2$ (0.3)**	**32**	**70**	**1:11**	**94**

[a] *Reaction conditions:* **1a** (0.05 mmol), **2b** (0.1 mmol), amine **C1** (20 mol%), and TEA (40 mol%) and additive in toluene (0.5 mL) at 40 °C. Then the products were reduced with $NaBH_4$.
[b] Combined yield of isolated isomers for two steps.
[c] Determined by ^1H NMR analysis of crude mixture.
[d] Determined by HPLC analysis on a chiral stationary phase for **4v**.
[e] ND = not determined.

of $CuBr_2$ (Table 3, entries 6 and 7). Poorer results were obtained when other Cu(II) and Zn(II) salts were used (Table 3, entries 8–10). In addition, similar results could be achieved by decreasing the loadings of $LiClO_4$ (Table 3, entry 11).

As a result, a few nitrones **1** were explored in the reactions with crontonaldehyde **2b** under the optimized catalytic conditions. The results are summarized in Table 4. The loadings of $CuBr_2$ had to be slightly modified to give optimal regioselectivity in most cases, while good to high ratios could be generally obtained (Table 4, entries 1–7). The asymmetric cycloaddition reaction of nitrone **1a** with crotonaldehyde **2b** still proceeded smoothly at a gram scale, albeit slightly decreased yields and stereoselectivity were obtained (Table 4, entry 8). Unfortunately, a nitrone with an *N*-CH_2CO_2Et group showed poor reactivity in the reaction with crotonaldehyde. In addition, poor regioselectivity or reactivity was observed when other enals were applied.[18]

Table 4. Substrate scope and limitations of switchable formal (3+2) cycloadditions of nitrones **1** and crotonaldehyde **2b**.[a]

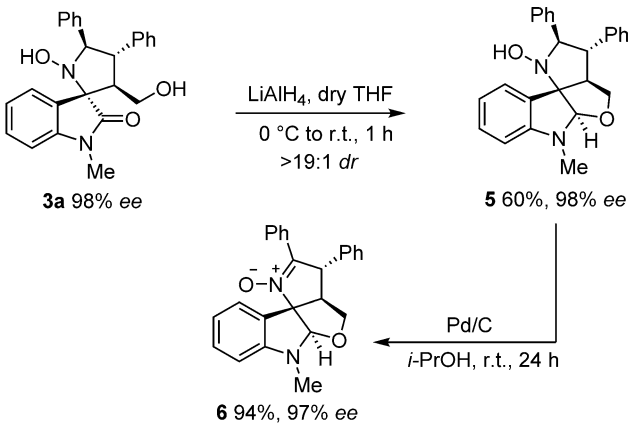


Entry	*x*	R, R^1	*t* [h]	**3**/**4**[b]	Yield[c] [%]	*ee*[d] [%]
1	0.3	Ph, H	32	1:11	**4v**, 64	94
2	0.5	4-ClC_6H_4, H	21	1:12	**4z**, 65	93
3	1.0	3-BrC_6H_4, H	25	1:7	**4a′**, 56	96
4	0.5	1-naphthyl, H	72	1:15	**4b′**, 56	86
5	0.3	3-furyl, H	22	1:11	**4c′**, 63	95
6	0.5	Ph, 5-Cl	22	1:7	**4d′**, 58	95
7	0.8	Ph, 5-OMe	22	1:12	**4e′**, 60	94
8[e]	0.3	Ph, H	72	1:8	**4v**, 51	92

[a] *Reaction conditions:* **1** (0.15 mmol), **2b** (0.3 mmol), amine **C1** (20 mol%), TEA (40 mol%), $LiClO_4$ (10 mol%) and $CuBr_2$ (*x* mol%) in toluene (1.5 mL) at 40 °C. Then the products were reduced with $NaBH_4$.
[b] Determined by ^1H NMR analysis of crude mixture.
[c] Yield of the isolated isomer **4** for two steps.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] With 3.76 mmol (1.0 g) of **1a**.

In addition, the cycloaddition product **3a** could be diastereoselectively converted to the fused tetrahydrofuro[2,3-*b*]indole **5**[20] in moderate yield with retained *ee* value. Interestingly, by treatment with 10% Pd/C, product **5** could be readily dehydrogenated to a new nitrone substance **6** in an excellent yield (Scheme 2). Unfortunately, attempts to reduce the hydroxylamino group of **3a** to give the corresponding pyrrolidine derivative failed, probably due to the steric hindrance.[18]

In conclusion, we have explored the asymmetric and regioselective formal (3+2) cycloadditions of nitrones from isatins and α,β-unsaturated aldehydes through the *in situ* formation of nitrone ylides under mild basic conditions. The substrate scope was generally substantial, and a spectrum of highly enantioenriched 1′-hydroxy-3,2′-pyrrolidinylspiro-oxindoles was constructed in moderate to good yields by employing



Scheme 2. Synthetic transformations of product **3a**.

the well-established iminium catalysis. Moreover, the regioselectivity could be finely switched by simply adding suitable metal salts when crotonaldehyde was used as the electrophile. Additional studies with such readily generated nitrone ylide species are under investigation.

Experimental Section

General Procedure for Asymmetric Formal (3+2) Cycloaddition of 1 and 2

A solution of nitrone **1** (0.15 mmol), enal **2** (0.18 mmol), triethylamine (0.03 mmol) and secondary amine catalyst **C1** (0.03 mmol) in MeCN (1.5 mL) was stirred at 40 °C for 12 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was directly dissolved in CH_2Cl_2 (1.5 mL). Then $NaBH_4$ (0.45 mmol) was added in one portion, and the mixture was stirred at ambient temperature for 12 h. After completion (monitored by TLC), the reaction was quenched with water and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated. The resulting crude product was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate (7:1 to 4:1) to afford the product **3**.

General Procedure for Switchable Formal (3+2) Cycloaddition of 1 and 2b

A solution of nitrone **1** (0.15 mmol), crotonaldehyde **2b** (0.3 mmol), triethylamine (0.06 mmol), secondary amine catalyst **C1** (0.03 mmol), $LiClO_4$ (0.015 mmol) and $CuBr_2$ (x mmol) in toluene (1.5 mL) was stirred at 40 °C. After completion (monitored by TLC), the solvent was removed under reduced pressure and the residue was directly dissolved in CH_2Cl_2 (1.5 mL). Then $NaBH_4$ (0.45 mmol) was added in one portion, and the mixture was stirred at room temperature for 12 h. After completion (monitored by TLC), the reaction was quenched with water and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated. The resulting crude product was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1 to 3:1) to afford the product **4**.

Acknowledgements

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[7] Only very limited examples of the (3+2) cycloadditions with nitrone ylides in a catalytic asymmetric manner were reported recently, but with very low *ee* values (up to 10% *ee*). See ref.[6]

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[9] Nitrones **1** were easily obtained as stable *E*-isomers. See the Supporting Information for details.

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[14] The aldehyde intermediate also could be isolated as a configurationally stable compound. See the Supporting Information for details.

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[16] A stepwise mechanistic proposal is provided in the Supporting Information.

[17] CCDC 1503539 (**3a**) and CCDC 1503540 (**4w**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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