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The highly enantioselective 1,3-dipolar cycloaddition of alkyl glyoxylate-derived nitrones to *E*-crotonaldehyde catalyzed by hybrid diamines

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ABSTRACT

1,3-Dipolar cycloaddition of alkyl glyoxylate-derived nitrones to *E*-crotonaldehyde can be catalyzed by hybrid diamines, obtained from (*S*)-BINAM and L-α-amino acids. The hybrid of (*S*)-BINAM and L-Phe was found to be the best organocatalyst. Products were obtained in good yield and diastereoselectivity as well as high enantioselectivity (82–91% ee). Subsequent transformations into functionalized pyrrolidinones have been demonstrated.

1,3-Dipolar cycloaddition (1,3-DC) of nitrones to alkenes provides isoxazolidines,[1] which are useful precursors for interesting heterocyclic products. The general utility of an asymmetric variant of this reaction has been demonstrated by syntheses of many optically active products.[2] Enantioselective protocols for 1,3-DC involving the use of metal complexes have been widely explored with limited levels of success.[3]

The use of chiral secondary amines as organocatalysts for this type of 1,3-DC reaction with α,β-unsaturated aldehydes is one of the most promising synthetic strategies to have emerged recently.[4] However, most reports concerning such organocatalyzed 1,3-DC, including our earlier paper,[5] describe reactions of aromatic nitrones, especially benzaldehyde or naphthaldehyde derivatives.

Therefore, in this study, we focused our attention on asymmetric 1,3-DC of alkyl glyoxylate-derived nitrones to *E*-crotonaldehyde. The possibility of ester group introduction into the isoxazolidine product allows further synthetic manipulations. Thus, glyoxylate nitrones were successfully applied as substrates for the diastereoselective synthesis of, for example, alkaloids, amino acids, and aminosugars.[2] To our knowledge, only two examples of enantioselective protocols for such substrates have been described.[6,7] The reaction of *t*-butyl glyoxylate nitrone (**1e**) with allyl alcohol catalyzed by a chiral zinc complex, leading to an isoxazolidine product (68%, 92% ee), was reported by Inomata's group.[6] Jørgensen and co-workers[7] reported the first inverse electron demand 1,3-DC of glyoxylate nitrones to vinyl ethers catalyzed by a chiral bisoxazoline–copper complex, however, only two examples of high enantioselectivity were observed.

Herein we report the first highly enantioselective organocatalytic 1,3-DC of glyoxylate-derived nitrones **1a–j** to *E*-crotonaldehyde (**2**) (Scheme 1). We initially investigated the reaction of **2** with *N*-benzyl-α-ethoxycarbonylmethanimine *N*-oxide (**1b**) as a model process to test our catalysts: commercially available MacMillan's imidazolidinone **C1**,[4a] and three hybrid diamines **C2–C4** obtained by us.[8] In the presence of **C1**, a nearly equimolar mixture of diastereomeric products **3b**[9] + **4b** was obtained in low yield (Table 1, entry 1). After reduction, the corresponding 3,4-*trans*-alcohol[10] was isolated with 58% ee. Since catalyst **C1** was inefficient in this case, we investigated the chiral salts of amines **C2–C4** (entries 2–4).

These salts were recently developed by us and used as efficient catalysts for the 1,3-DC of aromatic nitrones to α,β-unsaturated aldehydes.[5] We envisioned that the increased rigidity and bulkiness of our catalysts might lead to improved stereocontrol of the reaction. Among the salts tested, **C2***TfOH gave the best results in terms of yield and stereoselectivity. Under optimized conditions,[5] the mixture of products **3b + 4b** was obtained in 80% yield, in a 3.8:1 ratio, and 90% ee of the major diastereomer **3b** (entry 2). Next, we investigated the scope of the 1,3-DC reaction with nitrones of type **1**. As shown in Table 2, this reaction worked especially well for primary ester derived nitrones (entries 1, 2, and 4). Usually, enantiocontrol over 85% ee was observed. The best results were obtained for benzylic glyoxylate-derived nitrones (entries 7–10).

The presence of a substituent on the benzyl ring affected neither the stereoselectivity nor the yield of the reaction. The results

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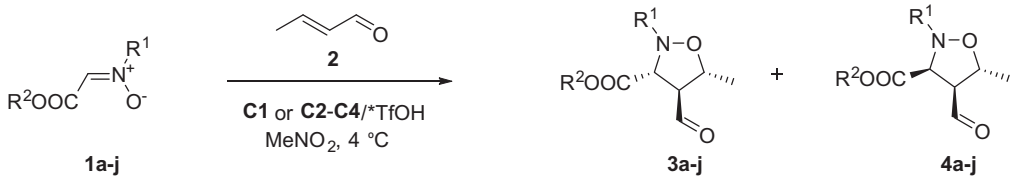
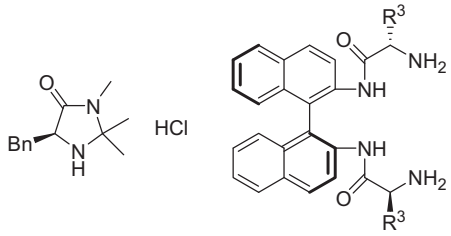


a: R^1=Bn, R^2=Me, **b**: R^1=Bn, R^2=Et, **c**: R^1=Bn, R^2=*i*-Pr, **d**: R^1=Bn, R^2=*n*-Bu, **e**: R^1=Bn, R^2=*t*-Bu, **f**: R^1=Bn, R^2=Cy, **g**: R^1=Bn, R^2=Bn, **h**: R^1=Bn, R^2=PMB, **i**: R^1=Bn, R^2=4-NO_2Bn, **j**: R^1=Me, R^2=Bn

Scheme 1.

Table 1
Screening of the catalysts in the model 1,3-DC reaction of **1b** with **2**[a]



C1

C2, R^3=Bn
C3, R^3=Me
C4, R^3=*i*-Bu

Entry[a]	Catalyst[b]	Yield[c] (%)	**3b**:**4b**[d]	ee (%) of **3**[e]
1	**C1**	20	1.5:1	58
2	**C2**	80	3.8:1	90
3	**C3**	82	1:1	60
4	**C4**	79	1:1	45

[a] The reactions were carried out on 0.25 mmol scale for 72 h.
[b] Except for **C1** (20 mol %), 10 mol % of the catalysts **C2**–**C4** in the presence of 9 mol % of TfOH were applied.
[c] Isolated combined yield of **3b** and **4b**.
[d] Determined after ^{1}H NMR analysis of the crude reaction mixture.
[e] Determined after reduction of the carbonyl group to the corresponding alcohol and HPLC analysis using chiral columns.

Table 2
Scope of glyoxylate nitrones **1** in the 1,3-DC reaction with **2** catalyzed by 10 mol % of **C2** in the presence of 9 mol % of TfOH[a]

Entry[a]	Product	Yield[b] (%)	Ratio of **3**:**4**[c]	ee (%) of **3**[d]
1	**3a**/**4a**	49	2.5:1	82
2	**3b**/**4b**	80	3.8:1	90
3	**3c**/**4c**	64	1:1	91
4	**3d**/**4d**	75	4.6:1	87
5	**3e**/**4e**	70	7:1	87
6	**3f**/**4f**	69	5.6:1	86
7	**3g**/**4g**	77	8.5:1	90
8	**3h**/**4h**	79	9.5:1	89
9	**3i**/**4i**	90	9.9:1	90
10	**3j**/**4j**	58[e]	6.6:1	88

[a] The reactions were carried out on 0.25 mmol scale for 72 h.
[b] Isolated combined yield of **3** and **4**.
[c] Determined after ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined after reduction of the carbonyl group to the corresponding alcohol and HPLC analysis using chiral columns.
[e] Isolated as the corresponding 3,4-*trans*-alcohol.

obtained with *t*-butyl nitrone **1e** were promising, but purification of the product by chromatography on silica gel was difficult. Only in the case of *i*-propyl glyoxylate nitrone **1c** were the results significantly worse in terms of diastereocontrol and yield (entry 3), although a drop in yield and enantioselectivity was also observed for the smallest methyl ester **1a** (entry 1). We believe that some of the lower yields may be explained by ester group lability under the acidic conditions of the reaction. In all examples, after reduction of the carbonyl group, the major diastereomer of the corresponding alcohol could be isolated in pure form *via* chromatography.

The configurations of products **3**, being 3,4-*trans*, 4,5-*trans* were deduced from their ^{1}H NMR spectra and confirmed by X-ray crystallographic analysis of compounds **3b** and **3g**, performed on their *N*-tosylhydrazones. From the same X-ray analyses, we determined the absolute configurations of these two compounds as (3*R*,4*S*,5*R*). The ORTEP projection of the *N*-tosylhydrazone of **3b** is shown in Figure 1.

Our earlier experiments on the influence of the acid additive suggest an iminium ion as a catalytic intermediate.[5] Moreover, the ^{1}H NMR spectra of catalyst **C2**, recorded in the presence of increasing amounts of TfOH, show an upfield shift of the amide proton (Δ ~0.2 ppm, 0.5 equiv TfOH), indicating an internal hydrogen-bonding interaction between the amide and trifluoromethanesulfonic acid. Analogously, the amine proton was shifted downfield (Δ ~0.5 ppm, 0.5 equiv TfOH), being consistent with ammonium salt formation. When the **C2***TfOH salt solution in nitromethane was treated with crotonaldehyde **2**, the mixture turned dark-red within a few minutes. This observation is also consistent with the possibility of the formation of a conjugated iminium ion.

As we did not succeed in growing crystals of catalyst **C2** or its salt that were suitable for X-ray crystallographic analysis, we performed other experiments to assess further the influence of the stereogenic elements of the catalyst on its activity. We have shown that only the *S* configuration of the binaphthyl moiety, combined with an L-amino acid, led to enhanced stereoselectivity.[5] To

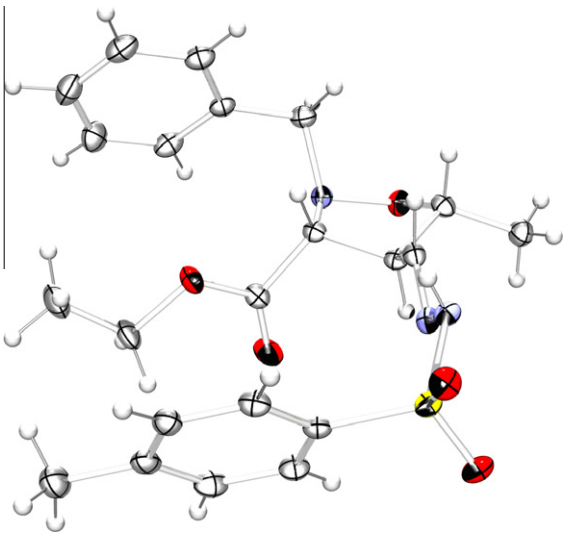


Figure 1. ORTEP projection of the *N*-tosylhydrazone of **3b**.

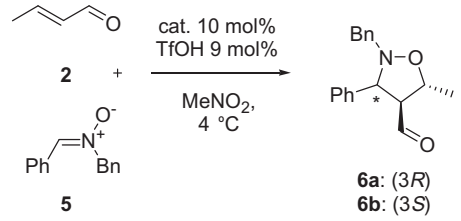
compare the influence of both axial chirality and the stereogenic center, we reinvestigated the reaction of aromatic nitrone **5** with *E*-crotonaldehyde (**2**), performed in the presence of two non-hybrid analogs of **C2**: (*S*)-BINAM glycine diamide **C6** and biphenyl L-Phe diamide **C7** (Table 3, entries 2 and 3). We also performed the same reaction in the presence of L-Phe methyl ester hydrochloride **C5** (entry 1). The selectivity for both **C5** and **C6** was low, indicating that none of the different stereogenic elements themselves were responsible for the high level of asymmetric induction. However, the biphenyl diamide produced the *endo* adduct **6a** in good yield and stereoselectivity: 84% yield, 3.8:1 dr, and 81% ee. This result confirms that the presence of both amino acid units is important for high asymmetric induction but, when combined with the axially chiral binaphthyl moiety, leads to increased diastero- and enantiocontrol.

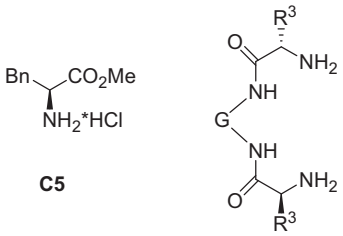
Cycloadduct **3b** was chosen for further studies toward synthetic applications of the obtained isoxazolidines. We envisioned that changing the carbonyl group at C-4 to an amine functionality and subsequent cleavage of the N–O bond of the starting isoxazolidine might lead to the formation of a new γ-lactam ring 2-pyrrolidinone derivative. Such cleavage is known to be facile, for example, by catalytic hydrogenation. A similar strategy for lactam formation was applied by Brandi et al.[11] for the synthesis of alkaloids.

The 2-pyrrolidinone moiety is present in many natural products,[12] compounds of medicinal interest,[13] and peptidomimetic building blocks.[14] Stereoselective synthesis of these compounds often requires multi-step procedures. Thus, development of new efficient methods for their enantioselective synthesis represents an attractive target.[15]

First, to demonstrate the preparative utility of our methodology, we performed the reaction of **1b** with **2** (Scheme 1), using a lower loading (5 mol %) of catalyst **C2** (with 4.5 mol % of TfOH). Diastereomerically pure **3b** was isolated in 65% yield and 87% ee. Thus, the enantioselectivity was only slightly affected by reducing the catalyst amount. Next, we converted **3b** into the corresponding amine by reductive amination with NH_4OAc and subjected it to catalytic hydrogenation. However, after consumption of the starting material, analysis of the reaction mixture showed only decomposition products.

Table 3
Comparison of the catalysts **C5**–**C7** and **C2** in the 1,3-DC reaction of **5** with **2**





C6, G=(*S*)-1,1-binaphth-2,2'-yl, R^3=H
C7, G=1,1'-biphen-2,2'-yl, R^3=Bn

Entry[a]	Catalyst[b]	Yield[c] (%)	**6a**:**6b**[d]	ee (%) of **6a**[e]
1	**C5**	78	1:1.3	23
2	**C6**	59	1:2	5
3	**C7**	84	3.8:1	81
4	**C2**	75	7:1	92[5]

[a] The reactions were carried out on 0.25 mmol scale for 72 h.
[b] Except for **C5** (10 mol %), 10 mol % of the catalysts **C2**, **C6**, and **C7** in the presence of 9 mol % of TfOH were used.
[c] Isolated combined yield of **6a** and **6b**.
[d] Determined after ^1H NMR analysis of the crude reaction mixture.
[e] Determined after reduction of the carbonyl group to the corresponding alcohol and HPLC analysis using chiral columns.

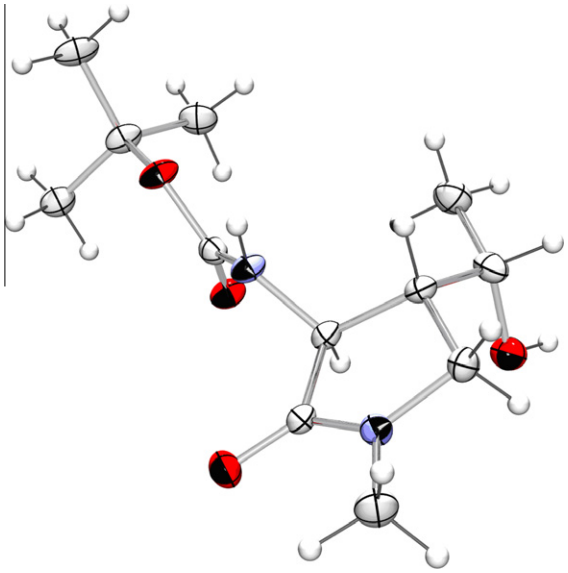
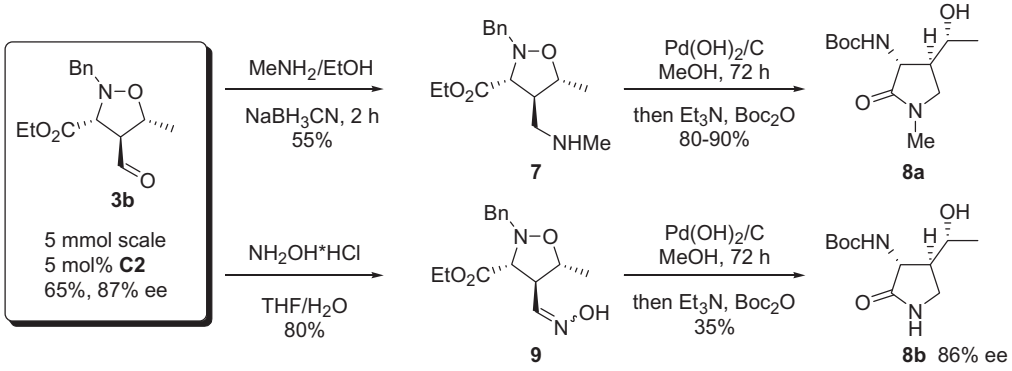


Figure 2. ORTEP projection of *N*-Me pyrrolidinone **8a**.



Scheme 2.

Since the intermediate amine seemed to be unstable, we decided instead to subject the corresponding oxime **9** to catalytic hydrogenation. This time, the *N*-Boc protected 2-pyrrolidinone **8b**[16] was isolated in 28% yield over three-steps (Scheme 2).

Next, we wanted to test the strategy with other substituted amines. When we subjected *N*-Me amine **7** to catalytic hydrogenation, the yield of the crucial γ-lactam formation step was in the range of 80–90%, and pyrrolidinone **8a**[17] was isolated in 50% yield over three-steps, as shown in Scheme 2. After recrystallization, compound **8a** was analyzed by X-ray crystallographic analysis and its relative configuration was confirmed (Fig. 2).

In conclusion, we have developed the first organocatalytic enantioselective reaction of alkyl glyoxylate-derived nitrones with *E*-crotonaldehyde.[18] The reaction is effective with organocatalyst loadings as low as 5 mol %. Enantioselectivities of up to 91% ee were observed. We also demonstrated the application of the obtained cycloadduct **3b** in short and simple syntheses of functionalized 2-pyrrolidinones.

Acknowledgment

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Crystallographic data (excluding structure factors) for the structures in this paper: *N*-tosylhydrazones of **3b** (CCDC 796643) and **3g** (CCDC 796644) and compound **8a** (CCDC 796645) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].

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9. *(3R,4S,5R)-2-Benzyl-3-ethoxycarbonyl-4-formyl-5-methylisoxazolidine* (**3b**): colorless oil, $[\alpha]_D = +50.1$ ($c = 0.75$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.83$ (d, $J = 1.4$, 1H, CHO), 7.38–7.26 (m, 5H, $H_{ar.}$), 4.57 (dq, $J_1 = 6.1$, $J_2 = 12.2$, 1H, $CHCH_3$), 4.18 (q, $J = 7$, 2H, $CO_2CH_2CH_3$), 4.12 (d, $J = 13.2$, 1H, CH_2Ph), 4.06 (d, $J = 5.2$, 1H, $CHCO_2Et$), 4.00 (d, $J = 13.2$, 1H, CH_2Ph), 3.55 (ddd, $J_1 = 1.4$, $J_2 = 5.2$, $J_3 = 6.4$, 1H, CHCHO), 1.47 (d, $J = 6.2$, 3H, $CHCH_3$), 1.26 (t, $J = 7$, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 198.1$, 170.1, 136.2, 129.3, 128.6, 127.8, 74.2, 66.8, 65.3, 62.0, 61.2, 19.4, 14.2.
10. *(3R,4R,5R)-2-Benzyl-3-ethoxycarbonyl-4-hydroxymethyl-5-methylisoxazolidine*: colorless crystals after recrystallization (>99% ee), mp 62.5–63.5 °C (hexane/2-propanol), $[\alpha]_D = +85.7$ ($c = 1.25$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.42$–7.22 (m, 5H, H_{ar}), 4.23–4.06 (m, 3H, overlapped CH_2Ph and $CHCH_3$), 4.14 (q, $J = 7$, 2H, $CO_2CH_2CH_3$), 3.77 (d, $J = 5.6$, 2H, CH_2OH), 3.54 (d, $J = 7$, 1H, $CHCO_2Et$), 2.64–2.57 (m, 1H, $CHCH_2OH$), 2.10 (br s, 1H, OH), 1.34 (d, $J = 6.2$, 3H, $CHCH_3$), 1.22 (t, $J = 7$, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.7$, 136.7, 129.4, 128.5, 127.7, 75.4, 70.1, 62.0, 61.9, 61.6, 56.9, 18.7, 14.3. LR ESI-MS: *m*/*z*: 302.1 for $[M+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{15}H_{21}NO_4+Na]^+$: 302.1368, found: 302.1376. HPLC conditions: DAICEL CHIRALPAK® AD-H, 2-propanol/hexane 5%, 1 ml/min, 35 °C, UV 215 nm, $t_1 = 16.2$ min (major enantiomer: 3*R*,4*R*,5*R*), $t_2 = 19.3$ min.
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16. *tert-Butyl (3R,4S,1′R)-[4-(1-hydroxyethyl)-2-oxo-pyrrolidin-3-yl]-carbamate* (**8b**): colorless solid, recrystallization from CH_2Cl_2/hexane, mp 129–130 °C. $[\alpha]_D = +24.0$ ($c = 0.7$, MeOH). ^1H NMR (200 MHz, CD_3CN): $\delta = 6.33$ (br s, 1H, NH), 5.70 (br s, 1H, NHBoc), 4.09–4.00 (m, 1H, $CHNHBoc$), 3.82–3.74 (m, 1H, $CHOH$), 3.55 (br s, 1H, CH_2), 3.30–3.20 (m, 1H, CH), 3.00–2.91 (m, 1H, CH_2), 1.41 (s, 9H, *t*-Bu), 1.10 (d, $J = 6.4$, 3H, $CHCH_3$). ^{13}C NMR (50 MHz, CD_3CN): $\delta = 80.7$, 69.2, 55.0, 50.7, 42.0, 28.9, 21.4. LR ESI-MS: *m*/*z*: 267.1 for $[M+Na]^+$, 511.3 for $[2M+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{11}H_{20}N_2O_4+Na]^+$: 267.1321, found: 267.1313. Optical purity (86% ee) was determined by HPLC analysis of its dibenzylic derivative.
17. *tert-Butyl (3R,4S,1′R)-[4-(1-hydroxyethyl)-1-methyl-2-oxo-pyrrolidin-3-yl]-carbamate* (**8a**): colorless solid, recrystallization from CH_2Cl_2/hexane afforded crystals (mp 125–128 °C), suitable for single crystal X-ray diffraction. $[\alpha]_D = -42.7$ ($c = 0.45$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 5.35$ (br s, 1H, NH), 4.10 (dd, $J_1 = 6.4$, $J_2 = 9.2$, 1H, $CHNHBoc$), 3.91–3.77 (m, 1H, $CHOH$), 3.34–3.24 (m, 1H, CH_2), 3.04–2.99 (m, 1H, CH_2), 2.89 (s, 3H, *N*-Me), 2.13 (quin, $J = 9$, 1H, CH), 1.46 (s, 9H, *t*-Bu), 1.18 (d, $J = 6.4$, 3H, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.6$, 158.2, 81.4, 69.4, 56.7, 50.7, 48.9, 30.4, 28.4, 20.7. LR ESI-MS: *m*/*z*: 281.1 for $[M+Na]^+$, 539.3 for $[2M+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{12}H_{22}N_2O_4+Na]^+$: 281.1477, found: 281.1472.
18. *General procedure for the 1,3-dipolar cycloaddition (1,3-DC)*: A solution of nitrone **1** (0.25 mmol, 1 equiv) in $MeNO_2$ (1 mL) was placed in a vial, and H_2O (13 μl, 0.75 mmol, 3 equiv), the catalyst (0.025 mmol, 0.1 equiv), and TfOH (20 μl of a 10% v/v solution in $MeNO_2$, 0.0225 mmol, 0.09 equiv) were added and the resulting mixture was cooled to 4 °C. Next, freshly distilled (*E*)-crotonaldehyde (**2**) was added [82 μl, 1 mmol, 4 equiv, followed by 3 equiv at 24 h intervals (two portions)] and the mixture was left to stir for 72 h, then it was filtered through a silica gel plug rinsing with EtOAc, and concentrated. The crude mixture was subjected to ^1H NMR analysis for determination of the diastereoselectivity (based on integration relative to the carbonyl peaks). After flash chromatography on silica gel (hexane–EtOAc), product **3** was isolated as an oil in 49–90% yield.
General procedure for reduction of the 1,3-DC products **3**: Product **3** was reduced to the corresponding alcohol with 1 equiv of $NaBH_4$ in MeOH at 0 °C for 30 min. After aqueous work-up, the diastereomerically pure 3,4-*trans*-alcohol was purified by flash chromatography on silica gel (hexane–EtOAc) and isolated in 60–70% yield. The ee values of the alcohols were determined by chiral HPLC. All new compounds obtained here had correct analytical and spectral data.