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Asymmetric conjugate addition of 5-benzylfurfurals to nitroalkenes using a diaminomethylenemalononitrile organocatalyst

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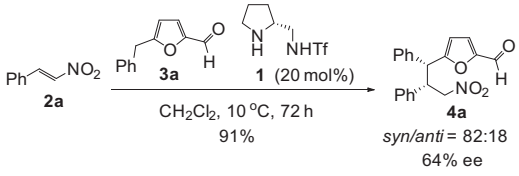
ABSTRACT

A pyrrolidine–diaminomethylenemalononitrile organocatalyst efficiently promotes the asymmetric direct bisvinylogous Michael addition of 5-benzylfurfural derivatives to nitroalkenes, affording the corresponding ε-regioselective addition products in high yields with up to 86% ee.

Asymmetric ε-regioselective reactions of polyunsaturated carbonyl compounds have attracted significant attention because the ε-position is far from the carbonyl group and the achievement of both high stereoselectivity and ε-regioselectivity is generally difficult. Bisvinylogous Mukaiyama aldol reactions are one of the most reliable synthetic methodologies for performing asymmetric ε-regioselective reactions, even though the preparation of unstable silyl enol ethers at a separate synthetic step is necessary.[1] A more convenient synthetic technique from the viewpoint of atom economy and green chemistry is the direct bisvinylogous-type reaction without the preparation of silyl enol ethers. However, the direct bisvinylogous-type reactions between carbonyl compounds and electrophiles using metal catalysts and organocatalysts are rare.[2–4] Organocatalysis reactions are valuable because they are environmentally benign and can be performed under mild reaction conditions. Therefore, the development of the direct bisvinylogous-type reaction with an organocatalyst is a highly desirable research theme in the field of modern organic chemistry.

Conversely, furan derivatives play an important role as valuable synthetic intermediates for the access of biologically active compounds and natural products.[5] To the best our knowledge, there has been only one example of the direct bisvinylogous Michael addition reaction of furfural derivatives to nitroalkenes with an organocatalyst.[4] Albrecht et al. reported that the sulfonamide organocatalyst **1** promoted the asymmetric direct bisvinylogous conjugate addition of 5-benzylfurfural (**3a**) to the nitroalkene **2a** through a trienamine intermediate (Scheme 1).[4] Unfortunately, the enantioselectivities of the products were moderate. We presume that satisfactory enantioselectivities were not obtained owing to the single hydrogen-bond donor of the sulfonamide group in catalyst **1**; the use of an organocatalyst bearing a double hydrogen-bond donor, which can activate the nitro groups of **2a** through a more rigid transition state, might improve the enantioselectivity. Representative double hydrogen-bond donor motifs include thiourea[6] and squaramide[7] groups; organocatalysts containing these motifs have been applied to versatile asymmetric reactions. We have reported diaminomethylenemalononitrile (DMM)[8] and diaminomethyleneindendione (DMI)[9] motifs as other types of double hydrogen-bond donors and have demonstrated that organocatalysts bearing these motifs can promote several valuable asymmetric reactions. Herein, we report that the DMM organocatalyst is a good catalyst for the asymmetric direct bisvinylogous Michael addition of 5-benzylfurfural derivatives to nitroalkenes.



Scheme 1. Albrecht's word.

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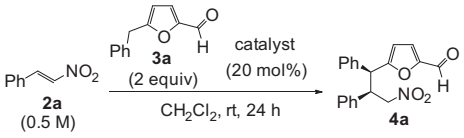
We investigated the catalysis of a model reaction between 5-benzylfuran-2-carbaldehyde (**3a**) and *trans*-β-nitrostyrene (**2a**) with different organocatalysts. First, organocatalysts **5** and **6** bearing a thiourea or a squaramide group as a representative double hydrogen-bond donor motif were used; however, no reactions were observed (Table 1, entries 1 and 2). The DMI catalyst **7**, which contained another type of double hydrogen-bond donor motif, was a poor catalyst; the corresponding adduct **4a** was obtained in low yield with low enantioselectivity (entry 3). The DMM catalyst **8** promoted the conjugate addition, resulting in the adduct **4a** in a high yield with moderate enantioselectivity (entry 4). The catalyst containing a DMM skeleton was preferable for the organocatalysis between **2a** and **3a** in comparison with the catalysts containing thiourea, squaramide, and the DMI motifs.

Second, we examined the direct bisvinylogous conjugate additions of 5-benzylfurfural (**3a**) in different solvents (Table 2). Among the examined reaction solvents, *m*-xylene was the most suitable reaction media, affording good enantioselectivity with up to 73% ee (entry 11). Further the optimization of the reaction conditions was performed (Table 3). High enantioselectivity was obtained when the concentrations of substrate **2a** were reduced to 0.25 M (entry 3). Both the yield and enantioselectivity decreased when the amount of **3a** was reduced to 1.0 or 0.5 equivalents (entries 5 and 6). The yield and stereoselectivity decreased when the amount of catalyst **8** was reduced from 20 mol% to 10 mol% (entry 7). Therefore, the optimal reaction conditions were determined to be those for entry 3.Fig. 1

With the optimized reaction conditions in hand, we investigated the scope and limitations of the Michael addition of various 5-benzylfurfural derivatives to nitroalkenes (Table 4).[10] The reactions of *trans*-β-nitrostyrene derivatives **2b–g** bearing electron-withdrawing groups such as bromo and chloro groups with 5-benzylfuran-2-carbaldehyde (**3a**) resulted in the corresponding adducts **4b–g** in high yields with good enantioselectivities (entries 1–6). Organocatalyst **8** promoted the reaction of **2a** with nitroalkenes bearing methoxy and methyl groups as electron donating groups to provide the corresponding adducts **4 h** and **4i**, respectively, in high yield with good stereoselectivities (entries 7 and 8). 5-Benzylfurfural derivatives bearing a bromo group at the *ortho*, *meta*, and *para*-positions were good substrates and afforded the adducts **4j–l** in high yields with good to high enantioselectivities (entries 9–11). 5-Benzylfurfural derivatives bearing methoxy and methyl groups at the *para*-position also smoothly reacted with **2a** to give the addition products **4 m** and **4n**, respectively, in high yields with good stereoselectivities (entries 12 and 13). All the enantioselectivities were higher than those previously reported (entries 1–3, 7–13).[4]

The stereochemistry of the addition products obtained using organocatalyst **8** was determined by comparison with reported chiral-phase HPLC retention times and through NMR spectroscopy analysis.[4] From these analyses, we infer that the direct bisvinylo-

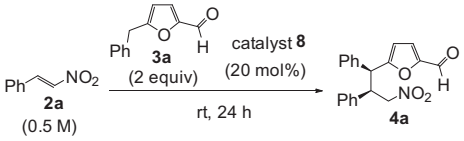
Table 1
Selection of organocatalysts.



Entry	Catalyst	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	**5**	trace	ND[d]	ND[d]
2	**6**	0	ND[d]	ND[d]
3	**7**	14	71:29	11
4	**8**	87	74:26	59

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by HPLC analysis.
[d] Not determined.

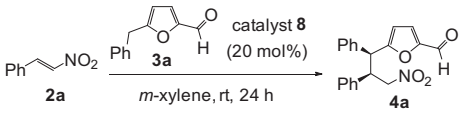
Table 2
Optimization of reaction solvents.



Entry	Solvent	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	H_2O	77	77:23	47
2	MeOH	44	70:30	37
3	DMF	68	71:29	23
4	THF	67	73:27	50
5	MeCN	56	77:23	58
6	EtOAc	79	77:23	69
7	Et_2O	93	80:20	68
8	CH_2Cl_2	87	74:26	59
9	toluene	89	75:25	70
10	*o*-xylene	98	76:24	71
11	*m*-xylene	92	78:22	73
12	*p*-xylene	84	77:23	70
13	hexane	84	79:21	51

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by HPLC analysis.

Table 3
Optimization of reaction conditions.



Entry	**3a** (equiv)	Conc.(M)	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	2.0	0.5	92	78:22	73
2	2.0	1.0	97	79:21	69
3	2.0	0.25	93	76:26	76[d]
4	2.0	0.17	89	73:27	71
5	1.0	0.25	62	74:26	71
6	0.5	0.25	69	71:29	65
7[e]	2.0	0.25	74	75:25	74

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by HPLC analysis.
[d] Enantioselectivity of minor *anti*-isomer is 60% ee.
[e] Catalyst **8** (10 mol%) was used.

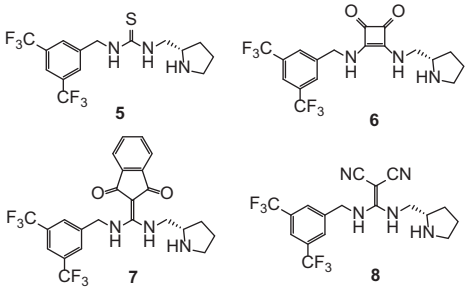


Fig. 1. Structure of organocatalysts.