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Organocatalytic Highly Enantioselective Conjugate Addition of Aldehydes to Alkylidine Malonates

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Abstract: The first highly enantioselective, direct organocatalytic conjugate addition of unmodified aldehydes to alkylidinemalonates is presented. The reaction gives access to β-formyl-substituted malonates and highly functionalized lactones with up to 14:1 *dr* and generally 94 to >99% *ee*.

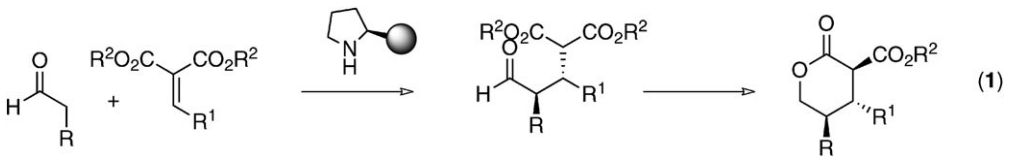
Keywords: aldehydes; alkylidenemalonates; asymmetric catalysis; chiral lactones; conjugate additions

The catalytic asymmetric conjugate addition of carbon-centered nucleophiles to alkylidinemalonates provides a practical route to synthetically and biologically important chiral compounds.[1] Most of these catalytic asymmetric strategies utilize organometallic-complexes as the catalysts.[1]

In the research field of organocatalysis,[2,3] there are several elegant reports on the amine-catalyzed asymmetric addition of ketones and aldehydes to nitrostyrenes.[4–6] Moreover, well-designed catalytic enantioselective conjugate additions of aldehydes to vinyl sulfones,[7] maleimides,[8] benzoquinones,[9] enones[10] and vinyl phosphonates[11] have recently been reported. However, only the amine-catalyzed conjugate addition of ketones to alkylidinemalonates is known.[12] In fact, initial attempts at employing unmodified aldehydes as donors failed.[12c] Thus, expansion of the scope of enamine catalysis to the use of aldehyde donors and to this class of Michael acceptors is a useful and challenging objective. Based on this, and the synthetic utility and biological importance of chiral malonates and lactones,[1,13] we began the task of developing an organocatalytic asymmetric conjugate addition of unmodified aldehydes to alkylidinemalonates [Eq. (1)].

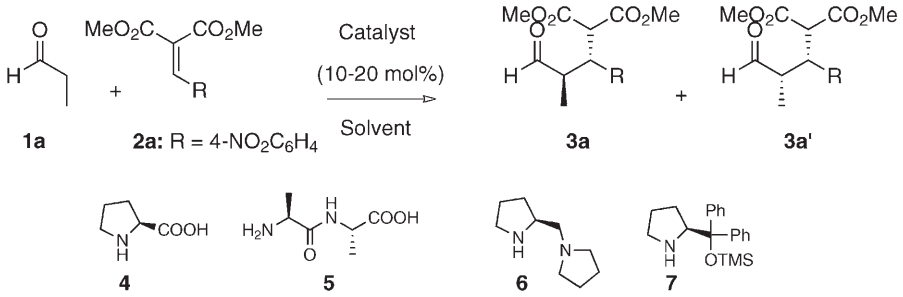
Herein, we report the first highly enantioselective chiral amine-catalyzed conjugate addition of unmodified aldehydes to alkylidenemalonates (generally 94 to >99% *ee*).

In an initial catalyst screen for the reaction between propionaldehyde **1a** (0.25 mmol) and alkylidine malonate **2a** (0.125 mmol), we found that proline, dipeptides and chiral pyrrolidines such as **4**–**7** catalyzed the asymmetric formation of formyl-substituted malonates **3a** and **3a′** (Table 1). It should be mentioned that the solvent that we believed would be best for each catalyst based on our previous experience was used. Of the screened catalysts, the protected diarylprolinol **7**[14] catalyzed the formation of the *anti*-isomer **3a** with high chemo- and enantioselectivity under several reaction conditions as determined by ^{1}H NMR and chiral-phase HPLC analysis (entries 6–10). For example, the reaction in $CHCl_3$ at −20 °C gave **3a** in 82% yield with 95% *ee* (entry 8). Decreasing the catalyst loading increased the diastereoselectivity from 5:1 to 10:1 at the expense of the efficiency (entry 9). To our delight, chiral amine **7** catalyzed the



(1)

Table 1. Selected reactions for the **4a**-catalyzed enantioselective domino reactions between **1a** and **2a**.



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	**4**	DMSO	rt	16	trace	n.d.	n.d.
2	**4**	DMF	rt	16	21	2:1	13
3	**5**	DMSO	rt	144	10[d]	1:1[d]	18[e]
4	**6**	$CHCl_3$	rt	16	60	1:1	34
5	**7**	$CHCl_3$	rt	16	73	2:1	86
6	**7**	CH_3CN	rt	6	63	5:1	91
7	**7**	toluene	rt	24	48	3:1	86
8	**7**	$CHCl_3$	-20	20	82	5:1	95
9	**7**	$CHCl_3$	-20	48	53[f]	10:1[f]	95
10	**7**	CH_3CN	4	16	88	10:1	95

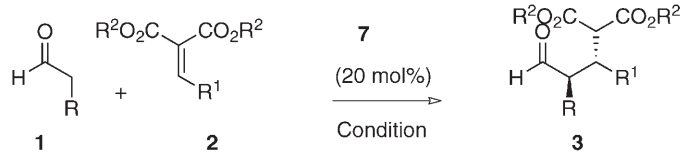
[a] Combined isolated yield of compounds **3a** and **3a′**.
[b] The *dr* (*anti*/*syn*) was determined by NMR analysis.
[c] Determined by chiral-phase HPLC analysis (OJ column).
[d] 10 equiv. H_2O were added.
[e] *ent*-**3a** was formed.
[f] 10 mol% catalyst.

asymmetric formation of **3a** in 88% yield with 10:1 *dr* (*anti*/*syn*) and 95% *ee* in CH_3CN at 4 °C (entry 10).

We also screened the conjugate reactions with chiral amine **7** at different temperatures and found that the conditions shown in entry 8 and entry 10 were optimal in $CHCl_3$ and CH_3CN, respectively. Thus, we decided to investigate the scope of the catalytic asymmetric conjugate addition in $CHCl_3$ at −20 °C or in CH_3CN at 4 °C employing chiral amine **7** as the catalyst (Table 2).

The organocatalytic asymmetric conjugate additions of aldehydes **1** to alkylidenemalonates **2** were highly chemo- and enantioselective and the corresponding α-aryl- or α-alkyl-β-formyl-substituted malonates **3a–j** were isolated in high yields with up to 14:1 *dr* and 95 to >99% *ee*. The reaction worked well for various functionalized aldehyde donors and both aliphatic and aromatic substituted alkylidenemalonates could be used as acceptors. For example, aldehyde **3i** was catalytically assembled from the reaction between aldehyde **1d** and alkylidene malonate **2a** in 86% yield and 98% *ee* (entry 9). The products **3** can also be converted to highly substituted lactones. To exemplify this, the aldehydes **3a** and **3j** and were converted to the corresponding lactones **8a** and **8j** with three contiguous chiral centers in 85 and 80% yield, respectively [Eq. (2)]. The relative configuration of chiral lactone **8j** was established by NOE experiments. The ab-

Table 2. Scope of the organocatalytic conjugate addition of aldehydes to alkylidinemalonates. (Conditions A: $CHCl_3$, −20 °C; Conditions B: CH_3CN, 4 °C.)

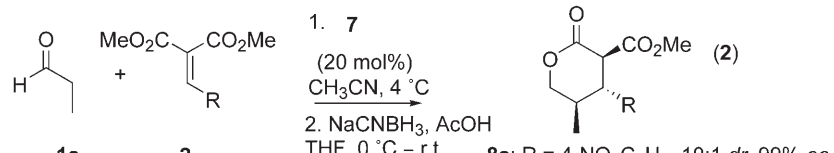


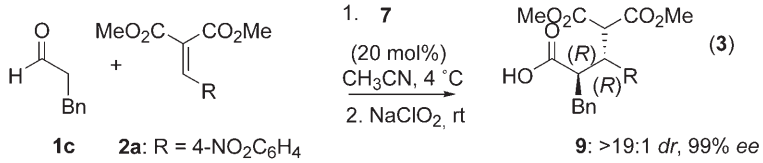
Entry	R	R^1	R^2	Prod	Cond	Time (h)	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	Me	4-$O_2NC_6H_4$	Me	**3a**	B	16	88	10:1	95
2	Me	3-$O_2NC_6H_4$	Me	**3b**	A	16	81	5:1	97
3	Me	4-ClC_6H_4	Me	**3c**	B	48	79	5:1	95
4	Me	4-BrC_6H_4	Me	**3d**	B	48	76	7:1	94
5	Me	4-BrC_6H_4	Bn	**3e**	B	48	68	7:1	95
6	Me	Ph	Me	**3f**	B	72	96[d]	7:1	>99
7	Et	4-$O_2NC_6H_4$	Me	**3g**	A	16	77	14:1	99
8	Bn	4-$O_2NC_6H_4$	Me	**3h**	B	48	73	8:1	98
9		4-$O_2NC_6H_4$	Me	**3i**	B	48	86	6:1	98
10	Me	*n*-Pr	Me	**3j**	B	48	84	4:1	95[e]

[a] Isolated yield of the pure product **3** after silica gel chromatography.
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral-phase HPLC analysis.
[d] The isolated yield based on recovered starting material.
[e] Determined by chiral-phase GC analysis after conversion to lactone **8**. Bn = benzyl.

solute and relative configuration of acid **9**, generated from the mild oxidation of **3h** and recrystallization, was assigned by X-ray crystallographic analysis and comparison to the literature[8,11] {[Eq. (3)], Figure 1}.[15]

Based on the absolute configuration of the product **9**, which was determined by X-ray analysis, we propose transition state **I** (Figure 2) to account for the stereochemical outcome of the chiral amine **7**-catalyzed reactions in Table 1. The *Si*-face of the chiral





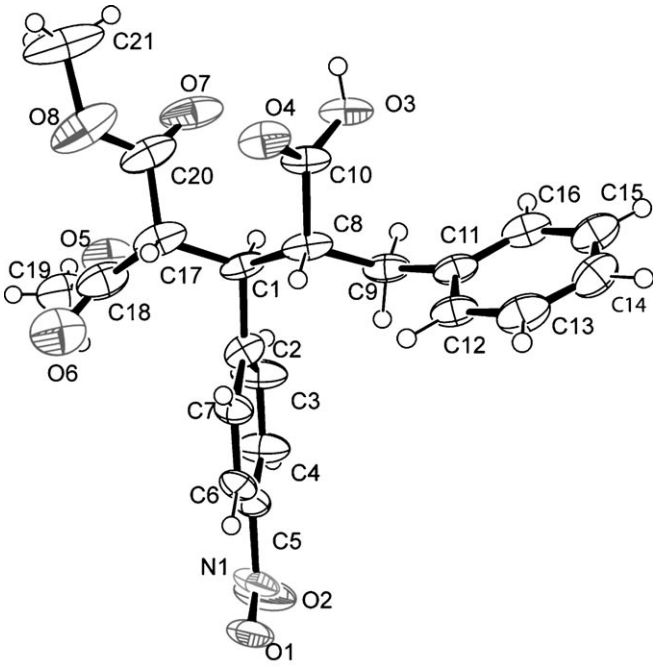


Figure 1. ORTEP picture of carboxylic acid **9** with ellipsoids at the 50% level. H atoms are drawn as sphere of arbitrary radii.

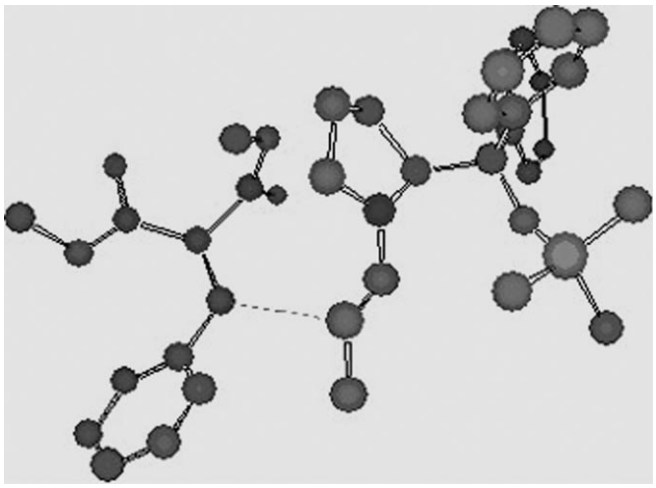


Figure 2. Proposed transition state model **I**.

enamine is efficiently shielded by the bulky aryl groups of **7**. Thus, the alkylidenemalonate is approaching the enamine from the *Re*-face with its substituent pointing away in order to avoid steric interactions.

In summary, we have developed an operationally simple protocol that employs unmodified and commercially available materials and catalysts for the first highly enantioselective (94 to >99% *ee*) catalytic conjugate addition of α-unsubstituted aldehydes to alkylidenemalonates. Mechanistic studies, synthetic applications of this transformation as well as development of other organocatalytic enantioselective conjugate addition reactions are ongoing in our laboratory.

Experimental Section

General Procedure for Chiral Amine 7-Catalyzed Conjugate Addition of Unmodified Aldehydes to Different Alkylidene Malonates

To a stirred solution of the catalyst **7** (20 mol%) in $CHCl_3$ (0.5 mL) at −20 °C or CH_3CN (0.5 mL) at +4 °C was added aldehyde **1** (0.25 mmol) and alkylidenemalonate (0.125 mmol). The reaction mixture was vigorously stirred for the time shown in Table 2 and monitored by TLC analysis. Next, the reaction mixture was directly loaded on the silica gel column and purified by silica gel chromatography (pentane: ethyl acetate = 8:1–4:1) to give product **3**.

Acknowledgements

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[15] CCDC 664013 contains 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.

