Organocatalytic enantioselective conjugate addition of aldehydes to maleimides†

Gui-Ling Zhao,[a] Yongmei Xu,[a] Henrik Sundén,[a] Lars Eriksson,[b] Mahmoud Sayah[a] and Armando Córdova*[a]

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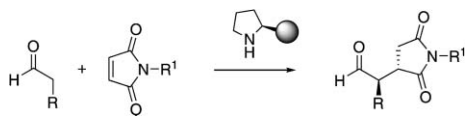
The highly enantioselective direct organocatalytic conjugate addition of aldehydes to maleimides is presented.

The asymmetric conjugate addition of carbon-centered nucleophiles to maleimides should provide a practical route to synthetically and biologically important chiral α-substituted succinimides.[1] However, there are only two effective catalytic asymmetric strategies that have been described to date, which utilize Rh-complexes,[2] or quinine[3] and quinidines[3] as the catalysts.

There are several elegant reports on the amine-catalyzed asymmetric addition of ketones and aldehydes to nitrostyrenes.[4–6] However, only the amine-catalyzed conjugate addition of acetone to maleimides is known, and no asymmetric induction was reported.[7] Thus, expanding the scope of enamine catalysis to this class of Michael acceptors is a useful and challenging objective. Based on the synthetic utility and biological importance of chiral α-substituted succinimides,[1] we embarked on the quest to develop an organocatalytic asymmetric conjugate addition of unmodified aldehydes to maleimides (eqn. (1)).


(1)

Herein, we report the first highly enantioselective enamine-catalyzed conjugate addition of unmodified aldehydes to maleimides (generally 97 → 99% ee).

In an initial catalyst screen for the reaction between propionaldehyde (**1a**) (0.50 mmol) and maleimide **2a** (0.25 mmol), we found that simple amino acids, dipeptides and chiral pyrrolidines such as **4**, **5**, **7**, **8** and **9** catalyzed the asymmetric formation of α-substituted succinimide **3a** (Table 1). Hence, both primary and secondary chiral amines can catalyze this transformation. To our delight, the protected diarylprolinol **8**[8] catalyzed the formation of **3a** with high chemo- and enantioselectivity under various reaction conditions (Table 1, entries 6–11). The highest diastereo- and enantioselectivity were achieved when $CHCl_3$ and CH_3CN were used as solvents. The other catalysts were also tested in a range of solvents, and the optimal results are shown in Table 1.

Thus, we decided to investigate the scope of the novel catalytic asymmetric conjugate addition with $CHCl_3$ as the solvent and chiral amine **8** as the catalyst (Table 2).

[a]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691, Sweden*
[b]*Department of Structural Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691, Sweden. E-mail: acordova1a@netscape.net; acordova@organ.su.se; Fax: +46 8 154908; Tel: +46 8 162479*
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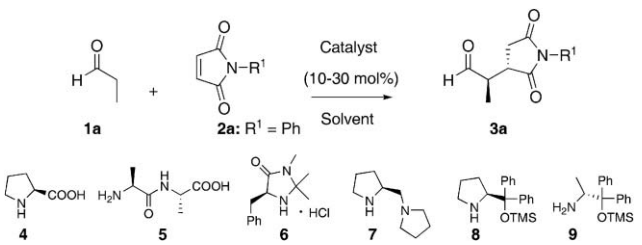
Table 1 Catalyst screen for the reaction between **1a** and **2a**

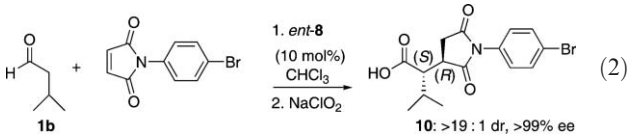


Entry	Catalyst	Solvent	Temp./°C	Time/h	Yield (%)[a]	dr[b]	ee (%)[c]
1	**4**	DMSO	rt	16	55[d]	4 : 1	−25
2	**5**	DMSO	rt	16	62[d]	1 : 1	38
3	**6**	$CHCl_3$	rt	144	Trace[e]	n.d.[i]	n.d.[i]
4	**7**	$CHCl_3$	rt	48	17[f]	1 : 6	40
5	**8**	$CHCl_3$	rt	14	87[g]	2 : 1	95
6	**8**	$CHCl_3$	4	36	93[g]	4 : 1	95
7	**8**	$CHCl_3$	−20	76	78[g]	5 : 1	97
8	**8**	CH_3CN	rt	48	83[g]	6 : 1	95
9	**8**	Hexane	4	96	52[g]	2 : 1	93
10	**8**	MTBE	4	47	36[g]	4 : 1	95
11	**8**	THF	rt	47	<10[g]	6 : 1	96
12	**9**	DMSO	rt	90	48[h]	1 : 1	−60

[a] Isolated yield of the pure product compound **3a**. [b] Determined by NMR analysis. [c] Determined by chiral phase HPLC analysis. [d] 30 mol% catalyst, 10 equiv. H_2O. [e] 15 mol% catalyst. [f] 30 mol% catalyst. [g] 10 mol% catalyst. [h] 20 mol% catalyst, 10 equiv. H_2O. [i] n.d. = not determined.

The organocatalytic asymmetric conjugate additions to **2a** were highly chemo- and enantioselective, and the corresponding α-substituted succinimides **3a–3e** were isolated in good-to-high yields with 97 → 99% ee. The reactions with other maleimides **2** were slower, highly chemoselective and gave the corresponding products **3** with excellent ee values (98%). The enantioselectivity of the reaction increased by decreasing the reaction temperature. However, the reaction rate decreased (see Table 2, entries 5 and 6). Moreover, product **3h**, with a quaternary carbon center, was also prepared in moderate enantioselectivity.

The absolute and relative configuration of acid **10**, generated from the mild oxidation of *ent*-**3f**, was assigned by X-ray crystallographic analysis (eqn. (2) and Fig. 1).[9]



(2)

Based on the X-ray analysis, we propose transition state (TS) **I** (Fig. 2) to account for the stereochemical outcome of the chiral amine **8**-catalyzed reactions in Table 1. The *Si*-face of the chiral

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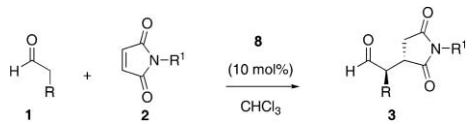
Table 2 Scope of the organocatalytic conjugate addition of aldehydes to maleimides



1 2 3

Entry	R	R^1	Product	Temp./°C	Time/h	Yield (%)[a]	dr[b]	ee (%)[c]
1	Me	Ph	**3a**	−20	76	78	5 : 1	97
2	*i*-Pr	Ph	**3b**	rt	24	70	8 : 1	99
3	*i*-Pr	Ph	**3b**	4	68	56	10 : 1	>99
4	*n*-Bu	Ph	**3c**	4	72	73	8 : 1	98
5	Bn	Ph	**3d**	4	72	91	2 : 1	83
6	Bn	Ph	**3d**	−20	120	41 (95)[d]	15 : 1	97
7	$TBSOCH_2$	Ph	**3e**	4	72	72	1 : 1	97
8	*i*-Pr	4-BrC_6H_4	**3f**	4	168	21 (96)[d]	8 : 1	98
9	*i*-Pr	Bn	**3g**	4	168	47 (91)[d]	15 : 1	98 (99)[e]
10		Ph	**3h**	rt	24	40 (92)[d]	—	51

[a] Isolated yield of the pure product **3** after silica gel chromatography. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral phase HPLC analysis. [d] The isolated yield, based on recovered starting material. [e] The ee after 72 h.

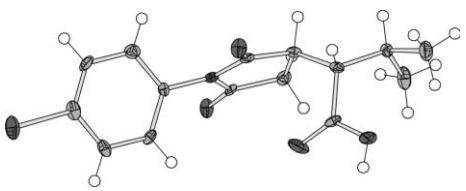


Fig. 1 ORTEP picture of carboxylic acid **10** with ellipsoids at the 50% level.

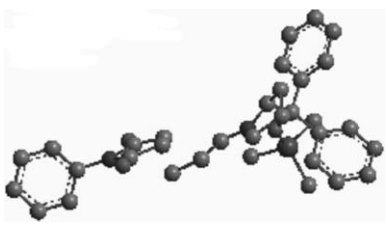


Fig. 2 Proposed TS **I**.

enamine is efficiently shielded by the bulky aryl groups of **8**. Thus, the maleimide is approaching the enamine from the *Re*-face, with its substituent at the nitrogen 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 (97 → 99% ee) catalytic conjugate addition of α-unsubstituted aldehydes to maleimides.

Mechanistic studies, synthetic applications of this transformation, as well as the development of other organocatalytic enantioselective reactions involving maleimides, are ongoing in our laboratory

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9 *Crystal data for* **10**: $C_{15}H_{16}BrNO_4$, M_w: 354.20 g mol^{-1}, monoclinic, a = 5.4015(2) Å, b = 10.6598(4) Å, c = 13.0093(5) Å, β = 99.248(4)°, V = 739.33(5) Å^3, T = 100(1) K, space group $P2_1$, Z = 2, μ = 2.795 mm^{-1}, $N_{measured}$ = 7190, N_{unique} = 3064, R_{int} = 0.0786, w$R2$ = 0.0460 (all data), $R1$ = 0.0363 (1436 $F^2 > 2\sigma(F^2)$). CCDC 623384. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614962f .