One-Pot Organocatalytic Asymmetric Synthesis of 1*H*-Pyrrolo[1,2*a*]indol-3(2*H*)-ones via a Michael–Hemiaminalization–Oxidation Sequence

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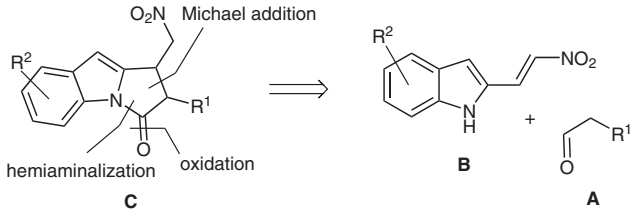
Dedicated to Professor Horst Kunz on the occasion of his 70th birthday

Abstract: An efficient one-pot organocatalytic asymmetric synthesis of 1,2-*cis*-disubstituted 1*H*-pyrrolo[1,2*a*]indol-3(2*H*)-ones in moderate to good overall yields (49–68%) is presented. The Michael–hemiaminalization–oxidation sequence occurs with very high asymmetric induction and, after purification, virtually stereoisomerically pure products were obtained (>98% de, >99% ee).

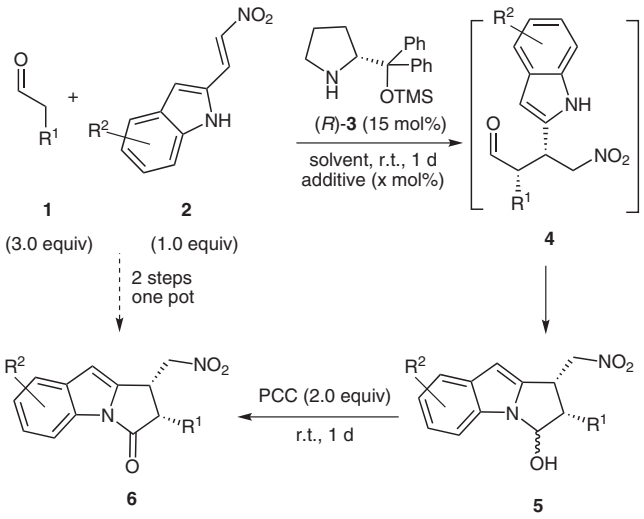
Key words: pyrrolo[1,2*a*]indolones, Michael addition, hemiaminalization, organocatalysis, one-pot reaction

Amine-catalyzed asymmetric Michael additions to nitroalkenes via enamine intermediates have received great interest and have been investigated intensively in recent years since their discovery in 2001.[1–3] Within this field, many efforts have been devoted to design new cascade reactions involving Michael additions to nitro olefins to afford structurally complex molecules with several stereocenters.[4] For example, we have successfully employed nitroalkenes as a component in an organocatalytic triple cascade for the stereoselective synthesis of tri- and tetrasubstituted cyclohexene carbaldehydes.[4a,b,d] Moreover, we focused on the application of Michael additions to nitroalkenes as key step in asymmetric syntheses of heterocycles.[5]



Scheme 1 Asymmetric synthesis of pyrrolo[1,2*a*]indolones **C** – retrosynthetic analysis

Indole is present as a characteristic subunit in a large number of alkaloids exhibiting biological activities.[6] Utilizing indole or its derivatives as a component in a cascade or one-pot reaction can open a direct entry to complex indole alkaloids.[7] For example, our group and Wang et al. reported independently a highly enantioselective synthesis of 3*H*-pyrrolo[1,2*a*]indoles via a domino aza-Michael–aldol condensation reaction.[7d,e] Furthermore, we have recently developed a new quadruple cascade for the asymmetric synthesis of 3-(cyclohexenylmethyl)indoles with excellent stereocontrol.[4k] Continuing our investigations in this field, we envisaged aldehydes **A** and (*E*)-2-(2-nitrovinyl)-1*H*-indoles **B** as potential substrates for a Michael addition–hemiaminalization–oxidation reaction,[8] which should provide an access to 1*H*-pyrrolo[1,2*a*]indol-3(2*H*)-ones **C**[9] bearing two stereogenic centers and a synthetically useful nitro group (Scheme 1).



Scheme 2 Asymmetric synthesis of pyrrolo[1,2*a*]indolones **6** from aldehydes **1** and 2-nitrovinyl-substituted indoles **2**

Initially, we performed the reaction between pentanal (**1a**, Scheme 2) and (*E*)-2-(2-nitrovinyl)-1*H*-indole (**2a**) in dichloromethane at room temperature using (*R*)-diphenylprolinol TMS-ether[10] [(*R*)-**3**, 15 mol%] as catalyst, which shows very good catalytic activity and selectivity in the Michael addition of aldehydes to nitrostyrenes.[11] The reaction was complete within one day, and the resulting Michael adduct **4a** underwent subsequently an intramolecular hemiaminalization affording 1*H*-pyrrolo[1,2*a*]indol-3(2*H*)-ol **5a** as product, not stable enough to be isolated through column chromatography. Therefore, we treated the reaction mixture with pyridinium chlorochromate after the full conversion of **2a**. In this way the Michael–hemianimalization product **5a** was readily oxidized to 1*H*-pyrrolo[1,2*a*]indol-3(2*H*)-one (**6a**, Table 2) in moderate yield (53%) and perfect diastereo- and enan-

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Table 1 Solvent and Additive Screening of the Michael–Hemiaminalization–Oxidation Sequence[a]

Entry	Solvent	Additive	x (mol%)	Yield (%)[b]	de (%)[c]	ee (%)[d]
1	CH_2Cl_2	–	–	53	>98	>99
2	CH_2Cl_2	AcOH	20	62	>98	>99
3	CH_2Cl_2	$PhCO_2H$	20	37	>98	>99
4	CH_2Cl_2	AcOH	60	37	>98	>99
5	CH_2Cl_2	AcOH	100	31	>98	>99
6	$CHCl_3$	AcOH	20	44	>98	>99
7	DCE	AcOH	20	38	>98	>99
8	MeCN	AcOH	20	41	>98	>99
9	THF	AcOH	20	0	–	–

[a] Reaction conditions: A mixture of pentanal (**1a**, 1.5 mmol, 3.0 equiv), (*E*)-2-(2-nitrovinyl)-1*H*-indole (**2a**, 0.5 mmol, 1.0 equiv), additive (x mol%) and catalyst (*R*)-**3** (15 mol%) in solvent (1.5 mL) was stirred for 1 d. Then pyridinium chlorochromate (1.0 mmol, 2.0 equiv) was added to the reaction mixture, which was stirred for 1 d.
[b] Yield of isolated product **6a**.
[c] Determined by ^{1}H NMR spectroscopy and by HPLC on the isolated product.
[d] Determined by HPLC analysis on a chiral stationary phase on the isolated product.

tioselectivity (>98% de, >99% ee, Table 1, entry 1). Next, two acids were tested as additives for this reaction in order to improve the yield. When acetic acid was employed as the additive, the yield was increased to 62%, while the stereoselectivities remained excellent (>98% de, >99% ee). In the case of benzoic acid, the product was obtained in a lower yield. Then we performed the reaction with 0.6 and 1.0 equivalents acetic acid, and the results indicated that the efficiency of this reaction diminished with an increasing amount of acetic acid (Table 1, entries 4 and 5). Subsequently, a solvent screening was undertaken using (*R*)-diphenylprolinol TMS-ether [(*R*)-**3**] as catalyst and acetic acid as additive (0.2 equiv). Perfect stereoselectivities were obtained in every solvent used, while no better yield was achieved (Table 1, entries 6–9). Notably, no Michael addition occurred when this reaction was conducted in THF (Table 1, entry 9).

Table 2 Scope of the Michael–Hemiaminalization–Oxidation Sequence[a]

6	R^1	R^2	Yield (%)[b]	de (%)[c]	ee (%)[d]
6a	*n*-Pr	H	62	>98	>99
6b	*n*-Bu	H	68	>98	>99
6c	All	H	56	>98	>99
6d	Bn	H	52	>98	>99
6e	*n*-Bu	5-Me	55	>98	>99
6f	*n*-Bu	5-Cl	58	>98	>99
6g	*n*-Bu	5-MeO	49	>98	>99

[a] Reaction conditions: A mixture of **1** (3.0 mmol, 3.0 equiv), **2** (1.0 mmol, 1.0 equiv), AcOH (20 mol%), and catalyst (*R*)-**3** (15 mol%) in CH_2Cl_2 (4 mL) was stirred at r.t. for 1 d. Then pyrindinium chlorochromate (2.0 mmol, 2.0 equiv) was added to the reaction mixture, which was stirred for 1 d.
[b] Yield of isolated product **6**.
[c] Determined by ^{1}H NMR spectroscopy and by HPLC on the isolated product.
[d] Determined by HPLC analysis on a chiral stationary phase on the isolated product.

Under the optimized reaction conditions, we investigated the scope of the reaction by varying the structure of both the aldehydes **1** and the 2-nitrovinyl indoles **2**. In the cases of aliphatic and aromatic aldehydes **1a–d** with **2a** the corresponding products **6a–d** were obtained in moderate to good yields (52–68%) and perfect stereoselectivities (>98% de, >99% ee). Next, we performed the reaction of hexanal (**1b**) with the substituted indoles **2b–d**. Generally, the electronic feature of the substituents did not show significant influence on the outcome of this reaction, and the products **6e–g** were furnished in moderate yields (49–58%) and in a virtually diastereo- and enantiomerically pure form (>98% de, >99% ee).

The relative and absolute configuration of the title compounds was unambiguously determined to be 1*S*,2*S* in the case of **6f** by X-ray structure analysis (Figure 1).

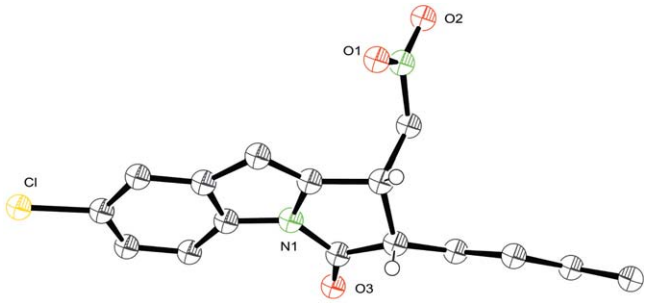

Figure 1 X-ray crystal structure of **6f**;[12] the Flack parameter[13] for the structure shown is 0.048(29)

In conclusion, we have developed a one-pot Michael addition–hemiaminalization–oxidation reaction employing simple aldehydes and 2-nitrovinyl-substituted indoles as substrates. This process is efficiently catalyzed by (*R*)-diphenylprolinol TMS-ether, and the resulting Michael adducts were directly converted into the 1,2-*cis*-disubstituted title compounds by treatment with pyridinium chlorochromate in moderate to good yields (49–68%). The Michael addition key step occurred with very high asymmetric induction and after the purification virtually stereoisomerically pure products were obtained (>98% de, >99% ee).[14]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) CCDC-798847 (**6f**) 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.

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(14) **General Procedure**
To a solution of aldehydes **1** (3.0 mmol, 3.0 equiv), (*E*)-2-(2-nitrovinyl)-1*H*-indoles **2** (1.0 mmol, 1.0 equiv), and AcOH (0.20 mmol, 20 mol%) in CH_2Cl_2 (4.0 mL) was added (*R*)-

diphenylprolinol TMS-ether [(*R*)-**3**] (0.15 mmol, 15 mol%). After stirring for 1 d, the reaction mixture was treated with pyridinium chloromate (2.0 mmol, 2.0 equiv) and stirred at r.t. for 1 d. The crude product was purified by flash chromatography on silica gel (pentane–Et_2O mixture) affording the corresponding 1*H*-pyrrolo[1,2*a*]indol-3 (2*H*)-ones **6** as a solid or sirup.

(1*S*,2*S*)-2-Butyl-7-chloro-1-(nitromethyl)-1*H*-pyrrolo[1,2-*a*]indol-3 (2*H*)-one (6f)

Isolated as a yellow solid (186 mg, 58%). The ee (>99%) was determined by HPLC on a chiral stationary phase [Chiralcel OD, *n*-heptane–EtOH (9:1), 1.0 mL/min), t_R = 11.52 min (major), 13.16 min (minor, based on the racemic mixture)]; mp 108 °C; $[\alpha]_D^{20}$ = 77.2 (*c* 0.32, $CHCl_3$). IR (KBr): 3293, 3196, 2955, 2924, 2867, 2160, 2064, 1725, 1662, 1598, 1582, 1554, 1498, 1446, 1391, 1360, 1317, 1264, 1201, 1167, 1146, 1055, 968, 946, 914, 893, 868, 810, 777, 754, 712, 693, 677, 655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.26–1.66 (m, 5 H), 1.88–2.00 (m, 1 H), 3.36–3.44 (m, 1 H), 4.32–4.40 (m, 1 H), 4.48–4.56 (m, 1 H), 4.71–4.77 (m, 1 H), 6.29 (s, 1 H), 7.25–7.29 (m, 1 H), 7.48 (d, *J* = 2.8 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.6, 26.1, 29.7, 34.4, 48.5, 74.8, 101.8, 114.6, 120.9, 124.6, 128.8, 130.0, 135.5, 142.0, 171.1 ppm. MS (EI, 70 eV): *m/z* (%) = 320 (33) [M^+], 273 (29), 219 (36), 217 (100). ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_3N_2{}^{35}Cl$: 320.0922; found: 320.0923.

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