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Efficient Synthesis of Highly Enantioenriched Δ¹-Pyrrolines

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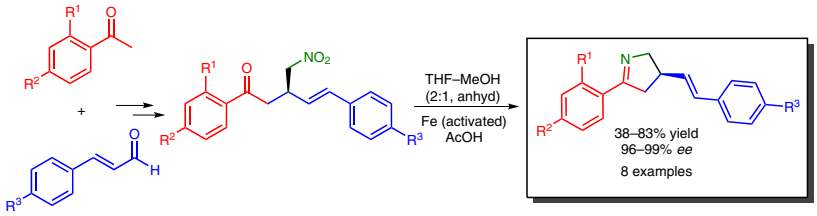

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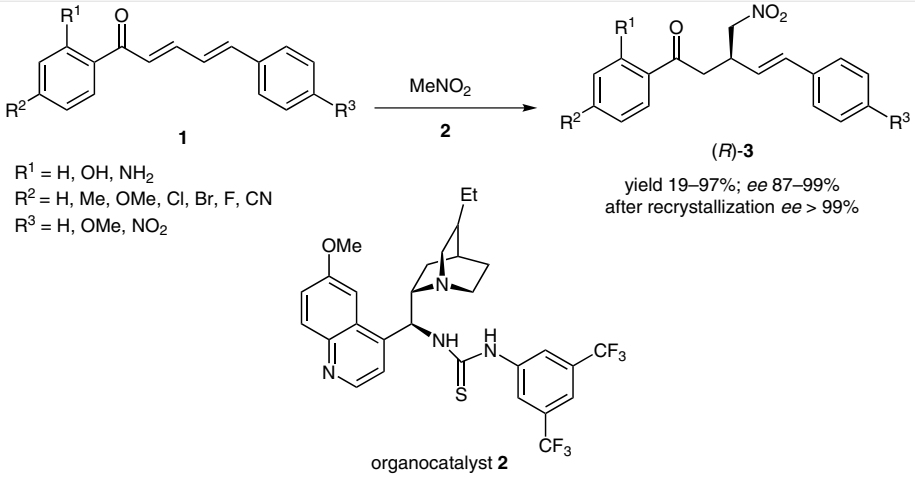
Abstract A general and efficient asymmetric synthesis of Δ¹-pyrrolines by a one-pot nitro-reduction, cyclization, and dehydration of (*R*,*E*)-1,5-diphenyl-3-(nitromethyl)-5-pent-4-en-1-ones with iron and aqueous hydrochloric acid has been developed. The Δ¹-pyrrolines were obtained with excellent enantioselectivities (up to 99%) and high yields (up to 83%).

Key words pyrrolines, reductive cyclization, Michael addition, stereoselectivity

Nitrogen-containing heterocycles are important core structures in natural and synthetic biologically active compounds.[2,3] In particular, 3,4-dihydro-2*H*-pyrroles,[4] also called Δ¹-pyrrolines, can be found in a wide variety of biologically active compounds such as hemes, chlorophylls and alkaloids, and these rings have been used as building blocks for the development of new drugs.[4] Recently, our group reported the synthesis of new boranil derivatives based on a Δ¹-pyrroline core leading to new fluorophores.[5] The synthesis of Δ¹-pyrrolines is well documented[2,4,6,7] and usually involves reductive cyclization of γ-nitro carbonyl compounds.[8,9] However, asymmetric versions of these reactions are scarce.[10,11] Shibata et al.[10] have recently reported the enantioselective synthesis of β-trifluoromethylated pyrrolines through organocatalyzed-conjugate addition of nitromethane to β-trifluoromethylated enones, followed by a nitro-reduction, cyclization and dehydration sequence in a one-pot procedure. Despite the very straightforward methodology, the need for a trifluoromethyl group restricts its scope and limits its application to particular cases.



Scheme 1 Enantioselective addition of nitromethane to (*E*,*E*)-1,5-diarylpenta-2,4-dien-1-ones **1** organocatalyzed by **2**

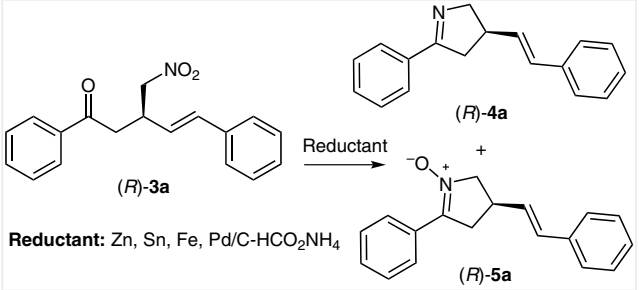
Table 1 Screening of Reduction Methods on the One-Pot Nitro-Reduction, Cyclization and Dehydration of (*R*)-**3a**

Entry	Conditions	Temp. (°C)	Time (h)	Yield (%)	
				(*R*)-**4a**	(*R*)-**5a**
1[a]	DMF–H_2O (1:1), Zn, conc. HCl	80	30	5	15
2[b]	$CHCl_3$, Sn, concd HCl	r.t.	15	31	35
3[c]	THF–MeOH (2:1), Fe, AcOH	65	15	58	10
4[c]	THF–MeOH (2:1), Fe (activated), AcOH	65	15	63	17
5[c]	THF–MeOH (2:1, anhyd), Fe (activated), AcOH	65	15	72	8
6[c]	THF–MeOH (2:1), Fe (activated), AcOH	80	15	36	14

[a] Reaction conditions: **3a** (0.169 mmol), concd HCl (0.34 mL), Zn powder (0.846 mmol), DMF–H_2O (1:1, 0.34 mL), 80 °C, 30 h.
[b] Reaction conditions: **3a** (0.169 mmol), concd HCl (5.6 mL), Sn powder (14.0 mmol), $CHCl_3$ (15 mL), r.t., 15 h.
[c] Reaction conditions: **3a** (0.31 mmol), AcOH (4.98 mmol), Fe (14.0 mmol), THF–MeOH (2:1, 6 mL), 65 °C, 15 h, nitrogen atmosphere.

Recent studies in our laboratory have led to the development of a new methodology for the asymmetric 1,4-Michael addition of nitromethane to 1,5-diarylpenta-2,4-dien-1-ones **1** (Scheme 1).[12,13] In the presence of organocatalyst **2**, (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones (*R*)-**3** have been obtained with excellent enantioselectivity (up to 99%) and isolated yields (up to 97%). We then wished to go one step further, and use these enantiomerically pure compounds for the synthesis of enantiopure Δ^1-pyrroline derivatives. In this communication, we present a general methodology for the synthesis of several highly enantioenriched Δ^1-pyrroline derivatives through a one-pot, nitro-reduction, cyclization, dehydration of the (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **3**.

To investigate the reactivity of the (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **3** towards the reductive cyclization of the nitro group, our investigation began with a screening of metal-mediated reduction methods that have already been described (Scheme 2,Table 1).[9,10,14] The first two reductive systems examined involved Zn/HCl (entry 1) and Sn/HCl (entry 2) and the Δ^1-pyrroline **4a** was obtained in low yields (5–31%). Nevertheless, through HPLC analysis, it was possible to note the absence of racemization of the asymmetric carbon, which allowed us to obtain Δ^1-pyrroline **4a** in excellent enantiomeric excess (>99%). However, formation of the corresponding Δ^1-pyrroline-*N*-oxide **5a** was also observed, in amounts higher than the desired product. Finally, reduction with Fe/AcOH provided better results, and Δ^1-pyrroline **4a** was obtained in good yield (entry 3). Further studies on the influence of the temperature, absence of water and oxygen, as well as the use of preactivated iron[15] were performed (entries 4–6). The best results were obtained by using a mixture of anhydrous tetrahydrofuran and methanol (2:1) under nitrogen, activated iron (14 mmol) as reducing agent, and acetic acid (4.98 mmol) as a proton source.



Scheme 2 Reduction methods tested on the one-pot nitro-reduction, cyclization, dehydration of (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **3**

It is worth mentioning that, under these conditions, not only was the Δ^1-pyrroline **4a** obtained in a very good yield (72%), but the formation of Δ^1-pyrroline-*N*-oxide **5a** was reduced to only 8% yield.

Table 2 Scope of the One-Pot Nitro-Reduction, Cyclization and Dehydration of **3**[a]

Entry	**3**	R^1	R^2	Yield (*R*)-**4** (%)	*ee* (*R*)-**4** (%)	Yield (*R*)-**5** (%)
1	**3b**	Me	H	83	>99	6
2	**3c**	OMe	H	73	>99	11
3	**3d**	Cl	H	49	>99	5
4	**3e**	F	H	67	>99	6
5	**3f**	Br	H	44	>99	9
6	**3g**	NO_2	H	40[b]	>99	0[c]
7	**3h**	H	OMe	38	>99	4

[a] Reaction conditions: **3b**–**h** (0.31 mmol), AcOH (4.98 mmol), Fe (14.0 mmol), THF–MeOH (2:1, 6 mL), 65 °C, 15 h, nitrogen atmosphere.
[b] (*R*,*E*)-2-(4-Aminophenyl)-4-styryl-Δ^1-pyrroline (**4g**) was obtained.
[c] (*R*,*E*)-1-(4-Aminophenyl)-3-(nitromethyl)-5-phenyl-5-pent-4-en-1-one (**3i**) was obtained in 57% yield.

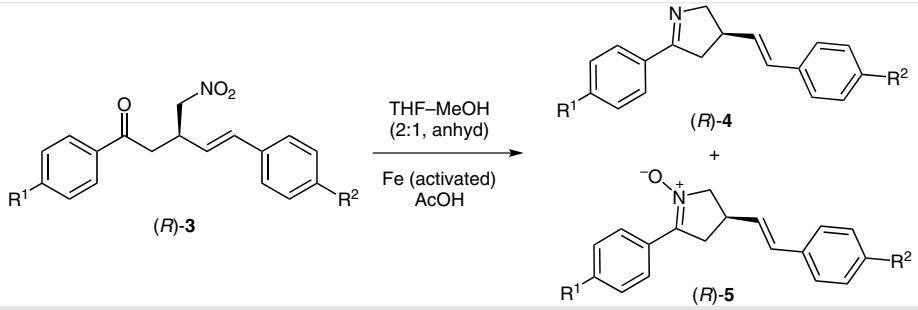
After establishing these optimal reaction conditions, the scope of the reaction was investigated by using a range of derivatives **3b**–**h** (Scheme 3,Table 2). The Δ¹-pyrrolines (*R*)-**4b**–**h**[16] were obtained in moderate to good yields (38–83%) and excellent enantiomeric excesses (99%) for all the synthesized derivatives (entries 1–7).

In the case of nitro derivative **3g** (Table 2, entry 6), it was observed that reduction of the aromatic nitro group resulted in the formation of (*R*,*E*)-2-(4-aminophenyl)-4-styryl-Δ¹-pyrroline (**4g**). Furthermore, for this derivative, the corresponding *N*-oxide (*R*)-**5** was not formed; instead, (*R*,*E*)-1-(4-aminophenyl)-3-(nitromethyl)-5-phenyl-5-pent-4-en-1-one (**3i**) was obtained.

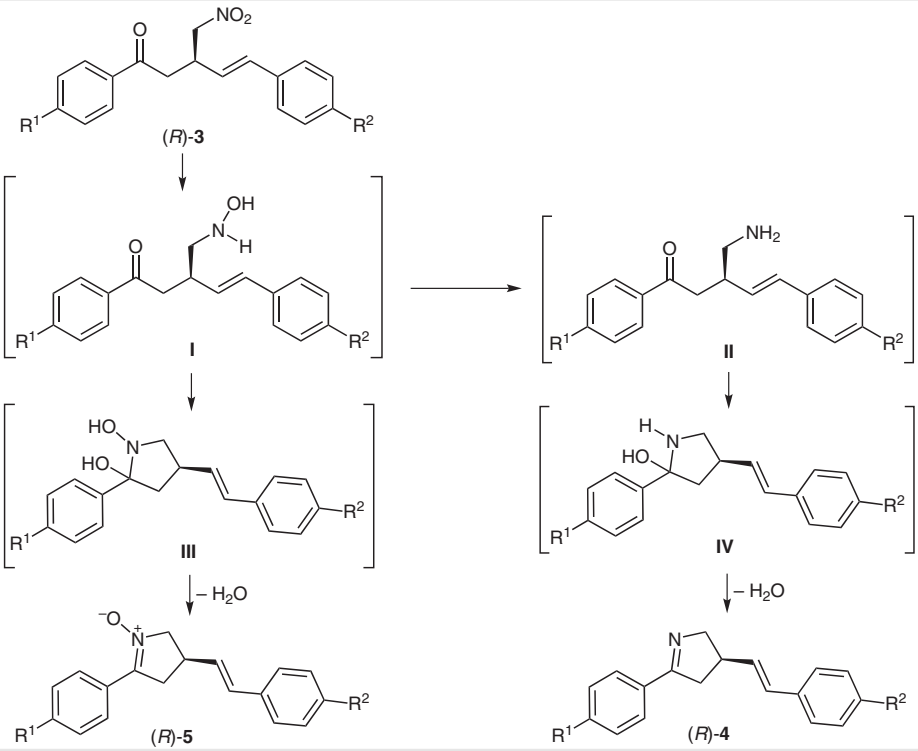
The mechanism for the formation of Δ¹-pyrrolines **4** involves reduction of the nitro group to the corresponding amine intermediate **II**, which, after a cyclization and dehydration sequence, affords the desired products. On the other hand, formation of Δ¹-pyrroline-*N*-oxides **5** as by-products results from cyclization of the partially reduced hydroxylamine intermediate **I** (Scheme 4).

The synthesis of the novel Δ¹-pyrroline derivatives (*R*)-**4b**–**h** occurred without racemization. All enantiomeric excesses were determined by HPLC analysis (see the Supporting Information). The absolute configuration of **4d** and **4e** were confirmed by X-ray diffraction studies (Figure 1).[17]

In conclusion, we have described a very efficient synthesis of Δ¹-pyrroline derivatives through a one-pot nitro-reduction, cyclization and dehydration sequence of (*R*,*E*)-



Scheme 3 Synthesis of highly enantioenriched Δ¹-pyrroline derivatives



Scheme 4 Proposed mechanism for the formation of the Δ¹-pyrrolines (*R*)-**4** and Δ¹-pyrroline-*N*-oxides **5**

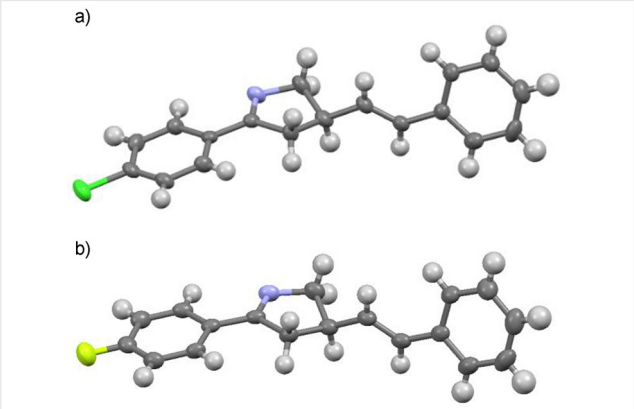


Figure 1 Molecular structure of **4d** (a) and **4e** (b). Thermal ellipsoids are shown at the 50% probability level, hydrogen atoms are shown with an arbitrary radius (0.30 Å). C, grey; N, blue; Cl, green; F, yellow; H, white

1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **3**. There was no racemization of the asymmetric carbon, and the *trans*-geometry of the double bond was retained. This methodology is being applied in our laboratory to the synthesis of Δ^1-pyrroline boranyl complexes.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380144.

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(15) A mixture of iron powder (30 g) and 10% HCl (25 mL) was stirred vigorously for 1 min. The solution was then filtered off and the iron powder was washed successively with distilled water (5 × 25 mL) and absolute EtOH (5 × 25 mL).
(16) **Synthesis of 4a–h; General Procedure:** To a solution of (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **3a**–**h** (0.31 mmol) in a mixture of THF–MeOH (2:1, 6 mL) was successively added at r.t., AcOH (4.98 mmol) and activated iron powder (14.0 mmol). The resulting mixture was heated at 65 °C for 15 h under a nitrogen atmosphere. After cooling to r.t., the reaction mixture was filtered through Celite and rinsed with EtOAc. The resultant solution was washed with sat. aq $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane–EtOAc, 80:20). Finally the residues were crystallized from hexane–EtOAc to furnish the desired compounds **4a**–**h**.
Compound 4a: Yield: 72%; brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.0, 2.3 Hz, 2 H, H-2′,6′), 7.45–7.19 (m, 8 H, H-3′,5′, H-4′, H-2″,6″, H-3″,5″, H-4″), 6.47 (d, *J* = 15.8 Hz, 1 H, H-β), 6.24 (dd, *J* = 15.8, 7.9 Hz, 1 H, H-α), 4.33 (dd, *J* = 15.6, 7.2 Hz, 2 H, H-5), 3.90 (dd, *J* = 15.6, 5.1 Hz, 1 H, H-5), 3.36–3.19 (m, 2 H, H-3, H-4), 2.97–2.81 (m, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7 (C-2), 137.1 (C-1″), 134.2 (C-1′), 132.2 (C-α), 130.5 (C-4′), 129.9 (C-β), 128.5 (C-3′,5′,C-3″,5″), 127.5 (C-2′,6′), 127.2 (C-4″), 126.0 (C-2″,6″), 67.2 (C-5), 41.8 (C-3), 41.3 (C-4). HRMS (ESI$^+$): *m*/*z* [$C_{18}H_{17}N$ + H]$^+$ calcd for $C_{19}H_{17}N$: 248.1434; found: 248.1433. HPLC (*i*-PrOH–hexane, 10:90; flow rate 0.7 mL/min; λ = 254 nm): t_r = 10.90 [(*R*)-**4a**] min (*ee* = 99%).
Compound 4e: Yield: 44%; salmon solid; mp 110.6–111.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.6 Hz, 2 H, H-2′,6′), 7.55 (d, *J* = 8.6 Hz, 2 H, H-3′,5′), 7.37–7.18 (m, 5 H, H-2″,6″, H-3″,5″, H-4″), 6.46 (d, *J* = 15.8 Hz, 1 H, H-β), 6.23 (dd, *J* = 15.8, 8.2 Hz, 1 H, H-α), 4.38–4.24 (m, 1 H, H-5), 3.94–3.82 (m, 1 H, H-5), 3.38–3.16 (m, 2 H, H-3, H-4), 2.92–2.79 (m, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C-2), 137.0 (C-1″), 133.2 (C-4′), 132.0 (C-α), 131.7 (C-3′,5′), 130.2 (C-β), 129.1 (C-2′,6′), 128.6 (C-3″,5″), 127.4 (C-4″), 126.1 (C-2″,6″), 125.1 (C-1′), 67.4 (C-5), 41.8 (C-3), 41.4 (C-4). HRMS (ESI$^+$): *m*/*z* [$C_{18}H_{16}BrN$ + H]$^+$ calcd for $C_{18}H_{17}BrN$: 326.0539; found: 326.0537. HPLC (*i*-PrOH–hexane, 10:90; flow rate 0.7 mL/min; λ = 254 nm): t_r = 13.07 [(*R*)-**4e**] min (*ee* = 99%).
(17) Crystal data for **4d**: $C_{18}H_{16}ClN$; *M* = 281.77; orthorhombic; space group P212121; *Z* = 4; *a* = 5.6675(7) Å, *b* = 7.8846(12) Å, *c* = 32.643(3) Å, *α* = *β* = *γ* = 90.00°; *V* = 1458.7(3) Å^3; colorless crystal with crystal size of 0.10 × 0.08 × 0.04 mm was used. Of a total of 2942 reflections collected, 2022 were independent (*R*int = 0.0968). Final *R*1 = 0.0614 [*I* > 2σ(*I*)] and *wR*2 = 0.1591 (all data). Crystal data for **4e**: $C_{18}H_{16}FN$; *M* = 265.32; orthorhombic; space group P212121; *Z* = 4; *a* = 5.6544(6) Å, *b* = 7.9709(8) Å, *c* =

31.048(3) Å, $\alpha = \beta = \gamma = 90.00°$; $V = 1399.4(2)$ Å^3; colourless flake with crystal size of 0.50 × 0.20 × 0.04 mm. Of a total of 3068 reflections collected, 2834 were independent (*R*int = 0.0380). Final *R*1 = 0.0336 [$I > 2\sigma(I)$] and *wR*2 = 0.0796 (all data). CCDC-1033064 and 1033065 contain 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/datarequest/cif.