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Reductive aldol reactions on aromatic heterocycles

Timothy J. Donohoe,[a,*] Karl W. Ace,[a] Paul M. Guyo,[a] Madeleine Helliwell [a,†] and Jeffrey McKenna [b]

[a]*Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*
[b]*Rhône-Poulenc Rorer, Dagenham Research Centre, Dagenham, RM10 3RX, UK*

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Abstract

The Birch reduction of both pyrroles and furans can be quenched with an aldehyde electrophile, thus constituting a reductive aldol reaction. Although the reaction was not stereoselective, the pyrrolines derived from reduction of pyrroles could be oxidised and then reduced with $NaBH_4$ to provide *syn*-aldol adducts with high levels of stereoselectivity. The relative stereochemistry of two adducts was proven by X-ray crystallography. © 2000 Elsevier Science Ltd. All rights reserved.

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The aldol reaction is one of the most important carbon–carbon bond forming reactions used in synthesis; one of the principal reasons for its success is that control of both relative and absolute stereochemistry is possible.[1] Normally, the enolate component of an aldol reaction is generated by reaction of a carbonyl compound with base: however, other methods of enolate generation include conjugate addition to unsaturated carbonyl compounds and reduction of, for example, α-halo carbonyl compounds. There is another popular way of generating enolates, which involves reduction of aromatic carboxylic acids with a group I metal in ammonia:[2] however, to the best of our knowledge, reaction of such enolates with carbonyl electrophiles (in what would then constitute a Birch reductive aldol reaction) is unknown.[3]

As part of a programme designed to study the partial reduction of heterocycles, we recently examined the reductive alkylation of electron deficient pyrroles[4] and furans:[5] we believe that addition of two electrons to such heterocycles generates a dianion and subsequently (after protonation at C-5 by ammonia) an enolate, Scheme 1. This enolate is a willing partner in many alkylation reactions and in this paper we wish to report on the use of aldehydes as electrophiles in the Birch reduction. Our study has concentrated on the development of the reductive aldol reaction of pyrroles, as the products so produced may have application in the synthesis of natural products such as lactacystin and oxazolamycin.

* Corresponding author. E-mail: t.j.donohoe@man.ac.uk (T. J. Donohoe)
† Author to whom correspondence regarding the X-ray crystal structure should be addressed.

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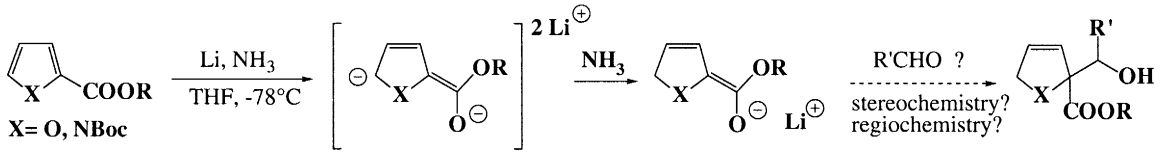
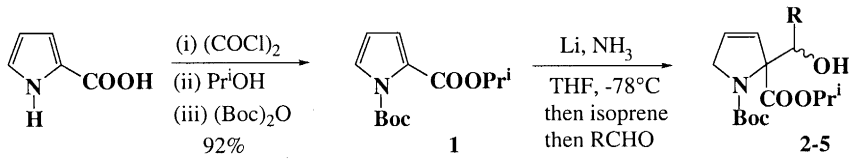


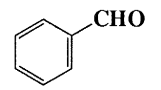
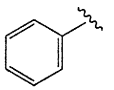
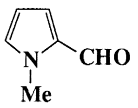
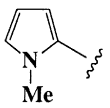
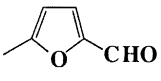
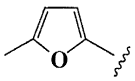
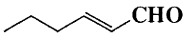
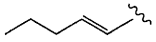
Scheme 1.

Compound **1** was prepared in a three high yielding steps from pyrrole-2 carboxylic acid and then subjected to reduction using lithium in ammonia/THF at −78°C. After quenching excess electrons with isoprene, the enolate was treated with a series of aldehydes (Scheme 2); in each case the result was a high yielding and regioselective aldol reaction (Table 1).[6]



Scheme 2.

Table 1
Each aldol adduct was formed as a 1:1 mixture of diastereoisomers

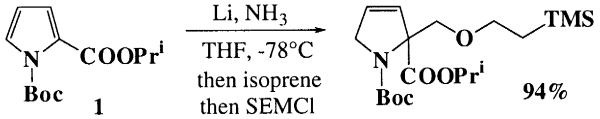
RCHO	R	Compound	Yield	RCHO	R	Compound	Yield
		**2**	91%			**4**	94%
		**3**	90%			**5**	78%

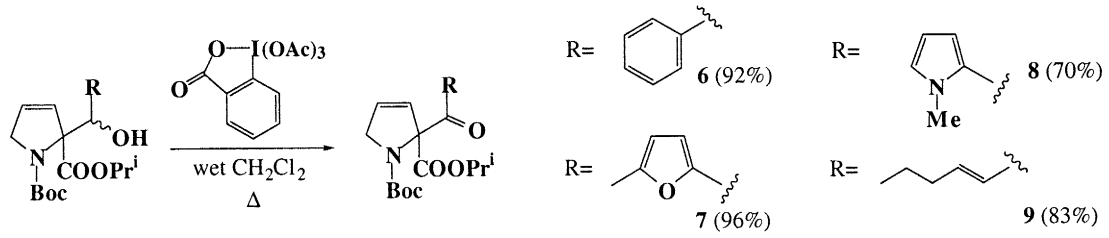
Presently, there are two limitations to this methodology: (i) the aldol adducts are formed as essentially 1:1 mixtures of diastereoisomers. It is unclear at this time whether the lack of stereoselectivity in the aldol reaction is a consequence of formation of a mixture of enolate geometric isomers or whether there is a lack of stereospecificity during the aldol reaction of either one of these isomers; and (ii) enolisable aldehydes, such as Pr^{i}CHO, protonate the enolate and so do not give aldol adducts using this protocol.‡

In an attempt to address the first issue raised above and control the stereochemistry of the aldol adducts **2**–**5**, we subjected each mixture to an oxidation/reduction sequence. Several oxidants were screened for the transformation of these hindered secondary alcohols to ketones, and only the Dess–Martin reagent, activated by water, gave good yields (Scheme 3).[7]

Ketones **6**–**9** were then reduced with sodium borohydride and cerium trichloride in isopropanol solvent (−78°C→rt) Scheme 4; we were delighted to observe high stereoselectivity for formation of the *syn* diastereoisomer. The $CeCl_3$ additive appeared to speed-up the rate of reduction, thus allowing (more

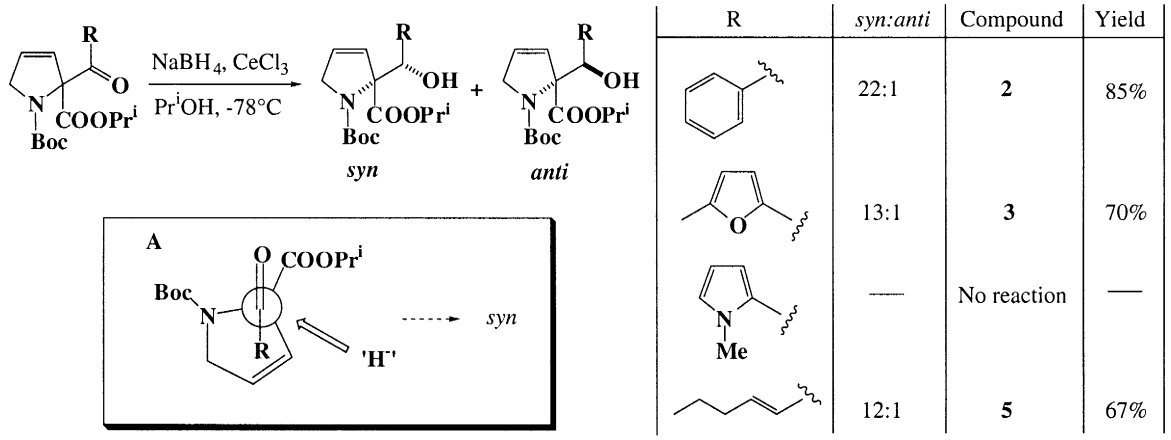
‡ Very reactive electrophiles such as formaldehyde were also not suitable for the reductive aldol reaction, although related compounds could be accessed by Birch reduction of **1**, followed by quenching with SEMCl.





Scheme 3.

selective) reaction at a lower temperature. Isopropanol tended to give slightly more stereoselective results than methanol solvent, and we presume that this is a consequence of a more bulky (and therefore more discriminating) alkoxyborohydride reducing agent. Compound **8** resisted attempts at reduction using $NaBH_4$ and use of more powerful reducing agents gave multi-component mixtures: presumably the ketone carbonyl in **8** is conjugated with the pyrrole nitrogen (ν C=O 1657 cm^{-1}) and is therefore relatively unreactive.



R	*syn:anti*	Compound	Yield
	22:1	**2**	85%
	13:1	**3**	70%
	—	No reaction	—
	12:1	**5**	67%

Scheme 4. The diastereoselectivity of the reaction was assessed by GC and in comparison with a 1:1 mixture of isomers from the Birch reduction. Compound **6** was reduced satisfactorily without cerium trichloride additive. Compound *syn*-**5** was formed with approximately 10% of a by-product which may be the 1,4 reduced adduct

We should like to note that the *syn* selectivity observed during reduction is consistent with the Felkin–Anh model so long as we assign the following sizes to groups attached to C-2 of the heterocycle, NBoc=large, $COOPr^i$=medium, and C=C=small (**A**, Scheme 4: this ordering seems reasonable on both steric and electronic grounds).[8]

The relative stereochemistry of the aldol adducts was difficult to ascertain by NMR spectroscopy and was secured by X-ray crystallographic analysis of *syn*-**2** (Fig. 1).

The relative stereochemistry of both *syn*-**3** and *syn*-**5** was assigned by analogy and in the knowledge that there were several features in the spectroscopic data of the *syn* diastereoisomers that helped to reinforce our assignment (for example, each *syn* isomer had a low field, D_2O exchangeable, doublet in the ^1H NMR spectrum). This data allowed us to assign one of the diastereoisomers of **4** as *syn*: this compound was separated and the structure proven by X-ray crystallography (Fig. 1).

In addition, we also attempted the reductive aldol reaction on furan **10** and obtained a good yield of product **11** (formed as a 1:1 mixture of diastereoisomers) (Scheme 5). Unfortunately, the ketone derived

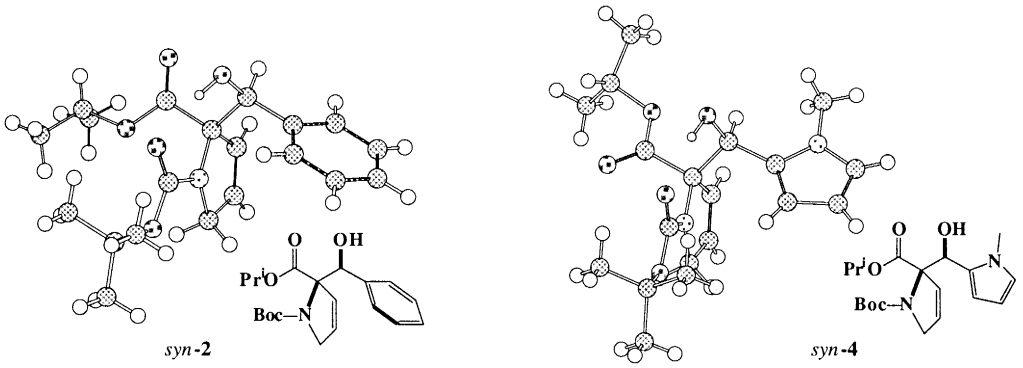
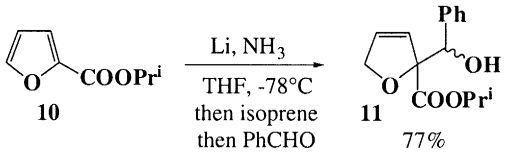


Fig. 1.

from oxidation of **11** was not reduced stereoselectively by the borohydride/$CeCl_3$ mixture; clearly, the Boc group on the nitrogen of **3**–**5** is essential in attaining a good selectivity.



Scheme 5.

To conclude, we have shown that aldehydes may be used as electrophilic partners for the Birch reaction. Although the adducts were formed as 1:1 mixtures of diastereoisomers, the *syn*-aldol compounds could be obtained readily via a two step oxidation/reduction procedure.

Representative experimental procedure: A solution of **1** (269 mg, 1.1 mmol), in THF (10 mL) was added dropwise to a blue solution of ammonia (50 mL), THF (10 mL) and lithium (19 mg, 2.7 mmol) at −78°C under nitrogen. After 15 min, isoprene (3 drops) was added followed by *trans*-hexenal (412 μL) and the reaction stirred at −78°C for 2 h. A saturated solution of NH_4Cl (10 mL) was added and the mixture warmed to room temperature, under a stream of nitrogen, to remove the ammonia. Brine (50 mL) was added and the mixture extracted with ethyl acetate (4×50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica (eluting with ethyl acetate:petrol, 1:9) gave **5** as a colourless oil (293 mg, 78%).

Acknowledgements

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