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Diastereoselective reductive aldol reactions of Boc-protected electron deficient pyrroles

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Abstract—An *anti*-selective reductive aldol reaction of a Boc-protected, 2-substituted pyrrole is reported. Reduction with LiDBB generates an exocyclic lithium enolate, but optimal stereoselectivity is obtained by transmetallation to magnesium with $MgBr_2 \cdot OEt_2$. The corresponding *syn*-aldols can easily be obtained (protected as carbamates) by subsequent inversion.

Partial reduction of a pyrrole, coupled with an aldol reaction is an attractive approach to the synthesis of many pyrrolidine-containing natural products. Lactacystin **1** (Fig. 1) (a potent inhibitor of proteasome-mediated degradation of ubiquitin-tagged proteins[1]) and kaitocephalin **2** (a novel NMDA and AMPA/KA receptor antagonist[2]) are both examples of structures which could be assembled using a reductive aldol reaction as a key step. Lactacystin would require an *anti*-selective† aldol reaction, whereas kaitocephalin would need the opposite (*syn*) stereochemical arrangement.

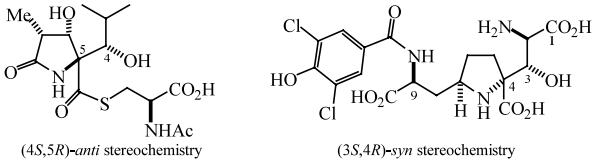
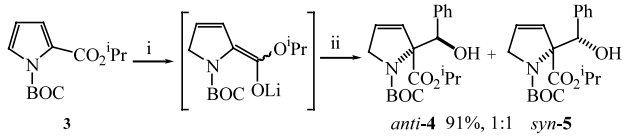


Figure 1. Structures of lactacystin and kaitocephalin.

In an earlier report[3] we disclosed details of a general procedure for the Birch reductive aldol reaction of aromatic heterocycles. One of the examples of this reaction was the reduction of pyrrole **3**, quenching with benzaldehyde to give the aldol products *anti*-**4** and *syn*-**5** (Scheme 1). However, this methodology has two drawbacks: (i) only non-enolisable aldehydes undergo the aldol reaction; (ii) the aldol products are formed as a 1:1 mixture of diastereoisomers.



Scheme 1. Reductive aldol reaction. *Reagents*: (i) Li, NH_3, THF, −78°C; (ii) PhCHO, then NH_4Cl.

We have recently reported another set of reaction conditions for accomplishing the partial reduction of aromatic compounds.[4] Termed 'ammonia free', these conditions involve lithium di-*tert*-butylbiphenylide (LiDBB) as a source of electrons and bis(methoxyethylamine) (BMEA) as a protonating agent, all in THF at low temperature (see Scheme 2).

It has now been discovered that enolisable aldehydes can be used successfully in the ammonia-free partial reduction and in marked contrast to the traditional Birch reduction,[3] no trace of dihydropyrrole was detected in the reaction mixture. It was surprising to discover during this investigation that reports of aldol reactions of exocyclic (extended) enolates are somewhat rare in the literature:[5] stereoselective examples are even rarer.[6] An improvement made to the previously published 'ammonia free' reaction conditions[4] was the

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† All aldol products are drawn in their 'chain-extended' form. In this way, use of the conventional aldol terminology '*anti*' and '*syn*' refers to the stereochemical relationship (as drawn) between the two groups on the α- and β-carbon atoms of the aldol adduct with highest priority under the Cahn–Ingold–Prelog classification.

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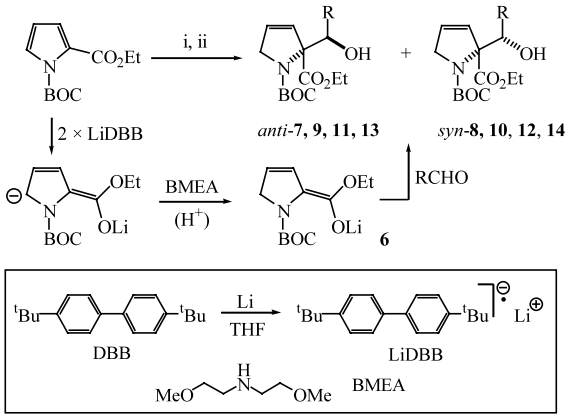


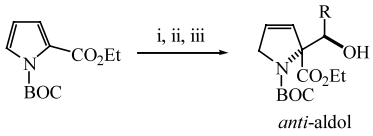
Scheme 2. Products of reductive aldol reaction under ammonia free conditions. *Reagents*: (i) LiDBB, BMEA, THF, −78°C, then $BrCH_2CH_2Br$; (ii) RCHO, then NH_4Cl.

Table 1. Results of aldol reactions of lithium enolate **6**

RCHO	Compounds	Yield (%)	d.r. (*anti*:*syn*)‡
MeCHO	*anti*-**7** and *syn*-**8**	69	1.8:1
^{i}PrCHO	*anti*-**9** and *syn*-**10**	74	8.0:1
^{t}BuCHO	*anti*-**11** and *syn*-**12**	71	5.3:1
PhCHO	*anti*-**13** and *syn*-**14**	73	1.8:1

development of a 'quench' for LiDBB prior to the addition of the aldehyde. Once the substrate has been reduced by the LiDBB solution, 1,2-dibromoethane is added to destroy any remaining LiDBB (an excess of this reagent does not react with the enolate at −78°C). Previously the electrophile (aldehyde) itself was responsible for quenching the LiDBB; this gave by-products that hampered the purification process. Scheme 2 and Table 1‡ show the results obtained for four simple aldehydes (RCHO), where R is Me, ^{i}Pr, ^{t}Bu or Ph. With the exception of benzaldehyde, none of these aldehydes give any aldol products in liquid ammonia. As well as being compatible with enolisable aldehydes, this reaction also showed promising signs of stereoselectivity (Table 1).

Encouraged by the inherent *anti*-selectivity§ of our reaction conditions, we investigated transmetallation of the lithium enolate **6** onto other metals commonly used in aldol reactions,[7] namely boron, magnesium, titanium and zinc. The use of dibutylboron triflate (Bu_2BOTf), chlorotitanium triisopropoxide and zinc bromide all failed to give improved ratios of *anti*-**7** to *syn*-**8** with acetaldehyde. The use of Bu_2BOTf was particularly troublesome, as the aldol boronates produced could not be successfully hydrolysed. However, transmetallation of the lithium enolate **6** with 1 equiv. of magnesium bromide diethyl etherate ($MgBr_2{\cdot}OEt_2$) improved the stereoselectivity for all of the aliphatic aldehydes used though no improvement was noticed for benzaldehyde. This improved aldol procedure is summarised in Scheme 3 and Table 2.

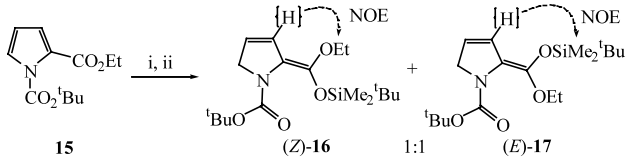


Scheme 3. *anti*-Aldol reaction with magnesium bromide as a Lewis acid. *Reagents*: (i) LiDBB, BMEA, THF, −78°C, then $BrCH_2CH_2Br$; (ii) $MgBr_2{\cdot}OEt_2$; (iii) RCHO, then NH_4Cl.

Table 2. Results of aldol reactions of magnesium enolate

RCHO	Compounds	Yield (%)	d.r. (*anti*:*syn*)†
MeCHO	*anti*-**7** and *syn*-**8**	70	7.6:1
^{i}PrCHO	*anti*-**9** and *syn*-**10**	72	>20:1
^{t}BuCHO	*anti*-**11** and *syn*-**12**	68	7.4:1
PhCHO	*anti*-**13** and *syn*-**14**	76	1.5:1

In order to understand better the origin of the diastereoselectivity of this aldol reaction we endeavoured to trap the exocyclic enolate (compound **6**, Scheme 2) as a silyl ketene acetal using *tert*-butyldimethylsilyl triflate. The trapping experiment revealed the presence of largely one enolate, only a trace of its geometrical isomer was detectable by 400 MHz ^{1}H NMR. To confirm the stereochemical identity of the enolate a sample of both enolate isomers was sought so that we could perform NOE experiments. It transpired that reduction of the pyrrole **15** with sodium naphthalenide (NaNp) and quenching with ^{t}BuMe$_2$SiOTf gave a 1:1 mixture of the two silyl ketene acetals (*Z*)-**16** and (*E*)-**17** (Scheme 4). A one-dimensional DPFGSE (double pulsed-field-gradient spin-echo)[8] NOE experiment performed on the mixture of silyl ketene acetals, established the enolate stereochemistry of each unambiguously.

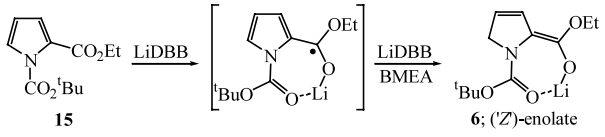


Scheme 4. Determination of enolate stereochemistry. *Reagents*: (i) NaNp, BMEA, THF, −78°C; (ii) ^{t}BuMe$_2$SiOTf, then pH 7 buffer.

‡ Diastereomeric ratios (d.r.) were determined by integration of the vinylic protons of the aldol products in the 400 MHz ^{1}H NMR spectrum of the crude reaction product.

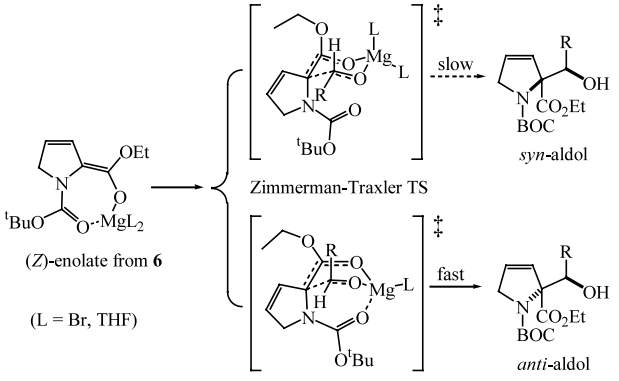
§ The relative stereochemistry has been proven by X-ray crystallography on a derivative of the adduct *anti*-**9**. Stereochemistry of the other compounds is assigned by analogy and by comparison of their spectroscopic data with compound *anti*-**9** (see Ref. 3).

Hence, we can be sure that the ('*Z*')-lithium enolate¶ **6** is generated on reduction of pyrrole **15** with LiDBB; chelation of Li^+ to the Boc group prior to the stereochemical determining event (which could be either the first or second electron transfer, Scheme 5) would explain this observation. It would also explain why generation of the enolate by reduction with sodium naphthalenide was non-stereoselective.



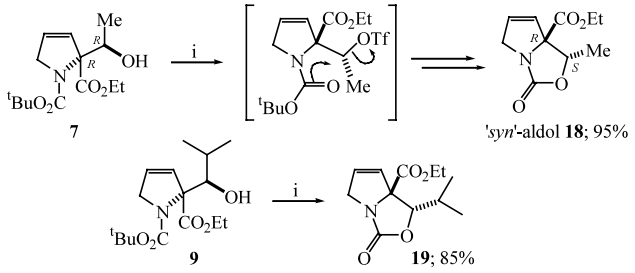
Scheme 5. Suggested explanation for observed enolate stereochemistry.

If a Zimmerman–Traxler transition state[9] is invoked (Scheme 6), with the R group of the aldehyde adopting an equatorial position in the chair transition state, the aldol reaction is predicted to be *syn*-selective! Through a series of control experiments, we were able to show that no equilibration was taking place and so an argument based on kinetic control is required. The observed diastereoselectivity may be rationalised by assuming that the metal atom retains its chelation to the carbonyl of the Boc group throughout the aldol reaction (Scheme 6). Three-point chelation of the metal atom will force a boat-like transition state to be adopted. In order to minimise interactions in the transition state, the R group of the aldehyde appears to be best accommodated in a pseudo-axial position, in this way the pyrroline ring and the R group of the aldehyde are kept furthest apart. The transition state thus depicted would lead to an *anti*-aldol product.



Scheme 6. Proposed explanation for *anti*-stereochemistry.

At this time, we have been unable to obtain the *syn* aldol isomers directly from the reductive aldol reaction. However we can achieve this transformation indirectly: the carbinol stereogenic centre could be inverted by using the Boc protecting group as an intramolecular nucleophile. Thus, treatment of *anti*-aldol **7** with trifluoromethanesulfonic anhydride and proton-sponge® in dichloromethane gave the *syn*-aldol (i.e. **8**) protected as its carbamate **18** (Scheme 7). Similarly, *anti*-aldol **9** could be cleanly inverted to give the carbamate **19**. The relative stereochemistry of the carbamate **19** has been proven by X-ray crystallography on a crystalline derivative.



Scheme 7. Protected *syn*-aldols prepared by stereochemical inversion. *Reagents*: (i) Tf_2O, proton-sponge®, CH_2Cl_2, −78°C to rt.

In conclusion, *anti*-selective reductive aldol reactions of Boc-protected, 2-substituted pyrroles have been demonstrated using enolisable aldehydes. The *anti*-aldols obtained in this way may be cleanly inverted in a single step to give the complementary *syn*-aldols protected as their carbamates. We anticipate that the methodology outlined in this letter will prove useful in the synthesis of natural products such as compounds **1** and **2**.

Representative procedure for the *anti*-selective reductive aldol reaction

Small strips of lithium foil (28 mg, 4.0 mmol) were placed in a Schlenk tube containing 4,4′-di-*tert*-butylbiphenyl (DBB) (1.1 g, 4.0 mmol) and some glass 'anti-bumping' granules. The tube was evacuated and purged with argon several times. The contents were stirred until the lithium foil was completely reduced to powder. Freshly distilled tetrahydrofuran (25 ml) was added (giving a turquoise solution) and the tube was cooled to −78°C under a positive pressure of argon. Pyrrole **15** (239 mg, 1.0 mmol) and bis-(methoxyethyl)amine (BMEA) (180 μl, 1.2 mmol) in freshly distilled THF (10 ml) were added dropwise over 5 min. (The turquoise colour persisted throughout the course of the substrate addition.) The reaction mixture was stirred at −78°C for a further 10 min and 1,2-dibromoethane (300 μl, 3.5 mmol) was added. After stirring for 15 min, magnesium bromide diethyl etherate (280 mg, 1.1 mmol) was added in one portion and the solution was stirred rapidly for 30 min. Isobutyraldehyde (200 μl, 2.2 mmol) was then added dropwise and after a further 10 min the reaction was quenched with saturated ammonium chloride solution (5 ml). The reaction mixture was warmed to room temperature and poured into dilute hydrochloric acid (1 M, 50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2×50

¶ To avoid confusion when describing enolate geometry, OM (where M is *any* metal) is always given precedence over OR under the Cahn–Ingold–Prelog classification. The major enolate **6** is assigned (*Z*)-stereochemistry irrespective of whether M is Li or Mg.

ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a crude product. Purification by chromatography on silica gel eluting with (i) petrol gave DBB (1.1 g) and (ii) petrol–acetone (4%) gave the aldols *anti*-**9** and *syn*-**10** (225 mg, 72%) in a 20:1 ratio as an oil. ^{1}H NMR data for compound *anti*-**9**: δ_H (400 MHz, $CDCl_3$) 6.01 (1H, dt, *J* 6.4 and 2.0 Hz, HC=CH), 5.96 (2H, s, HC=CH), 5.93 (1H, dt, *J* 6.4 and 2.0 Hz, HC=CH), 4.46–4.03 (10H, m, CH_2N, CH_2O and C*H*OH), 3.90 (1H, br. d, *J* 2.0 Hz, OH), 3.63 (1H, br. d, *J* 2.4 Hz, OH), 1.87–1.74 (2H, m, C*H*Me$_2$), 1.47 (9H, s, ^{t}Bu), 1.44 (9H, s, ^{t}Bu), 1.27 (3H, t, *J* 7.2 Hz, OCH$_2$*Me*), 1.23 (3H, t, *J* 6.8 Hz, CH$_2$*Me*), 1.00 (3H, d, *J* 7.2 Hz, Me), 0.98 (3H, d, *J* 6.4 Hz, Me), 0.90 (3H, d, *J* 6.8 Hz, Me) and 0.87 (3H, d, *J* 6.8 Hz, Me). (N.B. Doubling of ^{1}H NMR resonances due to Boc rotamers.)

Representative procedure for inversion of *anti*-aldols

anti-Aldol **9** (72 mg, 0.23 mmol) and proton-sponge® (98 mg, 0.46 mmol) were dissolved in dichloromethane (1.5 ml) and the reaction was cooled to −78°C under an argon atmosphere. Trifluoromethanesulfonic anhydride (60 μl, 0.36 mmol) was added and the orange solution stirred for one hour before warming to room temperature. The mixture was poured into dilute hydrochloric acid (1 M, 50 ml) and extracted with diethyl ether (3×50 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a crude product. Purification by chromatography on silica gel eluting with petrol–acetone (5%) gave the carbamate **19** as an oil (47 mg, 85%). ^{1}H NMR data for compound **19**: δ_H (400 MHz, $CDCl_3$) 6.18 (1H, dt, *J* 6.0 and 1.6 Hz, H_AC=CH_B), 5.99 (1H, ddd, *J* 6.0, 2.4 and 2.0 Hz, H_AC=CH_B), 4.52 (1H, d, *J* 8.4 Hz, C*H*^{i}Pr), 4.46 (1H, dt, *J* 15.6 and 2.0 Hz, CH_AH_BN), 4.21 (2H, q, *J* 6.8 Hz, OCH_2CH$_3$), 3.97 (1H, ddd, *J* 15.6, 2.8 and 1.6 Hz, CH$_A$$H_B$N), 1.86 (1H, dsp, *J* 8.4 and 6.8 Hz, C*H*Me$_A$Me$_B$), 1.28 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3), 1.07 (3H, d, *J* 6.8 Hz, CH*Me*$_A$Me$_B$) and 1.03 (3H, d, *J* 6.4 Hz, CHMe$_A$*Me*$_B$).

Acknowledgements

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