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Enantiopure oxazolidinones as chiral acids in the asymmetric protonation of *N*-Boc pyrrole derived enolates

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The first use of geminally disubstituted oxazolidinones as chiral protonating agents is described: these new acids are able to directly protonate an enolate generated by the ammonia free partial reduction of an electron deficient pyrrole and give up to 68% ee in the pyrroline product.

The reaction of metal enolates with a chiral proton source offers the opportunity to prepare enantiomerically enriched carbonyl compounds possessing an α-stereocentre (Scheme 1).[1] A substantial amount of information has been acquired regarding such a conceptually simple transformation with much progress made towards developing synthetically useful protocols. However, a number of drawbacks exist with such enantioselective protonation strategies.

A significant problem related to such an approach relates to the importance of controlling the *E*/*Z* geometry of the enolate during its formation. The presence of both geometrical enolates creates diastereomeric transition states leading to increased complexity in issues involving stereoselection.

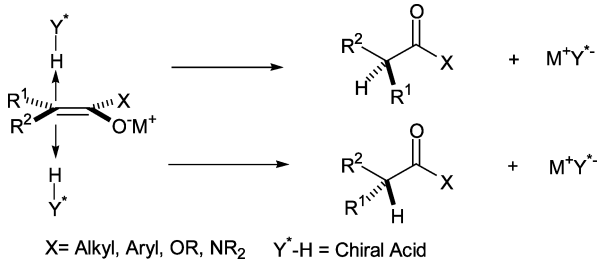
Recently, we have been engaged in a study regarding the utility of ester enolates formed *via* partial reduction of ester substituted *N*-Boc pyrroles under ammonia free (AF) conditions.[2] Accordingly, enolates thus generated have been successfully reacted with alkyl halides, aldehydes, ketones, chloroformates, and disulfides (Scheme 2).

Of note amongst these transformations are the highly diastereoselective reductive aldol reactions with aldehydes. Integral to such high diastereoselectivity is formation of the *Z*-lithium enolate under the ammonia free Birch conditions. This has been explained by invoking coordination of both ester and carbamate carbonyl groups to a lithium center during the reduction process (Scheme 2).

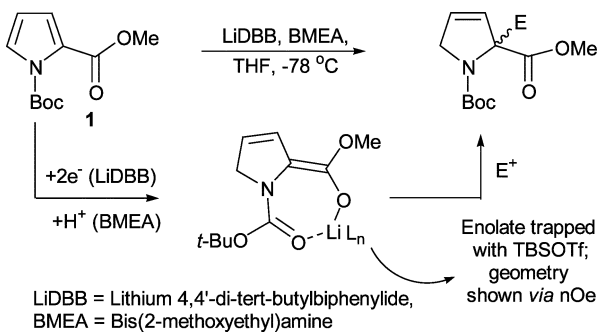
We believed such good *E*/*Z* control during the reduction would allow the possibility of investigating pyrrole derived enolates in enantioselective protonation reactions. Our goal was to locate an easily accessible proton source that would allow access to synthetically useful enantioenriched pyrroline systems. Initial focus centred upon use of amino acid derived nitrogen acids and in particular oxazolidinones (Scheme 3). A number of phenylalanine derived systems were initially examined in conjunction with the ammonia free reduction of pyrrole **1** using LiDBB in THF at −78 °C, with the results described in Table 1.

Initially the commercially available oxazolidinone **3** (R = H, Z = O) was examined and observed to furnish pyrroline (*R*)-**2** in 58% yield yet with disappointing enantiomeric excess of 11%.†[3,4] Progression to the 5 *gem* dimethyl analogue **4** led to a similar chemical yield yet with improved ee (46%).[5] Utilisation of commercially available 5 *gem* diphenyl analogue **5** showed that the observed ee increased to 68%.[6] Hence, the geminal functionality at the 5 position is seen to profoundly affect enantioselectivity. We have rationalised this increasing selectivity through a greater tendency to position the benzyl group over the acidic N–H bond where it interacts with the enolate. This trend would be expected to increase with greater steric bulk of R at C-5 (*cf.* H, Me, Ph) and thus higher facial selectivity is seen. Interestingly, changing the proton source from an oxazolidinone to an oxazolidinethione (**6**) resulted in formation of the opposite enantiomer of the pyrroline to that observed with proton sources **3–5**.

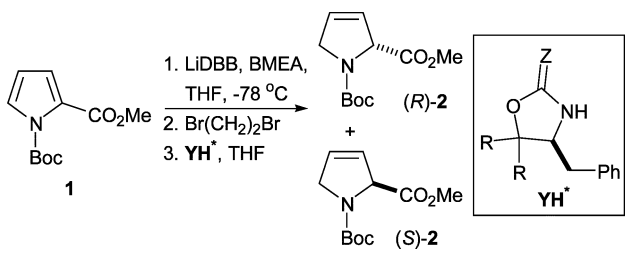
Next, we chose to alter the steric bulk of the pyrrole ester in conjunction with chiral proton source **5**. Accordingly, isopropyl and *tert*-butyl ester pyrroles were subjected to the same tandem reduction–chiral protonation protocol (Table 2). Interestingly, the observed enantioselectivity was observed to fall on increasing the steric bulk of the ester. This trend suggests that part of oxazolidinone **5** is directed towards the vicinity of the ester alkoxy moiety. As the alkoxy group increases in size the energy benefit of



Scheme 1 Enantioselective protonation of enolates.



Scheme 2 Ammonia free Birch reduction of pyrroles.



Scheme 3 Ammonia free Birch reduction of *N*-Boc pyrroles.

Table 1 Protonation enantioselectivity with chiral acids **3–6**

Entry	Oxazolidinone (YH*)	R	Z	Yield (%)	ee (*R*/*S*)
1	**3**	H	O	58	11 (*R*)
2	**4**	Me	O	57	46 (*R*)
3	**5**	Ph	O	50	68 (*R*)
4	**6**	Ph	S	55	31 (*S*)

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placing a group here reduces with a concomitant lowering in enantioselectivity, although the effect is small.

We were also intrigued about the role that coordination between the oxazolidinone C=O and enolate counter ion may play in the protonation reaction. We surmised the use of a metal which may enhance such coordination would improve the observed ee. However, when transmetallating from lithium to magnesium by addition of $MgBr_2{\cdot}OEt_2$, a substantial loss in facial selectivity was observed (Table 3). Moreover, the addition of TMEDA or HMPA, prior to protonation, may be expected to sequester the lithium cation and minimise coordination between enolate and **5**. In fact, this made only a small difference with a minimal fall in enantioselectivity for TMEDA. This suggests the protonation transition structure geometry is not influenced by coordination between **5** and the enolate metal counter ion.

We wish to propose a model (Fig. 1) that accounts for the observed facial selectivity based upon two assumptions. Firstly, that there is no coordination between the oxazolidinone carbonyl and enolate counter ion (*vide supra*; models based on chelation also predict the wrong outcome). Secondly, protonation of either enolate face occurs with the oxazolidinone benzyl group directed into the pocket of space between the pyrroline ring and the alkoxy moiety of the ester enolate (close to the C-3 hydrogen). With the benzyl group directed into this pocket, facial differentiation may be rationalised by the interactions of the oxazolidinone carbonyl group. Protonation on the favoured face sees the C=O directed above the *t*-Boc carbonyl carbon. In contrast, protonation on the unfavoured face sees the carbonyl positioned above the THF solvated enolate counter ion. We feel this steric interaction between the oxazolidinone carbonyl and THF solvated lithium enolate is the more costly interaction. In support of this model, as the size of the ester increases the size of the spatial pocket for the benzyl group diminishes, leading to reduced selectivity. Furthermore, this model predicts an unfavourable steric interaction between the pyrroline ring and the ring proton of **5** in the disfavoured case which is not predicted to occur in the favoured case.

Table 2 Effect of variation of pyrrole ester moiety

Entry	Oxazolidinone (YH*)	Ester	Yield (%)	ee (*R*/*S*)
1	**5**	Me	50	68 (*R*)
2	**5**	*i*-Pr	50	53 (*R*)
3	**5**	*t*-Bu	60	46 (*R*)

Table 3 Effect of additives on enantioselective protonation

Entry	Chiral acid (YH*)	Additive	Yield (%)	ee (*R*/*S*)
1	**5**	$MgBr_2{\cdot}OEt_2$	46	31 (*R*)
2	**6**	$MgBr_2{\cdot}OEt_2$	25	18 (*S*)
3	**5**	TMEDA	50	65 (*R*)
4	**6**	TMEDA	25	18 (*S*)
5	**5**	HMPA	45	44 (*R*)

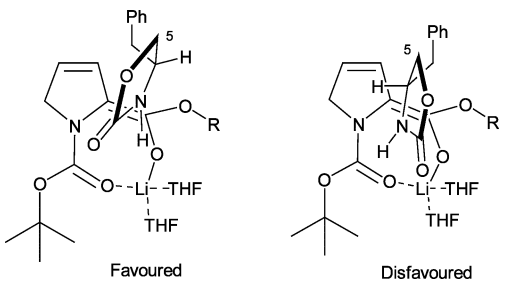
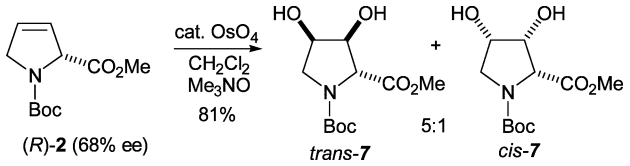


Fig. 1 Enantioselectivity model; for clarity the C-5 phenyls are omitted and the enantiomer of oxazolidinone is switched in the disfavoured case.



Scheme 4 Dihydroxylation of **2**. Formation of dihydroxyproline.

Recently, a number of multistep syntheses of *trans*-dihydroxy prolines have been reported.[7] This naturally occurring proline based amino acid (Scheme 4) was recently isolated from an adhesive protein produced by the marine mussel *Mytilus edulis*.[8] Rapid access to the enantioenriched pyrroline unit using our methodology has allowed a direct synthesis of such amino acids. Accordingly, treatment of (*R*)-**2** with catalytic OsO_4 and trimethylamine-*N*-oxide in dichloromethane furnished a 5 : 1 mixture of the protected amino acid *trans*-**7**.[9]

To conclude, we have developed a novel set of chiral acids that are compatible with the partial reduction reaction of aromatic compounds; moreover, the optimum chiral acid **5** is commercially available. Optimisation of the oxazolidinone structure and application to other systems are underway.

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Notes and references

† Representative procedure: Strips of lithium metal (23.4 mg, 3.37 mmol, 4.4 equiv.) and DBB (915 mg, 3.43 mmol, 4.4 equiv.) were ground together with anti-bumping granules in a Schlenk tube under a positive pressure of argon for 3 hours until a homogenous black powder formed. The mixture was cooled to −78 °C, solvated in THF (20 ml) and stirred for 10 minutes. Pyrrole **1** (174 mg, 0.77 mmol, 1.0 equiv.) and BMEA (136 μl, 0.99 mmol, 1.2 equiv.) in THF (5 ml) were added dropwise over 5 minutes and stirred for a further 5 minutes before the dropwise addition of 1,2-dibromoethane (until disappearance of the turquoise colour). The brown reaction mixture was stirred for 5 minutes before addition of (*S*)-**5** (535 mg, 1.62 mmol, 2.1 equiv.) in THF (30 ml) slowly down the side of the Schlenk wall. After 1 hour the reaction was quenched with sat. NH_4Cl (5 ml) and diluted with ether (20 ml) before being warmed to room temperature, poured into 1 M HCl (30 ml), extracted with ether (2 × 30 ml), washed with brine, dried over $MgSO_4$ and filtered through a pad of Celite. Removal of solvent *in vacuo* and purification on silica (petrol/ether 4 : 1) gave **2** (87 mg, 50%). Enantiomeric excess was determined through HPLC (Chiralpak AD) by comparison to a racemic standard. The configuration of the major enantiomer was determined through comparison of the specific rotation of **2** with that prepared from *trans*-hydroxy proline.[4]

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