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Enantioselective Partial Reduction of 2,5-Disubstituted Pyrroles via a Chiral Protonation Approach

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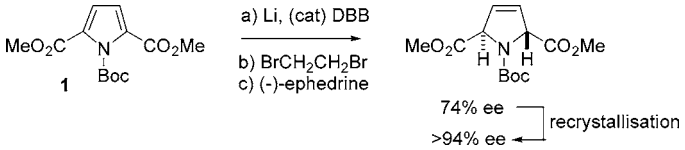
ABSTRACT



The partial reduction of 2,5-pyrrole diester 1 followed by enantioselective protonation in situ to furnish synthetically useful building blocks is described. An enantiomeric excess of up to 74% was achieved using (–)-ephedrine and related analogues as chiral proton sources. The pyrroline product obtained could be recrystallized to give enantiomerically pure material.

Our research over the past few years has focused on developing the partial reduction of heterocycles using Birch-type conditions.[1] Partial reduction of an aromatic heterocycle is a particularly useful transformation (as opposed to complete reduction) because it leaves an alkene unit intact for further elaboration.

When substituted heterocycles are reduced, one or more stereogenic centers are created and, therefore, a capacity for stereocontrol (relative and absolute) during the reaction would be a powerful tool. We chose to focus on reduction of compound **1** (which can be made in good yield and in one step from commercially available *N*-Boc pyrrole[2]) as this provides a useful building block for natural product synthesis. Partial reduction of **1** followed by protonation gave two possible diastereomeric products **2** with the two ester groups adopting either a *cis* or a *trans* relationship to each other depending on the reaction conditions (Scheme 1). Standard Birch conditions (i.e., sodium in liquid ammonia/THF at −78 °C, quenching with NH_4Cl) gave selectivity in favor of *trans*-**2** (Scheme 1, condition a);[3] the products were formed in a 6:1 ratio. Conversely, employing "ammonia-free" Birch conditions,[2,4] namely, lithium metal in THF with catalytic DBB (di-*tert*-butylbiphenyl) at −78 °C before quenching with a bulky proton source (2,6-di-*tert*-butylphenol) furnishes *meso cis*-**2** with a selectivity of >10:1 (Scheme 1, condition b).

The compound *trans*-**2** is a versatile starting material for natural products synthesis and has already been used to prepare (2*R*,5*R*)-bis(hydroxymethyl)-(3*R*,4*R*)-dihydroxypyrrolidine (DMDP)[2] and 5-*epi*-australine.[5] Therefore, we wished to develop a protocol for formation of the *trans*

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(1) (a) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667. (b) Donohoe, T. J.; Guyo, P. M.; Harji, R. R.; Helliwell, M. *Tetrahedron Lett.* **1998**, *39*, 3075. (c) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Chem. Commun.* **1999**, 141.
(2) Donohoe T. J.; Headley C. E.; Cousins R. P. C.; Cowley A. *Org. Lett.* **2003**, *5*, 999.
(3) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1327.
(4) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331.
(5) Donohoe, T. J.; Sintim, H. O. *Org. Lett.* **2004**, *6*, 2003.

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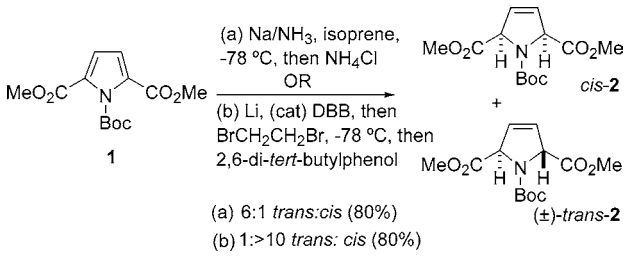
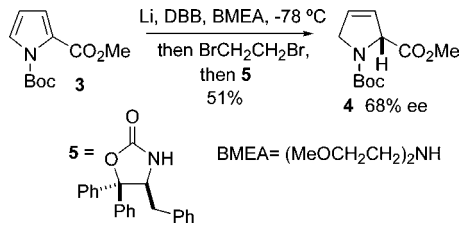
Scheme 1. Control of Relative Stereochemistry During Partial Reduction



diastereoisomer with enantioselectivity and envisaged that this could be achieved using a chiral protonation strategy. This method, first pioneered by Duhamel, involves protonation using a chiral proton source that is able to discriminate between the two faces of a prochiral enolate.[6] To date we have already had some success using this approach; pyrrole **3** can be reduced and protonated in 68% ee using **5** as a proton source (Scheme 2).[7]

Scheme 2. Control of Absolute Stereochemistry During Partial Reduction

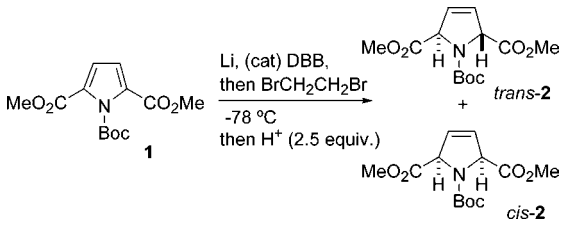


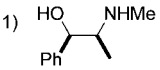
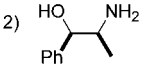
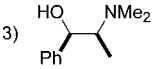
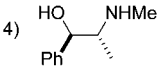
In addition to controlling the enantioselectivity of formation of *trans*-**2** from the reduction of **1**, the accompanying issue of diastereoselectivity must be addressed to minimize formation of the *meso cis*-diastereoisomer.

The enantioselective reduction of **1** was then examined utilizing a variety of chiral acids. Disappointing results were observed using oxazolidinones such as **5**, and therefore various alternative chiral proton sources were screened. It was found that 2.5 equiv of (−)-ephedrine gave the best results, furnishing **2** in 84% yield as a 1:1 mixture of diastereoisomers (which were separable by flash column chromatography). The *trans* diastereoisomer was found to have an enantiomeric excess of 74% (Scheme 3). Moreover, it was also possible to recrystallize this enantiomerically enriched product from light petroleum/ether, furnishing material with >94% ee (Scheme 3, entry 1).

The absolute stereochemistry of the product was proven by hydrogenation of the double bond and comparison of the

Scheme 3. Using Ephedrine To Control Absolute Stereochemistry



	source of H^+	yield (%)	trans/cis	ee (%)*
1)	 (-)-ephedrine	84	1:1	74 → >94 Δ
2)	 (-)-norephedrine	52	1:1	66
3)	 (-)-N-methylephedrine	83	1:1	74
4)	 (-)-pseudoephedrine	81	1:1	40

* ee determined by HPLC using a chiral column and in comparison with a racemic standard.
Δ recrystallisation from light petroleum:ether (73% yield).

sign of the specific rotation with literature values; *trans*-**2** as obtained above is predominantly the (*R*,*R*) isomer.[8]

Several ephedrine analogues were then examined as proton sources in an attempt to increase the enantioselectivity and also to gain some insight into the mechanism of the reaction. It would appear that the *N*-substituent does not greatly affect either the ee or the diastereomeric ratio: (−)-norephedrine and (−)-*N*-methyl ephedrine (Scheme 3, entries 2 and 3) give results comparable to those observed with ephedrine. It would appear that the absolute stereochemistry of the product is determined predominately by the carbon center bearing the hydroxyl group. Hence, (−)-pseudoephedrine, epimeric at the center bearing the nitrogen, gives the same absolute stereochemistry as (−)-ephedrine but with a lower enantiomeric excess (Scheme 3, entry 4).

Next we sought to understand more about the structural requirement for enantioselective protonation and performed some modifications to the ephedrine molecule.

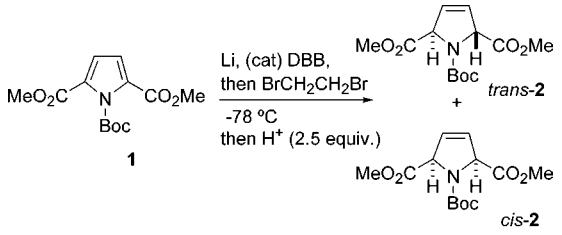
Ephedrine possesses two potentially acidic protons: the hydroxyl proton and the secondary amine proton. It is reasonable to assume that it is the acidic proton on the hydroxyl group that quenches the enolate; in support of this rationale, when *N*-methylephedrine (which possesses a tertiary rather than a secondary amino group) was used, the results were comparable to those observed with ephedrine, (Scheme 3, entry 3).

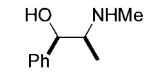
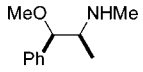
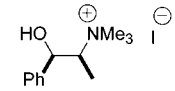
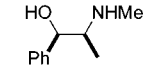
(6) Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. Martin, J.; Lasne, M. C.; Plaquevent, J.-C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181. For reviews, see: Fehr, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2567. Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1.

(7) Carbery, D. R.; Donohoe, T. J. *Chem. Commun.* **2004**, 722.

(8) Sasaki, N. A.; Sagnard, I. *Tetrahedron* **1994**, *50*, 7093.

Scheme 4. Probing the Ephedrine Structure



	source of H^+	yield (%)	trans/cis	ee (%)
1)	 (-)-ephedrine	84	1:1	74
2)		35	1:1	0
3)		83	1:1	0
4)	 (-)-ephedrine.1/2 H_2O	60	1:1	62

To further demonstrate that this is the case, the *O*-methyl derivative of ephedrine was prepared and used as a proton source (Scheme 4, entry 2). As before the product was formed as a 1:1 mixture of diastereoisomers; however, the yield was significantly lower (35%) and the product was racemic, implying that the amino NH is not sufficiently acidic to quench the enolate intermediate. We presume that the bisenolate remains in solution until it is quenched by the addition of NH_4Cl (resulting in racemic product).

The importance of chelation between the nitrogen and the oxygen of the proton source and a lithium counterion was investigated when we prepared the quaternary salt of ephedrine and used it as a proton source (Scheme 4, entry 3). In this case the diastereomeric ratio was 1:1 and the product was again racemic; from this observation it is reasonable to assume that the bidentate nature of the proton source plays an important role in coordinating to the lithium cation, making the transition state more rigid and resulting in the selectivity observed.

It would also appear that the presence of water in the reaction has little detrimental effect: use of ephedrine hemihydrate as a proton source gave a slightly lower ee and yield, but a reasonably high level of selectivity was still observed (Scheme 4, entry 4). This has interesting ramifications for the use of an auxiliary proton source and catalytic amounts of an ephedrine.[9]

The observed results can be further analyzed by considering the mechanism of reduction and the possibility of selectivity during each protonation (Figure 1). The reduction involves the addition of two electrons to **1** to form a

(9) See: Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891.

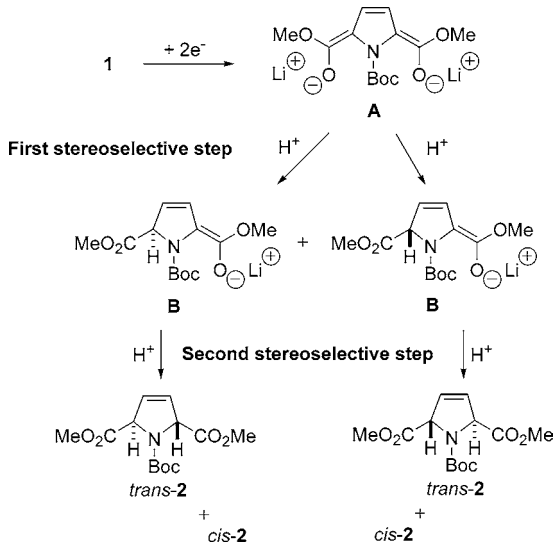
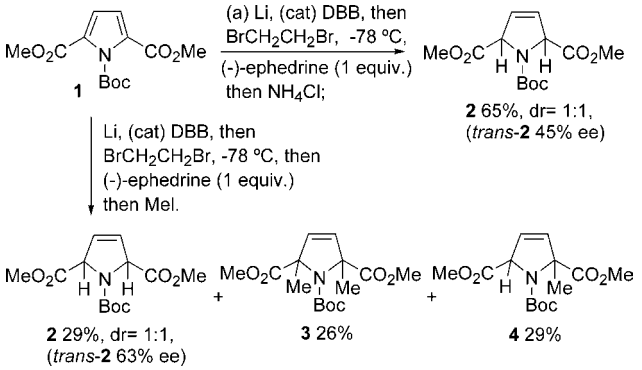


Figure 1. Mechanism for the partial reduction.

(relatively) stable dianion **A** (geometry not known). Upon quenching, intermediate **A** is then protonated twice to give the product (**1** → **A** → **B** → **2**).

We decided to explore this pathway by forming dianion **A** and then quenching it with 1 equiv of (−)-ephedrine followed by the addition of ammonium chloride (Scheme 5). This should allow us to probe the selectivity of the first

Scheme 5. Partial Quenching Experiments



protonation step as the ee of *trans*-**2** generated in this way should give us the selectivity of the first protonation. Intriguingly, the result of this experiment gave *trans*-**2** with 45% ee.[10] Initially, we suspected that this was an indication of a pathway that involved two stereoselective steps and resulted in chiral amplification.[11] However, a model that involves two stereoselective steps cannot predict both a high enantiomeric excess and a 1:1 mixture of diastereoisomers.

(10) Variation in time differences between the addition of ephedrine and the NH_4Cl quench made no difference to the outcome of this reaction. This control was performed to check if anion **B** was formed with high enantioselectivity and then racemizing; the results showed that it was not.

To check that the 1 equiv of ephedrine reaction was correct, we repeated the reduction of **1**, quenched with 1 equiv of (−)-ephedrine, and then flooded the reaction with methyl iodide (previous experiments had shown that the dianion **A** could be completely dimethylated when reacted with MeI). The results of this experiment were a surprise as they did not show complete monomethylation (of **B**) as expected from our model (Scheme 5). Instead, this experiment gave a mixture of both *cis*- and *trans*-**2**, dimethyl compound **3**, and monomethyl derivative **4**. The relative amounts of the four products did not vary significantly when we changed the time intervals between addition of the two electrophiles; the ee of *trans*-**2** was consistently 63%.

The results of these experiments hint at a complex behavior of the dianion **A** under these partial quenching conditions. If 1 equiv of ephedrine had protonated **A** once, then the outcome (after MeI quench) should be complete formation of monomethyl compound **4**. If, however, this dianion had reacted twice with the ephedrine (1 equiv), then we would expect *cis*- and *trans*-**2** (50%, with *trans*-**2** of 74% ee) together with the dimethyl compound **3** (50%) derived from dimethylation of the remaining dianion.

The fact that we observe products from at least two plausible reaction pathways implies that no single mechanism is sufficient to describe the product distribution under these conditions.

In fact, the results shown in Scheme 5 tell us that the reduction of **1**, quenching with ephedrine (1 equiv) and then ammonium chloride, does NOT give an insight into the facial selectivity for the first protonation step, and this makes the prospect of chiral amplification in the earlier system less likely.

We note that if either of the two protonation steps has zero facial selectivity and the other 6.7:1 selectivity, then the predicted outcome from the reaction with excess ephedrine would be dr of 1:1 and an ee of 74%—exactly what is observed. At present our intuition is that the reactive dianion **A** would be the likely contender for an intermediate showing low facial selectivity, although our experiments do not allow us to prove this.

To conclude, we have successfully developed a methodology for the synthesis of useful precursors for natural product synthesis using modified Birch conditions followed by a chiral protonation strategy. This uses cheap, readily available ephedrine as a proton source and furnishes material in high yields and high enantiomeric excess. The proton source is also available as both enantiomers, allowing access to the reduced pyrrole diester in both enantiomeric forms.

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Supporting Information Available: Copies of ^{1}H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org

OL049014Q

(11) We thank a referee for useful comments about our model and for the suggestion that *cis*- and *trans*-**2** might interconvert after the addition of ephedrine to dianion **A**. In a control experiment, exposure of *cis*-**2** to the lithium alkoxide of ephedrine at −78 °C showed that it was inert to deprotonation.