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Cycloaddition of Homochiral Imidazolinium Ylides: A Route to Optically Active Pyrroloimidazoles

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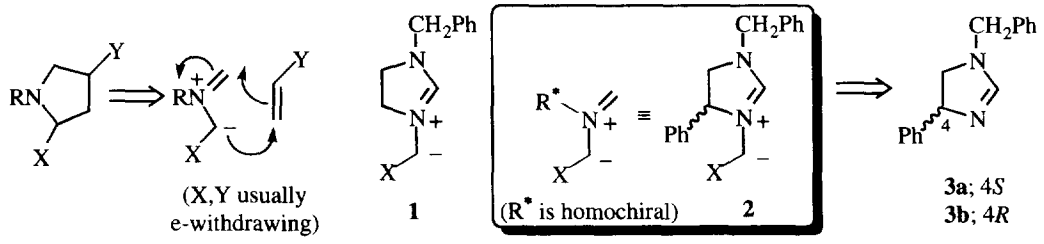
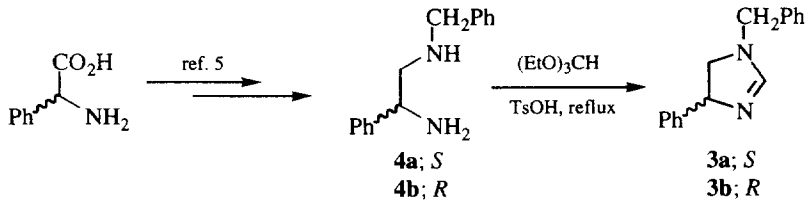
Abstract: The synthesis of either enantiomer of 1-benzyl-4-phenyl-2-imidazoline from phenylglycine is described. 'One-pot' generation and enantioselective 1,3-dipolar cycloaddition of homochiral azomethine ylides prepared from these imidazolines with a range of alkene dipolarophiles affords optically active hexahydropyrroloimidazole adducts.

The 1,3-dipolar cycloaddition of azomethine ylides to alkene dipolarophiles is a rapid way to assemble pyrrolidine rings, as shown schematically in Scheme 1. The stereodefined transition states of such pericyclic processes are also ideally suited to the asymmetric synthesis of such systems, as required for the many natural product targets containing pyrrolidine rings or fused pyrrolidines. One approach is to use a homochiral auxiliary substituent on nitrogen, but rotational freedom around the N-to-auxiliary bond presents difficulties for predicting facial selectivity. We have recently discovered a route to pyrrolidines using imidazolinium ylides **1**,[2] and now report the extension of this work to the homochiral 4-phenyl-imidazolinium ylides **2**, available as either enantiomer, wherein the auxiliary is conformationally restrained by virtue of the heterocyclic ring.[3] The facial selectivity of the ylides in cycloadditions is thus fully predictable. The phenyl substituent is designed to facilitate ultimate removal of the templating atoms.[4]



Scheme 1

The precursors to the ylides **2** are the imidazolines **3a,b**, easily prepared [$(EtO)_3CH$ solvent, toluene-p-sulphonic acid, reflux; *S* 86%, *R* 86%] from the homochiral diamines **4a,b**, Scheme 2, whose synthesis from *S*- or *R*- phenylglycine, respectively, we have recently reported.[5] Quaternisation of the imidazolines proved a very slow process even with active halides such as methyl bromoacetate, being incomplete after several days at 20°C, or 23 h at reflux in THF; addition of KI had no effect. However, given our findings[6] of the sensitivity of the imidazolinium salts to adventitious moisture, we developed a revised 'one-pot' protocol

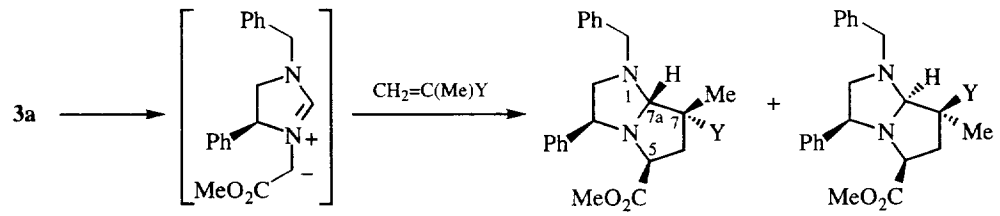


4a; *S*
4b; *R*

3a; *S*
3b; *R*

Scheme 2

whereby the salt is consumed as it is formed.[5] Thus, imidazolines **3** were separately mixed with alkylating agent and dipolarophile (3 mol equiv.) in dry THF and heated to reflux, when 1 mol equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added dropwise over 4h followed by a further 2h at reflux. Isolation then provided the hexahydropyrrolo[1,2-*a*]imidazole cycloadducts,[7] forming *three* of the five bonds of the new pyrrolidine ring in one pot. Using methyl bromoacetate as alkylating agent and methyl methacrylate as dipolarophile gave cycloadducts **5a**[8] (53%) from *S*-imidazoline **3a**, and **5b** (55%) from *R*-imidazoline **3b**, Scheme 3, as single enantiomers. With methacrylonitrile as dipolarophile, bicycles **5c** (24%, unoptimised) and **5d** (41%), respectively, were obtained as the major products.



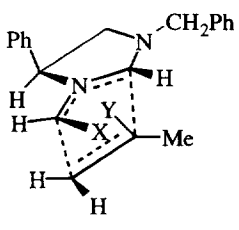
Y = CO_2Me — 53% **5a** (from *R*-enantiomer **3b**, 55% **5b**)

Y = CN — 24% **5c** (from *R*-enantiomer **3b**, 41% **5d**)

3% **5e** (from *R*-enantiomer **3b**, 5% **5f**)

Scheme 3

The absolute stereochemistry of the adducts is as illustrated and was secured by ^1H n.O.e. difference spectroscopy.[9] This stereochemical outcome of the cycloaddition is consistent with an *endo* approach of the dipole and dipolarophile, with the dipole having the *anti* geometry and facial selectivity provided by the 4-phenyl substituent in the dipole, as summarised in the transition state **6**.[2] We did not generally observe any other cycloadduct diastereoisomers with ester dipolarophiles, but with nitrile dipolarophiles a minor isomer corresponding to *exo* approach could be isolated. Thus, nitrile **5c** was isolated along with small amounts of **5e** (*endo*:*exo* 8:1), and nitrile **5d** with small amounts of **5f** (*endo*:*exo* 8:1). Interestingly, however, ^1H n.O.e.



6

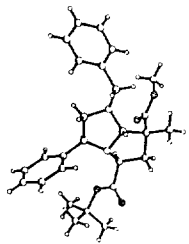
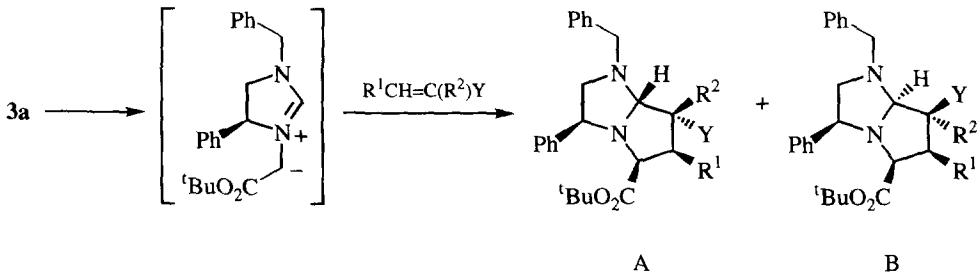


Figure 1

difference spectroscopy showed that the stereochemistry at C-7a in the *exo* adducts was opposite to that predicted by our transition state model for *exo* addition. It is likely that *exo* addition occurs in the expected fashion and is followed by an epimerisation at C-7a, since the alternative antarafacial addition across the dipole is energetically disfavoured.[10]

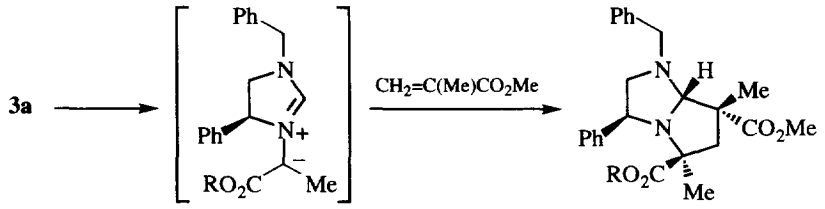
With *t*-butyl bromoacetate as alkylating agent, adducts **5g** and **5h** were produced using methyl methacrylate as dipolarophile from *S*- and *R*-imidazoline **3** respectively, Scheme 4. It proved possible to crystallise **5g**, and a single crystal X-ray analysis, Figure 1,[11] confirmed the structure to be as shown, in agreement with our ^{1}H n.O.e. studies. Methacrylonitrile afforded the corresponding adducts **5i** and **5j**; some *exo* adduct was also isolated: **5i** with **5k** (*endo:exo* 7:1); **5j** with **5l** (*endo:exo* 8:1). Using dipolarophiles lacking a substituent α to the activating group the corresponding cycloadducts were obtained. Thus methyl and *t*-butyl acrylates gave bicycles **5m** and **5n** , and **5o** and **5p** with the appropriate imidazolines.[12] In the case of *t*-butyl acrylate some of the *exo* isomer was also produced. Hence **5o** was isolated along with **5q** (*endo:exo* 20:1) and **5p** with **5r** (*endo:exo* 25:1). Once again ^{1}H n.O.e. studies showed that the *exo* adducts had the opposite stereochemistry at C-7a to that predicted by our transition state model. It was pleasing to find that the cycloadditions using *t*-butyl bromoacetate as alkylating agent were the most efficient to date. Extending the range of dipolarophiles we examined the addition of the 1,2-disubstituted alkene methyl (*E*)-crotonate which afforded bicycles **5s** (46%) and **5t** (26%, not optimised) from **3a** and **3b** respectively. Phenyl vinyl sulphone gave **5u** (33%) from **3b**, and methyl vinyl ketone afforded **5v** (71%).

Alternative alkylating agents were also investigated. Ethyl 2-bromopropionate afforded the C-5, C-7 quaternary adduct **5w** (29%) in the cycloaddition with imidazoline **3b** and methyl methacrylate, and *t*-butyl



Scheme 4

	Adduct A	Adduct B
R^1 = H, R^2 = Me, Y = CO_2Me	61% **5g** (from *R*-enantiomer **3b**, 62% **5h**)	
R^1 = H, R^2 = Me, Y = CN	27% **5i** (from *R*-enantiomer **3b**, 22% **5j**)	4% **5k** (from *R*-enantiomer **3b**, 3% **5l**)
R^1 = H, R^2 = H, Y = CO_2Me	65% **5m** (from *R*-enantiomer **3b**, 63% **5n**)	
R^1 = H, R^2 = H, Y = $CO_2{}^tBu$	59% **5o** (from *R*-enantiomer **3b**, 49% **5p**)	3% **5q** (from *R*-enantiomer **3b**, 2% **5r**)
R^1 = Me, R^2 = H, Y = CO_2Me	46% **5s** (from *R*-enantiomer **3b**, 26% **5t**)	
R^1 = H, R^2 = H, Y = SO_2Ph	33% **5u**	
R^1 = H, R^2 = H, Y = COMe	71% **5v**	



R = Et 29% **5w**

R = ^{t}Bu 23% **5x**

Scheme 5

2-bromopropionate afforded adduct **5x** (23%) from **3b** and methyl methacrylate, Scheme 5.

In conclusion, we have developed an enantioselective route to homochiral hexahydropyrrolo[1,2-*a*]-imidazoles via a 1,3-dipolar cycloaddition, allowing the generation of up to four stereocentres with complete stereocontrol and forming *three* of the five bonds of the new pyrrolidine ring in one pot. Extension of this work to the production of homochiral pyrrolidines by removal of the templating atoms is reported in the following Letter.[4]

References and Notes

1. Current address: Chemistry Department, Open University, Walton Hall, Milton Keynes MK7 6AA.
2. Jones, R.C.F.; Nichols, J.R.; Cox, M.T. *Tetrahedron Lett.*, **1990**, *31*, 2333.
3. For other examples of conformationally restrained azomethine ylides see: Harwood, L.M.; Lilley, I.A. *Tetrahedron Lett.*, **1993**, *34*, 537; Williams, R.M.; Zhai, W.; Aldous, D.J.; Aldous, S.C. *J. Org. Chem.*, **1992**, *57*, 6527. For a related example of an azomethine ylide with rotational freedom see: Rouden, J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.*, **1989**, *30*, 5133.
4. Jones, R.C.F.; Howard, K.J.; Snaith, J.S. following *Letter*.
5. Jones, R.C.F.; Turner, I.; Howard, K.J. *Tetrahedron Lett.*, **1993**, *34*, 6329.
6. Jones, R.C.F.; Howard, K.J. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2391.
7. All new compounds gave spectral data (IR, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
8. Data for **5a**: colourless oil, $[\alpha]_D^{22}$ –15.6 (*c* 1.04, EtOH) (Found: C, 70.85; H, 7.2; N, 6.9%; M$^+$, 408.2001; $C_{24}H_{28}N_2O_4$ requires C, 70.6; H, 6.9; N, 6.9%; M, 408.2049); ν_{max} (film)/cm^{-1} 3062, 3028, 2949, 2804, 1731, 1454, 1265, 1205, 1132, 700; δ_H (250 MHz; $CDCl_3$) 1.50 (3H, s, CH_3C), 2.20 (1H, dd, *J* 9.9 & 13.2, CC*H*H), 2.44 (1H, dd, *J* 9.2 & 10.0, PhCHC*H*H), 2.77 (1H, dd, *J* 6.8 & 13.2, CCH*H*), 3.21 (2H, m, PhC*H*H & PhCHCH*H*), 3.34 & 3.81 (6H, 2 x s, 2 x OCH_3), 4.08 (1H, dd, *J* 6.7 & 9.9, C*H*CO), 4.13 (2H, m, PhCH*H* & PhC*H*CH_2), 4.31 (1H, s, C-7a H), 7.25 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 22.97 (*C*H_3C), 43.33 (C*C*H_2), 51.47 & 51.91 (2 x OCH_3), 53.29*C*CH_3), 58.41 (Ph*C*H_2), 64.66 (PhCH*C*H_2), 66.98 (*C*HC=O), 69.39 (Ph*C*HCH_2), 96.19 (C-7a), 127.00, 127.09, 127.16, 128.04, 128.24 & 128.83 (6 x ArCH), 138.38 & 141.33 (2 x ArC), 174.63 & 175.28 (2 x C=O); *m/z* 408 (M$^+$, 4%), 309 (29), 308 (100), 249 (36), 217 (13), 130 (12), 104 (34), 91 (87).
9. For example, for **5a**, n.O.e. enhancements were observed between the protons on the following carbons: C5→C3, C6(pro-*S*)→C5, C7(Me)→C6(pro-*R*), C7(Me)→C7a
10. Preliminary molecular mechanics calculations (Macromodel 4.0, MM2) surprisingly show the product of *exo* addition **5e** as higher in energy than the expected product, 7a-*epi*-**5e**, by over 60 kJmol^{-1}; cf. Jones, R.C.F.; Howard, K.J. *Electronic Conference on Trends in Organic Chemistry (ECTOC-1) ISBN 0 85404 899 5*, Eds. Rzepa, H.S.; Goodman, J.M. (CD-ROM), Royal Society of Chemistry publications, 1995. see also http://www.ch.ic.ac.uk/ectoc/
11. Jones, R.C.F.; Howard, K.J.; Snaith, J.S.; Steel, P.J. manuscript in preparation.
12. There is no evidence for the ring opening equilibrium observed in the achiral series, ref. 2.

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