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Asymmetric synthesis of 3-phenyl-2,3-methanophenylalanine developed by panning catalysts in a library format

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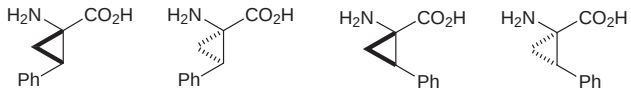
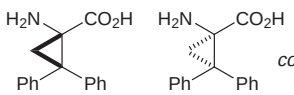
Optimal catalysts for the key cyclopropanation step in a synthesis of the title compound were identified by screening libraries of metal complex–ligand combinations; the synthesis was completed, and a derivative of the final product was crystallized to establish its solid state conformation.

Stereoisomers of 2,3-methanophenylalanine, 'cyclo-Phe', are useful phenylalanine surrogates for syntheses of conformationally constrained peptidomimetics.[1] They impart very specific steric perturbations at the *C*-terminal side or at the *N*-terminal side, depending on the cyclo-Phe isomer selected.[2] For some applications, however, it would be desirable to introduce this type of constraint at the *N*- and *C*-termini *simultaneously*. Consequently, we set about an asymmetric synthesis of 3-phenyl-2,3-methanophenylalanine, '3-Ph-cyclo-Phe'.



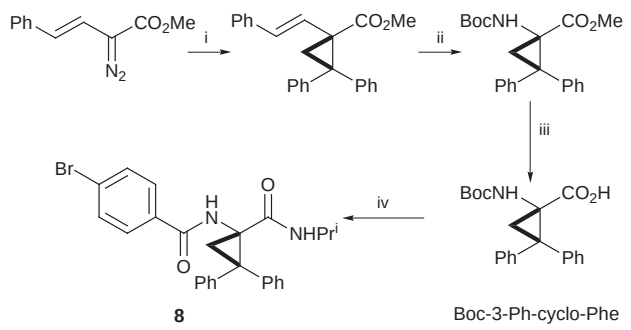
stereoisomers of cyclo-Phe



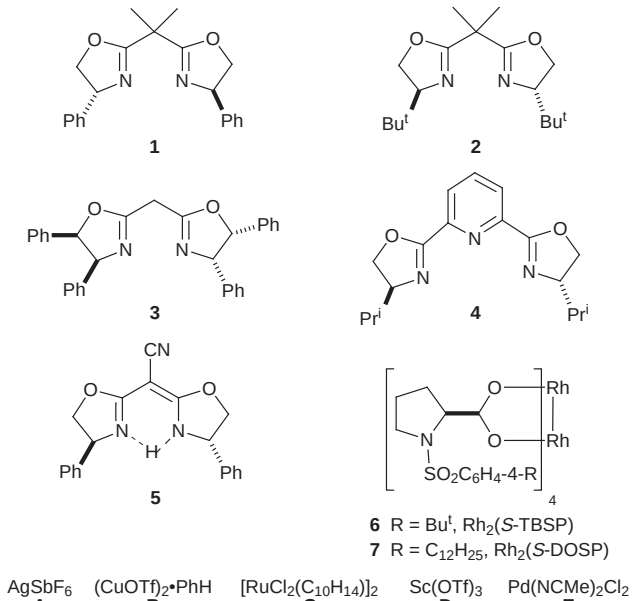
stereoisomers of 3-Ph-cyclo-Phe
constrain N- and C-termini simultaneously

Davies and co-workers have developed remarkably direct and effective syntheses of cyclo-Phe stereoisomers that involve enantio- and regio-selective cyclopropanations of phenylethene.[3] Doyle and co-workers have also shown 1,2-diphenylethene is a good substrate for asymmetric cyclopropanations using phenyl diazoacetate.[4] While it was apparent that the target compound identified above could be obtained using a modification of this approach (Scheme 1), the ideal catalyst for the cyclopropanation step was unknown. We therefore decided to screen some options in a library format.[5–9] This was done by manually weighing and pipetting catalysts and reagents into 24 glass vials set in wells drilled in a cooled aluminium block. Other papers from this laboratory describe the procedure used,[10] but some critical points are given here. All manipulations prior to the analysis were done in a glove box to maintain an inert atmosphere. After the reactions were mostly complete (TLC), the contents of each vial was manually filtered through a silica plug, an internal standard was introduced, and the sample was made up to a standard volume. The analysis was performed using an HPLC instrument equipped with an autosampler and a chiral column (Whelk-O *SS* , Regis Technologies). We estimate this protocol is one or two orders of magnitude faster than a conventional approach wherein a researcher would screen 2–3 reactions at a time.

Several generalities became apparent early in these investigations. First, the weighing errors with respect to the catalyst precursors became significant if the reactions were performed on 10 mg of diazo compound. The test reactions on a plate format were therefore performed on a 50 mg scale, and the important ones were checked on a larger scale. Second, pentane appeared to be the best solvent so this medium was used for all the latter screens. However, this provided a stringent test of reproducibility in these experiments because the data obtained using relatively insoluble catalyst precursors in this very apolar medium were related to the degree of agitation. Small stirrers were used in each well, but we were unable to arrange it so that they all spun smoothly; consequently, some reproducibility issues arose.† Nevertheless, the data obtained from the library screens did indicate promising catalysts for further development.



Scheme 1 *Reagents and conditions*: i, 1,1-diphenylethene (5 equiv.), Rh_2(*S*-TBSP)$_4$ (1 mol%), 0 °C, 24 h (86%, 97% ee); ii, cat $RuCl_3$, $NaIO_4$, MeCN–H_2O, CCl_4, 25 °C, 5 h then $(PhO)_2P(O)N_3$, NEt_3, Bu^tOH, reflux, 17 h (90% for 2 steps); iii, LiOH, aq. MeOH, reflux, 4 h (86%); iv, Pr^iNH_2, $Me_2NCFNMe_2{\cdot}PF_6$, CH_2Cl_2, Pr^iNEt_2, 0 °C, 30 min, then 50% TFA in CH_2Cl_2, 0–25 °C, 45 min, then 4-$BrC_6H_4CO_2H$, $Me_2NCFNMe_2{\cdot}PF_6$, CH_2Cl_2, Pr^iNEt_2, 25 °C, 45 min (32% for 3 steps).



AgSbF$_6$ **A** (CuOTf)$_2$•PhH **B** [RuCl$_2$(C$_{10}$H$_{14}$)]$_2$ **C** Sc(OTf)$_3$ **D** Pd(NCMe)$_2$Cl$_2$ **E**

Several libraries of catalysts were screened to check solvent effects, and metal–ligand combinations/ratios. This data, not shown here, enabled us to bias the screening process in later experiments. Consequently, Fig. 1 refers to a plate screen performed in the latter part of this work.

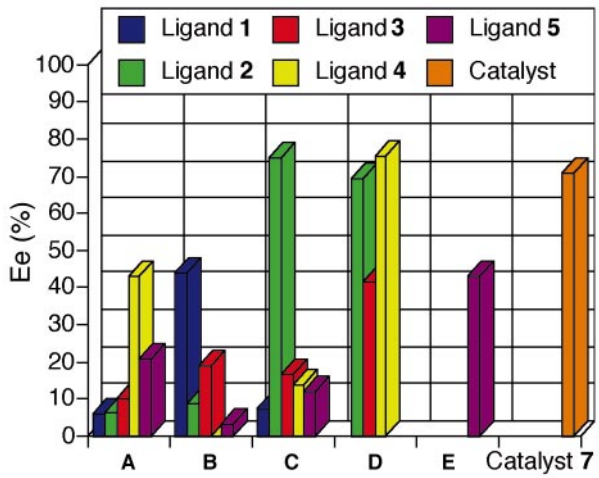


Fig. 1 Enantioselectivity data obtained from a library screen (% yields inset in columns). *Reaction conditions*: 1,2-diphenylethene (5 equiv.), metal (5 mol%), ligand:metal ratio = 1.5:1.0, pentane, 0 °C, 24 h.†

Table 1 Data for catalyst systems tested in conventional way[a]

Entry	Catalyst system	Metal/mol%	Ee (%)[b]	Yield (%)[c]
1[d]	**1B**	5.0	65[e]	62
2[d]	**2A**	5.0	24	2
3	**2B**	5.0	3 (9)	23 (4)[f]
4	**2C**	5.0	> 98 (75)	6 (14)[f]
5	**2D**	5.0	> 98 (69 and 78)	10 (6 and 24)[f]
6[d]	**2D**	5.0	> 98	1
7	**4D**	5.0	86 (75)	9 (16)[f]
8	**6**	10	94	85
9	**6**	5.0	97	88
10	**6**	1.0	97	86
11	**6**	0.1	89	63
12	**7**	1.0	> 98	50

[a] 50 mg scale, pentane, 0 °C, 1,2-diphenylethene (5 equiv.), ligand:metal = 1.5:1.0 for catalysts formed *in situ*. [b] Values in parentheses indicate data obtained in library screen. [c] Isolated yields unless otherwise indicated. [d] Reaction run at 25 °C. [e] > 95% ee after one recrystallization. [f] Measured *vs*. internal standard.

Data given in Fig. 1 and Table 1 indicate that the Davies/McKervey catalysts **6** and **7** were the most useful for the desired transformation. Other combinations gave poor yields and/or enantioselectivities except for the combination of copper triflate with ligand **1**. This gave product with a moderate enantioselectivity and yield, and the product could be crystallized to optical purity. This could be useful in some situations because the latter system, and the Davies/McKervey catalysts **6** and **7**, gave opposite enantiomers of the product.§

The synthesis of Boc-protected 3-Ph-cyclo-Phe was completed as indicated in Scheme 1. Absolute configurations here are assigned by extrapolation of Davies' model for enantioselective cyclopropanations with catalysts like **6** and **7**,[3,11] hence this must be regarded as a prediction rather than an established fact. Finally, a sample of this product was converted into diamide **8**, and single crystals of this material were formed for X-ray diffraction; a Chem3D diagram of the molecular structure is given in Fig. 2.¶ The observed φ,ψ angles (87.7, −152°) do not correspond closely with any idealized turn structure. The conformation seems to be governed by the phenyl rings adopting orientations with their faces beneath the *N*- and *C*-termini, with the *N*- and *C*-amide bonds in pseudo-parallel arrangements below these. Further studies are planned to elucidate less localized effects of 3-phenyl-cyclo-Phe on secondary structures.

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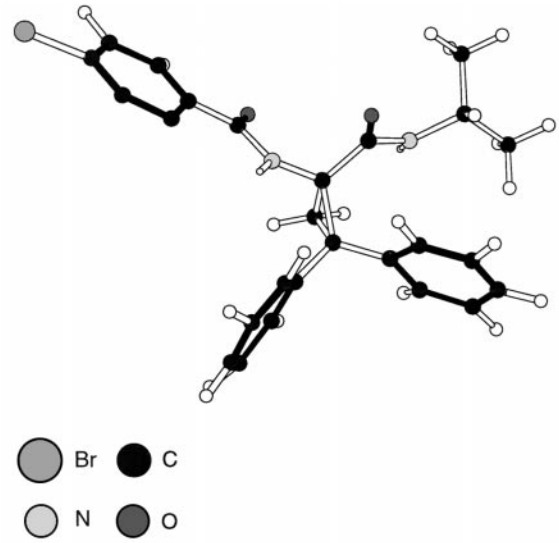

Fig. 2 Chem3D diagram of X-ray structure of 3-Ph-cyclo-Phe diamide.

Notes and references

† Four experiments were repeated on the same plate to check reproducibility in the same library; the worst correspondence of ee values was 26 *vs*. 6%, and the best was 19 *vs*. 18%. Table 1 shows the data obtained from experiments repeated on a larger scale, run in the conventional way. Five data points correspond to experiments that were performed in the plate format. The worst correspondence observed was for entry 5 (98 *vs*. 69% ee). In all five cases the ees obtained when the reactions were repeated on a large scale with efficient stirring were higher than those corresponding to the plate format.

‡ Percent yield for each well measured *vs*. an internal standard (1-acenaphthone): **1A** = 12%; **1B** = 23%; **1C** = 8%; **2A** = 18%; **2B** = 4%; **2C** = 14%; **2D** = 6%; **3A** = 12%; **3B** = 27%; **3C** = 2%; **3D** = 24%; **4A** = 41%; **4B** = 13%; **4C** = 1%; **4D** = 16%; **5A** = 29%; **5B** = 66%; **5C** = 1%; **5E** = 2%; catalyst **7** = 40%.

§ Both enantiomers of $Rh_2(TBSP)_4$ and of $Rh_2(DOSP)_4$ are commercially available from Aldrich, but in each case one is more expensive than the other.

¶ *Crystal data* for **8**: $C_{26}H_{25}N_2O_2Br{\cdot}1/2CH_2Cl_2$, M = 519.8 amu, triclinic, $P\bar{1}$, a = 12.423(3), b = 15.348(3), c = 16.332(3) Å, α = 63.02(2), β = 83.46(2), γ = 67.87(2)°, V = 2564(1) Å^3, Z = 2, T = 193(2) K, μ = 1.35 mm^{-1}, λ = 0.71073 Å, reflections measured: 5045, independent reflections: 4611, extinction coefficient = 0.0004(3), $R(F)$ [$I > 2\sigma(I)$] = 0.0865, $wR(F^2)$ [$I > 2\sigma(I)$] = 0.1118, $S(F^2)$ = 0.953. CCDC 182/1020.

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