Pergamon

Tetrahedron Letters 42 (2001) 8391–8394

TETRAHEDRON LETTERS

The synthesis of homochiral ligands based on [2.2]paracyclophane

Andrew Pelter,[a,*] Baldwin Mootoo,[b] Anderson Maxwell[b] and Alicia Reid[a,b]

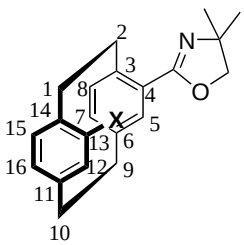
[a]*Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea, SA2 8PP, UK*
[b]*Department of Chemistry, University of the West Indies, St. Augustine, Trinidad and Tobago, West Indies*

Received 18 July 2001; revised 11 September 2001; accepted 21 September 2001

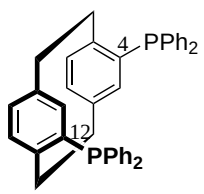
Abstract—A new *ortho*-lithiation of homochiral 4-*N*,*N*-diethylamido[2.2]paracyclophane **8** is the key to the production of a wide variety of 4,5-disubstituted homochiral ligands. ψ-Geminal bromination of **8** proceeds in high yields and the resulting bromide may be converted into a variety of 4,13-disubstituted ligands. The *o*-lithiation and ψ-geminal reactions can be used sequentially to give 4,5,12-trisubstituted compounds in which two liganding groups have the same geometrical relationship as in 'Phanephos'™. Homochiral oxazolines with only planar chirality have been made, one of which has been shown to be an effective catalyst for the Heck reaction.

Chiral synthesis is at the cutting edge of organic synthesis[1–3] due to the intellectual challenges posed and its potential importance, particularly in the pharmaceutical industry.[4] Due to the amplification of chirality, recent work has concentrated on catalytic reactions involving catalysts that may be homochiral or rendered so by ligation with homochiral ligands. Such ligands require a reasonably rigid framework and should be recoverable. Examples are 2,2-binaphthyls,[3] ferrocenes,[5] arene metal complexes[6] and metal carbonyl compounds[7] of planar chirality.

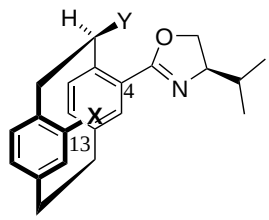
Some years ago we realised that substituted [2.2]paracyclophanes are readily available systems[8] that are chemically and chirally stable. The substituent groups on the [2.2]paracyclophane frame have rigidly defined geometrical relationships and it was surprising that the system had not received systematic investigation from the viewpoint of chiral synthesis.[9,10] We therefore incorporated the [2.2]paracyclophane (22PC) unit into unique amino acids of planar chirality[11–13] and showed that 4-alkylamino[2.2]paracyclophanes are effective chiral auxiliaries.[14] We further showed[13] that both secondary amide and oxazolinyl groups are ψ-geminal directing to give 4,13-disubstituted 22PC derivatives and produced racemic **1** and **2** as part of the first group of oxazolinyl[2.2]paracyclophanes (Fig. 1). We pointed out the potential of such compounds as chiral catalysts and indeed compound **1** has proved to be *a potent catalyst for the Heck reaction*.[15]



1 X = PPh_2 **2** X = SPh
6 X = H **7** X = Br



3



4 X =H, Y = SPh
5 X = $Ph_2C(OH)$, Y = H

Figure 1.

Keywords: homochiral ligands; [2.2]paracyclophane; *ortho*-lithiation; ψ-geminal substitution.
* Corresponding author. Tel.: +44 (0)1792 295258; fax: +44 (0)1792 295747; e-mail: a.pelter@swansea.ac.uk

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01808-1

In the recent expansion of chiral [2.2]paracyclophane investigations[16] particularly apposite, from our viewpoint, was the beautiful work of Pye and Rossen[17] who introduced homochiral (*S*)-[2.2] Phanephos™ **3** and its enantiomer as potent ligands for a variety of transition metal-catalysed reactions. Very recently Hou[18] introduced the bridge substituted oxazoline **4** for palladium-catalysed allylic alkylations. The synthesis of **4** was inefficient, bridge substitution occurring in only 12% yield. The same group[19] synthesised **5** and homologues as catalysts for the chiral addition of $ZnEt_2$ to aromatic aldehydes. In both cases the origin of chiral induction is not clear as more than one type of chirality is present.

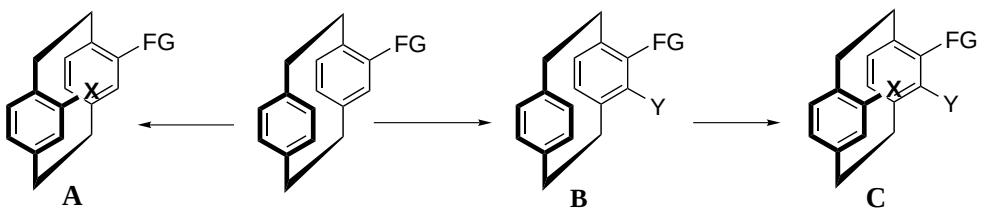
We now report that we have produced a novel *ortho*-lithiation reaction and combined it with ψ-geminal substitution to provide a flexible route to a wide variety of homochiral [2.2]paracyclophanes of potential use as ligands and as catalysts directly. The route is illustrated in Scheme 1. It depends critically on finding a substituent functional group that can have a dual role as an *ortho*-directing group for lithiation and is also capable of directing electrophilic substitution into the ψ-geminal (C-13) position. This would then give rise to the possibility of producing compounds belonging to classes A, B and C, the latter containing the 4,12 substitution pattern of Phanephos™ (Scheme 1).

We had already converted **6** into **7** and thence to **1** and **2** and therefore were sure that the oxazolinyl group was ψ-geminal directing. There are many examples[20] showing that oxazolinyl groups can direct lithiation to the *ortho*-position. However, extensive studies of the lithiation of **6** led only to mixtures, in which substitution at the bridge position (C-3) was evidenced in low yield but *ortho*-lithiation, though occurring, was not a clean reaction. These results parallel those of Hou.[18]

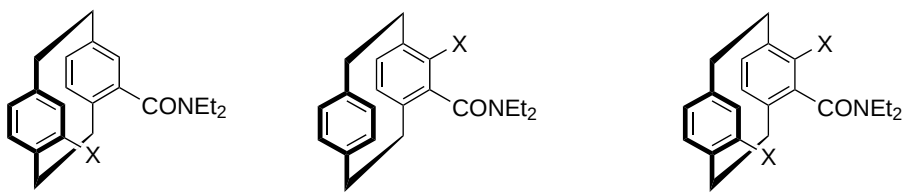
We tested a variety of groups such as CH_2OH, CH_2NEt_2 as *ortho*-directors (Scheme 1) but with no success, and we therefore turned to 4-*N*,*N*-diethylamido[2.2]paracyclophane **8**. Compound **8** was readily obtained in 92% yield from 4-carboxy[2.2]paracyclophane. One crystallisation of **8** of 97.4% e.e. gave an amide of >99.9% e.e. (chiral column), a very useful feature as compared with the acid. The recrystallised amide derived from the (−)-(*R*)-acid had mp 118–119°C, $[\alpha]_D^{20}$ −97.

Iron-catalysed bromination of **8** gave the desired ψ-geminal 4-bromo-13-(*N*,*N*-diethylamido)[2.2]paracyclophane **9**, mp 94–96°C, $[\alpha]_D^{20}$ −2.1, e.e. 98% (derived from acid of 98% e.e.) in 96% yield. Hence, we have established that the $CONEt_2$ group is ψ-geminal directing with regard to electrophilic substitution. Low temperature (78°C) lithiation of **9** and reaction with an appropriate reagent gave the 4,13-disubstituted compounds **10**–**13** (Fig. 2, Table 1).

Snieckus[21] found that lithiation of 2-methyl-*N*,*N*-diethylamidobenzene resulted in double benzylic lithiation, although in the absence of the 2-methyl group efficient *ortho*-lithiation occurred. As we necessarily have a methylene group in an *ortho*-position to the amide group then bridge substitution seemed likely. However, we were happy to find that *the use of t-BuLi/Et$_2$O/TMEDA led to ortho-lithiation of* ***8*** *in very high yield*. Following this important discovery, we were able to make a novel series of *ortho*-disubstituted[2.2]paracyclophanes **14**–**19** in good yields of which **14**–**17** were derived from (−)-(*R*)-amide (Fig. 2, Table 1).



Scheme 1.



8 X = H
9 X = Br
10 X = OH
11 X = CO_2Me
12 X = SPh
13 X = PPh_2

14 X = Br
15 X = OH
16 X = CO_2Me
17 X = SPh
18 X = $SnBu_3$
19 X = $SiMe_3$

20 X = Br
21 X = OH
22 X = CO_2Me
23 X = SPh

Figure 2.

Table 1. Physical characteristics of paracyclophanes **10**–**23** (Fig. 2) and **1**, **2**, **6**, **7** (Fig. 1)

Entry	Compound	Reagent	X^-	Mp (°C)	Yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)
1	**10**[b]	$B(OMe)_3/H_2O_2$	OH	152–155	57 (77[c])	−150.6	>99.9[d]
2	**11**	$ClCO_2Me$	CO_2Me	103–104	85	+3.50	98[e]
3	**12**[b]	$PhSO_2SPh$	SPh	139–141	83	~0.00	>99.9[d]
4	**13**	$ClPPh_2$	PPh_2	190–191	52	–	
5	**14**[b,h]	Br_2	Br	94–96	99	−38.5	98[e]
6	**15**	$B(OMe)_3/H_2O_2$	OH	67–69	82 (94[c])	−17.9	98[e]
7	**16**	$ClCO_2Me$	CO_2Me	110–111	87 (96[c])	+13.8	98[e]
8	**17**	$PhSO_2SPh$	SPh	92–95	92	−51.5	98[d]
9	**18**[f]	$ClSnBu_3$	$SnBu_3$	Oil	94	–	
10	**19**[b,f]	$ClSiMe_3$	$SiMe_3$	147–149	91 (96[c])	–	
11	**20**[i]	Br_2	Br	153–155	84 (98[c])	−28.8	>99.9[d]
12	**21**[b]	$B(OMe)_3/H_2O_2$	OH	115–116	80	−121.1	>99.9[d]
13	**22**[b]	$ClCO_2Me$	CO_2Me	139–142	72	+30	>99.9[d]
14	**23**[j]	$PhSO_2SPh$	SPh	193–194	76	+8.2	>99.9[d]
15	**6**	CCl_4/PPh_3	H	82–84	97	+105.4	94[g]
16	**7**	Br_2	Br	136–142	82 (85[c])	−30.6	94[g]
17	**2**	$PhSO_2SPh$	SPh	174–175	58	−22.9	94[g]
18	**1**	$ClPPh_2$	PPh_2	111–112	54	−12.7	94[g]

[a] Isolated yield of pure product.
[b] X-Ray structure obtained.
[c] Yield taking recovered starting material into account.
[d] From (−)-(*R*)-amide of >99.9% e.e.
[e] From (−)-(*R*)-amide of 98% e.e.
[f] From racemic amide.
[g] From (+)-(*S*)-acid of 94% e.e.
[h] **8** (2.22 mmol), *t*-BuLi (5.33 mmol), TMEDA (5.3 mmol), Et_2O (80 ml), −78°C then Br_2 (1.2 mmol).
[i] **14** (1.71 mmol), Br_2 (1.84 mmol), Fe (0.1 mmol), CH_2Cl_2 (35 ml), 40°C.
[j] **20** (0.43 mmol), *t*-BuLi (1.08 mmol), TMEDA (1.04 mmol), Et_2O (35 ml), −78°C then $PhSO_2SPh$ (2.16 mmol).

A key process in our approach (Scheme 1) to compounds of type C was the bromination of **14** to give **20**. In fact, as envisaged, this iron catalysed bromination proceeded in very good yield (Table 1, entry 11). Furthermore, double lithiation of **20** was successful and enabled us to produce essentially homochiral compounds **21**–**23** in good isolated yields (Table 1, entries 12–14, Figs. 3 and 4). In these compounds the two substituents (X) have the same relationship as in Phanephos™ and our approach thus constitutes a flexible route to a wide variety of such compounds.

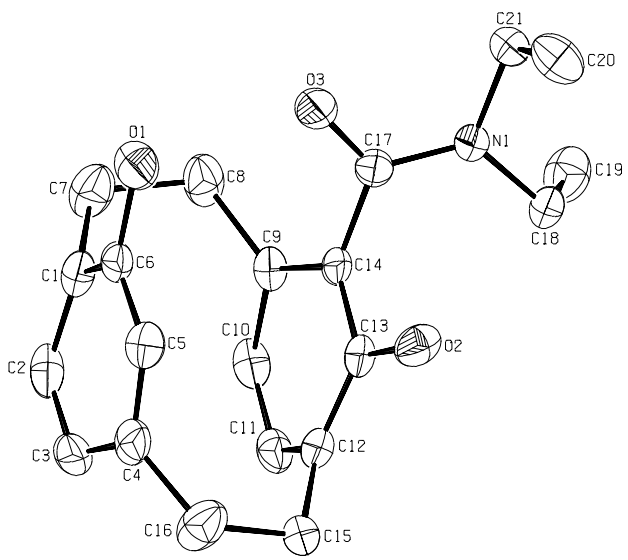


Figure 3. X-Ray structure of **21**.

Additionally to the above results, we here report that we have produced optically active **1** and **2** starting with (+)-(*S*)-4-carboxy[2.2]paracyclophane of 94% e.e. using methodology we have previously described.[13] We have already shown that one of these, **1**, is an efficient catalyst for the Heck reaction and for the addition of $ZnEt_2$ to benzaldehyde. We are now embarking on a systematic study of the catalytic properties of the compounds described above plus certain derivatives. Not all

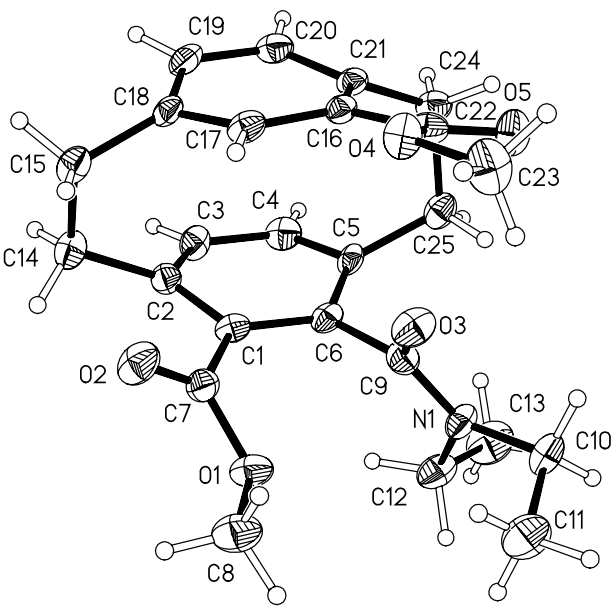


Figure 4. X-Ray structure of **22**.

are designed as transition metal ligands. Compounds derived from **10**, **11**, **17**, **21** and **22** will be tested for cooperative catalysis in biomimetic reactions.

The *ortho*-lithiation procedure described will have consequences far beyond those outlined above and will be of importance to all workers in the field of [2.2]paracyclophanes.

Acknowledgements

We thank the Leverhulme Trust, the British Council, the University of Wales, Swansea and UWI, St. Augustine for financial support of this work.

References

1. Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley-VCH: New York, 2001.
2. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd Ed.; Wiley-VCH: New York, 2000.
3. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; J. Wiley and Sons: New York, 1994.
4. Focus on Chirality, Pharm. News **2001**, *8*, 10–41.
5. (a) *Ferrocenes*, Togni, A.; Hayashi, T., Eds., VCH: Weinheim, 1995; (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.
6. Bolm, C.; Muniz, K. *Chem. Soc. Rev.* **1998**, *28*, 51.
7. Okamoto, K.; Kimachi, T.; Ibuka, T.; Takemoto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 463.
8. (a) Vögtle, F. *Cyclophane Chemistry*; J. Wiley and Sons: New York, 1993; (b) Cram, D. J.; Hornby, R. B.; Truesdale, E. A.; Reich, H. J.; Delton, M. H.; Cram, J. M. *Tetrahedron* **1974**, *30*, 1757.
9. Yanada, R.; Higashikawa, M.; Miwa, Y.; Taga, T.; Yoneda, F. *Tetrahedron Lett.* **1992**, *3*, 1387.
10. Reich, H. J.; Yelm, K. E. *J. Org. Chem.* **1991**, *56*, 5672.
11. Pelter, A.; Crump, R. A. N. C.; Kidwell, H. *Tetrahedron Lett.* **1996**, *37*, 1273.
12. Pelter, A.; Crump, R. A. N. C.; Kidwell, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3873.
13. Marchand, A.; Maxwell, A.; Mootoo, B.; Pelter, A.; Reid, A. *Tetrahedron* **2000**, *56*, 7331.
14. Pelter, A.; Crump, R. A. N. C.; Kidwell, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3173.
15. Pelter, A.; Beletskaya, I., unpublished experiments.
16. (a) Antonov, D. Y.; Belokon, Y. N.; Ikonnikov, N. S.; Orlova, S. A.; Pisarevsky, A. P.; Raevski, N. I.; Rozenberg, V. I.; Sergeeva, E. V.; Struchkov, Y. T.; Tararov, V. I.; Vorontsov, E. V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1873; (b) Sergeeva, E. V.; Rozenberg, V. I.; Vorontsov, E. V.; Danilova, T. I.; Starikova, Z. A.; Yanovsky, A. I.; Belokon, Y. N.; Hopf, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3445; (c) Belokon, Y.; Moscalenko, M.; Ikonnikov, N.; Yashkina, L.; Antonov, D.; Vorontsov, E.; Rozenberg, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3245; (d) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741; (e) Rozenberg, V. I.; Dubrovina, N. V.; Vorontsov, E. V.; Sergeeva, E. V.; Belokon, Y. N. *Tetrahedron: Asymmetry* **1999**, *10*, 511; (f) Wörsdörfer, U.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. *Synthesis* **1999**, *4*, 597; (g) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *Chem. Lett.* **2000**, *2*, 38; (h) Rozenberg, V. I.; Antonov, D. Y.; Zhuravsky, R. P.; Vorontsov, E. V.; Khrustalev, V. N.; Ikonnikov, N. S.; Belokon, Y. N. *Tetrahedron: Asymmetry* **2000**, *11*, 3245; (i) Bolm, C.; Kühn, T. *Synlett* **2000**, 899.
17. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207; (b) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 6462; (c) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441.
18. Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195.
19. Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Tao, A.; Cao, B.-X.; Sun, J. *Tetrahedron: Asymmetry* **2001**, *12*, 529.
20. Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
21. de Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.