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From central to planar chirality, the first example of atropenantioselective cycloetherification

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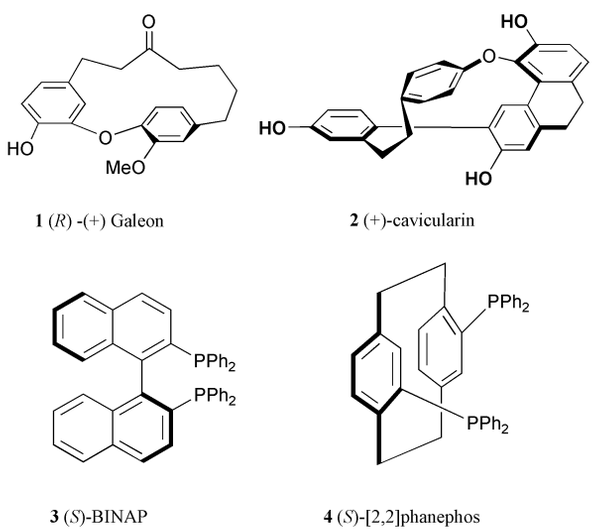
Using chiral quaternary ammonium hydroxide as base, cycloetherification of linear achiral diarylheptanoid 5, by way of an intramolecular S_NAr reaction, provides enantiomerically enriched cyclophane 6 in good to excellent yield.

A number of optically active natural products contain planar or axial chirality as the only asymmetric element. Galeon (**1**)[1] and cavicularin (**2**)[2] are such examples. Thus (*R*)-(+)-galeon displays planar chirality, while (+)-cavicularin possesses planar as well as axial chirality; both compounds are devoid of chiral centers (Fig. 1). On the other hand, ligands with axial chirality



1 (*R*) -(+) Galeon **2** (+)-cavicularin

3 (*S*)-BINAP **4** (*S*)-[2,2]phanephos

Fig. 1

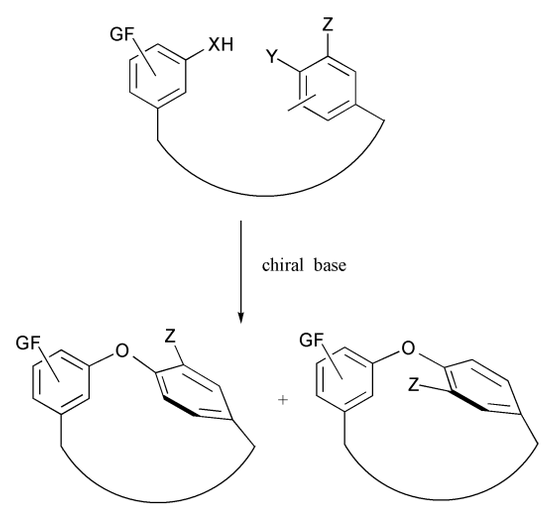
(*e.g.* BINAP, **3**)[3] and planar chirality (*e.g.* [2,2]phanephos, **4**)[4] have found widespread applications in catalytic asymmetric processes. The asymmetric synthesis of these classes of compounds is thus of considerable importance. While palladium catalyzed enantioselective Kumada coupling[5] and more recently, Suzuki coupling[6] have been developed for the synthesis of axially chiral biaryls, enantioselective cyclization leading to planar chiral cyclophanes, to the best of our knowledge, remains unknown.[7]

Since our original report,[8] cycloetherification based on intramolecular nucleophilic aromatic substitution (S_NAr) has been developed into a powerful methodology for the synthesis of macrocycles with *endo* aryl–aryl[9] and aryl–alkyl ether bonds.[10] *Atropdiastereoselective* cycloetherification has been observed sporadically.[10,11] However, no rationale could be advanced and indeed, the atropselectivity is very sensitive to subtle structural modifications and is difficult to predict. Recently, a highly atropdiastereoselective cyclization has been designed by Nicolaou and co-workers by the temporary introduction of a bulky substituent on the aromatic ring.[12] We have been interested in the development of an *atropenantioselective* cycloetherification process as shown in Scheme 1 and wish to report herein our preliminary results.

Table 1 Cycloetherification of **5**, a screening of chiral bases[a]

Entry	Substrate	Base	Yield of **6** (%)	Ee (%)[b]
1	**5a**	**7**	60	20
2	**5a**	**8**	90	3
3	**5a**	**9**	68	0
4	**5b**	**8**	87	0
5	**5b**	**9**	83	0
6	**5a**	**10**	60	6[c]

[a] The reaction was performed in DMF (0.05 M) at room temperature in the presence of one equivalent of chiral ammonium salt. [b] The enantiomeric excess was measured by HPLC using a chiral column (DAICEL DO), eluent: hexane–isopropanol 85 : 15, UV detection at 240 nm. [c] Enantioselectivity reversed.



Scheme 1

An achiral linear diarylheptanoid **5** (**5a** R = H, **5b** R = trimethylsilyl) was selected for our studies, since its cyclization will create concomitantly a planar chirality due to the presence of a nitro group *ortho* to the aryl ether linkage and the constrained ring system.[13] While potassium carbonate and caesium fluoride have previously been used to promote the cyclization of **5a** to provide cyclophane **6** in excellent yield, we found that tetrabutylammonium fluoride (TBAF) and tetrabutylammonium hydroxide were also able to promote the cyclization of **5a**. These results prompted us to investigate the projected *atropenantioselective* cyclization by using chiral quaternary ammonium salts. The following salts were synthesized from cinchonine and cinchonidine, respectively, according to standard procedures (Fig. 2).[14] The results of the cyclization, using DMF (0.05 M) as solvent, are summarized in Table 1.

As is seen, cyclization of **5a** promoted by chiral ammonium fluoride provided the cyclophane **6**† with negligible enantioselectivity (entries 2 to 5). The same is true with substrate **5b** wherein the phenol was protected as a trimethylsilyl ether (entry 4). However, a notable atropenantioselectivity was observed

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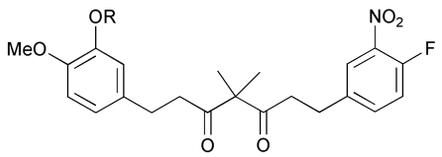
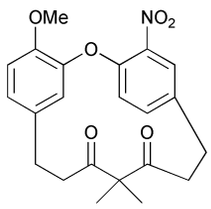
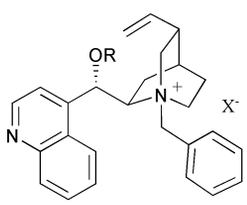


5a R = H
5b R = $SiMe_3$



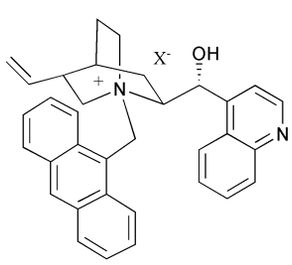
6

Cinchonine derived



7 R = H, X = OH
8 R = H, X = F
9 R = allyl, X = F

cinchonidine-derived



10 X = OH

Fig. 2

with the ammonium hydroxide, **5** producing **6** with 20% enantiomeric excess (entry 1). The *N*-anthracenylmethylcinchonidinium hydroxide was also tested for cyclization.[15] In this case, the opposite enantiomer was enriched under identical conditions, albeit with low ee (entry 6). The cyclophane **6** obtained was transformed to the diastereomeric mixture **11** (Fig. 3).[16] The diastereomeric excess calculated from the ^{1}H NMR spectra correlated well with the ee value determined from chiral HPLC analysis.

We assumed that the atropenantioselectivity of the cyclization should depend on the tightness of the ion pair formed between the phenoxide and the chiral ammonium base. The latter should in turn be influenced by the solvent polarity.[17] We thus examined the solvent effect using two pseudo-enantiomeric ammonium hydroxides (**7**, **10**) and the results are summarized in Table 2.

From DMF to toluene, the presumed ion pair $ArO^-NR_4^+$ should become tighter. Consequently, one may expect, at the expense of low reactivity, an increased enantioselectivity of the cyclization. However, experimental results indicated that there was no linear correlation between solvent polarity and atropenantioselectivity. Indeed, while the cyclization of **5** promoted

Table 2 Solvent effect on the cycloetherification of **5a**[a]

Entry	Solvent	Base	Time/h	Yield of **6** (%)	Ee (%)[b]
1	DMF	**7**	18	60	20
2	MeCN	**7**	24	83	0
3	Toluene	**7**	6 days	61	8
4	DMF	**10**	24	60	6
5	MeCN	**10**	24	79	2
6	Toluene	**10**	6 days	85	18[c]

[a] The reaction was performed at room temperature in the presence of one equivalent of chiral ammonium salt (0.05 M). [b] The enantiomeric excess was measured by HPLC using a chiral column (DAICEL DO), eluent: hexane–isopropanol 85 : 15, UV detection at 240 nm. [c] Enantioselectivity reversed.

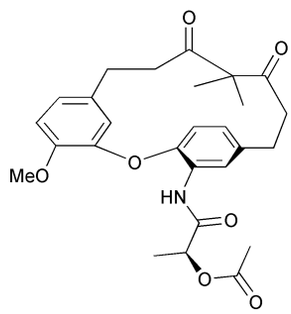


Fig. 3 The atropisomer shown in the figure is arbitrary.

by **10** provided a better ee in toluene (entries 6 *vs.* 4, 5), that promoted by **7** was best realized in DMF (entries 1 *vs.* 2, 3). This fact indicates that the chirality transfer from chiral ammonium salt to planar chiral cyclophane is more complex than we had envisaged.

The combination of butyllithium–sparteine[18] was next examined with the idea that the ion-pair ArO^-Li^+-sparteine should be even tighter, thus bringing the chiral environment nearer to the reactive sites. However, no cyclization occurred under a set of conditions varying temperatures, solvents and stoichiometries and only the starting material was recovered. This result is not unexpected in view of the counterion effect we observed previously on the intramolecular S_NAr reaction.[19]

In conclusion, we reported the first example of an enantioselective cycloetherification reaction. Although the atropenantioselectivity remained moderate, the results described here served as a proof-of-concept and laid down the foundation for future work.

Acknowledgements

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Notes and references

† Physical and spectroscopic data of cyclophane **6**. Mp: 148–151 °C; IR ($CHCl_3$) ν 3034, 3014, 1715, 1694, 1601, 1533, 1519, 1265, 1232, 1203, 1127 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.36 (s, 3H), 1.38 (s, 3H), 2.54–2.63 (m, 4H), 3.00–3.04 (m, 4H), 3.94 (s, 3H), 5.06 (d, J = 2.0 Hz, 1H), 6.5 (dd, J = 2.0, 8.2 Hz, 1H), 6.74 (d, J = 8.2 Hz), 7.11 (d, J = 8.3 Hz, 1H), 7.48 (dd, J = 2.2, 8.3 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 22.6, 26.2, 28.8, 39.2, 41.2, 56.6, 62.5, 112.2, 114.3, 122.4, 126.6, 127.1, 134.3, 136.3, 140.0, 143.1, 147.0, 149.0, 150.6, 207.0, 208.3; MS (FAB) *m/z* 397; Anal. calcd for $C_{22}H_{23}NO_6$: C, 66.49; H 5.83; N 3.52; Found: C, 66.16; H 5.85; N 3.45%.

1 K. E. Malterud, T. Anthonsen and J. Hjortas, *Tetrahedron Lett.*, 1976, 3069–3072.
2 M. Toyota, T. Yoshida, Y. Kan, S. Takaoka and Y. Asakawa, *Tetrahedron Lett.*, 1996, **37**, 4745–4748.

3 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, Inc., New York, 1994 .
4 P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante and P. J. Reider, *J. Am. Chem. Soc.*, 1997, **119**, 6207–6208.
5 (*a*) T. Hayashi, K. Hayashizaki, T. Kiyoi and Y. Ito, *J. Am. Chem. Soc.*, 1988, **110**, 8153–8156; (*b*) T. Hayashi, S. Nizuma, T. Kamikawa, N. Suzuki and Y. Uozumi, *J. Am. Chem. Soc.*, 1995, **117**, 9101–9102; (*c*) T. Kamikawa and T. Hayashi, *Tetrahedron*, 1999, **55**, 3455–3466.
6 (*a*) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.*, 2000, 1723–1724; (*b*) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12051–12052.
7 (*a*) For recent reviews on enantioselective synthesis and application of planar chiral (arene)chromium complexes and ferrocene derivatives, see: K. Kamikawa and M. Uemura, *Synlett*, 2000, 938–949; (*b*) C. Bolm and K. Muñiz, *Chem. Soc. Rev.*, 1999, **28**, 51–59; (*c*) C. J. Richards and A. J. Locke, *Tetrahedron: Asymmetry*, 1998, **9**, 2377–2407; (*d*) A. Togni, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1475–1477.
8 J. Zhu, *Synlett*, 1997, 133–144.
9 (*a*) For reviews, see: K. Burgess, D. Lim and C. I. Martinez, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1077–1078; (*b*) K. C. Nicolaou, C. N. C. Boddy, S. Bräse and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096–2152; (*c*) J. S. Sawyer, *Tetrahedron*, 2000, **56**, 5045–5065.
10 T. Temal-Laïb, J. Chastanet and J. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 583–590.
11 (*a*) M. Bois-Choussy, L. Neuville, R. Beugelmans and J. Zhu, *J. Org. Chem.*, 1996, **61**, 9309–9322; (*b*) R. Beugelmans, M. Bois-Choussy, C. Vergne, J. P. Bouillon and J. Zhu, *Chem. Commun.*, 1996, 1029–1030; (*c*) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow and J. L. Katz, *Angew. Chem. Int. Ed.*, 1998, **37**, 2700–2704; (*d*) D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter and J. L. Katz, *Angew. Chem., Int. Ed.*, 1998, **37**, 2704–2708.
12 K. C. Nicolaou and C. N. C. Boddy, *J. Am. Chem. Soc.*, 2002, **124**, 10451–10455.
13 G. Islas-Gonzalez and J. Zhu, *J. Org. Chem.*, 1999, **64**, 914–924.
14 Compound **7** was prepared from cinchonine in two steps: a) BnBr, acetone, reflux, 72h. b) Amberlyst A-26, MeOH. Treatment of compound **7** in MeOH with HF (1 M) gave **8** in quantitative yield. Cinchonidine derivative **10** was prepared in a similar fashion.
15 (*a*) B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1997, **38**, 8595–8598; (*b*) E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **119**, 12414–12415.
16 *Reagents and conditions*: a) $SnCl_2$, DMF, 50 °C, 7h. b) (*S*)-2-acetoxypropionyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature, 2 h.
17 A. Loupy, B. Tchoubar and D. Astruc, *Chem. Rev.*, 1992, **92**, 1141–1165.
18 D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2282–2316.
19 G. Islas-Gonzalez and J. Zhu, *Synlett*, 2000, 412–414.