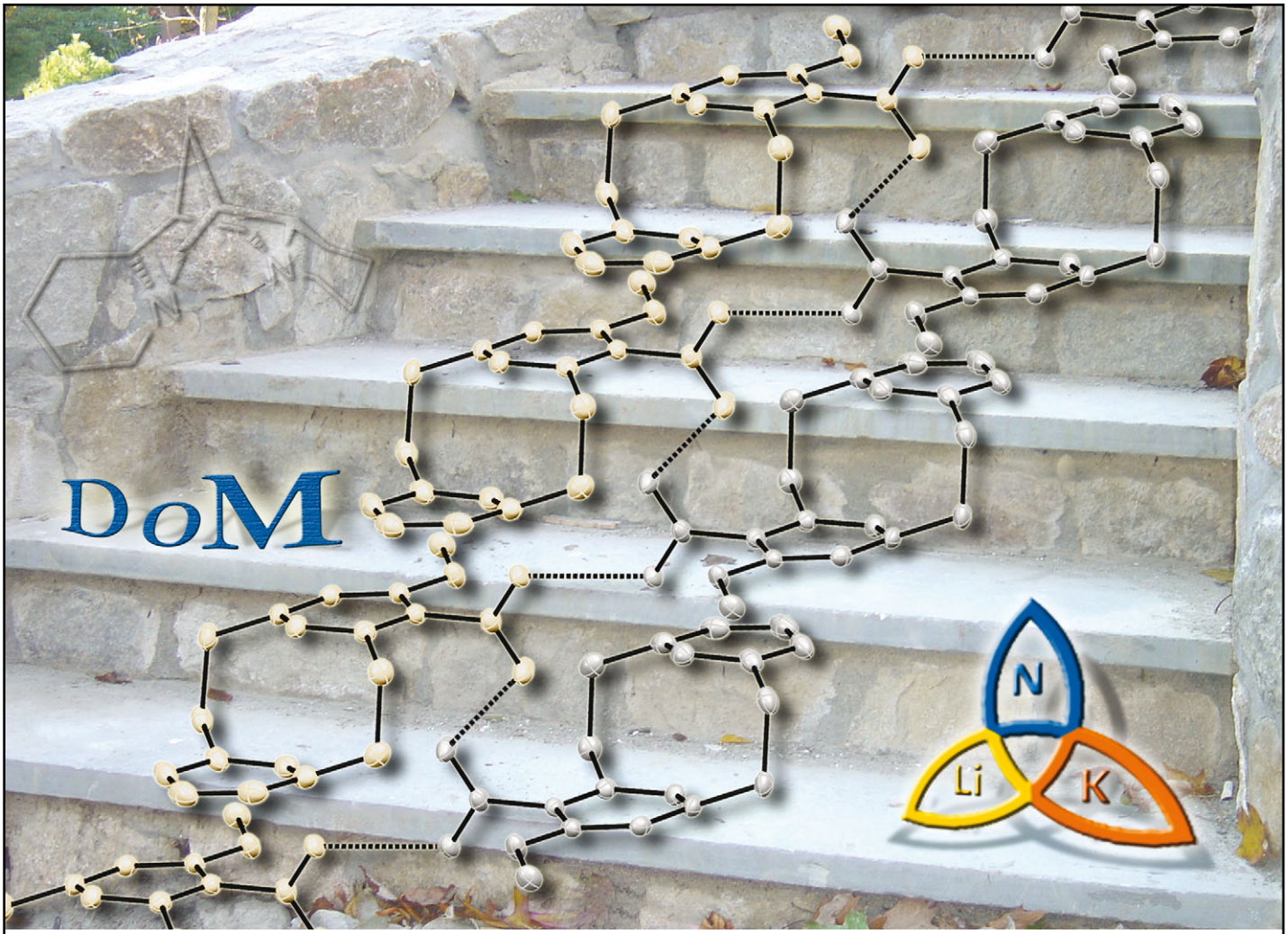

Showcasing research from Professor O'Shea's research group in Dublin, Ireland.

First asymmetric synthesis of planar chiral [2.2]metacyclophanes

We have illustrated a general three step asymmetric synthesis of planar chiral [2.2]metacyclophanes starting from inexpensive xylenes. The theme of our short synthetic strategy is the combination of selective benzylic and aryl metalations. The exploration of [2.2]metacyclophanes as potential planar chiral catalysts and ligands is now an exciting possibility.

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First asymmetric synthesis of planar chiral [2.2]metacyclophanes†

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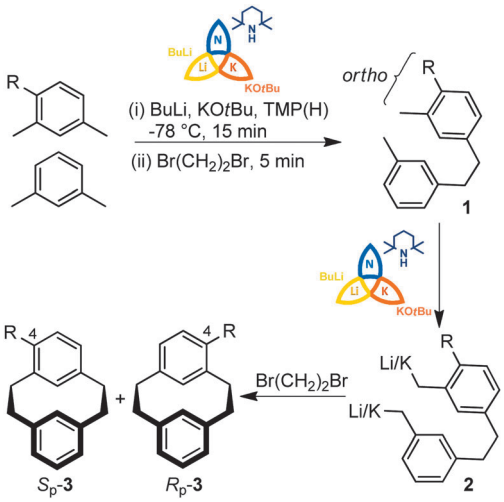
Marco Blangetti, Helge Müller-Bunz and Donal F. O'Shea*

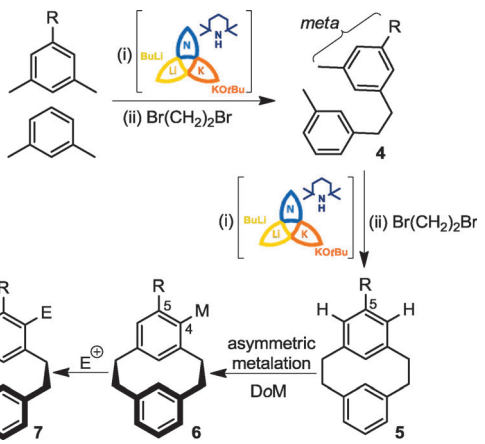
A general three step asymmetric synthesis of planar chiral [2.2]metacyclophanes utilizing selective benzylic and aryl metalations is described. The final enantioselective step is achieved using a (−)-sparteine mediated aryl metalation, following which electrophile reaction gives planar chiral cyclophanes with enantiomeric ratios (er) above 90 : 10.

Despite their first racemic synthesis in 1972, [2.2]metacyclophanes have failed to receive the same level of interest given to their isomeric relatives [2.2]paracyclophanes.[1] Planar chiral [2.2]paracyclophanes have recently found application as promising chiral ligands and have proven a valuable contribution to the growing family of planar chiral scaffolds.[2] As part of our ongoing interest in selective metalation strategies,[3] we recently developed a two step racemic synthesis of planar chiral [2.2]metacyclophanes from inexpensive *m*-xylenes.[4] Both transformative steps utilize LiNK metalation conditions (BuLi, KO*t*Bu, TMP(H)) for *m*-xylene benzylic deprotonation with subsequent *in situ* oxidative C–C coupling. For example, the synthesis of substrate **1** can be achieved by a hetero-oxidative coupling of *m*-xylene and 1-substituted-2,4-dimethylbenzenes.[4] Using LiNK conditions, a regioselective dimetalation at the thermodynamically favored benzylic positions provided **2** with *in situ* oxidative ring closure producing the racemic planar chiral cyclophane **3** (Scheme 1).

A consequence of the *ortho* substituent pattern of one of the aryl rings of **1** is that the R substituent is positioned at C-4 position of the cyclophane, rendering it planar chiral. This two-step strategy provides the very desirable feature of a short synthetic route to these chiral scaffolds but the additional challenge of an asymmetric synthesis remains unmet. Rather than attempt the development of asymmetric ring closure of substrates **2**, the success of which may vary with different R substituents, an alternative more general approach outlined in Scheme 2 was envisaged. This strategy would rely on the use of both thermodynamic and kinetic metalations to provide an asymmetric synthesis in three steps from *m*-xylenes. The first stage would exploit



Scheme 1 Racemic synthesis of planar chiral [2.2]metacyclophanes.



Scheme 2 Proposed asymmetric synthesis of planar chiral cyclophanes.

LiNK metalation/oxidative coupling of *m*-xylene and a 1-substituted-3,5-dimethylbenzene to provide **4** which has a *meta*-substitution pattern for the R substituent and methyl group (Scheme 2). Repeating the reaction sequence on **4** would produce the achiral cyclophane **5** with a

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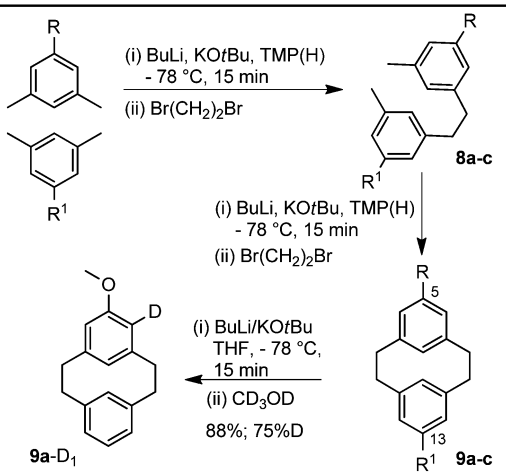
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data, HPLC, NMR spectra for all new compounds racemisation data for **11a–c**. CCDC 920658 and 920659. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc42275e

substituent (R) in C-5 position. If the R substituent is capable of directing a kinetic *ortho* metalation,[5] this would facilitate substitution at the C-4 position thereby rendering the cyclophane **6** chiral. If a metalation/electrophile trapping could be achieved in an asymmetric manner to produce **7**, then a diverse set of functional groups could be introduced *via* electrophile reaction. Enantioselective lithiations have been previously reported for the synthesis of planar chiral ferrocenes,[6] chromium–arenes[7] and 1,11-dioxa[*n*]paracyclophanes.[8]

In this report we outline our success with this strategy to deliver the first asymmetric synthesis of planar chiral [2.2]metacyclophanes. For this first preliminary account, two different directing groups OMe and $CON(iPr)_2$ were selected. The required 1,2-diarylethanes **8a** and **8b** were synthesized by cross-coupling of *m*-xylene with 1-methoxy-3,5-dimethylbenzene and *N*,*N*-diisopropyl-3,5-dimethylbenzamide respectively (Table 1, entries 1 and 2). To probe the effect of having both cyclophane aryl rings substituted, the bibenzyl **8c** was generated from a homo-coupling of 1-methoxy-3,5-dimethylbenzene (entry 3). Cyclophane ring closure was achieved by dimetalation/oxidative ring closure to produce achiral C-5 substituted cyclophanes **9a** and **9b** and the C-5/13 dimethoxy substituted derivative **9c** in yields from 31–42% (Table 1). To confirm the directed *ortho* metalation (DoM) strategy, **9a** was metalated under the kinetic conditions of BuLi/KO*t*Bu at −78 °C and treated with CD_3OD. ^2H NMR analysis showed 75% deuterium incorporated into the *ortho*-position of **9a**-D_1, with no deuterium observed in the other aryl ring or the bridging methylenes (Table 1).

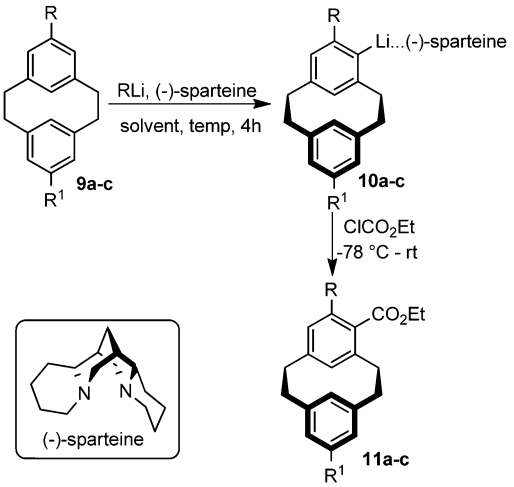
The natural product alkaloid (−)-sparteine, which can be isolated in significant quantities from *papilionaceous* plants, remains one of the most successful ligands for enantioselective organolithium chemistry.[9] Accordingly, an optimisation study of the (−)-sparteine mediated metalation of **9a** with varying alkyllithiums, solvents and temperatures was carried out with ethyl chloroformate used as electrophile (Table 2). Gratifyingly, optimal metalation conditions to produce **10a** were identified as *s*BuLi/(−)-sparteine in diethyl ether at −40 °C, which following treatment with chloroformate at −78 °C, gave the ester substituted cyclophane **11a** in 65% yield and an er of 91 : 9 (Table 2, entry 6). Using these conditions at lower temperatures (−78 °C) did not improve the er,

Table 1 Synthesis of achiral [2.2]metacyclophanes **9a–c**



Entry	R	R^1	8	Yield (%)	9	Yield (%)
1	MeO	H	**a**	40	**a**	42
2	$CON(iPr)_2$	H	**b**	30	**b**	31
3	MeO	MeO	**c**	92	**c**	35

Table 2 Optimisation of enantioselective metalation conditions



Entry	9	RLi	*T* (°C)	Solvent	Product	Yield (%)	e.r.[a]
1	**a**	BuLi	−78	Ether	—	—	—
2	**a**	BuLi	rt	Ether	**11a**	15	72 : 18
3	**a**	*s*BuLi	rt	Ether	**11a**	51	81 : 19
4	**a**	*s*BuLi	−78	Ether	**11a**	18	82 : 18
5	**a**	*s*BuLi	−60	Ether	**11a**	43	89 : 11
6	**a**	*s*BuLi	−40	Ether	**11a**	65	91 : 9
7	**a**	*s*BuLi	−20	Ether	**11a**	58	85 : 15
8	**a**	*s*BuLi	0	Heptane	**11a**	—	—
9	**b**	BuLi	−40	Ether	—	—	—
10	**b**	*s*BuLi	0	Heptane	—	—	—
11	**b**	*s*BuLi	−40	Ether	**11b**	73	74 : 26
12	**b**	*s*BuLi	−78	Ether	**11b**	76	85 : 15
13	**c**	BuLi	−78	Ether	—	—	—
14	**c**	*s*BuLi	−40	Ether	**11c**	46	91 : 9

[a] Compared to racemic samples generated using (i) *s*BuLi/PMDTA (ii) $ClCO_2Et$.

whereas at higher temperatures poorer *enantio*-discrimination was observed (entries 4, 5, and 7). Alternative conditions using BuLi as base or using *s*BuLi in a hydrocarbon solvent gave very poor metalations (entries 1, 2, and 8). For amido-substituted cyclophane **9b**, it was found that metalation at the lower temperature of −78 °C gave a better er of 85 : 15 when compared to −40 °C (entries 11 and 12). This is consistent with the fact that the $CON(iPr)_2$ group is a stronger *ortho*-directing group than OMe. Encouragingly, the dimethoxy-substituted cyclophane **9c** also gave an excellent er of 91 : 9 when reacted under identical conditions to that of **9a** (entry 14).

Assignment of the absolute configuration of the predominant enantiomer of **11a** was carried out using X-ray crystallography. The major isomer was purified by chiral HPLC and crystallized by the slow evaporation of a diethyl ether solution. Single crystal diffraction analysis showed it crystallized in the $P2_1$ space group with absolute configuration assigned as R_p (Fig. 1).[10a]

While **11a** had the expected structural features of a [2.2]metacyclophane ring,[11] it was interesting to observe that the C4/5 di-substitution pattern caused the ester group to rotate by 86.1° to the plane of the aromatic cyclophane ring. This contrasts to the mono C-4 carboxy substituted cyclophane in which the torsion angle is only 16.6°[4b] and can be rationalised by electronic repulsion between the oxygen atoms of the ester and ether groups. Ester saponification of a *rac*-**11a** was readily achieved with KOH in 2-propanol[12] to give the C4/C5 CO_2H/OMe substituted cyclophane **11d** which

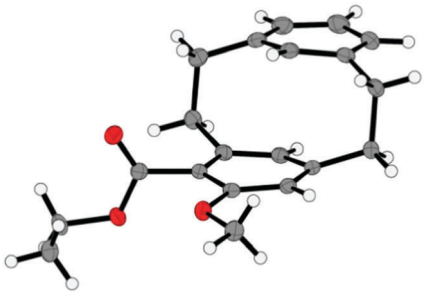


Fig. 1 Single molecule structure of R_p-**11a**. Thermal ellipsoids drawn at the 50% probability level.

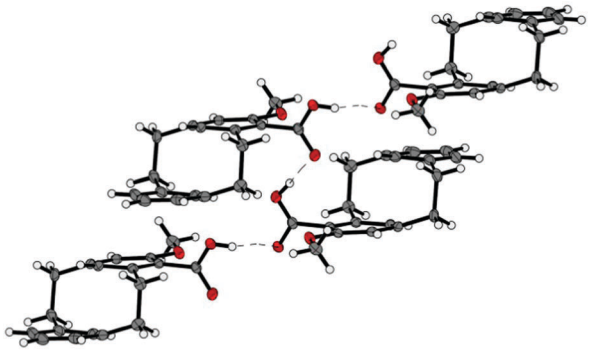
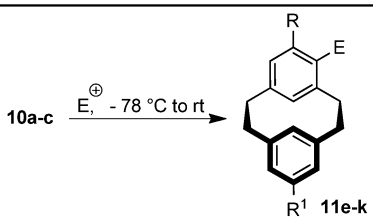


Fig. 2 X-Ray structure of *rac*-**11d** ($P2_1/c$ space group). Thermal ellipsoids drawn at the 50% probability level (CO_2H group disorder neglected).

was analysed by X-ray crystallography.[10b] As in the ester derivative above, the carboxylate group has a large torsion angle with respect to the aryl ring of 70.0°. Unusually, in the extended structure, the carboxylates of **11d** are hydrogen bonded to a neighbouring molecule by a single hydrogen bonding motif with an O···O distance of 2.63 Å as shown in Fig 2. This gives rise to a catemeric one-dimensional hydrogen bonded network in which neighbouring molecules of **11d** associate with each other *via* a two-point hydrogen bonding contact in a head-to-head staggered manner.[13] This contrasts with the mono-C4 carboxy substituted cyclophane which crystallized as the more common centrosymmetric carboxylate dimer.[4b]

Table 3 Electrophile reaction with **10a–c**



Entry	10	$E^{\oplus}$	11	E	Yield (%)	e.r.
1	**a**	DMF	**e**	CHO	68	91 : 9
2	**a**	I_2	**f**	I	59	93 : 7
3	**a**	$ClP(O)(OEt)_2$	**g**	$P(O)(OEt)_2$	58	95 : 5
4	**a**	$ClP(Ph)_2$	**h**	$P(O)Ph_2$	69	95 : 5[a]
5	**b**	DMF	**i**	CHO	59	84 : 16
6	**c**	$ClP(O)(OEt)_2$	**j**	$P(O)(OEt)_2$	40	90 : 10
7	**c**	DMF	**k**	CHO	58	91 : 9

[a] Oxidation occurred on work up.

The generality of this synthetic strategy was illustrated by reaction of the enantioselectively metalated cyclophanes **10a–c** with the series of electrophiles, DMF, I_2, diethyl chlorophosphate and chlorodiphenylphosphine (Table 3). In each case the reaction was successful with ers the same or slightly better than that obtained for ethyl chloroformate. This is indicative of the metalation reaction being the *enantio*-discriminating step with the er of the product not being overly electrophile dependent.

Finally, the racemisation barriers ($\Delta G^{\ddagger}$) of **11a–c** were determined as 141.6, 134.5 and 135.4 kJ mol^{-1} respectively, on the basis of the absolute rate equation, by experimentally following their racemisation in NMP at 453 K. These values are sufficiently high to encourage future investigation of [2.2]metacyclophanes as potential planar chiral catalysts and ligands.

In summary, the first general enantioselective synthesis of planar chiral [2.2]metacyclophanes has been accomplished. The structural features of the C4/C5 substituted derivatives identified by X-ray analysis may assist in predictive design of catalysts and ligands. The facile three step synthesis and relatively high inversion barrier to racemisation indicates their potential as planar chiral catalysts and ligands, which to date has not been explored. We thank the European Research Association ERA-Chemistry and the Irish Research Council (IRC) for financial support.

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