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The concise synthesis and resolution of planar chiral [2.2]paracyclophane oxazolines by C–H activation†

Shashank Tewari, Maulik N. Mungalpara, Suraj Patel and Gareth J. Rowlands *

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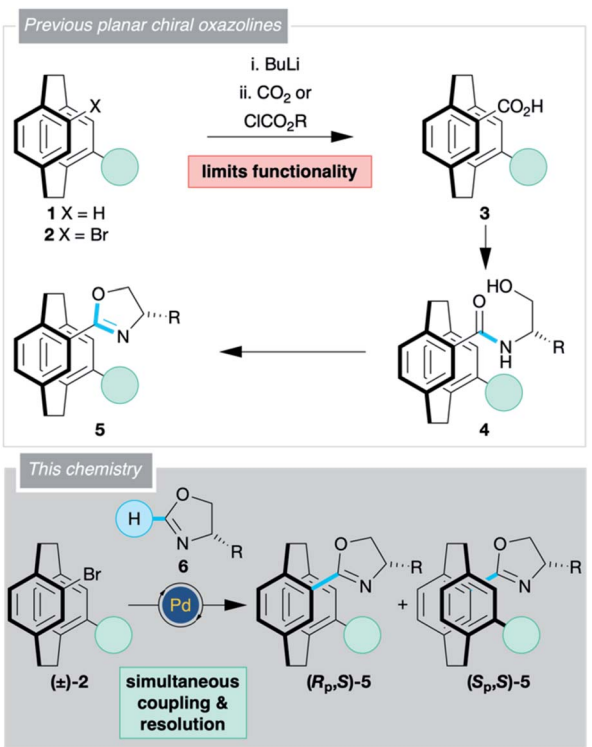
Planar chiral [2.2]paracyclophanes are resolved through the direct C–H arylation of enantiopure oxazolines, providing a convenient route to ligands and chiral materials. Preliminary results show that hydrolysis followed by decarboxylative phosphorylation leads to enantiopure [2.2]paracyclophane derivatives that are otherwise challenging to prepare.

[2.2]Paracyclophane **1** (X = H; Scheme 1) has garnered considerable attention as the core for planar chiral pre-ligands,[1,2] catalysts,[3,4] bioactive entities[5,6] and chiroptical materials.[7,8] The rigidity of the [2.2]paracyclophane provides an almost unrivalled opportunity to control the relative spatial position of various functional groups through a series of regioisomers.[4,9,10] The major roadblock hampering progress in [2.2]paracyclophane chemistry is the resolution of planar chirality, and there are only a limited number of commonly used enantiopure precursors, some of which are hard to obtain on a large scale.[11,12]

Oxazolines form a host of 'privileged' pre-ligands,[13–15] and it is no surprise that numerous oxazoline-substituted [2.2]paracyclophanes **5** have shown potential in asymmetric catalysis.[16–20] The oxazoline moiety aids the synthesis of these compounds, either by permitting resolution of the planar chirality,[16–19,21,22] or by directing functionalisation of the cyclophane backbone.[16,19,21,23] Every one of these oxazoline-containing [2.2]paracyclophanes **5** was synthesised from a bromo derivative **2** *via* the carboxylic acid **3**, then the amide **4**, and finally cyclisation (Scheme 1). This adds steps to the synthesis and limits the functionality found in the molecule as the acid is invariably formed by halogen–metal exchange.

Direct addition of an oxazoline **6** would allow simultaneous functionalisation and resolution of the planar chirality of [2.2]paracyclophane. Such a strategy would permit a more concise synthesis of [2.2]paracyclophane derivatives with a wider range of substituents. Previously, we have used C–H activation chemistry to synthesise planar chiral *N*-oxides,[24,25] and believed that the oxazoline C–H activation chemistry of Ackermann[26,27] and Lu[28] could be applied to [2.2]paracyclophane. Herein, we report the successful realisation of this strategy. Planar chiral oxazolines are accessed in a single step furnishing molecules that can be used as pre-ligands or as precursors to carboxylic acids that can be further derivatised by traditional means or decarboxylative couplings.

The coupling of oxazolines **6** and 4-bromo[2.2]paracyclophane **7** required little optimisation with the chemistry of Ackermann[26] transferring to paracyclophane without incident.



Scheme 1 Previous routes to oxazolines and proposed chemistry.

School of Natural Sciences, Massey University, Private Bag 11 222, Palmerston North, 4442, New Zealand. E-mail: g.j.rowlands@massey.ac.nz

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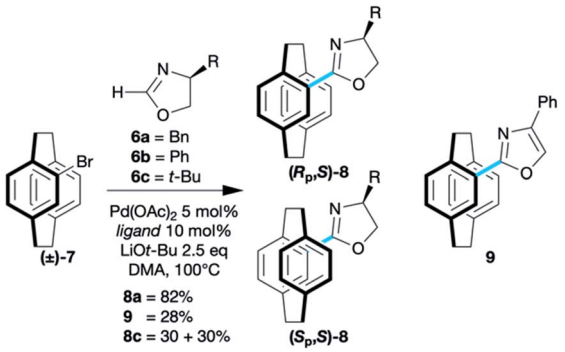


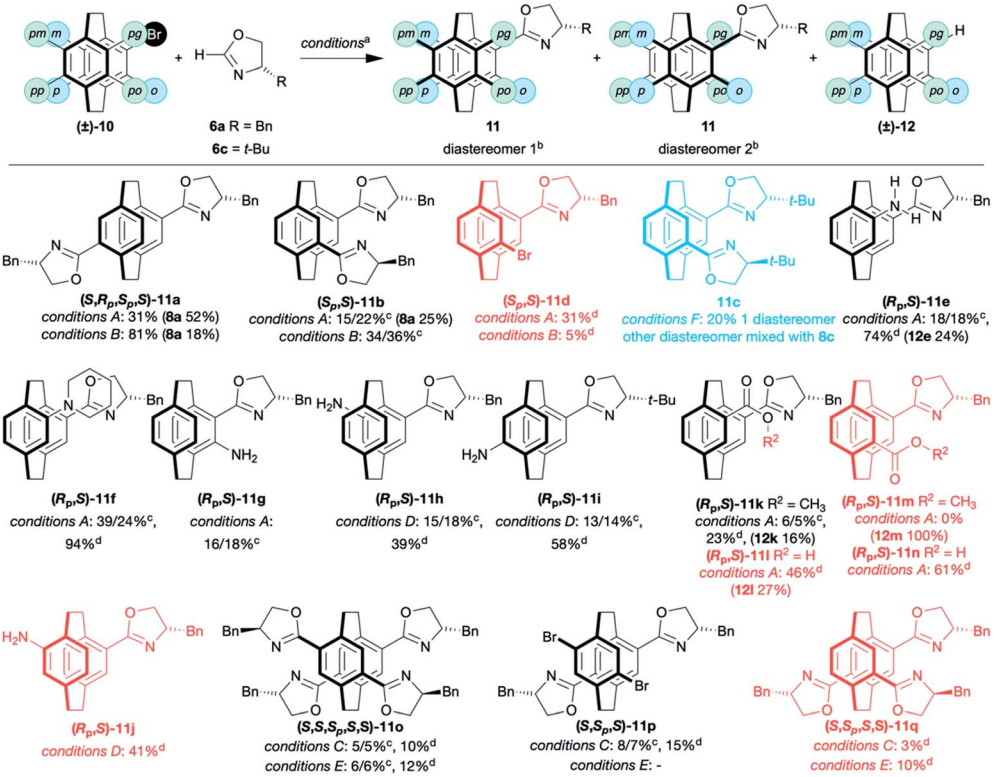
Scheme 2 Synthesis of 4-oxazolinyl[2.2]paracyclophanes **8a** and **8c**.

A range of (heteroatom-substituted) secondary phosphine pre-ligands [(HA)SPO] were screened, and di-*tert*-butylphosphine oxide (t-Bu$_2$SPO) gave a catalyst that showed complete conversion of simple [2.2]paracyclophane derivatives, such as 7 (**8a** 82%; **8c** 60% Scheme 2). More complex derivatives required the di-1-adamantylphosphine oxide (Ad$_2$SPO) otherwise returned unreacted starting material (see below).

Benzyloxazoline **8a** was formed as a mixture of diastereoisomers that are separable by column chromatography, but the similarity of the R_f values make resolution extremely challenging, with only the fractions at the beginning and end of a collection containing pure diastereoisomers. This led to screening a range of oxazolines. All coupled but with less satisfactory yields. The phenyloxazoline **6b** appears to couple with concomitant aromatisation furnishing oxazole **9**. For mono(oxazolines) **8**, *tert*-butyl derivative **6c** gave the best results in terms of resolution of planar chirality, with the diastereoisomers **8c** being readily separable.[21]

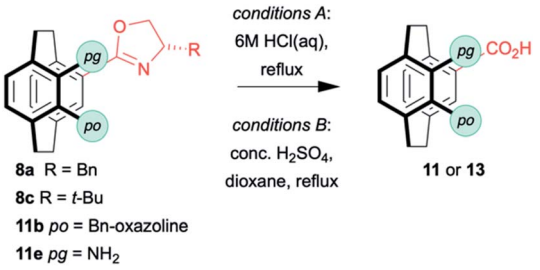
Next we established the scope of coupling reaction. Both the *pseudo-para*- (4,16)- (**11a**) and *pseudo-ortho*- (4,12)- bis(oxazolines) **11b** were readily prepared from the corresponding dibromo[2.2]paracyclophanes (Table 1). The *pseudo-para* isomer, 4,16-bis(4′-benzyloxazolin-2′-yl)[2.2]paracyclophane **11a**, is formed as a single stereoisomer due to its symmetry. The diastereoisomers of the more useful *pseudo-ortho* benzyl-substituted oxazoline **11b** were readily resolved,[17,20,29] but only one diastereoisomer of the *tert*-butyl derivative **11c** could be isolated. The other diastereoisomer co-ran with the two diastereomers of the product of protodebromination (**8c**). The

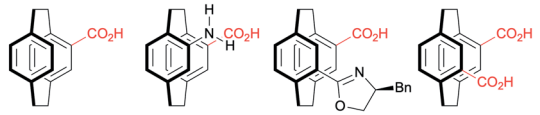
Table 1 Scope of oxazoline coupling (only single diastereoisomer of product shown)



[a] Conditions A: **6** (1.1 eq), Pd(OAc)$_2$ (5 mol%), (t-Bu)$_2$P(O)H (10 mol%), LiOt-Bu (2.5 eq); conditions B: **6** (2.2 eq), Pd(OAc)$_2$ (10 mol%), (t-Bu)$_2$P(O)H (20 mol%), LiOt-Bu (5.0 eq); conditions C: **6** (4.4 eq), Pd(OAc)$_2$ (40 mol%), (t-Bu)$_2$P(O)H (80 mol%), LiOt-Bu (10.0 eq); conditions D: **6** (1.1 eq), Pd(OAc)$_2$ (5 mol%), (Ad)$_2$P(O)H (10 mol%), LiOt-Bu (2.5 eq); conditions E: **6** (4.4 eq), Pd(OAc)$_2$ (40 mol%), (Ad)$_2$P(O)H (80 mol%), LiOt-Bu (10.0 eq); conditions F: **6** (2.2 eq), Pd(OAc)$_2$ (10 mol%), (Ad)$_2$P(O)H (20 mol%), LiOt-Bu (5.0 eq). [b] Only single diastereoisomer shown in table. Diastereoisomers in red cannot be separated. Diastereoisomers in blue are partially resolved. [c] Yield of separate diastereomers (diastereomer1)%/(diastereomer2)%. [d] Combined yield of all stereoisomers (includes mixed fractions).

Table 2 Hydrolysis of oxazolines[a]





[a] Conditions A: 6 M HCl(aq), reflux; conditions B: conc. H_2SO_4, dioxane, 110 °C. [b] Starting from a mixture of diastereomers. [c] Using pure diastereomer of **8**. [d] Hydrolysis reported in ref. 18. [e] Reacted for 12 hours. [f] Reacted for 24 hours.

synthesis of *pseudo-ortho*-bis(benzyloxazoline) **11b** has been performed on >1 g scale. The yields are lower but the separation easier. If a single equivalent of 2*H*-oxazoline **6a** is used in the coupling, it is possible to isolate the bromo mono(oxazoline) **11d**, but the reaction is non-selective, with a mixture of mono- along and bis(oxazoline) always formed.[16,18,30]

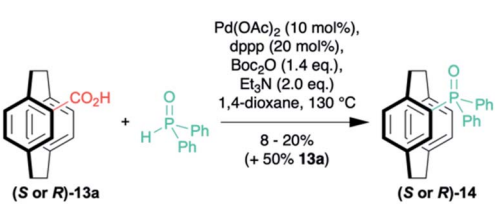
As is frequently observed with [2.2]paracyclophane derivatives, each regioisomer behaves differently, and it is hard to predict the influence of the substituents.[31,32] Using *t*-Bu_2SPO as pre-ligand, both primary and tertiary *pseudo-gem* amines gave the desired oxazolines as separable diastereoisomers **11e** and **11f**. The normally unreactive *ortho* substituted [2.2]paracyclophane derivative, 4-amino-5-bromo[2.2]paracyclophane,[33] appeared to give the amino-oxazoline **11g** as a pair of separable diastereomers in 34% yield, although these compounds proved to be unstable. All other amino[2.2]paracyclophanes gave unsatisfactory yields. The *pseudo-ortho*-amino-bromo[2.2] paracyclophane failed to couple and only furnished the product of protodebromination. On changing to Ad_2SPO, the *meta* **11h** and *pseudo-para* **11i**, were synthesised as separable diastereomeric amino oxazolines in moderate to good yields while the *pseudo-meta*-amino-bromo [2.2]paracyclophane gave **11j** as an inseparable mixture of diastereomers. It is unclear why this ligand is superior with these amino-bromo[2.2] paracyclophanes. Nitro-substituted [2.2]paracyclophanes (*pseudo-gem* and *pseudo-meta*) are unreactive. Esters proved problematic, giving low yields (**11k** and **11m**) and/or the product of protodebromination (**12**). We assume that the strongly basic conditions are incompatible with this functionality. This is supported by the fact the free acid reacts in good to moderate yields, 44% for *pseudo-gem* (**11l**) and 61% for *pseudo-ortho* (**11n**) (Table 1).

To push the limits of this coupling, we synthesised the 4,7,12,15-tetra(4′-benzyloxazolin-2′-yl)[2.2]paracyclophane **11o** from tetrabromo[2.2]paracyclophane.[34] Initial reaction with the *t*-Bu_2SPO ligand gave a complex mixture of regio- and stereoisomers. The resolved tetra(oxazoline) ligand **11o** was isolated in 10%. In addition, the *para*-bis(oxazoline)-dibromo[2.2] paracyclophane **11p** was isolated as separable diastereoisomers along with an unidentified regioisomer of the diastereomeric bis(oxazoline)-dibromo[2.2]paracyclophanes (not included in the yield). Finally, the two diastereoisomers of the protodebromo tris(oxazoline) **11q** were isolated. Altering the ligand to Ad_2SPO simplified the mixture and gave just the tetra(oxazoline) **11o** and tris(oxazoline) **11q**.

There are numerous reports describing the utility of [2.2] paracyclophane oxazolines. They have been used as pre-ligands,[16,18–20,29] or have directed further functionalisation of the [2.2]paracyclophane by either bromination[16,23] or metalation.[19,21] We believe straightforward elaboration of the amine or acid functionality will deliver modular pre-ligands, but here we want to increase the versatility of the oxazoline moiety and present preliminary results on the hydrolysis and decarboxylative phosphorylation of the oxazolines.

Oxazolines are robust, and hydrolysis is not straightforward. The hydrolysis of **11e** by heating to reflux in 6 M HCl has been reported to give **13b** in good yield (Table 2),[18] and these conditions worked for mono(benzyloxazoline) **8a** but failed to hydrolyse the mono(*tert*-butyloxazoline) **8c** or the bis(oxazoline) **11b**. More forcing conditions using concentrated sulfuric acid in dioxane at 110 °C lead to the clean hydrolysis of mono(oxazolines) while the *pseudo-ortho* bis(oxazoline) gives a mixture of the 4-acid-12-oxazoline **11n** and the desired 4,12-diacid **13c**. Fortunately, the products are easily separated based on solubility and recycling **11n** permits good overall yields of **13c** to be achieved. No sign of racemisation can be detected by optical rotation. While the conditions are harsh, the rapid synthesis of the oxazolines with concomitant resolution still make this methodology attractive if conducted early in a synthetic sequence.

It is possible to subject the enantiomerically enriched 4-carboxylic acid **13a** to a decarboxylative phosphorylation to give the phosphine oxide **14** in 8–20% (along with 50% unreacted starting material with no erosion of enantiopurity (Scheme 3).[35–37] So far, we have been unable to react the *pseudo-ortho*-diacid under the same conditions. Although the preliminary results are low yielding, they demonstrate that it is possible to isolate enantiomerically enriched phosphine oxide in just four steps. Only our own sulfoxide chemistry[38,39] is as efficient



Scheme 3 Decarboxylative phosphorylation.

and that methodology was limited by the need for a sulfoxide–lithium exchange with *tert*-butyllithium.

[2.2]Paracyclophane offers a useful planar chiral skeleton but its widespread adoption has been frustrated by a lack of simple methods to resolve the planar chirality. In this paper, we have shown how oxazolines can be coupled to bromo-derivatives to give separable diastereomers. The methodology permits a range of disubstituted [2.2]paracyclophanes to be rapidly prepared in enantiomerically pure form. We report the first example of a decarboxylative coupling on [2.2]paracyclophane. Optimisation of the decarboxylative coupling offers an exciting new route to enantiomerically enriched planar chiral molecules that are challenging to synthesise by conventional methods. We intend to extend the utility of this reaction to other derivatives, and will publish these studies in due course. Simpler, more rapid access to enantiomerically pure [2.2]paracyclophane derivatives will facilitate their wider use in catalysts, bioactive compounds, and materials.

Author contributions

ST and MNM contributed equally to this research.

Conflicts of interest

There are no conflicts to declare.

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