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Synthesis and use of chiral substituted benzenes containing 1,2-diols protected as cyclic acetals

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Dedicated to Professor S. V. Ley, FRS, on the occasion of his 65th birthday

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ABSTRACT

1,2-Dihydroxy benzenes have been protected as cyclic diacetals using 2,3-butane dione. These diacetals are extremely robust and can be further chemically diversified and resolved with chirality embedded in the 1,4-dioxane ring attached to the aromatic back bone as a result of the anomeric effect. These systems can serve as ligands, auxiliaries or organocatalysts for asymmetric synthesis.

1,2-Diacetal motifs have been extensively used as selective 1,2-diequatorial diol protecting groups[1] and also for stereo-controlled transformations[2] by virtue of their ability towards retention and transmission of chirality.[3] Several applications have been reported in the literature where the motif's chiral memory protocol can lend itself as a powerful synthetic tool for constructing asymmetric building blocks.[4] In all the reported studies on the use of 1,2-acetals, especially 2,3-butane diacetals (BDAs)[5] the diols that were protected for further synthetic manipulation were always those attached to at least one sp^3 carbon atom.[6] Until now no attempt has been made to ascertain if 1,2-diols attached to sp^2 carbon atoms such as catechol or 1,2-dihydroxy substituted benzenes can be protected as 1,2-diacetals. The present work was inspired by the pioneering contributions of Ley's group[1–4] and relates to the development of a synthetic protocol enabling the preparation of substituted racemic and optically active benzenes containing 1,2-diols protected as diacetal groups.

Considering that 1,2-diacetals are normally used to protect *anti* or diequatorial 1,2-diols it was envisaged that the protection of 1,2-diols attached to unsaturated sp^2 carbon atoms and aromatic species such as catechol or substituted 1,2-dihydroxy aromatic compounds with 2,3-butane dione[7] or any similar alkyl dione[8] may be tedious and require a multi-step approach.[9] However, we found that catechol when treated with trimethyl orthoformate and boron trifluoride diethyl etherate in methanol gave the required diacetal **1** which was isolated in good yield.

Having prepared the diacetal, we were keen to explore the possibility of making substituted benzenes with varying functionality and to obtain the compounds with this motif in its chiral form. We envisaged that making a BDA protected 1,2-dihydroxy aniline or benzoic acid would allow us to use such functional handles to facilitate resolution and isolate the enantiomerically enriched constituents. These compounds would now have a chiral framework in the form of a substituted diacetal functionality attached directly to the aromatic backbone allowing the molecule to possess chirality.

Accordingly, the BDA protected catechol **1** was subjected to a series of conditions that allowed us to obtain aniline **3** in its solid crystalline form as shown in Scheme 1. We now needed to find a suitable way to resolve the aniline where chirality was embedded in the 1,4-dioxane ring as a result of the favourable anomeric effects and equatorial placement of functionality. After several attempts we succeeded in finding a scalable method that allowed for the resolution of the BDA isomers. The procedure involved treating the aniline **3** with phthalic anhydride[10] and the resulting amide **4** was stirred with either (*R*) or (*S*) homochiral methylbenzylamine in isopropyl alcohol at room temperature overnight and during this time a colourless solid separated out which was filtered and dried.

This enriched diastereomeric salt which separated as colourless solid was suspended in methanol and heated to 60–65 °C for 15 min and filtered under hot conditions.

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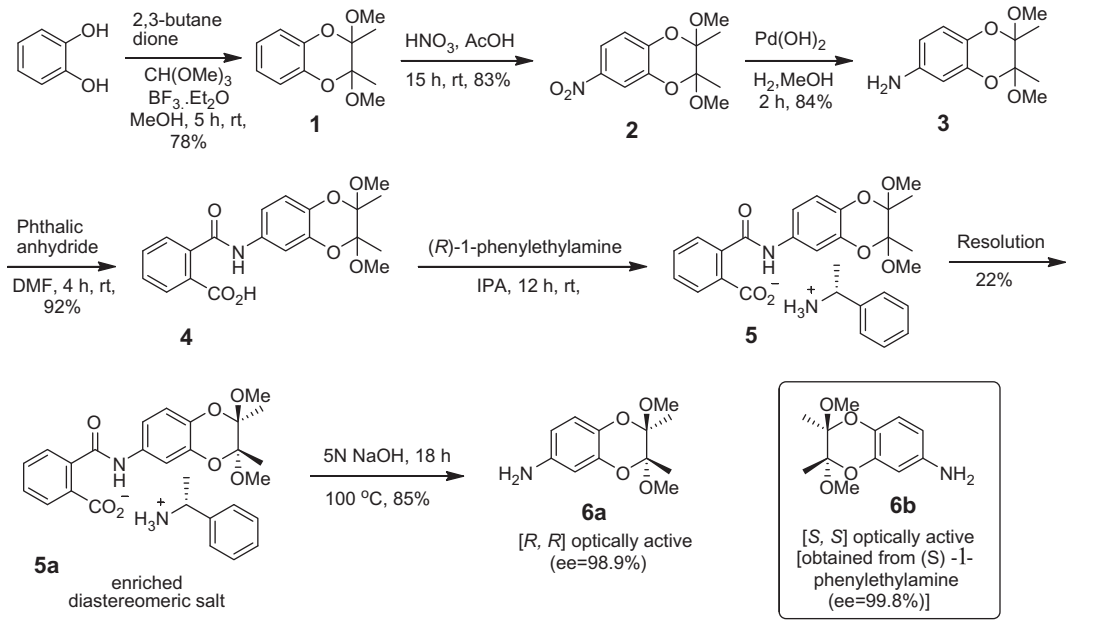


Scheme 1. Synthesis of chiral anilines.

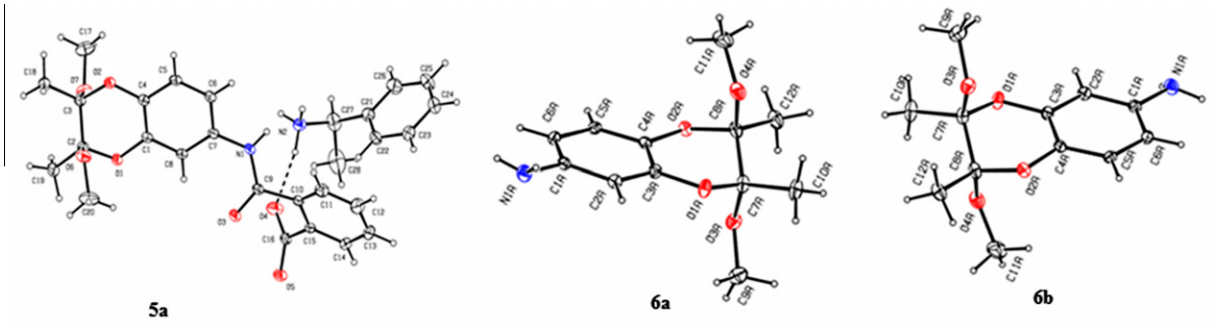
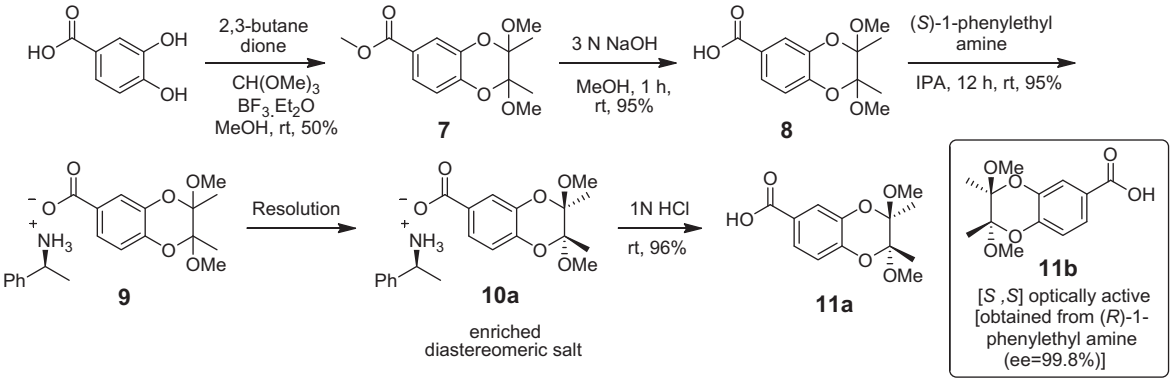


Figure 1. ORTEP diagram of compound **5a**, **6a** and **6b**.

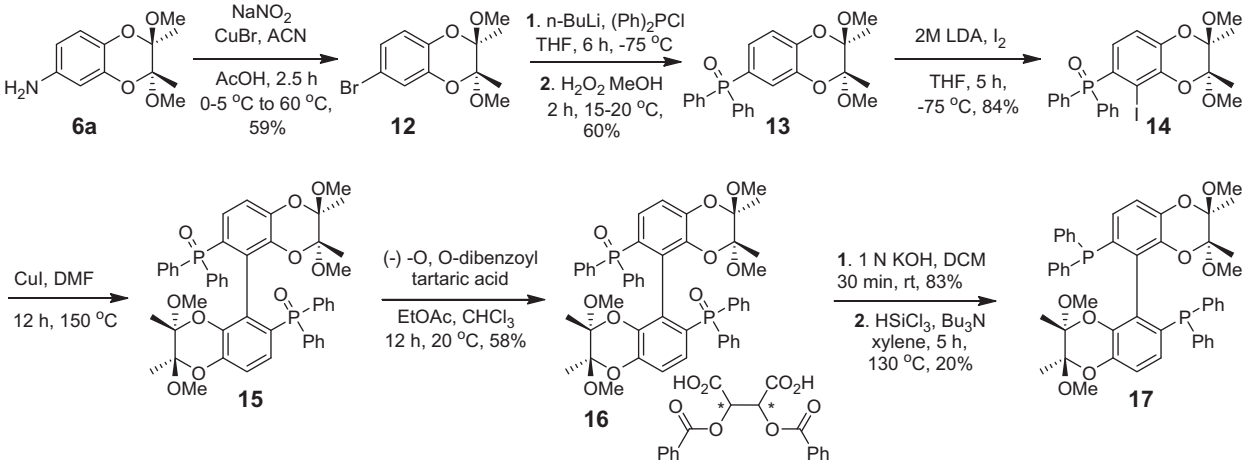


Scheme 2. Synthesis of chiral benzoic acids.

This process was repeated to yield a highly enriched diastereomeric salt. The stereochemistry of the optically active butane diacetal moiety was confirmed from X-ray data of the diastereomeric salt formed from the chiral methylbenzylamine[11] (Fig. 1). As expected the 1,2-dimethyl groups were in a pseudo equatorial position with the 1,2-dimethoxy groups in the pseudo axial positions. The salt formed with (*R*)-(+)-methylbenzylamine [(*R*)-(+)-1-phenylethylamine] gave the *R,R* isomer **5a**. Resolution of the diastereomeric salt prepared by treating the amide **4** with (*S*)-(−)-methylbenzylamine [(*S*)-(−)-1-phenylethylamine] gave the *S,S* isomer. The chiral anilines **6a** and **6b** were easily obtained by treating the above diastereomeric salts with aqueous 5 N sodium hydroxide. Having succeeded in resolving the anilines with the BDA rings attached in optically active forms, we looked into the

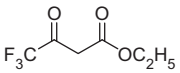
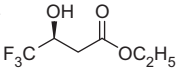
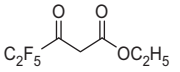
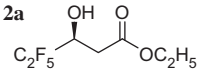
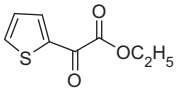
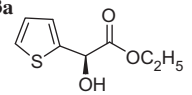
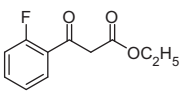
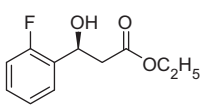
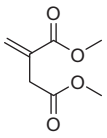
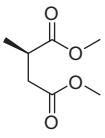
protection of 3,4-dihydroxy benzoic acid as a butane diacetal and again this was achieved using similar conditions that were applied to catechol (Scheme 2). The diastereomeric salt **10a** was prepared by stirring the acid **8** with a chiral α-methylbenzylamine to resolve the isomers. The salt formed with (*R*)-(+)-methylbenzylamine [(*R*)-(+)-1-phenylethylamine] gave the *S,S* isomer **11b** while the salt from (*S*)-(−)-methylbenzylamine [(*S*)-(−)-1-phenylethylamine] gave the *R,R* isomer **11a**. We now had two ways to prepare enantiomerically enriched 1,2-dihydroxy benzenes protected as butane diacetals with suitable functionality that could be used for further synthetic conversion and construction. The next objective was to ascertain the stability of the acetal functionality and find suitable applications for such systems. We set upon exploring the plausibility of using such compounds as ligands for asymmetric catalysis and in this regard decided to construct atropisomeric bisphosphines having the chiral BDA motif. The preparation of such ligands would allow us to subject the BDA functionality through a series of chemically diverse conditions that would allow us to test the stability of this group.

Our proposed plan was to subject the aniline to conditions required for diazotization to obtain a halide, preferably an aryl bromide as depicted in **12**. It was apparent that the aryl bromide **12** could then be converted into a phosphine oxide **13**[12] followed by *ortho*-lithiation to obtain iodide **14**. The subsequent homo coupling under Ullmann conditions followed by reduction would yield the bisphosphine ligand **17** with dual chirality resulting from the BDA components and the atropisomeric biphenyl structure. The BDA group proved to be extremely stable and no trace of any deprotected diol was noticed while performing the synthetic sequence. As envisaged, the bisphosphonate was obtained but surprisingly with a diastereomeric ratio of 84:16 for the resulting atropisomeric biphenyls. It appears that the chiral BDA component is having an effect in allowing for one diastereoisomer to form as the major product in the Ullmann reaction[13] (Scheme 3). The bisphosphines were further enriched to an optically pure form (>99% ee) using *O,O*-dibenzoyltartaric acid. The (+)-bisphosphine was enriched using (+)-*O,O*-dibenzoyltartaric acid[14] and the (−)-bisphosphine was enriched using (−)-*O,O*-dibenzoyltartaric acid.



Scheme 3. Synthesis of bisphosphine **17**.

Table 1
Asymmetric hydrogenation—comparative study

Entry	Substrate	Conditions[c]	Product	ee% (Reported)[a,b]
1		10 bar, 110 °C 1 h, EtOH	**1a** 	18.86 (23) **L1** 53.82 (49) **L2** 78.04 **L3**
2		10 bar, 110 °C 1 h, EtOH	**2a** 	49.00 (44) **L1** 74.22 (63) **L2** 89.78 **L3**
3		10 bar, 80 °C 24 h, EtOH	**3a** 	26.80 (56) **L1** 29.86 (63) **L2** 74.80 **L3**
4		10 bar, 80 °C 24 h, EtOH	**4a** 	43.38 (—) **L1** 57.82 (88) **L2** 81.50 **L3**
5		20 bar, 50 °C 24 h, MeOH	**5a** 	94.86 (90) **L1** 97.24 (93) **L2** 89.14 **L3**

[a] **L1** = (*R*)-BINAP, **L2** = (*R*)-SEGPHOS, **L3** = (*R*)-**17**.
[b] Enantiomeric excess measured by chiral HPLC and GC.
[c] Reactions were conducted on a 1-mmol scale with 1 mol % of in situ prepared $RuBr_2$[ligand] as catalyst. (—) = Not reported.

Atropisomeric ligands such as BINAP and several other related systems have proved to be excellent ligands for ruthenium catalysed asymmetric hydrogenations.[15] The aryl BDA ligand **17** was tested and compared for catalytic activity in asymmetric hydrogenations along with the commercially available BINAP[16] and SEGPHOS.[17] To ascertain if there could be any added value or enhancement of activity due to the presence of the BDA functionality, we only chose substrates that were reported in the literature[18] where the use of these popular ligands did not provide a high degree of selectivity resulting in low enantiomeric excess in the isolated products. A selective comparative study was done where BINAP[19] or SEGPHOS gave poor stereo-induction in ruthenium catalysed asymmetric hydrogenations. The results shown in Table 1 are very encouraging and clearly show that (*R*)-**17** can serve as a stable and selective ligand in promoting asymmetric catalysis.

In conclusion, we have described a method for protecting and isolating enantiomerically enriched anilines or benzoic acids containing 1,2-diols. These compounds can serve as precursors to construct novel and diverse chiral scaffolds. Future work will focus on the design of other aryl-BDA containing phosphines, amines, *N*-heterocyclic carbenes and other chelating systems and gauge their efficacy in asymmetric and organocatalytic reactions.

Acknowledgements

The authors would like to thank Dr. Ravi Kumar and the Indian Institute of Chemical Technology for the X-ray crystallography analysis.

Supplementary data

Supplementary data (Complete experimental details, copies of ^{1}H and ^{13}C NMR for all new compounds. ORTEP diagrams of **5a** (854474), 6a (854475) and **6b** (854476), HPLC and GC chromatograms.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.111.

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