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Preparation of enantiopure 4-arylmandelic acids via a Pd/C catalysed Suzuki coupling of enantiopure 4-bromomandelic acid

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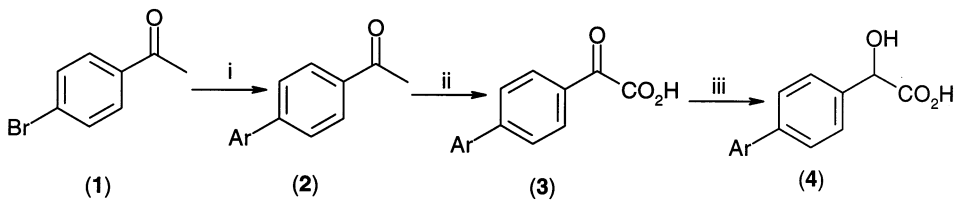
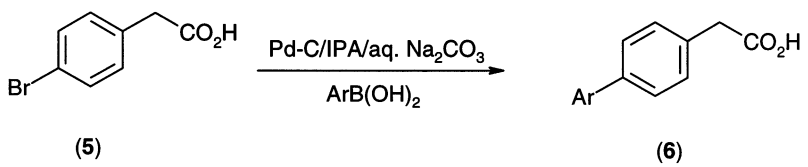
Abstract—A library of enantiomerically pure mandelic acid derivatives has been prepared using a palladium on carbon catalysed Suzuki reaction. The chirality was derived from enantiomerically pure 4-bromomandelic acid which was obtained by resolution with α-methylbenzylamine.

The Suzuki reaction has become a mainstay of modern synthetic organic chemistry for the preparation of biaryl compounds.[1] Recent contributions to this area have included reports on the use of Pd/C as an inexpensive and easily removed heterogeneous catalyst.[2] Surprisingly, this method has still not gained widespread acceptance.[3] Notable exceptions are to be found in Process Research and Development groups where the ease of removal of the catalyst has been an especially attractive feature.[4,5]

As part of our ongoing effort in high throughput diastereomeric salt screening for the preparation of chiral compounds by way of classical resolution, we had a need for an efficient synthesis of a range of 4-arylmandelic acid derivatives.[6] We were surprised to find no reported syntheses of these compounds in a single isomer form. The preparation of these compounds in a racemic form via Suzuki coupling has recently been reported (Scheme 1).[7] This three-step procedure utilises a ligand that is not commercially available,[8] toxic reagents and requires a chromatographic purification. Clearly such an approach was not suitable for the expeditious synthesis of a range of derivatives in single isomer form. Other approaches by way of a Friedel–Crafts reaction[9] or cyanohydrin chemistry[10] were also not practical.[11]



Scheme 1. Reagents: (i) $Pd(OAc)_2$/dioxane/(2′-dicyclohexylphosphanylbiphenyl-2-yl)dimethylamine; (ii) SeO_2/pyridine/105°C; (iii) H_2/PtO_2/HOAc.



Scheme 2.

Keywords: Suzuki reaction; biaryl compounds; 4-bromomandelic acid; palladium on carbon.

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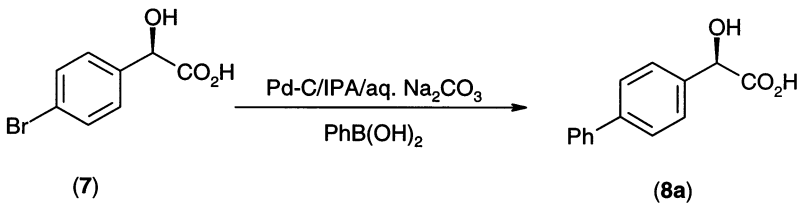


(7) (8a)

Scheme 3.

Table 1. Coupling of 4-bromomandelic acid with boronic acids

Entry	Compound	Yield (%)	e.e. (%)
1	(*R*)-**8a**	75	>99
2	(*R*)-**8b**	90	>99
3	(*S*)-**8c**	88	>99
4	(*S*)-**8d**	85	>99
5	(*R*)-**9a**	89	>99
6	(*R*)-**9b**	92	>99
7	(*S*)-**9c**	96	>99
8	(*R*)-**10**	99	>99

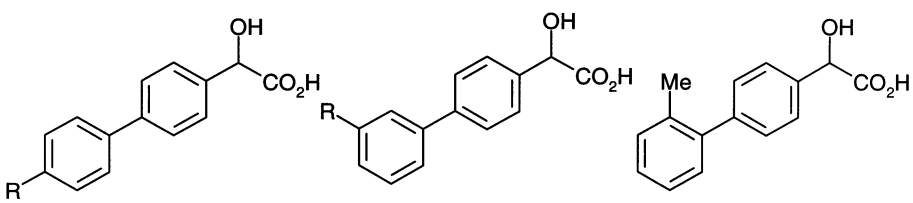
We were attracted to a report on the preparation of 4-arylphenylacetic acids (**6**) using a Pd/C catalysed Suzuki reaction (Scheme 2).[4] We reasoned that this approach was ideal for the rapid preparation of a family of chiral mandelic acid derivatives if we replaced the 4-bromophenylacetic acid with the single isomer 4-bromomandelic acid (**7**).

Compound (**7**) was obtained by resolution with α-methylbenzylamine.[12] With both enantiopodes of 4-bromomandelic acid (**7**) in hand we were now in a position to examine the Pd/C catalysed Suzuki reaction. At this stage we wanted to establish that there would not be any racemisation of the chiral centre under the basic reaction conditions. To test this issue, we first prepared racemic 4-phenylmandelic acid (**8a**) in a respectable 88% yield. Application of these conditions to (*R*)-(**3**) gave the desired (*R*)-(**8a**) in 75% yield (Scheme 3). Chiral HPLC analysis of (**8a**) confirmed that no racemisation had occurred during the coupling reaction.

Having satisfied ourselves that the procedure worked well we set about examining the scope of the reaction and preparing a small library of substituted mandelic acid resolving agents. The results with a range of other boronic acids are summarised in Table 1.[13,14] The enantiomeric excess of the products was determined by chiral HPLC.

From Table 1 it is apparent that a range of functional groups are tolerated within the boronic acid (Scheme 4). These include both electron-donating groups, for example methoxy, and electron-withdrawing groups, for example trifluoromethyl. Positional substitution was also well tolerated in the boronic acid. We have not yet examined the effect of positional isomers in the mandelic acid. In some cases small amounts of the corresponding *iso*-propyl ester contaminated the product. This was presumably formed by an acid catalysed esterification during work-up and could be avoided by distillation of the 2-propanol under vacuum at low temperature.

In conclusion, we have shown that the use of a Pd/C catalysed Suzuki coupling is a powerful reaction for the rapid generation of a library of chiral 4-aryl substituted mandelic acid derivatives. This study further exemplifies the utility of this procedure for the production of small libraries or families of compounds as well as for larger scale preparations. The reaction is noteworthy for giving high yields of the required product after simple filtration and precipitation with no evidence of racemisation. These compounds have been incorporated into our standard classical resolution screening library. Their utility as resolving agents is currently being determined.



(8) (9) (10)

a; R = H
b; R = Me
c; R = CF_3
d; R = F

a; R = Me
b; R = Cl
c; R = OMe

Scheme 4.

Acknowledgements

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12. The absolute stereochemistry of (**7**) was determined by single crystal X-ray of the least soluble salt.
13. General procedure: A solution of sodium carbonate (14.54 mmol, 1.25 equiv.) in water (6.25 ml) was added carefully to a stirred suspension of 4-bromomandelic acid (**3**) (11.63 mmol, 1.0 equiv.), arylboronic acid (12.79 mmol, 1.1 equiv.), 10% palladium on charcoal (0.23 mmol, 2 mol%) in 2-propanol (2.20 ml) and water (9.25 ml). The reaction was stirred at 62°C until complete, then it was cooled to ambient temperature and diluted with 70:15:1 2-propanol/water/2N NaOH solution (25 ml). The mixture was filtered and the catalyst was washed with the same solvent mixture (3×10 ml). The filtrate was diluted with water (25 ml) and acidified to ca. pH 2 with 2N HCl (14 ml). The 2-propanol was removed by vacuum distillation. The crystals that precipitated were filtered and washed with water (5×5 ml) (the pH of the washings was >pH 5), then dried under vacuum to yield the biaryl compound as a white solid.
14. All compounds were fully characterised.