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Efficient kinetic resolution in hydroboration of 1,2-dihydronaphthalenes

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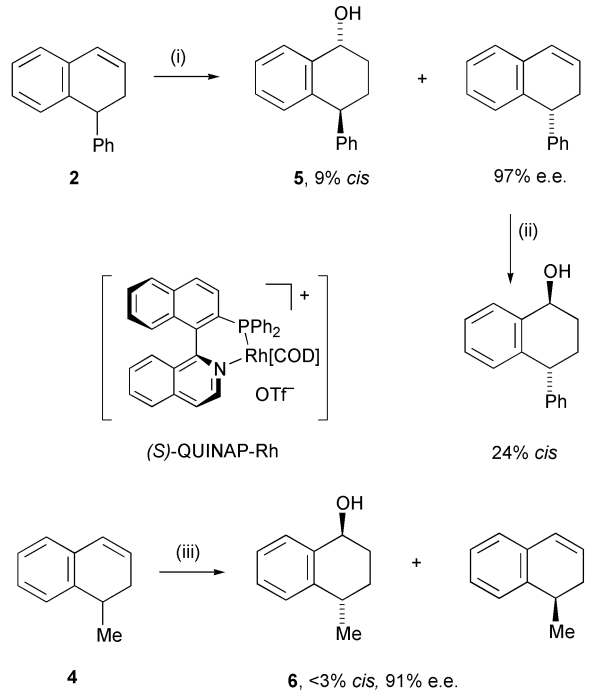
1-Substituted 1,2-dihydronaphthalenes undergo kinetic resolution during asymmetric hydroboration with Rh–QUINAP complexes.

In previous studies of asymmetric hydroboration employing catecholborane it has been established that cationic rhodium complexes of QUINAP are effective.[1] Especially when the reactant is a 1,2-disubstituted vinylarene, the results are superior to those obtained with diphosphine complexes.[2] The ensuing boronate ester can be converted into an alcohol, primary or secondary amine,[3a] homologous ester,[3b] carboxylic acid,[4] or homologous alcohol,[4] with retention of configuration.

Given the structure of Sertraline **1**, and the paucity of direct methods for the required introduction of two 1,4-disposed stereogenic centres in a tetrahydronaphthalene ring,[5] we considered the possibility of hydroboration routes starting with 1,2-dihydronaphthalenes. The parent alkene is one of the most favoured reactants for asymmetric hydroboration (96% ee, 99% regioselectivity)[1] The 1-substituted 1,2-dihydronaphthalenes **2** and **3** were prepared by Heck arylation–migration from the parent alkene with up to 70% regioselectivity,[6] and compound **4** was obtained from 4-methyltetralone ($LiAlH_4$ then DMSO, 150 °C, 46% overall).[7] Hydroboration–oxidation of compound **2** was carried out with (*R*)-QUINAP–Rh according to Scheme 1 with 60 mol% of catecholborane, resulting in recovery of the (*R*)-alkene in 38% yield and 97% ee.[8] The product alcohol **5** (46% yield) was a 91:9 *trans*:*cis* mixture of diastereomers. When the recovered alkene was hydroborated again with (*R*)-QUINAP–Rh, a much slower reaction resulted in a 76:24 *trans*:*cis* ratio of alcohols **5** in 63% yield after H_2O_2–NaOH oxidation, demonstrating the importance of reactant control[8] for the product isomeric composition. When compound **4** was the reactant employing 40 mol% of catecholborane, alcohol **6** was obtained in 80% yield based on the borane and >97:3 *trans*:*cis* ratio, with 91% ee in the *trans*-isomer.† These results indicate a highly selective kinetic resolution process with *S*-values in the region of 20.[9]



Scheme 1 (i) Catecholborane, 0.6 eq., 1 mol% (*R*)-catalyst, C_7H_8, 2 h, RT then 30% aq. H_2O_2, 0 °C, 1 h, flash silica, C_5H_{12} then $CHCl_3$; (ii) catecholborane, 1.2 eq. 4.5 mol% (*R*)-catalyst, 36 h, RT then 30% aq. H_2O_2, 0 °C, 1 h ; (iii) catecholborane, 0.4 eq., 1 mol% (*S*)-catalyst, otherwise as (i).

Remote stereoselectivity in addition reactions of 1-substituted 1,2-dihydronaphthalenes has been observed before, especially in epoxidation[10,11] and rationalised by Houk and coworkers.[11] Just as reagent approach is preferred from the face opposite to the ring substituent to minimise torsional strain, so also complexation occurs preferentially at the same face. The preferred conformation of a 1-substituted 1,2-dihydronaphthalene has the 1*R*-group in a quasiequatorial conformation in a flattened ring, indicated in Fig. 1. The allylic hydrogen *cis*-to the *R*-substituent is axial, and inhibits the approach of rhodium to that face of the alkene. Coordination then occurs preferentially to the opposite face,[12] and since the delivery of H–B to the reactant occurs by an intracomplex mechanism, the *trans*-product is favoured. These factors, coupled with the intrinsic enantioselectivity observed in hydroboration of this class of alkene, favours reaction of one enantiomer in the case of **2** or **4**.

The 3,4-dichloroaryl compound **3** was prepared as a potential precursor to Sertraline.[5,14] Hydroboration with as before (40 mol%) gave **7** in 91% yield based on catecholborane and 88% ee. Since this has been directly converted into (1*S*,4*S*)-Sertraline *via* the corresponding azide or ketone,[5] it completes a formal asymmetric synthesis. When (*S*)-QUINAP–Rh was employed as catalyst with 60 mol% of catecholborane, the (*S*)-alkene **3** was recovered in 78% yield (based on reagent) and 98% ee. The

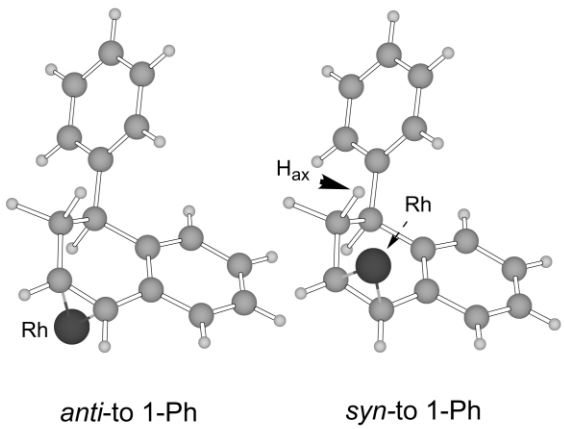


Fig. 1 Complexation of Rh to (*S*)-**2** in its MM2 preferred conformation. The *syn*-form incurs torsional strain between the allylic C–H and the coordinated metal fragment.

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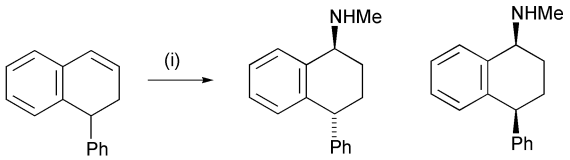
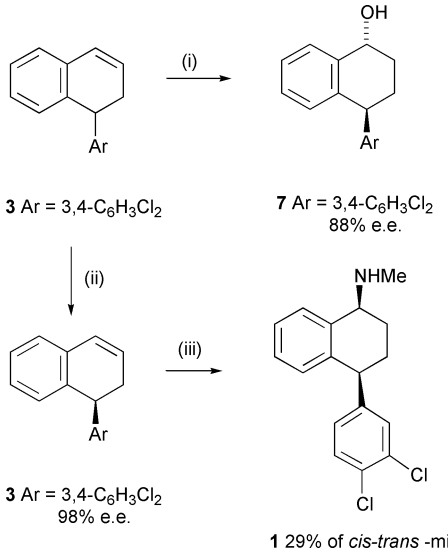


2 (+/–)-**8** 95 : 5

Scheme 2 (i) 1 mol% *rac*-catalyst, catecholborane, 1.0 eq., C_7H_8, RT, 2 h, then $ZnEt_2$ 1 eq., C_7H_8, MeNHCl, 1.2 eq., H_2O–Et_2O, 0 °C, 5 min followed by RT, 1 h, workup; (sample of **2** contained 42% of unreactive 2-Ph isomer (from Heck reaction).

feasibility of a direct amination experiment was tested by reacting compound **2** with racemic catalyst under the conditions of Scheme 2. The resulting boronate ester was treated first with $ZnEt_2$ and then with *in situ* generated MeNHCl. On workup the secondary amine **8** was isolated as a 95 : 5 *trans* : *cis* mixture in 47% yield.

On this basis similar conditions were applied to alkene (*S*)-**3** using the mismatched (*S*)-enantiomer of the catalyst in CH_2Cl_2 and a 5-fold excess of catecholborane to maximise the formation of the *cis*-product. The product, isolated in 26% yield, was a 71 : 29 *trans* : *cis* isomeric mixture (Scheme 3). The minor *cis*-isomer was shown to be Sertraline **1** by isolation (silica



3 Ar = 3,4-$C_6H_3Cl_2$

7 Ar = 3,4-$C_6H_3Cl_2$ 88% e.e.

3 Ar = 3,4-$C_6H_3Cl_2$ 98% e.e.

1 29% of *cis-trans* -mixture

Scheme 3 (i) Catecholborane, 0.4 eq., 1 mol% (*R*)-catalyst, C_7H_8, 2 h, RT then 30% aq. H_2O_2, 0 °C, 1 h, flash silica, C_5H_{12} then EtOAc : n-C_6H_{14} = 1 : 4; (ii) catecholborane, 0.6 eq., 1 mol% (*S*)-catalyst, C_7H_8, 2 h, RT then 30% aq. H_2O_2, 0 °C, 1 h, flash silica, n-C_6H_{14}; (iii) 10 mol% (*S*)-catalyst, catecholborane 5 eq., CH_2Cl_2, RT, 12 h, then styrene 5 eq., RT, 2 h., then *in vacuo*, $ZnEt_2$ 5.5 eq., C_7H_8, RT, 2 h, then MeNHCl, 6 eq., H_2O–Et_2O, 0 °C 5 min followed by RT, 1 h, workup.

chromatography (Biotage®, $CHCl_3$) and ^1H, ^{13}C NMR spectroscopic comparison with an authentic sample.

These results demonstrate for the first time both diastereoselectivity and kinetic resolution in asymmetric hydroboration.[15] The ease of separation of product and reactant after oxidative workup of the boronate ester enhances the synthetic utility of the procedure.

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Notes and references

† (1*S*,4*S*)-**6**, $[\alpha]^{25}_D$ +54.5 (*c* = 1.58, $CHCl_3$) for 91% ee; (1*R*,4*S*)-**7**, $[\alpha]^{25}_D$ +4.01 (*c* = 4.60, $CHCl_3$); (*S*)-**3**, $[\alpha]^{25}_D$ −42.5 (*c* = 3.35, $CHCl_3$) for 98% ee; HCl salt of (1*S*,4*S*)-**1**, $[\alpha]^{25}_D$ +37.5 (*c* = 0.45, MeOH).

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