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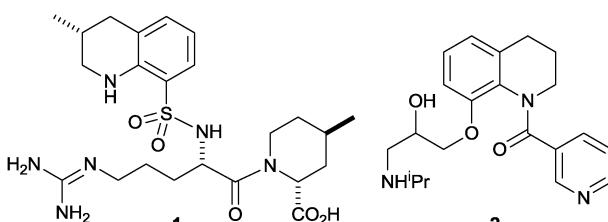
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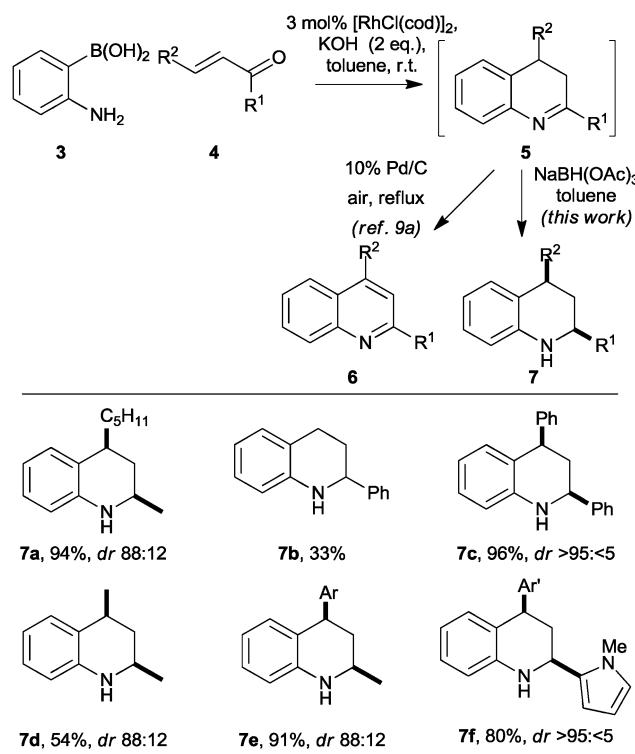
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**Rh-catalysed conjugate additions of 2-aminophenyl boronic acid derivatives were exploited in diastereoselective and asymmetric syntheses of tetrahydroquinolines. In both cases, combinatorial variation of the substitution of the tetrahydroquinoline ring system was possible.**

The tetrahydroquinoline ring system is an important synthetic target<sup>1</sup> that is found in many bioactive compounds including natural products (e.g. dynemicin A<sup>2</sup>) and drugs (e.g. the thrombin inhibitor argatroban<sup>3a</sup> **1** and the antiarrhythmic agent nicainoprol<sup>3b</sup> **2**). Established catalytic asymmetric synthetic approaches to tetrahydroquinolines include transition metal-catalysed hydrogenation and transfer-hydrogenation of quinolines,<sup>4</sup> organocatalytic reduction of quinolines<sup>5</sup> and dihydroquinolines,<sup>6</sup> hetero-Diels–Alder reactions of aniline-derived imines with electron-rich dienophiles (Povarov reactions)<sup>7</sup> and catalysed intramolecular hydride transfer/Mannich condensations.<sup>8</sup>



As part of a programme focused on the synthesis of diverse small molecule scaffolds,<sup>9</sup> we have exploited Rh-catalysed conjugate additions<sup>10</sup> in convergent heterocycle syntheses.<sup>9a,b</sup> For example, Rh-catalysed conjugate addition of 2-aminophenyl boronic acids **3** to enones **4** was followed by cyclisation<sup>‡</sup> ( $\rightarrow$  **5**) and oxidation to give quinolines **6** in good yield (Scheme 1).<sup>9a</sup>



**Scheme 1** Stereoselective synthesis of tetrahydroquinolines. Diastereomeric ratios (*dr*) are reported for the purified products. Ar = *p*-methoxyphenyl; Ar' = *p*-nitrophenyl.

The reaction presumably proceeds by intramolecular condensation of the initial conjugate addition adduct to yield a 3,4-dihydroquinoline **5** and, hence, the corresponding quinoline **6**.

Although the general approach might, in principle, be exploited in asymmetric heterocycle synthesis, it had only been demonstrated in the synthesis of achiral<sup>9a,b</sup> or racemic<sup>9b</sup> heterocycles. We recognized that Rh-catalysed conjugate addition chemistry might enable a new convergent, and potentially asymmetric,<sup>11</sup> synthesis of substituted tetrahydroquinolines **7** (Scheme 1). Initial studies focused on

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the convergent synthesis of the racemic tetrahydroquinoline **7a**. Thus, after completion of the Rh-catalysed conjugate addition reaction, the reaction mixture was diluted with toluene and treated with an excess of sodium triacetoxyborohydride: the tetrahydroquinoline **7a** was obtained in 94% yield with 88:12 diastereoselectivity.

Our initial studies into the scope of the convergent synthesis of racemic tetrahydroquinolines **7** are summarised in Scheme 1. The synthesis of the 2-substituted tetrahydroquinoline **7b** was lower yielding than that of the 2,4-disubstituted analogue **7a**. However, with all of the  $\alpha,\beta$ -disubstituted enones **4** studied, the reaction yielded the corresponding 2,4-disubstituted tetrahydroquinolines **7c–f** in reasonable to excellent yield with both aliphatic and aromatic  $R^1$  and  $R^2$  substituents. In each case, the products were obtained with good to excellent diastereoselectivity in favour of the *cis* isomer.

To enable substitution of the benzenoid ring, we investigated the use of 2-aminophenylpinacolboronates **8**, which may be prepared easily from the corresponding 2-bromoanilines (Scheme 2).<sup>12</sup> The reaction between the parent pinacolboronate **8** ( $R^3 = H$ ) with chalcone was slower than that of the corresponding boronic acid **3**. However, by increasing the catalyst loading (to 6 mol%), and the amount of base (to 2.5 eq.), the reaction was complete in a similar time, and a comparable yield of the tetrahydroquinoline **7c** was obtained (compare Scheme 1 with Scheme 2). Remarkably, the synthesis of the 2-substituted tetrahydroquinoline **7b** was much more effective with the pinacolboronate **8** ( $R^3 = H$ ) as the reactant, and a much improved 77% yield was observed (compare Scheme 1 with Scheme 2). In a similar vein, the 2,4-disubstituted tetrahydroquinolines **7g–i**

were obtained in good yield and with high diastereoselectivity. The accessibility of substituted 2-aminophenyl pinacolboronates enabled the synthesis of tetrahydroquinolines **7j–m** in which the benzenoid ring had been substituted.

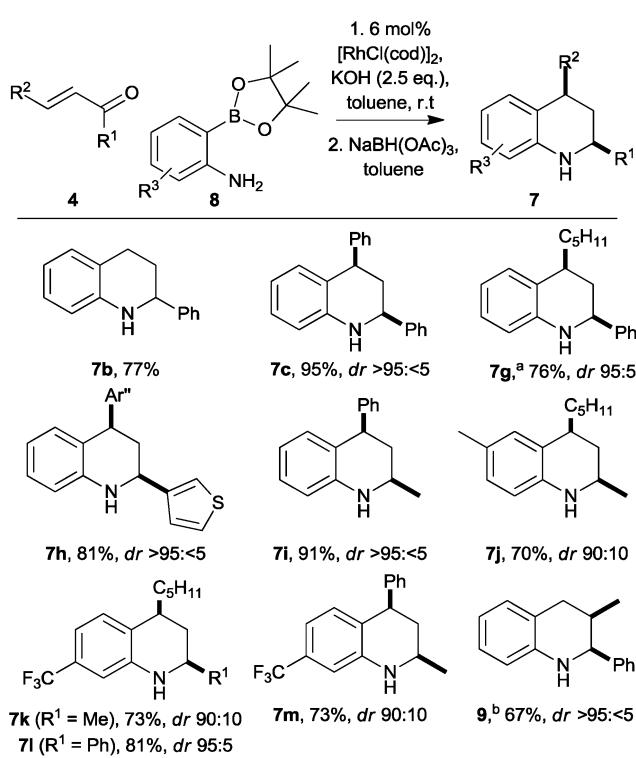
The syntheses of the 2,4-disubstituted tetrahydroquinolines **7** were all highly diastereoselective in favour of the *cis* diastereoisomer. The 1,3-diaxial orientations of H-2 and H-4 were determined by careful analysis of vicinal coupling constants<sup>13</sup> and, for **3h** and **3l**, observation of strong mutual *n*Oe interactions; in addition, the *cis* diastereoisomer of **3d** is a known compound.<sup>14</sup> The stereoselectivity may be explained in terms of axial attack<sup>15</sup> of the reducing agent on the 3,4-dihydroquinoline intermediate.

Extension to the synthesis of a 2,3-disubstituted tetrahydroquinoline was also possible (Scheme 2). Thus, with 2-methyl-1-phenyl prop-2-en-one, the known<sup>16</sup> tetrahydroquinoline **9** ( $J_{H2,H3} = 3.5$  Hz) was obtained in 67% yield as a  $>95 : <5$  mixture of diastereoisomers. As previously observed with the  $\beta$ -unsubstituted enone ( $\rightarrow$  **7b**; compare Scheme 1 with Scheme 2), the yield was higher with the pinacolboronate **8** ( $R^3 = H$ ) as the reactant (67%) than with the corresponding boronic acid **3** (58%).

We next focused on the development of an asymmetric tetrahydroquinoline synthesis. In studies directed towards an asymmetric synthesis of tetrahydroquinolones, we had found that addition of the pinacolboronate **8** ( $R^3 = H$ ) to methyl cinnamate gave racemic products with a wide range of chiral ligands; however, the corresponding Boc-protected substrate **10** ( $R^3 = H$ ) gave, with (*R,R,S,S*)-Duanphos as ligand,<sup>17,18</sup> a low yield of the corresponding tetrahydroquinolone in  $>98\%$  ee (ESI†). These initial results prompted us to investigate the addition of the Boc-protected pinacolboronates **10** to unsaturated ketones. In each case, the intermediate conjugate addition products were treated with triethylsilane in TFA to effect deprotection, cyclisation and reduction, and the enantiomeric excess of the corresponding tetrahydroquinolines **8** was determined by chiral HPLC (Table 1).

The reactions of the Boc-protected pinacolboronate **10** ( $R^3 = H$ ) with a range of  $\alpha,\beta$ -unsaturated ketones, catalysed by 6 mol% (*R,R,S,S*)-Duanphos[Rh(nbd)][BF<sub>4</sub>]<sup>–</sup>, were successful with both aromatic and aliphatic  $R^1$  and  $R^2$  groups (entries 1–4, Table 1). The use of the Boc-protected pinacolboronate **10** ( $R^3 = CF_3$ ) was also successful, and allowed variation of the substitution of the benzenoid ring (entries 5–7). The stereoselectivity of the reactions was remarkable: the products **7** were obtained with very high *cis* diastereoselectivity and with good to excellent enantiomeric excess. The absolute configuration of the tetrahydroquinolines **7c** and **7l** was determined by comparison of their experimental and simulated vibrational circular dichroism spectra.<sup>19</sup> This outcome is consistent with the observed sense of induction in reported asymmetric conjugate addition reactions using this catalyst system.<sup>18</sup>

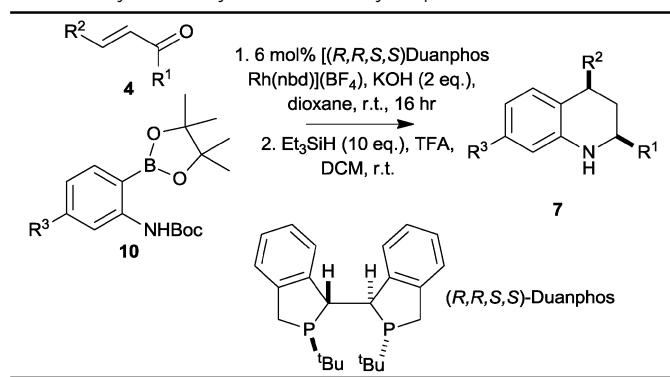
We also investigated the effect of generating the chiral catalyst *in situ*. Thus, the enantiomerically-enriched tetrahydroquinolines *ent*-**7c** and **7g** could be prepared using the combination of 3 mol% [Rh(nbd)Cl]<sub>2</sub> and 6 mol% of either (*S,S,R,R*) or (*R,R,S,S*)-Duanphos (entries 8 and 9, Table 1). The yield of the tetrahydroquinoline **7c** was higher under these conditions than with 6 mol% (*R,R,S,S*)-Duanphos[Rh(nbd)][BF<sub>4</sub>]<sup>–</sup> (compare entries 2 and 8).



Scheme 2 Stereoselective synthesis of tetrahydroquinolines. Diastereomeric ratios (dr) for purified products. <sup>a</sup> Performed at 50 °C. <sup>b</sup> Performed at 40 °C with 2-methyl-1-phenylprop-2-en-one; reduction conditions:  $\text{LiAlH}_4$ , toluene, r.t.  $\text{Ar}'' = p$ -chlorophenyl.



Table 1 Asymmetric synthesis of tetrahydroquinolines



Entry	Product	Yield/%	dr	ee <sup>a</sup> /%
1	7a	76	94:6	>98 <sup>b</sup>
2	7c	60	>95:5	>98
3	7h	45	>95:5	>98 <sup>b</sup>
4	7i	65	>95:5	>98
5	7k	72	>95:5	>98
6	7l	65	92:8	92
7	7m	72	>95:5	>98
8 <sup>c</sup>	ent-7c	78	>95:5	98
9 <sup>d</sup>	7g	62	>95:5	87

<sup>a</sup> Determined by chiral analytical HPLC. <sup>b</sup> The ee of the corresponding 3,5-dinitrobenzamide derivative was determined. <sup>c</sup> 3 mol% [Rh(nbd)Cl]<sub>2</sub> and 6 mol% (S,S,R,R)-Duanphos were used. <sup>d</sup> 3 mol% [Rh(nbd)Cl]<sub>2</sub> and 6 mol% (R,R,S,S)-Duanphos were used.

A novel convergent and stereoselective synthesis of tetrahydroquinolines exploited the Rh-catalysed addition of 2-amino-phenyl boronate derivatives to  $\alpha,\beta$ -unsaturated ketones as the key step. Remarkably, it was possible to develop a highly enantioselective variant of the reaction that exploited the specific combination of Duanphos as the chiral ligand and Boc-protected pinacolboronates as the reactants. The synthetic approach was modular, and will likely be adapted to synthesis of a range of other benzo-fused heterocyclic ring systems. We thank EPSRC and GlaxoSmithKline for funding, Douglas Minick for conducting VCD experiments, and Amgen and ChiralQuest for generous gifts of metal complexes.

## Notes and references

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