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# A convergent rhodium-catalysed asymmetric synthesis of tetrahydroquinolines†

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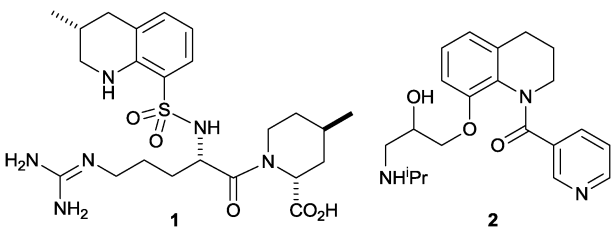
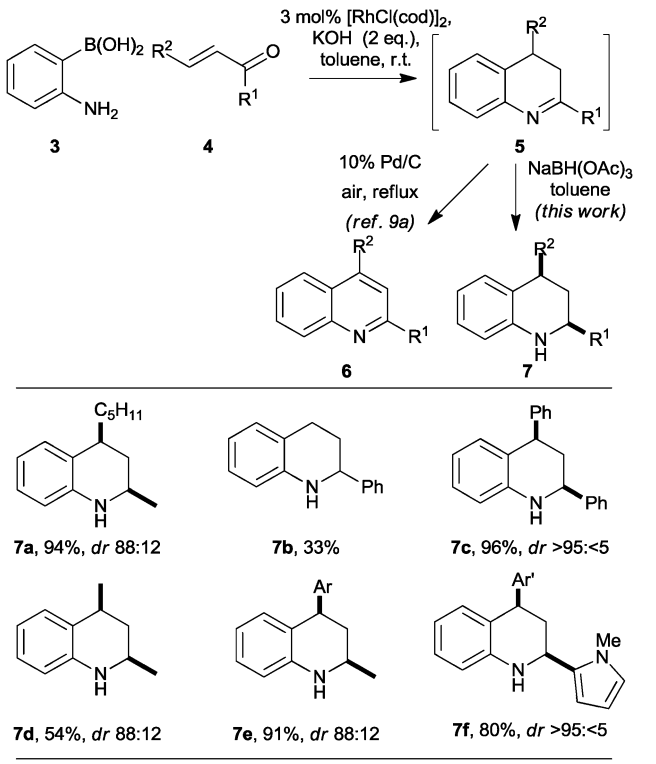
**Rh-catalysed conjugate additions of 2-aminophenyl boronic acid derivatives were exploited in diastereoselective and asymmetric syntheses of tetrahydroquinolines. In both cases, combinatorial variation of the substitution of the tetrahydroquinoline ring system was possible.**

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



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




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[9a,b] or racemic[9b] heterocycles. We recognized that Rh-catalysed conjugate addition chemistry might enable a new convergent, and potentially asymmetric,[11] synthesis of substituted tetrahydroquinolines **7** (Scheme 1). Initial studies focused on

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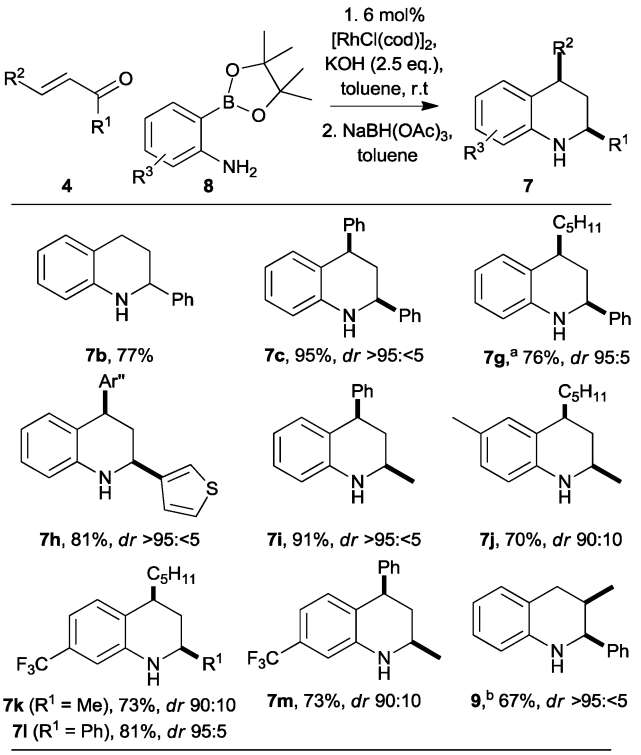
the convergent synthesis of the racemic tetrahydroquinoline **7a**. Thus, after completion of the Rh-catalysed conjugate addition reaction, the reaction mixture was diluted with toluene and treated with an excess of sodium triacetoxyborohydride: the tetrahydroquinoline **7a** was obtained in 94% yield 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 that that of the 2,4-disubstituted analogue **7a**. However, with all of the α,β-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).[12] 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.




Scheme 2 Stereoselective synthesis of tetrahydroquinolines. Diastereomeric ratios (dr) for purified products. [a] Performed at 50 °C. [b] Performed at 40 °C with 2-methyl-1-phenylprop-2-en-one; reduction conditions: $LiAlH_4$, toluene, r.t. Ar″ = *p*-chlorophenyl.

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[13] and, for **3h** and **3l**, observation of strong mutual nOe interactions; in addition, the *cis* diastereoisomer of **3d** is a known compound.[14] The stereoselectivity may be explained in terms of axial attack[15] 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[16] tetrahydroquinoline **9** ($^3J_{H2,H3}$ = 3.5 Hz) was obtained in 67% yield as a >95 : <5 mixture of diastereoisomers. As previously observed with the β-unsubstituted enone (→**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,[17,18] 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 α,β-unsaturated ketones, catalysed by 6 mol% (*R*,*R*,*S*,*S*)-Duanphos[Rh(nbd)][$BF_4$], 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.[19] This outcome is consistent with the observed sense of induction in reported asymmetric conjugate addition reactions using this catalyst system.[18]

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]$_2$ 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)][$BF_4$] (compare entries 2 and 8).

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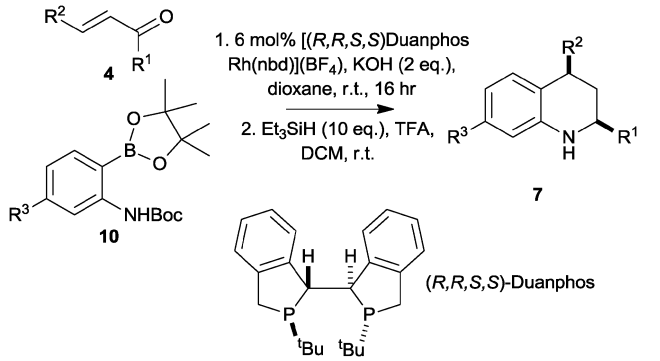
Table 1 Asymmetric synthesis of tetrahydroquinolines




| Entry | Product | Yield/% | dr | ee[a]/% |
|---|---|---|---|---|
| 1 | **7a** | 76 | 94 : 6 | >98[b] |
| 2 | **7c** | 60 | >95 : 5 | >98 |
| 3 | **7h** | 45 | >95 : 5 | >98[b] |
| 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[c] | *ent*-**7c** | 78 | >95 : 5 | 98 |
| 9[d] | **7g** | 62 | >95 : 5 | 87 |

[a] Determined by chiral analytical HPLC. [b] The ee of the corresponding 3,5-dinitrobenzamide derivative was determined. [c] 3 mol% $[Rh(nbd)Cl]_2$ and 6 mol% (*S*,*S*,*R*,*R*)-Duanphos were used. [d] 3 mol% $[Rh(nbd)Cl]_2$ 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-aminophenyl boronate derivatives to α,β-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.

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