



Cite this: *Chem. Commun.*, 2014, 50, 10222

Received 27th June 2014,  
Accepted 18th July 2014

DOI: 10.1039/c4cc04940c

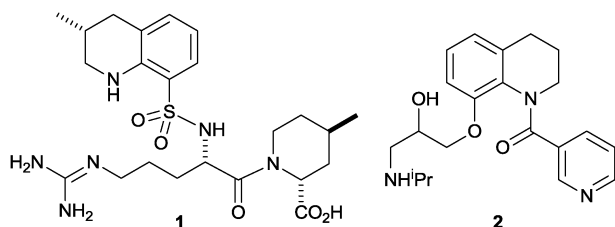
www.rsc.org/chemcomm

# A convergent rhodium-catalysed asymmetric synthesis of tetrahydroquinolines†

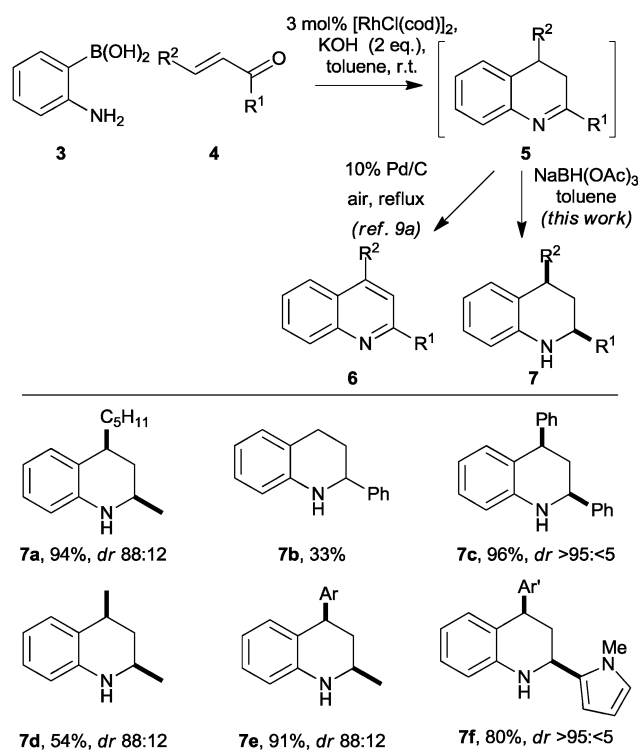
Ho Yin Li,<sup>a</sup> Joachim Horn,<sup>a</sup> Amanda Campbell,<sup>b</sup> David House,<sup>b</sup> Adam Nelson<sup>\*ac</sup> and Stephen P. Marsden<sup>\*a</sup>

**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‡ (→ **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

<sup>a</sup> School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

E-mail: a.s.nelson@leeds.ac.uk, s.p.marsden@leeds.ac.uk

<sup>b</sup> GlaxoSmithKline Medicines Research Centre, Stevenage, SG1 2NY, UK

<sup>c</sup> Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc04940c



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** ( $R^3 = \text{H}$ ) 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** ( $R^3 = \text{H}$ ) 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 nOe 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** ( $^3J_{\text{H2,H3}} = 3.5 \text{ Hz}$ ) 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** ( $R^3 = \text{H}$ ) 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** ( $R^3 = \text{H}$ ) to methyl cinnamate gave racemic products with a wide range of chiral ligands; however, the corresponding Boc-protected substrate **10** ( $R^3 = \text{H}$ ) gave, with (*R,R,S,S*)-Duanphos as ligand,<sup>17,18</sup> a low yield of the corresponding tetrahydroquinolone in  $>98\%$  ee (ESI<sup>†</sup>). 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** ( $R^3 = \text{H}$ ) with a range of  $\alpha,\beta$ -unsaturated ketones, catalysed by 6 mol% (*R,R,S,S*)-Duanphos[Rh(nbd)][BF<sub>4</sub>], 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** ( $R^3 = \text{CF}_3$ ) 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>

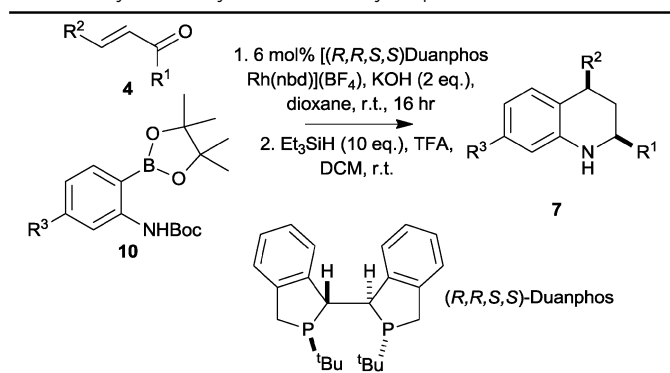
We also investigated the effect of generating the chiral catalyst *in situ*. Thus, the enantiomerically-enriched tetrahydroquinolines *ent*-**7c** and **7g** could be prepared using the combination of 3 mol% [Rh(nbd)Cl]<sub>2</sub> and 6 mol% of either (*S,S,R,R*) or (*R,R,S,S*)-Duanphos (entries 8 and 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>] (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: LiAlH<sub>4</sub>, toluene, r.t. Ar'' = *p*-chlorophenyl.



Table 1 Asymmetric synthesis of tetrahydroquinolines



Entry	Product	Yield/%	dr	ee <sup>d</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-aminophenyl 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

‡ See ref. 9a for evidence for the formation of 5 ( $R^1$  = Me;  $R^2$  = C<sub>5</sub>H<sub>11</sub>).

- 1 A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, 52, 15031.
- 2 M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. VanDuyne and J. Clardy, *J. Antibiot.*, 1989, 42, 1449.
- 3 (a) L. R. Bush, *Cardiovasc. Drug Rev.*, 1991, 9, 247; (b) S. Imanishi, T. Kimura and M. Arita, *Cardiovasc. Drug Rev.*, 1991, 9, 223.
- 4 For examples, see: (a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, 125, 10536; (b) M. T. Reetz and X. Li, *Chem. Commun.*, 2006, 2159; (c) W.-J. Tang, S.-F. Zhu, L.-J. Xu, Q.-L. Zhou, Q.-H. Fan, H.-F. Zhou, K. Lam and A. S. C. Chan, *Chem. Commun.*, 2007, 613; (d) C. Wang, C. Li, X. Wu, A. Pettman and J. Xiao, *Angew. Chem., Int. Ed.*, 2009, 48, 6524; (e) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu

- and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, 133, 9878; (f) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2008, 47, 8464.
- (a) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, 45, 3683; (b) Q.-S. Guo, D.-M. Du and J. Xu, *Angew. Chem., Int. Ed.*, 2008, 47, 759; (c) M. Rueping, T. Theissman, S. Raja and J. W. Bats, *Adv. Synth. Catal.*, 2008, 350, 1001; (d) M. Rueping and T. Theissman, *Chem. Sci.*, 2010, 1, 473; (e) M. Rueping, T. Theissman, M. Stoeckel and A. P. Antonchick, *Org. Biomol. Chem.*, 2011, 9, 6844; (f) Q. A. Chen, K. Gao, Y. Duan, Z. S. Ye, L. Shi, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, 134, 2442; (g) X.-F. Tu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2012, 51, 11346.
- Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, 131, 9182.
- (a) H. Ishitani and S. Kobayashi, *Tetrahedron Lett.*, 1996, 37, 1973. For select recent examples, see: (b) T. Akiyama, H. Morita and K. Fuchibe, *J. Am. Chem. Soc.*, 2006, 128, 13070; (c) H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.*, 2009, 131, 4598; (d) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi and A. Ricci, *Chem. Commun.*, 2010, 46, 327; (e) M.-S. Xie, X.-H. Chen, Y. Zhu, B. Gao, L.-L. Lin, X.-H. Liu and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2010, 49, 3799; (f) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao and E. N. Jacobsen, *Science*, 2010, 327, 986; (g) G. Dagousset, J. P. Zhu and G. Masson, *J. Am. Chem. Soc.*, 2011, 133, 14804; (h) C. Min, N. Mittal, D. X. Sun and D. Seidel, *Angew. Chem., Int. Ed.*, 2013, 52, 14084; (i) C. S. Luo and Y. Huang, *J. Am. Chem. Soc.*, 2013, 135, 8193; (j) J. Calleja, A. B. Gonzalez-Perez, A. R. de Lera, R. Alvarez, F. J. Fananas and F. Rodriguez, *Chem. Sci.*, 2014, 5, 996.
- (a) S. Murarka, I. Deb, C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2009, 131, 13226; (b) K. Mori, K. Ehara, K. Kurihara and T. Akiyama, *J. Am. Chem. Soc.*, 2011, 133, 6166; (c) Y.-K. Kang, S. M. Kim and D. Y. Kim, *J. Am. Chem. Soc.*, 2010, 132, 11847.
- (a) J. Horn, S. P. Marsden, A. Nelson, D. House and G. G. Weingarten, *Org. Lett.*, 2008, 10, 4117; (b) J. Horn, H. Y. Li, S. P. Marsden, A. Nelson, R. J. Shearer, A. J. Campbell, D. House and G. G. Weingarten, *Tetrahedron*, 2009, 65, 9002; (c) P. Tosatti, J. Horn, A. J. Campbell, D. House, A. Nelson and S. P. Marsden, *Adv. Synth. Catal.*, 2010, 352, 3153; (d) P. Tosatti, A. J. Campbell, D. House, A. Nelson and S. P. Marsden, *J. Org. Chem.*, 2011, 76, 5495.
- (a) M. Sakai, H. Hayashi and N. Miyaara, *Organometallics*, 1997, 16, 4229. For reviews, see: (b) T. Hayashi, *Synlett*, 2001, 879; (c) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, 103, 169; (d) H. J. Edwards, J. D. Hargrave, S. D. Penrose and C. G. Frost, *Chem. Soc. Rev.*, 2010, 39, 2093.
- (a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai and N. Miyaara, *J. Am. Chem. Soc.*, 1998, 120, 5579. For reviews, see ref. 10c,d and: (b) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, 103, 2829; (c) D. Mueller and A. Alexakis, *Chem. Commun.*, 2012, 48, 12037.
- O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem.*, 2000, 65, 9268.
- M. Karplus, *J. Am. Chem. Soc.*, 1963, 85, 2870.
- M. Ueda, S. Kawai, M. Hayashi, T. Naito and O. Miyata, *J. Org. Chem.*, 2010, 75, 914.
- R. V. Stevens, in *Strategies and Tactics in Organic Synthesis*, ed. T. Lindberg, Academic Press, 1984, vol. 1.
- S.-I. Murahashi, Y. Imada and Y. Hirai, *Bull. Chem. Soc. Jpn.*, 1989, 62, 2968.
- (a) D. Liu and X. Zhang, *Eur. J. Org. Chem.*, 2005, 646; (b) I. C. Lennon, *Chim. Oggi*, 2010, 28, 46.
- For an example of a Rh-catalysed conjugate addition with Duanphos as ligand, see: J. L. Zigterman, J. C. S. Woo, S. D. Walker, J. S. Tedrow, C. J. Borths, E. E. Bunel and M. M. Faul, *J. Org. Chem.*, 2007, 72, 8870.
- (a) P. J. Stephens, in *Computational Medicinal Chemistry for Drug Discovery*, ed. P. Bultinck, H. de Winter, W. Langenaeker and J. P. Tollenare, Marcel Dekker, New York, 2004, pp. 699–725; (b) T. Kuppens, P. Bultinck and W. Langenaeker, *Drug Discovery Today: Technol.*, 2004, 1, 269.

