Catalytic asymmetric hydroboration–amination

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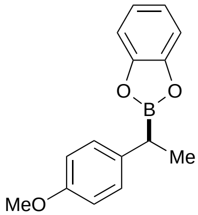
A one-pot asymmetric synthesis of primary amines from vinylarenes *via* catalytic hydroboration is described.

Despite considerable efforts to find alternatives, catecholborane is the most useful borane and rhodium complexes are the most useful catalysts in catalytic hydroboration.[1] Synthetic application of the resulting catecholborane adducts is however limited to oxidation with basic H_2O_2, and hence the asymmetric version[2] is in turn limited to the synthesis of secondary alcohols, for which many excellent alternative routes are already available.[3] Given the wealth of functional group transformations that can be performed with alkylboranes,[4] there is an incentive for developing further synthetic outlets for the catalysed case. Our initial efforts were directed to the reaction of isolated 1-phenylethylcatecholboronates† with electrophilic aminating agents such as $ClMgN(Me)OSiMe_3$, and although some success was achieved in controlling enantioselectivity, the chemoselectivity for secondary amine formation over alcohol was moderate.[5]

In considering a direct route from alkylcatecholboronates to amines, we were guided by prior results from Brown's research in which alkylboronates, which do not react directly with the standard aminating agent H_2NOSO_3H,[6] were converted by a practical, albeit multistep, route into amines *via* the more reactive dialkylborinate esters. In contrast, excess R_2Zn is reported to effect clean transmetallation of a range of dialkylvinylboranes,[7a] trialkylboranes,[7b] alkylboronates and alkyldithioboronates,[7c] thus providing a route to less accessible alkenyl and alkylzinc compounds. Reaction intermediates have not been reported, although it is likely that the trialkylborane is an intermediate in boronate ester transmetallations (*vide infra*).

Our own initial experiments were conducted in toluene solution by reacting an isolated sample of catecholboronate ester **1** with 1 equiv. of Et_2Zn; we were delighted to observe that a clean and quantitative displacement took place, resulting in the transfer of two ethyl groups to boron to form **2** and removal of the Zn from the reaction medium as an insoluble catecholate.[8] The resulting borane was characterized by ^1H NMR [$\delta_H(C_7D_8)$ 1.20 (q), 0.95(t)] and MS (*m/z* 205). Oxidation of the borane **2** under standard conditions (H_2O_2, NaOH) demonstrated that the configurational integrity of the stereogenic centre had been maintained. At this point we became aware of an early report that primary alkylcatecholboronates react with 2 equiv. of RMgBr by complete displacement of the catechol residue giving the mixed trialkylborane.[9] In accord with this, complete displacement of catecholate without precipitation was observed when the reaction between MeMgCl and borane **1** was carried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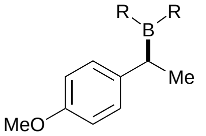
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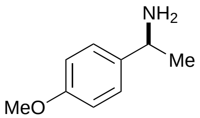
3 R = Me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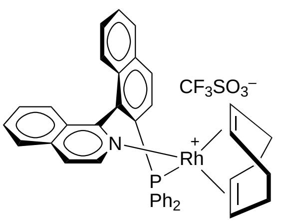
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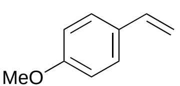
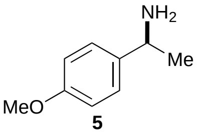
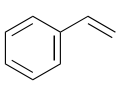
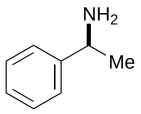
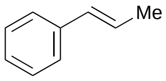
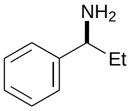
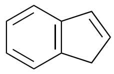
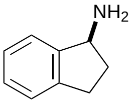
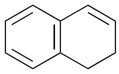
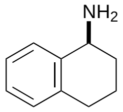
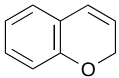
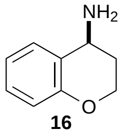
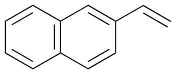
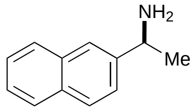
Table 1 Hydroboration–amination of vinylarenes[a]

Reactant	Product	Regio-select-ivity (%)[b]	Iso-lated yield (%)	Ee (%)[c]
 **6**	 **5**	> 98	56	98
 **7**	 **8**	> 98	54	87
 **9**	 **10**	> 98	50	90
 **11**	 **12**	> 98[d]	61	77
 **13**	 **14**	96	51	97
 **15**	 **16**	98[e]	64	89
 **17**	 **18**	92[f]	62	90

[a] Hydroboration–amination experiments as per typical protocol (see footnote ‡). [b] Minor component is regioisomeric primary amine. [c] Ees of amines or their acetamides were analysed by GC using a 25 m CHIRALDEX bonded silica column at 140–150 °C, achieving baseline separation in all cases. [d] From isolated organoborane. [e] Not previously obtained in enantiomerically enriched form, $[\alpha]_D^{23}$ −55.21 (*c* 0.36, $CHCl_3$) for acetylamino derivative; configuration assigned by comparison with (*S*)-chroman-4-ol (ref. 16) formed by hydroboration–oxidation. [f] Analysis by ^1H NMR using $Eu(tfc)_3$.

out in thf solution, the only product being **3** [δ_C 13.0 (J_{BC} 82 Hz)].[10] These displacement reactions were also shown to be occur with other arylalkylboronates prepared by catalytic hydroboration of vinylarenes with catecholborane.

With a clean route to enantiomerically enriched trialkylboranes in hand, attention was then turned to developing a synthetically useful amination procedure. It is known that in aminations with H_2NOSO_3H, methyl is a poor migrating group,[11] and a protocol was developed accordingly. It was established in an initial experiment that successive addition of 2 equiv. of MeMgCl and 3 equiv. of H_2NOSO_3H to an isolated sample of borane **1** (86% ee) in thf gave amine **5** in 83% ee and 65% yield. Catalytic hydroboration was then carried out for several vinylarenes in thf solution at ambient temperature, employing the rhodium complex of (*S*)-quinap (**4**) in the manner previously described.[12] On completion of the hydroboration reaction, 2 equiv. of MeMgCl (3 m solution in thf) were added followed after 30 min by 3 equiv. of H_2NOSO_3H. After stirring for 12 h the amine was isolated either directly, or as its acetamide (MeCOCl) and the ee analysed as described in Table 1. As far as can be determined, the ee values reflect the enantioselectivity of the catalytic hydroboration step, since H_2O_2–OH^- oxidation at the trialkylborane stage provides a secondary alcohol whose enantiomeric purity is the same or slightly lower than that of the primary amine (within experimental error). For the acyclic side-chain amines derived from alkenes **6**, **7**, **9** and **17**, the results follow quite closely those observed previously in hydroboration–oxidation, but superior results have been obtained for the slower-reacting dihydronaphthalene **13** and 4-chromene **15** by very careful attention to catalyst purity and freshness, although indene **11** was somewhat inferior. A one-stage asymmetric synthesis of 1-aminotetralin **14** in 97% ee is of potential practical significance.

In summary, we have developed a method for the catalytic asymmetric synthesis of primary amines from alkenes that complements existing methods, which are most commonly based on imine[13] or enamide reduction,[14] or allylic alkylation procedures.[15] The activation of catecholborane adducts offers the possibility of further extending the range of catalytic hydroboration (*e.g.* to Suzuki couplings and other C–C bond forming reactions) and provides an incentive for us to improve the scope and selectivity of the catalytic reaction itself.

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Footnote

† IUPAC name: *ortho*-phenylene 1-phenylethylboronate.

‡ Freshly prepared complex **4** (4.0 mg, 0.005 mmol, 1.0 mol%) and thf (0.5 ml) were placed in a vial under argon with the alkene (0.5 mmol). Freshly distilled catecholborane (53.3 µl, 59.5 mg, 0.5 mmol) was added with stirring, then left for 1 h. MeMgCl (3 m in thf, 333 µl, 1.0 mmol) was added and the solution stirred for 30 min. The reactant solution was added to predried H_2NOSO_3H (169 mg, 1.5 mmol), with 0.7 ml of thf or diglyme, and stirred under argon for *ca*. 15 h. HCl (1 m, 2 ml) was added, and the mixture poured into H_2O (4 ml). The aqueous layer was extracted with Et_2O (3×20 ml) and then was made strongly alkaline with NaOH (1 m, 3 ml). The mixture was then extracted with Et_2O (3×20 ml). The Et_2O extracts were combined and dried with magnesium sulfate, and the solvent removed *in vacuo*.

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