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Catalyzed hydroboration of allyl sulfonamides

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Dedicated to Professor M.F. Hawthorne on the occasion of his 75th birthday

Abstract

The hydroboration of allyl sulfonamides (4-$H_3CC_6H_4SO_2NRCH_2CH{=}CH_2$: R = H, **1**; Ph, **2**; Bz, **3**) with catecholborane (HBcat) using different rhodium catalysts has been examined using multinuclear NMR spectroscopy. Reactions give complex product distributions, regardless of the choice of catalyst, arising from a competing isomerization reaction. This isomerization reaction can be used with *N*-substituted allyl sulfonamides **2** and **3** to give the corresponding enamines (4-$H_3CC_6H_4SO_2CH{=}CH_2CH_3$), which in turn react with HBcat to give regioselective formation of one isomer (4-$H_3CC_6H_4SO_2NRCH_2CH_2$(Bcat)CH_3).

Keywords: Hydroboration; Catalysis; Isomerization; Sulfonamides; Aminoboron; Rhodium

1. Introduction

The hydroboration of alkenes and alkynes, which constitutes the addition of a B–H bond across a carbon–carbon multiple bond, is an extremely important reaction in organic synthesis [1]. Although simple boron hydride reagents such as borane ($H_3B{\cdot}X$, where X is a Lewis-base) and 9-borabicyclo[3.3.1]nonane react readily with alkenes at room temperature, hydroborations with catecholborane (HBcat, cat = 1,2-$O_2C_6H_4$) generally require elevated temperatures. The discovery that transition metals can be used to catalyze the addition of HBcat to organic substrates has become an important and well-established technique [2–15]. These reactions can have regio-, chemo-, or stereoselectivities, complementary, or more remarkably, opposite to those from products obtained via the uncatalyzed variant. For example, hydroborations of styrenes (Ar$CH{=}CH_2$) with HBcat proceed to give selectively either the expected anti-Markovnikov product (ArCH_2CH_2Bcat) or the Markovnikov product (ArCH(Bcat)CH_3), depending upon the choice of rhodium catalyst used to affect this transformation (Scheme 1) [3]. The unusual Markovnikov product is believed to arise when the rhodium centre can best stabilize a benzylic intermediate during the catalytic cycle.

Although a considerable amount of research has focused on the catalyzed hydroboration of simple unsaturated hydrocarbon systems, much less is known about analogous reactions with heteroatom-containing substrates [3,15–22]. For instance, rhodium catalyzed hydroborations of phenyl vinyl sulfide (Ph$SCH{=}CH_2$) and phenyl vinyl sulfone (Ph$SO_2CH{=}CH_2$) with HBcat give the unusual Markovnikov addition products, PhSCH(Bcat)CH_3 and PhSO_2CH(Bcat)CH_3, respectively [16]. Likewise, hydroborations of allyl phenyl sulfone (Ph$SO_2CH_2CH{=}CH_2$) using Wilkinson's catalyst and HBcat were reported to give PhSO_2CH_2-CH(OH)CH_3 upon oxidative work-up with NaOH/H_2O_2 [22]. These results, along with our interest in generating novel biologically-active boron compounds, prompted us to investigate the metal catalyzed hydroboration of allyl sulfonamides (Ar$SO_2NRCH_2CH{=}CH_2$) with HBcat using multinuclear NMR spectroscopy, the results of which are presented herein.

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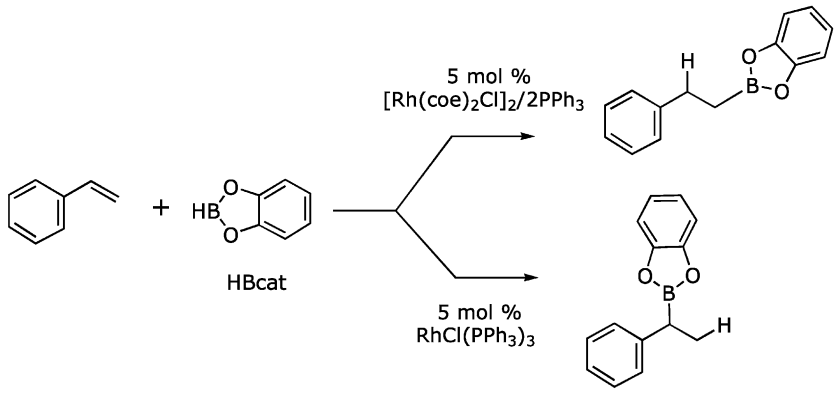


Scheme 1. The hydroboration of styrene with HBcat.

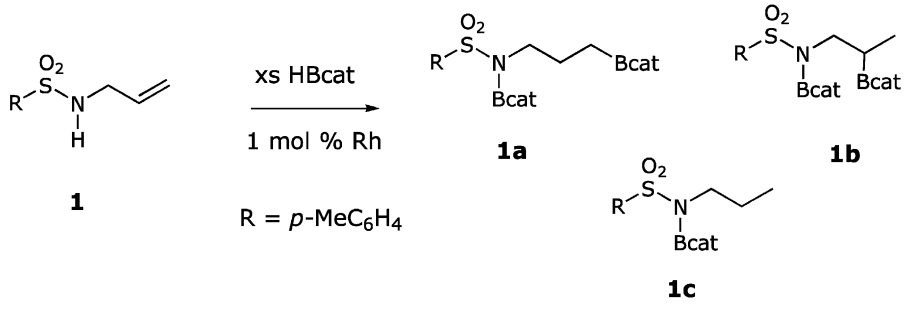
2. Results and discussion

The ability to make new organosulphur derivatives is of significant importance as these compounds have found extensive application in medicine over the past 30 years [23]. For instance, a major milestone in science this past century has been the discovery of the antibacterial properties of penicillin and other sulfonamide drugs. We therefore decided to investigate the hydroboration of allyl sulfonamides as a novel route of generating boron-containing organosulphur compounds.

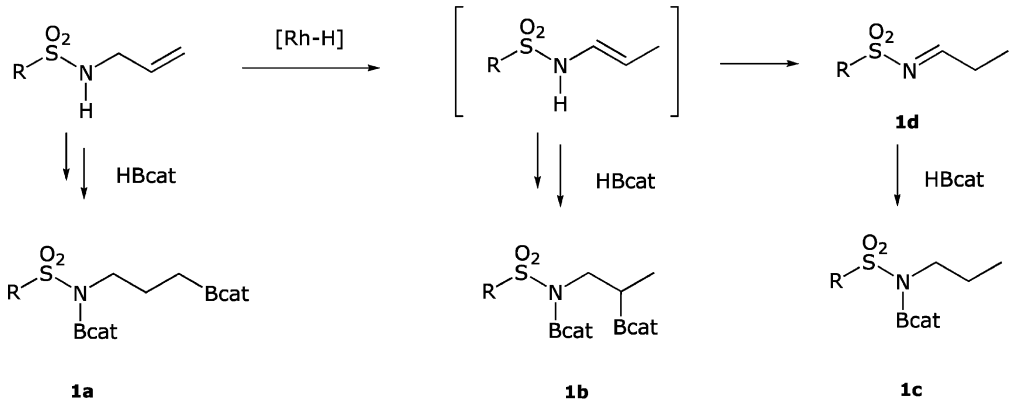
Sulfonamides **1**–**3** were prepared by the addition of *p*-toluenesulfonyl chloride to the corresponding allylamine, $RHNCH_2CH{=}CH_2$ (R = H, Ph, CH_2Ph). Hydroborations of 4-$H_3CC_6H_4SO_2NHCH_2CH{=}CH_2$ (**1**) with HBcat proceeded at room temperature to give the expected anti-Markovnikov product 4-$H_3CC_6H_4$-$SO_2NHCH_2CH_2CH_2$Bcat after 2 weeks. It is interesting to note that, under these conditions, HBcat failed to react with the N–H bond in **1** [17]. Reactions using a catalytic amount (1 mol%) of $RhCl(PPh_3)_3$ and an excess of HBcat (5 equiv) gave a mixture of both 4-$H_3CC_6H_4SO_2N$(Bcat)$CH_2CH_2CH_2$Bcat (**1a**) and 4-$H_3CC_6H_4SO_2N$(Bcat)CH_2CH(Bcat)CH_3 (**1b**) along with major amounts (ca. 80%) of hydrogenation product **1c** (Scheme 2), as monitored by multinuclear NMR spectroscopy [24]. As degradation of HBcat is often observed in these catalyzed reactions [3,24], an excess of HBcat was used to ensure complete conversion of the starting allyl sulfonamide. All attempts to improve regioselectivities using a number of different rhodium catalyst precursors proved unsuccessful.

Interesting, however, is the observation that the N–H bond has reacted with an equivalent of HBcat to form a new N–Bcat bond and, presumably, H_2. A peak at 25 ppm in the $^{11}B\{^1H\}$-NMR spectra is attributed to this new aminoboron species. This reaction represents an example of the rhodium catalyzed addition of a B–H bond to an amine [17] and suggests that product **1c** could therefore arise from a competing rhodium catalyzed hydrogenation reaction of the starting allyl sulfonamide **1**.

More remarkable, however, is the observation that catalyzed reactions using a deficiency of HBcat (1 mol%) quantitatively converted **1** into 4-$H_3CC_6H_4$-$SO_2N{=}CHCH_2CH_3$ (**1d**). This sulfonimine is presumably generated by a catalyzed isomerization of **1** [24,25], using a putative Rh–H species that forms when HBcat adds to the rhodium centre during the catalytic cycle [2]. We have found that **1d** could also be generated exclusively by the addition of a catalytic amount of $RhH(PPh_3)_4$ to **1** in the absence of HBcat. Subsequent addition of 1 equiv of HBcat can therefore be used, in either case, to give 'hydrogenation' product **1c** as the electron deficient boryl group adds to the electron rich



Scheme 2. The rhodium catalyzed hydroboration of allyl sulfonamide **1** with HBcat.



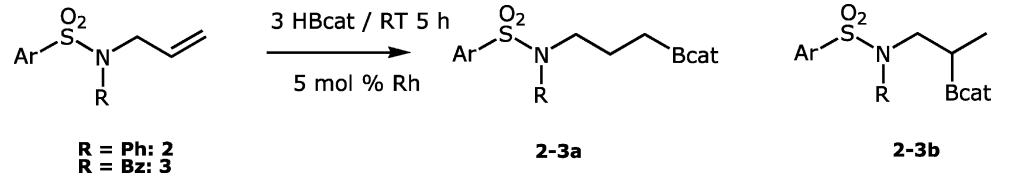
Scheme 3. Isomerization/hydroboration of allyl sulfonamide **1**.

imine nitrogen. It is therefore also plausible that the unexpected hydroboration product **1b** arises as a result of a metal catalyzed addition of HBcat to the transient enamine, which is produced in the first step of the isomerization process (Scheme 3).

Although we were unable to control selectivities in reactions with **1**, we decided to investigate hydroborations with *N*-phenyl substituted allyl sulfonamide **2** where isomerization to an imine is not possible. Mixtures of both hydroboration products **2a**–**b** were once again obtained under catalytic conditions using a variety of rhodium complexes (Table 1). For instance, regioselectivities of 90% for the expected anti-Markovnikov product were obtained (Table 1, entry 5) when the neutral catalyst system $[RhCl(coe)_2]_2/2PPh_3$ (coe = *cis*-cyclooctene) was used to affect this reaction. On the other hand, the Markovnikov isomer could be generated in 75% yield (based on ^{1}H-NMR spectroscopy) if an excess of phosphine was used with Wilkinson's catalyst (entry 4).

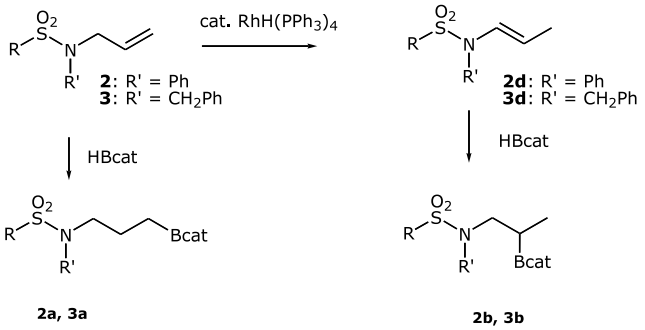
These selectivities appear to correlate with the competing isomerization reaction as we were able to generate the Markovnikov isomer **2b** in high yields using a tandem isomerization/hydroboration catalytic

Table 1
The rhodium catalyzed hydroboration of sulfonamide **2** with HBcat



Entry	Allyl	Catalyst system [a]	Solvent	**2a** [b]	**2b** [c]
1	**2**	$RhCl(PPh_3)_3$	C_6D_6	45	55
2	**2**	$RhCl(PPh_3)_3$	THF-d_8	50	50
3	**2**	$RhCl(PPh_3)_3$	CD_2Cl_2	35	65
4	**2**	$RhCl(PPh_3)_3+5PPh_3$	$CDCl_3$	25	75
5	**2**	$[Rh(coe)_2Cl]_2+2PPh_3$	$CDCl_3$	90	10
6	**2**	$[Rh(coe)_2Cl]_2+4PPh_3$	$CDCl_3$	85	15
7	**2**	$[Rh(cod)Cl]_2+AgBF_4+$dppe	THF-d_8	90	10
8	**2**	$Rh(acac)(coe)_2$	$CDCl_3$	85	15
9	**2**	$Rh(acac)(coe)_2+$dppm	$CDCl_3$	45	55
10	**2**	$Rh(acac)(coe)_2+$dppb	$CDCl_3$	80	20
11	**2**	$RhH(PPh_3)_4$	$CDCl_3$	0	100 [d]
12	**3**	$RhCl(PPh_3)_3$	$CDCl_3$	90	10

[a] acac = Acetylacetonato; cod = *cis*-cyclooctadiene; coe = *cis*-cyclooctene; dppb = 1,4-bis(diphenylphosphino)butane; dppe = 1,2-bis(diphenylphosphino)ethane; dppm = 1,1′-bis(diphenylphosphino)methane.
[b] Yields were ascertained using ^{1}H-NMR spectroscopy.
[c] All reactions contained minor amounts (< 5%) hydrogenation product.
[d] Tandem reaction involving complete isomerization of the allyl sulfonamide to an enamine, followed by addition of HBcat.



Scheme 4. Isomerization/hydroboration of allyl sulfonamides **2**–**3**.

reaction with $RhH(PPh_3)_4$ (entry 11). In these reactions, an initial catalyzed isomerization gave enamine intermediate **2d**, whereupon subsequent addition of HBcat using the same catalyst gave selective formation of **2b** (by multinuclear NMR spectroscopy). Small amounts of hydrogenation product ($< 5\%$) were also observed in these tandem reactions (Scheme 4).

This tandem catalytic reaction also worked for benzyl substituted sulfonamide **3**, albeit hydrogenation was more severe (ca. 20%) and reaction times were considerably longer. For instance, isomerization of **2** was usually complete within 1 day at room temperature but analogous reactions with the benzyl derivative required times of up to 1 week. This slow isomerization reaction is consistent with the 'hydroboration' results of **3** (Table 1, entry 12), which gave the anti-Markovnikov product **3a** in 90% yield, where isomerization/hydroboration is too slow to give any appreciable amounts of Markovnikov isomer **3b**.

Asymmetric variants of this tandem catalytic reaction will provide an avenue to generate enantiomerically enriched sulfonamides containing boronate esters. This work, along with assessing the anti-fungal and anti-bacterial activities of the resulting organosulphur complexes, is currently in progress and will be reported in due course.

3. Experimental

3.1. General

Reagents and solvents were purchased from Aldrich Chemicals and used as received. Rhodium catalysts $RhCl(PPh_3)_3$ [26], $[RhCl(coe)_2]_2$ [27], $[RhCl(cod)]_2$ [28], and $Rh(acac)(coe)_2$ [29], were prepared by established procedures. NMR spectra were recorded on a JEOL JNM-GSX270 FT NMR (^1H 270 and ^{11}B 87 MHz) spectrometer. Chemical shifts (δ) are reported in ppm [relative to internal Me_4Si (^1H) or external $BF_3{\cdot}OEt_2$ (^{11}B)] and coupling constants (J) in Hz. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), multiplet (m), broad (br), and overlapping (ov).

3.2. General procedure for the hydroboration reaction

Under an atmosphere of dinitrogen, 5 equiv of HBcat in 0.5 ml of the appropriate deuterated solvent were added to a 0.5 ml solution of the catalyst (1 mol%) and substrate. The reaction was allowed to proceed at room temperature (r.t.) for 5 h, at which point NMR data were collected.

3.3. Rhodium catalyzed hydroboration of *1* with HBcat

^1H-NMR ($CDCl_3$): $\delta = 7.94$–7.03 (ov m, Ar), 3.87 (2nd order m, $CH_2CH(Bcat)CH_3$, **1b**), 3.69 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **1a**), 3.50 (t, $J = 7$ Hz, $CH_2CH_2CH_3$, **1c**), 2.40 (s, Ar–CH_3), 2.38 (s, Ar–CH_3), 2.37 (s, Ar–CH_3), 2.09 (app quint, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **1a**), 1.72 (ov m, $CH_2CH(Bcat)CH_3$, **1b**, and $CH_2CH_2CH_3$, **1c**), 1.31 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **1a**), 1.23 (d, $J = 7$ Hz, $CH_2CH(Bcat)CH_3$, **1b**), 0.91 (t, $J = 7$ Hz, $CH_2CH_2CH_3$, **1c**); $^{11}B\{^1H\}$-NMR ($CDCl_3$): $\delta = 29.1$ (**1a**), 27.9 (**1b**), 24.6 (NBcat, **1a** and **1b**), 21.3 (B_2cat_3).

3.4. Rhodium catalyzed hydroboration of *2* with HBcat

^1H-NMR ($CDCl_3$): $\delta = 7.48$–6.95 (ov m, Ar), 3.83 (2nd order m, $CH_2CH(Bcat)CH_3$, **2b**), 3.64 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **2a**), 2.41 (s, Ar–CH_3), 2.40 (s, Ar–CH_3), 1.76 (app quint, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **2a**), 1.67 (app sext, $J = 7$ Hz, $CH_2CH(Bcat)CH_3$, **2b**), 1.34 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **2a**), 1.28 (d, $J = 7$ Hz, $CH_2CH(Bcat)CH_3$, **2b**); $^{11}B\{^1H\}$-NMR ($CDCl_3$): $\delta =$ 34.8 (**2a**), 28.2 (**2b**), 21.3 (B_2cat_3).

3.5. Rhodium catalyzed hydroboration of *3* with HBcat

^1H-NMR ($CDCl_3$): $\delta = 7.74$-7.04 (ov m, Ar), 4.36 (s, NCH_2Ph), 4.32 (s, NCH_2Ph), 3.38 (2nd order m, $CH_2CH(Bcat)CH_3$, **3b**), 3.19 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **3a**), 2.43 (s, Ar–CH_3), 2.41 (s, Ar–CH_3), 1.69 (app quint, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **3a**), 1.34 (app sext, $J = 7$ Hz, $CH_2CH(Bcat)CH_3$, **3b**), 1.11 (t, $J = 7$ Hz, $CH_2CH_2CH_2Bcat$, **3a**), 1.03 (d, $J = 7$ Hz, $CH_2CH(Bcat)CH_3$, **3b**); $^{11}B\{^1H\}$-NMR ($CDCl_3$): $\delta =$ 34.1 (**3a**), 29.4 (**3b**), 21.3 (B_2cat_3).

3.6. General procedure for the isomerization/hydroboration reaction

Under an atmosphere of dinitrogen, the allyl sulfonamide in 0.5 ml of the appropriate deuterated solvent was added to a 0.5 ml solution of $RhH(PPh_3)_4$ (5 mol%). The reaction was allowed to proceed at r.t. for 1 (**2d**) to 7 (**3d**) days, at which point NMR data were collected.

Upon conversion to the enamine, 3 equiv of HBcat in 0.5 ml of the appropriate deuterated solvent were added. The reaction was allowed to proceed at r.t. for 5 h, at which point NMR data were collected.

3.7. Enamine **2d**

^{1}H-NMR ($CDCl_3$): $\delta = 7.54$–6.87 (ov m, 10H, Ar and NC*H*=CHCH$_3$), 4.36 (ov d q, $J = 7$ Hz, 1H, NCH=C*H*CH$_3$), 2.42 (s, 3H, Ar–C*H*$_3$), 1.56 (d d, $J = 7$, 1 Hz, 3H, NCH=CHC*H*$_3$).

3.8. Rhodium catalyzed hydroboration of **2d** with HBcat

^{1}H-NMR ($CDCl_3$): $\delta = 7.48$–6.95 (ov m, Ar), 3.83 (2nd order m, 2H, C*H*$_2$CH(Bcat)CH$_3$), 2.41 (s, 3H, Ar–C*H*$_3$), 1.67 (app sext, $J = 7$ Hz, 1H, CH$_2$C*H*(Bcat)CH$_3$), 1.28 (d, $J = 7$ Hz, 3H, CH$_2$CH(Bcat)C*H*$_3$); ^{11}B{^{1}H}-NMR ($CDCl_3$): $\delta = 28.2$ (CBcat), 21.3 (B_2cat_3).

3.9. Enamine **3d**

^{1}H-NMR ($CDCl_3$): $\delta = 7.68$ (d, $J = 7$ Hz, 2H, Ar), 7.32–7.22 (ov m, 7H, Ar), 6.66 (d d, $J = 14$, 1 Hz, 1H, NC*H*=CHCH$_3$), 4.70 (ov d q, $J = 14$ Hz, 1H, NCH=C*H*CH$_3$), 4.46 (s, 2H, NC*H*$_2$Ph), 2.42 (s, 3H, Ar–C*H*$_3$), 1.54 (d d, $J = 7$, 1 Hz, 3H, NCH=CHC*H*$_3$).

3.10. Rhodium catalyzed hydroboration of **3d** with HBcat

^{1}H-NMR ($CDCl_3$): $\delta = 7.74$–7.04 (ov m, Ar), 4.32 (s, 2H, NC*H*$_2$Ph), 3.38 (2nd order m, 2H, C*H*$_2$CH(Bcat)CH$_3$), 2.43 (s, 3H, Ar–C*H*$_3$), 1.69 (app sext, $J = 7$ Hz, 1H, CH$_2$C*H*(Bcat)CH$_3$), 1.03 (d, $J = 7$ Hz, 3H, CH$_2$CH(Bcat)C*H*$_3$); ^{11}B{^{1}H}-NMR ($CDCl_3$): $\delta = 29.4$ (CBcat), 21.3 (B_2cat_3).

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