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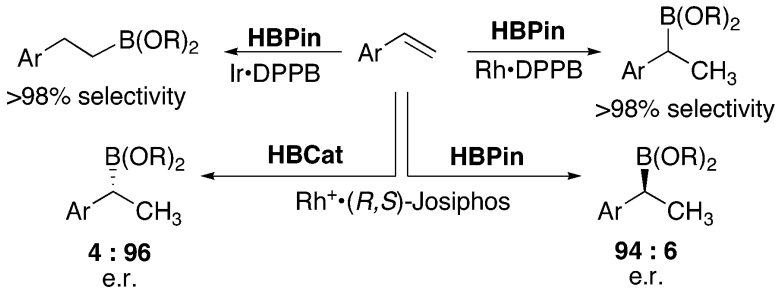

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Regio- and Enantiocontrol in the Room-Temperature Hydroboration of Vinyl Arenes with Pinacol Borane

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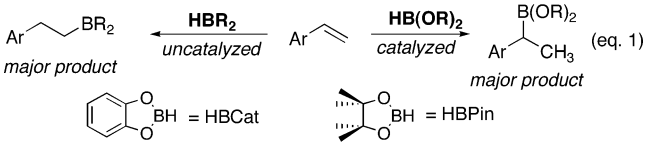
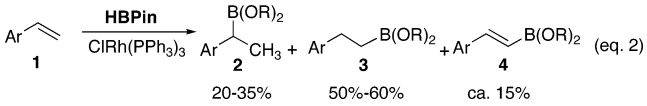
The Rh-catalyzed hydroboration[1] of vinyl arenes is a valuable reaction for the preparation of highly enantiomerically enriched alcohols,[2] amines,[3] and carboxylic acids.[4] The Rh catalyst serves to introduce asymmetry by means of the attached chiral ligands and also to invert the usual preference of the uncatalyzed hydroboration to occur in an anti-Markovnikov sense (eq 1).[1]



The use of catechol borane (HBCat) in the metal-catalyzed reaction is critical since the oxygen substituents on boron decrease the rate of the uncatalyzed (background) reaction substantially. However, catechol borane is air sensitive, difficult to handle, and decomposes in the presence of Rh complexes, phosphines, and other nucleophiles.[5]

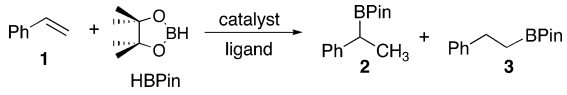
Therefore, we became interested in the use of pinacol borane (HBPin) as a substitute, since it is significantly more stable in air and to nucleophiles than HBCat.[6] The boronate ester products are also stable species that can be handled in air and purified by chromatography.[4,7] However, the greater steric bulk of pinacol borane makes achieving high branched selectivity more challenging. With use of $ClRh(PPh_3)_3$ as the catalyst, HBPin has been reported to give an unattractive mixture of products with **2** as a minor component (eq 2).[8] When $[Rh(COD)Cl]_2$ is employed, dehydrogenative borylation is the major pathway, giving compound **4** in 96% yield.[9]



Although pinacol borane has received very limited attention, recent results from the labs of Gevorgyan,[10a] Westcott,[10b] and Ramachandran[10c] have shown that it can be superior to catechol borane in the hydroboration of cyclopropenes, allylamines, and fluoroolefins.[10d] We find that under appropriate conditions, vinyl arenes can also react with high selectivities for either **2** or **3** using this reagent. Boronate esters such as **2** are important targets since they can be converted into a variety of NSAIDs such as Ibuprofen[4] and Naproxen. Thus, we report that the use of cationic Rh complexes modified by chelating phosphines gives high selectivities for **2**, while iridium catalysts give **3** as the only observable product. In the presence of chiral ligands for Rh, hydroboration with HBPin leads to high enantioselectivities at room temperature and *a reversal in the sense of enantioselection is observed compared to catechol borane*.

The hydroboration of styrene with HBPin was effectively catalyzed by cationic Rh complexes such as $[Rh(COD)_2]^+BF_4^-$ in a 1:1 mixture with bisphosphines such as DPPB or DPPP (Table 1). Under these conditions, the branched boronate ester (**2**) was obtained as the major product with greater than 96% selectivity (Table 1, entry 1).

Table 1. Hydroboration of Styrene with Pinacol Borane[a]



entry	catalyst	ligand	(L:M)[b]	**2**:**3**	yield[c]
1	$[Rh(COD)_2]BF_4$	DPPB	1:1	98:2	72%[d]
2	$[Rh(COD)_2]BF_4$	DPPB	2:1	95:5	70%
3	$[Rh(COD)_2]BF_4$	DPPB	1.2:1	96:4	84%
4	$[Rh(COD)Cl]_2$	DPPB	1:1	84:16	63%
5	$[Rh(COD)_2]BF_4$	DPPP	1:1	70:30	86%[e]
6	$[Rh(COD)_2]BF_4$	DPPP	2:1	98:2	56%[f]
7	$[Rh(COD)_2]BF_4$	DPPE	1:1	73:27	82%
8	$[Rh(COD)_2]BF_4$	DPPE	2:1		nr
9	$[Rh(COD)_2]BF_4$			67:33	68%[g]
10	$[Rh(COD)DPPE]BF_4$		1:1	65:35	99%[g]

[a] Reactions were performed with 5% catalyst in an N_2 glovebox. [b] Molar ratio. [c] Isolated yields after chromatography. [d] NMR yield = 62%, 1% cat. [e] NMR yield = 79%, 1% cat. [f] Yield = 18%, 1% cat. [g] NMR yield (1 h).

As shown in Table 1, high branched-to-linear ratios are always obtained in the case of DPPB and only a slight reduction in yield is observed running the reaction at 1% catalyst loading. Excess phosphine significantly improves the selectivity using DPPP as the ligand (compare entries 5 and 6); however, use of a full 2 equiv leads to a decrease in yield. This is especially obvious at low catalyst loadings, such that the 56% yield obtained in entry 6 is decreased to 18% at 1% catalyst loading. With DPPE, the addition of 2 equiv shuts down the reaction completely (entry 8). Since the selectivity in this case was similar to that obtained with cationic Rh alone (entry 9), we attemped the reaction with preformed $[Rh(DPPE)(COD)]^+$ complex (entry 10). As expected, the selectivity was similar, but the yield was higher with the preformed complex. Although we cannot exclude the possibility that dissociation of DPPE leads to the active catalyst, this is certainly not the case with DPPB, where significantly different B:L ratios are observed. With PPh_3 or $P(OPh)_3$, the regioselectivity was poor and vinylboronate **4** was observed in small amounts.

Remarkably, when iridium is employed as the catalyst, *a complete reversal in selectivity is obtained, with the linear isomer being the only observed product* (Table 2).[11] A variety of vinyl arenes reacted with >99% selectivity and greater than 90% yields. The change in regioselectivity likely stems from a change in mechanism from Rh−H insertion to Ir−B insertion, as proposed by Bonin and Micoun in their seminal paper on Ir-catalyzed hydroborations of diazines.[12a]

The asymmetric hydroboration of styrene was attempted using a variety of commonly employed chiral ligands (Table 3). Much to our surprise, with pinacol borane as the hydroborating reagent,

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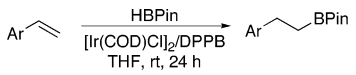
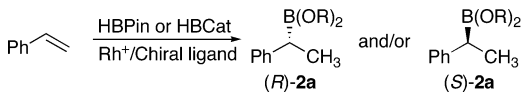
Table 2. Iridium-Catalyzed Hydroboration of Vinyl Arenes[a]



entry	substrate	L:B	yield[b]
1	styrene (**1a**)	>99:1	99%
2	*p*-methylstyrene (**1b**)	>99:1	95%
3	*p*-chlorostyrene (**1c**)	>99:1	99%
4	*p*-bromostyrene (**1d**)	>99:1	90%
5	*p*-methoxystyrene (**1e**)	>99:1	98%

[a] See Table 1. [b] Isolated yields after chromatography.

Table 3. Asymmetric Hydroboration of Styrene with HBPin and HBCat[a]



entry	ligand	reagent	temp (°C)	B:L	er[b] *R*:*S*	yield (%)
1	(*R*)-Binap	HBCat	−65	99:1	96:4	99[2a/4a]
2	(*R*)-Binap	HBCat	25	99:1	79:21	90[2a]
3	(*R*)-Binap	HBPin	25	56:44	30:70	30
4	(*R*,*S*)-Josiphos	HBCat	−70	99:1	96:4	65
5	(*R*,*S*)-Josiphos	HBCat	25	N.A.[c]	80:20	N.A.[c]
6	**(*R*,*S*)-Josiphos**	**HBPin**	**25**	**72:28**	**8:92**	**53(87)**[d]
7	(*S*) Quinap	HBCat	25	97:3	6:94	69
8	(*S*) Quinap	HBPin	25	65:35	9:91	30

[a] See footnote to Table 1. [b] Enantiomeric ratio; *R* and *S* refers to **2a**. Note that the *R*/*S* designation does not change after oxidation. [c] Not available.[2c] [d] Yield in parentheses corresponds to optimized case in dichloroethane.

the opposite enantiomer of the product was obtained using the same antipode of Binap (compare entries 2 and 3). Josiphos also gave the opposite enantiomer when HBPin was employed (entries 5 and 6). In this case, the reaction with HBPin *was more enantioselective* than with HBCat at 25 °C and approached the results obtained with HBCat at −78 °C. Reversals in asymmetric induction have been reported for hydrogenation[12b] and hydroboration[12a] reactions when different metals are employed, although in our case, the switch is caused merely by a change in the achiral reagent.

Quinap, a less sterically demanding ligand, reacts with good enantioselectivity, but the reversal in stereoinduction is not observed, suggesting that unfavorable steric interactions between the bulky BPin and PPh_2 substituents are indeed responsible for the change in enantioselectivity. The larger BPin group does not stack effectively with the aryl rings of the chiral ligand and substrate.[13a] Chelation of Rh to an oxygen on boron, which is predicted to be stabilizing,[13b] may also be disrupted with the bulkier pinacol borane.

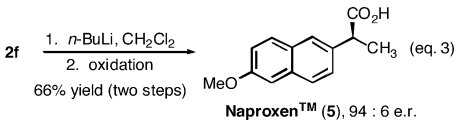
Under optimized conditions, (dichloroethane, Rh/Josiphos 1:1.2 ratio), the hydroboration of a variety of vinyl arenes was effected at 25 °C (Table 4). High enantioselectivies were observed in all cases. After hydroboration of 6-methoxy-2-vinylnaphthalene (**1f**), homologation and oxidation gives Naproxen in 66% yield (**5**, eq 3). This substrate gave the highest branched to linear selectivity and the highest enantioselectivity of any of olefins examined (entry 6). Other vinyl naphthalenes also react with high regio- and enantioselectivities (entries 7 and 8).

In conclusion, we have shown that vinyl arenes can be hydroborated with high regio- and enantiocontrol at 25 °C with HBPin.

Table 4. Enantioselective Hydroboration of Vinyl Arenes with Pinacol Borane and Rh·Josiphos[a]

entry	substrate	**2**:**3**	er (%)	yield[b]
1	styrene (**1a**)	83:17	92:8	87%
2	*p*-methylstyrene (**1b**)	82:18	94:6	39%
3	*p*-chlorostyrene (**1c**)	72:28	90:10	90%
4	*p*-bromostyrene (**1d**)	83:17	92:8	87%
5	*p*-methoxystyrene (**1e**)	83:17	88:12	69%
6	6-methoxy-2-vinylnaphthalene (**1f**)	95:5	94:6	83%
7	2-vinylnaphthalene (**1g**)	95:5	93:7	67%
8	6-methoxy-5-nitro-2-vinylnaphthalene (**1h**)	91:9	92:8	51%

[a] See footnote to Table 1. [b] Isolated yields after chromatography



Depending on the choice of catalyst (Rh or Ir), either the branched or the linear product can be obtained with greater than 95% selectivity. Reversals in enantioselectivity are observed with chiral bisphosphine-ligated catalysts when pinacol borane is employed in place of catechol borane.

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Supporting Information Available: Experimental procedures, conditions for determination of the enantiomeric ratio, and selected spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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