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# Enhanced regioselectivity of rhodium-catalysed alkene hydroboration in supercritical carbon dioxide

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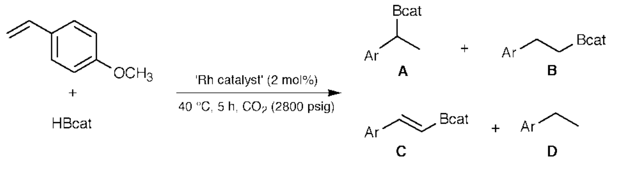
**Catalysed alkene hydroboration proceeds in supercritical $CO_2$ with several rhodium(I) complexes using tunable fluorinated ligands and shows higher regioselectivity relative to tetrahydrofuran or perfluoromethylcyclohexane.**

The power of homogeneous transition metal catalysis rests in chemists' ability to fine-tune the steric and electronic properties of the metal coordination environment and to optimize activity and selectivity by judicious choice of the reaction medium.[1] While a number of studies have employed fluorinated ligands [2–4] to conduct a variety of metal-catalysed reactions[5] in environmentally benign supercritical carbon dioxide ($scCO_2$), little work has been reported on catalyst tunability. Recently reported phosphines $PR_2R_F$[3,6,7] and phosphinites $PR_2(OR_F)$[6,7] ($R_F$ = $CH_2CH_2C_6F_{13}$) are easily prepared and offer the ability not only to enhance catalyst solubility, but to control the stereoelectronic environment of catalysts in $scCO_2$. We chose to investigate $Rh^I$-catalysed alkene hydroboration[8,9] due to the importance of boronate ester products in synthetic organic chemistry, medicinal chemistry, materials science and molecular recognition. The catalyzed reaction exhibits higher rates and complementary regioselectivity compared to the uncatalysed reaction, and efficient chirality transfer has been demonstrated in the asymmetric variant.[9] We now report the first demonstration of catalysed alkene hydroboration in $scCO_2$, the ability to tune both regio- and chemo-selectivity, and the discovery of much higher selectivity in $scCO_2$ compared to perfluoromethylcyclohexane ($CF_3C_6F_{11}$).

Catalyzed hydroboration of styrene derivatives with catecholatoborane (HBcat) was carried out in $scCO_2$ at 40 °C and 2800 psi for 5 h with a rhodium catalyst precursor and added phosphorus ligands using magnetically-stirred, high-pressure reactors with sapphire view windows that have been described elsewhere.[10] Addition of HBcat to vinylanisole using only the hexafluoroacetylacetonate (hfacac) rhodium complex $(hfacac)Rh(coe)_2$ **1** (coe = cyclooctene) as catalyst precursor[2] led to a homogeneous solution and, after 5 h, high conversion to a mixture of alkylboronate esters **A** and **B**, alkenylboronate ester **C**, and 4-ethylanisole **D** (Scheme 1, Table 1). Products **C** and **D** result from a competing dehydrogenative borylation pathway which is favoured by phosphine-free rhodium catalysts.[11] Addition of triphenylphosphine to **1** gave turbid solutions due to poor ligand and/or catalyst solubility in $scCO_2$. The fluorinated ligands, including **5**–**8** led to homogeneous solutions demonstrating that a single fluorinated substituent is sufficient to impart high solubility in $scCO_2$. As shown in Table 1, added ligands dramatically influence the regioselectivity of hydroboration. Triphenylphosphine, its 3,5-bis(trifluoromethyl)phenyl analog, and $P(R_F)_3$ all greatly increased hydroboration regiochemistry, but chemoselectivity was improved only marginally. Alkylboronate ester **A** was formed exclusively with cyclohexyl-substituted phosphine **8** (L : Rh ratio = 2 : 1), demonstrating the ability to control regioselectivity and chemoselectivity by tuning the solubility and stereoelectronic properties of ligands and metal catalysts in $scCO_2$.

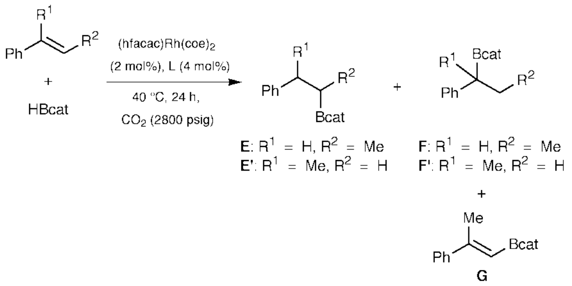


**Scheme 1**

**Table 1** Ligand effects on catalysed hydroboration of vinylanisole in $scCO_2$[a]

| Entry | L | Conversion (%) | Selectivity (%) A | B | C | D |
|---|---|---|---|---|---|---|
| 1 | No added ligand | 89 | 14 | 14 | 31 | 41 |
| 2 | $PPh_3$ (**2**) | 92 | 71 | 13 | 13 | 3 |
| 3 | $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ (**3**) | 94 | 75 | — | 19 | 6 |
| 4 | $P(R_F)_3$ (**4**)[b] | 94 | 82 | — | 17 | 1 |
| 5 | $Ph_2POR_F$ (**5**)[b] | 81 | 88 | — | 12 | — |
| 6 | $Cy_2POR_F$ (**6**)[b,c] | 89 | 90 | — | — | — |
| 7 | $Ph_2PR_F$ (**7**)[b] | 88 | 89 | — | 11 | — |
| 8 | $Cy_2PR_F$ (**8**)[b] | 100 | 100 | — | — | — |

[a] $(hfacac)Rh(coe)_2$ **1** (0.02 mmol), ligand L (0.04 mmol) and substrate (1.0 mmol). Conversion and product selectivity were determined by $^1H$ and $^{11}B$ NMR using hexamethyldisiloxane standard. [b] $R_F$ = $CH_2CH_2C_6F_{13}$. [c] Some polymeric material was observed in this reaction.



**Scheme 2**

In several studies of rhodium-catalyzed hydroboration of disubstituted alkenes, such as α- and β-methylstyrenes, monodentate ligands have been found to give poor selectivity to the desired Markovnikov addition product.[8] While conversions were low in some cases, the ability to control regiochemistry through tunable fluorinated ligands in $scCO_2$ is further illustrated in Scheme 2 and Table 2. For β-methylstyrene, the tris[3,5-bis(trifluoromethyl)phenyl]phosphine **3** and cyclohexyl-substituted ligands **6, 8** gave the highest activity, but with only fair regiocontrol. Ligands **4**, **5** and **7** gave alkylboronate ester **E** exclusively. The advantage of ligand tunability is also demonstrated for the reaction of α-methylstyrene and HBcat, as changing from cyclohexyl **6** to phenylphosphinite ligand **5** yields only the Markovnikov addition product **E′**.

Solvent effects play an important role in determining the selectivity of catalytic hydroboration reactions.[12] Gladysz and

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**Table 2** Hydroboration of α- and β-methylstyrene[a] in $scCO_2$

| Entry | L | Conversion (selectivity) (%) | |
|---|---|---|---|
| | | **E**:**F**:**G** | **E′**:**F′** |
| 1 | $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ (**3**) | 100 (0:24:76) | 90 (78:22) |
| 2 | $P(R_F)_3$ (**4**) | 56 (55:45:0) | 13 (100:0) |
| 3 | $Ph_2POR_F$ (**5**) | 13 (100:0:0) | 8 (100:0) |
| 4 | $Cy_2POR_F$ (**6**) | 3 (50:50:0) | 71 (89:11) |
| 5 | $Ph_2PR_F$ (**7**) | 19 (96:4:0) | 16 (100:0) |
| 6 | $Cy_2PR_F$ (**8**) | 38 (36:64:0) | 77 (71:29) |

[a] Conversion and selectivity were determined after 24 h.

**Table 3** Effect of solvent on the regioselectivity of vinylanisole hydroboration[a]

| Entry | L | Solvent | Conversion (%) | Selectivity (%) | | | |
|---|---|---|---|---|---|---|---|
| | | | | **A** | **B** | **C** | **D** |
| 1 | $P(R_F)_3$ (**4**) | THF | 82 | 66 | 15 | 13 | 6 |
| | | $CF_3C_6F_{11}$ | 84 | 57 | 16 | 19 | 8 |
| | | $scCO_2$ | 94 | 82 | — | 17 | 1 |
| 2 | $Ph_2POR_F$ (**5**) | THF | 100 | 52 | 21 | 16 | 11 |
| | | $CF_3C_6F_{11}$ | 98 | 37 | 23 | 23 | 17 |
| | | $scCO_2$ | 81 | 88 | — | 12 | — |
| 3 | $Cy_2POR_F$ (**6**) | THF | 94 | 20 | 37 | 35 | 8 |
| | | $CF_3C_6F_{11}$ | 89 | 24 | 26 | 37 | 13 |
| | | $scCO_2$[b] | 89 | 90 | — | — | — |
| 4 | $Ph_2PR_F$ (**7**) | THF | 93 | 84 | — | 12 | 4 |
| | | $CF_3C_6F_{11}$ | 90 | 80 | 4 | 12 | 4 |
| | | $scCO_2$ | 88 | 89 | — | 11 | — |
| 5 | $Cy_2PR_F$ (**8**) | THF | 100 | 32 | 34 | 17 | 17 |
| | | $CF_3C_6F_{11}$ | 91 | 25 | 41 | 17 | 17 |
| | | $scCO_2$ | 100 | 100 | — | — | — |

[a] Reactions in organic solvents were run in NMR tubes using 0.002 mmol **1**, 0.004 mmol ligand, and 0.1 mmol vinylanisole. Conversion and selectivity were determined by $^1H$ NMR. [b] Some polymeric material was observed in this reaction.

Horvath[13] reported an elegant study of alkene hydroboration in fluorous biphasic media using $RhCl[P(R_F)_3]_3$ derived from **4**; however, the regioselectivity for styrene derivatives was low. Comparing the reaction of vinylanisole and HBcat in $scCO_2$ to that in perfluoromethylcyclohexane led to some surprising results. Catalyst precursor **1** and ligand **4** showed significantly greater regiocontrol in $scCO_2$ (Table 3, entry 1). This trend held for ligands **5–8** and was particularly striking for $Cy_2PR_F$ (entry 5) which afforded a single product in $scCO_2$. Remarkably, the selectivity in $scCO_2$ for **4–8** was also considerably higher than that observed in THF. Ligand **4** is not soluble in THF; however, partially fluorinated ligands **5–8** and their rhodium complexes are fully soluble under the reaction conditions. In THF, product selectivity using the nonfluorinated analog of ligand **8** (*i.e.* $Cy_2PC_8H_{17}$) was found to be similar to that observed for ligand **8**, confirming the insulating effect of the two methylene spacers in the $R_F$ group.† There are several reports[4,5,14,15] of enhanced selectivity of catalysed reactions in $scCO_2$ compared to conventional organic solvents. Except for a few cases where density is controlled through pressure changes,[16] we are unaware of any examples presenting such a dramatic effect as that shown here. The origin of the higher selectivities for hydroborations is not clear. Since ligand-free rhodium complexes result in poor hydroboration selectivity,[11] stability and lability of the catalysts (*i.e.* keeping the ligand on the metal), which are likely solvent dependent, may play an important role. It is also possible that a Rh–$\eta^3$-benzyl intermediate[17] that would lead to **A** could be stabilized in $scCO_2$ relative to the $\eta^1$-regioisomer that would yield **B**.

In summary, we have demonstrated that catalysed alkene hydroboration can proceed in supercritical $CO_2$ without any difficulty from B–H reactivity with the solvent. Regiocontrol can be achieved using tunable ligands of the form $R_2PR_F$ and $R_2POR_F$. Furthermore, significantly higher regioselectivities can be obtained for these ligands in $scCO_2$, relative to fluorocarbons and even THF. Given further advancements in catalyst separations and recovery in $scCO_2$,[18] catalysis in this medium can complement fluorous phase approaches. We are currently assessing the effects of pressure (solvent density) on selectivity, monitoring reactive species by *in situ* NMR spectroscopy, and studying stoichiometric reactions of isolable 16 electron rhodium–boryl complexes.[19]

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## Notes and references

† Triphenylphosphine and catalyst precursor **1** (3:1) or Wilkinson's catalyst (ref. 9) lead to high selectivity > 95% to **A** in THF; however, these catalysts are not effective for methylstyrenes (ref. 19).

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