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Cobalt-catalysed Markovnikov selective hydroboration of vinylarenes†

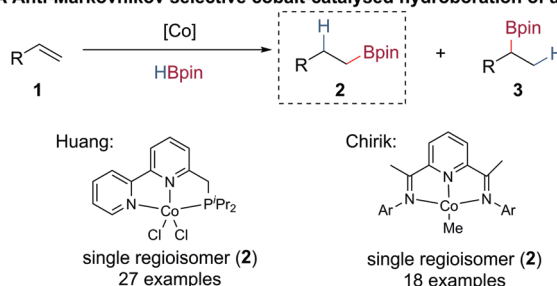
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A bipyridyl–oxazoline cobalt catalyst ^tBuBPOCoCl₂ has been developed for the Markovnikov selective hydroboration of alkenes using pinacolborane and NaO^tBu as the *in situ* activator with up to >98 : 2 branched : linear selectivity (24 examples, 45–92% isolated yield).

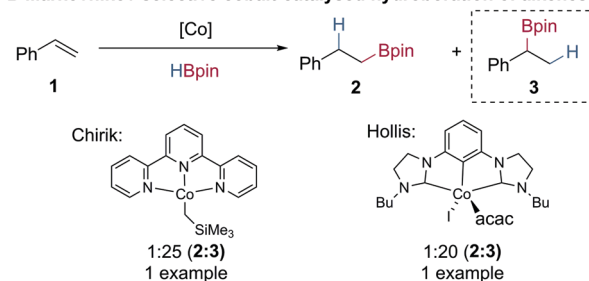
Metal-catalysed alkene hydroboration has received much attention, as the resulting boronic esters are versatile intermediates in the construction of various C–C and C–heteroatom bonds.¹ The majority of metal-catalysed alkene hydroboration reactions involve complexes of precious metals, such as Rh, Ru and Ir.² Although high chemoselectivity, regioselectivity, and enantioselectivity can be achieved, the low abundance and environmental concerns associated with these metals has driven investigations for Earth-abundant metal alternatives.^{3,4}

In recent years, a number of Earth-abundant and base metal complexes have been developed for alkene hydroboration. In most cases, these reactions are either highly anti-Markovnikov selective or give a mixture of both Markovnikov and anti-Markovnikov products.^{5–18} Huang reported that bipyridyl–phosphine cobalt complexes show high activity in the anti-Markovnikov hydroboration of alkenes.⁵ Additionally, Chirik developed bis(imino)pyridine cobalt methyl complexes for the anti-Markovnikov selective hydroboration of alkenes (Scheme 1A).⁶ Of direct significance to this manuscript, Chirik⁷ and Hollis⁸ have both reported unique cobalt catalysts capable of catalysing the Markovnikov selective hydroboration of styrene in 25 : 1 and 20 : 1 branched to linear ratio, respectively (Scheme 1B). Isomerisation–hydroboration using cobalt catalysis has also been reported by Chirik; which serves as an orthogonal procedure for the generation of branched boronic esters from aliphatic internal alkenes.⁹ However, a general reaction protocol with broad scope using a cobalt catalyst for the direct

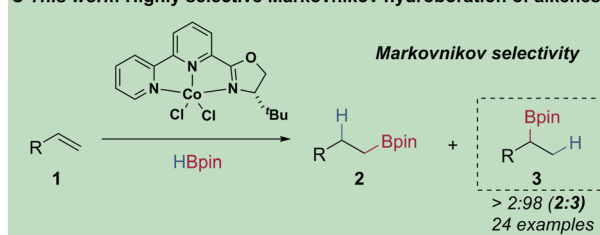
A Anti-Markovnikov selective cobalt-catalysed hydroboration of alkenes



B Markovnikov selective cobalt-catalysed hydroboration of alkenes



C This work: Highly selective Markovnikov hydroboration of alkenes



Scheme 1 (A) Anti-Markovnikov selective cobalt-catalysed alkene hydroboration. (B) Markovnikov selective cobalt-catalysed hydroboration of alkenes. (C) This work: ^tBuBPOCoCl₂-catalysed highly selective Markovnikov hydroboration of alkenes.

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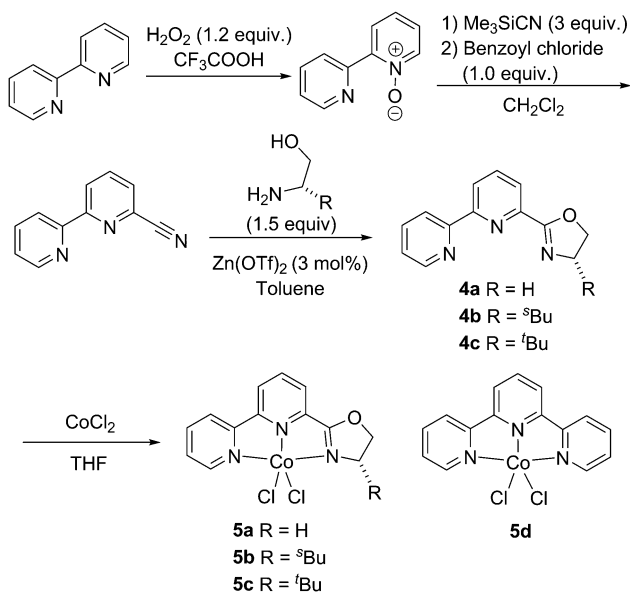
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Markovnikov selective hydroboration of alkenes has not been disclosed.

Herein, we report the preparation of bipyridyl–oxazoline cobalt(II) complexes and the application of these in cobalt-catalysed





Scheme 2 Synthesis of bipyridyl-oxazoline cobalt complexes **5a–5c** and terpyridine cobalt complex **5d**.

alkene hydroboration using NaO^tBu as the *in situ* pre-catalyst activator.¹⁸ This system presents a new and unique method for the generation of secondary boronic esters from readily available vinylarene starting materials with high regioselectivity, which is divergent from the majority of cobalt-catalysed alkene hydroboration reactions (Scheme 1C).

A series of cobalt complexes **5a–5c** bearing novel bipyridyl-oxazoline ligands was synthesised in four steps (Scheme 2). Reaction of 2,2'-bipyridine with hydrogen peroxide and trifluoroacetic acid gave 2,2'-bipyridine-1-oxide, which was reacted with trimethylsilyl cyanide and benzoyl chloride to give the bipyridyl-carbonitrile compound. Condensation of the bipyridyl-carbonitrile with various amino alcohols in the presence of $\text{Zn}(\text{OTf})_2$ produced the bipyridyl-oxazoline ligands **4a–4c** in moderate yields. The neutral bipyridyl-oxazoline cobalt(II) dichloride complexes **5a–5c** were formed in high yield by the addition of the corresponding ligand to anhydrous cobalt dichloride in anhydrous tetrahydrofuran (THF). Similarly, terpyridine complex **5d** was synthesised in the same manner from commercially available terpyridine. These cobalt complexes showed paramagnetically broadened and shifted resonances in the ^1H NMR spectra (see ESI†).

Initial studies focused on the hydroboration of styrene with pinacolborane (1.1 equiv.) using a range of cobalt pre-catalysts (1 mol%) and NaO^tBu (2 mol%) as the *in situ* activator in tetrahydrofuran at room temperature (Table 1). Hydroboration of styrene using $^t\text{BuBPOCoCl}_2$ **5a** and $^i\text{BuBPOCoCl}_2$ **5b** gave the branched hydroboration product in good yield and with 70:30 and 82:18 branched:linear regioselectivity, respectively (Table 1, entries 1 and 2). When the more bulky $^t\text{BuBPOCoCl}_2$ **5c** was used, hydroboration of styrene proceeded in excellent yield and with the highest selectivity for the Markovnikov regioisomer (97:3) (Table 1, entry 3). Terpyridine cobalt complex **5d** gave a moderate yield and good Markovnikov regioselectivity (91:1) (Table 1, entry 4). When the hydroboration of styrene, using

Table 1 Reaction optimisation for cobalt-catalysed hydroboration of styrene^a

Entry	[Co] (mol%)	Activator (mol%)	Solvent	Yield ^b (%)	Branched: linear
1	5a (1)	NaO^tBu (2)	THF	82	70:30
2	5b (1)	NaO^tBu (2)	THF	87	82:18
3	5c (1)	NaO^tBu (2)	THF	>95	97:3
4	5d (1)	NaO^tBu (2)	THF	69	91:9
5	5c (1)	NaO^tBu (2)	Neat	59	91:9
6	5c (1)	NaO^tBu (2)	EtOAc	77 ^c	96:4
7	5c (1)	NaO^tBu (2)	Toluene	>95	95:5
8	5c (1)	EtMgBr (2)	THF	85	90:10
9	5c (1)	NaBHET_3 (2)	THF	63 ^d	86:14
10 ^e	CoCl_2 (1)	NaO^tBu (2)	THF	—	—
11	—	NaO^tBu (2)	THF	—	—
12	5a (1)	—	THF	3	n.d.

^a Standard reaction conditions: styrene (0.5 mmol), HBpin (1.1 equiv.), [Co] (1.0 mol%) and NaO^tBu (2.0 mol%) in THF (3 ml) at 25 °C. ^b Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. ^c 2% hydrogenation product observed. ^d 5% hydrogenation product observed. ^e 30% hydrogenation product observed.

$^t\text{BuBPOCoCl}_2$ **5c**, was performed in the absence of solvent, good Markovnikov selectivity (91:1 b/l) was also achieved, but with decreased yield (Table 1, entry 5). Hydroboration of styrene proceeded well in ethyl acetate and toluene, albeit in reduced yield and regioselectivity compared to that in THF (Table 1, entries 6 and 7). Catalyst activation *in situ* with EtMgBr and NaBHET_3 gave both lower yields and regioselectivities compared to the activation using NaO^tBu (Table 1, entries 8 and 9). A control reaction using non-ligated anhydrous CoCl_2 under the optimised reaction conditions, showed no catalytic activity (Table 1, entry 10). Similarly, the reaction did not proceed in the absence of cobalt pre-catalyst or without added NaO^tBu (Table 1, entries 11 and 12).

Using the optimised reaction conditions, the substrate scope of the Markovnikov selective hydroboration was explored using a range of electronically and sterically differentiated styrene derivatives (Table 2). Hydroboration of styrene gave the secondary boronic ester in excellent isolated yield, and a 97:3 branched:linear selectivity (**3a**, 90%). Styrene derivatives bearing electron-donating groups such as iso-propyl, *tert*-butyl and methyl underwent successful hydroboration in excellent yield and regioselectivity (**3b–3e**, 72–87%). 4-Phenylstyrene gave the secondary boronic ester in good yield and regioselectivity (**3f**, 88%). Styrene derivatives bearing electron-withdrawing substituents including fluoro-, chloro-, bromo- and trifluoromethyl- also underwent successful hydroboration, giving the secondary boronic esters in moderate to excellent yields, with no cleavage of aryl-halide bond observed (**3g–3l**, 45–92%).^{19,20} Styrene derivatives bearing trialkylsilyl- and ether substituents also underwent successful hydroboration in good yields and selectivities to give the branched boronic esters (**3m–3o**, 70–87%).



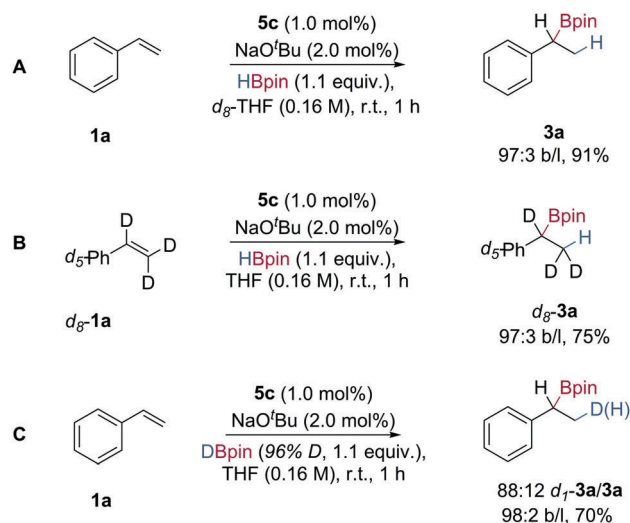
Table 2 Cobalt-catalysed Markovnikov selective hydroboration of vinylarenes using **5c**

$\text{R}-\text{CH}=\text{CH}_2$ 1a-x			5c (1.0 mol%) NaO^tBu (2.0 mol%) HBpin (1.1 equiv.), THF (0.16 M), r.t., 1 h	$\text{R}-\text{CH}_2-\text{CH}_2-\text{H}$ 3a-x
	3a	>95% (90%) (97:3)		
	3b	90% (81%) (>98:2)		
	3c	91% (87%) (97:3)		
	3d	83% (79%) (97:3)		
	3e	80% (72%) (95:5)		
	3f	93% (88%) (98:2)		
	3g	>95% (91%) (95:5)		
	3h	>95% (90%) (>98:2)		
	3i	>95% (92%) (96:4)		
	3j	88% (79%) (85:15)		
	3k	52% (45%) (96:4)		
	3l	84% (80%) (94:6)		
	3m	95% (87%) (97:3)		
	3n	85% (74%) (88:12)		
	3o	81% (70%) (94:6)		
	3p	83% ^{a,b} (75:25)		
	3q	85% ^{a,c} (86:14)		
	3r	81% (69%) (97:3)		
	3s	90% (79%) (98:2)		
	3t	90% (80%) (95:5)		
	3u	>95% (90%) (>98:2)		
	3v	90% (79%) (>98:2)		
	3w	72% (69%) ^b (70:30)		
	3x	67% (62%) (<2:98)		

Conditions: alkene (0.5 mmol), HBpin (1.1 equiv.), **5c** (1.0 mol%) and NaO^tBu (2.0 mol%) in THF (3 mL) at 25 °C, 1 h. Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses. Branched:linear ratios determined from integrals of product peaks in ^1H NMR of crude reaction mixtures. ^a Product decomposed on SiO_2 . ^b 10% alkene hydrogenation product observed in the crude reaction mixture. ^c 8% alkene hydrogenation product observed in the crude reaction mixture.

Hydroboration of primary and tertiary amine substituted substrates both gave the secondary boronic ester in good regioselectivity and yield (**3p–3q**, 83–85%). Styrene derivatives containing more than one unsaturated group, such as ester and nitrile substituents, were chemoselectively hydroborated at the alkene in excellent yield and regioselectivity, with no observed C–O or C–N bond cleavage, or reduction (**3r–3t**, 69–80%).²¹ Styrene derivatives bearing substituents at the β -position, such as *trans*- β -methylstyrene and indene were also reactive under the developed conditions, giving the product boronic esters with complete control of regioselectivity and in excellent yield (**3u–3v**, 79–90%). For alkyl alkenes, ketone containing alkene **1w** successfully gave the branched boronic ester **3w** in good yield with moderate regioselectivity and without ketone reduction. Hydroboration of 2,3-dimethyl-1-butene **1x** gave the linear boronic ester **3x** in good yield. Presumably, increased steric bulk of the 1,1-disubstituted alkene led to the anti-Markovnikov regioisomer. Oxidation of the secondary boronic ester products to the corresponding alcohols, and analysis by chiral HPLC, showed no enantioselectivity, indicating no stereoselection from the ligand.

In order to gain insight into the mechanism of the Markovnikov selective hydroboration of vinylarenes with HBpin, deuterium labelling experiments were performed. When the hydroboration of styrene was carried out in d_8 -THF, only the fully protio-boronic ester **3a** was obtained, indicating that both H and Bpin originate from pinacolborane (Scheme 3A). When the hydroboration of d_8 -styrene with HBpin was performed in THF, the mono-protio-boronic ester d_8 -**3a** was formed exclusively with 'H' at the terminal methyl group (Scheme 3B). When DBpin (96% D-content) was used in the hydroboration of styrene, a mixture of mono-deuterated boronic ester d_1 -**3a** and fully protio-boronic ester **3a** was formed, in a ratio of 88:12 D/H (Scheme 3C). The presence of (fully) protio-**3a** presumably arises from either β -hydride elimination of an intermediate organo-cobalt species,²² to generate a cobalt hydride that serves to add 'H' to styrene **1a**, or H/D exchange with extraneous water, either present in the reaction medium or on work-up.

**Scheme 3** Deuterium labelling studies of Markovnikov selective styrene hydroboration; isolated yields following flash column chromatography.

In conclusion, we have developed a Markovnikov selective cobalt-catalysed hydroboration of alkenes with pinacolborane at ambient temperature, using a bench-stable cobalt pre-catalyst bearing a bipyridyl-oxazoline ligand. This strategy has been applied to a variety of electronically and sterically differentiated styrene derivatives, bearing a range of functional groups, to give the secondary boronic esters in both high yield and regioselectivity.

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- It should be noted that we were unable to observe any products of H/D scrambling consistent with this scenario (e.g. d_n -styrene) in the crude reaction mixtures, but this may be due to loss of these low boiling point products on work-up.

