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Room Temperature Highly Enantioselective Nickel-Catalyzed Hydrovinylation

Nicolas Lassauque,[a] Giancarlo Franciò,[a,*] and Walter Leitner[a,*]

[a] Institut für Technische und Makromolekulare Chemie, RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany
Fax: (+49)-241-80-22177; e-mail: francio@itmc.rwth-aachen.de or leitner@itmc.rwth-aachen.de

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Abstract: At room temperature, nickel catalysts based on the new phosphoramidite (11b*R*)-*N*-[(*S*)-1-(naphthalen-1-yl)ethyl]-*N*-[(*S*)-1-(naphthalen-2-yl)ethyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine provide excellent selectivities for 3-arylbut-1-enes (93–99%) with high enantioselectivities (90–95% *ee*) and TOFs (up to 8300 h^{-1}) in the hydrovinylation of electron-rich and electron-poor vinylarenes. Within a few minutes, useful chiral building blocks and intermediates can be synthesized using this practical catalytic system.

Keywords: asymmetric catalysis; C–C coupling; olefin dimerization; phosphoramidite ligands

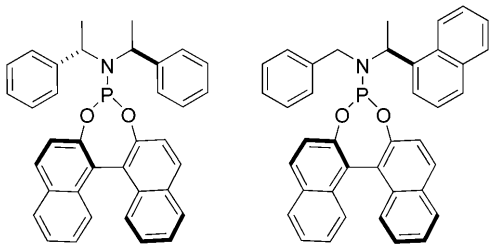


Figure 1. Benchmark phosphoramidite ligands for the Ni-catalyzed hydrovinylation.

The nickel-catalyzed heterodimerization of an olefin with ethylene (hydrovinylation) was one of the first examples of asymmetric catalysis ever reported.[1,2] Since this first pioneering study, major progress in this atom-efficient reaction has been achieved with the introduction of the unique Wilke ligand in the 1980s[3] and of modular phosphoramidite ligands more recently.[4,5] Although several protocols are known providing the desired chiral 3-arylbut-1-enes in high yields and enantioselectivities, all of them require the reaction to be carried out at very low temperature (typically −78 °C).[6,7] This hampers a widespread application of this useful coupling reaction. We disclose here readily accessible chiral ligands which for the first time enable highly enantioselective Ni-catalyzed hydrovinylation even at room temperature.

In 2002, we showed that chiral phosphoramidites led to the highly chemo- and enantio-selective Ni-catalyzed hydrovinylation of styrenes at low temperature. In particular, the Feringa ligand **1** (Figure 1), together with the metal precursor $[(allyl)NiCl]_2$ and NaBArF as the activator, resulted in a very active and highly selective catalytic system at −70 °C, but only moderate chemo- and enantioselectivity were observed at higher temperature.[4a] Since then, ligand **1** and related phosphoramidites have been successfully applied to other substrates under similar conditions.[5] As shown by a combination of experimental and computational studies,[8] a phenyl ring from the NCH-(CH_3)Ph side arm of **1** acts as a hemilabile donor in some intermediates of the catalytic cycle[9,10] and is decisive for both the catalyst activity and enantioselectivity.[8] Indeed, the presence of at least one 1-(aryl)ethyl group at the nitrogen guaranteed enhanced enantioselectivity in ligand frameworks as diverse as azaphospholenes,[3] phosphoramidites,[4a,5] and phosphorous triamides.[11] Recently,[12] Smith and RajanBabu applied ligand **2** (Figure 1) bearing an *N*-benzyl-1-(1′-naphthyl)ethylamine moiety in the Ni-catalyzed hydrovinylation of various substrates at −78 °C with *ee*s ≥ 94%. When *p*-isobutylstyrene was used as substrate only a minor depletion of the enantioselectivity was observed by raising the temperature from −78 °C to 0 °C (96% and 92%, respectively).[12b]

To study the role of the aryl group at the α-position to the nitrogen more systematically, we set out to explore the Ni-catalyzed hydrovinylation with all three possible combinations of (*R*)-binaphthol-based phosphoramidites comprising two chiral (*S*)-1-(naphthyl)ethyl groups at the nitrogen, i.e., the bis-(*S,S*)-[1-(1′-naphthyl)ethyl]amine (**3**), the bis-(*S,S*)-[1-(2′-naphthyl)ethyl]amine (**4**), and the new (*S*)-1-(1′-naphthyl)ethyl-(*S*)-1-(2′-naphthyl)ethylamine (**5**), respectively (Figure 2). Ligands **3**[13] and **4**[14] were prepared accordingly to literature procedures, while the new ligand **5** was synthesized starting from (*S*)-1-(1′-naphthyl)ethylamine as shown in Scheme 1 (see Supporting Information for full experimental details).[15]

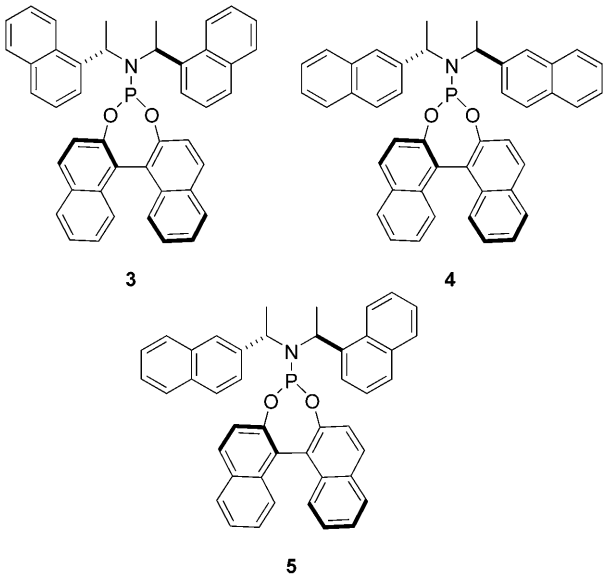
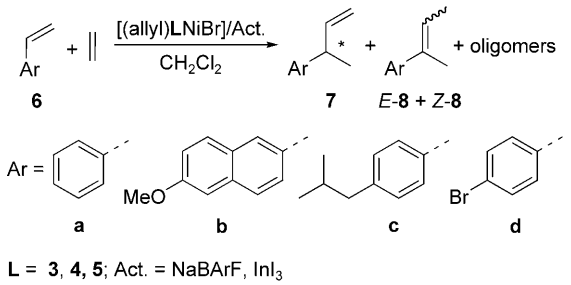


Figure 2. Phosphoramidite ligands used in this study.

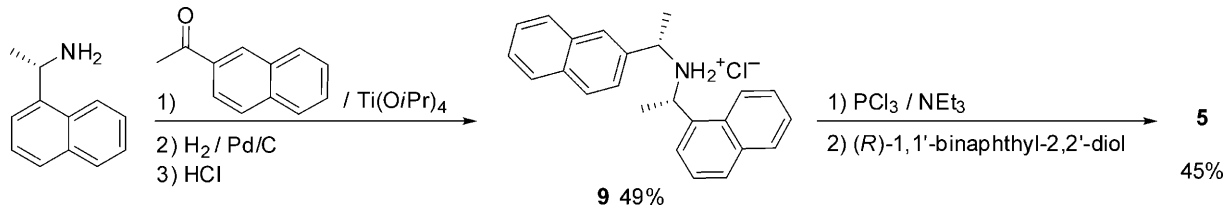
The pre-catalysts were formed mixing $[(allyl)NiBr]_2$ with two equivalents of the phosphoramidites **3–5** in CH_2Cl_2 for 10 min. Catalyst activation was carried out with NaBArF {BArF = B[3,5-$(CF_3)_2$-C_6H_3]$_4$}[16] or with InI_3.[17] The new catalytic systems were evaluated in the hydrovinylation of the benchmark substrate styrene (**6a**), 6-methoxy-1-vinylnaphthalene (**6b**) and *p*-isobutylstyrene (**6c**), which can serve as precursors for the synthesis of the anti-inflammatory drugs Naproxen® and Ibuprofen®, respectively,[3,12b,18] and *p*-bromostyrene (**6d**) as an example for an electron-poor substrate (Scheme 2). Representative results of this study are summarized in Table 1.



Scheme 2. Asymmetric hydrovinylation: substrates, ligands and activators used in this study.

When the catalyst system based on ligand **3** was applied in the hydrovinylation of styrene under standard conditions at −70 °C no significant conversion was observed. Even at 0 °C, only 40% conversion, very low chemo- (20%) and enantioselectivity (15%) were obtained, indicating that **3** is a poor ligand for this reaction. In sharp contrast, the isomeric ligand **4** forms an active and highly selective hydrovinylation catalyst. At a **6a**/Ni ratio of 250 and −70 °C, almost all of the substrate was selectively converted within 40 min into 3-phenylbut-1-ene (**7a**) with an *ee* of 97%, using either NaBArF or InI_3 as activator (entries 1 and 2). Even higher enantioselectivities were achieved with ligand **5**. Under standard conditions, almost perfect enantioselectivity was obtained in the hydrovinylation of styrene (99% *ee* with NaBArF, 98% *ee* with InI_3, entries 3 and 4). Thus, while the presence of a bis-(*S,S*)-[1-(1′-naphthyl)ethyl]amine group in **3** almost inhibits the catalytic cycle, the subtle modification from 1-naphthyl to 2-naphthyl of both or even one aryl moiety in **4** and in **5**, respectively, is sufficient and crucial for gaining activity and selectivity as well.

Similar high levels of enantioselectivity were obtained with ligand **4** also in the hydrovinylation of the other substrates **6b**, **6c** and **6d** with *ee*s ranging from 94% to 99% (entries 5, 6, 9, 13, and 14). Selectivities



Scheme 1. Synthesis of ligand **5**.

Table 1. Representative results of the asymmetric Ni-catalyzed hydrovinylation of vinylarenes with ligand **4** and **5**.[a]

Entry	Substrate	Activator	Ligand	Substrate/ [Ni]	T [°C]	t [min]	Conversion [%]	Selectivity for **7** [%]	*ee* (**7**) [%]	TOF_{av}[b] [h^{-1}]
1	**6a**	NaBArF	**4**	250	−70	40	97	>99	97 (*S*)	370
2	**6a**	InI_3	**4**	250	−70	40	97	>99	97 (*S*)	370
3	**6a**	NaBArF	**5**	250	−70	40	90	99	99 (*S*)	340
4	**6a**	InI_3	**5**	250	−70	40	>99	99	98 (*S*)	>380
5[c]	**6b**	NaBArF	**4**	125	−70	120	>99	>99	99 (*S*)	>62
6[c]	**6b**	InI_3	**4**	125	−70	120	>99	>99	99 (*S*)	>62
7[c]	**6b**	NaBARF	**5**	125	−70	120	>99	>99	>99 (*S*)	>62
8[c]	**6b**	InI_3	**5**	125	−70	120	>99	>99	>99 (*S*)	>62
9[d]	**6c**	NaBArF	**4**	250	−70	15	40	96	95 (*S*)	400
10[d]	**6c**	NaBArF	**5**	250	−70	15	34	99	96 (*S*)	340
11[d]	**6c**	NaBArF	**4**	250	−70	150	>99	80	95 (*S*)	>100
12[d]	**6c**	NaBArF	**5**	250	−70	150	>99	90	96 (*S*)	>100
13	**6d**	NaBArF	**4**	250	−70	30	95	>99	96 (*S*)	477
14	**6d**	InI_3	**4**	250	−70	30	99	98	94 (*S*)	>500
15	**6d**	NaBArF	**5**	250	−70	30	99	99	98 (*S*)	>500
16	**6d**	InI_3	**5**	250	−70	30	>99	>99	97 (*S*)	>500
17	**6a**	NaBArF	**5**	1000	0	30	82	>99	96 (*S*)	1640
18	**6a**	InI_3	**5**	1000	0	30	>99	99	95 (*S*)	>2000
19[e]	**6a**	NaBArF	**5**	1000	r.t.	17	98	98	93 (*S*)	3450
20	**6a**	InI_3	**5**	1000	r.t.	20	84	99	90 (*S*)	2520
21[f]	**6b**	NaBArF	**5**	250	r.t.	5	>99	94	95 (*S*)	>3125
22[f]	**6b**	InI_3	**5**	250	r.t.	5	>99	93	94 (*S*)	>3125
23[d]	**6c**	NaBArF	**5**	250	r.t.	2	>99	95	90 (*S*)	>8300
24[d]	**6c**	InI_3	**5**	250	r.t.	3	>99	92	89 (*S*)	>5000
25	**6d**	NaBArF	**5**	1000	r.t.	30	93	95	92 (*S*)	2790
26	**6d**	InI_3	**5**	1000	r.t.	30	76	95	90 (*S*)	2280

[a] *Reaction conditions:* [(allyl)**L**NiBr] = 0.012 mmol, activator = 1 equiv., CH_2Cl_2 = 3 mL.
[b] Turnover frequency for conversion of **6**.
[c] CH_2Cl_2 = 10 mL.
[d] *Reaction conditions:* [(allyl)**L**NiBr] = 0.006 mmol, activator = 1 equiv., CH_2Cl_2 = 1.5 mL.
[e] Isolated yield 83%.
[f] CH_2Cl_2 = 5 mL.

for the desired products **7b–d** were typically very high (>99%) and a slight decrease was observed upon complete substrate consumption only for **6c** (entry 11).[19] The catalyst performances achieved upon activation with NaBArF and with InI_3 are largely identical, confirming the efficiency of this Lewis acid for activation (*cf.* entries 5/6 and 13/14).[17] Again, even higher enantioselectivities coupled with chemoselectivities ≥99% have been obtained under the same conditions with ligand **5**. To the best of our knowledge, the enantiomeric excesses achieved with **5** are at the same excellent level (for **6b** and **6c**, entries 7 and 10, respectively) or even surpass (for **6a** and **6d**, entries 3 and 15, respectively) the highest *ee*s reported so far for these substrates.[2,20]

Encouraged by the extremely high selectivities obtained at low temperature, we carried out the hydrovinylation of styrene in the presence of **5** at higher temperature. At 0 °C almost full conversion, perfect chemoselectivity (>99%) and an enantioselectivity of 96% were achieved upon activation with NaBArF (entry 17), which are the highest values obtained for this transformation under these conditions.[21] Similar selectivities and higher activity were observed with InI_3 as activator under the same conditions (entry 18). Finally, these excellent levels of chemo- and enantioselectivities could be retained even by carrying out the reaction at room temperature (entries 19–26). Standard work-up provided essentially pure products in high yields (see Experimental Section for details).

With NaBArF activation, the desired products were obtained with chemoselectivities between 94% and 97% and enantioselectivities between 90% and 95%. Moreover, extremely high TOFs ranging from 2790 to >8300 h^{-1} were observed under these conditions. Comparable results were achieved again upon catalyst activation with InI_3 (chemoselectivities 92%–99%, *ee*s 89%–94%).[22] Thus, product **7b**, which is a possible precursor for Naproxen®, was obtained within 5 min in 94% GC yield and 95% *ee* by simply keeping under ethylene atmosphere a CH_2Cl_2 solution of **6b** and the catalyst components without external temper-

ature control (entry 21). Product **7c**, providing access to Ibuprofen®, was formed in less than 2 min in 95% GC yield and 90% *ee* (entry 23).

In summary, the subtle interplay of the steric bulk and hemilabile interaction of the naphthyl groups at the α-position to the nitrogen strongly controls the efficacy of the isomeric ligands **3**–**5**. Especially with the readily accessible ligand **5**, the hydrovinylation can now be carried out in a very simple protocol at room temperature to convert electron-rich and electron-poor substrates rapidly to chiral products in high yields and enantioselectivities. This further substantiates the role of hydrovinylation as a valuable and practical addition to the still limited tool box of asymmetric C–C coupling reactions.

Experimental Section

General Remarks

All manipulations were carried out under argon using Schlenk-tube techniques. NaBArF,[23] $[(\eta^3\text{-allyl})NiBr]_2$,[24] ligand **3**,[13] ligand **4**[13] and compound **6c**[25] were prepared according to literature procedures. InI_3 was provided by Acros Organics. 1-Acetylnaphthalene and 2-acetylnaphthalene were provided by Aldrich and used without further purification. (*S*)-1-(1′-Naphthyl)ethylamine and (*S*)-1-(2′-naphthyl)ethylamine were provided by BASF and used without further purification.

NMR spectra were measured at room temperature with a Bruker AV-400 or a Bruker AV-600 spectrometer. Chemical shifts are given relative to TMS by using the solvent signals as internal reference for ^{1}H as well as ^{13}C NMR and H_3PO_4 (85%) as external reference for ^{31}P NMR spectroscopy. Mass spectra (EI) were recorded on a Finnigan MAT 95 and optical rotations on a Jasco P-1020 polarimeter.

Synthesis of (*S*)-1-(1′-Naphthyl)ethyl-(*S*)-1-(2′-naphthyl)ethylammonium Chloride (9)[15]

A mixture of 2-acetylnaphthalene (2.926 g, 17.19 mmol), (*S*)-1-(1-naphthyl)ethylamine (2.94 g, 17.19 mmol) and titanium(IV) isopropoxide (22 mL, 72.6 mmol) in ethyl acetate (10 mL) was stirred for 30 min at room temperature. Then, 10% palladium on charcoal (90 mg, 0.5 mol%) was added and the mixture stirred overnight at room temperature under hydrogen (1 bar). An aqueous solution of sodium hydroxide (1 M, 50 mL) was then added to the mixture. After stirring for 10 min, the solution was filtered and the solid washed with ethyl acetate (3×20 mL). The organic layer was separated. The aqueous phase was extracted with ethyl acetate (3× 20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. A colourless oil was obtained, which was dissolved in an ethyl acetate/methanol mixture (75:25). A solution of HCl (1 M) was added dropwise until pH 1 was reached. The solution was then placed at −18 °C overnight. White crystals of the diastereomerically pure compound **9** formed; yield: 3.0 g (49%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.96$ (3 H, d, $J = 6.9$ Hz), 2.03 (3 H, d, $J = 6.9$), 4.12 (1 H, m), 4.76 (1 H, m), 6.7–8.6 (14 H, m), 10.74 (1 H, br), 10.86 (1 H, br); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.03$ (CH_3), 22.02 (CH_3), 51.50 (CH), 51.47 (CH), 121.53 ($C_{ar}H$), 124.77 ($C_{ar}H$), 125.63 ($C_{ar}H$), 125.95 ($C_{ar}H$), 126.23 ($C_{ar}H$), 126.33 ($C_{ar}H$), 126.35 ($C_{ar}H$), 126.74 ($C_{ar}H$), 127.63 ($C_{ar}H$), 128.16 ($C_{ar}H$), 128.86 ($C_{ar}H$), 128.88 ($C_{ar}H$), 129.21 ($C_{ar}H$), 129.39 ($C_{ar}H$), 130.33 (C_{ar}), 132.86 (C_{ar}), 132.95 (C_{ar}), 133.11 (C_{ar}), 133.42 (C_{ar}), 133.69 (C_{ar}); HR-MS (EI): $m/z = 325.18277$, calcd. for $C_{24}H_{23}N$: 325.18250; $[\alpha]_D^{20}$: 114.31 (*c* 0.8, CH_2Cl_2).

Synthesis of (11b*R*)-*N*-[(*S*)-1-(naphthalen-1-yl)ethyl]-*N*-[(*S*)-1-(naphthalen-2-yl)ethyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine (5)[15]

Et_3N (2.1 g, 20.8 mmol) was added at 0 °C through a septum to a solution of PCl_3 (0.571 g, 4.16 mmol) in CH_2Cl_2 (6 mL). After 5 min, compound **8** (1.5 g, 4.16 mmol) was added neat in one portion and the reaction mixture was stirred for 10 min at 0 °C and then for 5 h at room temperature. (*R*)-1,1′-Binaphthyl-2,2′-diol (1.19 g, 4.16 mmol) was added as a solid in one portion to the reaction mixture at 0 °C and the suspension was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. The yellow solid residue was dissolved in CH_2Cl_2 (5 mL) and filtered through a filter-cannula. The remaining solid residue was extracted twice with CH_2Cl_2 (2 mL). The combined solutions were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane:CH_2Cl_2 = 4:1) to obtain pure **5**; yield: 1.2 g (45%). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.90$ (6 H, br), 4.97 (1 H, br), 5.60 (1 H, br), 7.16–8.08 (26 H, m); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 21.18$ (CH_3), 24.29 (CH_3), 49.65 (CH), 52.50 (CH), 121.82 (C_{ar}), 122.39 ($C_{ar}H$), 122.56 ($C_{ar}H$), 122.79 ($C_{ar}H$), 124.24 (C_{ar}), 124.45 ($C_{ar}H$), 124.55 ($C_{ar}H$), 124.80 ($C_{ar}H$), 124.89 ($C_{ar}H$), 124.95 ($C_{ar}H$), 125.24 ($C_{ar}H$), 125.28 ($C_{ar}H$), 125.38 ($C_{ar}H$), 125.75 ($C_{ar}H$), 126.08 ($C_{ar}H$), 126.14 ($C_{ar}H$), 126.79 ($C_{ar}H$), 127.00 ($C_{ar}H$), 127.21 ($C_{ar}H$), 127.22 ($C_{ar}H$), 127.26 ($C_{ar}H$), 127.32 ($C_{ar}H$), 127.73 ($C_{ar}H$), 128.22 ($C_{ar}H$), 128.39 (C_{ar}), 128.41 ($C_{ar}H$), 128.43 ($C_{ar}H$), 129.64 ($C_{ar}H$), 130.47 ($C_{ar}H$), 130.51 (C_{ar}), 131.50 (C_{ar}), 132.07 (C_{ar}), 132.52 (C_{ar}), 132.89 (C_{ar}), 132.97 (C_{ar}) 133.33 (C_{ar}), 139.19 (C_{ar}), 139.77 (C_{ar}), 149.63 (C_{ar}), 150.36 (C_{ar}); ^{31}P{^{1}H} (243 MHz, $CDCl_3$): δ = 145.68; HR-MS (EI): m/z = 639.23244, calcd. for $C_{44}H_{34}O_2NP$: 639.23217. $[\alpha]_D^{20}$: −216.88 (*c* 0.9, CH_2Cl_2).

General Procedures for the Hydrovinylation Reactions

Pre-catalyst preparation: Pre-catalysts $[(\eta^3\text{-allyl})\{(R_a,S_C,S_C)\text{-}\mathbf{4}\}NiBr]$ (**9**) and $[(\eta^3\text{-allyl})\{(R_a,S_C,S_C)\text{-}\mathbf{5}\}NiBr]$ (**10**) were prepared by mixing in CH_2Cl_2 (5 mL) at 0 °C for 10 min the complex $[(\eta^3\text{-allyl})NiBr]_2$ (56.2 mg, 0.156 mmol) with the ligand (R_a,S_C,S_C)-**4** or (R_a,S_C,S_C)-**5** (200 mg, 0.312 mmol), respectively. After evaporation of the solvent under reduced pressure, an orange powder was obtained in both cases, which was used without further purification.

*Hydrovinylation of styrene **6a** at −70 °C* (Table 1, entries 3 and 4): A solution of pre-catalyst **10** (9.8 mg, 0.012 mmol) and styrene **6a** (0.35 mL, 3 mmol) in CH_2Cl_2 (3 mL) was cooled to −70 °C using a dry-ice/*i*-PrOH bath. The cold solution was then transferred *via* syringe to a Schlenk flask con-

taining the activator NaBArF (10.3 mg, 0.012 mmol) or InI_3 (5.6 mg, 0.012 mmol) at the same temperature. The resulting yellow mixture was allowed to warm to 0 °C for three minutes and then the now dark red solution was cooled down again to −70 °C. The reaction was started by exchanging the inert gas for ethylene by bubbling it through the solution for 5 s and keeping the Schlenk flask under an ethylene atmosphere at ambient pressure during the reaction. After 40 min, the catalyst was quenched with a solution of NH_3 (20% w/w, 1 mL). Ethylbenzene (0.4 mL, 3 mmol) was added as internal standard for the GC analysis and the solution was allowed to warm up to room temperature. The organic phase was separated, dried over Na_2SO_4, filtered through a pad of silica and analyzed *via* GC.

Hydrovinylation of styrene ***6a*** *at 0 °C* (Table 1, entry 17 and 18): The same procedure was followed as above except that both activation and reaction were performed at 0 °C.

Hydrovinylation of styrene ***6a*** *at room temperature* (Table 1, entry 19): A solution of pre-catalyst **10** (9.8 mg, 0.012 mmol) and styrene **6a** (1.40 mL, 12 mmol) in CH_2Cl_2 (3 mL) was added *via* syringe to a Schlenk flask containing the activator NaBArF (10.3 mg, 0.012 mmol). The reaction was started by exchanging the inert gas for ethylene by bubbling it through the solution for 5 s and keeping the Schlenk flask under an ethylene atmosphere at ambient pressure during the reaction. After 17 min, the catalyst was quenched with a solution of NH_3 (20% w/w, 1 mL). The organic phase was separated and the aqueous phase washed with CH_2Cl_2 (3×2 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed with a rotary evaporator to give a yellowish liquid. This liquid was passed through a short silica column (eluent *n*-pentane) and the solvent removed with a rotary evaporator affording pure product **7a** as a colourless liquid; yield: 1.31 g (83%).

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