# Nickel-Catalyzed Asymmetric Hydrovinylation Using Lewis Acid Activation

Nicolas Lassauque,<sup>[a]</sup> Giancarlo Franciò,<sup>[a]</sup> and Walter Leitner\*<sup>[a,b]</sup>

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A broad range of commercially available Lewis acids were investigated for their ability to activate and regulate nickel catalysts for asymmetric hydrovinylation processes using styrene as model substrate and ligand ( $R_a, S_C, S_C$ )-**5** as benchmark system. The colour change during the activation step associated with the halide abstraction furnishes helpful indications to adapt the activation conditions to the pre-catalyst/ Lewis acid system. In general, metal halide Lewis acids led to higher activities and enantioselectivities than the corre-

## Introduction

Asymmetric hydrovinylation is a powerful synthetic strategy to generate C-C bonds in a highly enantioselective and perfectly atom-efficient way (Scheme 1).<sup>[1]</sup> Formally, it comprises the addition of a vinylic C-H bond to another olefinic double bond, and highly selective catalytic systems for intermolecular,<sup>[1,2]</sup> and intramolecular<sup>[3,4]</sup> (cycloisomerisation) transformations have been developed. Among various transition metal complexes known to catalyze this reaction in principle, nickel catalysts are often the system of choice providing high activity combined with high chemo-, regio- and enantioselectivity.<sup>[2]</sup> The chiral information is introduced through chiral monodentate phosphorus ligands, whereby some of them bear an additional hemilabile donor group. Recently, we showed that phosphoramidites are extremely efficient chiral ligands for this transformation,<sup>[5]</sup> and they have gained increasing attention owing to their large substrate scope.<sup>[6,7]</sup>



Scheme 1. General asymmetric hydrovinylation reaction.

sponding triflates. In particular, the use of  $InI_3$  as co-catalyst resulted in the same chemo- and enantioselectivity and even higher activity than the benchmark system based on NaBArF. Moreover,  $InI_3$  is safe to handle and cheap, thus providing a simple and practical protocol for an efficient hydrovinylation reaction.

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The catalytic cycle of the nickel-catalyzed hydrovinylation occurs via cationic intermediates,<sup>[2]</sup> and the active species is typically generated from a neutral nickel halide precursor with a suitable co-catalyst. This activation step can be achieved by replacing the halide ligand with a weakly coordinating anion (WCA) (Scheme 2a). Silver salts,<sup>[8]</sup> ionic liquids,<sup>[9]</sup> and in particular NaBArF<sup>[10]</sup> have been used successfully for this purpose. Since the pioneering work of Wilke<sup>[1]</sup> and Bogdanovič,<sup>[11]</sup> it is well established that the nature of the WCA plays a decisive role in controlling the activity, chemoselectivity and even enantioselectivity. Such pronounced counterion effects on enantioselectivity are not restricted to nickel catalysts in hydrovinylation reactions, and other prominent examples include iridium-catalyzed hydrogenation,<sup>[12]</sup> ruthenium-catalyzed cyclopropanation<sup>[13]</sup> as well as acid-catalyzed hydroamination.<sup>[14]</sup>

$$\left\langle \left(-N_{i}\right)^{X} \xrightarrow{M^{+}WCA^{-}} \left\langle \left(-N_{i}\right)^{+}WCA^{-} + MX \right\rangle \right\rangle$$

$$\left\langle \left(-N_{i}\right)^{X} \xrightarrow{L \text{ lewis Acid (LA)}} \left\langle \left(-N_{i}\right)^{+}LAX^{-} \right\rangle \right\rangle$$

X = Cl, Br; L = ligand; M = Na, Ag

Scheme 2. Activation processes using (a) a weakly coordinating anion (WCA) and (b) a Lewis acid (LA).

A second method for activation of nickel catalyst is the use of Lewis acids (LA), which can abstract the halide ligand with formation of a corresponding adduct LAX<sup>-</sup> acting as weakly coordinating anion in this case (Scheme 2b). This approach was taken in the original standard protocol developed by Wilke et al.<sup>[15]</sup> which comprised aluminium



 <sup>[</sup>a] Institut für Technische und Makromolekulare Chemie, RWTH Aachen University, Worringer Weg 1, 52074 Aachen, Germany Fax: +49-241-8022177 E-mail: leitner@itmc.rwth-aachen.de

<sup>[</sup>b] Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany



Scheme 3. Benchmark hydrovinylation system.

sesquichloride as activator. BF<sub>3</sub> has also been used in early studies as activator in nickel-catalyzed hydrovinylation, but it was speculated that the LA interacts with the substrate (styrene) or the ligand (PPh<sub>3</sub>).<sup>[16]</sup> In(OTf)<sub>3</sub> has also been used successfully as activator in the palladium-catalyzed dimerisation of styrene with a Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> catalyst system.<sup>[17]</sup> This precatalyst does not contain halides, and it has also been speculated that the activation occurs by interaction with the substrate or formation of a Pd–In complex.

Given the large structural variety offered by LA activators and thus the strong regulating effect of the resulting counterion, it seems surprising that no more efforts have been made to systematically exploit this activation method. In the present study, we have investigated a broad range of Lewis acids for their ability to activate and regulate nickel catalysts for asymmetric hydrovinylation processes using styrene as model substrate and ligand ( $R_a, S_c, S_c$ )-5 as benchmark system (Scheme 3).

# **Results and Discussion**

The isolated complex  $[\eta^3-(allyl)Ni\{(R_a, S_C, S_C)-5\}Cl]$  (6) was used as hydrovinylation precatalyst<sup>[5a]</sup> for testing various Lewis acids as alternative activators. The activation step was carried out at -40 °C by introducing a dichloromethane solution of **6** in the presence of styrene (styrene/Ni = 1000) in a Schlenk flask containing 1.1 equiv. of the Lewis acid. After 5 min, the hydrovinylation was started at the same temperature by saturating the solution with ethylene and then maintaining an ethylene atmosphere (1 bar) over the reaction mixture. After stirring for a given reaction time (see Table 1), the reaction was quenched by adding an excess of aqueous ammonia solution. Following the standard workup procedure, conversion and enantioselectivity were determined by GC analysis (Experimental Section). Under these conditions, the benchmark activation procedure using NaBArF for halide exchange led to full conversion of 1

Entry	Activator	Activation temperature	Color change	Reaction temperature	Reaction time	Conversion	TOF <sup>[b]</sup>	Selectivity (3)	ee
		[°C]		[°C]	[h]	[%]	$[h^{-1}]$	[%]	[%]
1	Y(OTf) <sub>3</sub>	-40	no	-40	1	_		_	_
2	Bi(OTf) <sub>3</sub>	-40	yes	-40	1	31	310	97	70 (S)
3	Yb(OTf) <sub>3</sub>	-40	no	-40	1	5	50	99	n.d. <sup>[c]</sup>
4	La(OTf)3	-40	yes	-40	1	24	240	90	64 (S)
5	$In(OTf)_3$	-40	no	-40	1	7	70	99	n.d. <sup>[c]</sup>
6	$Gd(OTf)_3$	-40	no	-40	1	<1	_	_	_
7	Zn(OTf)	-40	no	-40	1	_	_	_	_
8	$Sc(OTf)_3$	-40	no	-40	1	_	_	_	_
9	$InI_3$	-40	yes	-40	0.5	94	1880	99	70 (S)
11	InBr <sub>3</sub>	-40	yes	-40	0.5	98	1960	99	66 (S)
10	BiBr <sub>3</sub>	-40	yes	-40	0.5	90	1800	99	68 (S)
12	$BiI_3$	-40	no	-40	0.5	_		_	_
13	LaI <sub>3</sub>	-40	yes	-40	0.5	18	360	99	66 (S)
14	$InI_3$	-70	yes	-70	2	82	410	99	92 (S)
15	InBr <sub>3</sub>	0	yes	-70	2	41	205	99	88 (S)
16	InCl <sub>3</sub>	0	no	-70	2	<1	_	_	_
17	BiBr <sub>3</sub>	-70	yes	-70	2	24	120	99	67 (S)
18	LaI <sub>3</sub>	-70	no	-70	2	3	15	99	n.d. <sup>[c]</sup>
19	$ZnCl_2$	-70	yes	-70	2	17	85	99	91 (S)
20	GaCl <sub>3</sub>	0	yes	-70	2	40	200	99	85 (S)
21	GaI <sub>3</sub>	0	yes	-70	2	16	80	99	87 (S)

Table 1. Hydrovinylation of styrene using catalyst 6 activated by metal halides.<sup>[a]</sup>

[a] For reaction conditions and analytic methods see Experimental Section. [b] Turnover frequency for conversion of 1. [c] Not calculated due to low conversion.



with a selectivity to **3** of 99% and an *ee* of 70% for the (*S*) enantiomer.

Initially, the performance of various metal triflates as Lewis acids was screened. Representative results are reported in Table 1 (Entries 1–8). No conversion was observed when the triflates of Y, Gd, Zn and Sc were used. In contrast, the triflates of Yb, In, La and Bi were able to activate **6** to some extent. In particular, conversions of 24% and 31% were obtained with La(OTf)<sub>3</sub> and Bi(OTf)<sub>3</sub>, respectively, corresponding to a TOF of up to 310 h<sup>-1</sup>. The desired product **3** was formed with high selectivity (90–99%), and enantioselectivity ranged between 64 and 70%. A slight colour change from pale yellow to yellow-orange was observed during the activation step with Bi(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, La(OTf)<sub>3</sub> and In(OTf)<sub>3</sub> as the Lewis acids, whereas no colour variation was detected with the triflates that did not lead to activation (Table 1).

A substantial increase of the catalytic activity was observed with simple halides as compared to the corresponding triflates as Lewis acids (Entries 9–13). In particular, InI<sub>3</sub>, InBr<sub>3</sub> and BiBr<sub>3</sub> were very efficient in the activation of **6** resulting in conversions, chemo- and enantioselectivities very similar to those of the benchmark **6**/NaBArF system under identical conditions. Almost full conversion, perfect selectivity towards **3** and enantioselectivities ranging from 66 to 70% were achieved. The slightly higher enantioselectivity achieved with InI<sub>3</sub> (70%) with respect to InBr<sub>3</sub> (66%) may be related to the larger charge delocalization and hence the weaker coordination ability of the resulting anion [InI<sub>3</sub>Cl]<sup>-</sup> in comparison with [InBr<sub>3</sub>Cl]<sup>-</sup>. BiI<sub>3</sub> showed no activity, most likely owing to its very poor solubility in CH<sub>2</sub>Cl<sub>2</sub>.

Again, the activation step was accompanied by a distinct colour change for the effective Lewis acids. By using  $InI_3$  and  $InBr_3$  the colour of the solution turned from pale yellow to deep red. This colour change is less pronounced in the case of BiBr<sub>3</sub> and hardly noticeable for LaI<sub>3</sub>. Representative snapshots of the catalyst solutions taken immediately after the activation are shown in Figure 1. The picture of a solution of catalyst **6** activated with NaBArF is included for comparison.



Figure 1. Dichloromethane solutions of **6** in the presence of styrene (a) and upon addition of different Lewis acids (b, c) and NaBArF (d).

The visual observation of the colour change was correlated with a change of the absorption properties by recording the UV/Vis spectra of the precatalyst after the activation.<sup>[18,19]</sup> Selected examples are shown in Figure 2. A strong redshift of the absorbance bands of the catalyst precursor **6** (black trace) was observed upon addition of an efficient activator such as NaBArF (6 + NaBArF, blue trace) and InI<sub>3</sub> (6 + InI<sub>3</sub>, orange trace). The resulting new spectra are largely identical with two maxima of absorbance around 370 and 477 nm, thus confirming that the mode of activation by the Lewis acids is halide abstraction to form a cationic species with a weakly coordinating anion as indicated in Scheme 2b. In contrast, only minor changes to the UV/Vis spectrum of the catalyst precursor were observed in the presence of LaI<sub>3</sub> (6 + LaI<sub>3</sub>, green trace) corresponding to inefficient catalyst formation.<sup>[19]</sup> The reduced signal intensity in this experiment was due to partial decomposition of complex 6 and formation of metal black.



Figure 2. UV/Vis spectra of **6** (black trace), **6** + LaI<sub>3</sub> (green trace), **6** + InI<sub>3</sub> (orange trace) and **6** + NaBArF (blue trace). Conditions: **1** (5 mL, 43.46 mmol); **6** (30 mg, 0.044 mmol) and activator (0.049 mmol) are dissolved in  $CH_2Cl_2$  (15 mL) at room temperature.

The colour change was used as a qualitative indicator for the formation of an active species during the further optimisation of the reaction conditions. Even at a reaction temperature of -70 °C (Entries 14-21), a number of metal halides induced significant activation, and very high to excellent chemo- and enantioselectivities were achieved. In certain cases, it was necessary to warm the reaction mixture to 0 °C for 5 min during the activation step, as no colour change was observed at -70 °C. By far the best results in terms of activity and selectivity were observed with InI<sub>3</sub> (Table 1, Entry 14) where the activation and reaction can both be performed at -70 °C. Most significantly, the results obtained with this activator led to identical selectivities and significant higher conversion as compared to the use of Na-BArF under identical conditions (6/NaBArF, -70 °C: 63%) conversion, >99% **3**, 93% *ee*).

#### Conclusion

We evaluated a wide range of Lewis acids for their ability to activate the nickel precursor **6** in the highly chemo- and enantioselective hydrovinylation of styrene. The observation of the colour change associated with the halide abstraction during the activation step proved to be a helpful tool to adapt the activation conditions to the precatalyst/Lewis acid system. In general, metal halides gave rise to more active and enantioselective catalytic systems than the corresponding triflates. Among these activators,  $InI_3$  appears to

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be the candidate of choice since it leads to the same chemoand enantioselectivity and even higher activity than the benchmark system based on NaBArF. In contrast to the activation with silver salts,<sup>[8]</sup> no filtration is needed before starting the reaction. Moreover, InI<sub>3</sub> is safe to handle, commercially available and relatively cheap, thus providing a simple and practical protocol for efficient hydrovinylation reaction.

# **Experimental Section**

**General:** All manipulations were carried out under argon by using classical Schlenk-tube techniques. NaBArF,<sup>[20]</sup> phosphoramidite  $(R_a, S_C, S_C)$ -5,<sup>[21]</sup> [ $\eta^3$ -(allyl)NiCl]<sub>2</sub>,<sup>[22]</sup> and [ $\eta^3$ -(allyl)Ni{ $(R_a, S_C, S_C)$ -5}Cl] (6)<sup>[5a]</sup> were prepared according to literature procedures. UV/ Vis spectra were recorded with an Avantes Ava-light DHS. All Lewis acids were provided by Aldrich except for InI<sub>3</sub> (Acros Organics) and ZnCl<sub>2</sub> (Fluka). All Lewis acids were dried under vacuum at 100 °C for 1 h before use.

General Procedure for the Hydrovinylation Reaction Using InI<sub>3</sub> as the Lewis Acid Activator at -70 °C: A solution of complex 6 (8.08 mg, 0.012 mmol) and styrene 1 (1.4 mL, 12.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was precooled and added via syringe to a Schlenk flask containing InI<sub>3</sub> (6.54 mg, 0.0132 mmol) at -70 °C. The resulting mixture was stirred under argon at -70 °C for 5 min, and then the gas was exchanged for ethylene by bubbling it through the solution for 5 s. The Schlenk flask was kept under ethylene at ambient pressure during the reaction. After 2 h, the reaction was quenched with a solution of NH<sub>3</sub> (20% w/w, 1 mL). Ethylbenzene (1.6 mL, 12.1 mmol) was added as internal standard for the GC analysis, and the solution was warmed up to room temperature. The organic phase was separated, dried with sodium sulfate and filtered through a pad of silica. Conversion and selectivity were determined by GC on a CP-Sil PONA CB column (50 °C, 8 °C/ min, 270 °C); retention times [min]: ethylbenzene 14.90; styrene 1 15.75; 3-phenyl-1-butene 3: 19.50; 2-phenyl-1-butene (E)-4: 20.50; 2-phenyl-1-butene (Z)-4: 22.80. The enantioselectivity was determined by GC on an Ivadex 7 IVA column (60 °C, 1 °C/min, 80 °C, 20 °C/min, 180 °C), retention times [min]: (R)-3-phenyl-1-butene: 15.48; (S)-3-phenyl-1-butene: 15.70.

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