Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500644

Enantioselective Nickel-Catalyzed Hydrocyanation using Chiral Phosphine-Phosphite Ligands: Recent Improvements and Insights

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Received: July 5, 2015; Revised: August 7, 2015; Published online: October 14, 2015

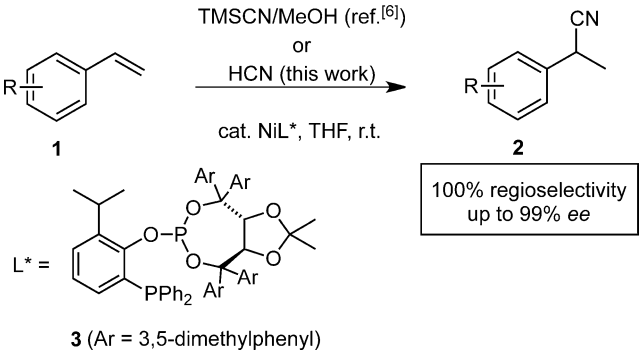
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500644.

Abstract: The asymmetric hydrocyanation of vinylarenes was investigated using hydrogen cyanide (HCN) in the presence of 5 mol% of a catalyst prepared from a phenol-derived chiral phosphine-phosphite ligand and bis(cyclooctadiene)nickel [$Ni(cod)_2$]. The reactions were performed in tetrahydrofuran (THF) at room temperature to give exclusively the branched nitriles with superior enantioselectivities of 88–99% *ee* for vinylarenes and 74–94% *ee* for vinylheteroarenes, respectively. Using styrene as a model substrate it was shown that the catalyst loading could be decreased to 0.42 mol% without any loss of selectivity (88% *ee*). The structure of the pre-catalyst, i.e., a tetrahedral Ni(0)(P,P-chelate)(cod) complex, was proven by X-ray and NMR analysis. Additional insight into the reaction course was gained by monitoring the hydrocyanation of styrene-d_8 by means of ^{2}D NMR spectroscopy.

Keywords: asymmetric synthesis; hydrocyanation; hydrogen cyanide (HCN); nickel; phosphine-phosphites

The hydrocyanation, that is, the conversion of alkenes into saturated nitriles, is widely known as the industrial production of adiponitrile from 1,3-butadiene involves two consecutive homogeneously Ni-catalyzed hydrocyanation steps.[1] Nevertheless, the hydrocyanation has found virtually no application in the synthesis of more complex products (e.g., in natural product synthesis) so far. A reason for this might be the lack of reliable general protocols especially with respect to stereocontrol. After some initial reports on asymmetric hydrocyanation,[2] a singular breakthrough was achieved by RajanBabu and Casalnuovo who showed that the conversion of 2-methoxy-6-vinylnaphthalene (MVN) proceeds with high enantioselectivity (95% *ee*) in the presence of a carbohydrate-derived diphosphinite ligand.[3] Later, the same authors also reported the hydrocyanation of aryl-1,3-dienes with up to 78% *ee*.[4] While important mechanistic insights into the Ni-catalyzed (asymmetric) hydrocyanation were reported by Vogt and co-workers,[5] selectivities for most substrates remained unsatisfactory (e.g., exceeded $\leq$60% *ee* for styrene).[6]

Recently, we disclosed a first general protocol for the highly enantioselective (up to 97% *ee*) Ni-catalyzed hydrocyanation of various vinylarenes employing the chiral phosphine-phosphite ligand **3** and TMSCN/MeOH as an *in situ* source of HCN (Scheme 1).[7] Modular ligands of this type are accessible in only a few steps[8] and have proven their utility already in numerous transition metal-catalyzed reactions.[9] While the *in situ* generation of HCN is attractive for small-scale laboratory applications, especially regarding safety aspects, the use of HCN itself as an atom-economic and much less expensive reagent is preferable for larger or even industrial scales. We



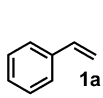
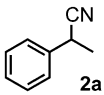
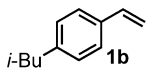
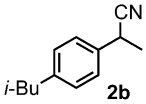
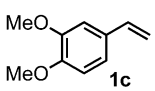
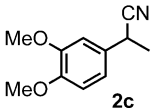
Scheme 1. Asymmetric hydrocyanation of styrenes.

here report the results of an extended study which demonstrates that the asymmetric Ni-catalyzed hydrocyanation of vinylarenes with HCN in the presence of ligand **3** leads to even improved selectivities and can be applied to a spectrum of synthetically relevant substrates (Scheme 1).

In a first series of experiments we picked three different vinylarenes to probe whether the reaction outcome using HCN is comparable with the one using TMSCN/MeOH.[7] For this purpose, the substrate was added to a solution of the catalyst (5 mol%) in THF under argon followed by addition of a solution of HCN in THF at room temperature over a period of 2 h. After chromatographic purification the selectivity was determined by means of GC on a chiral stationary phase.[10] Noteworthy, all three reactions (Table 1) reached full conversion after 2 h and proceeded with slightly improved enantioselectivities. This may be due to the complete absence of MeOH, which has been shown to give lower *ee*s than THF (the best performing solvent) alone in previous experiments.[7] No traces of the linear regioisomers could be detected.

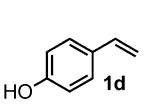
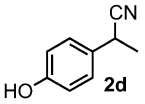
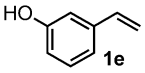
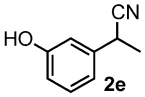
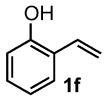
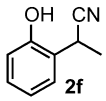
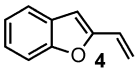
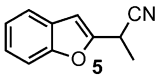
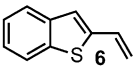
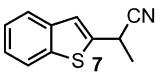
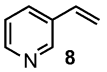
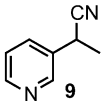
Encouraged by these initial results and to probe the scope of the methodology we investigated the hydrocyanation of a number of additional substrates using HCN. As Table 2 reveals, substrates **1d** and **1e** containing a free hydroxy function in *para* or *meta* positions are well tolerated, while **1f** with an *ortho* OH substituent showed no conversion at all. Remarkably, **1d** afforded the product (**2d**) with the highest selectivity (>99% *ee*) ever observed for this kind of transformation.

Table 1. Comparison of results using HCN instead of TMSCN/MeOH.

Entry	Substrate	Product	*ee*[a,c] (TMS-CN) [%]	*ee*[b,c] (HCN) [%]
1	 **1a**	 **2a**	86	88
2	 *i*-Bu **1b**	 *i*-Bu **2b**	92	93 (*S*)[7]
3	 MeO MeO **1c**	 MeO MeO **2c**	89	90

[a] *Reaction conditions:* 0.25 mmol substrate, 5 mol% of preformed catalyst [Ni(cod)$_2$/**3** = 1/1] in THF, slow addition (2 h) of TMSCN (1.5 equiv.) in THF/MeOH = 14/1 (0.125 M), room temperature.
[b] Slow addition (2 h) of HCN (1.5 equiv.) in THF (0.125 M).
[c] Determined by GC-FID on a chiral stationary phase, the absolute configuration of the products was not determined, unless otherwise indicated.

Table 2. Hydrocyanation of hydroxy-substituted styrenes and vinylheteroarenes.[a]

Entry	Substrate	Product	Isolated yield [%]	*ee*[b] [%]
1	 HO **1d**	 CN HO **2d**	73	>99
2	 HO **1e**	 CN HO **2e**	82	89
3	 OH **1f**	 OH CN **2f**	n.c.[c]	-
4	 O **4**	 CN O **5**	65	94
5	 S **6**	 CN S **7**	98	74
6	 N **8**	 CN N **9**	99	86

[a] *Reaction conditions:* substrate, 5 mol% of preformed catalyst [Ni(cod)$_2$/**3** = 1/1] in THF, slow addition (2 h) of HCN (1.5 equiv.) in THF (0.125 M), room temperature.
[b] Determined by GC-FID on a chiral stationary phase, the absolute configuration of the products was not determined.
[c] n.c. = no conversion.

The heteroaromatic vinylarenes **4**, **6**, and **8** also afforded the corresponding nitriles (**5**, **7**, and **9**, respectively) with high to excellent levels of selectivity under the standard conditions (Table 2, entries 4 and 5). These types of products had never been prepared by asymmetric hydrocyanation and are of potential interest as fine chemicals or intermediates in pharmaceutical chemistry. Again, all three reactions were found to proceed with complete regioselectivity and the pure products were isolated in good to excellent yields after column chromatography. In the case of **5** the lower yield results from incomplete conversion.

For the asymmetric hydrocyanation of styrene (**1a** to **2a**), the reaction was followed over time by taking samples, which were analyzed by GC. The obtained reaction profile indicated a rapid initial conversion (see the Supporting Information, Graph S1). Accordingly, the HCN addition time could either be shortened to 15 min or the catalyst loading could be decreased to 0.42 mol% (2 h) without loss of selectivity

Table 3. Further optimization of styrene hydrocyanation.[a]

Catalyst loading [mol%]	HCN addition time	Conversion [%]	*ee*[b] [%]
5	15 min	100	88
1.25	30 min	100	88
0.42	2 h	100	88

[a] *Reaction conditions:* substrate, preformed catalyst [$Ni(cod)_2$/**3** = 1/1] in THF, slow addition of HCN (1.5 equiv.) in THF (0.125 M), room temperature.
[b] Determined by GC-FID on a chiral stationary phase.

(at full conversion) (Table 3, see the Supporting Information, Graph S2).

The generally accepted and to quite some extent proven catalytic cycle for the Ni-catalyzed hydrocyanation of vinylarenes is shown in Scheme 2. After formation of the catalytically active complex (**I**), substrate and HCN addition lead, after hydrogen insertion, to the allyl-complex (**V**). The corresponding nitrile product is set free in a reductive elimination, which was proven to be the rate-, as well as the enantioselectivity-determining step.[2e,5,11]

Part of our investigations was also to prove the assumed catalyst structure (**I**). The comparison of ^{31}P NMR data of the free ligand (122 MHz, $CDCl_3$): $\delta = 149.57$ (d, $J = 73.3$ Hz), -18.72 (d, $J = 73.3$ Hz) with those of the Ni(**3**)(cod) complex (162 MHz, THF): $\delta = 130.23$ (d, $J = 44.5$ Hz), 25.25 (d, $J = 43.8$ Hz) indicated a 1:1 Ni to ligand ratio with both phosphorus atoms coordinated to the metal center, as a significant shift for both signals of the two P moieties (phosphine and phosphite) occurred (see the Supporting Information, Figure S1-3).

By slow diffusion of *n*-pentane into a solution of the isolated complex in THF under an inert atmosphere we were able to grow crystals of the complex Ni(**3**)(cod) suitable for X-ray single crystal analysis.[12] The structure of the complex (Figure 1) clearly resembles the assumed structure (**I**) with a tetrahedral coordination mode of the Ni(0) center.

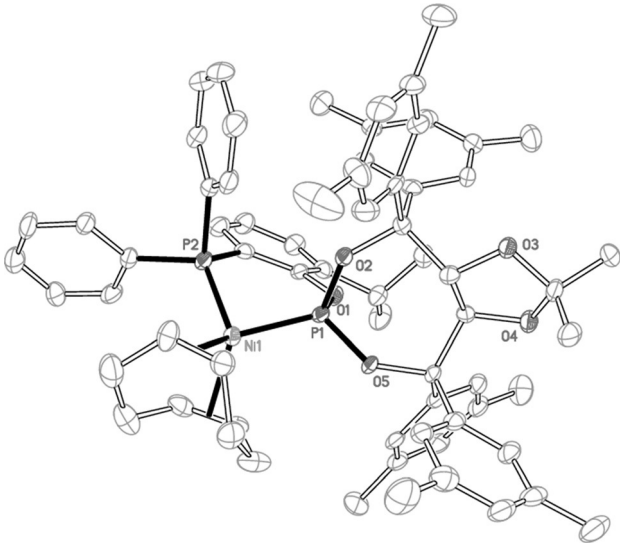
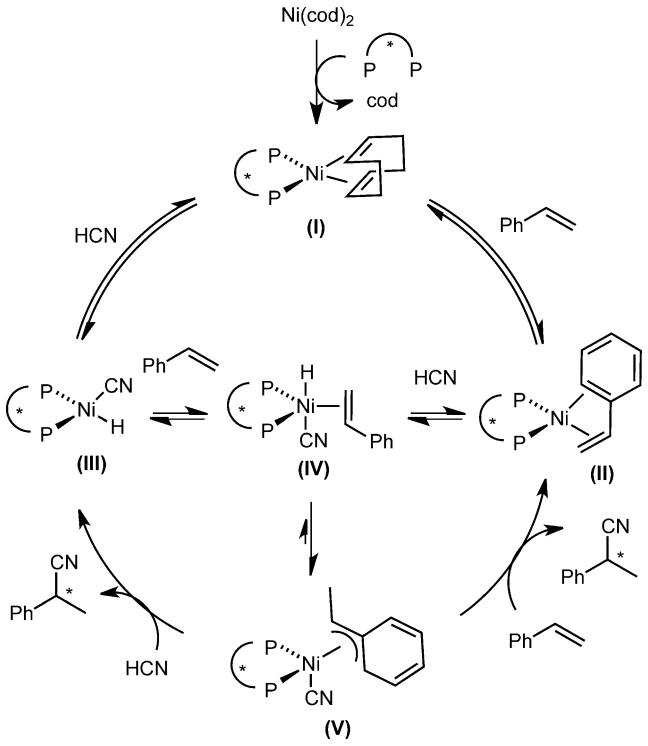


Figure 1. Molecular structure of the catalyst precursor Ni(**3**)(cod) in the crystal. Displacement ellipsoids are displayed at the 50% probability level. All hydrogen atoms and THF molecules in the crystal are omitted for clarity. Selected bond lengths (Å) and angles (deg) with standard uncertainties given in parentheses: Ni–P(1) = 2.0766(17), Ni–P(2) = 2.1265(18), Ni–C(1) = 2.081(7), Ni–C(2) = 2.092(7), Ni–C(5) = 2.074(6), Ni–C(6) = 2.101(7), P(1)–Ni–P(2) = 91.98(7).



Scheme 2. Proposed catalytic cycle for the hydrocyanation of styrene.[5]

We were also able to follow the conversion of deuterated styrene-d_8 by ^2D NMR (Figure 2). The comparison of the spectra of the free substrate (trace 1) compared to the one after addition of the catalyst (trace 2) proves the existence of a complex like (**II**), where the starting material is coordinated to the Ni center. After the addition of HCN we recorded the product spectrum (trace 3). Notably, no deuterium scrambling occurred, which suggests that formation of the intermediate allyl-complex (**V**) is irreversible or at least reversible to a very low extent.

To conclude, we could show that the previously used TMSCN/MeOH mixture can easily be replaced with HCN, which even improves the reaction out-

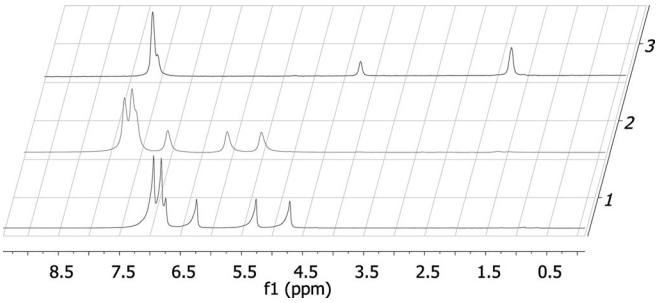


Figure 2. ^{2}D NMR spectra (61.42 MHz, THF) of free styrene-d_8 (trace 1), coordinated styrene-d_8 (trace 2) and the hydrocyanation product (trace 3).

come. Applying this methodology, the substrate scope of this important reaction could be significantly broadened and the catalyst performance was considerably improved. NMR and X-ray analyses revealed insights into the mechanism and origin of selectivity of the reaction. Further studies towards the application of the hydrocyanation reaction in natural product synthesis are currently under way.

Experimental Section

General Procedure for the Ni-Catalyzed Enantioselective Hydrocyanation with HCN

A Schlenk flask was charged with $Ni(cod)_2$ (3.4 mg, 0.0125 mmol, 0.05 equiv.), ligand (11.6 mg, 0.0125 mmol) and toluene (0.25 mL). The mixture was stirred for 5 min at room temperature and the toluene was removed under vacuum directly on the Schlenk line to yield the air-sensitive catalytically active complex. To this were added THF (2.0 mL) and the corresponding substrate (0.25 mmol, 1.0 equiv.). HCN (10.1 mg, 0.015 mL, 0.375 mmol, 1.5 equiv.) was dissolved in THF (3.0 mL) and immediately added to the substrate-containing mixture over a 2 h period by means of a syringe pump at room temperature. After completion of the addition, argon was bubbled through the reaction mixture for 10 min to remove traces of HCN. The solvents were removed under reduced pressure and the residue was submitted to column chromatography to yield the pure nitriles.

CAUTION! Hydrogen cyanide is very volatile and highly toxic. Distilled HCN is prone to very exothermic oligomerization when heated and should be stored at temperatures well below its melting point. Sensible precautions include working in a well ventilated fume hood equipped with HCN sensors (inside and outside the fume hood), and proper first aid cyanide kit and procedures should be in place. Excess HCN may be disposed by addition to aqueous sodium hypochlorite (which converts it to cyanate).

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie (doctoral stipend to A.F.) and by SusChemSys, a programme of the state of North Rhine-Westphalia, Germany, co-financed by the European Union through ERDF funds.

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[10] Lipodex E, 25 m × 0.25 mm capillary column, Macherey–Nagel.

[11] a) J. Wilting, C. Müller, A. C. Hewat, D. D. Ellis, D. M. Tooke, A. L. Spek, D. Vogt, *Organometallics* **2005**, *24*, 13–15; b) J. Wilting, M. Janssen, C. Müller, D. Vogt, *J. Am. Chem. Soc.* **2006**, *128*, 11374–11375.

[12] CCDC 1417330 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

