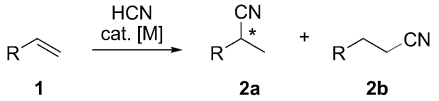
Hydrocyanation

DOI: 10.1002/anie.201208082

Enantioselective Nickel-Catalyzed Hydrocyanation of Vinylarenes Using Chiral Phosphine–Phosphite Ligands and TMS-CN as a Source of HCN**

*Anna Falk, Anna-Lena Göderz, and Hans-Günther Schmalz**

The transition-metal-catalyzed hydrocyanation of alkenes (Scheme 1) represents a highly attractive synthetic method from both an industrial and an academic point of view.[1]

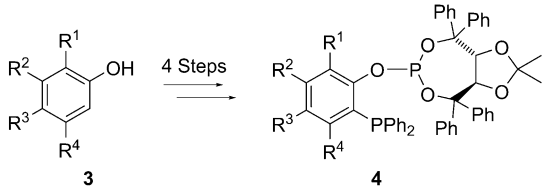


Scheme 1. Hydrocyanation of alkenes.

Starting from simple olefins (**1**) and HCN, this reaction offers a fully atom-economical access to nitriles (**2a** and **2b**), which are of value as polymer building blocks and intermediates for the synthesis of pharmaceuticals and other functionalized compounds (such as amines, carboxylic acid derivatives, aldehydes, ketones, N-heterocycles).[2] The by far most prominent application is the production of adiponitrile from 1,3-butadiene (> 1 000 000 tons per year) which exploits two Ni-catalyzed hydrocyanation steps (homogeneous catalysis).[3] Remarkably, there are almost no examples for the application of alkene hydrocyanation in the multistep synthesis of more complex organic compounds.

As Scheme 1 illustrates, the hydrocyanation of a terminal alkene (**1**) leads either to the (chiral) branched Markovnikov product **2a** or to the linear product **2b**. The general possibility to perform such transformations enantioselectively in the presence of a chiral ligand was first demonstrated by Elmes and Jackson in the Pd-catalyzed hydrocyanation of norbornene (30% *ee*).[4] Since then, only few reports on asymmetric hydrocyanation have appeared.[5–9] In 1992 RajanBabu and Casalnuovo succeeded in applying the Ni-catalyzed hydrocyanation of vinylarenes (**1**, R = aryl) in the synthesis of branched products of type **2a**.[6a] After intense optimization, these authors achieved the hydrocyanation of 2-methoxy-6-vinyl-naphthalene (MVN) with high enantioselectivity (95% *ee*) employing a carbohydrate-derived diphosphonite ligand;[6c] however, all other substrates only gave rise to much lower selectivities (< 60% *ee*). Vogt and co-workers tested (and optimized) chiral Xantphos-derived diphosphites for the asymmetric Ni-catalyzed hydrocyanation of vinylarenes and obtained moderate enantioselectivities (with 80% *ee* for MVN as the best substrate by far). Noteworthy, the selectivities reported for styrene as the parent substrate never exceeded 65% *ee*.[8,9] In a more recent paper, RajanBabu and co-workers also reported the hydrocyanation of aryl-1,3-dienes (up to 78% *ee*).[10] Thus, the search for reliable protocols for asymmetric hydrocyanation, which could be applied also in the context of complex-molecule total synthesis, still represents a challenging research task. We here disclose the results of a study which has led to the identification of a superior chiral ligand and the development of a practical procedure for the Ni-catalyzed hydrocyanation of various vinylarenes with high enantioselectivity (up to 97% *ee*).

Our investigation was triggered by the consideration that Taddol-derived phosphine–phosphites of type **4** might be suitable ligands for the Ni-catalyzed asymmetric hydrocyanation, because bidentate P,P ligands with a rather large bite angle promote reductive elimination.[1a] These ligands, which are accessible from the corresponding phenolic precursors (**3**) in only four steps (Scheme 2),[11] had proven their value in several other metal-catalyzed reactions,[12] and their modular nature allows a facile structural fine-tuning for individual applications.



Scheme 2. Modular phosphine–phosphite ligands of type **4**.

In a first series of experiments we tested eight of our ligands (**4a–h**) in the hydrocyanation of styrene (**5**) under standard conditions (THF, [Ni(cod)$_2$], 70 °C, 20 h) employing acetone cyanohydrin as an in situ source of HCN.[13] We were happy to find that our ligands indeed performed very well and we obtained only the branched product **6** with a respectable (at this time unsurpassed) selectivity of up to 68% *ee*

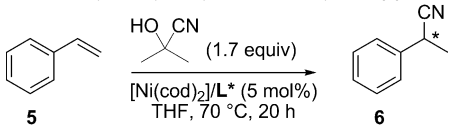
[*] Dipl.-Chem. A. Falk, B. Sc. A.-L. Göderz, Prof. Dr. H.-G. Schmalz
Department für Chemie, Universität zu Köln
Greinstrasse 4, 50939 Köln (Germany)
E-mail: schmalz@uni-koeln.de
Homepage: http://www.schmalz.uni-koeln.de

[**] This work was supported by the Fonds der Chemischen Industrie (doctoral stipend to A.F.). It was performed within the context of "SusChemSys", a program of the State of North Rhine-Westphalia (Germany), co-financed by the European Union through ERDF funds. We also thank Carl Dittmer, Köln, for contributing to the ligand synthesis. TMS = trimethylsilyl.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208082.

(Table 1). Interestingly, the substitution pattern of the ligand backbone had only little effect on the ligand performance (which is in contrast to our previous experiences with this kind of ligand).[12] In this initial screening, ligand **4b** was found to be most selective while **4a** with the bulky *tert*-butyl substituent as R^1 appeared to be most active.

Table 1: Initial screening of some chiral phosphine–phosphite ligands of type **4** in the Ni-catalyzed hydrocyanation of styrene (**5**).[a]



Entry	Ligand	Substitution pattern	*ee* [%][b]
1	**4a**	$R^1 = t$Bu; $R^2 = H$; $R^3 = t$Bu; $R^4 = H$	65
2	**4b**	$R^1 = i$Pr; $R^2 = H$; $R^3 = H$; $R^4 = H$	68
3	**4c**	R^1 = Ph; $R^2 = H$; $R^3 = H$; $R^4 = H$	67
4	**4d**	R^1 = Me; $R^2 = H$; $R^3 = H$; $R^4 = H$	63
5	**4e**	$R^1 = i$Pr; $R^2 = H$; $R^3 = H$; R^4 = Me	56
6	**4f**	$R^1 = t$Bu; $R^2 = H$; $R^3 = H$; $R^4 = H$	64
7	**4g**	R^1 = Me; $R^2 = H$; $R^3 = H$; R^4 = Me	56
8	**4h**	R^1 = Me; R^2 = Me; $R^3 = H$; $R^4 = H$	65

[a] Conditions: styrene (1 equiv), 5 mol% of preformed catalyst ([Ni(cod)$_2$]/L* 1:1), acetone cyanohydrin (1.7 equiv), THF, 70°C, 20 h. [b] Determined by GC-FID on a chiral stationary phase.

Employing ligands **4a** and **4b**, we next investigated the effect of the catalyst loading and the solvent on the reaction outcome (Table 2). We found that the amount of catalyst (preformed in toluene) only influenced the conversion rate while the selectivity was little affected (Table 2, entries 1–3). Using 5 mol% of catalyst we then screened a variety of (anhydrous) solvents. While the enantioselectivities remained almost unchanged, only the reactions in toluene and MeOH gave full conversions after 20 h (Table 2, entries 4, 7, 9, and 10).

Table 2: Ni-catalyzed hydrocyanation of styrene (**5**) to **6**: variation of catalyst amount and solvent.[a]

Entry	Ligand (L*)	Cat. loading [mol%]	Solvent	Conv. [%][b]	*ee* [%][b]
1	**4a**	2	THF	25	62
2	**4a**	5	THF	57	64
3	**4a**	10	THF	88	65
4	**4a**	5	toluene	100	60
5	**4a**	5	*n*-hexane	43	60
6	**4a**	5	DMSO	86	52
7	**4a**	5	MeOH	100	60
8	**4b**	5	THF	38	68
9	**4b**	5	toluene	95	63
10	**4b**	5	MeOH	100	64

[a] Conditions: styrene (1 equiv), preformed catalyst ([Ni(cod)$_2$]/L* 1:1), acetone cyanohydrin (1.7 equiv), 70°C, 20 h. [b] Determined by GC-FID on a chiral stationary phase (*n*-dodecane as internal standard).

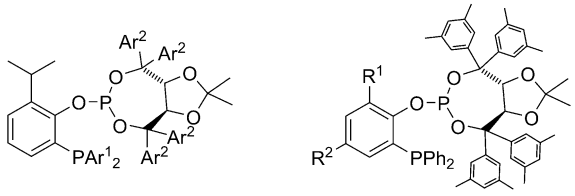
Having identified MeOH as a promising solvent, we examined the influence of the temperature. As Table 3 indicates, high conversions could be achieved within only 1 h even at room temperature using ligand **4a** (Table 3, entry 2). The yield of the isolated pure nitrile **6** (61% *ee*) was 94% in this case (1 mmol scale). Slightly improved enantioselectivities were observed at lower temperatures, however, at the expense of the reaction rate. The best selectivity (69% *ee*) combined with a satisfying conversion was observed for ligand **4b** at room temperature (Table 3, entry 6).

Table 3: Temperature effect on the Ni-catalyzed hydrocyanation of styrene using acetone cyanohydrin in MeOH.[a]

Entry	Ligand	*T* [°C]	*t* [h]	Conv. [%][b]	*ee* [%][b]
1	**4a**	70	1	100	60
2	**4a**	RT	1	100[c]	61
3	**4a**	0	17	31	64
4	**4a**	−10	17	1	66
5	**4b**	70	1	100	64
6	**4b**	RT	20	65	69

[a] Conditions: styrene, 5 mol% preformed catalyst ([Ni(cod)$_2$]/L* 1:1), 1.7 equiv acetone cyanohydrin, MeOH. [b] Determined by GC-FID on a chiral stationary phase. [c] Yield of the isolated product: 94%.

While we had obtained high conversions under mild conditions, the enantioselectivities (using ligands **4a** and **4b**, respectively) were still not satisfying. Thus, we decided to vary the ligand structure. For this purpose, we applied our modular synthetic scheme[11a,12e] to prepare a set of eight additional phosphine–phosphite ligands (**7a–d**, **8a–d**; Figure 1). Because the backbone substituent(s) had little impact on the selectivities (compare Table 1) we focused on the variation of the aryl substituents (Ar^2) at the Taddol unit.



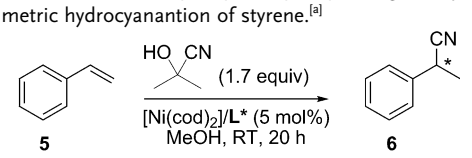
7a: Ar^1 = 4-MeOC$_6$H$_4$, Ar^2 = Ph
7b: Ar^1 = Ph, Ar^2 = 2-naphthyl
7c: Ar^1 = Ph, Ar^2 = 3,5-(CF$_3$)$_2$C$_6$H$_3$
7d: Ar^1 = Ph, Ar^2 = C$_6$F$_5$

8a: $R^1 = i$Pr, R^2 = H
8b: R^1 = Et, R^2 = H
8c: R^1 = Ph, R^2 = H
8d: $R^1 = t$Bu, $R^2 = t$Bu

Figure 1. A second set of phosphine–phosphite ligands tested.

Testing these ligands in the Ni-catalyzed hydrocyanation of styrene revealed that the structural modification of the Taddol unit indeed led to dramatic changes in the outcome of the reactions. Ligands **7c** and **8a** gave very good enantioselectivities (up to 82% *ee*) with the non-fluorinated ligand **8a** being much more active (Table 4, entries 3 and 5). Apparently the steric effect of the additional substituents in *meta* position of the Taddol aryl units is important for the superior performance of ligands **7c** and **8a**. Again, variation of the backbone substituent R^1 (ligands **8b–8d**) had little impact on the selectivities; only ligand **8d** with a bulky *tert*-butyl group in this position was significantly less selective and active. We therefore used ligand **8a** for the final optimization.

Table 4: Performance of new phosphine–phosphite ligands (Figure 1) in the asymmetric hydrocyanantion of styrene.[a]



Entry	Ligand (L*)	Conv. [%][b]	*ee* [%][b]
1	**7a**	22	64
2	**7b**	43	69
3	**7c**	8	82
4	**7d**	0	n.d.
5	**8a**	100	81
6	**8b**	73	81
7	**8c**	86	81
8	**8d**	14	74

[a] Conditions: styrene (1 equiv), 5 mol% of preformed catalyst ([Ni(cod)$_2$]/L* 1:1), acetone cyanohydrin (1.7 equiv), MeOH, RT, 20 h. [b] Determined by GC-FID on a chiral stationary phase.

Using **4b** as a reference and **8a** as the most promising ligand, we finally investigated the source of HCN as a reaction parameter we had not yet addressed. While industry does not hesitate to use HCN on a larger scale, our goal was to employ safe reagents that are easy to handle in a normal laboratory. In the experiments described above we used acetone cyanohydrin (added in one portion), which disintegrates during the reaction to form HCN and acetone. As an alternative, we envisioned that commercially available trimethylsilyl cyanide (TMS-CN) in the presence of a protic solvent such as MeOH could serve to generate HCN in situ in a controllable fashion.[14] To test this, we diluted TMS-CN with toluene and added it by means of a syringe pump to a solution of styrene and catalyst ([Ni(cod)$_2$]/**4b**) in MeOH at 20 °C. As the results shown in Table 5 (entries 1–3) indicate, product **6** was reliably formed with an enantioselectivity of 69% *ee* while the conversion of styrene was highly dependent on the addition time. Interestingly, too slow addition leads to a breakdown of the conversion, which indicates that the catalyst dies in the absence of enough fresh HCN. On the other hand, it is known that higher HCN concentrations have to be avoided to prevent the formation of catalytically inactive [NiL*CN$_2$] complexes.[3b,6b,15] Full conversion was achieved when the TMS-CN solution was added over a period of 5 h (Table 5, entry 3).[16]

Table 5: Enantioselective hydrocyanation of styrene using TMS-CN in the presence of MeOH as a source of HCN.[a]

Entry	Solvent	Addition time [h]	*T* [°C]	Ligand (L*)	Conv. [%][b]	*ee* [%][b]
1	MeOH	20	20	**4b**	2	69
2	MeOH	10	20	**4b**	27	69
3	MeOH	5	20	**4b**	100	69
4	THF	2	20	**8a**	100	86
5	THF	2	0	**8a**	65	89
6	THF	2	−20	**8a**	14	91

[a] Conditions: styrene, 5 mol% of preformed catalyst ([Ni(cod)$_2$]/L* 1:1), slow addition of TMS-CN (1.5 equiv) either as a 0.25 M solution in toluene (entries 1–3) or in THF/MeOH (14:1; entries 4–6). [b] Determined by GC-FID on a chiral stationary phase.

Using ligand **8a** we finally succeeded in achieving the hydrocyanation of styrene with 86% *ee* at full conversion (Table 5, entry 4). The key to this success was to switch back to THF as a solvent (which had furnished slightly better *ee* values in the initial screening, see Table 3) and to slowly add a solution of TMS-CN in THF/MeOH (which actually represents a dilute solution of HCN in THF).[17] A THF/MeOH ratio of 14:1 and an initial TMS-CN concentration of 0.125 M proved to be optimal for achieving high conversion (at a catalyst concentration of 0.006 M). The ideal addition time was 2 h at room temperature. At lower temperatures even somewhat higher enantioselectivities were obtained, however, with incomplete conversion (Table 5, entries 4–6).

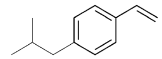
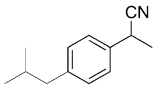
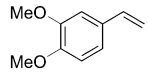
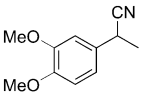
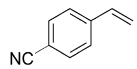
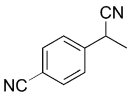
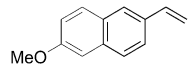
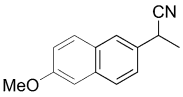
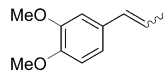
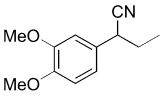
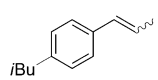
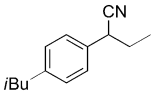
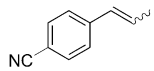
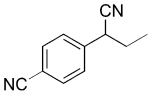
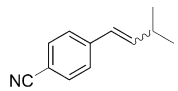
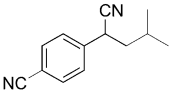
The applicability of the developed standard protocol was then probed by employing various substituted arylalkenes (Table 6). Much to our delight, good conversions and high to excellent enantioselectivities (up to 97% *ee*) were obtained in almost all cases. Electron-withdrawing and electron-donating substituents were tolerated, and even styrenes with a β substituent could be reacted (Table 6, entries 8–11).[18] All reactions proceeded very cleanly and with complete regioselectivity within the analytical limits (GC, NMR).

To demonstrate the preparative usefulness of the developed methodology we applied it in a gram-scale synthesis of the nitrile **10**, which is a precursor of the antiinflammatory drug Ibuprofen (**11**) (Scheme 3). We employed 1 g of substrate **9**[19] and the Ni-catalyzed hydrocyanation proceeded smoothly under the established conditions (with ligand **8a**) to afford pure **10** in quantitative yield with an enantiomeric excess of 92%. No traces of the linear regioisomer (of type **2b**) could be detected by GC or NMR analysis.

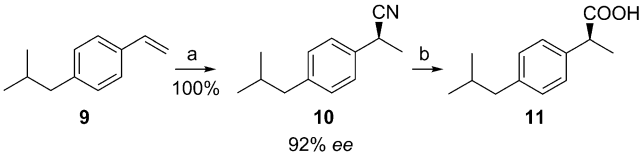
To determine the absolute configuration, a sample of **10** was hydrolyzed by treatment with a 3:3:1 mixture of sulfuric acid, acetic acid, and water at 120 °C. The resulting product showed a positive optical rotation and thus proved to be (*S*)-(+)-Ibuprofen (**11**). Consequently, the absolute configuration of nitrile **10** (and probably also the other structurally related hydrocyanation products obtained with ligand **8a**) could be assigned as *S*. Noteworthy, the $[\alpha]_D$ value of **11** corresponded to an enantiomeric purity of only 30% *ee* which indicates partial racemization under the harsh conditions of the nitrile hydrolysis.[20] Nevertheless, we would like to point out that the nitrile **10** (92% *ee*) should be converted efficiently into enantiomerically pure (*S*)-(+)-Ibuprofen (**11**) with the help of a suitable nitrilase (completion of the enantioselectivity through kinetic resolution or recrystallization).[21]

To conclude, we have devised a practical protocol for the asymmetric Ni-catalyzed hydrocyanation of vinylarenes. Using styrene (**5**), a hitherto "difficult" substrate, we succeeded in identifying the modular phosphine–phosphite **8a** as a tailored chiral ligand, which is available in both enantiomeric forms. We also showed that the handling of toxic HCN can be circumvented by employing TMS-CN as a safe reagent in the presence of MeOH. The developed method opens a reliable and scalable access to a broad spectrum of chiral nitriles with high levels of enantioselectivity. We are optimistic that these results form a valid basis for the future

Table 6: Enantioselective hydrocyanation of various arylalkenes under the optimized conditions using ligand **8a**.[a]

Entry	Substrate	Product	Conv. [%][b]	*ee* [%][b]
1			100	86
2			100	92
3			100	89
4			90	91
5			100	80
6			73	97
7			34	90
8[c]			15	81
9[d]			28	84
10[e]			83	83
11[f]			70	67

[a] Conditions: substrate, 5 mol% of preformed catalyst ([Ni(cod)$_2$]/**8a** 1:1) in THF, slow addition (2 h) of TMS-CN (1.5 equiv) in THF/MeOH (14:1; 0.125 M), RT. [b] Determined by GC-FID on a chiral stationary phase. [c] *E*/*Z* ratio (4:1). [d] *E*/*Z* ratio (1.4:1). [e] *E*/*Z* ratio (1:2.5). [f] *E*/*Z* ratio (1:4).



Scheme 3. Gram-scale synthesis of nitrile **10** and its conversion to (*S*)-(+)-Ibuprofen. Conditions: a) 5 mol% of the preformed catalyst ([Ni(cod)$_2$]/**8a** 1:1), THF, RT, slow addition (2 h) of TMS-CN (1.5 equiv) in THF/MeOH (14:1, 0.125 M); b) H_2SO_4/AcOH/H_2O (3:3:1), 120 °C.

application of asymmetric hydrocyanation reactions in multi-step syntheses of complex molecules in both industry and academia.

Experimental Section

Enantioselective hydrocyanation of 4-isobutylstyrene: Synthesis of (*S*)-(−)-2-(4-isobutylphenyl)propanenitrile (**10**): A round-bottomed Schlenk flask was charged with ligand **8a** (289.3 mg, 0.312 mmol, 0.05 equiv), [Ni(cod)$_2$] (85.8 mg, 0.312 mmol, 0.05 equiv), and toluene (6.2 mL). The mixture was stirred for 5 min and the solvent was removed on the Schlenk vacuum line. The residue was dried in vacuo for 20 min before it was re-dissolved in THF (52.0 mL), and 1-isobutyl-4-vinylbenzene (1.0 g, 6.24 mmol, 1.0 equiv) was added. A separate Schlenk flask was charged with THF (69.9 mL), MeOH (5.0 mL), and TMS-CN (1.17 mL, 9.36 mmol, 1.5 equiv) and the resulting solution was then slowly transferred to the stirred catalyst/substrate solution by means of a syringe pump over 2 h. When the addition was finished, the solvent was removed under reduced pressure. (**Caution**: This operation must be performed in a fume hood.) The residue was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 20:1) to afford product **10** (1.17 g, 6.24 mmol, 100%) as a colorless liquid. $[\alpha]_{589}^{20} = -16.4°$, $[\alpha]_{546}^{20} = -20.5°$, $[\alpha]_{405}^{20} = -43.1°$, $[\alpha]_{365}^{20} = -60.5°$ ($c = 0.5$ in $CHCl_3$). Further analytical data are given in the Supporting Information.

Received: October 8, 2012
Published online: December 20, 2012

Keywords: asymmetric catalysis · nickel · nitriles · phoshite ligands · trimethylsilyl cyanide

[1] a) "Hydrocyantion of Alkenes and Alkynes": T. V. RajanBabu, *Org. React.* **2011**, *75*, 1–73; b) L. Bini, C. Müller, D. Vogt, *Chem. Commun.* **2010**, *46*, 8325–8334; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; d) W. A. Nugent, T. V. RajanBabu, M. J. Burk, *Science* **1993**, *259*, 479–483.

[2] a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *Med. Chem.* **2010**, *53*, 7902–7917; b) M. B. Smith, J. March, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed., Wiley-Interscience, Hoboken, **2007**.

[3] a) C. A. Tolman, *J. Chem. Educ.* **1986**, *63*, 199; b) C. A. Tolman, R. J. McKinney, W. C. Seidel, J. D. Druliner, W. R. Stevens, *Adv. Catal.* **1985**, *33*, 1.

[4] P. S. Elmes, W. R. Jackson, *J. Am. Chem. Soc.* **1979**, *101*, 6128–6129.

[5] a) M. Hodgson, D. Parker, *J. Organomet. Chem.* **1987**, *325*, C27–C30; b) M. Hodgson, D. Parker, R. J. Taylor, G. Ferguson, *Organometallics* **1988**, *7*, 1761–1766.

[6] a) T. V. RajanBabu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1992**, *114*, 6265–6266; b) A. L. Casalnuovo, T. V. RajanBabu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882; c) T. V. RajanBabu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1996**, *118*, 6325–6326.

[7] a) M. J. Baker, P. G. Pringle, *J. Chem. Soc. Chem. Commun.* **1991**, 1292–1293; b) T. Horiuchi, E. Shirakawa, K. Nozaki, H. Takaya, *Tetrahedron: Asymmetry* **1997**, *8*, 57–63.

[8] M. Yan, Q.-Y. Xu, A. S. C. Chan, *Tetrahedron: Asymmetry* **2000**, *11*, 845–849.

[9] a) W. Goertz, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Chem. Eur. J.* **2001**, *7*, 1614–1618; b) J. Wilting, M. Janssen, C. Müller, D. Vogt, *J. Am. Chem. Soc.* **2006**, *128*, 11374–11375; c) J. Wilting, M. Janssen, C. Müller, M. Lutz, A. L. Spek, D. Vogt, *Adv. Synth. Catal.* **2007**, *349*, 350–356; d) L. Bini, C. Müller, D. Vogt, *ChemCatChem* **2010**, *2*, 590–608.

[10] B. Saha, T. V. RajanBabu, *Org Lett.* **2006**, *8*, 4657–4659.

[11] a) J. Velder, T. Robert, I. Weidner, J.-M. Neudörfl, J. Lex, H.-G. Schmalz, *Adv. Synth. Catal.* **2008**, *350*, 1309–1315; b) F. Blume,

S. Zemolka, T. Fey, R. Kranich, H.-G. Schmalz, *Adv. Synth. Catal.* **2002**, *344*, 868 – 883.

[12] a) S. Werle, T. Fey, J.-M. Neudörfl, H.-G. Schmalz, *Org. Lett.* **2007**, *9*, 3555 – 3558; b) T. Robert, J. Velder, H.-G. Schmalz, *Angew. Chem.* **2008**, *120*, 7832 – 7835; *Angew. Chem. Int. Ed.* **2008**, *47*, 7718 – 7721; c) W. Lölsberg, S. Ye, H.-G. Schmalz, *Adv. Synth. Catal.* **2010**, *352*, 2020 – 2031; d) T. Robert, Z. Abiri, J. Wassenaar, A. J. Sandee, S. Romanski, J.-M. Neudörfl, H.-G. Schmalz, J. N. H. Reek, *Organometallics* **2010**, *29*, 478 – 483; e) T. Robert, Z. Abiri, A. J. Sandee, H.-G. Schmalz, J. N. H. Reek, *Tetrahedron: Asymmetry* **2010**, *21*, 2671 – 2674; f) Q. Naeemi, T. Robert, D. P. Kranz, J. Velder, H.-G. Schmalz, *Tetrahedron: Asymmetry* **2011**, *22*, 887 – 892; g) A. Falk, L. Fiebig, J.-M. Neudörfl, A. Adler, H.-G. Schmalz, *Adv. Synth. Catal.* **2011**, *353*, 3357 – 3362.

[13] For the use of acetone cyanohydrin as a source of HCN in hydrocyanation reactions, see ref. [8]; see also M. de Greef, B. Breit, *Angew. Chem.* **2009**, *121*, 559 – 562; *Angew. Chem. Int. Ed.* **2009**, *48*, 551 – 554.

[14] To the best of our knowledge, TMS-CN has never been used as a HCN source in the metal-catalyzed hydrocyanation of alkenes; for an application in the Pd-catalyzed silylcyanation of alkynes, see a) N. Chatani, T. Hanafusa, *J. Chem. Soc. Chem. Commun.* **1985**, 838 – 839; b) N. Chatani, T. Takeyasu, N. Horiuchi, T. Hanafusa, *J. Org. Chem.* **1988**, *53*, 3539 – 3548; see also c) S. Arai, T. Sato, Y. Koike, M. Hayashi, A. Nishida, *Angew. Chem.* **2009**, *121*, 4598 – 4601; *Angew. Chem. Int. Ed.* **2009**, *48*, 4528 – 4531; for the in situ generation of HCN from TMS-CN/MeOH in the hydrocyanation of hydrazones, see: d) J. M. Keith, E. N. Jacobsen, *Org. Lett.* **2004**, *6*, 153 – 155.

[15] Addition of pure TMS-CN in one portion to substrate and catalyst in MeOH, toluene, THF, or mixtures of these led to conversions of less than 3%.

[16] This method was also used to synthesize racemic reference samples of various nitrile products (Table 6). See the Supporting Information for details.

[17] When the substrate and the catalyst were dissolved in THF/MeOH (14:1) and TMS-CN was added as a diluted solution in pure THF, a selectivity of 81% *ee* was observed, which is the same as that found for the reaction in pure MeOH.

[18] The fact that only the *E* isomer of the starting alkenes was detected (incomplete conversion) indicates that the *Z* isomers have significantly higher reactivity.

[19] Compound **9** was prepared from the corresponding aldehyde through Wittig olefination (see the Supporting Information for details).

[20] H. Kakeya, N. Sakai, T. Sugai, H. Ohta, *Tetrahedron Lett.* **1991**, *32*, 1343 – 1346.

[21] R. Kourist, P. Domínguez de María, K. Miyamoto, *Green Chem.* **2011**, *13*, 2607 – 2618.

