Homogeneous Catalysis

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Self-Assembled Bidentate Ligands for the Nickel-Catalyzed Hydrocyanation of Alkenes**

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Nitriles[1] are versatile intermediates in organic synthesis as they can be transformed into a wide variety of useful compounds, such as amines, aldehydes, ketones, and a range of carboxylic acid derivatives. A particularly appealing method for their synthesis consists of the formal addition of HCN across a C=C double bond,[2] commonly referred to as hydrocyanation. Although the reaction is most commonly catalyzed by catalysts incorporating (bidentate) phosphite or phosphinite ligands, the use of bidentate phosphine ligands has attracted considerable interest.[3–8] Van Leeuwen and co-workers showed that bidentate ligands with bite angles of approximately 105° have a beneficial effect on the activity of catalysts for the hydrocyanation of terminal alkenes.[9] The same research group was able to demonstrate that the use of electron-deficient ligands also leads to increased activity.[5] However, catalytic hydrocyanation remains underdeveloped and most of the research in the area has focused on the DuPont adiponitrile process.[10] In order to transform hydrocyanation into a synthetically useful reaction, it is of prime importance to develop more efficient catalyst systems.

We recently introduced the concept of self-assembly of bidentate ligands for combinatorial homogeneous catalysis.[11] Self-assembly of two complementary species through hydrogen bonding is a widely occurring phenomenon in nature, as exemplified by DNA base pairing between adenine (A) and thymine (T; (Scheme 1).[12]

Beyond the benefit of simplified ligand synthesis, the potential of our strategy lies in the possibility for the generation of combinatorial libraries of bidentate ligands through the simple mixing of suitably functionalized monodentate precursors.[13] This approach allowed us to identify uniquely active and selective catalysts for hydroformylation,[14] anti-Markovnikov hydration of terminal alkynes,[15] and asymmetric hydrogenation[16] and hydration of nitriles.[17] Interestingly, with bite angles close to 105° and being relatively electron poor, our self-assembled bidentate ligands display all of the features that seem to favor nickel-catalyzed hydrocyanation.

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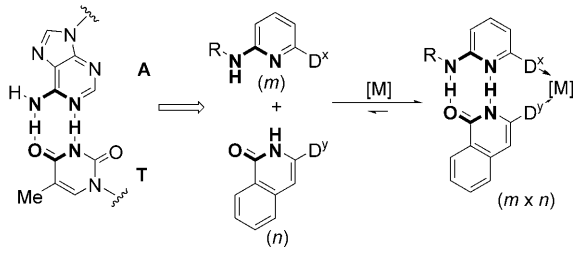
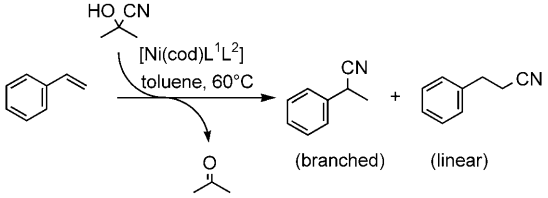


Scheme 1. Self-assembly through hydrogen bonding of the adenine–thymine and aminopyridine–isoquinolone systems. *m* and *n* represent the number of library components. D = donor atom.

In order to explore whether the heterodimeric chelate bonding mode operates under hydrocyanation conditions, the activity of [(cod)Ni(3-dpicon)(6-dppap)] (cod = cyclooctadiene) in the hydrocyanation of styrene with acetone cyanohydrin was compared to the activities of similar Ni^0 complexes that contain other combinations of mono- and bidentate ligands (Table 1).

Nickel(0) complexes that incorporate two equivalents of either 3-dpicon (Table 1, entry 10), or 6-dppap (entry 11) were barely active and gave yields comparable to those

Table 1: Nickel-catalyzed hydrocyanation of styrene.[a]



Entry			Additive	b [%][b]	l [%][b]
1	–	–	–	–[c]	–[c]
2	PPh_3	PPh_3	–	7	–[c]
3	$P(OPh)_3$	$P(OPh)_3$	–	14	1
4	dppe	–	–	1	–[c]
5	xantphos	–	–	88	1
6	dpephos	–	–	92	3
7[d]	dpephos	–	AcOH	89	6
8	3-dpicon	6-dppap	–	87	3
9	3-dpicon	6-dppap	AcOH	49	1
10	3-dpicon	3-dpicon	–	7	1
11	6-dppap	6-dppap	–	7	–[c]

[a] Reaction conditions: styrene/acetone cyanohydrin/$[Ni(cod)_2]/L^1/L^2$ = 1:1.25:0.05:0.05:0.05 in toluene (2 mL) for 20 h at 60 °C. [b] GC yield. [c] No reaction product detected. [d] The reaction was carried out 45 °C. Dppe = 1,2-bis(diphenylphosphino)ethane, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dpephos = bis(2-diphenylphosphinophenyl)ether, 3-dpicon = 3-diphenylphosphinoisoquinolone, 6-dppap = 6-diphenylphosphino-*N*-pivaloyl-2-aminopyridine.

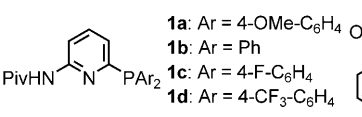
observed for other monodentate ligands such as PPh_3 (entry 2) and $P(OPh)_3$ (entry 3). However, upon mixing of equimolar amounts of $[Ni(cod)_2]$, 3-dpicon, and 6-dppap, a highly active hydrocyanation catalyst was obtained (Table 1, entry 8). The total yield of hydrocyanation products was as high as 90% and the branched reaction product was obtained as the major isomer (b:l = 97:3). This result strongly supports the assumption that the heterodimeric 3-dpicon/6-dppap ligand system acts like a bidentate ligand that is held together by a hydrogen-bonding network. Further evidence came from the observation that the heterodimeric 3-dpicon/6-dppap platform proved less efficient as a ligand system when the polarity of the reaction medium was increased (entry 9). This result may be related to the fact that hydrogen-bond formation becomes problematic under these conditions. As a consequence, the ligand system loses part of its bidentate character and displays catalytic activity comparable to that of systems made up of monodentate ligands. Under similar conditions, the activity of [(cod)Ni(dpephos)] remained unchanged (entry 7).

Ligand geometry is another important parameter in determining catalyst performance and deviations from the ideal geometry may lead to considerable loss of activity and/or selectivity. For example, Ni^0 complexes that incorporate a bidentate ligand with a small bite angle such as dppe (Table 1, entry 4) showed no catalytic activity. On the other hand, the use of xantphos (Table 1, entry 5) or dpephos (entry 6) gave rise to catalyst systems displaying activities and selectivities comparable to those observed for our heterodimeric 3-dpicon/6-dppap system. When the reaction was run without phosphorus-containing ligands (Table 1, entry 1) or in the absence of any metal source, hydrocyanation did not occur at all.

In order to obtain more information on the catalyst structure, a solution of $[Ni(cod)_2]$, 3-dpicon, and 6-dppap in degassed C_6D_6 was analyzed by NMR spectroscopy. The ^{31}P NMR spectrum of the solution featured doublets at $\delta =$ 36.0 ppm and at $\delta = 40.5$ ppm with a $^2J_{P-P}$-coupling constant of 3.3 Hz and confirmed the presence of two nonequivalent phosphine ligands coordinated to the same metal center. Additionally, ^1H NMR spectra showed a substantial shift of the NH signals of the 6-dppap and 3-dpicon ligands to low field after addition of $[Ni(cod)_2]$. These observations provide strong evidence for the expected heterodimeric chelate formation through a hydrogen-bonding network similar to Watson–Crick base pairing of adenine and thymine in DNA.

The next logical step involved the generation of a library of self-assembled bidentate ligand systems analogous to the 3-dpicon/6-dppap system in order to probe the influence of electronic effects on activity, selectivity, and stability of the ligands. It was in this step that our methodology was used to its full potential as a tool for the combinatorial synthesis of a library of bidentate ligands. From five phosphinoisoquinolone and four aminopyridyl phosphine ligands, a set of 20 bidentate ligand combinations was generated by simply mixing the components and $[Ni(cod)_2]$ in toluene. The resulting catalysts were explored with respect to their potential to catalyze the hydrocyanation of styrene with acetone cyanohydrin (Table 2). The ligands are represented in such a manner that

Table 2: Ligand matrix (5×4) of aminopyridine- or isoquinolone-derived self-assembled bidentate ligands in the nickel-catalyzed hydrocyanation of styrene.[a]



	1a	1b	1c	1d
2a	96%[b] (97:3)[c]	95% (97:3)	96% (96:4)	93% (95:5)
2b	97% (97:3)	90% (97:3)	94% (96:4)	89% (96:4)
2c	90% (96:4)	79% (95:5)	85% (95:5)	78% (94:6)
2d	62% (95:5)	52% (95:5)	64% (95:5)	55% (95:5)
2e	25% (96:4)	19% (96:4)	21% (96:4)	19% (96:4)

Reaction conditions: styrene/acetone cyanohydrin/$[Ni(cod)_2]/L^1/L^2$ = 1:1.25:0.05:0.05:0.05 in toluene (2 mL) for 20 h at 60°C. [b] Combined GC yield of branched and linear hydrocyanation products. [c] Regioselectivity (branched:linear).

the electron density on the phosphorus atom decreases from the top to the bottom and from the left to the right of the table. The major trends that can be seen in this study are that the catalytic activity decreases down a column and depends more on the nature of the isoquinolone than on the nature of its aminopyridine counterpart. According to the former trend, the most efficient catalysts are expected to be located in the upper (left) part of the table. Indeed, catalysts that incorporate ligands **1a**/**2a**, **1a**/**2b**, **1b**/**2a**, and **1d**/**2a** appeared to be excellent hydrocyanation catalysts and were more active than the parent system **1b**/**2b**. These results are in contrast with those of Van Leeuwen and co-workers, who observed that decreased electron density on the donor atom led to increased activity.[5] This discrepancy may be accounted for by the fact that the isoquinolone ligand is in itself electron deficient. Further decrease of the electron density may lead to a situation in which oxidative addition of HCN to Ni^0 becomes troublesome. In all cases, hydrocyanation occurred with yields greater than 95% and regioselectivities of up to 97:3 in favor of the branched reaction product. When the reaction was carried out at temperatures lower than 60°C, the catalyst-incorporating ligand **1a**/**2a** displayed the best overall performance and was selected for optimization purposes (Table 3).

Table 3: Influence of the reaction conditions on the nickel-catalyzed hydrocyanation of styrene with acetone cyanohydrin, using the **1a**/**2a** platform as a ligand system.[a]

Entry	1a [%]	2a [%]	[Ni] [%]	[Styrene] [mol L^{-1}]	[HCN] [mol L^{-1}]	T [°C]	Yield [%][b,c]
1	5	5	5	0.50	0.63	45	95 (97:3)
2	5	5	5	1.0	1.3	45	99 (95:5)
3	5	5	5	1.0	1.5	35	97 (94:6)
4	10	10	5	1.0	1.5	35	98 (98:2)
5	5	5	2.5	1.0	1.5	35	90 (99:1)

[a] Reactions were run for 20 h in toluene. [b] GC yield. [c] The value in parentheses refers to the observed b:l ratio.

Better results were obtained when the reaction was carried out at a styrene concentration of 1.0 mol L^{-1} instead of 0.50 mol L^{-1}. In this case, the total yield of hydrocyanation products was essentially quantitative (Table 3, entry 2). Furthermore, when the reaction was carried out with 1.5 equivalents instead of 1.3 equivalents of acetone cyanohydrin, the temperature could be lowered to 35 °C without a significant reduction in yield (Table 3, entry 3). Interestingly, at this temperature, the reaction mixture remained homogeneous throughout the reaction. This observation suggested that the catalyst did not decompose during the reaction and could be used in a second reaction cycle. Indeed, in an experiment that used a catalyst with ligand system **1a**/**2a**, the total yield of hydrocyanation products was as high as 97% after two reaction cycles. When a catalyst that incorporated a well-established bidentate ligand such as dpephos was used, the total yield of hydrocyanation products was not higher than 70% after two cycles. This result underlines the exceptional stability of our catalyst. On the other hand, the increase in concentration seemed to have a negative influence on the regioselectivity (Table 3, entry 1 versus entry 2). This issue was addressed by using a twofold excess of both **1a** and **2a** with respect to the metal (Table 3, entry 3 versus entry 4). Furthermore, the yield only slightly diminished when the catalyst load was lowered from 5.0 to 2.5 mol% (Table 3, entry 4 versus entry 5). As before, the reaction mixture remained homogeneous throughout the reaction, which suggested that the catalyst was stable under the reaction conditions. We therefore had good reason to believe that this minor loss of yield could be dealt with by increasing the reaction time. In summary, [Ni(**1a**/**2a**)$_2$] turned out to be capable of catalyzing the hydrocyanation of styrene under mild conditions with excellent yield and regioselectivity and at a catalyst load of 2.5 mol%.

The synthetic scope of [Ni(**1a**/**2a**)$_2$] was subsequently explored. In most cases, reacting 1 equivalent of alkene with 1.5 equivalents of acetone cyanohydrin in the presence of 2.5 mol% of [Ni(**1a**/**2a**)$_2$] for 25 hours in toluene at 35 °C gave the expected hydrocyanation products in high yields (Table 4). In all cases, the reactions proceeded with essentially complete regioselectivity in favor of the branched isomer. Various functional groups, including -OMe (Table 4, entry 1), -OAc (entry 2), -Me (entry 3), -Ph (entry 5), -CO_2Me (entry 6) and -F (entry 7), were tolerated. Interestingly, the hydrocyanation of (*E*)-1-phenylbuta-1,3-diene was also successfully accomplished and led to the exclusive formation of (*E*)-2-methyl-4-phenyl-3-butenenitrile (Table 4, entry 8).

Table 4: Regioselective hydrocyanation of functionalized alkenes with [Ni(**1a**/**2a**)$_2$] as the catalyst.[a]

Entry	Substrate	b:l	Yield [%][b]
1	4-OMe-$C_6H_4CH{=}CH_2$	>99:1	quant.
2	4-OAc-$C_6H_4CH{=}CH_2$	>99:1	quant.[c]
3	4-Me-$C_6H_4CH{=}CH_2$	>99:1	99
4	$C_6H_5CH{=}CH_2$	>99:1	89
5	4-Ph-$C_6H_4CH{=}CH_2$	>99:1	quant.
6	4-CO_2Me- $C_6H_4CH{=}CH_2$	>99:1	quant.
7	4-F-$C_6H_4CH{=}CH_2$	>99:1	quant.
8	(*E*)-1-phenylbuta-1,3-diene	[d]	86

[a] Reaction conditions: styrene/acetone cyanohydrin/[Ni(cod)$_2$]/L^1/L^2 = 1:1.5:0.025:0.05:0.05 in toluene (1 mL) for 25 h at 35 °C. [b] Yield of isolated product. [c] Yield after 40 h. [d] (*E*)-2-methyl-4-phenyl-3-butenenitrile was the only detectable reaction product.

It has been shown for the first time that heterodimeric self-assembled bidentate ligands can form complexes with Ni^0. Such complexes appeared to be promising catalysts for the hydrocyanation of styrene. From a 5×4 library of isoquinolone- or aminopyridine-derived self-assembled bidentate ligands, a catalyst with interesting activity, regioselectivity, and functional group tolerance was identified. Future efforts will focus on the extension of our methodology to enantioselective hydrocyanation.[18–22] Heterodimeric self-assembled bidentate ligands bearing chiral information were recently applied successfully to rhodium-catalyzed asymmetric hydrogenation.[16]

Experimental Section

General procedure: A resealable Schlenk flask was charged with [Ni(cod)$_2$] (0.050 mmol), **1a** (0.10 mmol), and **2a** (0.10 mmol) in a glovebox. The Schlenk flask was then connected to a conventional Schlenk line and toluene (1 mL) was added. The dark orange solution was stirred for 60 min at room temperature. A solution of substrate (2.0 mmol) in toluene (1 mL) was then added, followed by acetone cyanohydrin (1.5 mmol). The Schlenk flask was sealed and the reaction mixture stirred for 25 h at 35 °C. After cooling to room temperature, the homogeneous mixture was concentrated and the residue purified by flash chromatography on SiO_2.

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