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Journal of Molecular Catalysis A: Chemical 257 (2006) 48–52
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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The development of an enantioselective nickel hydrosilylation catalyst system via multi-substrate screening

Torsten Irrgang [a], Thomas Schareina [b], Rhett Kempe [a,b,*]

[a] *Lehrstuhl für Anorganische Chemie II, Universität Bayreuth, 95440 Bayreuth, Germany*
[b] *Leibniz-Institut für Organische Katalyse, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

Available online 11 May 2006

Dedicated to Bogdan Marciniec on the occasion of his 65th birthday.

Abstract

Multi-substrate screening (asymmetric hydrosilylation of ketones) comparing the catalytic behaviour of Ru, Ni, Pd, Rh and Ir DIOP-catalyst systems [DIOP = *O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] was performed. Initial screening studies revealed that beside the well explored rhodium complexes nickel-based catalysts show interesting selectivity and activity. Mechanistic studies indicate a long induction period in which the active and selective catalyst is formed. [Ni(DIOP)$_2$] which X-ray crystal structure was determined is not active under the applied conditions. Optimisation of the catalyst behaviour concluded from the mechanistic studies led to an improvement of the enantioselectivity by around 20% in comparison to the multi-substrate screening results.

Keywords: Asymmetric catalysis; Hydrosilylation; Ketones; Multi-substrate screening; Nickel; P ligands

1. Introduction

There is a continuing need of new chiral molecular catalysts (coordination compounds) for various enantioselective reactions. The development of highly active and selective homogeneous catalysts goes along with the exploration of a multidimensional parameter space [1] and thus many catalytically interesting metal ligand combinations may have missed. Multi-substrate screening is a very accurate and well documented way to reduce the numbers of experiments in asymmetric catalysis [2]. We report here on multi-substrate screening and mechanistic studies to identify a novel enantioselective nickel hydrosilylation catalyst system based on the known (and commercially available) DIOP ligand. Hydrosilylation of prochiral ketones catalysed by asymmetric transition metal complexes has become an attractive method for the synthesis of optically active alcohols [3]. Rh complexes represent the majority of described catalyst systems for these reactions [4]. Efficient catalyst systems for the enantioselective hydrosilylation of ketones based on nickel are rarely described despite the low price of this metal in comparison to rhodium [5].

* Corresponding author. Tel.: +49 921 55 2540; fax: +49 921 55 2157.
E-mail address: kempe@uni-bayreuth.de (R. Kempe).

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doi:10.1016/j.molcata.2006.04.002

2. Experimental

2.1. General

All syntheses were performed under purified nitrogen and argon using standard Schlenk and glove-box techniques. Solvents were dried by standard procedures. Unless otherwise indicated, all materials were commercially available and were used without further purification. NMR experiments were carried out using the Bruker ARX 250 spectrometer and the Varian Inova Unity 400 spectrometer. Chemical shifts are reported in ppm relative to the deuterated solvent. Elemental analyses were carried out by using a Vario elementar EL *III* analyser. Gas chromatographic analyses were accomplished on an Agilent 6890N network system equipped with 7683 series injector, auto sampler and Macherey-Nagel Lipodex-E capillary column (25 m × 0.25 mm).

2.2. Ketone libraries L1–L3

The ketone library L1 is a mixture of acetophenone (**1**), propiophenone (**2**), α-methylpropiophenone (**3**) and 2,2-dimethylpropiophenone (**4**). L2 is a mixture of acetophenone (**1**), propiophenone (**2**), 4-chloroacetophenone (**6**) and

4-fluoroacetophenone (**7**). The library L3 is a mixture of α-methylpropiophenone (**3**), 2,2-dimethylpropiophenone (**4**) and 2-acetylfurane (**5**).

2.3. [Ni(DIOP)$_2$]

To 0.138 g (0.5 mmol) [Ni(COD)$_2$] were added a solution of 0.498 g (1 mmol) (*R*,*R*)-DIOP in 4 mL toluene. The obtained intensive yellow solution was stirred and the crystallisation is starting after a few minutes. The precipitate was dissolved under heating and yellow crystals suitable for X-ray crystal structure analyses were obtained by cooling down to room temperature. Yield 0.48 g (92%). Anal. Calcd. for $C_{62}H_{64}NiO_4P_4 \times 0.5C_7H_8$: C, 71.40; H, 6.22. Found: C, 71.75; H, 6.47. ^{1}H NMR (250 MHz, CD_2Cl_2, 298 K): δ = 7.43 (bs, 2H), 7.21–7.04 (m, 9H), 3.20–3.18 (bd, 1H), 2.64–2.58 (bd, 1H), 2.35 (s, 0.38H, CH_3, toluene), 1.86–1.77 (q, 1H), 1.06 (s, 3H, CH_3) ppm. ^{13}C NMR (400 MHz, CD_2Cl_2, 296.1 K): δ = 133.18 (CH), 132.17 (CH), 129.15 (C), 128.34 (CH), 128.32 (CH), 127.91 (CH), 127.72 (CH), 125.42 (C), 107.00 ($(O)_2C(CH_3)_2$), 79.30 (CH), 27.14 (CH), 21.34 (CH) ppm. ^{31}P NMR (250 MHz, CD_2Cl_2, 298 K): δ = 222.24 ppm.

2.4. Initial screening

For the multi-substrate screening experiments a parallel Schlenk flask which allows parallel synthesis and screening steps outside a glove box were used [6]. The reaction flasks are loaded in a glove box to avoid the presence of moisture and oxygen. Generally, to 0.02 mmol of the metal salt, first, 1.5 mL of toluene and then 1 mL (0.02 mmol) of a stock solution of (*R*,*R*)-DIOP (0.1 g in 10 mL toluene) were added. To the stirred reaction mixtures 2.4 mmol of the silane, 0.5 mmol of dodecane as an internal standard and 0.5 mmol of the ketone libraries L1, L2 or L3 were added. The mixture obtained, were then stirred at room temperature for 22 h. The reactions were quenched with conc. HCl and extracted with ether. The conversions (conv.) and ee values were determined using GC (Macherey-Nagel Lipodex-E capillary column).

2.5. X-ray crystal structure analysis

X-ray crystal structure analyses were performed using a STOE-IPDS-diffractometer (graphite monochromated Mo Kα radiation, λ = 0.71073 Å). Structure solution and refinement were accomplished using SHELXS-86 [7], SHELXL-97 [8] and WinGX [9]. Crystallographic details are summarized in Table 1. CCDC-290298 contains the supplementary crystallographic data for this publication. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

2.6. Kinetic studies

To a stirred solution of 5.5 mg (0.02 mmol) [Ni(COD)$_2$] in 3 mL of toluene it was added slowly 1 mL of a toluene stock solution of (*R*,*R*)-DIOP [(0.0996 g (0.2 mmol) (*R*,*R*)-DIOP were dissolved in 10 mL of toluene]. The reaction solution became intensive yellow colour. After that 0.368 mL (2 mmol) diphenylsilane, 0.254 mL (2 mmol) dodecane as an internal standard and 0.234 mL (2 mmol) acetophenone were added. The mixture obtained, was then stirred at room temperature and samples were collected under argon pressure via septa with capillary tube at different times. The collected solutions were quenched with conc. HCl (0.4 mL) and then extracted with ether (2 mL). The conversions (conv.) and ee values were determined using GC from the ether/toluene phase.

Table 1
Details of the X-ray crystal structure analyses of [Ni(DIOP)$_2$(toluene)$_{2.5}$]

Formula	$C_{57.67}H_{61.33}Ni_{0.67}O_{2.67}P_{2.67}$
M (g mol^{-1})	918.79
Crystal system	Orthorhombic
Space group	P21212
a (Å)	24.980 (5)
b (Å)	25.427 (5)
c (Å)	11.822 (2)
V (Å^3)	7509 (2)
Z	6
Crystal size (mm)	0.40 × 0.40 × 0.30
ρ_{calcd} (g cm^{-3})	1.219
μ_{calcd} (mm^{-1}) (Mo Kα)	0.394
T (K)	200 (2)
θ range (°)	1.60–20.98
Reflections collected	27434
Independent reflections	7972
F_{000}	2924
R value [$I > 2\sigma(I)$]	0.0440
wR^2 (all data)	0.1126
Parameters	739

2.7. Catalyst optimisation

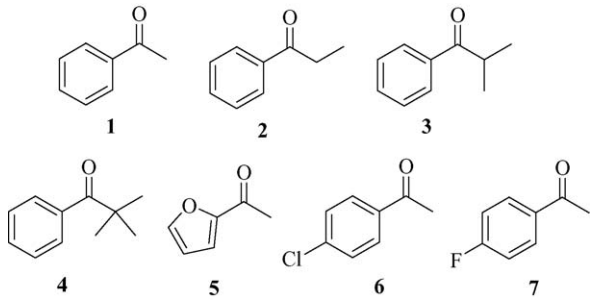
Generally, catalyst optimisations of the enantioselectivity were done with a small excess of diphenylsilane using [Ni(COD)$_2$] and (*R*,*R*)-DIOP (molar ratio 1:1) as catalyst system (1 mol%) and dodecane as internal standard in toluene.

Low temperature experiments of the hydrosilylation were done at 15 °C, at 5 °C (water/ice-mixture) and at −10 °C (ice/NaCl-mixture), respectively. Therefore, the samples were performed in a glove box at room temperature and then cooling down under stirring. Pre-formation experiments with acetone were performed for acetone/acetophenone in a 1:2 molar ratio at room temperature. For low temperature experiments in combination with pre-formation with acetone, using ketones **1**–**4**, molar ratios of acetone/ketones 2:1 at 15 °C and 3:1 at 5 °C were used.

3. Results and discussion

3.1. Screening procedure

Combinatorial screening the truly combinatorial approach in catalysis research could be done in at least three different ways: (1) multi-substrate single catalyst screening [10,2], (2)



Scheme 1. Ketones tested in the enantioselective hydrosilylation.

multi-catalyst single substrate screening [11] and (3) multi-substrate/catalyst screening. Since the accuracy decreases from 1 to 3 our interest was focused on multi-substrate screening. Since multi-substrate single catalyst screening involves the evaluation of the catalytic performance of one catalyst system with many substrates in one reaction flask such an approach is well suited to investigate the enantioselectivity of a catalyst system. It is assumed that parallel reactions take place, all substrates are converted at once with different reaction rates but more or less independent concerning there enantioselectivity. The ketones listed in Scheme 1 were tested.

In combination with the five silanes, diphenylsilane (**8**), triethylsilane (**9**), pentamethyldisiloxane (**10**), methylphenylsilane (**11**) and dimethylphenylsilane (**12**), as well as the six metal salts [Ni(COD)$_2$], [(DME)NiCl$_2$], [(COD)PdCl$_2$], [(COD)MCl]$_2$ and [(COD)RuCl$_2$] (COD = cyclooctadiene, DME = dimethoxyethane, M = Rh, Ir) the investigation of the catalytic performance of one chiral ligand would involve 210 single experiments. Three types of ketone libraries L1–L3 were used. The gas chromatogram (GC) of L1 and the corresponding alcohols, both enantiomers, are shown in Fig. 1. The data are indicative that conversion and enantioselectivity are well resolved for all products within one chromatogram. Educt peaks are also well resolved.

Using such ketone libraries, multi-substrate screening lowers the number of experiments. About 135 of the above

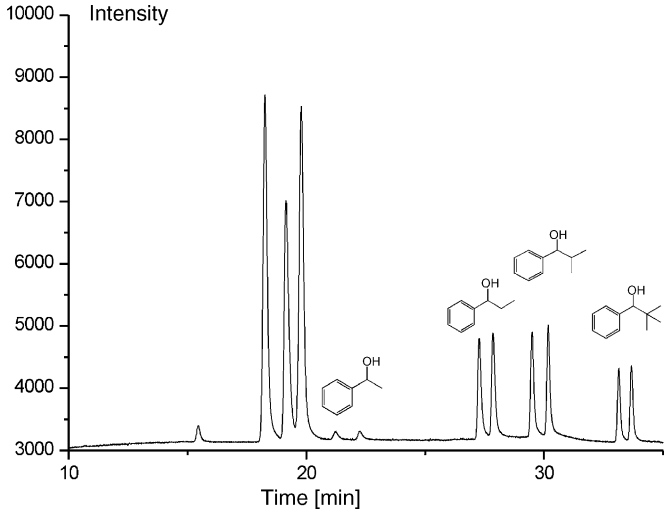


Fig. 1. GC data of a four-membered ketone/alcohol library.

Table 2
Results of the initial screening (ee (conversion) in %; L1–L3 see ketone libraries)

	8	9	10	11	12
Ni(0)					
1^{L2}	46 (78)	0 (0)	0 (0)	8 (94)	0 (0)
2^{L2}	43 (58)	0 (0)	0 (0)	29 (92)	0 (0)
3^{L3}	41 (>99)	0 (0)	0 (0)	12 (54)	0 (0)
4^{L3}	15 (>99)	0 (0)	0 (0)	12 (94)	0 (0)
5^{L3}	62 (>99)	0 (0)	0 (0)	50 (99)	0 (0)
6^{L2}	47 (91)	0 (0)	0 (0)	11 (96)	4 (2)
7^{L2}	35 (75)	0 (0)	0 (0)	5 (97)	7 (2)
Rh					
1^{L1}	36 (>99)	0 (0)	26 (46)	16 (78)	0 (0)
2^{L1}	21 (>99)	0 (0)	7 (47)	10 (58)	0 (0)
3^{L1}	25 (>99)	0 (0)	19 (42)	14 (95)	0 (0)
4^{L1}	3 (>99)	0 (0)	44 (>99)	51 (46)	0 (0)
Ir					
1^{L1}	2 (35)	0 (0)	0 (0)	11 (87)	0 (0)
2^{L1}	0 (0)	0 (0)	0 (0)	9 (>99)	0 (0)
3^{L1}	0 (0)	0 (0)	0 (0)	13 (79)	0 (0)
4^{L1}	0 (0)	0 (0)	0 (0)	28 (>99)	0 (0)

mentioned 210 hydrosilylation reactions were carried out using DIOP as the chiral ligand [DIOP = *O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]. These 135 experiments including the following metal salts [Ni(COD)$_2$], [(DME)NiCl$_2$], [(COD)PdCl$_2$], [(COD)IrCl]$_2$, [(COD)RhCl]$_2$ and [(COD)RuCl$_2$]. There performance of these metal salts and DIOP in the presence of the silanes **8**–**12** as well as all combinations with the ketones **1**–**4** were explored. It means $6 \times 5 \times 4 = 120$ experiments. In addition to that we investigated the catalytic performance of [Ni(COD)$_2$] and DIOP in the presence of the silanes **8**–**12** and the ketones **5**–**7** due to the promising performance of the catalyst systems based on [Ni(COD)$_2$]. It means additional 15 experiments.

The results of the initial screening experiments are shown in Table 2. The best results (enantioselectivity/conversion) were observed for Ni(0) with **8** [entries 1–8-Ni(0) till 7–8-Ni(0)]. In comparison to rhodium [entries 1–8-Rh till 4–8-Rh] the Ni(0) catalyst system [entries 1–8-Ni(0) till 4–8-Ni(0)] shows 10–20% higher ee values. We were surprised by the promising catalytic performance of the Ni(0) catalyst system and decided to explore a Ni(II) precursor to see how important the oxidation state of the starting complex is. Using [(DME)NiCl$_2$], [(COD)PdCl$_2$] and [(COD)RuCl$_2$] as metal complex sources did not give any or if very low conversion. Thus this data are not shown in Table 2. In addition, [(COD)PdCl$_2$] shows low activity with pentamethyldisiloxane (**10**) for ketones **1** (ee = 3, conv. = 43%) and **2** (ee = 4, conv. = 8%).

Diphenylsilane was shown to give the best conversion. The best enantioselectivity in combination with a quantitative conversion was observed for ketone **5** (62% under screening conditions). The results obtained for the Ni catalyst systems are interesting since they showed the best enantioselectivity under screening conditions. The enantioselectivity was in the same range as observed for DIOP rhodium catalyst systems [12]. Enantioselective hydrosilylation of ketones using nickel-based

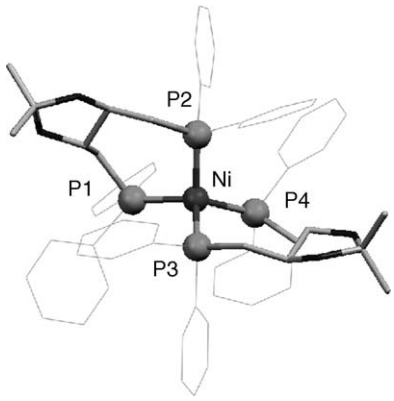


Fig. 2. Molecular structure of [Ni(DIOP)$_2$]; phenyl substituents of the phosphanes are plotted as "wire frames" due to clarity; selected bond length and angles (Å,°) P1 Ni 2.2088 (14), P2 Ni 2.2089 (14), P3 Ni 2.2025 (13), P4 Ni 2.2105 (14), P1 Ni P2 104.25 (5), P3 Ni P4 104.91 (5).

catalysts are rarely described in comparison to rhodium despite the much lower price of the group 10 metal [13]. Thus, we became interested in the nature of the Ni catalyst system.

Reaction of two equivalents of DIOP with [Ni(COD)$_2$] smoothly generates yellow [Ni(DIOP)$_2$] which crystallizes out of toluene. X-ray crystal structure analysis of [Ni(DIOP)$_2$] revealed it to be a tetrahedral coordinated complex (Fig. 2).

Using [Ni(DIOP)$_2$] as a catalyst did not give any conversation. The bis-DIOP coordinated nickel complex seems to be a very stable, coordinatively saturated compound which is not able to catalyse hydrosilylation efficiently. It was concluded, the formation of [Ni(DIOP)$_2$] can be avoided due to the presence of ketones and/or silanes under catalytic conditions.

Time dependant product formation indicated the existence of an induction period and revealed that enantioselectivity increases by the time (Fig. 3). We propose the formation of [(DIOP)Ni(COD)] under catalytic conditions followed by a slow hydrosilylation of the coordinated COD to generate the catalytically active species. It was concluded that preformation with a non-prochiral ketone like acetone should increase the enantioselectivity. In case the non-prochiral ketone is hydrosilylated faster than the ketones **1**–**7** the higher enantioselective catalyst system which is formed during the induction period is formed during the hydrosilylation of the non-prochiral ketone dominantly and

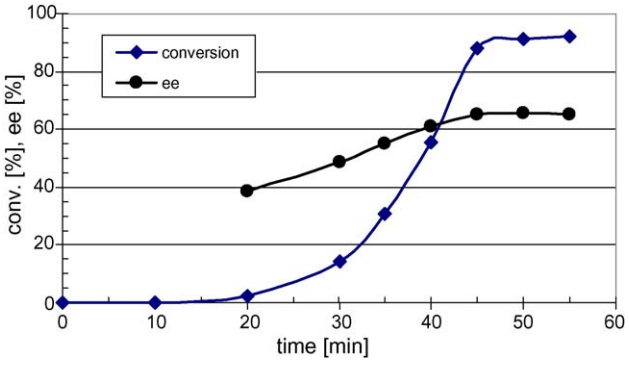


Fig. 3. Time dependence of conversion and ee (%) in the hydrosilylation of **1** using diphenylsilane.

Table 3
Best results for the hydrosilylation of the ketones **1-4** (for ketones see Scheme 1) using diphenylsilane

Ketone	Conversion (%)	ee (%)
1	>99	71
2	>99	66
3	>99	41
4	>99	22

not during the hydrosilylation of any of the prochiral ketones. Hydrosilylation with the prochiral ketones only goes along with the unselective conversion of a significant amount of these educts during the induction period which means lower enantioselctivity. Optimisation of the enantioselectivity was accomplished using **1** and later applied to the other members of the ketone library L1. When the reaction temperature was lowered to −10 °C, no conversion was observed. The decrease in temperature goes along with a tremendous lengthen of the induction period and with the crystallisation of unwanted by-products like [Ni(DIOP)$_2$]. An improvement of the enantioselectivity was observed by preformation with acetone at room temperature (25 °C) followed by a reaction at slightly lower temperatures (10 °C) after the end of the induction period. All these optimisation experiments—preformation with acetone and mixed temperature experiments **1** led to an improved ee of 71% (quantitative conversion; molar ratio acetone: **1** = 2:1; T = 15 °C) (Table 3).

Improved enantioselectivity could be observed at 15 °C for ketones **2** and **4** as well (Table 3).

4. Conclusions

Multi-substrate screening is an efficient tool to discover novel enantioselective catalyst systems. The introduction of "unconventional" and especially low priced metals in the screening process can lead to novel catalyst systems. Insight how the catalysts work is especially important since the screenings do not provide enough information in this regard. We introduced a novel nickel hydrosilylation catalyst system which is of higher enantioselectivity as the corresponding Rh catalyst. Considering the fact that enantioselective nickel-based ketone hydrosilylation catalysts are nearly unknown an interesting alternative to rhodium might have been discovered.

Acknowledgment

Financial support from the BMBF, the DEGUSSA AG and the Fonds der Chemischen Industrie is gratefully acknowledged.

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