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Conjugate Addition of Diethylzinc to Enones Catalyzed by Homogeneous and Supported Chiral Ni-complexes. Cooperative Effect of the Support on Enantioselectivity

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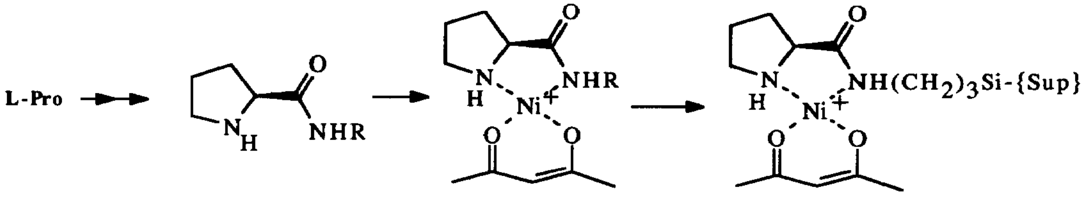
Abstract: *Chiral t-butylaminocarbonylpyrrolidine acetylacetonate Ni(II) hexafluorophosphate and the corresponding supported complexes on silica and on a modified USY-zeolite are readily prepared. The application of these free and supported complexes as catalysts in the addition of diethylzinc to a series of different substituted enones affords chiral β-ethylated ketones in high yields with an enantiomeric excess up to 95%.*

Several methods have been described for enantioselective conjugate addition of organometallic reagents to enones that provide useful chiral β-substituted ketones. Mainly, they require stoichiometric or even excess amounts of chiral reagents[1], but only a few papers have been reported on this reaction where the chiral inductor was used in catalytic quantities[2], and in all cases it was not easily recovered. There remains therefore the unresolved problem of developing an enantioselective catalyst, that could easily be recovered and reused, for this reaction. We describe herein the preparation of *t*-butyl- and 3-(triethoxysilyl)propyl-aminocarbonylpyrrolidine acetylacetonate Ni(II) hexafluorophosphates [**2a,b**] and the corresponding complexes anchored by covalent bonding to silica or a modified USY-zeolite, and their application as catalysts in the enantioselective 1,4-addition of diethylzinc to different substituted enones.

The ligands **1a,b** were prepared in three steps from (*L*)-proline; protection as the *N*-carbobenzyloxy derivative, amide formation by treatment with the corresponding amine in the presence of ethyl chloroformate and triethylamine and finally deprotection using Pd/C as catalyst with cyclohexene as the hydrogen source[3].

The reaction of $(acac)_2$ Ni(II) with nitrogen ligands **1a,b**, in the presence of a non coordinative anion (hexafluorophosphate or perchlorate) yields the corresponding cationic Ni-complexes **2a,b** in almost quantitative yield, as amorphous solids, where an acetylacetonate anion has been replaced by the bidentate N,N-ligand (**2a** or **2b**)[4] (*Scheme I*).

The complex **2b**, bearing a reactive triethoxysilyl group, was reacted with silica[5] and a modified USY-zeolite[6] that presents a well developed supermicropore system and a large quantitiy of silanol groups on its surface, to give immobilized complexes **Sil-2b** and **Zeol-2b** respectively.



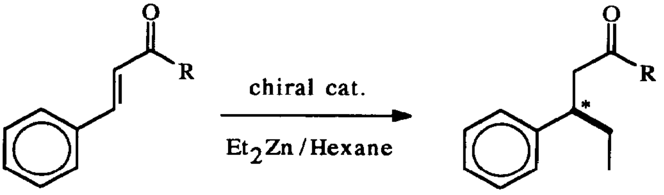
1 **2a,b** **Sil-2b, Zeol-2b**

R = a: $C(CH_3)_3$; b: $(CH_2)_3Si(OEt)_3$

The supporting process involves hydrolysis of $(EtO)_3Si$ groups on the complex and reaction with silanols on the framework of support forming stable covalent bonds $(Si\text{-}O)_3SiR$ without changing the environment around the metal[7]. The process was completed by stirring the inorganic solid into a solution of **2b** in toluene at room temperature for 24 hours. The crude catalyst was then submitted to Soxhlet extraction [CH_2Cl_2/Et_2O (1/1)], in order to remove any residual non-bonded complex, and was finally dried at 50°C under 0.01 torr.

The loading of metal was always 1.0 ± 0.1% wt measured by atomic absorption of digested samples. The soluble and immobilized catalysts, where Ni-complexes are covalently bonded to the silanol present in the support surface, are stable under air at room temperature for long periods and no special storage conditions were required. The structure of the immobilized complexes appears to be the same as the non-anchored complexes since the frequencies and relative intensities of i.r. spectra are comparable for both types of materials.

The enones of type **3** (R = Ph, Me) were reacted with diethylzinc, following the standard homogeneous conditions[8], in the presence of the chiral Ni-complex **2a** (5% molar amount) in hexane/THF[9] at -10°C. After column chromatography, the ketones (*R*)-**4** (R = Ph, Me) were obtained in good yield (75-85%) with moderate *e.e*'s (75-77%) (Table 1).



3a,b **4a,b**

R = a: Ph; b: Me

When the additions, were catalyzed by supported nickel-complexes **Sil-2b** and **Zeol-2b** the ethylation took place more slowly than under homogeneous conditions, to give ketones (*R*)-**4** with similar yields, after filtration and column chromatography. The *e.e.*'s of 3-alkylketones are improved over those obtained with homogeneous catalysts, as shown in Table 1, presumably due to the additional steric constrains at the surface of the support. In USY-zeolite anchored complexes, where the reactions must take place within mesopores containing the anchored Ni-complex, this effect is more evident and *e.e*'s up to 95% are obtained (Table 1).

Table 1. Conjugate addition of Et_2Zn to enones-**3** catalyzed by chiral Ni-complexes

Entry	Subst.	Catal.	Solvent	Temp.(°C)	Time (h)	Yield(%)[a]	*ee*(%)[b]
1	**3a**	**2a**	THF	20	2	73	32
2	**3a**	**2a**	Hexane/THF	-10	2	75	77
3	**3a**	**Sil-2b**	THF	20	14	70	34
4	**3a**	**Zeol-2b**	THF	20	14	85	46
5	**3a**	**Zeol-2b**	Hexane/THF	-10	18	80	91
6	**3b**	**2a**	THF	20	6	50	29
7	**3b**	**2a**	Hexane/THF	-10	18	85	75
8	**3b**	**Sil-2b**	THF	20	18	49	37
9	**3b**	**Zeol-2b**	THF	20	22	61	38
10	**3b**	**Zeol-2b**	Hexane/THF	-10	24	74	95

[a] After column chromatography (silica, ethyl acetate:hexane [1:30])

[b] Based on rotation values[10] (Also by NMR with $Eu(hfc)_3$ for entries 7 and 10)

When reactions were carried out at room temperature in THF yields and enantioselectivities decreased, but the observed surface effects were comparable with optical selectivities being enhanced compared with homogeneous catalysts.

The relatively high enantioselectivities observed with a Ni(II)/N,N-ligand ratio (1:1), compared to reported ratios of more than 10 for high selectivity, could be explained because the chiral inductor is incorporated into the catalyst and possible catalysis by the achiral $(acac)_2$ Ni(II)[11] cannot take place as happens in the homogeneous catalysis studies.

The reaction of methyl (Z)-cinnamate with Et_2Zn under the same conditions affords a mixture of diastereomeric compounds resulting from addition of the primary Michael-adduct to a second molecule of ester, and the mono adducts are not isolated.

Thus, heterogenization of chiral nickel catalysts by supporting adequately substituted complexes on inorganic matrices, particularly USY-zeolites, plays a decisive role in increasing the enantioselectivity of diethylzinc additions to enones. This is in addition to the increased ease of handling, greater stability and simple recovery and recycling of catalyst, and thus constitutes a powerful alternative to homogeneous catalysis.

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4. The nickel complexes are tetrahedral species, as shown by their absorption spectra: λ - 294 nm, ε - 9400 (F.A. Cotton, G. Wilkinson, "Advanced Inorganic Chemistry" 5th Ed., Wiley, New York 1988, p. 741. The analytical data of C, H, N, Ni confirm the proposed stoichiometries (N,N-ligand, Ni, acac, F_6P; 1:1:1:1).

5. Merck silica (particle size 63-200 μm) was used after heating to 415 K under 0.01 torr for 3 hours before use to remove most of the superficial water.

6. Modified USY-zeolite were prepared by steam calcination at 1300 K of an 80% NH_4^+ exchanged NaY zeolite, followed by treatment with a 1N citric acid solution at 403 K for 6 hours. The final zeolite presented a well developed supermicropore system (pore diameter 12-30 A). The controlled dealumination promotes destruction of some sodalite units, which allows direct communication between α-catges generating cavities wider than 12 Å. The formation of supermicropores and large mesopores has been detected by N_2 adsorption-desorption (-60 % of total pore volume corresponding to 12-30 Å diameter mesopores). The unit cell size of the final zeolite was 24.40 Å, the bulk being Si/Al = 4.2, with 95% crystallinity. The zeolite was dired at 415 K under 0.01 torr before carrying out the anchoring process.

7. For silica supported reagents see B.L. Booth, G.C. Ofunne, C. Stacey, P.J.T. Tait, *J. Organomet. Chem.*, **315**, 143, (1986) and references cited.

8. Typical experimental procedure: To a suspension of 20 mg (0.047 mmol) of $[Ni(acac)L]PF_6$ **2a** in 20 ml of dry hexane, cooled to -10°C was added a solution of 200 mg (0.96 mmol) of 1,3-diphenylpropenone in 2 ml of dry THF. The mixture was stirred under argon for 30 min and 1.5 ml of 1M solution of Et_2Zn in hexane (1.5 mmol) was added. After 2 h at this temperature, the reaction was quenched by addition of 15 ml of saturated aqueous solution of NH_4Cl. The mixture was thoroughly extracted with ethyl acetate and the combined organic extracts were successively washed with water and brine, and dried over sodium sulphate. Evaporation under reduced pressure gave a crude product which was purified by chromatography (silica gel-hexane:ethyl acetate 30:1). Pure 1,3-diphenylpentan-1-one (174 mg, 75%) was obtained.

9. The substrate was added dissolved in the minimum amount of tetrahydrofuran, that allows that reactions take place with reagents in solution.

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