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COMMUNICATIONS

Published on Web 10/21/2004

Nickel(II)-Catalyzed Highly Enantioselective Hydrophosphination of Methacrylonitrile

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Received August 20, 2004; E-mail: togni@inorg.chem.ethz.ch

Chiral phosphines, as ligands in transition metal complexes, efficiently create asymmetric catalysts for enantioselective transformations.[1] However, chiral phosphines are expensive, and their syntheses frequently require a resolution or are limited to the use of starting materials derived from enantiopure natural products. An alternative synthetic strategy might involve the enantioselective transition-metal-catalyzed addition of a P−H bond to a C═C double bond (eq 1).[2]

(1)

Although hydrophosphinations have proven valuable for the synthesis of achiral or chiral phosphines (when involving stereospecific reactions),[3−7] methodologies for enantioselective P−H additions are limited. Among the few asymmetric catalyses, Pt^0-(MeDuphos) complexes catalyze hydrophosphinations of Michael acceptors via P−H bond oxidative addition and olefin insertion, but unfortunately the reaction's enantioselectivity is low.[8] Additionally, lanthanide-catalyzed intramolecular hydrophosphinations give chiral cyclic phosphines with good diastereomeric ratios.[9] Interestingly, the mechanisms of lanthanide-catalyzed hydrophosphinations and hydroaminations appear to be closely related.[10]

We have recently described enantioselective intermolecular hydroaminations of vinyl nitriles that are catalyzed by the dicationic nickel complex [Ni(Pigiphos)(THF)]$(ClO_4)_2$ ([**1**]$(ClO_4)_2$) containing the C_1-symmetric trisphosphine Pigiphos (Scheme 1; the (*R*)-(*S*)-enantiomer of Pigiphos was used exclusively).[11,12]

Preliminary studies suggested that coordination of the vinyl nitrile to the dicationic Ni^{II} center activates its C═C bond toward 1,4-addition of the amine. On the basis of this proposal, we speculated that [**1**]$(ClO_4)_2$ might also catalyze hydrophosphinations. Herein, we report a new method for the preparation of a series of enantioenriched (2-cyanopropyl)phosphines and present results that implicate 1,4-conjugate addition for P−C bond formation.

Initially, we attempted the nickel-catalyzed addition of Cy_2PH (**2a**) to methacrylonitrile under conditions similar to those developed for our hydroaminations (5 mol % [**1**]$(ClO_4)_2$ in THF).[12] After 1 h, the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture displayed a new singlet at −8.12 ppm. Unfortunately, the reaction did not proceed to completion under these conditions even after extended reaction times (<2 weeks). However, under optimized conditions (methacrylonitrile as solvent and 10 mol % [**1**]$(ClO_4)_2$), the reaction is complete after ca. 5 h at room temperature. Three multiplets (2.18, 1.48, and 1.44 ppm, 1 H each) in the ^1H NMR spectrum of the product indicated the formation of the anti-Markovnikov addition product $Cy_2PCH_2CHMeCN$ (**3a**). The ee (65%) was determined by coordination of **3a** to an enantiopure chiral Pd complex.[8,13]

‡ X-ray crystallographic studies.

Scheme 1

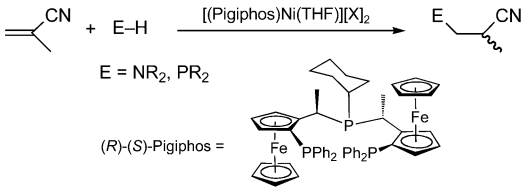


Table 1. Solvent, Counterion, and Temperature Effects on the Reaction of $^tBu_2PH$ and Methacrylonitrile Catalyzed by $[\mathbf{1}]^{2+}$

entry	solvent	counterion	temp	% ee
1	methacrylonitrile	ClO_4	rt	65
2	F_3CCH_2OH	ClO_4	rt	45
3	acetone	ClO_4	rt	77
4	thf	BPh_4	rt	67
5	acetone	BF_4	rt	50
6	acetone	BF_4	−78 °C → rt	84
7	acetone	ClO_4	−25 °C	89

We then surveyed the reaction of a few primary and secondary phosphines with methacrylonitrile in the presence of [**1**]$(ClO_4)_2$ at room temperature. Ph_2PH (**2b**, 10 equiv) forms $Ph_2PCH_2CHMeCN$ (**3b**) quantitatively, but with low ee (14%). Mes_2PH does not react (only starting material is detected by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy) after 2 weeks at room temperature, and the primary phosphines $CyPH_2$ and (1-MeCy)PH_2 do not give isolable hydrophosphination products. The best results are obtained for the reaction of methacrylonitrile and $^tBu_2PH$ (**2c**, 98 equiv) to form $^tBu_2PCH_2CHMeCN$ (**3c**, 65% ee).

Noting that the bulky dialkylphosphines gave more promising results, we focused on the effects of the counterion, solvent, and temperature in the Ni-catalyzed reaction of $^tBu_2PH$ and methacrylonitrile (Table 1). The enantioselectivities follow the trend F_3CCH_2OH < thf ≈ methacrylonitrile < acetone, and the use of [**1**]$(BF_4)_2$ gives lower enantioselectivities than observed with [**1**]$(ClO_4)_2$ at room temperature (Table 1, entries 1−5). However, addition of ^{t}-Bu_2PH to a −78 °C acetone solution of [**1**]$(BF_4)_2$ and methacrylonitrile affords **3c** in 84% ee (entry 6). The highest enantioselectivity is obtained from [**1**]$(ClO_4)_2$ in acetone at −25 °C (entry 7, 89% ee). The catalyst is highly active under these conditions, giving 600 turnovers after 48 h and 900 turnovers after 1 week (0.1 mol % catalyst). Hydrophosphinations with $^iPr_2PH$ or (1-adamantyl)$_2PH$ to give **3d** (49 turnovers, 24 h, 69% ee) or **3e** (100 turnovers, 96 h, 94% ee) are also optimal in acetone at −25 °C (Table 2).[14] Although the Pigiphos ligand is sterically demanding, conversion and enantioselectivity of the hydrophosphination are apparently enhanced by bulky, nucleophilic phosphine substrates.

This suggests a pathway involving coordination of methacrylonitrile to the nickel center followed by nucleophilic attack of the secondary phosphine. To investigate this possibility, methacryloni-

10.1021/ja0449574 CCC: $27.50

Table 2. [**1**]$(ClO_4)_2$-Catalyzed Reaction of R_2PH and Methacrylonitrile[a]

entry	phosphine	turnover	time (h)	yield (%)[b]	ee (%)
1[c]	Cy_2PH	10	8	71	70
2[c]	Ph_2PH	15	24	10	32
3[d]	$^iPr_2PH$	49	24	not isolated	78
4[d]	$^tBu_2PH$	100	8	97	89
5[d]	Ad_2PH[e]	100	96	95	94

[a] Catalyst loadings range from 1 to 10 mol %, either [**1**]$(ClO_4)_2$ or generated in situ from Pigiphos and $[Ni(H_2O)_6][ClO_4]_2$, and reactions were performed at −25 °C. [b] Isolated yields are based on moles of the R_2PH starting material. [c] Reactions were performed in methacrylonitrile. [d] Reactions were performed in acetone. [e] Ad = 1-adamantyl.

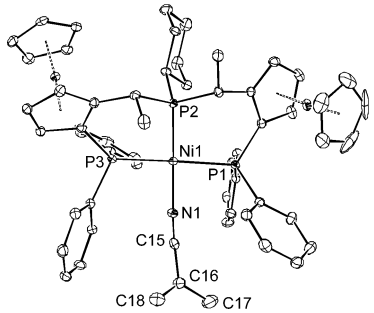
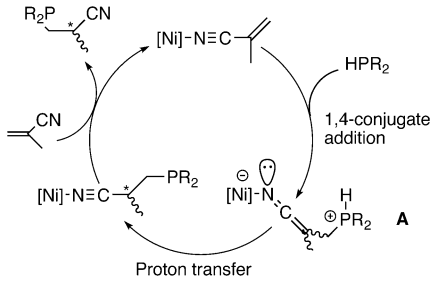


Figure 1. ORTEP diagram of the dication of [Ni(Pigiphos)(NCMeCCH$_2$)]-$(ClO_4)_2$ ([**5**]$(ClO_4)_2$). Hydrogen atoms are omitted for clarity.

trile (1−10 equiv) was added to a mixture of Pigiphos and [Ni-$(H_2O)_6](ClO_4)_2$ in THF-d_8 to form [Ni(Pigiphos)(NCMeCCH$_2$)]-$(ClO_4)_2$ ([**5**]$(ClO_4)_2$). The ^{31}P chemical shifts and coupling constants for [**5**]$(ClO_4)_2$ and the acetonitrile complex [Ni(Pigiphos)(NCCH$_3$)]-$(ClO_4)_2$ are similar, suggesting that in solution the methacrylonitrile is coordinated to Ni via the nitrile nitrogen.[15,16] This bonding mode is maintained in the solid state, as evidenced by the X-ray crystal structure illustrated in Figure 1. In the dication $[\mathbf{5}]^{2+}$, the nickel atom is bonded to its ligands in a distorted square planar geometry,[17] in which the nickel dication and nitrogen atom of the nitrile are displaced 0.33 and 1.15 Å, respectively, from a plane defined by the three phosphorus atoms. Notably, the two axial faces of the complex are distinguished by this displacement, and the methacrylonitrile ligand is sterically contained within a chiral environment created by the Ph_2P phenyl groups.[17]

Reaction of $[\mathbf{5}]^{2+}$ and R_2PH (R = Cy, Ph, ^{t}Bu; 1−2 equiv) in THF-d_8 gives $R_2PCH_2CHMeCN$. Furthermore, yields and enantioselectivities of hydrophosphination products from [**1**]$(ClO_4)_2$ and [**5**]$(ClO_4)_2$ as catalysts are indistinguishable. These results suggest that the dication $[\mathbf{5}]^{2+}$ is an intermediate in the catalytic cycle (Scheme 2). Note that in this mechanism, P−C bond formation produces a phosphonium ion and an axially chiral azaallenyl ligand coordinated to the chiral $[Ni(Pigiphos)]^{2+}$ fragment (i.e., two diastereoisomers of type **A**). Stereospecific proton transfer from the pendant phosphonium to the N═C═*C*RR′ carbon of each diastereoisomer generates the α-stereogenic center. Compound [**5**]-$(ClO_4)_2$ is also an intermediate in the [**1**]$(ClO_4)_2$-catalyzed asymmetric hydroamination.[12] Accordingly, there are similar solvent and counterion effects in the hydroamination and hydrophosphination reactions. Additionally, the absolute configuration of the major enantiomer of hydroamination and hydrophosphination, respectively, demonstrates that the sense of chiral induction is the same in both reactions.[15,17b]

Scheme 2. Proposed Catalytic Cycle



These similarities suggest that $[Ni(Pigiphos)(L)]^{2+}$ complexes may be able to catalyze the asymmetric addition of other E−H nucleophiles to vinyl nitriles for the synthesis of highly enantioenriched organic compounds containing main group elements. Along these lines, we are currently working to further develop the synthetic utility of this class of asymmetric transformation.

Acknowledgment is made to H. Rüegger for NMR assistance. This work was funded by COST-D24.

Supporting Information Available: Experimental section including X-ray crystallographic data for **5**$(ClO_4)_2$ and for the complexes used in the determinations of absolute configurations (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) See Supporting Information. (b) Absolute configurations were determined by X-ray crystallographic analysis of adducts derived from **3** and an enantiopure Pd complex of known absolute configuration. Note that the sense of chiral induction is the same in both reactions, although the descriptor of the absolute configuration of the major enantiomers changes from *R* (hydroamination) to *S* (hydrophosphination) due to different priority sequences of the substituents at the respective stereogenic center.

JA0449574