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Highly Enantioselective Nickel-Catalyzed Hydrovinylation with Chiral Phosphoramidite Ligands

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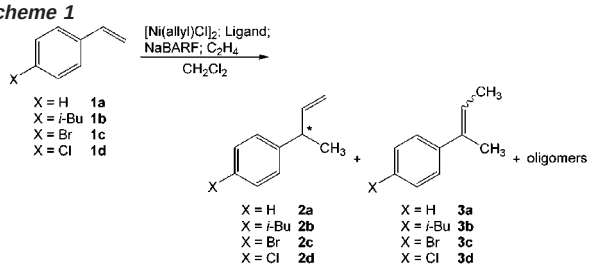
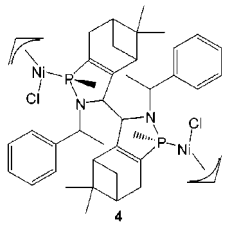
The development of highly stereoselective carbon−carbon bond-forming reactions continues to be one of the major challenges in fine chemical synthesis.[1] The nickel-catalyzed hydrovinylation is a metal-mediated coupling reaction with a remarkable potential for enantioselective synthesis.[2,3] It comprises the formal addition of a hydrogen atom and a vinyl group to a prochiral olefin and gives access to high-value products in a very elegant and atom-efficient way. Using ethene as the cheapest vinylic coupling partner, the transformation results effectively in a chain elongation of two carbon atoms simultaneously creating a stereogenic center in allylic position (Scheme 1).

Scheme 1



In contrast to many other enantioselective catalytic processes,[4] ligand development for this particular reaction is still in its infancy. The state of the art is defined by catalyst **4** containing a ligand that



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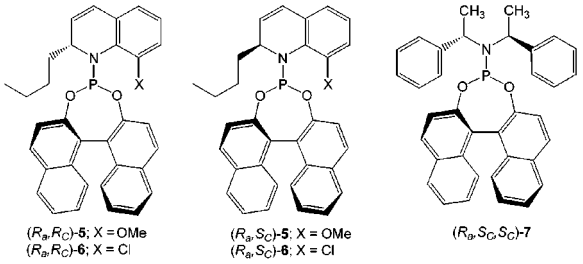
was found by serendipity in the pioneering investigations of Wilke and co-workers.[5] After activation with a suitable chloride-abstracting reagent, this system provides high chemo- and stereoselectivities in chlorinated solvents at very low temperatures[3b] and in compressed CO_2[6] or ionic liquid/CO_2 systems[7] around ambient temperature. The scope of this "chiral pool"-derived ligand is, however, rather limited, and only one enantiomer of the desired products **2a**−**d** is readily accessible. All attempts to optimize or simplify the ligand framework of **4** have remained unsuccessful thus far.[8]

The only other promising class of Ni catalysts[9] for asymmetric hydrovinylation contains atropisomeric ligands such as MOP and was investigated by the group of RajanBabu.[10a] Their results suggested that the nature of the chloride-abstracting agent and the presence of hemilabile donor groups had a synergistic influence on the catalyst perfomance.[10b] Enantioselectivities of up to 80% ee were obtained at substrate-to-nickel ratios of 70:1 under optimized conditions.[10b]

In the search for new hydrovinylation catalysts that allow for systematic modification of a readily accessible ligand framework, we have turned our attention to chiral phosphoramidites.[11] The selection of the representative examples **5**−**7** was guided by the rather heuristic design principle that an efficient ligand system for asymmetric hydrovinylation should possess a P−N bond and contain more than one element of chirality, one of them preferentially being an atropisomeric unit. In addition, the set of ligands should allow to assess the potential influence of additional donor groups. The most significant results obtained with catalysts formed from **5**−**7** and $[Ni(allyl)Cl]_2$ and using NaBARF (BARF = tetrakis-[3,5-bis(trifluormethyl)phenyl]borate) as activator are summarized in Table 1.[12]



The (R_a,R_C) diastereomer of the new ligand **5** gave an active catalytic system for the hydrovinylation of styrene **1a**, but the optical induction remained disappointingly low (entry 1). The C2 epimer (R_a,S_C)-**5**, however, provided reasonable enantioselectivity at moderate conversion (entry 2). An even more dramatic difference in activity and selectivity was observed for the two diastereomers of the chloride-substituted ligand BINAPHOSQUIN (**6**).[13] The (R_a,S_C) configuration in **6** led to an extremely active catalyst resulting preferably in styrene dimerization and trimerization (entry 3). The large tendency for oligomerization could not be suppressed even at −78 °C or upon reducing the loading of (R_a,S_C)-**6**/Ni. In contrast, the other diastereomer (R_a,R_C)-**6** formed a less active catalyst, yielding **2a** very selectively with a remarkable ee of 87% (*S*) (entry 4). It is interesting to note that the two ligand systems **5** and **6** give rise to products with the opposite preferred stereochemistry and that the opposite configuration at C2 is required to obtain the highest asymmetric induction.[14]

The results obtained with ligands **5**−**6** further substantiate the cooperative effect of axial and central chirality and indicate also a

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Table 1. Ni-Catalyzed Enantioselective Hydrovinylation of Vinyl Arenes **1a**−**d** Using Chiral Phosphoramidites **5**−**7** as Ligands and NaBARF as Activator[12]

entry	ligand	substrate	*T* [°C]	*p* (C_2H_4) [bar]	*t* [h]	**1**/Ni	conv. [%]	selectivity [%] **2**	**3**	oligomers[a]	ee (**2**) [%]
1	(R_a,R_C)-**5**	**1a**	0	44	1	280	99.7	85.4	13.3	<1.5	7.6 (*R*)
2	(R_a,S_C)-**5**	**1a**	−30	49	2	280	13.5	93.3	3.1	3.7	56.4 (*R*)
3	(R_a,S_C)-**6**	**1a**	−32	12	2	300	100	<1	<1	100	−
4	(R_a,R_C)-**6**	**1a**	−32	12	2	300	33.1	96.2	0.4	3.7	87.2 (*S*)
5	(R_a,S_C,S_C)-**7**	**1a**	−70	∼1	4	620	100	84.9	4.3	8.1	94.8 (*S*)
6a	(R_a,S_C,S_C)-**7**	**1a**	−65	∼1	4	4600	89.2	100	<1	<1	91.1 (*S*)
6b			−65→rt	∼1	16	5490	82.7	96.4	<1	3.0	91.4 (*S*)
7	(R_a,S_C,S_C)-**7**	**1a**	0	∼1	2	13270	100	78.1	9.1	12.7	76.2 (*S*)
8[b]	(R_a,S_C,S_C)-**7**	**1a**	−50	∼1	0.3	1330	99.5	99.1	0.9	<1	89.7 (*S*)
9	(R_a,S_C,S_C)-**7**	**1b**	−70	∼1	4	1330	28.4	28.4	<1	<1	67.7(*S*)
10	(R_a,S_C,S_C)-**7**	**1c**	−70	∼1	5	2650	83.4	98.8	1.2	<1	91.9 (*S*)
11	(R_a,S_C,S_C)-**7**	**1d**	−30	∼1	4	660	100	81.2	6.8	12.0	90.8 (*S*)

[a] Oligomerization products of **1** and secondary hydrovinylation products of **2** and **3** are summarized as "oligomers", see Supporting Information for details. [b] $NaAl[OC(CF_3)_2Ph]_4$ was used as activator.

strong influence of additional donor groups. The best result (87% ee at −32 °C) was, however, achieved with ligand **6** containing the weaker donor group at C8. We therefore extended our study to Feringa's ligand system **7**[15] combining central and axial chirality but lacking an obvious additional donor group.[16]

Employing the standard procedure under particularly mild conditions, a Ni catalyst based on (R_a,S_C,S_C)-**7** gave quantitative conversion of **1a** with 84.9% selectivity for the desired product **2a** and an excellent enantioselectivity of 94.8% (*S*) (entry 5). Moreover, the catalyst system proved extremely efficient and remarkably robust for the hydrovinylation of **1a**. Almost 90% conversion and perfect chemoselectivity was achieved within 4 h at −65 °C even at a substrate-to-nickel ratio of 4600:1 (entry 6a). Further addition of substrate to this reaction mixture led again to almost complete conversion within 16 h (entry 6b) corresponding to a total turnover number of ca. 8340. Chemo- and enantioselectivity remained uniformly high under these conditions. At 0 °C, a styrene conversion of 69% was reached at a substrate-to-nickel ratio of ca. 13000:1 within 30 min. These data correspond to an initial turnover frequency approaching 18 000 h^{-1} even under the conservative assumption that all Ni centers were available in active form. Consumption of **1a** was quantitative after a total reaction time of 2 h, but the reaction was slightly less selective at this temperature (entry 7).

A highly active and selective system was also formed from [Ni(allyl)Cl]$_2$ and (R_a,S_C,S_C)-**7** using $NaAl[OC(CF_3)_2Ph]_4$ as activator (entry 8).[6] Other salts such as $NaBF_4$ or $LiNTf_2$ were considerably less effective. A first screening of the substrate scope indicates that electron-deficient vinyl arenes are hydrovinylated with activity and selectivity similar to those for **1a** (entry 10 and 11), whereas electron-donating substituents such as in **1b** lead to somewhat less satisfactory results (entry 9).

Our results show that chiral phosphoramidites are the first efficient *and* modular ligand system for highly enantioselective hydrovinylation. The large potential for structural variation and the straightforward synthesis of these ligands make them currently the best lead structure for catalyst development in this field. Our ongoing efforts in this area include the combination of their molecular design with novel reaction and separation processes.[6,7]

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The catalyst precursors were either preformed or formed in situ by addition of ligands **5**−**7** to [Ni(allyl)Cl]$_2$ in a 2:1 ratio. Substrates **1a**−**d** were added to their solutions in CH_2Cl_2, followed by activation of the catalyst precursors with a slight excess of NaBARF at room temperature. The resulting orange solutions were cooled to the desired temperature and pressurized or purged with ethene under stirring for the reaction times listed in Table 1. Conversion, product composition, and enantiomeric purity of **2** were determined by GC and GC-MS techniques after quenching with 2 mL of concentrated aqueous ammonia and standard workup. Details of the experimental and analytical procedures are given in the Supporting Information.

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(14) The assignment of the absolute configuration at C2 is based on X-ray data of **6** and comparison of NMR data within the series of ligands **5**−**6** (cf. ref 11c). The $^{31}P\{^1H\}$ resonances of **5** are found at δ 146.9 (R_a,S_C) and δ 142.8 (R_a,R_C).

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(16) The potential influence of the phenyl groups in the amine part remains to be addressed in future investigations.

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