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Tunable Ligands for Asymmetric Catalysis: Readily Available Carbohydrate-Derived Diarylphosphinites Induce High Selectivity in the Hydrovinylation of Styrene Derivatives

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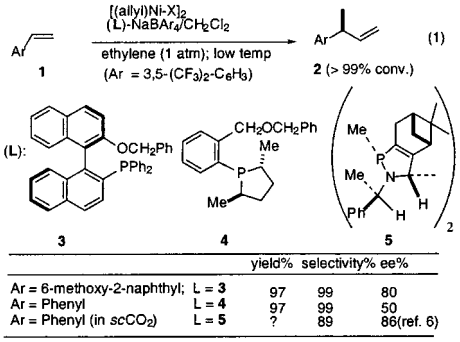
The asymmetric hydrovinylation of olefins is one of a handful of catalytic asymmetric reactions that uses a feedstock carbon source for the synthesis of potentially valuable fine chemical intermediates.[1] In 1998 we reported[2] a new protocol for this remarkable reaction that gave a nearly quantitative yield of the product.[3] In our initial efforts to find a broadly applicable asymmetric version of this reaction, we considered the requirement of a coordination site for ethylene on the putative cationic nickel hydride intermediates, and chose (*R*)-2-diphenylphosphino-2′-alkoxy-1,1′-binaphthyl (**3,** MOP) in which the −OR group would play the role of a hemilabile ligand. Further we showed that there is a strong synergistic relationship between such a ligand and the counterion that is used.[4] For example, AgOTf additive, which gave in many cases, isolated yields >95% with Ph_3P as a ligand, gave low yields in the hydrovinylation reactions using the hemilabile ligands such as MOP (**3**) or the phospholane **4.** In sharp contrast, the use of Na^+ $^-B[3,5\text{-}(CF_3)_2\text{-}C_6H_3)]_4$ (Na^+ $^-$BARF) fully restored the activity of the catalyst giving isolated yields up to 97% for various vinyl arenes (eq 1).[4] Beneficial effects of highly dissociated counterions in hydrovinylation of styrene using the original Wilke's azaphospholene ligand (**5**)[5] in supercritical CO_2 have since been reported by Leitner et al.[6] Even though the initial studies with MOP (**3**) and 1-aryl-2,5-phospholane (**4**) ligands provided a number of useful parameters to optimize the efficiency of the catalyst, the enantioselectivity in the hydrovinylation of styrene derivatives remained modest (best: 50%, using phospholane **4**).



		yield%	selectivity%	ee%
Ar = 6-methoxy-2-naphthyl;	L = **3**	97	99	80
Ar = Phenyl	L = **4**	97	99	50
Ar = Phenyl (in *sc*CO_2)	L = **5**	?	89	86(ref. 6)

In continued efforts to improve the selectivity, we have screened a large number of ligands, and recently discovered that easily accessible carbohydrate-derived phosphinites[7] serve as excellent ligands for this exacting reaction. The details of these investigations are reported in this communication.

From our initial survey of ligands, we discovered that simple diarylphosphinites (for example, **6**−**8**, Figure 1)[8] were viable ligands for the nickel-catalyzed hydrovinylation of styrene (isolated yield and ee of product shown in brackets). Not unexpectedly,[4] several others (including some phosphines), some carrying good Lewis

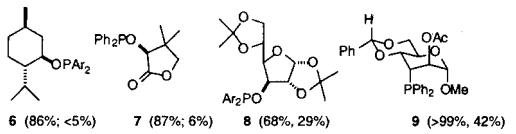


Figure 1. Selected[8] monophosphinites and phosphines for hydrovinylation of styrene (yield and ee of 3-phenyl-1-butene is shown in brackets).

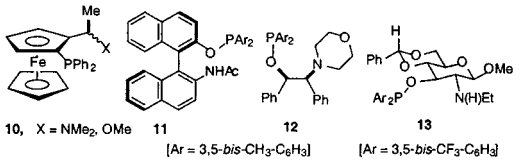


Figure 2. Prototypical ligands[8] that gave low (<5%) turnover in the hydrovinylation.

basic groups (e.g., **10**−**13**, Figure 2),[8] were found to be totally ineffective. On the basis of these studies, diarylphosphinites from 2-acetamido-2-deoxyglycopyranoside were chosen for further development. Two practical considerations make this an obvious choice among the ligands we tested: (a) the modular construction of the ligand allows sufficient flexibility to fine-tune the steric and electronic properties of the ligating atom(s), and (b) the configuration of the ring carbons could be changed either through diastereoselective functional group manipulations or by choosing alternate sugars to build the scaffold.

The hydrovinylation of styrene was carried out as follows. The catalyst precursor was prepared by mixing stoichiometric amounts (1:1 Ni/**L**) of allyl nickel bromide dimer and the ligand in CH_2Cl_2, followed by exchanging the bromide ion by addition of Na BARF. The precipitated salts were removed by filtration through Celite. Oxygen-free ethylene was introduced into the flask after cooling the Ni-complex to the appropriate temperature (−70 to −55 °C), followed by the substrate dissolved in CH_2Cl_2. After ∼2 h, the reaction was quenched with ammonium chloride and the product isolated, by evaporation of the solvent. Selectivity factors were determined by NMR spectroscopy, GC and HPLC. Table 1 shows the yield, selectivity, and enantiomeric excess obtained when various β-acylaminophosphinites are used as ligands for hydrovinylation of styrene.[8] In general, outstanding selectivity for the primary product, 3-phenyl-1-butene is observed with these ligands. Among this set of ligands, an α-glycoside appears to give better yields than a β-glycoside (entry 1 vs 2). Whether a 3,5-bis-CH_3-C_6H_3-substituent or a 3,5-bis-CF_3-C_6H_3-substituent on phosphorus is better depends on the configuration of the carbon to which is attached the diarylphosphinite moiety (entries 2 and 3). In the *gluco*-series (entry 2) the CF_3-aromatic substituent is better, whereas in the *allo*-series (entry 3) the CH_3-aromatic substituent is better. For higher enantioselectivity the *allo*-configuration (entry 3) is clearly superior as compared to the *gluco*-derivative (entry 2). Finally, the acyl group

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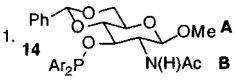
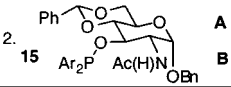
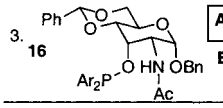
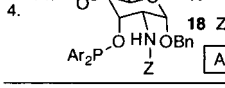
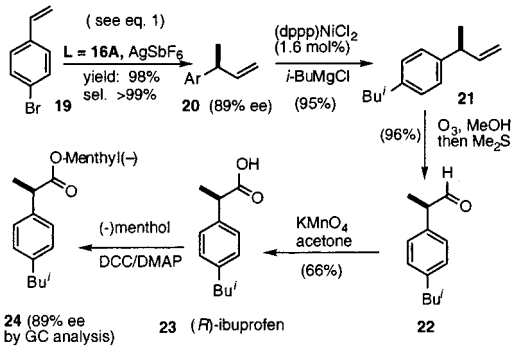
Table 1. Hydrovinylation of Styrene Using Sugar−Phosphinite Ligands[1]

No.	ligand	Ar	yield[2]	selectivity[3]	%ee[4]
1.	 **14**	**A**	62	>99	32 (*S*)
		B	35	>99	28 (*S*)
2.	 **15**	**A**	93	96	9 (*S*)
		B	93	>99	45 (*S*)
3.	 **16**	**A**	89	89	81 (*S*)
		B	42	>99	62 (*S*)
4.		**17** Z = CF_3CO	40[5]	40	87 (*S*)
		18 Z = PhCO	23[5]	23	82 (*S*)
		Ar = **A**			

[1] See eq 1. **A** Ar = 3,5-$(CH_3)_2$−C_6H_3; **B** Ar = 3,5-$(CF_3)_2$-C_6H_3. [2] Isolated yield of 3-phenyl-1-butene. [3] Percentage of 3-phenyl-1-butene among all products. [4] Determined by HPLC. [5] Conversion >99%.

Scheme 1. Synthesis of Ibuprofen via Asymmetric Hydrovinylation



on nitrogen showed a pronounced effect on the selectivity of the reaction (entry 4). All are exceptionally good ligands (>99% conversion), with the N-CH_3CO-ligand giving the best selectivity (entry 3, **A**). The N-COPh and N-$COCF_3$ derivatives promote concomitant isomerization of the initially formed 3-phenyl-1-butene to a mixture of 2-phenyl-2-butenes under the reaction conditions, reducing the selectivity for the former to 23 and 40%, respectively (entry 4).

In overall yield and selectivity, the diarylphosphinite **16A** is one of the best ligands for the Ni-catalyzed asymmetric hydrovinylation of styrene.[9] Most gratifyingly, ligand **16 A**[10] is also one of the best ligands for the hydrovinylation of 4-bromostyrene, giving *98% isolated yield (>99% selectivity for the desired product) with 89% enantiomeric excess* (Scheme 1). A study of the effect of the counteranion on this reaction shows that SbF_6^- is marginally better than BARF, whereas BF_4 and OTf are greatly inferior.[11] The enantiomeric excess of this key compound {$([\alpha]^{25}_D = +9.9 \pm 0.1$ (*c* 7.02, $CHCl_3$)}, from which a number of 2-arylpropionic acids could be prepared by cross-coupling chemistry (vide infra), was determined by three independent methods, all agreeing within experimental error. The ee's for compound **20** (Ar = 4-bromophenyl) and the corresponding debrominated derivative, 3-phenyl-1-butene (prepared by treatment of **20** with Mg in MeOH, >99% yield) were determined by HPLC on a Chiralcel OJ column. Kumada coupling of **20** and *i*-BuMgBr in the presence of 1 mol % of (dppe)$NiCl_2$ (Scheme 1) gave **21** (89%ee, HPLC). Subsequent ozonolysis and oxidation of the resulting aldehyde[12] gave ibuprofen, whose configuration and enantiomeric excess were established by conversion to the known (−)-menthyl esters (**24**).[2a] Gas chromatograpic analysis of **24** using Chirasil-L-val column revealed baseline separation, with a diastereomeric excess of 89% for the (*R*)-ibuprofen ester. This confirms the overall selectivity and the absolute configuration of the primary product of hydrovinylation.

Finally, studies with 4-isobutylstyrene serve as a reminder that a single ligand is unlikely to have broad applicability and that further fine-tuning may be needed before practical levels of asymmetric induction can be achieved for individual substrates. The most promising ligand, **16A**, produced a very efficient catalyst (1 mol % loading, >99% yield and selectivity) for the hydrovinylation of this substrate, albeit with a modest 74% ee for the product.[8] Nonetheless, this represents one of the highest overall selectivity in the synthesis of this key intermediate.[13]

In summary, discovery of a new, tunable ligand class for efficient asymmetric hydrovinylation of vinyl arenes is reported. Also disclosed are the highest overall yields and selectivities for the hydrovinylation of 4-bromostyrene and 4-isobutylstyrene, two important precursors for the synthesis of commercially important 2-arylpropionic acids. Further studies are in progress.

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Supporting Information Available: Details of the synthesis of ligands and characterization and analytical data of products including GC and HPLC data for key compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a more complete list and experimental procedures see Supporting Information.

(9) For a compilation of best practices, see ref 1b. See also ref 6a for a reaction done in *sc* CO_2 using **5** and BARF as a counteranion.

(10) Other related ligands gave the following yield/selectivity (for 4-aryl-1-butene)/ee for 4-bromostyrene: **15A** 88/>99/13; **15B** 41/>99/47; **16B** 19/>99/43.

(11) The following yield/selectivity (for 3-aryl-1-butene)/ee were obtained for various salts when used in conjunction with **16A**: $AgSbF_6$ 98/>99/89; NaBARF 94/94/89: $AgBF_4$ 24/>99/86; AgOTf 70/>99/74.

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(13) According to our results, the $[\alpha]_D$ values for **21** previously reported in the literature[5b,13a] and the ee's based on these numbers alone may need reevaluation.[8] We obtained a value of +6.80 ± 0.1 (*c* 2.09, $CHCl_3$) for (*S*)-**21** of 74% ee. (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.

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