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Nickel(0)-Catalyzed Asymmetric Hydrocyanation of 1,3-Dienes

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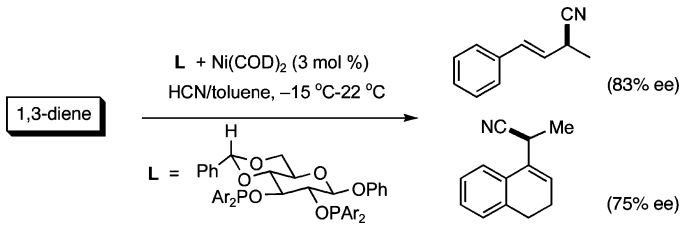
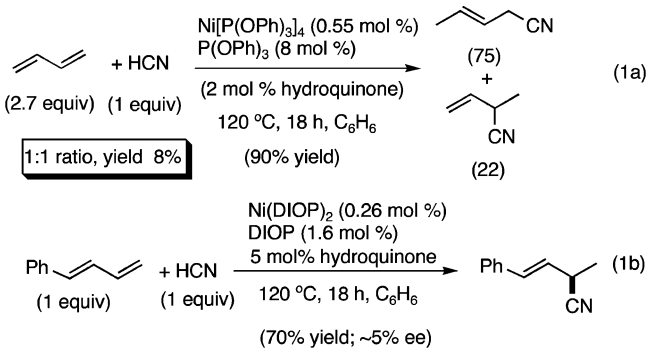
ABSTRACT



1,2-Bis-diarylphosphinites are excellent ligands for the Ni(0)-catalyzed hydrocyanation of certain types of 1,3-dienes. 1-Phenyl-1,3-butadiene, 1-vinyl-3,4-dihydronaphthalene, and 1-vinylindene undergo highly regioselective hydrocyanation under ambient conditions to give exclusively the 1,2-adducts in good to excellent yields. Using bis-1,2-diarylphosphinites derived from D-glucose, the highest enantioselectivities to-date for asymmetric hydrocyanation of 1,3-dienes (70–83% ee's) have been obtained.

Hydrogen cyanide is an abundantly available feedstock that is used extensively in industry for the production of polymer intermediates including adiponitrile, acrylamide, and methyl acrylate.[1] The studies in support of the development of the adiponitrile process from 1,3-butadiene and HCN by the Dupont researchers led to many key discoveries in organometallic chemistry.[2] Cyanohydrins derived from carbonyl compounds are intermediates for several pharmaceutical and agricultural products.[3] However, most applications of HCN as a starting material in *asymmetric synthesis* have been limited to 1,2- and 1,4-additions to carbonyl derivatives.[3,4] In contrast, except for a few vinylarenes, relatively little attention has been paid to *asymmetric* hydrocyanation of alkenes, even though excellent catalytic efficiency (for 6-methoxy-2-vinylnaphthalene, ~2000 h^{-1}) has been demonstrated for this reaction.[5] In the *only* other successful example of an asymmetric hydrocyanation reported, norbornene gives up to 55% ee for the *exo*-carbonitrile at 100 °C (1 mol % catalyst, 24 h).[6]



The lack of interest in this reaction can be traced to the early results on hydrocyanations of simple alkenes and

(1) (a) Casalnuovo, A. L.; RajanBabu, T. V. Transition-Metal-Catalyzed Alkene and Alkyne Hydrocyanations. In *Transition Metals for Organic Synthesis 2nd ed.*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; p 149. (b) Huthmacher, K.; Krill, S. Reactions with Hydrogen Cyanide (Hydrocyanation). In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Ed.; VCH: Weinheim, 1996; Vol. I; p 465. (c) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*; VCH: Weinheim, 1993; p 43.

(2) (a) Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. Homogeneous Nickel-Catalyzed Olefin Hydrocyanation. *Adv. Catal.* **1985**, *33*, 1. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (c) Tolman, C. A. *J. Chem. Educ.* **1986**, *63*, 199.

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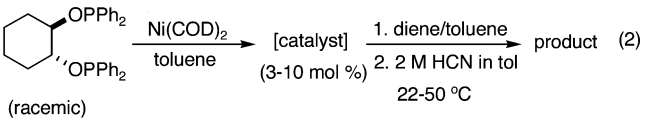
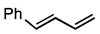
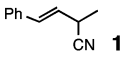
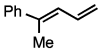
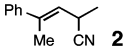
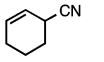
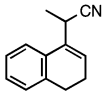
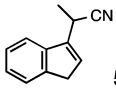
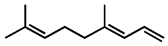
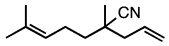
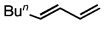
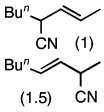
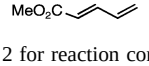
dienes, which seemed to suggest that the reaction needed to be run at high temperatures, and often, isomeric mixtures of nitriles were obtained.[2a,7] These problems are highlighted in eqs 1a and 1b, which illustrate two of the typical protocols including the only asymmetric hydrocyanation of a diene reported to-date. Complexes Ni$\mathbf{L}_n$ [$n = 4$: $\mathbf{L} = P(OPh)_3$; $n = 2$: $\mathbf{L}$ = DIOP] catalyze the addition of HCN to a number of 1,3- and 1,4-dienes at 90−120 °C to give a mixture of nitriles. We recently uncovered new reaction conditions under which readily available, tunable bis-1,2-diarylphosphinites were found to be good ligands in Ni(0)-catalyzed, *low-temperature* hydrocyanation of 1,3-dienes. In this paper, we report the first examples of a *low temperature* hydrocynation of dienes including asymmetric variations.



With the goal of examining the scope of the reaction, the initial experiments were carried out on a number of 1,3-dienes using bis-1,2-diphenylphosphinite derived from racemic *trans*-1,2-cyclohexanediol. A typical protocol representing the new reaction conditions is shown in eq 2, and the results for a variety of dienes are tabulated in Table 1.[8,9]

Table 1. Hydrocyanation of 1,3-Dienes under Ambient Conditions[a]

entry	substrate	product(s)	yield (%)[b]
1.		 **1**	87
2.[c]		 **2**	32
3.		 **3**	>95[d]
4.		 **4**	80
5.		 **5**	71
6.[c]		 **6**	83
7.[c]		 **7** **8**	82
8.		No reaction	0

[a] See eq 2 for reaction conditions. [b] Rest, starting material. [c] 50 °C, 24 h. [d] Estimated by GC and NMR.

A mixture of the ligand and Ni(COD)$_2$ was stirred in toluene at room temperature, and to this was added the diene followed by 2 M solution of HCN in toluene. The mixture was stirred for the prescribed length of time, the solvent was evaporated, and the product was isolated by column chromatography. Only limited optimization of reaction conditions has so far been attempted. 1-Phenyl-1,3-butadiene under these conditions gave, exclusively, 87% of the 1,2-adduct (entry 1). The only other component of the product mixture was unreacted starting material, which was easily removed by chromatography. With additional substitution at the 1-position (entry 2) the reaction proceeds more slowly, yet giving the expected product in high selectivity. 1,3-Cyclohexadiene is an excellent substrate, giving an excellent yield (GC and NMR) of the expected hydrocyanation product at room temperature (entry 3). Dienes with an exocyclic vinyl group (entries 4 and 5) are an interesting class of compounds, useful for the installation of chiral centers at the position of attachment on the ring as well as at the exocyclic positions of the side chain.[10] Here also exclusive formation of the expected 1,2-adduct was observed. Geraniol-derived diene

(3) Kruse, C. G. Chiral Cyanohydrins—Their Manufacture and Utility as Chiral Building Blocks. In *Chirality in Industry − The Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. N., Sheldrake G. N., Crosby, J., Eds.; Wiley: New York, 1992; p 279.

(4) Reviews: (a) North, M. *Synlett* **1993**, 807. (b) Mori, A.; Inoue, S. Cyanation of Carbonyl and Imino Groups. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, p 983. For more recent results, see: (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012 and references therein. (d) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514.

(5) (a) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869. (b) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325. (c) RajanBabu, T. V.; Casalnuovo, A. L. Hydrocyanation of Carbon−Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. I; p 367.

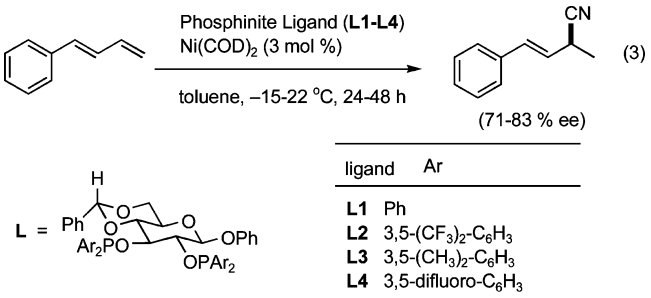
(6) Yan, M.; Xu, Q.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 845. Other reports: (b) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1997**, *8*, 57. (c) Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292. (d) Hodgson, M.; Parker, D. *J. Organomet. Chem.* **1987**, *325*, C27.

(7) (a) Drinkard, W. C.; Lindsey, R. V. Jr.. US Patent 3,496,215, 1970. (b) Keim, W.; Behr, A.; Lühr, H.-O.; Weisser, J. *J. Catal.* **1982**, *78*, 209. (c) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (d) Campi, E. M.; Elmes, P. S.; Jackson, W. R.; Lovel, C. G.; Probert, M. K. S. *Aust. J. Chem.* **1987**, *40*, 1053. (e) Bäckvall, J. E.; Andell, O. S. *Organometallics*, **1986**, *5*, 2350.

(8) See the Supporting Information for details including precautions to be undertaken when using HCN as a reagent.

(9) **Toxicity of Hydrogen Cyanide.** Hydrogen cyanide is a highly toxic, volatile liquid (bp 27 °C) that is also susceptible to explosive polymerization in the presence of base catalysts. It should be handled only in a well-ventilated fume hood or drybox. Sensible precautions include not working alone and having available proper first aid equipment. When handling large quantities of HCN, it should be handled by a team of at least two technically qualified individuals who have received appropriate medical training for treating HCN poisoning (for details see: *Prudent Practices for Handling Hazardous Chemicals in Laboratories*; National Academy Press: Washington, DC, 1981; pp 45−47). HCN prepared by the Ziegler procedure (Ziegler, K. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 341) was diluted with cold (<5 °C) toluene to make a 2 M solution which was kept inside the freezer compartment of a drybox. The solution was further stabilized by adding ~20 mg of P_2O_5 to ~100 mL of the above solution. Excess HCN maybe disposed of by burning or in the case of small amounts by addition to aqueous sodium hypochlorite (which converts it to the cyanate). In the present case, no more than 2 mmol (2 mL of toluene solution) was used at one time.

in entry 6 gave, surprisingly, a single tertiary nitrile, in >95% regioselectivity, thus generating an all-carbon quaternary center in that process. None of the expected 1,2-adduct was observed under the reaction conditions. 1-Butyl-1,3-butadiene, as expected,[7] gave a mixture of 1,2- and 1,4-adducts in good yields. Under these conditions, methyl penta-1,3-dienoate (entry 8) failed to react. The starting material was recovered unchanged.

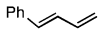
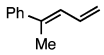
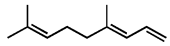


Encouraged by the moderate reaction conditions under which the hydrocyanation of 1,3-dienes proceed, the asymmetric reaction was attempted (eq 3) using various carbohydrate ligands[11] including vicinal diarylphosphinites **L1-L4**, derived from D-glucose. We have used this class of ligands for a variety of reactions[12] including, Ni(0)-catalyzed hydrocyanation of vinylarenes.[5a] 1-Phenyl-1,3-butadiene gave 87% yield and 78% ee for the 1,2-addition product using the bis-3,5-dimethylphenylphosphinite (**L3**) as the ligand (Table 2, entry 1). This 1,3-diene is very reactive, and the reaction can be carried out at −15 °C, using otherwise identical conditions, to get an ee of 83%. The product was converted into known (*S*)-(*E*)-2-methyl-4-phenylbut-3-en-1-ol[13] by reduction with DIBAL followed by treatment of the resulting aldehyde with $NaBH_4$. The configurations of this alcohol and that of the starting nitrile were assigned by comparison of the $[\alpha]_D$ values and chromatographic retention times.

The major enantiomer of the product from 1-vinyl-3,4-dihydronaphthalene (entry 2) was identified after conversion (DDQ in benzene) to the known[5a] fully aromatic compound, (*S*)-2-(1-naphthyl)propionitrile. Configuration of the product of entry 3 was assigned by analogy. Those of entries 4 and 5 have not been assigned.

(10) For the use of asymmetric hydrovinylation in this context, see: Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006,** *128*, 54.
(11) For a more complete list, see the Supporting Information.
(12) (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) Rh-catalyzed hydrogenation: RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. (c) Pd-catalyzed allylation: Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.
(13) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

Table 2. Asymmetric Hydrocyanation of 1,3-Dienes[a]

entry	substrate	L	% yield[b]	% ee[c]
1.		**L1**	92	72
		L2	75	78
		L3	87	78 (83)[d]
2.		**L1**	64	39
		L2	63	75
		L3	73	50
3.		**L1**	68	66
		L2	61	68
		L3	62	70
		L4	46	74
4.		**L2**	56	68
5.		**L2**	48	19

[a] See eq 3 and the Supporting Information for reaction conditions and stereochemical assignments. [b] Rest, starting material. [c] Determined by GC using a Cyclodex-B column or HPLC using Chiralcel OD, OJ or Chiralpak AS-H columns.[8] [d] At −15 °C (52% conversion).

Hydrocyanations of other 1,3-dienes were similarly carried out, and the results are shown in Table 2. In general, moderate to high ee's are obtained for the substrates shown except in entry 5.

In summary, a new protocol for the asymmetric hydrocyanation of 1,3-dienes is reported. We are currently examining modifications of the phosphinite ligands with the goal of improving the scope and the enantioselectivity of the reaction.

Acknowledgment. Financial assistance for this research by the National Science Foundation (CHE-0308378, CHE-0610349) and the Petroleum Research Fund of the American Chemical Society (42964-AC1) is gratefully acknowledged.

Supporting Information Available: Full experimental details of typical hydrocyanation reactions, precautions for the use of HCN, and spectroscopic and chromatographic data for characterization of compounds listed. This material is available free of charge via the Internet at http://pubs.acs.org.

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