CHAPTER 1

HYDROCYANATION OF ALKENES AND ALKYNES

T. V. (BABU) RAJANBABU

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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rajanbabu.1@osu.edu
Organic Reactions, Vol. 75, Edited by Scott E. Denmark et al.

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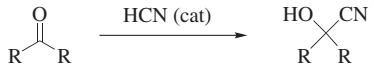
ACKNOWLEDGMENTS

I thank Scott Rychnovsky, Bert Ciganek, Danielle Soenen, and Linda Press and several members of the Editorial Board of *Organic Reactions* for many suggestions to improve the content and presentation of this article. I am grateful for a highly fruitful collaboration with Dr. Al Casalnuovo in developing the asymmetric hydrocyanation of vinylarenes. Research at the Ohio State University was supported by the Petroleum Research Fund of the American Chemical Society and the U.S. National Science Foundation. This article is dedicated to

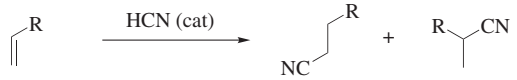
many talented scientists at DuPont, most notable among them Drs. Bill Drinkard, Chad Tolman, and Ron McKinney, who, during the course of developing the DuPont adiponitrile process, formulated many important concepts that helped define the role of ligands in homogeneous catalysis by organometallic complexes.

INTRODUCTION

Hydrogen cyanide is an abundantly available feedstock that is useful for the synthesis of organonitrile intermediates which serve as precursors for amines, amides, isocyanates, carboxylic acids, and esters.[1] Many of these compounds are used in the manufacture of polymers, agrichemicals, cosmetics, and pharmaceuticals. Hydrogen cyanide itself is relatively unreactive, but in the presence of a catalyst HCN adds to carbonyl compounds, alkenes, and alkynes, offering a direct and economical way to such organonitrile intermediates (Eqs. 1–5).[2–6]

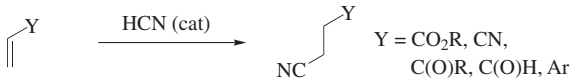


(Eq. 1)

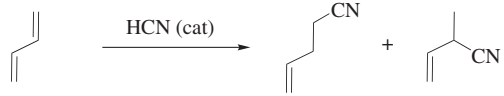


anti-Markovnikov Markovnikov

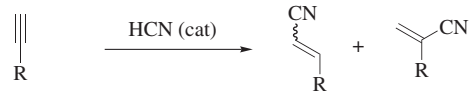
(Eq. 2)



(Eq. 3)



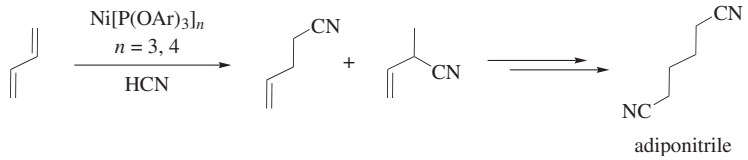
(Eq. 4)



(Eq. 5)

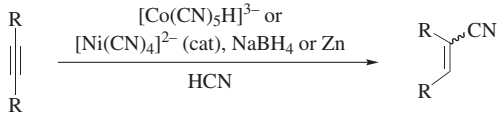
Hydrocyanation of activated substrates such as carbonyl compounds, imines, and electron-deficient alkenes (Eq. 3) usually occurs in the presence of a base, including cyanide ion itself.[7–9] Conjugate addition of HCN to α,β-unsaturated carbonyl compounds also proceed in the presence of Lewis acids such as alkylaluminum reagents (Nagata reaction),[10–12] aluminum salen complexes,[13] and gadolinium alkoxides.[14] Addition of HCN to an unactivated alkene or alkyne is best accomplished with a transition-metal-catalyst, usually a Ni or Pd complex. The classic example, which represents a very successful commercial application of this process, is DuPont's production of the nylon-66 precursor, adiponitrile, via hydrocyanation of 1,3-butadiene (Eq. 6).[15,16] This discovery sparked many seminal mechanistic investigations of transition-metal-catalyzed reactions.[17–23]

Concepts that emerged from these studies include the proposal that many catalytic processes proceed through coordinatively unsaturated 16-electron (or lower) intermediates,[24] and the importance of steric (e.g., ligand cone-angle θ) and electronic effects (e.g., Tolman χ-factor) on ligand substitution reactions.[20,22,25] Hydrocyanation of alkenes continues to offer opportunities for ligand/catalyst tuning to achieve higher efficiencies and selectivities at all levels in a key carbon–carbon bond-forming reaction.[26,27,27a]



adiponitrile (Eq. 6)

Until the late 1960s, the major industrial synthesis of acrylonitrile involved either the addition of HCN to acetylene at high temperature with no catalyst, or addition in the presence of a Cu(I)-catalyst at 80–90°.[1,3,7,28] Reactions involving low-valent Ni, Pd, and Co-complexes have since largely replaced these processes.[29,30] Zero-valent Ni arylphosphite complexes, and to a lesser extent, zero-valent palladium arylphosphine or arylphosphite complexes, catalyze addition of HCN to alkynes. On the basis of the initial discovery of the hydrocyanation of alkynes with stoichiometric $[Co(CN)_5H]^{3-}$, a new process using substoichiometric amounts of $Ni(CN)_4^{2-}$ and stoichiometric amounts of a reducing agent ($NaBH_4$ or Zn) has been reported for the addition of elements of HCN across an acetylene (Eq. 7).[31]



(Eq. 7)

This chapter focuses primarily on the metal-catalyzed hydrocyanation of alkenes and alkynes. Coverage of the catalyzed, conjugate addition of HCN to α, β-unsaturated carbonyl compounds will be limited to a brief mention of the results that appeared since the publication of the *Organic Reactions* chapter on the Nagata reaction.[10] Acetone cyanohydrin and trimethylsilyl cyanide (TMSCN), both commercially available reagents, can be used for the in situ generation of HCN. In some transition-metal-catalyzed additions, TMSCN acts as a surrogate for HCN, giving products where the TMS group replaces the hydrogen. Preparatively, these reagents provide some advantages since the handling of toxic HCN is avoided. Reactions of these reagents are included under the appropriate substrates, so that direct comparison of yield and selectivity can be made. Heterogeneous vapor-phase hydrocyanations catalyzed by metal oxides,[7,32–34] Lewis acids,[7] and transition metals,[32] and 1,2-additions of HCN to carbonyl compounds,[35] imines, or other related compounds[9] are not included here. Mowry's exhaustive review (1942)[7] should be consulted for early reports on the addition of alkali

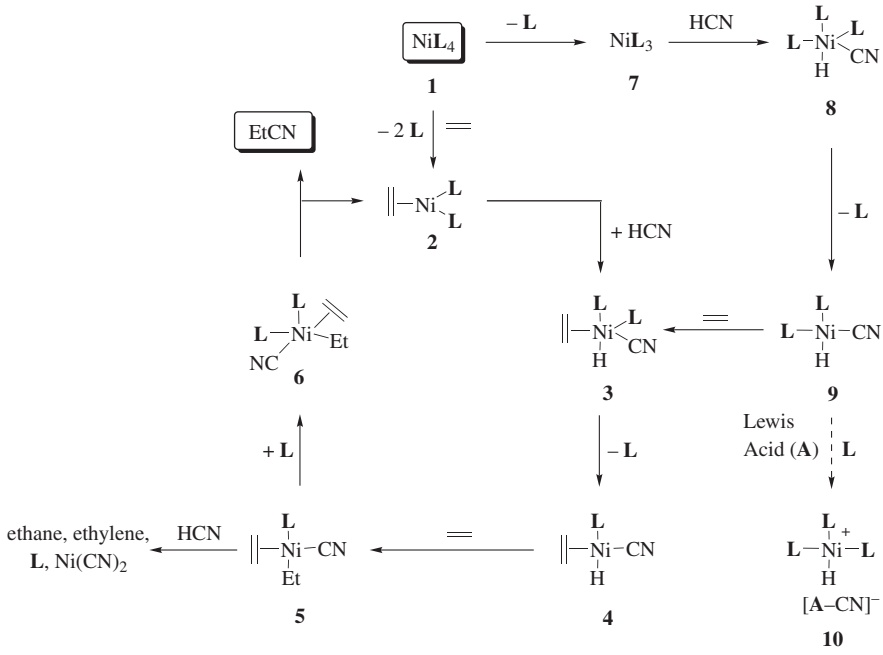
and alkaline earth metal salts to highly activated alkenes such as alkylidene malonates, cyanoacetates, and nitroalkenes. These reactions are often accompanied by side reactions, rearrangements of the primary products, and multiple additions. Because of the large commercial interest in hydrocyanation, many proprietary aspects of these reactions appear in the patent literature. Only the most relevant patents related to synthetic chemistry along with their *Chemical Abstracts* citations are mentioned in this article. This chapter covers the literature on hydrocyanation up to the end of 2008.

MECHANISM AND STEREOCHEMISTRY

Hydrocyanation of Alkenes

Mechanism. Some of the earliest work on homogeneous hydrocyanation of alkenes uses dicobalt octacarbonyl[36,37] and Cu(I)[38] salts as catalysts. For example, catalysis with dicobalt octacarbonyl effects hydrocyanation of simple terminal alkenes, styrene, conjugated dienes, and norbornenes. Unlike the nickel-catalyzed process (see below), the major products correspond to an overall Markovnikov addition of HCN (Eq. 2). Unfortunately, for many of these reactions, a relatively high reaction temperature (130°) is needed and a relatively low catalyst turnover is obtained (1–8 mol nitrile per mol Co). The use of other Co, Fe, Ni, and Pd complexes also appears in the patent literature.[2,3] Very little mechanistic information is available on most of these reactions. In sharp contrast, the mechanism of the Ni$\mathbf{L}_n$-catalyzed reaction [$\mathbf{L} = (ArO)_3P$, $n = 3, 4$] is one of the most extensively studied, in part due to the commercial importance of the DuPont adiponitrile process. A comprehensive review[16] and full details of a mechanistic study[39] have been published and should be consulted for details. An abbreviated mechanism for the hydrocyanation of ethylene is shown in Scheme 1.

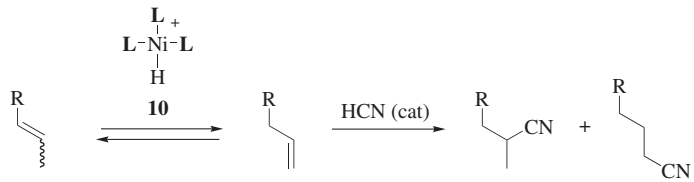
The typical hydrocyanation catalysts are zero-valent triarylphosphite-nickel complexes, $Ni[P(OAr)_3]_n$ ($n = 3, 4$; Ar = Ph or 2-, 3-, or 4-tolyl). These catalysts tolerate a broad range of substrates and functional groups. The initial step is the dissociation of the arylphosphite ligands from the Ni$\mathbf{L}_4$ complex **1** to give a coordinatively unsaturated Ni-complex that readily forms an alkene intermediate **2** (Scheme 1). Oxidative addition of HCN to this complex gives **3**. This intermediate can also be arrived at by oxidative addition of HCN to **7** and subsequent substitution of a ligand in **8** by the alkene. Loss of a ligand from **3** gives **4**. Insertion of ethylene into the metal–hydrogen bond gives **5** with a σ-bonded ethyl group and a π-bonded ethylene. With an excess of the ligand, complex **6** is produced which proceeds to give the product EtCN along with the active catalyst. The last step is essentially irreversible unless the product is an allyl cyanide. If the starting alkene is electron-deficient (tetrafluoroethylene or acrylonitrile), the reductive elimination from **6** is slow and the turnover is essentially blocked. Intermediate **5** is also the source of a deleterious side reaction which forms catalytically inactive $Ni(CN)_2$ if excess HCN is present in the medium. Several of



Scheme 1. Mechanism of the Ni-catalyzed hydrocyanation of ethylene.

the intermediates in the catalytic cycle have been identified by low-temperature spectroscopic techniques.[16]

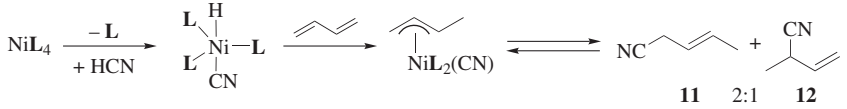
Regioselectivity. Lewis acids such as $AlCl_3$, $ZnCl_2$, or BPh_3 facilitate the addition reactions of terminal alkenes, which are otherwise slow.[21,40] In these reactions, overall anti-Markovnikov additions are observed. Internal alkenes hydrocyanate much slower than terminal alkenes and give a preponderance of linear products when isomerization is possible (Eq. 8).[21] Lewis acids (**A**) promote alkene isomerization by increasing the concentration of the cationic nickel hydride (**10**) via cyanide abstraction from the intermediate **9** by the Lewis acid. (see Scheme 1).



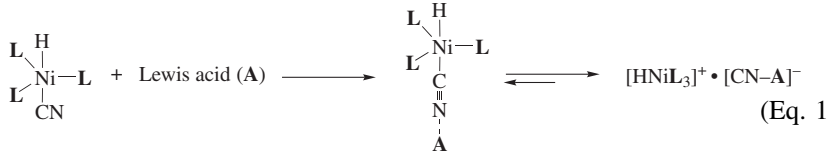
(Eq. 8)

1,3-Butadiene is readily hydrocyanated, and the resulting allylic nitriles, 3-pentenenitrile (**11**) and 2-methylbutenenitrile (**12**), are produced in a ratio of 2:1 by reductive elimination from stable and often detectable η^3-allyl nickel

cyanides (Eq. 9). In the DuPont adiponitrile process, this reductive elimination is reversible and the nickel-catalyzed equilibration of the regioisomeric allylic nitriles is achieved at higher temperatures to favor 3-pentenenitrile (**11**). Isomerization of the 3-pentenenitrile (**11**) to the desired 4-pentenenitrile (**13**) is catalyzed by a cationic nickel hydride **10** that is generated by removal of CN^- by a Lewis acid promoter (**A** in Eq. 10). This isomerization (Eq. 11) is the result of kinetic control made possible by coordination of the CN^- to Ni.[41] Insertion of the double bond in **13** into the [Ni–H] bond of complex **10** followed by reductive elimination yields adiponitrile (**14**) (Eq. 12). It is clear that the size of the Lewis acid dictates the regioselectivity in this process, where only very little of the 2-methylglutaronitrile (**15**) is formed.

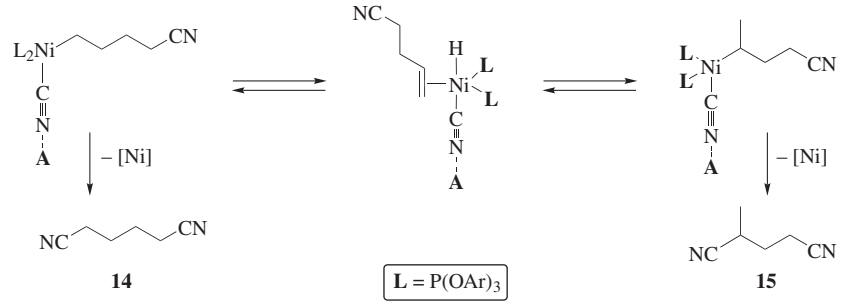


(Eq. 9)



(Eq. 10)

(Eq. 11)

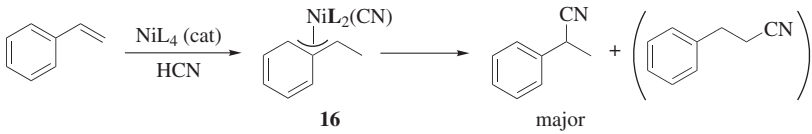


(Eq. 12)

Unconjugated dienes such as 1,5-cyclooctadiene give products typical of conjugated dienes because alkene isomerization is available through a classic insertion/β-hydride elimination mechanism.[42]

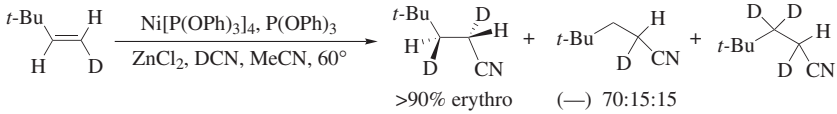
Vinylarenes, similar to conjugated dienes, give rise to η^3-benzylnickel cyanides (see Scheme 2). As a result, an overall Markovnikov addition to yield mostly the

internal nitrile ensues after the reductive elimination of Ni$\mathbf{L}_2$ (Eq. 13).[16] Addition of Lewis acids to the reaction increases the proportion of the terminal nitrile.[43] The reductive elimination from the (benzyl)Ni(CN) complex **16** (or from intermediate **6** in case of simple alkenes, Scheme 1) is known to be the turnover-limiting step in the catalytic cycle.



(Eq. 13)

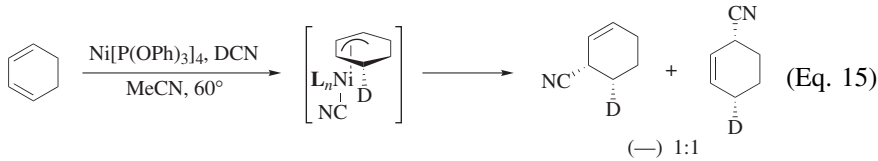
Stereoselectivity. The stereoselectivity of hydrocyanation has been studied in some detail and it has been established that the addition of HCN to olefins is stereospecifically *syn*.[23,40] Addition of HCN to 3,3-dimethyl-1-butene leads to anti-Markovnikov addition of HCN with a regioselectivity of more than 99%.[40] Addition of DCN to (*E*)-1-deuterio-3,3-dimethyl-1-butene leads predominantly to the erythro product, confirming the *syn*-addition mode (Eq. 14).[23] Significant amounts of a geminal dideuterated hydrocyanation product are also observed in this reaction, which supports the intermediacy of Ni–H intermediates. A similar reaction catalyzed by Pd(DIOP)$_2$ also leads to *syn*-addition of DCN to 4-*tert*-butylcyclohexene and *tert*-butylethylene.[44] Under these conditions norbornene gives exclusively *cis-exo*-bicyclo[2.2.1]heptane-3-*d*-2-nitrile.[44]



(Eq. 14)

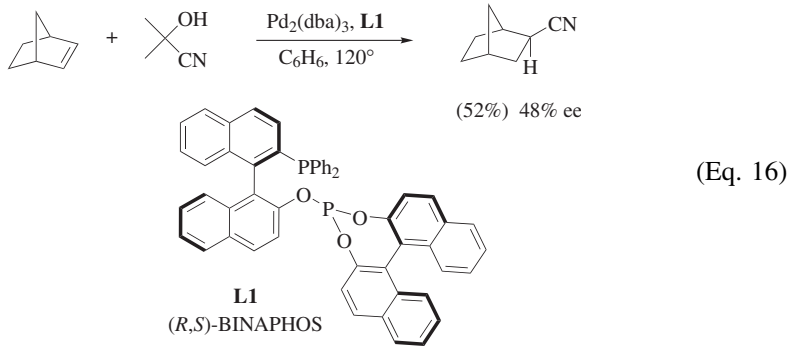
Hydrocyanation of a 1,3-diene follows a mechanism similar to that of an isolated alkene with some significant differences. In this reaction, Lewis acids are not needed and the reaction proceeds to give excellent yields.[16,42] For example, addition of DCN to 1,3-cyclohexadiene results in a smooth conversion to two monodeuterated nitriles which are 1,2 and 1,4-addition products (Eq. 15).[23] The fact that recovered cyclohexadiene does not contain any deuterium suggests that the initial metal hydride addition is irreversible in this reaction. It has been shown that the addition of HNi$\mathbf{L}_3$(CN) [$\mathbf{L}$ = P(O-2-tolyl)$_3$] to butadiene is also essentially irreversible.[21] Careful analysis of the products from 1,3-cyclohexadiene suggests a *syn*-addition of DCN takes place in 1,2- and 1,4-fashions with equal propensity. Other evidence accumulated from a variety of studies including some dealing with asymmetric hydrocyanation of dienes and vinylarenes[45,46] support the intermediacy of an η^3-allyl($\mathbf{L}_n$)Ni–CN complex (Eq. 9) or an η^3-benzyl

($\mathbf{L}_n$)Ni–CN complex (Eq. 13) in the respective hydrocyanations (see below under Asymmetric Hydrocyanation of Dienes and Vinylarenes).



(Eq. 15)

Asymmetric Hydrocyanation. *Asymmetric Hydrocyanation of Norbornene*. Most of the early studies on the transition-metal-catalyzed asymmetric hydrocyanation of alkenes deal with the hydrocyanation of norbornene or its derivatives. Although high facial selectivities are observed, only modest enantioselectivities and yields are obtained in this reaction.[44,47–49] A Pd-catalyzed hydrocyanation of norbornene using the (*R*,*S*)-BINAPHOS ligand **L1** gives 48% ee for the indicated (2*S*)-product (Eq. 16).[50,51]

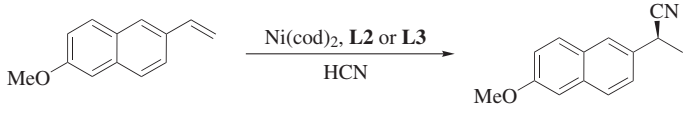


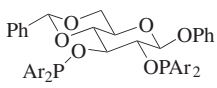
(Eq. 16)

Asymmetric Hydrocyanation of Vinylarenes. The highest enantioselectivities have been obtained for the asymmetric hydrocyanation of vinylarenes using carbohydrate-based [arylphosphinite]nickel complexes as catalysts. When the 2,3-disubstituted gluco-diarylphosphinite ligand **L2** is used, for example, the naproxen precursor, 6-methoxy-2-vinylnaphthalene, is hydrocyanated with complete regioselectivity in 85–95% ee (*S*) (Eq. 17).[45,26] This catalyst system is remarkably active, giving maximum reaction rates of 2000 turnovers h^{-1} (turnover = moles of alkene/mole of Ni/unit time) and 700–800 total turnovers at room temperature.

A key finding of this work is the importance of ligand electronic effects in asymmetric catalysis. A study of the effect of the aryl substituents on phosphorus shows a pronounced increase in the enantioselectivity as the electron-withdrawing power of the substituent increases. For example, the ee in the hydrocyanation of 6-methoxy-2-vinylnaphthalene increases from 16% to 78% as the *meta*-substituents in **L2** are varied in the series Me, H, F, CF_3 ($\sigma_m = -0.07$, 0, 0.34, and 0.43,

respectively). On the other hand, ligand electronic asymmetry appears to be important in the fructose-based phosphinite ligand system **L3**. In this system, the electronic differentiation of the two phosphorus sites is used to maximize the enantioselectivity. Thus, the incorporation of a more electron-withdrawing aryl group in the C_4 position rather than in the C_3 position is crucial to obtaining the highest ee's. For example, for ligand **L3** (Eq. 17) the following selectivities are observed in the hydrocyanation of 6-methoxy-2-vinylnaphthalene: $Ar^1 = 3,5\text{-}(CF_3)_2C_6H_3$, $Ar^2 = C_6H_5$, 58% ee; $Ar^1 = Ar^2 = 3,5\text{-}(CF_3)_2C_6H_3$, 56% ee; $Ar^1 = Ar^2 = C_6H_5$, 43% ee; $Ar^1 = C_6H_5$, $Ar^2 = 3,5\text{-}(CF_3)_2C_6H_3$, 89% ee. A detailed account of the origin of these remarkable ligand effects and its relation to the mechanism of the asymmetric hydrocyanation has been published,[45] and the original papers should be consulted for details. Only the essential highlights are included here.

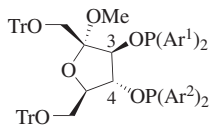




L2

	Ar
L2a	$3,5\text{-}(CF_3)_2C_6H_3$
L2b	$3,5\text{-}F_2C_6H_3$
L2c	C_6H_5
L2d	$3,5\text{-}Me_2C_6H_3$

(Eq. 17)



L3

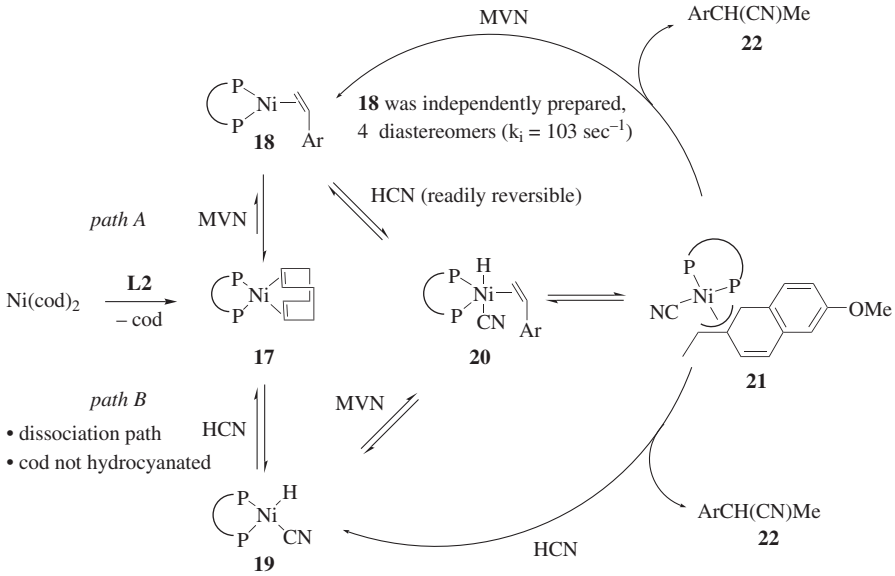
	Ar^1	Ar^2
L3a	$3,5\text{-}(CF_3)_2C_6H_3$	$3,5\text{-}(CF_3)_2C_6H_3$
L3b	Ph	Ph
L3c	$3,5\text{-}(CF_3)_2C_6H_3$	Ph
L3d	Ph	$3,5\text{-}(CF_3)_2C_6H_3$

Studies of the reaction mechanism (Scheme 2) using a series of ligands **L2** with electronically different substituents on the aromatic groups on phosphorus implicate a Ni**L2**(cod) catalyst composition **17** as the resting state in the absence of HCN.[45] However, the enantioselectivity *does not* depend on the differentiation of the *re* and *si* faces of the vinylarene in Ni**L2**(vinylarene) complex **18** that is formed from **17** by ligand exchange. Deuterium labeling studies suggest that the rate of reductive elimination from a Ni**L2**(benzyl)CN complex **21** to give product **22** increases relative to β-hydride elimination (**21** → **20**) as the electron-withdrawing power of the aryl substituent on phosphorus increases.

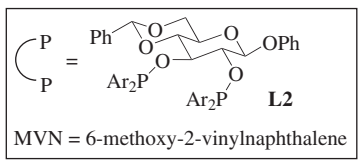
The origin of the relationship between higher enantioselectivities and electron-withdrawing aryl substituents remains speculative because the rates of many of the fundamental processes are largely unknown. Although the steric effects

are determinants of the sense of stereoinduction, the data clearly show that an electronic component is also present in this Ni$\mathbf{L}_n$-catalyst system that can be used to enhance the inherent preference for the (*S*)-nitriles. A series of kinetic and isotopic labeling studies suggests that the barrier for alkene insertion and/or reductive elimination (Scheme 2) is disproportionately lower for the *S*-pathway as the electron-density at nickel is reduced, and this is the origin of the enhanced selectivity.[45]

Asymmetric Hydrocyanation of 1,3-Dienes. Addition of HCN to 1,3-cyclohexadiene in the presence of a chiral phosphite ligand **L5**, shown in Eq. 18, gives (*R*)-2-cyclohexenenitrile in 86% ee and 45% yield.[52] The 3′-methyl group in **L5** is critical for a highly enantioselective reaction since in its absence (e.g., using ligand **L4**) the selectivity is only 43% ee. Mechanistic studies in this system using DCN confirmed the earlier conclusion[45] that the enantioselectivity-determining step involves the reductive elimination from the σ-Ni(**L**)CN-allyl complex.

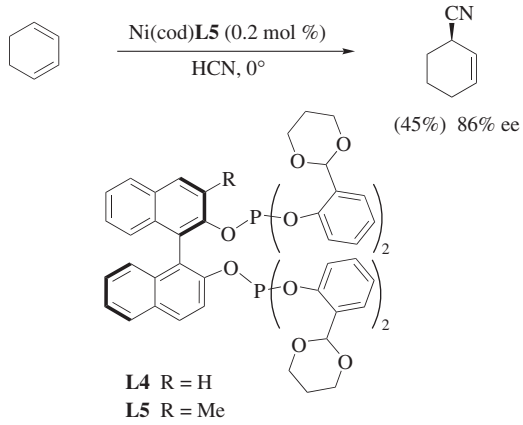


precedent for **19**: Pd(DIOP)(norbornadiene) + HCN



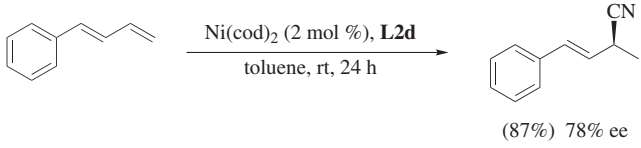
- **17** observed by ^{31}P and ^{1}H NMR
- same species (**17**) observed at the end of reaction
- very little Ni**L2**(MVN) (**18**) forms from Ni**L2**(cod) (**17**) + MVN
- complex **17** is catalyst resting state in the absence of HCN
- complex **21** is catalyst resting state at steady-state

Scheme 2. Details of the mechanism of the Ni-catalyzed hydrocyanation of a vinylarene.



(Eq. 18)

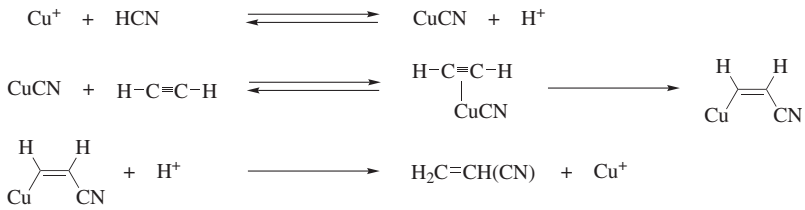
Carbohydrate-derived vicinal bis-diarylphosphinites (**L2**) previously used for asymmetric hydrocyanation of vinylarenes (Eq. 17) give moderate selectivities in Ni(0)-catalyzed asymmetric hydrocyanation of 1-phenyl-1,3-butadiene (Eq. 19) and other 1,3-dienes.[53]



(Eq. 19)

Hydrocyanation of Alkynes

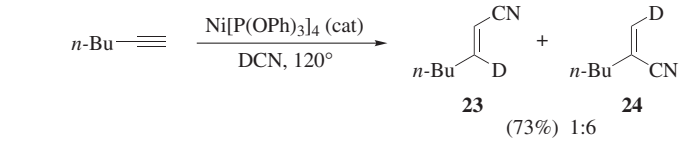
Copper(I)-Catalyzed Hydrocyanation of Acetylene. In this reaction, a dilute mixture of acetylene and hydrogen cyanide is fed into a solution of copper(I) and ammonium chloride at 70–90°. A possible mechanism for this reaction is shown in Scheme 3.[28]



Scheme 3. Mechanism of Cu(I)-catalyzed hydrocyanation of acetylene.

Nickel(0)-Catalyzed Reactions. The mechanism of the Ni(0)(arylphosphite)-catalyzed hydrocyanation of acetylene is thought to be similar to that of alkene hydrocyanation, including the *syn*-stereoselectivity (Eq. 20).[54,55] The

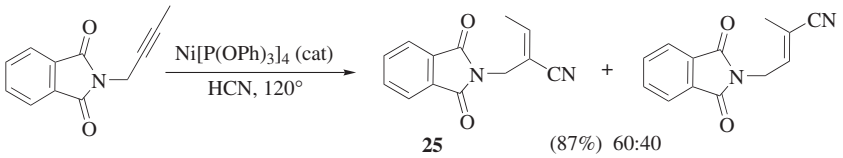
regioselectivity of the reaction is largely determined by steric effects, especially when bulky substituents are present. Terminal alkynes with small and moderately sized aliphatic substituents give mostly the internal nitrile (Eq. 20, **23**:**24** = 1:6), reflecting the increased stability of the secondary C_σ–Ni bonding compared to the C–Ni bond with the terminal carbon. *tert*-Butyl and phenyl acetylenes give terminal nitriles. In hydrocyanations of alkynes containing heteroatoms on one of the substituents, there is a slight preference for the nitriles in which the nitrile group is attached to the carbon carrying the heteroatom (e.g., product **25**, Eq. 21). Hydrocyanation of internal alkynes favors the product in which the nitrile group is attached to the least hindered position. Electronic effects can play an important role in reactions of substrates with small electron-withdrawing substituents. For example, dimethyl acetylenedicarboxylate gives predominantly the *anti*-adduct, albeit in a low yield. [29]



23 **24**

(73%) 1:6

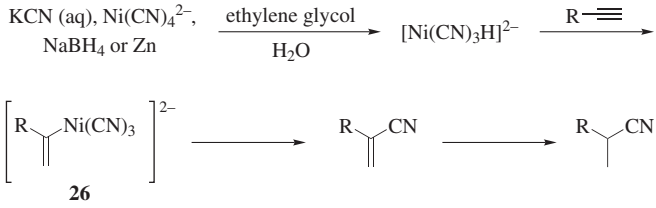
(Eq. 20)



25 (87%) 60:40

(Eq. 21)

Potassium Tetracyanonickelate(II)-Catalyzed Reactions. The hydrocyanation/hydrogenation conditions using $K_2Ni(CN)_4$ as a catalyst (Eq. 22), which is applicable to both terminal and internal alkynes (but not to alkenes), is surprisingly ineffective for symmetrical alkynes.[31] Internal nitriles are strongly favored by this catalyst system, but unlike the nickel phosphite-catalyzed process, the regioselectivity is insensitive to substituent steric effects. Deuterium labeling studies show that borohydride is the hydrogen source for the hydrocyanation, whereas the solvent provides the hydrogens for the subsequent alkene hydrogenation. A mechanism consistent with the observed results including kinetic studies, the selective formation of the internal nitrile, and the *cis* configuration of the intermediate unsaturated nitrile involves the initial hydride transfer from a nickel–hydride species to the acetylene *without* initial formation of a π-acetylene–cyanonickelate intermediate. Subsequent cyanation of this intermediate (e.g., **26**) followed by hydrogenation gives the expected product. Formation of a $[Ni(CN)_3H]^{2-}$-complex from $[Ni(CN)_4]^{2-}$ and the solvent or sodium borohydride is assumed.[31] Presumably, the borohydride is a better source of hydrogen (as a hydride), which is consistent with the incorporation of deuterium upon use of sodium borodeuteride.



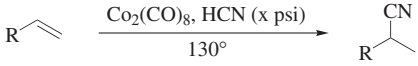
(Eq. 22)

The stoichiometric hydrocyanation of acetylenes by $CoCl_2$ and KCN under an atmosphere of hydrogen also involves formation of the related $[Co(CN)_5H]^-$ intermediate, which forms a σ-vinyl–Co intermediate.[56] The proposed mechanisms of these fascinating reactions should be considered tentative at best.

SCOPE AND LIMITATIONS

Transition-Metal-Catalyzed Hydrocyanation of Unactivated Alkenes

Addition of HCN to unactivated alkenes is a sluggish reaction that proceeds at high temperature in the gas phase over alumina,[57] cyanide-on-alumina,[57] or cobalt-on-alumina[58] catalysts. In homogeneous medium, the reaction is catalyzed by Co, Ni, and Pd complexes. For example, $Co_2(CO)_8$ facilitates the addition of HCN to alkenes in a Markovnikov fashion at 130°.[36] Propene and 1-butene give the corresponding internal nitriles in 65% and 67% conversions at 130° and with moderate pressures in an autoclave (Eq. 23). As the size of the alkyl group on the double bond increases, the conversions decrease. In the case of 1-octene, addition of triphenylphosphine improves the conversion (up to 24%). Functionalized alkenes such as methyl 5-pentenoate and 5-cyanopentene give only moderate yields under these conditions.



R	x	Time (h)	% Conv.	
Me	110	15	65	
Et	40	8	67	
n-C_6H_{13}	46	8	5	
n-C_6H_{13}	43	8	24	*Ph_3P added*

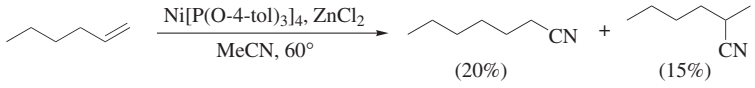
(Eq. 23)

The best results in the hydrocyanation of unactivated alkenes are obtained with $Ni[P(OAr)_3]_n$ ($n = 3$, Ar = 2-tolyl; $n = 4$, Ar = 4-tolyl), which show favorable ligand dissociation kinetics needed for the alkene activation. Olefins form complexes with $\mathbf{L}_2Ni(0)$ with equilibrium constants decreasing in the order ethylene>styrene>propene>1-hexene>disubstituted alkenes. The complexes $Ni\mathbf{L}_2$(olefin) [$\mathbf{L} = P(O\text{-}2\text{-tolyl})_3$] can be isolated for ethylene and styrene (Scheme 1).[16] Addition of HCN to this complex results in complete conversion to alkylnickel cyanide intermediates and subsequently to the products, propionitrile from

ethylene and 2-phenylpropionitrile from styrene. Other alkenes give similar intermediates, but in lower yields. Hydrocyanation of propene gives a 70:30 ratio of terminal to internal products. Isobutylene gives exclusively 3-methylbutyronitrile with cyanide addition occurring at the least hindered position. A similar regioselectivity is reported for *tert*-butylethylene.[23] Cyclopentene, cyclohexene, cyclooctene, trimethylsilylethylene, and 1,1,1-trifluropropene give the expected products in hydrocyanations using $Ni[P(O\text{-}2\text{-}tolyl)_3]_3$ not promoted by a Lewis acid.[16] Unfortunately, details of the preparative aspects of these reactions are sparse.

The unpromoted reactions discussed thus far generally give only a few turnovers. Since the disclosure of soluble Ni(0)[15] and Pd(0)[59] catalysts for homogeneous alkene hydrocyanation, the use of Lewis acids to promote this reaction has received a great deal of attention. The half-life of propene hydrocyanation by $Ni[P(O\text{-}2\text{-}tolyl)_3]_3$ is ~60 minutes at 0°.[16] The addition of Lewis acids dramatically alters the rate of the reaction, with $AlCl_3$ having the most pronounced effect: the half life at −25° is 10 minutes. Triphenylboron slows down the reaction, yet produces the best terminal to internal selectivity in the hydrocyanation of propene (89:11).

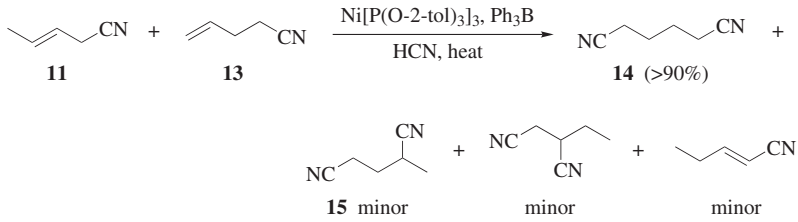
Hydrocyanation of 1-hexene catalyzed by $Ni[P(O\text{-}4\text{-}tolyl)_3]_4$ in the presence of excess ligand and a promoter Lewis acid such as $ZnCl_2$ gives two nitriles in terminal to internal ratio of 4:3 (Eq. 24).[40] The increased activity in the presence of added ligand is thought to be due to the prevention of the formation of the catalytically inactive $\mathbf{L}_2Ni(CN)_2$ species. In many hydrocyanation reactions slow addition of HCN helps to slow down this deactivation process. The Lewis acid promoter acts as a cyanide acceptor and has a pronounced effect on the branched to linear ratio of products. Among the Lewis acids, $ZnCl_2$ gives one of the best selectivities in favor of the terminal nitrile of 1-hexene (terminal:internal = 78:22), whereas $AlCl_3$ is the best for internal nitrile (terminal:internal = 69:31). In the hydrocyanation of hexene with $Ni[P(O\text{-}2\text{-}tolyl)_3]_3$ in the presence of $(4\text{-}tolyl)_3B$, the regioselectivity for the terminal product increases to 91%. Likewise, using *p*-cresol as the solvent ($Ni[P(O\text{-}4\text{-}tolyl)_3]_4$:$P(O\text{-}4\text{-}tolyl)_3$:$ZnCl_2$ = 1:5:2, 60°) gives a higher proportion of the terminal product (terminal:internal = 86:14) compared with acetonitrile (terminal:internal = 78:22).[40] Isobutylene and 2,3-dimethyl-1-butene give a terminal to branched ratio of 99:1.



(Eq. 24)

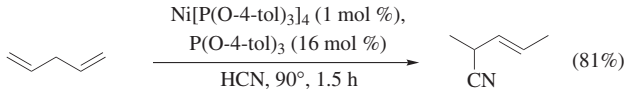
Hydrocyanation of a mixture of 3-pentenitrile (**11**) and 4-pentenenitrile (**13**) is an important step in the DuPont process for the manufacture of adiponitrile from 1,3-butadiene, and many protocols for this reaction have been described in the patent literature.[16] In this process, a mixture of mononitriles obtained from Ni(0)-catalyzed hydrocyanation of 1,3-butadiene (see below under "Hydrocyanation of 1,3-Dienes") is treated with HCN and a mixture of a $Ni[P(O\text{-}2\text{-}tol)_3]_3$ and Ph_3B (Eq. 25).[21,60] Because the isomerization of the internal alkene **11** to the terminal

alkene **13** catalyzed by $\mathbf{L}_3$NiH(CN) (Eq. 11) is faster than the hydrocyanation of the former (Eq. 12), the major product formed is adiponitrile (**14**). More robust chelating phosphites based on various biaryl scaffolds are also viable ligands,[61] including a self-assembled bidentate ligand.[61a] Many different examples have been described in the patent literature.[62]

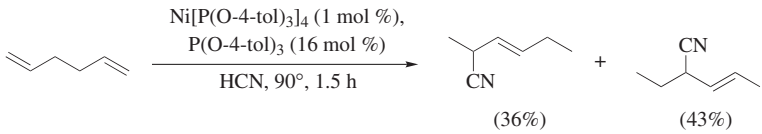


(Eq. 25)

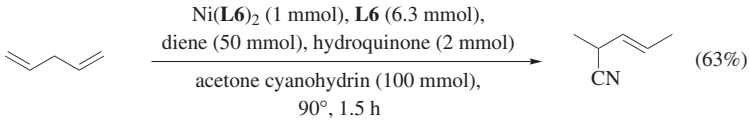
Under similar conditions non-conjugated dienes undergo hydrocyanation to give major products in which the terminal alkene is isomerized (Eqs. 26 and 27).[42] The reaction shown in Eq. 28 demonstrates the use of acetone cyanohydrin in place of toxic HCN and the use of a different chelating diphosphine (**L6**).[63]



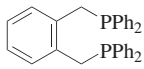
(Eq. 26)



(Eq. 27)

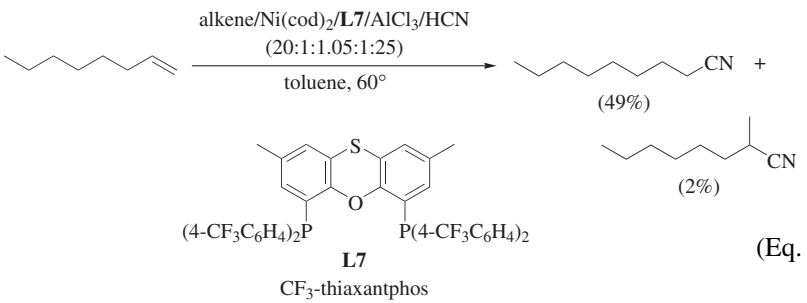


(Eq. 28)



L6

Rigid bidentate phosphines with an optimum bite angle of more than 100° show pronounced activity for the hydrocyanation of unactivated alkenes in the presence of Lewis acids.[64,65] Thus, Ni(cod)$_2$ in the presence of a diphosphine **L7** and $AlCl_3$ effects the hydrocyanation of 1-octene with up to 49:1 terminal to internal ratio of the isomeric nitriles (Eq. 29).[65]



(Eq. 29)

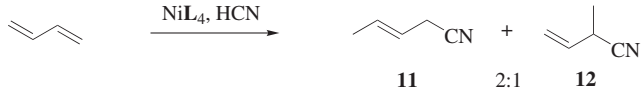
Alkenes bearing halogen, oxygen, carbonyl substituents, or other electron-withdrawing groups do not react with HCN under Ni(0)-catalysis. Mechanistic studies indicate that the final reductive elimination step is retarded by these substituents.[16]

Transition-Metal-Catalyzed Hydrocyanation of Activated Alkenes

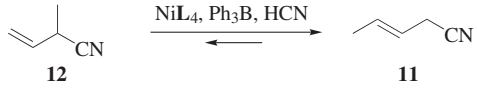
Hydrocyanation of 1,3-Dienes. Even though copper[66,67] and cobalt[3] salts and complexes have been used for the hydrocyanation of 1,3-dienes, nickel-catalyzed reactions are unparalleled in their efficiency and selectivity, and most of the known examples deal with homogeneous catalyzed reactions involving this metal. Because of the huge commercial interest in this reaction, much of the work appears in the patent literature. Only the most relevant results where full details of the preparative aspects are available are discussed here.

The DuPont process for the production of adiponitrile via hydrocyanation of butadiene represents one of the most successful commercial applications of this reaction. As shown in the accompanying equations, a triarylphosphite nickel complex catalyzes the hydrocyanation of butadiene in a multi-step process to give overall anti-Markovnikov addition of two molecules of HCN. The reaction is carried out in two stages. In the initial hydrocyanation, butadiene gives mostly a ~2:1 mixture of isomeric C_5 nitriles, 3-pentenenitrile (**11**) and 2-methyl-3-butenenitrile (**12**), which are resistant to further reaction with HCN in the absence of a Lewis acid (Eq. 30). In a second stage, the initial product is isomerized to a mixture of 3-and 4-pentenenitriles (**11** and **13**) using a $Ni[P(OAr)_3]_n (n = 3$ or 4) complex and a Lewis acid such as Ph_3B or $ZnCl_2$ (Eqs. 31 and 32). Concurrent isomerization of **11** to **13** and anti-Markovnikov HCN addition to **13** follows (Eqs. 32 and 33). Under the optimum conditions, the hydrocyanation of **13** proceeds faster than all the other reactions, and adiponitrile (**14**) is formed in very high yield and selectivity (Scheme 4). The added Lewis acid promoter increases the rate of hydrocyanation of **13** and controls the selectivities in the isomerization reactions.[21,60] Major side products, 2-methylglutaronitrile (**15**) and ethylsuccinonitrile (**27**), arise from hydrocyanation of various intermediates. 2-Pentenenitrile (**28**), which is one of the isomerization products of 3-pentenenitrile, acts as an inhibitor in the process. Fortunately, only a very small amount of this

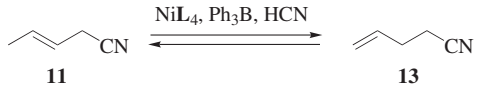
nitrile is formed under production conditions.



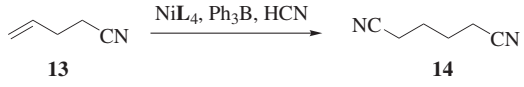
(Eq. 30)



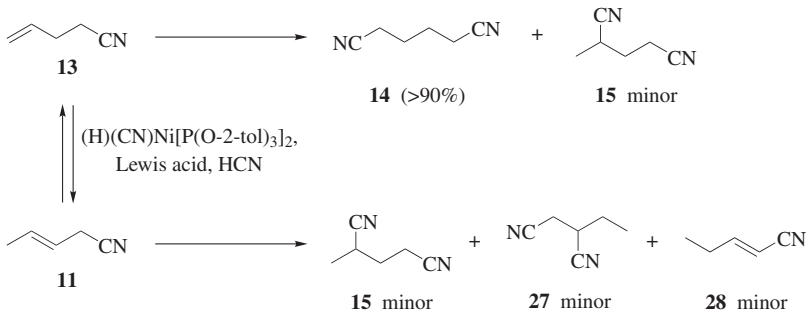
(Eq. 31)



(Eq. 32)



(Eq. 33)



Scheme 4. Side-reactions accompanying butadiene hydrocyanation.

A chelating phosphite ligand based on 2,2′-biphenol makes a robust Ni(**L8**)$_2$ complex (Fig. 1) which, remarkably, is stable when exposed to air for 14 days even in a toluene solution.[61,61a] This complex is more efficient in the initial hydrocyanation of butadiene compared with the more sensitive Ni[P(O-4-tolyl)$_3$]$_4$, yielding more than four times the turnover of the latter. Similar chelating phosphites have been described in the patent literature.[62] Two other recently developed ligands are shown in Fig. 1. The Ni-complexes of the phosphonite ligand **L9** show excellent activity and high selectivity in the hydrocyanation of butadiene.[68,68a] The triptycene-based ligand **L10** with a large bite-angle is exceptionally good in giving a high yield and a very high ratio (93:2) of 3-pentenenitrile (**11**) to 2-methyl-3-butenenitrile (**12**), especially when the reaction is carried out in dioxane (Eq. 34).[27] As might be inferred, Ni(0)-complexes of ligand **L9** and

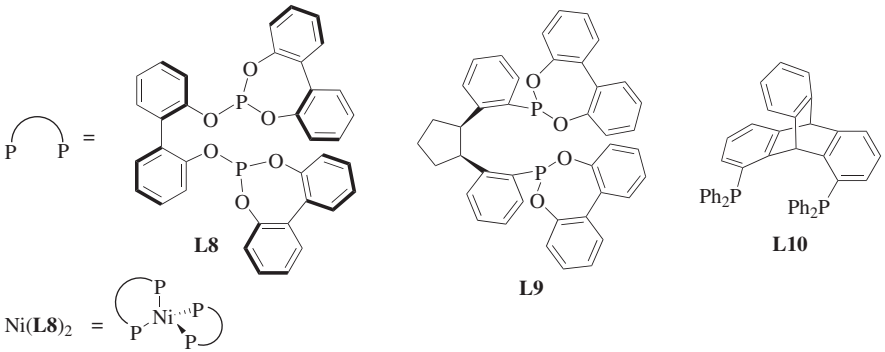
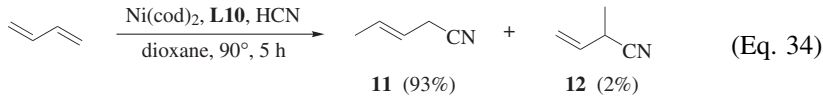


Figure 1. New ligands for hydrocyanation of 1,3-butadiene.

L10 are also good catalysts for the conversion of 2-methyl-3-butenenitrile to 3-pentenenitrile even in the absence of Lewis acids. How much this contributes to the overall higher selectivity for the formation of 3-pentenenitrile remains to be established.

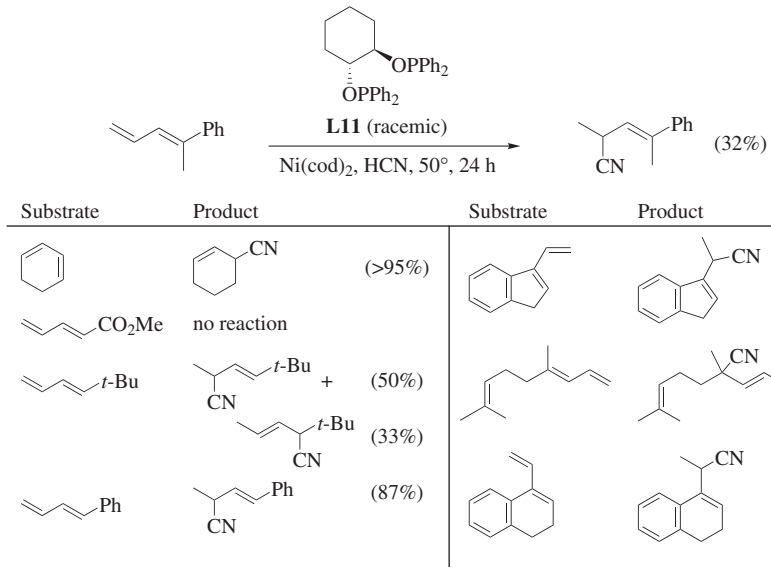


11 (93%) **12** (2%) (Eq. 34)

The feasibility of hydrocyanation of other dienes catalyzed by $Ni[P(OAr)_3]_n$ ($n = 3$ or 4) has been demonstrated. These include reactions of 1-vinyl-1-cyclohexene,[16] norbornadiene,[16] dicyclopentadiene,[16] allene,[16] 1,5-cyclooctadiene,[16] 1,3-cyclooctadiene,[16] cyclopentadiene,[16] 1,3-cyclohexadiene,[23] 1-methyl-1,3-butadiene, 2-methyl-1,3-butadiene, and 1,4-dimethyl-1,3-butadiene.[42] To be of practical synthetic value, further optimization of reaction conditions will be required for most of these substrates.

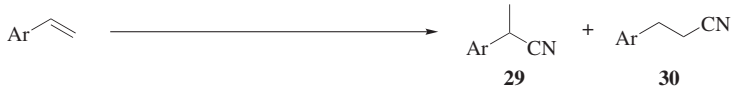
A simple analog of carbohydrate-derived 1,2-bis(diarylphosphinites) (**L2**, Eq. 17), **L11**, has been used extensively in asymmetric hydrogenation and hydrocyanation reactions (see below under "Asymmetric Hydrocyanation of Vinylarenes"). The 1,2-bis(diphenylphosphinite) derived from *trans*-1,2-cyclohexanediol (**L11**) readily forms Ni-complexes that catalyze addition of HCN to a variety of 1,3-dienes at 25–50°.[53] The examples shown in Eq. 35 are typical.

Thus, sequential additions of 1,3-cyclohexadiene and HCN to a catalyst prepared from the ligand and $Ni(cod)_2$ give the expected product in >95% yield. The yields of other dienes vary with the structure of the dienes. Higher temperatures are needed for more substituted, less reactive dienes such as 1-phenyl-1-methyl-1,3-butadiene and 2,6-dimethylnona-2,6,8-triene. Depending on the structure of the diene, both 1,2- and 1,4-additions are observed.



(Eq. 35)

Hydrocyanation of Vinylarenes. Hydrocyanations of styrene and various other vinylarenes have been investigated in detail.[16,26,43] The internal nitrile **29** is obtained as the major product with $Ni[P(O\text{-}4\text{-}tolyl)_3]_4$ (Eq. 36). This can be explained on the basis of the formation of a stable η^3-intermediate (see Scheme 2, **21**)[45] whose presence can be inferred from UV spectroscopy.[16] High activity and selectivity for the formation of the internal isomer **29** has been observed using finely tuned Xantphos ligands (e.g., **L7**, see Eq. 29 for ligand structure) having a natural bite angle of 105–106°.[65] Several other catalysts that give very high regio- and enantioselectivities are discussed under "Asymmetric Hydrocyanation Reactions."

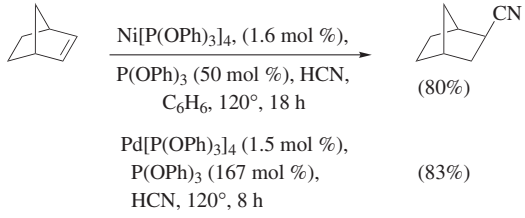


29 **30**

	Ar	**29** + **30**	**29**:**30**
$Ni[P(O\text{-}4\text{-}tol)_3]_4$ (5 mol %), $P(O\text{-}4\text{-}tol)_3$ (10 mol %), HCN (excess), $ZnCl_2$ (2 mol %), 88°, 3 h	4-*i*-BuC_6H_4	(68%)	90:10
$Ni[P(O\text{-}4\text{-}tol)_3]_4$ (5 mol %), $P(O\text{-}4\text{-}tol)_3$ (10 mol %), HCN (excess), $ZnCl_2$ (2 mol %), 88°, 5.5 h	6-OMe-2-naphthyl	(93%)	95:5
Ni(cod)**L7**/**L7**/styrene/HCN (1:1.05:20:25), toluene, 60°, 16 h	Ph	(90%)	99:1

(Eq. 36)

Hydrocyanation of Strained Alkenes. Hydrocyanation of norbornene is catalyzed by both $Pd[P(OPh)_3]_4$[59] and $Ni[P(OPh)_3]_4$[47,59] to give the *exo*-adduct exclusively (Eq. 37).

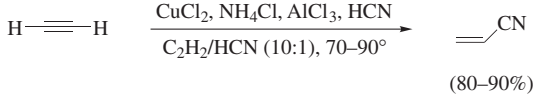


(Eq. 37)

Conjugate Addition of HCN to Activated Alkenes. As discussed in the introduction, this topic is beyond the scope of the current chapter. An excellent review of recent work has been published,[8] and the reader is directed to this source. Other pertinent references can be found in recent papers that deal with asymmetric C–CN bond-forming reactions.[13,14,69,70]

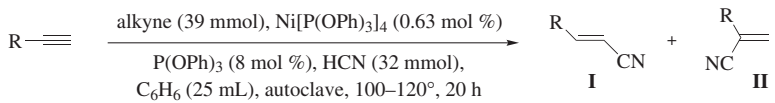
Transition-Metal-Catalyzed Hydrocyanation of Alkynes

A major manufacturing process for acrylonitrile used to be the addition of HCN to acetylene (Eq. 38) until it was replaced by the cooxidation of propylene and ammonia (the SOHIO process).[28] The need for strong acids such as HCl for catalytic activity suggests the intermediacy of a C_σ–Cu species. As expected, the major byproducts in the reaction are acetaldehyde and vinylacetylene.



(Eq. 38)

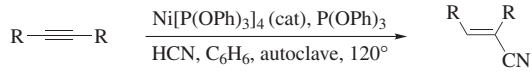
Addition of HCN catalyzed by $Ni[P(OAr)_3]_4$ to straight-chain terminal alkynes with moderately sized substituents leads to mostly the internal products (Eq. 39).[71,72] In this example, the relative stability of the secondary Ni–C_σ bond overwhelms the steric effect of the alkyl group. Symmetric alkynes give varying yields of the product (Eq. 40). Bulky substituents direct the cyano group to the terminal position, indicating that there is also a pronounced steric effect on the regioselectivity of this reaction. A similar trend is observed in silyl-substituted alkynes with 1-triphenylsilyl-1-hexyne giving exclusively the terminal nitrile (Eq. 41).[73] Trimethylsilylacetylene gives a terminal to internal ratio of 25:75 and *tert*-butyldimethylsilylacetylene gives a ratio of 35:65. The size of the silyl group can be used to control the regioselectivity in hydrocyanation reactions of disubstituted acetylenes (Eq. 41).[74] In general, the reactions proceed with *syn*-stereoselectivity. In many of these reactions, acetone cyanohydrin can be used in place of the toxic HCN, thus making this a preparatively useful reaction for the synthesis of vinyl nitrile intermediates.[72,74]



R	I + II	I:II
n-Pr	(78%)	12:88
n-Bu	(73%)	14:86
t-Bu	(15%)	88:12
t-Bu	(45%)	80:20[a]
n-C_6H_{13}	(60%)	14:86
Ph	(45%)	90:10

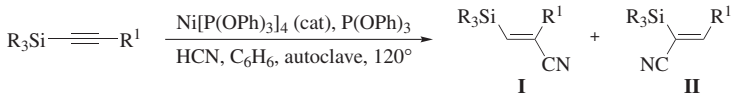
[a] Slow addition, 60°

(Eq. 39)



(Eq. 40)

R = Ph (93%)
R = CO_2Me (27%) *possibly* E-*isomer*



Me_3Si–

R^1	I + II	I:II
H	(74%)	25:75
Me	(87%)	80:20
n-Bu	(90%)	72:28
Ph	(80%)	20:80

acetone cyanohydrin, refluxing toluene

***t*-$BuMe_2Si$–**

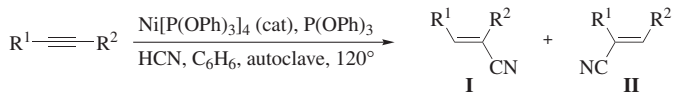
R^1	I + II	I:II
H	(57%)	35:65
Me	(88%)	98:2
n-Bu	(85%)	97:3
Ph	(73%)	90:10

Ph_3Si–

R^1	I + II	I:II
n-Bu	(75%)	100:0

(Eq. 41)

Hydrocyanations of alkynes with functionalized substituents such as hydroxy,[75] alkoxy,[76] and phthalimido (PhT)[77] have been carried out (Eq. 42). The coordinating properties of these groups can alter the commonly observed regioselectivity in some of these reactions. The products from α- and β-hydroxyalkylalkynes have been converted into α-alkylidene-γ-lactones[76] and the phthalimido-bearing nitriles[77] have been used for the synthesis of various β- and γ-amino acids via hydrogenation of the double bond followed by hydrolysis of the nitrile.[78,79]

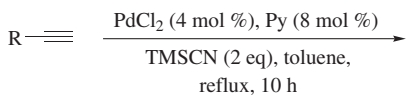


R^1	R^2	I + II	I:II
Me	CH_2OH	(72%)	1:1
H	$(CH_2)_2OBn$	(78%)	19:3
H	CH_2PhT	(88%)	4:1
H	CH_2PhT	(72%)	1:1
Me	$(CH_2)_2PhT$	(88%)	9:1

(Eq. 42)

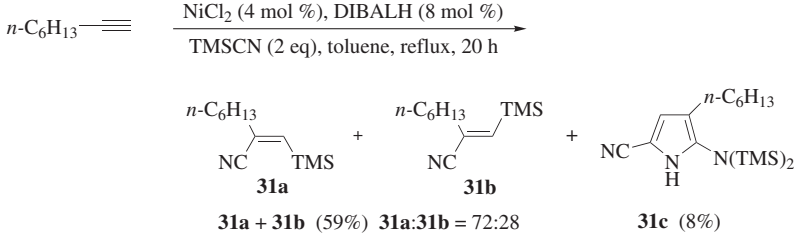
Addition of Trimethylsilyl Cyanide to Alkynes

Addition of trimethylsilyl cyanide to terminal alkynes is a synthetically useful reaction that is catalyzed by $PdCl_2$ in the presence of pyridine (Py) (Eq. 43).[80] The reaction is regioselective in that the more highly substituted nitrile is the major product, which arises via a *syn*-addition of TMSCN to the alkyne, giving predominantly the (*Z*)-alkene. A less general Ni(0)-catalyzed addition (Eq. 44)[80] is complicated by competitive addition of TMSCN to the initial product, yielding pyrrole carbonitriles (e.g., **31c**). Reaction with internal alkynes is sluggish and in general gives a mixture of products including pyrrole derivatives.



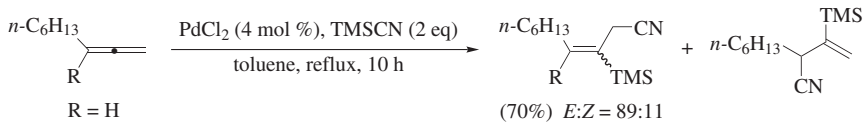
R	I + II	I:II
$TMSO(CH_2)_2$	(34%)	88:12
n-C_6H_{13}	(41%)	85:15
Ph	(90%)	95:5
4-$MeOC_6H_4$	(90%)	95:5
2-naphthyl	(90%)	95:5

(Eq. 43)



(Eq. 44)

Allenes also react with TMSCN in the presence of a $PdCl_2$/pyridine catalyst to afford vinylsilanes in which silicon is bound to the central carbon of the allene.[81] When R = H, a side product (3–20%) in which the cyanide is trapped at the C3 position is also formed (Eq. 45).

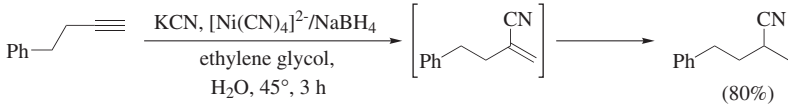


(Eq. 45)

Cyanonickelate- and Cyanocobaltate-Catalyzed Hydrocyanation of Alkynes

An intriguing catalyst system for alkyne hydrocyanation that does not utilize organophosphorus-stabilized nickel or palladium complexes or HCN involves cyanometalates of cobalt and nickel in mixed aqueous media. On the basis of initial work involving the stoichiometric hydrocyanation of alkynes with $[Co(CN)_5H]^{3-}$,[82] a catalyst employing $Ni(CN)_4^{2-}$ for the hydrocyanation of alkynes has been developed.[31,56] As shown in Eq. 46, treatment of an alkyne with

KCN, a reducing agent such as Zn or $NaBH_4$, and a substoichiometric amount of $Ni(CN)_4^{2-}$ leads to alkyne hydrocyanation and subsequent hydrogenation of the initially formed unsaturated nitrile. Attractive features of this system include the use of an air- and moisture-stable catalyst precursor, the use of the cyanide ion as both a reagent and a ligand for the catalyst, and the ease of separating an aqueous catalyst solution from the product and substrate. One major drawback is the low catalyst turnover (<8 mol RCN/mol Ni).

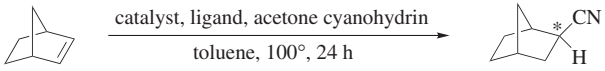


(Eq. 46)

Asymmetric Hydrocyanation Reactions

Markovnikov addition of HCN to an alkene can in principle serve as an entry into chiral compounds that can be transformed into a wide array of useful products.[26,83] In spite of the extensive work on hydrocyanation of alkenes, only limited research activity has been directed toward finding an asymmetric variation of this reaction.

Bicyclo[2.2.1]heptanes. Most of the early studies in this area focused on the HCN additions to norbornene and its derivatives (Eq. 47). Although these reactions give exclusively the *exo*-isomer, the highest enantiomeric excess reported to date for this class of substrates is only ~55%, using a binaphthol-derived phosphite **L12** (Fig. 2) as a ligand for Ni(0).[51] Other ligands that have been investigated for this reaction include **L13**,[49] **L1**,[50], DIOP,[47] and BINAP,[48] whose structures are shown in Fig. 2. The yields and enantioselectivites obtained with these ligands using either their nickel or palladium complexes are also shown (Eq. 47).



Catalyst, Ligand		% ee	Config.
$Ni(cod)_2$, **L12**	(—)	55	—
$Ni(\mathbf{L13})_2$, Ph_3B	(58%)	38	*R*
$Ni(cod)_2$, **L1**	(52%)	40	*S*
$Pd(\mathbf{L1})_2$, **L1**	(52%)	48	*S*
$Ni[(R,R)\text{-DIOP}]_2$, (*R*,*R*-DIOP)	(20%)	14	*R*
$Pd[(S,S)\text{-DIOP}]_2$, (*S*,*S*-DIOP)	(94%)	32	*S*
$Pd[(R)\text{-BINAP}]_2$, (*R*)-BINAP	(6%)	40	*R*

(Eq. 47)

Norbornadiene and benzonorbornene have also been hydrocyanated with low enantioselectivites using (−)-$Pd(DIOP)_2$ complexes.[47] The ligand **L12** gives an ee of 73% in the asymmetric hydrocyanation of vinyl acetate in a low-yielding reaction.[51]

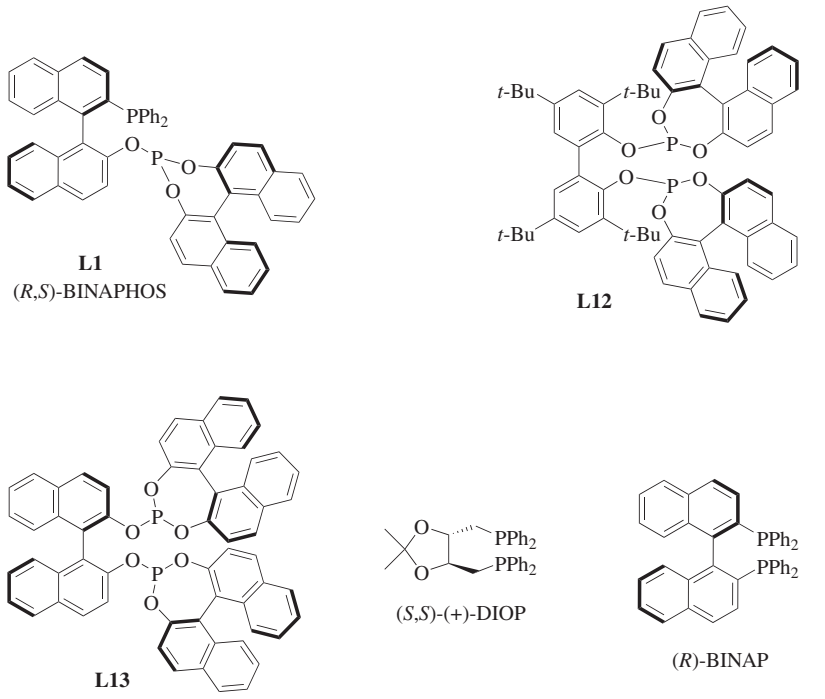
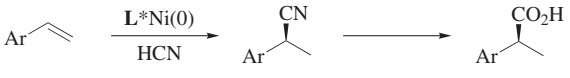


Figure 2. Ligands for asymmetric hydrocyanation of alkenes.

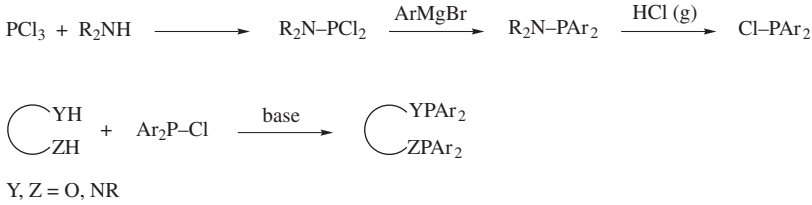
Vinylarenes. An important class of compounds that can be readily prepared from vinylarenes via the asymmetric hydrocyanation route are the 2-arylpropionitriles, precursors for the widely used antiinflammatory 2-arylpropionic acids (Eq. 48).[84,85] Of these, only naproxen [(*S*)-2-(6-methoxynaphthyl) propionic acid] is sold as an enantiomerically pure drug. Racemic ibuprofen and naproxen have been prepared by the $Ni[P(O\text{-}4\text{-}tolyl)_3]_4$-catalyzed hydrocyanation of the corresponding vinylarene (Eq. 36) followed by hydrolysis of the resulting 2-arylpropionitrile.



(Eq. 48)

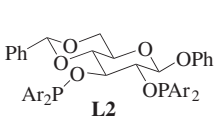
Ar = 4-isobutylphenyl (ibuprofen)
Ar = 6-methoxy-2-naphthyl (naproxen)

The most active ligands for the hydrocyanation of vinylarenes are vicinal diarylphosphinites derived from 1,2-diols. Readily accessible diarylchlorophosphines can be coupled to several commercially available diols and amino alcohols (Scheme 5). Hydrocyanations of prototypical vinylarenes using phosphinites from dimethyl tartrate, binaphthol, propranolol, pseudoephedrine, prolinol, pinenediol,



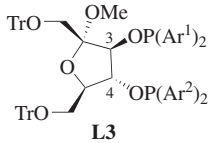
Scheme 5. Synthesis of diarylphosphinites.

and various steroidal diols as ligand precursors give excellent yields and regioselectivities, yet only disappointing enantioselectivities.[83] However, these studies established that the 1,2-bis(diarylphosphinites) could serve as broadly applicable ligands for the Ni(0)-catalyzed hydrocyanation of vinylarenes.



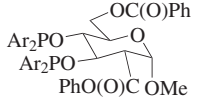
L2

	Ar
L2a	3,5-$(CF_3)_2C_6H_3$
L2b	3,5-$F_2C_6H_3$
L2c	C_6H_5
L2d	3,5-$Me_2C_6H_3$



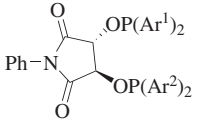
L3

	Ar^1	Ar^2
L3a	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$
L3b	Ph	Ph
L3c	3,5-$(CF_3)_2C_6H_3$	Ph
L3d	Ph	3,5-$(CF_3)_2C_6H_3$



L14

	Ar
L14a	3,5-$(CF_3)_2C_6H_3$
L14b	Ph
L14c	3,5-$Me_2C_6H_3$



L15

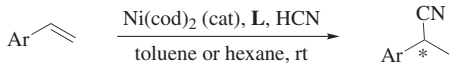
	Ar^1	Ar^2
L15a	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$
L15b	Ph	Ph
L15c	Ph	3,5-$(CF_3)_2C_6H_3$

Figure 3. Carbohydrate-derived ligands for asymmetric hydrocyanation of vinylarenes.

The highest enantioselectivities for the asymmetric hydrocyanation of vinylarenes have been obtained using finely tuned carbohydrate-derived phosphinite–Ni catalysts. Several 1,2- and 1,3-diarylphosphinite ligands are synthesized from tartaric acid and from various sugars including glucose, galactose, fructose,

2-acetamidoglucose, lactose, and trehalose.[83] The structures of four of these scaffolds **L2**, **L3**, **L14**, and **L15**, along with the substituents on the *P*-aryl groups, are shown in Fig. 3.

The results of hydrocyanation of vinylarenes using these ligands are shown in Eq. 49 and the tables that follow.[83] Inspection of the results in Table A suggests that the local chirality defined by the phosphinoxy-bearing carbons controls the absolute configuration of the major product. Thus, ligands of the type 2,3-*O*-disubstituted D-gluco-bis(diarylphosphinite) (**L2**) give the (*S*)-nitrile as the major product, whereas the corresponding 3,4-bis-*O*-diarylphosphinites (**L14**) give the (*R*)-nitrile. In a related observation, 3,4-disubstituted methyl α-D-fructofuranoside 3,4-*O*-bis(diarylphosphinites) (**L3**) also give the (*R*)-nitrile. These and other initial results suggest that the phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**L2**) is the best and most accessible sugar backbone, and further variations of the *P*-aryl-substituent on this sugar backbone have been undertaken to enhance the observed enantioselectivity. As shown in Table B, two strongly electron-withdrawing CF_3-substituents at the 3- and 5-positions of the arylphosphinites (ligand **L2a**) give the highest selectivity in the asymmetric hydrocyanation of a number of vinylarenes. The ee's decrease dramatically (from >85% to 16% for 6-methoxy-2-vinylnaphthalene) as the electron-withdrawing power of the *P*-aryl substituent decreases (for **L2a**–**L2d**, $\sigma_m = 0.43, 0.34, 0, -0.07$ respectively).



(80–95%) (Eq. 49)

The asymmetric hydrocyanations of a series of 4-substituted styrenes show that the electron-deficient catalysts indeed give the highest ee's in every case examined (e.g., for 4-methylstyrene: **L2a**, 70%; **L2b**, 47%; **L2c**, 1%).[45] Yet the electronic nature of the substrate also seems to play an important role. For example, the following ee's are observed using **L2a** for a series of substituted styrenes: 4-Me, 70%; 4-Ph, 68%; 4-phenoxy, 60%; 4-*i*-Bu, 56%; 4-MeO, 52%; 4-Cl, 40%; 4-F, 28%; 4-CF_3, 14%.

Fine-tuning of the diaryl phosphinites derived from the methyl α-fructofuranoside (**L3**) produces electronically 'symmetrical' and 'unsymmetrical' bis(diaryl) phosphinite ligands that afford (*R*)-2-arylpropionitriles (Table C).[86] As anticipated from previous work, electron-donating substituents on the phosphorus aryl groups give the lowest enantioselectivities. Symmetrical electron-deficient

TABLE A. EFFECT OF SUGAR BACKBONE ON CONFIGURATION OF THE HYDROCYANATION PRODUCT OF 6-METHOXY-2-VINYLNAPHTHALENE

Ligand	Ar	% ee	Config.
L2c	Ph	35	*S*
L14b	Ph	20	*R*
L3b	Ph	43	*R*

TABLE B. EFFECT OF ELECTRON-WITHDRAWING GROUPS ON ENANTIOSELECTIVITY

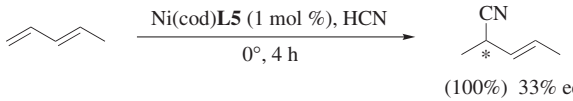
	Ligand, % ee, *S*			
Vinylarene	**L2a**	**L2b**	**L2c**	**L2d**
6-MeO-2-vinylnaphthalene	85–91	78	35	16
2-vinylnaphthalene	77	75	46	45
1-vinylnaphthalene	68	—	63	—
acenaphthene	59	—	0	—
3-fluoro-4-phenylstyrene	55	—	10	—
4-isobutylstyrene	56	38	6	—
4-trifluoromethylstyrene	14	9	1	—

TABLE C. EFFECT OF ELECTRONIC ASYMMETRY ON ENANTIOSELECTIVITY OF THE HYDROCYANATION PRODUCT OF 6-METHOXY-2-VINYLNAPHTHALENE

Ligand	% ee, *R*	Ligand	% ee, *S*
L3a	56	**L15a**	70
L3b	43	**L15b**	54
L3c	58	**L15c**	77
L3d	89		

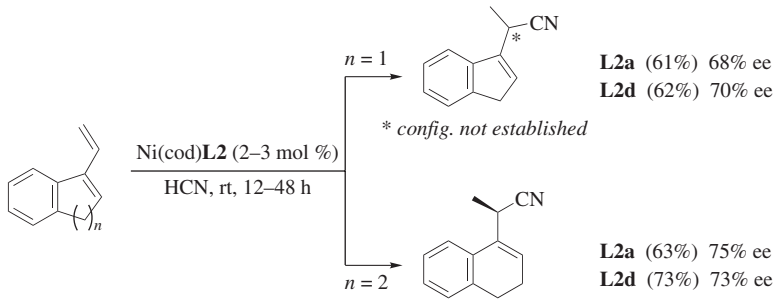
phosphinites increase the selectivity to some extent. But the highest enantioselectivities (89–95% ee) are obtained with C_3 of the sugar carrying an electron-rich phosphinite, and the C_4 carrying an electron-deficient phosphinite (ligand **L3d**). A similar observation is also made using (3*S*,4*S*)-tartranil phosphinites (**L15**): the highest ee, 77% (*S*), is obtained with a mixed phenyl/3,5-bis(trifluoromethyl)phenyl derivative (**L15c**) whereas the C_2-symmetric 3,5-bis(trifluoromethyl)phenyl- and phenylphosphinite derivatives **L15a** and **L15b** give 70 and 54% ee, respectively.

1,3-Dienes. Asymmetric hydrocyanation of 1,3-dienes continues to be a challenge. The best results reported to date are for a low-yielding reaction of 1,3-cyclohexadiene with HCN using a Ni(0)-complex of a binaphthol-derived phosphite **L5** (Eq. 18).[87] Under the same conditions, 1-methylbutadiene gives an ee of 33% (Eq. 50).

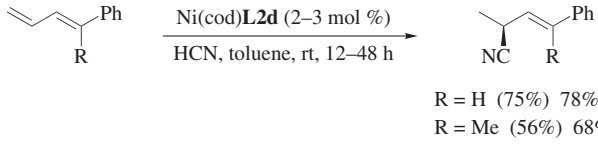


(100%) 33% ee (Eq. 50)

The D-glucose-derived ligands **L2a** and **L2d** (Fig. 3) used for asymmetric hydrocyanation of vinylarenes are moderately effective for the hydrocyanation of special classes of 1,3-dienes, as shown in Eqs. 51 and 52.[53]



(Eq. 51)



(Eq. 52)

Limitations and Future Prospects

Currently, synthetically useful hydrocyanation reactions are limited to vinylarenes, certain types of 1,3-dienes, and alkynes. Reactions of unactivated terminal alkenes proceed in moderate yields and regioselectivities. Intermediacy of an allylnickel complex in the 1,3-diene hydrocyanation leads to good-to-moderate regioselectivity in reactions of substituted 1,3-dienes. Isomerization of double bonds under hydrocyanation conditions limits the utility of internal and unconjugated dienes. The regioselectivity in the hydrocyanation of internal alkynes is poor, although terminal silyl substitution and judicious use of alkynes carrying heteroatom-substituted side-chains do provide a synthetically viable route to complex vinyl nitriles. Unactivated alkenes are less reactive and need Lewis acids to promote the reaction. While the $Co_2(CO)_8$-mediated reactions give the Markovnikov products selectively from terminal alkenes, high temperatures, prolonged reaction times, and low turnovers in the catalyst are major drawbacks of this otherwise worthwhile hydrofunctionalization reaction. A systematic investigation of the cobalt-mediated reaction might be a highly profitable area for future research. Reactions of allenes have not been explored to a great extent. Asymmetric hydrocyanation is another potentially important area that has been poorly developed. Enantioselectivities above 90% ee have been achieved only for vinylnaphthalene derivatives. Substituted dienes, which undergo hydrocyanation reactions even in the absence of Lewis acids, could in principle serve as highly valuable precursors if the problems of regio- and stereoselectivities can be solved. Alkenes carrying electron-withdrawing substituents do not participate in metal-catalyzed hydrocyanation reactions. These substrates are ideally suited for the base- or Lewis acid catalyzed reactions. Finally, the toxicity of HCN is an important consideration, even though with proper precautions it can be readily

handled as borne out by the use of billions of pounds of HCN in the chemical industry. Use of acetone cyanohydrin and TMSCN as surrogates for the toxic HCN should alleviate some of the safety concerns.

APPLICATIONS TO SYNTHESIS

The synthesis of adiponitrile by the Ni(0)-catalyzed hydrocyanation of 1,3-butadiene is one of the largest industrial applications of homogeneous catalysis.[22,88] The nitrile is reduced and the resulting hexamethylenediamine is used for various applications including the manufacture of nylon-66. The antiinflammatory 2-arylpropionic acids ibuprofen and naproxen have been synthesized in racemic form by hydrocyanation of the corresponding vinylarenes.[43] An asymmetric version of this reaction would be useful for the synthesis of enantiopure (*S*)-naproxen since the precursor 2-arylpropionitrile can be recrystallized to enantiomeric purity.[89] Hydrocyanation of functionalized alkynes has been used for the syntheses of α-alkylidene-γ-lactones[76] and β- and γ-amino acids.[78,79] Conjugate addition of HCN or its surrogates including asymmetric enantioselective versions have been reported and these reactions have been used extensively in synthesis. A discussion of these reactions is beyond the scope of this chapter and other sources should be consulted for details.[8,13,14]

COMPARISON WITH OTHER METHODS

Nitriles can be prepared by replacement of halides and activated alcohol derivatives (e.g., tosylates, mesylates).[90–94] These reactions proceed better in polar aprotic solvents such as DMSO.[95–97] Phase-transfer catalysts (e.g., hexadecyltributylphosphonium bromide) permit the synthesis of octylcyanide from 1-chlorooctane.[98–100] Catalysis by crown ethers such as 18-crown-6 is also useful for the synthesis of a variety of primary and, occasionally, secondary cyanides from the corresponding halides.[101] Dehydrations of aldehyde oximes, carboxamides,[102] and reactions of carbonyl compounds with tosylmethyl isocyanide (TosMIC)[103,104] also give nitriles. Ring-opening reactions of epoxides,[105–108] aziridines,[109,110,111] and activated cyclopropanes[112,113] offer other attractive routes to highly functionalized nitriles. Vinylnitriles, the products of alkyne hydrocyanation, can be synthesized by Pd(0)-catalyzed reaction of vinyl bromides with cyanide ion in a stereospecific reaction.[114] A mild cobalt-catalyzed hydrocyanation of olefins using a combination of tosyl cyanide and phenylsilane proceeds with Markovnikov regioselectivity and is useful for the synthesis of even tertiary cyanides from 1,1-disubstituted alkenes.[115]

EXPERIMENTAL CONDITIONS

Safety in the Use of Hydrogen Cyanide

Hydrogen cyanide is a highly toxic, volatile liquid (bp 26°) that is also susceptible to explosive polymerization in the presence of base catalysts. Considering

its extensive use in industry, reports of accidents are rare, pointing to the extreme diligence and attention paid during manufacturing processes. In the laboratory it should be used only in small quantities in a well-ventilated hood. Other sensible precautions include not working alone and having available proper first aid equipment, HCN monitors, and Scott Air Packs. Large quantities of HCN should be handled by a team of at least two technically qualified individuals who have received appropriate medical training for treating HCN poisoning.[116] On an industrial scale, HCN is disposed of by burning. Smaller amounts such as are used in a typical laboratory setting can be disposed of by adding to an equimolar mixture of sodium hydroxide and sodium hypochlorite (which converts it to the cyanate).

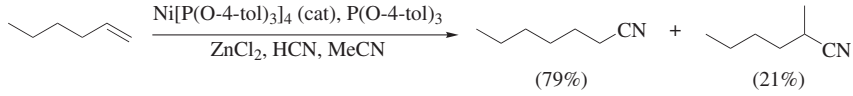
Sources of Hydrogen Cyanide

Hydrogen cyanide is commercially available from Fumico Inc. (PO Box 3459, Amarillo, TX 79106). Commercial HCN is stabilized with small amounts of strong acids such as H_2SO_4. In the laboratory HCN may be prepared by adding concentrated sulfuric acid to sodium cyanide and distilling the product formed into a cold trap, as described by Ziegler and co-workers.[117,118] Small amounts of HCN may be purified by vacuum transfer through Drierite. A standard solution of HCN may be prepared by adding the appropriate amount of pre-cooled solvent to a measured volume of HCN collected in a cold trap. Such solutions, stabilized by adding a trace of P_2O_5, can be stored in a freezer for subsequent use. Small amounts of uninhibited HCN should be stored below its mp (-13°). It is most conveniently transferred cold at low temperature using a pre-cooled cold syringe (density 0.687 g mL^{-1}). Acetone cyanohydrin and trimethylsilyl cyanide, often used as alternatives, are commercially available and should be treated with care, especially if formation of HCN or large concentrations of cyanide salts are possible under the reaction conditions or during work up.

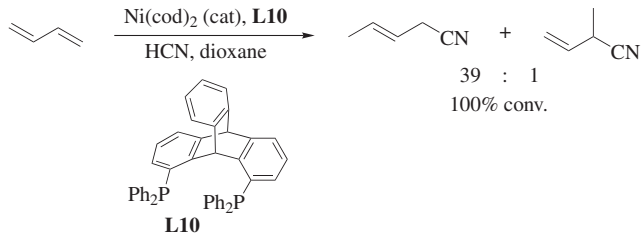
Catalysts

Because of the air sensitivity of nickel(0) complexes, small-scale reactions start with preparation of these complexes in a drybox or under strict anaerobic conditions. The most commonly used arylphosphite–Ni complexes Ni[P(O-2-tolyl)$_3$]$_3$,[119] Ni[P(O-4-tolyl)$_3$]$_4$,[120] and Ni[P(O-phenyl)$_3$]$_4$,[121] are prepared by well-known procedures. The hydrocyanation reactions may be carried out neat in the starting alkene, diene, or alkyne, or in various solvents including benzene, toluene, xylenes, acetonitrile, or dioxane. Because one of the major catalyst deactivation paths involves the reaction between Ni(0)[L]$_n$ and HCN to form $Ni(CN)_2$, it is often advantageous to add HCN slowly to a mixture of the substrate and the precatalyst in the appropriate solvent. Excess amounts of HCN are purged before isolating the product using standard organic chemistry techniques. In one of the most common protocols, especially when chelating ligands are involved, the catalyst is generated in situ by the reaction of a readily available Ni(0) source such as Ni(cod)$_2$ with the ligand. Catalytically active Ni(0) complexes can also be prepared by reduction of Ni(II) salts[122] with activated zinc in the presence of a ligand.[45]

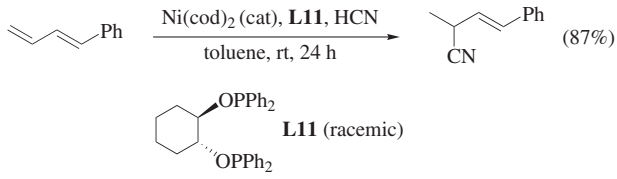
EXPERIMENTAL PROCEDURES



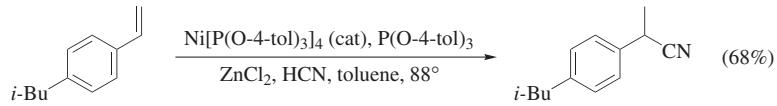
Heptanenitrile and 2-Methylhexanenitrile [Ni(0)-Catalyzed, Lewis Acid Promoted Hydrocyanation of a Terminal Alkene].[40] Tetrakis(tri-4-tolylphosphite)Ni(0) (1.4 g, 0.001 mol), $ZnCl_2$ (0.024 g, 0.002 mol) and tri-4-tolylphosphite (1.75 g, 0.005 mol) were charged to the reaction flask under heavy nitrogen purge. Hex-1-ene (25 mL, 0.2 mol) and acetonitrile (25 mL) were then added and the mixture was heated with stirring to 60°. When equilibrium temperature had been reached, HCN was continuously fed into the reaction mixture by passing a stream of dry nitrogen through a trap containing liquid HCN at 0°. After 2.5 hours, 1.90 mL (0.05 mol) of HCN had been added to the system. GC analysis on a 10-ft. column (10% SE-30 on Chromosorb W) indicated that the nitriles produced (total, 5.5 g) consisted of 79.4% heptanenitrile and 20.6% 2-methylhexanenitrile. The nitriles were identified by NMR, IR, and mass spectrometry, and their properties matched those of the commercially available materials.



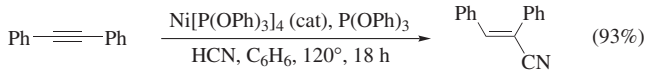
3-Pentenenitrile [Ni-Catalyzed Hydrocyanation of a 1,3-Diene].[27] A solution of ligand **L10** (11.5 mg, 0.018 mmol) in 2 mL of solvent was added to $Ni(cod)_2$ (5.0 mg, 0.018 mmol). Cooled liquid butadiene (200 μL, 2.29 mmol, 125 equiv) was added by an Eppendorf pipette, followed by 50 μL of *n*-decane as an internal standard. The solution was transferred into a 15-mL Schlenk tube equipped with a Teflon-coated stirring bar. A round-bottom Schlenk flask was filled with 1 mL of dioxane and an excess of HCN (13 μmol/min), which was taken up in a 5-mL syringe and was added to the reaction mixture by syringe pump during 3 hours (closed system). The mixture was stirred for another 5 hours at 90°. The reaction product was cooled to 0° and flushed with a gentle stream of argon for 1 minute to remove traces of HCN. Samples were analyzed by GC, using *n*-decane as internal standard. The reaction showed 100% conversion after 5 hours, with 93.3% of the product as *trans*-3-pentenenitrile and 2.4% as 2-methyl-3-butenenitrile. All the reactions were carried out in duplicate, showing a variability for conversion and selectivity of ±2% and ±1%, respectively.



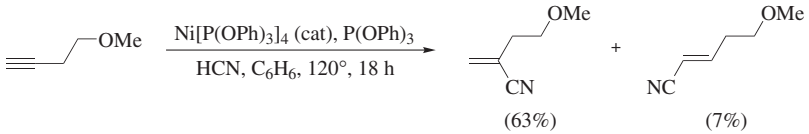
(*E*)-2-Methyl-4-phenylbut-3-enenitrile [Ni(0)-Catalyzed Hydrocyanation of an Activated Diene.][53] To a mixture of the 1,2-bisdiphenylphosphinite ligand **L11** (0.05 mmol) and $Ni(cod)_2$ (0.05 mmol) in the drybox was added 0.2 mL of toluene, and the mixture was stirred for 5 minutes at room temperature. Subsequently, 0.2 mL of a toluene solution of the diene (0.5 mmol) was added dropwise, and the reaction mixture was stirred for 10 minutes at room temperature. Then 0.2 mL of 2 M HCN in toluene was added slowly, dropwise, and the reaction mixture was stirred for 20 hours at room temperature. The reaction flask was removed from the drybox, and N_2 gas was passed into the reaction mixture in a well-ventilated hood to remove excess HCN. On larger scales, the HCN/N_2 mixture should be trapped in a solid KOH tower. The crude mixture was passed through a small pad of silica to remove the catalyst and the solvent was removed under vacuum. The product was purified by silica gel column chromatography using 100% hexane to hexane/Et_2O (19:1) as eluents to afford the pure product (87% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (d, $J = 7.5$ Hz, 3 H), 3.52 (m, 1 H), 6.07 (dd, $J = 6.5$, 15.5 Hz, 1 H), 6.75 (d, $J = 16$ Hz, 1 H), 7.3–7.42 (m, 5 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 19.06, 28.38, 120.9, 124.38, 126.57, 128.29, 128.74, 132.55, 135.74.



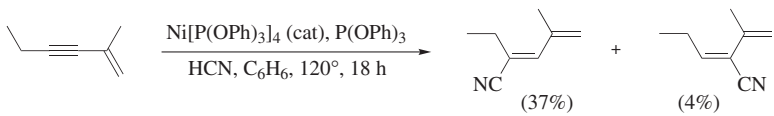
2-(4-Isobutylphenyl)propionitrile [Ni(0)-Catalyzed Hydrocyanation of a Vinylarene].[43] Tetrakis(tri-4-tolylphosphite)nickel(0) (1.50 g, 1.0 mmol) and tri-4-tolyl phosphite (0.30 mL, 1.0 mmol) were dissolved in toluene (30 mL). Zinc chloride (0.06 g, 0.5 mmol) was dissolved in propionitrile (0.5 mL) and then added to the catalyst mixture, which was subsequently heated to 88° under nitrogen. 4-Isobutylstyrene (3.45 g, 21.5 mmol) was added by syringe pump; 0.30 g was added initially and the remainder added at 1.33 mL/h. After the initial addition of the substrate, HCN/N_2 was fed at 3 mL/min for 3 hours and then at 1 mL/min for 3 hours. Silica gel chromatography of the reaction mixture (hexane/EtOAc) afforded the title product (2.66 g, 14.2 mmol, 68% yield) as a colorless liquid; ^1H NMR (360 MHz, $CDCl_3$) δ 0.90 (d, $J = 7$ Hz, 6 H), 1.61 (d, $J = 7$ Hz, 3 H), 1.76–1.94 (m, 1 H), 2.47 (d, $J = 7$ Hz, 2 H), 3.86 (q, $J = 7$ Hz, 1 H), 7.14 (d, $J = 8$ Hz, 2 H), 7.25 (d, $J = 8$ Hz, 2 H). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.31; H, 8.95; H, 7.47.



(*E*)-2,3-Diphenylprop-2-enenitrile [Ni(0)-Catalyzed Hydrocyanation of a Disubstituted Alkyne].[55] Into a 75-mL stainless-steel autoclave was placed $Ni[P(OPh)_3]_4$ (0.24 g, 0.2 mmol), $P(OPh)_3$ (0.8 g, 2.5 mmol), diphenylacetylene (7 g, 39 mmol), HCN (1.25 mL, 32 mmol), and benzene (25 mL). The vessel was heated at 120° for 18 hours. After the reaction mixture was cooled, benzene was removed by distillation. Column chromatography (basic alumina, activity II, elution with 10% ether in light petroleum), followed by distillation, afforded the unsaturated nitrile (6.12 g, 93% yield) as colorless crystals; mp 48–49°; bp 130° (oven temperature)/0.01 mmHg; IR 2225 cm^{-1}; ^1H NMR (60 MHz) δ 7.33 (s, 5 H, Ar), 7.47 (s, 6 H, Ar-H); ^{13}C NMR (22.62 MHz) δ 114.43, 120.15, 128.61, 128.93, 129.13, 129.32, 129.84, 132.70, 133.61, 144.21; MS *m/z*: 205. No trace of polymerized or disubstituted material was detected. When the HCN was replaced by acetone cyanohydrin the yield of the nitrile was 57%.

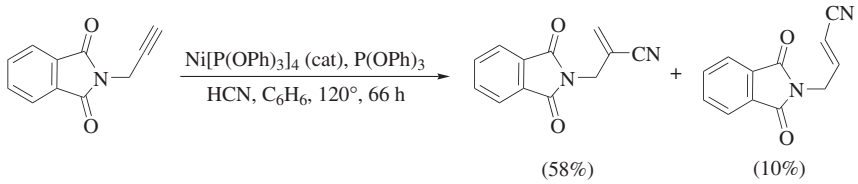


2-Cyano-4-methoxybut-1-ene and (*E*)-5-Methoxypent-2-enenitrile [Ni(0)-Catalyzed Hydrocyanation of an Alkynol Ether].[76] 4-Methoxybut-1-yne (0.84 g, 10 mmol), $Ni[P(OPh)_3]_4$ (0.23 g, 0.17 mmol), $P(OPh)_3$ (0.25 g, 0.65 mmol), HCN (0.4 mL, 10 mmol), and benzene (20 mL) were placed in a stainless-steel autoclave under nitrogen and heated at 120° for 18 hours. The benzene was removed and Kugelrohr distillation of the residue gave a mixture of nitriles as a clear liquid (0.8 g, 70% yield), bp 150° (oven temperature)/15 mmHg. 2-Cyano-4-methoxybut-1-ene: IR 2240 cm^{-1}; ^1H NMR (300 MHz) δ 2.5 (t, $J = 6.2$ Hz, 2 H), 3.55 (s, 3 H), 3.56 (t, $J = 6.2$ Hz, 2 H), 5.80 (s, 1 H), 5.91 (s, 1 H). (*E*)-5-Methoxypent-2-enenitrile: ^1H NMR (300 MHz) δ 2.50 (m, 2 H), 3.34 (s, 3 H), 3.49 (t, $J = 6.0$ Hz, 2 H), 5.43 (dt, $J = 16.3$, 1.8 Hz, 1 H), 6.74 (dt, $J = 16.4$, 6.8 Hz, 1 H); MS *m/z*: 111.

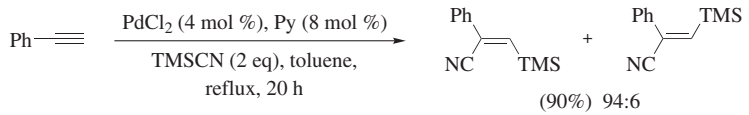


2-Ethyl-4-methylpenta-2,4-dienenitrile and 2-(1′-Methylethenyl)pent-2-enenitrile [Ni(0)-Catalyzed Hydrocyanation of an Enyne].[123] A mixture of 2-methylhex-1-en-3-yne (0.94 g, 10 mmol), $Ni[P(OPh)_3]_4$ (0.23 g, 0.18 mmol), $(PhO)_3P$ (0.15 mL, 0.57 mmol), HCN (0.39 mL, 10 mmol), and benzene

(20 mL) was placed in a stainless-steel autoclave under nitrogen, and heated at 120° for 18 hours. After removal of the benzene, Kugelrohr distillation gave the title nitriles as a colorless oil (0.5 g, 41% yield); bp 130° (oven temperature)/15 mmHg; IR 2225, 1620, 1595 cm^{-1}. The ratio of isomers determined by NMR spectroscopy was 90:10 2-ethyl-4-methylpenta-2,4-dienenitrile/2(1′-methylethenyl)pent-2-ene-nitrile. 2-Ethyl-4-methylpenta-2,4-dienenitrile:^{1}H NMR (300 MHz) δ 1.19 (t, $J = 7.5$ Hz, 3 H), 1.92 (s, 3 H), 2.43 (dq, $J = 7.5$, 1.2 Hz, 2 H), 5.07 (s, 1 H), 5.23 (t, $J = 1.2$ Hz, 1 H), 6.62 (d, $J = 0.8$ Hz, 1 H); MS m/z: $[M]^+$ calcd for $C_8H_{11}N$, 121.0891; found, 121.089. 2-(1′-Methylethenyl)pent-2-ene-nitrile:^{1}H NMR (300 MHz) δ 1.06 (t, $J = 7.5$ Hz, 3 H), 1.95 (d, 3 H), 2.34 (dq, $J = 7.5$ Hz, 2 H), 5.04 (s, 1 H), 5.23 (s, 1 H), 6.38 (t, $J = 7.6$ Hz, 1 H); MS m/z: 121.

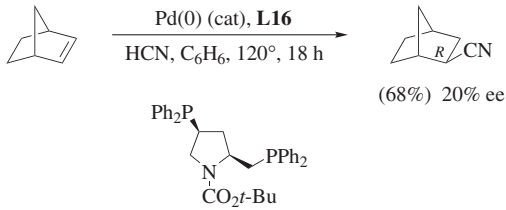


2-(2′-Cyanoprop-2′-enyl)phthalimide [Hydrocyanation of a Phtalimidomethylalkyne].[79] The substrate (5 mmol), $Ni[P(OPh)_3]_4$ (100 μmol), $P(OPh)_3$ (1 mmol), and dry degassed benzene (10 mL) were placed, in that order, in an autoclave under a nitrogen atmosphere. Hydrogen cyanide (5 mmol) was added using a gas-tight syringe. In some cases, when ambient temperature exceeded 20°, a larger volume of HCN was used. The reactor was sealed and heated at 120° for 66 hours. The autoclave was cooled, the excess hydrogen cyanide was vented, and the benzene was removed. The catalyst was precipitated with $CHCl_3$ and removed by filtration, and the solvent was removed in vacuo. Silica gel chromatography of the crude product (EtOAc/light petroleum) gave a mixture of the title compound and (*E*)-2-(3-cyanoprop-2-enyl)phthalimide in a ratio of 85:15 as a white solid (68% yield); mp 71–72°; ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6, 116.6, 118.0, 123.8, 131.7, 132.9, 134.5, 167.1. The ^{1}H NMR spectral data were consistent with the literature.[77] Major isomer: mp 68–70°; IR 2230, 1780, 1720 cm^{-1}; ^{1}H NMR (300 Mz) δ 4.47 (t, $J = 1.3$ Hz, 2 H), 6.02 (t, $J = 1.3$ Hz, 1 H), 6.09 (t, $J = 1.3$ Hz, 1 H), 7.82 (m, 4 H). Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.9; H, 3.8; N, 13.2. Found: C, 67.9; H, 3.6; N, 13.1. Minor isomer: ^{1}H NMR (300 MHz) δ 4.44 (dd, $J = 5.5$, 1.8 Hz, 2 H), 5.52 (dt, $J = 16.3$, 1.8 Hz, 1 H), 6.73 (dt, $J = 16.3$, 5.5 Hz, 1 H), 7.82 (m, 4 H).



(*Z*)-2-Phenyl-3-(trimethylsilyl)prop-2-enenitrile [Addition of TMSCN to an Alkyne Catalyzed by $PdCl_2$/Pyridine].[80] To a solution containing phenylacetylene (0.55 mL, 5 mmol) and Me_3SiCN (1.34 mL, 10 mmol) in toluene

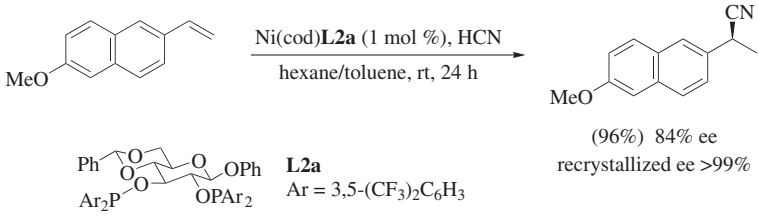
(10 mL) were added $PdCl_2$ (36 mg, 0.2 mmol) and pyridine (32 μL, 0.4 mmol). The mixture was heated at reflux under nitrogen with stirring for 20 hours. Monitoring of the reaction by GC showed that the reaction was complete within 10 hours. GC analysis of the reaction mixture showed the formation of 2-phenyl-3-(trimethylsilyl)prop-2-enenitrile in 93% yield ($Z:E = 94:6$). The solution was evaporated in vacuo, and the residue was chromatographed on silica gel [hexane/EtOAc (9:1)], followed by bulb-to-bulb distillation, to give the product mixture in 90% yield; bp 130–140° (25 mmHg); IR (neat) 3060, 2960, 2890, 2220 (CN), 1560 (C=C), 1490, 1450, 1250, 975, 860, 840, 755, 685 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.35 (s, 9 H, $SiCH_3$), 7.10 (s, 1 H, =CH), 7.37–7.41 (m, 2 H, Ph), 7.61–7.63 (m, 3 H, Ph); ^{13}C NMR ($CDCl_3$) δ −1.40 ($SiCH_3$), 117.9 (CN, $^3J_{CN-H} = 17$ Hz), 125.7, 127.9, 128.9, 129.6, 135.1 (Ph, =C), 147.6 (=CH); MS m/z: [M^+] 201. Anal. Calcd for $C_{12}H_{15}NSi$: C, 71.59; H, 7.51; N, 6.96. Found: C, 71.84; H, 7.27; N, 6.99.



L16
(*S*,*S*)-BPPM

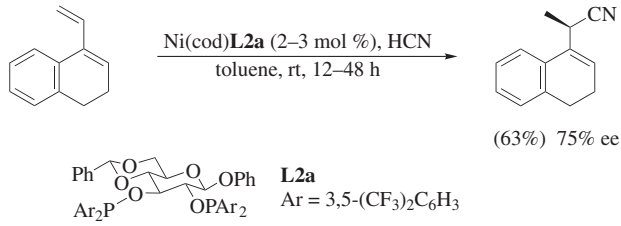
***exo*-(2*R*)-Cyanonorbornane [Pd-Catalyzed Asymmetric Hydrocyanation of a Strained Alkene].**[48] A Carius tube was charged with bis(dibenzylideneacetone)palladium (13.6 mg, 0.024 mmol), (2*S*, 4*S*)-*tert*-butoxycarbonyl-4-(diphenylphosphino)-2-((diphenylphosphino)methyl)pyrrolidine (**L16**, (*S*,*S*)-BPPM, 112 mg, 0.203 mmol), and a solution of bicyclo[2.2.l]heptene (2.68 g, 28.6 mmol) in benzene (5 mL). Hydrogen cyanide (385 mg, 14.3 mmol) was distilled into the tube, and a further addition of benzene (7 mL) was made. The tube was sealed under argon (500 mm Hg) and heated to 120° for 18 hours. Unreacted hydrogen cyanide, excess norbornene, and benzene were removed by distillation at atmospheric pressure, and the residue was distilled to yield a colorless oil, bp 80° (6 mmHg), which solidified to a colorless wax at room temperature [1.175 g, 68% yield (based on HCN)]; $[\alpha]_D$ − 5.8° (*c* 0.9, $CHCl_3$). The product was confirmed to be pure bicyclo[2.2.1]heptane-*exo*-carbonitrile by GC (by comparison of the retention time to that of an authentic sample). Acid hydrolysis (6 M HCl, 110°, 3 hours) of the nitrile according to a published procedure[124] gave the corresponding acid as a colorless solid that was purified by sublimation (60°, 0.1 mmHg) to give bicyclo[2.2.l]heptene-*exo*-2-carboxylic acid (1.0 g) as a colorless solid; mp 57–58°; $[\alpha_D]$ −5.45 (*c* 1.0, EtOH). The enantiomeric purity of this acid was determined independently by ^1H NMR analysis of the (*S*)-methyl mandelate ester. To a solution of the *exo*-2-norbornanecarboxylic acid (140 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at −10° was added (*S*)-methyl mandelate (183 mg,

1.1 mmol), 4-(dimethy1amino)pyridine (2.5 mg), and dicyclohexylcarbodiimide (206 mg, 1.0 mmol). After the mixture was stirred at -10° for 3 hours, the dicyclohexylurea was removed by filtration, the solvent was removed under reduced pressure, and the residue was purified by preparative TLC [SiO_2, EtOAc/hexane (1:1)] to yield the desired ester as a homogeneous colorless oil; ^{1}H NMR (C_6D_6) δ 1.01−1.39 (6 H, m, H-5, H-6, H-7), 1.61 (1 H, dd, H-4), 2.09 (2 H, m, H-3), 2.38 (1 H, m, H-2), 2.54 + 2.87 (1 H, br s + br s, H-1), 3.19 (3 H, s, CO_2CH_3), 6.077 + 6.066 (1 H, s + s, CHOCO), 7.09 (3 H, m), 7.46 (2 H, d, *ortho* arom). Integration of the resonances at δ 6.077/6.061 and 2.87/2.54 ppm gave ratios of 60:40 and 40.5:59.5 ($\pm$1%), respectively, in agreement with the chiroptical data (20% ee). Hydrocyanations using (*R*)-BINAP [40% ee (*R*)], (*R*,*R*)-DIOP [86% yield, 9% ee (*R*)], and (*S*,*S*)-DIOP [13% ee (*S*)] ligands were carried out using similar procedures.



(*S*)-2-(6-Methoxy-2-naphthalene)propionitrile [Asymmetric Hydrocyanation of a Vinylarene].[45] To a solution of $Ni(cod)_2$ (0.059 g, 0.22 mmol) and the ligand **L2a** (0.271 g, 0.22 mmol) in 10 mL of hexane were added 6-methoxy-2-vinylnaphthalene (4.00 g, 21.7 mmol) and 110 mL of hexane. An approximately 2 M solution of HCN in toluene (11 mL, 22 mmol) was added to the resulting slurry by addition funnel over 2.5 hours. The initially heterogeneous solution became an orange-brown homogeneous solution about half-way through the addition, and then the product precipitated as a white powder. GC analysis showed an 84% conversion at the end of the addition; therefore, an additional 3 mL of the HCN solution was added over 1 hour. After the reaction mixture was stirred overnight, benzene was added to dissolve all of the solids. GC analysis showed >99% conversion. HPLC analysis of a small sample isolated by silica gel chromatography (hexane/Et_2O 90:10) showed 84% ee. The solids that precipitated initially were enriched up to 93% ee. Recrystallization provided optically pure nitrile. After concentration of the reaction mixture in vacuo, the remaining solids were slurried in 200 mL of hexane and collected by filtration, affording 3.555 g of an off-white solid. The filtrate was concentrated in vacuo to about 50 mL, and a second crop of product was isolated by filtration (yield 0.468 g). A third crop of product was then isolated by silica gel chromatography of the filtrate (90:10 hexane/Et_2O), yield 0.380 g. The total yield was 4.403 g (96%). Two recrystallizations from 10% Et_2O/hexanes afforded pure product in greater than 99% ee as judged by HPLC analysis on a Chiralcel OJ column using hexane/2-propanol (90:10) as eluent; mp 99 -100°; $[\alpha]_D$ -29.4 ± 0.8 (*c* 1, $CHCl_3$); ^{1}H

NMR ($CDCl_3$) δ 1.70 (d, $J = 7$ Hz, 3 H), 3.92 (s, 3 H), 4.00–4.04 (q, $J = 7$ Hz, 1 H), 7.14 (d, $J = 2.6$ Hz, 1 H), 7.19 (dd, $J = 9.1$, 2.6 Hz, 1 H), 7.39 (m, 1 H), 7.72–7.77 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 31.2, 55.3, 105.6, 119.5, 121.7, 124.9, 125.3, 127.9, 128.7, 129.3, 132.0, 134.0, 158.1.



(*R*)-2-(3,4-Dihydro-1-naphthalene)propionitrile [Asymmetric Hydrocyanation of a 1,3-Diene].[53] To a mixture of the phosphinite ligand **L2a** (2.1 mol%) and $Ni(cod)_2$ (2 mol%) in a drybox was added 0.2 mL of toluene, and the mixture was stirred for 5 minutes at room temperature. To this solution a 0.2-mL toluene solution of the diene (0.5 mmol) was added dropwise. The solution turned brown, and the mixture was stirred for 10 minutes at room temperature. Then 0.14 mL of 2 M HCN in toluene was added slowly, dropwise, and the reaction was stirred for another 12 hours. Additional $Ni(cod)_2$ (1 mol %) and 2 M HCN in toluene (0.1 mL) were added, respectively, and the reaction mixture was stirred for an additional 12 to 48 hours. The reaction flask was removed from the drybox and N_2 gas was passed into the reaction mixture in a well-ventilated hood to remove any excess HCN. On a larger scale, the HCN/N_2 effluent should be trapped in a solid KOH tower. The crude mixture was passed through a small pad of silica to remove the catalyst. The solvent was removed under vacuum and the product was further purified by short silica gel column chromatography using a gradient of 100% hexane to hexane/Et_2O (19:1) to afford the pure product (63% yield). The enantiomeric ratio of the final product was determined by HPLC on a Chiralcel OJ column (hexanes/2-propanol 95:5, 0.5 mL/min, 254 nm, t_R 20.53 min, t_R 23.62 min; 75% ee); $[\alpha]^{20}_D$ −61° (*c* 0.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.6 (d, $J = 7.5$ Hz, 3 H), 2.35–2.39 (m, 2 H), 2.79 (t, $J = 8$ Hz, 2 H), 3.92 (q, $J = 7$ Hz, 1 H), 6.36 (t, $J = 4.5$ Hz, 1 H), 7.20–7.28 (m, 4 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 18.9, 22.9, 27.9, 28.0, 121.7, 121.8, 126.6, 127.2, 127.6, 128.2, 131.8, 132.7, 136.9. The configuration was established by comparison of the optical rotation of the fully aromatic derivative (prepared by reaction of the product with DDQ in benzene) with that of an authentic sample.

TABULAR SURVEY

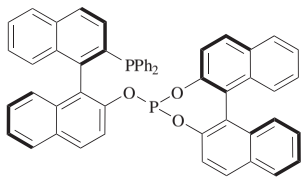
The literature up to the end of 2008 is included in the Tabular Survey. Tables are classified according to type of substrates except for the section on asymmetric hydrocyanations, which is dealt with separately. Table 1 presents the substrates that are not described by Tables 2–4. In all tables and sub-tables the substrates are

organized in the order of increasing carbon count. Under the heading 'conditions' the best available set of parameters to carry out the transformation that is available in open literature is provided. In many instances, more optimized conditions may be available in the patent literature, which should be consulted for specific compounds. It should be noted that the complex $Pd(DIOP)_2$ or $Ni(DIOP)_2$ and the corresponding ligand have opposite optical rotations, e.g., (−)-DIOP forms (+)-$Pd(DIOP)_2$ and (+)-$Ni(DIOP)_2$, respectively.

The following abbreviations are used in the tables:

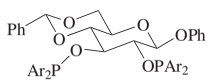
Ac	acetyl
All	allyl
cod	1,5-cyclooctadiene
conv.	conversion
dba	dibenzylideneacetone
DEIPS	diethylisopropylsilyl
DIBALH	diisobutylaluminum hydride
Dppp	1,3-bis(diphenylphosphino)propane
EG	ethylene glycol
MCPBA	*m*-chloroperoxybenzoic acid
Pht	*N*-phthalimidoyl
Rac	racemic
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
TMS	trimethylsilyl
TOF	turnover frequency
tol	tolyl, methylphenyl
TON	turnover number

CHART 1. LIGANDS FOR METAL-CATALYZED HYDROCYANATION OF ALKENES



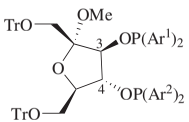
L1

(*R*,*S*)-BINAPHOS



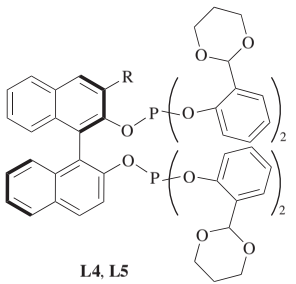
L2

	Ar
2a	3,5-$(CF_3)_2C_6H_3$
2b	3,5-$F_2C_6H_3$
2c	C_6H_5
2d	3,5-$Me_2C_6H_3$



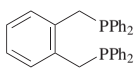
L3

	Ar^1	Ar^2
3a	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$
3b	Ph	Ph
3c	3,5-$(CF_3)_2C_6H_3$	Ph
3d	Ph	3,5-$(CF_3)_2C_6H_3$



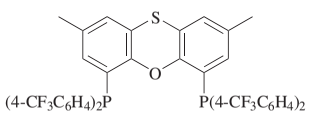
L4, **L5**

	R
4	H
5	Me



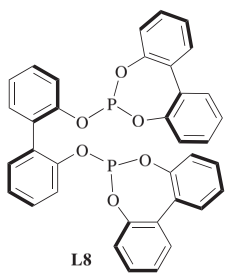
L6

phmep

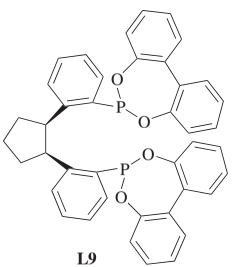


L7

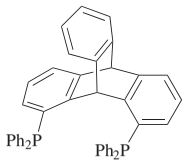
CF_3-thiaxantphos



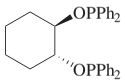
L8



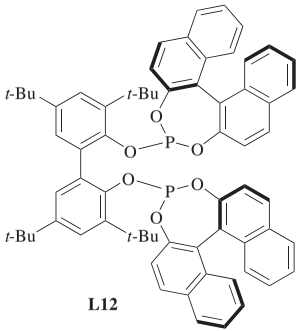
L9



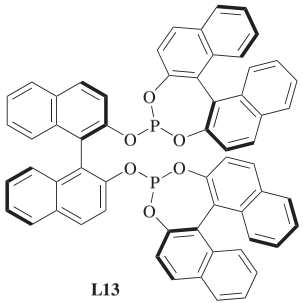
L10



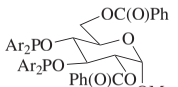
L11 (racemic)



L12

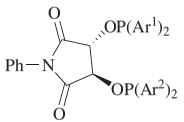


L13



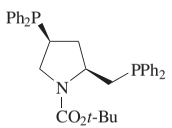
L14

	Ar
14a	3,5-$(CF_3)_2C_6H_3$
14b	Ph
14c	3,5-$Me_2C_6H_3$

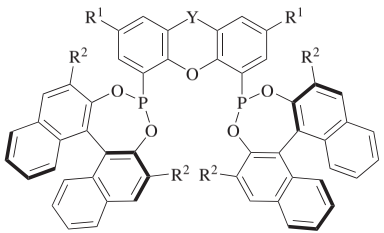


L15

	Ar^1	Ar^2
15a	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$
15b	Ph	Ph
15c	Ph	3,5-$(CF_3)_2C_6H_3$



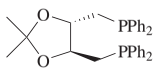
L16
(*S*,*S*)-BPPM



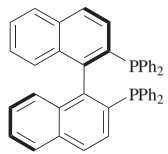
L17

	Y	R^1	R^2
17a	CMe_2	H	H
17b	S	Me	H
17c	S	Me	Me

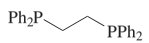
CHART 1. LIGANDS FOR METAL-CATALYZED HYDROCYANATION OF ALKENES (*Continued*)



(*S*,*S*)-(+)-DIOP



(*R*)-BINAP



diphos

TABLE 1. HYDROCYANATION OF ALKENES

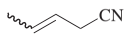
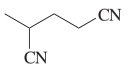
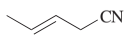
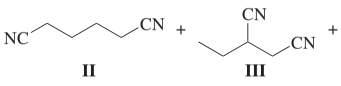
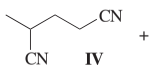
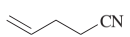
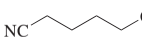
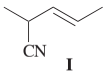
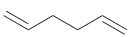
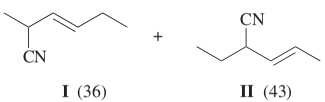
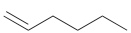
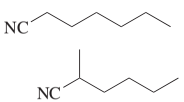
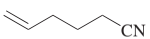
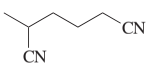
	Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_2		$Co_2(CO)_8$	Alkene (excess), cat (17 g), HCN (27 g), sealed vessel (200 psi), 130°, 7 h	 63% conv.	36
C_3		$Co_2(CO)_8$	Alkene (150 g), cat (17 g), HCN (14 g), sealed vessel (110 psi), 130°, 15 h	 65% conv.	36
C_4		$Co_2(CO)_8$	Alkene (56 g), cat (17g), HCN (14 g), sealed vessel (40 psi), 130°, 8 h	 67% conv. **I**	36
		$Co_2(CO)_8$	Alkene (56 g), cat (17g), HCN (14 g), sealed vessel (32 psi), 130°, 8 h	**I** 9% conv.	36
		$Co_2(CO)_8$	Alkene (56 g), cat (17g), Ph_3P (8.5 g), HCN (14 g), sealed vessel (39 psi), 130°, 8 h	**I** 24% conv.	36
C_5		$Co_2(CO)_8$	Alkene (40.5 g), cat (17 g), HCN (27 g), 130°, 14.5 h	 7% conv.	36
	 **I**	$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (2.49 mmol), cat (8.3 mmol), $ZnCl_2$ (2 mmol), HCN, 68°	 **II** + **III** +  **IV** + isomers of **IV**	21, 16
				II + **III** + **IV** + **V** (~100), **II**:**III**:**IV**:**V** = 35:7:1:39	
		$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (1.02 mmol), cat (2 mmol), $P(O\text{-}4\text{-}tol)_3$ (7.8 mmol), $Ph_3Sn^+TsO^-$ (0.18 mmol), HCN (excess), 50°	**II** + **IV** (~100), **II**:**IV** = 91.4:7.4	60
		$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (0.2 mmol), cat (0.05 mmol), Ph_3B (0.05 mmol), HCN (0.2 mmol), rt	 (98)	21

TABLE 1. HYDROCYANATION OF ALKENES (*Continued*)

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
	$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (100 mmol), cat (1 mmol), $P(O\text{-}4\text{-}tol)_3$ (16 mmol), HCN (100 mmol), 90°, 1.5 h	 **I** (81), 82% conv.	42
	$Ni[(-)\text{-DIOP}]_2$ [a]	Alkene (390 mmol), cat (1 mmol), (–)-DIOP (6.3 mmol), HCN (275 mmol), 90°, 1.5 h	**I** (74)	63
	$Ni(\mathbf{L6})_2$	Alkene (50 mmol), cat (1 mmol), **L6** (6.3 mmol), acetone cyanohydrin (100 mmol), 90°, 1.5 h	**I** (63)	63
C_6				
	$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (100 mmol), cat (1 mmol), $P(O\text{-}4\text{-}tol)_3$ (16 mmol), HCN (100 mmol), 90°, 1.5 h	 **I** (36) + **II** (43)	42
	$Ni[(-)\text{-DIOP}]_2$ [a]	Alkene (390 mmol), cat (1 mmol), (–)-DIOP (6.3 mmol), HCN (275 mmol), 90°, 1.5 h	**I** (38) + **II** (45)	63
	$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (200 mmol), cat (1 mmol), $P(O\text{-}4\text{-}tol)_3$ (5 mmol), $ZnCl_2$ (2 mmol), HCN (added slowly), MeCN (25 mL), 60°, 2.5 h	 (20) + (5)	40
	$Co_2(CO)_8$	Alkene (19 g), cat (17 g), HCN (14 g), 130°, 8 h	 36% conv.	36

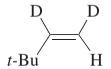
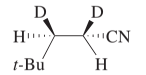
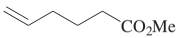
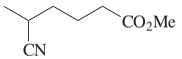
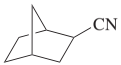
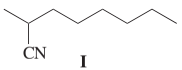
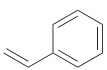
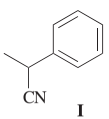
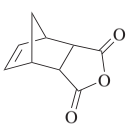
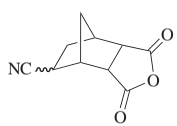
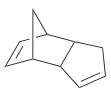
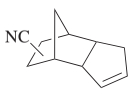
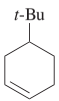
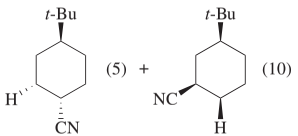
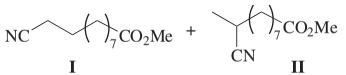
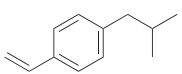
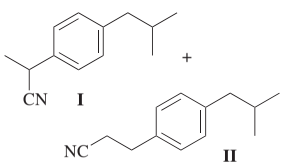
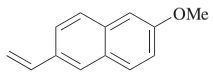
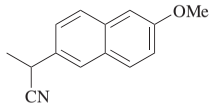
		$Pd[(-)\text{-}DIOP]_2$ [a]	cat (0.3 mol %), HCN, 120°, 18 h	 (10)		125, 44
C_7		$Co_2(CO)_8$	Alkene (22 g), cat (17 g), HCN (27 g), sealed vessel (28 psi), 130°, 8 h		19% conv.	36
		$Pd[P(OPh)_3]_4$	Alkene (1.24 M), cat (0.01 M), $P(OPh)_3$ (1.1 M), HCN (0.66 M)	 (83) **I**		59, 47
		$Ni[P(OPh)_3]_4$	Alkene (64 mmol), cat (0.09 mmol), $P(OPh)_3$ (0.6 mmol), HCN (82 mmol), C_6H_6	**I** (80)		47
		$Pd(diphos)_2$	Various conditions	**I** (—)		47
C_8		$Co_2(CO)_8$	Alkene (56 g), cat (17 g), Ph_3P (8.5 g), HCN (27 g), sealed vessel (46 psi), 130°, 8 h	 **I**	24% conv.	36
		$Ni(cod)_2$	Alkene/cat/**L7**/$AlCl_3$/HCN (20:1:1.05:1:25), toluene, 60°	 + **I** (2) (49)		126
		$Co_2(CO)_8$	Alkene (104 g), cat (17 g), hydroquinone (2 g), HCN (14 g), sealed vessel (25 psi), 130°, 8 h	 **I**	52% conv.	36
		$Ni(cod)_2$ + **L7**	Alkene (1.3 mmol), $Ni(cod)_2$ (0.065 mmol), **L7** (0.065 mmol), HCN (excess), toluene (2 mL), 60°, 16 h	**I** (90)		65
C_9		$Co_2(CO)_8$	Alkene (164 g), cat (68 g), Ph_3P (20 g), HCN (54 g), 130°, 8 h		28% conv.[b]	36

TABLE 1. HYDROCYANATION OF ALKENES (*Continued*)

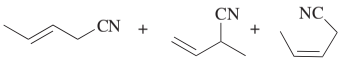
Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 	$Co_2(CO)_8$	Alkene (60 g), cat (17 g), PPh_3 (8.5 g), HCN (14 g), 130°, 15.5 h	 24% conv.[b]	36
	$Ni[P(OPh)_3]_4$	Alkene (65 mmol), cat (2.1 mmol), $P(OPh)_3$ (9.7 mmol), $ZnCl_2$ (4 mmol), HCN (50 mmol), toluene, 60°	 (5) + (10)	44
C_{11} 	$Ni(cod)_2$	Alkene/cat/**L7**/$AlCl_3$/HCN (20:1:1.05:1:25), toluene, 60°	 **I** + **II** **I** + **II** (36), **I**:**II** = 75:25	126
C_{12} 	$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (21.5 mmol), cat (1.0 mmol), $P(O\text{-}4\text{-}tol)_3$ (1.0 mmol), $ZnCl_2$ (0.35 mmol), HCN (excess), 88°, 3 h	 **I** + **II** (68), **I**:**II** = 90:10	43

C_{13}		$Ni[P(O\text{-}4\text{-}tol)_3]_4$	Alkene (15.6 mmol), cat (1.0 mmol), $P(O\text{-}4\text{-}tol)_3$ (1.0 mmol), HCN (excess), toluene (15 mL)		(93)	43

[a] The complex $Pd(DIOP)_2$ or $Ni(DIOP)_2$ and the corresponding ligand have opposite optical rotations.

[b] The position of the nitrile is unknown.

TABLE 2. HYDROCYANATION OF 1,3-DIENES

Diene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_4 	CuBr	Diene (52 mmol), cat (2.5 mmol), Cl_3CCO_2H (3 mmol), HCN (107 mmol), MeCN, 79°, 16 h	 **I** (68) **II** (4) (3)	66, 67
	$Ni[P(OPh)_3]_4$	Diene (100 mmol), cat (1 mmol), $P(OPh)_3$ (16 mmol), HCN (100 mmol), 90°, 90 min	**I** (64) + **II** (34)	42
	$Ni[P(OPh)_3]_4$	Diene (410 mmol), cat (1 mmol), $P(OPh)_3$ (14 mmol), hydroquinone (2 mmol), HCN (180 mmol), 90°, 90 min	**I** (68) + **II** (20)	63
	$Ni(cod)_2$ + **L9**	HCN/diene (3:4), **L9**/Ni (21:20), Ni (0.1 mol %), 120°, 3 h	**I** (45) + **II** (37), TON 644, TOF 215	68
	$Ni(cod)_2$ + $P(O\text{-}4\text{-}tol)_3$	HCN/diene (3:4), $P(O\text{-}4\text{-}tol)_3$/Ni (6:1), Ni (0.2 mol %), 120°, 3 h	**I** (5) + **II** (3), TON 30, TOF 10	68
	$Ni(cod)_2$ + **L10**	Diene (2.25 mmol), $Ni(cod)_2$ (0.018 mmol), **L10** (0.018 mmol), acetone cyanohydrin (2.7 mmol), solvent (2 mL), 90°, 5 h	**I** + **II**: Solvent / **I** / **II**: dioxane (81) (4); toluene (31) (17)	27
	$Ni(cod)_2$ + **L10**	Diene (2.25 mmol), $Ni(cod)_2$ (0.018 mmol), **L10** (0.018 mmol), HCN (excess), dioxane (2 mL), 90°, 5 h	**I** (93) + **II** (2)	27
	$Ni(\mathbf{L8})_2$	Diene (46 mmol), cat (0.088 mmol), acetone cyanohydrin (34 mmol), 140°, 18 h	**I** (35) + **II** (29)	61

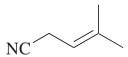
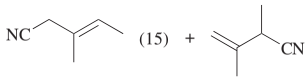
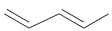
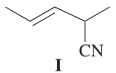
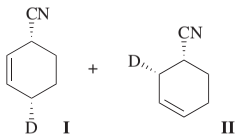
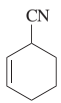
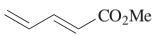
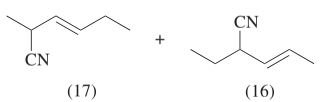
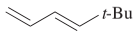
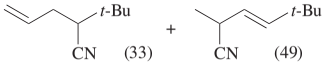
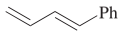
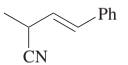
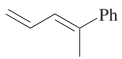
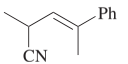
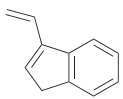
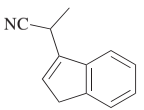
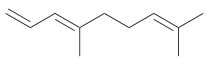
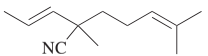
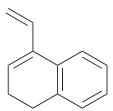
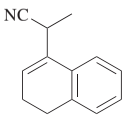
C_5				
	CuBr	Diene (52 mmol), cat (2.5 mmol), Cl_3CCO_2H (3 mmol), HCN (107 mmol), MeCN, 79°, 16 h	 (39) + oligomers	66, 67
	$Ni[P(OPh)_3]_4$	Diene (100 mmol), cat (1 mmol), $P(OPh)_3$ (16 mmol), HCN (100 mmol), 90°, 90 min	 (15) + (11)	42
	CuBr	Diene (52 mmol), cat (2.5 mmol), Cl_3CCO_2H (3 mmol), HCN (107 mmol), MeCN, 79°, 16 h	 **I** (12) + oligomers	66, 67
	$Ni[P(OPh)_3]_4$	Diene (100 mmol), cat (1 mmol), $P(OPh)_3$ (16 mmol), HCN (100 mmol), 90°, 90 min	**I** (74)	42
C_6				
	$Ni[P(OPh)_3]_4$	Diene (3 mmol), cat (0.06 mmol), $P(OPh)_3$ (0.18 mmol), DCN (3 mmol), MeCN, 60°, 2 h	 **I** + **II** (38), **I**:**II** = 1:1[a]	23
	$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (5 mol %), **L11** (5 mol %), toluene, rt, 20 h	 (>95)	53
	$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (5 mol %), **L11** (5 mol %), toluene, rt, 20 h	no reaction	53
	$Ni[(-)\text{-DIOP}]_2$[b]	Diene (390 mmol), cat (1 mmol), DIOP (6.3 mmol), HCN (275 mmol), 90°, 1.5 h	 (17) (16)	63

TABLE 2. HYDROCYANATION OF 1,3-DIENES (*Continued*)

	Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (10 mol %), **L11** (10 mol %), toluene, 50°, 20 h	 (33) + (49)	53
C_{10}		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (10 mol %), **L11** (10 mol %), toluene, rt, 20 h	 (87)	53
C_{11}		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (10 mol %), **L11** (10 mol %), toluene, 50°, 24 h	 (32)	53
		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (5 mol %), **L11** (5 mol %), toluene, rt, 48 h	 (71)	53
		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (10 mol %), **L11** (10 mol %), toluene, 50°, 24 h	 (83)	53
C_{12}		$Ni(cod)_2$ + **L11**	Diene/HCN (1:1), $Ni(cod)_2$ (10 mol %), **L11** (10 mol %), toluene, rt, 24 h	 (80)	53

[a] Deuterio-1,3-cyclohexadiene is not formed.

[b] The complex $Pd(DIOP)_2$ or $Ni(DIOP)_2$ and the corresponding ligand have opposite optical rotations.

TABLE 3A. HYDROCYANATION OF ALKYNES USING HCN

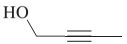
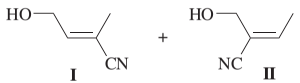
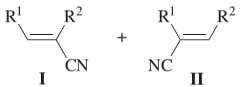
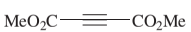
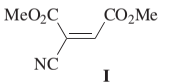
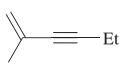
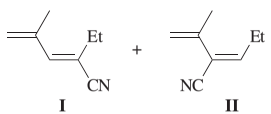
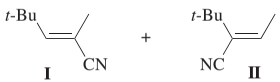
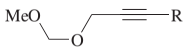
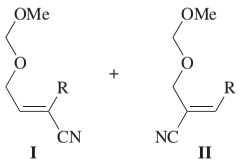
Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_2	$CuCl_2$, NH_4Cl, $AlCl_3$	Alkyne/HCN (10:1), 70–90°	 (80–90)	7
C_4 	$Ni[P(OPh)_3]_4$	Alkyne (5 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 60°, 20 h	 **I** + **II** (62), **I**:**II** = 55:45	75
	$Ni(\mathbf{L6})_2$	Alkyne (5 mmol), cat (0.1 mmol), **L6** (0.7 mmol), HCN (5.2 mmol), C_6H_6 (20 mL), 60°, 18 h	**I** + **II** (72), **I**:**II** = 50:50	75
$C_{5–8}$ 	$Ni[P(OPh)_3]_4$	Alkyne (21 mmol), cat (0.54 mmol), $P(OPh)_3$ (2.4 mmol), $ZnCl_2$ (1 mmol), HCN (32 mmol in 5 mL toluene), 60°, 10 h		
R			**I** + **II** / **I**:**II**	
n-Pr			(40) 1:19	72
n-Bu			(33) 1:24	72, 71
t-Bu			(45) 4:1	72, 71
n-C_6H_{13}			(45) 2:23	72, 71
Ph			(35) 17:3	72, 71
$C_{5–11}$ 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h	**I** + **II**	
R			**I** + **II** / **I**:**II**	
n-Pr			(60) 13:87	72
n-Bu			(73) 14:86	72, 71
t-Bu			(15) 88:12	72, 71
n-C_6H_{13}			(60) 14:86	72, 71
Ph			(48) 98:2	72, 71
$PhCH_2OCH_2CH_2$			(78) 15:85	76

TABLE 3A. HYDROCYANATION OF ALKYNES USING HCN (*Continued*)

Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{5-24}	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat, $P(OPh)_3$ (2.5 mmol), cyanide source (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h	 **I** **II**	73, 74

R^1	R^2	Cyanide Source	Alkyne/Cat	**I** + **II**	**I**:**II**
TMS	H	acetone cyanohydrin	195:1	(74)	1:3
TMS	Me	acetone cyanohydrin	195:1	(90)	4:1
TMS	Me	acetone cyanohydrin	45:1[a]	(87)	4:1
TBS	H	HCN	45:1	(57)	7:13
TBS	Me	HCN	45:1	(88)	49:1
TMS	*n*-Bu	acetone cyanohydrin	90:1[a]	(90)	18:7
TMS	Ph	HCN	90:1	(80)	1:4
TBS	Ph	HCN	45:1	(74)	9:1
Ph_3Si	*n*-Bu	HCN	18:1[b]	(75)	1:0

C_6 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h	 (27) **I**	72, 71
		Alkyne (21 mmol), cat (0.54 mmol), $P(OPh)_3$ (2.4 mmol), $ZnCl_2$ (1 mmol), HCN (32 mmol in 5 mL toluene), 60°, 10 h	**I** (5)	72, 71
C_7 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h	 **I** **II** **I** + **II** (41), **I**:**II** = 2:3	123

	$Ni[P(OPh)_3]_4$	Alkyne (21 mmol), cat (0.54 mmol), $P(OPh)_3$ (2.4 mmol), $ZnCl_2$ (1 mmol), HCN (32 mmol in 5 mL toluene), 60°, 10 h	 **I** + **II** (78), **I**:**II** = 9:1	72, 71
C_{7-11} 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h		76

R	**I** + **II**	**I**:**II**
CH_2OMe	(71)	1:1
n-Bu	(90)	1:1
Ph	(61)	1:3

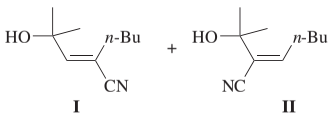
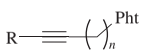
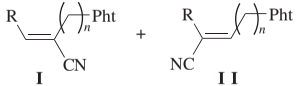
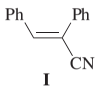
C_9 	$Ni[P(OPh)_3]_4$	Alkyne (5 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 60°, 20 h	 **I** + **II** (84), **I**:**II** = 50:50	75
	$Ni(\mathbf{L6})_2$	Alkyne (5 mmol), cat (0.1 mmol), **L6** (0.7 mmol), HCN (5.2 mmol), C_6H_6 (20 mL), 120°, 18 h	**I** + **II** (79), **I**:**II** = 75:25	75

TABLE 3A. HYDROCYANATION OF ALKYNES USING HCN (*Continued*)

Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-17} 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.2 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°		78, 77

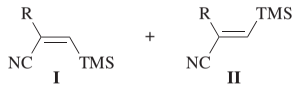
R	*n*	Time (h)	I + II	I:II
H	1	66	(88)	4:1
H	2	20	(88)	9:1
Me	1	20	(72)	1:1
Ph	1	20	(76)	9:1

C_{14} 	$Ni[P(OPh)_3]_4$	Alkyne (39 mmol), cat (0.9 mmol), $P(OPh)_3$ (2.5 mmol), HCN (32 mmol), C_6H_6 (25 mL), autoclave, 120°, 20 h	 (93)	72, 71
	$Ni[P(OPh)_3]_4$	Alkyne (21 mmol), cat (0.54 mmol), $P(OPh)_3$ (2.4 mmol), $ZnCl_2$ (1 mmol), HCN (32 mmol in 5 mL toluene), 60°, 10 h	**I** (82)	72, 71

[a] The reaction is performed in toluene and without autoclave.

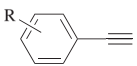
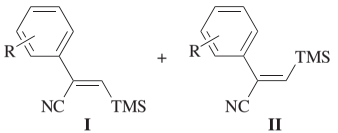
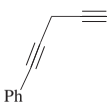
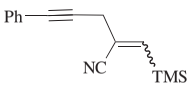
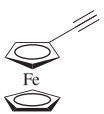
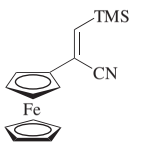
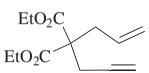
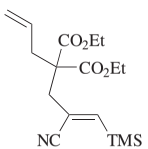
[b] This substrate requires 72 h reaction time.

TABLE 3B. HYDROCYANATION OF ALKYNES USING TMSCN

Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{5-12} R—≡	$PdCl_2$			80

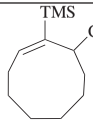
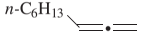
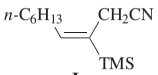
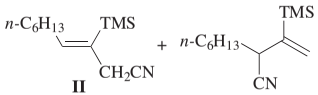
R	Conditions	I + II	I:II
$NCCH_2CH_2$	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	(63)	84:16
$AcOCH_2CH_2$	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	(36)	80:20
$TMSOCH_2CH_2$	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	(34)	88:12
Ph	Alkyne (5 mmol), cat (0.2 mmol), pyridine (0.4 mmol), TMSCN (10 mmol), toluene (10 mL), reflux, 10 h	(90)	95:5
n-C_6H_{13}	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	(41)	85:15
2-naphthalene	Alkyne (5 mmol), cat (0.2 mmol), pyridine (0.4 mmol), TMSCN (10 mmol), toluene (10 mL), reflux, 10 h	(90)	95:5

TABLE 3B. HYDROCYANATION OF ALKYNES USING TMSCN (*Continued*)

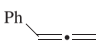
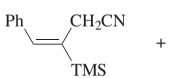
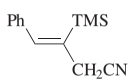
Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{8-9} 	$PdCl_2$	Alkyne (5 mmol), cat (0.2 mmol), pyridine (0.4 mmol), TMSCN (10 mmol), toluene (10 mL), reflux, 10 h	 **I** + **II**	80
C_{11} 	$PdCl_2$	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	 (47), *Z*:*E* = 87:13	80
C_{12} 	$PdCl_2$	Alkyne (5 mmol), cat (0.2 mmol), pyridine (0.4 mmol), TMSCN (10 mmol), toluene (10 mL), reflux, 10 h	 (52)	80
C_{13} 	$PdCl_2$	Alkyne (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 10 h	 (36)	80

R	I + II	I:II
4-F	(38)	—
4-Cl	(47)	94:6
2-Cl	(23)	81:19
2-OMe	(85)	83:17
4-OMe	(90)	95:5

TABLE 3C. HYDROCYANATION OF ALLENES USING TMSCN

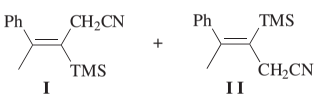
Allene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9 	$PdCl_2$	Allene (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 20 h	 (54) **I**	81
	$NiCl_2$, DIBALH	—	**I** (78)	80
	Pd or Ni salt	Allene (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 20 h	 + **I**  **II** + **III** (3–20%)	81

Cat	I + II	I:II
$PdCl_2$	(70)	89:11
$PdCl_2$, pyridine	(66)	95:5
$PdBr_2$, pyridine	(87)	89:11
$NiCl_2$, DIBALH	(54)	72:28

Allene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd or Ni salt	Allene (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 20 h	 +  **II**	81

Cat	I + II	I:II
$PdCl_2$, pyridine	(67)	88:12
$PdBr_2$, pyridine	(75)	89:11
$NiCl_2$, DIBALH	(48)	54:46

TABLE 3C. HYDROCYANATION OF ALLENES USING TMSCN (*Continued*)

Allene	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 	Pd or Ni salt	Allene (2.5 mmol), cat (0.1 mmol), pyridine (0.2 mmol), TMSCN (5 mmol), toluene (5 mL), reflux, 20 h	 **I** + **II**	81

Cat	I + II	I:II[a]
$PdBr_2$, pyridine	(60)	67:33
$NiCl_2$, DIBALH	(58)	64:36

[a] The product configuration assignment is tentative.

TABLE 3D. HYDROCYANATION OF ALKYNES USING CYANOMETALLATES

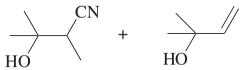
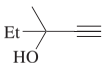
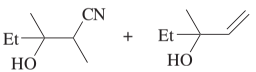
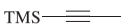
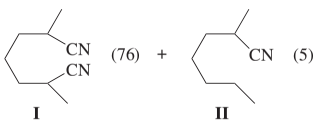
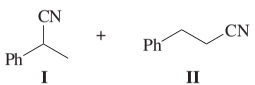
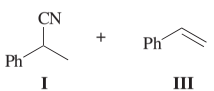
Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
	$K_2[Ni(CN)_4]$	Alkyne/cat (2:1), $K_2[Ni(CN)_4]/NaBH_4$ (4 mmol), H_2O, 45°, 4 h	 (49) + (12)	31
C_6				
	$K_2[Ni(CN)_4]$	Alkyne/cat (2:1), $K_2[Ni(CN)_4]/NaBH_4$ (4 mmol), H_2O, 45°, 4 h	 (59) + (10)	31
	$K_2[Ni(CN)_4]$	Alkyne/cat (2:1), $K_2[Ni(CN)_4]/NaBH_4$ (4 mmol), H_2O, 45°, 8 h	 (92)	31
C_7				
	$K_2[Ni(CN)_4]$	$K_2[Ni(CN)_4]/NaBH_4$ (4 mmol), EG, 45°, 6 h	 (76) + (5) **I** **II**	31
	$K_2[Ni(CN)_4]$	$K_2[Ni(CN)_4]/Zn$ (4 mmol), H_2O, 45°, 6 h	**I** (28) + **II** (53)	31
C_8				
	$K_2[Ni(CN)_4]$	Alkyne/cat/$NaBH_4$/KCN (8:1:5:10), H_2O/EG (9:1), 9 h	 **I** **II** **I** + **II** (90), **I**:**II** = 97:3	31
	$K_2[Ni(CN)_4]$	Alkyne/cat/Zn/KCN (2:1:5:2), H_2O, 2 h	 **I** **III** **I** + **III** (95), **I**:**III** = 93:7	31

TABLE 3D. HYDROCYANATION OF ALKYNES USING CYANOMETALLATES (*Continued*)

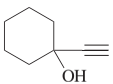
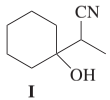
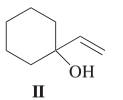
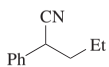
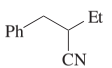
Alkyne	Catalyst	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8				
Ph—≡	$K_3[Co(CN)_5]$	Alkyne (5 mmol), alkyne/cat (1:1), $CoCl_2$ (5 mmol), KCN (24.5 mmol), H_2O (25 mL), 45°, 24 h	 (18) +  (2)	82
	$K_3[Co(CN)_5]$	Alkyne (5 mmol), alkyne/cat (1:1), $CoCl_2$ (5 mmol), KCN (24.5 mmol), H_2O (25 mL), 45°, 10 h	 (71) +  (13)	82
	$K_2[Ni(CN)_4]$	Alkyne (8 mmol), $K_2[Ni(CN)_4]$/ $NaBH_4$ (4 mmol), H_2O, 45°, 4 h	**I** (77) + **II** (14)	31
C_9				
Ph—≡	$K_2[Ni(CN)_4]$	Alkyne (8 mmol), $K_2[Ni(CN)_4]$/ $NaBH_4$ (4 mmol), H_2O/EG, 45°, 4 h	 (40) +  (23)	31
C_{10}				
Ph—≡—Et	$K_2[Ni(CN)_4]$	Alkyne (8 mmol), $K_2[Ni(CN)_4]$/ $NaBH_4$ (4 mmol), H_2O/EG, 45°, 8 h	 (43) +  (28)	31

TABLE 4A. ASYMMETRIC HYDROCYANATION OF MONOENES AND 1,3-DIENES

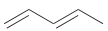
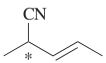
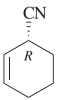
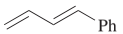
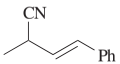
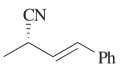
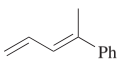
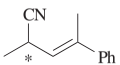
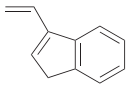
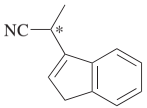
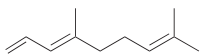
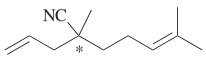
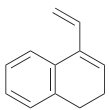
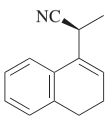
	Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_4		$Ni(cod)_2$ + **L12**	Alkene/$Ni(cod)_2$/**L12**/acetone cyanohydrin (100:1:7:110), toluene, 100°, 24 h	 24% conv., 83% selectivity,[a] 73% ee[b]	51
C_5		$Ni(cod)_2$ + **L5**	Alkene/$Ni(cod)_2$/**L5**/HCN (100:1:1.1:200), toluene (1.2 mL), 60°, 4 h	 (100), 33[b]	87
C_6		$Ni(cod)_2$ + **L4** or **L5**	Alkene/$Ni(cod)_2$/**L**/HCN (100:1:1.1:200), toluene (1.2 mL), 4 h		87
				Ligand / Temp (°) /	
				L4 80 (100), 43	
				L5 80 (100), 63	
				L5 0 (45), 86	
C_{10}		$Ni[(-)\text{-DIOP}]_2$[c]	Alkene (7.4 mmol), cat (0.019 mmol), (–)-DIOP (0.12 mmol), hydroquinone (0.4 mmol), HCN (7.4 mmol), C_6H_6, 120°, 18 h	 (70), <5	63
		$Ni(cod)_2$ + **L2**	Alkene (0.5 mmol), $Ni(cod)_2$ (3 mol %), **L2** (2.1 mol %), HCN (0.48 mmol), toluene, 12–48 h	 Ligand /	53
				L2a (75), 78	
				L2c (92), 72	
				L2d (87), 78	
C_{11}		$Ni(cod)_2$ + **L2a**	Alkene (0.5 mmol), $Ni(cod)_2$ (3 mol %), **L2a** (2.1 mol %), HCN (0.48 mmol), toluene, 12–48 h	 (56), 68[b]	53

TABLE 4A. ASYMMETRIC HYDROCYANATION OF MONOENES AND 1,3-DIENES (*Continued*)

	Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_{11}		$Ni(cod)_2$ + **L2**	Alkene (0.5 mmol), $Ni(cod)_2$ (3 mol %), **L2** (2.1 mol %), HCN (0.48 mmol), toluene, 12–48 h	 Ligand: **L2a** (61), 68[b]; **L2b** (46), 74[b]; **L2c** (68), 66[b]; **L2d** (62), 70[b]	53
		$Ni(cod)_2$ + **L2a**	Alkene (0.5 mmol), $Ni(cod)_2$ (3 mol %), **L2a** (2.1 mol %), HCN (0.48 mmol), toluene, 12–48 h	 (48), 19[b]	53
C_{12}		$Ni(cod)_2$ + **L2**	Alkene (0.5 mmol), $Ni(cod)_2$ (3 mol %), **L2** (1 mol %), HCN (0.48 mmol), toluene, 12–48 h	 Ligand: **L2a** (63), 75; **L2c** (64), 39; **L2d** (73), 50	53

[a] The selectivity refers to formation of the internal nitrile versus other products. No terminal nitrile was observed.

[b] The configuration of the product was not specified.

[c] The complex $Pd(DIOP)_2$ or $Ni(DIOP)_2$ and the corresponding ligand have opposite optical rotations.

TABLE 4B. ASYMMETRIC HYDROCYANATION OF BICYCLIC ALKENES

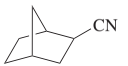
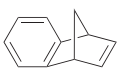
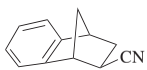
Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_7 	$Ni(cod)_2$ + **L1**	Alkene/$Ni(cod)_2$/**L1** (200:1:2), alkene/acetone cyanohydrin (>1:1), C_6H_6, 100°, 24 h	 (+)-**I** (52), 40	50
	$Pd_2(dba)_3$ + **L1**	Alkene (6 mmol), $Pd_2(dba)_3$ (0.03 mmol), **L1** (0.03 mmol), acetone cyanohydrin (5.5 mmol), C_6H_6 (0.5 mL), 120°, 18 h	(+)-**I** (52), 48	50
	Pd[(+)-DIOP]$_2$ [a]	Alkene (64 mmol), cat (0.09 mmol), (+)-DIOP (0.6 mmol), HCN (32 mmol), C_6H_6 (25 mL), 80°	(+)-**I** (94), 32	124, 47
	Pd[(+)-DIOP]$_2$ [a]	Alkene (28 mmol), cat (0.02 mmol), (+)-DIOP (0.2 mmol), HCN (14 mmol), C_6H_6 (7 mL), 120°, 18 h	(+)-**I** (94), 13	48
	Ni[(+)-DIOP)]$_2$ [a]	Alkene (64 mmol), cat (0.09 mmol), (+)-DIOP (0.6 mmol), HCN (32 mmol), C_6H_6 (25 mL), 80°	(–)-**I** (20), 14	124, 47
	Pd(**L16**)$_2$	Alkene (28 mmol), cat (0.02 mmol), **L16** (0.2 mmol), HCN (14 mmol), C_6H_6 (7 mL), 120°, 18 h	(–)-**I** (68), 20	48
	Pd[(*R*)-BINAP]$_2$	Alkene (28 mmol), cat (0.02 mmol), (*R*)-BINAP (0.2 mmol), HCN (14 mmol), C_6H_6 (7 mL), 120°, 18 h	(–)-**I** (6), 40	48

TABLE 4B. ASYMMETRIC HYDROCYANATION OF BICYCLIC ALKENES (*Continued*)

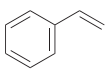
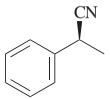
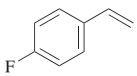
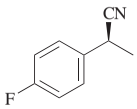
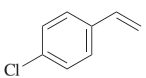
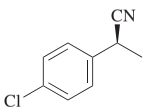
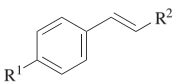
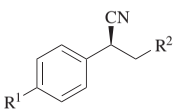
Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_7 	Ni(**L13**)$_2$	Alkene (48 mmol), cat (0.068 mmol), acetone cyanohydrin (24 mmol), 120°, 40 h	 (42), 33 (–)-**I**	49
	Ni(**L13**)$_2$	Alkene (48 mmol), cat (0.068 mmol), BPh_3 (0.34 mmol), acetone cyanohydrin (24 mmol), 100°, 40 h	(–)-**I** (58), 38	49
	Ni(cod)$_2$ + **L12**	Alkene/Ni(cod)$_2$/**L12**/acetone cyanohydrin (100:1:7:110), toluene, 100°, 24 h	**I**[b] 89% conv., 84% selectivity,[c] 55% ee	51
	Pd[(+)-DIOP]$_2$ [a]	Alkene (64 mmol), cat (0.09 mmol), (+)-DIOP (0.025 mmol), HCN (64 mmol), C_6H_6, 130°	 (40), 17	124, 47
C_{11} 	Pd[(+)-DIOP]$_2$ [a]	Alkene (37 mmol), cat (0.09 mmol), (+)-DIOP (0.6 mmol), HCN (32 mmol), C_6H_6 (25 mL), 130°, 18 h	 (83), 12	124, 47

[a] The complex Pd(DIOP)$_2$ or Ni(DIOP)$_2$ and the corresponding ligand have opposite optical rotations.

[b] The product configuration was not reported.

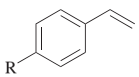
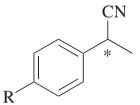
[c] The selectivity refers to formation of the nitrile versus other products.

TABLE 4C. ASYMMETRIC HYDROCYANATION OF VINYLARENES

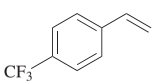
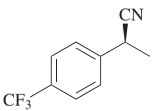
Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_8 	$Ni(cod)_2$ + **L17**	Alkene (1.3 mmol), $Ni(cod)_2$ (0.065 mmol), **L17** (0.062 mmol), HCN (1.04 mmol), toluene (2 mL), 60°, 16 h	 Ligand: **L17a** (61), 12; **L17b** (81), 14; **L17c** (17), 42	127
	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >90% conv. Ligand: **L2a** 28; **L2b** 15; **L2c** 4	45
	$Ni(cod)_2$ + **L2a**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2a** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >90% conv., 40% ee	45
C_{8-9} 	$Ni(cod)_2$ + **L4** or **L5**	Alkene/$Ni(cod)_2$/**L**/HCN (100:1:1.1:200), toluene (1.2 mL), 4 h		87

R^1	R^2	Ligand	Temp (°)	
H	H	**L4**	60	(100), 43
H	H	**L4**	0	(69), 47
H	H	**L5**	60	(100), 34
H	H	**L5**	0	(100), 49
Me	H	**L4**	0	(100), 54
Me	H	**L5**	0	(100), 50
H	Me	**L5**	60	(24), 30

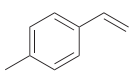
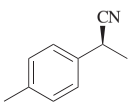
TABLE 4C. ASYMMETRIC HYDROCYANATION OF VINYLARENES (*Continued*)

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_{8-12} 	$Ni(cod)_2$ + **L12**	Alkene/$Ni(cod)_2$/**L12**/acetone cyanohydrin (100:1:x:110), toluene, 100°, 24 h		51

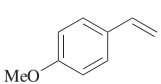
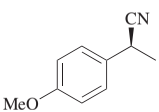
R	x	Conv. (%)	Selectivity (%)[a]	% ee[b]
H	1.2	48	70	49
F	7	98	94	49
Me	7	98	80	41
MeO	7	98	83	40

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_9 	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >90% conv.	45

Ligand	% ee
L2a	14
L2b	9
L2c	<5

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >90% conv.	45

Ligand	% ee
L2a	70
L2b	47
L2c	<5

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >90% conv.	45

Ligand	% ee
L2a	52
L2b	39
L2c	6

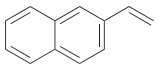
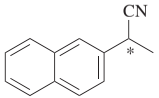
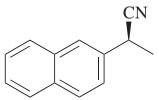
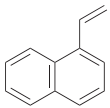
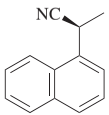
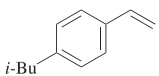
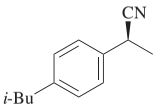
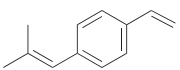
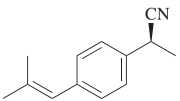
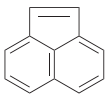
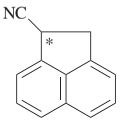
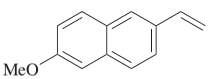
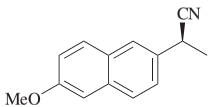
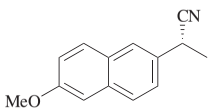
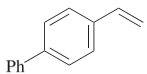
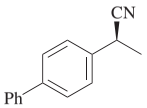
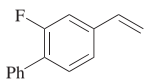
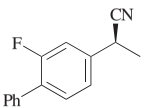
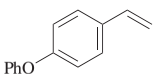
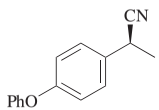
C_{12} 	$Ni(cod)_2$ + **L12**	Alkene/$Ni(cod)_2$/**L12**/acetone cyanohydrin (100:1:7:110), toluene, 100°, 24 h		20% conv., 94% selectivity,[a] 38% ee[b]	51
	$Ni(cod)_2$ + **L2**	Alkene (22 mmol), $Ni(cod)_2$ (1 mol %), **L2** (1 mol %), HCN (22 mmol), toluene, 24 h	 >95% conv.	Ligand / % ee: **L2a** 77; **L2b** 75; **L2c** 46; **L2d** 25	45
	$Ni(cod)_2$ + **L2**	Alkene (22 mmol), $Ni(cod)_2$ (1 mol %), **L2** (1 mol %), HCN (22 mmol), toluene, 24 h	 >95% conv.	Ligand / % ee: **L2a** 68; **L2c** 63	45
	$Ni(cod)_2$ + **L17**	Alkene/$Ni(cod)_2$/**L17**/HCN (100:1:1.05:125), toluene (2 mL), 60°, 16 h	 **I**	Ligand: **L17a** (29), 19; **L17b** (58), 15; **L17c** (22), 63	127
	$Ni(cod)_2$ + **L2**	Alkene (7.92 mmol), $Ni(cod)_2$ (0.16 mol %), **L2** (0.16 mol %), HCN (11 mmol in toluene), hexane, 24 h	**I**	Ligand: **L2a** (77), 56; **L2b** (—), 38; **L2c** (—), 6	45
	$Ni(cod)_2$ + **L2a**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2a** (2 mol %), HCN (0.65 mmol), hexane, 24 h		(—), 63	45

TABLE 4C. ASYMMETRIC HYDROCYANATION OF VINYLARENES (*Continued*)

Alkene	Catalyst	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
C_{12} 	$Ni(cod)_2$ + **L2**	Alkene (22 mmol), $Ni(cod)_2$ (1 mol %), **L2** (1 mol %), HCN (22 mmol), toluene, 24 h	 >95% conv.	45
			Ligand % ee[b] **L2a** 59 **L2c** 0	
C_{13} 	$Ni(cod)_2$ + **L17**	Alkene/$Ni(cod)_2$/**L17**/HCN (20:1:1.05:205), toluene (2 mL), 60°, 16 h	 **I**	127
			Ligand **L17a** (99), 31 **L17b** (99), 30 **L17c** (99), 29	
	$Ni(cod)_2$ + **L2**	Alkene (22 mmol), $Ni(cod)_2$ (1 mol %), **L2** (1 mol %), HCN (22 mmol), toluene, 24 h	**I** >95% conv.	45
			Ligand % ee **L2a** 84[c] **L2b** 78 **L2c** 35 **L2d** 16	
	$Ni(cod)_2$ + **L14**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L14** (2 mol %), HCN (0.65 mmol), 24 h	 **II** >95% conv.	89
			Ligand % ee **L14a** 33 **L14c** 13	
	$Ni(cod)_2$ + **L3**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L3** (2 mol %), HCN (0.65 mmol), rt, 24 h	**II** >95% conv.	86
			Ligand % ee **L3a** 56 **L3b** 43 **L3c** 58 **L3d** 89[d]	

	$Ni(cod)_2$ + **L15**	Alkene, $Ni(cod)_2$ (2 mol %), **L15** (2 mol %), HCN, 24 h	**II** (—)	Ligand / % ee: **L15a** 70; **L15b** 54; **L15c** 77		86
C_{14} 	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 >95% conv.	Ligand / % ee: **L2a** 68; **L2b** 41; **L2c** 8		45
	$Ni(cod)_2$ + **L2**	Alkene (22 mmol), $Ni(cod)_2$ (1 mol %), **L2** (1 mol %), HCN (22 mmol), toluene, 24 h	 90% conv.	Ligand / % ee: **L2a** 55; **L2c** 10		45
	$Ni(cod)_2$ + **L2**	Alkene (0.65 mmol), $Ni(cod)_2$ (2 mol %), **L2** (2 mol %), HCN (0.65 mmol), hexane, 24 h	 90% conv.	Ligand / % ee: **L2a** 60; **L2b** 38; **L2c** 7		45

[a] The selectivity refers to formation of the branched nitrile versus other products. No linear nitrile was observed.

[b] The absolute configuration of the product was not reported.

[c] Recrystallization of the product increases the enantiomeric excess from 84 to 99% ee.

[d] The enantiomeric excess increases from 89 to 95% ee when the reaction is performed at 0°.

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[3] James, B. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; pp 353–360.
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