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Stereocontrolled Cyanohydrin Ether Synthesis through Chiral Brønsted Acid-Mediated Vinyl Ether Hydrocyanation

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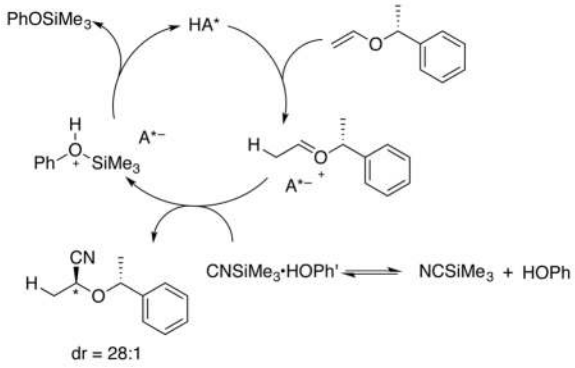
Abstract



Vinyl ethers can be protonated to generate oxocarbenium ions that react with Me_3SiCN to form cyanohydrin alkyl ethers. Reactions that form racemic products proceed efficiently upon converting the vinyl ether to an α-chloro ether prior to cyanide addition in a pathway that proceeds through Brønsted acid-mediated chloride ionization. Enantiomerically enriched products can be accessed by directly protonating the vinyl ether with a chiral Brønsted acid to form a chiral ion pair. Me_3SiCN acts as the nucleophile and PhOH serves as a stoichiometric proton source in a rare example of an asymmetric bimolecular nucleophilic addition reaction into an oxocarbenium ion. Computational studies provide a model for the interaction between the catalyst and the oxocarbenium ion.

Introduction

Nitriles are remarkably versatile entities that can serve as precursors to diverse functional groups such as carboxylic acids, amides, amines, ketones, and aldehydes.[1] Moreover the cyano group is proving to be an effective subunit for applications in medicinal chemistry[2] and is present in numerous natural products.[3] The broad utility of nitriles has led to efforts for their enantioselective synthesis. These studies have largely focused on asymmetric cyanohydrin formation,[4] and several successful preparations from of silyl ketene imine reactions have also been reported.[5] Asymmetric cyanohydrin synthesis generally commences with the addition of cyanide to an aldehyde or ketone and concludes with trapping the resulting hydroxy group as an ester or a silyl ether, though a few examples of direct asymmetric cyanohydrin formation are known.[6] The direct formation of

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Supporting Information
^1H and ^{13}C NMR spectra for all new compounds, HPLC traces for enantiomeric ratio determinations, methods for determining product absolute stereochemistry, and coordinates for computationally-derived structures. This material is available free of charge via the Internet http://pubs.acs.org.

enantiomerically enriched cyanohydrin alkyl ethers has not been reported despite their synthetic utility. Cyanohydrins are unstable under basic conditions and are weak nucleophiles, rendering their direct alkylation implausible. Cyanohydrin alkyl ethers are available as racemic mixtures through Lewis acid-mediated acetal ionization reactions followed by quenching the resulting oxocarbenium ions with Me_3SiCN.[7] Stereocontrol in these reactions is rare for acyclic substrates, though a good level of diastereocontrol was observed in the addition to an α-(trimethylsilyl)benzyl-substituted oxocarbenium ion.[8] Difficulties in controlling the stereochemical outcomes in additions of cyanide to oxocarbenium ions result from the high reactivity and minimal steric demands of the nucleophile and the high reactivity of the electrophile.[9]

Cyanohydrin alkyl ethers have proven to be particularly effective substrates for amide formation through nitrile hydrozirconation, acylation, and nucleophilic addition.[10] Multiple applications in target-,[11] diversity-,[12] and function-oriented[13] synthesis led us to explore the potential for directly preparing enantiomerically enriched cyanohydrin alkyl ethers through a catalytic, asymmetric pathway. This manuscript describes a protocol for synthesizing these structures through Brønsted acid-mediated enol ether hydrocyanation that proceeds through alkene protonation followed by cyanide addition. A general protocol for accessing racemic structures is presented followed by a description of an asymmetric variant in which asymmetric Brønsted acids serve to generate chiral ion pairs that engage in stereoselective cyanide addition reactions. These reactions, where Me_3SiCN serves as the nucleophile and phenol is used as a proton source, are rare illustrations of asymmetric bimolecular Brønsted acid-catalyzed asymmetric additions into oxocarbenium ions and are the first examples in which a silylated nucleophile couples with readily accessible enol ether substrates. The results of these studies are analyzed through a computationally based model that defines the interactions between the catalyst and the oxocarbenium ion, explains the observed stereochemical outcomes, and defines the current scope of the process.

Results and Discussion

Our initial objective was to develop a route for cyanohydrin alkyl ether formation through alkyl enol ether protonation. Enol ethers are attractive oxocarbenium ion precursors in comparison to more commonly employed acetals, particularly for substrates that contain structurally complex or valuable alkoxy groups. These substrates are readily accessed through cross-coupling[14] or vinyl transfer[15] reactions, and do not require that an equivalent of the alkoxy group be lost through cyanation. Despite these benefits, examples of enol ethers as precursors to cyanohydrin ethers are quite rare.[16] Our initial approach to the problem (Scheme 1) illustrated a significant obstacle to their use in these reactions. Adding a catalytic quantity of anhydrous HCl to a mixture of benzyl vinyl ether (**1**) and Me_3SiCN provided cyanohydrin ether **2** in only 18% yield. The remainder of the material resulted from oligomerization through nucleophilic enol ether addition into oxocarbenium ion intermediates. This problem was solved by quantitatively converting the enol ether to an electrophile prior to the addition of Me_3SiCN through forming α-chloro ether **3** from **1** and HCl (1.1 equiv). The addition of Me_3SiCN (2 equiv) to the crude chloro ether led to the formation of **2** in 81% yield for the one pot transformation. The mechanism of this transformation could proceed through chloride ionization by a Brønsted acid or by Me_3SiCN. The cyanation step was suppressed by the addition of 2,6-di-*tert*-butylpyridine, suggesting that the oxocarbenium ion **4** arises from Brønsted acid-mediated ionization in accord with observations from the Jacobsen group.[17] The addition of chloride to Me_3SiCN creates the highly reactive nucleophile **5** that adds to **4** to form the product.[18]

The scope of the process is illustrated through the examples shown in Table 1. Substrates with longer alkoxy groups react smoothly (entry 1), and functional groups such as alkenes,

silyl ethers, and sulfides are tolerated (entries 2–4). Ethers with branched alkoxy groups react efficiently, though little stereocontrol is observed (entry 5). The vinyl group can be lengthened (entries 6 and 7), and cyclic enol ethers react well (entry 8). These transformations illustrate the generality of cyanohydrin ether formation through Brønsted acid-mediated enol ether hydrocyanation and provide an entry into the development of an asymmetric variant.

These results led us to explore the potential of replacing HCl with a chiral Brønsted acid[19] to form asymmetric ion pair intermediates[20] (Scheme 2). Thus we prepared chloro ether **3** and added Me_3SiCN at 0 °C in the presence of thiophosphoryl triflimide **22**[21] (3 mol%). This reaction provided **2** with an enantiomeric ratio (er) of 57.5:42.5, thereby successfully demonstrating that a modest degree of asymmetric induction is possible for this process though the results are not preparatively useful. Success in this protocol requires that the liberated HCl from oxocarbenium ion generation engage in an exchange reaction with the silylated catalyst that forms from the cyanation step to regenerate the chiral Brønsted acid and form Me_3SiCl. However if this process is not rapid or is not thermodynamically viable then the potential for a non-selective HCl-catalyzed background reaction is high.

The capacity for a non-selective background reaction led us to re-examine vinyl ethers as substrates. Chiral Brønsted acids have been used to generate oxocarbenium ion intermediates for reactions in which a proton is lost from a nucleophile, such as an alcohol or active methylene compound, to regenerate the acid directly.[22] Silylated nucleophiles can be utilized when a silyl group scavenger is formed upon oxocarbenium ion generation.[17a,23] All reported cases of bimolecular additions into oxocarbenium ions utilized either sterically hindered nucleophiles[22a] or highly specific electrophiles.[17a,22g,23] Asymmetric Brønsted acid-catalyzed additions of silylated nucleophiles to vinyl ether-derived oxocarbenium ions are unexplored processes. The obstacle to these reactions lies in the need to regenerate the Brønsted acid when a silyl cation acts as the electrofuge. Alcohols have been added to quench silyl electrofuges and regenerate Brønsted acids in enantioselective enolsilane[24] and silyl ketene imine[25] protonation reactions. These results inspired the proposed catalytic cycle for the transformation that is shown in Scheme 3. Enol ether protonation will generate a chiral ion pair. We postulate that Me_3SiCN will be activated by complexation with an alcohol to form a pentavalent silyl isocyanide nucleophile in accord with Woerpel's studies[8] on the reactive intermediates in the addition of silyl cyanides to oxocarbenium ions. Cyanide transfer yields the cyanohydrin ether and an ion pair from the protonated silyl ether and the conjugate base of the catalyst. Proton transfer regenerates the catalyst and yields a silyl ether.

Initial catalyst screening was conducted with **1** as the substrate in CH_2Cl_2 at rt. The Brønsted acid loading was set at 3 mol% and phenol was used as the stoichiometric proton source. The results are shown in Table 2. The absolute stereochemistry of the major isomer was determined through comparison to authentic material that was prepared from methyl lactate. Thiophosphoryl triflimide **22** provided an 65:35 enantiomeric ratio (entry 1), indicating that this protocol is superior to oxocarbenium ion formation through chloro ether ionization. Changing the substitution pattern of the aryl groups (**23**, entry 2) and introducing a triphenylsilyl group onto the binaphthyl core (**24**, entry 3) led to significantly diminished stereocontrol. Adamantyl-substituted catalyst **25** provided an increase in selectivity (entry 4). Selectivity was further improved by employing biaryl-substituted catalyst **26** (entry 5). The triflimide group proved to be essential for the reaction, with **27** proving to be an ineffective catalyst (entry 6). Phosphoryl triflimide **28** was also ineffective (entry 7), demonstrating the importance of the sulfide group in this process. Thus acid **26** was selected as the lead catalyst for this process. Changing the cyanide source to HCN with no incorporation of phenol resulted in low conversion and diminished enantioselectivity (not

shown). This suggests that the Me_3SiCN and phenol interact to form the relevant nucleophile in this reaction, and that this nucleophile is not HCN. ^{13}C NMR studies confirmed that PhOH and Me_3SiCN interact in solution,[26] as has been previously described.[27] The generation of a more reactive nucleophile through this interaction is consistent with the higher yield of these reactions in comparison to the studies with catalytic activation by HCl. Stereocontrol was modestly improved by adding PhOH slowly in an effort to minimize the background reaction[28] and side reactons such as mixed acetal formation. Lowering the temperature to −40 °C resulted in higher selectivity, providing **2** with an 83.3:16.7 er (entry 8). A limited solvent screen was conducted, with the best result being observed with $PhCF_3$, consistent with other results from addition reactions to chiral ion pairs.[26] The minimum temperature for this reaction is −25 °C because of the freezing point of $PhCF_3$, yet the process provided **2** in 85% chemical yield with an er of 85:15 (entry 9). Stereocontrol was not improved by increasing the catalyst loading to 10 mol% (not shown). Nearly identical results can be obtained when the catalyst loading is reduced to 0.5 mol%, however (entry 10). Lowering the catalyst loading to 0.1 mol% resulted in a reaction that was unacceptably slow.

The identification of optimal conditions allowed us to explore the scope of the process (Table 3). The process proved to be relatively insensitive to changes in the alkoxy group, with longer chains and branching being tolerated (entries 1, 2, and 4). Substrates with larger aromatic groups such as naphthalenes (entry 7) also react smoothly. Functional groups such as alkenes (entry 3), esters (entry 5) and sulfides (entry 6) are compatible with the reaction conditions. One limitation to this method is that alkoxy groups that can fragment to form a stable carbocation following oxocarbenium ion formation, such as *tert*-butyl ethers, do not yield the cyanohydrin ether product (not shown). Extending the alkenyl group caused a reduction in efficiency that was more pronounced at greater chain lengths (entries 8 and 9). (*Z*)-Enol ethers proved to be superior substrates relative to the corresponding (*E*)-enol ethers, though identical levels of stereocontrol were observed regardless of the substrate alkene geometry (entries 9 and 10). This suggests that the same reactive intermediate was formed from either isomer but the (*Z*)-isomer is protonated more rapidly than the (*E*)-isomer. Chiral substrates can show matched or mismatched selectivity in these reactions, as evidenced by the reaction of the phenethyl vinyl ether enantiomers in entries 11 and 12. Reactions with these compounds under HCl-mediated conditions showed little stereocontrol. The reaction of (*R*)-enantiomer **42** in the presence of **26**, however, proved to be highly diastereoselective. The reaction of (*S*)-enantiomer **14** showed little diastereoselectivity, similar to the HCl-mediated process.

Chiral Brønsted acid catalysis can also be used to prepare enantiomerically enriched cyanohydrin ethers from conventional acetal precursors (Scheme 4). Dibenzyl acetal **45** reacts with Me_3SiCN in the presence of **26** to provide **(*S*)-2** in 85% yield and with an er of 82.5:17.5. These numbers are comparable to the values that were observed with the corresponding vinyl ether substrate. Dimethyl acetal **46** reacts under these conditions to yield **(*S*)-17** in 91% yield and with an er of 73:27. Again these values are similar to the results in the vinyl ether series, indicating that the choice of a vinyl ether or acetal substrate should generally be dictated by synthetic accessibility since reaction outcomes are negligibly different. Acetals, however, are clearly superior substrates to poorly reactive (*E*)-vinyl ethers in these processes. The similarities between the outcomes of reactions with acetals and enol ethers suggests that they proceed through the same intermediates, and the acetals do not react through through a pathway in which one of the enantiotopic alkoxy groups is preferentially activated by the catalyst to generate a tight ion pair between the oxocarbenium ion and the departing alcohol.[29] NMR studies showed that phosphoryl triflimides are silylated by Me_3SiCN in the absence of phenol[25] to form a Lewis acid that most likely

serves as the active catalyst in these processes. Trimethylsilyl ethers are observed as products in these reactions in accord with this hypothesis.

Oxocarbenium ions do not possess obvious sites for hydrogen bonding to the catalyst, in contrast to carbonyl and imine groups, obscuring the development of a predictive model for ion pairing. Thus we initiated computational studies using density functional theory (DFT) to gain insight into the origins of the asymmetric induction and to explain the substrate scope. These studies were conducted with Gaussian 09[30] using B3LYP[31] as the exchange-correlation function. The interaction between the oxocarbenium ion of ethyl vinyl ether with the conjugate base of catalyst **22** was utilized to develop a model for these transformations. Peripheral atoms were treated with the 3–21G[32] basis set while contact atoms were treated with the 6–311G[33] basis set. The phosphorus and sulfur atoms were described by the 6–311G(3df, 3pd)[34] basis set. Energy minima were determined by optimizing structures from several starting geometries. Minima were confirmed by frequency calculations.

The lowest energy structure for the ion pair is shown in Figure 1. This structure shows interactions between the sulfur of the catalyst and the carbon of the oxocarbenium ion. Additionally the nitrogen of the triflimide group in catalyst interacts with the hydrogen on the electrophilic carbon of the oxocarbenium ion. Corey has postulated that this type of interaction can be important in structures between aldehydes and Lewis acids[35] and recent work has postulated these interactions to be relevant for chiral phosphoric acid-catalyzed additions to aldehydes.[36] The Mulliken charge on the indicated hydrogen was calculated to be +0.22, supporting the postulated electrostatic attraction. Additionally the fluorine atoms of the trifluoromethyl group in the catalyst are proximal to the hydrogen atoms of the electron deficient hydrogens of the alkoxy group. Although the existence of defined C–H•••F–C hydrogen bonds is controversial,[37] electrostatic and van der Waals attractions between organofluorine compounds and electron deficient hydrogens are well established[38] and could contribute to defining the orientation of the substrate in the catalyst. The Mulliken charges on these hydrogens were calculated to be +0.2, again supporting the possibility for an electrostatic interaction. Thus the *Si*-face of the oxocarbenium ion is blocked and the *Re*-face is open for nucleophilic attack. This correlates with the observed (*S*)-stereoisomer being the major product in these reactions. Lengthening the alkyl group of the electrophilic arm of the oxocarbenium ion results in a steric clash with a triisopropylphenyl group of the catalyst, while the other arm of the electrophile can be extended without impediment. This explains the diminished stereocontrol that is observed when the alkenyl group of the substrate is extended.

The substantial difference in the matched and mismatched outcomes from the α-methylbenzyl ether substrates was not expected based on the minimal diastereocontrol that was observed through the HCl-mediated pathway, but can be rationalized through a molecular modeling based on the ion pair structure.[26] The methyl group of (*R*)-substrate **42** fills a pocket of the catalyst (Figure 2, top image), thereby placing the sterically undemanding benzylic hydrogen across from the trajectory of the nucleophile. Placing the corresponding methyl group of (*S*)-substrate **14** in the same orientation creates steric interactions between the phenyl group and the catalyst. Therefore the benzylic hydrogen rotates into that position (Figure 2, bottom image), leading to a conformation in which the methyl and phenyl groups block the trajectory of the nucleophile into the *Re*-face. Therefore neither face of the oxocarbenium ion is open for nucleophilic attack and the reaction most likely proceeds through an intermediate that is not intimately associated with the chiral counterion.

Conclusions

We have demonstrated that vinyl ethers undergo smooth acid-mediated hydrocyanation reactions to yield cyanohydrin ethers. Racemic product formation proceeds most efficiently when the vinyl ether is quantitatively converted to a chloro ether followed by Brønsted acid-mediated ionization to form an oxocarbenium ion that reacts with Me_3SiCN. Useful levels of enantioselectivity can be achieved by forming the oxocarbenium ion directly through protonating the vinyl ether with a chiral Brønsted acid, in which catalyst regeneration is effected by the addition of phenol. Acetals are also suitable substrates for this process, yielding products with similar levels of enantiocontrol. These processes represent the first examples of asymmetric Brønsted acid-mediated addition reactions of silylated nucleophiles with vinyl ethers and acetals and are rare cases[17a,22a,22g23] in which enantioselectivity has been observed in bimolecular reactions into oxocarbenium ions. Computational studies suggest that the attraction in the ion pair arises from associations between the conjugate base of the catalyst with the electrophilic carbon and its attached hydrogen in the oxocarbenium ion. This model accurately explains several experimental observations in this study. The protocols that were developed for asymmetric additions of silylated nucleophiles into oxocarbenium ions coupled with the model for ion pair association will be beneficial for broadening the scope of this useful reaction class to include other silyl-containing nucleophiles.

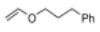
Experimental Section

General protocols

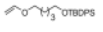
Chemical shifts for proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, CD_2Cl_2 = 5.32 ppm and for ^{13}C NMR: $CDCl_3$ = 77.23 ppm. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; dd = doublet of doublets; ddd = doublet of doublet of doublets; td = triplet of doublets). High resolution mass spectrometry (HRMS) were determined with a time of flight (TOF) detector. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. High performance liquid chromatography (HPLC) was performed with a refractive index detector using chiral stationary columns (0.46 cm x 25 cm). Optical rotations were recorded on a digital polarimeter with a sodium lamp at ambient temperature as follows: $[\alpha]_\lambda$ (c, g/100 mL). Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride was distilled under N_2 from CaH_2. α,α,α-Trifluorotoluene, HCl solution (2.0 M in diethyl ether), ethyl acetate, diethyl ether, toluene, and hexanes were used as purchased. Trimethylsilyl cyanide was freshly fractionally distilled prior to use and used under Ar atmosphere. Analytical TLC was performed on pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was performed with 32–63 60 Å silica gel. All reactions were performed in oven or flame-dried glassware under argon with magnetic stirring unless otherwise noted. Substrates **1**,[39] **8**,[40] **29**,[41] **31**,[42] and **42**[43] were prepared according to reported protocols.

General procedure for preparing vinyl ether substrates.[17]

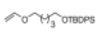
To a solution of the alcohol (1.0 equiv) in ethyl vinyl ether (10 equiv) was added $Hg(OAc)_2$ (0.1 equiv). The reaction mixture was stirred at reflux under N_2 for 24 h, then the excess ethyl vinyl ether was removed under vacuum. The crude product was purified by flash chromatography using CH_2Cl_2 and hexanes as the eluent.



(3-(Vinyloxy)propyl)benzene (6)—The general procedure for the vinyl ether formation was followed with ethyl vinyl ether (10.8 mL, 110 mmol), 3-phenylpropan-1-ol (1.5 mL, 11 mmol), and $Hg(OAc)_2$ (176 mg, 0.55 mmol). The crude product was purified by flash chromatography (20% CH_2Cl_2 in hexane) to give **6** as a colorless oil (1.04 g, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.22-7.20 (m, 3H), 6.50 (dd, 1H, *J* = 14.4, 6.8 Hz), 4.19 (dd, 1H, *J* = 14.4, 2.0 Hz), 4.00 (dd, 1H, *J* = 6.8, 2.0 Hz), 3.71 (t, 2H, *J* = 6.4 Hz), 2.75 (t, 2H, *J* = 7.2 Hz), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 141.7, 128.6, 128.6, 126.1, 86.6, 67.1, 32.3, 30.9; IR (neat) 3116, 3027, 2946, 2870, 1614, 1319, 1203, 1083, 815, 747, 699 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}O$ $[M+H]^+$ 163.1117, found 163.1109.



***tert*-Butyldiphenyl((5-(vinyloxy)pentyl)oxy)silane (10)—**The general procedure for vinyl ether formation was followed with ethyl vinyl ether (6.9 mL, 72 mmol), 5-((*tert*-butyldiphenylsilyl)oxy)pentan-1-ol (2.5 g, 7.2 mmol), and $Hg(OAc)_2$ (115 mg, 0.375 mmol). The crude product was purified by flash chromatography (20% to 40% CH_2Cl_2 in hexane) to give **10** as a colorless oil (1.67 g, 63%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.45-7.37 (m, 6H), 6.47 (dd, 1H, *J* = 14.0, 6.5 Hz), 4.18 (dd, 1H, *J* = 14.5, 2.0 Hz), 3.98 (dd, 1H, *J* = 6.5, 2.0 Hz), 3.69 (t, 2H, J = 6.5 Hz), 3.67 (t, 2H, *J* = 6.5 Hz), 1.69-1.64 (m, 2H), 1.63-1.58 (m, 2H), 1.50-1.44 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 135.8, 134.3, 129.7, 127.8, 86.4, 68.1, 63.9, 32.4, 29.0, 27.1, 22.5, 19.4; IR (neat) 3071, 3049, 2934, 2859, 1612, 1428, 1203, 1111, 822, 703 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}O_2Si$ $[M+H]^+$ 369.2244, found 369.2232.



Benzyl(2-(vinyloxy)ethyl)sulfane (12)—The general procedure for vinyl ether formation was followed with ethyl vinyl ether (2.3 mL, 23 mmol), 2-(benzylthio)ethan-1-ol (390 mg, 2.3 mmol), and $Hg(OAc)_2$ (73 mg, 0.23 mmol). The crude product was purified by flash chromatography (15% CH_2Cl_2 in hexane) to give **12** as a colorless oil (347 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 6.46 (dd, 1H, *J* = 14.0, 6.8 Hz), 4.19 (dd, 1H, *J* = 14.0, 2.0 Hz), 4.04 (dd, 1H, *J* = 6.8, 2.0 Hz), 3.82 (t, 2H, *J* = 6.8 Hz), 3.80 (s, 2H), 2.71 (t, 2H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 138.3, 129.1, 128.7, 127.2, 87.1, 67.7, 36.8, 30.1; IR (neat) 3114, 3062, 3028, 2921, 2870, 1616, 1454, 1320, 1194, 1070, 819, 702 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{14}OS$ $[M]^+$ 194.0765, found 194.0794.

(*S*)-(1-(Vinyloxy)ethyl)benzene (14)—The general procedure for vinyl ether formation was followed with ethyl vinyl ether (8.0 mL, 83 mmol), (*S*)-phenylethanol (1.00 mL, 8.3 mmol), and $Hg(OAc)_2$ (262 mg, 0.83 mmol). The crude product was purified by flash chromatography (15% CH_2Cl_2 in hexane) to give **14** as a colorless oil (763 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.33 (dd, 1H, *J* = 14.0, 6.4 Hz), 4.91 (q, 1H, *J* = 6.4 Hz), 4.27 (d, 1H, *J* = 14.4 Hz), 4.00 (d, 1H, *J* = 6.8 Hz), 1.54 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 143.1, 128.7, 127.7, 125.9, 89.4, 77.5, 23.8; IR (neat) 3030, 2980, 2931, 1637, 1188, 1085, 759, 699 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O$ $[M]^+$ 148.0888, found 148.0898. $[\alpha]_D^{25} = -71.1$ (*c* 1.0, $CHCl_3$).

(*E*)-(3-methoxyallyl)benzene (16) and (*Z*)-(3-methoxyallyl)benzene (41)—Prepared following Negishi's protocol,[44] with the crude product being purified by MPLC (medium pressure liquid chromatography, 100% hexane to 10% CH_2Cl_2 in hexane) for three times. The faster eluting product is the minor isomer **41**: ^1H NMR (400 MHz, CD_2Cl_2) δ 7.28-7.24 (m, 2H), 7.21-7.19 (m, 2H), 7.17-7.14 (m, 1H), 6.02 (d, 1H, *J* = 6.0 Hz), 4.55 (q, 1H, *J* = 7.6 Hz), 3.62 (s, 3H), 3.38 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 141.9, 128.5, 128.5, 125.9, 105.7, 59.8, 30.3.

The slower eluting product is the major isomer **16:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.24-7.18 (m, 3H), 6.43 (d, 1H, *J* = 12.6 Hz), 4.91 (dt, 1H, *J* = 12.6, 7.5 Hz), 3.55 (s, 3H), 3.28 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 141.9, 128.6, 128.5, 126.2, 102.1, 56.1, 34.2.

(*E*)-(Dec-1-en-1-yloxy)cyclohexane (18)[45]—To a solution of (*E*)-1-iododec-1-ene (798 mg, 3 mmol) and cyclohexanol (632 μL, 6 mmol) in toluene (1.5 mL) was added CuI (57 mg, 0.3 mmol), Cs_2CO_3 (1.46g, 4.5 mmol) and tetramethyl-1,10-phenanthroline (141 mg, 0.6 mmol). The reaction tube was sealed with a screw cap, and stirred at 85 °C for 20 h. The resulting suspension was cooled to room temperature, and passed through a short pad of silica gel eluting with Et_2O. The filtrate was concentrated under vacuum, and the crude product was purified by flash chromatography (100% hexane to 5% Et_2O in hexane) to give as a colorless oil (385 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, *J* = 12.3 Hz), 4.89 (dt, 1H, *J* = 12.3, 7.2 Hz), 3.65-3.56 (m, 1H), 1.90-1.88 (m, 4H), 1.76-1.74 (m, 2H), 1.56-1.51 (m, 1H), 1.43-1.27 (m, 18H), 0.89 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 106.6, 78.1, 32.3, 32.1, 30.8, 29.7, 29.5, 29.3, 27.9, 25.8, 24.0, 22.9, 14.3; IR (neat) 2928, 2855, 1671, 1452, 1164, 922 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{16}H_{31}O$ $[M+H]^+$ 239.2375, found 239.2377.

3-(Vinyloxy)propyl benzoate (35)—The general procedure for vinyl ether formation was followed with ethyl vinyl ether (12 mL, 130 mmol), 3-hydroxypropyl benzoate (2.27 g, 12.6 mmol), and $Hg(OAc)_2$ (401 mg, 1.26 mmol). The crude product was purified by flash chromatography (5% EtOAc in hexane) to give **35** as a colorless oil (1.51 g, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 6.8 Hz), 7.57 (t, 1H, *J* = 6.6 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 6.49 (dd, 1H, *J* = 14.0, 6.8 Hz), 4.45 (t, 2H, *J* = 6.4 Hz), 4.22 (dd, 1H, *J* = 14.4, 2.0 Hz), 4.03 (dd, 1H, *J* = 6.8, 2.0 Hz), 3.86 (t, 2H, *J* = 6.0 Hz), 2.15 (quin, 2H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 151.8, 133.0, 130.4, 129.7, 128.5, 86.8, 64.5, 61.9, 28.6; IR (neat) 3117, 3064, 2962, 2881, 1721, 1617, 1452, 1275, 1199, 1112, 820, 712 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{14}O_3$ $[M]^+$ 206.0943, found 206.0937.

2-((Vinyloxy)methyl)naphthalene (37)—The general procedure for vinyl ether formation was followed with ethyl vinyl ether (1.9 mL, 20 mmol), 2-napthalenemethanol (316 mg, 2.0 mmol), and $Hg(OAc)_2$ (32 mg, 0.1 mmol). The crude product was purified by flash chromatography (10% to 20% CH_2Cl_2 in hexane) to give **37** as the desired product (152 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.84 (m, 4H), 7.51-7.47 (m, 3H), 6.64 (dd, 1H, *J* = 14.4, 6.8 Hz), 4.95 (s, 2H), 4.38 (dd, 1H, *J* = 14.4, 2.0 Hz), 4.13 (dd, 1H, *J* = 6.8, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 134.6, 133.5, 133.2, 128.5, 128.1, 127.9, 126.6, 126.4, 126.3, 125.6, 87.8, 70.4; IR (neat) 3055, 2923, 2867, 1616, 1319, 1196, 959, 816, 752 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_{12}O$ $[M]^+$ 184.0888, found 184.0896.

(*Z*)-((Prop-1-en-1-yloxy)methyl)benzene (39)[46]—To a solution of allyl benzyl ether (592 mg, 4.0 mmol) in DMSO (40 mL) was added *t*-BuOK (1.63 g, 10 mmol) under Ar atmosphere. After stirring at 60 °C for 2 h, the reaction mixture was diluted with Et_2O, washed with H_2O (3x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **39** as a colorless oil (460 mg, 78%, *Z:E* = 97:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 6.05 (dq, 1H, *J* = 6.0, 1.5 Hz), 4.81 (s, 2H), 4.46 (app quin, 1H, *J* = 6.6 Hz), 1.64 (dd, 3H, *J* = 6.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 138.0, 128.6, 127.9, 127.4, 101.9, 73.6, 9.5. These data are consistent with reported literature values.[47]

General procedure for vinyl ether hydrocyanation via α-chloroether formation

To a solution of the vinyl ether (1.0 equiv) in freshly distilled methylene chloride (0.1 M) at −40 °C under Ar was added a solution of HCl (1.1 equiv, 2.0 M in diethyl ether) dropwise. After 5 min, TMSCN (2 equiv) was added to the reaction mixture. The mixture was stirred at −40 °C for 1 h, then was quenched by Et_3N (0.3 mL) followed by saturated $NaHCO_3$ solution. After warming up to room temperature, the reaction mixture was extracted with methylene chloride (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

2-(Benzyloxy)propanenitrile (2)—The general procedure for hydrocyanation was followed with **1** (54 mg, 0.4 mmol), HCl solution (220 μL, 0.44 mmol), TMSCN (100 μL, 0.8 mmol), and CH_2Cl_2 (4 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **2** as a colorless oil (52 mg, 81%). For characterization data see the procedure for preparing enantioenriched material.

2-(3-Phenylpropoxy)propanenitrile (7)—The general procedure for hydrocyanation was followed with **6** (49 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **7** as a colorless oil (52 mg, 92%). For characterization data see the procedure for preparing enantioenriched material.

2-(Hex-5-en-1-yloxy)propanenitrile (9)—The general procedure for hydrocyanation was followed with **8** (38 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (10% Et_2O in pentane) to give **9** as a colorless oil (35 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 17.1, 10.2, 6.6 Hz), 5.06-4.95 (m, 2H), 4.22 (q, 1H, *J* = 6.9 Hz), 3.76 (dt, 1H, *J* = 8.7, 6.3 Hz), 3.47 (dt, 1H, *J* = 8.7, 6.3 Hz), 2.09 (q, 2H, *J* = 6.9 Hz), 1.69-1.60 (m, 2H), 1.57 (d, 3H, *J* = 6.6 Hz), 1.53-1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 119.3, 115.0, 70.6, 64.7, 33.5, 28.9, 25.4, 20.0; IR (neat) 3078, 2941, 2870, 1641, 1443, 1331, 1113, 1077, 997, 912 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_9H_{16}ON$ $[M+H]^+$ 154.1226, found 154.1218.

2-((5-((*tert*-Butyldiphenylsilyl)oxy)pentyl)oxy)propanenitrile (11)—The general procedure for hydrocyanation was followed with **10** (74 mg, 0.2 mmol), HCl solution (110 μL, 0.22 mmol), TMSCN (50 μL, 0.4 mmol), and CH_2Cl_2 (2 mL). The crude product was purified by flash chromatography (3% to 5% EtOAc in hexane) to give **11** as a colorless oil (76 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.45-7.37 (m, 6H), 4.20 (q, 1H, *J* = 6.5 Hz), 3.74 (dt, 1H, *J* = 9.0, 6.5 Hz), 3.68 (t, 2H, *J* = 6.5 Hz), 3.44 (dt, 1H, *J* = 9.0, 6.5 Hz), 1.64-1.58 (m, 4H), 1.56 (d, 3H, *J* = 7.0 Hz), 1.48-1.42 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 134.3, 129.7, 127.8, 119.3, 70.7, 64.7, 63.9, 32.4, 29.2, 27.1, 22.4, 20.0, 19.4; IR (neat) 3050, 2997, 2941, 1589, 1473, 1113, 823, 706, 613 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{34}O_2NSi$ $[M+H]^+$ 396.2353, found 396.2343.

2-(2-(Benzylthio)ethoxy)propanenitrile (13)—The general procedure for hydrocyanation was followed with **12** (58 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **13** as a colorless oil (60 mg, 85%). For characterization data see the procedure for preparing enantioenriched material.

2-((*S*)-1-Phenylethoxy)propanenitrile (15)—The general procedure for hydrocyanation was followed with **14** (104 mg, 0.7 mmol), HCl solution (385 μL, 0.77

mmol), TMSCN (175 μL, 1.4 mmol), and CH_2Cl_2 (7 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give two diastereomers (112 mg, 91%, d.r. = 1.2:1). The faster eluting product was the major diastereomer **44**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 4.75 (q, 1H, *J* = 6.4 Hz), 3.97 (q, 1H, *J* = 6.8 Hz), 1.52 (d, 3H, *J* = 6.4 Hz), 1.51 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 129.1, 128.6, 126.6, 119.4, 77.9, 61.7, 24.1, 20.1; IR (neat) 3032, 2982, 2887, 1453, 1057, 763, 702 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.1016. $[\alpha]_D^{25}$ = −323.3 (*c* 1.0, $CHCl_3$).

The slower eluting product was the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 4.68 (q, 1H, *J* = 6.8 Hz), 4.31 (q, 1H, *J* = 6.8 Hz), 1.58 (d, 3H, *J* = 6.4 Hz), 1.51 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.8, 128.5, 126.6, 119.4, 78.2, 62.2, 22.6, 20.4; IR (neat) 3032, 2981, 2889, 1453, 1029, 762, 701 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.1018. $[\alpha]_D^{25}$ = −8.7 (*c* 1.0, $CHCl_3$).

 2-Methoxy-4-phenylbutanenitrile (17)—The general procedure for hydrocyanation was followed with **16** (30 mg, 0.2 mmol), HCl solution (110 μL, 0.22 mmol), TMSCN (50 μL, 0.4 mmol), and CH_2Cl_2 (2 mL) at 0 °C. The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **17** as a colorless oil (29 mg, 83%). For characterization data see the procedure for preparing enantioenriched material.

 2-(Cyclohexyloxy)undecanenitrile (19)—The general procedure for hydrocyanation was followed with **18** (72 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **19** as a colorless oil (75 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (t, 1H, *J* = 6.8 Hz), 3.58-3.52 (m, 1H), 1.96-1.71(m, 6H), 1.55-1.38 (m, 4H), 1.30-1.27(m, 16H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6, 77.9, 66.0, 34.2, 32.8, 32.0, 31.1, 29.6, 29.5, 29.4, 29.2, 25.7, 25.1, 24.0, 23.9, 22.9, 14.3; IR (neat) 2930, 2857, 1453, 1337, 1099 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{17}H_{31}NO$ $[M]^+$ 265.2406, found 265.2394.

 Tetrahydro-2*H*-pyran-2-carbonitrile (21)—The general procedure for hydrocyanation was followed with **20** (72 mg, 0.8 mmol), HCl solution (440 μL, 0.88 mmol), TMSCN (200 μL, 1.6 mmol), and CH_2Cl_2 (8 mL). The crude product was purified by flash chromatography (6% EtOAc in hexane) to give **21** as a colorless oil (58 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (t, 1H, *J* = 4.5 Hz), 3.94-3.86 (m, 1H), 3.81-3.74 (m, 1H), 1.96-1.80 (m, 3H), 1.78-1.74 (m, 1H), 1.68-1.63 (m, 2H). These data are consistent with reported literature values.[48]

General procedure for the asymmetric cyanide addition to vinyl ethers

To a solution of catalyst **26** (0.03 equiv) in anhydrous $PhCF_3$ at room temperature under Ar was added TMSCN. The reaction mixture was stirred at rt for 10 min, then was cooled to −25 °C. A solution of vinyl ether (1.0 equiv) in $PhCF_3$ (0.3 mL) was added to the reaction mixture dropwise. The vial containing vinyl ether was rinsed with $PhCF_3$ (0.3 mL) and the rinses were also transferred to the reaction mixture to give 0.1 M solution. After 5 min, phenol (1.0 equiv) in $PhCF_3$ (0.6 mL) was added via a syringe pump using a 3 mL syringe at a rate of 0.03 mL/h over 20 h. The reaction mixture was allowed to stir for another 4 h at this temperature. The reaction mixture was then quenched with Et_3N and saturated $NaHCO_3$ solution. After warming up to room temperature, the reaction mixture was extracted with

Et_2O (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

 (*S*)-2-(Benzyloxy)propanenitrile ((*S*)-2)—The general asymmetric hydrocyanation procedure was followed with **1** (107 mg, 0.8 mmol), catalyst **26** (5 mg, 0.0004 mmol, 0.005 equiv), TMSCN (200 μL, 1.6 mmol), phenol (76 mg, 0.8 mmol) and trifluorotoluene (6 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **(*S*)-2** as a colorless oil (108 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 5H), 4.86 (d, 1H, *J* = 11.4 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.27 (q, 1H, *J* = 6.6 Hz), 1.60 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 128.9, 128.6, 128.4, 119.0, 72.3, 63.5, 20.0; IR (neat) 3066, 3034, 2996, 2872, 1455, 1330, 1111, 746, 699 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{10}H_{11}NO$ $[M]^+$ 161.0841, found 161.0828. These data are consistent with reported literature values.[49] HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 7.7 min, t_{minor} = 8.7 min. er = 85:15. $[\alpha]_D^{25}$ = −123.3 (*c* 1.0, $CHCl_3$). Please see the Supporting Information for the determination of the absolute stereochemistry of the major product.

 (*S*)-2-Phenethoxypropanenitrile (30)—The general asymmetric hydrocyanation procedure was followed with **29** (45 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **30** as a colorless oil (41 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 4.22 (q, 1H, *J* = 6.9 Hz), 4.00 (dt, 1H, *J* = 8.7, 6.9 Hz), 3.67 (dt, 1H, *J* = 8.7, 6.9 Hz), 2.94 (t, 2H, *J* = 6.9 Hz), 1.56 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 129.1, 128.7, 126.7, 119.1, 71.4, 64.8, 36.1, 20.0; IR (neat) 3029, 2995, 2871, 1497, 1475, 1330, 1115, 750, 700 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.1014. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 10.0 min, t_{minor} = 13.6 min. er = 87.5:12.5. $[\alpha]_D^{25}$ = −61.3 (*c* 1.0, $CHCl_3$). Racemic material was prepared through the cyanation of the α-chloroether.

 (*S*)-2-(3-Phenylpropoxy)propanenitrile ((*S*)-7)—The general asymmetric hydrocyanation procedure was followed with **6** (49 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-7** as a colorless oil (51 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 4.20 (q, 1H, *J* = 6.9 Hz), 3.77 (dt, 1H, *J* = 9.3, 6.3 Hz), 3.46 (dt, 1H, *J* = 9.0, 6.3 Hz), 2.72 (t, 2H, *J* = 7.5 Hz), 2.00-1.91 (m, 2H), 1.58 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.7, 128.6, 126.2, 119.3, 69.9, 64.8, 32.3, 31.1, 20.1; IR (neat) 3027, 2941, 2870, 1453, 1329, 1116, 748, 701 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{12}H_{15}NO$ $[M]^+$ 189.1154, found 189.1147. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 8.8 min, t_{minor} = 10.2 min. er = 86:14. $[\alpha]_D^{25}$ = −46.6 (*c* 1.0, $CHCl_3$).

 (*S*)-2-(Cinnamyloxy)propanenitrile (32)—The general asymmetric hydrocyanation procedure was followed with **31** (48 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (4% to 5% EtOAc in hexane) to give **32** as a colorless oil (43 mg, 77%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 6.70 (d, 1H, *J* = 15.9 Hz), 6.26 (ddd, 1H, *J* = 15.9, 6.9, 5.4 Hz), 4.47 (ddd, 1H, *J* = 12.0, 5.4, 1.2 Hz), 4.35 (q, 1H, *J* = 6.9 Hz), 4.21 (ddd, 1H, *J* = 12.3, 6.9, 1.2 Hz), 1.61 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 134.9, 128.8, 128.4, 126.9, 123.7, 119.1, 71.0, 63.4, 20.0; IR (neat) 3027, 2995, 2941, 2863, 1449, 1329, 1111, 969, 747, 693 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{13}NO$ $[M]^+$ 187.0997, found 187.1012. HPLC (Lux

cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 15.2 min, t_{minor} = 20.8 min. er = 82:18. $[\alpha]_D^{25}$ = −96.9 (*c* 1.0, $CHCl_3$). Racemic material was prepared through cyanation of the α-chloroether.

(*S*)-2-(Cyclohexyloxy)propanenitrile (34)—The general asymmetric hydrocyanation procedure was followed with **33** (50 mg, 0.4 mmol), catalyst **26** (14.6 mg, 0.0012 mmol), TMSCN (101 μL, 0.8 mmol), phenol (37 mg, 0.4 mmol) and trifluorotoluene (4 mL). The crude product was purified by flash chromatography (3% to 5% EtOAc in hexane) to give **34** as a colorless oil (44 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (q, 1H, *J* = 6.8 Hz), 3.60-3.54 (m, 1H), 1.97-1.89 (m, 2H), 1.80-1.71 (m, 2H), 1.56 (d, 3H, *J* = 6.8 Hz), 1.45-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.0, 77.9, 61.5, 32.9, 31.2, 25.7, 24.1, 24.0, 20.7; IR (neat) 2936, 2860, 1451, 1375, 1113, 1070, 981 cm^{-1}; HRMS (EI) *m/z* calcd for $C_9H_{15}NO$ $[M]^+$ 153.1154, found 153.1162. $[\alpha]_D^{25}$ = −72.5 (*c* 1.0, $CHCl_3$). The enantiomeric ratio was determined from a derivative. Please see the Supporting Information for details.

(*S*)-3-(1-Cyanoethoxy)propyl benzoate (36)—The general asymmetric hydrocyanation procedure was followed with **35** (62 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (2% EtOAc in toluene) to give **36** as a colorless oil (61 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.2 Hz),7.45 (t, 2H, *J* = 7.6 Hz), 4.50-4.38 (m, 2H), 4.25 (q, 1H, *J* = 6.8 Hz), 3.94 (dt, 1H, *J* = 9.2, 6.0 Hz), 3.63 (dt, 1H, *J* = 9.2, 6.0 Hz), 2.10 (quin, 2H, *J* = 6.4 Hz), 1.57 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 133.2, 130.4, 129.8, 128.6, 119.0, 67.2, 64.9, 61.8, 29.0, 20.0; IR (neat) 3064, 2962, 1719, 1276, 1115, 713 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1130, found 234.1122. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 14.5 min, t_{minor} = 16.1 min. er = 83:17. $[\alpha]_D^{25}$ = −37.8 (*c* 1.0, $CHCl_3$).

(*S*)-2-(2-(Benzylthio)ethoxy)propanenitrile ((*S*)-13)—The general asymmetric hydrocyanation procedure was followed with **12** (58 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-13** as a colorless oil (50 mg, 71%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 4.23 (q, 1H, *J* = 6.8 Hz), 3.88 (dt, 1H, *J* = 9.6, 6.4 Hz), 3.79 (s, 2H), 3.57 (dt, 1H, *J* = 9.2, 6.8 Hz), 2.66 (t, 2H, *J* = 6.4 Hz), 1.58 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 129.1, 128.8, 127.4, 118.9, 70.1, 64.8, 36.9, 30.4, 20.0; IR (neat) 3062, 3028, 2920, 2870, 1453, 1329, 1114, 1073, 1016, 704 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{15}NOS$ $[M]^+$ 221.0874, found 221.0893. $[\alpha]_D^{25}$ = −39.6 (*c* 1.0, $CHCl_3$). The enantiomeric ratio was determined from a derivative. Please see the Supporting Information for details.

(*S*)-2-(Naphthalen-2-ylmethoxy)propanenitrile (38)—The general asymmetric hydrocyanation procedure was followed with **37** (55 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (7% EtOAc in hexane) to give **38** as a colorless oil (56 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.84 (m, 4H), 7.54-7.47 (m, 3H), 5.02 (d, 1H, *J* = 12.0 Hz), 4.71 (d, 1H, *J* = 12.0 Hz), 4.30 (q, 1H, *J* = 6.8 Hz), 1.62 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 133.5, 133.4, 128.8, 128.2, 127.9, 127.6, 126.6, 126.6, 125.9, 119.0, 72.4, 63.4, 20.0; IR (neat) 3049, 2990, 2919, 1463, 1336, 1136, 863, 824, 748 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{13}NO$ $[M]^+$ 211.0997, found 211.1007. HPLC (Lux cellulose-3), hexane/*i*-PrOH 65:35, 1 mL/min, t_{major} = 12.9 min, t_{minor} = 19.3 min. er = 84.5:15.5. $[\alpha]_D^{25}$ = −117.5 (*c* 1.0, $CHCl_3$).

(*S*)-2-(Benzyloxy)butanenitrile (40)—The general asymmetric hydrocyanation procedure was followed with **39** (44 mg, 0.3 mmol), catalyst **26** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (2% EtOAc in hexane) to give **40** as a colorless oil (39 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.33 (m, 5H), 4.87 (d, 1H, *J* = 11.5 Hz), 4.55 (d, 1H, *J* = 11.5 Hz), 4.12 (t, 1H, *J* = 6.5 Hz), 1.91 (quin, 2H, *J* = 7.5 Hz), 1.09 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 128.9, 128.6, 128.4, 118.4, 72.4, 69.1, 27.1, 9.4; IR (neat) 3033, 2974, 2938, 2880, 1455, 1335, 1110, 742, 699 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.0980. HPLC (Lux cellulose-3), hexane/*i*-PrOH 95:5, 1 mL/min, t_{major} = 7.3 min, t_{minor} = 8.7 min. er = 80.5:19.5. $[\alpha]_D^{25}$ = −94.5 (*c* 1.0, $CHCl_3$).

(*S*)-2-Methoxy-4-phenylbutanenitrile ((*S*)-17)—The general asymmetric hydrocyanation procedure was followed with **41** (24 mg, 0.16 mmol), catalyst **26** (17.6 mg, 0.014 mmol), TMSCN (80 μL, 0.64 mmol), phenol (15 mg, 0.16 mmol) and trifluorotoluene (1.6 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-17** as a colorless oil (24 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, 2H, *J* = 7.2 Hz), 7.24 (t, 1H, *J* = 7.2 Hz), 7.20 (d, 2H, *J* = 7.2 Hz), 3.98 (t, 1H, *J* = 6.4 Hz), 3.50 (s, 3H), 2.83 (t, 2H, *J* = 7.6 Hz), 2.24-2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 128.9, 128.7, 126.7, 118.2, 69.7, 58.2, 35.1, 30.9. These data are consistent with reported literature values.[50] HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 7.6 min, t_{minor} = 8.4 min. er = 74:26. $[\alpha]_D^{25}$ = +17.1 (*c* 1.0, $CHCl_3$).

When using (*E*)-vinyl ether **16** (44 mg, 0.3 mmol), catalyst **26** (33 mg, 0.027 mmol), TMSCN (152 μL, 1.2 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3.0 mL): the crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-17** as a colorless oil (7 mg, 13%, 22% conversion based on crude NMR). er = 74:26.

(*S*)-2-((*R*)-1-phenylethoxy)propanenitrile (43)—The general asymmetric hydrocyanation procedure was followed with **42** (59 mg, 0.4 mmol), catalyst **26** (14.6 mg, 0.0012 mmol), TMSCN (101 μL, 0.8 mmol), phenol (37 mg, 0.4 mmol) and trifluorotoluene (4 mL). The crude product was passed through a short pad of silica gel (5% EtOAc in hexane) to remove the catalyst. The eluent was then concentrated under vacuum for HPLC analysis. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, $t_{minor, RR}$ = 6.3 min, $t_{major, SR}$ = 7.2 min. d.r. = 28:1. The crude product was further purified by flash chromatography (3% EtOAc in hexane) to give **43** as a colorless oil (56 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 4.68 (q, 1H, *J* = 6.5 Hz), 4.31 (q, 1H, *J* = 7.0 Hz), 1.57 (d, 3H, *J* = 7.0 Hz), 1.51 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.8, 128.5, 126.6, 119.4, 78.2, 62.2, 22.6, 20.4; IR (neat) 3034, 2980, 2933, 1453, 1377, 1109, 762, 700 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.0986. $[\alpha]_D^{25}$ = +9.4 (*c* 1.0, $CHCl_3$). Please see the Supporting Information for the determination of the relative stereochemistry.

(*S*)-2-((*S*)-1-phenylethoxy)propanenitrile (44)—The general asymmetric cyanation procedure for vinyl ethers was followed by using vinyl ether **14** (59 mg, 0.4 mmol), catalyst **26** (14.6 mg, 0.0012 mmol), TMSCN (101 μL, 0.8 mmol), phenol (37 mg, 0.4 mmol) and trifluorotoluene (4 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give two diastereomers (57 mg, 81%, d.r. = 1.2:1, crude NMR ratio 1.4:1). The faster eluting product was the major diastereomer **44**. For characterization see **15.**

General procedure for the asymmetric cyanide addition to acetals

To a solution of catalyst **26** (0.03 equiv) in anhydrous α,α,α-trifluorotoluene at room temperature under Ar was added TMSCN. The reaction mixture was stirred at room temperature for 15 min, then was cooled to −25 °C. A solution of the acetal (1.0 equiv) in trifluorotoluene (0.6 mL) was added to the reaction mixture via a syringe pump using a 3 mL syringe at a rate of 0.03 mL/h over 20 h. The reaction mixture was allowed to stir for another 4 h at this temperature after the addition was complete. The reaction mixture was then quenched with Et_3N and saturated $NaHCO_3$ solution. After warming to room temperature, the reaction mixture was extracted with Et_2O (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

 **(*S*)-2-(Benzyloxy)propanenitrile ((*S*)-2)—**The general asymmetric acetal cyanation procedure was followed with **45** (73 mg, 0.3 mmol), catalyst **26** (11 mg, 0.009 mmol, 0.03 equiv), TMSCN (76 μL, 0.6 mmol) and trifluorotoluene (2.5 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **(*S*)-2** as a colorless oil (41 mg, 85%), er = 82.5:17.5. Spectral and HPLC data are consistent with previously reported values.

 **(*S*)-2-Methoxy-4-phenylbutanenitrile ((*S*)-17)—**The general asymmetric acetal cyanation procedure was followed with **46** (36 mg, 0.2 mmol), catalyst **26** (7 mg, 0.006 mmol, 0.03 equiv), TMSCN (100 μL, 0.8 mmol) and trifluorotoluene (2 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-17** as a colorless oil (32 mg, 91%), er = 73:27. Spectral and HPLC data are consistent with previously reported values.

Density Functional Theory (DFT) Calculations

All calculations were preformed with the Gaussian 09B.01 program, using the hybrid B3LYP as the exchange/correlation functional. Peripheral atoms, shown in Figure S0, were treated with 3–21G basis set while other atoms were treated with 6–311G basis set. For the S and P atoms, the 6–311G(3df, 3pd) basis set was used. A large number of initial structures were used to initiate the geometry optimizations, and local minimas were confirmed by frequency calculations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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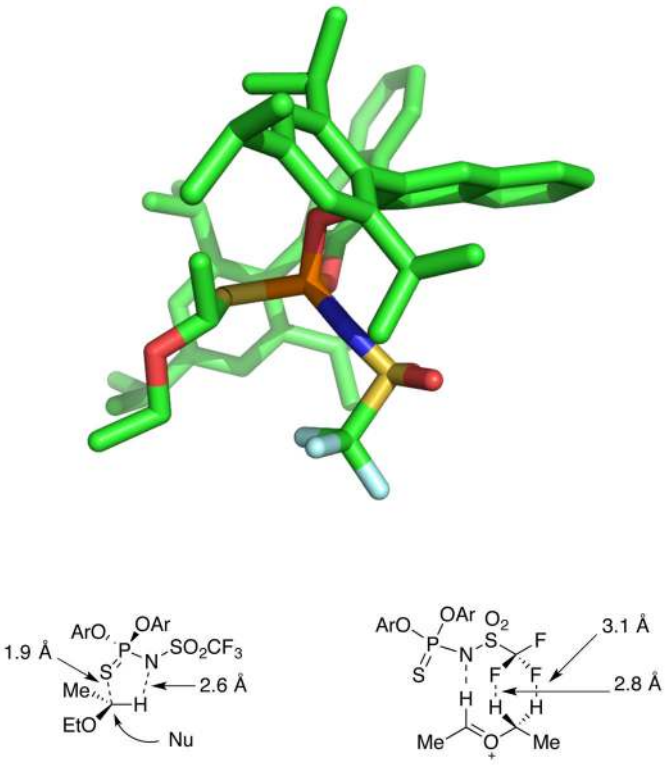


Figure 1.

Modeled structure of the ion pair from the reaction of ethyl vinyl ether with catalyst **22** (top) and illustrations of the relevant interactions and nucleophilic approach trajectory (bottom). Hydrogens have been removed for clarity. Green = carbon, red = oxygen, gold = sulfur, light blue = fluorine, dark blue = nitrogen.

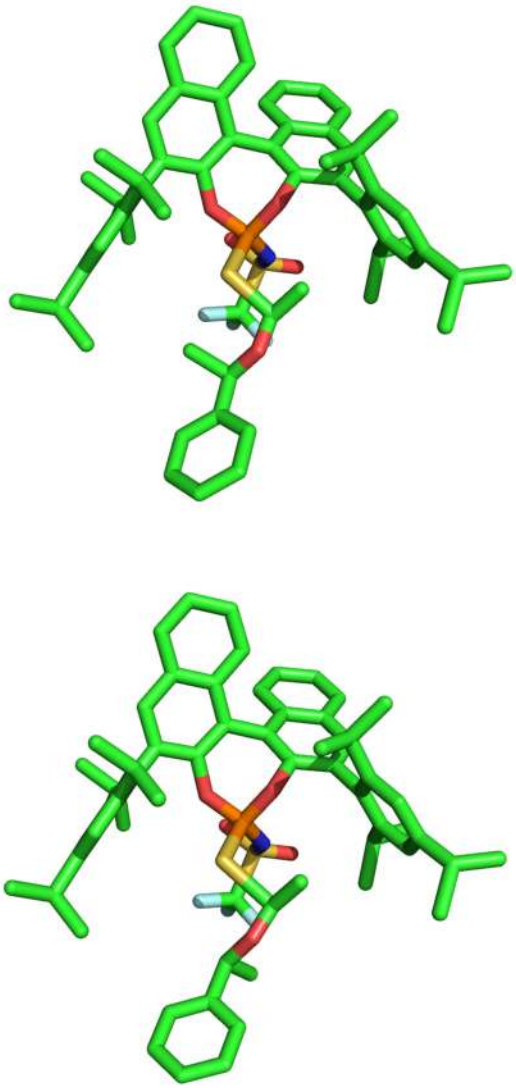
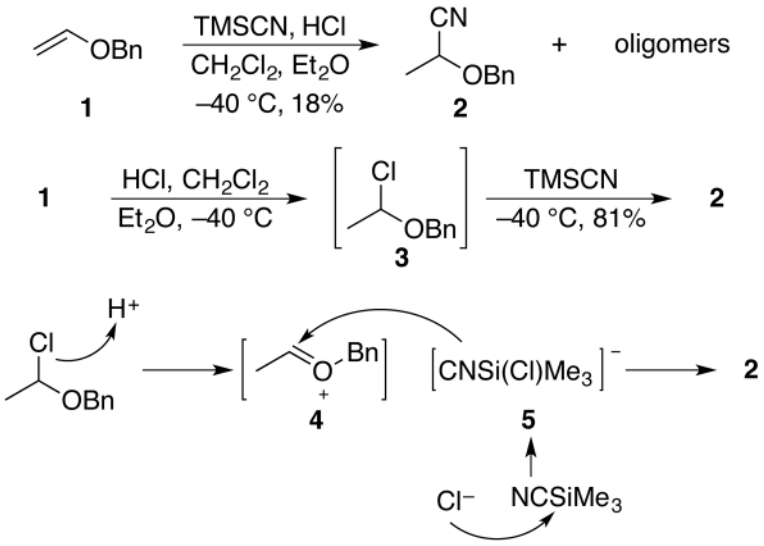
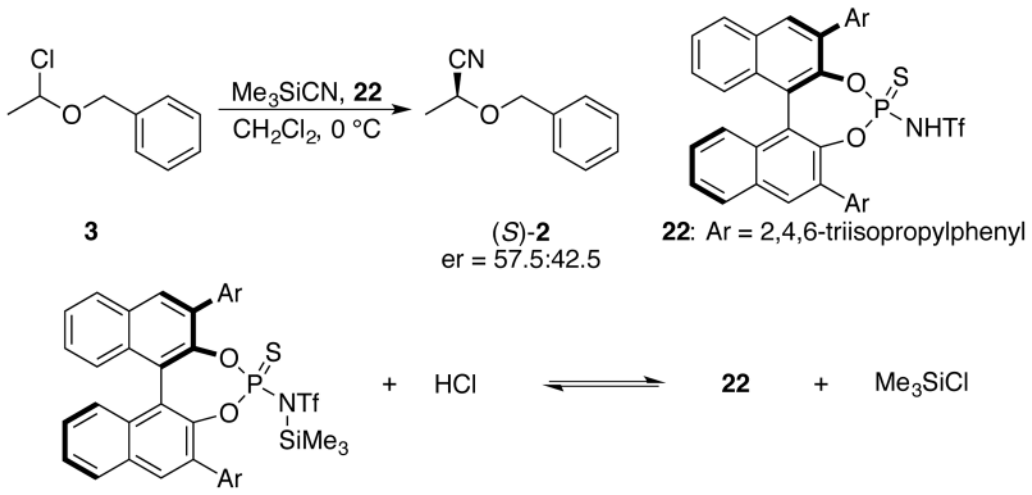


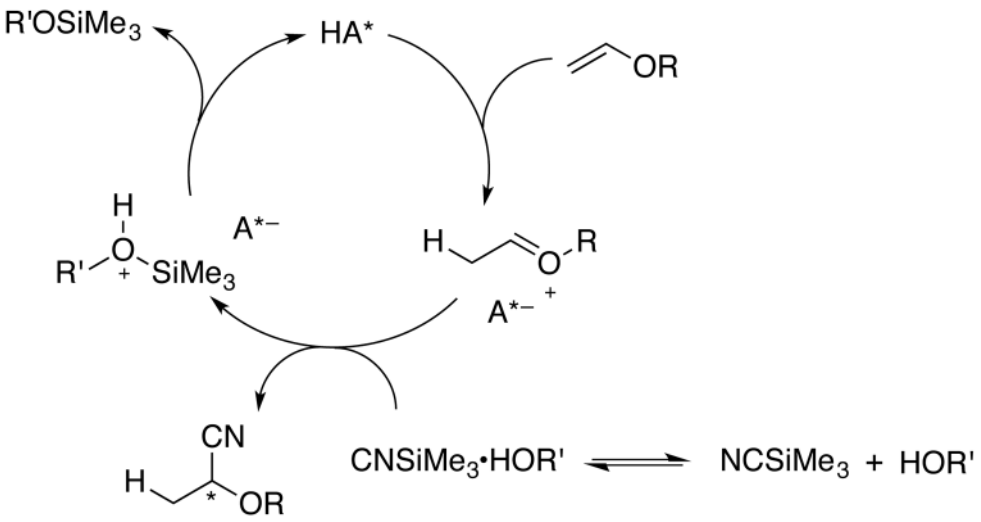
Figure 2.
Modeled structures of the ion pairs derived from **42** (top) and **14** (bottom) with catalyst **22**. Hydrogens have been deleted for clarity.



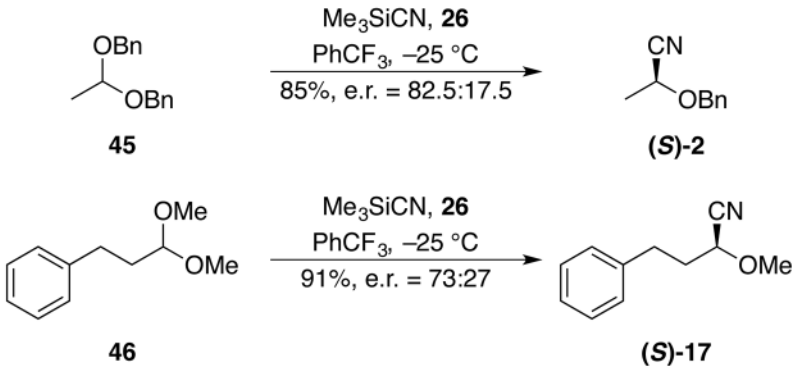
Scheme 1.
Cyanohydrin ether formation through enol ether hydrocyanation.



Scheme 2.
Chiral Brønsted acid-initiated chloride ionization and cyanation.



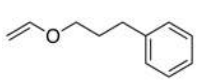
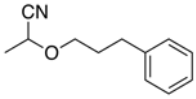
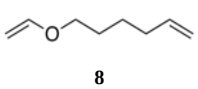
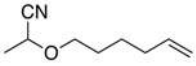
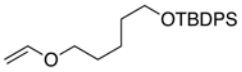
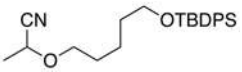
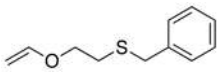
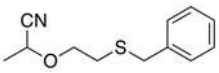
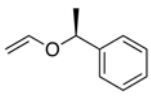
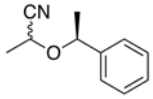
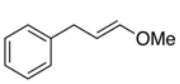
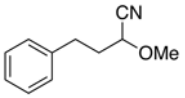
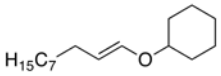
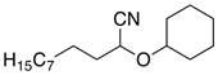
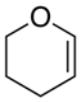
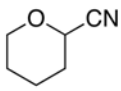
Scheme 3.
Direct enol ether hydrocyanation with catalyst regeneration. HA* = chiral Brønsted acid.



Scheme 4.
Application to acetal substrates.

Table 1

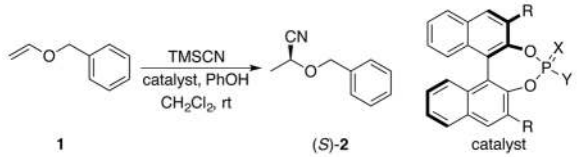
Scope of the enol ether hydrocyanation reaction.[a]

entry	substrate	product	yield
1	 **6**	 **7**	92%
2	 **8**	 **9**	76%
3	 **10**	 **11**	96%
4	 **12**	 **13**	85%
5	 **14**	 **15**	91% (dr = 1.2:1)
6	 **16**	 **17**	83%
7	 **18**	 **19**	94%
8	 **20**	 **21**	65%

[a]Representative procedure: HCl (1.1 equiv) is added to the vinyl ether in CH_2Cl_2 at −40 °C. Me_3SiCN (2 equiv) is added upon complete starting material consumption and the reaction is stirred at −40 °C until product formation is complete.

Table 2

Catalyst screening.

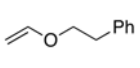
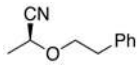
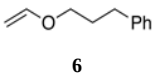
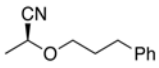
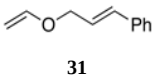
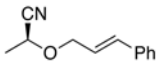
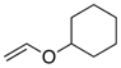
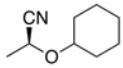
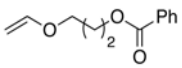
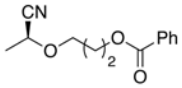
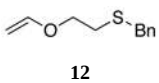
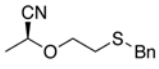
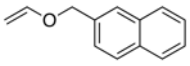
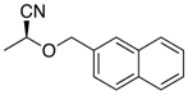
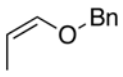
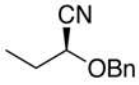
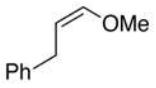
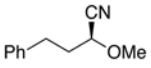
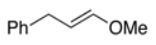
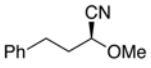
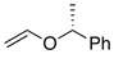
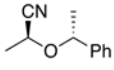


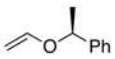
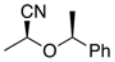
entry	catalyst	er
1	**22**: R = 2,4,6-triisopropylphenyl, X = S, Y = NHTf	65:35
2	**23**: R = 3,5-di(trifluoromethyl)phenyl, X = S, Y = NHTf	51.5:48.5
3	**24**: R = triphenylsilyl, X = S, Y = NHTf	52:48
4	**25**: R = 2,6-diisopropyl-4-adamantlyphenyl X = S, Y = NHTf	68:32
5	**26**: R = 2,6-diisopropyl-4-(2,4,6-triisopropylphenyl)- phenyl, X = S, Y = NHTf	71.5:28.5
6	**27**: R = 2,4,6-triisopropylphenyl, X = O, Y = SH	–
7	**28**: R = 2,4,6-triisopropylphenyl, X = O, Y = NHTf	–
8	**26**, −40 °C	83.3:16.7
9	**26**, $PhCF_3$ solvent, −25 °C	85:15 85% yield
10	**26**, $PhCF_3$ solvent, −25 °C, 0.5 mol% catalyst	85:15 84% yield

[a]Representative procedure: A solution of phenol (1.0 equiv) was added dropwise over 20 h to a solution of the vinyl ether (1.0 equiv), the catalyst (0.03 equiv), and Me_3SiCN (2.0 equiv). The reactions were complete shortly after the phenol addition was complete. Enantiomeric ratios were determined by HPLC with a Lux Cellulose 3 column.

Table 3

Substrate scope for the asymmetric reaction.[a]

entry	substrate	product	yield (%)	er
1	 **29**	 **30**	78	87.5:12.5
2	 **6**	 **(*S*)-7**	90	86:14
3	 **31**	 **32**	77	82:18
4	 **33**	 **34**	72	84:16
5	 **35**	 **36**	84	83:17
6	 **12**	 **(*S*)-13**	71	83:17
7	 **37**	 **38**	88	84.5:15.5
8	 **39**	 **40**	74	80.5:19.5
9	 **41**	 **(*S*)-17**	86	74:26
10	 **16**	 **(*S*)-17**	13	74:26
11	 **42**	 **43**	80	dr = 28:1

entry	substrate	product	yield (%)	er
12	 **14**	 **44**	81	dr = 1.4:1

[a]Please see the Supporting Information for precise experimental details.