Stereoselective Synthesis of Spirooxindole Amides and Cyanohydrin Alkyl Ethers

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A new family of spirooxindole amides were synthesized by a sequence of hydrozirconation, acylation, and intramolecular cyclization reactions. Three of the four possible diastereomers can be obtained as the major isomers through this process. The spirooxindole structure has many points for diversification, and a 37-membered library was synthesized through this approach by collaborators. A comparison with known compound collections showed that this new spirooxindole library possessed good chemical diversity.

Cyanohydrin alkyl ethers, the key intermediate in the above multi-component hydrozironation reaction, were effectively synthesized through a Brønsted acid-mediated hydrocyanation of vinyl ethers. The enantiomerically enriched product can be obtained by asymmetric hydrocyanation of vinyl ethers catalyzed by a chiral Brønsted acid, and the catalyst can be regenerated by PhOH. As far as we know, this research represents the first example of chiral Brønsted acid mediated intermolecular addition of silylated nucleophiles with vinyl ethers. The ion pair interaction between the conjugate base of the chiral Brønsted acid and the oxocarbenium ion was revealed by computational modeling, which explained the origin of the enantioselectivity and the substrate scope of this reaction.

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PREFACE

First of all, I would like to thank my advisor, Professor Paul Floreancig, for providing me with these challenging and interesting projects. Without his guidance and encouragement, I will never become an organic chemist, and my understanding to chemistry would be confined to a much lower level.

Next, I would like to thank Professor Brummond, Professor Cohen, Professor Wipf and Professor Xie for their guidance and advice in comprehensive examination, graduation proposal writing, and dissertation studies. I also would like to express my gratitude to my proposal mentor, Professor Horne, for his patience and instructions in teaching me how to express my own research ideas.

To all of past and present group members, I wish to thank you all for your help and encouragement in the past five years. I cherish the every moment we share the joy and sadness together. I also would like to thank all of my past and present collaborators and friends in the department of chemistry and school of medicine for the constructive suggestions and innovative discussions.

Finally, I would like to thank my parents for their love and support. I may know much more chemistry than you do, but you know how to raise a son and guide him to achieve his goal. I dedicate this document to you.

1.0 STEREOSELECTIVE SYNTHESIS OF SPIROOXINDOLE AMIDES THROUGH NITRILE HYDROZIRCONATION

1.1 INTRODUCTION

The spirooxindole unit, characterized by a unique spiro fusion of a heterocycle or carbocycle at the C3 position of an oxindole, is present in numerous biologically active natural products such as gelsemine,[1] and spirotryprostatin B[2] (Figure 1.1). In addition, the rigid spirooxindole core provides a good template for the synthesis of natural product-like compounds as potential medicinal agents. Many elegant methods have been developed to construct the spirooxindole core structure,[3] which further promotes structure-activity studies, and preparation of diverse

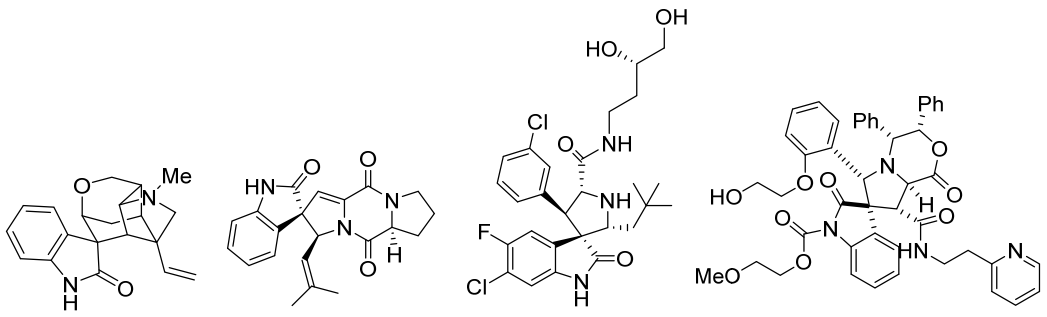
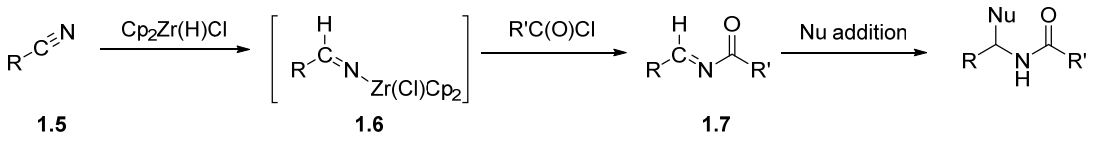


Figure 1.1 Structures of important spirooxdindoles

spirooxindole structures. Schreiber and co-workers developed a spirooxindole library through diversity-oriented synthesis (DOS), and found lead compound **1.4** as an adjuvant of the actin polymerization inhibitor latrunculin B.[4] Wang and co-workers applied structure-based design to develop MI-219 (**1.3**) as an anti-cancer drug candidate that operates through MDM2 inhibition.[5] In accord with our continued interest in preparing structurally diverse amides, we sought to develop a new protocol for diastereoselective synthesis of spirooxindoles.

1.2 Multicomponent amide synthesis through nitrile hydrozirconation

Diversity oriented synthesis, which could possibly play a vital role in drug discovery, requires access to a collection of many compounds with molecular complexity and structural diversity.[6] While the complexity of a molecule is important to its possible biological activity, the structural diversity, which can be achieved by altering building blocks, stereochemistry, and molecular scaffolds, is essential to identify new protein targets and their regulators.[6] The Floreancig group's multicomponent method towards syntheses of structurally diverse amides is one of these approaches.[7] Nitriles (**1.5**) react readily with the Schwartz reagent ($Cp_2Zr(H)Cl$) to form metalloimines (**1.6**) that add into acyl chlorides to yield acylimines (**1.7**). A wide range of amide-containing structures can be obtained when different nucleophiles react with these acylimines (Scheme 1.1).

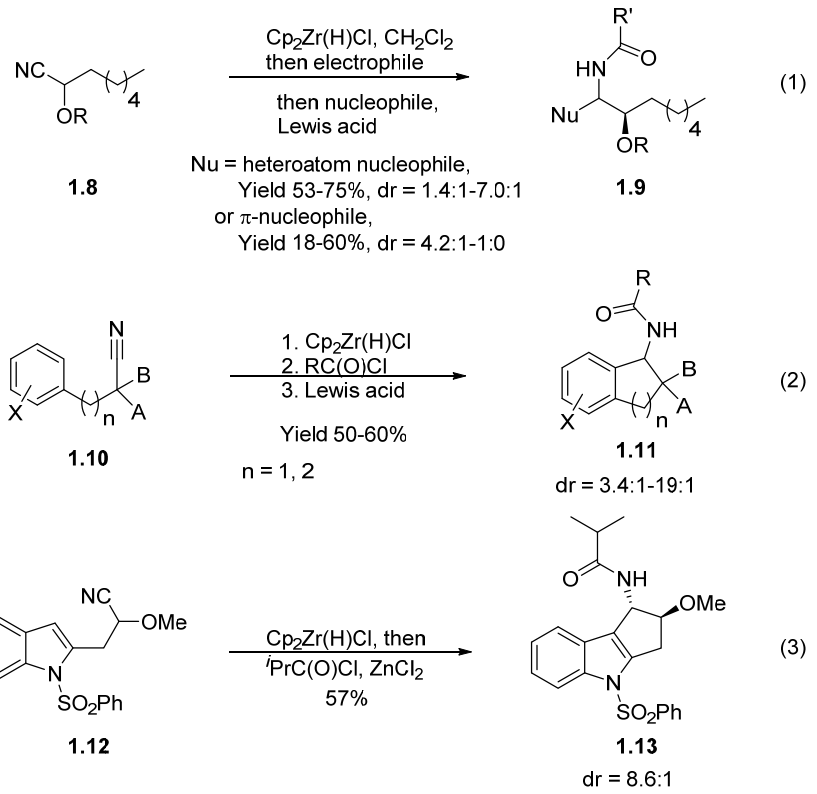


1.5 **1.6** **1.7**

Scheme 1.1 Diverse amides formation through nitrile hydrozirconation

1.2.1 Previous work on amides formation from nitrile hydrozirconation

Dr. Shuangyi Wan first demonstrated that heteroatom nucleophiles, such as water, methanol, phenol, thiophenol, and *tert*-butyl alcohol, are suitable nucleophiles to attack acylimines to generate "oxidized" amides in good yield and moderate to good diastereoselectivity (Scheme 1.2, reaction 1).[7d] Following that work, Mr. Mikkel DeBenedetto showed that π-nucleophiles add diastereoselectively into nitrile-derived acylimines to give α-branched amides (Scheme 1.2, reaction 1).[7c] It is worth noting that unlike alcohols and thiols, weakly reactive π-nucleophiles require acylimine activation by a Lewis acid to promote addition. Zinc bromide led to the formation of the *syn*-isomer, and gave single diastereomer for methallyl trimethylsilane. Enolsilanes and indoles also gave good selectivity when used as nucleophiles with this reaction. Dr. Qing Xiao further expanded the scope of the reaction by developing a Lewis acid-mediated intramolecular Friedel-Crafts alkylation reaction (Scheme 1.2, reaction 2).[7b] Indanyl and tetrahydronaphthyl amides can be formed with good to excellent levels of diastereocontrol. In addition to substituted benzene derivatives, indole can also be used as a nucleophile to generate bicylic *β*-alkoxy amides (Scheme 1.2, reaction 3).



Scheme 1.2 Previous work on amides formation through nitrile hydrozirconation

The nucleophilic addition to acylimines through nitrile hydrozirconation is also a powerful approach to access biologically active natural products. Our group successfully used this method for the total synthesis of pederin and psymberin, which are potent cytotoxins towards a number of cancer cell lines with IC_{50} values at nanomolar or lower concentrations (Figure 1.2).[8] By using different alcohols, acid chlorides and nitriles, a number of analogs were readily prepared through this late stage multicomponent approach for construction of *N*-acyl aminal linkages. The structure-activity relationships were further elucidated, and a number of more potent cytotoxins were identified (Figure 1.2).

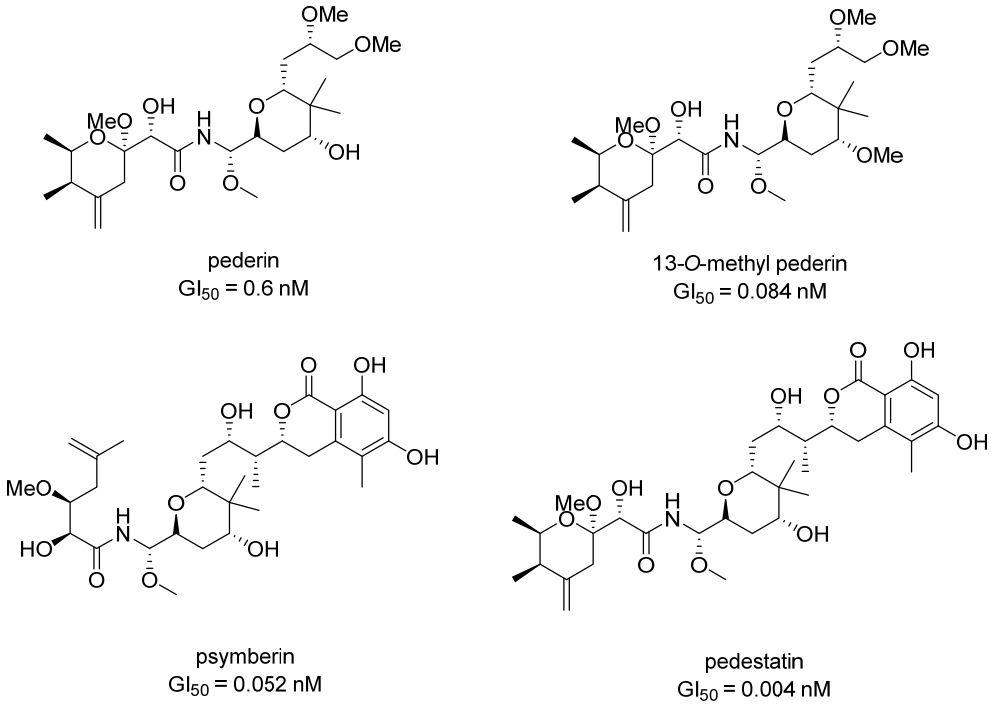
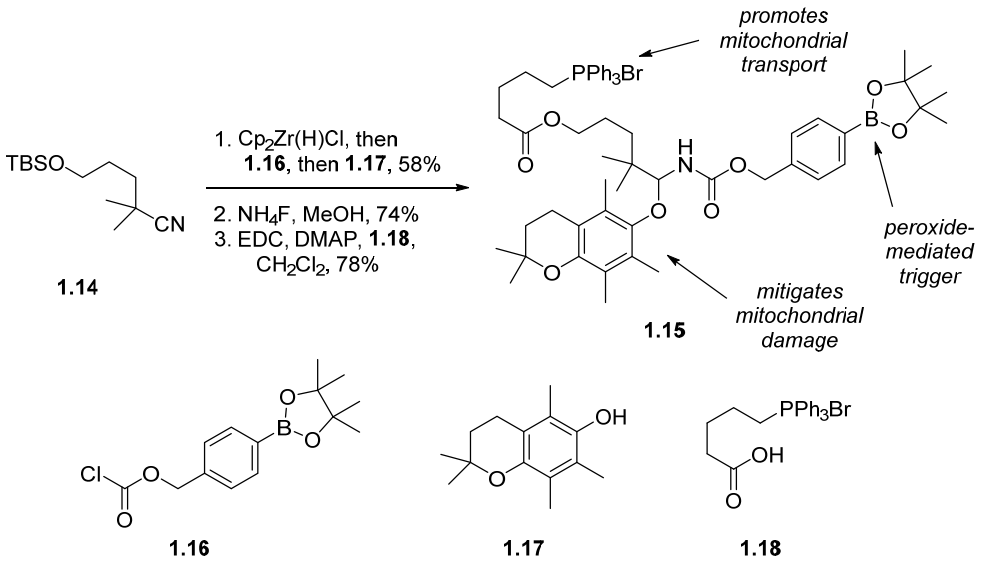


Figure 1.2 Pederin, psymberin and their analogs

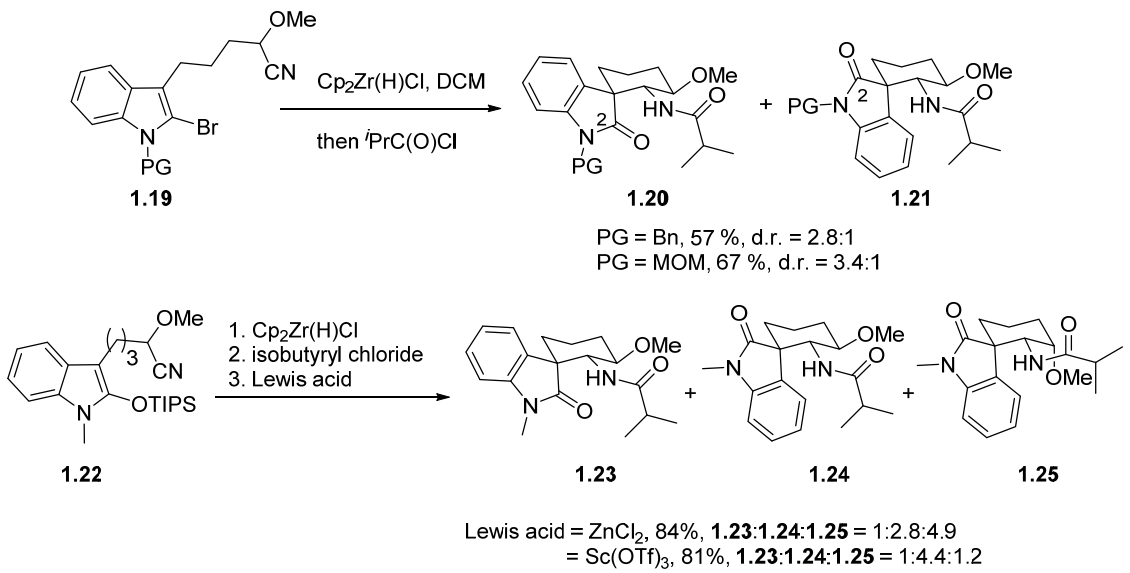
This approach can also be applied to build compounds for drug delivery. As shown in Scheme 1.3, α-alkoxy carbamate **1.15** was synthesized, which consist of a cargo, a triggering group and a targeting group. Upon peroxide stimulus, the boronate is oxidized to phenoxide, which then initiates the breakdown of acyl aminal to release alcohols. Pentamethyl chromanol could be released from carbamate **1.15**, and can mitigate damages caused by active oxygen species.[9]



Scheme 1.3 Synthesis of alkoxy carbamate 1.15

1.2.2 Previous work on spirooxindole synthesis through nitrile hydrozirconation

We concluded that indoles are good nucleophiles for nitrile-derived acylimine for intermolecular addition and intramolecular Friedel-Crafts reaction, based on our previous study.[7b] Furthermore, we envisioned that nucleophilic attack from 3-position of 2-haloindoles, followed by water addition to the iminium ion intermediate would lead to spirooxindole structure. Therefore, nitrile hydrozirconation should be applicable for spirooxindole synthesis.

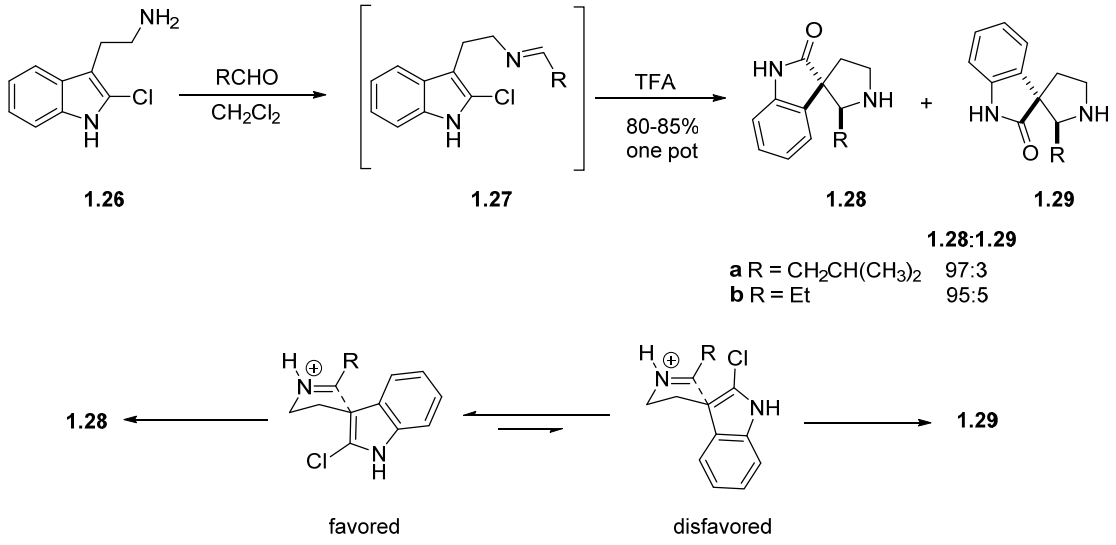


Scheme 1.4 Previous work on spirooxindole synthesis through nitrile hydrozirconation

Dr. Qing Xiao first used isobutyryl chloride as the electrophile and 2-bromoindole **1.19** as the oxindole surrogate to demonstrate the feasibility of this idea (Scheme 1.4). Two diastereomers were obtained in good yield, with the C2-center of the oxindole of the major diastereomer adopts an axial orientation. Additionally 2-silyloxyindole **1.22** was synthesized to study whether steric bulk at the 2-position influenced stereoselectivity (Scheme 1.4). Unlike 2-bromoindole **1.19**, 2-silyloxyindole **1.22** needed one full equivalent of Lewis acid to promote the reaction, and different Lewis acids were screened for their effects on diastereoselectivity. The results showed that the diastereoselectivity at the quaternary center was inverted with the C-2 center of the oxindole of the major diastereomer adopting an equatorial orientation. When $Sc(OTf)_3$ was used as the Lewis acid, the major diastereomer adopted the *trans* relationship between the amide and the methoxy groups (diastereomer **1.24**). In contrast, the *cis* relationship (diastereomer **1.25**) is favored when $ZnCl_2$ was employed to the reaction, possibly due to the stronger chelating ability of $ZnCl_2$ relative to $Sc(OTf)_3$.

1.3 SPIROOXINDOLE SYNTHESIS THROUGH NITRILE HYDROZIRCONATION

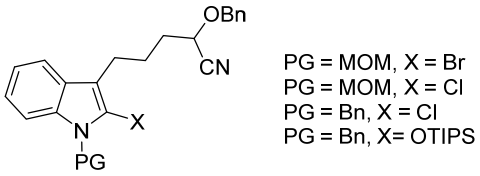
The spirooxindole structure built by Dr. Xiao is structurally unique. The synthesis sequence featured by hydrozirconation, acylation and intramolecular addition leads to the complex spirocyclic structure with two new stereocenters in one pot from acyclic indolyl cyanohydrin ethers. In addition to the building block diversity made possible by the addition of different acid chlorides, the stereochemical diversity is also possible because it is influenced by different oxindole surrogates and Lewis acids chelating abilities. Therefore, this synthetic sequence is a promising diversity oriented synthesis (DOS) strategy. We sought to optimize the substrate and reaction conditions to pursue improved stereocontrol as well as the possibility for further structural modification. Different acid chlorides will also be examined to explore the scope of this reaction.



Scheme 1.5 Horne's spirooxindole synthesis through 2-chloroindole

Studies by Horne and co-workers provided guidance for improving diastereoselectivity.[10] As shown in Scheme 1.5, condensation of 2-chlorotryptamine (**1.26**) with isovaleraldehyde affords imine **1.27**, which then cyclizes under acidic conditions to give spirooxindole **1.28** with good yield and high stereoselectivity. The author implied that the stereoselectivity is highly influenced by the steric interaction between the substituent on the spiro-pyrrolidine ring and the substituent at the 2-position of indole. This finding is in accord with Dr. Xiao's observation on the reverse of stereoselectivity by using 2-bromoindole and 2-silyloxyindole. Therefore, the 2-chloroindole subunit was chosen as the new oxindole surrogate for spirooxindole synthesis, with the expectation that the smaller chlorine group will lead to improved diastereoselectivity. The 2-triisopropylsiloxyl group was selected as the bulky counterpart of the chlorine group for further stereocontrol.

A benzyl group was chosen as the protecting group for the cyanohydrin instead of methyl group in the previous study to facilitate further structure modification. Methoxymethyl (MOM) and benzyl groups were chosen as the protecting groups on the nitrogen of the indole substrate. These protecting groups can be easily removed after spirooxindole formation.[11] Additionally the different electronic and physical properties of these two protecting groups may lead to different stereochemical outcomes. Thus, the following substrates (Figure 1.3) were selected for the study of nitrile hydrozirconation sequence.

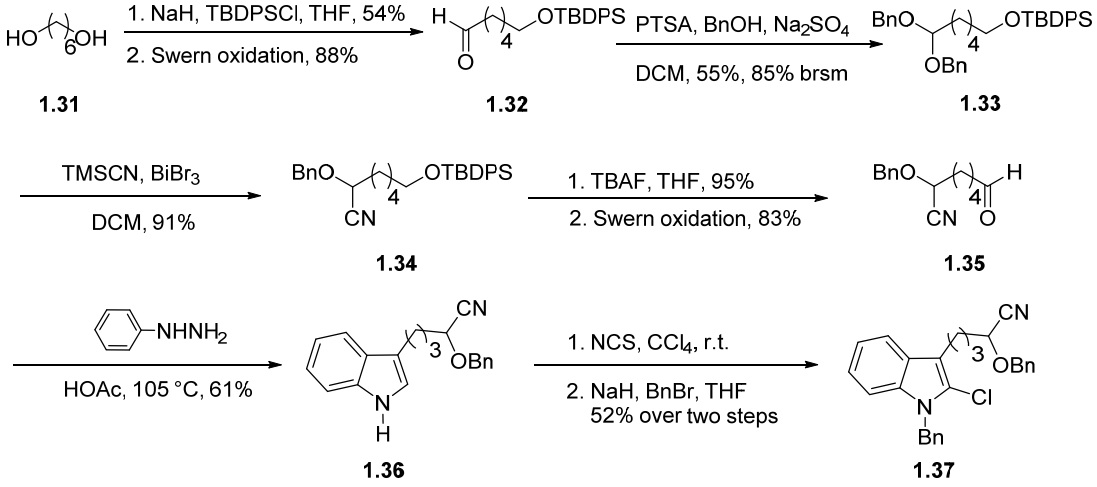


1.30

Figure 1.3 Design of the substrate

1.3.1 Substrate Synthesis

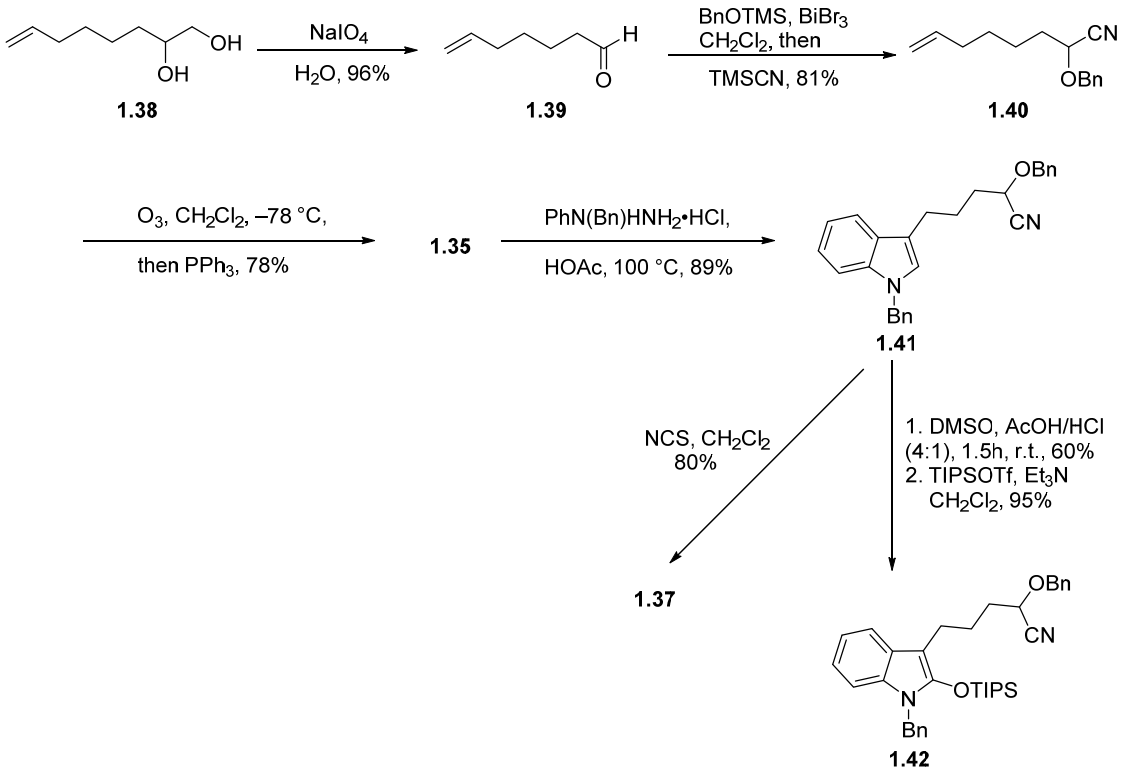
The substrate synthesis follows Dr. Qing Xiao's protocol. As shown in Scheme 1.6, aldehyde **1.32** was obtained by Swern oxidation of mono-*tert*-butyldiphenylsilyl (TBDPS) protected of 1,6-hexanediol (**1.31**). Benzyl alcohol (BnOH) was condensed with aldehyde **1.32** under *p*-toluenesulfonic acid (PTSA) catalysis to yield benzyl acetal **1.33**, which was then treated with trimethylsilyl cyanide (TMSCN) and bismuth tribromide ($BiBr_3$) to afford benzyl cyanohydrin ether **1.34**. After TBDPS group deprotection and Swern oxidation, aldehyde **1.35** was obtained in good yield. Aldehyde **1.35** then reacted with phenylhydrazine to construct indole **1.36**, which underwent chlorination and benzylation to give 2-chloroindole **1.37**.



Scheme 1.6 Substrate synthesis for nitrile hydrozirconation

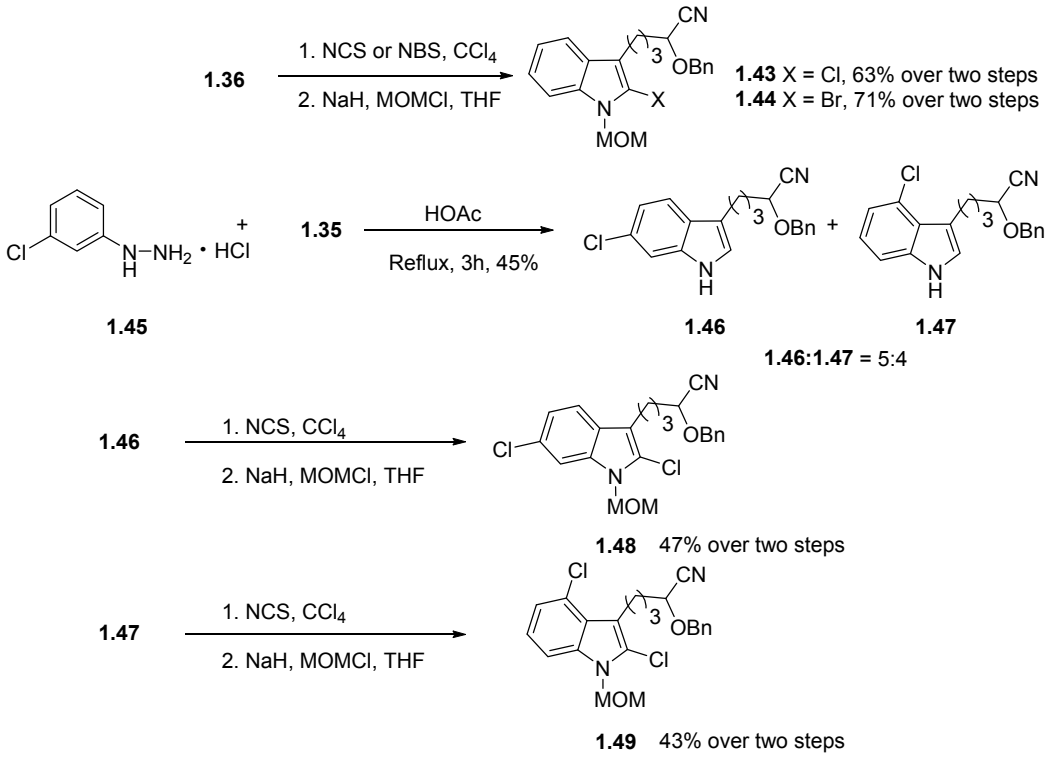
Even though the above method started from cheap starting material, 9 steps were required to prepare the desired substrate. Therefore, further efforts were made to improve the efficiency of this synthetic sequence (Scheme 1.7). Aldehyde **1.39**, prepared through a known periodate mediated cleavage of commercially-available 7-octene-1,2-diol (**1.38**),[12] was converted to

cyanohydrin ether **1.40** through a one-pot sequential acetalization reaction with BnOTMS and $BiBr_3$ followed by TMSCN addition[7a]. Ozonolysis and Fischer indole synthesis with commercially available benzyl phenylhydrazine hydrochloride provided **1.41**, which then reacted with NCS to afford the cyclization substrate **1.37**. It is worth noting that this sequence also facilitated the synthesis of the 2-silyloxyindole substrate. The corresponding silyloxyindole substrate **1.42** was prepared by oxidizing **1.41** to form the oxindole followed by silylation with TIPSOTf and Et_3N (Scheme 1.7)[13]. The established indole oxidation protocol using DMSO and HCl[14] was not effecient for the oxidation step. The conversion was low even after stirring for 24 h. However, good yield and quick conversion was achieved when AcOH was used as the co-solvent.[15]



Scheme 1.7 Modified substrate synthesis for nitrile hydrozirconation

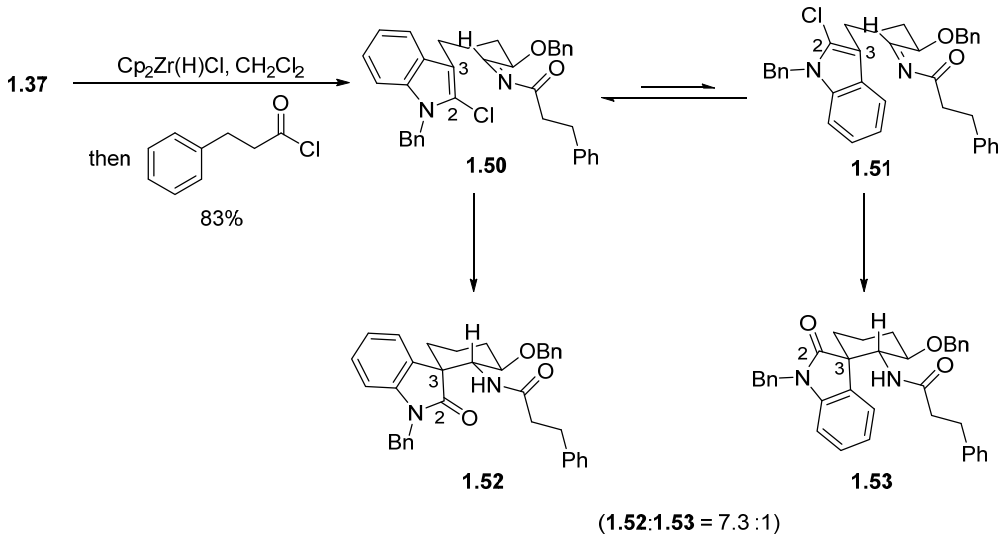
The MOM protected 2-haloindole substrates **1.43** and **1.44** were synthesized by halogenation of indole **1.36**, followed by MOM protection of the indole fragment (Scheme 1.8). 6-Chloroindole substrate **1.48** was chosen because of the significant biological activity enchancement observed by Wang and co-workers for this substituent in the spirooxindole structure.[5b] **1.46** and its regioisomer **1.47** were obtained in a combined yield of 45% (**1.46**:**1.47** = 5:4) by using the commercially available 3-chlorophenylhydrazine hydrochloride for Fisher indole synthesis. Even though these two isomers have similar polarity, they are separable by flash chromatography, and the application of medium pressure liquid chromatography (MPLC) can greatly facilitate the separation. These results indicated that indoles with different substitution patterns should be accessible by the following the same sequence featured by Fisher indole synthesis, halogenation and protection.



Scheme 1.8 Synthesis of diverse 2-haloindole substrates

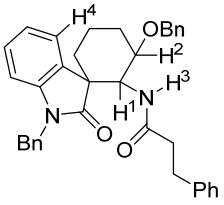
1.3.2 Spirooxindole formation from acyclic indole substrates

Spirooxindole formation is demonstrated in Scheme 1.9. Treatment of 2-chloroindole **1.37** with $Cp_2Zr(H)Cl$ followed by acylation with hydrocinnamyl chloride formed an acylimine that folded preferentially into a reactive conformation (**1.50**) in which the benzyloxy and acylimine groups adopted pseudoequatorial orientations and the C2-center of the indole occupied a pseudoaxial orientation. The minor conformation (**1.51**) placed the C2-center of the indole in a pseudoequatorial orientation. Nucleophilic addition at the 3-position of the indole followed by hydrolysis of the chloroiminium ion intermediate provided spirooxindoles **1.52** and **1.53** in 73% and 10% yields respectively. This selectivity indicates that the aryl group is sterically more demanding than the chloro substituent in the transition states, consistent with observations by Overman and Panek.[16]



Scheme 1.9 Spirooxindole formation through nitrile hydrozirconation, acylation, and intramolecular addition

The structures of the products were assigned based on extensive analyses of their NOESY and COSY spectra (Figure 1.4). Four characteristic hydrogens in these diastereomers



were instructive for stereochemistry determination: H^1 – the hydrogen on the tertiary carbon connected to the amido group; H^2 – the hydrogen on the tertiary carbon connected to the benzyloxy group; H^3 – the amide hydrogen; H^4 – the hydrogen in the 4-position of the oxindole. The stereochemical orientations of the alkoxy and amide groups in the six-membered ring were determined by the coupling constants and splitting pattern of H^1 and H^2. For compounds **1.52** and **1.53**, which adopted the *trans* relationship between the amide and benzyloxy groups, the coupling constant between these two hydrogens is around 10 Hz, with H^1 being an apparent triplet, and H^2 being an apparent doublet of triplets. The stereochemistry of the quaternary carbon can be deduced from the NOE signals. An NOE signal between H^1 and H^4 was observed for compound **1.52**, with C2-center of the oxindole in an axial orientation. Conversely, an NOE signal between H^2 and H^4 was observed for compound **1.53**, which placed C2-center of the oxindole in the equatorial orientation. In addition, NOE studies also provided information about the conformation of amide. For both diastereomers, an NOE signal between H^2 and H^3 was observed, indicating a defined amide structure with H^1 and H^3 *trans* to each other as shown by structure **1.54**.

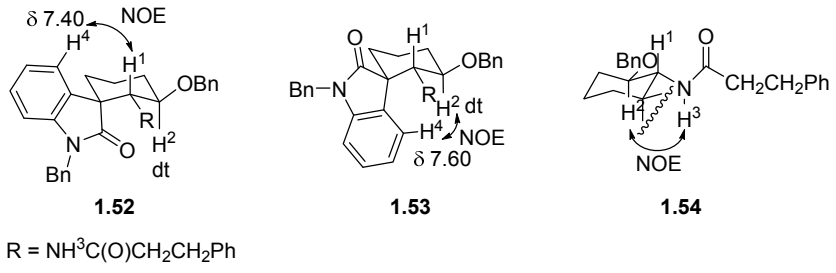
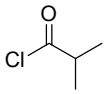
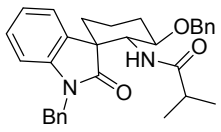
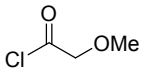
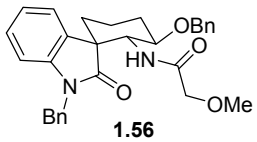
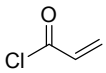
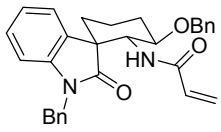


Figure 1.4 Structure determination for diastereomers 1.52 and 1.53

Based on this study, 2-chloroindole **1.37** was used to examine the scope of the reaction as shown in Table 1.1. Aliphatic, branched aliphatic, α,β-unsaturated, and heteroatom-functionalized acid chlorides serve as suitable electrophiles for the transformation.

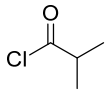
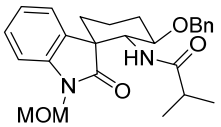
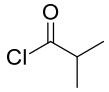
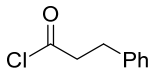
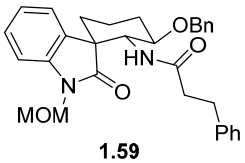
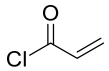
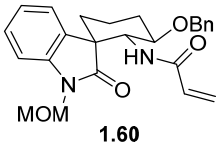
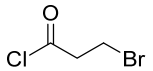
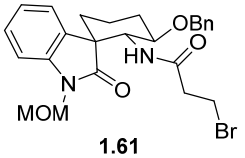
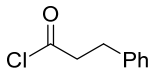
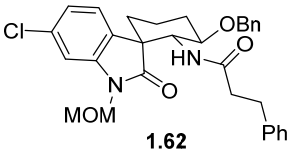
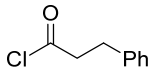
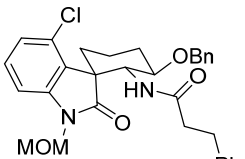
Table 1.1 Acid chloride scope for spirooxindole synthesis[a]

entry	substrate	acid chloride	major product	dr[b]	Yield (%)[c]
1	**1.37**		 **1.55**	3.6:1	87
2	**1.37**		 **1.56**	9.1:1[d]	46
3	**1.37**		 **1.57**	20:1	53

[a] Representative procedure: $Cp_2Zr(H)Cl$ (1.25 eq) was added to a 0.1 M solution of the indole nitrile in CH_2Cl_2 under Ar. After stirring at rt for 15 min the acid chloride was added. The mixture stirred overnight at rt. [b] Ratio of isolated, purified diastereomers. [c] Combined yield of diastereomers. [d] Single isomer at the quaternary center - dr refers to the ratio of *trans* and *cis* amido ethers.

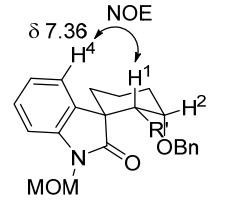
N-Methoxymethylindoles are also effective substrates as shown in Table 1.2. As expected, 2-chloroindoles showed better diastereoselectivity than 2-bromoindoles (entries 1 and 2), which may be attributed to a more favored transition conformation caused by the smaller size of the chlorine atom. *N*-Methoxymethylindoles are not as reactive as *N*-benzylindoles due to the inductive attenuation of indole nucleophilicity by the methoxy group and in some cases a catalytic amount of $Sc(OTf)_3$ was required to promote the cyclization (entries 4 and 5). For acryloyl chloride (entry 4), the acyliminium ion generated after addition of the acid chloride was

Table 1.2 Cyclization with N-methoxymethylindoles[a]

entry	substrate	acid chloride	major product	dr[b]	Yield (%)[c]
1	**1.43**		 **1.58**	11.8:1	51
2	**1.44**		**1.58**	2.7:1	59
3	**1.43**		 **1.59**	15:1	64
4[e]	**1.43**		 **1.60**	8.2:1[d]	46
5[e]	**1.43**		 **1.61**	6.7:1[d]	54
6	**1.48**		 **1.62**	1:0	50
7	**1.49**		 **1.63**	1:0	36

[a] Representative procedure: $Cp_2Zr(H)Cl$ (1.25 eq) was added to a 0.1 M solution of the indole nitrile in CH_2Cl_2 under Ar. After stirring at rt for 15 min the acid chloride was added. The mixture stirred overnight at rt. [b] Ratio of isolated, purified diastereomers. [c] Combined yield of diastereomers. [d] Single isomer at the quaternary center - dr refers to the ratio of *trans* and *cis* amido ethers. [e] $Sc(OTf)_3$ (0.1 eq) was added to promote cyclization.

not sufficiently electrophilic to promote attack from the indole to form the cyclized product in the absence of a Lewis acid. Cyclization can occur efficiently for 3-bromopropionyl chloride (entry 5), but stirring overnight under these conditions led to halogen exchange of bromine with chlorine (confirmed by mass spec). In the presence of a catalytic amount of $Sc(OTf)_3$, these two problems were resolved, and a minor amount of stereoisomer that has a *cis*-relationship between the amide and benzyloxy groups was obtained (compound **1.61'**, Figure 1.5), presumably resulting from a chelation-controlled transition state. Chlorination on the benzene ring of the indole, in anticipation of further structural manipulations of the spirooxindole products, is compatible with the reaction conditions (entries 6 and 7). These substrates reacted somewhat less efficiently than the corresponding non-halogenated substrate due to inductive deactivation by the chloro group and, in the case of **1.49**, steric interactions in the transition state. However useful quantities of the products could be isolated.



1.61'

R' = $NH^3C(O)CH_2CH_2Br$

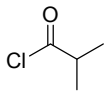
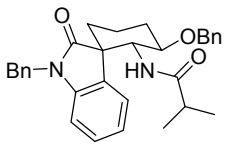
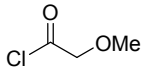
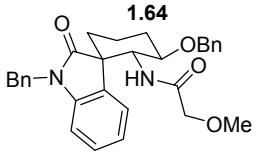
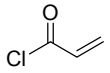
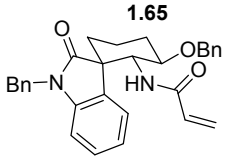
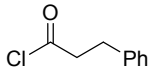
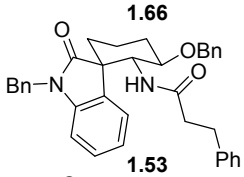
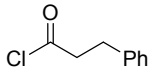
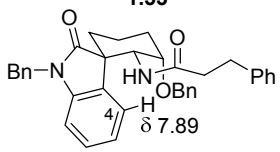
Figure 1.5 Structure determination for 1.61'

The structure of the minor diastereomer **1.61'** was determined by NMR studies. The *cis* relationship between the amide and benzyloxy groups was deduced from the coupling constant and splitting pattern of H^1 and H^2. The coupling constant of these two protons is approximately 4

Hz, with H^1 being a doublet of doublets, and H^2 being a doublet of triplets. In addition, the NOE signal between H^1 and H^4 implies the C2-center of the oxindole core occupies the axial position.

As an expansion of Dr. Xiao's work to invert the stereochemistry of the quaternary carbon using 2-silyloxyindoles, substrate **1.42** was utilized for cyclization reactions, and the results of this study are shown in Table 1.3. Several issues related to these transformations are worth noting. The overall yield of spirooxindole products from these reactions is comparable to the yields from the chloroindole substrates, indicating that the potentially labile enolsilane moiety is compatible with the reaction conditions. The reactions of **1.42** are slower than the reactions of the chloroindole substrates and require a full equivalent of Lewis acid despite the presence of the strongly donating silyloxy group. We attribute this effect to the steric demands in the cyclization transition states. Control of the quaternary center is good to excellent, though the *trans*:*cis* ratio between the benzyloxy and amide groups is lower than what was observed for the chloroindole substrates. The *trans* and *cis* stereoisomers were separable by flash chromatography, with the *cis* isomer reproducibly being the less polar stereoisomer. On the basis of the unusually downfield ^{1}H NMR chemical shift (7.89 ppm) of the C4 hydrogen in the *cis*-isomer (compound **1.67**, Table 1.3), we postulate that the polarity arises from a hydrogen bond between the oxygen and the arene hydrogen.[17] Changing the Lewis acid from $Sc(OTf)_3$ to $ZnCl_2$ results in the *cis*-isomer being the major product (entry 5) as a result of chelation between the acylimine and the benzyloxy groups.

Table 1.3 Cyclizations with silyloxyindole substrates[a]

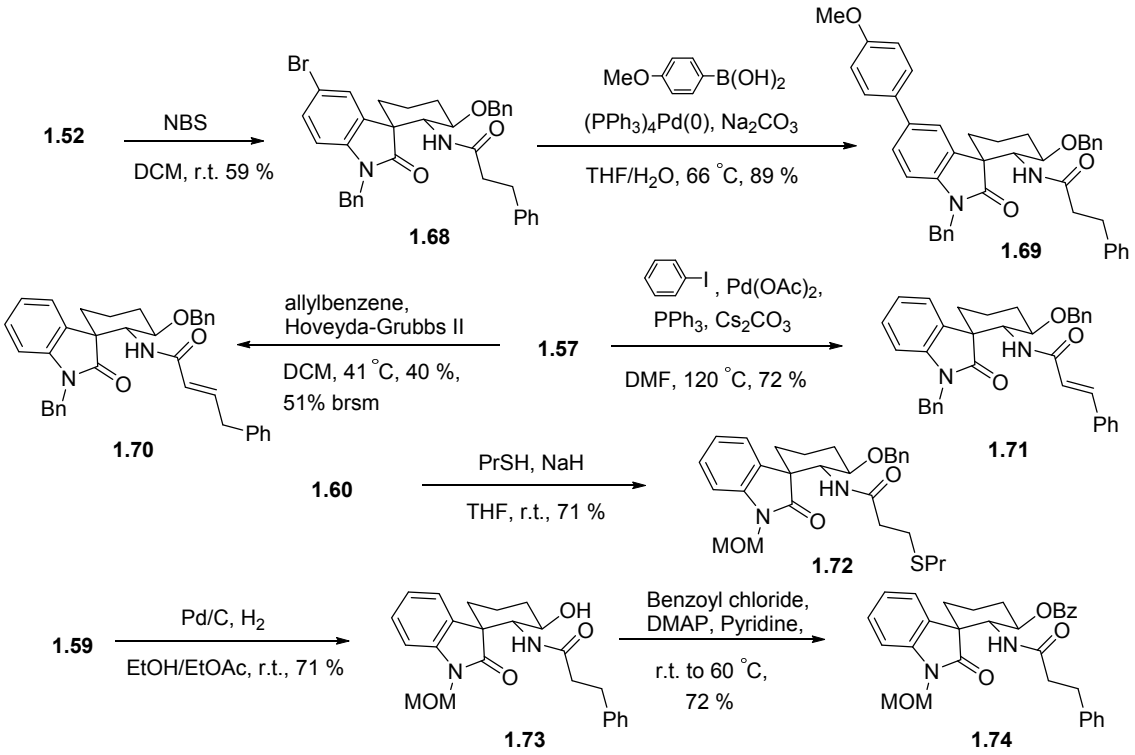
entry	substrate	acid chloride	major product	dr[b]	Yield (%)[c]
1	**1.42**		 **1.64**	4.1:1 (2.1:1)	68 (46)
2	**1.42**		 **1.65**	12:1 (1.7:1)	67 (42)
3	**1.42**		 **1.66**	7.2:1 (3.7:1)	38 (30)
4	**1.42**		 **1.53**	4.5:1 (2.4:1)	66 (47)
5[d]	**1.42**		 **1.67**	18:1 (1.8:1)	58 (37)

[a] Representative procedure: $Cp_2Zr(H)Cl$ (1.25 eq) was added to a 0.1 M solution of the indole nitrile in CH_2Cl_2 under Ar. After stirring at rt for 15 min the acid chloride and $Sc(OTf)_3$ were added. The mixture stirred overnight at rt. [b]The ratio refers to the quaternary center. The value in parentheses refers to the ratio of the major stereoisomer to all other stereoisomers. [c] Combined yield of all stereoisomers. The yield of the major stereoisomer is in parentheses. [d] $ZnCl_2$ was used instead of $Sc(OTf)_3$.

1.3.3 Further structure modification of the spirooxindole products

The spirooxindole products were designed to have numerous points for structural diversification as a prelude to library synthesis. Several of these opportunities are shown in Scheme 1.10. Regioselective oxindole bromination can be achieved with NBS, and the resulting aryl bromide **1.68** engages in a Suzuki reaction,[18] as seen in the preparation of **1.69** from **1.52**. Acrylamides

1.57 and **1.60** are highly versatile, undergoing Heck reaction[19] to form **1.71**, and cross metathesis[20] to form **1.70**, and thiolate addition to form **1.72**.[21] Benzyl ether cleavage was effected through standard hydrogenolysis conditions to afford the corresponding alcohol **1.73**, which underwent subsequent acylation to afford **1.74**.



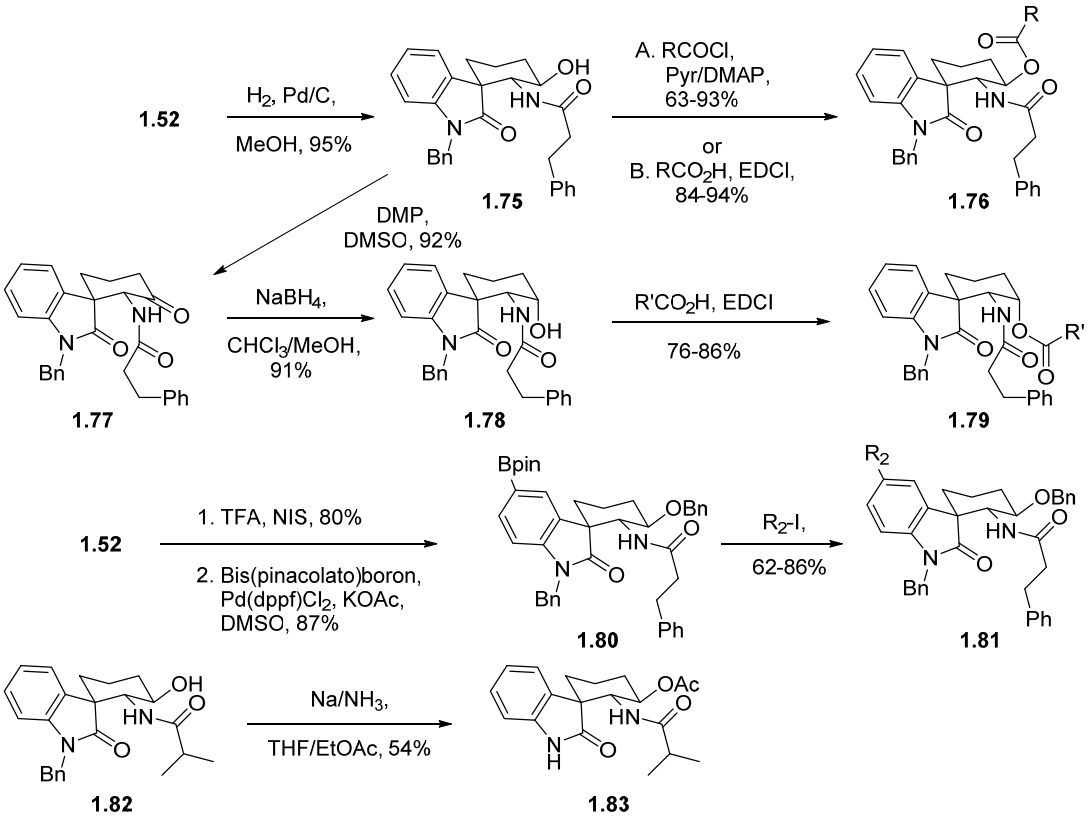
Scheme 1.10 Spirooxindole functionalizations

1.3.4 Construction of a spirooxindole amide library

The spirooxindole products are structurally unique, and diversification can be easily achieved either by using different acid chlorides during the reaction sequence or modifications after spirooxindole formation. In addition, good stereocontrol at the spirooxindole quaternary carbon

can be achieved by choosing different acyclic indoles as the starting material. As an application of our methodology to diversity oriented synthesis, a spirooxindole amide library was synthesized by the University of Pittsburgh Center for Chemical Methodologies and Library Development (UP-CMLD), and I participated in the synthetic route development part.

As shown in Scheme 1.11, the benzyl protecting group of **1.52** on the alcohol was selectively removed by hydrogenation, and the free alcohol **1.75** can be acylated with different acid chlorides or acids to give new esters **1.76**. Furthermore, the free alcohol can also be used to generate more stereoisomers. After Swern oxidation, the ketone **1.77** was obtained, and it was then selectively reduced (d.r. > 20:1) to generate **1.78**, in which the hydroxyl group is in the axial position opposite to starting material **1.75**. The subsequent acylation reaction then led to the *syn*-amido ester **1.79**, which is complementary to the original *trans*-amido ester **1.76**. It is worth noting that the configuration of **1.79** could not be obtained as the major isomer in the previous hydrozirconation, acylation and nucleophilic addition sequence. Thus, all four possible diastereomers of the spirooxindole structure can be selectively produced as major isomers. In addition, this stereochemistry inversion strategy can also be employed to the diastereomer **1.53**, which is the epimer of **1.52** at the 3-position of the spirooxindole core. Additional structure complexity can be achieved by Suzuki coupling with **1.80**. *N*-Debenzylation of the spirooxindole core under dissolving metal conditions[22] gave more polar product **1.83**. This spirooxindole structure with lower molecular weight is expected to have improved pharmacological property, according to Lipinski's rule of five.[23] Additionally, the free N-H bond of the spirooxindole could provide different biological properties through hydrogen bonding with protein targets.[5b] Finally, the single X-ray crystallography of **1.84** was obtained (Figure 1.6), confirming the previous structure assignments by NOE studies.



Scheme 1.11 Spirooxindole library synthesis

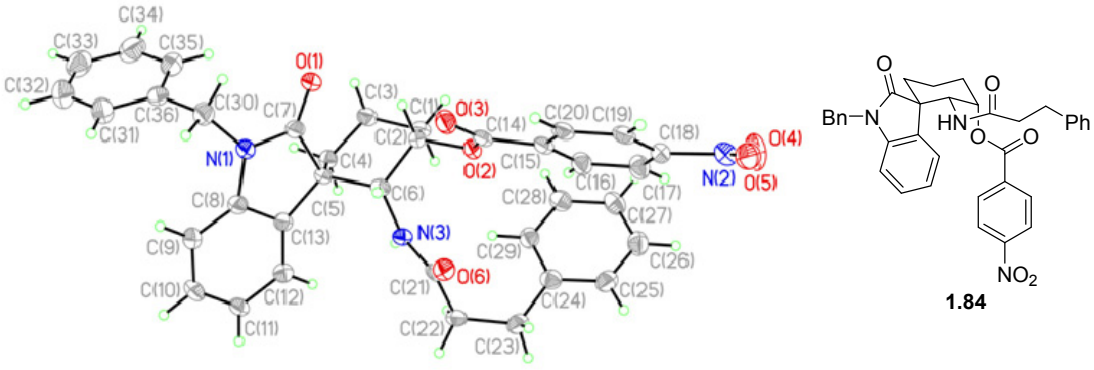


Figure 1.6 X-ray structure of 1.84

Using the above diversification methods, a library of 37-membered spirooxindoles was synthesized by Dr. Tsegay and Dr. Hong at UP-CMLD. The structural novelty of this library was studied by Dr. Xie and coworkers through chemistry space BCUT metrics as well as 2D finger-print calculations.[24] The results showed that this library has good chemical novelty when compared against NIH MLSMR (Molecular Libraries Small Molecule Repository), and Maybridge compound collections. These spirooxindoles have been deposited to NIH MLSMR, and some of these compounds were identified biologically active after preliminary high throughput screening (Appendix C).

1.4 CONCLUSIONS

We have demonstrated that the acyclic indolyl cyanohydrin ethers can be transformed to spirooxindole amides through a sequence of hydrozirconation, acylation and intramolecular nucleophilic addition. Three of the four possible diastereomers can be prepared as major products through this process. The quaternary stereocenter can be controlled by adjusting the steric bulk of the substituent at the 2-position of the indole substrate. Meanwhile, by using a chelating or non chelating Lewis acid, the relative stereochemistry between the amide and benzyloxy groups can also be influenced. Furthermore, the stereochemistry of the benzyloxy group can also be inverted through hydroxyl group oxidation and stereoselective reduction sequence. The novel spirooxindole structure has many sites for diversification, and a 37-membered library was synthesized. A comparison with known compound collections showed that the new spirooxindoles possessed good chemical diversity.

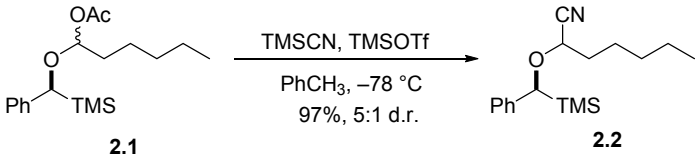
2.0 STEREOCONTROLLED CYANOHYDRIN ETHER SYNTHESIS THROUGH CHIRAL BRØNSTED ACID-MEDIATED VINYL ETHER HYDROCYANATION

2.1 INTRODUCTION

The stereocontrolled spirooxindole amide synthesis has demonstrated that cyanohydrin alkyl ethers are important building blocks for the amide formation through hydrozirconation, acylation, and nucleophilic addition. The direct formation of enantiomerically enriched cyanohydrin alkyl ethers has not been reported despite its synthetic utility. Major efforts for the synthesis of chiral nitrile containing compounds have focused on the asymmetric cyanohydrin formation. Excellent enantioselectivity can be achieved by cyanide addition to an aldehyde or ketone,[25] and many catalysts are effective to mediate this transformation.[26] Chiral cyanohydrins can be transferred to silyl ethers,[27] esters,[28] and acetals[29] without loss of stereochemistry. However, the alkylation of cyanohydrins to yield cyanohydrin alkyl ethers are implausible, because cyanohydrins are not stable under basic conditions, and cyanohydrins are weak nucleophiles for direct alkylation due to the strong inductive effect of the cyano group. Therefore, a new strategy is needed towards the direct synthesis of enaniomerically enriched cyanohydrin alkyl ethers.

Racemic cyanohydrin alkyl ethers can be generated by Lewis acid catalyzed acetal ionization reactions followed by quenching the resulting oxocarbenium ions with TMSCN.[30]

Absolute stereocontrol in these reactions is rare for acyclic substrates, though a good level of diastereocontrol was achieved by Rychnovsky and co-workers.[31] In their study, TMSCN added diastereoselectively to the α-(trimethylsilyl)benzyl-substituted oxocarbenium ion to yield the cyanohydrin alkyl ether in 5:1 d.r.. Even though the complicated auxiliary and substrate syntheses limit the application of this strategy, it demonstrates the feasibility of enantioselective synthesis of cyanohydrin alkyl ethers through stereoselective cyanide addition to oxocarbenium ions.



Scheme 2.1 Rychnovsky's diastereoselective cyanide addition to oxocarbenium ions

Encouraged by our previous application of cyanohydrin alkyl ethers in target-, diversity-, and function-oriented synthesis, we initiated a study directed towards the enantioselective synthesis of cyanohydrin alkyl ethers through catalytic asymmetric cyanide addition to oxocarbenium ions.

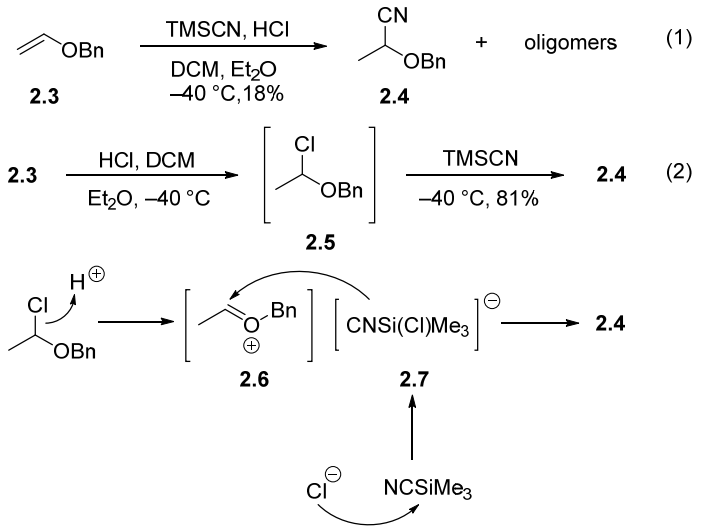
2.2 SYNTHESIS OF ACHIRAL CYANOHYDRIN ALKYL EHTER THROUGH CYANATION OF ENOL ETHER

In the previous spirooxindole synthesis, the Lewis acid catalyzed ionization of acetals and the following cyanation was used as the established protocol for the synthesis of cyanohydrin alkyl

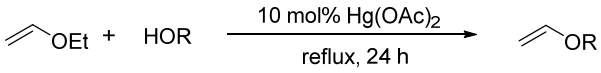
ethers. However, if the substrate contains structurally complex or valuable alkoxy groups, this approach will become inappropriate for the synthesis of such cyanohydrin alkyl ethers. Enol ethers are attractive substrates for the synthesis of cyanohydrin alkyl ethers without loss of precious alkoxy groups. Oxocarbenium ions can be generated upon protonation, and the following cyanation should give cyanohydrin alkyl ethers. These substrates are readily accessed through cross-coupling[32] or vinyl transfer reactions.[33] Despite these benefits, examples of enol ethers as precursors to cyanohydrin alkyl ethers are quite rare in the literature. Our initial attempts of using this substrate for the cyanohydrin ether synthesis illustrated the obstacle to its application in synthesis (Scheme 2.2, reaction 1). Adding anhydrous HCl to a mixture of benzyl vinyl ether (**2.3**) and TMSCN provided cyanohydrin ether **2.4** in only 18% yield. The remainder of the material ended up oligomerized through nucleophilic enol ether addition into the oxocarbenium ion intermediates.

The oligomerization pathway could be alleviated by converting the enol ether to an electrophile prior to the addition of TMSCN. This was accomplished through quantitatively forming α-chloro ether **2.5** from **2.3** and HCl (Et_2O solution, 1.1 equiv). The addition of TMSCN (2 equiv) to the crude chloro ether led to the formation of **2.4** in 81% yield for the one pot transformation (Scheme 2.2, reaction 2). The mechanism of this transformation could proceed through chloride ionization by a Brønsted acid or direct addition by TMSCN. 2,6-di-*tert*-Butylpyridine was added to the *in situ* generated chloro ether before the addition of TMSCN to elucidate the mechanism, and no cyanohydrin ether was generated. The suppressed cyanation step suggested that the oxocarbenium ion **2.6** arises from Brønsted acid-mediated ionization of choloro ether **2.5**, which was in accord with observations from the Jacobsen group.[34] Woerpel and co-workers demonstrated that the nuclophilic addition of TMSCN to oxocarbenium ions

involved an ionic pentacoordinate siliconate as the real nucleophile.[35] We propose that chloride adds to TMSCN to create the activated cyanide species **2.7**, which then adds to the oxocarbenium ion **2.6** to form **2.4** (Scheme 2.2).



Scheme 2.2 Cyanohydrin ether formation through vinyl ether hydrocyanation

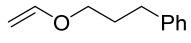
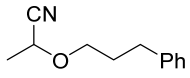
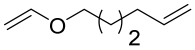
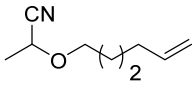
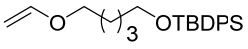
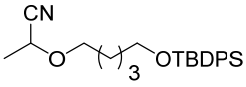
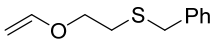
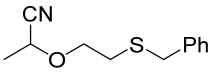
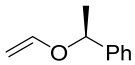
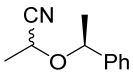
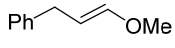
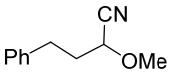
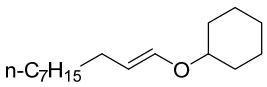
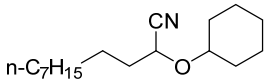
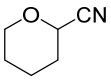
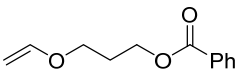
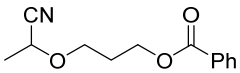


Scheme 2.3 General vinyl ether substrate synthesis

The scope of this reaction is shown in Table 2.1. Vinyl ether substrates were readily synthesized by using different alcohols via mercury acetate catalyzed vinyl transfer reaction with ethyl vinyl ether (Scheme 2.3).[33] Vinyl ethers with longer alkenyl groups (**2.18** and **2.20**, Table 2.1) were synthesized through metal-catalyzed coupling reactions.[36] Substrates with longer alkoxy groups react smoothly (entry 1), and functional groups such as alkenes, silyl ethers and sulfides are tolerated (entries 2-4). Vinyl ethers with branched alkoxy groups react smoothly, but little stereocontrol is observed (entry 5). The vinyl group can be extented (entries 6 and 7), and

cyclic enol ethers react well (entry 8). The ester gives decreased yield (entry 9) possibly due to the instability of the ester group to the oxocarbenium ion intermediate. These transformations demonstrate that cyanohydrin alkyl ethers can be formed through Brønsted acid-mediated vinyl ether hydrocyanation, and this method is superior to the convential acetal ionization approaches toward synthesis of cyanohydrin ethers with complex alkoxy groups.

Table 2.1 Scope of the enol ether hydrocyanation reaction

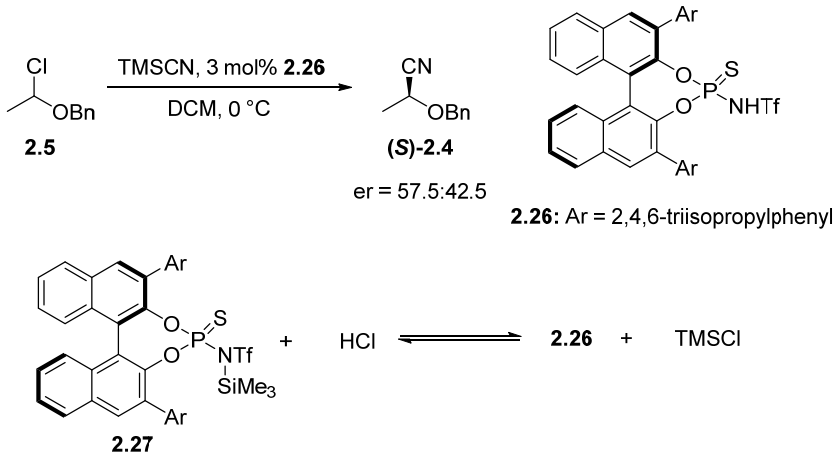
entry	substrate	product	yield
1	 **2.8**	 **2.9**	92%
2	 **2.10**	 **2.11**	76%
3	 **2.12**	 **2.13**	96%
4	 **2.14**	 **2.15**	85%
5	 **2.16**	 **2.17**	91% dr = 1.2:1
6	 **2.18**	 **2.19**	83%
7	 **2.20**	 **2.21**	94%
8	 **2.22**	 **2.23**	65%
9	 **2.24**	 **2.25**	48%

[a] Representatvie procedure: HCl (2.0 M Et_2O solution, 1.1 equiv) is added to the vinyl ether in CH_2Cl_2 at –40 °C. TMSCN (2 equiv) is added upon complete starting material consumption and the reaction is stirred at –40 °C until product formation is complete.

2.3 ASYMMETRIC CYANOHYDRIN ALKYL ETHER SYNTHESIS MEDIATED BY CHIRAL BRØNSTED ACID

2.3.1 Chiral Brønsted acid mediated cyanation of α-chloro ethers

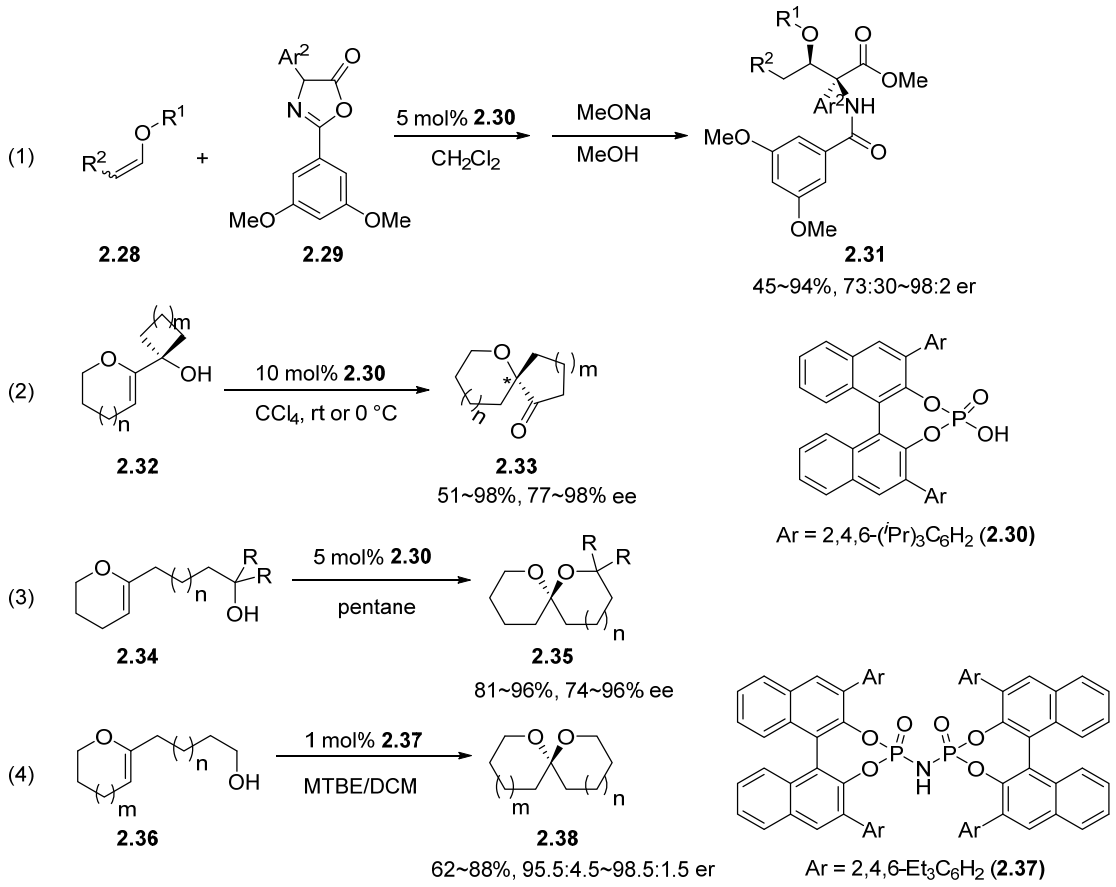
The Brønsted acid mediated hydrocyanation reaction in the previous chapter prompted us to explore the potential of replacing HCl with a chiral Brønsted acid[37], with the expectation that the chiral ion pair[38] formed between the oxocarbenium ion and the conjugate base of chiral Brønsted acid would lead to enantioselective cyanide addition. Thus we prepared α-chloroether **2.5** and added TMSCN at 0 °C in the presence of thiophosphoryl triflimide **2.26**[39] (3 mol%). This reaction provided **2.4** with an enantiomeric ratio (er) of 57.5:42.5. Even though the results are not preparatively useful, it demonstrates that the tight ion pair strategy could lead to some degree of enantiocontrol. After examining the possible reaction mechanism, we noticed that HCl could be released from the ionization of the α-chloro ethers mediated by the chiral Brønsted acid. In order to achieve high enantioselectivity, the liberated HCl must engage in a fast exchange reaction with the silylated catalyst to regenerate the chiral Brønsted acid and form TMSCl. If this process is not rapid or is not thermodynamically viable, HCl will promote the non-selective pathway and lead to low enantioselectivity. Therefore, the chiral Brønsted acid mediated cyanation of α-chloroethers is not effective to achieve high enantioselectivity.



Scheme 2.4 Chiral Brønsted acid-mediated choride ionization and cyanation

2.3.2 Chiral Brønsted acid catalyzed hydrocyanation of vinyl ethers

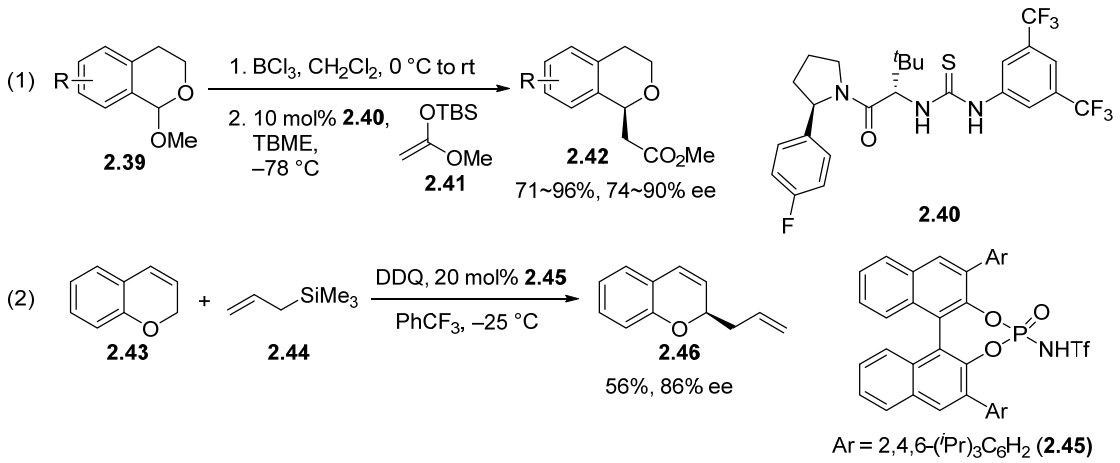
The non-selective background reaction catalyzed by HCl led us to reexamine vinyl ethers alone as substrates. However, there are not many examples using vinyl ethers as oxocarbenium ion precursors for asymmetric synthesis. Terada and co-workers developed an enantioselective aldol-type reaction catalyzed by chiral phosphoric acid **2.30** (Scheme 2.5, reaction 1).[40] Vinyl ethers were protonated by **2.30** to give oxocarbenium ions, which then reacted with the enol form of the azlactone to produce the addition product. Tu and co-workers reported that chiral Brønsted acids promote a semipinacol rearrangement of vinyl ethers to give spiroethers (Scheme 2.5, reaction 2).[41] Recently, Nagorny[42] and List[43] demonstrated separately the asymmetric spiroacetalization of cyclic vinyl ethers catalyzed by chiral Brønsted acid (Scheme 2.5, reaction 3 and 4). These examples show that oxocarbenium ions can be readily generated through chiral Brønsted acid catalyzed protonation of vinyl ethers, and the acid can be regenerated from the protons lost from nucleophiles, such as active methylene compounds or alcohols.



Scheme 2.5 Chiral Brønsted acid mediated vinyl ether transformations

Silylated nucleophiles can be utilized for the asymmetric addition to oxocarbenium ions when a silyl group scavenger is generated upon formation of oxocarbenium ions. Jacobsen and co-workers developed a thiourea-catalyzed enantioselective addition reaction to oxocarbenium ions in which silyl ketene acetals were used as nucleophiles and 1-chloroisochroman was employed as the oxocarbenium precursor (Scheme 2.6, reaction 1).[34a] Our group recently demonstrated that a chiral Brønsted acid can mediate asymmetric addition of allyl trimethylsilane (**2.44**) to benzopyrylium ions, which were generated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of 2*H*-chromene (**2.43**) (Scheme 2.6, reaction 2).[44] All the above

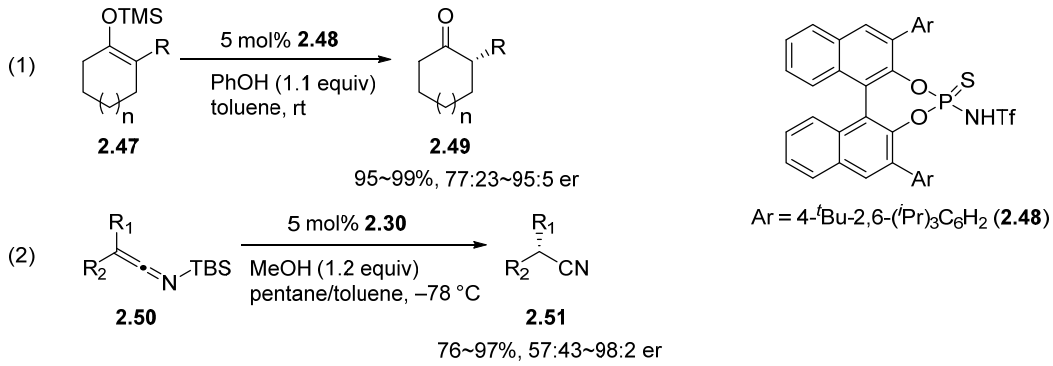
reported cases of intermolecular additions to oxocarbenium ions utilized sterically hindered nucleophiles[40] or highly specific electrophiles[34a, 44].



Scheme 2.6 Addition of silylated nucleophiles to oxocarbenium ions through organocatalysis

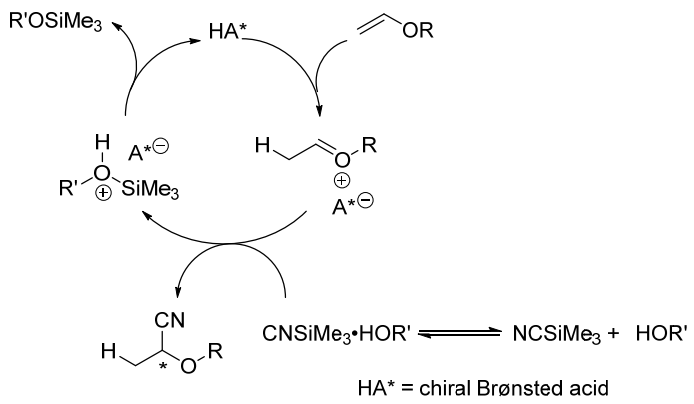
The Brønsted acid-catalyzed asymmetric addition of silylated nucleophiles to vinyl ether-derived oxocarbenium ions has not been explored. The generation of oxocarbenium ions and the following nucleophilic addition are feasible, but the consumption of the Brønsted acid will terminate the catalytic cycle. Because there is no other silyl group scavengers generated in the reaction, the catalyst will be silylated, which subsequently blocks the oxocarbenium ion formation pathway. Yamamoto and co-workers developed an enantioselective protonation reaction of enolsilanes using a chiral Brønsted acid as the catalyst (Scheme 2.7, reaction 1).[45] In this reaction, phenol functions as both the proton source and the silyl group scavenger, and only catalytic amount of chiral Brønsted acid is necessary for the transformation. List and co-workers recently demonstrated that methanol could serve as proton source for the asymmetric protonation of silyl ketene imine (Scheme 2.7, reaction 2).[46] Therefore, we envisioned that alcohols could be

used to regenerate the chiral Brønsted acid from its silylated form and to quench silyl electrofuges upon silylated nucleophile addition to oxocarbenium ions.



Scheme 2.7 Asymmetric protonation reactions mediated by chiral Brønsted acid and alcohols

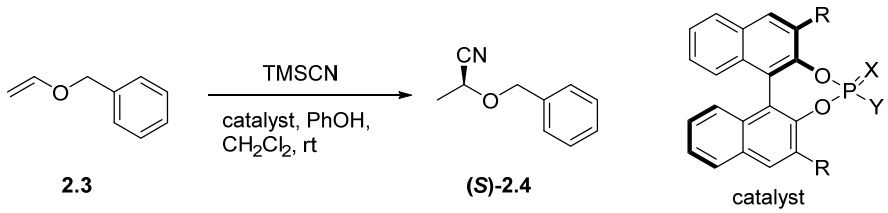
A proposed catalytic cycle for the asymmetric addition of TMSCN to vinyl ether-derived oxocarbenium ions is shown in Scheme 2.8. Protonation of the enol ether will generate a chiral ion pair. The TMSCN will be activated by complexation with an alcohol in accord with Woerpel's studies.[35] The subsequent cyanide transfer yields the cyanohydrin ether and an ion pair between the protonated silyl ether and the conjugate base of the catalyst. The chiral Brønsted acid is then regenerated by the proton transfer and a silyl ether is also produced.



Scheme 2.8 Direct enol ether hydrocyanation with catalyst regeneration

Catalysts were first screened for reactivity and selectivity. The reaction was conducted with **2.3** as the substrate in CH_2Cl_2 at rt, and phenol was used as the stoichiometric proton source. The results are shown in Table 2.2. Thiophosphoryl triflimide **2.26** provided an enantiomeric ratio of 65:35 (entry 1), indicating that this protocol is superior to the asymmetric cyanation of α-chloroethers. Changing the substitution pattern of the aryl groups (**2.52**, entry 2) and introducing a triphenylsilyl group onto the binaphthyl core (**2.53**, entry 3) led to almost no stereoselectivity. This implied that the diisopropyl group at the 2,6-positions of the triisopropylphenyl group is essential for the stereocontrol. Selectivity was further improved by introducing more steric demanding groups at the 4-position of the triisopropylphenyl group (entry 4-5) and the optimal selectivity was achieved by using biary-substituted catalyst **2.55** (entry 5). The triflimide group proved to be essential for the reactivity, with phosphoric acid **2.56** (entry 6) and thiophosphoric acid **2.57** (entry 7) proving to be ineffective catalysts. Phosphoryl triflimide **2.58** led to decomposition of the substrate (entry 8), demonstrating the importance of the sulfide group in this process. Thus acid **2.55** was selected as the lead catalyst for this process.

Table 2.2 Catalyst screening



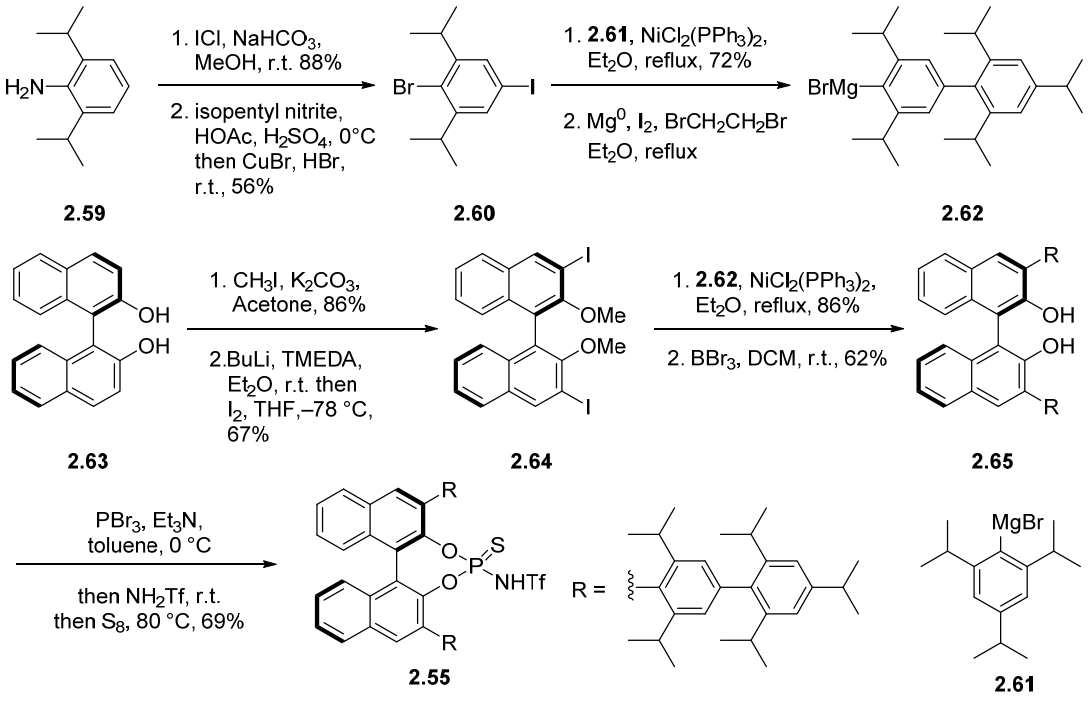
2.3 **(*S*)-2.4** catalyst

entry	catalyst (mol%)	t (h)	er
1	**2.26** (3.0): R = 2,4,6-Triisopropylphenyl, X= S, Y = NHTf	0.5	65:35
2	**2.52** (3.0): R = 3,5-di(trifluoromethyl)phenyl, X= S, Y = NHTf	0.5	51.5:48.5
3	**2.53** (3.0): R = triphenylsilyl, X= S, Y = NHTf	0.5	52:48
4	**2.54** (3.0): R = 2,6-diisopropyl-4-amamantlyphenyl X= S, Y = NHTf	0.5	68:32
5	**2.55** (3.0): R = 2,6-diisopropyl-4-(2,4,6-triisopropylpenyl) -phenyl, X= S, Y = NHTf	0.5	71.5:28.5
6	**2.56** (10.0): R = phenyl, X= O, Y =OH	12	-
7	**2.57** (10.0): R = 2,4,6-Triisopropylphenyl, X= O, Y = SH	12	-
8	**2.58** (10.0): R = 2,4,6-Triisopropylphenyl, X= O, Y = NHTf	0.5	-

[a]Representative procedure: The catalyst and Me_3SiCN (2.0 equiv) were first stirred at rt in DCM for 10 min. The vinyl ether (1.0 equiv) in DCM was added to the reaction mixture, followed by addition of phenol (1.0 equiv). Enantiomeric ratios were determined by HPLC with a Lux Cellulose 3 column.

The synthesis of chiral Brønsted acid **2.55** shown in Scheme 2.9, represents the general procedure for the synthesis of sterically bulky chiral Brønsted acids. Acid **2.55** was first reported by Yamamoto,[47] however no synthetic details were included. Thus, herein we provided the synthetic sequence towards this acid. The intermediate **2.60**[48] and **2.64**[49] were synthesized according to the reported procedure. Even though the Kumada coupling[50] between **2.61** and **2.64** proceeded smoothly in both THF and Et_2O for the preparation of catalyst **2.26**, the coupling reaction towards the synthesis of sterically bulky BINOL derivative **2.65** must be conducted in Et_2O. THF can promote the generation of Grignard reagent **2.62**, but no coupling product between **2.62** and **2.64** was obtained. The Grignard reagent **2.62** is difficult to form in Et_2O possibly due to the steric bulk of its bromide precursor. However, the reaction proceeded when

magnesium strip was successfully activated by dibromoethane. Once Grignard reagent **2.62** is generated, the bulky BINOL derivative **2.65** can be obtained by nickel-catalyzed Kumada coupling[51] and methyl ether cleavage. The subsequent formation of triflimide and sulfur oxidation gave chiral Brønsted acid **2.55** in good yield.[47]



Scheme 2.9 Synthesis of chiral Brønsted acid 2.55

The reaction conditions were optimized after identifying the suitable catalyst (Table 2.3). HCN was tested for this reaction as it is the most direct proton and cyanide source.[52] The cyanohydrin ether **2.4** was isolated in 35% yield with 69:31 er (entry 1) when HCN was used at −40 °C alone. However, when a 1:1 mixture of TMSCN and HCN was used as the cyanide source, **2.4** was obtained in 60% yield and 77:23 er (entry 2). Therefore, HCN is not an effective cyanide source for the oxocarbenium ion addition, and it leads lower enantioselectivity as previously observed by Shibasaki and co-workers.[53] Additionally, when TMSCN is present in

the reaction mixture, HCN is not the real nucleophile that is involved in this chiral Brønsted acid-mediated asymmetric hydrocyanation reaction. However, HCN can serve as the proton source for this reaction. When HCN was added slowly to the reaction mixture over 20 h, an improved enantioselectivity was observed (entry 3). This implied that the low selectivity pathway involving HCN as the nucleophile is suppressed by slow addition, and in this protocol HCN functions as a proton source instead of the nucleophile. Lowering temperature to −60 °C gave no further selectivity improvement (entry 4).

Solvent screening revealed that $PhCF_3$ was the optimal solvent in terms of enantioselectivity and the chemical yield (entries 5-6). ^{i}PrOH was also tested as the proton source instead of PhOH, but it led to decreased yield because of competitive mixed acetal formation (entry 7). Hence, PhOH was identified as a better proton source than alkyl alcohols. The selectivity was improved at −25 °C to give an er of 80.5:19.5 while PhOH was added slowly to minimize side reactions such as the mixed acetal formation (entry 8). Replacing TMSCN with bulky TBSCN resulted in decreased selectivity and chemical yield (entry 9). After optimization of the reaction conditions, optimal catalyst **2.55** was used to give **2.4** in 85% chemical yield with an er of 85:15 (entry 10). Even though the minimum reaction temperature for $PhCF_3$ is −25 °C, the selectivity and the yield obtained under this condition is better than using CH_2Cl_2 as solvent at −40 °C (entry 11). When HCN was used as the proton source, a similar selectivity and yield can be achieved (entry 12). However, PhOH is a better proton source for the reaction due to safety and availability. Enantioselectivity was not improved by increasing the loading of the catalyst to 10 mol% (entry 13). Reducing the loading of the catalyst to 0.5 mol% did not influence the selectivity and the chemical yield (entry 14). Even though synthesis of catalyst **2.55**

takes several steps, the low catalyst loading will greatly facilitate further application of this protocol.

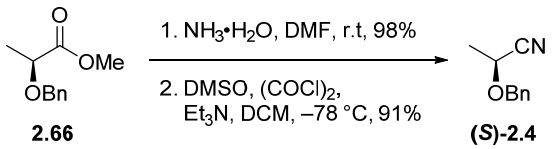
Table 2.3 Condition optimization[a]

entry	Temp (°C)	catalyst	solvent	proton source	cyanide scource	er	yield (%)[b]
1	–40	**2.26**	DCM		HCN	69:31	35
2	–40	**2.26**	DCM		TMSCN+HCN (1:1)	77:23	60
3	–40	**2.26**	DCM	HCN	TMSCN	80.5:19.5	58
4	–60	**2.26**	DCM	HCN	TMSCN	80.5:19.5	60
5[c]	rt	**2.26**	$PhCH_3$	PhOH	TMSCN	63.5:36.5	68
6[c]	rt	**2.26**	$PhCF_3$	PhOH	TMSCN	68.5:31.5	87
7[c]	rt	**2.26**	$PhCF_3$	^{i}PrOH	TMSCN	68.5:31.5	37
8	–25	**2.26**	$PhCF_3$	PhOH	TMSCN	80.5:19.5	85
9	–25	**2.26**	$PhCF_3$	PhOH	TBSCN	78.5:21.5	54
10	–25	**2.55**	$PhCF_3$	PhOH	TMSCN	85:15	85
11	–40	**2.55**	DCM	PhOH	TMSCN	83.5:16.5	65
12	–25	**2.55**	$PhCF_3$	HCN	TMSCN	84.5:15.5	87
13[d]	–25	**2.55**	$PhCF_3$	PhOH	TMSCN	84.5:15.5	90
14[e]	–25	**2.55**	$PhCF_3$	PhOH	TMSCN	85:15	84

[a]Representative procedure: A solution of proton source (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 cyanide source (2.0 equiv). The reactions were complete shortly after the proton source addition was complete. Enantiomeric ratios were determined by HPLC with a Lux Cellulose 3 column. [b]Isolated yield. [c]Proton source was added in one portion, and the reaction finished in 30 min. [d]10 mol% catalyst was used. [e]0.5 mol% catalyst was used.

The absolute stereochemistry of the major isomer of cyanohydrin ether **2.4** was determined by comparison with the authentic material that was prepared by methyl lactate (Scheme 2.10). (*S*)-2-(Benzyloxy)propanoate (**2.66**) was first transformed to a primary amide, which was then oxidized under Swern conditions to give the cyanohydrin ether **2.4**. The optical rotation of this authentic sample is −169.1 (*c* 1.0, $CHCl_3$), and the HPLC analysis showed the purity of this sample is over 99:1 er. The cyanohydrin ether **2.4** obtained by asymmetric

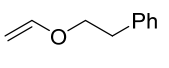
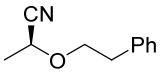
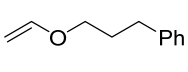
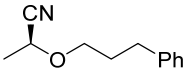
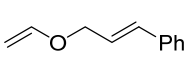
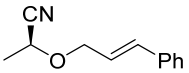
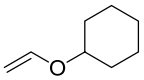
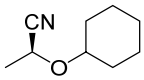
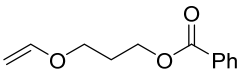
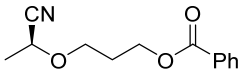
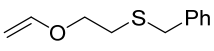
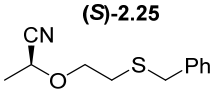
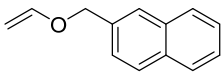
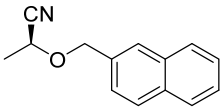
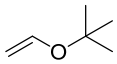
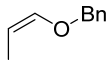
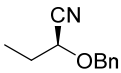
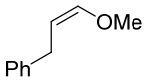
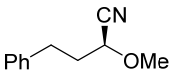
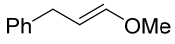
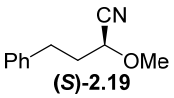
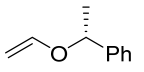
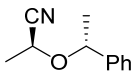
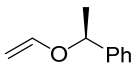
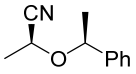
cyanation (Table 2.3, entry 14) has an optical rotation of −123.3 (*c* 1.0, $CHCl_3$), and hence, the absolute stereochemistry of the major isomer is *S*. This result was also confirmed by HPLC retention time comparison.



Scheme 2.10 Determination of the absolute stereochemistry of 2.4

The scope of this reaction was further explored, and the results are summarized in Table 2.4. The reaction was insensitive to alkoxy group changes. Similar levels of stereocontrol were observed for alkoxy groups with longer chains (entries 1 and 2), branching (entry 4), and larger aromatic groups (entry 7). Functional groups such as alkenes (entry 3), esters (entry 5) and sulfides (entry 6) are compatible with the reaction conditions. It is worth noting that ester **2.25** was obtained in higher yield in this protocol than the cyanation of α-chloroethers (entry 9, Table 2.1). This result implied that the hydrocyanation of vinyl ethers mediated by a chiral Brønsted acid is more efficient than the cyanation of α-chloroethers. Unfortunately, vinyl ethers with alkoxy groups that can fragment to form a stable carbocation following oxocarbenium ion formation, such as *tert*-butyl vinyl ether (**2.75**), do not yield the cyanohydrin ether product (entry 8). Extending the alkenyl group caused a reduction in enantioselectivity that was more pronounced at greater chain lengths (entries 9 and 10). (*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 10 and 11). This implies that the same reactive intermediate was formed from either isomer. The (*Z*)-isomer more readily

Table 2.4 Substrate scope for the asymmetric reaction[a]

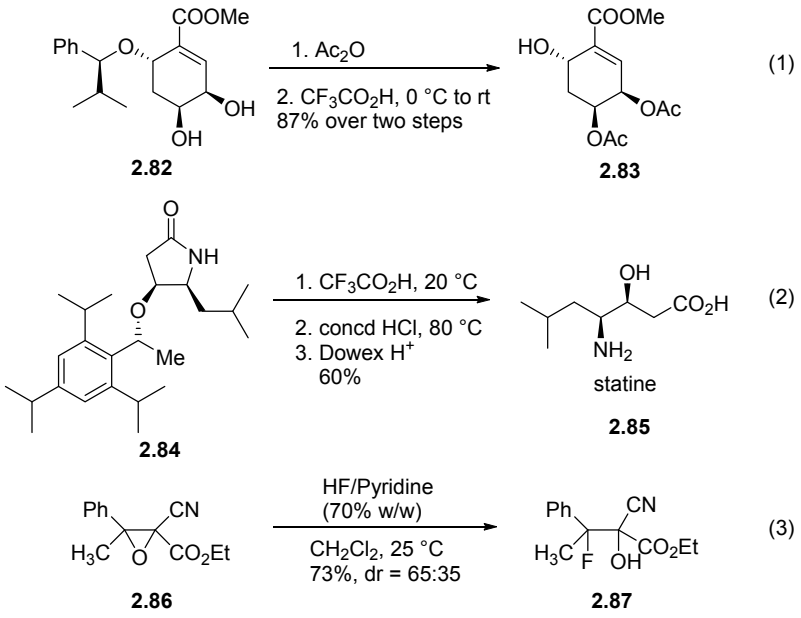
entry	substrate	product	yield (%)[b]	er
1	 **2.67**	 **2.68**	78	87.5:12.5
2	 **2.8**	 **(*S*)-2.9**	90	86:14
3	 **2.69**	 **2.70**	77	82:18
4	 **2.71**	 **2.72**	72	84:16
5	 **2.24**	 **(*S*)-2.25**	87	83:17
6	 **2.14**	 **(*S*)-2.15**	71	83:17
7	 **2.73**	 **2.74**	88	84.5:15.5
8[c]	 **2.75**	–	–	–
9	 **2.76**	 **2.77**	74	80.5:19.5
10[d]	 **2.78**	 **(*S*)-2.19**	86	74:26
11[d]	 **2.18**	 **(*S*)-2.19**	13	74:26
12	 **2.79**	 **2.80**	80	dr = 28:1[e]
13	 **2.16**	 **2.81**	81	dr = 1.4:1[f]

[a]Representative procedure: A solution of PhOH (1.0 equiv) was added dropwise over 20 h to a solution of the vinyl ether (1.0 equiv), catalyst **2.55** (0.03 equiv), and TMSCN (2.0 equiv) in $PhCF_3$ at –25 °C. The reactions were quenched 4 h later after PhOH addition was complete. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [b]Isolated yield. [c]The reaction was carried out in CD_2Cl_2 at rt, and PhOH was added in one portion. [d]9 mol% catalyst was used. [e]Determined by HPLC analysis. [f]Determined by crude NMR.

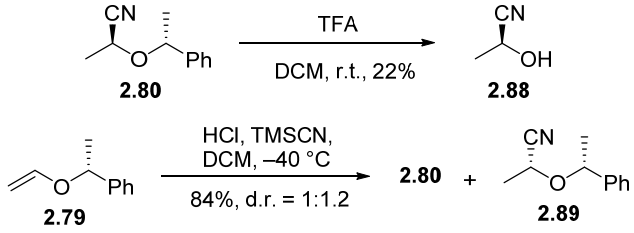
undergoes the hydrocyanation process because it is presumably protonated more rapidly than the (*E*)-isomer. Chiral substrates can show matched or mismatched selectivity in these reactions, as demonstrated by the reaction of the methylbenzyl vinyl ether enantiomers in entries 12 and 13. Reactions with these compounds under HCl-mediated conditions showed little stereocontrol (entry 5, Table 2.1). However, the reaction of (*R*)-enantiomer **2.79** in the presence of **2.55** proved to be highly diastereoselective. The reaction of (*S*)-enantiomer **2.16** showed little diastereoselectivity, similar to the HCl-mediated process.

The stereochemistry of **2.80** was determined by the conversion to the corresponding cyanohydrin through cleavage of the methylbenzyl group. Posner and Greene showed that benzylic C-O bonds of chiral secondary alcohols can be cleaved by trifluoroacetic acid without loss of the stereochemistry of the hydroxyl group (Scheme 2.11, reactions 1 and 2).[54] Baklouti and co-workers demonstrated that the ring opening fluorination of the cyanohydrin ether derivative **2.86** went through the S_N1 pathway under acidic conditions (Scheme 2.11, reaction 3).[55] Therefore, trifluoroacetic acid was used to cleave the methylbenzyl group of **2.80** to give cyanohydrin **2.88** in 22% yield (Scheme 2.12, reaction 1). The low yield is possibly due to the volatility of cyanohydrin **2.88**. The measured optical rotation for **2.88** is −32 (*c* 0.23, $CHCl_3$), which is consistent with the reported value[56] for the (*S*)-lactonitrile ($[\alpha]_D^{25} = -30$ (*c* 1.0, $CHCl_3$)). Therefore, the stereochemistry of the cyanohydrin ether group of **2.80** was determined to be *S*. The diastereoselectivity for the asymmetric cyanation of **2.79** was determined by HPLC using a Lux cellulose-3 column. **2.80** and its diastereomer **2.89** were synthesized through cyanation of the α-chloroether (Scheme 2.12, reaction 2), and these two diastereomers can be readily separated by flash chromatography. The retention times for both of the diastereomers were recorded, and the diastereoselectivity for the chiral Brønsted acid catalyzed hydrocyanation

reaction was determined to be 28:1 by comparison of the crude product with the purified samples.



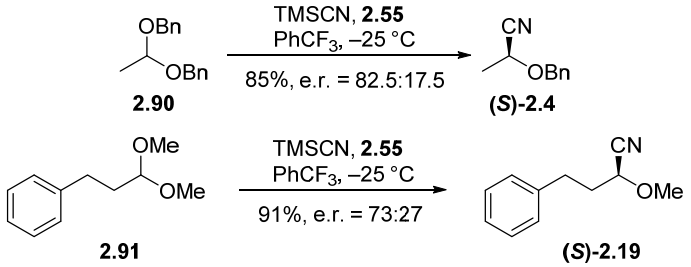
Scheme 2.11 Cleavage of C-O benzylic bonds under acidic unditions



Scheme 2.12 Determination of the absolute stereochemistry and diatereoselectivity of 2.80

Acetals can also be used as substrates for the preparation of enantiomerically enriched cyanohydrin ethers (Scheme 2.12). Dibenzyl acetal **2.90** reacts with TMSCN in the presence of **2.55** to give **(*S*)-2.4** in 85% yield and with an er of 82.5:17.5. Dimethyl acetal **2.91** reacts under these conditions to yield **(*S*)-2.19** in 91% yield and with an er of 73:27. Both enantioselectivity

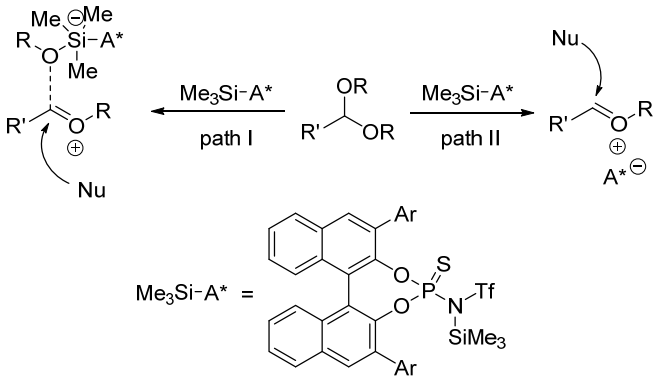
and chemical yield are similar to the results in vinyl ether series, and hence, the choice of a vinyl ether or acetal substrate is determined by synthetic accessibility. Acetals, however, are clearly superior substrates to poorly reactive (*E*)-vinyl ethers in these processes.



Scheme 2.13 Application to acetal substrates

A plausible mechanism for this process is shown in Scheme 2.14. The silylated thiophosphoryl triflimide possibly serves as the active catalyst in these processes. NMR studies showed that thiophosphoryl triflimides were silylated by TMSCN to form a Lewis acid in the absence of phenol, consistent with observations by Yamamoto and List[46-47] in reactions between chiral Brønsted acids and silylated substrates. Trimethylsilyl ethers were observed as products in accord with this hypothesis. Sammakia and co-workers demonstrated that Lewis acid-mediated cleavage of acetals and nucleophilic addition predominately undergoes S_N1 pathway to generate oxocarbenium ions.[57] Therefore, it can be postulated that one of the enantiotopic alkoxy groups is preferentially activated by the silylated chiral Brønsted acid to form a tight ion pair between the oxocarbenium ion and the departing alcohol, followed by nucleophilic addition (Scheme 2.14, path I). However, the similarities between the outcomes of reactions with acetals and vinyl ethers suggest that they proceed through the same intermediates as shown in Scheme 2.8,

probably involving the direct interaction between the oxocarbenium ion and the conjugate base of the chiral Brønsted acid (Scheme 2.14, path II).



Scheme 2.14 Possible pathways towards activation of acetals

2.3.3 Computational studies

Unlike carbonyl and imine containting compounds, which are widely used as substrates for chiral Brønsted acid catalyzed reactions, oxocarbenium ions do not possess Lewis basic sites for hydrogen bonding to the catalyst. As far as we know, there is no established model for the ion pair interaction between the oxocarbenium ion and the conjugate base of chiral Brønsted acid. 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. Mr. Xiaoge Su from Professor Jordan's group at the University of Pittsburgh conducted these studies with Gaussian 09.[58] B3LYP[59] was used as the exchange correlation function. The interaction between the oxocarbenium ion of ethyl vinyl ether with the conjugate base of catalyst **2.26** was utilized to develop a model for these transformations. Peripheral atoms, which constitute the aromatic part

of the chiral Brønsted acid **2.26**, were treated with the 3-21G[60] basis set while contact atoms were treated with the 6-311G[61] basis set. The phosphorus and sulfur atoms were described by the 6-311G(3df, 3pd)[62] basis set. Energy minima were determined by optimizing structures from several starting geometries, which were derived from the crystal structure of the sodium salt of **2.26**,[45] and the minima were confirmed by frequency calculations.

The lowest energy structure for the ion pair is shown as model **A** in Figure 2.1. 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 the catalyst interacts with the hydrogen on the electrophilic carbon of the oxocarbenium ion. Corey postulated that this type of interaction can be important in structures between aldehydes and Lewis acids.[63] Recent work in chiral phosphoric acid-catalyzed additions to aldehydes indicated that these interactions are essential for stereocontrol.[64] The Mulliken charge on the 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 carbon of the alkoxy group. Even though the existence of defined C–H•••F–C hydrogen bonds is debatable,[65] electrostatic and van der Waals attractions between organofluorine compounds and electron deficient hydrogens are well established,[66] thus these interactions 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. Model **A** shows that the *Si*-face of the oxocarbenium ion is blocked by a triisopropylphenyl group of the catalyst and the *Re*-face is open for nucleophilic attack. Thus, the (*S*)-stereoisomer is predicted to be the major product, and this result is consistent with the experimental result. Additionally, extending the length of the alkenyl group results in a steric clash with a triisopropylpenyl group

of the catalyst, while the alkoxy group of the substrate can be lengthened without impediment. This explains whey the stereoselectivity is insensitive to alkoxy group changes, but it diminishes when the alkenyl group of the substrate is extended.

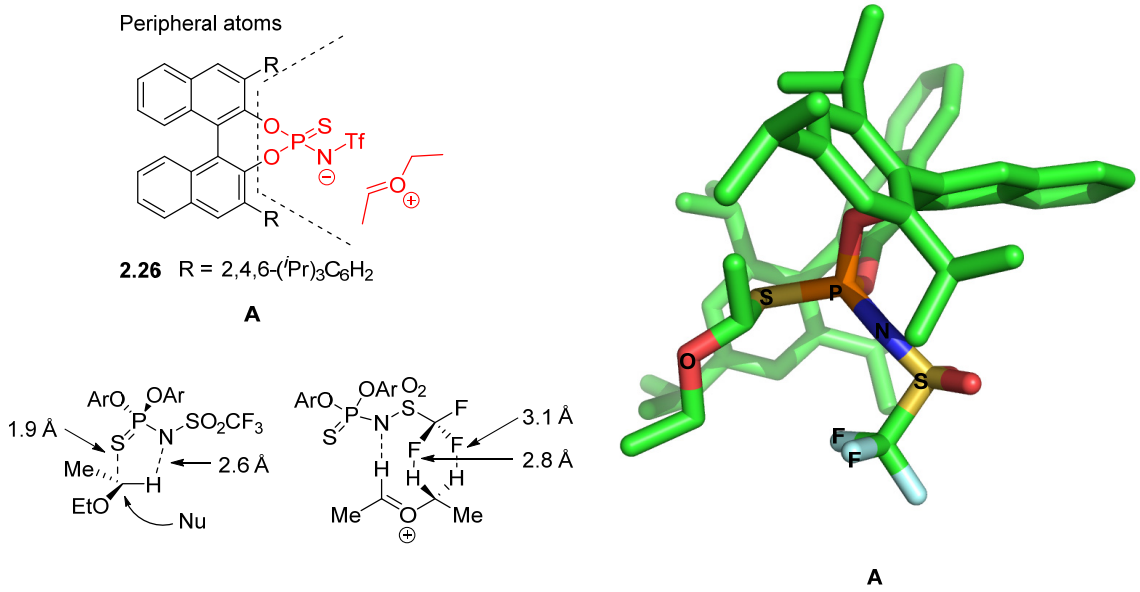


Figure 2.1 Modeled structure of the ion pair from the reaction of ethyl vinyl ether with catalyst 2.26. Hydrogens have been removed for clarity. Green = carbon, red = oxygen, gold = sulfur, light blue = fluorine, darkblue = nitrogen.

The substantial diastereoselectivity differences in the matched and mismatched outcomes from the α-methylbenzyl vinyl ether substrates were not expected based on the minimal diastereocontrol that was obtained through the HCl-mediated pathway. This result can be rationalized by model **A**. Overlapping methylbenzyl vinyl ethers with ethyl vinyl ether in model **A**, the models for the ion pair between the conjugate base of **2.26** and the oxocarbenium ions of methylbenzyl vinyl ethers were obtained. The methyl group of (*R*)-substrate **2.78** fills a pocket of the catalyst (Figure 2.2, model **B**) leaving an open *Re*-face for the nucleophilic addition. In

contrast, the trajectory of the nucleophile towards the *Re*-face of (*S*)-substrate **2.16** was blocked by the methyl group (Figure 2.2, model **C**). Rotation of the methyl group to avoid the interaction with the nucleophile will lead to a steric clash between the phenyl group and the catalyst. 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.

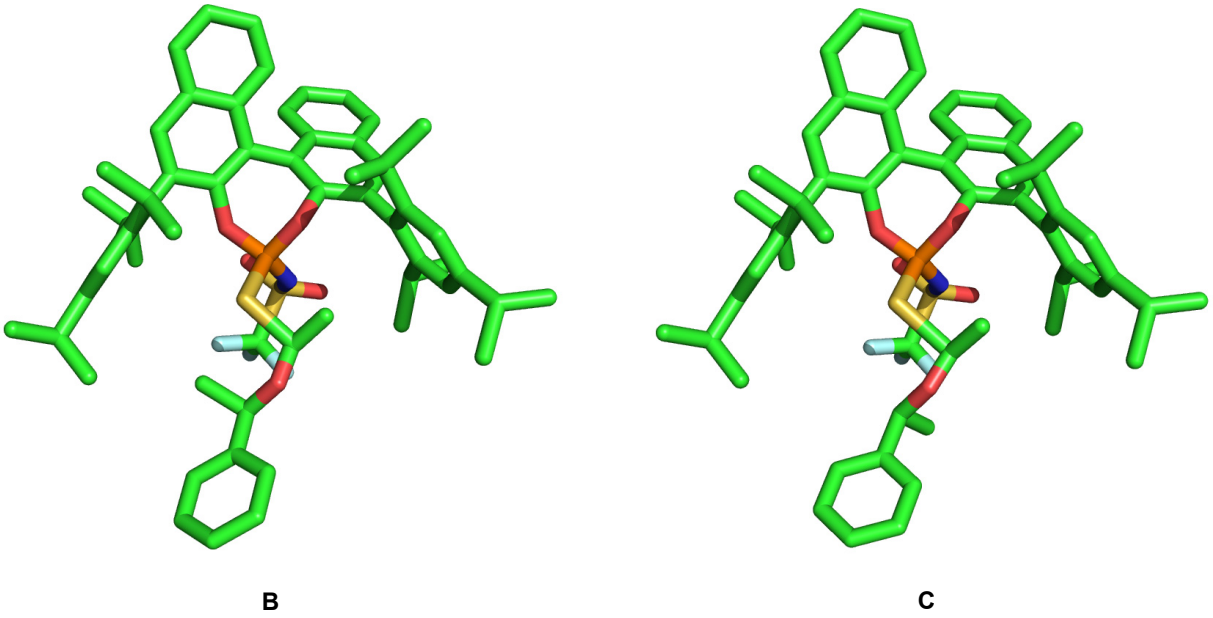


Figure 2.2 Modeled structures of the ion pairs derived from 2.79 (B) and 2.16 (C) with catalyst 2.26. Hydrogens have been removed for clarity.

2.4 CONCLUSIONS

We have shown that cyanohydrin alkyl ethers could be effectively synthesized by acid mediated hydrocyanation of vinyl ethers. Racemic product formation proceeds smoothly through

conversion of vinyl ethers to chloroethers followed by Brønsted acid-mediated oxocarbenium ion formation and subsequent TMSCN addition. The enantiomerically enriched products can be achieved by asymmetric cyanation of the oxocarbenium ion, which was generated by protonation of vinyl ethers with a chiral Brønsted acid. Only a catalytic amount of the chiral Brønsted acid is needed for the transformation, and the silylated catalyst can be regenerated by using phenol as the proton source. In addition to vinyl ethers, acetals can also be used as substrates for oxocarbenium ion formations and the similar level of enantiocontrol was achieved. These processes represent the first examples of chiral Brønsted acid mediated asymmetric addition of silylated nucleophiles with vinyl ethers and acetals. Computational studies revealed the unique ion pair interaction between the conjugate base of the chiral Brønsted acid and the oxocarbenium ion, which well explained many experimental observations. The protocol that was developed for the asymmetric addition of TMSCN to oxocarbenium ions, as well as the model for novel chiral ion pair interactions will benefit further studies towards asymmetric addition of other silylated nucleophiles to oxocarbenium ions.

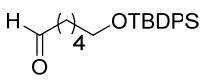
APPENDIX A

STEREOSELECTIVE SYNTHESIS OF SPIROOXINDOLE AMIDES THROUGH NITRILE HYDROZIRCONATION (SUPPORTING INFORMAITON)

General Information Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz, a Bruker Avance 600 spectrometer at 600 MHz if specified. The chemical shifts 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, DMSO = 2.50, for ^{13}C NMR: $CDCl_3$ = 77.23, DMSO = 39.52. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublet; td = triplet of doublets; dtd = doublet of triplet of doublets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. 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. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride was distilled under N_2 from CaH_2. The Schwartz

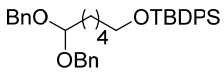
reagent was prepared following the reported procedure,[67] and stored under argon atmosphere in freezer. All acid chlorides were freshly distilled prior to use. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under argon with magnetic stirring unless otherwise noted. All the reactions that use the Schwartz reagent were performed under argon unless otherwise specified. All products in this manuscript are racemic mixtures but are drawn and named as single enantiomers to indicate their relative stereochemistry.

3-((*tert*-Butyldiphenylsilyl)oxy)propanal (1.32)



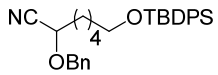
To a solution of 1,6-hexanediol (18.92g, 160 mmol) in dry THF (160 mL) at 0°C was added NaH (60% dispersion in mineral oil, 6.4g, 160 mmol), and the suspension was stirred at rt for 1 h. TBDPSCl (40.9 mL, 160 mmol) was added dropwise over 10 min at 0°C, and then the solution was stirred at rt overnight followed by quenching the reaction with H_2O. Extract the solution with ether (2x), and then dry the combined organic layer over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash chromatography (10% to 45% EtOAc in Hexane) to give mono-TBDPS protected 1,6-hexanediol as colorless oil (30.747g, 54%). To a solution of oxalyl chloride (5.56 mL, 64.7 mmol) in anhydrous CH_2Cl_2 (250 mL) under argon atmosphere at –78 °C was added DMSO (6.12 mL, 86.2 mmol) in CH_2Cl_2 (35 mL) dropwise. The resulting solution was stirred at that temperature for 30 min, and then the above alcohol (15.37 g, 43.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise. 30 min later, triethylamine (30.2 mL, 215.5 mmol) was added to the solution. The solution was allowed to stir for another 30 min, before warming up to room temperature. The solution was then stirred at room temperature for 30 min, and quenched with brine. The mixture was extracted with CH_2Cl_2 (2x), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (10% EtOAc in hexane) to give **1.32** as colorless oil (27.04g, 88%).^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.67-7.66 (m, 4H), 7.43-7.37 (m, 6H), 3.67 (t, 2H, J = 6.0 Hz), 2.41 (t, 2H, J = 7.0 Hz), 1.65-1.52 (m, 4H), 1.44-1.41 (m, 2H), 1.05 (s, 9H).

(3,3-bis(Benzyloxy)propoxy)(*tert*-butyl)diphenylsilane (1.33)



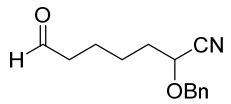
To a solution of **1.32** (1.00 g, 2.82 mmol) in CH_2Cl_2 (5.6 mL) was added BnOH (730 μL, 7.05 mmol), *p*-toluenesulfonic acid monohydrate (PTSA•H_2O) (6 mg, 0.03 mmol) and Na_2SO_4 (800.0 mg, 5.6 mmol). After stirring at room temperature overnight, the solution was diluted with CH_2Cl_2 and then filtered. Wash the filtrate with brine, and dry over Na_2SO_4. After removing the solvent at reduced pressure, the residue was purified by flash chromatography (3% to 5% EtOAc in Hexane) to give **1.33** as colorless oil (854 mg, 55%, 85% brsm), and recover aldehyde **1.32** (345 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 4H, *J* = 6.5 Hz), 7.44-7.36 (m, 11H), 7.32-7.29 (m, 5H), 4.75 (t, 1H, *J* = 5.5 Hz), 4.67 (d, 2H, *J* = 12.0 Hz), 4.58 (d, 2H, *J* = 12.0 Hz), 3.66 (t, 2H, *J* = 6.0 Hz), 1.78-1.75 (m, 2H), 1.59-1.57 (m, 2H), 1.41-1.39 (m, 4H), 1.07 (s, 9H).

2-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)butanenitrile (1.34)



To a solution of **1.33** (851 mg, 1.54 mmol) in CH_2Cl_2 (1.6 mL) was added TMSCN (307 μL, 2.30 mmol) and $BiBr_3$ (67 mg, 0.15 mmol) at room temperature. The solution was stirred for 3 h, and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (2x), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated at reduced pressure, and purified by flash chromatography (5% to 10% EtOAc in hexane) to give **1.34** as a colorless oil (663 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 4H, *J* = 7.0 Hz), 7.43-7.36 (m, 11H), 4.85 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 11.5 Hz), 4.12 (t, 1H, *J* = 6.5 Hz), 3.65 (t, 2H, *J* = 6.5 Hz), 1.87-1.82 (m, 2H), 1.57-1.55 (m, 2H), 1.49-1.44 (m, 2H), 1.39-1.05 (m, 2H), 1.07 (s, 9H).

2-(Benzyloxy)-7-oxoheptanenitrile (1.35)

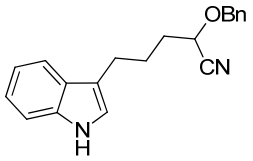


To a solution of **1.34** (6.05 g, 12.8 mmol) in THF (125 mL) was added TBAF (1 M solution in THF, 15.4 mL) dropwise at room temperature. The solution was stirred for 1.5 h, and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography to give the desired alcohol as colorless oil (2.85 g, 95%). To a solution of oxalyl chloride (1.57 mL, 18.3 mmol) in anhydrous CH_2Cl_2 (70 mL) under argon atmosphere at –78 °C was added DMSO (1.73 mL, 24.4 mmol) in CH_2Cl_2 (10 mL) dropwise. The resulting solution was stirred at that temperature for 30 min, and then the above alcohol (2.85 g, 12.2 mmol) in CH_2Cl_2 (15 mL) was added dropwise. After 30 min, triethylamine (8.5 mL, 61 mmol) was added to the solution. The solution was allowed to stir for another 30 min, before warming to room temperature. The solution was then stirred at room temperature for 30 min, and quenched with brine. The mixture was extracted with CH_2Cl_2 (2x), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (15% to 30% EtOAc in hexane) to give **1.35** as light yellow oil (2.356g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 1.6 Hz), 7.41-7.33 (m, 5H), 4.86 (d, 1H, *J* = 11.6 Hz), 4.53 (d, 1H, *J* = 11.6 Hz), 4.17 (t, 1H, *J* = 6.4 Hz), 2.47 (dt, 2H, *J* = 1.6, 6.8 Hz), 1.93-1.87 (m, 2H), 1.70-1.61 (m, 2H), 1.58-1.53 (m, 2H).

2-(Benzyloxy)-5-(1*H*-indol-3-yl)pentanenitrile (1.36)

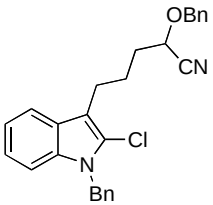
To a solution of **1.35** (925 mg, 4.00 mmol) in HOAc (20 mL) was added phenylhydrazine (397 μL, 4.00 mmol). The solution was stirred at 105 °C overnight under N_2. The solution was cooled

to rt and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with saturated $NaHCO_3$ solution (2x). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (10% to 25% EtOAc in hexane) to give **1.36** as a slightly red oil (746 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.38-7.35 (m, 6H), 7.21 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 6.98 (s, 1H), 4.84 (d, 1H, *J* = 11.5 Hz), 4.50 (d, 1H, *J* = 11.5 Hz), 4.17 (t, 1H, *J* = 6.0 Hz), 2.81 (t, 2H, *J* = 6.5 Hz), 1.96-1.94 (m, 4H).



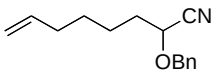
5-(1-Benzyl-2-chloro-1*H*-indol-3-yl)-2-(benzyloxy)pentanenitrile (1.37)

To a solution of **1.36** (660 mg, 2.17 mmol) in CCl_4 (15 mL) was added *N*-chlorosuccinimide (NCS) (292 mg, 2.19 mmol) at room temperature. The solution was stirred for 2 h, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (8% to 20% EtOAc in hexane) to give 2-chloroindole as slightly yellow oil (556 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.50 (d, 1H, *J* = 8.0 Hz), 7.40-7.36 (m, 5H), 7.30 (d, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 7.16 (t, 1H, *J* = 7.5 Hz), 4.85 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 11.5 Hz), 4.18 (t, 1H, *J* = 6.0 Hz), 2.80 (t, 2H, *J* = 6.5 Hz), 1.95-1.92 (m, 4H). To a solution of the above 2-chloroindole (204 mg, 0.6 mmol) in DMF (6.5 mL) was added NaH (60% in mineral oil, 31 mg, 0.78 mmol) at 0 °C under argon. After that, the ice bath was removed, and the suspension was allowed to stir at rt for another 30 min followed by addition of BnBr (107 μL, 0.9 mmol). The solution was stirred for 5 h, and then carefully quenched by ice water. The mixture was extracted with EtOAc (2x), and the combined organic layer was washed with brine.



The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (10% to 25% EtOAc in hexane) to give **1.37** as slightly yellow oil (177 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J* = 7.5 Hz), 7.37-7.33 (m, 4H), 7.29-7.22 (m, 5H), 7.17 (t, 1H, *J* = 7.5 Hz), 7.12 (t, 1H, *J* = 7.0 Hz), 7.08 (d, 2H, *J* = 7.0 Hz), 5.38 (s, 2H), 4.83 (d, 1H, *J* = 11.5 Hz), 4.49 (d, 1H, *J* = 11.5 Hz), 4.17 (t, 1H, *J* = 5.5 Hz), 2.84 (app s, 2H), 1.95-1.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.1, 135.6, 128.9, 128.8, 128.6, 128.4, 127.6, 126.9, 126.5, 123.6, 122.3, 120.2, 118.4, 118.4, 111.0, 109.9, 72.4, 67.6, 47.0, 33.0, 25.0, 23.5; IR (neat) 3060, 3031, 2928, 2865, 1456, 1334, 1102, 739, 697 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{25}N_2OCl$ $[M]^+$ 428.1655, found 428.1647.

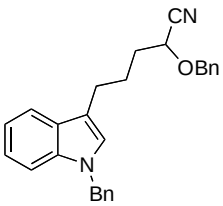
2-(Benzyloxy)oct-7-enenitrile (1.40)



To a solution of 6-heptenal (**1.39**) (168 mg, 1.50 mmol) and BnOTMS (649 mg, 3.60 mmol) in CH_2Cl_2 (2.5 mL) was added $BiBr_3$ (34 mg, 0.075 mmol). The suspension was stirred overnight, and then TMSCN (394 μL, 3.1 mmol) and $BiBr_3$ (32 mg, 0.075 mmol) were added. The suspension was stirred for another 4 h and then quenched with saturated $NaHCO_3$. The mixture was extracted with EtOAc (3x), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (5% to 10% EtOAc in hexane) to give **1.40** as a colorless oil (277 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H), 5.79 (ddt, 1H, *J* = 6.6, 10.2, 17.1 Hz), 5.02 (d, 1H, *J* = 17.1 Hz), 4.97 (d, 1H, *J* = 9.6 Hz), 4.86 (d, 1H, *J* = 11.7 Hz), 4.53 (d, 1H, *J* = 11.7 Hz), 4.16 (t, 1H, *J* = 6.6 Hz), 2.05 (q, 2H, *J* = 6.6 Hz), 1.91-1.85 (m, 2H), 1.54-1.48 (m, 2H), 1.46-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.1, 128.8, 128.6,

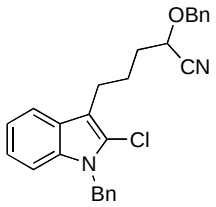
128.3, 118.4, 115.0, 72.3, 67.7, 33.5, 33.4, 28.3, 24.3; IR (neat) 3068, 3033, 2930, 2864, 1640, 1456, 1100, 913, 740 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{19}NO$ $[M]^+$ 229.1467, found 229.1460.

5-(1-Benzyl-1*H*-indol-3-yl)-2-(benzyloxy)pentanenitrile (1.41)



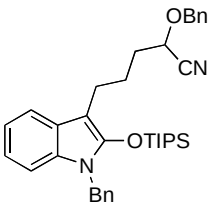
To a solution of **1.40** (1.90 g, 8.3 mmol) in CH_2Cl_2 (84 mL) was treated with O_3 at −78 °C until the blue color persisted. PPh_3 (8.7 g, 33.1 mmol) was then added and the solution was allowed to warm to rt. After stirring for 1 hour, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (5% to 40% EtOAc in hexane) to give the aldehyde **1.35** as colorless oil (1.48 g, 78%), and all spectral data for this compound were identical to those from TBDPS deprotection of **1.34** followed by Swern oxidation. To a solution of the aldehyde (400 mg, 1.73 mmol) in HOAc (9 mL), was added 1-benzyl-1-phenylhydrazine hydrochloride (406 mg, 1.73 mmol). The solution was stirred at 100 °C for 1 h under N_2. The solution was cooled to rt and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with saturated $NaHCO_3$ solution (2x). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (5% to 10% EtOAc in hexane) to give **1.41** as a slightly red oil (610 mg, 89%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, 1H, *J* = 7.5 Hz), 7.37-7.25 (m, 9H), 7.18 (t, 1H, *J* = 7.2 Hz), 7.13-7.08 (m, 3H), 6.89 (s, 1H), 5.28 (s, 2H), 4.83 (d, 1H, *J* = 11.4 Hz), 4.49 (d, 1H, *J* = 11.4 Hz), 4.17 (t, 1H, *J* = 6.0 Hz), 2.80 (t, 2H, *J* = 6.3 Hz), 1.95-1.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 136.8, 136.1, 128.9, 128.8, 128.5, 128.4, 128.1, 127.7, 126.9, 125.7, 121.9, 119.1, 118.5, 114.8, 109.8, 72.3, 67.7, 50.0, 33.3, 25.4, 24.5; IR (neat) 3030, 2926, 2866, 1466, 1454, 1331, 1101, 739 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{26}N_2O$ $[M]^+$ 394.2045, found 394.2043.

5-(1-Benzyl-2-chloro-1*H*-indol-3-yl)-2-(benzyloxy)pentanenitrile (1.37) through modified sequence



To a solution of **1.41** (250 mg, 0.63 mmol) in CH_2Cl_2 (5.3 mL) was added *N*-chlorosuccinimide (NCS) (85 mg, 0.63 mmol) at room temperature. The solution was stirred for 1 h, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc in hexane) to give **1.37** as slightly yellow oil (217 mg, 80%). All spectral data were consistent with products that had previously been prepared.

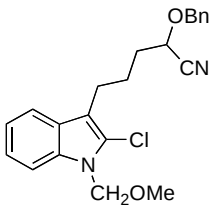
5-(1-Benzyl-2-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)-2-(benzyloxy)pentanenitrile (1.42)



To a solution of **1.41** (135 mg, 0.34 mmol) in premixed solvent (4:1; AcOH:concentrated HCl; v:v) was added DMSO (468 μL, 6.8 mmol) dropwise at room temperature. The solution was stirred for 1.5 h, and then poured into saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (2x), and the combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography (10% to 30% EtOAc in hexane) to give the oxindole as yellow oil (84 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 11H), 7.18 (t, 1H, J = 7.6 Hz), 7.03 (t, 1H, J = 7.6 Hz), 6.74 (d, 1H, J = 7.6 Hz), 4.97 (d, 1H, J = 12.0 Hz), 4.86 (dd, 1H, J = 4.0, 11.6 Hz), 4.83 (d, 1H, J = 12.0 Hz), 4.51 (dd, 1H, J = 3.6, 11.6 Hz), 4.13 (dt, 1H, J = 3.2, 6.4 Hz), 3.54 (t, 1H, J = 6.0 Hz), 2.04-1.92 (m, 2H), 1.91-1.90 (m, 2H), 1.60-1.56 (m, 2H). To a solution of the oxindole (838 mg, 2.04 mmol) in CH_2Cl_2 (17 mL) under argon at 0 °C were added Et_3N (566 μL, 4.08 mmol) and TIPSOTf (553 μL, 2.04 mmol). The ice bath was removed and the solution was stirred at rt for 1.5 h. The reaction was quenched with saturated $NaHCO_3$

solution. The aqueous layer was extracted with CH_2Cl_2 (2x), and then the combined organic layer was dried over Na_2SO_4. The mixture was filtered and concentrated, then the resulting residue was purified by flash chromatography (4% to 10% EtOAc in hexane with 0.5% Et_3N) to give **1.42** as a slightly yellow oil (1.09 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, *J* = 7.2 Hz), 7.38-7.32 (m, 5H), 7.24 (app d, 2H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 7.2 Hz), 7.06-6.98 (m, 5H), 5.22 (s, 2H), 4.80 (d, 1H, *J* = 11.6 Hz), 4.46 (d, 1H, *J* = 11.6 Hz), 4.15 (t, 1H, *J* = 6.0 Hz), 2.73 (t, 2H, *J* = 7.0 Hz), 1.99-1.85 (m, 4H), 1.27 (septet, 3H, *J* = 7.6 Hz), 1.08 (d, 18H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 137.8, 136.1, 131.6, 128.6, 128.6, 128.2, 127.4, 127.1, 126.3, 119.7, 119.4, 118.4, 117.5, 109.2, 93.1, 72.2, 67.8, 45.1, 33.5, 25.5, 23.2, 17.9, 13.8; IR (neat) 3061, 3031, 2946, 2867, 1620, 1578, 1469, 1414, 1339, 1008, 769, 737 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{47}N_2O_2Si$ $[M+H]^+$ 567.3407, found 567.3363.

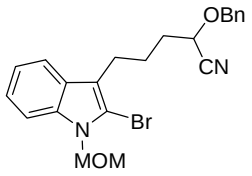
2-(Benzyloxy)-5-(2-chloro-1-(methoxymethyl)-1*H*-indol-3-yl)pentanenitrile (1.43)



To a solution of **1.36** (610 mg, 2.00 mmol) in CCl_4 (15 mL) was added *N*-chlorosuccinimide (NCS) (268 mg, 2.00 mmol) at room temperature under argon atmosphere. The solution was stirred for 2 hours, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (8% to 20% EtOAc in hexane) to give the desired 2-chloroindole as slightly yellow oil (519 mg). To a solution of the above 2-chloroindole (519 mg, 1.53 mmol) in THF (16 mL) was added NaH (60% in mineral oil, 80 mg, 2.0 mmol) at 0 °C under argon. After that, the ice bath was removed, and the suspension was allowed to stir at rt for another 30 min followed by addition of MOMCl (175 μL, 2.3 mmol). The solution was stirred for 1 hour, and then quenched by ice water. The mixture was extracted with EtOAc (2x), and the combined organic

layer was washed with brine. The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (15% to 30% EtOAc in hexane) to give **1.43** as slightly yellow oil (481 mg, 63% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.36-7.35 (m, 5H), 7.24 (t, 1H, *J* = 7.2 Hz), 7.17 (t, 1H, *J* = 7.2 Hz), 5.52 (s, 2H), 4.83 (d, 1H, *J* = 11.4 Hz), 4.50 (d, 1H, *J* = 11.4 Hz), 4.17 (t, 1H, *J* = 6.0 Hz), 3.29 (s, 3H), 2.80 (t, 2H, *J* = 6.0 Hz), 1.92-1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 135.9, 128.7, 128.5, 128.3, 127.1, 123.3, 122.7, 120.8, 118.4, 118.3, 112.0, 109.9, 73.9, 72.3, 67.5, 56.1, 32.9, 24.8, 23.3; IR (neat) 3032, 2935, 2360, 2340, 1455, 1322, 1099, 742, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{23}N_2O_2Cl$ $[M]^+$ 382.1448, found 382.1449.

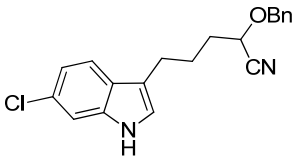
2-(Benzyloxy)-5-(2-bromo-1-(methoxymethyl)-1H-indol-3-yl)pentanenitrile (1.44)



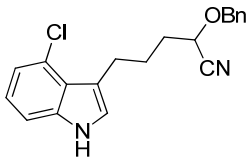
To a solution of **1.36** (400 mg, 1.30 mmol) in CH_2Cl_2 (21 mL) was added *N*-bromosuccinimide (NBS) (234 mg, 1.30 mmol) in small portions at room temperature under argon atmosphere. The solution was stirred for 35 min, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (100% toluene) to give the desired 2-bromoindole as slightly yellow oil. To a solution of the above 2-bromoindole (375 mg, 0.98 mmol) in THF (10 mL) was added NaH (60% in mineral oil, 51 mg, 1.27 mmol) at 0 °C under argon. After that, the ice bath was removed, and the suspension was allowed to stir at rt for another 30 min followed by addition of MOMCl (108 μL, 1.43 mmol). The solution was stirred for 30 min, and then quenched by ice water. The mixture was extracted with EtOAc (2x), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, concentrated at reduced pressure, and purified by flash chromatography (15% to 30% EtOAc in hexane) to give **1.44** as

slightly yellow oil (395 mg, 71% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 1H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.37-7.33 (m, 5H), 7.24 (t, 1H, *J* = 7.5 Hz), 7.15 (t, 1H, *J* = 7.5 Hz), 5.54 (s, 2H), 4.83 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.17 (t, 1H, *J* = 6.0 Hz), 3.29 (s, 3H), 2.80 (t, 2H, *J* = 7.5 Hz), 1.93-1.90 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.2, 128.9, 128.6, 128.5, 127.9, 122.8, 120.8, 118.5, 118.4, 115.7, 112.9, 110.2, 75.4, 72.5, 67.7, 56.2, 33.1, 25.0, 24.6; IR (neat) 3031, 2932, 2867, 2360, 1592, 1453, 1318, 1093, 911, 741, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{23}N_2O_2Br$ (M^+) 426.0943, found 426.0946.

2-(Benzyloxy)-5-(6-chloro-1*H*-indol-3-yl)pentanenitrile (1.46)

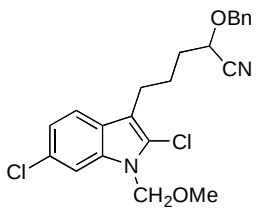


To a solution of **1.35** (1.35 g, 5.84 mmol) in HOAc (35 mL) was added 3-chlorophenylhydrazine hydrochloride (1.57, 8.8 mmol). The solution was refluxed for 3 hours under N_2. The solution was cooled to rt and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with saturated $NaHCO_3$ solution (2x). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (10% to 25% EtOAc in hexane) to give the desired product as a slightly yellow oil (898 mg, 45%, **1.46**:**1.47** = 5:4) with **1.46** as the faster eluting product. ^{1}H NMR (300 MHz, $CDCl_3$) for **1.46** δ 7.94 (s, 1H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.38-7.31 (m, 6H), 7.08 (dd, 1H, *J* = 1.8, 8.4 Hz), 6.96 (app d, 1H, *J* = 2.4 Hz), 4.84 (d, 1 H, *J* = 11.4 Hz), 4.50 (d, 1H, *J* = 11.7 Hz), 4.16 (t, 1H, *J* = 6.0 Hz), 2.77 (t, 2H, *J* = 6.3 Hz), 1.98-1.87 (m, 4H). ^{1}H NMR (300 MHz, $CDCl_3$) for **1.47** δ 8.02 (s,



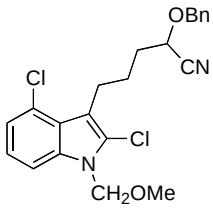
1H), 7.36 (app s, 5H), 7.25-7.24 (m, 1H), 7.07 (app d, 2H, *J* = 5.1 Hz), 6.98 (app d, 1H, *J* = 3.6 Hz), 4.85 (d, 1 H, *J* = 11.4 Hz), 4.52 (d, 1H, *J* = 11.1 Hz), 4.18 (t, 1H, *J* = 6.0 Hz), 3.02 (t, 2H, *J* = 6.6 Hz), 2.06-1.90 (m, 4H).

2-(Benzyloxy)-5-(2,4-dichloro-1-(methoxymethyl)-1*H*-indol-3-yl)pentanenitrile (1.48)



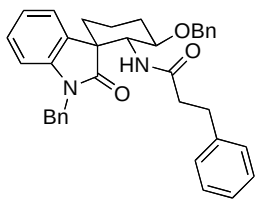
Follow the same procedure for the preparation of **1.43**, and use **1.46** instead of **1.36** give **1.48** as slightly yellow oil (258 mg, 47% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.32 (m, 6H), 7.14 (app d, 1H, *J* = 1.5 Hz), 7.13 (app s, 1H), 5.51 (s, 2H), 4.84 (d, 1H, *J* = 11.7 Hz), 4.52 (d, 1H, *J* = 11.4 Hz), 4.20 (t, 1H, *J* = 6.3 Hz), 3.29 (s, 3H), 3.02 (t, 2H, *J* = 6.9 Hz), 2.03-1.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.1, 128.7, 128.4, 128.3, 125.6, 125.0, 123.9, 123.1, 122.0, 118.4, 112.4, 108.7, 74.2, 72.3, 67.7, 56.1, 32.9, 26.5, 24.0; IR (neat) 3062, 3031, 2939, 2867, 1457, 1430, 1323, 1187, 1102, 914, 739 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{23}N_2O_2Cl_2$ $[M]^+$ 416.1058, found 416.1054.

2-(Benzyloxy)-5-(2,6-dichloro-1-(methoxymethyl)-1*H*-indol-3-yl)pentanenitrile (1.49)

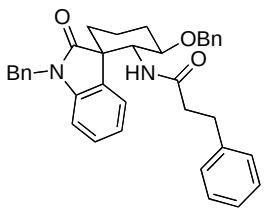


Follow the same procedure for the preparation of **1.43**, and use **1.47** instead of **1.36** give **1.49** as slightly yellow oil (190 mg, 43% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 1H, *J* = 1.5 Hz), 7.40-7.35 (m, 6H), 7.13 (dd, 1H, *J* = 1.5, 8.4 Hz), 5.47 (s, 2H), 4.83 (d, 1H, *J* = 11.7 Hz), 4.50 (d, 1H, *J* = 11.4 Hz), 4.16 (t, 1H, *J* = 5.7 Hz), 3.29 (s, 3H), 2.77 (t, 2H, *J* = 6.3 Hz), 1.89-1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 136.0, 128.8, 128.6, 128.4, 125.7, 123.9, 121.6, 119.4, 118.3, 112.2, 110.2, 74.1, 72.4, 67.5, 56.2, 33.0, 24.8, 23.4; IR (neat) 3064, 3032, 2935, 2868, 1465, 1394, 1334, 1099, 913, 807, 741 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O_2Cl_2Na$ $[M+Na]^+$ 439.0956, found 439.0959.

***N*-((1*S*,2*R*,3*R*)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.52)**



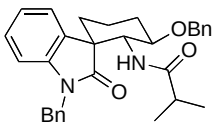
To a solution of **1.37** (98 mg, 0.23 mmol) in CH_2Cl_2 (2.3 mL) was added $Cp_2Zr(H)Cl$ (74 mg, 0.29 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (43 μL, 0.29 mmol) was added and the mixture was stirred overnight. The mixture was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (103 mg, 83%, 7.3:1). The faster eluting product **1.52** was the major diastereomer and was isolated as a white solid **(**mp 138.7 °C-140.8 °C**)**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.39 (d, 1H, *J* = 7.5 Hz), 7.32-7.06 (m, 15H), 6.90 (d, 2H, *J* = 7.8 Hz), 6.70 (d, 1H, *J* = 7.2 Hz), 4.92 (d, 1H, *J* = 15.6 Hz), 4.86 (d, 1H, *J* = 9.9 Hz), 4.79 (d, 1H, *J* = 15.6 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.62 (t, 1H, *J* = 9.9 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.24 (dt, 1H, *J* = 4.5, 10.8 Hz), 2.58-2.37 (m, 3H), 2.19 (qt, 1H, *J* = 3.9, 13.2 Hz), 2.07-1.97 (m, 1H), 1.91-1.78 (m, 2H), 1.74-1.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 171.9, 142.0, 141.1, 139.2, 136.3, 131.8, 129.0, 128.5, 128.5, 128.2, 127.9, 127.7, 127.4, 126.1, 123.9, 123.3, 108.6, 76.3, 90.9, 55.4, 54.4, 43.6, 38.1, 35.2, 31.3, 31.0, 19.0; IR (neat) 3323, 3060, 3029, 2931, 2864, 1699, 1655, 1611, 1543, 1492, 1366, 1027, 1100, 1028, 741 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{36}N_2O_3Na$ $[M+Na]^+$ 567.2624, found 567.2648.



The slower eluting product was repurified by preparative TLC (10% EtOAc in CH_2Cl_2) to give minor diastereomer **1.53** as a white solid (mp 171.2 °C-175.0 °C): ^{1}H NMR (400 MHz, DMSO) δ 7.60 (d, 1H, *J* = 7.2 Hz), 7.29-7.19 (m, 13H), 7.14-7.11 (m, 1H), 7.08-7.03 (m, 3H), 6.88 (d, 1H, *J* = 9.6 Hz), 6.86 (d,

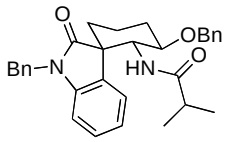
1H, *J* = 7.6 Hz), 4.97 (d, 1H, *J* = 15.6 Hz), 4.68 (d, 1H, *J* = 15.6 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 4.47 (t, 1H, *J* = 10.4 Hz), 4.45 (d, 1H, *J* = 11.6 Hz), 3.84 (dt, 1H, *J* = 4.4, 10.8 Hz), 2.55 (t, 2H, *J* = 8.4 Hz), 2.36 (app d, 1H, *J* = 9.6 Hz), 2.21-2.13 (m, 1H), 2.06-1.98 (m, 1H), 1.94-1.85 (m, 2H), 1.81-1.77 (m, 1H), 1.50-1.42 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 177.2, 171.2, 142.9, 141.4, 139.3, 136.6, 130.0, 128.4, 128.2, 128.0, 127.9, 127.2, 125.9, 125.7, 121.9, 108.9, 77.4, 70.6, 54.8, 54.0, 42.6, 36.9, 33.7, 31.1, 30.9, 19.7; IR (neat) 3272, 3061, 3028, 2925, 2854, 1712, 1650, 1609, 1546, 1464, 1363 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{36}N_2O_3Na$ $[M+Na]^+$ 567.2624, found 567.2604.

_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)isobutyramide (1.55)



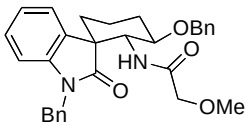
To a solution of **1.37** (104 mg, 0.24 mmol) in CH_2Cl_2 (2.4 mL) was added $Cp_2Zr(H)Cl$ (78 mg, 0.30 mmol). The reaction mixture was stirred for 15 min. Isobutyryl chloride (31 μL, 0.30 mmol) was added and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (100 mg, 87%, 3.6:1). The faster eluting product was the major diastereomer **1.55** and was isolated as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, 1H, *J* = 7.5 Hz), 7.30-7.27 (m, 10H), 7.13 (t, 1H, *J* = 7.5 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 6.70 (d, 1H, *J* = 7.5 Hz), 4.98 (d, 1H, *J* = 15.5 Hz), 4.83 (d, 1H, *J* = 9.5 Hz), 4.78 (d, 1H, *J* = 15.5 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 4.60 (t, 1H, *J* = 10.0 Hz), 4.49 (t, 1H, *J* = 12.0 Hz), 4.28 (dt, 1H, *J* = 4.0, 10.5 Hz), 2.40 (d, 1H, *J* = 11.5 Hz), 2.23 (app q, 1H, *J* = 13.5 Hz), 1.90 (t, 1H, *J* = 13.5 Hz),

1.81 (app d, 1H, *J* = 13.5 Hz), 1.74-1.70 (m, 2H), 1.63-1.57 (m, 1H), 0.78 (d, 3H, *J* = 6.5 Hz), 0.42 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 176.5, 142.0, 139.2, 136.4, 131.6, 129.0, 128.4, 128.0, 127.7, 127.6, 127.5, 124.0, 123.3, 108.4, 76.2, 71.0, 55.0, 54.6, 43.7, 35.9, 34.9, 31.2, 19.6, 19.1, 18.9; IR (neat) 3337, 3060, 3030, 2867, 1694, 1611, 1491, 1466, 1365, 1208, 1173, 1098, 740, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{31}H_{34}N_2O_3$ $[M]^+$ 482.2569, found 482.2569.



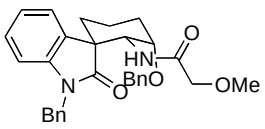
The slower eluting product was minor diastereomer **1.64** and was isolated as a white solid (mp 158.1 °C-161.2 °C): ^{1}H NMR (300 MHz, DMSO) δ 7.59 (d, 1H, *J* = 7.5 Hz), 7.27-7.22 (m, 11H), 7.07 (t, 1H, *J* = 7.2 Hz), 6.84 (t, 1H, *J* = 7.5 Hz), 6.70 (d, 1H, *J* = 9.6 Hz), 4.86 (d, 1H, *J* = 15.9 Hz), 4.78 (d, 1H, *J* = 15.9 Hz), 4.62 (d, 1H, *J* = 11.4 Hz), 4.47 (d, 1H, *J* = 11.4 Hz), 4.40 (t, 1H, *J* = 10.2 Hz), 3.86 (dt, 1H, *J* = 4.5, 10.5 Hz), 2.37 (app d, 1H, *J* = 14.1 Hz), 2.12 (quintet, 1H, *J* = 6.9 Hz), 1.90-1.76 (m, 3H), 1.47-1.41 (m, 2H), 0.74 (d, 3H, *J* = 6.6 Hz), 0.70 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO) δ 177.2, 175.6, 143.0, 139.2, 136.4, 130.0, 128.5, 127.9, 127.2, 127.0, 126.9, 125.9, 121.8, 108.8, 77.1, 70.5, 54.4, 54.1, 42.7, 33.8, 33.5, 31.0, 19.8, 19.6, 18.9; IR (neat) 3345, 3060, 3032, 2934, 2870, 1712, 1678, 1609, 1489, 1463, 1364, 1209, 1105, 743, 697 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{31}H_{34}N_2O_3$ $[M]^+$ 482.2569, found 482.2579.

_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-2-methoxyacetamide (1.56)



To a solution of **1.37** (118 mg, 0.28 mmol) in CH_2Cl_2 (2.8 mL) was added $Cp_2Zr(H)Cl$ (89 mg, 0.34 mmol). The reaction mixture was stirred for 15 min. Methoxyacetyl chloride (31 μL, 0.34 mmol) was added and the mixture was stirred

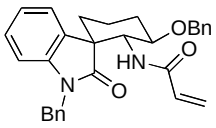
overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (61 mg, 46%, 9.1:1). The faster eluting product was major diastereomer **1.56** and was isolated as a white solid (mp 121.0 °C-123.8 °C): ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 (d, 1H, *J* = 7.2 Hz), 7.34-7.25 (m, 10H), 7.11 (t, 1H, *J* = 7.6 Hz), 7.05 (d, 1H, *J* = 7.2 Hz), 6.61 (d, 1H, *J* = 7.2 Hz), 6.22 (d, 1H, *J* = 10.4 Hz), 4.99 (d, 1H, *J* = 15.6 Hz), 4.83 (d, 1H, *J* = 15.6 Hz), 4.72 (d, 1H, *J* = 11.6 Hz), 4.64 (t, 1H, *J* = 10.4 Hz), 4.52 (d, 1H, *J* = 11.6 Hz), 4.31 (dt, 1H, *J* = 4.4, 10.8 Hz), 3.61 (d, 1H, *J* = 15.2 Hz), 3.49 (d, 1H, *J* = 15.2 Hz), 3.07 (s, 3H), 2.42 (d, 1H, *J* = 12.8 Hz), 2.23 (qt, 1H, *J* = 3.6, 13.6 Hz), 1.91 (app dt, 1H, *J* = 4.0, 14.0 Hz), 1.84-1.80 (m, 1H), 1.71 (app dquint, 1H, *J* = 3.2, 13.6 Hz), 1.60-1.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 169.5, 141.9, 139.0, 135.8, 131.6, 128.8, 128.2, 128.0, 127.6, 127.3, 127.2, 127.1, 123.5, 123.1, 108.6, 71.6, 71.2, 58.8, 54.8, 54.2, 43.6, 35.5, 30.9, 18.8; IR (neat) 3063, 3032, 2931, 1695, 1613, 1519, 1366, 1204, 1110, 1027, 741 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_4Na$ $[M+Na]^+$ 507.2260, found 507.2279.



The slower eluting *syn*-diastereomer was repurified by preparative TLC (10% EtOAc in CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 7.2 Hz), 7.33-7.24 (m, 10H), 7.16 (t, 1H, *J* = 8.0 Hz), 7.07 (d, 1H, *J* = 10.4 Hz), 6.97 (t, 1H, *J* = 7.6 Hz), 6.70 (d, 1H, *J* = 7.6 Hz), 5.01 (d, 1H, *J* = 15.6 Hz), 4.80 (d, 1H, *J* = 15.6 Hz), 4.60 (dd, 1H, *J* = 4.0, 10.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.05 (quintet, 1H, *J* = 4.0 Hz), 3.89 (d, 1H, *J* = 14.8 Hz), 3.82 (d, 1H, *J* = 14.8 Hz), 2.18-2.12 (m, 1H), 2.10-2.03 (m, 1H), 1.99-1.95 (m, 1H), 1.91-1.81 (m, 2H), 1.66-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 169.9, 142.6, 138.4, 136.1, 132.3, 129.0, 128.5, 128.1, 127.8, 127.7, 127.4, 124.9, 122.1,

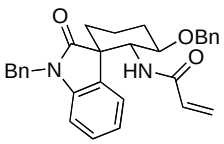
109.5, 73.6, 72.2, 70.5, 59.5, 51.3, 49.4, 44.1, 29.9, 27.3, 19.0; IR (neat) 3061, 2938, 1711, 1681, 1610, 1465, 1360, 1110, 1026, 918 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_4Na$ $[M+Na]^+$ 507.2260, found 507.2239.

_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)acrylamide (1.57)



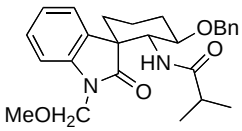
To a solution of **1.37** (109 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was added $Cp_2Zr(H)Cl$ (82 mg, 0.32 mmol). The reaction mixture was stirred for 15 min. Acryloyl chloride (26 μL, 0.32 mmol) was added and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (62 mg, 53%, 20:1). The faster eluting product was major diastereomer **1.57** and was isolated as a white solid **(**mp 157.0 °C-161.2 °C): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, *J* = 7.6 Hz), 7.32-7.21 (m, 10H), 7.13 (dt, 1H, *J* = 3.6, 7.6 Hz), 7.07 (dt, 1H, *J* = 3.6, 7.6 Hz), 6.67 (d, 1H, *J* = 7.6 Hz), 5.95 (dd, 1H, *J* = 3.6, 16.8 Hz), 5.60 (dd, 1H, *J* = 10.4, 17.2 Hz), 5.43 (dd, 1H, *J* = 3.6, 7.6 Hz), 4.99-4.95 (m, 2H), 4.80 (d, 1H, *J* = 15.6 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.67 (t, 1H, *J* = 10.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.25 (dt, 1H, *J* = 4.8, 10.4 Hz), 2.41 (app d, 1H, *J* = 3.2, 12.8 Hz), 2.18 (qt, 1H, *J* = 4.0, 13.6 Hz), 1.90 (dt, 1H, *J* = 4.0, 14.0 Hz), 1.81 (app d, 1H, *J* = 12.8 Hz), 1.72 (app dt, 1H, *J* = 3.2, 13.6 Hz), 1.65-1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 165.4, 142.0, 139.1, 136.2, 131.8, 130.8, 129.1, 128.5, 128.2, 127.9, 127.8, 127.2, 126.4, 123.8, 123.5, 108.7, 76.6, 91.0, 55.4, 54.4, 43.5, 35.4,

30.9, 19.1; IR (neat) 3289, 3060, 3031, 2930, 2863, 1701, 1611, 1540, 1492, 1365, 1206, 986, 739 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{30}N_2O_3Na$ $[M+Na]^+$ 489.2154, found 489.2176.



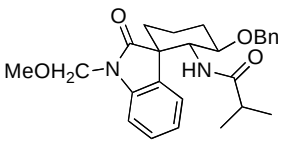
The slower eluting product was repurified by preparative TLC (10 % EtOAc in CH_2Cl_2) to give minor diastereomer **1.66** as a white solid (mp 222.6 °C-226.9 °C): ^1H NMR (400 MHz, DMSO) δ 7.63 (d, 1H, *J* = 7.6 Hz), 7.32-7.17 (m, 12H), 7.07 (d, 1H, *J* = 7.2 Hz), 6.78 (d, 1H, *J* = 8.0 Hz), 6.14 (dd, 1H, *J* = 9.6, 16.8 Hz), 6.01 (dd, 1H, *J* = 2.0, 16.8 Hz), 5.52 (dd, 1H, *J* = 2.4, 10.0 Hz), 5.08 (d, 1H, *J* = 16.0 Hz), 4.63-4.55 (m, 3H), 4.46 (d, 1H, *J* = 11.6 Hz), 3.90 (dt, 1H, *J* = 4.0, 10.8 Hz), 2.38 (app d, 1H, *J* = 11.6 Hz), 1.92-1.78 (m, 3H), 1.52-1.43 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 177.1, 164.6, 142.8, 139.2, 136.2, 132.0, 129.9, 128.5, 128.0, 128.0, 127.2, 127.1, 126.8, 126.0, 125.0, 121.9, 109.0, 77.3, 70.7, 55.0, 54.0, 42.5, 33.8, 31.1, 30.7, 19.7; IR (neat) 3245, 3061, 2934, 2856, 1709, 1658, 1610, 1551, 1465, 1361, 734 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{30}N_2O_3Na$ $[M+Na]^+$ 489.2154, found 489.2141.

_N_-((1_S_,2_R_,3_R_)-3-(Benzyloxy)-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)isobutyramide (1.58)



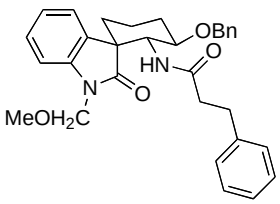
To a solution of **1.43** (99 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $Cp_2Zr(H)Cl$ (84 mg, 0.32 mmol). The reaction mixture was stirred for 15 min. Isobutyryl chloride (34 μL, 0.32 mmol) was added and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give the product as two diastereomers (59 mg, 51%, 11.8:1). The faster eluting isomer was major

product **1.58**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, 1H, *J* = 7.5 Hz), 7.37-7.30 (m, 5H), 7.22 (t, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 6.92 (d, 1H, *J* = 7.5 Hz), 5.12 (d, 1H, *J* = 10.5 Hz), 5.09 (d, 1H, *J* = 11.0 Hz), 4.90 (d, 1H, *J* = 10.0 Hz), 4.69 (d, 1H, *J* = 11.5 Hz), 4.60 (t, 1H, *J* = 10.0 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.22 (dt, 1H, *J* = 4.5, 10.5 Hz), 3.34 (s, 3H), 2.39 (d, 1H, *J* = 9.5 Hz), 2.15 (q, 1H, *J* = 13.5 Hz), 1.93-1.86 (m, 2H), 1.79 (app d, 1H, *J* = 14.0 Hz), 1.70 (app d, 1H, *J* = 14.0 Hz), 1.63-1.60 (m, 1H), 0.84 (d, 3H, *J* = 6.5 Hz), 0.60 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 176.7, 141.3, 139.2, 131.2, 128.6, 128.5, 127.7, 127.6, 124.2, 123.8, 108.9, 76.3, 71.4, 71.1, 56.6, 55.2, 54.9, 36.0, 35.3, 31.1, 19.9, 19.1, 19.0; IR (neat) 3333, 3059, 2931, 2869, 1710, 1667, 1523, 1490, 1467, 1361, 1089, 744 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$ 436.2362, found 436.2366.

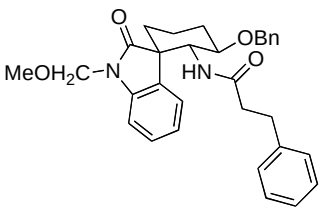


Slower eluting minor product: ^{1}H NMR (500 MHz, DMSO) δ 7.60 (d, 1H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.5 Hz), 7.29-7.22 (m, 5H), 7.13 (t, 1H, *J* = 7.5 Hz), 7.07 (d, 1H, *J* = 8.0 Hz), 6.68 (d, 1H, *J* = 10.0 Hz), 4.99 (s, 2H), 4.60 (d, 1H, *J* = 11.5 Hz), 4.46 (d, 1H, *J* = 11.5 Hz), 4.33 (t, 1H, *J* = 10.0 Hz), 3.83 (dt, 1H, *J* = 5.0, 11.5 Hz), 3.14 (s, 3H), 2.35 (app d, 1H, *J* = 6.0 Hz), 2.09 (quintet, 1H, *J* = 6.5 Hz), 1.87-1.81 (m, 2H), 1.74 (m, 1H), 1.45-1.41 (m, 2H), 0.74 (d, 3H, *J* = 6.5 Hz), 0.67 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO) δ 177.8, 175.6, 142.3, 139.2, 129.6, 128.0, 127.9, 127.2, 127.1, 125.9, 122.3, 109.1, 77.0, 70.7, 70.5, 55.6, 54.5, 54.3, 33.6, 33.5, 31.0, 19.7, 19.6, 18.9; IR (neat) 3322, 3060, 2936, 2871, 1723, 1659, 1527, 1465, 1358, 1241, 1095, 915, 742, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$ 436.2362, found 436.2360.

***N*-((1*S*,2*R*,3*R*)-3-(Benzyloxy)-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.59)**



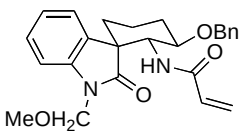
To a solution of **1.43** (83 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $Cp_2Zr(H)Cl$ (81 mg, 0.31 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (46 μL, 0.31 mmol) was added and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (83 mg, 64%, 15:1). The faster eluting product was major diastereomer **1.59** and was isolated as a white solid (mp 163.0 °C-164.8 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 7.41 (d, 1H, *J* = 7.2 Hz), 7.31-7.23 (m, 6H), 7.20-7.12 (m, 4H), 6.95-6.91 (m, 3H), 5.09 (d, 1H, *J* = 10.5 Hz), 5.04 (d, 1H, *J* = 10.5 Hz), 4.94 (d, 1H, *J* = 9.6 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.62 (t, 1H, *J* = 9.9 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.19 (dt, 1H, *J* = 4.5, 10.2 Hz), 3.27 (s, 3H), 2.55 (app dt, 1H, *J* = 3.0, 9.5 Hz), 2.38 (app d, 1H, *J* = 17.4 Hz), 2.19-2.08 (m, 1H), 2.06-1.93 (m, 2H), 1.87 (dd, 1H, *J* = 3.6, 12.9 Hz), 1.80-1.75 (m, 1H), 1.72-1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 172.0, 141.1, 139.1, 131.3, 128.6, 128.5, 128.3, 128.2, 127.7, 127.6, 124.0, 123.8, 109.0, 76.4, 71.2, 71.0, 56.3, 55.2, 55.0, 38.4, 35.7, 31.5, 30.9, 19.0; IR (neat) 3251, 3058, 2932, 2865, 1709, 1645, 1551,1492, 1362, 1088, 743 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{34}N_2O_4Na$ $[M+Na]^+$ 521.2416, found 521.2448.



The slower eluting product was isolated as a white solid (mp 193.1 °C-196.8 °C): ^{1}H NMR (300 MHz, DMSO) δ 7.62 (d, 1H, *J* = 7.5 Hz), 7.35 (d, 1H, *J* = 7.2 Hz), 7.27-7.07 (m, 10H), 7.02 (app d, 1H, *J* = 6.9 Hz), 6.92 (d, 1H, *J* = 9.9 Hz), 4.99 (s, 2H), 4.62 (d, 1H, *J* = 11.7 Hz), 4.45 (d, 1H, *J* = 11.7

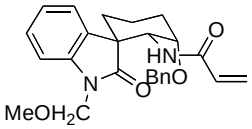
Hz), 4.40 (t, 1H, *J* = 10.2 Hz), 3.83 (dt, 1H, *J* = 3.9, 10.5 Hz), 3.10 (s, 3H), 2.36 (app d, 1H, *J* = 12.3 Hz), 2.11-1.99 (m, 2H), 1.87-1.75 (m, 4H), 1.47-1.40 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 177.7, 171.2, 142.2, 141.4, 139.3, 129.6, 128.1, 128.0, 127.9, 127.2, 125.9, 125.7, 122.3, 109.3, 77.2, 70.7, 70.6, 55.3, 54.8, 54.3, 36.9, 33.7, 31.1, 31.0, 19.6; IR (neat) 3260, 3061, 3025, 2935, 2855, 1723, 1648, 1549, 1465, 1357, 1082, 741 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{34}N_2O_4Na$ $[M+Na]^+$ 521.2416, found 521.2440.

_N_-((1_S_,2_R_,3_R_)-3-(Benzyloxy)-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)acrylamide (1.60)



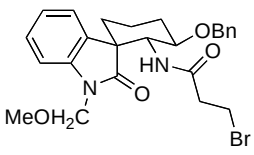
To a solution of **1.43** (98 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $Cp_2Zr(H)Cl$ (79 mg, 0.31 mmol). The reaction mixture was stirred for 15 min at room temperature. Acryloyl chloride (26 μL, 0.32 mmol) was added and the mixture was stirred for 30 min. $Sc(OTf)_3$ (13 mg, 0.026 mmol) was added and the solution was stirred for another 1.5 hours. The reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (3x), and the combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give product as two diastereomers (49 mg, 46%, 8.2:1). The faster eluting product was major diastereomer **1.60** and was isolated as a white solid (mp 126.5 °C-128.8 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 7.41 (d, 1H, *J* = 7.2 Hz), 7.31-7.20 (m, 6H), 7.12 (t, 1H, *J* = 7.2 Hz), 6.93 (d, 1H, *J* = 7.8 Hz), 6.01 (d, 1H, *J* = 16.8 Hz), 5.70 (dd, 1H, *J* = 10.5, 17.1 Hz), 5.45 (d, 1H, *J* = 10.2 Hz), 5.10 (app s, 2H), 5.04 (d, 1H, *J* = 9.9 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.67 (t, 1H, *J* = 10.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.22 (dt, 1H, *J* = 4.8, 10.8 Hz), 3.30 (s, 3H), 2.40 (app d, 1H, *J* = 12.3 Hz), 2.11 (dt, 1H, *J* = 3.6, 13.2 Hz),

1.89 (dt, 1H, *J* = 3.6, 13.8 Hz), 1.81-1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 165.5, 141.0, 139.0, 131.0, 130.8, 128.5, 128.4, 127.8, 127.6, 126.4, 123.9, 109.1, 76.6, 71.3, 71.0, 56.4, 55.2, 54.9, 35.9, 30.9, 19.0; IR (neat) 3291, 3059, 2934, 2864, 1711, 1664, 1612, 1540, 1362, 1230, 1089, 914, 744 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_2O_4Na$ $[M+Na]^+$ 443.1947, found 443.1939.



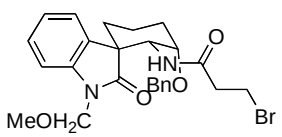
The slower eluting product was repurified by chromatography (10% to 25% EtOAc in CH_2Cl_2) to provide the minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 7.5 Hz), 7.32-7.26 (m, 6H), 7.06 (app t, 2H, *J* = 7.5 Hz), 6.18 (dd, 1H, *J* = 1.8, 17.1 Hz), 6.08 (d, 1H, *J* = 9.9 Hz), 6.03 (d, 1H, *J* = 9.9 Hz), 5.60 (dd, 1H, *J* = 1.8, 10.2 Hz), 5.15 (d, 1H, *J* = 11.1 Hz), 5.10 (d, 1H, *J* = 11.1 Hz), 4.64 (dd, 1H, *J* = 4.2, 9.9 Hz), 4.55 (d, 1H, *J* = 11.7 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.02 (quintet, 1H, *J* = 4.2 Hz), 3.32 (s, 3H), 2.17-2.11 (m, 1H), 2.06-1.96 (m, 1H), 1.91-1.82 (m, 3H), 1.69-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 165.6, 141.6, 138.3, 132.0, 131.1, 128.6, 128.6, 128.1, 127.8, 126.6, 124.7, 122.8, 109.8, 73.7, 71.6, 70.7, 56.4, 51.7, 50.2, 30.6, 27.4, 18.6; IR (neat) 3323, 3059, 2939, 1723, 1660, 1610, 1539, 1466, 1349, 1240, 1086, 744 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_2O_4Na$ $[M+Na]^+$ 443.1947, found 443.1955.

_N_-((1_S_,2_R_,3_R_)-3-(Benzyloxy)-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-bromopropanamide (1.61)



To a solution of **1.43** (113 mg, 0.30 mmol) in CH_2Cl_2 (3.0 mL) was added $Cp_2Zr(H)Cl$ (95 mg, 0.37 mmol). The reaction mixture was stirred for 15 min. 3-Bromopropionyl chloride (37 μL, 0.37 mmol) was added and the mixture was stirred for 15 min, followed by addition of $Sc(OTf)_3$ (15 mg, 0.03 mmol). The

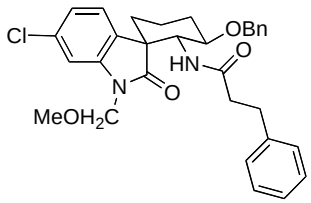
solution was stirred for another 30 min, then was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (3x), and the combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure the residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give the product as two diastereomers (80 mg, 54%, 6.7:1). The faster eluting product was the major diastereomer **1.61** and was isolated as a white solid (mp 169.8 °C-174.5 °C): ^{1}H NMR (300 MHz, $CDCl_3$) 7.33 (d, 1H, J = 7.5 Hz), 7.30-7.21 (m, 6H), 7.18 (d, 1H, J = 7.5 Hz), 7.08 (d, 1H, J = 7.5 Hz), 6.89 (d, 1H, J = 7.5 Hz), 5.06 (s, 2H), 5.01 (d, 1H, J = 9.9 Hz), 4.67 (d, 1H, J = 12.0 Hz), 4.54 (t, 1H, J = 9.9 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.18 (dt, 1H, J = 4.5, 10.5 Hz), 3.29 (s, 3H), 3.19 (t, 2H, J = 7.5 Hz), 2.43-2.33 (m, 2H), 2.21-2.13 (m, 1H), 2.11-2.02 (m, 1H), 1.85 (dt, 1H, J = 3.6, 14.1 Hz), 1.77-1.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 169.1, 141.0, 138.9, 130.9, 128.4, 128.2, 127.6, 127.5, 123.7, 123.6, 109.0, 76.2, 71.1, 71.0, 56.3, 55.1, 54.7, 39.8, 35.5, 30.8, 26.9, 18.8; IR (neat) 3251, 3063, 2932, 1703, 1647, 1558, 1490, 1361, 1115, 1089 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_2O_4BrNa$ $[M+Na]^+$ 523.1208, found 523.1210.



The slower eluting product was repurified by preparative TLC (20% EtOAc in CH_2Cl_2) to provide the minor diastereomer **1.61'**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 1H, J = 7.2 Hz), 7.33-7.30 (m, 6H), 7.06 (app t, 2H, J = 7.5 Hz), 6.00 (d, 1H, J = 9.6 Hz), 5.15 (d, 1H, J = 10.8 Hz), 5.09 (d, 1H, J = 10.8 Hz), 4.55 (dd, 1H, J = 4.2, 10.2 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.46 (d, 1H, J = 11.7 Hz), 4.00 (quintet, 1H, J = 4.2 Hz), 3.50 (t, 2H, J = 6.9 Hz), 3.33 (s, 3H), 2.76-2.59 (m, 2H), 2.18-2.12 (m, 1H), 2.03-1.81 (m, 4H), 1.68-1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 169.8, 141.6, 138.3, 131.8, 128.7, 128.6, 128.2, 127.9, 124.8, 122.8, 109.8, 73.6, 71.6, 70.7, 56.5, 51.6, 50.3, 39.9, 30.6, 27.5, 27.3, 18.5; IR (neat) 3340, 3059, 2939, 2876, 1720, 1655, 1611, 1541, 1466,

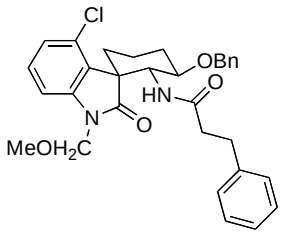
1349, 1245, 1086, 914, 746 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_2O_4BrNa$ $[M+Na]^+$ 523.1208, found 523.1165.

_N_-((1_S_,2_R_,3_R_)-3-(Benzyloxy)-6'-chloro-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.62)



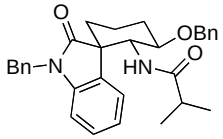
To a solution of **1.48** (95 mg, 0.23 mmol) in CH_2Cl_2 (2.3 mL) was added $Cp_2Zr(H)Cl$ (73 mg, 0.28 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (42 μL, 0.28 mmol) was added and the mixture was stirred overnight at rt. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc) to give **1.62** as single diastereomer (61 mg, 50%, white solid, mp 193.0 °C-195.2 °C). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.11 (m, 10H), 6.95-6.93 (m, 3H), 5.01 (s, 2H), 4.95 (d, 1H, *J* = 9.6 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 9.9 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.17 (dt, 1H, *J* = 4.5, 10.5 Hz), 3.24 (s, 3H), 2.66-2.60 (m, 2H), 2.37 (app d, 1H, *J* = 9.9 Hz), 2.23-1.99 (m, 3H), 1.85 (dt, 1H, *J* = 3.9, 13.8 Hz), 1.77-1.62 (m, 2H), 1.54-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 172.1, 142.1, 140.9, 139.0, 134.0, 129.6, 128.6, 128.5, 127.7, 126.2, 125.1, 123.6, 109.9, 76.2, 71.2, 70.9, 56.3, 54.9, 54.8, 38.2, 35.6, 31.3, 30.8, 18.9; IR (neat) 3249, 3057, 3028, 2935, 2869, 2362, 1707, 1647, 1610, 1549, 1448, 1094 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{33}N_2O_4ClNa$ $[M+Na]^+$ 555.2027, found 555.2028.

***N*-((1*S*,2*R*,3*R*)-3-(Benzyloxy)-4'-chloro-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.63)**



To a solution of **1.49** (82 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added $Cp_2Zr(H)Cl$ (63 mg, 0.25 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (37 μL, 0.25 mmol) was added and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in hexane to 100% EtOAc, then 5% EtOAc in CH_2Cl_2) to give product **1.63** as single diastereomer (38 mg, 36%, white solid, mp 159.8 °C-161.6 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.08 (m, 10H), 6.98 (app d, 2H, *J* = 7.8 Hz), 6.84 (d, 1H, *J* = 7.5 Hz), 5.21 (t, 1H, *J* = 9.6 Hz), 5.06 (d, 1H, *J* = 10.8 Hz), 5.00 (d, 1H, *J* = 10.8 Hz), 4.88 (d, 1H, *J* = 9.3 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.15 (dt, 1H, *J* = 4.5, 11.1 Hz), 3.26 (s, 3H), 2.72-2.60 (m, 3H), 2.37 (app d, 1H, *J* = 12.6 Hz), 2.21-1.97 (m, 3H), 1.75-1.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 171.8, 142.8, 141.0, 138.9, 131.8, 129.5, 128.4, 128.3, 128.1, 127.6, 127.5, 126.6, 126.0, 125.3, 107.6, 76.5, 71.1, 70.7, 56.3, 56.2, 52.1, 38.2, 31.3, 30.4, 29.8, 18.5; IR (neat) 3295, 3061, 3028, 2935, 2864, 1715, 1657, 1607, 1456, 1361, 1092 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{33}N_2O_4ClNa$ $[M+Na]^+$ 555.2027, found 555.2047.

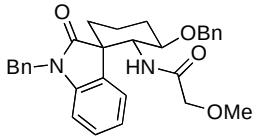
***N*-((1*R*,2*R*,3*R*)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)isobutyramide (1.64)**



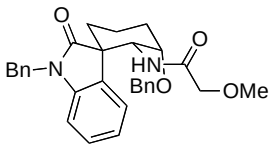
To a solution of **1.42** (120 mg, 0.21 mmol) in CH_2Cl_2 (2.1 mL) was added $Cp_2Zr(H)Cl$ (68 mg, 0.26 mmol). The reaction mixture was stirred for 15 min.

Isobutyryl chloride (27 μL, 0.26 mmol) was added and the mixture was stirred for 20 min, followed by addition of $Sc(OTf)_3$ (103 mg, 0.21 mmol). After stirring overnight the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in CH_2Cl_2 to 100%) to give the product as four diastereomers (69 mg, 68%). The fastest eluting product was a mixture of two inseparable diastereomers (12 mg, 1:0.72). By comparison to the available spectrum, they are **1.55** and its epimer at the benzyloxy position. The second fastest eluting product was repurified by preparative TLC (35% EtOAc in hexane) to yield the minor diastereomer (10 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, *J* = 7.6 Hz), 7.38-7.21 (m, 10H), 7.15 (t, 1H, *J* = 7.6 Hz), 6.88 (t, 1H, *J* = 7.6 Hz), 6.71 (d, 1H, *J* = 7.6 Hz), 5.23 (d, 1H, *J* = 9.6 Hz), 4.96 (d, 1H, *J* = 15.6 Hz), 4.79 (d, 1H, *J* = 15.6 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 4.70 (dd, 1H, *J* = 3.6, 10.0 Hz), 4.37 (d, 1H, *J* = 11.2 Hz), 3.97-3.95 (m, 1H), 2.29 (app dt, 1H, *J* = 3.2, 14.4 Hz), 2.10-1.95 (m, 3H), 1.77-1.63 (m, 3H), 0.85 (d, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 175.7, 143.5, 138.4, 136.3, 130.0, 128.9, 128.7, 128.4, 128.1, 128.0, 128.0, 127.7, 127.6, 122.0, 108.9, 76.0, 72.0, 53.3, 51.4, 44.2, 35.5, 34.3, 27.6, 19.5, 19.4, 15.9; IR (neat) 3349, 3060, 3031, 2929, 2869, 1715, 1678, 1609, 1494, 1466, 1364, 1207, 1089, 751 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{31}H_{34}N_2O_3$ $[M]^+$ 482.2569, found 482.2567. The third eluting product **1.64** was the major diastereomer (47 mg, 46%). All spectral data for this compound were identical to the minor product from the cyclization of **1.37**.

***N*-((1*R*,2*R*,3*R*)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-2-methoxyacetamide (1.65)**



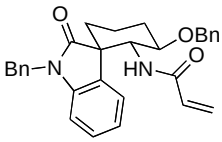
To a solution of **1.42** (114 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added $Cp_2Zr(H)Cl$ (65 mg, 0.25 mmol). The reaction mixture was stirred for 15 min. Methoxyacetyl chloride (23 μL, 0.25 mmol) was added and the mixture was stirred for 20 min, followed by addition of $Sc(OTf)_3$ (96 mg, 0.20 mmol). After stirring overnight, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined



organic layer was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in CH_2Cl_2 to 100% EtOAc) to give product as four diastereomers (65 mg, 67%). The fastest eluting product was minor diastereomer **1.56** (3 mg). The second fastest eluting product was the minor diastereomer (2 mg) which was the epimer of **1.56** at the benzyloxyl position as shown before. The last eluting fraction was a mixture of two inseparable diastereomers (60 mg, 1:2.1), which were repurified by preparative TLC (10% EtOAc in CH_2Cl_2) for characterization purpose, and give the third eluting product as the minor diastereomer, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, 1H, *J* = 7.2 Hz), 7.34-7.23 (m, 10H), 7.15 (t, 1H, *J* = 7.8 Hz), 6.87 (t, 1H, *J* = 7.2 Hz), 6.72 (d, 1H, *J* = 7.8 Hz), 6.45 (d, 1H, *J* = 10.2 Hz), 5.10 (d, 1H, *J* = 15.0 Hz), 4.75 (dd, 1H, *J* = 3.6, 10.2 Hz), 4.73 (d, 1H, *J* = 11.4 Hz), 4.42 (d, 1H, *J* = 11.4 Hz), 3.94 (m, 1H), 3.68 (d, 1H, *J* = 15.0 Hz), 3.49 (d, 1H, *J* = 15.0 Hz), 2.28 (app d, 1H, *J* = 13.8 Hz), 2.10-1.98 (m, 2H), 1.74 (app t, 1H, *J* = 13.2 Hz), 1.68 (app d, 2H, *J* = 11.9 Hz). The slow eluting product was the major diastereomer **1.65** and was isolated as a white solid (mp 164.2 °C-165.8 °C): ^{1}H NMR (600 MHz, DMSO) δ 7.61 (d, 1H, *J* = 7.8 Hz), 7.31-7.28 (m, 5H), 7.26-7.22 (m, 6H), 7.06 (d, 1H, *J* = 7.2 Hz), 6.92 (d, 1H, *J* = 7.8 Hz), 6.11 (d, 1H, *J* = 10.2 Hz),

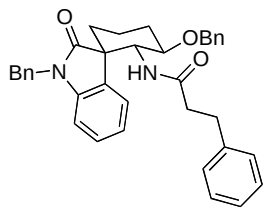
5.00 (d, 1H, *J* = 15.6 Hz), 4.70 (d, 1H, *J* = 15.6 Hz), 4.64 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.43 (t, 1H, *J* = 10.8 Hz), 3.86 (dt, 1H, *J* = 4.2, 10.8 Hz), 3.57 (d, 1H, *J* = 15.6 Hz), 3.43 (d, 1H, *J* = 15.6 Hz), 2.81 (s, 3H), 2.41 (app d, 1H, *J* = 15.6 Hz), 1.93-1.78 (m, 3H), 1.51-1.44 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 177.1, 168.2, 142.9, 139.1, 136.4, 129.4, 128.5, 128.4, 128.0, 127.3, 127.2, 127.1, 125.6, 122.0, 109.2, 77.2, 71.1, 70.2, 58.2, 54.1, 53.8, 42.7, 33.5, 30.7, 19.6; IR (neat) 3271, 3060, 3031, 2929, 2853, 1714, 1608, 1521, 1464, 1364, 1113, 1070, 737 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_4Na$ $[M+Na]^+$ 507.2260, found 507.2251.

_N_-((1_R_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)acrylamide (1.66)

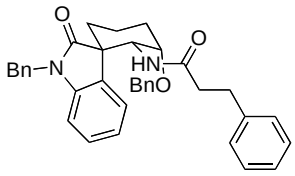


To a solution of **1.42** (105 mg, 0.19 mmol) in CH_2Cl_2 (1.9 mL) was added $Cp_2Zr(H)Cl$ (60 mg, 0.23 mmol). The reaction mixture was stirred for 15 min. Acryloyl chloride (19 μL, 0.23 mmol) was added and the mixture was stirred for 20 min, followed by addition of $Sc(OTf)_3$ (93 mg, 0.20 mmol). After stirring overnight, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in CH_2Cl_2 to 100% EtOAc) to give product as four diastereomers (33 mg, 38%). The fastest eluting product **1.57** was the minor diastereomer (1 mg). The second fastest eluting product was a mixture of two inseparable diastereomers (6 mg, 1:1). The third eluting product **1.66** was the major diastereomer (26 mg). This product showed identical spectral data to the minor product from the cyclization of **1.37**.

***N*-((1*R*,2*R*,3*R*)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.53)**



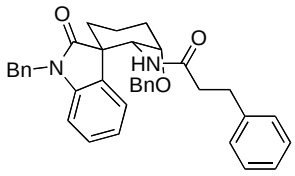
To a solution of **1.42** (113 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added $Cp_2Zr(H)Cl$ (65 mg, 0.25 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (37 μL, 0.25 mmol) was added and the mixture was stirred for 20 min, followed by addition of $Sc(OTf)_3$ (98 mg, 0.20 mmol). After stirring overnight, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (5% to 100% EtOAc in CH_2Cl_2) to give product as four diastereomers (72 mg, 66%). The fastest eluting product was a mixture of two inseparable diastereomers (13 mg, 1:1). By comparing with the available spectra, they are **1.52** and its epimer at the benzyloxy position.



The second fastest eluting product was *syn*-diastereomer **1.67** (8 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, *J* = 7.6 Hz), 7.35-7.12 (m, 14H), 7.03 (app d, 2H, *J* = 7.2 Hz), 6.87 (dt, 1H, *J* = 3.6, 7.6 Hz), 6.71 (d, 1H, *J* = 8.0 Hz), 5.16 (d, 1H, *J* = 9.6 Hz), 5.05 (d, 1H, *J* = 15.6 Hz), 4.75 (dd, 1H, *J* = 4.0, 10.0 Hz), 4.68 (d, 1H, *J* = 15.6 Hz), 4.64 (d, 1H, *J* = 11.2 Hz), 4.20 (d, 1H, *J* = 11.2 Hz), 3.87-3.86 (m, 1H), 2.75-2.61 (m, 2H), 2.25 (d, 1H, *J* = 14.0 Hz), 2.20-2.12 (m, 1H), 2.09-1.93 (m, 3H), 1.76-1.72 (m, 1H), 1.66-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 171.0, 143.4, 141.0, 138.4, 136.3, 129.9, 128.9, 128.7, 128.6, 128.4, 128.4, 128.2, 128.0, 128.0, 127.8, 127.6, 126.3, 122.1, 109.0, 76.2, 71.9, 53.2, 51.7, 44.2, 38.0, 34.3, 31.3, 27.7, 15.9; IR (neat) 3087, 3029, 2936, 2866, 1711, 1670, 1609, 1494, 1466, 1364, 733 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{36}N_2O_3Na$ $[M+Na]^+$ 567.2624, found 567.2598. The third eluting product **1.53** was the

major diastereomer (51 mg). All spectral data for this compound were identical to those from the minor isomer of the cyclization of **1.37**.

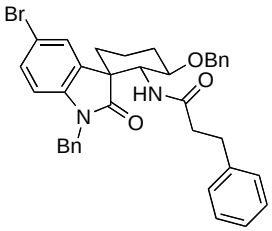
_N_-((1_R_,2_R_,3_S_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.67)



To a solution of **1.42** (62 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) was added $Cp_2Zr(H)Cl$ (35 mg, 0.13 mmol). The reaction mixture was stirred for 15 min. Hydrocinnamoyl chloride (19 μL, 0.13 mmol) was added and the mixture was stirred for 20 min, followed by addition of $ZnCl_2$ (0.13 mL 1M solution). After stirring overnight at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in CH_2Cl_2 to 100% EtOAc) to give the product as four diastereomers (33 mg, 66%). The fastest eluting product was a mixture of two inseparable diastereomers (2 mg, 3:2). By comparing with the available spectrum, they are **1.52** and its epimer at the benzyloxy position. The second fastest eluting material was the major product **1.67** (22 mg) and the third eluting product **1.53** as the minor product (11 mg). All spectral data were consistent with products that had previously been prepared.

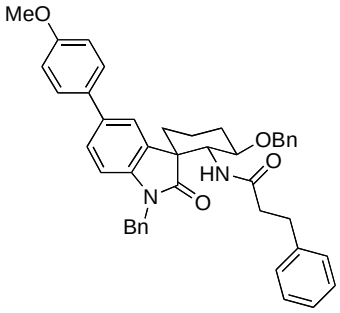
_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-5'-bromo-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.68)

To a solution of **1.52** (250 mg, 0.46 mmol) in CH_2Cl_2 (9 mL) was added NBS (82 mg, 0.46 mmol) at 0 °C. The ice bath was removed and the mixture was stirred for 1h. NBS (20 mg, 0.11



mmol) was added and after 40 min the solvent was removed under reduced pressure. The residue was purified by chromatography (15% to 30% EtOAc in hexane) to give the aryl bromide as white solid **1.68** (170 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.51 (d, 1H, *J* = 2.0 Hz), 7.34-7.11 (m, 14H), 6.92 (app d, 2H, *J* = 6.8 Hz), 6.53 (d, 1H, *J* = 8.0 Hz), 4.89 (d, 1H, *J* = 16.0 Hz), 4.88 (d, 1H, *J* = 8.4 Hz), 4.74 (d, 1H, *J* = 15.6 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.57 (t, 1H, *J* = 10.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.21 (dt, 1H, *J* = 4.4, 10.4 Hz), 2.56 (t, 2H, *J* = 8.0 Hz), 2.39 (app dd, 1H, *J* = 3.2, 12.8 Hz), 2.16 (qt, 1H, *J* = 3.6, 9.2 Hz), 2.06 (quint, 1H, *J* = 7.6 Hz), 1.93 (app dd, 1H, *J* = 7.6, 14.8 Hz), 1.84 (dt, 1H, *J* = 4.0, 12.8 Hz), 1.79 (app d, 1H, *J* = 12.8 Hz), 1.71 (app dt, 1H, *J* = 3.2, 14.0 Hz), 1.62-1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 171.9, 141.0, 140.9, 139.0, 135.8, 133.9, 131.1, 129.1, 128.5, 128.4, 128.2, 127.6, 127.6, 127.3, 127.2, 126.1, 115.9, 110.0, 76.2, 70.7, 55.0, 54.6, 43.6, 38.0, 35.1, 31.2, 30.7, 18.9; IR (neat) 3306, 3062, 3029, 2931, 2864, 1702, 1606, 1484, 1426, 1358, 1205, 1169, 1098, 737 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{35}N_2O_3NaBr$ $[M+Na]^+$ 645.1729, found 645.1726.

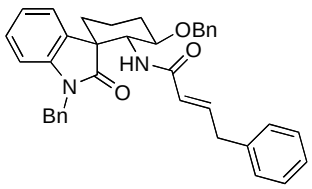
_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-5'-(4-methoxyphenyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.69)



To a solution (40 mg, 0.06 mmol) of the aryl bromide **1.68** in THF/H_2O (1 mL, 3:1) in a sealed tube was added $(PPh_3)_4Pd$ (7 mg, 0.006 mmol), 4-methoxyphenylboronic acid (20 mg, 0.13 mmol), and Na_2CO_3 (27 mg, 0.26 mmol). The atmosphere was exchanged for argon then the tube was sealed and immersed in a preheated oil bath (66 °C). The reaction stirred at 66 °C for 5 h, then the solution was extracted with EtOAc

(2x). The combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (15% to 30% EtOAc in hexane) to give biaryl **1.69** (37 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.60 (d, 1H, *J* = 1.8 Hz), 7.52 (app d, 2H, *J* = 8.7 Hz), 7.35-7.21 (m, 11H), 7.15-7.10 (m, 3H), 6.97 (app d, 2H, *J* = 8.7 Hz), 6.87 (app d, 2H, *J* = 7.8 Hz), 6.74 (d, 1H, *J* = 8.1 Hz), 5.00 (d, 1H, *J* = 10.2 Hz), 4.94 (d, 1H, *J* = 15.6 Hz), 4.84 (d, 1H, *J* = 15.6 Hz), 4.74 (t, 1H, *J* = 10.2 Hz), 4.71 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.29 (dt, 1H, *J* = 4.2, 10.5 Hz), 3.85 (s, 3H), 2.56-2.37 (m, 3H), 2.22 (qt, 1H, *J* = 3.6, 12.6 Hz), 2.14-2.04 (m, 1H), 2.00-1.83 (m, 3H), 1.80-1.69 (m, 2H), 1.61-1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 172.0, 159.1, 141.0, 140.8, 139.2, 136.3, 136.3, 133.8, 132.3, 129.1, 128.5, 128.5, 128.3, 128.2, 127.9, 127.5, 127.3, 126.6, 126.1, 122.9, 114.4, 108.7, 76.4, 70.8, 55.5, 55.3, 54.6, 43.7, 38.2, 35.4, 31.5, 31.0, 19.0; IR (neat) 3324, 3062, 3030, 2933, 2864, 1696, 1612, 1543, 1491, 1453, 1365, 1247, 1100, 1027, 909, 813, 732 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{43}H_{42}N_2O_4$ $[M]^+$ 650.3144, found 650.3148.

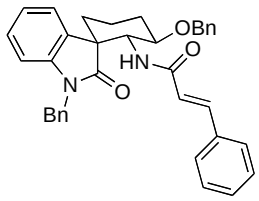
(*E*)-*N*-((1*S*,2*R*,3*R*)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-4-phenylbut-2-enamide (1.70)



To a solution of **1.57** (23 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) in a sealed tube were added the second generation Hoveyda-Grubbs catalyst (2 mg) and allylbenzene (19 μL, 0.15 mmol). The atmosphere was exchanged with argon, then the tube was immersed in a preheated oil bath (41 °C). The reaction was stirred for 18 h, then the solvent was removed under reduced pressure and the residue was purified by preparative TLC (5% EtOAc in CH_2Cl_2) to yield **1.70** (11 mg, 40%, 51% brsm) and starting material (5 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, *J* = 7.6 Hz), 7.33-7.22 (m,

13H), 7.16-7.06 (m, 4H), 6.75 (dt, 1H, *J* = 6.8, 15.2 Hz), 6.66 (d, 1H, *J* = 7.6 Hz), 5.27 (d, 1H, *J* = 15.2 Hz), 4.96 (d, 1H, *J* = 15.6 Hz), 4.91 (d, 1H, *J* = 10.0 Hz), 4.80 (d, 1H, *J* = 15.6 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 4.68 (t, 1H, *J* = 10.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.24 (dt, 1H, *J* = 4.4, 10.4 Hz), 3.39 (t, 1H, *J* = 6.4 Hz), 2.41 (d, 1H, *J* = 10.0 Hz), 2.19 (q, 1H, *J* = 13.2 Hz), 1.91 (dt, 1H, *J* = 3.6, 14.0 Hz), 1.82 (app d, 1H, *J* = 14.0 Hz), 1.74-1.70 (m, 1H), 1.62-1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 165.7, 143.1, 142.0, 139.1, 138.2, 136.2, 131.9, 129.0, 129.0, 128.9, 128.4, 128.1, 127.8, 127.8, 127.5, 127.2, 126.7, 124.6, 123.8, 123.4, 108.7, 76.7, 70.9, 55.3, 54.4, 43.5, 38.3, 35.5, 30.9, 19.1; IR (neat) 3416, 3060, 3029, 2931, 2864, 1696, 1640, 1612, 1537, 1493, 1365, 1174, 1098, 980 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{37}H_{36}N_2O_3Na$ $[M+Na]^+$ 579.2624, found 579.2679.

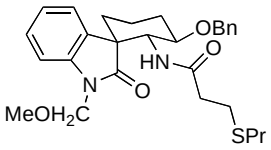
_N_-((1_S_,2_R_,3_R_)-1'-Benzyl-3-(benzyloxy)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)cinnamamide (1.71)



To a solution of **1.57** (30 mg, 0.06 mmol) in DMF (0.5 mL) in a sealed tube was added $Pd(OAc)_2$ (0.7 mg), PPh_3 (1.7 mg, 0.0064 mmol), iodobenzene (7.2 μL, 0.06 mmol) and Cs_2CO_3 (23 mg, 0.07 mmol). The atmosphere was exchanged with argon, then the tube was sealed and immersed in a preheated oil bath (120 °C). The reaction stirred for 12 h, then the mixture was diluted with EtOAc and washed with brine (2x). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography (10% to 50% EtOAc in hexane) to yield **1.71** as a slightly red solid (25 mg, 72%, mp 185.4 °C-189.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H, *J* = 8.0 Hz), 7.39-7.35 (m, 6H), 7.31-7.24 (m, 9H), 7.16-7.08 (m, 2H), 6.68 (d, 1H, *J* = 8.0 Hz), 5.82 (d, 1H, *J* = 15.6 Hz), 5.00 (app d, 2H, *J* = 15.6 Hz), 4.83 (d,

1H, *J* = 15.6 Hz), 4.76-4.71 (m, 2H), 4.49 (d, 1H, *J* = 12.0 Hz), 4.29 (dt, 1H, *J* = 4.8, 10.8 Hz), 2.44 (d, 1H, *J* = 12.8 Hz), 2.23 (qt, 1H, *J* = 3.6, 13.6 Hz), 1.94 (dt, 1H, *J* = 4.0, 14.0 Hz), 1.85 (app d, 1H, *J* = 14.0 Hz), 1.78-1.73 (m, 1H), 1.66-1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 165.6, 142.0, 141.0, 139.1, 136.3, 134.9, 131.9, 129.8, 129.0, 128.9, 128.5, 128.2, 128.0, 127.9, 127.8, 127.5, 127.3, 123.8, 123.4, 120.5, 108.8, 76.7, 71.0, 55.4, 54.5, 43.5, 35.3, 31.0, 19.1; IR (neat) 3304, 3060, 3030, 2932, 2864, 1699, 1663, 1612, 1492, 1366, 1209, 1027, 1098, 978, 910, 734 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}N_2O_3Na$ $[M+Na]^+$ 565.2467, found 565.2432.

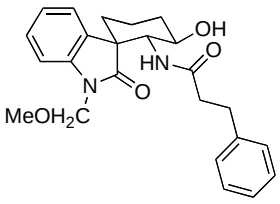
_N_-((1_S_,2_R_,3_R_)-3-(Benzyloxy)-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-(propylthio)propanamide (1.72)



To a suspension of NaH (6 mg, 0.15 mmol) in THF (0.6 mL) at 0 °C under argon was added 1-propanethiol (10 μL, 0.11 mmol). After 15 min a solution of **1.60** (31 mg, 0.074 mmol) in THF (0.6 mL) was added dropwise at 0 °C. The ice bath was removed and the reaction stirred at for 1 h. The reaction mixture was quenched with water and extracted with EtOAc (2x). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography (5% to 15% EtOAc in CH_2Cl_2) to give sulfide **1.72** (26 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 1H, *J* = 7.2 Hz), 7.32-7.24 (m, 5H), 7.22 (d, 1H, *J* = 7.6 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 6.93 (d, 1H, *J* = 7.6 Hz), 5.25 (d, 1H, *J* = 9.6 Hz), 5.11 (d, 1H, *J* = 10.8 Hz), 5.08 (d, 1H, *J* = 10.8 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 4.58 (t, 1H, *J* = 10.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.21 (dt, 1H, *J* = 4.8, 10.8 Hz), 3.23 (s, 3H), 2.43-2.36 (m, 2H), 2.30-2.23 (m, 3H), 2.15-2.06 (m, 2H), 2.01-1.93 (m, 1H), 1.88 (dt, 1H, *J* = 3.6, 14.0 Hz), 1.78 (app d, 1H, *J* = 14.4 Hz), 1.71-1.68 (m, 1H),

1.60-1.55 (m, 1H), 1.47 (sextet, 2H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 171.2, 141.2, 139.1, 131.2, 128.5, 128.3, 127.7, 127.6, 123.9, 123.7, 109.0, 76.4, 71.3, 71.1, 56.4, 55.3, 54.9, 37.0, 35.6, 34.2, 31.0, 27.6, 22.9, 19.0, 13.6; IR (neat) 3247, 3061, 2932, 2869, 1706, 1643, 1555, 1491, 1362, 1294, 1116, 1088, 740 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_2O_4NaS$ $[M+Na]^+$ 519.2293, found 519.2319.

_N_-((1_S_,2_R_,3_R_)-3-Hydroxy-1'-(methoxymethyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-2-yl)-3-phenylpropanamide (1.73)



To a solution of **1.59** (50 mg, 0.10 mmol) in EtOH/EtOAc (2 mL, 1:1) was added Pd/C (7 mg). The atmosphere was exchanged with H_2 and the mixture was stirred for 24 h. The suspension was diluted with EtOAc then was filtered through a short pad of silica gel. Removal of the solvent provided the alcohol as a white solid **1.73** (29 mg, 71%, mp 219.2 °C-220.8 °C) that was directly used for next step without further purification: ^{1}H NMR (300 MHz, DMSO) δ 7.30 (d, 2H, J = 7.5 Hz), 7.22-6.89 (m, 7H), 5.08 (d, 1H, J = 10.8 Hz), 4.98 (d, 1H, J = 11.1 Hz), 4.40 (d, 1H, J = 5.1 Hz), 4.25-4.15 (m, 2H), 3.19 (s, 3H), 2.31-2.23 (m, 2H), 2.11-2.00 (m, 4H), 1.92-1.83 (m, 1H), 1.62-1.45 (m, 3H); ^{13}C NMR (75 MHz, DMSO) δ 178.1, 171.7, 141.5, 141.4, 131.4, 128.2, 127.9, 127.4, 125.6, 123.7, 122.2, 108.4, 70.5, 66.7, 56.9, 55.5, 53.9, 37.1, 34.8, 34.2, 31.3, 18.7; IR (neat) 3424, 3269, 2938, 1694, 1640, 1554, 1453, 1369, 1077 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O_4Na$ $[M+Na]^+$ 431.1947, found 431.1955.

(1*S*,2*R*,3*R*)-1'-(Methoxymethyl)-2'-oxo-2-(3-phenylpropanamido)spiro[cyclohexane-1,3'-indolin]-3-yl benzoate (1.74)

To a solution of the alcohol **1.73** (11mg, 0.027 mmol) and a catalytic amout of DMAP in pyridine (0.5 mL) was added benzoyl chloride (31 μL, 0.27 mmol). The mixture was stirred for 30 h, then another portion of benzoyl choride (31 μL, 0.27 mmol) was added. After 18 h the temperature was raised to 60 °C. After stirring for 4 h the mixture was diluted with EtOAc, and then washed with saturated $NaHCO_3$ solution. After removal of the solvent, the residue was purified by flash chromatography (20% to 40% EtOAc in hexane) to yield benzoate **1.74** (10 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 7.2 Hz), 8.02 (d, 2H, *J* = 7.2 Hz), 7.62 (t, 1H, *J* = 7.6 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.48 (t, 1H, *J* = 7.6 Hz), 7.45-7.40 (m, 3H), 7.16 (t, 1H, *J* = 7.6 Hz), 7.11-7.04 (m, 3H), 6.96 (d, 1H, *J* = 7.6 Hz), 6.80-6.78 (m, 2H), 5.97 (dt, 1H, *J* = 4.8, 10.8 Hz), 5.50 (d, 1H, *J* = 10.0 Hz), 5.12 (d, 1H, *J* = 10.8 Hz), 5.09 (d, 1H, *J* = 10.8 Hz), 4.83 (t, 1H, *J* = 10.4 Hz), 2.46-2.37 (m, 2H), 2.35-2.26 (m, 2H), 2.03-1.93 (m, 3H), 1.89-1.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 172.3, 167.0, 141.3, 140.8, 133.8, 133.4, 130.7, 130.4, 130.1, 130.0, 128.7, 128.6, 128.5, 128.0, 126.1, 123.9, 123.8, 109.3, 71.9, 71.3, 56.4, 55.1, 54.8, 38.3, 35.5, 31.5, 31.2, 19.0; IR (neat) 3350, 3062,3030, 2935, 1713, 1613, 1537, 1361, 1273, 1117, 713 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{32}N_2O_5Na$ $[M+Na]^+$ 535.2209, found 535.2236.

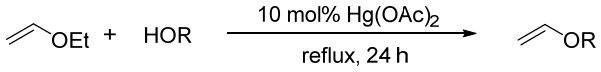
APPENDIX B

STEREOCONTROLLED CYANOHYDRIN ETHER SYNTHESIS THROUGH CHIRAL BRØNSTED ACID-MEDIATED VINYL ETHER HYDROCYANATION (SUPPORTING INFORMATION)

General Information Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, and a Bruker Avance 500 spectrometer at 500 MHz. The chemical shifts 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, 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 and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. 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 on a Shimadzu UFLC Series with a refractive index detector using chiral stationary columns (0.46 cm x 25 cm) from Daicel (OD) or Phenomenex

(Lux 5μ cellulose-3). Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter with 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 was used commercially available dehydrated solvent from Aldrich and used under Ar atmosphere. Trimethylsilyl cyanide was freshly fractionally distilled prior to use. Hydrogen chloride solution (2.0 M in diethyl ether) was used commercially available from Aldrich and used under Ar atmosphere. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under argon with magnetic stirring unless otherwise noted. Substrate **2.3** was prepared according to Tanner's protocol.[68] Substrate **2.10** was prepared according to Rutjes' protocol.[69] Substrate **2.67** was prepared according to Taylor's protocol.[70] Substrate **2.69** was prepared according to the Maruoka's protocol.[71] Substrate **2.79** was prepared according to Boger's protocol. [72]

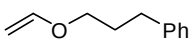
General procedure for the preparation of vinyl ether substrate[33]



Scheme S2.1 General vinyl ether substrate synthesis

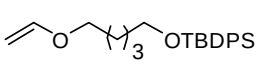
To a solution of the alcohol (1.0 equiv) in ethyl vinyl ether (10 equiv) was added $Hg(OAc)_2$ (0.1 equiv). The reaction mixture was reflux under N_2 for 24 h, and the excess ethyl vinyl ether was removed under vacuum. The crude product was purified by flash chromatography using CH_2Cl_2 and hexanes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

(3-(Vinyloxy)propyl)benzene (2.8)



The general procedure for the vinyl ether formation was followed with ethyl vinyl ether (10.80 mL, 110 mmol), 3-phenylpropan-1-ol (1.50 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 **2.8** as a colorless oil (1.04 g, 58%). ^{1}H 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 $C_{11}H_{15}O$ $[M+H]^+$ 163.11174, found 163.11085.

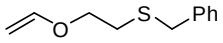
***tert*-Butyldiphenyl((5-(vinyloxy)pentyl)oxy)silane (2.12)**



The general procedure for the 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 **2.12** as a colorless oil (1.67 g, 63%). ^{1}H 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,

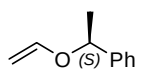
2.0 Hz), 3.68 (t, 2H, *J* = 6.5 Hz), 3.67 (t, 2H, *J* = 7.0 Hz), 1.69-1.64 (m, 2H), 1.63-1.58 (m, 2H), 1.50-1.44 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 135.8, 134.3, 129.7, 127.8, 86.4, 68.1, 63.9, 32.4, 29.0, 27.1, 22.5, 19.4; IR (neat) 3071, 3049, 2934, 2859, 1612, 1428, 1203, 1111, 822, 703 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}O_2Si$ $[M+H]^+$ 369.22443, found 369.22317.

Benzyl(2-(vinyloxy)ethyl)sulfane (2.14)



The general procedure for the 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 **2.14** as a colorless oil (347 mg, 78%). ^{1}H 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.

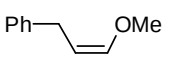
(*S*)-(1-(Vinyloxy)ethyl)benzene (2.16)



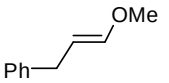
The general procedure for the vinyl ether formation was followed with ethyl vinyl ether (8.0 mL, 83 mmol), (*S*)-phenylethanol (1.00 mL, 8.3 mmol), and $Hg(OAc)_2$ (262 mg, 0.83 mmol). The crude product was purified by flash chromatography (15% CH_2Cl_2 in hexane) to give **2.16** as a colorless oil (763 mg, 62%). ^{1}H 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 $C_{10}H_{12}NO$ $[M]^+$ 148.0888, found 148.0898. $[\alpha]_D^{25}$ = –71.1 (*c* 1.0, $CHCl_3$).

(*E*)-(3-methoxyallyl)benzene (2.18) and (*Z*)-(3-methoxyallyl)benzene (2.78)

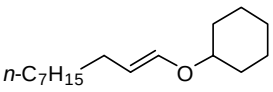


Prepared following Nigishi's protocol,[73] and the crude product was purified by MPLC (medium pressure liquid chromatography, 100% hexane to 10% CH_2Cl_2 in hexane) for three times. The faster eluent is the minor isomer **2.78**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28-7.24 (m, 2H), 7.21-7.19 (m, 2H), 7.17-7.14 (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 eluent gives the major isomer **2.18**: ^{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.

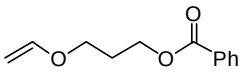
(*E*)-(Dec-1-en-1-yloxy)cyclohexane (2.20)[36]



To a solution of (*E*)-1-iododec-1-ene (798 mg, 3 mmol) and cyclohexenol (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.

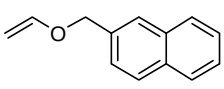
The filtrate was then concentrated under vacuum, and the crude product was purified by flash chromatography (100% hexane to 5% Et_2O in hexane) to give **2.20** as a colorless oil (385 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, *J* = 12.3 Hz), 4.89 (dt, 1H, *J* = 12.3, 7.2 Hz), 3.65-3.56 (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 (2.24)



The general procedure for the vinyl ether formation was followed with ethyl vinyl ether (12 mL, 126 mmol), 3-hydroxypropyl benzoate (2.273 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 **2.24** as a colorless oil (1.510 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.

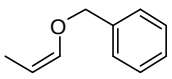
2-((Vinyloxy)methyl)naphthalene (2.73)



The general procedure for the vinyl ether formation was followed with ethyl vinyl ether (1.92 mL, 20 mmol), 2-napthalenemethanol (316 mg, 2 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 **2.73** 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 (2.76)[74]



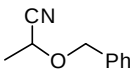
To a solution of allyl benzyl ether (592 mg, 4 mmol) in DMSO (40 mL) was added *t*-BuOK (1.12 g, 10 mmol) under Ar atmosphere. After stirring at 60 °C for 2 h, the reaction mixture was diluted with Et_2O, washed with H_2O (3x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **2.76** 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.[75]

General procedure for the cyanation of α-chloroether:

To a one neck round bottom flask with a magnetic stirring bar, a solution of the vinyl ether (1.0 equiv) in freshly distilled methylene chloride (0.1 M) was added under Ar. After cooling to –40 °C (cooling bath temperature), a solution of HCl (1.1 equiv, 2.0 M in diethyl ether) was added

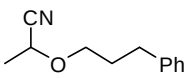
dropwise to the reaction over 20 sec. After 5 min, TMSCN (2 equiv) was added dropwise to the reaction mixture over about 30 sec. The mixture was stirred at this temperature for 1 h, and it was then quenched at –40 °C by Et_3N (0.3 mL) followed by saturated $NaHCO_3$ solution (0.5 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ solution (6 mL), and transfered to a separatory funnel. After separation, the aqueous layer was extracted with CH_2Cl_2 again (10 mL). The combined organic layer was dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

2-(Benzyloxy)propanenitrile (2.4)



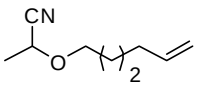
The general procedure for hydrocyanation was followed with **2.3** (54 mg, 0.4 mmol), HCl solution (220 μL, 0.44 mmol), TMSCN (100 μL, 0.8 mmol), and CH_2Cl_2 (4 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give **2.4** as a colorless oil (52 mg, 81%). For characterization data see the procedure for preparing enantioenriched material.

2-(3-Phenylpropoxy)propanenitrile (2.9)



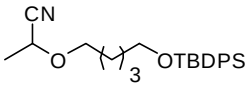
The general procedure for hydrocyanation was followed with **2.8** (49 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **2.9** as a colorless oil (52 mg, 92%). For characterization data see the procedure for preparing enantioenriched material.

2-(Hex-5-en-1-yloxy)propanenitrile (2.11)



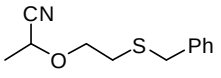
The general procedure for hydrocyanation was followed with **2.10** (38 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (10% Et_2O in pentane) to give **2.11** as a colorless oil (35 mg, 76%). ^{1}H 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 $C_9H_{16}ON$ $[M+H]^+$ 154.12264, found 154.12182.

2-((5-((tert-Butyldiphenylsilyl)oxy)pentyl)oxy)propanenitrile (2.13)



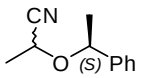
The general procedure for hydrocyanation was followed with **2.12** (74 mg, 0.2 mmol), HCl solution (110 μL, 0.22 mmol), TMSCN (50 μL, 0.4 mmol), and CH_2Cl_2 (2 mL). The crude product was purified by flash chromatography (3% to 5% EtOAc in hexane) to give **2.13** as a colorless oil (76 mg, 96%). ^{1}H 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 $C_{24}H_{34}O_2NSi$ $[M+H]^+$ 396.23533, found 396.23431.

2-(2-(Benzylthio)ethoxy)propanenitrile (2.15)

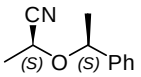


The general procedure for hydrocyanation was followed with vinyl ether **2.14** (58 mg, 0.3 mmol), HCl solution (165 μL, 0.33 mmol), TMSCN (75 μL, 0.6 mmol), and CH_2Cl_2 (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **2.15** as a colorless oil (60 mg, 85%). For characterization data see the procedure for preparing enantioenriched material.

2-((*S*)-1-Phenylethoxy)propanenitrile (2.17)

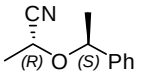


The general procedure for hydrocyanation was followed with **2.16** (104 mg, 0.7 mmol), HCl solution (385 μL, 0.77 mmol), TMSCN (175 μL, 1.4 mmol), and CH_2Cl_2 (7 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give two diastereomers (112 mg, 91%, d.r. = 1.2:1). The faster eluting product was the major diastereomer **2.81**: ^{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,



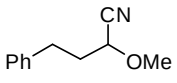
1453, 1057, 763, 702 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.1016. $[\alpha]_D^{25}$ = –323.3 (*c* 1.0, $CHCl_3$).

The slower eluting product was the minor diastereomer: ^{1}H NMR (400 MHz,



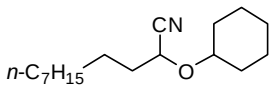
$CDCl_3$) δ 7.41-7.31 (m, 5H), 4.68 (q, 1H, *J* = 6.8 Hz), 4.31 (q, 1H, *J* = 6.8 Hz), 1.58 (d, 3H, *J* = 6.4 Hz), 1.51 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.8, 128.5, 126.6, 119.4, 78.2, 62.2, 22.6, 20.4; IR (neat) 3032, 2981, 2889, 1453, 1029, 762, 701 cm^{-1}; HRMS (EI) *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 (2.19)



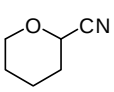
The general procedure for the cyanation of α-chloroether was followed with **2.18** (30 mg, 0.2 mmol), HCl solution (110 μL, 0.22 mmol), TMSCN (50 μL, 0.4 mmol), and CH_2Cl_2 (2 mL) at 0 °C. The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **2.19** as a colorless oil (29 mg, 83%). For characterization data see the procedure for preparing enantioenriched material.

2-(Cyclohexyloxy)undecanenitrile (2.21)



The general procedure for hydrocyanation was followed by using vinyl ether **2.20** (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 **2.21** 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 (2.23)



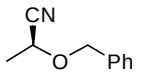
The general procedure for hydrocyanation was followed with **2.22** (72 mg, 0.8 mmol), HCl solution (440 μL, 0.88 mmol), TMSCN (200 μL, 1.6 mmol), and CH_2Cl_2 (8 mL). The crude product was purified by flash chromatography (6% EtOAc in hexane) to give **2.23** as a colorless oil (58 mg, 65%). ^{1}H NMR (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.[76]

General procedure for the asymmetric cyanide addition to vinyl ethers:

To a single neck round bottom flask equiped with a magnetic stirring bar, a solution of catalyst **2.55** (0.03 equiv) in anhydrous trifluorotoluene was added at room temperature under Ar atmosphere followed by TMSCN. The reaction mixture was stirred at room temperature for 10 min, then was cooled to –25 °C (cooling bath temperature). A solution of vinyl ether (1.0 equiv) in trifluorotoluene (0.3 mL) was added to the reaction mixture dropwise over 30 sec. The vial containing vinyl ether was rinsed with trifluorotoluene (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 trifluorotoluene (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 (0.3 mL) and saturated $NaHCO_3$ solution (0.5 mL) at –25 °C. After warming to room temperature, the reaction mixture was diluted with Et_2O and saturated $NaHCO_3$ solution, and transfered to a separatory funnel. After separation, the aqueous layer was extracted with Et_2O again. The combined organic layer was dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

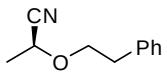
(*S*)-2-(Benzyloxy)propanenitrile ((*S*)-2.4)



The general asymmetric hydrocyanation procedure was followed with **2.3** (107 mg, 0.8 mmol), catalyst **2.55** (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*)-2.4** 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.[77] 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, $CHCl_3$).

The absolute configuration was assigned by comparison of HPLC retention times with a sample of known configuration which was obtained by alternative synthesis (see determination of absolute configurations section).

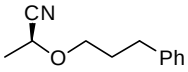
(*S*)-2-Phenethoxypropanenitrile (2.68)



The general asymmetric hydrocyanation procedure was followed with **2.67** (45 mg, 0.3 mmol), catalyst **2.55** (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 **2.68** 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

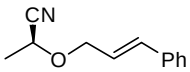
MHz, $CDCl_3$) δ 138.2, 129.1, 128.7, 126.7, 119.1, 71.4, 64.8, 36.1, 20.0; IR (neat) 3029, 2995, 2871, 1497, 1475, 1330, 1115, 750, 700 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.1014. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 10.0 min, 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*)-2.9)



The general asymmetric cyanation procedure was followed with **2.8** (49 mg, 0.3 mmol), catalyst **2.55** (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*)-2.9** as a colorless oil (51 mg, 90%). ^1H 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, $CHCl_3$).

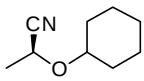
(*S*)-2-(Cinnamyloxy)propanenitrile (2.70)



The general asymmetric cyanation procedure was followed with **2.69** (48 mg, 0.3 mmol), catalyst **2.55** (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

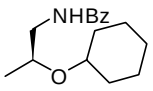
chromatography (4% to 5% EtOAc in hexane) to give **2.70** as a colorless oil (43 mg, 77%).[1]H NMR (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 6.70 (d, 1H, *J* = 15.9 Hz), 6.26 (ddd, 1H, *J* = 15.9, 6.9, 5.4 Hz), 4.47 (ddd, 1H, *J* = 12.0, 5.4, 1.2 Hz), 4.35 (q, 1H, *J* = 6.9 Hz), 4.21 (ddd, 1H, *J* = 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, $CHCl_3$). The racemates were prepared through the cyanation of α-chloroether.

(*S*)-2-(Cyclohexyloxy)propanenitrile (2.72)



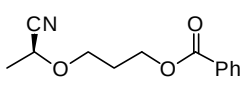
The general asymmetric cyanation procedure was followed with **2.71** (50 mg, 0.4 mmol), catalyst **2.55** (14.6 mg, 0.0012 mmol), TMSCN (101 μL, 0.8 mmol), phenol (37 mg, 0.4 mmol) and trifluorotoluene (4 mL). The crude product was purified by flash chromatography (3% to 5% EtOAc in hexane) to give **2.72** 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 by the obtained reduction and acylation product on HPLC. Racemic material was prepared through cyanation of the α-chloroether.

(*S*)-*N*-(2-(Cyclohexyloxy)propyl)benzamide



Cyanohydrin ether **2.72** (19 mg, 0.13 mmol) in anhydrous Et_2O (0.2 mL) was added to an $LiAlH_4$ solution (0.13 mL of 1 M solution in Et_2O, 0.13 mmol) at 0 °C under Ar, and then the ice bath was removed. The reaction mixture was stirred at room temperature for 45 min, and it was then carefully quenched with H_2O followed by 20% NaOH solution. The mixture was extracted with EtOAc (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was then dissolved in CH_2Cl_2 (1 mL), followed by addition of Et_3N (42 μL) and benzoyl chloride (14 μL) at room temperature. The reaction mixture was stirred for 30 min, and then quenched with H_2O. The mixture was then exacted with CH_2Cl_2 (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography (10% to 20% EtOAc in hexane) to give the product as a colorless oil (16 mg, 47% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.76 (m, 2H), 7.53-7.49 (m, 1H), 7.47-7.43 (m, 2H), 6.57 (s, 1H), 3.81-3.73 (m, 2H), 3.37-3.31 (m, 1H), 3.22-3.15 (m, 1H), 1.89-1.87 (m, 2H), 1.77-1.72 (m, 2H), 1.56-1.54 (m, 1H), 1.34-1.22 (m, 5H), 1.19 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 135.0, 131.6, 128.8, 127.0, 75.8, 71.5, 45.4, 33.9, 32.9, 25.9, 24.6, 24.5, 18.7; IR (neat) 3325, 3064, 2931, 2856, 1643, 1544, 1144, 1093, 802, 696 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1807, found 262.1797. HPLC (OD), hexane/*i*-PrOH 95:5, 1 mL/min, t_{minor} = 8.3 min, t_{major} = 9.9 min. er = 84:16. $[\alpha]_D^{25}$ = +32.2 (*c* 1.0, $CHCl_3$).

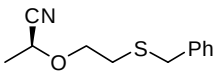
(*S*)-3-(1-Cyanoethoxy)propyl benzoate ((*S*)-2.25)



The general asymmetric cyanation procedure was followed with **2.24** (62 mg, 0.3 mmol), catalyst **2.55** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6

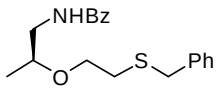
mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (2% EtOAc in toluene) to give **(*S*)-2.25** as a colorless oil (61 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.2 Hz),7.45 (t, 2H, *J* = 7.6 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, $CHCl_3$). Racemic material was prepared through the cyanation of the α-chloroether.

(*S*)-2-(2-(Benzylthio)ethoxy)propanenitrile ((*S*)-2.15)



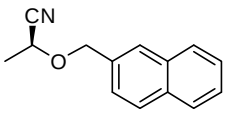
The general asymmetric cyanation procedure was followed with **2.14** (58 mg, 0.3 mmol), catalyst **2.55** (11 mg, 0.0009 mmol), TMSCN (76 μL, 0.6 mmol), phenol (28 mg, 0.3 mmol) and trifluorotoluene (3 mL). The crude product was purified by flash chromatography (4% EtOAc in hexane) to give **(*S*)-2.15** 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 by the obtained reduction and acylation product on HPLC.

(*S*)-*N*-(2-(2-(Benzylthio)ethoxy)propyl)benzamide



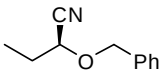
Cyanohydrin ether **(*S*)-2.15** (25 mg, 0.11 mmol) in anhydrous Et_2O (0.3 mL) was added to an $LiAlH_4$ solution (0.11 mL of 1 M solution in Et_2O, 0.11 mmol) at 0 °C under Ar, and then the ice bath was removed. The reaction mixture was stirred at room temperature for 45 min, and it was then carefully quenched with H_2O followed by 20% NaOH solution. The mixture was extracted with EtOAc (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was then dissolved in CH_2Cl_2 (1 mL), followed by addition of Et_3N (35 μL) and benzoyl chloride (12 μL) at room temperature. The reaction mixture was stirred for 30 min, and then quenched with H_2O. The mixture was then exacted with CH_2Cl_2 (2x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography (15% to 25% EtOAc in hexane) to give the product as a colorless oil (25 mg, 69% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.52-7.49 (m, 1H), 7.43-7.40 (m, 2H), 7.31-7.23 (m, 5H), 6.88 (s, 1H), 3.82 (ddd, 1H, *J* = 14.0, 7.0, 3.5 Hz), 3.77 (dt, 1H, *J* = 10.0, 6.0 Hz), 3.72 (s, 2H), 3.68-3.58 (m, 1H), 3.44 (ddd, 1H, *J* = 10.0, 8.0, 6.0 Hz), 3.24 (ddd, 1H, *J* = 14.0, 8.0, 4.0 Hz), 2.71-2.61 (m, 2H), 1.21 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 138.1, 134.5, 131.4, 128.9, 128.6, 128.5, 127.1, 127.1, 74.6, 67.2, 44.7, 36.7, 31.8, 17.4; IR (neat) 3334, 3061, 3028, 2971, 2925, 2868, 1644, 1336, 1290, 1120, 707 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{19}H_{24}NO_2S$ $[M+H]^+$ 330.1528, found 330.1520. HPLC (Lux cellulose-3), hexane/*i*-PrOH 80:20, 1 mL/min, t_{minor} = 9.8 min, t_{major} = 10.6 min. er = 83:17. $[\alpha]_D^{25}$ = –2.2 (*c* 1.0, $CHCl_3$).

(*S*)-2-(Naphthalen-2-ylmethoxy)propanenitrile (2.74)



The general asymmetric cyanation procedure was followed with **2.73** (55 mg, 0.3 mmol), catalyst **2.55** (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 **2.74** 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, $CHCl_3$). Racemic material was prepared through the cyanation of the α-chloroether.

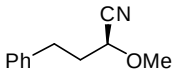
(*S*)-2-(Benzyloxy)butanenitrile (2.77)



The general asymmetric cyanation procedure was followed with **2.76** (44 mg, 0.3 mmol), catalyst **2.55** (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 **2.77** 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, $CHCl_3$). Racemic material was prepared through cyanation of the α-chloroether.

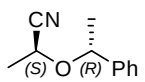
(*S*)-2-Methoxy-4-phenylbutanenitrile ((*S*)-2.19)



The general asymmetric cyanation procedure was followed with **2.78** (24 mg, 0.16 mmol), catalyst **2.55** (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*)-2.19** 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.[78] 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 **2.18** (44 mg, 0.3 mmol), catalyst **2.55** (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*)-2.19** as a colorless oil (7 mg, 13%, 22% conversion based on crude NMR). er =74:26.

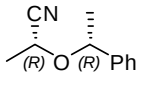
(*S*)-2-((*R*)-1-phenylethoxy)propanenitrile (2.80)



The general asymmetric cyanation procedure was followed with **2.79** (59 mg, 0.4 mmol), catalyst **2.55** (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 **2.80** 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, $CHCl_3$).

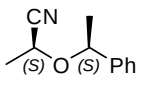
The absolute configuration of cyanohydrin ether was assigned by comparison of optical rotation with the known cyanohydrin which was obtained by cleavage of the 1-phenylethanol group (see determination of absolute configurations section).



The general procedure for the cyanation of the α-chloroether was followed to generate both of the diastereomers by using (*R*)-(1-vinyloxy)ethyl)benzene **2.79** (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 as two diastereomers (103 mg, 84%, d.r. = 1.2:1). The faster eluting product was the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 4.75 (q, 1H, *J* = 6.6 Hz), 3.97 (q, 1H, *J* = 6.6 Hz), 1.52 (d, 3H, *J* = 6.6 Hz), 1.51 (d, 3H, *J* = 6.9 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) 3033, 2981, 2887, 1454, 1110, 1057, 763, 702 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ $[M]^+$ 175.0997, found 175.0990. $[\alpha]_D^{25}$ = +306.0 (*c* 1.0, $CHCl_3$). HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{RR} = 6.4 min.

The slower eluting product was the minor diastereomer **2.80**: For characterization, see above. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{SR} = 7.1 min.

(*S*)-2-((*S*)-1-phenylethoxy)propanenitrile (2.81)



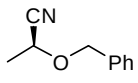
The general asymmetric cyanation procedure was followed with **2.16** (59 mg, 0.4 mmol), catalyst **2.55** (14.6 mg, 0.0012 mmol), TMSCN (101 μL, 0.8 mmol), phenol (37 mg, 0.4 mmol) and trifluorotoluene (4 mL). The crude product was purified by flash chromatography (3% EtOAc in hexane) to give two diastereomers (57 mg, 81%, d.r. = 1.2:1, crude NMR ratio 1.4:1). The faster eluting product was the major diastereomer **2.81**. For characterization data see the procedure for preparing **2.17**.

General procedure for the asymmetric cyanide addition to acetals:

To a single neck round bottom flask equiped with a magnetic stirring bar, a solution of catalyst **2.55** (0.03 equiv) in anhydrous trifluorotoluene was added at room temperature under Ar atmosphere followed by addition of TMSCN. The reaction mixture was stirred at room temperature for 15 min and then cooled to –25 °C (cooling bath temperature). 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 addition. The reaction mixture was then quenched with Et_3N (0.3 mL) and saturated $NaHCO_3$ solution (0.5 mL) at –25 °C. After warming to room temperature, the reaction mixture was diluted with Et_2O and saturated $NaHCO_3$ solution, and transferred to a separatory funnel. After separation, the aqueous layer was extracted with Et_2O

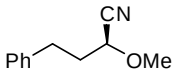
again. The combined organic layer was dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography.

(*S*)-2-(Benzyloxy)propanenitrile ((*S*)-2.4)



The general asymmetric acetal cyanation procedure was followed with **2.90** (73 mg, 0.3 mmol), catalyst **2.55** (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*)-2.4** as a colorless oil (41 mg, 85%), er = 82.5:17.5. Spectral and HPLC data are consistent with previously reported values.

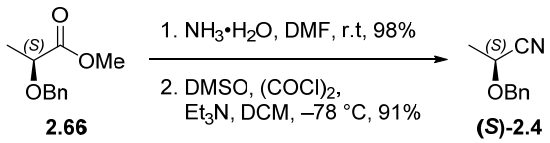
(*S*)-2-Methoxy-4-phenylbutanenitrile ((*S*)-2.19)



The general asymmetric acetal cyanation procedure was followed with **2.91** (36 mg, 0.2 mmol), catalyst **2.55** (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*)-2.19** as a colorless oil (32 mg, 91%), er = 73:27. Spectral and HPLC data are consistent with previously reported values.

Determination of the absolute stereochemistry:

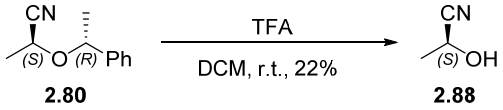
For (*S*)-2-(Benzyloxy)propanenitrile ((*S*)-2.4)



Scheme S2.2 Determination of the absolute stereochemistry of 2.4

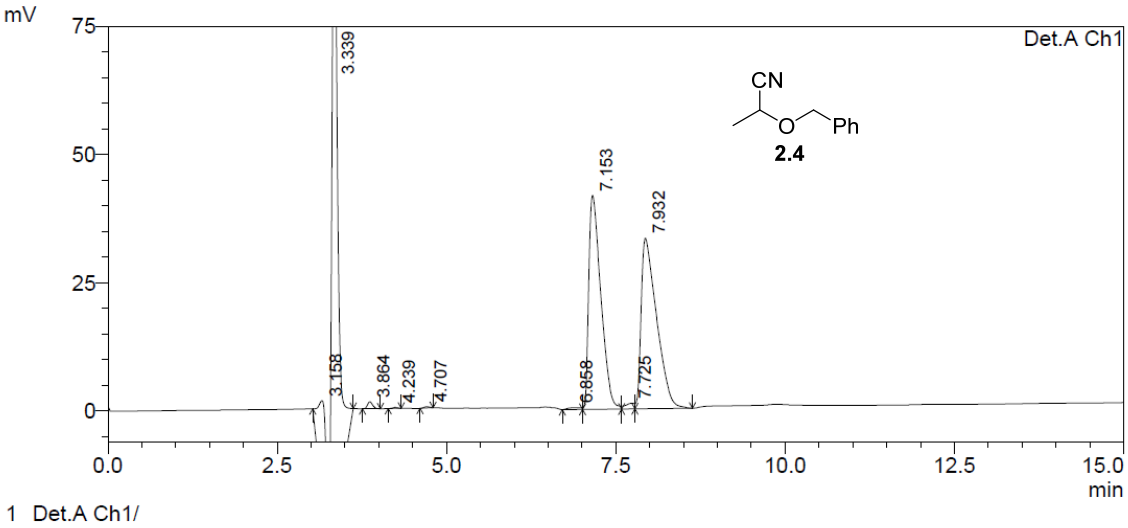
To a solution of methyl (*S*)-2-(benzyloxy)propanoate (**2.66**)[79] (194 mg, 1.0 mmol) in DMF (5 mL) was added NH_3•H_2O (10 mL) at room temperature. The reaction mixture was stirred overnight, and then diluted with EtOAc and washed with H_2O (3x). The organic layer was dried over Na_2SO_4, and concentrated under vacuum to give the pure amide as a white solid (176 mg, 98%), which was directly used for the next step. To a solution of oxalyl chloride (39 μL, 0.45 mmol) in CH_2Cl_2 (3 mL) was added DMSO (43 μL, 0.6 mmol) in CH_2Cl_2 at –78 °C under Ar. After 20 min, the amide (54 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL) was added to the reaction mixture dropwise. The reaction mixture was stirred for another 30 min, before adding Et_3N (125 μL, 0.9 mmol). The solution was allowed to stir for another 30 min, and then warmed up to the room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl solution, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified with flash chromatography (3% EtOAc in hexane) to give the cyanohydrin ether **(*S*)-2.4** (44 mg, 91%). The spectra data are consistent with previous results. HPLC (Lux cellulose-3), hexane/*i*-PrOH 90:10, 1 mL/min, t_{major} = 7.3 min, t_{minor} = 8.3 min. er > 99:1. $[\alpha]_D^{25}$ = –169.1 (*c* 1.0, $CHCl_3$).

For (*S*)-2-((*R*)-1-phenylethoxy)propanenitrile (2.88)[54]



Scheme S2.3 Determination of the absolute stereochemistry of 2.80

To a solution of **2.80** (26 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (69 μL, 0.9 mmol) at room temperature. The reaction mixture was stirred overnight, and then concentrated under vacuum. The crude product was purified by flash chromatography (7% to 25% EtOAc in hexane) to give (*S*)-lactonitrile (**2.88**) as a colorless oil (2.3 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (app quin, 1H, J = 6.4 Hz), 2.32 (d, 1H, J = 5.6 Hz), 1.63 (d, 3H, J = 6.8 Hz). These data are consistent with reported literature values.[80] $[\alpha]_D^{25}$ = –32 (*c* 0.23, $CHCl_3$). (Literature value[56] for (*S*)-lactonitrile: $[\alpha]_D^{25}$ = –30 (*c* 1.0, $CHCl_3$), ee>98%)



1 Det.A Ch1/

Detector A

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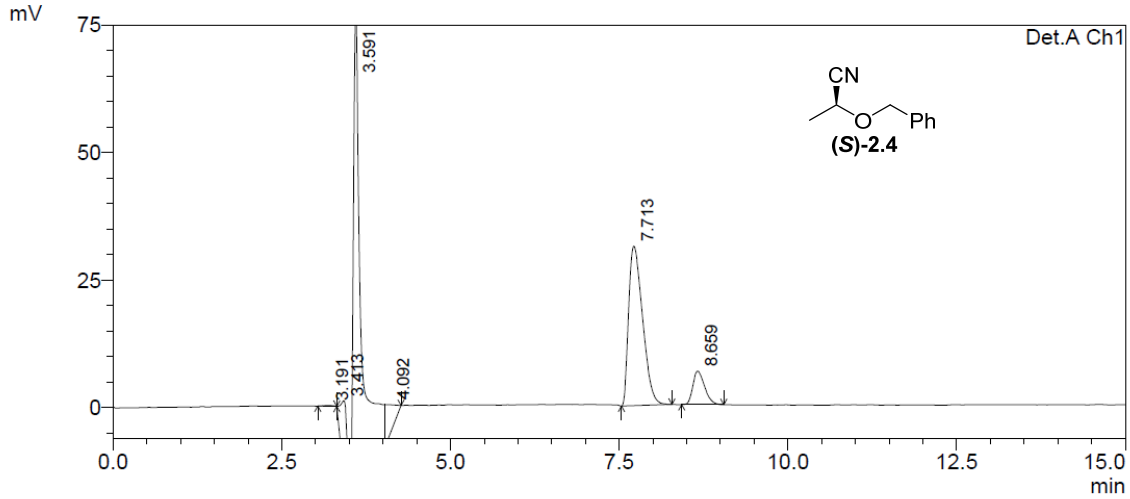

1 Det.A Ch1/

Detector A

ID#	Name	Ret. Time	Area	Height
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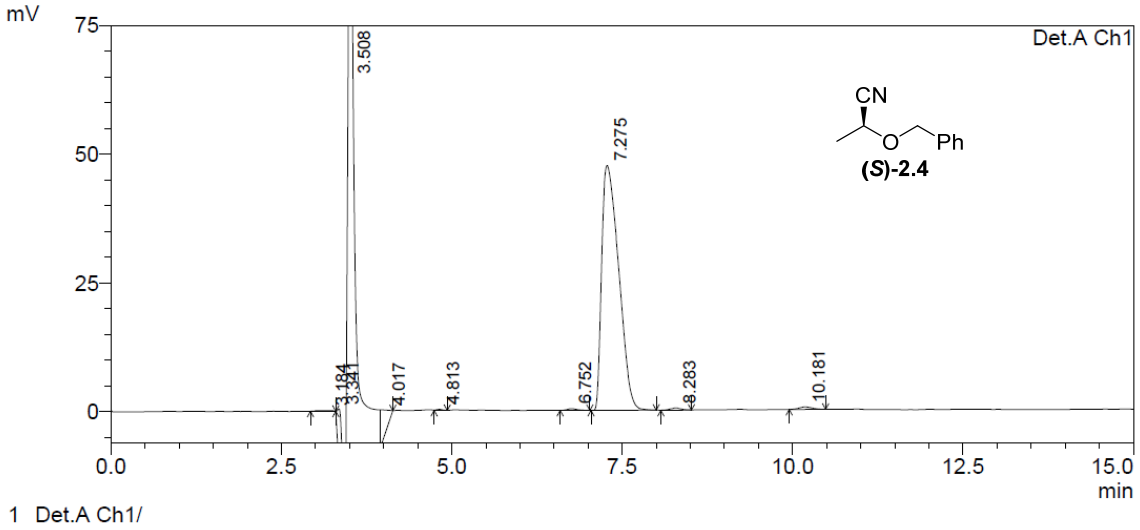

Detector A

ID#	Name	Ret. Time	Area	Height
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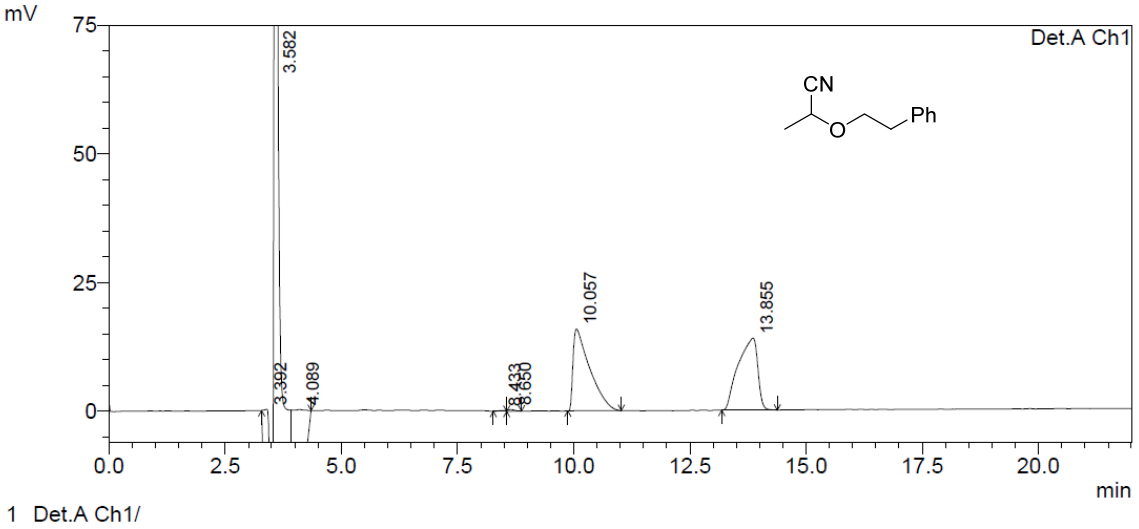
Figure S2.1 HPLC tracer of 2.4



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT10.057	10.057	397186	15892
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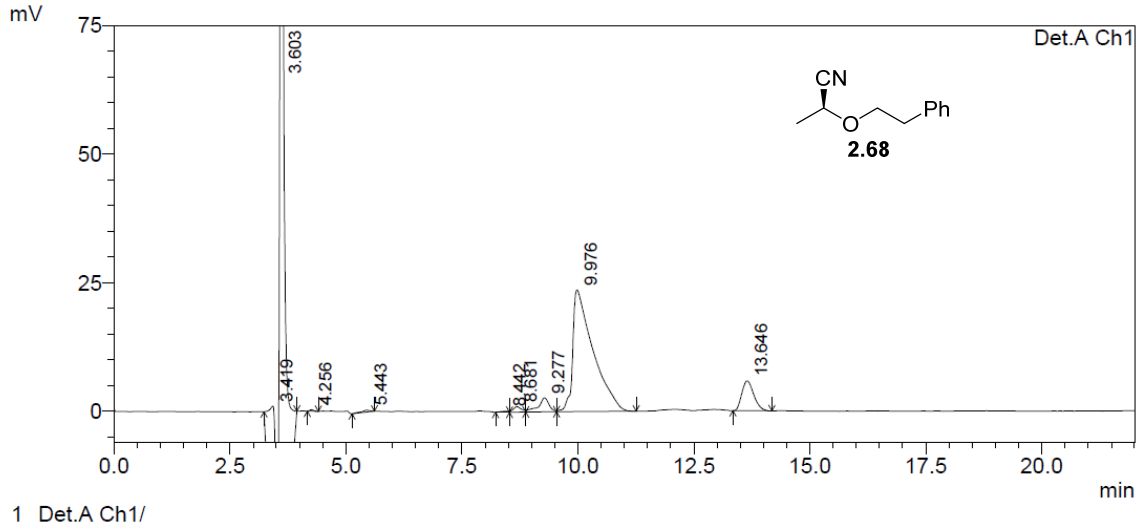
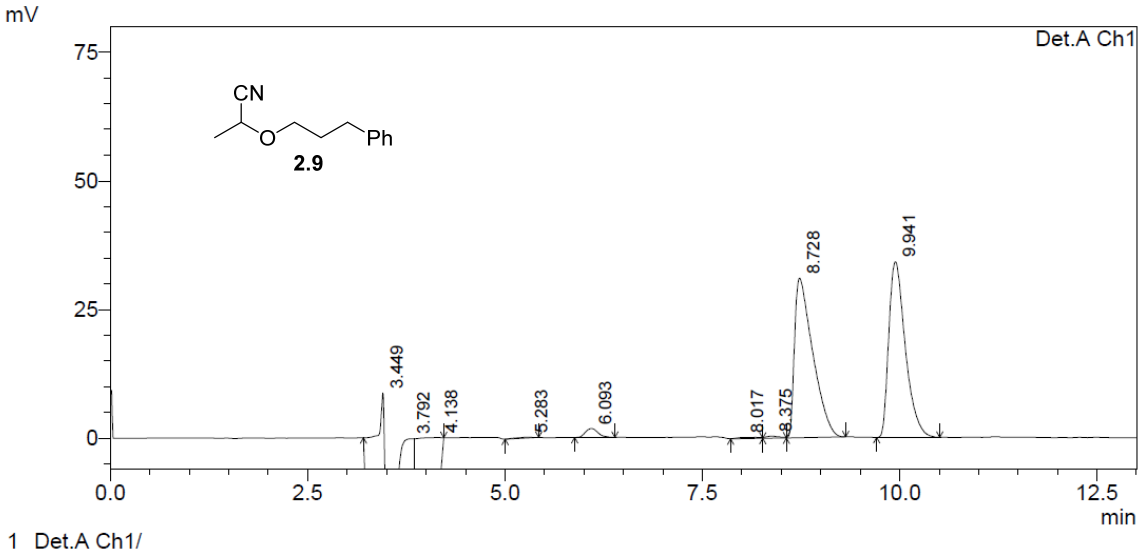


Detector A

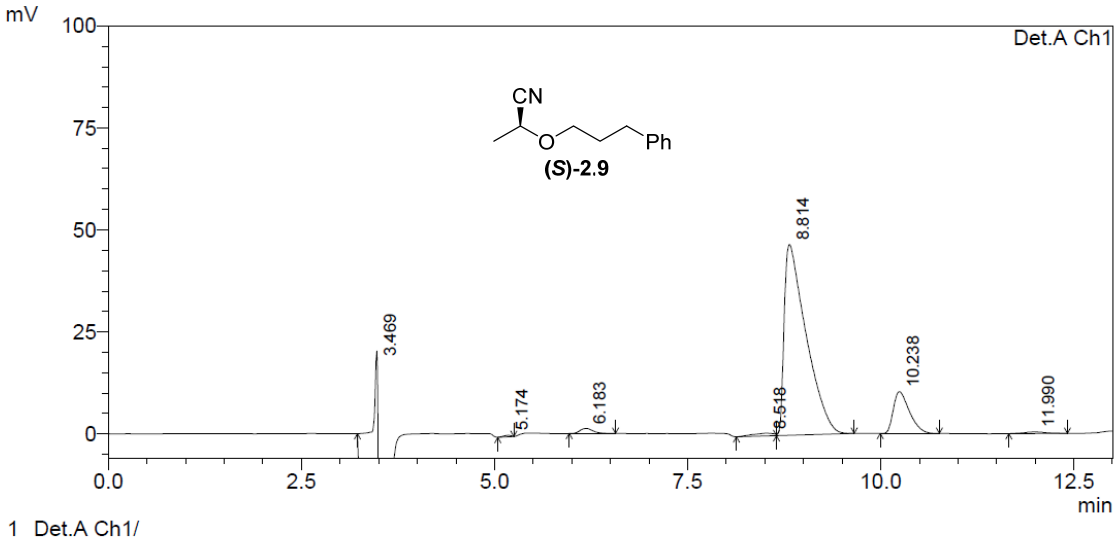
ID#	Name	Ret. Time	Area	Height
1	RT9.976	9.976	721928	23676
2	RT13.646	13.646	104043	5794

Figure S2.2 HPLC tracer of 2.68



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT8.728	8.728	497048	30988
2	RT9.941	9.941	497275	34136



Detector A

ID#	Name	Ret. Time	Area	Height
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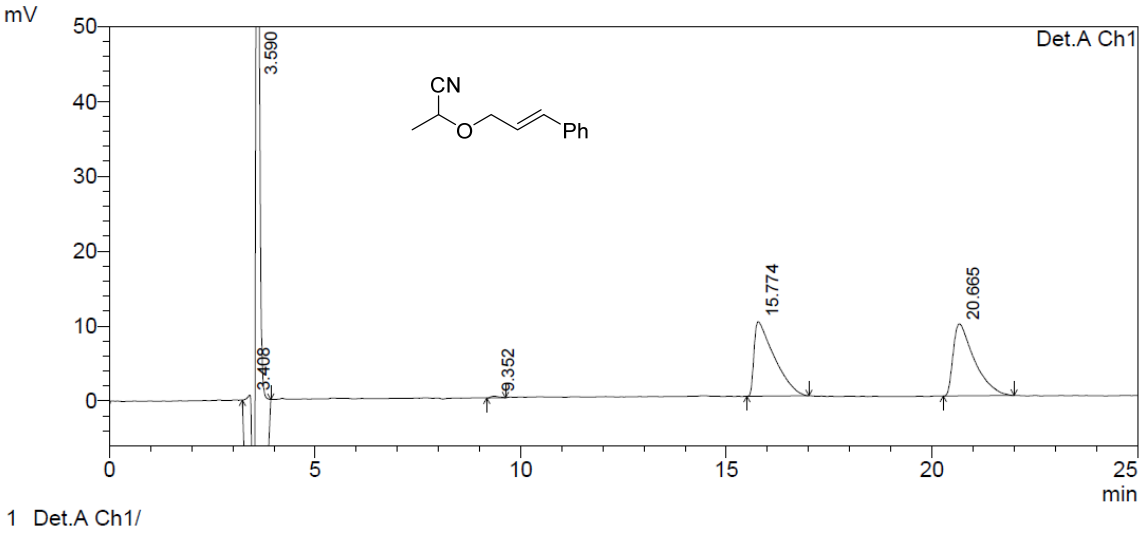
Figure S2.3 HPLC tracer of 2.9



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT15.774	15.774	338780	9946
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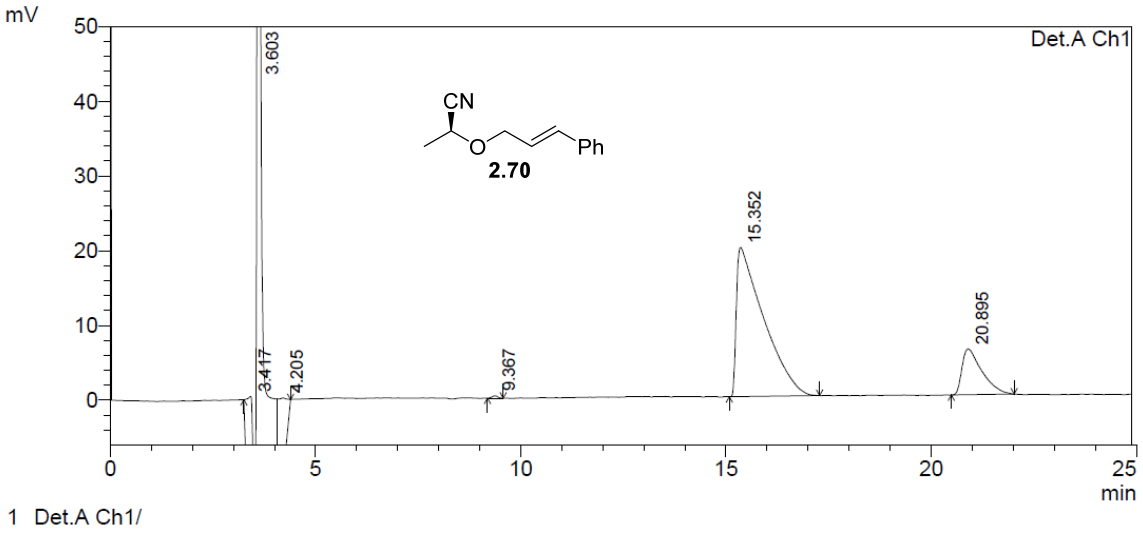

Detector A

ID#	Name	Ret. Time	Area	Height
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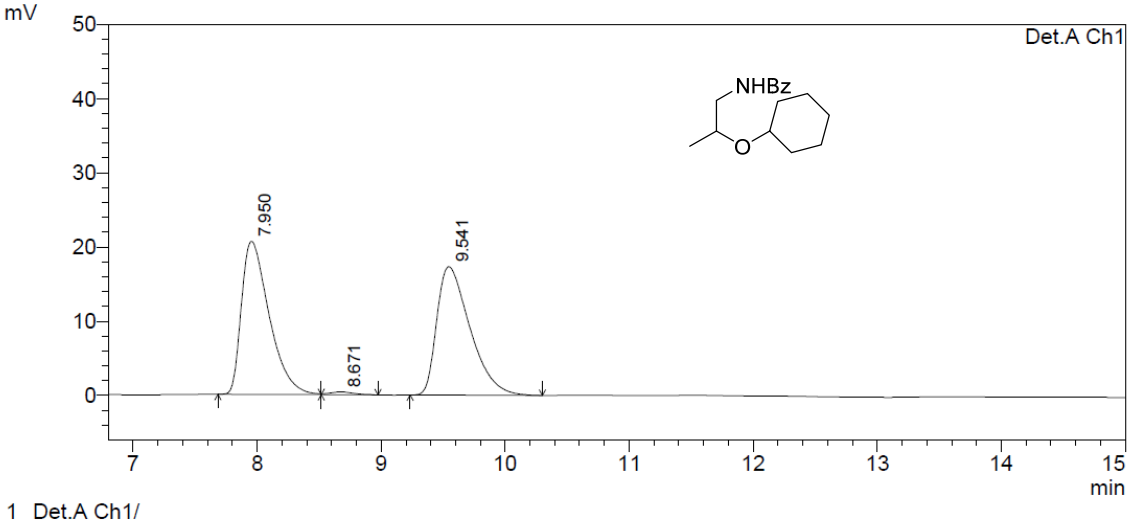
2	RT20.895	20.895	207115	6145

Figure S2.4 HPLC tracer of 2.70



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT7.950	7.950	321349	20639
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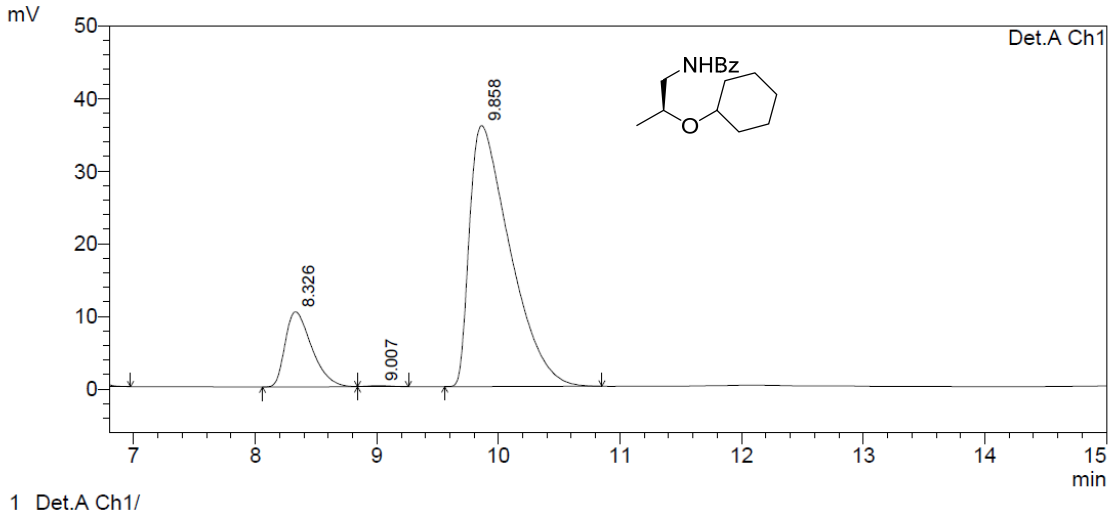
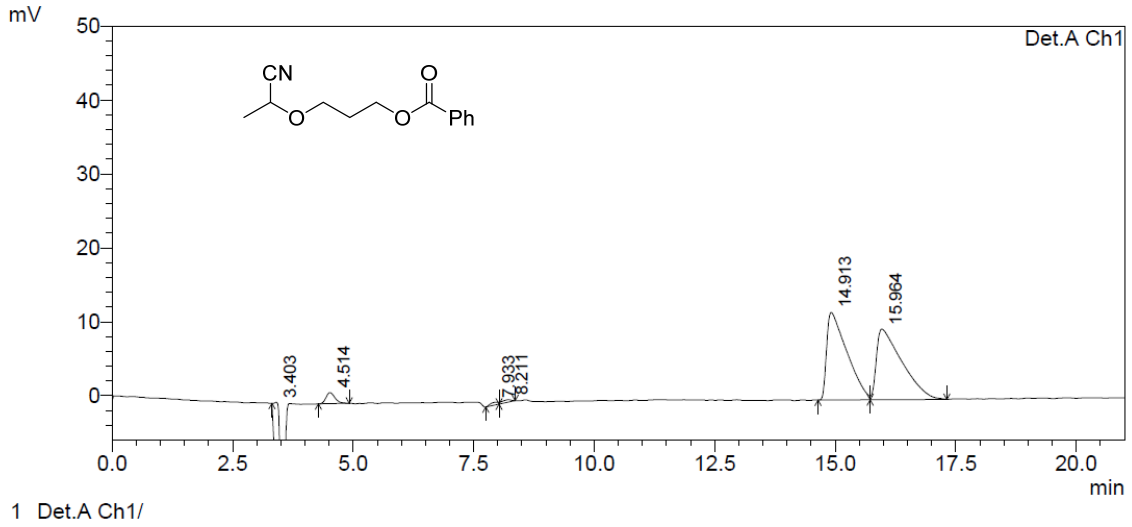


Detector A

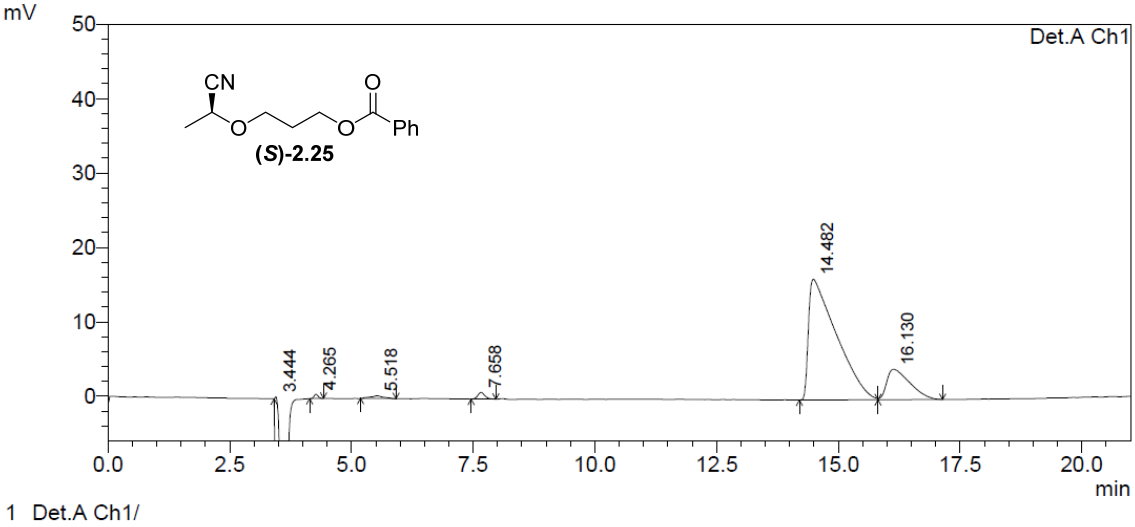
ID#	Name	Ret. Time	Area	Height
1	RT8.326	8.326	157833	10353
2	RT9.858	9.858	833012	35940

Figure S2.5 HPLC tracer of the derivative of 2.72



Detector A

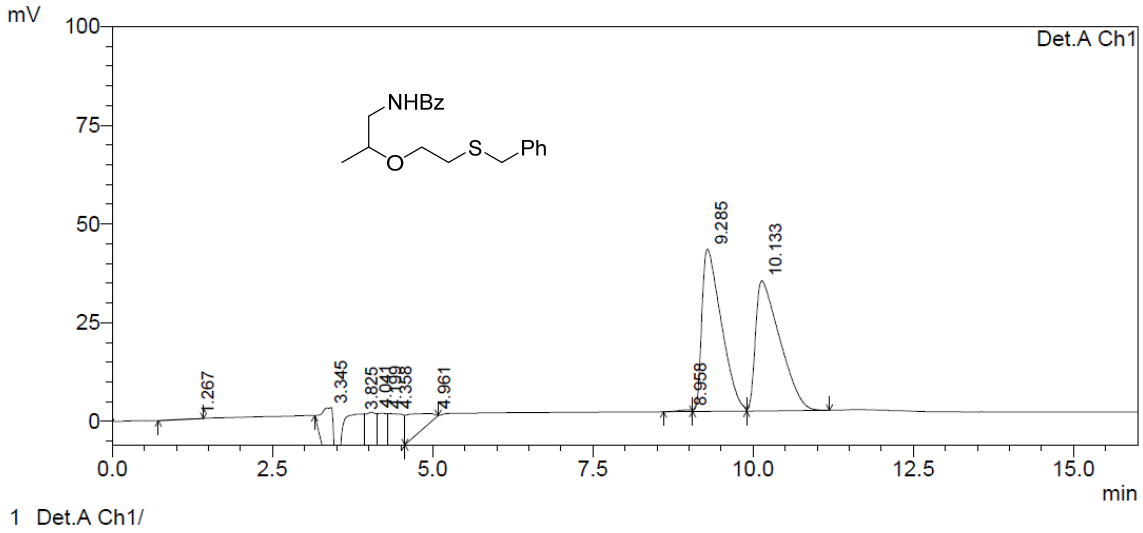
ID#	Name	Ret. Time	Area	Height
1	RT14.913	14.913	346444	11860
2	RT15.964	15.964	352633	9569



Detector A

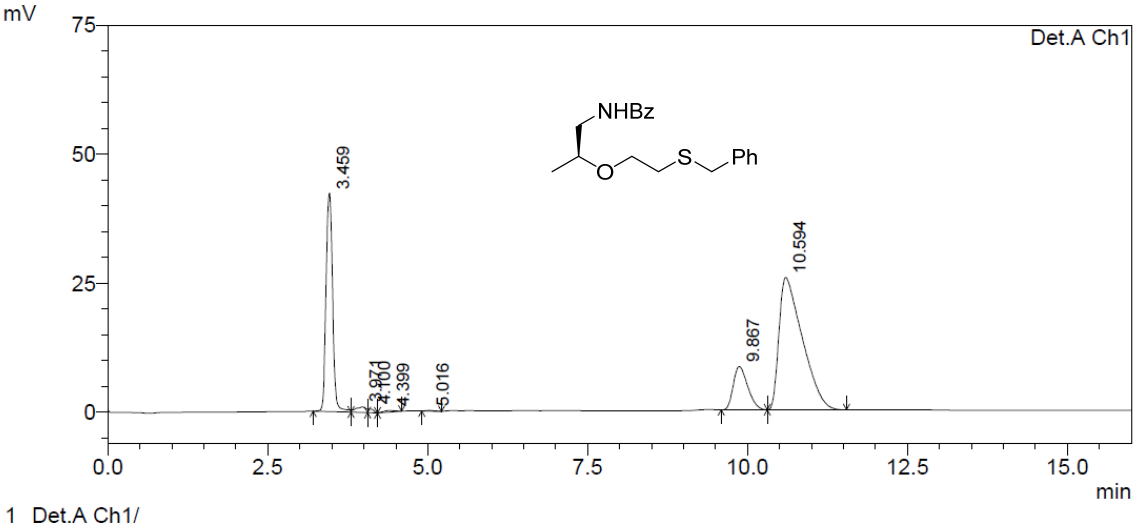
ID#	Name	Ret. Time	Area	Height
1	RT14.482	14.482	646318	16231
2	RT16.130	16.130	134270	4094

Figure S2.6 HPLC tracer of 2.25



Detector A

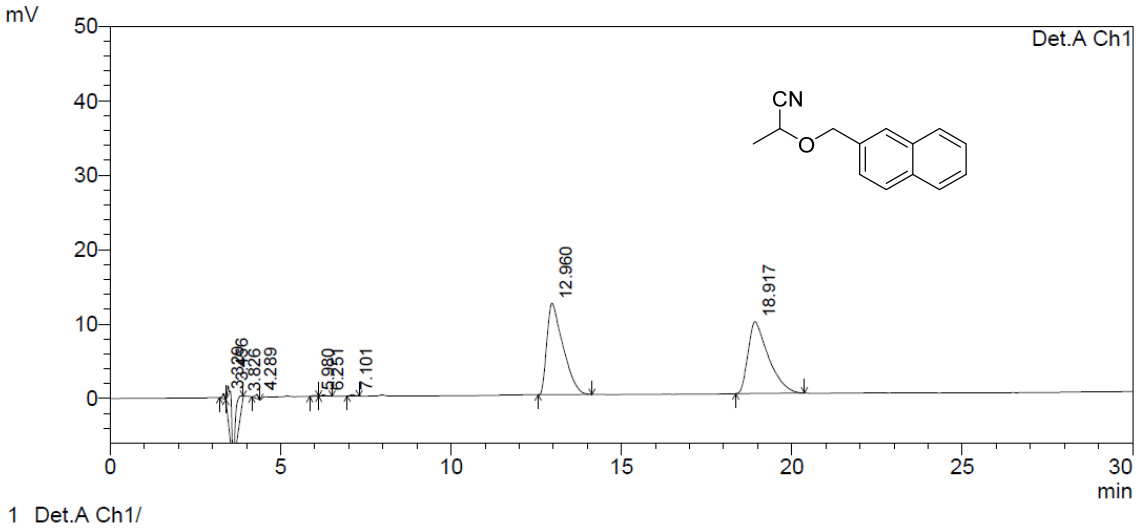
ID#	Name	Ret. Time	Area	Height
1	RT9.285	9.285	869433	41115
2	RT10.133	10.133	873551	32960



Detector A

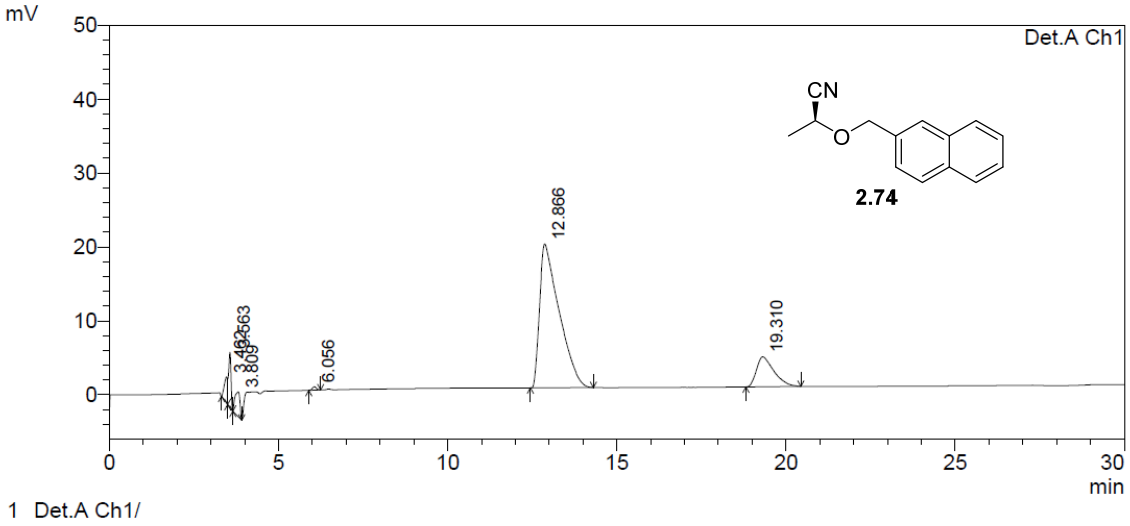
ID#	Name	Ret. Time	Area	Height
1	RT9.867	9.867	132308	8411
2	RT10.594	10.594	650967	25640

Figure S2.7 HPLC tracer of the derivative of 2.15



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT12.960	12.960	403545	12291
2	RT18.917	18.917	399696	9647



Detector A

ID#	Name	Ret. Time	Area	Height
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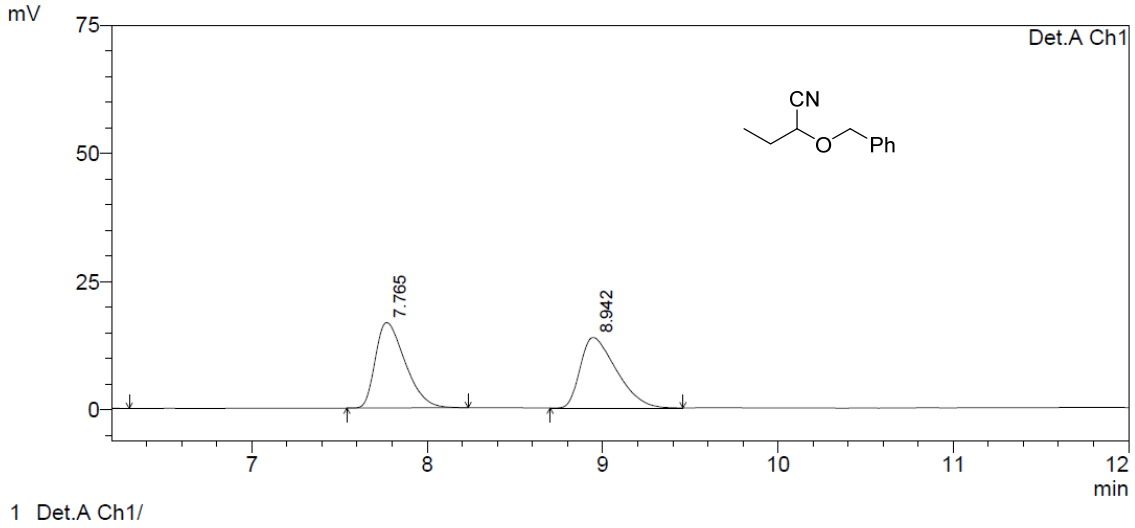
2	RT19.310	19.310	144216	4058

Figure S2.8 HPLC tracer of 2.74



Detector A

ID#	Name	Ret. Time	Area	Height
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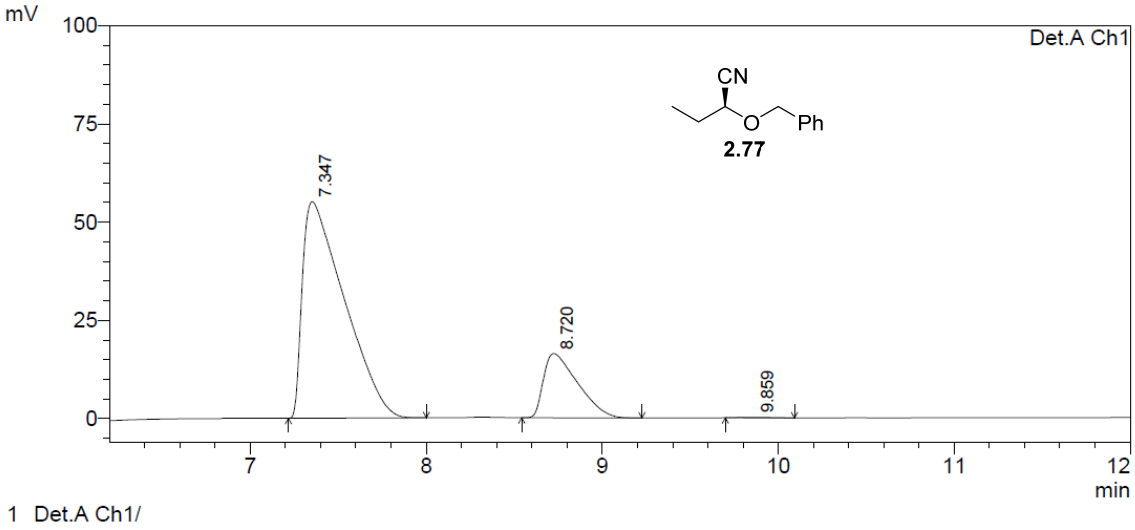

Detector A

ID#	Name	Ret. Time	Area	Height
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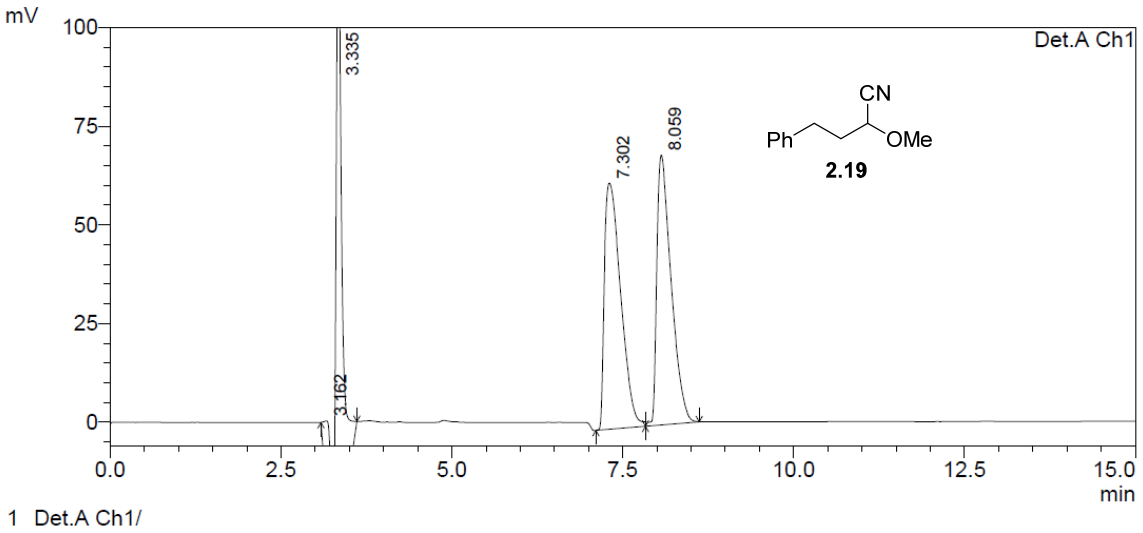
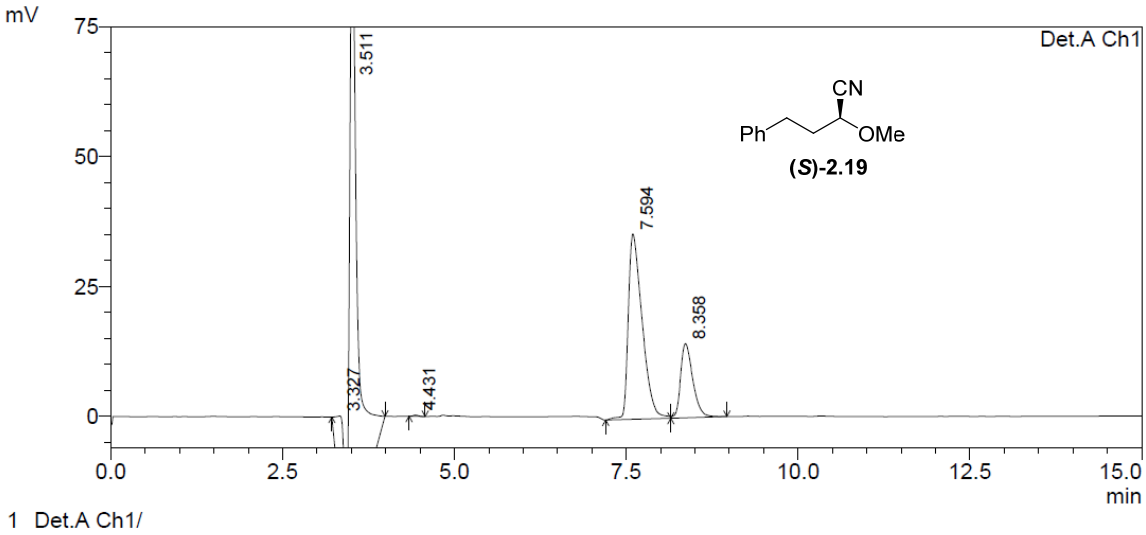
Figure S2.9 HPLC tracer of 2.77



Detector A

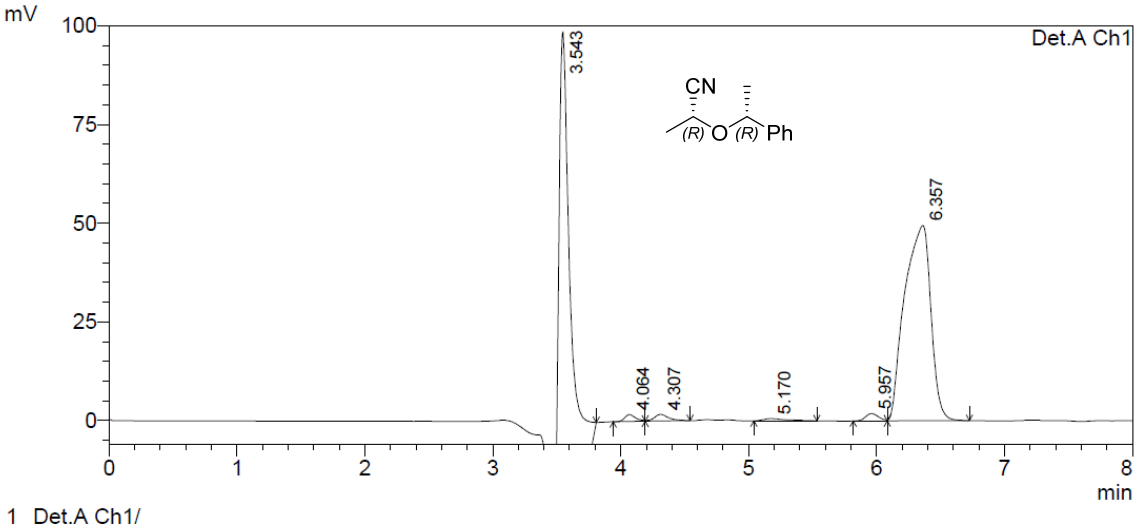
ID#	Name	Ret. Time	Area	Height
1	RT7.302	7.302	1035371	62356
2	RT8.059	8.059	993414	68370



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT7.594	7.594	503437	35690
2	RT8.358	8.358	176696	14272

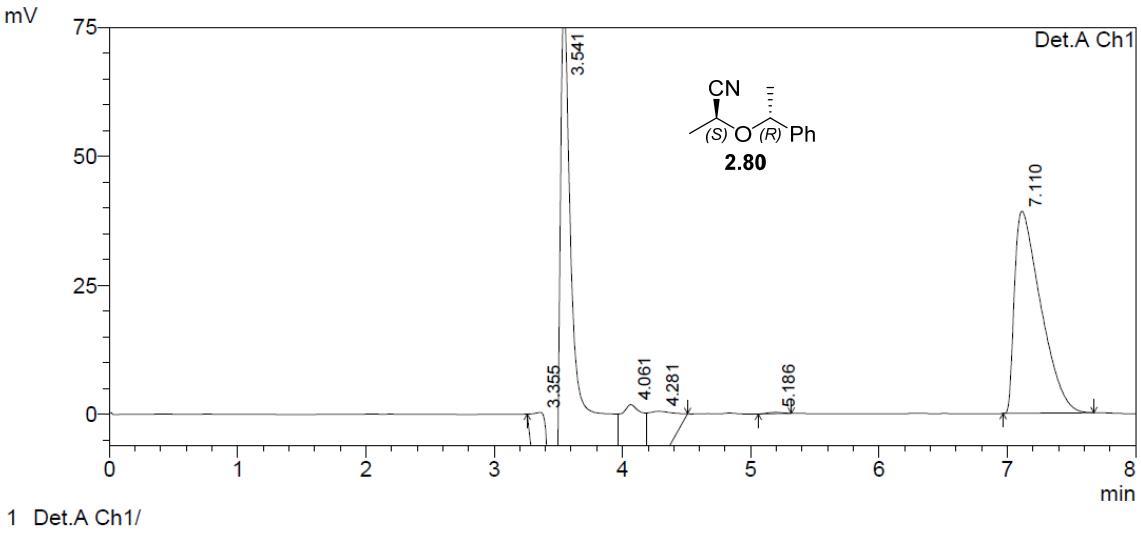
Figure S2.10 HPLC tracer of 2.19



1 Det.A Ch1/

Detector A

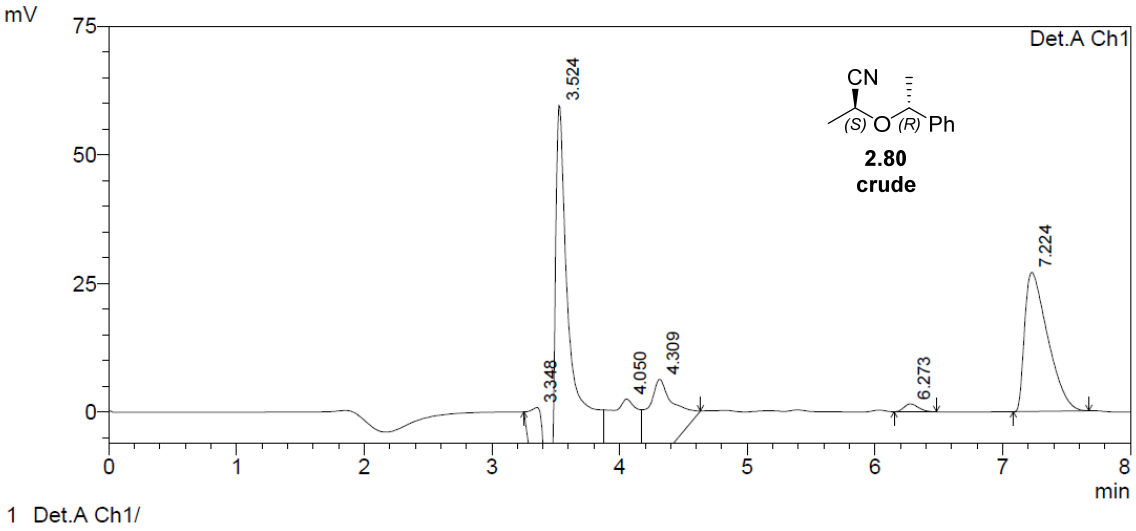
ID#	Name	Ret. Time	Area	Height
1	RT6.357	6.357	701604	49469



1 Det.A Ch1/

Detector A

ID#	Name	Ret. Time	Area	Height
1	RT7.110	7.110	558335	39185



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT6.273	6.273	11849	1518
2	RT7.224	7.224	340058	27054

Figure S2.11 HPLC tracer of 2.80

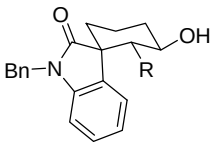
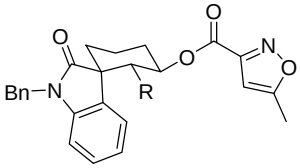
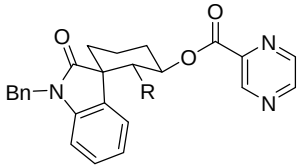
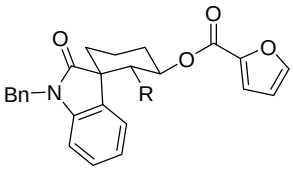
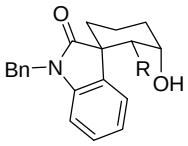
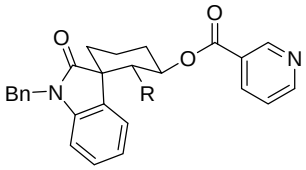
APPENDIX C

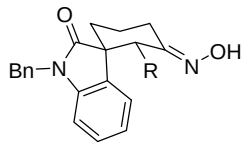
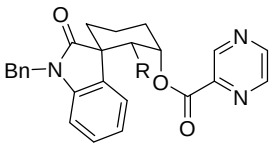
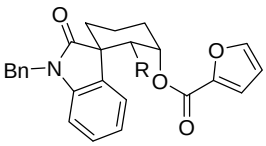
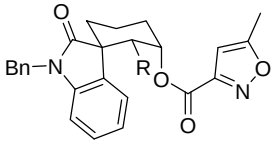
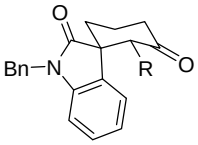
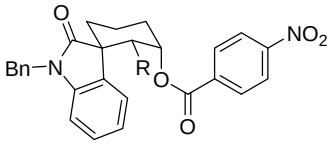
SPIROOXINDOLE LIBRARY COMPOUNDS AND THE PRELIMINARY HIGH THROUGHPUT SCREENING RESULTS

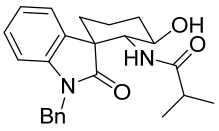
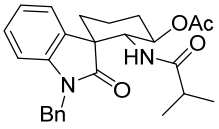
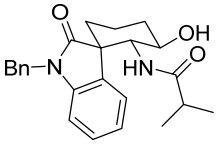
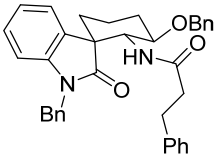
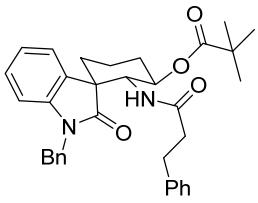
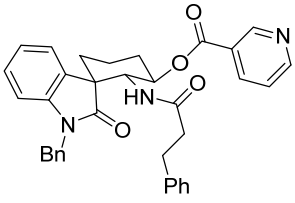
The spirooxindole library compounds were deposited to NIH MLSMR (Molecular Libraries Small Molecule Repository) in April, 2012. Some of the library compounds have been identified to have some biological activity after preliminary high throughput screening. The compound number is provided in the following table, together with the name of the active bioassay.

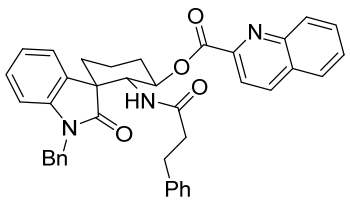
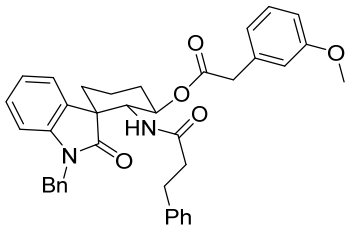
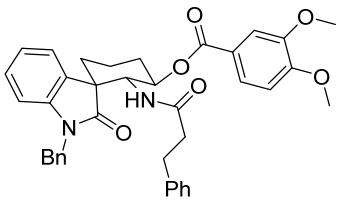
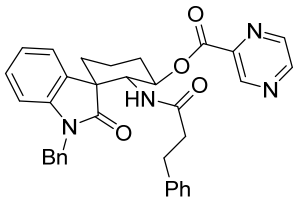
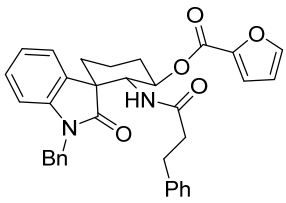
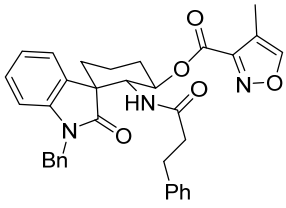
Compounds MLS004342609, MLS004342611, and MLS004342628 are exosite inhibitors for ADAM10 (A Disintegrin and Metalloproteinase Domain-containing Protein 10), which is a major determinant of HER2 (Human Epidermal Growth Factor Receptor 2) shedding. The inhibition of ADAM10 may provide a therapeutic approach for treating cancers with active HER2 signaling, like breast cancer.[81] Compounds MLS004342594 and MLS004342615 are inhibitors for MBD2 (Methyl-CpG-Binding Domain Protein 2), which mediates epigenetic gene silencing and relates to human cancers.[82] The discovery of new MBD2 inhibitors could lead to restoring gene fuction by reactivating the silenced genes in cancer cells.

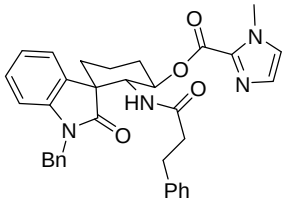
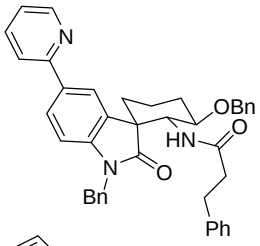
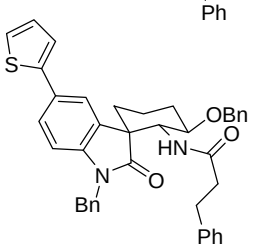
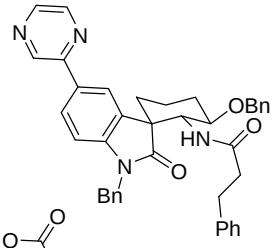
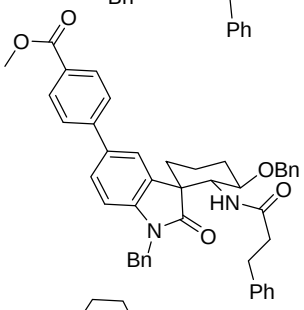
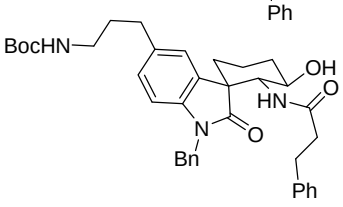
Table S3.1 Spirooxindole library and the related biological activity

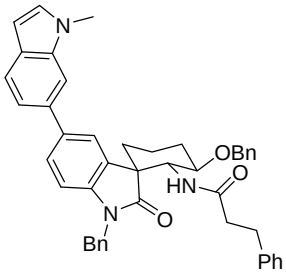
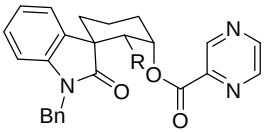
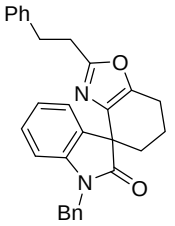
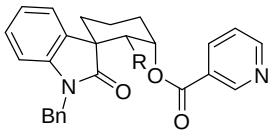
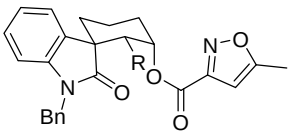
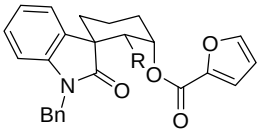
Structure	Substrate SID	Compound Name	Active Bioassay Name
 R = NHC(O)CH_2CH_2Ph	144097065	MLS004342589	
 R = NHC(O)CH_2CH_2Ph	144097066	MLS004342590	
 R = NHC(O)CH_2CH_2Ph	144097067	MLS004342591	
 R = NHC(O)CH_2CH_2Ph	144097068	MLS004342592	
 R = NHC(O)CH_2CH_2Ph	144097069	MLS004342593	
 R = NHC(O)CH_2CH_2Ph	144097070	MLS004342594	TRFRET-based biochemical primary high throughput screening assay to identify inhibitors of 5-meCpG-binding domain protein 2 (MBD2)-DBD binding to methylated oligonucleotide

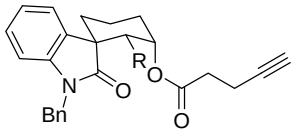
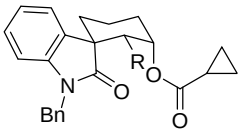
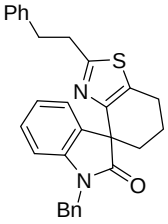
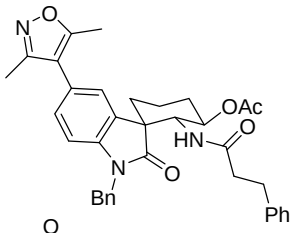
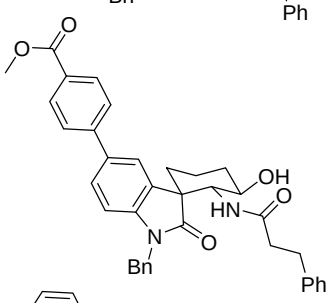
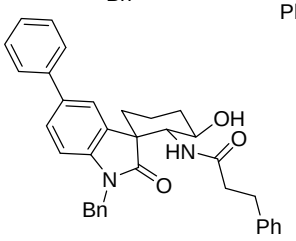
Structure	Substrate SID	Compound Name	Active Bioassay Name
 R = NHC(O)CH_2CH_2Ph	144097071	MLS004342595	
 R = NHC(O)CH_2CH_2Ph	144097072	MLS004342596	
 R = NHC(O)CH_2CH_2Ph	144097073	MLS004342597	
 R = NHC(O)CH_2CH_2Ph	144097074	MLS004342598	
 R = NHC(O)CH_2CH_2Ph	144097075	MLS004342599	
 R = NHC(O)CH_2CH_2Ph	144097076	MLS004342600	

Structure	Substrate SID	Compound Name	Active Bioassay Name
	144097077	MLS004342601	
	144097078	MLS004342602	
	144097079	MLS004342603	
	144097080	MLS004342604	
	144097081	MLS004342605	
	144097082	MLS004342606	

Structure	Substrate SID	Compound Name	Active Bioassay Name
	144097083	MLS004342607	
	144097084	MLS004342608	
	144097085	MLS004342609	QFRET-based biochemical primary high throughput screening assay to identify exosite inhibitors of ADAM10.
	144097086	MLS004342610	
	144097087	MLS004342611	QFRET-based biochemical primary high throughput screening assay to identify exosite inhibitors of ADAM10.
	144097088	MLS004342612	

Structure	Substrate SID	Compound Name	Active Bioassay Name
	144097089	MLS004342613	
	144097090	MLS004342614	
	144097091	MLS004342615	TRFRET-based biochemical primary high throughput screening assay to identify inhibitors of 5-meCpG-binding domain protein 2 (MBD2)-DBD binding to methylated oligonucleotide
	144097092	MLS004342616	
	144099194	MLS004342617	
	144097093	MLS004342618	

Structure	Substrate SID	Compound Name	Active Bioassay Name
	144097094	MLS004342619	
 R = $NHC(O)CH_2CH_2Ph$	144097095	MLS004342620	
	144097096	MLS004342621	
 R = $NHC(O)CH_2CH_2Ph$	144097097	MLS004342622	
 R = $NHC(O)CH_2CH_2Ph$	144097098	MLS004342623	
 R = $NHC(O)CH_2CH_2Ph$	144099195	MLS004342624	

Structure	Substrate SID	Compound Name	Active Bioassay Name
 R = NHC(O)CH_2CH_2Ph	144097099	MLS004342625	
 R = NHC(O)CH_2CH_2Ph	144097100	MLS004342626	
	144097101	MLS004342627	
	144097102	MLS004342628	QFRET-based biochemical primary high throughput screening assay to identify exosite inhibitors of ADAM10.
	144097103	MLS004342629	
	144097104	MLS004342630	

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