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Helicoselective Synthesis of Dioxo[6]helicenes and Design of Original P-Stereogenic Brønsted Acid Organocatalysts.

Peng Liu

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N° BU:

THÈSE

Helicoselective Synthesis of Dioxo[6]helicenes and Design of Original *P*-Stereogenic Brønsted Acid Organocatalysts

Présentée par

Peng LIU

Pour obtenir le grade de **Docteur en Sciences** de l'Université Aix-Marseille

Spécialité : Chimie Organique

École Doctorale des Sciences Chimiques - ED 250

Institut des Sciences Moléculaires de Marseille (*iSm2*)-UMR 7313

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Abbreviations

B	BARF	tetrakis[3,5-	P	<i>p</i> -TSA	<i>para</i> -toluenesulfonic acid	
	BINOL	1,1'-Bi-2-naphthol		R	RCM	ring-closing metathesis
	Boc	<i>tert</i> -butyloxycarbonyl			rt	room temperature
C	cat	catalyst	S	SEGPPOS	SEAGULL PHOS	
	CPA	chiral phosphoric acid		SOMO	singly occupied molecular	
	CPME	cyclopentyl methyl ether		SPINOL	1,1'-spirobiindane-7,7'-diol	
D	dba	dibenzylideneacetone	T	SPO	secondary phosphine oxide	
	DBU	1,8-Diazabicyclo[5.4.0]undec-7-		TEA	triethylamine	
	DCM	dichloromethane		temp	temperature	
	DDQ	2,3-dichloro-5,6-dicyano-1,4-		<i>t</i> Bu	<i>tert</i> -butyl	
	DFT	<i>density functional theory</i>		THBC	tetrahydro- β -carboline	
	(DHQD) ₂ PHAL	hydroquinidine 1,4-phthalazinediyl		THF	<i>tetrahydrofuran</i>	
	DIPEA	diisopropylethylamine		THIQ	tetrahydroisoquinoline	
	DMAP	4-dimethylaminopyridine		TLC	<i>thin layer</i> chromatography	
	DMF	dimethylformamide		TMEDA	tetramethylethylenediamine	
	DMSO	dimethyl sulfoxide		TUC	thiourea catalyst	
	DNA	deoxyribonucleic acid		U	UV	ultraviolet
	DKR	dynamic kinetic resolution			VAPOL	4,4'-dihydroxy-2,2'-diphenyl-
	dr	diastereomeric ratio			VCD	vibrational circular dichroism
E	ECD	electronic circular dichroism	VQM	vinylidene quinone methide		
	ee	enantiomeric excess				
H	HOMO	highest occupied molecular orbital				
	HPLC	high pressure liquid				
	HRMS	high resolution mass spectrometry				
I	<i>i</i> Pr	isopropyl				
M	MOM	methoxymethyl ether				
	MS	molecular sieves				
	MW	microwaves				
N	NBS	N-bromosuccinimide				
	NBP	N-Bromophthalimide				
	NHC	nucleophilic heterocyclic carbene				
	NMR	Nuclear Magnetic Resonance				
	NTs	N-tosyl				
O	OAc	acetoxy				
	Ox	oxidation				

General introduction

It has been nearly 400 years, since the early chemist Boyle proposed the concept of element. This also marks the initial establishment of the discipline of chemistry.¹ Since that time, various natural science together with chemistry have flourished. The joint efforts of generations of scientists have continued to promote the progress and development of human society.

Chemistry, as an ancient and brand-new discipline, has become a very important discipline after hundreds of years of development. Chemistry is the science of studying the composition, properties, structure, and changing laws of matter at the molecular and atomic levels, the science of creating new matter. Among various branches, organic chemistry is a science that studies the composition, structure, properties, preparation methods, and applications of organic compounds.²

In 1874, the French chemist Leber and the Dutch chemist Van Tov respectively proposed a new concept: isomers. They believe that the molecule is a three-dimensional entity, the four valence bonds of a carbon atom are symmetrical in space, and point to the four vertices of a regular tetrahedron, respectively, and the carbon atom is located in the center of the regular tetrahedron. When a carbon atom is connected to four different atoms or groups, a pair of stereoisomers are generated, which are physical and mirror images of each other, or the chiral relationship of the left and right hands. This pair of compounds is an optical isomer or enantiomers. This phenomenon is called enantiomerism. These two molecules, which form a real object and a mirror image, are opposite to each other but cannot be completely coincidently called chiral molecules. Leber's and Van Tov's theory is the basis of stereochemistry³ in organic chemistry.

¹ K. R. Williams, *J. Chem. Educ.* **2009**, 86, 2, 148.

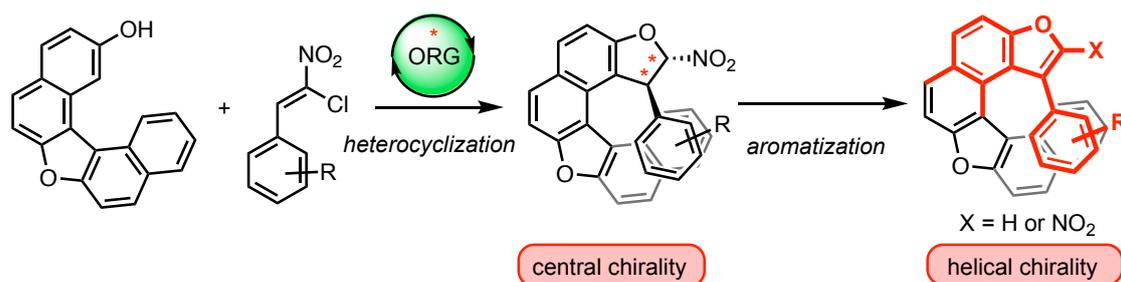
² E. W. Vitz, *J. Chem. Educ.* **1979**, 56, 5, 327.

³ a) J. D'Angelo, M. B. Smith, *Hybrid Retrosynthesis*, **2015**. b) J. D. Rawn, R. Ouellette, *Organic Chemistry (Second Edition)*, **2018**. c) R. Ouellette, J. D. Rawn, *Organic Chemistry Study Guide*, **2015**, 1st edition.

In the past 100 years, science has evolved tremendously, allowing human kind to develop an extraordinary rationalization of natural phenomena. These incredible changes, were driven by revolutionary discoveries, such as the creation of a consistent model for the structure of the atom in chemistry. Also, in organic chemistry, incredible progresses have been made. At the beginning of the century organic chemists started by preparing and characterizing molecules with only few atoms, while today we are able to synthesize much more sophisticated structures. Despite these achievements, the challenge of controlling both the efficiency and the stereoselectivity of a reaction remains open. The present manuscript compiles our recent contributions to this field based both on the development of new enantioselective organocatalytic reactions and on the design of new chiral organocatalysts.

In the first introductory chapter, we discuss the definition of chirality as a transversal topic in science. Then, we will present the different strategies to control chirality in organic synthesis, with a special attention to enantioselective organocatalysis.

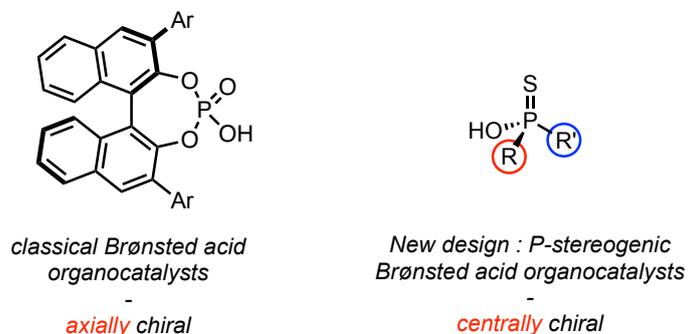
In the second chapter, we will discuss our results on the enantioselective synthesis of new heterohelicenes based on an organocatalytic heterocyclization/aromatization sequence (Scheme 1).



Scheme 1. Enantioselective synthesis of heterohelicenes

In the third chapter, we have developed a new kind of Brønsted acid catalyst, which possesses a stereogenic phosphorous atom (Scheme 2). Compared with traditional

chiral phosphoric acid catalysts (CPA), which display axial chirality, our new catalysts have important advantages and could be very complementary of the classical ones.



Scheme 2. New design for Brønsted acid organocatalysis

The research in this thesis provides a new method for the synthesis and application of helically chiral compounds, and also gives new insight for the development and application of original Brønsted acid organocatalysts.

Chapter 1: Background of chirality in science

1.1) Research and definition of chirality

During the past fifty years, the interest in the phenomenon of chirality has grown constantly, both among the academic and the industrial communities. The term *chirality* derives from the Greek “χειρ” which means “hand”. This word is used for objects that are mirror images one of each other, just like hands. A chiral object is not superimposable to his mirror image. These objects possess no symmetry element of the second kind, such as a mirror plane, a center of inversion or a rotation-reflexion axis.⁴ The couple of not superimposable objects are said to be chiral and are called enantiomers. Whenever we encounter a mix of 1:1 enantiomers we call it a racemic mixture.⁵ To understand better the phenomenon of chirality and its implications in modern science, we will trace back the first time it has been recognized.

In 1848, Louis Pasteur, examining a racemic mixture of tartaric acid crystals with a microscope, discovered that they had a peculiarity: they formed two different types of crystals, each being the mirror image of the other (Figure 1).⁶ One further discovery was that one kind of crystal rotated polarized light clockwise while the other anticlockwise. The next step was Pasteur’s formulation of a molecular theory that postulated the existence of molecules belonging to two types: one “left-handed” and one “right-handed”.

⁴IUPAC. *Compendium of Chemical Terminology*, Blackwell Scientific Publications, Oxford, **1997**.

⁵ (a) H. W. Moseley, *J. Chem. Educ.* **1928**, *5*, 1, 50. (b) J. Chen, A. S. Myerson, *CrystEngComm*, **2012**, *14*, 8326. (c) Y. Tobe, *Mendeleev Commun.* **2003**, *13*, 93.

⁶ J. Gal, *Nature Chem.* **2017**, *9*, 604.



Figure 1. Large crystals of sodium ammonium tartrate prepared by the seeding method. Left, (-)-enantiomer; right, (+)-enantiomer

However, it was not until 1893, that a formal definition of chirality or “handedness” was formulated by Lord Kelvin during a conference at the Oxford University Junior Science Club: “I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself”.⁷ The couple of enantiomers were lately labeled D/(+)-enantiomer in the case of clockwise rotation and L/(-)-enantiomer in the case of anticlockwise rotation.

The classical example of object having the property of being chiral is human’s hands. In Nature both enantiomers can exist, but in many cases only one is effectively observed, we call this preference “handedness” of Nature. An example of enantiomers existing in nature are helical seashells belonging to the family of *Liguus Virgineus*, which exist only in their left-hand helix seashell, or the orbit of an electron in the proximity of the nucleus, which exists only as a right-hand helix (Figure 2).⁸

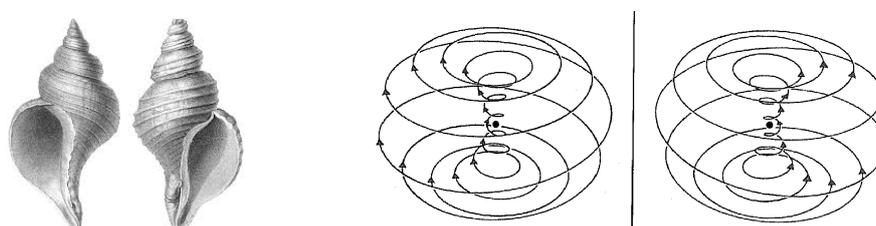


Figure 2. *Liguus Virgineus* (left) and orbital of an electron (right)

⁷ W. T. Kelvin, *The Molecular Opticics of Cristals*, 1894.

⁸ R. A. Hegstrom, D. K. Kondepudi, D. K. *Scientific American*, 1990, 108.

This concept of handedness, or chirality, is extremely general and finds applications in many fields, from cosmology to chemistry and biology.

1.2) Different types of chirality

There are four main types of chiral molecules (Figure 3).⁹ First, the central chirality is due to the asymmetry of any atom in the molecule, resulting in the presence of a stereogenic center. The second type is axial chirality, which is found in allene-type or biphenyl-type molecules. The third type is planar chirality, which is exhibited by molecules like (*E*)-cyclooctene, some poly-substituted metallocenes, and certain monosubstituted paracyclophanes. The last one is known as helical chirality, which is less common in compounds as compared with central or axial chirality. In this thesis, our work mainly focused on the studies of central and helical chiralities.

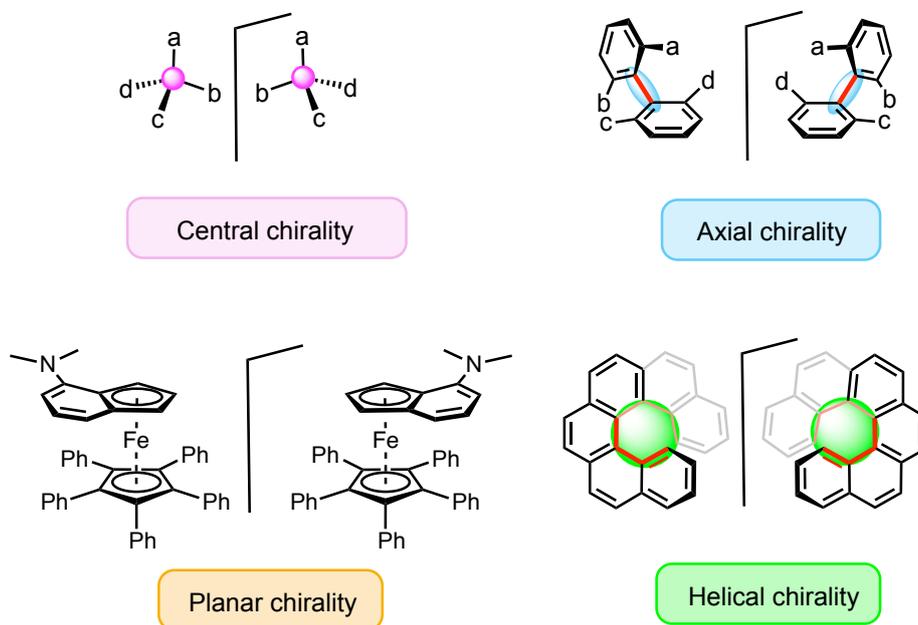


Figure 3. Different kinds of chiral molecules

⁹ E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, Univ. Science Books, 2005.

1.3) The importance of controlling chirality

On Earth, the phenomenon of homochirality is encountered: the almost exclusive presence of only one of the two possible enantiomers of certain molecules. Since life on Earth developed prevalently on L-aminoacids and D-sugars, the tridimensional structure of biological aggregates like proteins or nucleic acids are also chiral. Proteins such as enzymes, for example, have a chiral folding and that use only enantiopure substrates to perform their transformations.¹⁰ Therefore, when designing a new biologically active compound, it is important to be able to control which of the two enantiomers to synthesize. A famous case in medicine history is the one of thalidomide, an antiemetic drug, which was largely prescribed in the 50s and 60s to pregnant women. At the time, pharmacological studies were performed on racemates, not taking into account the possible effects of each enantiomer. In the case of thalidomide, the (*S*)-enantiomer (Figure 4) was responsible of the desired antiemetic activity. However, the (*R*)-enantiomer caused mutation of the fetus. Furthermore, recent studies have demonstrated that even the pure (*S*)-enantiomer racemizes *in vivo*.¹¹

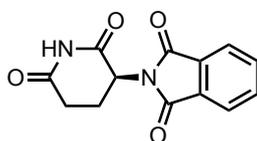


Figure 4. Structure of (*S*)-thalidomide

This and other similar cases culminated in the drafting of strict guidelines for registration of chiral drugs, where both the enantiomers need to be tested for biological activity.¹² However, to perform such tests, each potential drug must be available as pure single enantiomer. In principle, three approaches may be adopted to achieve that:

¹⁰ D. G. Blackmond, *Cold Spring Harb. Perspect. Biol.* **2010**.

¹¹ T. Ito, H. Ando, T. Suzuki, T. Ogura, K. Hotta, Y. Imamura, Y. Yamaguchi, H. Handa, *Science*, **2010**, 327, 1345.

¹² G. D. Lin, Q.-D. You, J.-F. Feng *Chiral Drugs: Chemistry and Biological action* Wiley-VCH: Weinheim, Germany **2011**.

resolution of a racemic, stereoselective synthesis starting from chiral pool and conversion of an achiral or prochiral substrate into a chiral one by enantioselective catalysis.¹³ The last methodology involves a transfer of chirality, meaning that one molecule of chiral catalyst can produce several hundreds or even thousands of enantioenriched molecules. In this manuscript, we will focus our attention mainly on the last method.

A catalyst is a molecule that is able to accelerate the reaction rate by decreasing the activation energy and that is regenerated at the end of the reaction. Enantioselective catalysis goes much further, since it is able to produce the enantiomeric products in unequal amounts. This happens thanks to the interaction between the catalyst and the substrates at the transition state. In enantioselective catalyzed systems, two diastereomeric transition states are created, one of which will be favored (less energetic) over the other one leading to an enantiomeric excess in the product (Figure 5).¹⁴

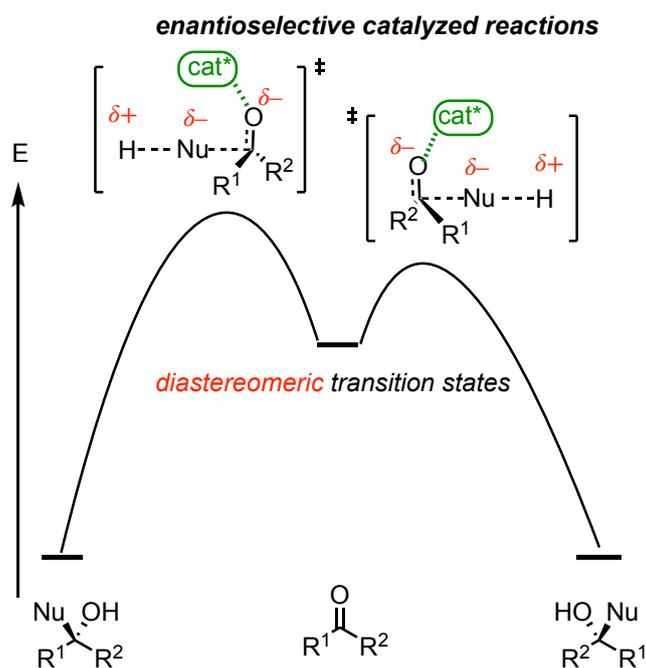


Figure 5. Scheme of catalyzed enantioselective reaction

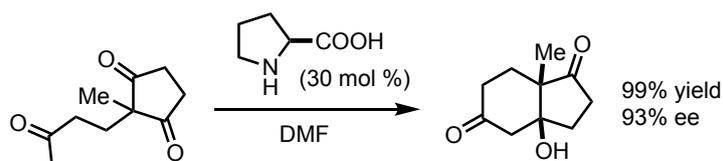
¹³ S. Bhadur, D. Mukesh, *Homogeneous Catalysis: Mechanisms and Industrial Applications* Wiley and Sons, Inc., **2000**.

¹⁴ J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, Oxford, **2012**.

1.4) Different strategies to control chirality

In the field of enantioselective catalysis, there are three basic modes for controlling chirality, which are metal catalysis, organic catalysis and biocatalysis. In the past two decades, organic catalysis has been revived and developed due to its various advantages, such as cheapness, stability and availability. However, even if smart solutions have been elaborated over the years, much development is still needed. No catalyst is general enough, and unremitting efforts are still needed to develop various efficient catalysts to adapt to the progress and development of organic chemistry.

In the Scheme 3, this is the proline-catalyzed intramolecular enantioselective aldol reaction,¹⁵ which is one of the earliest work in the field of enantioselective organocatalysis catalysis in 1971.



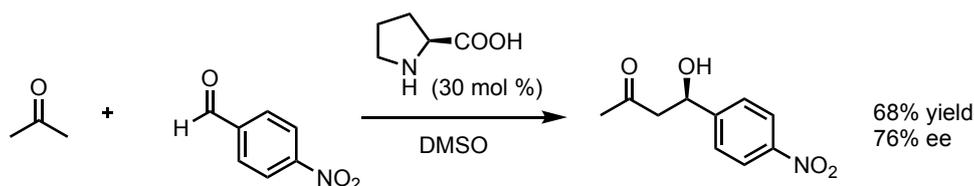
Scheme 3. Hajos–Parrish–Eder–Sauer–Wiechert reaction

Thirty years later, List reported the proline-catalyzed direct intermolecular enantioselective aldol reactions (Scheme 4).¹⁶ although the enantiomeric excess is moderate (76% ee), this conceptualization of organic catalysis has brought unprecedented enthusiasm and an explosion in the number of publications reporting the use of organocatalysis.¹⁷

¹⁵ U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl.* **1971**, 10, 496.

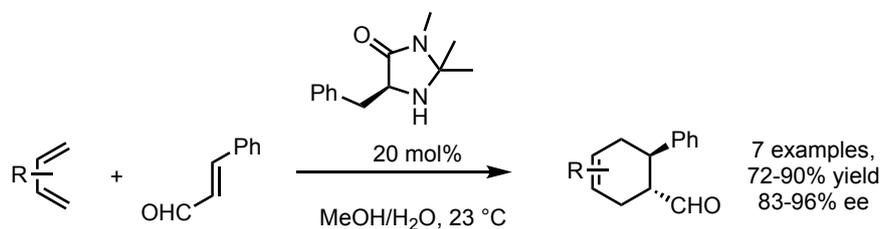
¹⁶ B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395.

¹⁷ a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 6798. b) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620. c) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem., Int. Ed.* **2003**, 42, 2785. d) M. Arno, Domingo, L. R. Theor. *Chem. Acc.* **2002**, 108, 23. e) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala,



Scheme 4. The concepts of organocatalysis and its revival

Another pivotal contribution to the birth of organocatalysis comes from the work of MacMillan (Scheme 5). In the same year as List, he published the first enantioselective organocatalyzed Diels-Alder reaction. Thanks to an imidazolidinone catalyst, highly enantioenriched cyclohexenes could be obtained.¹⁸



Scheme 5. MacMillan's enantioselective Diels-Alder reaction

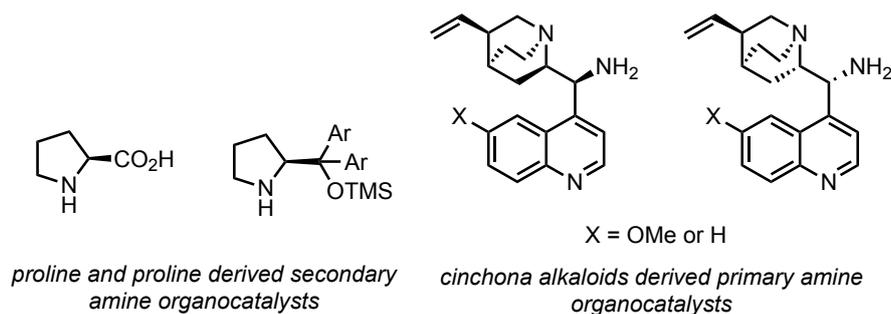
1.5) The different activation modes of organocatalysis

Small organic molecules can be used as catalysts for enantioselective reactions and this is today a mature field of research, even if it is only developed very well during the last twenty years. Organocatalysis has some advantages and is very complementary to other catalyses (metal- and biocatalysis). Organocatalysts are in general non-sensitive towards moisture and air, inexpensive and easy to prepare, available in both enantiomers, non-toxic and simple to use.

R. Hobi, *Helv. Chim. Acta*, **2007**, 90, 425. f) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkowicz, R. R. Terrell, *J. Am. Chem. Soc.* **1963**, 85, 207. g) A. Córdova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W. W. Liao, W. W. *Chem. Commun.* **2005**, 3586.

¹⁸ K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243.

Several years ago, the concept named enantioselective aminocatalysis was established by using chiral primary and secondary amines as efficient and powerful catalysts. If proline-derived catalysts are very popular, primary amine catalysts derived from cinchona alkaloids are also used to promote the functionalization of sterically hindered carbonyl compounds (Scheme 6).¹⁹ There are four different structures of this kind of catalysts.



Scheme 6. Different families of aminocatalysts

We will discuss the two main activation modes dealing with either covalent or non-covalent interactions. The covalent activation means that a covalent bond is formed between the catalyst and one of the starting materials in the reaction process. Enamine is a traditional covalent activation. Beside this, iminium activation, SOMO and nucleophilic activation (NHC, DMAP) also belong to the covalent activation.

1.5.1) Covalent activation

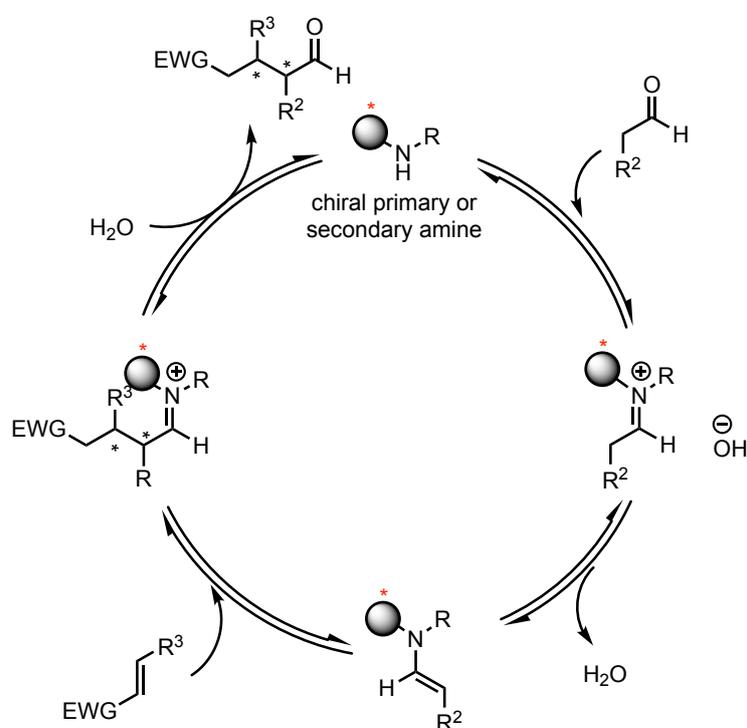
1.5.1.1) Enamine activation

Enamine activation can be sometimes recognized as bifunctional catalysis because the chiral amine-containing catalyst interacts with the carbonyl compound to form the

¹⁹ a) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.* **2011**, 1, 354. b) J. Duan, P. Li, *Catal. Sci. Technol.* **2014**, 4, 311. c) C. E. Song, *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis*, **2009**, Wiley-VCH Verlag GmbH & Co. KGaA. d) P. J. Boratyński, M. Zielińska-Błajet, J. Skarzewski, *The Alkaloids: Chemistry and Biology*, **2019**, 82, 29. e) K. M. Kacprzak, *Chemistry and Biology of Cinchona Alkaloids*, **2013**, 21, 606.

enamine intermediate and then engages with the electrophilic partner by either hydrogen-bonding or electrostatic interactions.

The Scheme 7 is showing the mechanism of α -functionalization of carbonyl compounds, which proceeds by enamine activation. The catalytic cycle starts from the condensation of the chiral amine catalyst and the aldehyde compound, to form the iminium ion. The iminium ion is in equilibrium with enamine intermediate. This enamine has a higher HOMO orbital compared with the free carbonyl compound, thus is activated toward performing a nucleophilic addition on an electrophile and then forms an iminium ion. Finally, the hydrolysis of this resulting functionalized iminium ion will liberate the aldehyde product and the amine catalyst will be available for another catalytic cycle.²⁰

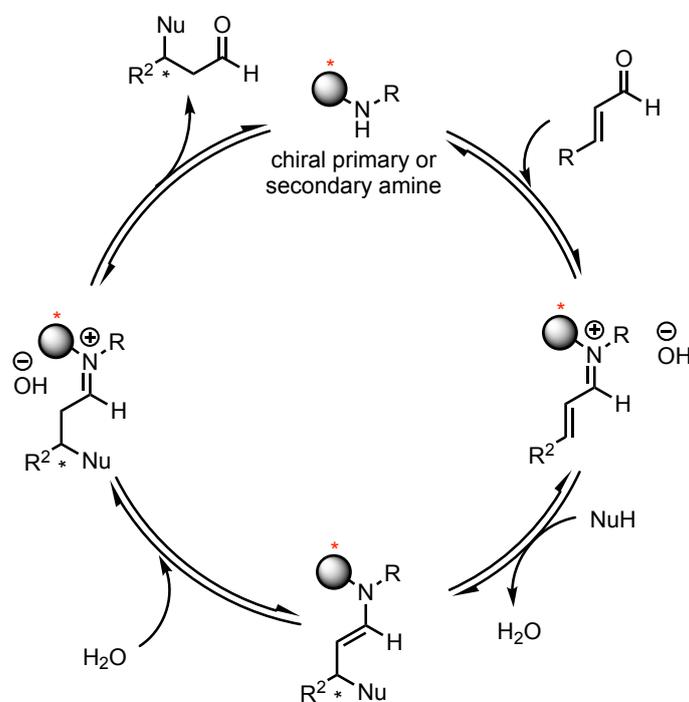


Scheme 7. Amino-catalyzed α -functionalization of aldehydes

²⁰ a) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, 38, 2178. b) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, 47, 632.

1.5.1.2 Iminium activation

Comparing with the α -functionalization of carbonyl compounds, the β -functionalization of α,β -unsaturated aldehydes proceeds by the iminium activation cycle. The initial step is condensation between the amine catalyst and the unsaturated aldehyde, it will form a conjugated iminium ion intermediate. Then the addition of a nucleophile to the β -carbon atom of the iminium ion will lead to the functionalized enamine. It is in tautomeric equilibrium with the corresponding iminium ion. As a result, the iminium ion is hydrolyzed to release the final product and catalyst to enter in the next catalytic cycle (Scheme 8).²¹



Scheme 8. Amino-catalyzed β -functionalization of α,β -unsaturated aldehydes

²¹ A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, 107, 5416.

1.5.2) Non-covalent activation

1.5.2.1) Hydrogen-Bond catalysis

The hydrogen-bonding interaction plays an important role in the molecular recognition and activation processes of various biological reactions, which are normally mediated by the enzymes or the antibodies in living organisms. Initially, the hydrogen-bonding was thought to be insufficiently strong to be used in enantioselective catalysis until the late 90s when Jacobsen²² and Corey²³ independently reported enantioselective Strecker reaction, which used the hydrogen-bonding organocatalysts that activate imine electrophiles. Many different chiral hydrogen-bond catalysts have been developed over the years,²⁴ including cinchona alkaloid derivatives, thiourea/urea, squaramide catalysts and the most popular Brønsted acids such as chiral phosphoric acid derivatives (CPAs).

a) Urea/thiourea

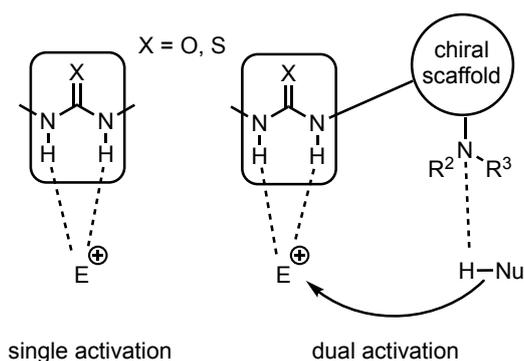
The urea and thiourea derivatives have been intensively investigated in the area of molecular recognition due to their strong hydrogen-bonding activity. They can be used to recognize carboxylic acids, sulfonic acids, nitrates, and others through multi-hydrogen bonding. The realization that urea and thiourea are compatible with a big range of Lewis bases has allowed the development of bifunctional catalytic systems, while adding an extra level of complexity to catalyst design, it will provides new opportunities regarding not only the rate-enhancing simultaneous activation of both the electrophile and nucleophile, but also in terms of enantioselective control thanks to the catalysts chiral environment (Scheme 9).²⁵

²² M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 4901.

²³ E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, 1, 157.

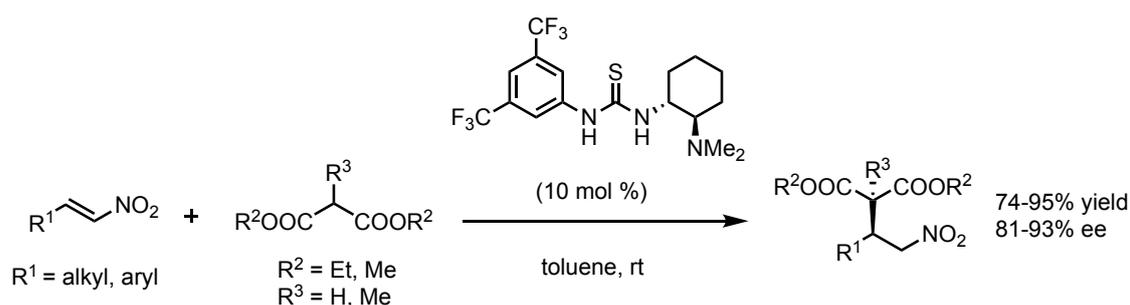
²⁴ a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, 107, 5713. b) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, 32, 289.

²⁵ a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, 3, 4299. b) S. J. Connon, *Chem. Eur. J.* **2006**, 12, 5418. c) S. J. Connon, *SYNLETT*, **2009**, 3, 354. d) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, 38, 1187.



Scheme 9. Dual activation concept using bifunctional thiourea

The first enantioselective Michael addition was reported by Takemoto's group in 2003 by using the bifunctional amine thiourea-organocatalyst (TUC) (Scheme 10).²⁶ This kind of bifunctional organocatalyst promotes the enantioselective Michael reaction between malonates and nitroolefins which has marked an important breakthrough in enantioselective organocatalysis.²⁷



Scheme 10. First enantioselective Michael addition catalyzed by a bifunctional amine thiourea organocatalyst (TUC)

e) W.-Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, 1, 1298. f) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, 14, 1724.

²⁶ a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, 125, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X.-N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, 127, 119.

²⁷ For metal catalysis, see: a) J. Ji, D.M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger, H. E. Morton, *J. Am. Chem. Soc.* **1999**, 121, 10215; b) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, 124, 8192; c) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, 124, 5262; d) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, 124, 13097; e) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, 126, 11148.

b) Squaramides

Squaramides were also initially used as synthetic anion receptors due to the special properties of the molecular recognition.²⁸ The most significant difference between thioureas and squaramides is the relative distance and spacing between the two N-H groups (Figure 6). The Takemoto²⁹ and Rawal³⁰ groups have calculated the distances for *N,N'*-dimethylthiourea and *N,N'*-dimethylsquaramide to be approximately 2.13 Å and approximately 2.72 Å.



Figure 6. Comparison between squaramide and thiourea motives

Because of a larger distance between the two N-H groups and some further structural alterations, the pKa value of the squaramide moiety is lower compared to their thiourea (Figure 7).³¹ So, the activity of the corresponding squaramide catalyst is slightly raised.

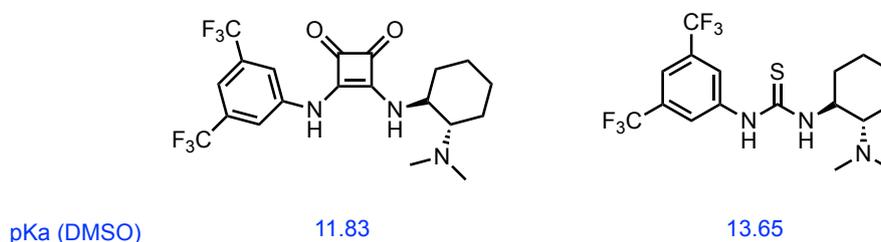


Figure 7. Comparison of pKa values between squaramide and thiourea catalysts

²⁸ a) B.-L. Zhao, J.-H. Li, D.-M. Du, *Chem. Rec.* **2017**, 17, 1. b) F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, 6, 645. c) X.-J. Cai, Z. Li, W.-H. Chen, *Mini-Reviews in Organic Chemistry*, **2018**, 15, 148. d) X. Ni, X. Li, Z. Wang, J.-P. Cheng, *Org. Lett.* **2014**, 16, 1786.

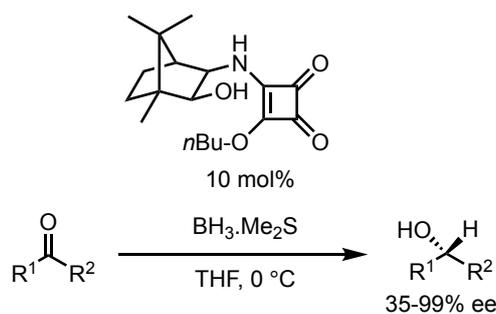
²⁹ T. Okino, Y. Hoashi, T. Furukawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, 127, 119.

³⁰ J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, 130, 14416.

³¹ a) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, 14, 1724. b) Xiang Ni, Xin Li,* Zhen Wang, and Jin-Pei Cheng, *Org. Lett.* **2014**, 16, 1786.

Due to the special structure, the squaramide moiety forms stronger hydrogen bonds with the substrates bearing nitro, carbonyl, imino, nitrile functionalities, etc. The squaramides effectively act as the H-bond donor catalysts making them an effective alternative to thiourea catalysts. In the next part, more examples of details about the use of squaramides in organocatalysis will be discussed.

Xie reported the first example using a chiral squaramide in enantioselective catalysis (Scheme 11).³² The enantioselective reduction of prochiral ketones was made with borane dimethyl sulfide combined with catalytic amounts of chiral squaric amino alcohols, the final secondary alcohols can be obtained with enantiomeric excesses up to 99%. In this example, the squaramide derivative was used as a chiral ligand, but not as a bifunctional catalyst.



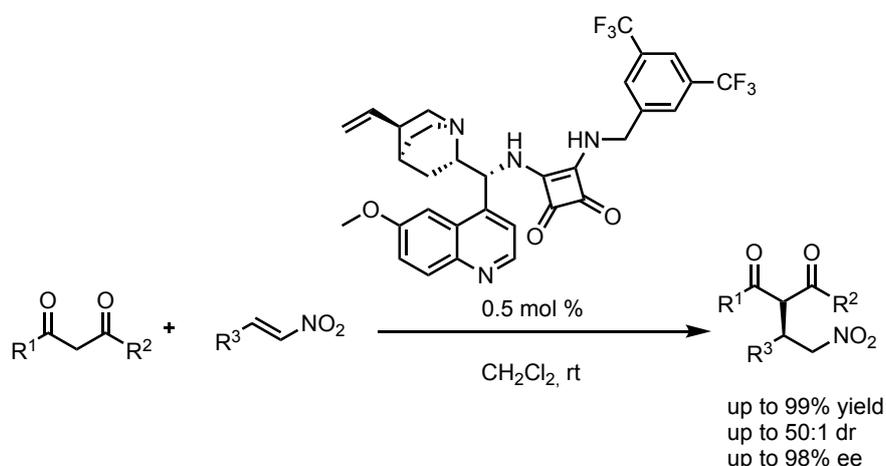
Scheme 11. Reduction of ketones using a squaramide ligand

Later, the application of cinchona alkaloid-based squaramide catalysts in organic reaction increased rapidly. In 2008, Rawal reported the synthesis of nitrodione³³ with very good results, up to 98% yield, 99% ee and 50:1 dr by using 1,3-diketones and nitroalkenes as starting materials and a cinchona alkaloid-based squaramide as chiral catalyst (Scheme 12). This kind of catalyst was proved to be superior especially the activity, it requires very low catalyst loadings such as 0.1 mol% to complete the

³² H. H. Zou, J. Hu, J. Zhang, J.-S. You, D. Ma, D. Li, R.-G. Xie, *J. Mol. Catal. A*, **2005**, 242, 57.

³³ J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, 130, 14416.

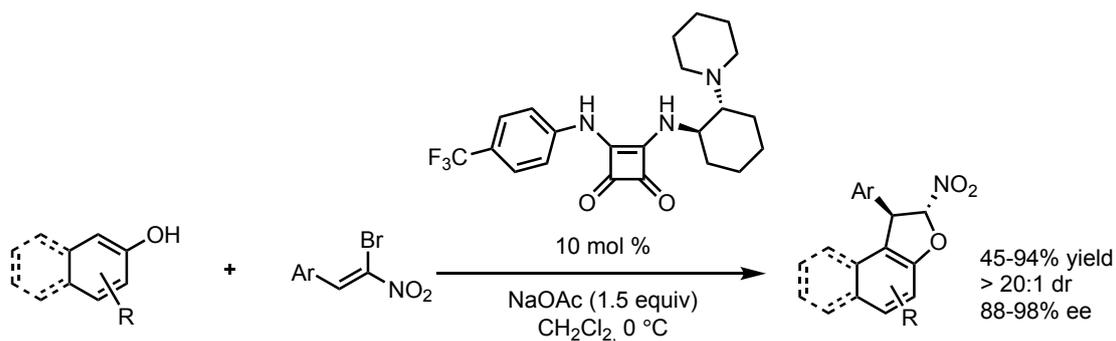
conversion. When using less reactive nucleophiles, only 2 mol% catalyst were needed in the reaction.



Scheme 12. Chiral bifunctional squaramide organocatalyzed Michael addition

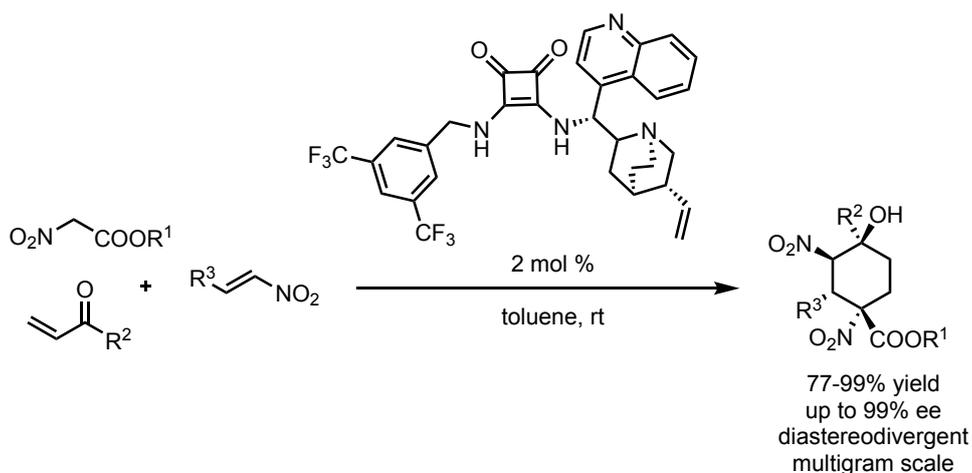
Since this important work by Rawal and co-workers, many methodologies using squaramide organocatalysts in domino reactions were described, a selection of these methodologies will now be presented. In 2013, Alemán and co-workers published a research work about the synthesis of *trans*-dihydroarylfurans by the Friedel-Crafts/substitution domino reaction catalyzed by a bifunctional squaramide catalyst (Scheme 13).³⁴ Using (*Z*)-bromonitroalkenes and naphthol or phenol derivatives as starting materials, the chiral *trans*-dihydroarylfuran derivatives can be efficiently synthesized with moderated to good yield and very good enantiomeric excesses by using a squaramide catalysis. The author found the key of this catalytic system is the neutralization of the generated HBr by a stoichiometric amount of base, sodium acetate in this case. This efficient heterocyclization domino process has been an important source of inspiration for our work on the enantioselective synthesis of heterohelicenes, which will be discussed later in this manuscript.

³⁴ C. Jarava-Barrera, F. Esteban, C. Navarro-Ranninger, A. Parra, J. Alemán, *Chem. Commun.* **2013**, 49, 2001.



Scheme 13. Enantioselective synthesis of *trans*-dihydroarylfurans

In 2014, Carrillo and Vicario reported a stereoselective and diastereodivergent synthesis of cyclohexanes containing four stereocenters through the enantioselective domino cascade reaction employing hydrogen-bond catalysis (Scheme 14).³⁵ The products were obtained with great efficiency with enantiomeric excesses up to > 99%.

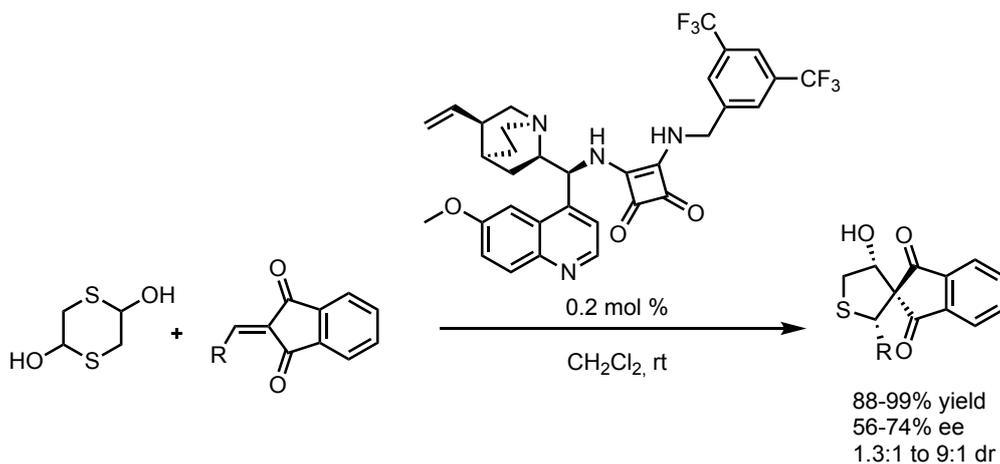


Scheme 14. Diastereodivergent access to densely functionalized cyclohexanes

In 2016, Enders group developed a novel enantioselective domino thia-Michael/aldol reaction by using 2-arylidene-1,3-indandiones and 1,4-dithiane-2,5-diol catalyzed by

³⁵ J. I. Martinez, L. Villar, U. Uria, L. Carrillo, E. Reyes, J. L. Vicario, *Adv. Synth. Catal.* **2014**, 356, 3627.

only 0.2 mol% of a squaramide (Scheme 15).³⁶ This domino transformation provides a rapid method to the tetrahydrothiophene which bears spiro indane-1,3-dione derivatives with very good yields, moderate to good diastereoselectivities and moderate enantioselectivities.

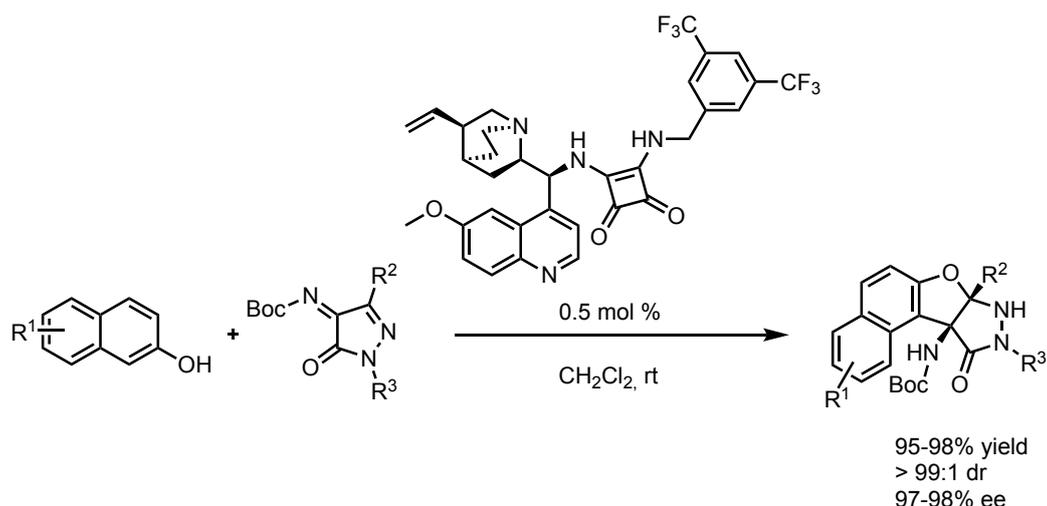


Scheme 15. Squaramide-catalyzed thia-Michael/aldol domino reactions

In 2017, Enders group described the use of a bifunctional squaramide catalyst to promote an aza-Friedel-Crafts/*N*, *O*-acetalization domino reaction (Scheme 16).³⁷ They used 2-naphthols and pyrazolinone ketimines as starting materials and the method requires a catalyst loading of only 0.5 mol% of the bifunctional squaramide. It is possible to scale up the reaction to multi-gram amounts, and it also provides a new series of furanonaphthopyrazolidinone derivatives bearing two contiguous stereogenic centers with excellent yields from 95 to 98% and good stereoselectivity (up to >99:1 dr and 98% ee).

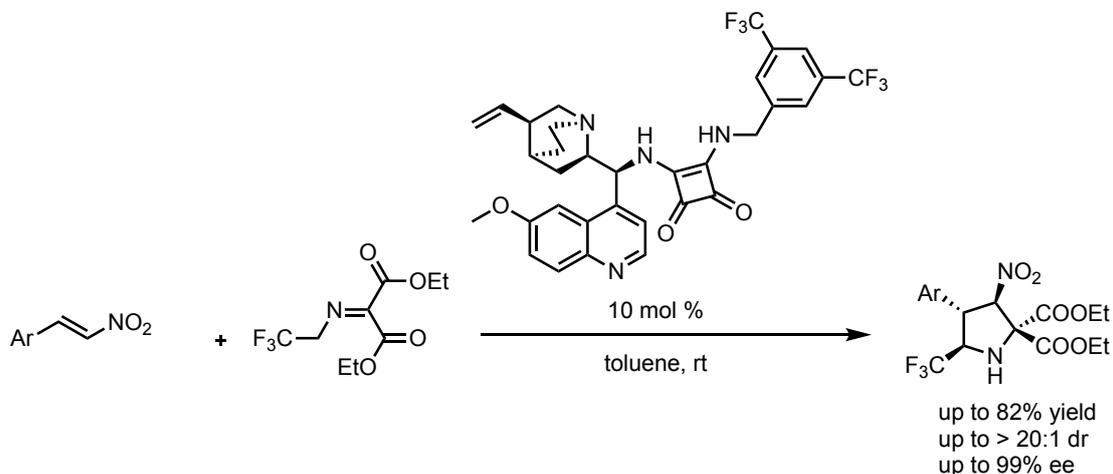
³⁶ S. Mahajana, P. Chauhana, M. Blümela, R. Puttreddyb, K. Rissanenb, G. Raabea, D. Enders, *Synthesis*, **2016**, 48, 1131.

³⁷ U. Kaya, P. Chauhan, S. Mahajan, K. Deckers, A. Valkonen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2017**, 56, 15358.



Scheme 16. Squaramide-catalyzed enantioselective Friedel–Crafts/*N*, *O*-acetalization

The same year, Enders group reported a bifunctional squaramide-catalyzed domino Michael/aza-Henry (a formal (3+2)-cycloaddition) for the synthesis of 3-nitro-5-trifluoromethyl-substituted pyrrolidines (Scheme 17).³⁸ The products contain three contiguous stereogenic centers and are efficiently prepared with excellent yields and very good stereoselectivities.



Scheme 17. Squaramide-catalyzed domino Michael/aza-Henry

³⁸ Q. Liu, K. Zhao, Y. Zhi, G. Raabe, D. Enders, *Org. Chem. Front.* **2017**, 4, 1416.

1.5.2.2 Brønsted acid

In the area of organocatalysis, chiral Brønsted acid catalysis is another type of non-covalent activation. It is related to the activation of the bifunctional thiourea or squaramide organocatalysts in a sense that these catalytic species activate the electrophile. However, in the case of Brønsted acid organocatalysts, a real protonation of the electrophile occurs, while the former provides catalytic activation through simple hydrogen bond.³⁹ Brønsted acids have been proven to be the highly efficient and very versatile catalysts for enantioselective catalysis. In this field, in the past years, chiral phosphoric acids (CPAs) derived from BINOL (Figure 8) are the most widely used organocatalysts. They can be recognized also as bifunctional organocatalyst since they possess a Brønsted acid site as well as a Lewis basic site.

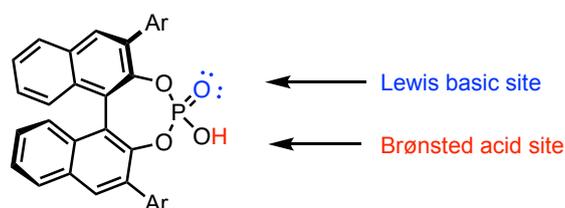
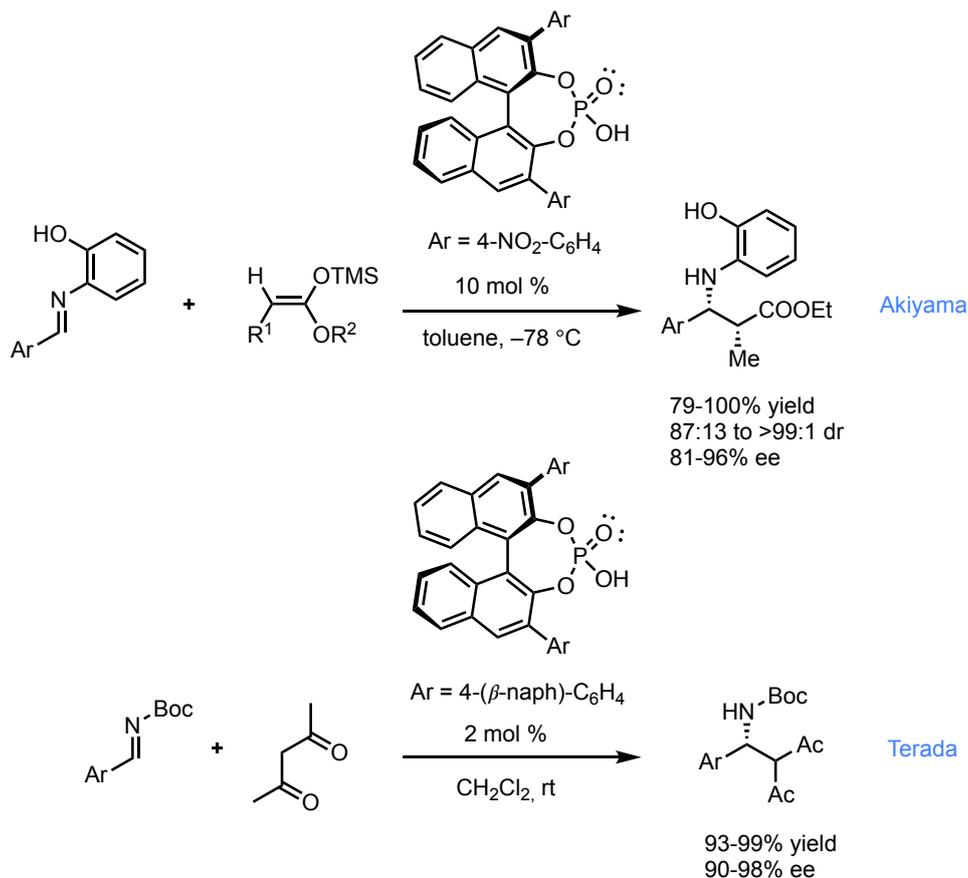


Figure 8. Chiral BINOL-derived phosphoric acids.

Two very important and pioneer work were published in 2004: Akiyama and Terada separately reported enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid, which constitute the first reports about the chiral CPA-catalyzed organic reactions (Scheme 18).⁴⁰

³⁹ B. List, *Asymmetric Organocatalysis*, **2009**, Springer.

⁴⁰ a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566. b) M. Terada, D. Uragushi, *J. Am. Chem. Soc.* **2004**, 126, 5356. c) For mechanistic studies: M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, 129, 6756.



Scheme 18. Pioneer CPA-catalyzed Mannich reaction

This type of activation has been mainly used to promote Diels-Alder⁴¹, Aza-Diels-Alder,⁴² Mannich,⁴³ Strecker,⁴⁴ Pictet-Spengler,⁴⁵ and Biginelli,⁴⁶ reactions. The enantioselective Brønsted acid catalysis is no longer restricted to the reactive substrates. It is certain that the carbonyl compounds can also be activated through these stronger Brønsted acid catalysts. In the enantioselective formation of C–C, C–H, C–O, C–N, and

⁴¹ a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; b) M. Rueping, C. Azap, *C. Angew. Chem. Int. Ed.* **2006**, *45*, 783.

⁴² D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626.

⁴³ a) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett.* **2003**, 1919; b) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.

⁴⁴ M. Rueping, E. Sugiono, C. Azap, *Angew. Chem. Int. Ed.* **2006**, *45*, 2617.

⁴⁵ J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086.

⁴⁶ X. H. Chen, X. Y. Xu, H. Liu, L. F. Cun, L. Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 1086.

C–P bonds, the CPAs were proved to be the very useful catalysts.⁴⁷ By using them in organic synthesis, people have achieved great success and the operation is normally very simple with the mild reaction conditions. The widely use of these catalyst is due to their easy modulation of the Brønsted acidity strength (Figure 9).⁴⁸

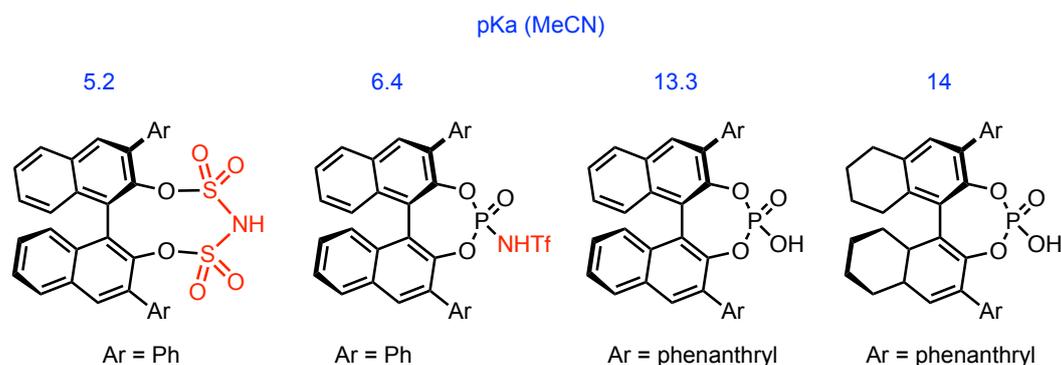


Figure 9. Acidity scale for selected BINOL-derived Brønsted acids.

Although this kind of BINOL-derived phosphoric acids was very useful and has many advantages, alternative design is still needed to answer some of the limitations of these catalyst such as their rather difficult synthesis (several steps) and the need to incorporate large aryl groups at 3 and 3' position. In chapter 3, we will describe our results in these directions.

⁴⁷ D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, 291, 395.

⁴⁸ D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, 114, 9047.

Chapter 2: Simultaneous Control of Central and Helical Chiralities: Expedient Helicoselective Synthesis of Dioxa[6]helicenes

2.1) Introduction

Helical chirality is a type of chirality which arises from the screw-shape skeleton of polycyclic aromatic compounds, or from the tertiary structure of complex macromolecules such as DNA. In this paragraph, we will focus only on helicenes, which are molecules formed by *ortho*-fused aromatic rings. As previously discussed, if we add to a benzene molecule other aromatic rings in the *ortho* position, the steric hindrance generated in the structure will cause the skeleton to spiral up and adopt a helical shape in order to ease that hindrance.⁴⁹ The shape adopted by such molecules to ease strain generates a pair of enantiomers, which can be named according to the direction of the spiral: if the helix spirals downwards in a anticlockwise sense it will be named the *M*, on the other side, if the helix spirals downward in an clockwise direction it will be named *P* (Figure 10).

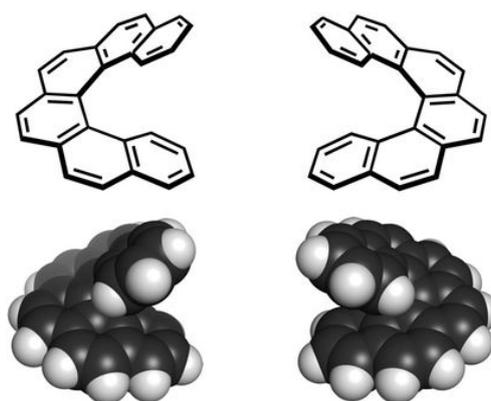


Figure 10. (*M*)- and (*P*)-[6]helicene

⁴⁹ Chen, C. F.; Shen, Y. *Helicene Chemistry, from Synthesis to Applications*, Springer, 2017.

2.2) State of the art on the enantioselective synthesis of heterohelicenes

Although the stereoselective synthesis of carbohelicenes is a relatively mature field,⁵⁰ only a few efficient enantioselective catalytic approaches to heterohelicenes have been proposed within the last decade.⁵¹ This is mainly due to the decreased barriers to enantiomerization generally observed in this class of helicenes, which constitutes an important synthetic challenge that we wish to undertake in this thesis. Moreover, the presence of one or more heteroatoms in a chiral non-racemic helix induces structural and physico-chemical modifications and usually resulting in additional properties. Indeed, within the last few years, [n]heterohelicenes revealed as promising scaffolds

⁵⁰ For reviews, see: b) M. Gingras, G. Felix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007; c) S. Shirakawa, S. Liu, S. Kaneko, *Chem. Asian J.* **2016**, *11*, 330; For a recent chiral-Au-catalyzed synthesis of carbo[6]helicenes, see: E. González-Fernández, L. D. M. Nicholls, L. D. Schaaf, C. Farès, C. W. Lehmann, M. Alcarazo, *J. Am. Chem. Soc.* **2017**, *139*, 1428.

⁵¹ For selected diastereoselective approaches to optically active (hetero)helicenes, see: a) J. Žádný, A. Jančařík, A. Andronova, M. Šámal, J. V. Chocholoušová, J. Vacek, R. Pohl, D. Šaman, I. Císařová, I. G. Stará, I. Starý, *Angew. Chem. Int. Ed.* **2012**, *51*, 5857; b) K. Yavari, S. Moussa, B. Ben Hassine, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem. Int. Ed.* **2012**, *51*, 6748; c) D. Waghray, G. Bagdziunas, J. Jacobs, L. Van Meervelt, J. V. Grazulevicius, W. Dehaen, *Chem. Eur. J.* **2015**, *21*, 18791; d) A. M. del Hoyo, A. Urbano, M. C. Carreño, *Org. Lett.* **2016**, *18*, 20; e) J. Klívar, A. Jančařík, D. Šaman, R. Pohl, P. Fiedler, L. Bednářová, I. Starý, I. G. Stará, *Chem. Eur. J.* **2016**, *22*, 14401; f) J. Nejedlý, M. Šámal, J. Rybáček, M. Tobrmanová, F. Szydło, C. Coudret, M. Neumeier, J. Vacek, J. V. Chocholoušová, M. Buděšínský, D. Šaman, L. Bednářová, L. Sieger, I. G. Stará, I. Starý, *Angew. Chem. Int. Ed.* **2017**, *56*, 5839; For selected resolution of racemates: g) M. Miyasaka, A. Rajca, M. Pink, S. Rajca, *Chem. Eur. J.* **2004**, *10*, 6531; h) J. Míšek, F. Teplý, I. G. Stará, M. Tichý, D. Šaman, I. Císařová, P. Vojtíšek, I. Starý, *Angew. Chem. Int. Ed.* **2008**, *47*, 3188; i) L. Severa, D. Koval, P. Novotná, M. Ončák, P. Sázelová, D. Šaman, P. Slavíček, M. Urbanová, V. Kašička, F. Teplý, *New J. Chem.* **2010**, *34*, 1063; j) J. Doucet, G. R. Stephenson, *Chem. Eur. J.* **2015**, *21*, 13431; k) J. Doucet, G. R. Stephenson, *Chem. Eur. J.* **2015**, *21*, 18677; l) M. S. Sundar, A. V. Bedekar, *RSC Adv.* **2016**, *6*, 46258; For selected chiral HPLC separations of racemates: m) S. Graule, M. Rudolph, N. Vanthuyne, J. Autschbach, C. Roussel, J. Crassous, R. Réau, *J. Am. Chem. Soc.* **2009**, *131*, 3183; n) K. Nakano, H. Oyama, Y. Nishimura, S. Nakasako, K. Nozaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 695; o) M. Akiyama, K. Nozaki, *Angew. Chem. Int. Ed.* **2017**, *56*, 2040; p) T. Otani, A. Tsuyuki, T. Iwachi, S. Someya, K. Tateno, H. Kawai, T. Saito, K. S. Kanyiva, T. Shibata, *Angew. Chem. Int. Ed.* **2017**, *56*, 3906.

for a wide range of applications because of the fine-tuning of their properties by the nature and the relative position of the heteroatom. Notably, recent developments are concerned with catalysts design and their utilization in enantioselective reactions,⁵² molecular recognition,⁵³ material science, including cryptography,⁵⁴ light-emitting devices,⁵⁵ spin filter⁵⁶ or molecular machines⁵⁷ and some biologically active agents.⁵⁸ Only few direct catalyst-controlled enantioselective approaches have been proposed, all within the last ten years (Scheme 19). The most popular ones are the transition metal-

⁵² For reviews: a) P. Aillard, A. Voituriez, A. Marinetti, *Dalton Trans.* **2014**, *43*, 15263; b) M. J. Narcis, N. Takenaka, *Eur. J. Org. Chem.* **2014**, *2014*, 21; For other recent contributions: c) A. Matsumoto, K. Yonemitsu, H. Ozaki, J. Mišek, I. Starý, I. G. Stará, K. Soai, *Org. Biomol. Chem.* **2017**, *15*, 1321; d) P. Aillard, D. Dova, V. Magné, P. Retailleau, S. Cauteruccio, E. Licandro, A. Voituriez, A. Marinetti, *Chem. Commun.* **2016**, *52*, 10984.

⁵³ a) Y. Xu, Y. X. Zhang, H. Sugiyama, T. Umano, H. Osuga, K. Tanaka, *J. Am. Chem. Soc.* **2004**, *126*, 6566; b) Q. Huang, L. Jiang, W. Liang, J. Gui, D. Xu, W. Wu, Y. Nakai, M. Nishijima, G. Fukuhara, T. Mori, Y. Inoue, C. Yang, *J. Org. Chem.* **2016**, *81*, 3430.

⁵⁴ a) N. Saleh, M. Srebro, T. Reynaldo, N. Vanthuyne, L. Toupet, V. Y. Chang, G. Muller, J. A. G. Williams, C. Roussel, J. Autschbach, J. Crassous, *Chem. Commun.* **2015**, *51*, 3754; b) N. Saleh, B. Moore, M. Srebro, N. Vanthuyne, L. Toupet, J. A. G. Williams, C. Roussel, K. K. Deol, G. Muller, J. Autschbach, J. Crassous, *Chem. Eur. J.* **2015**, *21*, 1673.

⁵⁵ a) T. Caronna, R. Sinisi, M. Catellani, L. Malpezzi, S. V. Meille, A. Mele, *Chem. Commun.* **2000**, 1139; b) W. Hua, Z. Liu, L. Duan, G. Dong, Y. Qiu, B. Zhang, D. Cui, X. Tao, N. Cheng, Y. Liu, *RSC Adv.* **2015**, *5*, 75.

⁵⁶ V. Kiran, S. P. Mathew, S. R. Cohen, I. Hernández Delgado, J. Lacour, R. Naaman, *Adv. Mater.* **2016**, *28*, 1957.

⁵⁷ a) For a general review including some applications of heterohelicenes: Y. Shen, C.-F. Chen, *Chem. Rev.* **2012**, *112*, 1463; b) T. R. Kelly, X. Cai, F. Damkaci, S. B. Panicker, B. Tu, S. M. Bushell, I. Cornella, M. J. Piggott, R. Salives, M. Cavero, Y. Zhao, S. Jasmin, *J. Am. Chem. Soc.* **2007**, *129*, 376.

⁵⁸ K.-I. Shinohara, Y. Sannohe, S. Kaieda, K.-I. Tanaka, H. Osuga, H. Tahara, Y. Xu, T. Kawase, T. Bando, H. Sugiyama, *J. Am. Chem. Soc.* **2010**, *132*, 3778.

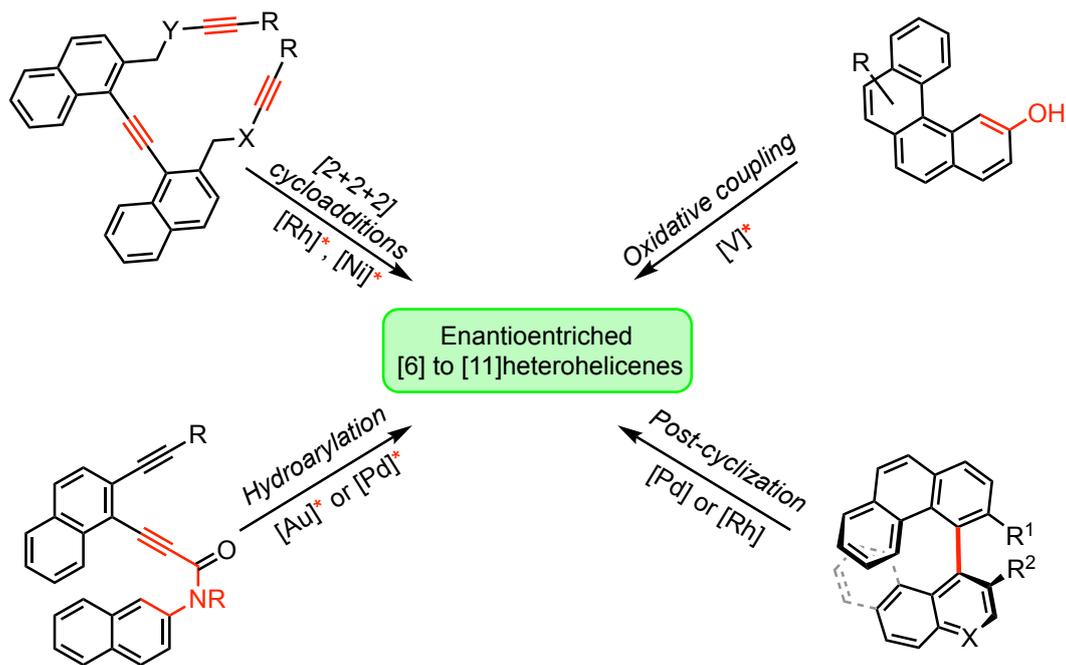
catalyzed intra- and intermolecular [2+2+2] cycloadditions⁵⁹ or hydroarylations.⁶⁰ However, these two approaches require the multistep preparation of elaborated achiral functionalized multi-propargylic precursors and limiting their practicability. In addition, a chiral vanadium-catalyzed oxidative coupling/heterocyclization sequence with benzo[*c*]phenanthrenols has been proposed recently for the synthesis of symmetrical furan-containing oxa[9]helicenes.⁶¹ It presumably proceeds *via* a transient axially chiral intermediate that rearomatizes by tautomerization. In complement, explicit axial-to-helical conversion of chirality is involved in various metal-catalyzed post-cyclizations of non-racemic biaryl atropisomers with moderate to excellent stereoselectivities.⁶²

⁵⁹ a) For a recent account: K. Tanaka, Y. Kimura, K. Murayama, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 375; b) For a related enantioselective synthesis of disila[7]helicenes with a chiral Ir(I) complex: T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tsuchikama, K. Endo, *Chem. Commun.* **2012**, *48*, 1311; K. Murayama, Y. Oike, S. Furumi, M. Takeuchi, K. Noguchi, K. Tanaka, *Eur. J. Org. Chem.* **2015**, 1409; d) M. Šámmal, S. Čercheja, J. Rybáček, J. V. Chocholousová, J. Vacek, L. Bednárová, D. Saman, I. G. Stará, I. Starý, *J. Am. Chem. Soc.* **2015**, *137*, 8469; e) I. Gay Sánchez, M. Šámmal, J. Nejedlý, M. Karras, J. Klívar, J. Rybacek, M. Budesinsky, L. Bednarova, B. Seidlerova, I. G. Stará, I. Starý, *Chem. Commun.* **2017**, *53*, 4370.

⁶⁰ a) T. Shibuya, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, *50*, 3963; b) K. Nakamura, S. Furumi, M. Takeuchi, T. Shibuya, K. Tanaka, *J. Am. Chem. Soc.* **2014**, *136*, 5555.

⁶¹ a) M. Sako, Y. Takeuchi, T. Tsujihara, J. Koderá, T. Kawano, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2016**, *138*, 11481; b) For a related Cu-chiral amine catalyzed oxidative coupling: M. Karikomi, M. Toda, Y. Sasaki, M. Shibuya, K. Yamada, T. Kimura, M. Minabe, K. Hiratani *Tetrahedron Lett.* **2014**, *55*, 7099.

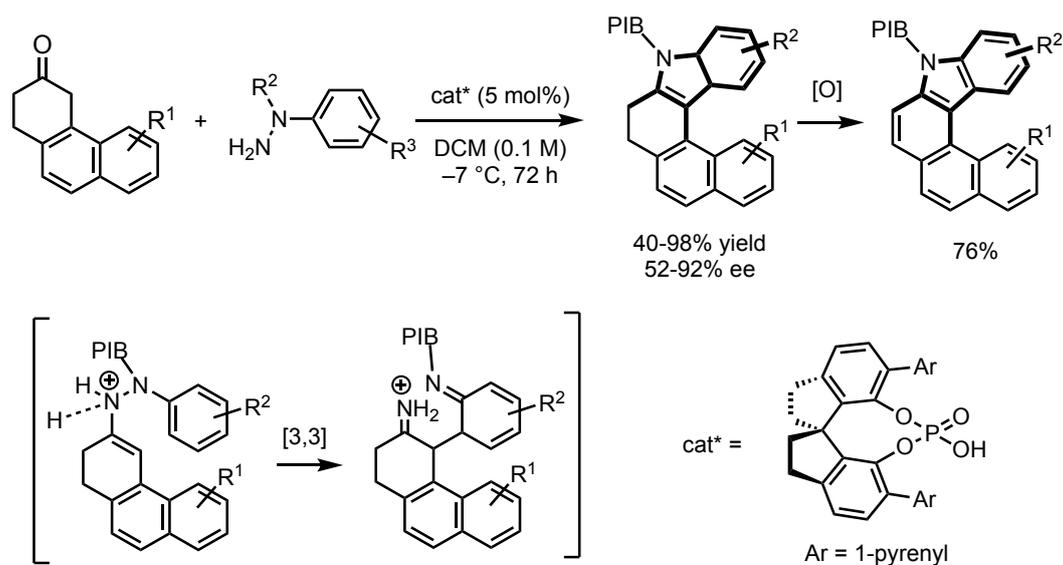
⁶² a) E. Kaneko, Y. Matsumoto, K. Kamikawa, *Chem. Eur. J.* **2013**, *19*, 11837; b) M. Murai, R. Okada, A. Nishiyama, K. Takai, *Org. Lett.* **2016**, *18*, 4380.



Scheme 19. Metal-catalyzed approaches to enantioenriched [n]heterohelices

Beside all these transition metal-promoted cyclizations, the first organocatalytic approach involves an elegant CPA-catalyzed enantioselective Fischer indole synthesis from hydrazines and phenanthrenones (Scheme 20).⁶³ The transient generation of two sp^3 -stereogenic centers is triggered by a [3,3]-sigmatropic rearrangement furnishing a series of new configurationally stable partially saturated indolohelices after *in situ* heterocyclization. Oxidative aromatization to the fully π -conjugated heterohelices proved possible.

⁶³ L. Kötzner, M. J. Webber, A. Martínez, C. De Fusco, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 5202.



Scheme 20. Organocatalyzed enantioselective synthesis of heterohelicenes

2.3) Importance of the heteroatom in the heterohelicene structures

The nature and the position of the heterocycle involved in a helical structure are crucial with respect to the configurational stability of the helix and constitute essential parameters for the development of new configurationally stable [n]heterohelicenes (Figure 11). In this context, both experimental evidences⁶⁴ and DFT calculations⁶⁵ clearly confirm the significant configurational stability following the van der Waals radius order $O < N \ll S$.^{66a} This beneficial effect is because bigger heteroatoms cause wider internal angles between the two formal C–C double bonds involved in the annulation to form the helix. In the case of thiophenes, this bond angle is larger than

⁶⁴ K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 7136.

⁶⁵ S. Arae, T. Mori, T. Kawatsu, D. Ueda, Y. Shigeta, N. Hamamoto, H. Fujimoto, M. Sumimoto, T. Imahori, K. Igawa, K. Tomooka, T. Punniyamurthy, R. Irie, *Chem. Lett.* **2017**, *46*, 1214.

⁶⁶ a) J. Elm, J. Lykkebo, T. J. Sørensen, B. W. Laursen, K. V. Mikkelsen, *J. Phys. Chem. A* **2011**, *115*, 12025; b) G. Lamanna, C. Faggi, F. Gasparrini, A. Ciogli, C. Villani, P. J. Stephens, F. J. Devlin, S. Menichetti, *Chem. Eur. J.* **2008**, *14*, 5747.

for furans and pyrroles^{67a} resulting in a better configurational stabilization of up to 50 kJ.mol⁻¹ in some thiahelicenes compared to the corresponding oxahelicenes.⁶⁶⁻⁶⁸

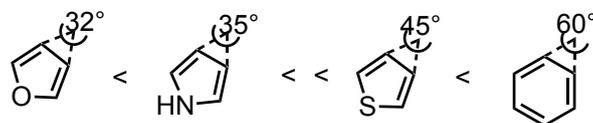


Figure 11. Variation of the bond angles

Finally, when azahelicenes are concerned, increased barriers to enantiomerization of up to 35 kJ.mol⁻¹ have been calculated when the free NH is replaced by a NTs (Figure 12), while a *Nt*-Bu has almost no effect, reflecting the importance of the nitrogen atom substitution.⁶⁵ Because of these geometrical factors, heterohelicenes have usually larger pitches and therefore lower barriers to enantiomerization than carbohelicenes. This partially explains why the enantioselective synthesis of small configurationally stable heterohelicenes is particularly challenging and yet an unsolved problem.

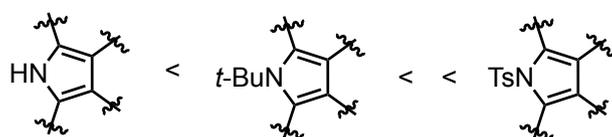


Figure 12. Effect of the *N*-substitution on azaheterohelicenes configurational stability

⁶⁷ a) For pioneer observations, see: H. Wynberg, M. B. Groen, H. Schadenberg, *J. Org. Chem.* **1971**, *36*, 2797 and ref therein; b) G. Pieters, A. Gaucher, S. Marque, F. Maurel, P. Lesot, D. Prim, *J. Org. Chem.* **2010**, *75*, 2096; c) In the 1,*n*-diaz[5]pyridohelicene series similar beneficial effects of about 7 and 14 kJ.mol⁻¹ have been calculated for thiophene and selenophene nucleus, respectively comparatively to the corresponding furan: B. M. Alzoubi, *Z. Anorg. Allg. Chem.* **2014**, *640*, 986.

⁶⁸ a) S. K. Collins, M. P. Vachon, *Org. Biomol. Chem.* **2006**, *4*, 2518; b) A. Rajca, M. Pink, S. Xiao, M. Miyasaka, S. Rajca, K. Das, K. Plessel, *J. Org. Chem.* **2009**, *74*, 7504; c) M. Miyasaka, M. Pink, S. Rajca, A. Rajca, *Angew. Chem. Int. Ed.* **2009**, *48*, 5954.

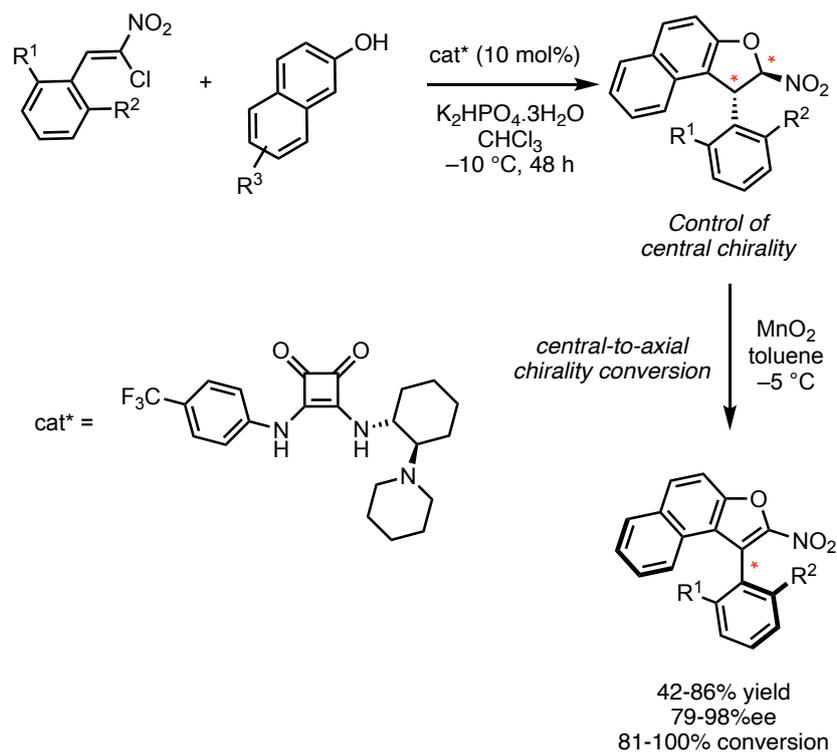
2.4) Presentation of our strategy for the enantioselective synthesis of heterohelicenes

2.4.1) Previous work of the laboratory: atroposelective synthesis of 3-arylfurans

Within the laboratory, a new practical robust and reliable general enantioselective organocatalytic strategy was developed to access challenging 3-arylfuran atropisomers (Scheme 21).⁶⁹ Atropisomeric species featuring one five-membered rings are quite difficult to construct in a stereoselective manner. This is due to the increased distance between the ortho-substituents next to the axis, which is responsible for lower barriers to rotation, hampering their configurational stability. Organocatalysis offers the mildness for an efficient stereocontrol during the elaboration of the key centrally chiral dihydrofuran intermediate, which is obtained from a domino reaction between β -naphthol derivatives and α -chloronitroalkene.⁷⁰ Upon oxidative aromatization, the dihydrofurans converts to the corresponding optically active axially chiral furan atropisomers with excellent central-to-axial conversion of chirality in most cases.

⁶⁹ a) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez, *J. Am. Chem. Soc.* **2017**, *139*, 2140.

⁷⁰ a) C. Jarava-Barrera, F. Esteban, C. Navarro-Ranninger, A. Parra, J. Alemañ, *Chem. Commun.* **2013**, *49*, 2001. b) M. Rueping, A. Parra, U. Uria, F. Besselièvre, E. Merino, *Org. Lett.*, **2010**, *12*, 5680. c) D. Becerra, W. Raimondi, D. Dauzonne, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2017**, *49*, 195.



Scheme 21. Enantioselective synthesis of furan atropisomers

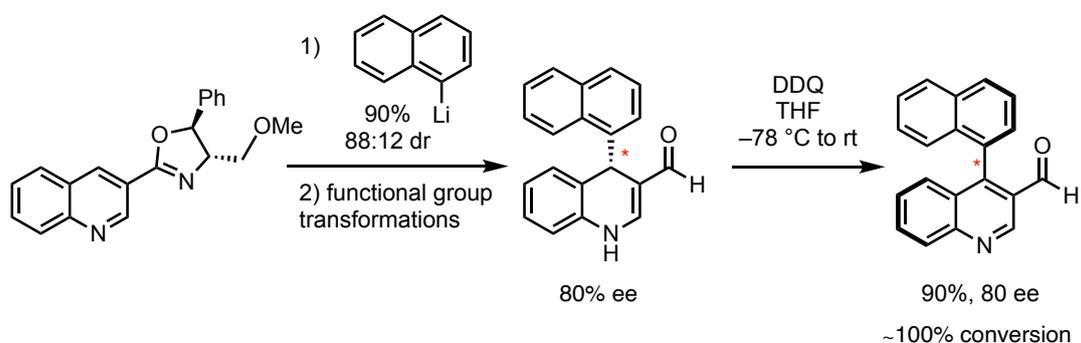
The central-to-axial conversion of chirality upon aromatization of partially saturated cyclic intermediates is known for years and commonly used for the synthesis of allenes,⁷¹ but was surprisingly underexploited until recently for the construction of axially chiral biaryls. Back in 1965, the concept of central-to-axial chirality conversion was proposed to attribute the absolute configuration of the natural product chaparrin.⁷² However, it became a viable synthetic approach for atropisomers only seventeen years later with the first diastereoselective approach by Meyers and co-workers (Scheme 22)⁷³ and is still a source of inspiration.⁷⁴

⁷¹ For a recent review on allenes, see: W.-D. Chu, Y. Zhang, J. Wang, *Catal. Sci. Technol.* **2017**, *7*, 4570.

⁷² A. I. Meyers, D. G. Wettlaufer, *J. Am. Chem. Soc.* **1984**, *106*, 1135.

⁷³ T. R. Hollands, P. de Mayo, M. Nisbet, P. Crabbé, *Can. J. Chem.* **1965**, *43*, 3008.

⁷⁴ A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2018**, *57*, 7136.



Scheme 22. First example of central-to-axial chirality conversion by Myers

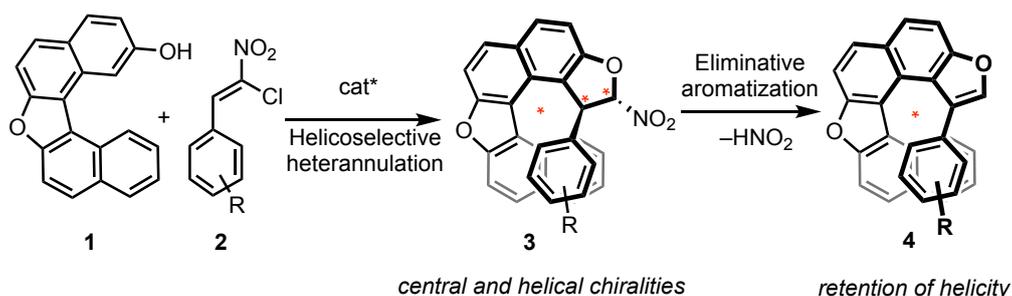
In most diastereoselective approaches,⁷⁵ the original stereogenic center(s) was(were) accessed from the chiral pool^{75a,b} or by resolution,^{75c-f} limiting both scope and efficiency.

⁷⁵ For selected pioneer and selected more recent examples, see: a) A. I. Meyers, K. A. Lutomski, *J. Am. Chem. Soc.* **1982**, *104*, 879; b) J. M. Wilson, D. J. Cram, *J. Am. Chem. Soc.* **1982**, *104*, 881; c) B. Koop, A. Straub, H. J. Schäfer, *Tetrahedron: Asymmetry* **2001**, *12*, 341; d) T. Hattori, M. Date, K. Sakurai, N. Morohashi, H. Kosugi, S. Miyano, *Tetrahedron Lett.* **2001**, *42*, 8035; e) Y. Nishii, K. Wakasugi, K. Koga, Y. Tanabe, *J. Am. Chem. Soc.* **2004**, *126*, 5358; f) Y. Liu, K. Lu, M. Dai, K. Wang, W. Wu, J. Chen, J. Quan, Z. Yang, *Org. Lett.* **2007**, *9*, 805; g) T. Leermann, P.-E. Broutin, F. R. Leroux, F. Colobert, *Org. Biomol. Chem.* **2012**, *10*, 4095; h) Q. Dherbassy, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2018**, *57*, 4668; i) J. Rae, J. Frey, S. Jerhaoui, S. Choppin, J. Wencel-Delord, F. Colobert, *ACS Catal.* **2018**, *8*, 2805; j) H. Forkosh, V. Verzhinin, H. Reiss, D. Pappo, *Org. Lett.* **2018**, *20*, 2459.

2.4.2) Strategy for the enantioselective synthesis of heterohelicenes

Based on our recent interest for the synthesis of axially chiral 3-arylfuran atropisomers,⁷⁶ we devise a new expedient helicoselective access to helically chiral related fused furans **3**. We thus reasoned that the use of an extended aromatic bis-nucleophile **1** in combination with a α -chloronitroalkene **2**, in the presence of a bifunctional organocatalyst (cat*), would give the centrally and helically chiral fused dihydrofuran **3** through an unprecedented helicoselective Michael/*O*-alkylation heteroannulation sequence (Scheme 23). The following aromatization by elimination of nitrous acid, would provide the corresponding oxa[6]helicene **4** with conservation of the helical chirality.

It must be admitted here that our first idea was to design an innovative central-to-helical chirality conversion. The dihydrofuran drawn below possess both central and helical chiralities and this was not anticipated. Therefore, the aromatization step is not a conversion of chirality, since helical chirality is present at the dihydrofuran stage.



Scheme 23. Strategy for the enantioselective synthesis of heterohelicenes

⁷⁶ a) Raut, V. S.; Jean, M.; Vanthuynne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez J. *J. Am. Chem. Soc.* **2017**, *139*, 2140-2143. b) Bao, X.; Rodriguez, J.; Bonne, D. *Chem. Sci.* **2020**, *11*, 403-408.

Before showing our results concerning this strategy, a literature survey of enantioselective methods allowing the simultaneous control of multiple stereogenic elements within a molecule is necessary.

2.5) Simultaneous control of multiple stereogenic elements

In recent years, several groups reported the simultaneous control of multiple stereogenic elements within the same molecule. Several strategies have been elaborated, such as the use of chiral substrate that induce the control of another stereogenic element, via diastereoselective approaches.⁷⁷ In this part, we will only detail the enantioselective approaches, classified by the type of stereogenic elements.

2.5.1) Installation of central and axial chiralities

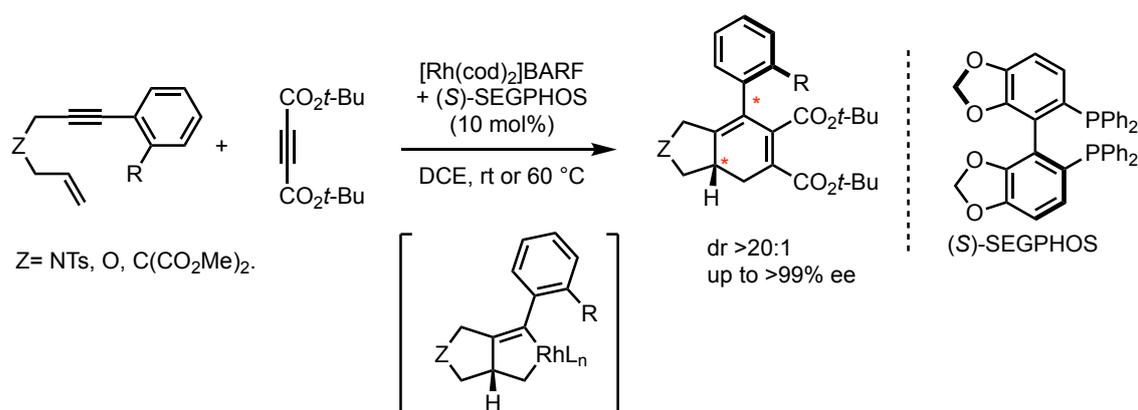
The most common installation of two different stereogenic element concerns the introduction of central and axial chiralities. The following examples have been classified according to the different types of reaction involved.

2.5.1.1) [2+2+2] cycloaddition

In 2008, the group of Shibata reported their research about Rh-catalyzed [2+2+2] cycloaddition to construct fused cyclohexadienes bearing central and axial chiralities (Scheme 24). They first optimized the reaction between nitrogen-tethered enyne with a naphthyl group on its terminal alkyne and 1,4-dimethoxybut-2-yne as a model reaction. After examination of several chiral ligands for the cationic Rh complex in 1,2-dichloroethane, the SEGPHOS was found to give the best yield but moderate diastereoselectivity ($dr = 2:1$) within one hour. The enantiomeric excess of the major diastereomer was 80% ee while the minor diastereomer was isolated with ee > 99%.

⁷⁷ For a recent review, see: O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223. For selected recent examples, see: a) C. Bolm, M. Kesselgruber, K. Muniz, G. Raabe, *Organometallics*, **2000**, 19, 1648; b) W.-W. Chen, Q. Zhao, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2010**, 12, 1072; c) A.-M. Hoyo, A. Urbano, M.-C. Carreño, *Org. Lett.* **2016**, 18, 20; d) S. Lin, D. Leow, K.-W. Huang, C.-H. Tan, *Chem. Asian J.* **2009**, 4, 1741; e) X. Xue, Z. Gu, *Org. Lett.* **2019**, 21, 3942.

They further investigated the reaction conditions to improve diastereoselectivity successfully after increasing the reaction temperature to 60 °C along with the dropwise addition of acetylene dicarboxylate. From the research, it is concluded that the central chirality is generated at the ring-fused position of the bicyclic rhodacyclopentene intermediate by the oxidative coupling of the metal center with an enyne. They also proposed that the axial chirality is not controlled at this stage, but during the following reaction with the alkyne, which induces the axial chirality control.⁷⁸



Scheme 24. Rh-catalyzed [2+2+2] cycloaddition

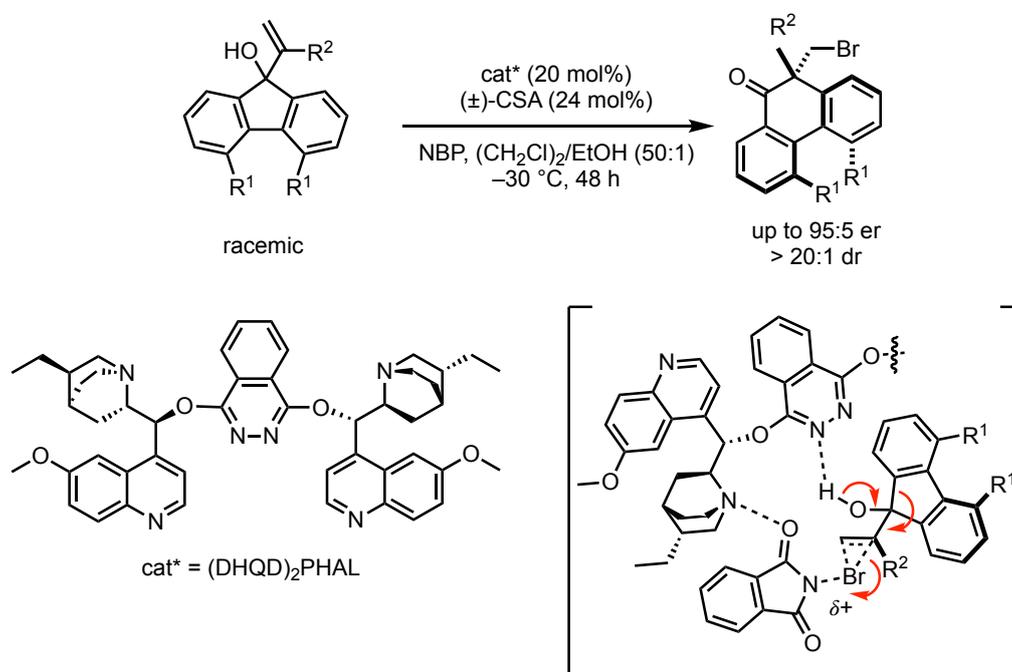
2.5.1.2) Dynamic kinetic resolution (DKR)

The second strategy to install both central and axial chiralities is the DKR, which is the most used strategy. The group of Yeung described an access to axially chiral biaryls via an organocatalytic enantioselective semipinacol rearrangement in 2018 (Scheme 25).⁷⁹ Racemic biaryl fluorenes starting materials were used as substrates in the initial study together with *N*-bromosuccinimide (NBS) as the brominating reagent. When (DHQD)₂PHAL was used as catalyst, it could promote the rearrangement of starting materials to give the ring-expanded product in 75% yield but with moderate

⁷⁸ T. Shibata, M. Otomo, Y. Tahara, K. Endo, *Org. Biomol. Chem.* **2008**, 6, 4296.

⁷⁹ Y. Liu, Y.-L. S. Tse, F. Y. Kwong, Y.-Y. Yeung, *ACS Catal.* **2017**, 7, 4435.

enantioselectivity. After the optimization of conditions, notably by use of *N*-bromophthalimide (NBP) as the brominating agent and racemic camphor sulfonic acid as the additive provided an appreciable improvement of the enantioselectivity and excellent diastereoselectivity, the substrate scope was investigated. A plausible mechanism is proposed, they speculate that NBP could be activated by the protonated quinuclidine while the basic nitrogen of phthalazine of the catalyst could deprotonate the hydroxyl hydrogen atom of substrate to give the intermediate. Subsequently, semipinacol rearrangement triggered by the electrophilic bromine atom could yield the atropisomeric product.

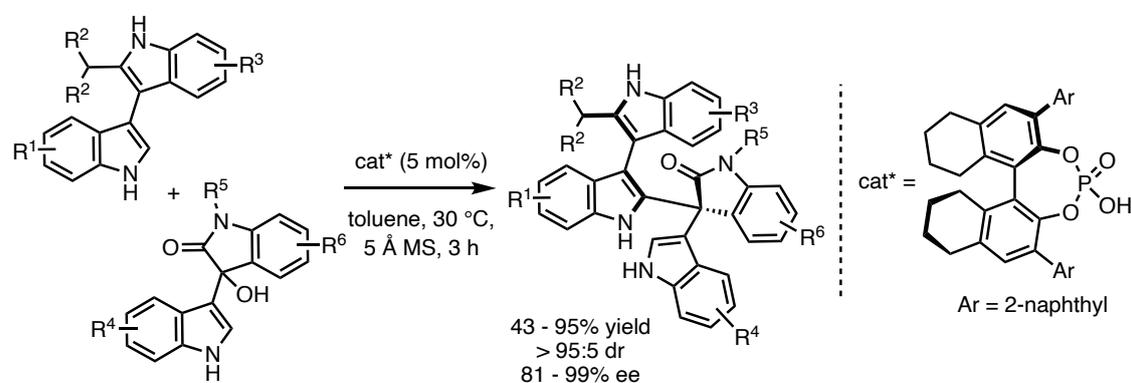


Scheme 25. DKR-Semipinacol Rearrangement

The group of Shi reported an efficient access to axially chiral bi-indole skeletons from pre-functionalized bi-indoles in which free-rotation around the axis is possible (Scheme 26).⁸⁰ The smart choice of an isatin-derived 3-indolylmethanol as the bulky

⁸⁰ C. Ma, F. Jiang, F. T. Sheng, Y. Jiao, G. J. Mei, F. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 3014.

electrophile under CPA-activation not only blocks the rotation and creates the axial chirality but also forges a stereogenic quaternary carbon atom. The highly congested tri-indolic molecules are formed in high yields and excellent diastereo- and enantioselectivities. This is also the first highly enantioselective construction of axially chiral 3,3'-bisindole structures, a nice example for simultaneous control of axial and central chirality in one step. This also provides a new strategy for catalytic enantioselective construction of axially chiral 3,3'-bisindole backbones from prochiral substrates.

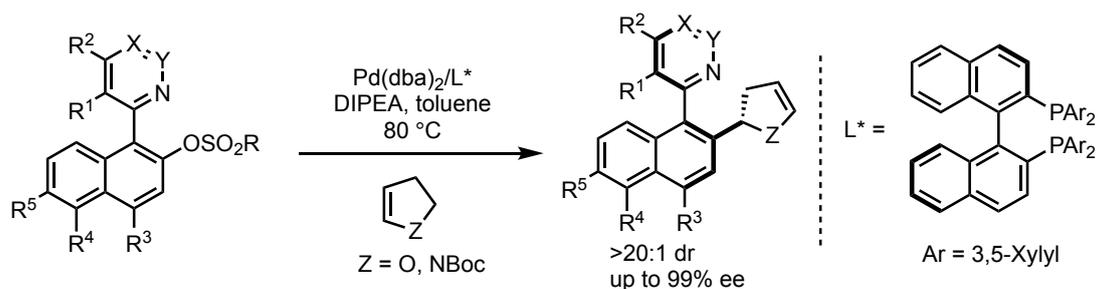


Scheme 26. The strategy for constructing an axially chiral 3,3'-bisindole backbone

Lassaletta and co-workers described an enantioselective coupling of 2,3-dihydrofuran with a variety of quinoline, quinazoline, phthalazine, and picoline derivatives which takes place with simultaneous installation of central and axial chiralities (Scheme 27).⁸¹ Excellent diastereo- and enantiomeric excesses were obtained when the Pd-catalyzed enantioselective Heck reaction of heterobiaryl sulfonates with electron-rich olefins was used, with the catalyst loadings reduced down to 2 mol% for large scale reactions. Computational studies suggest that a β -hydride elimination is the stereocontrolling step,

⁸¹ J. A. Carmona, V. Hornillos, P. Ramírez-López, A. Ros, J. Iglesias-Sigüenza, E. Gómez-Bengoa, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2018**, 140, 11067.

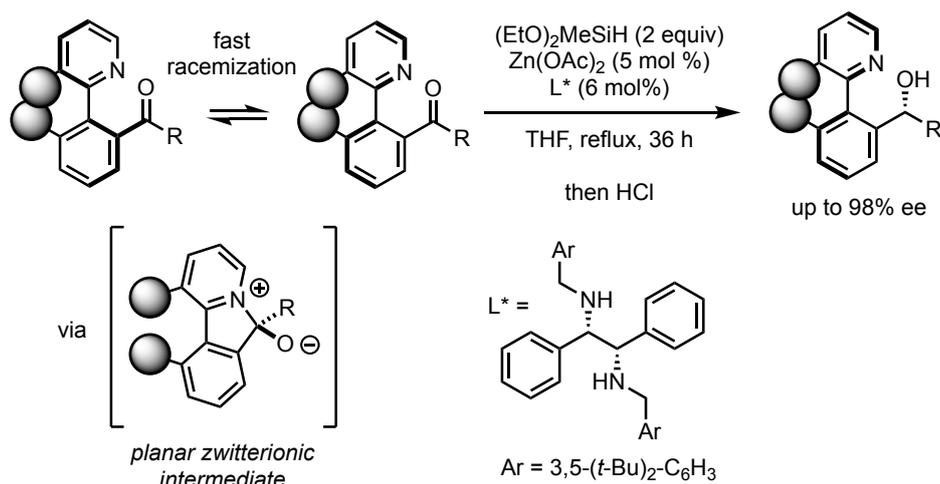
in agreement with the observed stereochemical outcome of the reaction. This transformation represents the first example of the use of an enantioselective Heck reaction to resolve both a stereogenic axis and a stereocenter simultaneously, showing a broad scope of axially chiral heterobiaryl compounds with electron-rich cyclic and acyclic olefins.



Scheme 27. Enantioselective Heck coupling by Lassaletta.

The same group also reported the diastereo- and highly enantioselective DKR of configurationally labile heterobiaryl ketones (Scheme 28).⁸² The DKR proceeds by zinc-catalyzed hydrosilylation of the carbonyl group, leading to secondary alcohols bearing axial and central chiralities. The strategy relies on the racemization of the stereogenic axis via a planar zwitterionic intermediate that takes place thanks to a Lewis acid-base interaction between a nitrogen atom in the heterocycle and the ketone carbonyl. The synthetic utility of the methodology is demonstrated through stereospecific transformations into *N,N*-ligands or appealing axially chiral, bifunctional thiourea organocatalysts. The weak Lewis acid-base interaction is the key for the atroposelective Zn-catalyzed hydrosilylation of heterobiaryl ketones via DKR.

⁸² V. Hornillos, J. A. Carmona, A. Ros, J. Iglesias-Sigüenza, J. López-Serrano, R. Fernández, J. M. Lassaletta, *Angew. Chem. Int. Ed.* **2018**, *57*, 3777.

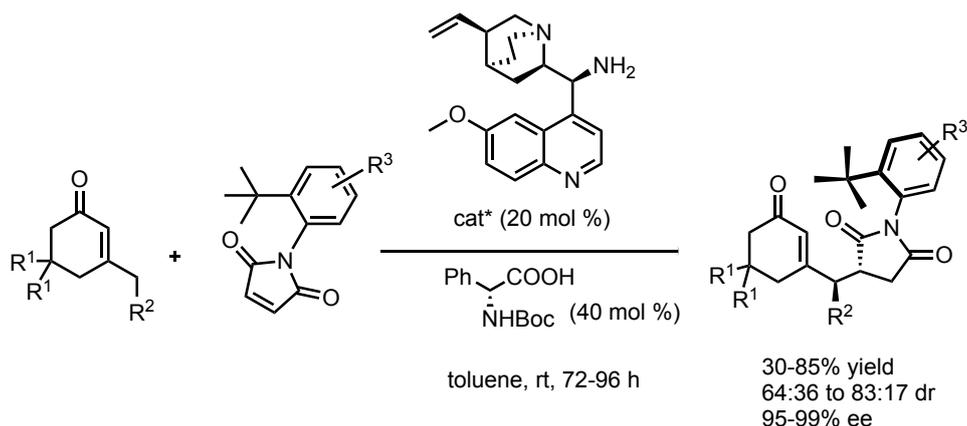


Scheme 28. Zn-catalyzed enantioselective hydrosilylation

2.5.1.3) Desymmetrization

In 2014, the group of Bencivenni described a method dealing with the aminocatalytic desymmetrization of *N*-arylmaleimides *via* vinylogous Michael addition of 3-substituted cyclohexenones to *N*-(2-*tert*-butylphenyl) succinimides with remote control of the axial chirality (Scheme 29).⁸³ 9-Amino(9-deoxy)epi-quinine catalyzed the enantioselective desymmetrization which, led to atropisomeric succinimides with two adjacent stereocenters. Primary amine catalysis was fundamental for the enantioselective desymmetrization to occur with simultaneous and exclusive remote control of the chiral axis and the newly formed stereocenters.

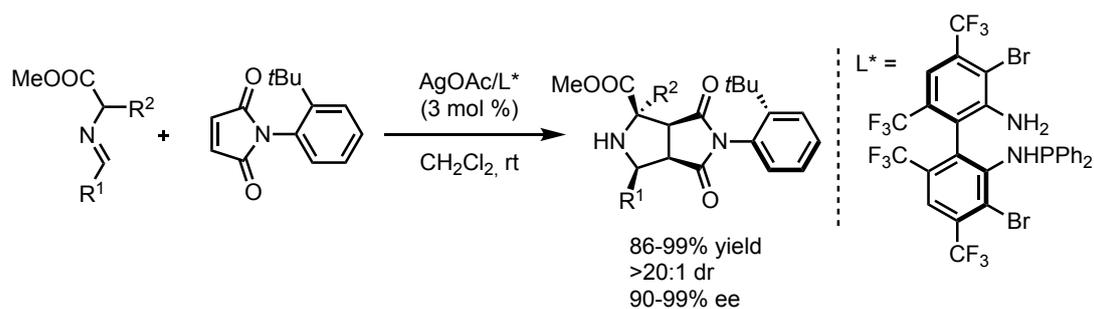
⁸³ N. D. Iorio, P. Righi, A. Mazzanti, M. Mancinelli, A. Ciogli, G. Bencivenni, *J. Am. Chem. Soc.* **2014**, 136, 10250.



Scheme 29. Aminocatalytic desymmetrization for remote control of axial chirality

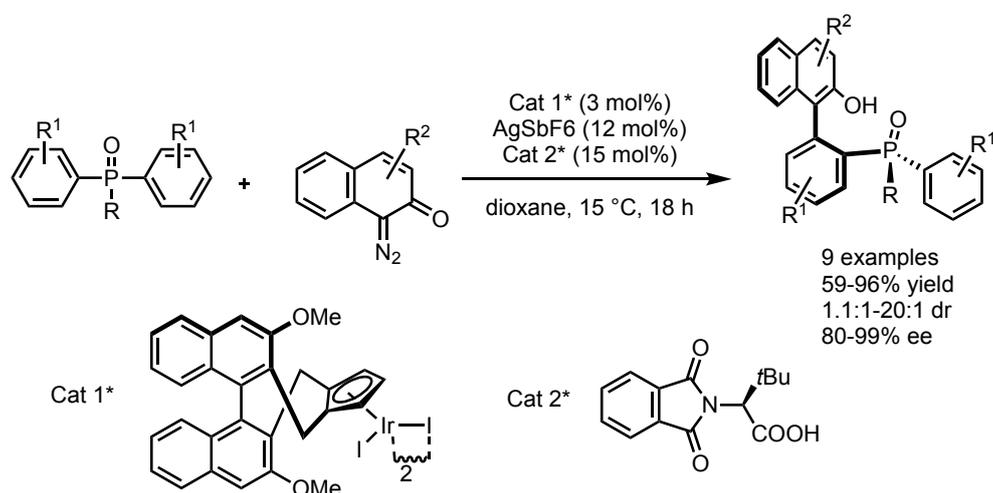
In 2016, the group of Wang also reported the atroposelective desymmetrization of *N*-arylmaleimide *via* 1,3-dipolar cycloaddition of azomethine ylides catalyzed by silver(I) (Scheme 30).⁸⁴ This is an efficient method for the access to octahydropyrrolo[3,4-*c*]pyrrole derivatives. The reaction proceeds *via* 1,3-dipolar cycloaddition of *in situ* generated azomethine ylides to afford a facile access to a series of biologically important and enantioenriched octahydropyrrolo[3,4-*c*]pyrrole derivatives in generally high yields (up to 99%) with excellent levels of diastereo-/enantioselectivities (up to >20:1 dr, 99% ee). The absolute configuration of the generated chiral axis has been identified as (*M*) through single-crystal X-ray diffraction analysis. The enantioenriched octahydropyrrolo[3,4-*c*]pyrroles possess four adjacent stereocenters and a C–N stereogenic axis. This novel desymmetrization process works well with a broad substrate scope to afford the corresponding annulation products with great yields and excellent stereoselectivity control.

⁸⁴ H.-C. Liu, H.-Y. Tao, H. Cong, C.-J. Wang, *J. Org. Chem.* **2016**, 81, 3752.



Scheme 30. Atroposelective desymmetrization of *N*-arylmaleimide

In 2018, the group of Cramer described an enantioselective C–H arylation of phosphine oxides with *o*-quinone diazides catalyzed by an iridium (III) complex bearing an atropisomeric cyclopentadienyl ligand and phthaloyl *tert*-leucine as co-catalyst (Scheme 31).⁸⁵ The method allows notably the selective assembly of axially and *P*-chiral compounds in excellent yields and generally good diastereo- and enantioselectivities. Enantiospecific reductions provide monodentate chiral phosphorus (III) compounds, which have structures and biaryl backbones useful as ligands in enantioselective catalysis.

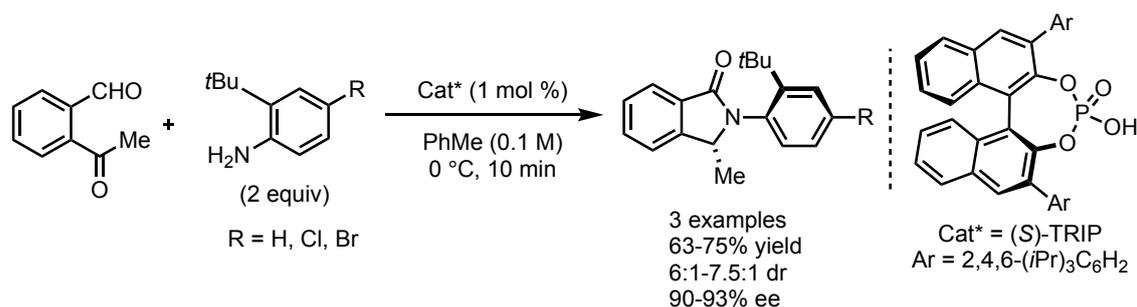


Scheme 31. Enantioselective C-H arylation of phosphine oxides

⁸⁵ Y.-S. Jang, Ł. Wozniak, J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2018**, 57, 12901.

2.5.1.4) Other organocatalyzed reaction

The group of Seidel described a catalytic enantioselective synthesis of isoindolinones thanks to the condensation of 2-acylbenzaldehydes and anilines (Scheme 32).⁸⁶ In the presence of 1 mol% of the CPA catalyst, reactions reach completion within 10 min and provided products with up to 98% enantiomeric excess. Anilines with an ortho *t*-butyl group form atropisomeric products, thereby enabling the simultaneous generation of axial and central chiralities from simple achiral substrates.



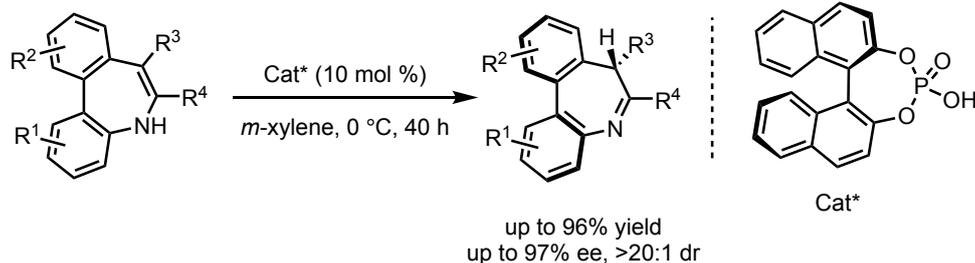
Scheme 32. Enantioselective condensation between 2-acylbenzaldehydes and anilines

The group of Luan reported the first example of catalytic enantioselective tautomerization of structurally labile but isolable enamines to access to chiral imine-tautomers (Scheme 33).⁸⁷ Kinetically stable enamine-based dibenzo[*b,d*]azepines were tautomerized by a simple chiral BINOL-phosphoric acid, which provides a variety of seven-membered imine products bearing both central and axial stereogenic elements in good yields (up to 96%) with excellent enantio- and diastereoselectivities (up to 97% ee, >20:1 dr). This kind of enantiomerically enriched seven-membered *N*-heterocycles possess a tertiary carbon stereogenic center and a biaryl axis with great enantio- and diastereoselectivities. This highly atom-economical process, represents a rare example of transferring one class of kinetically stable enols or enols equivalents into their

⁸⁶ C. Min, Y. Lin, D. Seidel, *Angew. Chem. Int. Ed.* **2017**, 56, 15353.

⁸⁷ J. Liu, X. Yang, Z. Zuo, J. Nan, Y. Wang, X. Luan, *Org. Lett.* **2018**, 20, 244.

enantioenriched keto tautomers by using an enantioselective tautomerization strategy.

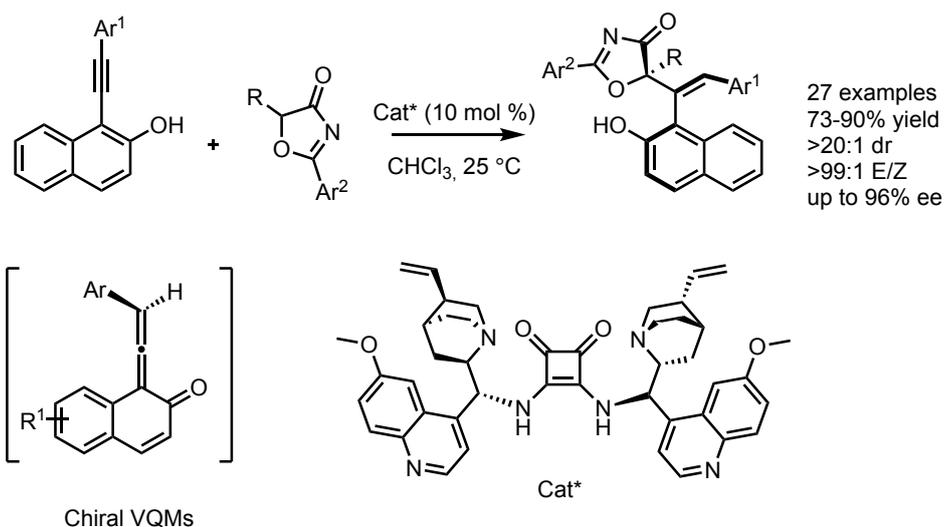


Scheme 33. Catalytic enantioselective tautomerization of enamines

Vinylidene quinone methides (VQMs) are highly electrophilic intermediates, which have shown huge potential for the construction of axially chiral compounds (Scheme 34).⁸⁸ A critical feature of VQMs is their intrinsic axial chirality that can be controlled during their generation from 2-alkynylnaphthols with a chiral non-racemic organocatalyst. In this context, Liu, Yan and Li described an enantioselective one-pot construction of intriguing molecules bearing *E,Z* configurations, stereogenic carbon atoms and axially chiral styrenes. They employed 5*H*-oxazol-4-ones as the nucleophilic partner with in situ generated VQM intermediate under hydrogen-bonding organocatalysis. The method enabled the rapid construction of a series of stereochemically complex products with excellent *E,Z* selectivity, diastereoselectivity (>20:1 dr), and enantioselectivity (up to 96% ee). The reaction proceeds under mild reaction conditions, tolerates a range of functional groups, and is applicable to gram-scale synthesis.⁸⁹

⁸⁸ J. Rodriguez, D. Bonne, *Chem. Commun.* **2019**, 55, 11168.

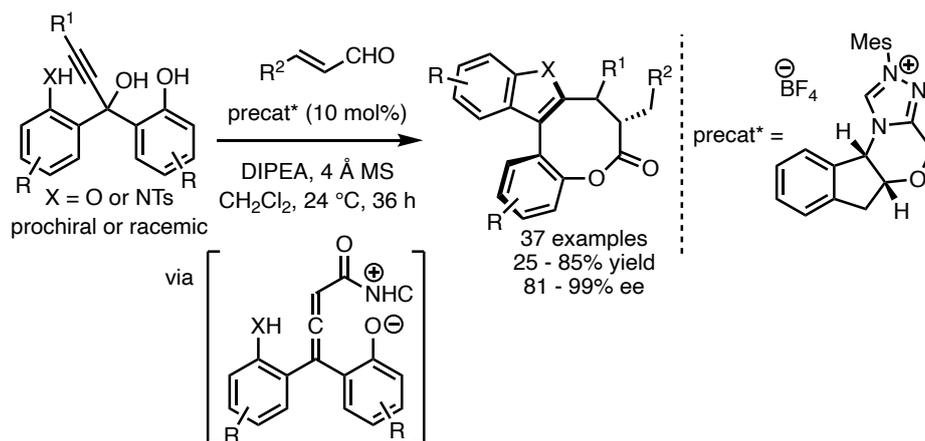
⁸⁹ A. Huang, L. Zhang, D. Li, Y. Liu, H. Yan, W. Li, *Org. Lett.* **2019**, 21, 95.



Scheme 34. Enantioselective nucleophilic addition on VQM intermediates

In their quest to N-heterocyclic carbene (NHC)-catalyzed enantioselective acylation of prochiral triols (Scheme 35, X = O), the group of Wong and Zhao serendipitously discovered the formation of bridged biaryls bearing an eight-membered lactone when the triol (X = O) or the aminophenol (X = NTs) was reacted with enals in the presence of azolium pre-catalyst under basic conditions.⁹⁰ The scope is wide for this unique class of atropisomers displaying either a benzofuran or an indole ring. Mechanistic investigations were realized by DFT calculations and suggest an initial formation of a highly reactive chiral *o*-quinone methide that evolves by 1,6-conjugate addition of the *in situ* generated azolium enolate. The resulting chiral allene acylazolium intermediate undergoes a bi-directional heterocyclization giving the final product with both axial and central chiralities.

⁹⁰ S. Lu, J.-Y. Ong, H. Yang, S. B. Poh, X. Liew, C. S. D. Seow, M. W. Wong, Y. Zhao, *J. Am. Chem. Soc.* **2019**, *141*, 17062.

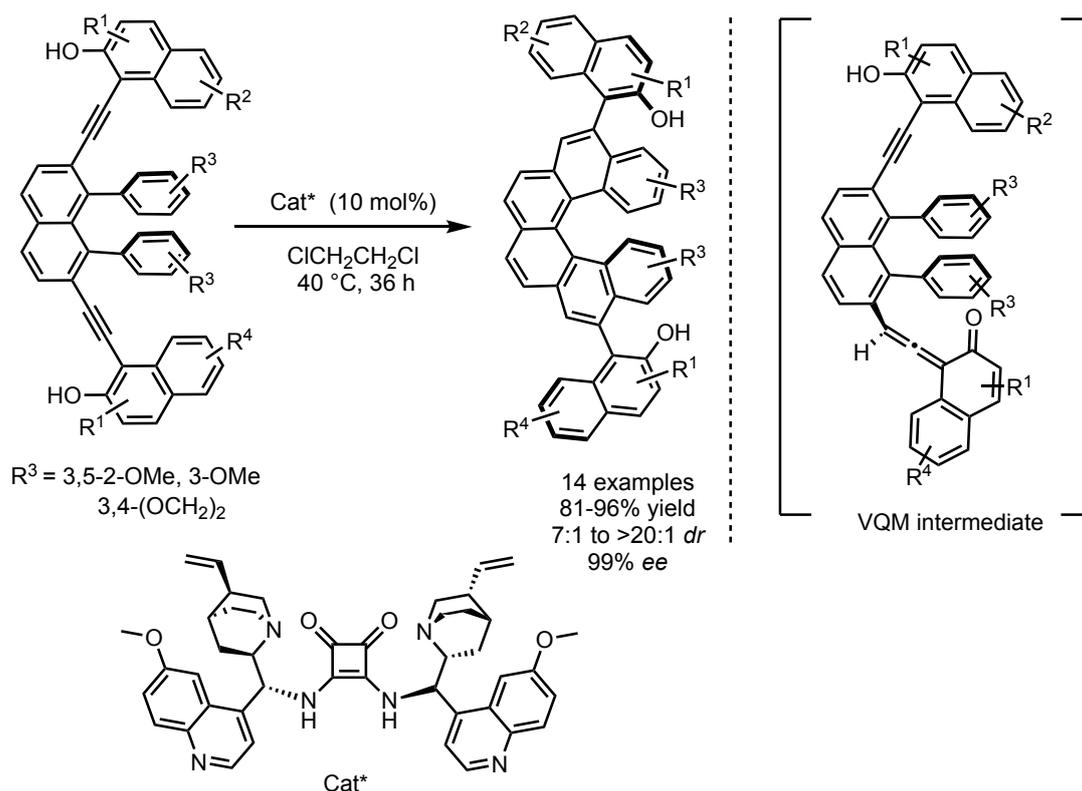


Scheme 35. Atroposelective synthesis of biaryls bearing an eight-membered lactone

2.5.2) Installation of planar and axial chiralities

In 2015, Kamikawa, Takahashi and Ogasawara reported an elegant strategy leading to axially chiral *N*-arylindole compounds *via* an enantioselective desymmetrizing ring-closing metathesis (RCM) (Scheme 36).⁹¹ They started from functionalized prochiral planar (π -arene)chromium complexes bearing an indolyl substituent whose orientation is fixed in the *anti*-configuration, with respect to the chromium atom. The reactions were run in benzene at 40 °C with 10 mol% of *in situ* generated chiral molybdenum catalyst. The presence of an electron-rich phosphine coordinated to the chromium is crucial to obtain high yields and enantioselectivities. With these reaction conditions, chiral chromium complexes were produced very efficiently and both axial and planar chirality were simultaneously installed and controlled during this transformation. The authors showed the possibility of decomplexing under very soft reaction conditions, destroying the planar chirality and releasing the axially chiral *N*-arylindole in excellent yield with retention of the enantiomeric purity.

⁹¹ K. Kamikawa, S. Arai, W.-Y. Wu, C. Nakamura, T. Takahashi, M. Ogasawara, *Chem. Eur. J.* **2015**, 21, 4954.



Scheme 37. Enantioselective synthesis of axially chiral carbo[6]helicenes.

This literature survey shows that the methodologies allowing the simultaneous control of two different stereogenic elements are not common. Moreover, there is no example where both central and helical chiralities are installed and controlled within a molecule.

2.6) Configurational stability of the target

The inversion of configuration of stereogenic tetrasubstituted sp^3 -hybridized carbon atoms calls for chemical operations (breaking then making a covalent bond). On the contrary, the inversion of configuration of stereogenic axes and helices generally only requires flexibility and molecular motion. For atropisomers and helicenes, these dynamic phenomena can be accurately monitored: (i) either directly by dynamic chiral

HPLC when the corresponding barriers to enantiomerization ΔG^\ddagger are in the magnitude of 85–100 kJ.mol⁻¹; (ii) or by studying the kinetics of racemization for compounds with $\Delta G^\ddagger > 100$ kJ.mol⁻¹. It is assumed that the enantiomers of helically chiral structures are isolable for $\Delta G^\ddagger > 100$ kJ.mol⁻¹, corresponding to a half-life time $t_{1/2}$ higher than 5 hours at 25 °C.⁹³

In the case of our targeted dioxa[6]helicenes, the required configurational stability is anticipated to be secured by a remote steric effect of the bulky aryl group at the 3-position of the furan ring of **4b** (Figure 13), insuring an increased barrier to enantiomerization. This is indeed corroborated by comparison of configurational stability of the corresponding carbo[6]helicene with the targeted oxa[6]helicenes. The presence of two five-membered furan rings results in a more open helical pitch⁹⁴ responsible for a much lower barrier to enantiomerization of $\Delta G^\ddagger = 71.5$ kJ/mol for configurationally labile ($t_{1/2} = 0.5$ s) unsubstituted dioxa[6]helicene **4a** compared to the $\Delta G^\ddagger = 151.3$ kJ/mol for stable carbo[6]helicene.⁹⁵ Gratifyingly, a strong beneficial remote steric effect of the phenyl substituent at the 3-position of the furan ring in **4b** increases the barrier to enantiomerization up to $\Delta G^\ddagger = 138.8$ kJ/mol, corresponding to a half-life of one year at 80 °C, arguing for a high configurational stability.

⁹³ For a monograph: C. Wolf in *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*. RSCPublishing: **2007**, chap.3, 153.

⁹⁴ For the pioneer observation, see: M. B. Groen, H. Schadenberg, H. Wynberg, *J. Org. Chem.* **1971**, 36, 2797.

⁹⁵ It is established that each enantiomer of a helical structure is isolable when the half-life time $t_{1/2}$ is higher than 5 hours at 25 °C meaning a barrier to enantiomerization $\Delta G^\ddagger > 100$ kJ/mol.

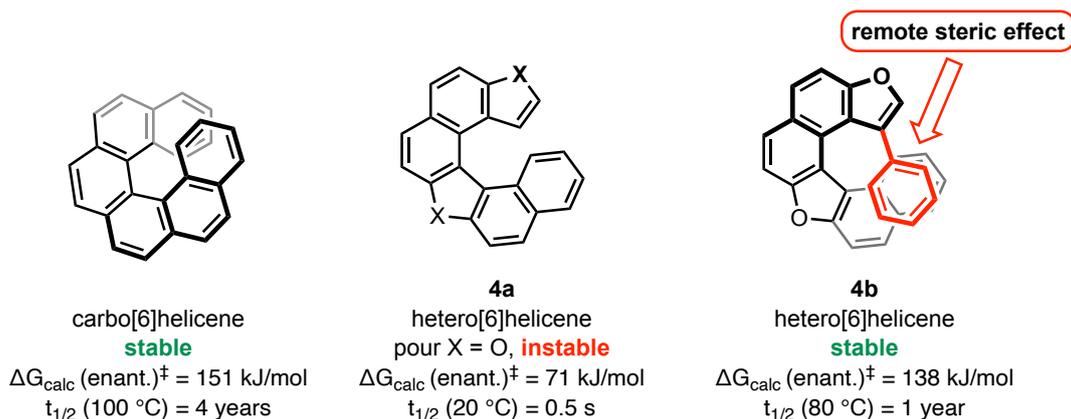
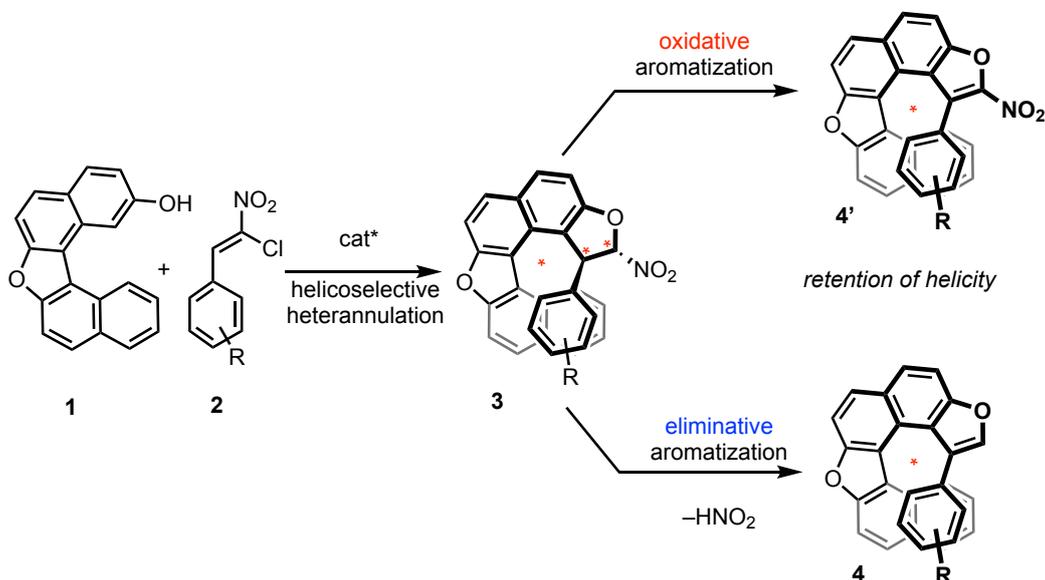


Figure 13. Barriers to enantiomerization for carbo[6]helicene and oxa[6]helicenes.⁹⁶

Our strategy is the organocatalytic synthesis of dihydrofurans from easy accessible starting materials and their aromatization to the desired heterohelicenes (Scheme 38). Two possibilities for the aromatization are possible: 1) the oxidation of the dihydrofuran or 2) the elimination of nitrous acid under basic conditions. These two approaches have been explored and will be discussed later.



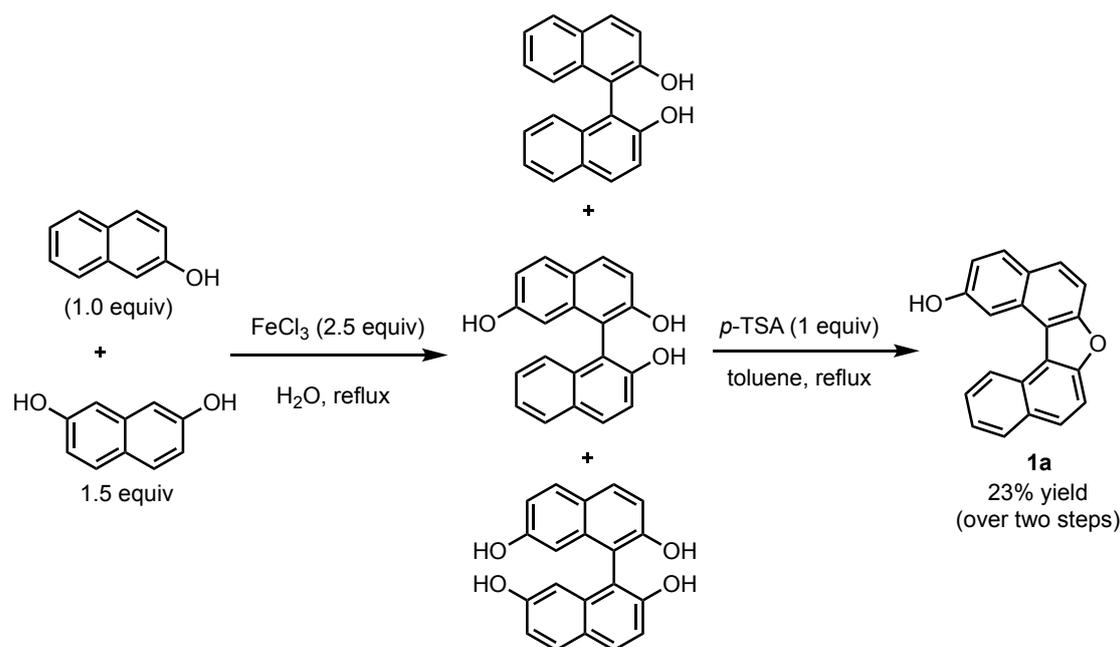
Scheme 38. Strategy for the enantioselective synthesis of helicenes

⁹⁶ Calculated values at the B3LYP/6-31G(d) level of theory, in collaboration with Prof. Stéphane Humbel, iSm2, CTOM.

2.7) Enantioselective synthesis of dihydrofurans bearing central and helical chiralities

2.7.1) Synthesis of the starting materials

In 2015, Bedekar⁹⁷ reported the synthesis of racemic 7,12,17-trioxa[11]helicene, and this provided us a good method to synthesize the starting materials (Scheme 39). The first step is the oxidative cross-coupling between dihydroxynaphthalene and 2-naphthalene which yield three products that can be separated by flash column chromatography on silica gel. Then, *p*-TSA under reflux promoted the dehydrative cyclization to get the desired dinaphtho[2,1-*b*:1',2'-*d*]furan-2-ol **1a** with an acceptable overall yield of 23% for two steps.

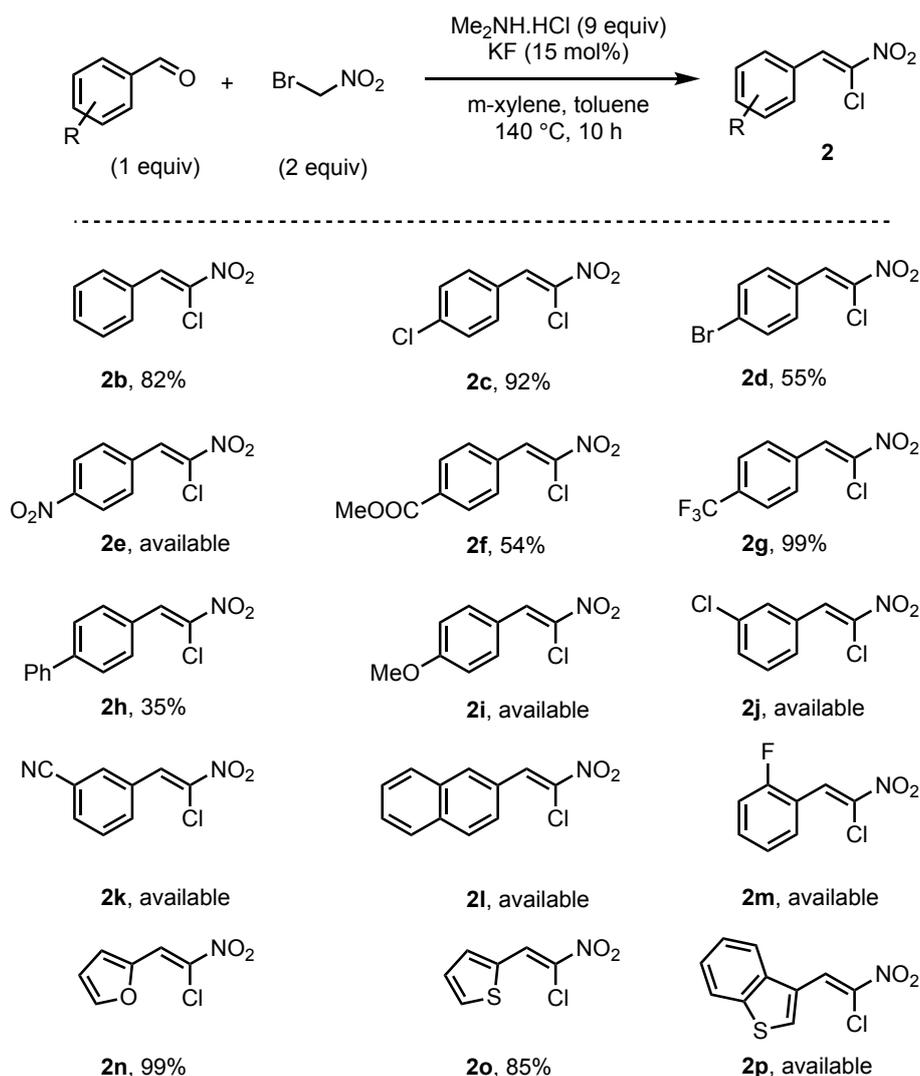


Scheme 39. Synthetic route for dinaphtho[2,1-*b*:1',2'-*d*]furan-2-ol **1a**.

⁹⁷ M. S. Sundar, A. V. Bedekar, *Org. Lett.* **2015**, 17, 5808.

In addition, various chloronitroalkenes **2** were synthesized using the following reaction, reported by Dauzonne and co-workers.⁹⁸ The substituted benzaldehydes, bromonitromethane, and dimethylamine hydrochloride were used as the starting materials, using potassium fluoride as the catalyst, the above compounds were put in the mixed solvents with toluene and *m*-xylene and connected to the Dean- Stark trap. The mixture was heated at 160 °C with azeotropic removal of water. The pure product was obtained after purification by flash column chromatography on silica gel. Apart from those already available in our laboratory, we have synthesized eight new α -chloronitroalkenes (Scheme 40).

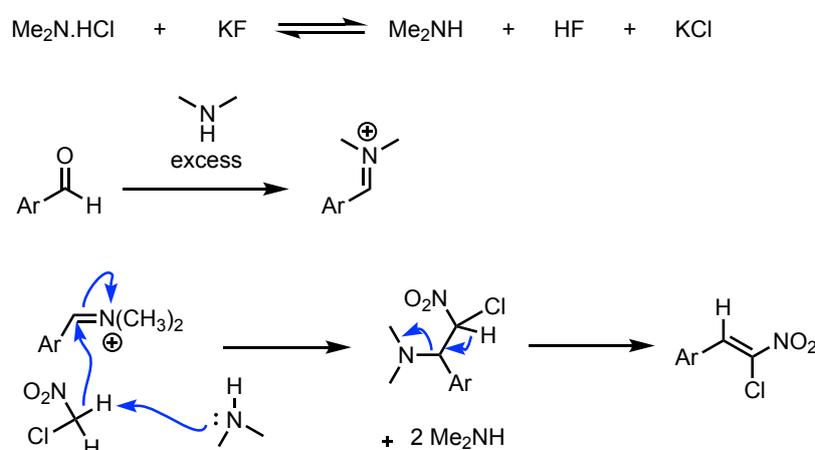
⁹⁸ D. Dauzonne, R. Royer, *Synthesis*, **1987**, 1020.



Scheme 40. Synthesis of new α -chloro- α -nitroalkenes

A plausible mechanism to account for the formation of α -chloro- α -nitroalkenes could be as follows (Scheme 41). The dimethylammonium chloride, insoluble in xylene, disappears quickly at the start of the reaction, after about 30 min of reaction, there is the appearance of a solid composed of a complex mixture of dimethylammonium salts (bromide, fluoride and chloride) and potassium chloride. Obtaining almost exclusively the chlorinated product from bromonitromethane as the starting material is due to the use of a large excess of dimethylammonium chloride, which induces an exchange of halogen on bromonitromethane via nucleophilic substitution with chloride anion. The

reacting entity is then chloronitromethane formed *in situ*. It should be noted that in some cases a small amount of the corresponding bromonitroalkene (5%) is obtained as a mixture with the desired product. The presence of a small amount of KF (15 mol% relative to the aldehyde used) makes it possible to continuously shift the equilibrium leading to the formation of free amine. Then, the formation of iminium ion is possible. Dimethylamine could then deprotonate the chloronitromethane to generate the nitronate anion, which could add on the corresponding iminium ion. Finally, elimination of dimethylamine would give the desired (*Z*)- α -chloronitroalkene.

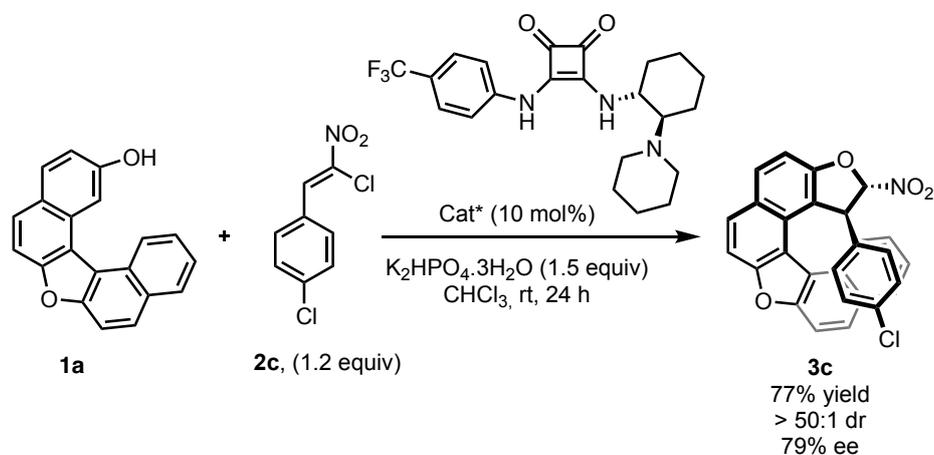


Scheme 41. Mechanism of synthesis of α -chloronitroalkenes

2.7.2) Preliminary results and reaction optimization

A model reaction was tested using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1a** (1.0 equiv) and (*Z*)-1-chloro-4-(2-chloro-2-nitrovinyl)benzene **2c** (1.2 equiv), (Scheme 42). Potassium phosphate dibasic trihydrate (1.5 equiv) was used as the base to neutralize the HCl formed *in situ*. Squaramide catalyst (10 mol%) was then added followed by chloroform (0.1 M). The resulting solution was stirred at room temperature for 6 days. Under the above conditions, the final product **3c** could be obtained with encouraging 77% yield and 79% ee with a perfect 1,2-*trans* diastereoselectivity. Given the important steric hindrance, this was a promising result and we realized that the product may

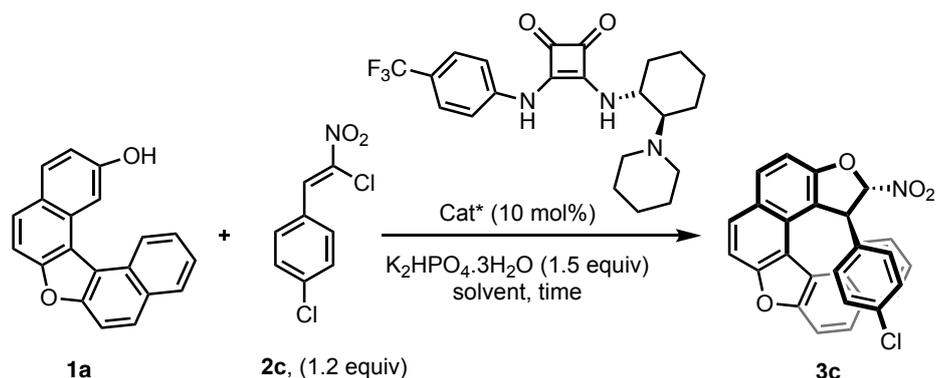
display both central and helical chiralities. This will be checked later by chiroptical studies.



Scheme 42. Preliminary studies towards enantioselective synthesis of dihydrofurans

We next followed by the optimization of the reaction conditions to improve both the yield and the enantiomeric excess (Table 1). At first, other solvents were tested with the above squaramide catalyst. But, as the scheme shows, chloroform is still the best solvent. When the methanol was used as solvent, the enantiomeric excess was very low (9% ee). Using acetonitrile, toluene and THF as solvents, only trace of product was formed (the ee was not measured in these cases). The next step was the evaluation of the catalytic activity of other squaramides and thioureas.

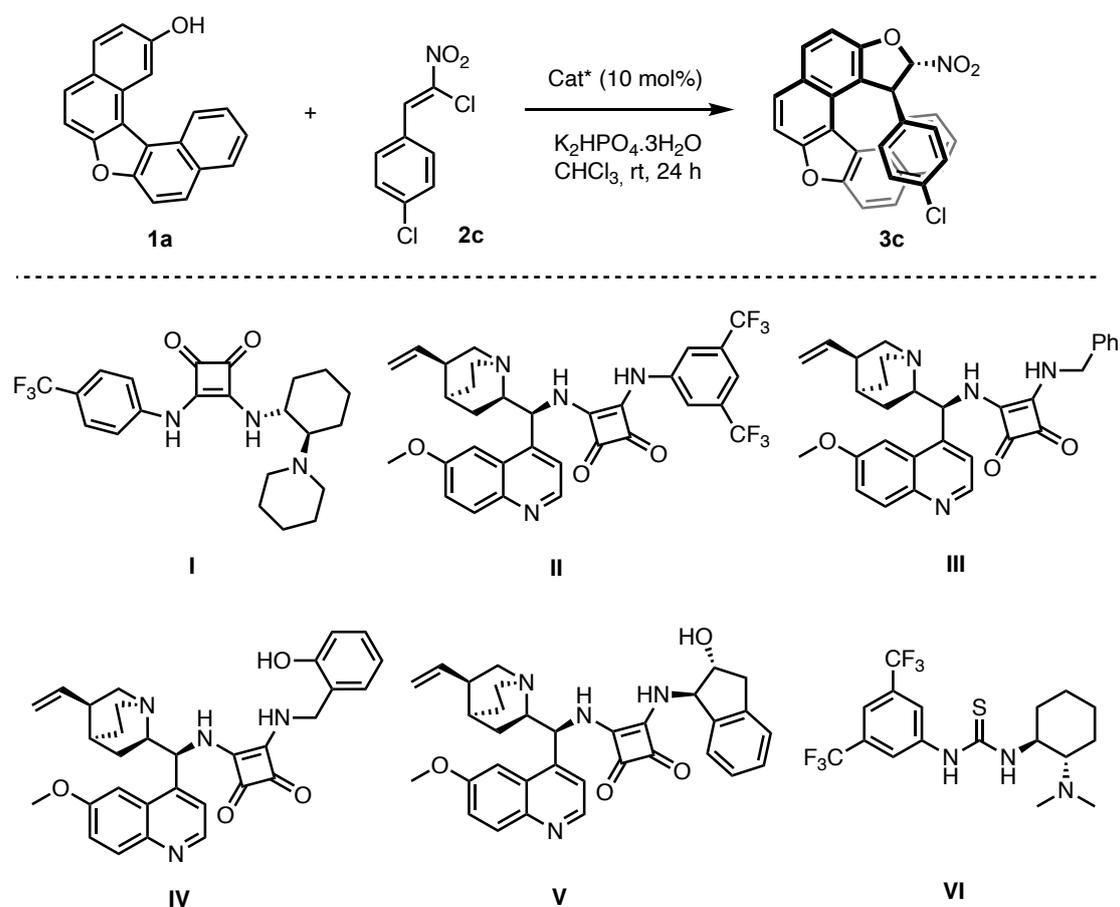
Table 1. Solvent optimization



Entry	solvent	time	yield of 3c (%)	ee of 3c (%)
1	MeOH	6 d	49%	71
2	MeCN	24 h	trace	nd
3	THF	25 h	trace	nd
4	toluene	24 h	trace	nd

Five alternative catalysts were used in the reaction to improve the enantiomeric excess. Table 2 shows the structure of each catalysts, including the squaramides and thiourea catalysts. Entry 1 is the initial result, so other five different kinds of catalysts were used to optimize the enantiomeric excess. It is glad to find that catalysts **III**, **IV**, **V** and **VI** are more efficient than catalyst **I**, at least in term of enantioselectivity. When using the catalyst **III**, the enantiomeric excess is the highest (96% ee) and the yield is also very good (81%, entry 3). Then, other solvents were used with the catalyst **II** to optimize the solvent with this catalyst (entries 7 and 8), but no unprovment was found with THF or toluene, chloroform remaining the best solvent for this reaction (entry 3).

Table 2. Catalyst optimization

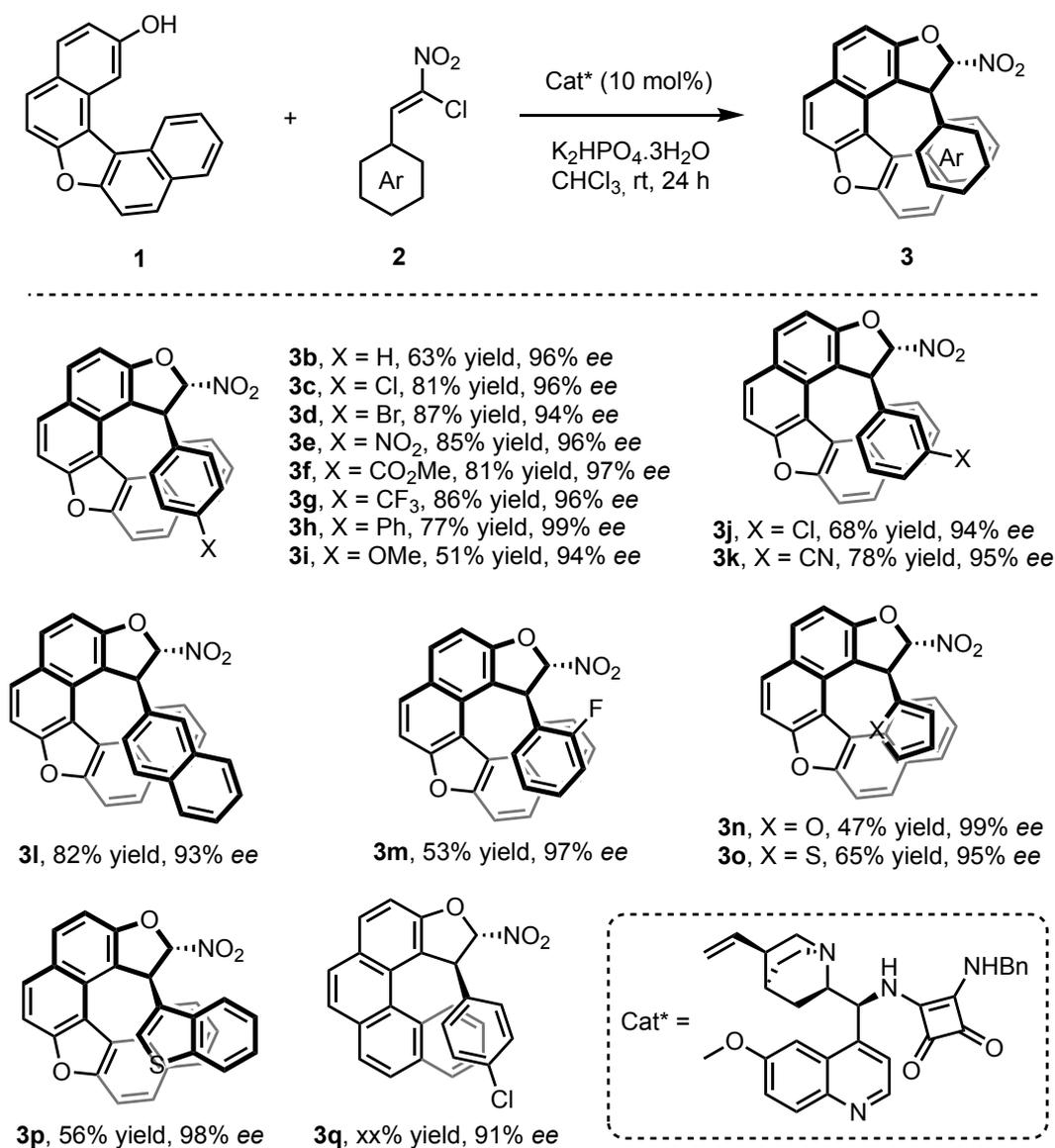


Entry	Catalyst	Yield of 3c (%)	ee of 3c (%)
1	I	77	79
2	II	59	71
3	III	81	96
4	IV	19	88
5	V	85	88
6	VI	42	94
7 ^a	III	9	50
8 ^b	III	26	88

^aTHF was used as the solvent. ^bToluene was used as the solvent.

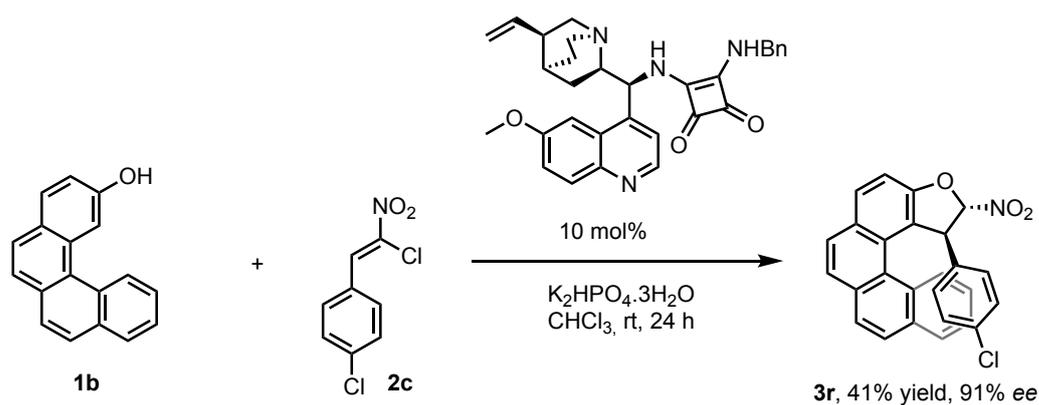
2.7.3) Reaction scope

With optimized reaction conditions in hand, we next explored the generality of this new domino organocatalyzed helicoselective synthesis of dihydrofurans **3**. Substituents at the *para* position of the phenyl ring were all compatible with this protocol as well as a naphthyl group, affording the corresponding products with excellent stereocontrol (**3c-i** and **3l**, 93-99% ee), even if the yield was moderate in the case of the 4-methoxyphenyl group (**3i**, 51% yield). Substituents in *meta* (**3j-k**) and *ortho* (**3m**) positions of the phenyl ring were also tolerated with slightly diminished yield but again, excellent enantioselectivities were observed. Chloronitroalkenes bearing heteroaryl rings such as furan, thiophene and benzothiophene behave with comparable efficiency, with good yields and excellent enantioselectivity (**3n-p**).



Scheme 43. Reaction scope for the dihydrofuran synthesis.

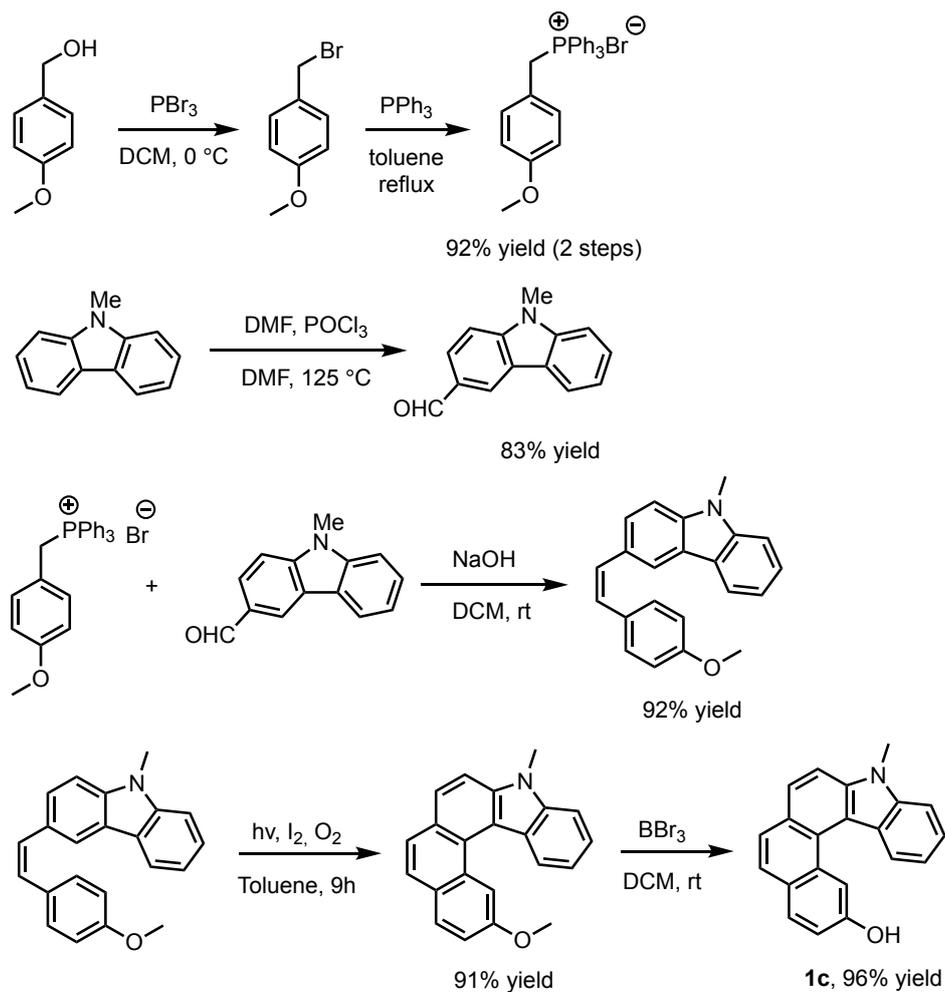
We next investigate the use of benzo[*c*]phenanthren-2-ol **1b** under the reaction conditions (Scheme 44). Pleasingly, the corresponding dihydrofuran **3r** was obtained in good yield and excellent enantioselectivity, even if in this case the presence of an inherent helicity has not been investigated yet in this particular case of oxa[5]helicene.



Scheme 44. Towards a hetero[5]helicene.

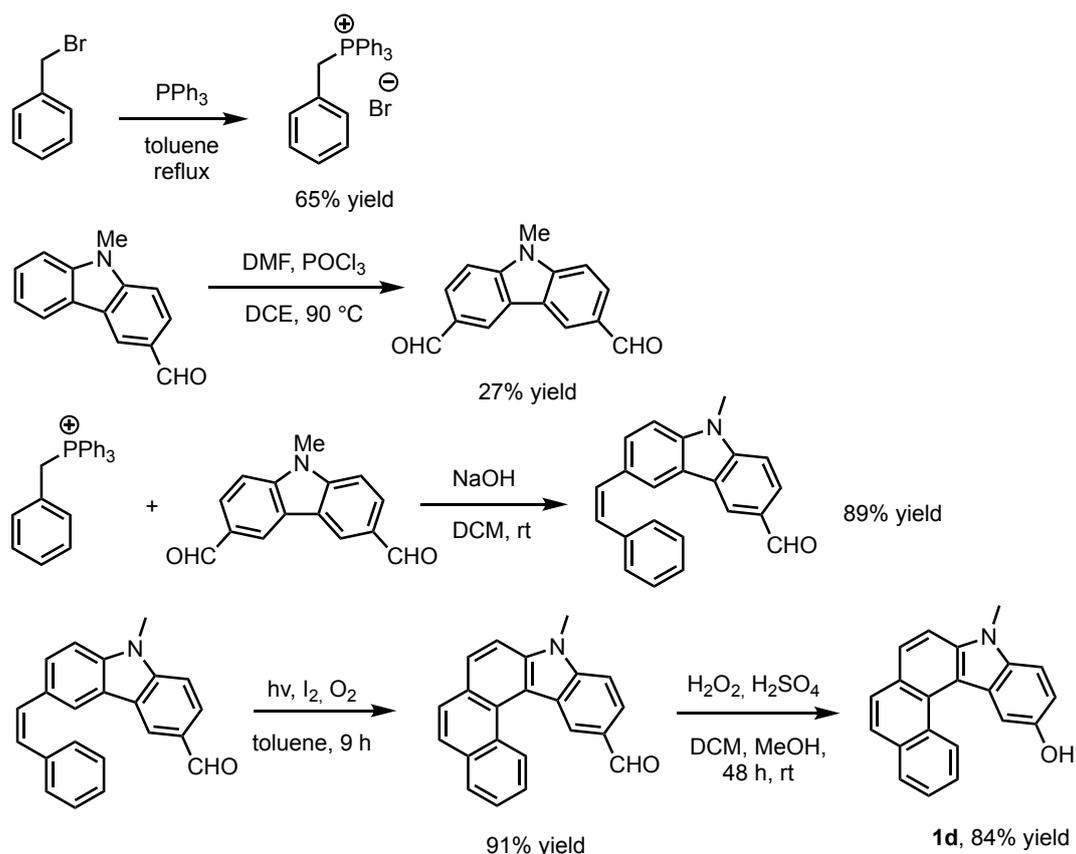
We next investigated the use of alternative bis-nucleophiles with other heteroatoms. Moorthy's report about stabilization and helicity-dependent reversion of colored *o*-quinonoid intermediates of helical chromenes,⁹⁹ provide us with an efficient synthetic pathway to access to our desired new starting materials (Scheme 45). Hence, phosphonium bromide salt was obtained from (4-methoxyphenyl)methanol in two steps (92%), while a Vilsmeier-Haack formylation allowed to obtain the corresponding 3-formylcarbazole derivative. Then, the Wittig reaction between the previously synthesized substrates afforded the desired alkene which underwent oxidative photocyclization to give the methoxy-substituted aza[5]helicene in excellent yield (91%). Finally, methoxy ether deprotection gave the desired 9-methyl-9*H*-naphtho[2,1-*c*]carbazol-2-ol **1c** in 96% yield.

⁹⁹ J. N. Moorthy, S. Mandal, A. Mukhopadhyay, S. Samanta, *J. Am. Chem. Soc.* **2013**, 135, 6872.



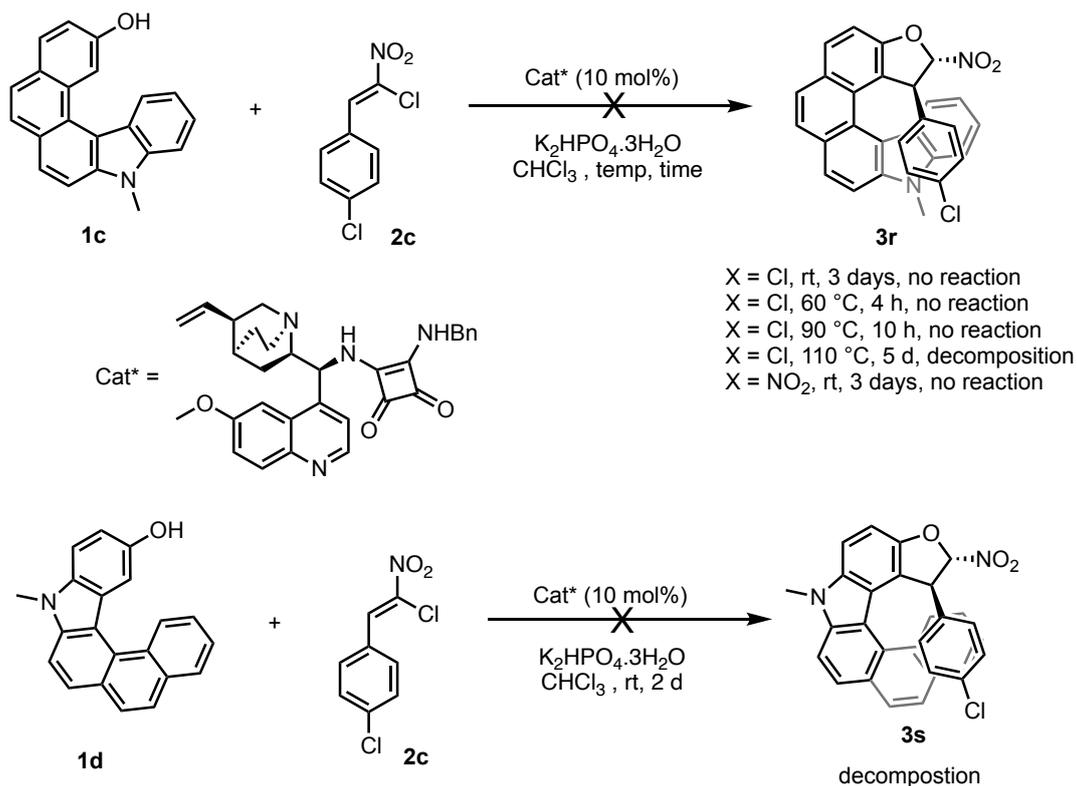
Scheme 45. Synthesis of 9-methyl-9H-naphtho[2,1-c]carbazol-2-ol **1c**

A similar strategy allowed us to synthesize 9-methyl-9H-naphtho[2,1-c]carbazol-12-ol **1d**, a regioisomer of previously synthesized hydroxycarbazole derivative (Scheme 46).



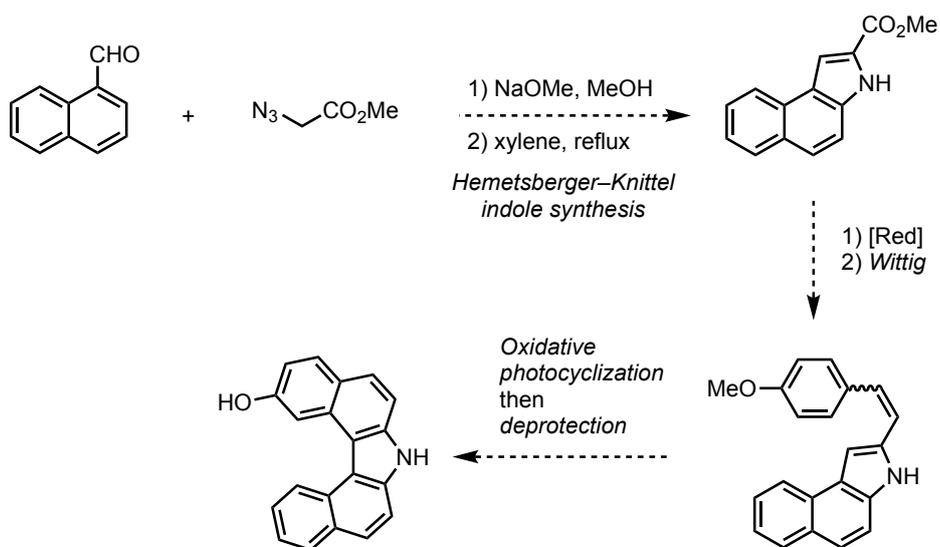
Scheme 46. Synthesis of 9-methyl-9H-naphtho[2,1-c]carbazol-12-ol **1d**

We started our investigation with 9-methyl-9H-naphtho[2,1-c]carbazol-2-ol **1c** as an alternative starting material which would allow the enantioselective synthesis of oxa,aza[6]helicenes **3r** with central chirality. Unfortunately, this substrate remained unreactive in the standard reaction conditions. Increasing the temperature has no effect as well as increasing the amount of catalyst (30 mol%) or using a more reactive 4-nitrophenyl-substituted chloronitroalkene. This surprising result is difficult to rationalize but we may argue for a slightly higher steric hindrance of the substrate when switching the oxygen atom by a *N*-Me substituent. When the reaction was conducted with **1d** as substrate, only decomposition of the substrates was observed after 2 days of reaction, and no product **3s** could be isolated.



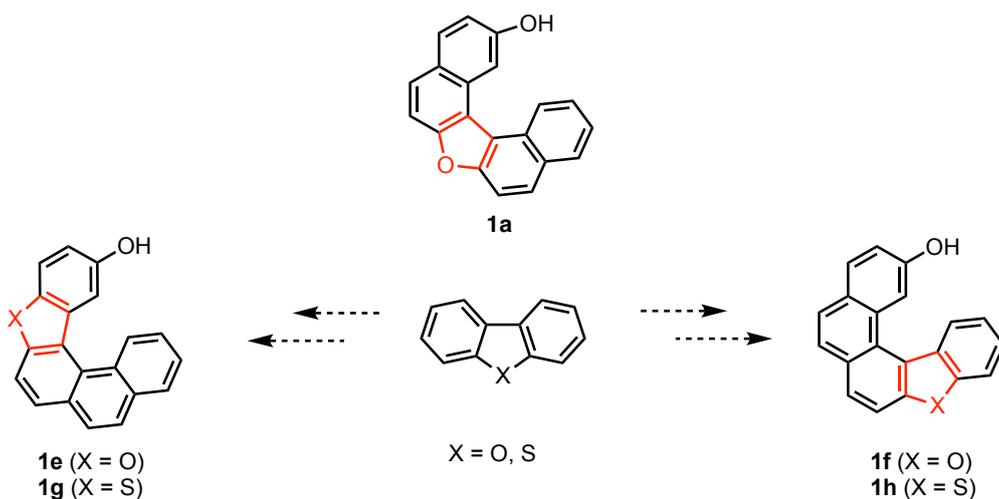
Scheme 47. Towards aza[6]helicenes

In order to solve and understand this problem of reactivity, several substrates may be envisaged to be tried in this reaction. First, we may try the NH analogue of dinaphtho[2,1-b:1',2'-d]furan-2-ol. Its synthesis is not described but should be easy accessible following the following synthetic scheme (Scheme 48). The methyl 3*H*-benzo[*e*]indole-2-carboxylate could be obtained from 1-naphthaldehyde and methyl 2-azidoacetate by a sequence Knoevenagel/Hemetsberger-Knittel synthesis. Then, as before, Wittig olefination, oxidative photocyclization and deprotection should allow to afford the desired 7*H*-dibenzo[*c,g*]carbazol-2-ol.



Scheme 48. Perspective: synthesis of 7*H*-dibenzo[*c,g*]carbazol-2-ol.

In addition, we may also envisage the synthesis of **1e** and **1f**, which are regioisomers of dinaphtho[2,1-*b*:1',2'-*d*] furan-2-ol **1a** by changing the position of the furan ring (Scheme 49). These should be easy accessible using previously used synthetic sequence (Scheme 45 and Scheme 46) from dibenzo[*b,d*]furan. Sulfur analogues **1g** and **1h** may also be obtained following this synthetic pathway from dibenzo[*b,d*]thiophene.

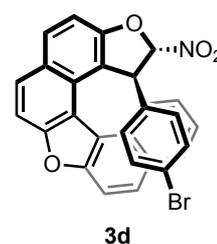


Scheme 49. Perspective: regioisomers of dinaphtho[2,1-*b*:1',2'-*d*] furan-2-ol

To the best of our knowledge, our preliminary results represent the first example of simultaneous control of central and helical chiralities by a catalytic chemical transformation offering unprecedented chiral platform molecules for the synthesis of a new family of heterohelicenes. We then focused on the determination of the absolute configuration of these intriguing centrally and helically chiral molecules.

2.7.4) Determination of the absolute configuration

To ascertain the expected helicoselectivity resulting in the simultaneous control of central and helical chiralities we needed an accurate assignment of the relative and absolute configurations of this mixed-chiral dihydrofuran. Since no exploitable crystals could be obtained with **3d**, we tackled this key point by a complete chiroptical spectroscopy study combining vibrational and electronic circular dichroisms (VCD, ECD) with density functional theory (DFT) calculations, in collaboration with Nicolas Vanthuyne, Marion Jean (chiral HPLC analysis) and Jean-Valère Naubron (VCD, ECD analysis).¹⁰⁰



A good agreement between experimentally recorded VCD (vibrational circular dichroism) and ECD (electronic circular dichroism) spectra of **3d** and the simulated VCD and ECD spectra of the (*M,S,S*)-**3d** enantiomer allowed the assignment of absolute configurations (Figure 14 and Figure 15). However, the measured VCD bands intensities are stronger than that calculated based on the SMD model. In general, this can be related to the dynamic nature of the solute-solvent intermolecular interactions that affect the experimental VCD spectrum. Besides, the calculated ECD spectrum for (*M,S,S*)-**3d** is also in very good agreement with the one recorded for dihydrofuran **3d**, confirming the VCD conclusion. The calculated spectra reproduce well both the high

¹⁰⁰ a) T. Bürgi, A. Urakawa, B. Behzadi, B.; K.-H. Ernst, A. Baiker, *New. J. Chem.* **2004**, *26*, 332. b) G. Pieters, A. Gaucher, J. Marrot, F. Maurel, J.-V. Naubron, M. Jean, N. Vanthuyne, J. Crassous, D. Prim, *Org. Lett.* **2011**, *13*, 4450.

and low-energy bands of the experimental spectrum allowing the definitive determination of the absolute configuration of **3d** as (*M,S,S*).

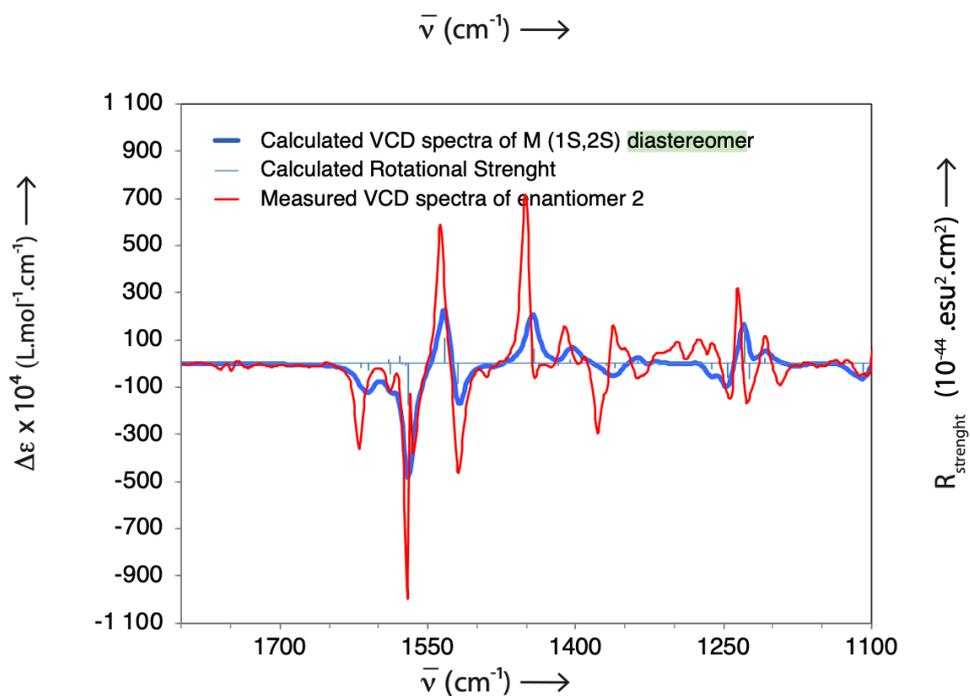


Figure 14. VCD spectroscopy studies comparing the experimental spectra of the second eluted enantiomer with the simulated spectra of the (*M,S,S*)-**3d** enantiomer

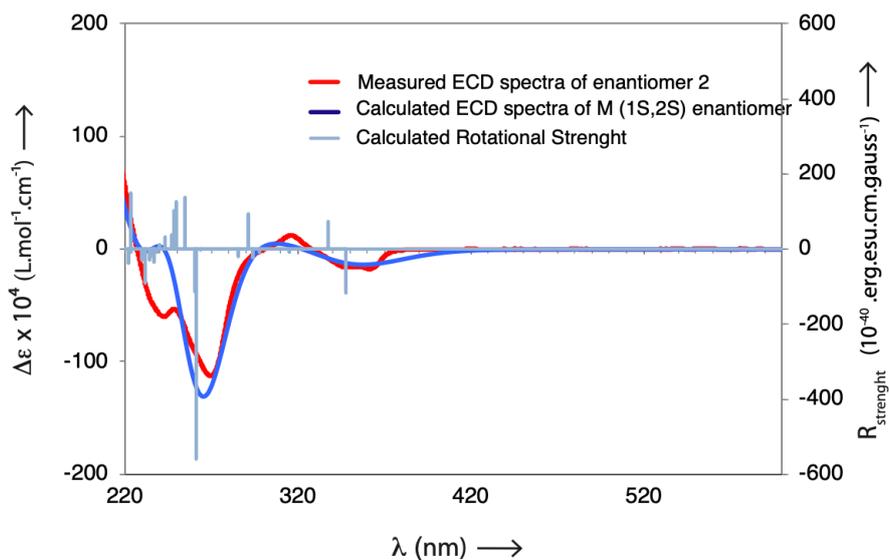


Figure 15. ECD spectroscopy studies comparing the experimental spectra of the second eluted enantiomer with the simulated spectra of the (*M,S,S*)-**3d** enantiomer

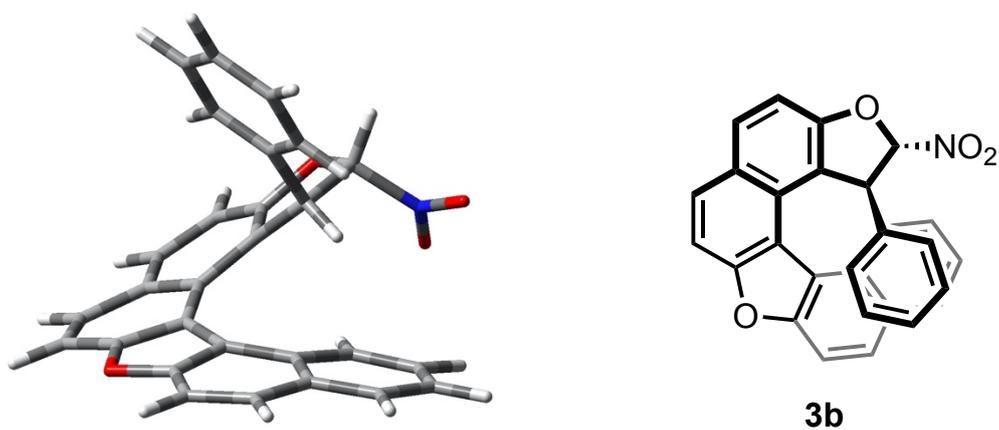
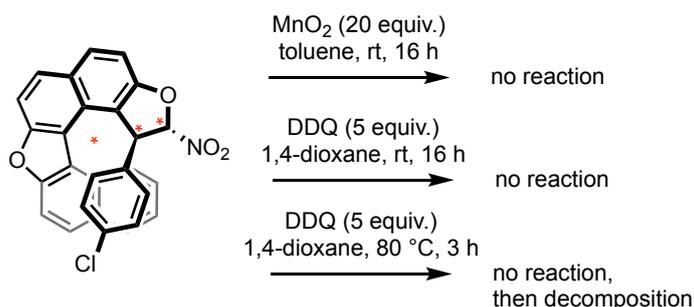


Figure 16. Optimized geometries of the (*M,S,S*)-**3b** enantiomer (with SMD(acetonitrile)/B3LYP/6-311+G(d,p))

2.8) Aromatization to dioxo[6]helicenes

2.8.1) Primary investigations

Based on our previous experience on the enantioselective synthesis of furan atropisomers,¹⁰¹ the oxidation was investigated first (Scheme 50). The reaction was conducted using 20 equivalents of MnO₂ as the oxidant, but the starting material was not reacting under these conditions and started to decompose after prolonged time. We next tried other oxidants: using 5 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in this reaction resulted also in the recovery of the starting material. Heating the reaction mixture at 80 °C for 3 hours did not allow the oxidation into the corresponding furan. Decomposition was observed when increasing the reaction time under these conditions. One hypothesis of these unsuccessful attempts for oxidation is the high steric hindrance in this substrate.

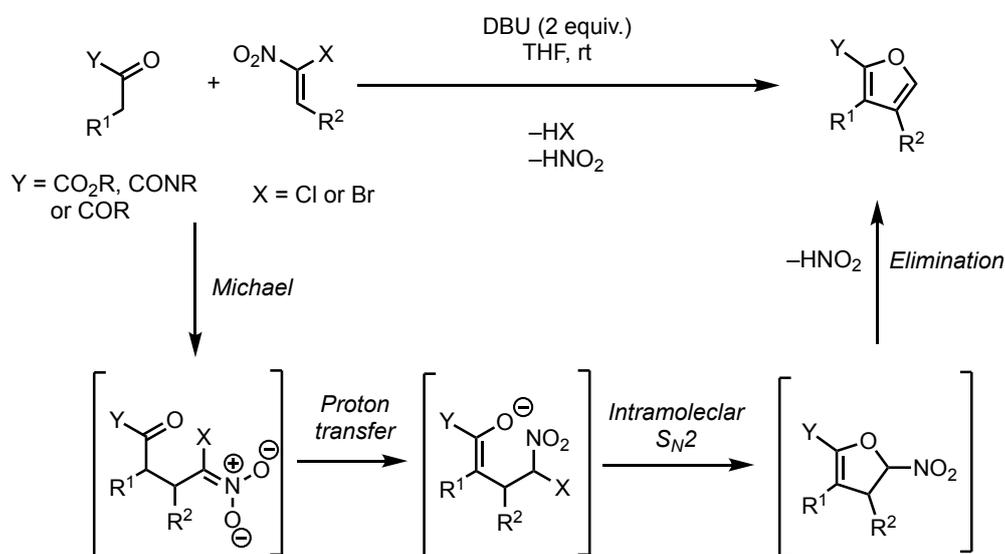


Scheme 50. Oxidation attempts

We next focus our effort on the aromatization by elimination of HNO₂. In 2012, our laboratory published another synthesis of achiral furan starting from 1,2-dicarbonyl compounds and (*Z*)-1-(2-halo-2-nitrovinyl)arene. Upon Michael addition/subsequent intramolecular S_N2 reaction and elimination of HNO₂ the desired furans were obtained

¹⁰¹ V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez *J. Am. Chem. Soc.* **2017**, *139*, 2140.

in generally good isolated yield (Scheme 51).¹⁰² DBU was found to be the best base to promote this reaction.

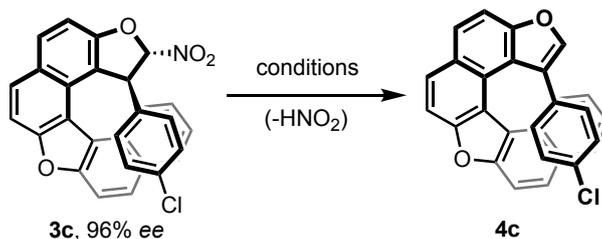


Scheme 51. Formal [3+2] cycloaddition to prepare functionalized furans

We naturally tried to use the same reaction conditions for the elimination of chiral dihydrofuran **3c** (Table 3). The use of DBU as a strong organic base in THF at room temperature (entry 1) led to no reaction and slow decomposition over time. The estimated high barrier to enantiomerization of our oxa[6]helicenes (see Figure 13, half-life of **4b** = 21 days at 100 °C) made us confident about the possibility of using harsher reaction condition without racemization. Increasing the temperature in short reaction time with microwave activation (entry 2, 60 °C, 10 min) led to low conversion. Finally, further increasing the temperature to 100 °C for 20 min led to the formation of the desired product **4c** in good yield (entry 3, 54%) and most importantly, under such relatively harsh conditions, the aromatization proceeded with very high enantiopurity retention, leading to configurationally stable dioxo[6]helicene.

¹⁰² Raimondi, W.; Dauzonne, D.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Eur. J. Org. Chem.* **2012**, 354, 6119.

Table 3. Optimization of the aromatization by elimination



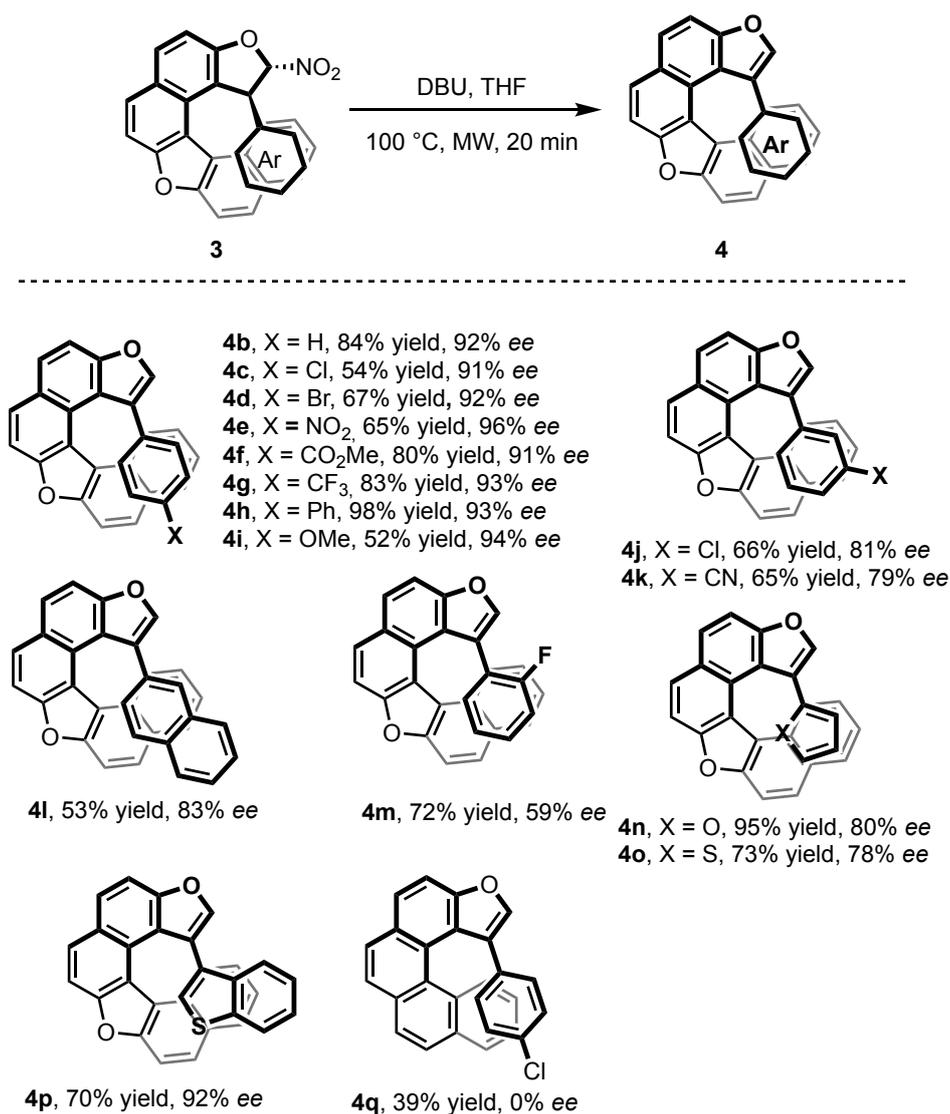
Entry	Conditions	xx
1	DBU ^a , THF, rt, 72 h	complex mixture
2	DBU ^a , THF, 60 °C, MW, 10 min	< 10%
3	DBU ^a , THF, 100 °C, MW, 20 min	54%, 91% ee

^a(5 equiv)

2.8.2) Reaction scope for the elimination reaction

Then, the scope of this eliminative aromatization was investigated and is described in the Scheme 52. The synthesis of dioxo[6]helicenes **4** *via* aromatization of dihydrofuran **3** is applicable to a broad range of substrates. The presence of a *para*-substituted aryl group (**4c-i**) as well as a simple phenyl (**4b**) group is suitable affording good to excellent yields as well as excellent retention of the helical stereogenic information (94-100% retention). The presence of a substituent in the *meta* position or a 2-naphthyl group gave the corresponding products in good yields (**4j-l**) but with slight erosion of the enantiopurity (79-83% *ee*). This tendency was even more noticeable for *ortho*-substituted group, where product **4m** was recovered with 59% *ee* starting from dihydrofuran **4m** with 97% *ee*. Interestingly, smaller heteroaryl groups such as furan and thiophene could be introduced at the peripheral region of the final helicene (**4n** and **4m**, 80% *ee* and 78% *ee*, respectively) with a more efficient helical retention for the bulkier benzothiophene (**4p**, 92% *ee*). Unfortunately, when these reaction conditions were applied to the dihydrofuran **3q**, the desired oxa[5]helicene **4q** was obtained but with complete loss of the enantiopurity (39% yield, 0% *ee*). The lower barrier to

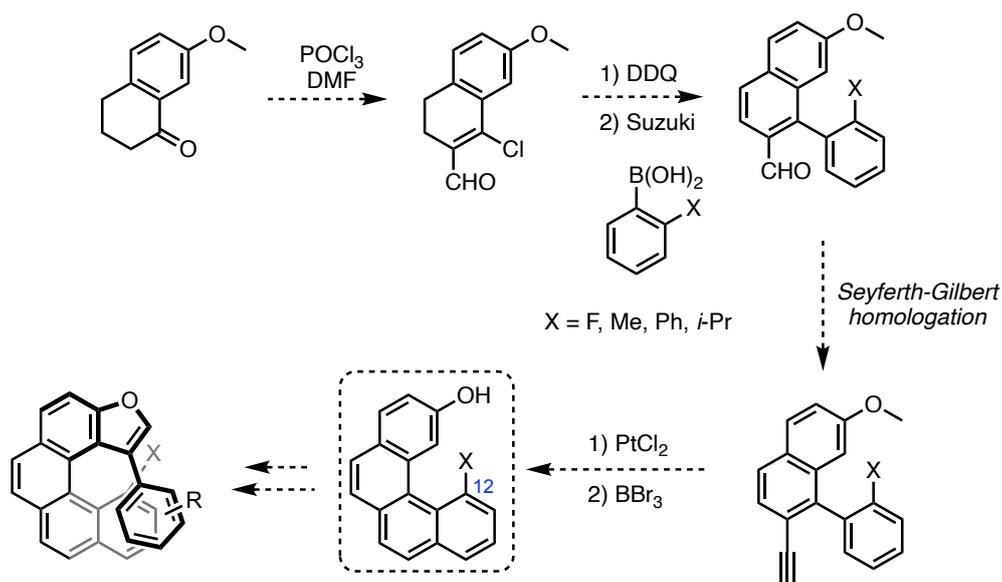
enantiomerization in this particular case (one furan ring less by comparison with the other dioxo[6]helicene) could explain its fast racemization under this harsh reaction conditions. The barrier to enantiomerization for **4q** was calculated to be 111.9 kJ.mol⁻¹, corresponding to a half-life of 7 min at 100 °C,¹⁰³ which could explain its easy racemization during the course of the reaction (MW, 100 °C, 30 min). In this particular case, further optimizations to develop the elimination at room temperature are necessary in order to preserve the enantiopurity of the dihydrofuran **3q**.



Scheme 52. Scope of the synthesis of dioxo[6]helicenes.

¹⁰³ Correlation between energy and selectivity, Pr. J. Lacour website, <https://www.unige.ch/sciences/chiorg/lacour/correl>

The racemization of **4q** prompted us to design future substrates with an additional substituent at position 12 (X = F, Me, Ph or *i*Pr) allowing to reach higher barriers to enantiomerization in the final oxa[5]helicenes (Scheme 53). Hence, based on the synthesis reported by Sasai and co-workers, these substrates could be synthesized in 6 steps from commercially available methoxytetralone.



Scheme 53. Towards oxa[5]helicenes

2.8.3) Absolute configuration

The same complete chiroptical spectroscopy study (VCD, ECD, DFT) with **4d** as model compound allowed the definitive determination of its absolute configuration as (*M*)-**4d** (Figure 17 and Figure 18).

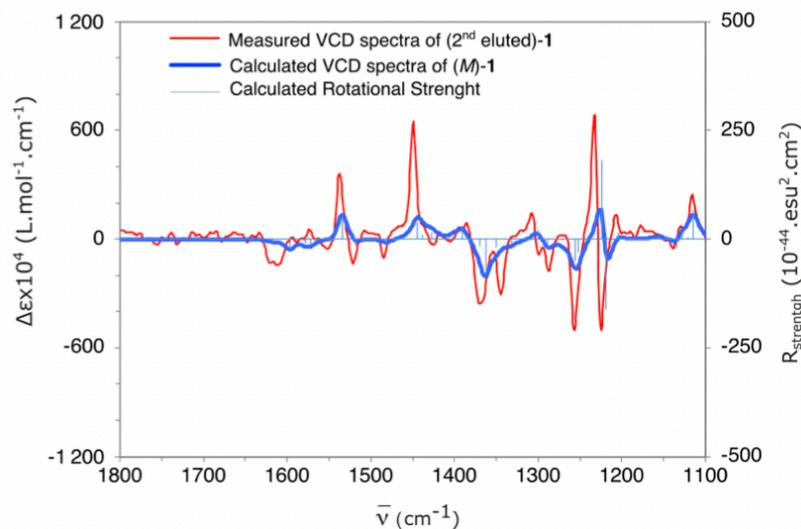


Figure 17. VCD spectroscopy studies comparing the experimental spectra of the second eluted enantiomer with the simulated spectra of the (*M*)-**4d** enantiomer.

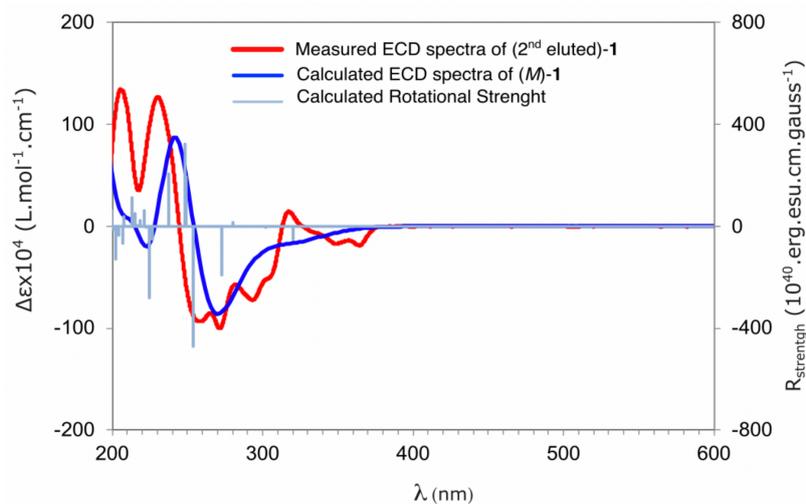


Figure 18. ECD spectroscopy studies comparing the experimental spectra of the second eluted enantiomer with the simulated spectra of the (*M*)-**4d** enantiomer.

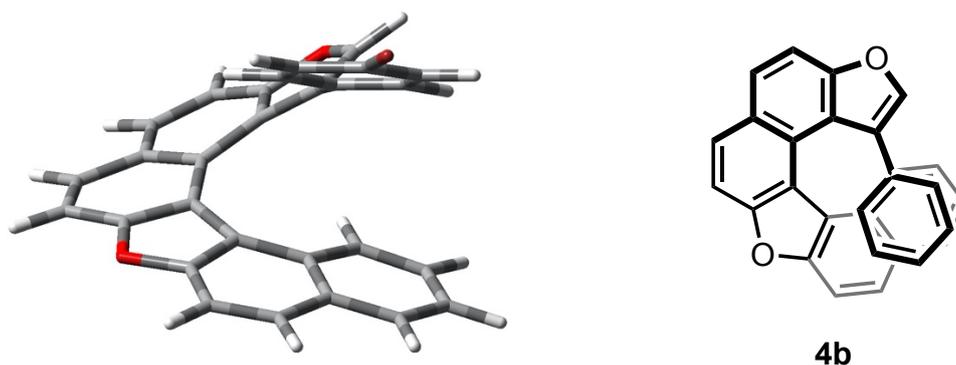
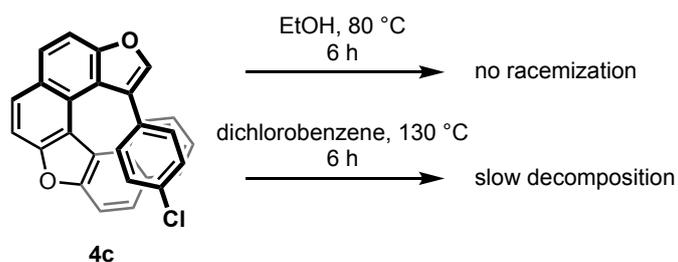


Figure 19. Optimized geometries of the (*M*)-**4b** enantiomer (with SMD(acetonitrile)/B3LYP/6-311+G(d,p))

2.8.4) Barriers to enantiomerization barriers

In order to better understand the effect of substituents on the retention of the helicity, studies on barriers to enantiomerization were performed. No racemization occurred when a sample of **4d** was refluxed in EtOH (80 °C) for several hours (Scheme 54). Increasing the temperature to 130 °C (dichlorobenzene) for several hours resulted in the slow decomposition of the starting material, preventing the experimental determination of its barrier to enantiomerization, that should be above 140 kJ.mol⁻¹.



Scheme 54. Racemization experiments.

In collaboration with Pr. Stéphane Humbel (iSm2, équipe CTOM), theoretical calculations were achieved by density functional theory (DFT), and the barrier to enantiomerization of **4c** was found to 142.2 kJ.mol⁻¹. Removing the 4-chlorophenyl

group had a dramatic effect on this value (**4a**, $\Delta G^{\ddagger}_{\text{rot}} = 71.5 \text{ kJ.mol}^{-1}$), demonstrating the crucial role of the remote steric effect in such furan-containing heterohelicenes. The nature of the substituent on the phenyl group have only moderate effect on the barrier to enantiomerization (for example, X = H, **4b**, $\Delta G^{\ddagger}_{\text{rot}} = 138.8 \text{ kJ.mol}^{-1}$). In addition, switching the phenyl group by a 2-furanyl moiety has no significant effect on the barrier to enantiomerization (**4n**, $\Delta G^{\ddagger}_{\text{rot}} = 136.2 \text{ kJ.mol}^{-1}$), and does not explain the difference in the retention of the helicity (96% and 81% of retention for **4c** and **4n**, respectively). As discussed before for product **4q**, its barrier to enantiomerization was calculated to be $111.9 \text{ kJ.mol}^{-1}$, corresponding to a half-life of 7 min at $100 \text{ }^{\circ}\text{C}$,¹⁰⁴ which could explain its easy racemization during the course of the reaction (MW, $100 \text{ }^{\circ}\text{C}$, 30 min).

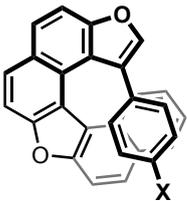
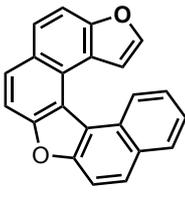
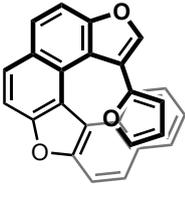
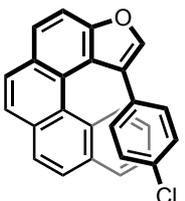
helicene				
Barriers to enantiomerization (kJ.mol ⁻¹)	4b (X = H), 138.8 4c (X = Cl), 142.2 4e (X = NO ₂), 144.5 4i (X = OMe), 142.8	71.5	136.2	111.9

Figure 20. Determination of barriers to enantiomerization by DFT.

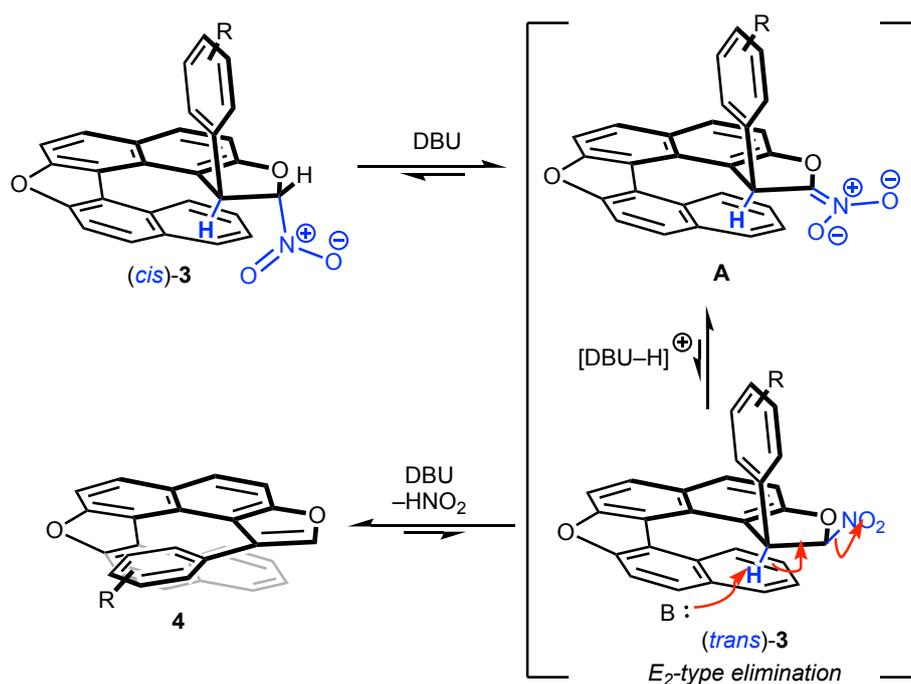
2.8.5) Reaction mechanism

From a mechanistic point of view, the aromatization with conservation of the helical chirality raises some interrogations whether it follows an intramolecular *syn*- or an intermolecular *anti*-elimination (E_i vs E_2). Recently, Zhu and co-workers reported a organocatalyzed kinetic resolution of diastereomerically pure dihydronitropyrroles using a bifunctional thiourea organocatalyst leading to enantioenriched 3-arylpyrrole

¹⁰⁴ Correlation between energy and selectivity, Pr. J. Lacour website, <https://www.unige.ch/sciences/chiorg/lacour/correl>

atropisomers.¹⁰⁵ A *syn*-elimination of HNO₂ was proposed to explain the crucial role of the chiral organocatalyst, which could favorably interact with the substrate *via* hydrogen bonding interactions. In the present case, DBU alone could not participate in such mechanism and its use at room temperature or up to 60 °C revealed inefficient. Moreover, in a control experiment, compound **3c** was heated in toluene (MW, 100 °C, 30 min) without DBU leaving it unchanged, which also excludes a thermal E_i elimination.¹⁰⁶

With these experimental observations, an alternative base-promoted E₂-type mechanism was envisaged. The *cis* relative configuration between the nitro group and its β-hydrogen atom in (*cis*)-**3** (Scheme 5) would then require a prior epimerization to (*trans*)-**3** *via* nitronate intermediate **A**. Compound (*trans*)-**3** would subsequently undergo a rapid aromatization *via* DBU-promoted E₂-elimination of HNO₂.

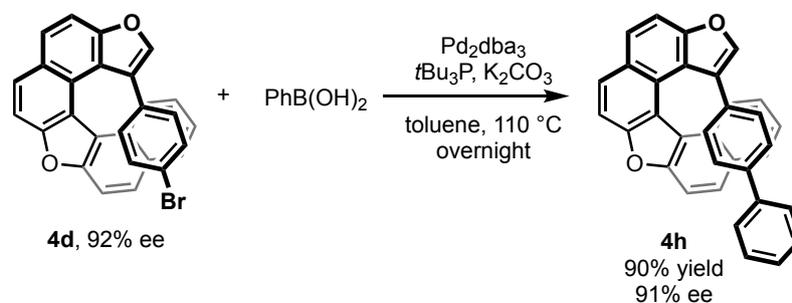


Scheme 34: Mechanism for the DBU-promoted E₂-elimination

¹⁰⁵ S.-C Zheng, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2019**, *58*, 9215.

¹⁰⁶ a) R. Chen, X. Fan, Z. Xu, Z. He, *Tetrahedron Lett.* **2017**, *58*, 3722. b) D. Dauzonne, H. Josien, P. Demerseman, *Tetrahedron*, **1990**, *46*, 7359.

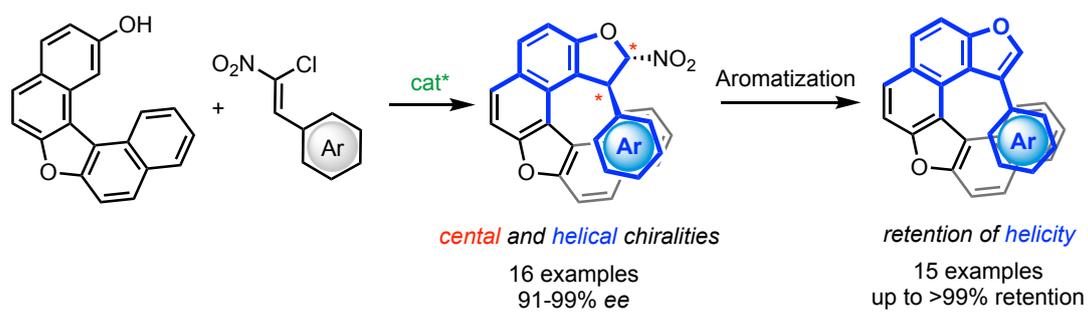
To demonstrate the synthetic usefulness of this methodology, **4d** was converted to **4h** *via* Suzuki cross-coupling reaction. Compound **4h** was isolated in excellent yield and the enantiopurity was retained even after prolonged time at 110 °C, confirming an unusual high barriers to enantiomerization for this class dioxo[6]helicene.



Scheme 55. Synthetic transformation of **4d**.

2.9) Conclusion

In conclusion of this chapter, we have developed an expedient helicoselective synthetic access to a new family of configurationally stable dioxo[6]helicenes from simple achiral precursors (Scheme 56). The helicity is created and controlled during an organocatalyzed domino Michael/*C–O* alkylation step, which delivers mixed-chiral 2-nitrodihydrofurans featuring both two stereogenic carbon atoms and a helical shape as single diastereomers in high enantiopurities. Interestingly, this represents the first case of a catalytic chemical transformation in which both central and helical chiralities are controlled simultaneously, offering unprecedented chiral platform molecules for the synthesis of enantioenriched heterohelicenes by simple base-promoted elimination of HNO_2 with excellent conservation of the helical information in most cases.



Scheme 56. Expedient helicoselective synthesis of dioxo[6]helicenes

Chapter 3: Design, synthesis and evaluation of original P-stereogenic organocatalysts

3.1) Brønsted acid catalysis, with traditional CPA catalysts

Organocatalysis was conceptualized in 2000 and never stopped growing since then.¹⁰⁷ In 2004, the groups of Akiyama¹⁰⁸ and Terada¹⁰⁹ have introduced independently the use of 3,3'-diaryl-BINOL-derived CPAs¹¹⁰ for the enantioselective activation of aromatic imines in the Mannich reaction opening a new era for enantioselective organocatalysis with Brønsted acids (Scheme 57). Since then, a huge amount of efforts has been devoted to the development of elaborated C₂-axially chiral catalysts including sterically crowded atropisomeric BINOL or spirocyclic SPINOL derivatives.¹¹¹ Other C₂-symmetric chiral CPAs based on VAPOL and VANOL have been successfully developed but present similar drawbacks such as high prices and long synthetic sequences for their preparation.¹¹²

¹⁰⁷ *Comprehensive Organocatalysis: Catalysts, Reactions and Applications*, P. I. Dalko, , Wiley-VCH, Weinheim, **2013**.

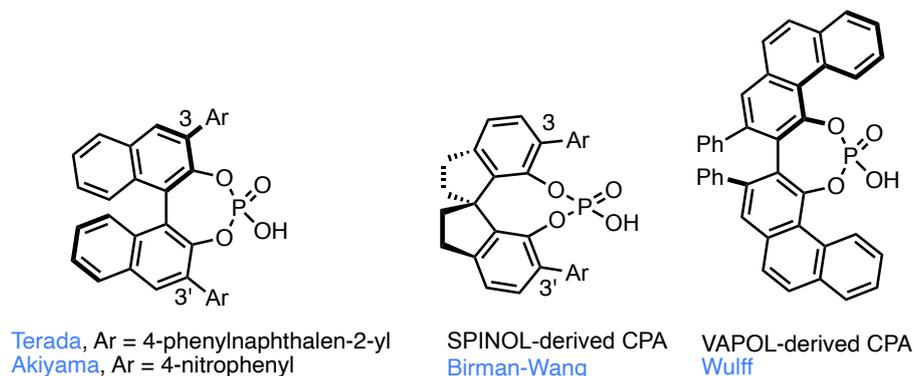
¹⁰⁸ K. Fuchibe, J. Itoh, T. Akiyama, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

¹⁰⁹ D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.

¹¹⁰ D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

¹¹¹ (a) V. B. Birman, A. L. Rheingold, K.-C. Lam, *Tetrahedron: Asymmetry* **1999**, *10*, 125. (b) F. Xu, D. Huang, W. Shen, X. Lin, Y. Wang, *J. Org. Chem.* **2010**, *75*, 8677. (c) C.-H. Xing, Y.-X. Liao, J. Ng, Q.-S. Hu, *J. Org. Chem.* **2011**, *76*, 4125.

¹¹² (a) A. A. Desai, L. Huang, W. D. Wulff, G. B. Rowland, J. C. Antilla, *Synthesis* **2010**, 2106. (b) A. A. Desai, W. D. Wulff, *Synthesis* **2010**, 3670. (c) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696.



Scheme 57. Traditional Brønsted acid organocatalysts.

The concept behind this design, lies upon the modulation of the 3,3'-disubstitution to shape a large enough chiral pocket able to accommodate both the nucleophile and the electrophile *via* a Lewis base/Brønsted acid dual activation or providing a chiral counter-anion cavity efficient to control highly enantioselective reactions by strict ion pairing interactions (Figure 21).¹¹³

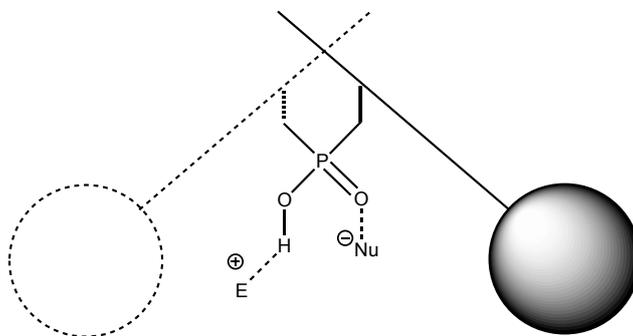


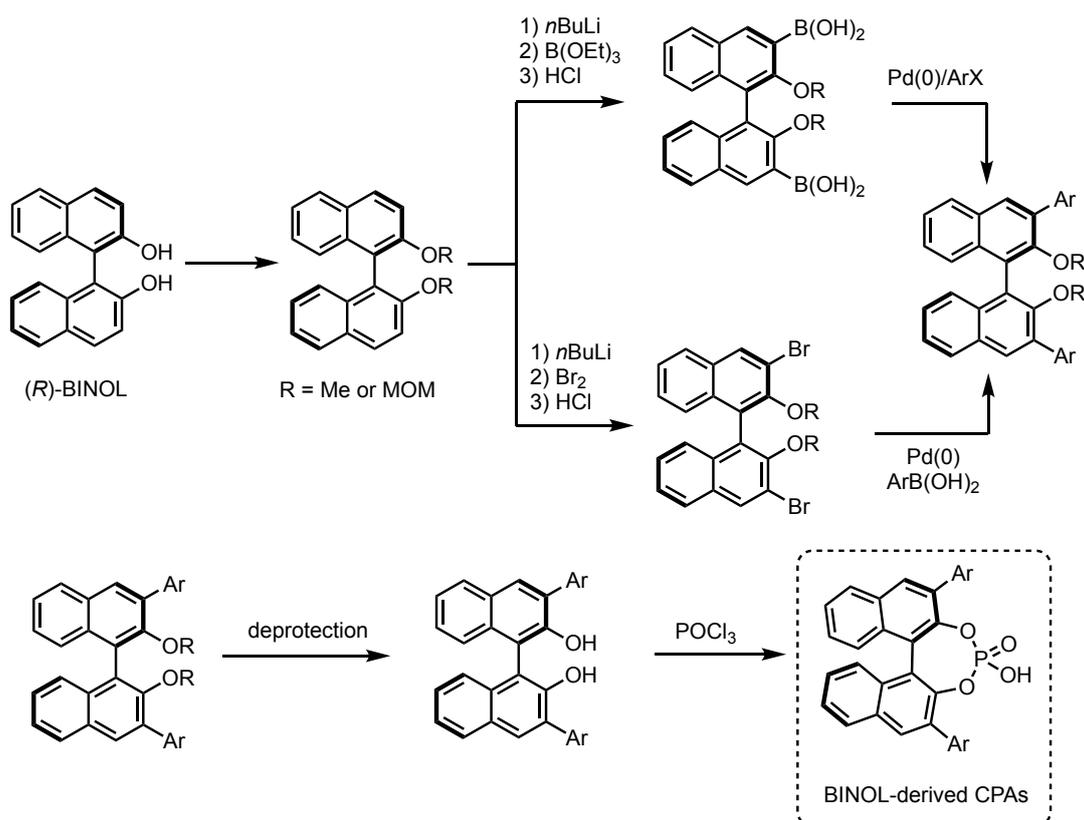
Figure 21. Model for bifunctional CPA-catalyzed reactions.

Although, successful in many inter- or intramolecular transformations involving activation of iminium or oxocarbenium ions, the scale up and the potential industrial development of this family of catalysts is hampered by a low variability and in most

¹¹³ (a) *Asymmetric Ion-Pairing Catalysis*, K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, 52, 534.
(b) *Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications*, M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, 52, 518.

cases a tedious multistep synthetic access (minimum 5 steps from enantiopure C_2 -axially chiral precursors).

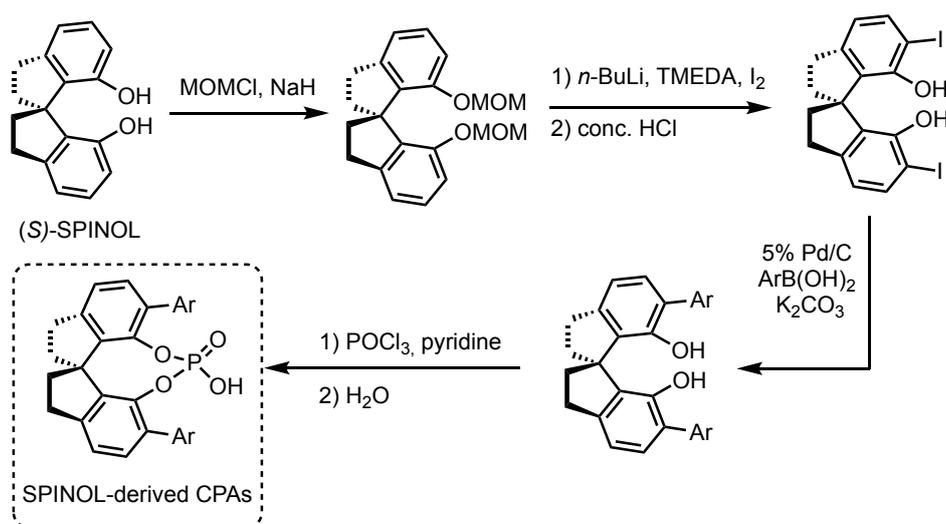
The synthesis of BINOL-derived CPAs was summarized in the Scheme 58. In order to change the substituents at the 3,3'-positions, the common method which was used widely starts with the commercially available BINOL in either (*R*) or (*S*) configuration. Then the protection of the hydroxyl groups gives the protected product, which can be treated by two different synthetic routes. The first route is the installation of boronic esters at the 3,3'-positions by using the lithiation-borylation reactions. The second one is the lithiation-halogenation reactions which can also be carried out to obtain the desired products. Both of these two different intermediates can be used in the next palladium-catalyzed cross-coupling reactions with an appropriate coupling partner to get the product which has aryl groups at the 3,3'-positions. Then, a deprotection step followed by a phosphorylation reaction allow to obtain the final catalyst.¹¹⁴



Scheme 58. Synthesis of BINOL-derived CPAs

¹¹⁴ D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, 114, 9047.

The synthesis of SPINOL-derived CPAs is presented in Scheme 59. At first, (*S*)-SPINOL was protected with the MOM group to afford the protected product. Then, lithiation and subsequent iodination reactions followed by deprotection of hydroxyl groups give the iodo-functionalized SPINOL derivative. Next, Suzuki coupling reaction, realized using 5% Pd/C as the catalyst, allow to functionalized 3 and 3' positions with large aryl groups. Finally, phosphorylation of the coupling product will afford the desired CPAs.¹¹⁵



Scheme 59. Synthesis of SPINOL-derived CPAs

Hence, the development of new strategies to design efficient, easily accessible, sterically and electronically widely flexible chiral Brønsted acids becomes very attractive and highly desirable.

In this chapter, the objectives are the design and synthesis of a complementary class of Brønsted acid organocatalyst in which the chirality comes from the presence of a stereogenic phosphorous atom. In addition, we will see that this design revealed successful in the enantioselective Pictet-Spengler reaction, which opens new synthetic opportunities for both hydrogen-bonding and ion-pairing enantioselective organocatalyses.

¹¹⁵ F. Xu, D. Huang, C. Han, W. Shen, X. Lin, Y. Wang, *J. Org. Chem.* **2010**, *75*, 8677.

3.2) Design of original P-stereogenic Brønsted acid organocatalysts

We propose an original and complementary design for simple and easily accessible Brønsted acids in which the chirality is now centered on the phosphorus atom.^{116,117} This is made possible by using thiophosphinic acids **5** that are configurationally stable unlike their phosphoric ($R^1, R^2 = OR$) or phosphonic ($R^1, R^2 \neq OR$) analogues because of the tautomeric equilibrium existing for these compounds (Scheme 60, eq. 1).¹¹⁸ Thiophosphinic acids can also exist as two thiono/thiolo tautomeric structures but this does not affect their configurational stability. Indeed, studies indicate that the equilibrium is strongly displaced toward the thiono form.¹¹⁹ These species have mainly been used as efficient chiral solvating agents for the determination of the enantiomeric excesses of chiral compounds with a stereogenic carbon atom.¹²⁰ For the use of these molecules as new flexible Brønsted acids, and compared to classical C_2 -symmetric CPAs two important parameters can be easily tuned: the Brønsted acidity and the steric environment by modulation of R^1 and R^2 directly connected to the phosphorus atom (Scheme 60, eq. 2). This fine tuning will allow combining a beneficial electronic effect and a favorable spatial arrangement for an intimate and efficient dual activation

¹¹⁶ a) M. Dutartre, J. Bayardon, S. Jugé, *Chem. Soc. Rev.* **2016**, *45*, 5771. b) O. I. Kolodiazny, *Top. Curr. Chem.* **2015**, *360*, 161. c) S. Takizawa, E. Rémond, F. Arteaga Arteaga, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé, H. Sasai, *Chem. Commun.* **2013**, *49*, 8392. d) O. I. Kolodiazny, *Tetrahedron: Asymmetry* **2012**, *23*, 1.

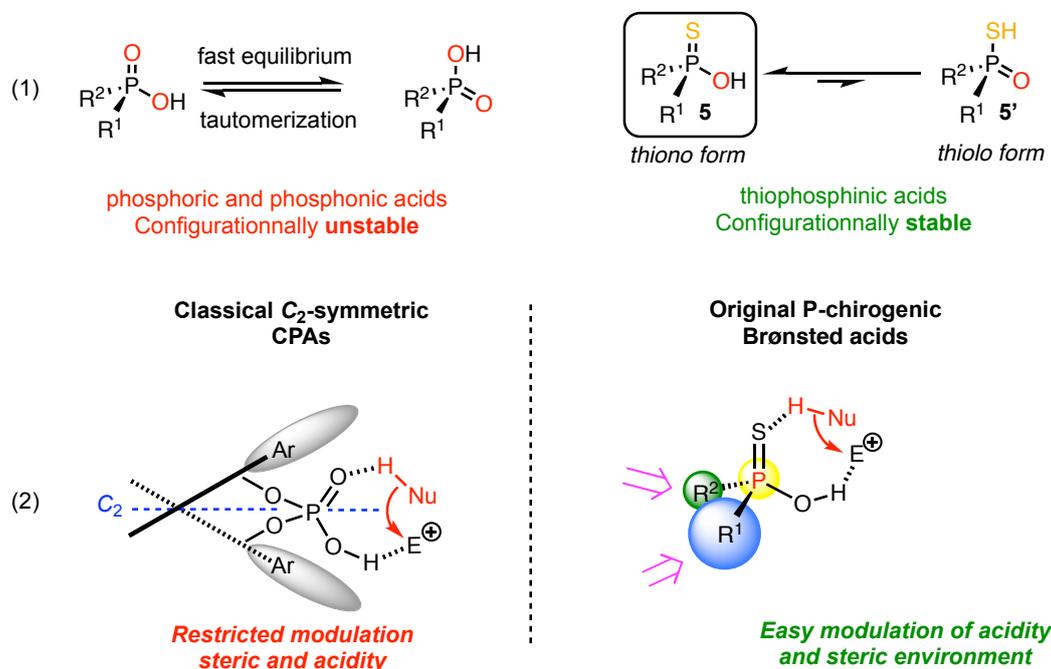
¹¹⁷ For examples of non *P*-chirogenic organocatalysts, see: a) A. Voituriez, A. Marinetti, M. Gicquel, *Synlett* **2015**, *26*, 142. b) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174. c) J. Stemper, K. Isaac, J. Pastor, G. Frison, P. Retailleau, A. Voituriez, J.-F. Betzer, A. Marinetti, *Adv. Synth. Catal.* **2013**, *355*, 3613. d) M. Gicquel, Y. Zhang, P. Aillard, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem. Int. Ed.* **2015**, *54*, 5470.

¹¹⁸ S. Vassiliou, *Curr. Org. Chem.* **2011**, *15*, 2469.

¹¹⁹ K. Swierczek, A. S. Pandey, J. W. Peters, A. C. Hengge, *J. Med. Chem.* **2003**, *46*, 3703.

¹²⁰ a) J. Drabowicz, P. Pokora-Sobczak, D. Krasowska, Z. Czarnocki, *Phosphorus, Sulfur, and Silicon* **2014**, *189*, 977. b) M. Moriyama, *J. Synth. Org. Chem. Jap.* **1984**, *42*, 355.

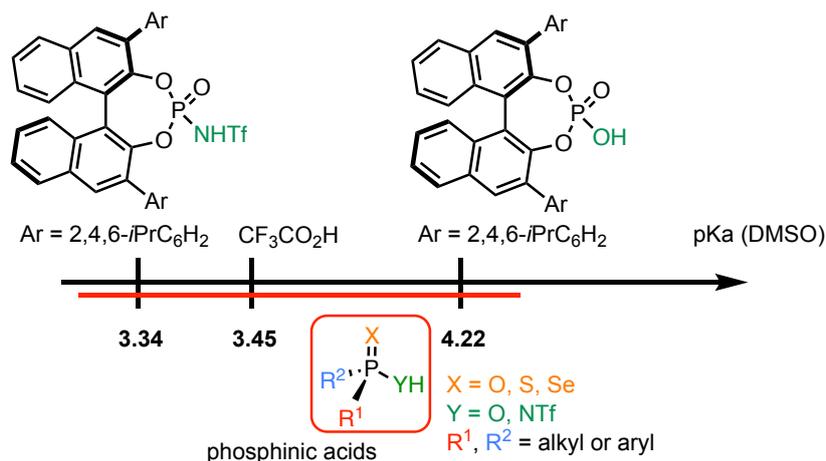
triggering versatile enantioselective transformations *via* hydrogen-bonding or ion-pairing organocatalysis.



Scheme 60. Design of original P-stereogenic Brønsted acids

The important features of this design are the easy modulation of pK_a of the organocatalyst, and this will have important consequences on the rate constant of the reactions. In general, the more acidic catalysts result in higher rate constants.¹²¹ In term of acidity scale, the easy modulation of all groups around the phosphorous atom should allow us to finely tune the acidity covering pK_a values between 3 and 5, a common range found for classical CPAs (Scheme 61). However, the enantioselectivity will mostly depend of the catalyst shape and architecture, by varying the nature of R¹ and R² groups.

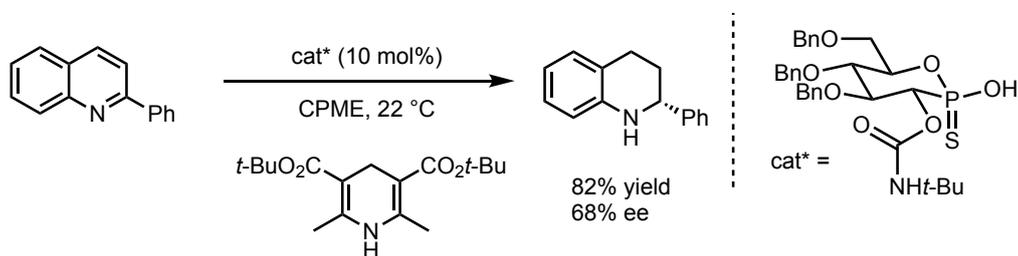
¹²¹ K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito, *Angew. Chem. Int. Ed.* **2013**, 52, 11569.



Scheme 61. Acidity scale of the phosphinic acids.

3.3) State of the art

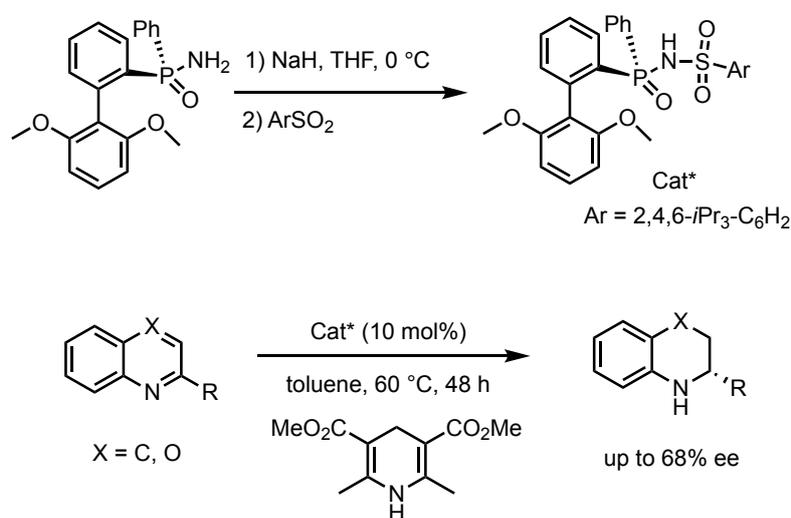
The first example of a *P*-chiral Brønsted acid has been reported by Guinchard and Voituriez in 2014 (Scheme 62).¹²² This thiophosphonic Brønsted acid was used in the enantioselective organocatalyzed transfer hydrogenation of quinolines and the desired products were obtained with a maximum of 68% ee. The main drawback in this design is the very low variability of the catalyst based on a sugar-like backbone, which importantly limits its applications. Nevertheless, this recent result demonstrates that *P*-stereogenicity can be a new answer in enantioselective Brønsted acid organocatalysis but necessitates a completely new design of the catalyst scaffold.



Scheme 62. *P*-stereogenic thiophosphonic acid catalyst of Guinchard and Voituriez.

¹²² A. Ferry, J. Stemper, A. Marinetti, A. Voituriez, X. Guinchard, *Eur. J. Org. Chem.* **2014**, 188.

Last year, in 2019, the group of Senanayake described the new class of *P*-stereogenic Brønsted acid organocatalysts (Scheme 63).¹²³ These catalysts were made from the *P*-stereogenic phosphinamides and were successfully applied to promote the reduction of quinoline derivatives via transfer hydrogenation. The moderate stereoselectivity is induced by the *P*-chiral environment, which can be tuned by the substituents linked to the phosphorous atom.



Scheme 63. *P*-stereogenic phosphinamide of Senanayake

3.4) Synthesis of original *P*-Stereogenic organocatalysts

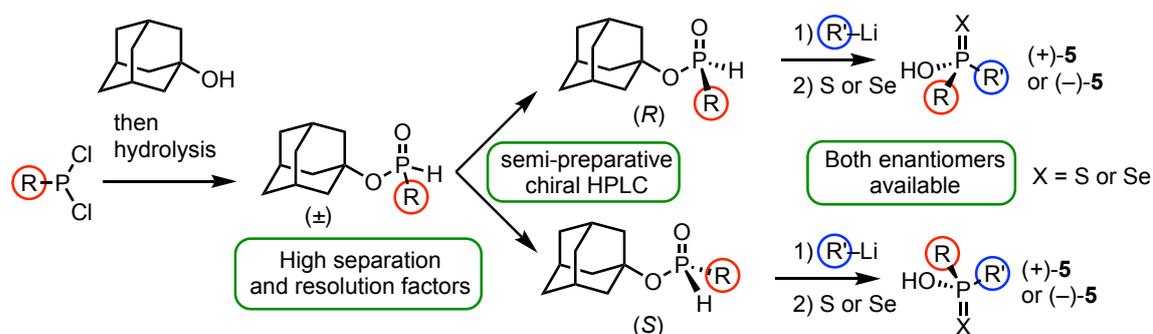
P-chirogenic mono-phosphines are particularly useful compounds in enantioselective catalysis,¹²⁴ however, their use have been severely restricted due to the lack of simple

¹²³ Z. S. Han, H. Wu, B. Qu, Y. Wang, L. Wu, L. Zhang, Y. Xu, L. Wu, Y. Zhang, H. Lee, F. Roschangar, J. J. Song, C. H. Senanayake, *Tetrahedron Lett.* **2019**, 60, 1834.

¹²⁴ A. Grabulosa, *Catalysis Series*; The Royal Society of Chemistry, **2011**.

methods to access them in enantiopure form.^{116, 125} Recently, a new versatile methodology based on resolution of H-adamantylphosphinates has been developed in our institute for the facile preparation of each enantiomer of *P*-stereogenic compounds (Scheme 64).¹²⁶ The synthetic route involves the reaction of 1-adamantol with various aryl-dichlorophosphines.

H-Adamantylphosphinates possess remarkable and unusual ease to separate on semi-preparative chiral HPLC. For example, semi-preparative equipment (1 cm diameter column, available in the institute allowed the separation of 25 g of the racemic mixture of compound with R = Ph in 56 h, into 12 g of each enantiomer with excellent enantiopurity (ee > 99%). In a subsequent step, the secondary phosphine oxide (SPO) is then formed from enantiopure H-adamantylphosphinates through the stereospecific substitution of adamantyl group by an alkyl- or an aryl-lithium (R'-Li). The final thiophosphinic acids **5** are obtained by simple reaction with sulfur proceeding with total retention of configuration.¹²⁷ The corresponding selenophosphinic acids can be obtained the same way using selenium powder instead of sulfur.¹²⁸ The ease of access of large quantities of the two optically pure enantiomers of a potential catalyst is a key point of this project.



¹²⁵ a) T. Chen, L.-B. Han, *Synlett* **2015**, 26, 1153. b) D. Héroult, D. H. Nguyen, D. Nuel, G. Buono *Chem. Soc. Rev.* **2015**, 44, 2508. c) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, 251, 25. d) S. Lemouzy, L. Giordano, D. Héroult, G. Buono, *Eur. J. Org. Chem.* **2020**, 3351.

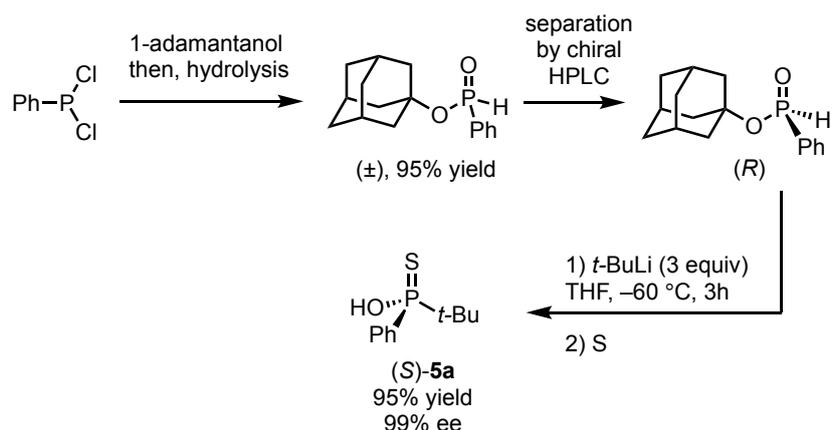
¹²⁶ D. Gatineau, D. H. Nguyen, D. Héroult, N. Vanthuyne, J. Leclaire, *J. Org. Chem.* **2015**, 80, 4132.

¹²⁷ (a) Q. Xu, C.-Q. Zhao, L.-B. Han, *J. Am. Chem. Soc.* **2008**, 130, 12648. (b) J. Michalski, Z. Skrzypczynski, *J. Organomet. Chem.* **1975**, 97, 31.

¹²⁸ C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, 130, 9246.

Scheme 64. Synthesis of enantioenriched thiophosphinic acids from adamantanol.

Chiral thiophosphinic acid **5a** was synthesized using the above strategy (Scheme 65). Firstly, reaction between 1-adamantanol and dichlorophenylphosphine, followed by hydrolysis furnished the racemic H-adamantylphosphinate. The latter was separated using semipreparative chiral HPLC on Lux-Cellulose-2 (250 × 10 mm) in methanol at 5 mL/min and 30 °C with UV detection 235 nm, 0.1 mL of a 175 mg/mL racemic solution injected every 2.4 min. After 700 injections, 6.0 g of adamantan-1-yl (*S*)-phenylphosphinate (ee > 99%) and 6.2 g of adamantan-1-yl (*R*)-phenylphosphinate (ee = 99%) were obtained. The (*R*) enantiomer was reacted with *t*-BuLi, and the obtained *t*-butylphenylphosphinate was oxidized with sulfur to afford the desired chiral thiophosphinic acid **5a** in excellent yield and no erosion of the enantiomeric excess (99% ee).

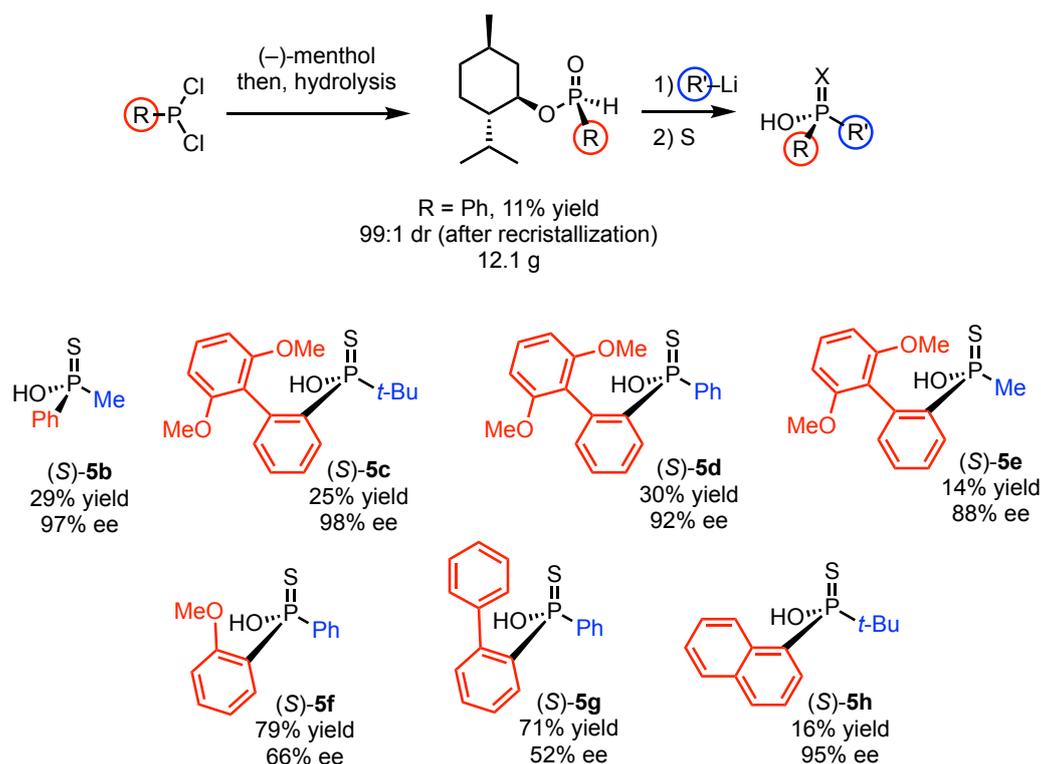


Scheme 65. Synthesis of chiral thiophosphinic acid **5a**

An alternative diastereoselective route was used also using (–)-menthol as the chiral auxiliary (Scheme 66).¹²⁹ Hence, most *O*-menthylphosphinates could be obtained as single diastereomers after multiple recrystallizations. As before, nucleophilic substitution with inversion of configuration was accomplished using the corresponding lithium reagent. Then, oxidation with sulfur, with retention of the configuration,

¹²⁹ This work was done in collaboration with Xiaoze BAO, a postdoc of our group (03/2018-07/2019)

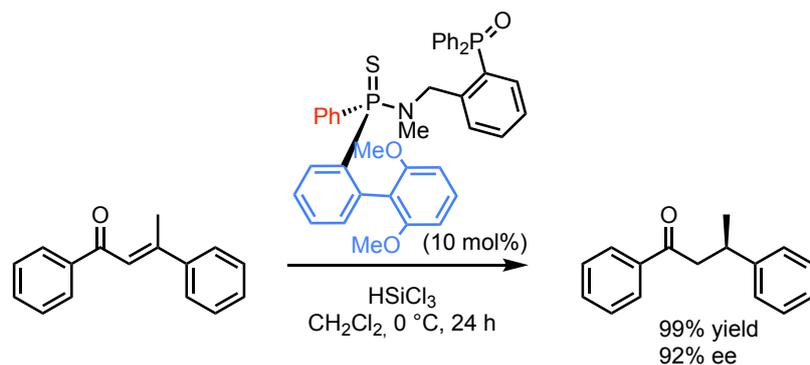
allowed the formation of the desired Brønsted acid organocatalyst. The yields given are for the two last steps (nucleophilic substitution and oxidation with sulfur). Thiophosphinic acids **5f** and **5g** were obtained with moderate enantiomeric excess (66% and 52% ee, respectively) because of unsuccessful recrystallization of the corresponding *O*-menthylphosphinates in the first step. For these catalysts, the synthetic path from *O*-adamantylphosphinates should be preferred but has not been tried yet.



Scheme 66. Synthesis of enantioenriched thiophosphinic acids from (–)-menthol.

The idea of introducing a sterically demanding *o,o'*-disubstituted biphenyl moiety comes from a work from Han and co-workers, which has recently demonstrated its efficiency in P-chirogenic Lewis base catalysts for the enantioselective reduction of chalcone derivatives (Scheme 67).¹³⁰ We thought that this group could play also an important role in the stereo-discriminating step.

¹³⁰ Z. S. Han, L. Zhang, Y. Xu, J. D. Sieber, M. A. Marsini, Z. Li, J. T. Reeves, K. R. Fandrick, N. D. Patel, J.-N. Desrosiers, B. Qu, A. Chen, D. M. Rudzinski, L. P. Samankumara, S. Ma, N. Grinberg, F. Roschangar, N. K. Yee, G. Wang, J. J. Song, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2015**, *54*, 5474.

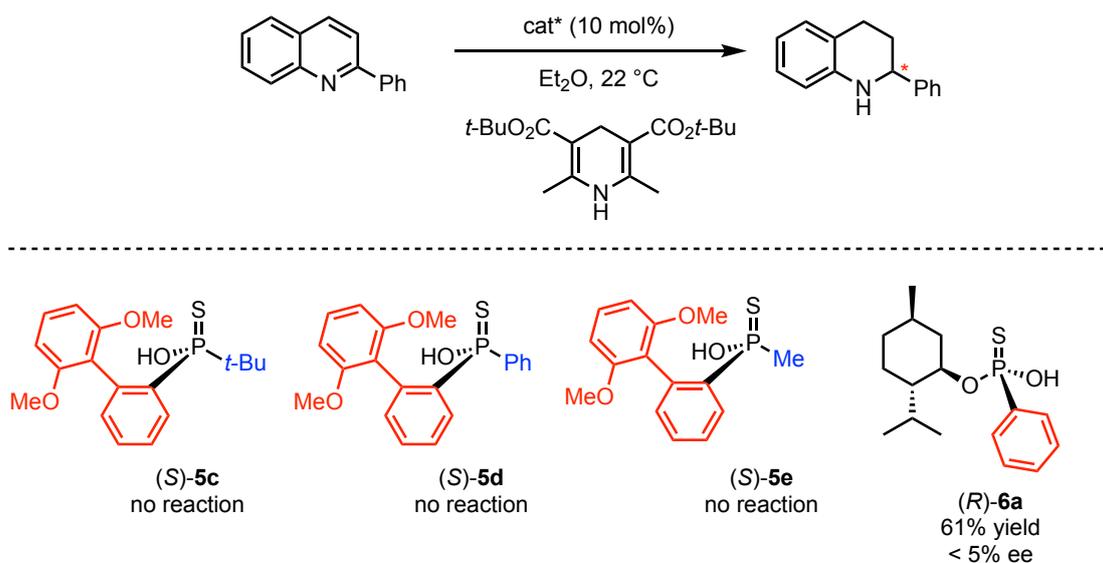


Scheme 67. Enantioselective reduction catalyzed by *P*-stereogenic phosphinamide.

3.5) Application of new P-Stereogenic organocatalysts

3.5.1) Application in enantioselective organocatalyzed transfer hydrogenation of quinolines

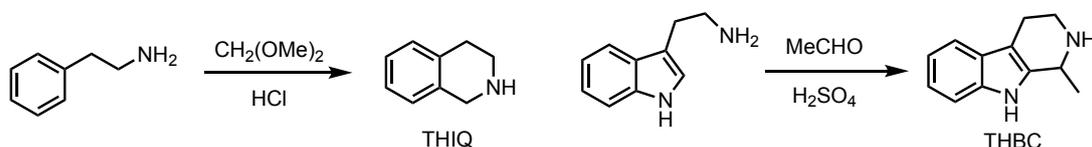
We first evaluated the catalytic activity of the thiophosphinic acids **5** in the transfer hydrogenation of 2-phenylquinolone (Scheme 68). Unfortunately, very disappointing results were obtained: the use of chiral thiophosphinic acids **5c**, **5d** or **5e** led to no reaction. The use of more acidic thiophosphonic acid **6a** allowed the formation of the desired product but with no enantioselectivity.



Scheme 68. Chiral thiophosphinic and thiophosphonic acids catalyzed enantioselective transfer hydrogenation

3.5.2 Application in enantioselective Pictet-Spengler Reaction

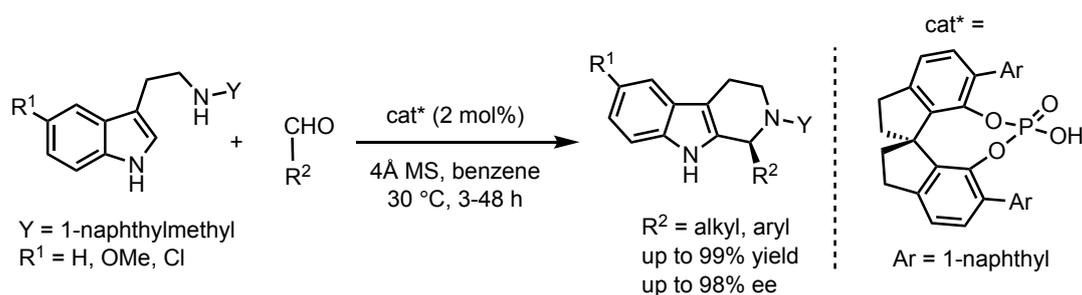
The Pictet-Spengler reaction was discovered at the University of Geneva in 1911 by the chemists Pictet and Spengler. The alkaloid tetrahydroisoquinoline (THIQ) and tetrahydro- β -carboline (THBC) alkaloid skeletons were obtained by reacting the corresponding primary amine with an aldehyde or an acetal under acidic condition (Scheme 69). This is a new and simple way to achieve the chemical synthesis of alkaloids. The reaction was named the Pictet-Spengler reaction later and now it is a very well-known reaction.¹³¹



Scheme 69. The first Pictet-Spengler reactions

¹³¹ J. Stockigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, 50, 8538.

The catalytic activity of the chiral phosphinic acids were first evaluated in a known version of the enantioselective Pictet-Spengler reaction. This reaction has been described by Lin and Wang in 2012. Chiral SPINOL-phosphoric acids were used as highly enantioselective catalysts for the enantioselective Pictet-Spengler reaction of *N*-naphthylmethyl tryptamines with a series of aliphatic and aromatic aldehydes, affording optically active tetrahydro- β -carbolines in excellent yields and ee values (Scheme 70).¹³²

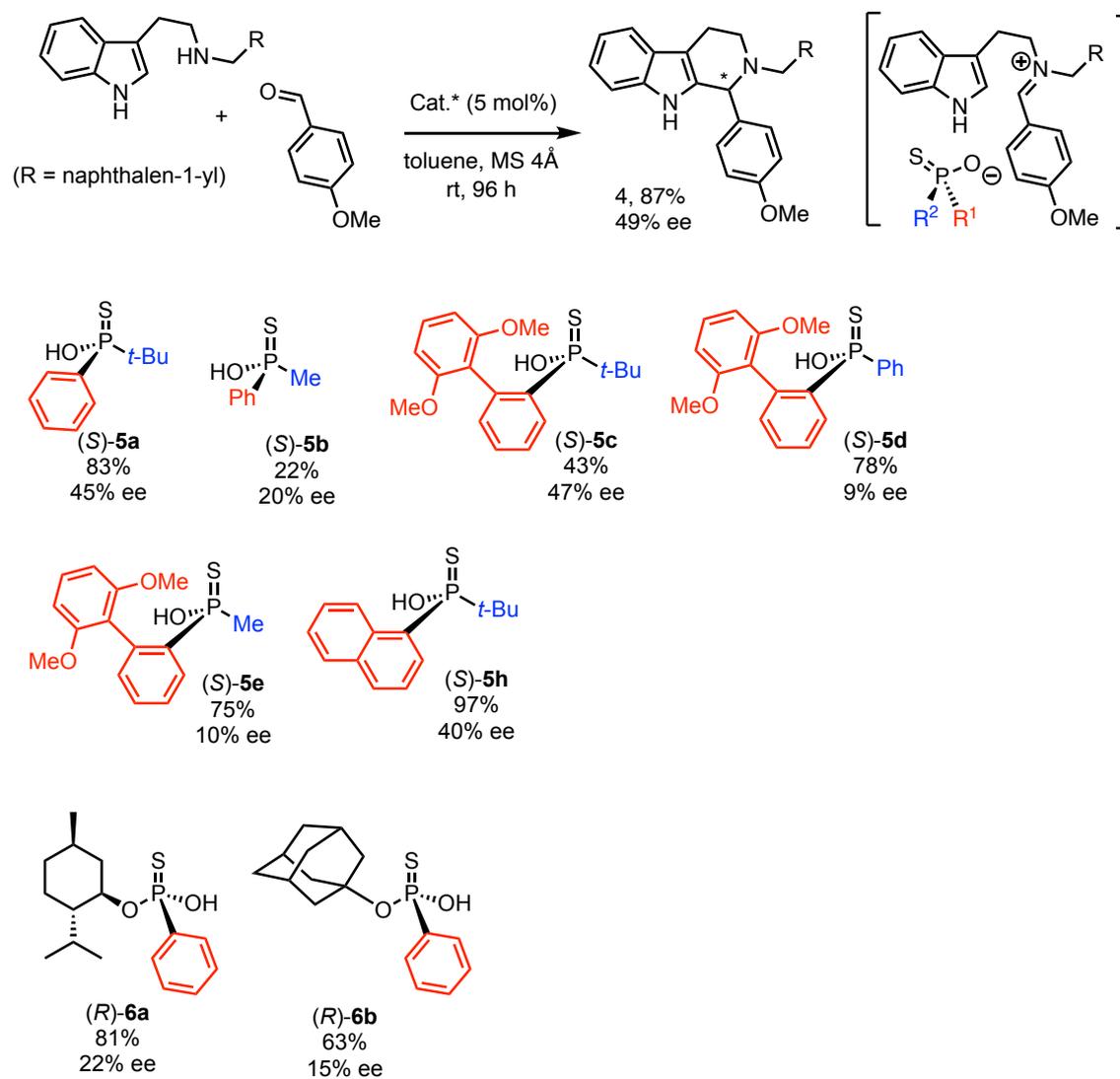


Scheme 70. Enantioselective Pictet-Spengler reaction

The synthesized catalysts with high enantiomeric excess were evaluated in this model reaction in order to validate our concept. We verified that the uncatalyzed reaction was not operating as no product was isolated without any catalyst. From these initial attempts, the *tert*-butyl group seems to play a crucial role in the stereo differentiation of the iminium ion face. Indeed catalysts **5a**, **5c** and **5h** bearing a *tert*-butyl group gave the best enantiomeric excesses, from 40 to 45% ee. Replacing this group by a phenyl or a methyl group had a detrimental effect on the enantioselection that dropped between 10 and 20% ee catalysts **5b**, **5d** and **5e**. *O*-menthylphosphinates and *O*-adamantylphosphinates were converted to the corresponding thiophosphonic acid organocatalysts **6a** and **6b** by oxidation with sulfur and these catalysts were evaluated. Unfortunately in these two cases, the enantioselectivity was kept down to 22 and 15% ee, respectively. This might be due to the increase distance of the steric hindrance from the reactive center. Even if these results could be improved, they validate our concept

¹³² D. Huang, F. Xu, X. Lin, Y. Wang, *Chem. Eur. J.* **2012**, *18*, 3148

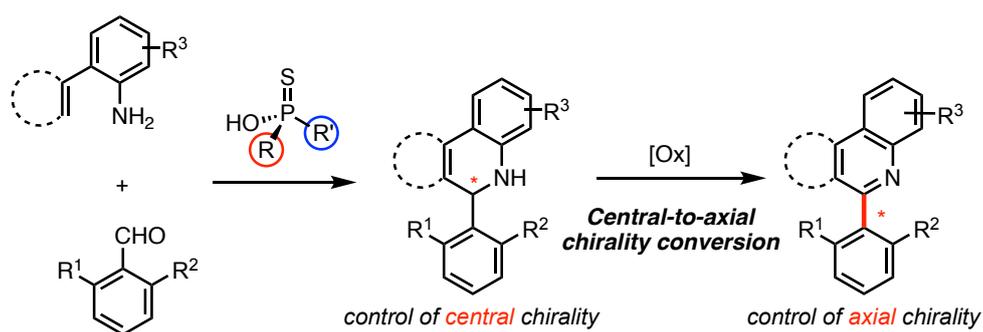
of designing original P-stereogenic Brønsted organocatalysts. We next planned to use them in new Pictet-Spengler-like reactions.



Scheme 15. Chiral thiophosphinic and thiophosphonic acids catalyzed enantioselective Pictet-Spengler reaction

3.5.3 Application in atroposelective annulation reaction

A key synthetic challenge for organocatalysis is the control of axial chirality, which constitutes an important emerging research area.¹³³ In this context, we wanted to exploit our new designed catalysts for the enantioselective synthesis of synthetically useful and biologically relevant axially chiral *N*-heterocycles such as quinolines (Scheme 71).



Scheme 71. Enantioselective synthesis of quinoline atropisomers

Indeed, non-racemic axially chiral molecules are of prime interest first for their challenging synthesis but also for their presence in numerous natural products¹³⁴ and bioactive scaffolds¹³⁵ and finally because of their ligand ability with various metal¹³⁶ or their direct organocatalytic activities.¹¹⁰ If many approaches exist for the synthesis

¹³³a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418. b) G. Bencivenni, *Synlett* **2015**, *26*, 1915. b) Y.-B. Wang, B. Tan, *Acc. Chem. Res.* **2018**, *51*, 534. c) T.-Z. Li, S.-J. Liu, W. Tan, F. Shi, *Chem. Eur. J.* **2020**, DOI : 10.1002/chem.202001397.

¹³⁴ G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563.

¹³⁵ J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398.

¹³⁶ E. Fernández, P. J. Guiry, K. P. T. Connole, J. M. Brown, *J. Org. Chem.* **2014**, *79*, 5391.

of biaryl atropisomers,¹³⁷ the enantioselective construction of atropisomeric heteroaryl structures is much more challenging.¹³⁸

Our strategy involves the utilization of a Brønsted acid organocatalyst to promote an enantioselective intramolecular annulation to the corresponding fused-dihydropyridine intermediates and to rely on the concept of central-to-axial chirality conversion¹³⁹ triggered by the oxidative aromatization recently developed in our group.¹⁴⁰

We selected 2-aminophenylindole and 2-methoxy-1-naphthaldehyde as starting materials and the reaction were run in the presence of 10 mol% of catalyst for 72 h at room temperature (Table 4). The intermediate **7** was not isolated, and an oxidant was added directly into the reaction mixture. The final axially chiral quinoline **8** could then be isolated and the results are displayed in the next table. The barrier to enantiomerization has been experimentally evaluated to 137 kJ/mol, which avoids any racemization at room temperature. Surprisingly, thiophosphinic acid **5a** gave no reaction, possibly due to too weak acidity of this catalyst or to the non-reactivity of the selected substrates. Therefore, to check the feasibility of the transformation, we then switched to the more classical BINOL-derived CPAs, which gave better results. Catalyst **CPA-1** allowed the formation of the desired product, although very por

¹³⁷ Special issue, Colobert, F. (Ed.), *Methods for Controlling Axial Chirality, Tetrahedron* **2016**, *72*, 5157.

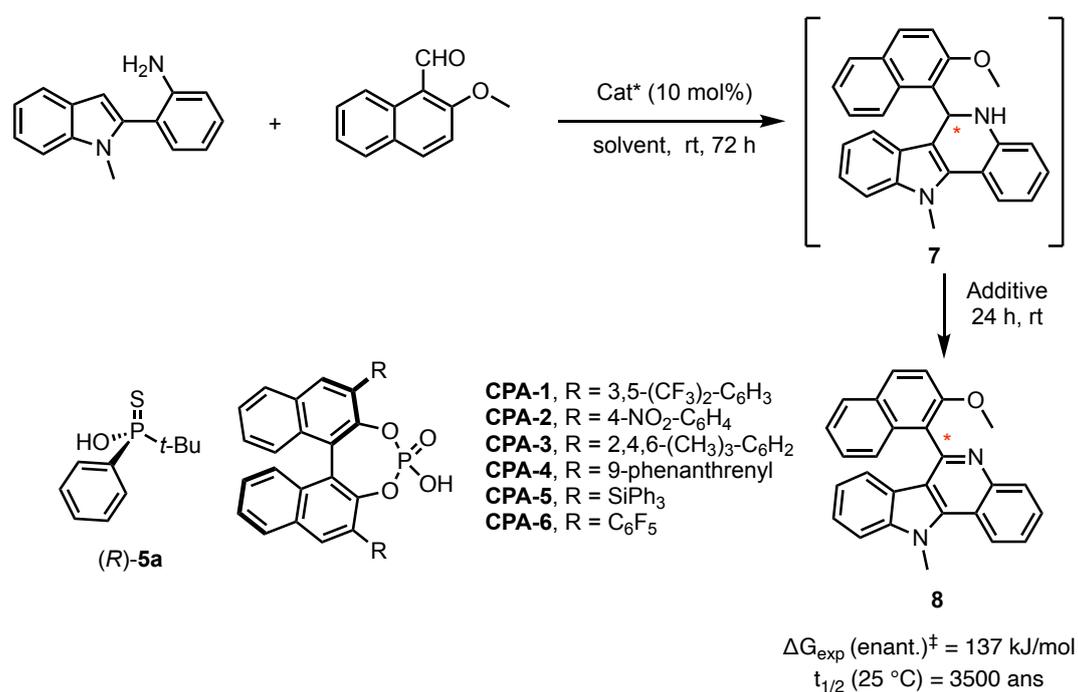
¹³⁸ a) E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru, *Chem. Rev.* **2015**, *115*, 11239. b) D. Bonne, J. Rodriguez, *Chem. Commun.* **2017**, *53*, 12385-12393. c) D. Bonne, J. Rodriguez, *Eur. J. Org. Chem.* **2018**, 2417.

¹³⁹ In its strict definition, conversion of chirality is a chemical process consisting in the destruction of a stereogenic element on a molecule with the simultaneous installation of another stereogenic element of a different nature. For further details, see: Wolf, C. in *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, RSC, Cambridge, **2007**, pp. 233. For seminal studies, see: (a) J. A. Berson, E. J. Brown, *J. Am. Chem. Soc.* **1955**, *77*, 450. (b) A. I. Meyers, D. G. Wettlaufer, *J. Am. Chem. Soc.* **1984**, *106*, 1135.

¹⁴⁰ a) O. Quinonero, M. Jean, N. Vanthuyne, C. Roussel, D. Bonne, T. Constantieux, C. Bressy, X. Bugaut, J. Rodriguez, *Angew. Chem. Int. Ed.* **2016**, *55*, 1401. b) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez, *J. Am. Chem. Soc.* **2017**, *139*, 2140. c) X. Bao, J. Rodriguez, D. Bonne, *Chem. Sci.* **2020**, *11*, 403.

enantiomeric excess was obtained after the oxidation (entries 3-5). DDQ and MnO₂ gave similar results and were superior oxidizing agent than hypervalent iodine reagent for this transformation. Other catalysts were evaluated (entries 6-10) and we found that catalyst **CPA-6** with C₆F₅ aryl groups gave a good yield with promising enantioselectivity (40 % ee, entry 10). Finally, other solvent were tried (entries 11-15) but none of them were superior to toluene which is the best one.

Table 4. Enantioselective synthesis of quinoline atropisomers



entry	catalyst	solvent	additive	yield (%)	ee (%)
1	(<i>R</i>)- 5a	toluene	MnO ₂	no reaction	-
2	CPA-1	toluene	MnO ₂	93	9
3	CPA-1	toluene	DDQ	90	9
4	CPA-1	toluene	PhI(OAc) ₂ , Cs ₂ CO ₃	76	0
5	CPA-2	toluene	DDQ	82	10
6	CPA-3	toluene	DDQ	77	0
7 ^a	CPA-4	toluene	DDQ	86	12
8 ^b	CPA-5	toluene	DDQ	82	37
9	CPA-6	toluene	DDQ	72	40
10	CPA-6	THF	DDQ	65	0
11	CPA-6	CHCl ₃	DDQ	27	15
12	CPA-6	MeOH	DDQ	73	0
13	CPA-6	CH ₃ CN	DDQ	57	0
14	CPA-6	cyclohexane	DDQ	47	10

The reaction was conducted with indole derivative (0.05 mmol, 1 equiv), aldehyde (1.5 equiv) and catalyst (10 mol%) in solvent (0.5 mL).

Of course, this study is not over and I could not finalize it. Efforts are still needed to reach higher enantiomeric excesses. We are currently synthesizing more acidic P-stereogenic catalysts that could possibly perform well in this reaction. The scope of this reaction could then be evaluated. For this moment, as we were not able to isolate cleanly the dihydroquinoline intermediate, there is no clear explanation of the moderate ee

obtained: is the first step moderately enantioselective or is the conversion of chirality not efficient?

In addition, given the high barrier to enantiomerization, mono-*ortho*-substituted aldehydes should be possible substrates in this transformation, which would easily broaden the substrate scope (Figure 22).

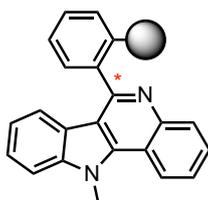


Figure 22. mono-*ortho*-aryl-substituted axially chiral quinoline

3.6) Summary and perspective

Brønsted acid enantioselective organocatalysis is generally realized using C_2 -symmetrical BINOL- or SPINOL-derived phosphoric acid. In this chapter, we have shown that an alternative is possible: P-stereogenic Brønsted acid are catalyzing the Pictet-Splengler reaction with moderate enantioselectivity. This is a first step and further optimization is necessary to reach higher enantiomeric excess and to make these catalysts more general. Increasing their acidity is a first possibility (Se, NHTf, etc.). Another one would be the installation of an additional function (Lewis basic site) that could bind with a nucleophile would lead to a more rigid transition with increased stereo-differentiation (Figure 23).

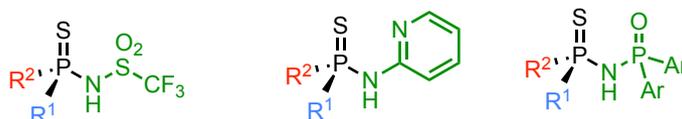


Figure 23. Other chiral thiophosphinic acids

General conclusion

(In English)

To conclude the thesis, at first, the expedient helicoselective synthetic access to a new series of configurationally stable dioxo[6]helicenes from simple achiral precursors was developed. The helicity is created and controlled during an organocatalyzed domino Michael/C–O alkylation step, which delivers mixed-chiral 2-nitrodihydrofurans featuring both two stereogenic carbon atoms and a helical shape as single diastereomers with high enantiomeric excesses. Interestingly, this represents the first case of a catalytic chemical transformation in which both central and helical chiralities are controlled simultaneously, offering unprecedented chiral platform molecules for the synthesis of enantioenriched heterohelicenes by simple base-promoted elimination of HNO₂ with excellent conservation of the helical information in most cases. Secondly, the idea was originated from the thiophosphinic acid, we designed a new structure of *P*-stereogenic chiral Brønsted acid, the chirality is now centered on the phosphorus atom, this opens new synthetic opportunities for both hydrogen-bonding and ion-pairing enantioselective organocatalysis. Up to now, we have successfully synthesized several different new catalysts and applied them in enantioselective organocatalytic reactions. Such as the use of *P*-chirogenic organocatalysts in Pictet-Spengler reaction, promising enantiomeric excess and good yield were obtained, the use of these catalysts in other reactions is still under further research.

(In French)

Cette thèse est composée de deux parties principales. Premièrement, l'accès synthétique hélicosélectif à une nouvelle série de dioxo[6]hélécènes dioxo configurationnellement stables à partir de précurseurs achiraux simples a été développé. L'hélice est créée et contrôlée au cours d'une réaction domino organocatalysée comprenant une alkylation de Michael suivie d'un couplage C–O, qui fournit les 2-nitrodihydrofuranes chiraux

sous forme d' uniques diastéréomères avec de hautes puretés optique présentant à la fois une chiralité centrale (deux atomes de carbone stéréogènes) et une chiralité hélicoïdale. Il s'agit du premier cas d'une transformation chimique dans laquelle les chiralités centrales et hélicoïdales sont contrôlées simultanément. Ceci donne accès à des molécules chirales très originales pour la synthèse d'hétérohelicènes optiquement actifs par élimination de HNO_2 avec une excellente rétention la chiralité hélicoïdale dans la plupart des cas. Dans une second partie, une nouvelle classe d'organocatalyseurs de type acides de Brønsted a été développée dans laquelle la chiralité est centrée sur l'atome de phosphore. Les acides thiophosphiniques P-stéréogènes chiraux optiquement actifs ont été synthétisés., ce qui ouvre de nouvelles opportunités en l'organocatalyse énantiosélective. Ces nouveaux organocatalyseurs ont notamment été utilisés dans la réaction de Pictet-Spengler et les produits ont été obtenus avec de bons rendements et énantiosélectivité modérée (jusqu'à 47% ee). Cette première étape valide le concept initial mais une optimisation supplémentaire est nécessaire pour atteindre des excès énantiomériques plus élevés et pour rendre ces organocatalyseurs plus généraux.

Chapter 4: Experimental procedures and characterization of compounds

4.1) General information

Reactions were run under argon atmosphere in oven-dried glassware. Unless specified, commercial reagents and solvents were used as received. Commercially available catalysts were purchased from Sigma-Aldrich. CHCl_3 was dried using a M-Braun SPS- 800 system.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Macherey-Nagel) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and further visualization was achieved by staining p-anisaldehyde and heating by a hot air gun. Flash column chromatography was performed using silica gel (35–70 μm , 60 A, Acros). Organic extracts were dried over anhydrous Na_2SO_4 .

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a Bruker AV 300 and AV 400 spectrometer. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent (CDCl_3 : δ 7.26 (CHCl_3)). Data are reported as follows: chemical shift (multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, m = multiplet), coupling constant(s) (Hz), integration). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker AV 300 and AV 400 MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.16 (CHCl_3)). Data are reported as follows: chemical shift (δ scale).

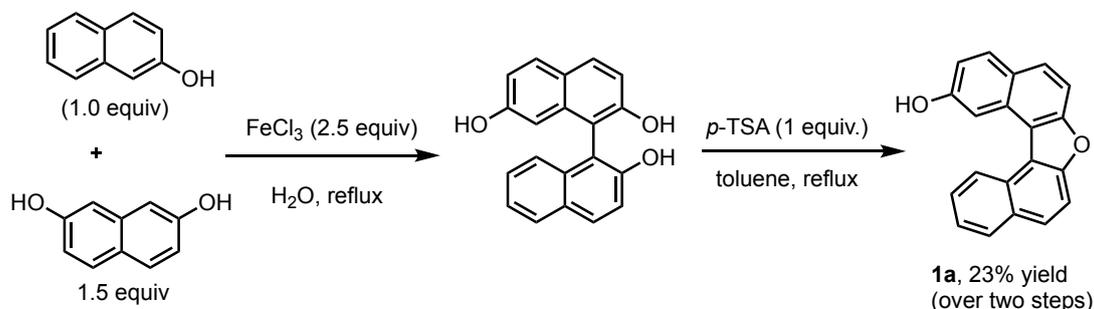
HPLC analyses for the determination of enantiomeric excesses were performed on a Merck-Hitachi system equipped with Chiralpak AZ-H, Chiralpak IA, Chiralpak IB,

Chiralpak IC, Chiralpak ID, Chiralpak IE, Chiralpak IF, Lux-Cellulose-2 and Lux-Cellulose-4. Optical Rotations were recorded on an Anton Paar MCP 200 Polarimeter at 589 nm and 25 °C and specific rotations are reported as follows: specific rotation (concentration in grams/100 mL of solution, solvent).

High resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 HDMS apparatus using a positive electrospray (ESI) ionization source.

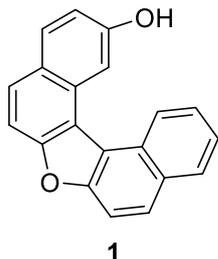
4.2) Experimental procedure for chapter 2

4.2.1) Synthesis of dinaphtho[2,1-b:1',2'-d]furan-2-ol **1a**



A solution of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (21.09 g, 78.04 mmol) in 100 mL water was added dropwise for 1 h at 100 °C to the solution of 2,7-dihydroxynaphthalene (5.0 g, 31.22 mmol) and 2-hydroxynaphthalene (6.75 g, 46.88 mmol) in 250 mL of water. The reaction mixture was refluxed for 24 h, cooled to room temperature and extracted with ethyl acetate (2 x 250 mL). The organic phases were dried over sodium sulphate and concentrated under reduced pressure to obtain the crude black mass. Purification of compound by column chromatography on silica gel using gradient petroleum ether: ethyl acetate 100:00 to 70:30 as eluent to separate the three binaphthol derivatives. The 1,1'-binaphthalene-2,2',7-triol (1 g, 3.31 mmol) was refluxed in toluene (20 mL) in the presence of $p\text{-TsOH}$ (0.63 g 3.31 mmol) for 24 h. After quenching with saturated potassium carbonate solution, the crude product was extracted with ethyl acetate. The combined extracts were washed with water (2 x 100 mL) and the organic layer was dried over Na_2SO_4 and evaporated to obtain crude solid. The crude product was purified by column chromatography over silica gel using light petroleum ether/ethyl acetate as eluent (100:00 to 90:10) furnishing the dinaphtho[2,1-b:1',2'-d]furan-2-ol **1a** as a white solid (23% yield over two steps).

dinaphtho[2,1-b:1',2'-d]furan-2-ol 1a



Data for 1

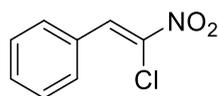
¹H NMR (CDCl₃, 400 MHz) δ 9.12 (d, *J* = 8.8 Hz, 1H, ArH), 8.50 (d, *J* = 2.4 Hz, ArH), 8.09 (d, *J* = 8.8 Hz, 1H, ArH), 7.99 (d, *J* = 8.4 Hz, 1H, ArH), 7.97 (d, *J* = 8.4 Hz, 1H, ArH), 7.90 (d, *J* = 8.8 Hz, 1H, ArH), 7.85 (d, *J* = 8.8 Hz, 1H, ArH), 7.77 (td, *J* = 6.8, 1.2 Hz, 1H, ArH), 7.71 (d, *J* = 8.8 Hz, 1H, ArH), 7.61 (td, *J* = 6.8, 1.2 Hz, 1H, ArH), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H, ArH), 5.37 (s, 1H, OH). ¹³C NMR (CDCl₃, 100 MHz) δ 155.05 (Cq), 154.13 (Cq), 154.05 (Cq), 131.43 (CH), 131.21 (Cq), 130.04 (Cq), 129.55 (CH), 128.75 (Cq), 128.49 (Cq), 128.28 (CH), 128.10 (CH), 126.36 (Cq), 126.10 (CH), 125.58 (CH), 124.34 (CH), 118.46 (Cq), 115.54 (CH), 112.37 (CH), 110.37 (CH), 109.08 (CH).

4.2.2) Experimental procedures for the synthesis and characterization of chloronitroalkene 2

The α -chloro- α -nitroalkenes were prepared according to the literature known procedure with slight modification. Substituted benzaldehyde (4.0 mmol, 1.0 equiv), bromonitromethane (1.1 g, 8.1 mmol, 2.0 equiv), dimethylamine hydrochloride (2.96 g, 36.3 mmol, 9.0 equiv), potassium fluoride (35.0 mg, 0.6 mmol, 0.15 equiv), toluene (3.8 mL) and *m*-xylenes (11.3 mL) were combined in a 50 mL round bottomed flask and connected to a Dean-Stark trap. The mixture was heated at 130 °C with azeotropic removal of water for 12 hours. The reaction was cool down to room temperature and

saturated sodium bisulfite (NaHSO₃, 5.0 mL) was poured in it. The reaction mixture was vigorously stirred before being partitioned between aqueous and organic layer. After separation of organic layer, the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford a brown oil. The oily residue was subsequently purified on a silica column using ethyl acetate/hexane mixture to produce the product. The corresponding bromonitroalkene is sometimes isolated (5 %) along with the desired product, which can be used as such in the domino Michael/*O*-alkylation reaction without any interference.

(*Z*)-(2-chloro-2-nitrovinyl)benzene 2b

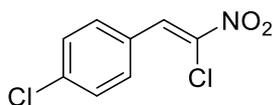


2b

Data for 2b

¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.77 (d, *J* = 6.5 Hz, 2H), 7.42 (q, *J* = 5.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.6, 131.9, 131.6, 131.2 (2C), 129.7 (2C), 129.1.

(Z)-1-chloro-4-(2-chloro-2-nitrovinyl)benzene 2c

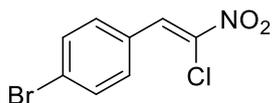


2c

Data for 2c

¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 138.4, 133.5, 133.2, 129.0, 128.8 (2C), 128.7 (2C).

(Z)-1-bromo-4-(2-chloro-2-nitrovinyl)benzene 2d

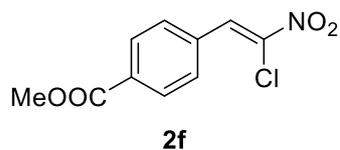


2d

Data for 2d

¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 138.0, 132.5, 132.4, 130.5 (2C), 128.5 (2C), 126.7.

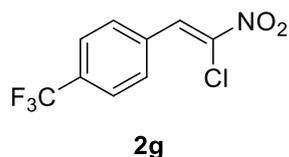
methyl (Z)-4-(2-chloro-2-nitrovinyl)benzoate 2f



Data for 2f

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.14 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.3$ Hz, 2H), 3.96 (s, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.9, 139.5, 138.4, 129.8 (2C), 129.3, 129.0 (2C), 128.8, 51.5.

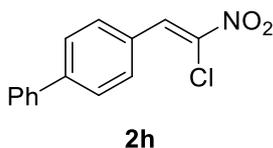
(Z)-1-(2-chloro-2-nitrovinyl)-4-(trifluoromethyl)benzene 2g



Data for 2g

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.38 (s, 1H), 7.94 (d, $J = 8.2$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.5, 138.4, 130.2, 128.9 (2C), 128.8, 125.0 (2C), 124.1.

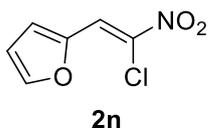
(Z)-4-(2-chloro-2-nitrovinyl)-1,1'-biphenyl 2h



Data for 2h

¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.64 (m, 2H), 7.48 (m, 2H), 7.41 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 140.8, 140.0, 138.4, 134.1, 129.2 (2C), 128.8, 127.9 (2C), 127.8 (2C), 127.6, 126.9 (2C).

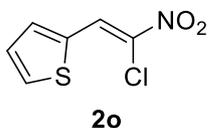
(Z)-2-(2-chloro-2-nitrovinyl)furan 2n



Data for 2n

¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.75 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.32 (d, *J* = 3.7 Hz, 1H), 6.68 (ddd, *J* = 3.7, 1.8, 0.5 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 151.5, 144.4, 143.7, 128.8, 112.7, 109.5.

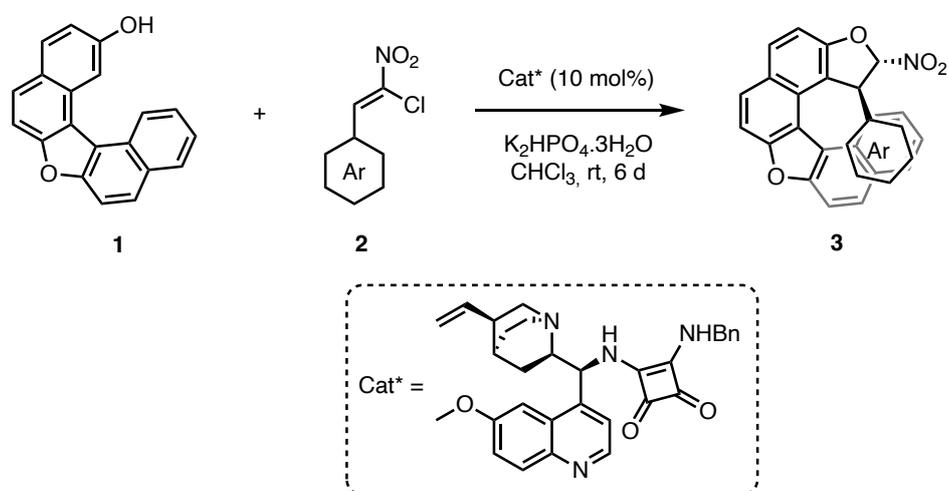
(Z)-2-(2-chloro-2-nitrovinyl)thiophene 2o



Data for 2o

¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.67 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.04 (d, *J* = 3.7 Hz, 1H), 6.97 (ddd, *J* = 3.7, 1.8, 0.5 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 144.4, 137.8, 130.5, 129.1, 128.8, 128.3.

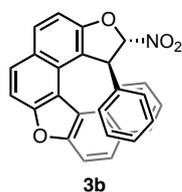
4.2.3) Experimental procedures for the enantioselective synthesis and characterization of dihydrofurans **3**



General Procedure A

A fifteen-centimeter-long sealed tube was charged with dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (1.0 equiv) and the appropriate chloronitroalkene **2** (1.2 equiv). Potassium phosphate dibasic trihydrate (1.5 equiv) and the squareamide catalyst (10 mol%) were added followed by chloroform (0.1 M). The resulting solution was stirred at room temperature for 6 days then the reaction was directly purified via flash column chromatography using eluent as stated.

(*M,S,S*)-**3b**



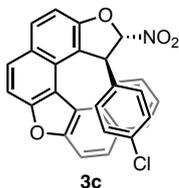
3b was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-(2-chloro-2-nitrovinyl)benzene **2b** (43.9 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether

(1/100 to 5/100) provided the title compound **3b** (54.3 mg, 63% yield) as a light yellow oil.

Data for **3b**

R_f: 0.62 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 6.55) = +254.24; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.24 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.89 (dd, *J* = 8.8, 3.5 Hz, 2H), 7.71 – 7.63 (m, 2H), 7.63 – 7.50 (m, 3H), 6.89 – 6.83 (m, 1H), 6.75 (m, 2H), 6.22 (s, 1H), 6.06 – 5.94 (m, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.12, 155.80, 153.90, 137.94, 132.70, 131.03, 129.35, 128.99, 128.83, 128.71 (2C), 128.51, 128.18, 127.85, 126.55 (2C), 126.19, 125.76, 125.10, 125.04, 119.82, 119.08, 116.57, 112.45, 111.45, 111.21, 110.37, 57.04; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 454.1049, calc'd C₂₈H₁₇NO₄Ag requires 454.1050; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **96% ee**, **t_{r1}** : 5.64 min, **t_{r2}** : 6.88 min.

(*M,S,S*)-**3c**



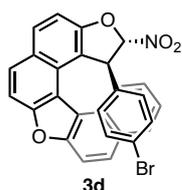
3c was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-chloro-4-(2-chloro-2-nitrovinyl)benzene **2c** (52.1 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3c** (75.4 mg, 81% yield) as a light yellow oil.

Data for **3c**

R_f: 0.62 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 5.77) = -134.57; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.19 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 8.07 (d, *J* =

7.4 Hz, 1H), 7.91 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 8.9$ Hz, 1H), 7.64 (m, 3H), 7.55 (d, $J = 8.8$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 2H), 6.21 (s, 1H), 5.97 (s, 1H), 5.92 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 158.05, 155.84, 153.97, 136.37, 133.79, 132.95, 131.02, 129.37, 129.07, 128.94 (2C), 128.90, 128.39, 128.30, 127.92 (2C), 126.01, 125.82, 125.16, 124.93, 119.42, 118.89, 116.45, 112.57, 111.38, 111.06, 110.41, 56.36; HRMS-ESI⁺ (m/z): found $[\text{M}+\text{Ag}]^+$ 573.9808, calc'd $\text{C}_{28}\text{H}_{16}\text{ClNO}_4\text{Ag}$ requires 573.9806; HPLC analysis (Lux-Cellulose-2, Heptane/isopropanol (95/5), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 210 nm) indicated 96% ee, $t_{\text{r}1}$: 7.64 min, $t_{\text{r}2}$: 11.29 min.

(*M,S,S*)-3d



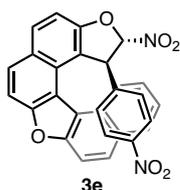
3d was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-bromo-4-(2-chloro-2-nitrovinyl)benzene **2d** (62.6 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3d** (88.6 mg, 87% yield) as a yellow oil.

Data for 3d

R_f : 0.55 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , $c = 7.53$) = +376.06; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.19 (m, 1H), 8.13 (d, $J = 8.8$ Hz, 1H), 8.06 (m, 1H), 7.91 (dd, $J = 8.9, 1.3$ Hz, 2H), 7.72 (d, $J = 8.9$ Hz, 1H), 7.68 – 7.58 (m, 3H), 7.55 (m, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.20 (s, 1H), 5.97 (d, $J = 1.0$ Hz, 1H), 5.86 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 158.06, 155.86, 153.98, 136.90, 132.97, 131.89 (2C), 131.03, 129.38, 129.08, 128.91, 128.38, 128.32, 128.25 (2C), 126.00, 125.83, 125.17,

124.93, 121.97, 119.34, 118.89, 116.45, 112.60, 111.40, 110.96, 110.41, 56.43; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 617.9297, calc'd C₂₈H₁₆NO₄BrAg requires 617.9298; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **94% ee**, **t_{r1}** : 5.96 min, **t_{r2}** : 7.56 min.

(M,S,S)-3e

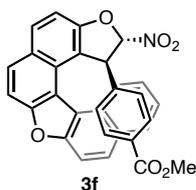


3e was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-(2-chloro-2-nitrovinyl)-4-nitrobenzene **2e** (54.7 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **3e** (80.9 mg, 85% yield) as a light yellow oil.

Data for 3e

R_f: 0.21 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 6.66) = +580.19; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.18 (m, 2H), 8.09 (m, 1H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.69 – 7.54 (m, 6H), 6.39 (s, 1H), 6.16 (d, *J* = 8.7 Hz, 2H), 5.99 (s, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.17, 155.93, 154.05, 147.47, 144.77, 133.45, 131.06, 129.43, 129.25, 129.04, 128.53, 128.27, 127.63 (2C), 125.99, 125.86, 125.30, 124.79, 124.00 (2C), 118.60, 118.59, 116.26, 112.69, 111.61, 110.52, 110.30, 56.44; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 583.0049, calc'd C₂₈H₁₆N₂O₆Ag requires 583.0054; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (60/40), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **96% ee**, **t_{r1}** : 9.03 min, **t_{r2}** : 10.23 min.

(*M,S,S*)-**3f**

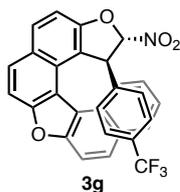


3f was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and methyl (*Z*)-4-(2-chloro-2-nitrovinyl)benzoate **2f** (57.8 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **3f** (79.2 mg, 81% yield) as a yellow oil.

Data for 3f

R_f: 0.12 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 6.06) = +546.56; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.21 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.92 – 7.89 (m, 2H), 7.70 – 7.54 (m, 5H), 7.41 (d, *J* = 7.8 Hz, 2H), 6.30 (s, 1H), 6.08 – 6.02 (m, 3H), 3.70 (s, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 166.33, 158.11, 155.83, 153.94, 142.74, 133.03, 131.02, 130.00 (2C), 129.75, 129.36, 129.10, 128.89, 128.37, 128.33, 126.64 (2C), 126.01, 125.84, 125.17, 124.91, 119.22, 118.83, 116.39, 112.56, 111.37, 110.82, 110.43, 56.76, 52.13; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 596.0257, calc'd C₃₀H₁₉NO₆Ag requires 596.0258; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **97% ee**, **t_{r1}** : 7.41 min, **t_{r2}** : 9.94 min.

(M,S,S)-3g

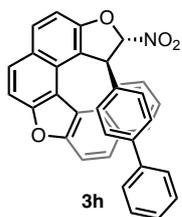


3g was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-(2-chloro-2-nitrovinyl)-4-(trifluoromethyl)benzene **2g** (60.2 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3g** (85.8 mg, 86% yield) as a light green oil.

Data for **3g**

R_f: 0.52 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 7.19) = +635.14; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.19 (m, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.65 (m, *J* = 8.9 Hz, 2H), 7.64 – 7.52 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.31 (s, 1H), 6.12 (d, *J* = 8.1 Hz, 2H), 6.00 (d, *J* = 1.0 Hz, 1H). **¹⁹F NMR (282 MHz, CDCl₃)** δ –62.96. **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.16, 155.90, 154.02, 141.76 (q, ⁵*J*_{C-F} = 1.5 Hz), 133.16, 131.05, 130.17 (q, ²*J*_{C-F} = 33 Hz), 129.39, 129.14, 128.95, 128.40, 128.35, 127.00 (2C), 125.96, 125.91, 125.79 (q, ⁴*J*_{C-F} = 3.8 Hz, 2C), 125.21, 124.86, 123.6 (q, ¹*J*_{C-F} = 270 Hz), 118.96, 118.78, 116.40, 112.61, 111.49, 110.77, 110.44, 56.60; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 606.0075, calc'd C₂₉H₁₆NF₃O₄Ag requires 606.0077; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **96% ee**, **t_{r1}** : 4.91 min, **t_{r2}** : 6.08 min.

(*M,S,S*)-**3h**

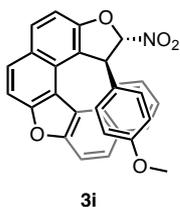


3h was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-4-(2-chloro-2-nitrovinyl)-1,1'-biphenyl **2h** (62.2 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3h** (78.1 mg, 77% yield) as a light yellow oil.

Data for **3h**

R_f: 0.44 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 5.47) = +815.29; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.16 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.48 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.22 – 7.09 (m, 5H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.17 (s, 1H), 6.01 – 5.94 (m, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.13, 155.86, 153.96, 140.67, 140.10, 136.93, 132.76, 131.07, 129.39, 129.03, 128.87, 128.73 (2C), 128.54, 128.23, 127.47, 127.39 (2C), 126.96 (2C), 126.87 (2C), 126.20, 125.81, 125.14, 125.06, 119.81, 119.11, 116.62, 112.53, 111.43, 111.28, 110.43, 56.74; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 530.1364, calc'd C₃₄H₂₁NO₄Ag requires 530.1363; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **99% ee**, **t_{r1}** : 6.54 min, **t_{r2}** : 8.63 min.

(*M,S,S*)-3h

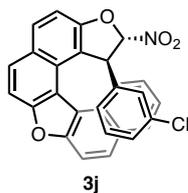


3i was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-(2-chloro-2-nitrovinyl)-4-methoxybenzene **2i** (51.1 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **3i** (47.1 mg, 51% yield) as a light yellow oil.

Data for 3i

R_f: 0.30 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 4.89) = +187.69; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.22 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.88 – 7.76 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 6.27 (d, *J* = 8.7 Hz, 2H), 6.16 (s, 1H), 5.98 (s, 1H), 5.90 (d, *J* = 8.7 Hz, 2H), 3.50 (s, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 159.00, 157.96, 155.79, 153.91, 132.60, 131.02, 130.03, 129.37, 128.96, 128.85, 128.52, 128.16, 127.68 (2C), 126.17, 125.74, 125.10, 120.22, 119.15, 116.61, 114.47, 114.06 (2C), 112.49, 111.64, 111.19, 110.38, 56.43, 55.09; **HRMS-ESI⁺ (m/z)**: found [M+Ag]⁺ 568.0313, calc'd C₂₉H₁₉NO₅Ag requires 568.0309; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **94% ee**, **t_{r1}** : 6.08 min, **t_{r2}** : 7.65 min.

(*M,S,S*)-**3j**

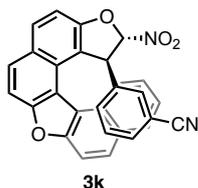


3j was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-(2-chloro-2-nitrovinyl)-3-chlorobenzene **2j** (52.1 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3j** (63.2 mg, 68% yield) as a light yellow oil.

Data for **3j**

R_f: 0.53 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 3.35) = +484.73; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.22 – 8.17 (m, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 8.07 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.68 – 7.58 (m, 3H), 7.55 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.84 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H), 6.67 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.22 (s, 1H), 6.00 (d, *J* = 0.8 Hz, 1H), 5.99 (t, *J* = 1.6 Hz, 1H), 5.86 (dt, *J* = 7.9, 1.6 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.07, 155.87, 153.98, 139.81, 134.53, 133.05, 131.07, 129.94, 129.38, 129.12, 128.93, 128.41, 128.33, 128.21, 126.77, 125.99, 125.84, 125.17, 124.89, 124.79, 119.13, 118.88, 116.40, 112.52, 111.37, 110.97, 110.42, 56.50; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 573.9805, calc'd C₂₈H₁₆NO₄ClAg requires 573.9806; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **94% ee**, **t_{r1}** : 4.95 min, **t_{r2}** : 6.14 min.

(M,S,S)-3k

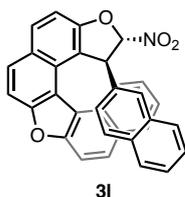


3k was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-3-(2-chloro-2-nitrovinyl)benzonitrile **2k** (49.9 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **3k** (71.1 mg, 78% yield) as a light yellow oil.

Data for **3k**

R_f: 0.11 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 5.11) = +293.89; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.21 – 8.15 (m, 2H), 8.14 – 8.05 (m, 1H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.73 (m, 1H), 7.73 – 7.59 (m, 3H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.16 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.87 (td, *J* = 7.7, 0.8 Hz, 1H), 6.31 (s, 1H), 6.24 – 6.22 (m, 2H), 5.97 (d, *J* = 1.0 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 189.99, 158.13, 155.90, 154.03, 139.34, 137.33, 133.44, 131.73, 131.22, 131.07, 130.22, 129.61, 129.44, 129.27, 129.10, 128.53, 128.27, 125.95, 125.29, 124.80, 118.56, 117.92, 116.24, 112.94, 112.60, 111.56, 110.54, 110.50, 56.34; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 563.0157, calc'd C₂₉H₁₆N₂O₄Ag requires 563.0156; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **95% ee**, **t_{r1}** : 14.36 min, **t_{r2}** : 16.86 min.

(M,S,S)-3I



3I was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-2-(2-chloro-2-nitrovinyl)naphthalene **2I** (55.9 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3I** (78.9 mg, 82% yield) as a light yellow oil.

Data for **3I**

R_f: 0.45 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 6.16) = +849.00; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.29 (d, *J* = 8.6 Hz, 1H), 8.15 (d, *J* = 11.6 Hz, 1H), 8.13 – 8.09 (m, 1H), 7.91 (dd, *J* = 8.9, 4.1 Hz, 2H), 7.73 – 7.59 (m, 5H), 7.54 – 7.44 (m, 1H), 7.31 – 7.13 (m, 4H), 6.39 (s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.19 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.11 (d, *J* = 1.0 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.05, 155.78, 153.88, 135.26, 132.87, 132.80, 132.63, 131.07, 129.36, 129.03, 128.85, 128.78, 128.57, 128.13, 127.78, 127.39, 126.22, 126.18, 126.12, 126.01, 125.82, 125.17, 125.13, 123.92, 119.86, 119.12, 116.50, 112.54, 111.36, 111.25, 110.42, 57.12; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 588.0359, calc'd C₃₂H₁₉NO₄Ag requires 588.0360; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **93% ee**, **t_{r1}** : 6.16 min, **t_{r2}** : 7.96 min.

(*M,S,S*)-**3m**

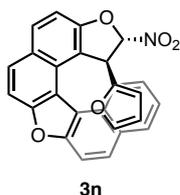


3m was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-1-(2-chloro-2-nitrovinyl)-2-fluorobenzene **2m** (48.2 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3m** (47.6 mg, 53% yield) as a light yellow oil.

Data for **3m**

R_f: 0.40 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 5.30) = +231.36; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.24 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), (m, 3H), 7.62 – 7.56 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 6.92 – 6.81 (m, 1H), 6.65 – 6.55 (m, 2H), 6.45 (td, *J* = 8.1, 1.2 Hz, 1H), 6.03 (s, 1H), 5.48 (td, *J* = 7.7, 1.6 Hz, 1H); **¹⁹F NMR (282 MHz, CDCl₃)** δ -117.73 (ddd, *J* = 10.2, 7.5, 5.3 Hz). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 159.89 (d, ¹*J*_{C-F} = 186 Hz), 158.96, 158.86, 153.95, 132.98, 131.01, 129.74, 129.66, 129.31, 128.89 (d, ²*J*_{C-F} = 10.1 Hz), 128.59, 128.33, 127.99 (d, ³*J*_{C-F} = 2.4 Hz), 126.27, 125.91, 125.14, 124.71, 124.58 (d, ²*J*_{C-F} = 10.4 Hz), 124.16 (d, ³*J*_{C-F} = 2.7 Hz), 118.86, 117.74, 116.60, 115.68, 115.46, 112.22, 111.29, 110.73 (d, ⁴*J*_{C-F} = 0.8 Hz), 110.37, 50.52; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 556.0106, calc'd C₂₈H₁₆NO₄FAg requires 556.0109; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **97% ee**, **t_{r1}** : 5.34 min, **t_{r2}** : 6.22 min.

(*M,S,S*)-**3n**

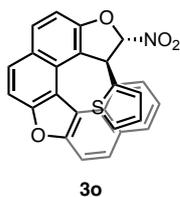


3n was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-2-(2-chloro-2-nitrovinyl)furan **2n** (41.5 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3n** (39.6 mg, 47% yield) as a light yellow oil.

Data for **3n**

R_f: 0.52 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 3.96) = +490.32; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.17 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 9.4 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.64 – 7.52 (m, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 2.7 Hz, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 5.73 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.71 (d, *J* = 3.3 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.39, 155.94, 154.02, 149.38, 142.64, 133.08, 131.10, 129.24, 129.10, 128.90, 128.50, 128.32, 126.20, 125.98, 125.16, 124.64, 119.11, 116.61, 116.53, 112.51, 111.27, 110.59, 110.19, 108.65, 107.40, 50.96; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 527.9995, calc'd C₂₆H₁₅NO₅Ag requires 527.9996; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **99% ee**, **t_{r1}** : 5.34 min, **t_{r2}** : 6.25 min.

(M,S,S)-3o

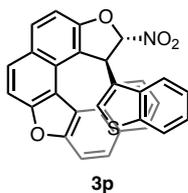


3o was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-2-(2-chloro-2-nitrovinyl)thiophene **2o** (45.4 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3o** (56.8 mg, 65% yield) as a light yellow oil.

Data for **3o**

R_f: 0.53 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 2.62) = +1199.92; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.19 (d, *J* = 6.5 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 11.1 Hz, 1H), 7.63 – 7.56 (m, 3H), 7.52 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.72 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.51 (s, 1H), 6.40 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.10 (d, *J* = 0.9 Hz, 1H), 5.83 (ddd, *J* = 3.6, 1.2, 0.6 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 157.76, 155.86, 153.97, 140.68, 137.16, 134.52, 133.12, 131.07, 129.38, 129.06, 128.89, 128.28, 126.76, 125.89, 125.31, 125.12, 124.99, 124.63, 119.63, 119.09, 116.58, 112.49, 111.32, 110.98, 110.55, 52.36; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 545.9766, calc'd C₂₆H₁₅NO₄SAg requires 545.9765; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **95% ee**, **t_{r1}** : 5.27 min, **t_{r2}** : 6.31 min.

(*M,S,S*)-**3p**

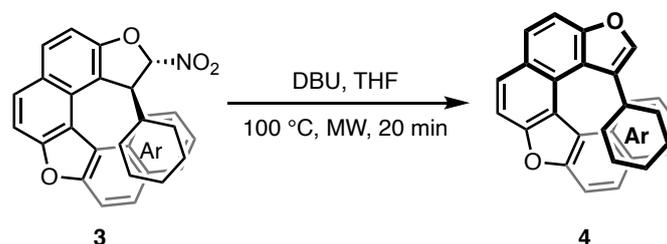


3p was prepared following general procedure **A** using dinaphtho[2,1-b:1',2'-d]furan-2-ol **1** (56.8 mg, 0.2 mmol) and (*Z*)-3-(2-chloro-2-nitrovinyl)benzo[*b*]thiophene **2p** (57.4 mg, 0.24 mmol) for 6 days. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **3o** (54.5 mg, 56% yield) as a light yellow oil.

Data for **3p**

R_f: 0.55 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 6.62) = +356.41; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.25 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.95 (dd, *J* = 8.4, 3.8 Hz, 2H), 7.92 – 7.87 (m, 1H), 7.78 – 7.67 (m, 2H), 7.69 – 7.60 (m, 2H), 7.57 – 7.52 (m, 2H), 7.16 – 7.00 (m, 3H), 6.75 (s, 1H), 6.03 (d, *J* = 0.9 Hz, 1H), 5.44 (s, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.59, 155.82, 153.98, 140.37, 136.56, 133.43, 132.99, 131.81, 131.07, 129.03, 128.86, 128.23, 125.72, 124.97, 124.79, 124.64, 124.48, 124.04, 123.08, 122.76, 122.27, 120.81, 118.65, 117.81, 116.67, 112.29, 111.39, 110.47, 109.69, 51.23; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 595.9924, calc'd C₃₀H₁₇NO₄SAg requires 595.9923; **HPLC analysis** (Lux-Cellulose-4, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **98% ee**, **t_{r1}** : 5.11 min, **t_{r2}** : 6.25 min.

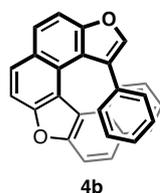
4.2.4) Experimental procedures of elimination and characterization of helicenes **4**



General procedure B

The eight-centimeter-long sealed G10 tube for microwaves was charged with compound **3** (1.0 equiv) and the DBU (5.0 equiv), followed by THF (0.1 M). The resulting solution was put into the microwaves at $100\text{ }^\circ\text{C}$ for 30 minutes then the reaction was directly purified via flash column chromatography using eluent as stated.

(*M*)-**4b**



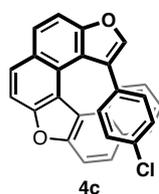
4b was prepared following general procedure **B** using **3b** (43.1 mg, 0.1 mmol) and DBU (74.7 μL , 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4b** (32.2 mg, 84% yield) as a light yellow oil.

Data for **4b**

R_f : 0.81 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , $c = 6.45$) = -287.94 ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 8.16 – 8.10 (m, 1H), 8.05 (d, $J = 8.8$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 7.85 (dd, $J = 8.8, 2.2$ Hz, 2H), 7.78 (s, 1H), 7.70 – 7.56 (m, 3H), 7.33 – 7.19

(m, 2H), 6.75 – 7.69 (m, 2H), 6.60 – 6.51 (m, 1H), 6.51 – 6.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 155.70, 155.30, 152.99, 141.20, 131.97, 130.18, 128.83, 128.74, 128.05, 127.89, 127.79(2C), 127.58, 127.25, 126.69, 126.35, 126.10(2C), 125.92, 124.93, 123.81, 122.94, 121.33, 120.59, 118.10, 111.77, 111.72, 110.83; HRMS-ESI⁺ (m/z) : found $[\text{M}+\text{Ag}]^+$ 491.0196, calc'd $\text{C}_{28}\text{H}_{16}\text{O}_2\text{Ag}$ requires 491.0196; HPLC analysis (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated 92% ee, $t_{\text{r}1}$: 3.65 min, $t_{\text{r}2}$: 4.18 min.

(M)-4c



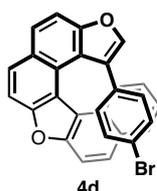
4c was prepared following general procedure **B** using **3c** (46.5 mg, 0.1 mmol) and DBU (74.7 μL , 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **4c** (22.6 mg, 54% yield) as a light yellow oil.

Data for 4c

R_f : 0.50 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , $c = 4.51$) = +112.88; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.05 (d, $J = 8.8$ Hz, 1H), 8.03 – 7.99 (m, 2H), 7.84 (dd, $J = 8.8$, 0.7 Hz, 2H), 7.77 (s, 1H), 7.73 (ddd, $J = 8.2$, 1.3, 0.7 Hz, 1H), 7.68 (s, 2H), 7.30 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.20 (ddd, $J = 8.3$, 6.9, 1.3 Hz, 1H), 6.58 (d, $J = 7.9$ Hz, 2H), 6.36 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 155.67, 155.32, 153.06, 141.05, 135.94, 131.70, 130.32, 130.22, 129.02, 128.77, 128.13, 127.88, 127.81, 126.88, 126.14, 126.10, 126.05 (2C), 125.67, 124.98, 123.98, 122.66, 120.92, 120.38, 117.79, 111.97, 111.79, 110.92; HRMS-ESI⁺ (m/z) : found $[\text{M}+\text{Ag}]^+$ 526.9791, calc'd $\text{C}_{28}\text{H}_{15}\text{ClO}_2\text{Ag}$ requires 526.9799; HPLC analysis (Chiralpak IF, Heptane/ Ethanol

(95/5), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 290 nm) indicated **91% ee**, $t_{\text{r}1}$: 4.70 min, $t_{\text{r}2}$: 5.22 min.

(M)-4d

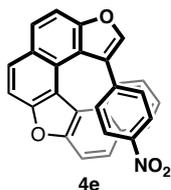


4d was prepared following general procedure **B** using **3d** (50.9 mg, 0.1 mmol) and DBU (74.7 μL , 0.5 mmol) for half an hour. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **4d** (31.3 mg, 67% yield) as a yellow oil.

Data for 4d

R_f : 0.62 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl_3 , $c = 5.77$) = -263.06 ; **$^1\text{H NMR}$ (400 MHz, CDCl_3)** δ (ppm) 8.05 (d, $J = 8.8$, 1H), 8.01 (d, $J = 8.8$, 1H), 8.02 – 7.97 (m, 1H), 7.84 (dd, $J = 8.8$, 0.9 Hz, 2H), 7.77 (s, 1H), 7.75 (ddd, $J = 8.1$, 1.4, 0.7 Hz, 1H), 7.69 (s, 2H), 7.31 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.19 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 6.51 (s, 3H); **$^{13}\text{C NMR}$ (75 MHz, CDCl_3)** δ (ppm) 155.66, 155.31, 153.04, 140.97, 130.73, 130.22, 129.34, 128.95 (2C), 128.76, 128.67, 128.12, 127.84 (2C), 126.88, 126.11, 126.10, 124.98, 123.99, 122.63, 120.90, 120.32, 119.94, 117.76, 111.97, 111.78, 110.91, one carbon signal is missing; **HRMS-ESI⁺ (m/z)** : found $[\text{M}+\text{Ag}]^+$ 570.9286, calc'd $\text{C}_{28}\text{H}_{15}\text{BrO}_2\text{Ag}$ requires 570.9291; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **92% ee**, $t_{\text{r}1}$: 3.86 min, $t_{\text{r}2}$: 4.31 min.

(M)-4e

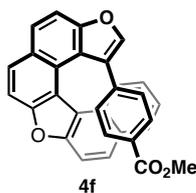


4e was prepared following general procedure **B** using **3e** (47.6 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for half an hour. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **4e** (27.9 mg, 65% yield) as a yellow oil.

Data for 4e

R_f: 0.31 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, $c = 5.58$) = -38.71 ; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) δ 8.09 (d, $J = 8.7$ Hz, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.99 – 7.93 (m, 1H), 7.88 (dd, $J = 8.7, 2.2$ Hz, 2H), 7.87 (s, 1H), 7.68 (d, $J = 8.9$ Hz, 1H), 7.66 – 7.62 (m, 1H), 7.60 – 7.56 (m, 1H), 7.34 – 7.18 (m, 4H), 6.79 (d, $J = 8.2$ Hz, 2H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.87, 155.46, 153.26, 145.49, 141.85, 138.90, 130.06, 128.92, 128.40, 128.34, 128.12, 128.09, 127.85, 127.46, 127.19, 125.93, 125.61, 125.20, 124.20, 122.38, 121.13 (2C), 120.59, 119.75, 117.59, 112.31, 111.81, 111.25; **HRMS-ESI⁺ (m/z)** : found $[M+Ag]^+$ 536.0048, calc'd C₂₈H₁₅NO₄Ag requires 536.0047; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **96% ee**, **t_{r1}** : 5.72 min, **t_{r2}** : 6.46 min.

(M)-4f

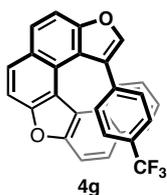


4f was prepared following general procedure **B** using **3f** (48.9 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **4f** (35.4 mg, 80% yield) as a deep yellow oil.

Data for 4f

R_f: 0.31 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl₃, $c = 7.07$) = -214.87 ; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.14 – 7.98 (m, 3H), 7.86 (dd, $J = 8.8, 2.2$ Hz, 2H), 7.83 (s, 1H), 7.65 (d, $J = 8.8$ Hz, 1H), 7.63 – 7.59 (m, 1H), 7.59 – 7.52 (d, $J = 8.8$ Hz, 1H), 7.32 – 7.18 (m, 2H), 7.11 (d, $J = 7.6$ Hz, 2H), 6.74 (d, $J = 7.9$ Hz, 2H), 3.79 (s, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 166.80, 155.78, 155.36, 153.14, 141.62, 136.83, 130.11, 128.81, 128.58, 128.11, 128.05, 127.72, 127.46 (2C), 127.36 (2C), 127.28, 127.06, 126.57, 126.04, 125.05, 124.00, 122.70, 120.92, 120.16, 117.92, 111.99, 111.76, 111.04, 51.96; **HRMS-ESI⁺ (m/z)** : found $[M+\text{Ag}]^+$ 549.0251, calc'd C₃₀H₁₈O₄Ag requires 549.0251; **HPLC analysis** (Lux-Amylose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **91% ee**, **t_{r1}** : 6.74 min, **t_{r2}** : 11.03 min.

(M)-4g

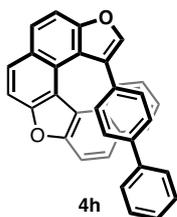


4g was prepared following general procedure **B** using **3g** (49.9 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for half an hour. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **4g** (37.5 mg, 83% yield) as a deep yellow oil.

Data for 4g

R_f: 0.60 (10% EtOAc in Pet. Et.); [α]_D²⁵ (CHCl₃, *c* = 7.50) = -227.33; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.06 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.89 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.79 (dd, *J* = 8.8, 1.8 Hz, 2H), 7.82 (s, 1H), 7.68 – 7.57 (m, 3H), 7.29 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.20 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 2H); **¹⁹F NMR (282 MHz, CDCl₃)** δ -63.10. **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.75, 155.37, 153.11, 141.40, 135.54 (q, ⁵*J*_{C-F} = 1.0 Hz), 130.23, 128.83, 128.49, 128.24, 128.15, 127.93 (2C), 127.70 (q, ²*J*_{C-F} = 24 Hz), 127.09, 126.07, 125.95, 124.99, 123.93, 122.67 (q, ⁴*J*_{C-H} = 3.9 Hz), 122.58, 120.82, 120.17, 117.74, 111.89, 111.81, 111.01; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 559.0070, calc'd C₂₉H₁₅F₃O₂Ag requires 559.0070; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (90/10), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **93% ee**, **t_{r1}** : 3.68 min, **t_{r2}** : 4.03 min.

(M)-4h

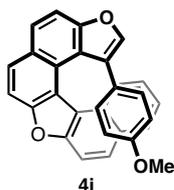


4h was prepared following general procedure **B** using **3h** (50.7 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **4h** (45.0 mg, 98% yield) as a deep yellow oil.

Data for **4h**

R_f: 0.61 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 9.02) = -134.28; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.10 – 8.07 (m, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.80 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.75 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.30 – 7.16 (m, 5H), 6.73 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 7.9 Hz, 2H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.68, 155.31, 152.97, 141.42, 141.03, 138.77, 130.87, 130.15, 128.91, 128.78, 128.60 (2C), 128.28 (2C), 128.08, 127.69, 127.64, 127.00 (2C), 126.97, 126.82, 126.72, 126.33, 124.98, 124.89 (2C), 123.88, 122.91, 121.24, 120.69, 118.00, 111.79 (2C), 110.83; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 567.0510, calc'd C₃₄H₂₀O₂Ag requires 567.0509; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **93% ee**, **t_{r1}** : 4.44 min, **t_{r2}** : 5.83 min.

(M)-4i

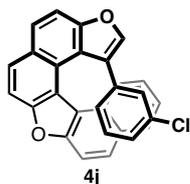


4i was prepared following general procedure **B** using **3i** (46.1 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 7/100) provided the title compound **4i** (21.5 mg, 52% yield) as a deep yellow oil.

Data for 4i

R_f: 0.40 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl₃, $c = 4.31$) = -68.06 ; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.10 – 8.05 (m, 1H), 8.04 (d, $J = 8.7$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.82 (dd, $J = 8.8, 3.3$ Hz, 2H), 7.74 (s, 1H), 7.68 – 7.61 (m, 3H), 7.28 (ddd, $J = 6.1, 5.2, 1.0$ Hz, 1H), 7.21 (ddd, $J = 6.1, 5.2, 1.0$ Hz, 1H), 6.60 (d, $J = 8.0$ Hz, 2H), 5.97 (d, $J = 8.9$ Hz, 2H), 3.49 (s, 3H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 157.74, 155.60, 155.30, 152.95, 140.62, 130.32, 129.13 (2C), 128.94, 128.74, 128.10, 127.77, 127.50, 126.74, 126.54, 126.46, 124.86, 124.46, 123.91, 122.96, 121.42, 120.91, 118.00, 111.80 (2C), 111.77, 110.72, 55.31, one carbon signal is missing; **HRMS-ESI⁺ (m/z)** : found $[M+Ag]^+$ 521.0300, calc'd C₂₉H₁₈O₃Ag requires 521.0301; **HPLC analysis** (Chiralpak AZ-H, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **94% ee**, **t_{r1}** : 4.74 min, **t_{r2}** : 5.63 min.

(M)-4j

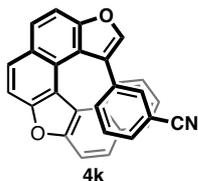


4j was prepared following general procedure **B** using **3j** (46.5 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4j** (27.6 mg, 66% yield) as a light yellow oil.

Data for 4j

R_f: 0.72 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl₃, *c* = 5.51) = -250.42; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.10 – 8.03 (m, 2H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.79 (s, 1H), 7.70 – 7.64 (m, 3H), 7.34 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.26 – 7.20 (m, 1H), 6.72 (s, 1H), 6.57 – 6.50 (m, 2H), 6.36 (t, *J* = 7.8 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.73, 155.43, 153.27, 141.34, 133.79, 132.40, 130.30, 128.83, 128.42, 128.12, 128.10, 128.08, 127.99, 127.85, 127.19, 127.01, 126.14, 126.04, 126.00, 125.04, 123.99, 122.61, 121.06, 120.22, 117.89, 112.00, 111.78, 111.04; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 526.9798, calc'd C₂₈H₁₅O₂ClAg requires 526.9799; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **81% ee**, **t_{r1}** : 3.70 min, **t_{r2}** : 4.15 min.

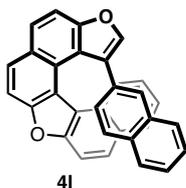
(M)-4k



4k was prepared following general procedure **B** using **3k** (45.6 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for half an hour. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 10/100) provided the title compound **4k** (26.6 mg, 65% yield) as a deep yellow oil.

Data for 4k

R_f: 0.30 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 5.32) = -111.22; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.08 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.87 (dd, *J* = 8.8, 2.7 Hz, 2H), 7.81 (s, 1H), 7.72 – 7.68 (m, 2H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.38 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.03 (brs, 1H), 6.87 – 6.78 (m, 2H), 6.49 (t, *J* = 7.7 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.81, 155.54, 153.35, 141.48, 133.37, 131.81, 131.45, 130.24, 129.33, 128.87, 128.33 (2C), 128.28, 127.83, 127.29, 126.60, 125.93, 125.28, 125.22, 124.32, 122.40, 120.71, 119.88, 118.45, 117.54, 112.27, 111.86, 111.21, 110.13; **HRMS-ESI⁺ (m/z)** : found $[M+Ag]^+$ 516.0148, calc'd C₂₉H₁₅NO₂Ag requires 516.0148; **HPLC analysis** (Lux-Cellulose-2, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **79% ee**, **t_{r1}** : 8.54 min, **t_{r2}** : 11.10 min.

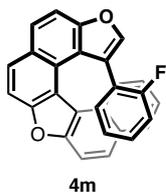


4I was prepared following general procedure **B** using **3I** (48.1 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4I** (23.1 mg, 53% yield) as a deep yellow oil.

Data for 4I

R_f: 0.72 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 4.60) = -52.42; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.08 (d, *J* = 8.8 Hz, 1H), 8.09 – 8.05 (m, 1H), 8.04 (d, *J* = 8.8, 1H), 7.89 (s, 1H), 7.87 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.30 – 7.03 (m, 8H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 11.2, 2.0 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.73, 155.28, 153.06, 141.32, 131.81, 131.63, 129.77, 129.36, 128.83, 128.70, 128.08, 127.54, 127.49, 127.36, 127.22, 126.97, 126.81, 126.56, 126.77, 126.04, 125.57, 125.21, 125.17, 124.97, 123.75, 122.99, 121.04, 120.71, 118.14, 111.82, 111.52, 110.89; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 541.0353, calc'd C₃₂H₁₈O₂Ag requires 541.0352; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **83% ee**, **t_{r1}** : 3.97 min, **t_{r2}** : 4.53 min.

(M)-4m

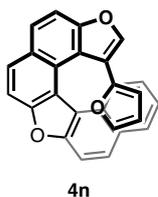


4m was prepared following general procedure **B** using **3m**(44.9 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4m** (28.9 mg, 72% yield) as a light yellow oil.

Data for **4m**

R_f: 0.70 (10% EtOAc in Pet. Et.); $[\alpha]_{\text{D}}^{25}$ (CHCl₃, $c = 5.79$) = -103.41 ; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.09 – 7.98 (m, 3H), 7.96 (d, $J = 2.6$ Hz, 1H), 7.85 (dd, $J = 8.8, 4.4$ Hz, 2H), 7.68 – 7.59 (m, 3H), 7.37 – 7.27 (m, 2H), 6.59 – 6.41 (m, 2H), 6.30 (dd, $J = 10.4, 8.5$ Hz, 1H), 6.06 (t, $J = 7.7$ Hz, 1H); **¹⁹F NMR (282 MHz, CDCl₃)** δ -113.25. **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 158.40 (d, $^1J_{\text{C-F}} = 184$ Hz), 155.25, 155.09, 153.12, 143.31, 129.93, 129.59, 128.96, 128.88, 128.20, 128.00, 127.81, 127.72, 127.71, 126.85, 125.77, 125.11 (d, $^4J_{\text{C-F}} = 1$ Hz), 123.86, 121.78 (d, $^3J_{\text{C-F}} = 2.5$ Hz), 121.07, 120.47 (d, $^2J_{\text{C-F}} = 10.7$ Hz), 118.11, 113.98, 113.76, 111.69, 111.64, 110.90; **HRMS-ESI⁺ (m/z)** : found $[\text{M}+\text{Ag}]^+$ 430.1124, calc'd C₂₈H₁₅O₂FAg requires 430.1129; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **59% ee**, **t_{r1}** : 3.63 min, **t_{r2}** : 4.06 min.

(M)-4n

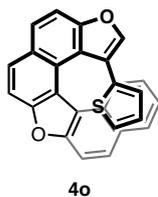


4n was prepared following general procedure **B** using **3n** (42.1 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4n** (35.5 mg, 95% yield) as a deep purple oil.

Data for **4n**

R_f: 0.80 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, $c = 7.01$) = -2464.74; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.21 – 8.13 (m, 1H), 8.04 (d, $J = 8.7$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.96 (s, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.78 – 7.71 (m, 3H), 7.36 – 7.24 (m, 2H), 6.53 (dd, $J = 1.8, 0.8$ Hz, 1H), 5.51 (dd, $J = 3.4, 1.8$ Hz, 1H), 5.47 (dd, $J = 3.4, 0.8$ Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.56, 155.28, 153.11, 146.33, 141.49, 140.38, 130.37, 129.14, 128.99, 128.16, 127.85, 127.79, 127.22, 126.28, 125.07, 123.93, 123.06, 121.54, 119.75, 118.46, 118.33, 111.99, 111.54, 111.16, 110.04, 108.23; **HRMS-ESI⁺ (m/z)** : found [M+Ag]⁺ 480.9988, calc'd C₂₆H₁₄O₃Ag requires 480.9988; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{\max} : 254 nm) indicated **80% ee**, **t_{r1}** : 3.76 min, **t_{r2}** : 4.29 min.

(M)-4o

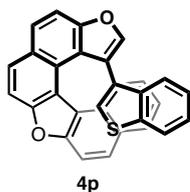


4o was prepared following general procedure **B** using **3o** (43.7 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4o** (28.5 mg, 73% yield) as a deep purple oil.

Data for 4o

R_f: 0.81 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl₃, *c* = 5.69) = -251.05; **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.22 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), (7.88 – 7.80 (m, 3H), 7.76 – 7.67 (m, 3H), 7.33 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.29 – 7.23 (m, 1H), 6.53 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.15 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.10 (dd, *J* = 5.1, 3.6 Hz, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.51, 155.50, 152.99, 141.42, 133.07, 130.31, 129.07, 128.91, 128.09, 127.93, 127.70, 127.03, 126.31, 126.38, 125.36, 125.14, 123.99, 123.56, 122.85, 121.64, 121.02, 120.74, 118.09, 111.93, 111.67, 111.07; **HRMS-ESI⁺ (m/z)**: found [M+Ag]⁺ 498.9758, calc'd C₂₆H₁₄O₂SAg requires 498.9758; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **78% ee**, **t_{r1}** : 3.86 min, **t_{r2}** : 4.54 min.

(M)-4p

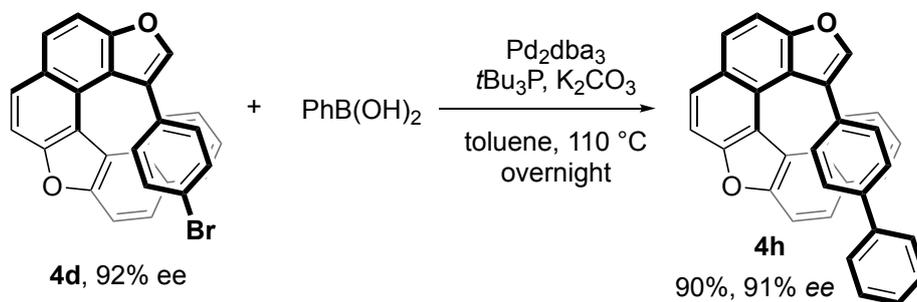


4p was prepared following general procedure **B** using **3p** (48.7 mg, 0.1 mmol) and DBU (74.7 μ L, 0.5 mmol) for 30 min. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 4/100) provided the title compound **4p** (30.8 mg, 70% yield) as a deep yellow oil.

Data for 4p

R_f : 0.70 (10% EtOAc in Pet. Et.); $[\alpha]_D^{25}$ (CHCl_3 , $c = 6.16$) = -227.17 ; **$^1\text{H NMR}$ (400 MHz, CDCl_3)** δ (ppm) 8.09 – 8.01 (m, 3H), 7.96 (d, $J = 8.3$ Hz, 1H), 7.86 (dd, $J = 16.9, 8.7$ Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.42 – 7.36 (m, 2H), 7.24 – 7.16 (m, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 6.96 (t, $J = 7.5$ Hz, 1H), 6.75 (t, $J = 7.8$ Hz, 1H), 6.41 (s, 1H); **$^{13}\text{C NMR}$ (75 MHz, CDCl_3)** δ (ppm) 155.35, 155.19, 153.03, 141.47, 139.06, 137.36, 129.65, 128.97, 128.44, 128.31, 127.85, 127.50, 127.15, 126.86, 125.27, 125.26, 124.49, 123.71, 123.66, 123.28, 123.13, 123.10, 122.05, 121.25, 121.21, 120.57, 117.96, 111.76, 111.48, 110.92; **HRMS-ESI⁺ (m/z)** : found $[\text{M}+\text{Ag}]^+$ 441.0942, calc'd $\text{C}_{30}\text{H}_{16}\text{O}_2\text{SAg}$ requires 441.0944; **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 $^\circ\text{C}$, λ_{max} : 254 nm) indicated **92% ee**, t_{r1} : 4.11 min, t_{r2} : 5.13 min.

4.2.5) General procedure for the derivatization of Suzuki coupling reaction



General Procedure C

A fifteen-centimeter-long sealed tube was charged with **4d** (1.0 equiv) and the phenylboronic acid (1.5 equiv). Tris(dibenzylideneacetone)dipalladium (5 mol%), tri-*tert*-butylphosphine (15 mol%) and the potassium carbonate (2.0 equiv) were added into the tube, followed by toluene (0.1 M). The resulting solution was stirred at 80 °C for 11 hours under argon atmosphere, then the reaction was directly purified via flash column chromatography using eluent as stated.

(*M*)-**4h**

4h was prepared following general procedure **C** using **4d** (46.2 mg, 0.1 mmol) and the phenylboronic acid (18.3 mg, 1.5 equiv). Tris(dibenzylideneacetone)dipalladium (4.6 mg, 5 mol%), tri-*tert*-butylphosphine (3.1 mg, 15 mol%) and the potassium carbonate (27.8 mg, 2.0 equiv) was added into the tube, followed by toluene (1 mL, 0.1M), heating for 11 hours under argon atmosphere. Flash column chromatography eluting with EtOAc/petroleum ether (1/100 to 5/100) provided the title compound **4h** (41.4 mg, 90% yield) as a yellow oil.

Data for **4h**

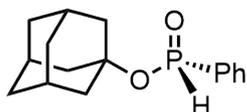
R_f ¹H NMR and ¹³C NMR were identical as previously isolated. **HPLC analysis** (Lux-Amylose-1, Heptane/Ethanol (80/20), Flow : 1 mL/min, Temp : 25 °C, λ_{max} : 254 nm) indicated **91% ee**, **t_{r1}** : 4.16 min, **t_{r2}** : 5.73 min.

4.3) Experimental procedures for chapter 3

4.3.1) Synthesis and characterization of enantioenriched adamantly hydrogenophosphate

A solution of adamantanol (8.5 g, 56 mmol) and pyridine (4.5 mL, 56 mmol) in dichloromethane (100 mL) was added dropwise at 0 °C to a solution of dichloroarylphosphine (56 mmol) in dichloromethane (20 mL). After 15 h at room temperature, water (40 mL) was added slowly at 0 °C. The two layers were separated, and the aqueous phase was extracted with hexane (3 × 20 mL). The organic layers were collected and concentrated under reduced pressure. Hexane (100 mL) was added to the resulting crude product, and the organic phase was washed with 10% aqueous sodium bicarbonate solution (100 mL). The aqueous phase was extracted with hexane (3 × 30 mL). The

organic layers were collected, dried over MgSO₄, filtered, and concentrated under reduced pressure to give adamantlyhydrogenophenylphosphinates.

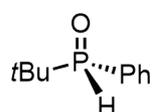


¹H NMR (400 MHz, CDCl₃) δ 1.65 (bs, 6H), 2.13 (bs, 6H), 2.21 (bs, 3H), 7.44–7.56 (m, 3H), 7.79 (d, *J* = 553.3 Hz, 1H), 7.71–7.82 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 30.7 (3C), 35.3 (3C), 43.7 (d, *J* = 4.9 Hz, 3C), 82.1 (*d*, *J* = 8.8 Hz), 128.1 (d, *J* = 13.8 Hz, 2C), 130.4 (d, *J* = 11.6 Hz, 2C), 131.3 (d, *J* = 137.5 Hz), 132.1 (d, *J* = 2.8 Hz); ³¹P NMR (81 MHz, CDCl₃) δ 15.2 (s). Chiral HPLC : analytical separation on Lux Cellulose-2 in hexane/ethanol (1/1) at 1 mL/min and 25 °C with UV detection at 254 nm and polarimetry: **tr**₁ = 6.30 min (S_P)-(-), **tr**₂ = 11.12 min (R_P)-(+), *k*₁ = 1.1 (S_P)-(-), *k*₂ = 2.7 (R_P)-(+), α = 2.46, R_s = 13.3. Semipreparative separation on Lux-Cellulose-2 (250 × 10 mm) in methanol at 5 mL/min and 30 °C with UV detection 235

nm, 0.1 mL of a 175 mg/mL racemic solution injected every 2.4 min. After 700 injections, 6.0 g of (SP)-(-)-3a (ee > 99%) and 6.2 g of (RP)-(+)-3a (ee = 99%).

4.3.2) Experimental procedure for the synthesis and characterization of optically active SPOs

A dry Schlenk tube was charged under an argon atmosphere with a solution of alkyllithium (2.2 mmol) in THF (5 mL) and cooled to $-50\text{ }^{\circ}\text{C}$. A solution of phosphinate (1 mmol) in THF (2 mL) was added dropwise, the reaction mixture was stirred at $-50\text{ }^{\circ}\text{C}$ for 2 h and the solution was warmed to $-20\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at this temperature for 3 h. The reaction mixture was then diluted with Et₂O (5 mL) and NH₄Cl saturated aqueous solution (5 mL). The organic phase was separated off, and the aqueous phase was extracted with AcOEt (2 × 5 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under vacuum. Purification of the crude product by chromatography on a short plug of deactivated silica gel (10% H₂O), using Et₂O/light petroleum/MeOH 4/1/0.05 as eluent, afforded SPO.

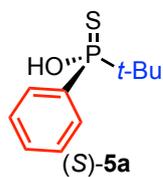


¹H NMR (400 MHz, CDCl₃): δ 7.70–7.66 (m, 2H), 7.58 (dt, *J* = 1.3, 7.1 Hz, 1H), 7.52–7.48 (m, 2H), 7.03 (d, *J* = 450.0 Hz, 1H), 1.15 (d, *J* = 16.6 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 132.5 (2C), 131.0, 129.0 (2C), 128.5, 32.0, 23.5 (3C). ³¹P NMR (81 MHz, CDCl₃): δ 47.43.

4.3.3) Experimental procedures for the synthesis and characterization of (S_P)-(-)-*tert*-butylphenylthiophosphinic acid

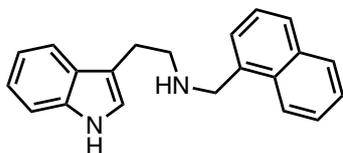
A mixture of *tert*-butylphenylphosphine oxide (99% ee, 45.5 mg, 0.25 mmol) and sulfur (8 mg, 0.25 mmol) was heated under N₂ in dry THF (0.5 mL) for 1.5 h. A complete conversion of the starting material was confirmed. Solvent was pumped off. The residue

was recrystallized in hexane to give pure *tert*-butylphenylthiophosphinic acid (44 mg, 0.206 mmol, 82% yield).



^1H NMR : δ 7.81-7.67 (m, 2H), 7.48-7.44 (m, 1H), 7.39-7.36 (m, 2H), 1.16 (d, J_{HP}) 17.4 Hz, 9H). ^{13}C NMR (100 MHz, CDCl_3) : δ 131.2 (3C), 128.7 (2C), 128.5, 49.9, 24.2 (3C); ^{31}P NMR : δ 98.7.

4.3.4) Experimental procedure for the synthesis and characterization of N-(naphthalen-1-ylmethyl)tryptamine

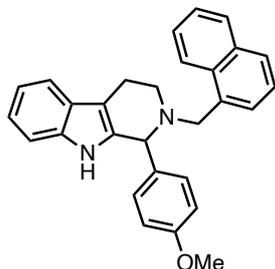


To a solution of tryptamine (1.60 g, 10 mmol) in MeOH (40 mL) was added aldehyde (11 mmol) and the mixture was stirred at room temperature for 36 h. The mixture was cooled to 0 °C and solid NaBH₄ (228 mg, 6 mmol) was added in two portions. Then the solution was allowed to warm to room temperature and was stirred for another 30 min. The solvent was removed, diluted with EtOAc and quenched with saturated aqueous NaHCO₃. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate / petroleum ether = 1/1, with 2% TEA) to give the product as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.64 (br, 1H), 3.00-3.11 (m, 4H), 4.23 (s, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 7.08-7.12 (m, 1H), 7.15-7.20 (m, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.34-7.45 (m, 4H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.80-7.83 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.10 (br, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 25.7, 49.8, 51.4, 111.1, 113.7, 118.8, 119.2, 121.9, 122.0, 123.5, 125.3, 125.5, 125.8, 126.0, 127.3, 127.6, 128.6, 131.7, 133.7, 135.8, 136.3.

4.3.5) Experimental procedures for the synthesis and characterization of Pictet-Spengler reaction

A mixture of *N*-α-naphthylmethyl tryptamine (0.1 mmol), catalyst (0.002 mmol), 4 Å molecular sieves (0.15 g, powdered) in 1 mL toluene was stirred for 5 min at room temperature under a nitrogen atmosphere. Subsequently, aldehyde (0.3 mmol) was added, and the mixture was stirred at rt for the appropriate time. The reaction was

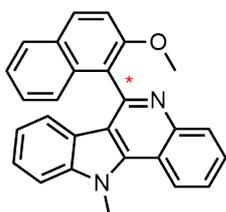
monitored with TLC. After the reaction was completed, the reaction mixture was directly purified by flash column chromatography (ethyl acetate / petroleum ether = 1/15 to 1/8, with 2% TEA) to give the desired product.



1-(4-methoxyphenyl)-2-(naphthalen-1-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole

^1H NMR (400 MHz, CDCl_3) δ 2.63-2.86 (m, 3H), 3.17-3.22 (m, 1H), 3.75-3.78 (m, 4H), 4.29 (d, $J = 13.6$ Hz, 1H), 4.64 (s, 1H), 6.87 (d, $J = 8.4$ Hz, 2H), 7.06-7.21 (m, 3H), 7.30-7.55 (m, 8H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 48.2, 55.2, 56.4, 64.5, 109.2, 110.8, 113.9, 118.2, 119.3, 121.4, 124.7, 125.2, 125.5, 127.1, 127.2, 127.6, 128.3, 130.5, 132.3, 133.2, 133.7, 134.99, 135.04, 136.2, 159.4.

4.3.6) Experimental procedures for the synthesis and characterization of 6-(2-methoxynaphthalen-1-yl)-11-methyl-11H-indolo[3,2-*c*]quinolone



A mixture of 2-(1-methyl-1H-indol-2-yl)aniline (45.0 mg, 0.2 mmol) and 2-methoxy-1-naphthaldehyde (56.0 mg, 0.30 mmol) and catalyst (10 mol%) was stirred under N_2 in dry toluene (2.0 mL) at room temperature for 72 h. Then, DDQ (10 equiv) was added in this reaction which was stirred at room temperature for another 24 h. TLC was used to confirmed the consumption of the intermediate and then the solvent was pumped off.

The residue was purified to give pure 6-(2-methoxynaphthalen-1-yl)-11-methyl-11H-indolo[3,2-c]quinolone (44 mg, 0.206 mmol, 82% yield).

6-(2-methoxynaphthalen-1-yl)-11-methyl-11H-indolo[3,2-c]quinolone

¹H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 9.2 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.66 (m, 2H), 7.62 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.56 – 7.34 (m, 6H), 7.19 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.41 (s, 3H), 3.90 (s, 3H).