Stereochemistry and Recent Applications of Axially Chiral Organic Molecules

Stereochemistry and Recent Applications of Axially Chiral Organic Molecules.

Michele Mancinelli,[a] Giorgio Bencivenni,[a] Daniel Pecorari,[a] Andrea Mazzanti*[a]

Dedicated to Prof. Lodovico Lunazzi on the occasion of his 80th birthday

[a] Dr. M. Mancinelli, Prof. Dr. G. Bencivenni, D. Pecorari, Prof. Dr. A. Mazzanti
Department of Industrial Chemistry "Toso Montanari"
University of Bologna
Viale Risorgimento 4 – 40136 Bologna, Italy
E-mail: andrea.mazzanti@unibo.it
https://www.unibo.it/sitoweb/andrea.mazzanti/

Abstract: This minireview covers the literature of the last decade related to the stereochemistry of axially chiral molecules. The first section reviews the use of dynamic NMR and dynamic HPLC for the ranking of the steric size of common organic moieties. The second and third sections describe the recent advances in the preparation of new atropisomeric scaffolds, and in the asymmetric synthesis of stereogenic axes by means of atroposelective organocatalysis.

1. Introduction

"Another possibility - and one at first sight perhaps more acceptable from the point of view of strain of the carbon atoms by which the two nuclei are united - is that the two benzene nuclei possess a common axis, but do not lie in the same plane." [1] In 1922 Kristie and Kenner demonstrated that 2,2'-dinitrodiphenyl-6,6'dicarboxylic acid could be separated into two optically active antipodes due to the frozen rotation about the aryl-aryl single bond. The term "atropisomerism" was then coined by Kuhn[2] in 1933 to define the stereoisomerism due to the hindered rotation about a single bond. The terminology comes from the Greek word "*tropos*" (i.e. "it turns") with the negative prefix "*a*", indicating something that "does not turn", and it has been periodically updated during the decades.

From many points of view the term atropisomerism is strictly correlated with the concept of conformation as defined by D.H.R. Barton in the middle of the 20th century: *"The most general definition of conformation is as follows: the conformations of a molecule (of defined constitution and configuration) are those arrangements in space of the atoms of the molecule which are not superimposable upon each other.*[3]

Atropisomers are indeed molecular conformations where the conformational rearrangement (i.e. racemization) has very high energy barrier, thus very long lifetimes. Being the rate constant related to the temperature at which it is measured (at constant activation energy), the concept of atropisomerism is closely linked with the temperature at which it is considered. Oki defined atropisomers the conformers that interconvert with a half-life of more than 1000 seconds at a given temperature. [4] Therefore, an energy barrier of 24 kcal/mol is well sufficient to allow for the isolation of atropisomers at +25 °C, but the same energy barrier lead to unstable conformations if the temperature is raised by only 20 °C.

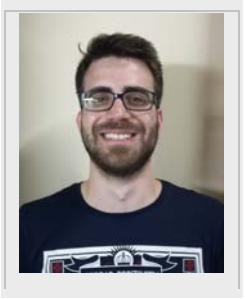
Atropisomerism is an alternative way to introduce chirality into molecules lacking classical stereocenters, and in recent years it has been considered and developed for the design of new axially chiral drugs,[5, 6] following the discovery of many biologically active compounds with axial chirality.[7]

Due to the growing importance of enantiopure axially chiral compounds, many efforts have been devoted to the discovery of new atropisomeric scaffolds, and to the search of atroposelective reactions.[8] Within this realm, the atropo-selective organocatalytic approach is a raising topic in the recent literature.[9-10]

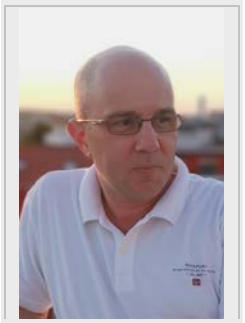
The first section of the present review covers the more classical field of atropisomerism, where conformational analysis of stereogenic axes of different bis-aromatic systems allows to evaluate the steric hindrance caused by a variety of chemical moieties. The second section covers the preparation of stable atropisomers with different atom combinations generating the stereogenic axis, whereas the third part shows some recent examples of atropisomeric compounds where stereogenic axes are forged by atroposelective organocatalytic reactions. The selections presented in this minireview (mainly related to the literature of the last decade) reflect the personal interests of the authors, so that other excellent examples may not have been reported.

Michele Mancinelli graduated in Chemistry at the University of Camerino in 2005 and received his Ph.D. degree in Chemistry from the University of Bologna in 2009. After a postdoctoral period, he became in 2019 a Fixed-term researcher in the Department of Industrial Chemistry "Toso Montanari", Rimini. His research interests cover the preparation of atropisomers with B-C stereogenic axes, atropisomeric drugs, and the determination of their absolute configuration by Electronic and Vibrational Dichroism.

Giorgio Bencivenni graduated in 2003 in Industrial Chemistry at the University of Bologna, and in 2008 he obtained his Ph.D. in Chemistry. From 2008 to 2014 he has been post-doctoral associate. In 2015 he became fixed-term Senior Assistant Professor at the Department of Industrial Chemistry "Toso Montanari" of the University of Bologna. From 2018 he is Associate Professor of Organic Chemistry. His research interests are mainly focused on atroposelective organocatalytic transformations and vinylogous reactivity.



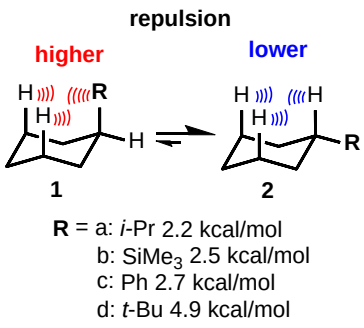
Daniel Pecorari received his master degree at the University of Bologna in Industrial Chemistry in 2017. He then moved to the University of Ferrara. From 2018 he is a Ph.D. student in the Department of Industrial Chemistry "Toso Montanari", University of Bologna. His research interests are in organic asymmetric systems, focused on atrop-isomeric drugs.



Andrea Mazzanti graduated in 1994 and in 1999 obtained his Ph.D. in Chemistry at the Department of Organic Chemistry "A. Mangini", University of Bologna. He became Assistant Professor in 2001 and Associate Professor in 2010. From 2018 he is Full Professor of Organic Chemistry in the Department of Industrial Chemistry "Toso Montanari", University of Bologna. In 2004 he has been recipient of the "Ciamician Medal" of the Organic Chemistry Division of the Italian Chemical Society, and in 2013 of the Award "Structural Determination of Organic Compounds" from the same Division of Organic Chemistry. His whole career is dedicated on the conformational analysis and structural characterization of organic compounds, with a particular focus on the preparation of novel atropisomeric molecules and on the determination of the absolute configuration of organic compounds.

2. Steric factors

Steric hindrance plays a key role in the rotational transition state for bond rotation (racemization in the case of classic atropisomers). A way to rank the different steric hindrance of common moieties was therefore required in order to allow to forecast the thermal stability of novel atropisomeric moieties. For many years the most popular benchmarks for steric hindrance has been the so-called *A-values*.[11-13] This scale is based on the free energy differences between the axial and equatorial conformations of monosubstituted cyclohexanes (Scheme 1). As any other scale, however, it has its built-in limits. The main is related with the underlying geometries, where the axial substituent to be evaluated slightly interferes with two hydrogen atoms in the axial positions.



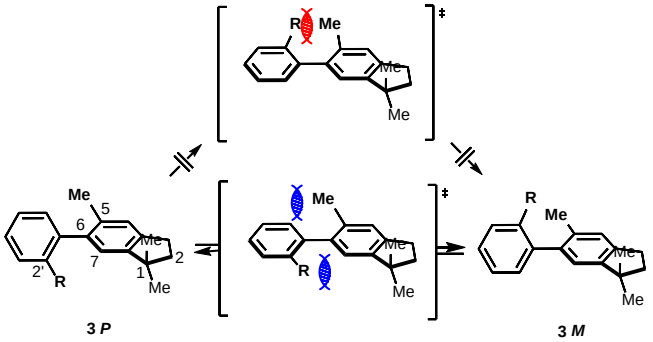
Scheme 1. Model proposed for the *A-value* scale of steric hindrance.

This lateral contact causes friction, rather than to give rise to true repulsive forces. As a consequence, the *A-values* of numerous prominent substituents fall in the 0 – 1 kcal/mol range and only few exceeds the 2 kcal/mol limit (Scheme 1: 2.2, 2.5, 2.7, 4.9 kcal/mol, for isopropyl, trimethylsilyl, phenyl and *tert*-butyl, respectively). It should be also kept into account that the accuracy in the high energy range of this scale is limited by the Boltzmann distribution, that makes negligible the population of the axial conformation when its energy is bigger than 3.0 kcal/mol (axial conformer population less than 0.6%).

On the other hand, chemical reactions are influenced by steric hindrance when a "not guilty" molecular fragment gets in the way of the substrate-approaching reagent, without being actively involved in the transformation event. For this reason, a steric scale based on transition state models is a better simulation of a real situation. The structure of a planarized biphenyl carrying at one *ortho*-position a substituent X that collides with a hydrogen atom (or another substituent X') in the *ortho'*-position across the space mimics this kind of scenario more faithfully than the cyclohexane model. To quantify such steric effects, the rotational barrier of smartly designed bis-aryl compounds merely needs to be determined.

Following Christie and Kenner's first example, there were many further investigations,[14] mainly based on measuring racemization rates or mutarotation of highly substituted biphenyls, with aryl-aryl rotational barriers greater than about 20 kcal/mol. This usually meant the compounds were biphenyl derivatives with three or four *ortho*-substituents around the stereogenic axis, although, it was soon evident that two suitably large *ortho*-substituents could provide sufficiently long lifetimes.[15-18]

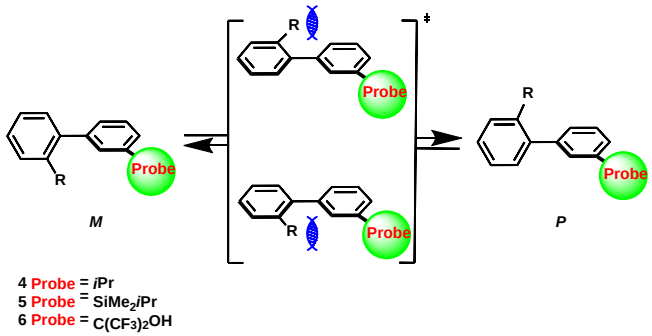
With the advent of variable-temperature NMR (dynamic NMR or DNMR) spectroscopy,[19] racemization barriers much lower than 20 kcal/mol could be measured, thus many more compounds with one *ortho*-substituent in each ring were studied.[20-25] This phase reached its climax with the systematic study by Bott, Field, and Sternhell (BFS).[26] To detect the racemization rate of the aryl-aryl stereogenic axis, they designed a molecular scaffold containing a chirality probe (Scheme 2) and observed the coalescence temperatures of the two anisochronous methyl signals with high accuracy. The rate constants could be converted into the racemization energy by Eyring equation. To evaluate their data, the authors made the plausible assumption that the 5-methyl group and the 2'-X substituent avoid to bump into each other and rather would to face both a small hydrogen atom at the coplanar transition state (Scheme 2).



Scheme 2. The model proposed by Sternhell.

They also postulated additivity of the 2'-X/7-H and 6'-H/5-CH_3 interactions. This second consideration was less obvious but it enabled them to derive X/H increments for all substituents probed. In fact, they needed just to divide the experimentally established barrier of 19.4 kcal/mol for the torsional motion of 1,1,2',5-tetramethyl-6-phenylindane by two in order to obtain the H/CH_3 increment. All further X/H increments resulted by the subtraction of this number (9.7 kcal/mol) from the other barriers. On the basis of the contribution of each substituent to the experimental barrier, they proposed the concept of the effective van der Waals radius of a substituent.

However, some calculations in 2002 [27] suggested an activation energy of 17.6 kcal/mol for the racemization of 2,2'-dichlorobiphenyl, whereas a rotational barrier of 13.0 kcal/mol should be derived from the BFS approach. This observation questioned the accuracy and reliability of the additive rule. In the same period it was shown that the rotational barrier of mono-substituted biphenyls could be detected and measured by means of low-temperature DNMR.[28] However, the chemical compounds were *para*-disubstituted phenyl rings and diastereoisomers were observed, thus a different chemical system was developed to come back to the original concept of aryl-aryl racemization barriers. Three stereochemical probes were designed in order to detect the racemization barriers with DNMR. The first one was a simple isopropyl group (Scheme 3, compounds **4**),[29, 30] that allowed the measurement of racemization barrier for a series of *ortho*-substituents.



Scheme 3. Chemical scaffold for the measurement of "*B-values*".

Lineshape simulations of the NMR spectra at different temperatures allowed the accurate determination of many rate constants, hence the activation energies (Figure 1). The observed values confirmed that the aryl-aryl rotation had negligible activation entropy, as usual in conformational processes.[31]

Unfortunately, the isopropyl probe showed its limitations in the cases where the barriers to be measured were very small, mainly because of the small difference in chemical shift of the two methyl groups. A second issue of this probe was the possible buttressing effect[32] exerted on the hydrogen in position 2 by the probe itself. For these reasons the stereochemical probe was updated to isopropyl-dimethylsilyl (Scheme 3, compounds **5**).[33] The longer and more flexible carbon-silicon bond develops a much smaller buttressing effect on the planar transition state and the probe could be used both in the ^{1}H and ^{13}C NMR spectra. A large series of chemical systems were investigated with this probe, yielding the "*B-value*" steric scale, in analogy with the "*A-value*" early proposed (Table 1).[34, 35]

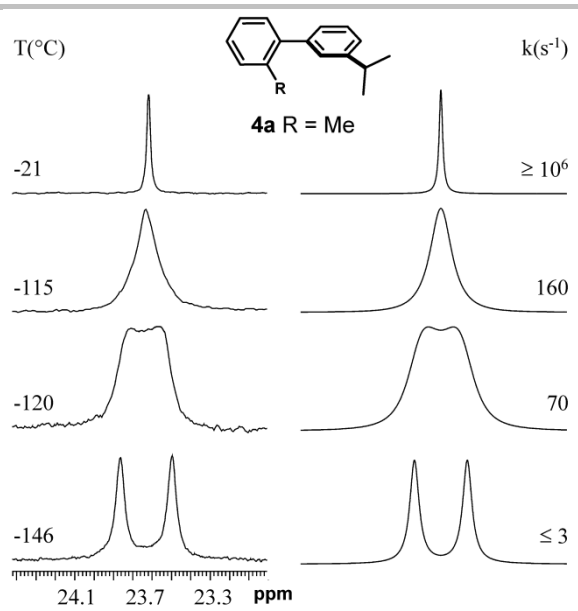


Figure 1. Left: temperature dependence of the ^{13}C NMR (150.8 MHz) isopropyl methyl signal of **4a** in $CHF_2Cl/CHFCl_2$ Right: selected examples of line shape simulation obtained with the rate constants indicated. Adapted with permission from *J.Org. Chem.* **2006**, *71*, 5474-5481. Copyright 2006 American Chemical Society.

Table 1: Summary of B-Values obtained by DNMR (values in kcal/mol).

ortho subst.	$\Delta G^{\neq}$ exp.	$\Delta E^{\neq}$ calc.	*ortho* subst.	$\Delta G^{\neq}$ exp.	$\Delta E^{\neq}$ calc.
Me	7.4[a]	7.1	CHO[b]	10.2[b]	11.0
Et	8.7[a]	8.6	COOH[b]	7.7[b]	8.5
i-Pr	11.1[a]	11.1	COOMe[b]	7.7[b]	8.3
t-Bu	15.4[a]	15.3	MeCO[d]	8.0	8.3
CF_3	10.5[b]	9.2	*t*-BuCO[d]	6.7	7.2
$C(CF_3)_2OH$	16.5[b]	16.9	SCH_3[c]	8.6	8.4
CH_2OH	7.9[b]	7.8	SPh[c]	8.3	8.8
C_6H_5	7.5[b]	7.4	SOPh[c]	8.6	8.1
C_6F_5	7.7[b]	8.1	SO_2Ph[c]	12.8	10.3
NH_2	8.1[a]	8.4	SePh[c]	9.1	9.2
NO_2	7.6[a]	7.8	TePh[c]	9.9	10.2
NMe_2	6.9[a]	6.8	$P(CH_3)_2$[c]	9.1	10.0
$^+NMe_3$	18.1[a]	18.2	$PO(CH_3)_2$[c]	11.8	13.3
F	4.4[d]	4.3	PPh_2[c]	9.4	9.2
Cl	7.7[a]	7.3	$POPh_2$[c]	10.2	11.3
Br	8.7[a]	8.5	$P(C_6H_{11})_2$[c]	11.8	9.5
I	10.0[a]	9.9	$PO(C_6H_{11})_2$[c]	12.7	12.9
OH	5.4[d]	5.3	$Si(CH_3)_3$[c]	10.4	10.0
OMe	5.6[a]	4.5	$Si[CH(CH_3)_2]_3$[c]	12.1	11.2
OCF_3	5.5[b]	4.8	$Sn(CH_3)_3$[c]	9.1	8.8
OCH_2OCH_3	5.7[c]	6.1	$Si(CH_3)_2C_2H_5$[c]	9.9	10.2
$CH=CH_2$	8.2[b]	8.5	$Si(CH_3)_2Ph$[c]	9.8	10.9
C≡CH	6.0[b]	5.3			

[a] ref [33], [b] ref [34], [c] ref [35], [d] ref [30].

During these investigations, it was also shown that DFT calculations could reliably predict the experimental values of the rotational barriers,[36] paving the way to the *in-silico* design of atropisomeric systems based on aryl-aryl stereogenic axes (see the second chapter). A third stereochemical probe was designed to measure the *B-values* of the two smallest chemical moieties, i.e. fluorine and hydroxyl.[37] The new probe took advantage from the use of two diastereotopic CF_3 groups (Scheme 3, compound **6**), that showed huge chemical shift differences in the ^{19}F NMR spectrum, thus allowing to push to the limit the DNMR technique.[38]

In 2015 and 2016 two different scaffold were proposed for the evaluation of steric factors. The basic idea was to raise the rotational barrier to yield stable or metastable atropisomers, where the racemization barrier could be measured, after HPLC separation on chiral stationary phase(CSP-HPLC), with standard techniques and without the need for a chirality probe. Roussel, Farran and co-authors proposed the N-Arylthiazine-2-thione template to evaluate the rotational barriers of a wide series of substituents (Figure 2),[39] whereas Orelli and Roussel proposed the 2,3-dihydro-1H-pyrimido[1,2-a]quinoxaline 6-oxide and the homologous 1,2-dihydroimidazo[1,2-a]quinoxaline 5-oxide as the core to which various *ortho*-substituted aryl rings were connected.[40]

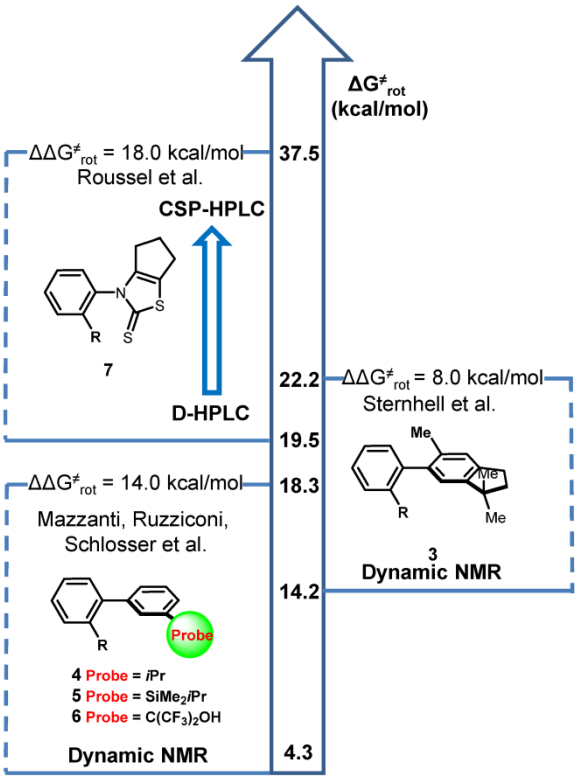


Figure 2. Chemical scaffolds used to evaluate steric factors. Adapted with permission from *J. Org. Chem.* **2017**, *82*, 10188-10200. Copyright 2017 American Chemical Society.

The two different molecular scaffolds allowed the measurement of racemization energies in two completely different energy scales (Figure 2). The DNMR technique allowed to observe small racemization energies, and therefore to reliably consider a negligible entropic contribution in the transition state. The DHPLC and HPLC techniques allowed to measure lifetimes in a more accurate way, but they suffer from problems due to interactions with the stationary phase (DHPLC) and a possible entropy of activation (HPLC). This latter factor is mainly due to the molecular distortion needed in a high energy transition state.[36] A direct comparison between the two more recent approaches and the BFS one allows to observe that the major discrepancies are in the OH/Me/CN triad and in the Me/Cl/Phenyl one (Figure 3).

A subsequent study where 1-aryl-2-iminoazacycloalkanes were used as the chemical scaffold confirmed this trend.[41]

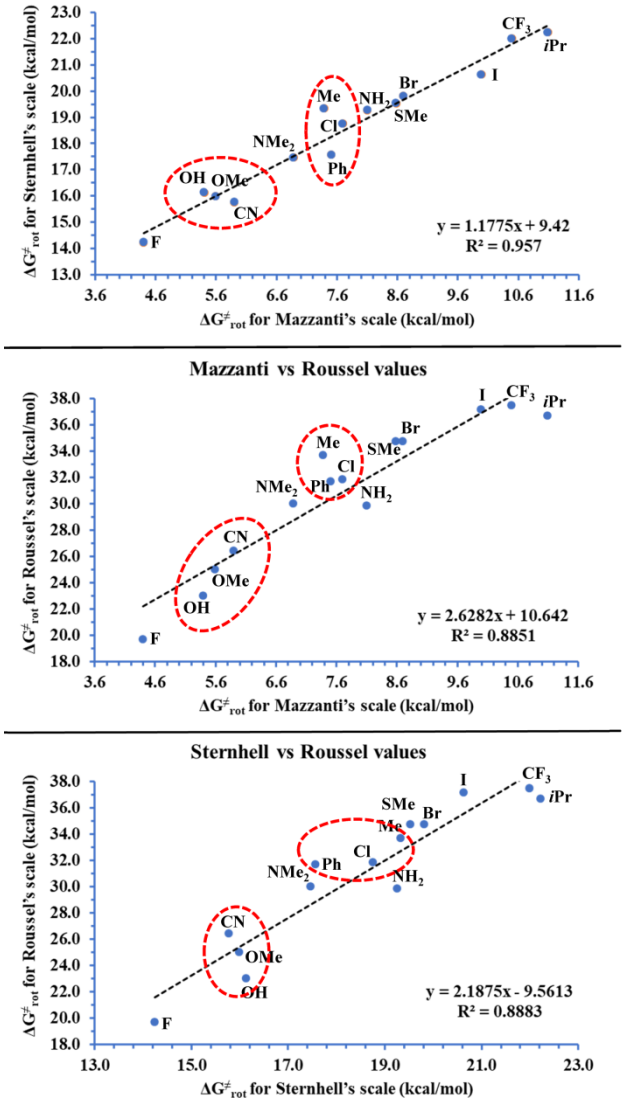


Figure 3. Correlation among the three sets of rotational barriers. Adapted with permission from *J. Org. Chem.* **2017**, *82*, 10188-10200. Copyright 2017 American Chemical Society.

3. Atropisomerism

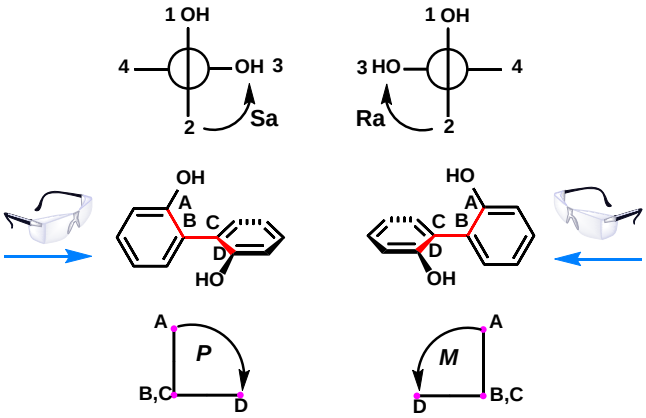
After its discovery in 1922 and the refinement of its definition in 1933, for many decades atropisomerism has been largely overlooked as an "alien" subclass of stereoisomerism, alternative to classical stereogenic centers and not deserving of being a valuable source of chirality, but only an academic curiosity.[42] This situation changed firstly with the preparation of atropisomeric catalysts (e.g. BINAP)[43] and then with the

discovery of many bioactive natural compounds containing stereogenic axes.[44, 45] About a decade ago, Clayden and LaPlante stressed the implications of atropisomerism in drug discovery,[Errore. Il segnalibro non è definito., Errore. Il segnalibro non è definito., 46, 47] and the importance of axial chirality sources in the pharmaceutical realm is still actual.[48-50] In the field of organocatalysis the use of atropisomeric phosphoric acids is now ubiquitous.[51]

Atropisomers generated by the frozen rotation of a C_{sp}^2-C_{sp}^2 stereogenic axis represent the most common cases,[52] but many other combinations have been shown to yield atropisomeric pairs.[53] Hereafter some case studies are presented where different atoms are involved in the stereogenic axis.

3.1. Nomenclature of stereogenic axes

As atropisomerism is a different source of chirality, the standard IUPAC rules for the terminology had to be updated. In actual IUPAC recommendations,[54] two approaches are considered. The first one uses the R_a and S_a stereochemical labels, where the subscript "a" indicates the presence of axial chirality. Once the stereogenic axis is determined, a Newman projection along this axis is used. The four substituents are named in terms of "far" and "close" to the observer and the CIP rules are used to rank the groups within each pair. The stereochemical label is then assigned by considering the "close" substituents having higher priority with respect to the far ones (Scheme 4, top).



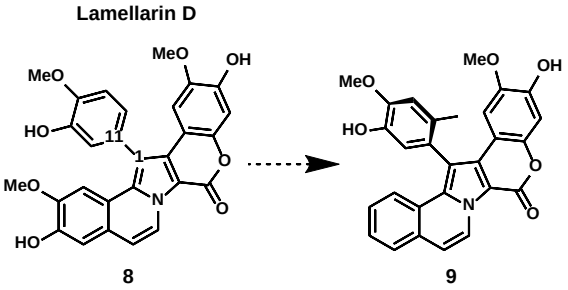
Scheme 4. R_a/S_a and *M*/*P* nomenclature of stereogenic axes.

The second approach relies on the dihedral angle concept to assign the *M* and *P* stereochemical labels. The four points defining the dihedral angle are found by using the standard CIP rules, with the two central points (B and C in Scheme 4, bottom) corresponding to the stereogenic axis. Once defined, the rotation going from the nearest, highest ranking atom (A), towards the far highest ranking atom (D) can be clockwise (thus *P*) or counterclockwise (thus *M*).[55] With respect to the R_a/S_a nomenclature, the *M*/*P* one is applicable to virtually all the cases where a stereogenic axis or an helical disposition of atoms is present (e.g. helicenes). It can be also easily applied to sp^3-sp^2 stereogenic axes, whereas the assignment of the two CIP priorities required for the R_a/S_a nomenclature in the sp^3 branch of the stereogenic axis is less straightforward.

3.2. Carbon-carbon stereogenic axes

Atropisomers due to the restricted rotation of a C-C bond represent the great majority of cases, and their asymmetric synthesis has been periodically reviewed.[56] In the emerging field of atropisomeric drugs some examples of C-C stereogenic axes have been recently proven to yield high-activity compounds.

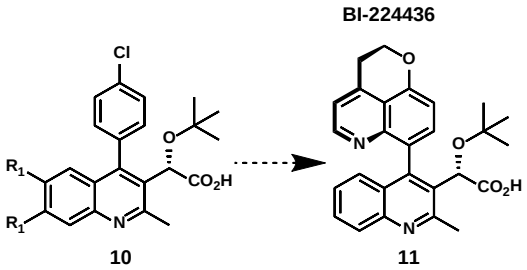
In 2013 the total synthesis of atropisomeric 16-lamellarines was presented.[57] Natural lamellarines (e.g. compound **8** in Scheme 5) are not atropisomeric due to the relatively fast rotation of the C1-C11 carbon bond. In their paper, Iwao and co-authors raised the C-C rotational barrier by adding a methyl in the *ortho*-position of the phenyl ring (compound **9** in Scheme 5).



Scheme 5. Route to atropisomeric 16-Lamellarines.

The two atropisomers were resolved by CSP-HPLC and it was shown that the R_a atropisomer (i.e. *M*) showed an effective inhibition of all protein kinases tested within this study, whereas the S_a (i.e. *P*) atropisomer selectively inhibited only some kinases (GSK-3α/β, PIM1 and DYRK1A).

In 2014, a Boehringer research group presented the preparation of compound **11** as a structure-activity-relationship (SAR) study starting from compound **10** (Scheme 6) to target the HIV-1 integrase.[58]



Scheme 6. SAR development to atropisomeric BI-224436 (**11**)

Compound **11** is a highly hindered bis-aryl system that yield stable diastereoisomers due to the simultaneous presence of a stereogenic carbon and a stereogenic axis. In this case the thermodynamically less stable diastereoisomers due to the stereogenic axis was shown to be the most active compound, and the challenging task of its diastereoselective preparation was realized slightly after. [59]

In 2019, Bristol-Meyers Squibb researchers proposed compound **12** as a very active compound towards the same HIV-1 integrase target. [60] Within this study, they confirmed that atropisomerism at the C-C stereogenic axis was a key factor for the drug effectiveness, being "*R*" (i.e. *M* or R_a) the most active

configuration of the stereogenic axis (Figure 4). This study showed also that the lateral chain was an important factor for the overall activity, in that it was necessary to gain better interactions with the active protein pocket.

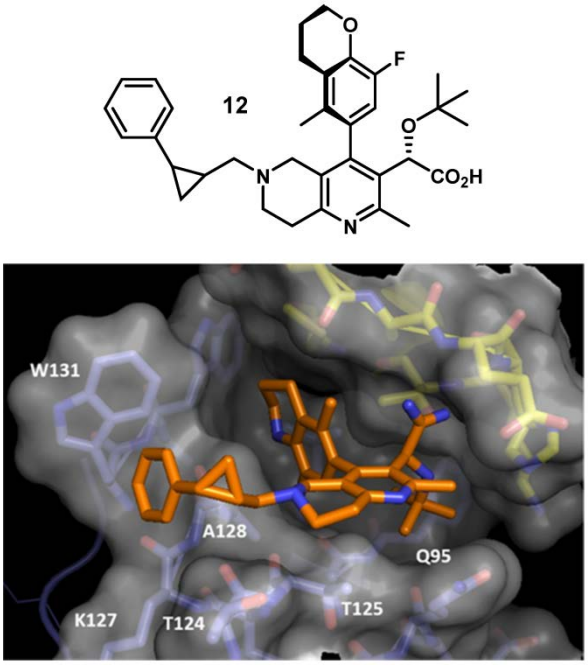
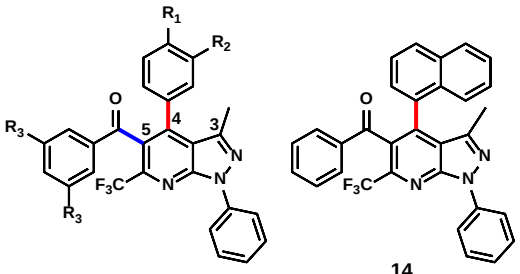


Figure 4. Chemical structure of **12** and its X-ray structure when bound to HIV-1 integrase. Adapted with permission from *J. Med. Chem.* **2019**, *62*, 1348-1361. Copyright 2019 American Chemical Society.

Within the field of new atropisomeric systems, unusual carbon-carbon atropisomers were observed in highly substituted 4-arylpyrazolo[3,4-*b*]pyridines, where a classical aryl-aryl stereogenic axis was associated with a less common C_{sp}^2-CO stereogenic axis (compounds **13a-e** and **14** in Scheme 7).[61] Due to the steric hindrance exerted by the large CF_3 group and by the methyl in position 3 of the pyrazolo-pyridine, both the stereogenic axes had very high barriers to rotation. Despite the absence of any *ortho*-substituents, four slowly interconverting stereoisomers were observed at ambient temperature and the aryl-aryl rotational barrier exceeded the 19 kcal/mol limit. In the presence of a more hindered aryl ring, such as the 1-naphthyl ring, the racemization barrier could not be measured and it was estimated as > 35 kcal/mol.

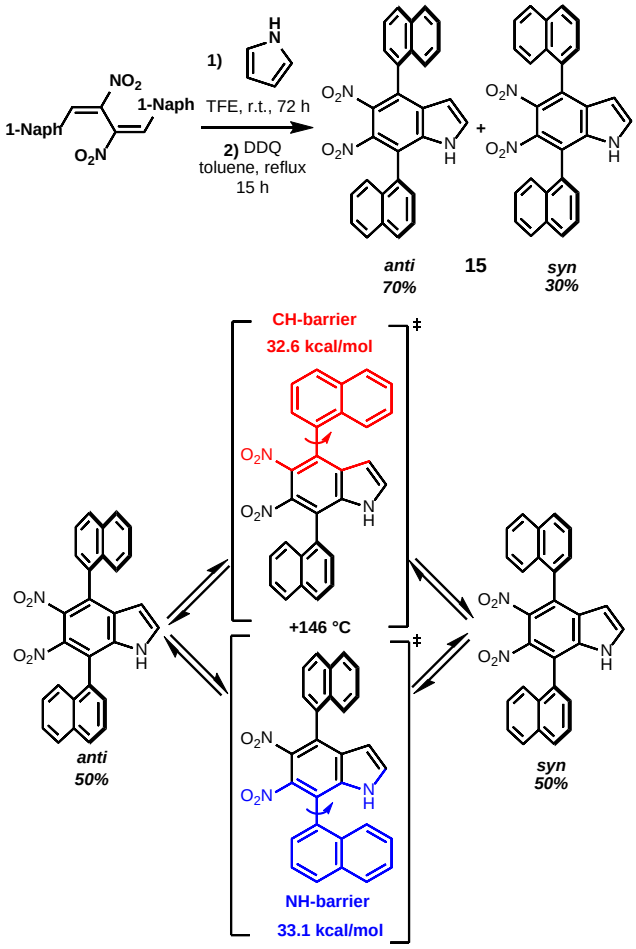


13a R_1 = OMe, R_2 = H, R_3 = H
13b R_1 = Me, R_2 = H, R_3 = H
13c R_1 = H, R_2 = Et, R_3 = H
13d R_1 = H, R_2 = i-Pr, R_3 = H
13e R_1 = H, R_2 = i-Pr, R_3 = Me

14
$\Delta G^{\neq}_{rac}$ **> 35 kcal/mol**

Scheme 7. Pyrazolo-pyridines with two stereogenic axes.

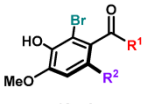
Heterocyclic derivatives with axial chirality were also prepared by benzannulation, yielding 5,6-dinitroindoles (**15**) with two stereogenic axes in positions 4 and 7 (Scheme 8).[53g]



Scheme 8. Atropisomeric bis-aryl indoles.

Due to the steric hindrance exerted by the two nitro groups, the aryl-aryl rotational barriers were found to be higher than 30 kcal/mol. In these compounds a direct comparison of the steric hindrance exerted by the NH and CH moiety to aryl rotation was feasible. Two derivatives where NH and CH moiety were modified to N-Me and C-Br were prepared to selectively raise the rotational barriers of one of the two naphthyl rings. The two diastereomerization energy values were then accurately measured. It was found that the steric hindrance to diastereomerization due to N-H (33.1 kcal/mol) is slightly larger than that of the C-H moiety (32.6 kcal/mol).

In addition to the cumulative effect of the steric size of the *ortho*-substituents on the torsional barriers of stereogenic axes, it has recently been confirmed that the size of the ring that takes part in the formation of a stereogenic axis is closely involved in the activation energy of the rotational barrier. In their paper Miller and co-authors [62] determined the racemization barrier of a series of troponoids (**16a-d**), that were correlated with the values of their analogues benzenoids (**17a-d**, Figure 5). The different constraints due to the different angle of the seven-membered cycle in the transition state lead to a raise in the racemization barrier of 5-9 kcal/mol with respect to the analogue benzenoid compound.



R1	R2	Benzenoids No.	$T_{1/2}$ (s)	$\Delta G^{\neq}$ (kcal/mol)	Troponoids No.	$T_{1/2}$ (s)	$\Delta G^{\neq}$ (kcal/mol)
Ph	Me	**16a**	6×10^{-4}	13.4	**17a**	2×10^{2}	20.9
$N(CH_2)_5$	H	**16b**	0.2	16.9	**17b**	1×10^{2}	20.5
$N(CH_2)_5$	Me	**16c**	5×10^{4}	24.2	**17c**	8×10^{9}	31.2
$N(i\text{-}Pr)_2$	Me	**16d**	2×10^{5}	24.9	**17d**	2×10^{11}	33.2

Figure 5. Correlation among the three sets of rotational barriers. Adapted with permission from *Org. Lett* **2019**, *21*, 2412-2415. Copyright 2019 American Chemical Society.

On the other side, also five-membered rings and not-aromatic rings are able to produce stable atropisomers, [63] such as maleimides **18**. [64] Due to the steric hindrance caused by the two carbonyl moieties, stable atropisomers are generated when two aryl rings are present in position 2 and 3 of the ring (Figure 6). The meso/racemic pair could be easily assigned thanks to the benzyl chirality probe on maleimide, and an atropimerization barrier of 28.6 kcal/mol was measured when the two substituents were 2-methylnaphthyls.

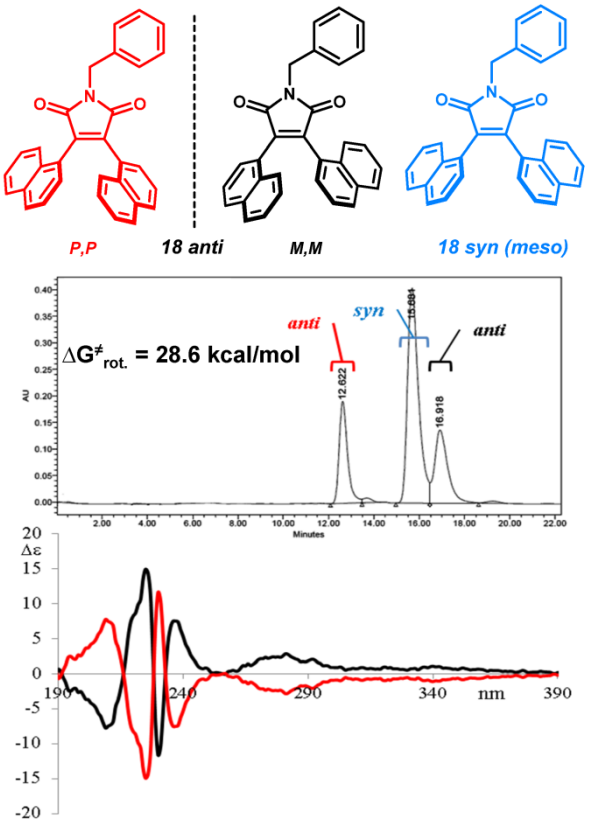
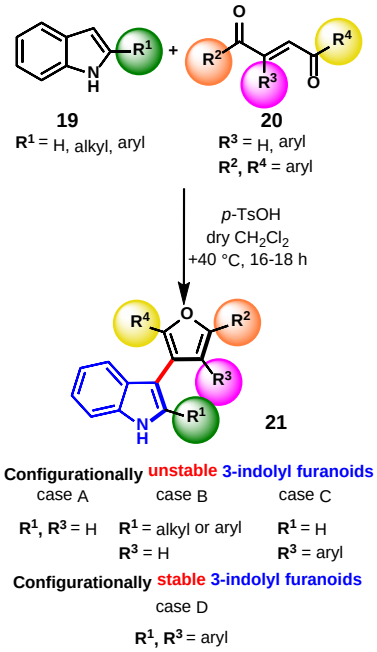


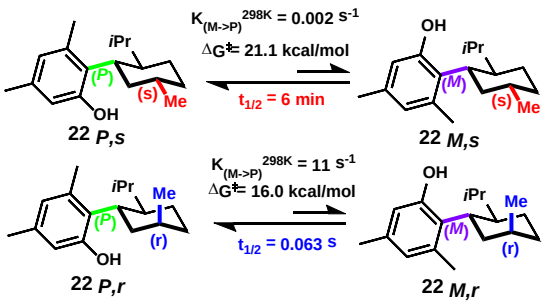
Figure 6. CSP-HPLC separation of the *meso* and atropisomeric pair of compound **18**. Bottom are shown the electronic circular dichroism (ECD) spectra of the two atropisomers. Adapted with permission from *J. Org. Chem.* **2013**, *78*, 3709-3719. Copyright 2013 American Chemical Society.

Stable atropisomers of C-C axes with two five-membered rings have been recently reported for some indolyl furanoids (compounds **21** in Scheme 9).[65] Due to the smaller angle that reduces the steric hindrance, stable atropisomers were obtained only when the C-C stereogenic axis was surrounded by four substituents (mainly phenyl groups) in the *ortho* positions of the furan and in the 2-position of indole. However, although the atropisomers could be separated, their lifetime did not exceed the 30 days limit, and more sterically demanding substituents are required to yield more stable atropisomers.



Scheme 9. C-C axially chiral five-membered rings.

The rotational barriers about the single C_{sp}^2 -C_{sp}^3 bonds are generally very small and the conformational isomers (or atropisomers) due to the stereogenic axis cannot be isolated at room temperature. However, some cases are present in the literature.[66-70] Berber and Clayden have recently shown the preparation of atropisomeric phenylcyclohexanes **22**.[71, 72] The stereogenic axis is generated, by hydrogenation of some cannabidiols, between a sterically hindered phenyl ring and a substituted cyclohexane (Scheme 10).



Scheme 10. Atropisomers of phenylcyclohexanes.

In these cases, the conformational control arises from a combination of the steric effect on the substituents on the *ortho*

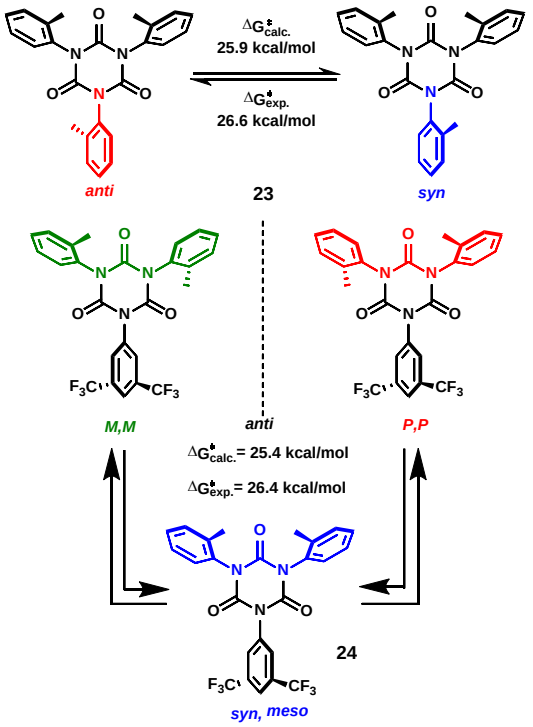
position at the axis of chirality but it is also influenced by the substituents in equatorial or axial position in the cyclohexane ring.

For example, more stable atropisomers were obtained with an equatorial methyl group at the C1 carbon of cyclohexane and hindered *ortho* substituents in the aromatic branch (21.1 kcal/mol, from **22-*M,s*** to **22-*P,s***), while an axial methyl at the C1 on cyclohexane decreases significantly the rotational barrier (16 kcal/mol, from **22-*M,r*** to **22-*P,r***). Dynamic NMR, EXSY and DFT calculations were employed to analyze different compounds with different steric hindrance, and to rationalize how the barriers are influenced by the equatorial or axial disposition of the substituents on cyclohexane.

3.3. Carbon-nitrogen stereogenic axes

Being the C-C axis the most common source of atropisomerism, also the carbon-nitrogen stereogenic axis can yield thermally stable atropisomers.[73] Barbiturates are the most studied class of biologically active compounds having a C_{sp}^2-N stereogenic axis,[74] but also lactams,[75] imides[76] and azalidine-4-ones.[77] As shown in the first section, C-N axis was employed in some models for the steric evaluation of *ortho*-substituents in the aryl ring,[39] and some organocatalytic atroposelective synthesis have been recently reported.[78, 79]

Isocyanurate is a six-membered ring and, although not aromatic, is nevertheless a rather rigid system. DFT calculations predicted that the stereoisomers arising from the restricted rotation of the aryl groups in 1,3,5-tri-*ortho*-tolyl-isocyanurate **23** (see Scheme 11) had an interconversion barrier as high as 25.9 kcal/mol,[80] so small substituents as methyl are large enough to develop stable atropisomers. When one of the three aryl rings is different from the other two (**24**), the racemic pair could be resolved on CSP-HPLC, with a 26.4 kcal/mol racemization barrier.



Scheme 11. Atropisomeric isocyanurates.

When the heteroaromatic scaffold of xanthine was considered,[81] both position 1 and 3 were amenable to generate stereogenic axes with the opportunity to yield stable atropisomers (Figure 7).

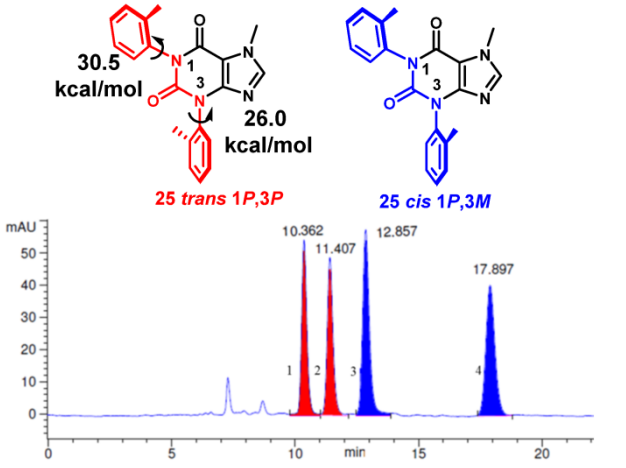
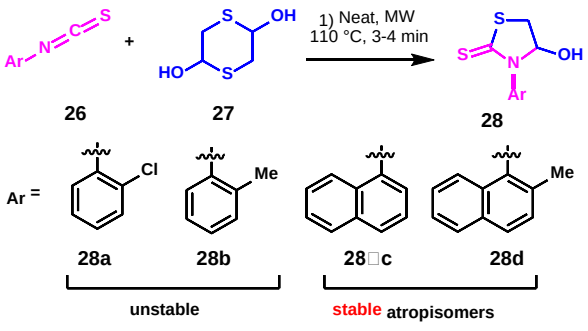


Figure 7. Top: *trans* and *cis* diastereomers of **25**. Bottom: CSP-HPLC chromatogram. Reproduced with permission from *J. Org. Chem.* **2017**, *82*, 6874-6885. Copyright 2017 American Chemical Society.

A class of 1-aryl and 1-3-bis-aryl xanthines was therefore prepared to evaluate the steric requirements needed to produce stable heteroaromatic atropisomers or diastereoisomers with one or two C_{sp}^2-N stereogenic axes. It was shown that a simple *ortho*-tolyl ring (*B*-value = 7.4 kcal/mol) produced enough steric hindrance to rotation to yield stable atropisomers of compound **25** in both positions of the xanthine core ($\Delta G^{\neq}$ = 30.5 kcal/mol for the aryl ring in the 1-position and 26.0 kcal/mol for the 3-position).

A domino reaction between aryl-isocyanates and 1,4-dithiane-2,5-diol[82] was used for the synthesis of axially chiral N-arylthiazolinethione derivatives **28** (Scheme 12).[83] The more flexible five-membered ring of arylthiazolidine-2-thiones implies more flexibility in the transition state, thus lower rotational barriers at the C_{sp}^2-nitrogen stereogenic axis.

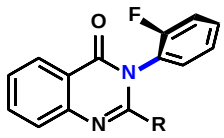


Scheme 12. Atropisomers of arylthiazolidine-2-thiones.

While atropisomeric pairs were observed with *ortho*-substituted phenyl rings (**28a** and **28b**) by DNMR in the +50÷+120 °C range, more stable atropisomers were resolved using the 1-naphthyl (**28c**) and 2-methyl-1-naphthyl (**28d**) ring. Due to the presence of two stereogenic elements, four stereoisomers were observed at low temperature by CSP-HPLC,

and two different barriers leading to racemization and diastereomerization were found to take place. Variable-temperature HPLC on achiral and chiral stationary phases allowed to assign the lower diastereomerization barrier to the configurational inversion at the stereogenic carbon atom, whereas the higher barrier was due to the C-N rotation of the aromatic ring.

In two very recent papers, [53a,84] Kitagawa and Roussel showed an example of C-N atropisomers where the steric hindrance in the aryl counterpart was the very small fluorine atom. 2-Alkyl-3-(2-fluorophenyl)quinazolin-4-ones and 3-(2-fluorophenyl)-4-methylthiazoline-2-thione yield N-aryl atropisomers, whose enantiomers were isolated at ambient temperature (compounds **29a-c** in Scheme 13).

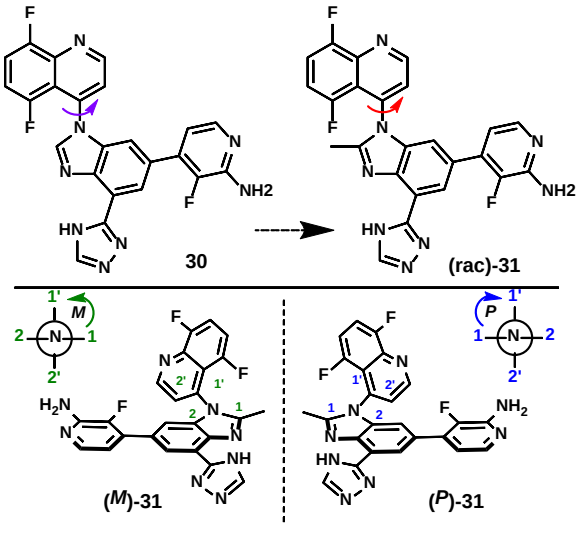


	R	ΔG≠ (kcal/mol)
29a	Et	26.5
29b	Me	26.1
29c	*i*Pr	26.2

Scheme 13. Atropisomeric 1-aryl-quinazolin-4-ones

Some examples of amines bearing C-N stereogenic axes have been presented too. The atropisomers of acyclic amines bearing a bulky adamantane moiety and a *ortho*-disubstituted phenyl ring could be resolved by complexation with an enantiopure palladium complex. [85] Their resolution could be exploited also by simple crystallization due to the tendency to produce conglomerates.

In 2018 Perreault and co-authors from Gilead Science proposed an atropisomeric drug as a selective inhibitor of PI3Kβ kinase. [86] Starting form a known active compound (**30** in Scheme 14), the rotational barrier of the difluoroquinoline ring was raised to ≈35 kcal/mol by the presence of a methyl in position 2 of the imidazole (compound **31**).



Scheme 14. Preparation of atropisomeric PI2Kβ Inhibitor

Biological tests showed that the *P* atropisomer was 10^2-10^4 times more active towards PI3Kβ with respect to the *M* atropisomer, and by one magnitude order with respect to the starting drug candidate **30**.

In the framework of an investigation of Bruton's tyrosine kinase (BTK) inhibitors, Watterson and co-authors prepared a carbazole derivative as a new candidate. [87] During the early stage of the study, they observed the formation of four interconverting atropisomers by means of CSP-HPLC (Figure 8).

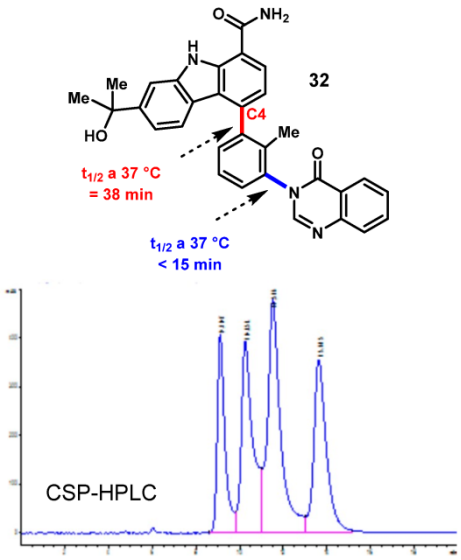
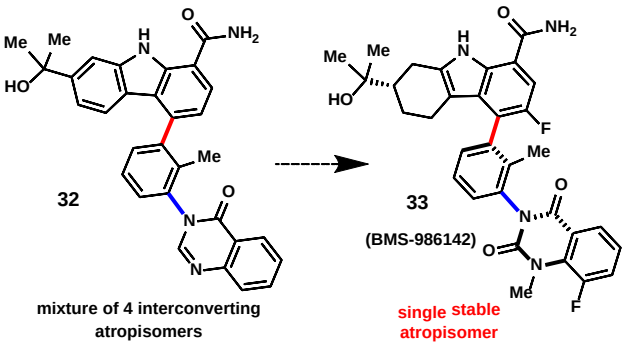


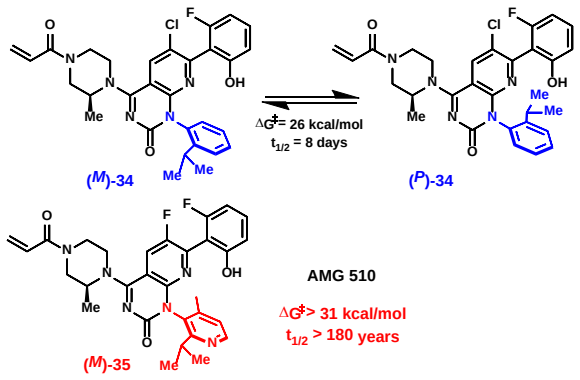
Figure 8. The four atropisomers of compound **32** due to the two stereogenic axes, observed by means of CSP-HPLC. Adapted with permission from *J. Med. Chem.* **2016**, *59*, 9173-9200. Copyright 2016 American Chemical Society.

One of the stereogenic axes was generated by the carbazole-phenyl bis-aryl branch, while the second one was a C-N stereogenic axis with quinazolin-4(3H)-one. However, the lifetimes of these atropisomers were too short to be useful and manageable. Some attempts to *lower* the atropimerization barrier lead to compounds with reduced effectiveness. On the contrary, higher activity compounds were designed by SAR by *increasing* the atropimerization barrier (Scheme 15). The most active compound **33** ultimately possesses a classical stereocenter and two stereodefined stereogenic axes. The latter has been subsequently prepared in an atroposelective and effective way.[88, 89]



Scheme 15. SAR development to BMS-986142.

A similar situation was observed during the preparation of an inhibitor of KRAS^{G12C} protein. [90] The main candidate aza-quinolinone **34** (Scheme 16) showed very good activity, but its development as pure substance was hampered by atropisomerism with a low energetic barrier (26 kcal/mol), yielding undesired racemization in a few days.



Scheme 16. SAR development to AMG 510.

The C-N rotational barrier was raised by varying the pattern at the 2 and 6 position of the aromatic ring, until compound **35** was identified as a stable atropisomer with very good biological parameters (cellular assays, permeability and oral bioavailability).

3.4. Carbon-boron stereogenic axes

Azaborines are aromatic compounds where the carbon-carbon aromatic bond has been substituted by the isoelectronic boron-nitrogen moiety.[91] The ionic component of this bond significantly alters both molecular and solid-state electronic and optical properties of the system by modifying the character of the frontier molecular orbitals, and the intermolecular interactions present in solid phases. The feasibility of a thermally stable boron-carbon stereogenic axis has been shown in 2016 for compound **36** (Figure 9).[92]

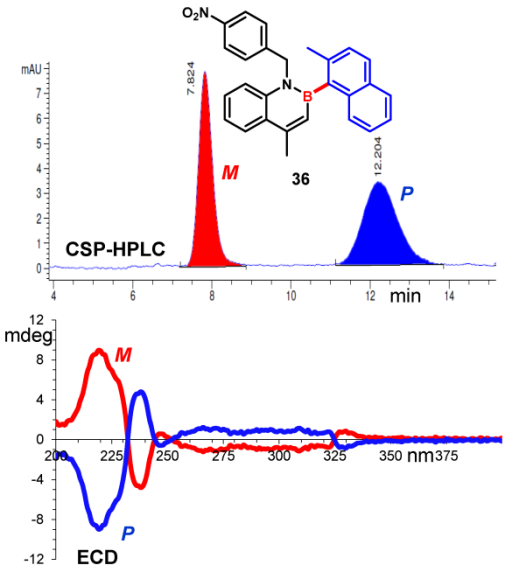


Figure 9. CSP-HPLC separation of the two atropisomers of **36,** and their corresponding ECD spectra. Adapted with permission from *Org. Lett.* **2016**, *18*, 2692. Copyright 2016 from American Chemical Society.

While the endocyclic B-N bond length was similar to the carbon-carbon one, the C_{sp}^2-boron bond distance was found to be 1.58 Å, longer than the isostere carbon compound. This suggested that the rotational barrier was lower than that of a classical aryl-aryl compound. Indeed, the atropimerization energy barrier was found to be smaller by about 6 kcal/mol in the medium-energy range (i.e. 19.0 kcal/mol vs 25.2 kcal/mol of the C-C isostere). However, using highly hindered aryl rings, such as 2-methylnaphthyl (compound **36**), the two atropisomers could be effectively resolved on CSP-HPLC (Figure 9).The B-N rotational barrier was determined as 33.0 kcal/mol by monitoring the racemization of an enantiopure sample, whereas the racemization barrier of the analogous bis-aryl compound cannot be determined because it exceeded 40 kcal/mol. DFT calculations had suggested that the rotational energy difference between the two compounds was within the 12-14 kcal/mol range (thus about 46 kcal/mol for the aryl-aryl compound).

To evaluate the value of this difference a different scaffold was designed in order to lower the C-B rotational barrier, still maintaining the thermal stability of the atropisomers (Figure 10).[93]

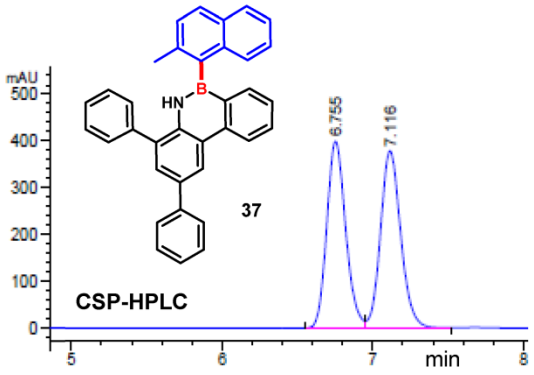


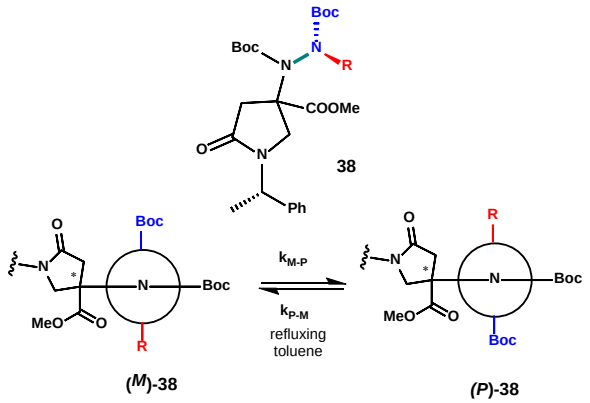
Figure 10. CSP-HPLC separation of the two atropisomers of **37**. Adapted with permission from *J. Org. Chem.* **2019**, *84*, 12253-12258. Copyright 2019 American Chemical Society.

A racemization barrier of 26.0 kcal/mol was determined in the analogue of a 1-1'-binaphthyl compound (compound **37**, DFT calculation had suggested 25.3 kcal/mol), whereas the barrier for the analogous isostere was estimated as larger than 38.0 kcal/mol (calculated value 38.0 kcal/mol). Considering the benchmark results of DFT calculations for **37**, the real C-C barrier could be estimated as about 39 kcal/mol. This result showed that the longer C-B bond had a huge influence on the thermal stability of C-B atropisomers, being the energy barrier smaller by about 12-13 kcal/mol with respect to the C-C analogues.

3.5. Nitrogen-nitrogen stereogenic axes

N-N stereogenic axes are uncommon and scarce literature is present. Rinaldi and co-workers have recently synthetized novel atropisomers with hindered rotation around a N-N bond, in a synthetic procedure to obtain α-amino acids containing a quaternary stereogenic centre (compound **38** in Scheme 17).[94] In this strategy the alkylation on one nitrogen atom of one hydrazidic moiety hinders the rotation of the N-N bond, thus

driving the four substituents in a perpendicular conformation, with total loss of conjugation between the two nitrogen atoms.



Scheme 17. Axially chiral hydrazines

The steric hindrance to rotation raises the rotational energy barrier up to 31.3 kcal/mol This unusual resistance to atropimerization for a nitrogen-nitrogen single bond was studied experimentally and computationally, ascribing the behaviour mainly to the loss in conjugation between the hydrazidic nitrogen and the Boc group.

3.6. Miscellanea

Some examples of unusual atropisomeric scaffolds have been recently presented in the literature. A series of compounds containing four stereogenic axes were reported in 2018 by Curran and Roussel.[95] Compound **39** [(3Z,9Z)-4,9-dimethyl-5,8-diphenyl-1,2,5,8-dithiadiazecine-6,7-(5H,8H)-dione] was serendipitously isolated during the oxidation of thiazoline-2-thione with metachloroperbenzoic acid. The 10-membered ring contains a CO-CO, two N-C_{sp}^2 and a S-S stereogenic axes. However, only a racemic mixture was observed by CSP-HPLC instead of the expected 16 stereoisomers, and the racemization barrier was determined as 24.7 kcal/mol at +30 °C. DFT calculations allowed to determine the pathway to racemization, that requires rotation about all the four axes. Due to the presence of four stereogenic axes, each stereoisomer converts into another one by four possible routes, and a four-dimensional distorted hypercube was necessary to visualize the whole stereochemical network (Figure 11). The calculated energies for all the 8 diastereoisomers confirmed that one diastereoisomer (*MPPP*/*PMMM*) was much more stable than the others, in agreement with the structure observed in the solid state by X-ray diffraction. The complete enantiomerization process between the two observed enantiomers proceeds through two different pathways with similar energies and by combination of inversion of the C-C axis and inversion of the N-alkenyl axes.

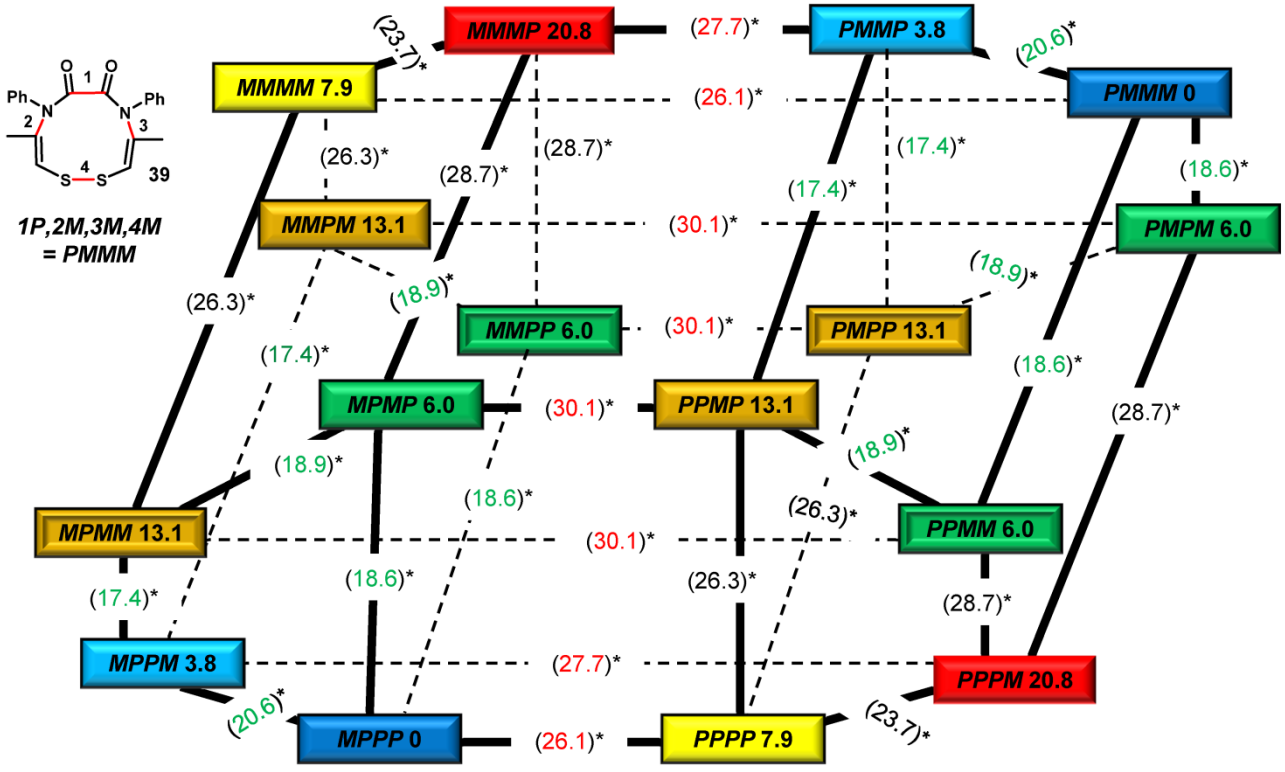


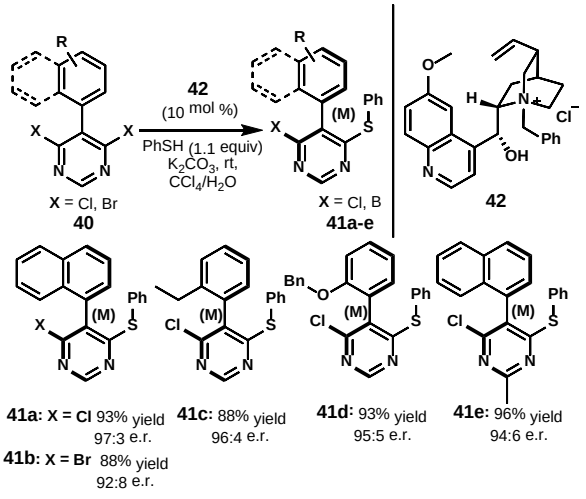
Figure 11. Stereochemical network connecting the 16 stereoisomers of compound **39**. The numbers in parenthesis represent the energy required for interconversion (in kcal/mol). The numbers after the stereochemical descriptors are the ground state energy related to the most stable stereoisomer *MPPP*/*PMMM*. Adapted with permission from *J. Org. Chem.* **2018**, *83*, 7566-7573. Copyright 2018 American Chemical Society.

4. Atroposelective organocatalysis

The use of organocatalysis for atroposelective reactions is a challenging task that nowadays attracts an always increasing numbers of research groups in chemical science.[56,96] As the logical consequence of the classical definition of atropisomers, which has been addressed for the description of frozen rotation in biaryls, the most studied type of molecules possessing high energy barrier to rotation is that of C-C atropisomers. In this field recent advances have been principally concentrated on the development of direct arylation reactions followed by rapid central to axial chirality conversion[97] for the realization of molecular structures that found broad applications as catalyst, ligands for asymmetric synthesis and fine chemicals.[8, 98] Carbon-heteroatom atropisomers received less attention and only in recent years various research groups reported interesting examples for their enantioselective preparation using organocatalysis as the strategy of choice.[96f,99]

Within the atroposelective approach, desymmetrization reactions are widely used for the asymmetric synthesis of atropisomeric bis-aryls.[100] Important contributes have been recently reported by the research groups of Smith, Tan and Akiyama. Three different desymmetrization reactions have been studied, each one with a different catalytic system and with a complete differentiation of the target prochiral molecules. This aspect highlights the versatility of organocatalysis to promote unprecedented atroposelective transformations using different kind of catalytic activation.

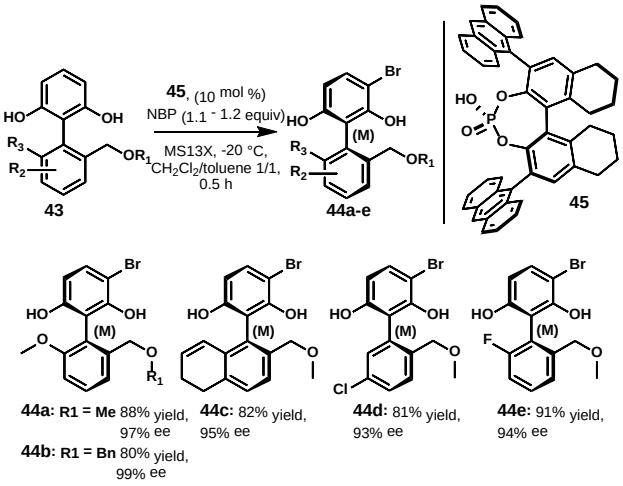
In 2014 Smith developed an asymmetric desymmetrization *via* nucleophilic aromatic substitution for the synthesis of atropisomeric pyrimidines **41a-e** using *N*-benzylquininium chloride **42** as phase transfer organocatalyst (Scheme 18).[101] The reaction proceeded smoothly using thiols as nucleophiles. High enantioselectivity and yields were observed for a large series of substituents. It was demonstrated that the atroposelectivity of the reaction was enhanced by using an excess of thiol because of a kinetic resolution which released a minor amount of the achiral doubly substituted product.



Scheme 18. Smith's approach for the organocatalytic atroposelective nucleophilic aromatic substitution.

The resulting compounds were comparable to biphenyl compounds bearing three *ortho* substituents. Compound **41d** was used for the representative determination of the rotational energy barrier of these bis-aryl pyrimidines. Through a kinetic measurement of the $t_{1/2}$ of racemization in isopropanol at +25 °C, a racemization barrier $\Delta G^{\neq}_{rot}$ = 28.0 kcal/mol was estimated.

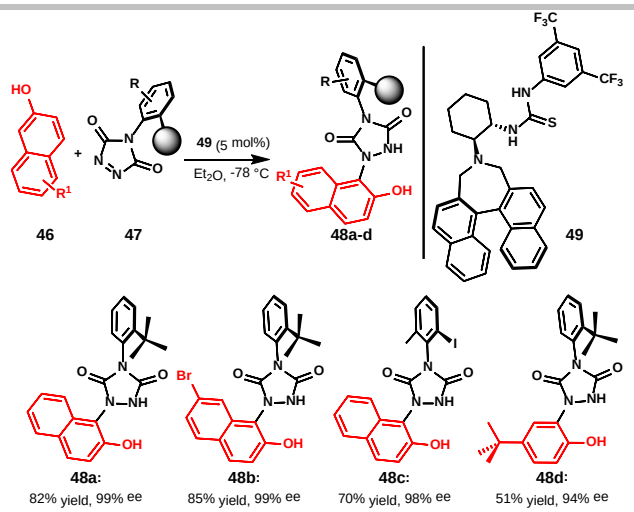
The use of enantiopure phosphoric acids as catalysts revealed to be highly effective when Akiyama in 2013 reported the atroposelective electrophilic bromination of bis-aryl diols **44** (Scheme 19).[102] The reaction was an interesting example of desymmetrization, where the role played by an intramolecular hydrogen bonding interaction between the phenolic hydroxy group and the O-alkyl group are supposed to be fundamental for both the reactivity and the enantioselectivity of the process. Using the partially hydrogenated phosphoric acid **45,** bearing 9-anthryl groups in combination with N-bromophthalimide (NBP), a large number of substrates **43** could be selectively brominated at the 4-position of highly electron-rich 2-arylresorcinol ring.



Scheme 19. Akiyama's atroposelective desymmetrization of biaryls via electrophilic bromination.

Also in this case, an increment of the enantioselectivity of the process was observed, as the result of a kinetic resolution occurring when an excess of brominating agent reacts with the minor enantiomer faster than with the major one.

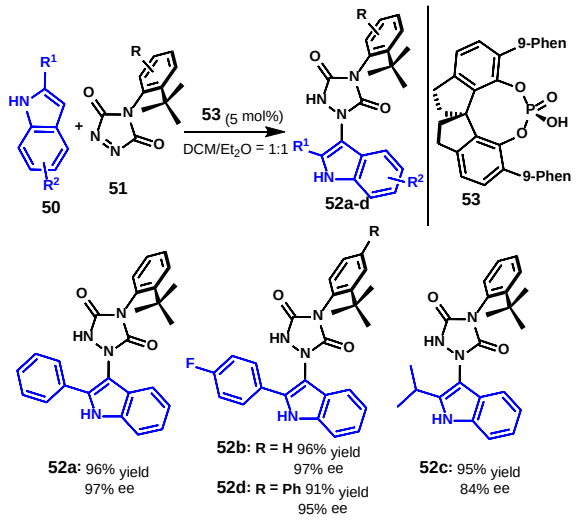
In 2016 Tan and co-authors developed the atroposelective synthesis of urazole-type molecules **48** through a Friedel-Craft type desymmetrization reactions (Scheme 20).[103] 4-Aryl-1,2,4-triazole-3,5-dione (ATAD) was reacted with β-naphthols or indoles under two different catalytic activations. The presence of a bulky *t*-butyl group in the 4-aryl ring makes very slow the C-N rotation. Albeit a symmetry plane is still present, the two faces are enantiotopic and amenable to be asymmetrically functionalized. A chiral tertiary amine (**46**) was used for the reaction of β-naphthols, whereas a chiral phosphoric acid, was employed for the reaction of indoles. Regardless of the activation mode employed, the remote control over the stereogenic axis was realized through a selective H-bonding interaction between one of the prochiral carbonyl group of ATAD and the hydrogen bond donor functionality of the catalyst.



Scheme 20. Tan's atroposelective desymmetrization of ATAD via N-arylation of naphthols.

When β-naphthols were employed, the catalyst of choice was a chiral diamine skeleton functionalized with an axially chiral binaphthyl system, which was effective at 5% loading. Good reactivity and enantioselectivity was observed with several substituents (**48a-d** in Scheme 20). Phenols could be efficiently employed and iodine group can replace the *t*-butyl group as the shielding group in ATAD. An important feature of this desymmetrization is the practical application of these new product as efficient chiral ligand for the Sc-catalyzed addition of indoles to isatins, a reaction that afforded promising values of enantiocontrol and yields.

A 9-phenanthryl-SPINOL-derived phosphoric acid **53** was used as catalyst when indoles were used (Scheme 21). The desymmetrization reaction was very fast at -78 °C and gave easy access to a large number of indole and triazoledione derivatives **52** in high yield and enantiocontrol, highlighting the efficient remote control by the catalyst on the forged stereogenic axis.

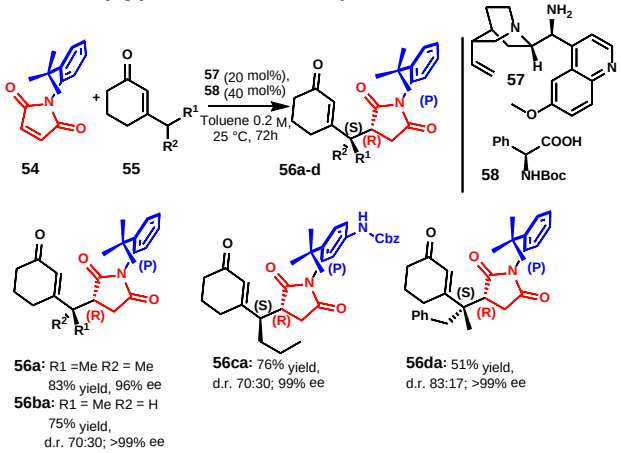


Scheme 21. Tan's atroposelective desymmetrization of ATAD with indoles.

Recently we focused our attention to the realization of organocatalytic desymmetrizations which enables the control of stereogenic axis using organic molecules as catalyst. Our target molecules were compounds bearing a C-N stereogenic axis such as succinimides,[78, 79, 104] C_{sp}^3-C_{sp}^2 atropisomers[105] and alkylidenecyclohexanes,[106] where the axial chirality originates because of the locked rotation around a double bond, rather than for steric interaction with hindered substituents.

N-2-terbutylphenylmaleimides **54** are characterized by the restricted rotation along the carbon nitrogen single bond because of the high steric hindrance exerted by the two carbonyl groups. Similarly with the case of ATAD, the energy required for the rotation ($\Delta G^{\neq}_{rot}$) along the C-N bond is higher than 31 kcal/mol, thus implying that a symmetry plane splits the molecule into two enantiotopic *Re* and *Si* faces.

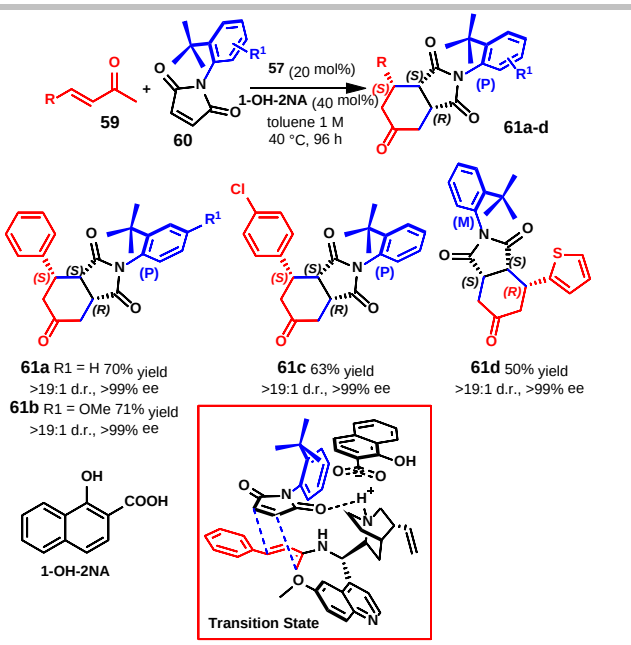
With this consideration in mind, a desymmetrization reaction using the vinylogous addition of 3-alkyl-cyclohexenones **55** as nucleophiles was planned to yield compounds **56** (Scheme 22).[78] The key feature of this reaction was the simultaneous remote control of two chirality sources (centers and axes), realized by means of 9-Amino(9-deoxy)epi-quinine **57** and N-Boc-L-Phenylglycine **58** as co-catalyst.



Scheme 22. Representative examples for the desymmetrization of prochiral maleimides via vinylogous Michael addition. The major diastereoisomer is reported.

After the formation of the vinylogous intermediate the catalyst selectively anchors the maleimide carbonyl group, thus directing the addition to only one of the two prochiral carbons of the double bond. The selective recognition of one of the two enantiotopic sides of the maleimide symmetry plane is realized by this kind of interaction, and an effective desymmetrization was realized. The reaction could tolerate the presence of various substituents on the aromatic ring of maleimide and a large numbers of alkyl cyclohexenones could be employed. Indeed, by reacting enones with two alkyl substituents at the vinylogous position, the simultaneous control of adjacent quaternary and tertiary stereocenters and a stereogenic axis was realized. The diastereomerization barrier of the C-N stereogenic axis was evaluated to be 32.0 kcal/mol at +130°C, in agreement with the value previously reported by Curran on similar systems.[107]

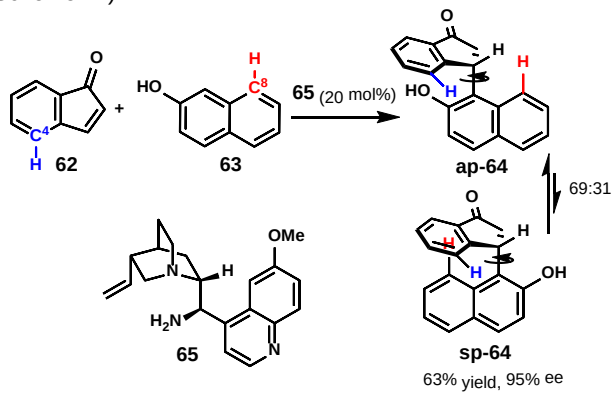
Since maleimides are powerful dienophiles, the feasibility to engage 2-*t*-butylmaleimides derivatives in a formal Diels-Alder reaction with a dienamine was explored.[79] The diene can be derived from α,β-unsaturated linear ketones upon activation by catalyst **57** (Scheme 23).



Scheme 23. Representative examples for the desymmetrization of prochiral maleimides via Diels-Alder cycloaddition. The major diastereoisomer is reported.

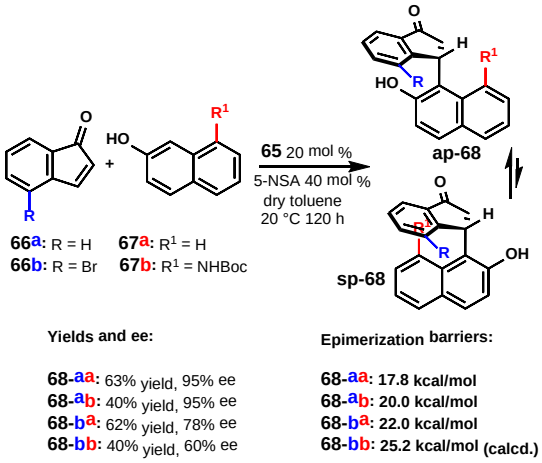
The stereochemistry of the atropisomeric succinimide is influenced by the shielding effect of the *t*-butyl group, which forces the chiral dienamine to engage the *endo* addition exclusively to the bottom face of the dienophile, as depicted in the proposed TS (red box in Scheme 23). The role of the chiral primary amine is fundamental to drive the control of both the classical stereocenters and the stereogenic axis. With this Diels-Alder reaction a large number of enones and maleimides could be reacted under mild reaction conditions, obtaining good yields and excellent diastereo- and enantioselectivities (compounds **61**).

An atroposelective arylation yielding C_{sp}^3-C_{sp}^2 atropisomers, was realized for the first time through the organocatalytic Friedel-Crafts arylation of inden-1-ones with β-naphthols.[105] Using β-naphthol and inden-1-one, it was observed that the reaction yielded compound **64** as an equilibrium mixture of synclinal (*sp*) and antiperiplanar (*ap*) conformational diastereoisomers (Scheme 24).[108]



Scheme 24. Enantioselective synthesis of naphthyl indanones.

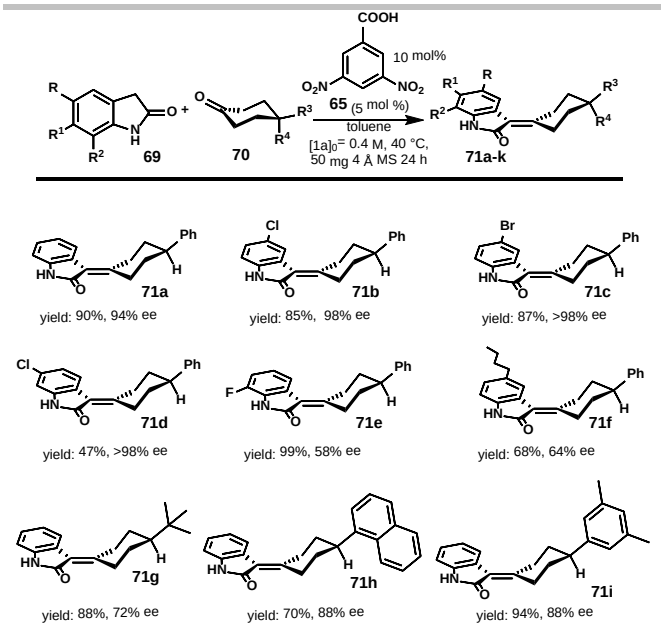
Variable-temperature ^{1}H-NMR allowed to determine that the rotational barrier of the newly formed C_{sp}^2-C_{sp}^3 single bond was only 17.9 kcal/mol, thus only the configuration of stereogenic carbon could be controlled. We then focused on the possibility to increase the rotational barrier to a value that could ensure the first example of an organocatalyzed synthesis of C_{sp}^3-C_{sp}^2 atropisomers. This target was achieved by mixing together inden-1-ones and β-naphthols with increasing steric hindrance at the C4 and C8 position, respectively (Scheme 25). The result obtained revealed a substantial increment of the rotational barrier, that was measured for compounds **67ab** and **67ba**, for which the amount of minor diastereoisomer was still detectable.



Scheme 25. Atroposelective preparation of naphthyl indanones with C_{sp}^3-C_{sp}^2 stereogenic axes.

In the cases of compounds like **67-bb,** where two substituents were simultaneously present in both reagents, the exclusive presence of a single conformational diastereoisomer was observed. This result did not allow the experimental determination of the rotational barrier which was estimated via DFT calculation as 25.2 kcal/mol. The phenomena observed is in line with a dynamic thermodynamic resolution[109] where the newly forged stereogenic center is able to control the stereogenic axis by means of the steric interactions, which are responsible of the energy bias between the two *ap*/*sp* conformers.

Focusing on the development of novel methodologies for the synthesis of axially chiral compounds, our attention was recently directed to the olefination reactions to produce alkylidenecyclohexanes,[12,55] which are, together with allenes,[110] two "classical" examples of axially chiral compounds, fully stable at the stereogenic axis. The primary amine 9-*epi*-NH_2-QDA (**65**) was used to promote the Knoevenagel reaction of oxindoles with 4-substituted cycloexanones to yield enantioenriched cyclohexylidene oxindoles **71** (Scheme 26).[106] In general, good yield and enantioselectivity were obtained and in some cases the enantioselection could be enhanced thanks to a selective precipitation of the racemate from the reaction mixture during the reaction work up. The reaction mechanism was modelled using by DFT calculations, that suggested a point-to-axial chirality conversion after the nucleophilic addition of oxindoles to the iminium ion.



Scheme 26 Knoevenagel condensation of oxindoles with prochiral 4-phenylcyclohexanones.

5. Conclusions and perspectives

The concept of frozen rotation of a single bond yielding separable stereoisomers is almost one hundred years old, but it is living a new youth. The recent advances in DFT calculations showed that it is possible to design novel atropisomers with high reliability, and the pharmaceutical field is eager of new candidate drugs with unconventional chiral features (BTK inhibitors are a paradigmatic example).

However, the concepts of atropisomerism and stereogenic axis must evolve towards a new reality based on the concept of chirality in its broadest sense, and not strictly tied to rigid classifications. What awaits us in the near future of "unconventional chirality"? Recent papers have shown that it is possible to find new and unusual atropisomeric molecular scaffolds, not linked to the classicism of bis-aryls, and that atropisomeric modification of biologically active molecules that do not contain elements of classical chirality is possible. Within the asymmetric synthesis realm, the rising star of atroposelective organocatalysis will certainly be one of the key methods for the asymmetrical preparation of a large number of axially chiral molecules.

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Keywords: Atropisomers • dynamic-NMR • stereogenic axes • organocatalysis.

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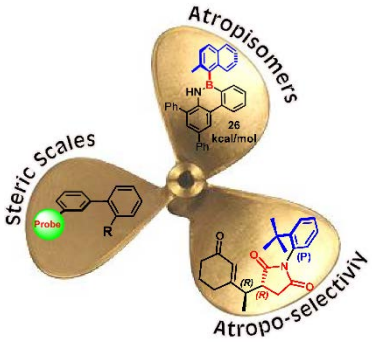
Axial Chirality



This minireview summarizes the recent applications of axially chiral organic molecules. Steric scales ranking, novel atropisomeric scaffolds and recent atroposelective organocatalytic approaches are reviewed considering the literature of the last decade