
Advances in

HETEROCYCLIC CHEMISTRY

VOLUME **105**

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PREFACE

Volume 105 of our series contains four chapters. Alkorta and Elguero (Institute of Medicinal Chemistry Madrid, Spain) and Roussel, Vanthuyne, and Piras (University of Marseille, France), two experienced teams, have combined to consider atropisomerism and axial chirality in heteroaromatics. Conformers arising from (i) restricted rotation about a single bond, and (ii) axial chirality treating stereoisomerism resulting from planar arrangements of four groups in pairs above a chirality axis can be isolated as separate chemical species. These phenomena are of great importance in a wide variety of heterocycles of diverse ring sizes and types. The authors bring together with a remarkable precision this highly diverse subject.

The second chapter is also concerned with stereochemistry but of a very different type. Eusebio Juaristi and Yamir Bandala [of the National University Autonoma Mexico City] discuss anomeric effects in saturated heterocyclic ring systems, bringing together the diverse literature on how these influence the physical and chemical properties of this important group of compounds with particular reference to six membered saturated rings containing hetero atoms.

The third chapter is devoted to the Biginelli condensation which is the most important method for the construction of dihydropyrimidin ring systems. This subject which has expanded remarkably in the last twenty years is thoroughly surveyed by Kawaljit and Kamaljit Singh both of Guru Nanak Dev University, Amritsar, India.

The final chapter covering recent work on regioselective direct arylation at positions two and three of indoles is treated expertly by Lebrasseur and Larrosa (Queen Mary University, London) who demonstrate convincingly why the classically important subject of indole chemistry is still of great importance and interests.

Alan Katritzky
University of Florida

Atropisomerism and Axial Chirality in Heteroaromatic Compounds

**Ibon Alkorta^a, José Elguero^a, Christian Roussel^b,
Nicolas Vanthuyne^b and Patrick Piras^b**

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1. INTRODUCTION

As often happen with chemistry concepts, atropisomerism was introduced with one example, which was both limited and clear. Then, it expanded to a general concept that lost its clarity. For this reason it is necessary to define clearly the subject of this review. Atropisomerism in heteroaromatic compounds refers to restricted rotation about a sp^2 – sp^2 bond between two rings one of them or both being an aromatic heterocycle.

There are a series of IUPAC's definitions worth to remember here:

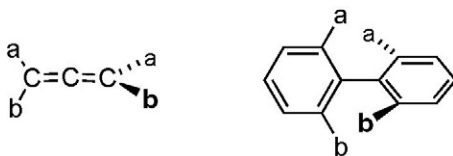
Atropisomers

A subclass of *conformers* that can be isolated as separate *chemical species* and which arise from restricted rotation about a single bond (see *rotational barrier*), for example, *ortho*-substituted biphenyl, 1,1,2,2-tetra-*t*-butylethane

Axial chirality

Term used to refer to stereoisomerism resulting from the nonplanar arrangement of four groups in pairs about a *chirality* axis. It is exemplified by allenes $abC=C=Ccd$ (or $abC=C=Cab$) and by the atropisomerism of *ortho*-substituted biphenyls.

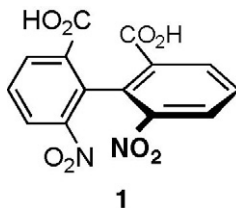
The *configuration* in molecular entities possessing axial chirality is specified by the stereodescriptors R_a and S_a (or by P or M).



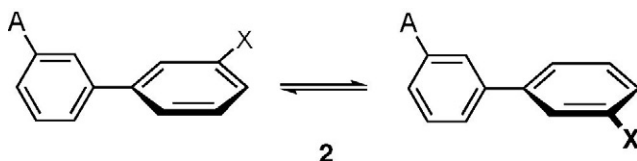
Chirality axis (also axis of chirality)

An axis about which a set of ligands is held so that it results in a spatial arrangement that is not superposable on its mirror image. For example with an allene $abC=C=Ccd$ the chiral axis is defined by the $C=C=C$ bonds: and with an *ortho*-substituted biphenyl the atoms C-1, C-1', C-4, and C-4' lie on the chiral axis.

As it can be seen, IUPAC definition covers more situations than the present review that is restricted to biphenyl heterocyclic analogues. Natta and Farina (72MI1) offer an interesting discussion on this subject (they used the term *atropisomerism*, also found in the old references). In the authoritative book by Eliel et al. (94MI1), Chapter 14-5 is devoted to biphenyls atropisomerism. They report that this type of enantiomerism was discovered by Christie and Kenner in 1922 (22JCS614) in the case of 6,6'-dinitro-2,2'-diphenic acid (1) that they were able to resolve. It was later called (33MI1) “atropisomerism.” An important aspect of all the concepts related to a barrier is (we quote) “It is immediately obvious that the term suffers from all the problems discussed previously: How slow must be the interconversion of the enantiomers (i.e., how long is their half-life) before one speaks of atropisomerism? At what temperature is the measurement to be made? Does atropisomerism still exists when isolation of stereoisomers becomes difficult or impossible but their existence can be revealed by NMR (or other spectral) study and so on.”



This is one of the most delicate points concerning atropisomerism. Oki ([83TS\(14\)1](#)) defined in 1983 the condition for the existence of atropisomerism as one where the isomers can be isolated and have a half-life $t_{1/2}$ of at least 1000 s (this corresponds to 93.3 kJ mol⁻¹ at 300K). According to Eliel *et al.*, though this definition is entirely arbitrary, it is convenient and quite essential if the concept of atropisomerism is to be maintained at all ([94MI1](#)). Consider however the following imaginary example. Compound **2** although nonplanar should have a low racemization barrier being devoid of *ortho*-substituents. It could crystallize with both enantiomers, the *R_a* and *S_a*, in the same unit cell or in separate crystals (spontaneous resolution). In the last case, both enantiomers have been isolated but they racemize very fast in solution: could we speak of atropisomerism?

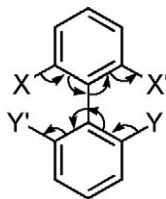


The barrier of rotation about an sp²–sp² bond is related to *ortho* steric effects in heteroaromatic compounds ([88AHC173](#)). In this review (see pages 256–272 in [88AHC173](#)) there is an abundant bibliography about this topic.

Atropisomers are a particular class of conformers that are enantiomers (with the same energy and all the characteristics of enantiomers such as not being superimposable mirror images, opposite ORD, ECD, and VCD) *and* that can be interconverted through a suitable process (see below). We are of the opinion that the occurrence of a stereogenic element is more important than the interconversion barrier, the limit of which is very variable (see cryo-chiral chromatography) and completely arbitrary. We think the suitable term should be “isolable atropisomers” in opposition to “labile atropisomers” when the interconversion is too fast for isolation.

Another point that is important is the occurrence of interconversion of atropisomers (enantiomers) by a process that involves other species than the actual atropisomers. We have observed racemization of atropisomers occurring through a ring opening instead of the rotation along the chirality axis in the intact enantiomers ([88JOC5076](#)). It means that a distinction shall be done between the processes that involve one or several rotations about bonds and those occurring within an unstable intermediate corresponding to a change in the actual

structure of the atropisomers (catalysis, protonation, ring opening-ring closure, etc.).



3

Heterocyclic analogues to biphenyl provide a large variety of geometrical situations in addition to the differences in conjugation. For instance, the interannular distance C–C = 1.48 Å in biphenyls (71T991), N–C = 1.40 Å in *N*-phenylazoles (78T1139), and N–N = 1.36 Å in *N,N*-linked biazoles (84CJC687). In addition, the bond angles (see 3), which are decisive in determining the resulting distances between interacting groups, vary widely from six-membered rings to five-membered rings with different heteroatoms.

In this review an aromatic compound is any five- or six-membered cyclic structure that is formally aromatic or that one of its tautomers or resonance forms is aromatic (76MI1), that is, not only pyridine but also pyridones, and not only thiazole but also thiazolinethiones. We will include systems, like phthalimide, that although nonaromatic have all its ring atoms in a plane or close to it, that is, the critical condition is the absence of sp^3 atoms in the ring, thus 3,5-dihydroxypyrazoles will be considered but their tautomers pyrazolidine-3,5-diones will not.

In Figure 1 are represented some examples of the systems we will discuss in this review. A considerable number of papers have been devoted to the experimental and theoretical determination of the interannular angles in the equilibrium conformation of these systems, they will be cited only when relevant to the discussion.

The systems are 4 (rotation about a C–C bond such as in pyridines); 5 (rotation about a C–N bond such as in pyrroles); 6 (rotation about a N–N bond such as in *N,N'*-bipyrroles); 7 (rotation about a C–C bond such as in pyridines *ortho-ortho'*-linked); 8 (rotation about a C–N bond such as in pyrroles *ortho-ortho'*-linked); 9 (rotation about a N–N bond such as in *N,N'*-bipyrroles *ortho-ortho'*-linked); 10 (rotation about N-metal bonds), and 11 (rotation about N-metal bonds *ortho-ortho'*-linked, although most cases are *ortho-ortho'*-linked, we do not exclude other bridges).

On the other hand, we will not consider the atropisomerism of porphyrines 12 and related compounds that is a very large field in itself (99MI1, 96MI1, 97MI1, 10JPP630, 10MI1, 11JA582). Nor systems such as

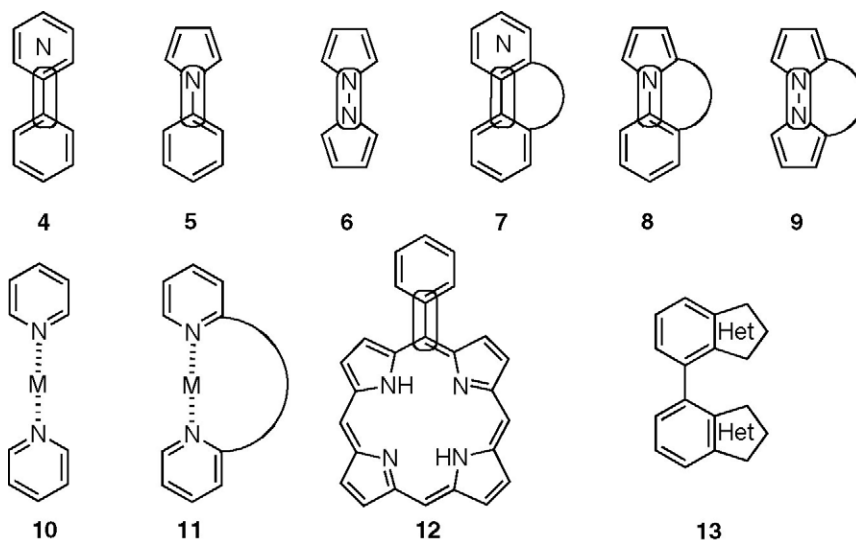


Figure 1. Structures 4–11 covered in this review.

13 where two benzoheterocycles (quinolines, indoles, benzimidazoles, etc.) are linked through their benzene rings, considering that they belong more properly to biphenyls. Note that not necessarily are examples of all the above possibilities.

2. METHODOLOGIES

We will describe the main methodologies used to study atropisomerism taking into account the rotation barriers, first the static methods and then the dynamic ones. Chapter 2 is closely related to Chapter 4 of Wolf's "*Dynamic Stereochemistry of Chiral Compounds: principles and applications*" (08MI1).

2.1 X-ray crystallography

With rare exceptions, X-ray (or neutron) diffraction provides only a static picture of atropisomerism, but this picture is essential for knowing the torsion angle and the preferred conformation. We have reported in Table 1 a summary of important references followed by a more detailed discussion of the most relevant or original.

Alcalde *et al.* (87JOC5009, 94AHC(60)197) reported the X-ray molecular structures of betaines 14 and 15. The first is planar (dihedral angle 1.9°) while the second is almost perpendicular (dihedral angle 84.4°).

Table 1. X-ray structures of compounds related to atropisomerism

Compound	Rings	Bond	Reference
<i>N</i> -(<i>p</i> -Bromophenyl)sydnone	5-6	NC	(63AX471)
1-(2',4'-Dinitrophenyl)-4-bromopyrazole ^a	5-6	NC	(69AX(B)1637)
1-(2',4'-Dinitrophenyl)-4-chloropyrazole ^a	5-6	NC	(70AX(B)380)
1-(3-Methyl-1-isoquinolyl)-3-phenyl-5-hydroxypyrazole ^b	5-6	NC	(71CB2694)
1- <i>p</i> -Nitrophenyl-3-methyl-4-bromopyrazole	5-6	NC	(72AX(B)791)
1-Phenyl-3-methyl-5-pyrazolinone	5-6	NC	(73CSC469)
1-Phenyl-3-hydroxy-5-methylpyrazole	5-6	NC	(73CSC473)
(<i>R</i>)-(+)-4,4'-Dibromo-2,2'-dicarbomethoxy-3,3'-bithienyl	5-5	CC	(75CS204)
(<i>R</i>)-(–)-2,2'-Dibromo-4,4'-dicarbomethoxy-3,3'-bithienyl	5-5	CC	(76CS66)
1-Phenyl-3-dimethylamino-4-cyano-5-aminopyrazole	5-6	NC	(77AX(B)413)
1-(2',4'-Dinitrophenyl)imidazo[4,5- <i>b</i>]pyridine	5-6	NC	(80AX(B)1217)
3-(Methylthio)-4-(<i>p</i> -nitrophenyl)-1,2,4-triazole	5-6	NC	(80JHC1077)
1,2-Bis(8-naphthyl)-1,2,3,4- <i>defl</i> chrysenyl-4-phenyl-1,2,4-triazolidine-3,5-dione	5-6	NC	(88CB1647)
(<i>S,S</i>) and (<i>S,R</i>) Atropisomers of 4-(2-thienyl)-4 <i>H</i> -1,2,4-triazole	5-5	NC	(92CPB220)
3- and 5-(2'-hydroxyphenyl)pyrazoles ^b	5-6	CC	(92JA5039)
3-Phenylpyrazoles	5-6	CC	(92JCS(P2)1737)
3,5-Bis(4-methylpyrazol-1-yl)-4-methylpyrazole ^c	5-5	NC	(93CJC1443)
10,10'-Biacrydinyl-9,9'-dione (6-6 NN), 9-(10'-bromo-9'-anthryl)carbazole (5-6 NC), 9,9'-bicarbazyl aza derivatives of 9-phenylcarbazole ^d	5-5	NN	(93JCS(P2)757) (93JCS(P2)1547)
2,2'-Bithienyl 94AX(C)1942).	5-5	CC	(94AX(C)1941, (94AX(C)1942).
1-Methyl-2-phenylimidazole, 1-methyl-4-phenylimidazole	5-6	CC	(94JHC899)
2,5-Bis(pyrazol-1'-yl)-1,4-dihydroxybenzene ^b (Rh complex)	5-6	NC	(94JOM(467)293)
2,3-Bis(benzimidazol-1'-yl)-1,4-dihydroxybenzene	5-6	NC	(94T12489)
(<i>R</i>)-(–)-1-(1-isoquinoliny)-2-naphthalenemethanol	6-6	CC	(94TA45)
1,1'-Bisisoquinoline (Ru and Os complexes)	6-6	CC	(95JA2000)
optically pure 2,2'-bis(diphenylphosphino)-3,3'-bibenzo[<i>b</i>]thiophene and 3,3'-bibenzo[<i>b</i>]furan	5-5	CC	(96JOC6244)
an atropisomer derived from 3,3'-bithiophene	5-5	CC	(97JOC4465)
1,1'-Bibenzimidazole (5-5 NN) and 2,2'-biindole derivatives	5-5	CC	(97JOM(529)445)
6,6'-Dimethyl-2,2'-bipyridyl	6-6	CC	(98AX(C)661)
2,2'-Bibenzoxazole	5-5	CC	(98AX(C)668)
2-(2'-Hydroxyphenyl)imidazoles ^b	5-6	CC	(98JMS(440)193)
1-(4'-Hydroxyphenyl)-1,2,4-triazole (5-6 CC)	5-6	NC	(99AX(C)1160)
9-(4-Cyanophenyl)carbazole	5-6	NC	(99AX(C)1299)
3-trifluoromethyl-5-(2-thienyl)pyrazole	5-5	CC	(00JMS(526)59)
2,4,6-Tris(azol-1-yl)-1,3,5-triazines	5-6	NC	(01H905)
2-(1'-Pyridin-2'-one)benzimidazole ^c	5-6	NC	(01JPC(B)12759)
3-Phenyl and 5-phenyl-1 <i>H</i> -pyrazole, 3-phenyl-1 <i>H</i> -indazole	5-6	CC	(02HCA2763)
4(5)-Phenylimidazole	5-6	CC	(02JCS(P2)564)

(continued)

Table 1 (continued)

Compound	Rings	Bond	Reference
4-amino-2,6-bis(pyrazol-1-ylmethyl)-5-(pyrazol-1-yl)pyrimidine	5-6	NC	(02NJC926)
1-(2'-Pyridyl and 1'-isoquinolyl)-1 <i>H</i> -benzotriazole	5-6	NC	(03DT992)
Tris(3',5'-dimethylpyrazol-1-yl)- <i>s</i> -triazine	5-6	NC	(03KGS1584)
<i>meso</i> - <i>N,N</i> -Diarylimidazolium and <i>rac</i> - <i>N</i> -aryl-thiazolium salts	5-6	NC	(04EJOC2025)
axially chiral quinazoline ligands	6-6	CC	(04JOC6572)
1-(2',4'-Dinitrophenyl)-1,2,3-triazole ^a	5-6	NC	(05AJC817)
chiral bipyridines	6-6	CC	(05CEJ3049)
(<i>P</i>)-(<i>R,R</i>)-Bipyridine- <i>N</i> -oxides	6-6	CC	(05JOC5235)
Axially chiral <i>N</i> -aryl indoles	5-6	NC	(06OL1097)
3(5)-Ethyl-5(3)-phenyl-1 <i>H</i> -pyrazole	5-6	CC	(06SC349)
2-Phenylbenzimidazole	5-6	CC	(06ZK281)
1,1'-Bipyrrole	5-5	NN	(07JOC9395)
2-Phenyl-2 <i>H</i> -benzotriazole	5-6	NC	(07MI2201)
4-(1 <i>H</i> -1,2,4-Triazol-3-yl)-4 <i>H</i> -1,2,4-triazole	5-5	NC	(08CC4159)
4,6-Bis(pyrazol-1-yl)pyrimidines, 3,6-bis(pyrazol-1-yl)pyridazines			
Cu(I) complexes	5-6	NC	(08IC413)
Atropisomeric 4,4'-biquinazoline Ir(III) complex	6-6	CC	(08ICC564)
<i>N</i> -Arylimidazole part of a macrocyclic pentapeptide	5-6	NC	(09JOC8212)
2,3'-Biindole	5-5	CC	(10CC4554)
Axially chiral <i>N</i> -aryl indoles	5-6	NC	(10CEJ6752)
Polythiophenes	5-5	CC	(10TL2956)

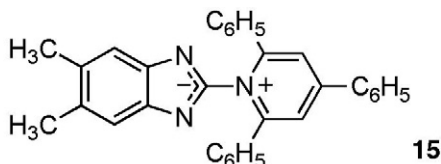
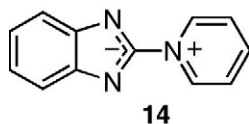
^aThe NO₂ group is on the same side as the pyridine-like N₂ atom.

^bThere is an intramolecular O-H...N hydrogen bond.

^cThere is an intramolecular N-H...N hydrogen bond.

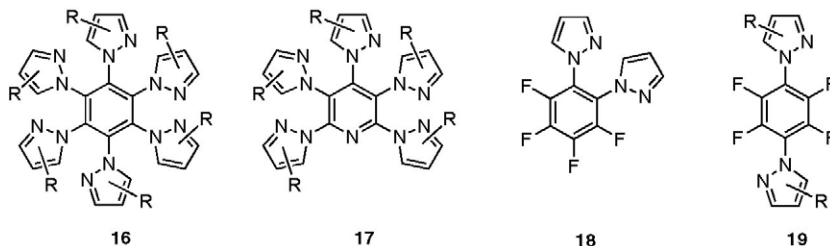
^dPresence of C-H...N intramolecular hydrogen bonds (IMHB).

^eThere is an intramolecular N-H...O hydrogen bond.

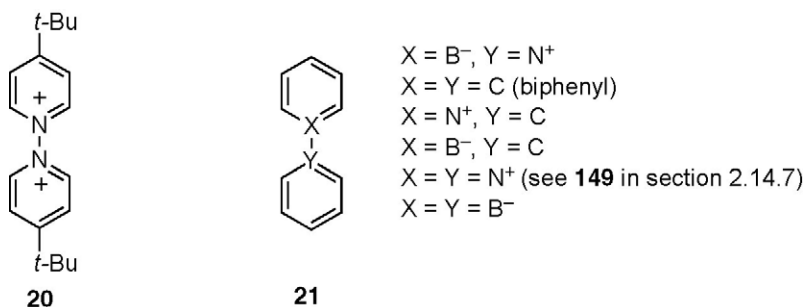


Claramunt et al. dedicated several publications to the study of the structure of polyazolyl-benzenes (propellenes) (97MI2). These compounds present several N-C bonds between five (azoles) and six-membered rings (benzenes). Besides the dihedral angles the position (up or down) of the azolyl residues are characteristic of these compounds: hexa(3,5-dimethylpyrazol-1-yl)benzene (**16**, R = 3,5-dimethyl) (95JCS(P2)1359), hexakis(pyrazol-1-yl)benzene (**16**, R = H) (96JPOC137, 02EJIC3178), 1,2,4,5-tetrakis(pyrazol-1'-yl)-3,6-bis(3'',5''-dimethylpyrazol-1'-yl)benzene (**16**, R = H

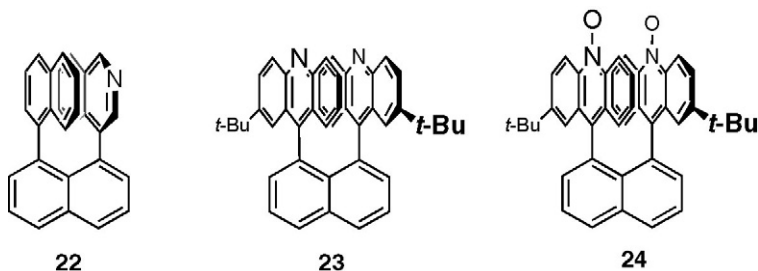
and $R = 3,5$ -dimethyl) (96JPOC717, 99JIP169), polypyrazolylpyridines (17, $R = H$ and $R = 3,5$ -dimethyl) (96T11075), poly(pyrazol-1-yl)benzenes 18 and 19 ($R = H$ and $R = 3,5$ -dimethyl) (97NJC195), and hexa(imidazol-1-yl)benzene (99JMS(478)285).



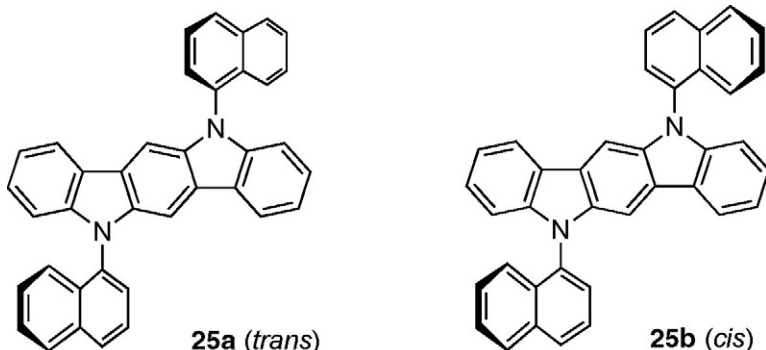
Bock et al. (95CEJ557) determined the structure of 4,4-di(*tert*-butyl)-*N,N*-bipyridinium diperchlorate (20), an analogue of biphenyl with perpendicular pyridine rings. In the following discussion they compare, using AM1 calculations, the rotational profiles of a series of related molecules 21.



Zoltewicz et al. studied in a series of papers the atropisomerism of cofacial pyridine rings and in one of them they described the *anti* structure of 3-aza-1,1':8',1''-ternaphthalene (22) (97T5379).



In a series of remarkable papers Wolf et al. also using a naphthalene to build up cofacial structures described the acridinyl derivatives 23 and 24 (06CCC4242, 08JOC4267).



5,11-Dihydro-5,11-di-1-naphthylindolo[3,2-*b*]carbazole, a hole-transport molecule for organic light-emitting diodes, presents atropisomerism (**25a** and **25b**) (99JA5097). A single-crystal X-ray diffraction analysis on crystals selected from the sublimed product shows that the two naphthyl rings in compound **25** have two different orientations in the solid state, which can be attributed to the coexistence of the *trans* and the *cis* isomers. The occupancy factors for the two sites were found to be approximately 0.50:0.50. Since the *cis* form is chiral, it contains two enantiomers, while the *trans* form is achiral.

Finally, some compounds presenting atropisomerism were determined inside protein cavities, such as C-aryl and C-pyridylimidazoles (03NSB764, 08JMC4122).

2.2 Electron diffraction

Although having plenty of possibilities this technique has been only used once (no example of atropisomers study using MW spectroscopy was reported). Almenningen *et al.*, well known in this field, studied 2,2'-dithienyl founding an angle of twist of 34° (58ACS1671).

2.3 Electronic spectra (visible and UV)

Several authors noted that hindering the planarity (steric inhibition of resonance) modifies the absorption (hypsochromic – blue shift – and hypochromic effects), others using Braude's equation determined the torsion angles θ about the bond linking both rings. According to Braude and Sondheimer (54NAT117, 55JCS3773), the interplanar angle θ is calculated from $\cos^2\theta = \varepsilon/\varepsilon_0$, where ε_0 and ε are the molar absorptivities for a model compound where θ is assumed to be 0° for the studied compound at λ_{\max} of the π to π^* transitions, respectively. Other authors use $\cos\theta = \varepsilon/\varepsilon_0$ (04JPOC686). These relationships apply in cases in which ε_0 is reduced without a concurrent hypsochromic shift (62MI1).

Qualitative conclusions about steric inhibition of resonance were drawn for 1-phenylpyrroles when the 2,5-positions were substituted by methyl groups (loss of coplanarity) (53JCS3802) (see also 65JOC190, 68BCSJ2849). Similar observations were reported for phenyl-1,2,4-triazoles (54JCS4256), for 1-aryltetrazoles (55LA(591)200), for *N*- and *C*-phenylpyrazoles (56G797, 67RTC1249, 95JOC3427) for 1-*p*-nitrophenylpyrazoles (56JOC97), for *N*-phenyl-1,2,3-triazoles and benzotriazoles (58G977, 61CCC67) for *N*-aryl-benzotriazole *N*-oxides (58G1035), for 1-aryl-pyrazoles (59JA5637, 60JOC1355, 63ZOK511), 1-phenylimidazoles (64ZOK632), arylfurans and arylthiophenes (66HCA1794), 2-arylbenzotriazoles (92JA964), 2-(1-pyrrolyl, diazoly, and for triazolyl)-substituted 5-nitropyridines with nonlinear optical properties (94BCJ1936).

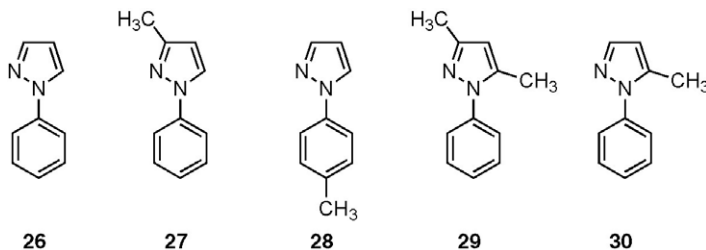
Braude's equation in its most usual form ($\cos^2\theta = \varepsilon/\varepsilon_0$) has been applied to 2-arylindoles (61JOC220), 1-arylpyrazoles (65CHC613, 66BSF3744, 66T2703), 1-arylimidazoles (70CHC194), and 3(5)-phenylpyrazoles (91G477) to calculate the torsion angles.

2.4 Dipole moments

Since the measured dipole moments can be estimated by a vector sum that depends on the conformation, this method has been used for *N*-phenylpyrroles (51ZFK897, 52JCS1467, 71JCS(B)1811), *N*-pyridylpyrazoles (70CHC45, 70ZOK1104), *N*-(benzimidazol-2-yl)azoles (70CHC515), *N*-arylimidazoles and benzimidazoles (70CHC194, 70CHC759), and 3(5)-phenylpyrazoles (95BSB383). Most of these contributions are from Russian authors and have been summarized in a review (71CHC809).

2.5 Depolarized Rayleigh scattering (DRS)

A method of great interest but seldom used to determine the conformation of heterocyclic analogues of biphenyl. The only reported example concerns the study of 1-arylpyrazoles by Rioux and Clément (70BSF2139, 70BSF2144). The calculated dihedral angles were $11 \pm 3^\circ$ (26), $9 \pm 3^\circ$ (27), $7 \pm 3^\circ$ (28), $37 \pm 3^\circ$ (29); this last value agrees with that determined using the Braude's equation (Section 2.3) for 30: 33° (66T2703).

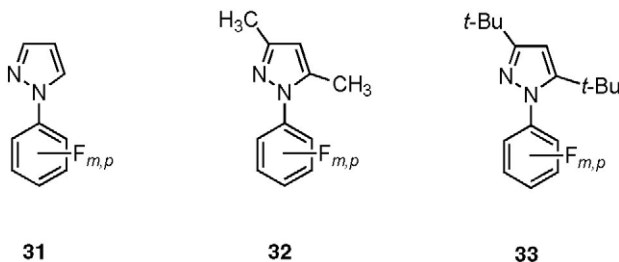


2.6 Basicity measurements (pK_a) and reactivity

Steric inhibition of resonance increases the basicity of *N*-arylpyrazoles by about 0.5 pK_a units when a methyl group is introduced at position 5 (68BSF5009), the effect increases with larger groups (68BSF707). Pozharskii, Simonov et al. determined the basicity and the reactivity (rates of the Menshutkin reaction, ethyl iodide in acetone at 50 °C) for pairs of *N*-aryl imidazoles and benzimidazoles (68CHC373, 70CHC194). They conclude that the difference is due to a decrease of the resonance interaction in the benzimidazoles by a loss of planarity. They estimated the dihedral angle of *N*-phenylbenzimidazole: 41–43° (dipole moments, Section 2.4), 39° (ionization constants) and 40° (Menshutkin reaction). The rates of *N*-methylation of *N*-arylpyrazoles and *N*-arylimidazoles were determined by Deady et al. (75AJC1861); they concluded that in pyrazoles the steric effects to quaternization are much more important than in imidazoles.

2.7 Substituent constants (Hammett)

For a long time, the properties of heterocycles linked to aryl rings have been used to determine substituent constants, Hammett or subsequent modifications. As early as 1958 (58MI89), Rao determined the Hammett σ and Taft σ_I and σ_R values for the 1-tetrazolyl substituent using ultraviolet spectroscopy. The values of the constants are sensitive to steric hindrance. These calculations were extensively covered by Kauer and Sheppard (67JOC3580) that calculated σ_m , σ_p , σ_I , σ_R , and σ_R° for 1-aryl-5-substituted-1*H*-1,2,3,4-tetrazoles. The σ_m (0.52) and σ_p (0.50) constants of the 2*H*-benzotriazolyl substituent were determined from the ionization of the corresponding phenols and anilines as well as by IR spectroscopy. The similar values indicate that the conjugation of the triazole nucleus with the benzene ring is almost negligible (69CCC72). The most systematic publication deals with the determination of σ_p values for all *N*-azolyl substituents (74JCS(P2)449); it was noted that steric hindrance increases σ_p . A further paper by the same group extends that work to Taft σ_R and σ_R° values using ^{19}F NMR spectroscopy (81JCR(S)364). The values change significantly with the steric effect of the 5-substituent, σ_R and $\sigma_R^\circ = 0.30$ and -0.06 (31), 0.28 and -0.11 (32) and 0.16 and -0.03 (33).

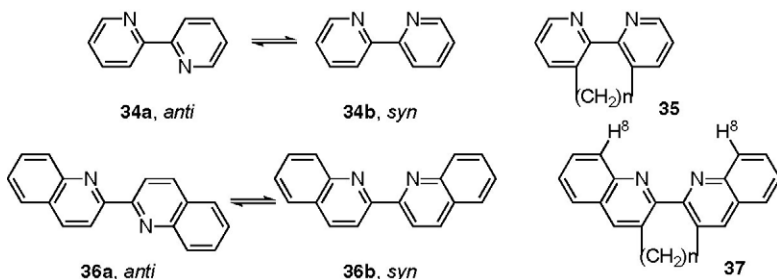


2.8 Static NMR

Undoubtedly, NMR is one of the methods of choice to study atropisomerism. Together with crystallography (2.1), HPLC (2.11), and theoretical calculations (2.14), NMR is the technique that has contributed most to the understanding of this phenomenon. We have separated, in some cases rather artificially, the use of NMR to study static aspects of atropisomerism (torsion angles, preferred conformation, equilibrium constants) from its dynamic use (barriers, 2.9).

2.8.1 Conformation and steric effects

Qualitative conclusions about steric effects have been reached using in general ^1H and ^{13}C NMR spectroscopy of solutions. Examples are 4-phenylpyrazole (67RTC1249), 1-phenylpyrrole (67T4469), 1- and 2-aryltetrazoles and tetrazolium salts (76T499, 77T1399), 3,3'-biindoles (82JA3628), acridine tweezers (89JA1373), and 2-substituted 1-aryl-3,5-diphenylpyrroles (with LSR) (99MC74).



Thummel et al. reported a conformational study of 2,2'-bipyridine **34** using as model compounds with restricted mobility **35** (3,3'-polymethylenes, $n = 1-4$) (85JOC3824). In another publication they examine the case of 2,2'-biquinolines **36** (85JOC666); for the annulated derivatives **37** they found a linear relationship between the torsion angle θ and the signal of H_8 proton. It was noted that in the case of N,N' -linked biazoles (aza derivatives of **6**), the conformation modifies the chemical shift of the α -protons on the opposite ring (80JCR(S)50). The conformation and *ortho* steric effects of a series of 2-(pyrazol-1-yl)quinolines was studied by ^1H and ^{13}C NMR (96JHC323); it was noted that the preferred conformation avoids lone pair (LP) proximities unless there is a bulky substituent (*t*-Bu) that results in an orthogonal conformation. 1-(2',4'-Dinitrophenyl)benzimidazole adopts a conformation with the 2'-nitro group toward the H_2 of the benzimidazole (72BSF2916).

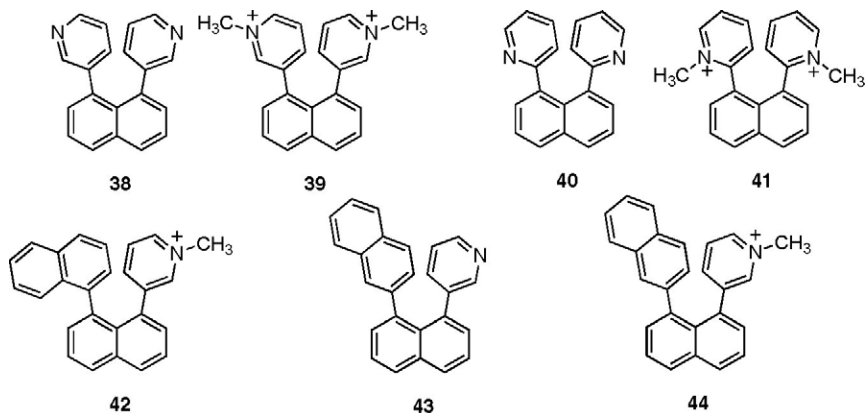
2.8.2 Determination of isomeric composition

The isomeric composition of phenyl groups bearing several (azol-1-yl) substituents was described in terms of up/down (**u/d**) conformations.

They were determined by NMR using symmetry considerations and bidimensional experiments. In this way were studied hexakis(pyrazol-1-yl)benzene (**16**, R = H) (96JPOC137), octakis (pyrazol-1-yl)naphthalene (00ARK(iv)612), hexakis(imidazol-1-yl)benzene (99JMS(478)285, 98MC (AHC)475). Phenyl derivatives containing both several hydroxy and pyrazol-1-yl substituents were also studied and the effect of intramolecular hydrogen bonds (IMHB) on the conformation established (01ARK(i)172, 01ARK(i)183), in the second publication the NMR experiments were carried out on the solid state (CPMAS NMR).

2.8.3 Determination of atropisomeric composition

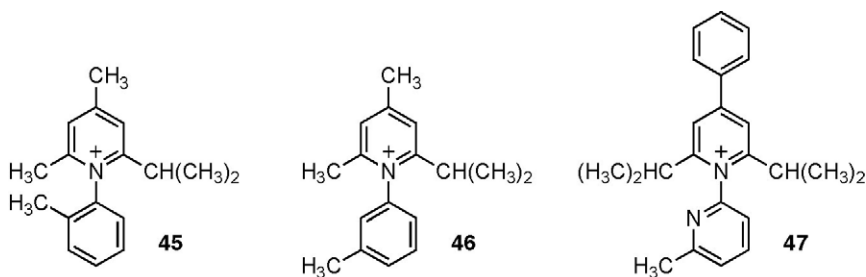
There have been several reports where NMR was used to determine the diastereomeric composition of atropisomeric mixture. In a series of remarkable papers (related to **22**), Zoltewicz *et al.* discussed the *anti/syn* isomerism of derivatives **38–44**. For 1,8-di(pyridin-3-yl)naphthalene (**38**) and its double quaternary salt **39**, they determined by signal integration of ^1H NMR the *anti/syn* ratio (96JOC7018). In the case of 1,8-di(pyridin-2-yl)naphthalene (**40**), the barrier was too low and only average signals were observed in a wide range of temperatures (97JOC2763); only with the much hindered quaternary salt **41** the *anti/syn* ratio can be measured. The study of the **42–44** series, together with nonheterocyclic analogues, allows one to conclude that polar- π and cation- π stabilizing interactions between constrained cofacial aromatic rings are present favoring the more sterically hindered diastereomers (01JOC7227).



Apart from the analysis of the diastereomeric species, static NMR is largely used to reveal atropenantiomerism. The compounds are equipped with a suitable probe to reveal the axial chirality through diastereotopicity of the observed elements. Methylene protons in CH₂R substituents are splitted to produce AB(X) coupling figures and the methyl groups of

gem-dimethyl substituents offer both ^1H and ^{13}C probes. The absence of splitting may be due to a too low barrier producing coalescence or to coincidental shifts, temperature or (and) solvent changes are tried. Colebrook et al. provided the first examples in heterocyclic atropisomers (72TL5239).

Uncuta and Balaban discussed the case of the *N*-arylpyridinium derivatives **45** and **46** (76RRC251). Only in the case of the *o*-tolyl derivative **45**, the methyl groups of the *i*Pr appear anisochronous being diastereotopic; the *m*-tolyl derivative **46** has a barrier to internal rotation too low and the rotation is too fast on the NMR time scale (at -60°C and 80 MHz in CDCl_3 , some signals of **46** broadened). Note that the *p*-tolyl derivative is achiral and should not give any splitting of the methyl groups originating from the hindered rotation about the *N*-aryl bond.



It is worth recalling that NMR probes can also detect local chirality due to atropisomerism in the absence of global molecular chirality. Pyridinium salt **47** is definitively achiral due to a symmetry plane however the methyl groups of each flanking *i*Pr groups are diastereotopic thanks to the high barrier of the *N*-(2-pyridyl) group (83OMR587).

Atropisomerism may also be revealed by the addition of optically pure reagents in the course of static NMR experiments: lanthanide shifts reagents (73JCS(CC)537, 89JCS(P2)713, 94MI225, 98MI419, 08T1371, 99MC74), Pirkle alcohol (85T229), or beta-cyclodextrin (^{19}F NMR) (00TA4771).

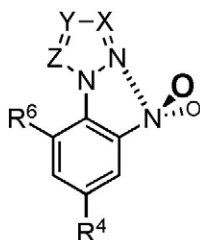
2.8.4 Intramolecular hydrogen bonds (IMHBs)

When the α C-H of one ring is on the same side that the α N atom of another ring the preferred conformation is such as they place themselves in proximity; some authors have considered that this attractive interaction is actually a weak IMHB of the C-H \cdots N type. On ^1H NMR the proximity of the LP of a N atom results in a deshielding: 2,2'-bipyridines (65JPC4166, 65RTC1399), 5-aryltetrazoles (68CJC2855), and 1-arylpurazoles (66AJC1935, 70BSF1346) [annulated, *o,o'*-linked, derivatives, Section 7] were used to establish this fact (70BSF1345). N-H \cdots N IMHBs stabilized the conformation of 2,4-biimidazole (01JCS(P1)1216) a result established

by ^1H , ^{13}C , and ^{15}N NMR. Therefore, the IMHB is responsible for planar or nearly planar conformations (see for instance compound **34bH⁺**).

2.8.5 Orthogonal effects

Paulini *et al.* introduced the term “orthogonal multipolar interactions” to describe situations that were not previously recognized ([05AG\(IE\)1788](#)). Among these interactions, there is one relevant for the present work, that present between the *o*-nitro substituent on the 1-aryl ring and the N_2 atom of an azole.



48, X, Y, Z, CH, benzo, or N; R^4 , R^6 , H or NO_2

Based on ^1H NMR chemical shifts we described in 1970 that the nitro group of 1-(2',4'-dinitrophenyl)pyrazoles prefers to be on the side of the N_2 rather than on the side of H_5 ([70BSF1346](#)). Then we extended this observation to 1-(2',4'-dinitrophenyl)benzazoles ([70MI307](#)) and more recently using the name “orthogonal effect” to other 1-(2',4'-dinitrophenyl)azoles ([04AJC1103](#)) including CPMAS NMR results ([08MRC697](#)). The orthogonal effect although weaker than HBs plays a role in stabilizing planar conformations.

2.8.6 ^1H NMR: relationship between $\Delta\delta(o-m)$ and steric effects

It has been known for a long time that the difference between the ^1H chemical shifts of the *ortho* and *meta* positions of *N*-aryl heterocycles depends on steric effects in a way that is possible to establish a relationship between $\Delta\delta(o-m)$ and the torsion angle θ . For examples of the sensitivity to steric effects see *N*-arylazoles ([64CJC1605](#), [66BSF3727](#), [66JOC1878](#), [67SA\(A\)2243](#), [68JCS\(B\)211](#)) and phenylpyridazines ([66ACS258](#)). In the case of bipyridines and bridged 2,2'-bipyridinium salts, an estimation of the torsion angles was achieved by comparing the chemical shifts of ring protons with those obtained with other methods ([67AJC1195](#), [67AJC1227](#)). Using the ring current effects as calculated by the Johnson and Bovey theory and the measured $\Delta\delta(o-m)$ values, the torsion angles θ of several phenyl purines were determined ([74T3405](#)).

2.8.7 ^{13}C NMR chemical shifts: relationship with steric effects

In a similar way to the preceding section, Begtrup reported in 1973 that the ^{13}C chemical shifts of the phenyl ring in 1-phenylazoles are very sensitive

to steric effects (73ACS3101). They extended the results to a large family of substituted 1-phenylazoles showing that the signal of different carbons is able to distinguish between hindered and unhindered molecules (74ACS(B)61). Related works on *N*-arylpyrazoles and *N*-arylpyrazolium salts were reported afterwards (89MRC603, 92MRC455). Faure et al. (78MI1) used the fact that $\Delta\delta(o-m)$ does not change to establish that the dihedral angles were the same in a series of phenylthiazoles.

Based on Begtrup's data, Fong for the first time used a quantitative relationship to calculate torsion angles θ from the difference in ^{13}C chemical shifts of carbons *meta* and *para* of the phenyl ring, $\Delta\delta(m-p)$ (80AJC1763). It is not a direct equation but uses Taft $\sigma_{\text{R}}^{\circ}$ values of the azolyl substituents (Section 2.7), $\cos^2\theta = (\sigma_{\text{R}}^{\circ})_{\theta} / (\sigma_{\text{R}}^{\circ})_0$.

2.8.8 Effect of metal coordination on the conformation

Rebek et al. studied the effect of complexation on the conformation of bridged (crown ether) bipyridines (79JA4333). They noted that the free crown may adopt a variety of conformations in solution, wherein the size of the crown cavity is related to the dihedral angle θ . In the free crown ether this angle is shown at its maximum value (slightly less than 180°). Binding to an alkali metal gathers the oxygen atoms and in particular the benzylic oxygens close to each other. This fixes the position of the benzyl hydrogens and the size of the dihedral angle θ (ca. 90°) modifying the interaction of the bipyridine toward metals. The same author has reported the use of bipyridyl-metal chelation to enhance reaction rates by modifying the dihedral angles (85JA7487). An allosteric effect was demonstrated on the complex of a *N,N*-bonded bi(2*H*)indazole crown ether with PdCl_2 , in which conformational changes induced by complexation caused transport rates by the crown to be lowered, without inversion of the K^+/Na^+ selectivity (88JOC2055).

In the case of hexakis(pyrazol-1-yl)benzene (**16**, $\text{R} = \text{H}$), the effect of metal complexation on the **u/d** composition has been studied (07POL4373).

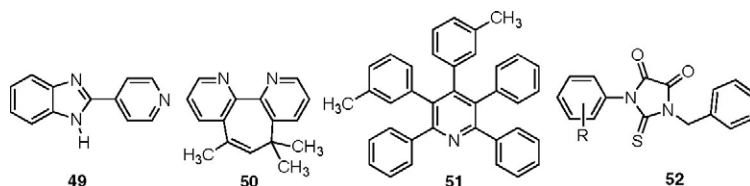
2.8.9 Other examples

Lunazzi et al. have determined the conformation of 2,2'-bithienyl by means of a liquid crystal (nematic phase) NMR study (73JCS(P2)751); they found 78% of *s-trans* and 22% of *s-cis* rotamers (the estimated interconversion barrier is about 20 kJ mol^{-1} , see Section 2.9). The same compound using the same approach was studied by Khetrpal and Kunwar (74MP(28)441), the θ angles determined by X-ray (Section 2.1) and electron diffraction (Section 2.2) are 0° and 34° , respectively; they concluded that 2,2'-bithienyl is a mixture of *cis*- and *trans*-planar structures but they were unable to calculate the proportions (for theoretical calculations, see Section 2.14.3).

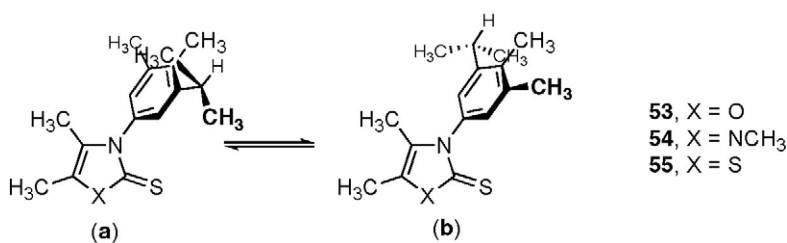
2.9 Dynamic NMR (DNMR)

Dynamic nuclear magnetic resonance (DNMR) spectroscopy covers the investigation of temperature-dependent NMR spectra and the calculation of rate constants and Arrhenius (E_a) or Eyring (ΔG^\ddagger) parameters from these spectra (83TS(14)1, 08MI1). Barriers determined by DNMR usually are in the 20–100 kJ mol⁻¹ range. The lower domain of barrier range is more easily addressed with high field NMR whereas the higher domain is more conveniently addressed by low field NMR. In general, it is difficult to determine ΔS^\ddagger (J K⁻¹ mol⁻¹) with accuracy being 1000 times smaller than ΔH^\ddagger (kJ mol⁻¹). DNMR may address diastereomerization barriers or enantiomerization barriers. It is worth recalling that at least two diastereomerization barriers that differ by the (ΔG^0) difference in the ground state of the diastereomers should be reported. Enantiomerization barrier is the unique barrier to transform one enantiomer into the other.

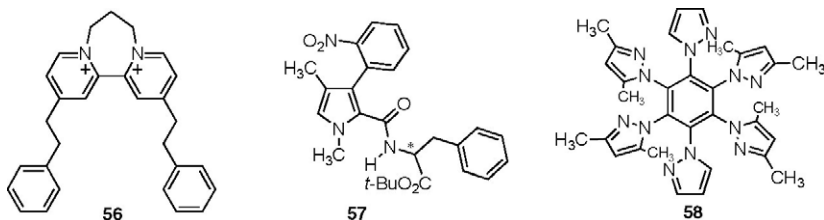
Lunazzi measured the interconversion barrier of 2,2'-bithienyl to be 21 ± 8 kJ mol⁻¹ in a liquid crystalline solvent (see Section 2.8.9) (74JA1305). When a barrier between two diastereomers is given, one should provide the direction since two barriers $A \rightarrow B$ and $B \rightarrow A$ differ by the stability of the two diastereomers. The barrier to rotation of 2-(pyridin-4-yl)-1*H*-benzimidazole (**49**) is too low to be measured by DNMR (estimated to be <11 kJ mol⁻¹) (77H911). The racemization barrier of a *ortho-ortho'*-bridged bipyridine derivative **50** (61 kJ mol⁻¹) has been measured (78JA4315), the barrier decreases by monoprotection, **50H**⁺ (42 kJ mol⁻¹) and increases to 70 kJ mol⁻¹ by double protonation, **50H**₂²⁺. Line-shape analysis of the ¹H NMR spectra of pentaarylpyridine **51** yielded a free energy of activation for rotation around the bonds joining the central ring and the peripheral rings bearing *meta* methyl groups of $\Delta G^\ddagger_{265} = 61.5$ kJ mol⁻¹ (80JOC2511). Dynamic ¹H NMR spectroscopy of 1-aryl-3-benzyl-2-thioxoimidazolidine-4,5-dione (**52**) indicates that a degenerate racemization (atropisomerism) is observed at 245–260 K; the calculated free energy of racemization was 50.5–53.5 kJ mol⁻¹ (84MI45).



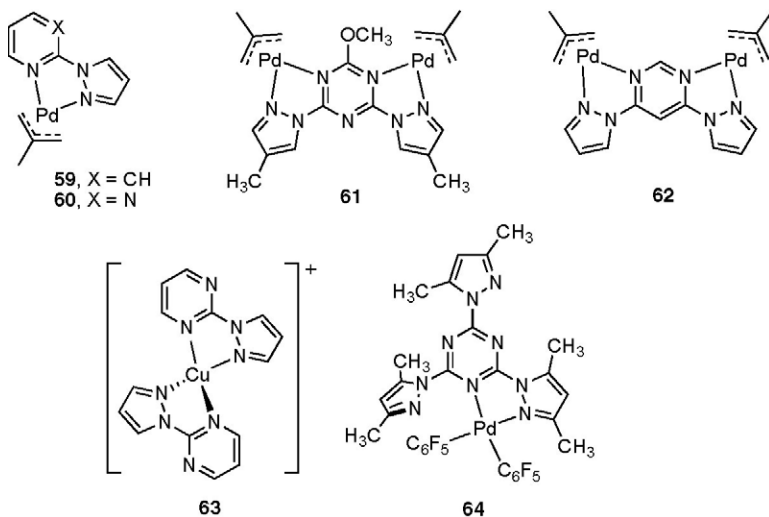
Djafri *et al.* have determined by ¹H DNMR the barriers to rotation of aryl groups (unsubstituted in the *ortho* positions) in position 3 of 4,5-dimethyl-oxazoline-2-thiones (**53**), -imidazoline-2-thiones (**54**), and -thiazoline-2-thiones (**55**) (85JCS(P2)273); the barriers were 38.9, 51.5, and 74.0 kJ mol⁻¹, respectively. They conclude that the ring element X (O, NCH₃, S) affects the barriers mainly by its influence on the geometry of the ring.



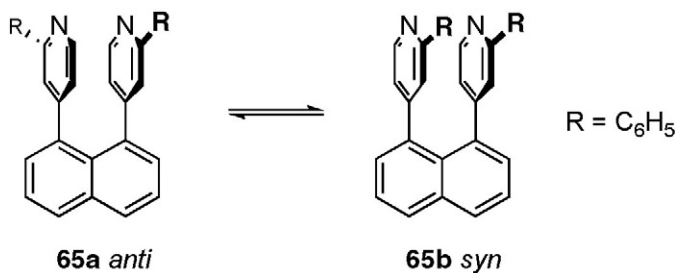
Font and co-workers (87JOC521) measured for **56** a barrier of 69 kJ mol⁻¹, very close to that of **50H₂²⁺**. The barrier about the C–C bond of the chiral 3-arylpyrrole **57** has been determined to be 96 kJ mol⁻¹ (93BSF779). In an hexakis(pyrazol-1-yl)benzene, **58**, with two kinds of pyrazole rings, the experimental barrier, 94 kJ mol⁻¹ (97JCS(P2)2173), corresponds to the transition state connecting the **ududud** isomer to the **uduudd** one.



Jalón and co-workers determined rotational barriers of a large number of metal (generally Pd) complexes: **59** and **60** (96CB589), **61** (98IC6606), **62** (00IC1152), **63** (01NJC1050), and **64** (03IC885) among many other.



Wolf and Tumambac (03JPC(A)815) reported the study of a compound related to **38**, the 1,8-bis(2,2'-diphenyl-4,4'-dipyridyl)naphthalene (**65**). Rate constants obtained between -65.0 and 40.3 °C allowed the determination of the Gibbs standard activation energy ΔG^\ddagger for the diastereoisomerization of **65** as 70.4 kJ mol $^{-1}$. The rotational activation enthalpy ΔH^\ddagger and the rotational activation entropy ΔS^\ddagger were calculated from the Eyring plot as 57.5 kJ mol $^{-1}$ and -43.4 J K $^{-1}$ mol $^{-1}$, respectively.



2.10 Resolution

Diastereomers present different physical and chemical properties. Thus, the resolution of enantiomers by the formation of diastereomers is one of the most classical methods to achieve this goal.

Covalent bonding of a racemate with an optimized optically pure derivatizing agent affords diastereomeric species that can be separated by conventional methods such as preparative chromatography, selective extraction or selective crystallization. After separation the pure enantiomers can be recovered by elimination or transformation of the derivatizing agent. Chiral atropisomers can be resolved according to these procedures when the operating conditions for binding and cleavage of the derivatizing agent are carefully optimized to prevent thermal racemization. The method is exemplified in some biheteroaryl synthesis through coupling reactions of optically pure derivatized monoaryl compounds (97JOC4465). Dynamic kinetic resolution may be envisioned as a resolution method, the barrier in the derivatized compound shall be higher than in the starting material.

Crystallization of diastereomeric salts obtained from an optically pure acid or an optically pure base is a classical method for the resolution of atropisomeric heterocycles presenting the complementary basic or acid functions. The method requires several trials to find the optimal resolving agent. Atropisomers bearing mono or diphosphine groups are separated using optically pure Pd(II) complexes. Table 2 reports some selected examples.

Few examples of enzymatic resolution applied to heterocyclic atropisomers have been reported. Atropisomers of 1,1'-bis(hydroxyalkyl)-3,3'-

Table 2. Examples of crystallization of diastereomeric salts

Atropisomeric species	Resolving agent	Reference
1-(2-Carboxyphenyl)-2,5-dimethyl-1 <i>H</i> -pyrrole-3-carboxylic acid	Brucine	(31JA374)
4,4'-Dicarboxy-1,1',3,3',5,5'-hexamethyl-2,2'-bipyrryl	Brucine	(53JOC1413)
1,1'-Biisoquinolyl	(+) Tartaric acid; racemization in the salt	(54JCS3464)
4,4'-Biquinolyl	(+) Tartaric acid	(52JCS4133)
5,5'-Biquinolyl	(+) Tartaric acid	(52JCS4133)
4,4'-Biisoquinolyl	(+) Tartaric acid	(54JCS3464)
5,5'-Biisoquinolyl	(+) Tartaric acid	(54JCS3464)
8,8'-Biisoquinolyl	(+) Tartaric acid	(54JCS3464)
4,4'-Dicarboxy-2,2',5,5'-tetraethyl-3,3'-bithienyl	Cinchonidine	(67AK115)
1-Aryl-4,6-dimethyl-2(1 <i>H</i>)-pyrimidones	D-Camphor sulfonic acid	(78H469)
(4,4',6,6'-Tetramethyl-3,3'-bi-1-benzothi-ene-2,2'-diyl)bis(diphenylphosphane)dioxide	(-)-2,3-O,O'-Dibenzoyl-L-tartaric acid	(95JCS(CC)685)
1,1'-Bis-dimethylaminomethyl-2,2'-bis-diphenylphosphino[3,3']biindolyl	Bis[(<i>R</i>)-dimethyl(1-(1-naphthyl)ethylamino)-C ² , N)palladium chloride]	(96TA285)
1-[2-carboxy-6-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrole-2-carboxylic acid	(<i>S</i>)-1-Phenylethanamine	(99T7881)
3,3'-Bi(1-benzothiophene)-2,2'-dicarboxylic acid	Quinine	(03CCCC1020)
1-[(3-Carboxy-1,10-biphenyl)-2-yl]pyrrole-2-carboxylic acid	(<i>S</i>)-1-Phenylethanamine	(09CHI905)
1-(2-Carboxymethyl-6-ethylphenyl)-1 <i>H</i> -pyrrole-2-carboxylic acid	(<i>R</i>)-1-Phenylethanamine	(09TA98)

biindolizines were obtained in enantiomerically pure forms by selective transesterification by vinyl acetate catalyzed by *Candida Antartica* (Novozym 435) (96TA3365). Lipase from *Mucor miehei* was successfully employed to resolve (\pm)-3,3'-bis(hydroxymethyl)-2,2'-bipyridine *N,N*-dioxide enantiomers in EtOH/vinyl acetate (06TA12). Patent literature reported the preparation of optically pure PH 79704 atropisomer at the kg scale by Novozyme Savinase enzymatic resolution of a precursor at 30 °C and pH 9.1 (08WO72079).

One may foresee some interesting developments in enzymatic dynamic kinetic resolution of an atropisomeric framework when the barrier in the transformed product is higher than in the starting material.

Another emerging resolution technique is applicable to atropisomers that form conglomerates. Chiral symmetry breaking of C–N axial chirality for *N*-aryl-2(1*H*)-pyrimidinone conglomerates was achieved by crystallization induced enantiomer transformation without any outside chiral

source (03AG(IE)4360). This work was extended recently to 1-(1-naphthyl)-4,6-dimethylpyrimidin-2(1*H*)-thione that also forms a conglomerate. Eighty-nine to ninety percent enantiomeric excesses were obtained by crystallization with seeding and stirring, stirring alone yielded 41–88% *ees* with random preference in one enantiomeric form, seeding alone resulted in 8–37% in the same enantiomeric form as the seeding crystals (10OBC5418).

2.11 HPLC and other chromatographies

In the last 30 years, the so-called chiral chromatographies have been a cornerstone in the tremendous developments of all the aspects of chirosciences. Three techniques have been developed for the analysis of enantiomers: (a) liquid chromatography on chiral support and elution with an achiral solvent that comprises also supercritical CO₂; (b) gas chromatography on a chiral stationary phase (CSP), and (c) liquid chromatography on an achiral support with a chiral additive in the mobile phase. The resolution of atropisomers that do not presents suitable functional group for classical resolution by formation of diastereomers with optically pure amines or acids became reachable.

All three techniques have been unequally exemplified in the separation of heterocyclic atropisomers. GC on a 10% permethyl-(α -cyclodextrin (Chirasil-Dex, Chrompack) chemically bonded to a dimethyl polysiloxane backbone (CB-(α -PMCD) coupled with EI–MS was employed to elucidate the structure of a hexachlorinated bipyrrrole which was obtained as a by-product during the synthesis of the achiral heptachloro-1(1'-methyl-1,2(1'-bipyrrrole (02AC4287). Two baseline separated peaks were obtained in ca. 20 min confirming the chiral structure of the by-product.

Another example of chiral GC has been recently reported on the same chiral support for the analysis of enantiomers of 5,5'-dichloro-1,1'-dimethyl-3,3',4,4'-tetrabromo-2,2'-bipyrrrole. Partial racemization of the optically pure sample occurred in the injector (10JC(A1217)2050). The high-temperature ranges, which are operated both in the column and in the injector, obviously require great care in the analysis of atropisomeric systems.

The use of a chiral additive in the mobile phase has been exemplified by Roussel and Favrou who studied the separation of several *N*-aryl-thiazoline-2-thione atropisomers on an achiral column with β or γ cyclodextrin in the mobile phase. It is worth recalling that the association constants between each enantiomer and the chiral selector can be determined by varying the chiral additive concentration (93CHI471, 93JIP283).

Liquid chromatography on a chiral support occupies a special place in the study of atropisomers since analytical conditions may be easily scaled up to collect optically pure samples for off-line studies. Subambient

temperatures can be applied for the analysis and the collect of atropisomers presenting short half-lives.

More than 250 CSPs have been commercially available among more than ca. 1500 CSPs, which have been reported in the literature (08JPBA839).

Since the pioneering work of Mannschreck in Germany who performed chiral separation of heterocyclic atropisomers on home-made microcrystalline cellulose triacetate or cellulose tribenzoate glass-columns, the field has been constantly expanding (83JC(282)89, 84EJMC381, 85JC(329)307, 85MI3, 85T229, 86JC(351)346, 89JCS(P2)713, 90JCS(P2)619, 90MI2, 92JHC327). Low pressure liquid chromatography on these supports looks quite obsolete in comparison with the modern HPLC columns, the peaks were very broad, the analysis times were quite long and the solvent was limited to a mixture of lower alcohols and water. We experienced separation that provided one enantiomer after 3 h and the second next day. Nevertheless, these separations were performed at the semipreparative scale and the flow was passed through a 1 mL polarimeter or CD cell opening the way to dual detection with collection of the enantiomers according to their sign. For fast exchanging atropisomers, when the maximum angle value on the polarimeter was reached (or a large enough angular deviation to get good precision in the data), the thermostated cell was quickly disconnected, allowed to equilibrate its temperature for 2 min and then closed with normal plugs. The chromatography was continued and the remaining atropisomers recovered in a flask. The racemization rate can be directly monitored from the trapped atropisomer since first order kinetic does not require the initial concentration to be known (86NJC399). The use of cellulose triacetate for the resolution of atropisomers was exemplified in other studies (88JOC5076, 88NJC947, 89JC(462)95, 90NJC169, 94CHI251, 00EJOC1081), and provided enriched samples for the determination of the order of elution on other chiral supports such as BSA (89CHI154, 92JC(A591)65). Tris-(*p*-methylbenzoyl) cellulose beads were employed to separate *N*-aryl-thiazoline-2-thione atropisomers (93CHI207, 94CHI251).

1,1'-Trimethylene-2,2'-bipyridine-3,3'-dicarboxylic acid and 1,1'-tetramethylene-2,2'-bipyridine-3,3'-dicarboxylic acid atropisomers were baseline separated in 10 days on potato starch after tremendous effort to prepare the column. The authors stated that "attempts to resolve theses acids were only successful with specially conditioned columns of starch" (95JPC14161). It is highly probable that more convenient chiral HPLC conditions are now available.

The Daicel polysaccharide CSPs that became available in 1985 have been largely used in the field of atropisomeric heterocycles both at the analytical or semipreparative scale. Cellulose tris(*p*-methylbenzoate), cellulose tris(3,5-dimethylphenylcarbamate), amylose tris(3,5-dimethylphenyl-carbamate), and amylose tris[(*S*)alpha-phenethyl]carbamate were

coated on silica and marketed under the trade name Chiralcel OJ, Chiralcel OD, Chiralpak AD, and Chiralpak AS respectively. All are available under various particle sizes.

Selected examples of resolution of heterocyclic atropisomers can be found on OJ columns: (93JLC859, 96JC(A722)177, 97TA341, 98JOC2597, 98JOC2634, 01SL1551, 01TA341, 03EJOC3818, 04T4513, 10TA711; on OD column: 92JCS(CC)905, 92TL3169, 92TL7173, 94JCS(CC)653, 94TL8631, 94TL9729, 96JA9188, 96JCS(P1)183, 96JOC710, 96JOC8002, 96JOC9344, 96PHA379, 97EN449, 97T4601, 99SL783, 99TA25, 99TA2975, 00CHI510, 00JOC3154, 00TA2647, 00TL7723, 01BMCL177, 01CHI56, 01JCS(P1)1785, 01JCS(P2)961, 01JOC5940, 02ARK(x)72, 03JOC6329, 06T295, 06T968, 06TA3185, 08CEJ4899, 08OL1373; on AD column: 96JCS(P1)183, 96PHA379, 97JCS(CC)551, 98JA11880, 01CHI56, 02JOC2769, 02TL1539, 03AG(IE)3674, 04AG(IE)3795, 04CEJ6531, 04H223, 04JOC2048, 04T4513, 05OL4045, 08BMC9519, 08JPBA1120, 09CHI160; on AS column 97EN449, 98JOC2634, 02JPBA431).

The number of available polysaccharide based CSPs coated on silica has increased in the last few years by the introduction of new carbamate substituents on cellulose and amylose or by the production of “generic” Daicel phases. All these CSPs in which the selector is coated on silica suffer from solvent restrictions. On the other hand, the recently introduced immobilized polysaccharide phases Chiralpak IA (05JC(A1075)65, 05LOC433), IB, and IC allow a large range of eluents that were not permitted for the coated versions.

Molecular CSPs are obtained by a covalent link between an optically pure molecular selector and silica through a spacer. The so called Whelk CSPs [(3*R*,4*S*) or (3*S*,4*R*)-4-(3,5-dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene] from Regis present two perpendicular planes one being a π -donor and the second a π -acceptor. They have been used for the resolution of atropisomeric heterocycles (96JC(A753)109, 96JC(A726)91, 98CHI253, 05JOC2930, 06JOC2854). The availability of the two enantiomeric CSPs is quite useful to control the order of elution.

Some rare examples of separation on other CSPs have been reported: Sumipax OA 2000 (88JCS(P1)313), home made tyrosine phase (92CHI36); Ceramospher Ru-(I) (96H415), Chiralpak OP(+) (08T11335); Chirex 3018 (05CHI559), and ULMO (10JC(A1217)1017).

Another advantage of HPLC comes from specific chirality detectors on line such as a polarimeter and a CD that may be used to monitor the order of elution. We strongly recommend the use of these detectors when running chiral separations. Both detectors are silent for *meso* compounds and active for *D* and *L* forms (00EJOC1081, 04JC(A1037)311, 07CC1745). Figure 2 reports a chromatogram obtained on an immobilized CSP from Daicel (Chiralpak IB) of a mixture of atropisomers presenting a *meso* and *D*, *L* forms. The polarimetric response is silent for the third peak that is the

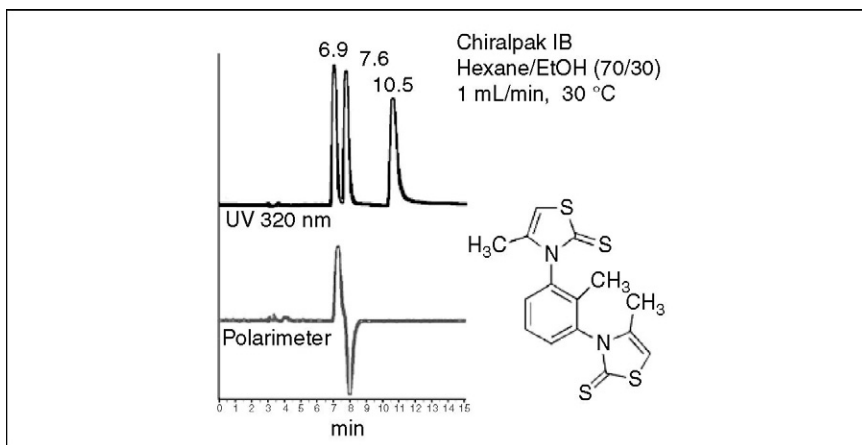


Figure 2. Assignment of *meso* and *D,L* forms with polarimetric detection.

meso form while the first and the second peak correspond to the dextrogyre and levogyre enantiomer (in the mobile phase), respectively.

It is worth recalling that the optical rotation (sign and magnitude) of an enantiomer is depending on the solvent and the wavelength. Polarimetric detection gives the sign of the enantiomer in the mobile phase. Changing a mobile phase might change the sign of the peak for the same absolute configuration. As an example 3-(2-methoxyphenyl)-4-methyl-1,3-thiazole-2(3*H*)-thione atropisomers give an opposite sign of optical rotation in acetonitrile or EtOH (03JC(A995)79). For the majority of the enantiomers (including atropisomers), the optical rotation magnitude decreases when the wavelength increases. In that case the observed sign will be the same whatever the wavelength at which the polarimeter is operating. In the case of a Cotton effect the magnitude and the sign of the optical rotation might vary with the wavelength for the same enantiomer (03JC(A995)79). The sign of the observed peak for the same enantiomer might change with the detector wavelength technology. A PDR polarimeter operates at a single laser wavelength of 670 nm whereas a JASCO polarimeter operates simultaneously in the 350–900 nm wavelength range. In the case of a Cotton effect the two detectors might result in an opposite sign for the same enantiomer under identical conditions.

Jasco ECD detectors on line are operated at a single wavelength that can be varied. It is clear that depending on the wavelength, positive or negative responses can be obtained for the same enantiomer. Figure 3 reports the chromatogram of atropisomers of a *N*-aryl-thiazoline-2-thione with inversion of the CD sign between 220 and 254 nm. The separation was performed on the recently introduced TCI chiral BP-S from Tokyo Chemical Industry.

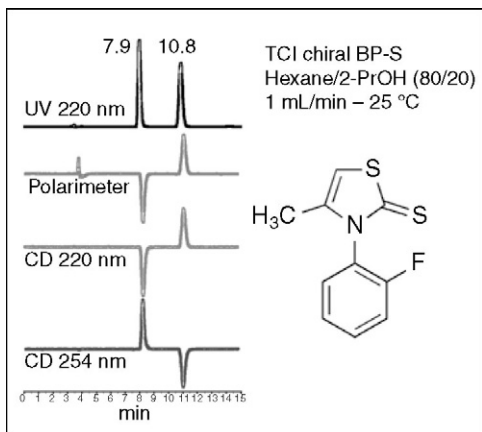


Figure 3. Chromatogram of atropisomers of a *N*-aryl-thiazoline-2-thione.

Modern ECD detectors on line allow the recording of the complete CD trace, which can be used for the determination of the absolute configuration by comparison with calculated ECD spectra or application of empirical rules ([01JA2703](#), [05JNP686](#), [08OL1373](#)).

The use of chiral HPLC (separative method) in tandem with a chirality detector (chirality assessment) presents a decisive advantage in the determination of absolute configuration of a series of 1-(thi)oxothiazoliny-3-(thi)oxothiazoliny-1-yl toluene atropisomers by the chemical transformation method. Such a correlation method could be performed on a mixture of a very limited quantity of compounds, without the tedious purification steps that are normally required in the classical chemical correlation method ([02CHI665](#)).

Racemization of enantiomers on the column may result in several typical peak shapes that are temperature dependent. At high temperature a single peak is observed due to a fast exchange between the enantiomers, at low temperature the exchange may be sufficiently slow to produce baseline separated peaks. In between, two peaks are linked by a plateau that is parallel to the baseline. Polarimetric or CD detectors reveal that the plateau is silent whereas the two flanking peaks give opposite sign. The plateau height increases with the temperature. The observation of a plateau between exchanging enantiomers gave rise to dynamic chiral HPLC (DHPLC) studies. [Figure 4](#) illustrates the occurrence of a plateau during the chiral HPLC of the atropisomers of one *N*-aryl-thiazolin-2-alkylimine on Lux-Cellulose-2 from Phenomenex. The polarimeter response shows that the plateau corresponds to the racemate while the first peak to the (+) enantiomer and the second to the (–) one.

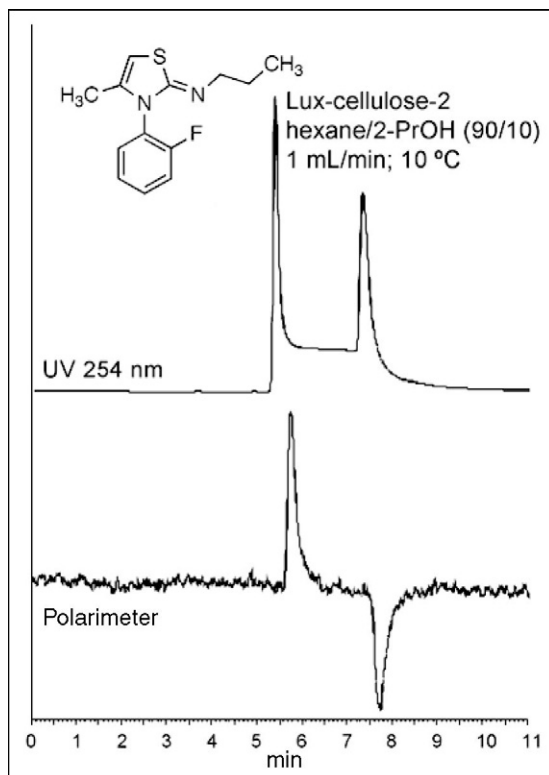
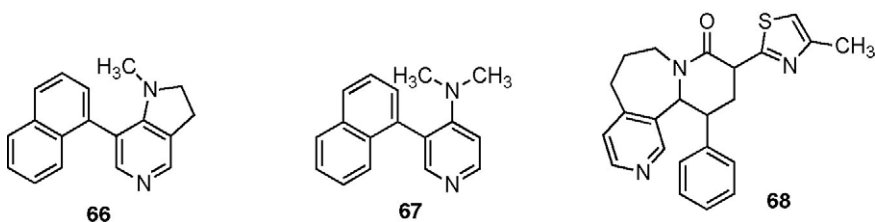


Figure 4. Occurrence of a plateau during the chiral HPLC of the atropisomers of one *N*-aryl-thiazolin-2-alkylimine.

From the shape of the exchanging peaks the enantiomerization rate at the given temperature can be evaluated using the Trapp and Schurig equation (01CHI403, 02CHI465), which works perfectly in the case of a chromatogram with minimal tailing peaks and a plateau parallel to the base line. Computer programs have been developed for line shape fitting. The two more recent are DCXplorer freely available from Oliver Trapp (Ruprecht-Karls-Universität Heidelberg, Germany) (06CHI489) and Auto-DHPLCy2k developed by Marco Pierini (Sapienza Università di Roma, Italy). Uray et al. recently compared the two kinds of software in barrier determination from a very poor separation of atropisomeric 4,4'-bisquinoline-2-ones with highly tailing peaks (10JC (A)1017). This is an interesting methodological study, however, frankly speaking, it is probably more rewarding to optimize the separation in order to get a nice plateau rather than to push the softwares beyond their application range.

DHPLC filled the gap of a barrier range, which was not previously accessible before. When the barriers are too low for the collection of the enantiomer before off-line thermal racemization and too high for DNMR experiments, DHPLC is useful. The domain can be extended by running the chiral separation at very low temperatures (cryo-chromatography).

Spivey *et al.* reported examples of chromatograms with a plateau shape on Chiralcel OD for 3-(1-naphthyl)-pyridine derivative atropisomers **66** and **67** ([99JOC9430](#), [01JOC7394](#)). The barriers (85.9 kJ mol^{-1} at 20°C) were determined by fitting the simulated chromatogram with the experimental one. It corresponds to a half-life for racemization of 1.9 min at 20°C .

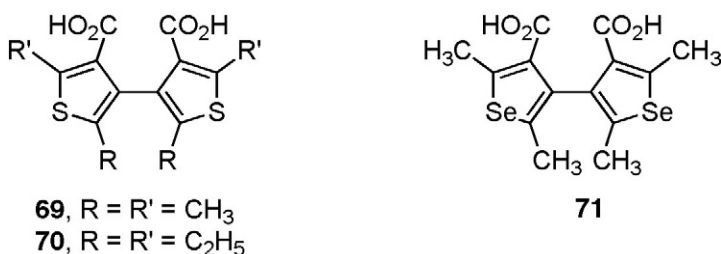


Gibson *et al.* determined for **68** a barrier equal to 92.7 kJ mol^{-1} ($t_{1/2} = 31 \text{ min}$ at 20°C) by thermal racemization after collecting enriched enantiomers from a sample which showed “a slightly raised baseline between the peaks, consistent with interconversion of species on the column” ([02JOC9354](#)). This is a typical example of a borderline for which the barrier might be determined either by DHPLC (at slightly higher temperature) or off-line thermal racemization after quick collection of the enantiomer.

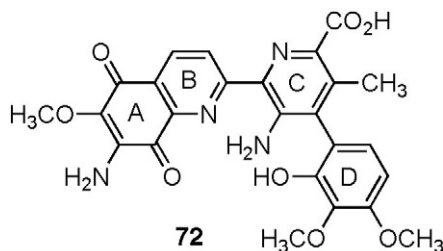
Other examples of plateaus in atropisomeric *N*-aryl-*N'*-aryl-2-iminothiazoline ([08ARK\(viii\)28](#), [08JOC403](#)) or in *N*-aryl-thiazolin-2-one series have been reported ([05LOC433](#)).

2.12 Optical methods (CD)

Håkansson *et al.* ([75CS131](#)) reported the determination of the absolute configurations of 4,4'-dicarboxy-2,2',5,5'-tetraalkyl-3,3'-bithienyl (**69** and **70**), and 4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-biselenienyl (**71**). Compound **69** was related by chemical methods to hexamethyl-3,3'-bithienyl, the absolute configuration of which was known. Compounds **69** and **70** were related by the quasi-racemate method. Biselenienyl **71** and bithienyl **69** had previously been related by the same method. They conclude that the levorotatory forms of **69**, **70**, and **71** have the (*R*)-configuration. CD studies were carried out using for comparison 3,3',6,6'-tetramethyl-2,2'-diphenic acid.

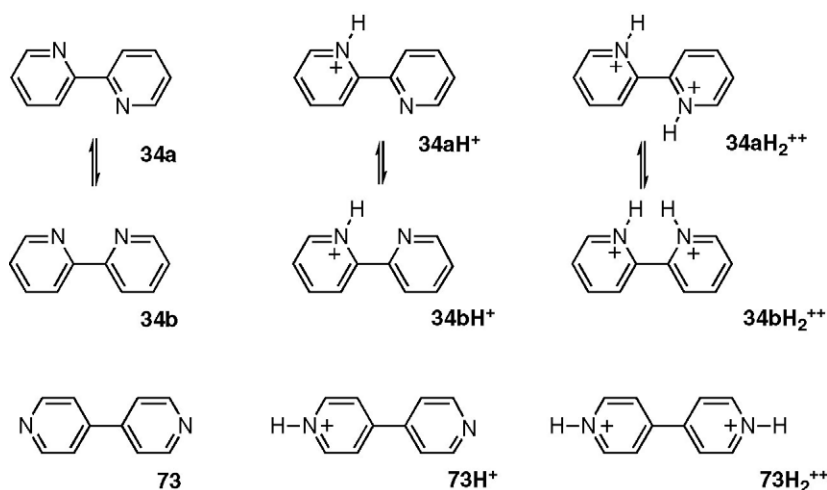


Håkansson and Wiklund (75CS173) extended these studies to many other bithienyls, for instance several bromo and methyl substituted 3,3'-bithienyls of (*R*)-configuration with flexible substituents such as carboxylic groups, hydroxymethyl groups, and bromomethyl groups at the 2,2'- or 4,4'-positions. The compounds with flexible substituents at the 2- and 2'-positions exhibit CD spectra similar to those of bridged and open methyl and bromo substituted 3,3'-bithienyls, characterized by a negative CD band near or above 250 nm followed by a positive band at shorter wavelengths. The 3,3'-bithienyl-4,4'-dicarboxylic and -4-monocarboxylic acids and their esters have CD spectra of an entirely different type. These are characterized by a negative Cotton effect near 240 nm, which is changed to positive on ionization in the case of the 4,4'-dicarboxylic acids.



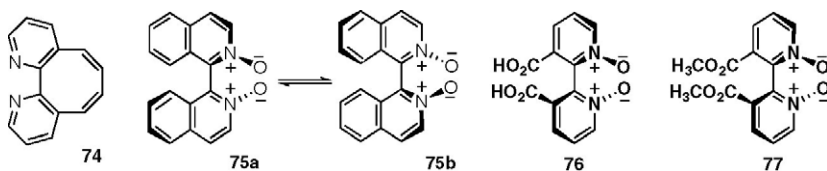
The chiroptical properties of streptonigrin (**72**) (from *Streptomyces floculus*) and its monoxime were recorded (81T2929). This is the first case of atropisomerism arising from a phenylpyridine in a natural product. Accepting that the solid-state conformation is retained in solution in ethyl acetate, the optical activity arises from the skewed rings C and D. Rotation about the bond between rings C and D is prevented by steric hindrance of amine and methyl groups of one ring and the OH group of the other. The rate of racemization of the compound would be slow because of the buttressing effect, caused by bulky substituents in the 3 and 3' positions. CD values were used with comparison with model compounds.

Magnetic circular dichroism (MCD) was used to determine the conformation and the dihedral angles of bipyridyls (84BCSJ341).



Using MCD, the effect of the protonation on the conformation of 2,2'-bipyridine (34) and 4,4'-bipyridine (73) was studied. According to the authors, 2,2'-bipyridine exists in a planar *trans*-structure, **34a** ($\theta = 0^\circ$), the monoprotection maintains the *trans*-structure **34aH⁺** but θ increases to 30° and the diprotection led to **34aH₂⁺⁺** with $\theta = 40^\circ$. In the case of 73, the θ angles are 30° for both **73** and **73H₂⁺⁺**. As we will see in Section 2.14 these conclusions are only in part confirmed by high-level calculations.

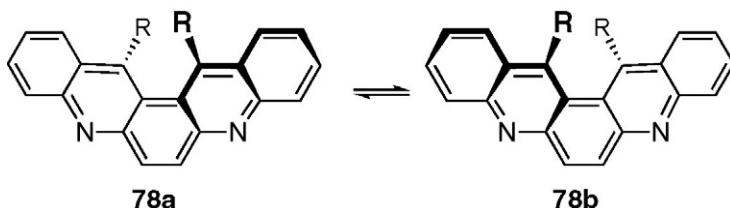
Sandström *et al.* (92JCS(P2)1625) reported the enantiomer resolution, barrier to ring inversion ($\Delta G^\ddagger_{322} = 104.3 \text{ kJ mol}^{-1}$, $\Delta H^\ddagger = 102.7 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -5.0 \text{ J K}^{-1} \text{ mol}^{-1}$), circular dichroism spectrum and absolute configuration of cycloocta[2,1-*b*:3,4-*b'*]dipyridine (74).



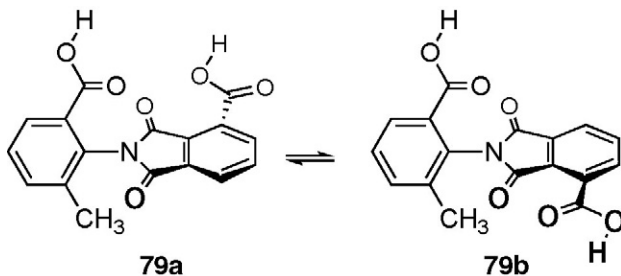
The theoretical CD spectrum of **74** was obtained by representing the calculated transitions as Gaussians, and it shows a considerable similarity with the experimental spectrum, both with respect to the sequence of the band signs and with respect to the intensities. Therefore, it seems reasonable to assume that the first eluted enantiomer has the *R* configuration.

Both atropisomers of 1,1'-bisquinoline *N,N'*-dioxide (75) were obtained by preparative HPLC with a Chiralcel OD column. The mirror images of the CD spectra thus obtained, (+)-**75** and (–)-**75**, ensure that these are a pair of enantiomers (92JHC931).

A related work reported the preparation, resolution, and absolute configuration of 2,2'-bipyridine-3,3'-dicarboxylic acid 1,1'-dioxide (*S*)-(+)-**76** and its ester (*S*)-(-)-**77** (95TA1279). Crystallization of the corresponding brucine salts afforded both enantiomers (-)-**76** and (+)-**76**. Treatment with diazomethane converted the levorotatory acid (-)-**76** into the dextrorotatory methyl ester (+)-**77**. Alternatively, racemate (\pm)-**77** was easily resolved by preparative chromatography on triacetylcellulose. Since CD results were inconclusive, the authors resorted to determining the absolute configuration of the barium salt of acid (+)-**76** by X-ray diffraction using the Bijvoet's anomalous dispersion method (49MI313). This revealed that acid (+)-**76** has the *S*-configuration. For interconversion of the enantiomers of **77**, the free activation energy ΔG^\ddagger amounted to $106.5 \text{ kJ mol}^{-1}$ at 50°C ($\Delta H^\ddagger = 94.7 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -3.7 \text{ J K}^{-1} \text{ mol}^{-1}$). On the other hand, the optically active acid **76** is entirely stable in 0.1 M aqueous NaOH at room temperature; at high temperatures, in the same solvent, it racemized only very slowly ($\Delta G^\ddagger = 132.8 \text{ kJ mol}^{-1}$ at 93.3°C).



The one-pot synthesis of helical aromatics, 13,14-dialkyldibenzo[*b,j*][4,7]-phenanthrolines (**78**) together with their stability against racemization and the assignment of absolute configuration assisted by experimental and theoretical circular dichroism were reported by Tanaka et al. (04JOC7794). For $R = \text{CH}_3$, $\Delta H^\ddagger = 87.5 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -24.1 \text{ J K}^{-1} \text{ mol}^{-1}$ (and not kJ mol^{-1} as reported). The absolute configuration of these molecules was established on the basis of the CD exciton chirality method (exciton-coupled CD) together with theoretically calculated spectra.



A small, axially chiral diacid **79** was designed with chiral memory based on restricted rotation (09OL2599). The chiral memory properties of diacid **79** were initially studied using CD spectroscopy. Heating a racemic sample with a chiral alkaloid (quinine or quinidine) led to an enantiomeric excess of up to 40% *ee*. The guest-induced chirality was preserved on cooling to rt, which was maintained even in the absence of guest ($t_{1/2}$ = 14 year). The chiral enrichment process was also reversible, allowing the diacid to be used as a chiral switch.

2.13 Racemization, enantiomerization, and diastereomerization barriers (kinetics)

The following scheme (Figure 5) defines the relationship between the different entities according to the inter-ring dihedral angle for the rotation about the pivot bond. In this scheme, one or two phenyl groups may be replaced by a heterocyclic framework. The two planar conformations corresponding to $\theta = 0$ and 180° are diastereomers, they correspond to the ground states in the case of high conjugation, weak repulsive interactions X-A; Y,B; X-B; Y-A or attractive interactions X-A; Y,B; X-B; Y-A (09JPC(A))

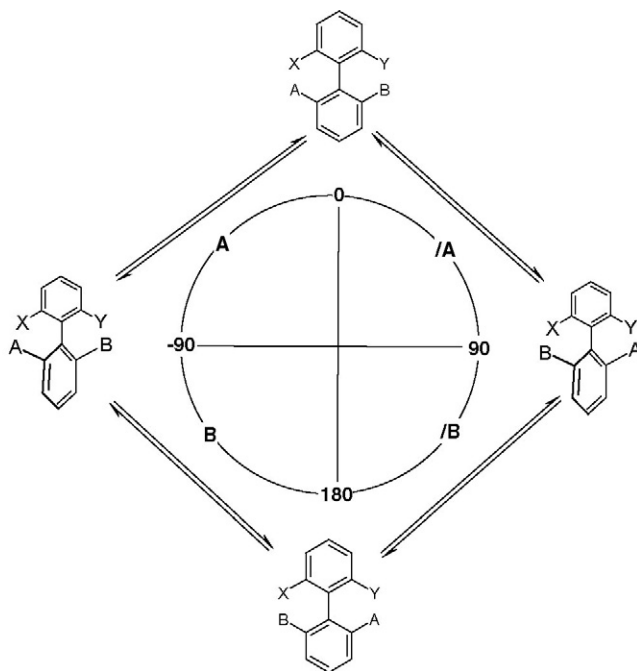


Figure 5. Relationships between the different entities according to the inter-ring dihedral angle for rotation about the pivot bond.

56). One ground state may be planar while the other one may be slightly twisted and composed of two enantiomers belonging to the mirrored quadrants A and /A or B and /B. The two ground states may be slightly twisted giving rise to four stereomers composed of two pairs of fast exchanging enantiomers. The passage from one pair to the other pair will go through the enantiomeric pair at $+90^\circ$ and -90° with the same probability.

In the absence of additional chiral interaction, any conformer belonging to the A quadrant will have its equally populated enantiomer in the /A quadrant while any conformer belonging to the B quadrant will have its enantiomer in the /B quadrant. Conformers belonging to the A and B or /A and /B quadrants are diastereomers. When the angles of twist increase for steric or electronic reasons the occurrence of two pairs of enantiomers will be maintained unless the angle reaches a value equal to 90° for which the two pairs degenerate into a single pair of enantiomers. When the angles of twist are very high one will get a fast exchanging pair of diastereomers and slow exchanging pairs of enantiomers through one or two diastereomeric planar transition states near 0 or 180° . It is worth noting that the passage through the two diastereomeric planar TSs will not be equally probable and will depend on the energy difference between these two states.

It follows from the above considerations that in the case of high conjugation and small steric interaction due to the A, B, X, Y substituents, two diastereomerization barriers between the two (nearly) planar ground states will be obtained: one for the *syn(cis)* to the *anti(trans)* form and one for the reverse reaction. They reflect the difference in energy between the *cis* and *trans* forms.

In the case of a highly twisted framework, the barrier will correspond to the transformation of an enantiomer into its antipode. A single barrier will be obtained in both directions since the enantiomers have the same energy. The resulting apparent barrier comprises the passage by the two concurrent diastereomeric transition states and should be accordingly corrected when compared with a theoretical calculation.

The enantiomerization is the reversible transformation of one atropenantiomer into its mirror image while racemization is the irreversible process leading to a 50:50 mixture of two enantiomers (95CHI396).

The barrier height governs the stability of the species and the method to be employed for its determination. Dynamic NMR will be used for barriers ranging from 40 to 85 kJ mol^{-1} , the atropisomers shall be equipped with sensor giving rise to diastereotopic signals (72TL5239, 75CB1682, 75CJC3431, 76CS120, 80JA5618, 80TL2379). DNMR provides the enantiomerization rate constant. In the absence of these groups, DNMR might also be performed in the presence of a chiral additive in the solvent. Dynamic HPLC on a chiral support covers the barrier range between 85 and 105 kJ

mol^{-1} (see chiral chromatography). The barrier range can be extended toward the lower side using cryo-chromatography. DHPLC provides the enantiomerization rate constant. The barriers above 105 kJ mol^{-1} can be determined on line by trapping an enriched sample in the thermostated cell of a polarimeter or a CD detector at the output of a chromatogram on a chiral support. The decay of the polarimeter or CD signal is recorded as a function of time. Since the racemization of the sample obeys strictly a first order kinetic law with a known final composition of 50:50, the knowledge of the initial concentration is not required. In another method the enantiomer can be obtained by conventional resolution methods or chiral HPLC and submitted to thermal racemization in an appropriate solvent. Chiral chromatography (08T1371) or chiroptical methods (50CJC26) can be used to monitor the composition of the mixture of the enantiomers as a function of time. Anytime chiroptical methods are used, the obtained rate constant is the racemization rate constant k_{rac} . The enantiomerization rate constant can be obtained from the relation $2 k_{\text{enant}} = k_{\text{rac}}$.

The determination of the rate constant at different temperatures allows the derivation of the ΔH^\ddagger and ΔS^\ddagger of the enantiomerization process (67AK115, 74CS226, 80JCS(P1)1599).

When two diastereomers A and B are in equilibrium (Figure 6), the diastereomerization rate constants $A \rightarrow B$ (k_1) and $B \rightarrow A$ (k_2) are different. They are related by the equilibrium constant $K = k_2/k_1$. Thermal diastereomerization can be monitored by NMR, achiral, or chiral chromatography.

As a typical example, the barriers around the two *N*-aryl axes in bis-(thi)oxo-thiazoline are very different and the diastereoisomerization occurred by rotation of the sole thiazolinone. Starting from the pure *syn* form, the ratio of the diastereomers was monitored by NMR versus time allowing the determination of $k_{\text{obs}} = k_1 + k_2$ at the given temperature. The ratio of diastereomers at equilibrium provided $K = k_2/k_1$. The higher stability of the *anti* form resulted from a better accommodation of the dipolar

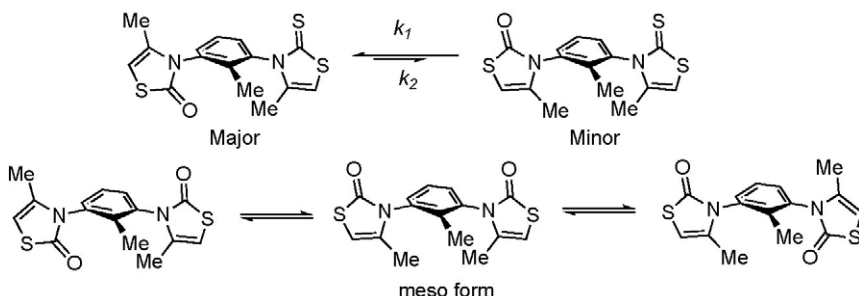
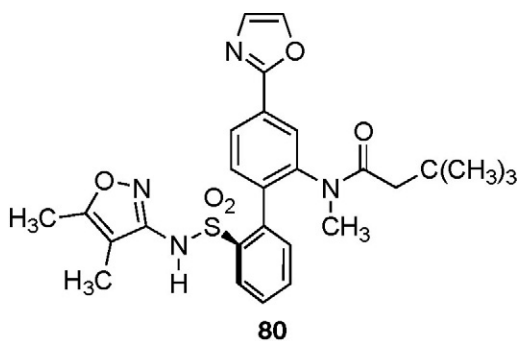


Figure 6. Case of two diastereomers A and B in equilibrium.

interaction. The barriers were also evaluated for the 1,3-bis-thiazolinone derivative in which the rotation is permitted around the two axes giving rise to *meso* and *D,L* atropisomers (00H1699).

Tumambac and Wolf (05JOC2930) have reported a detailed kinetic analysis of the stereodynamics in axially chiral 1,8-bis(2,2'-diphenyl-4,4'-diquinolyl)naphthalene and 1,8-bis(2,2'-diisopropyl-4,4'-diquinolyl)naphthalene *N,N'*-dioxide in which *meso* and *D,L* forms are in equilibrium and were isolated by chiral chromatography.

The determination of the rotation process and the associated barrier to rotation is of primary importance in the field of atropisomerism. It opens the way to dynamic kinetic resolution or spontaneous resolution. The knowledge of the barrier is also important for the development of an atropisomeric drug. If the enantiomerization occurs rapidly at the physiological medium and temperature (37 °C) a racemic drug will be developed. If the barrier is very high single enantiomer will be developed. It is worth recalling that the binding of an atropisomeric drug with proteins might result in a considerable change in the barrier to rotation. The barrier might increase or decrease. An example has been reported for an atropisomeric biphenyl type drug BMS-207940 (**80**) that is out of the scope of this review. The racemization rate was 10 times faster in the presence of human serum or human serum albumin than in pure water. Furthermore, the rate was dependent on the initial concentration of the atropisomers (05JC(A1078)67).



Cases in which the barrier increases upon binding have not yet been disclosed. One may foresee many new studies in that direction for the atropisomeric drugs.

2.14 Theoretical calculations

Biphenyl, like benzene, methane, acetylene, pyridine, furan, and so on, is one of the paradigmatic molecules of organic chemistry. Biphenyl and several of its derivatives, including the important catalyst 1,1'-binaphthol,

have been the subject of many theoretical studies. As Johansson and Olsen pointed out “From an electronic structure point of view, biphenyl is a surprisingly challenging molecule. Especially, pinpointing the energetics of the internal rotation around the central C–C bond connecting the two benzene units has proven problematic” (08JCTC1460).

Theoretical papers on biphenyl are very numerous and we will cite only a few recent ones. According to Hosoya (05M1037), biphenyl can be considered to consist of two unlinked aromatic rings. Taubert et al. (10IJQC848) reached the same conclusion (they studied also phenol-imidazole). The experimental barriers around the planar and perpendicular conformations were for the first time accurately reproduced by Johansson and Olsen (08JCTC1460). Several *ab initio* methods were used by Grein to calculate the dihedral angle and energy barriers of biphenyl (03THE(624)23). Prampolini et al. (10JCTC2536) analyzed its potential energy surface.

The heterocyclic analogues of biphenyl, that this review survey, have also been studied but in a much lesser degree. The evolution of computational chemistry allows predicting that only HF, DFT, and higher level methods will survive in the near future. For this reason we will not report semiempirical (mostly PM3, MNDO, and AM1) nor molecular mechanic calculation results save in exceptional cases.

Taking into account the ring size and the nature of the atoms involved in the central bond, it is possible to classify the calculated molecules into nine sections.

2.14.1 C–C, 6-6 Derivatives

These compounds have been much studied and since 1980, *ab initio* studies were published. Barone et al. in 1986 summarized and extended their previous results in the field of azabiphenyls (Figure 7) calculated at the STO-3G level (86IJQC541).

Among other properties, the authors reported the dihedral angle θ and the planar (TS₀) and perpendicular (TS₉₀) barriers. For instance, for **107**, $\theta = 40^\circ$, TS₀ = 3.7, and TS₉₀ = 5.7 kJ mol^{−1} (80CPL(69)530). The potential curves were adjusted to a Fourier expansion, $\Delta E(\theta) = E(\theta) - E(0^\circ) = \sum 1/2V_j[1 - \cos(j\theta)]$. The main conclusions were that the STO-3G basis set overestimates conjugative attraction and that the repulsions decrease in the order H...H > LP...LP >> LP...H.

Although none carried out such a comprehensive study, Göller and Grummt calculated compounds **81**, **88**, **34**, and **100** with different high-level methods reporting θ values for the minima and different TSs (00CPL(321)399, 02CPL(354)233). They describe the LP...H interaction as strongly stabilizing. Solvent effects on 2,2'-bipyridine (**34**) were calculated showing that polar media shifted the equilibria toward the less stable *s-cis* isomer

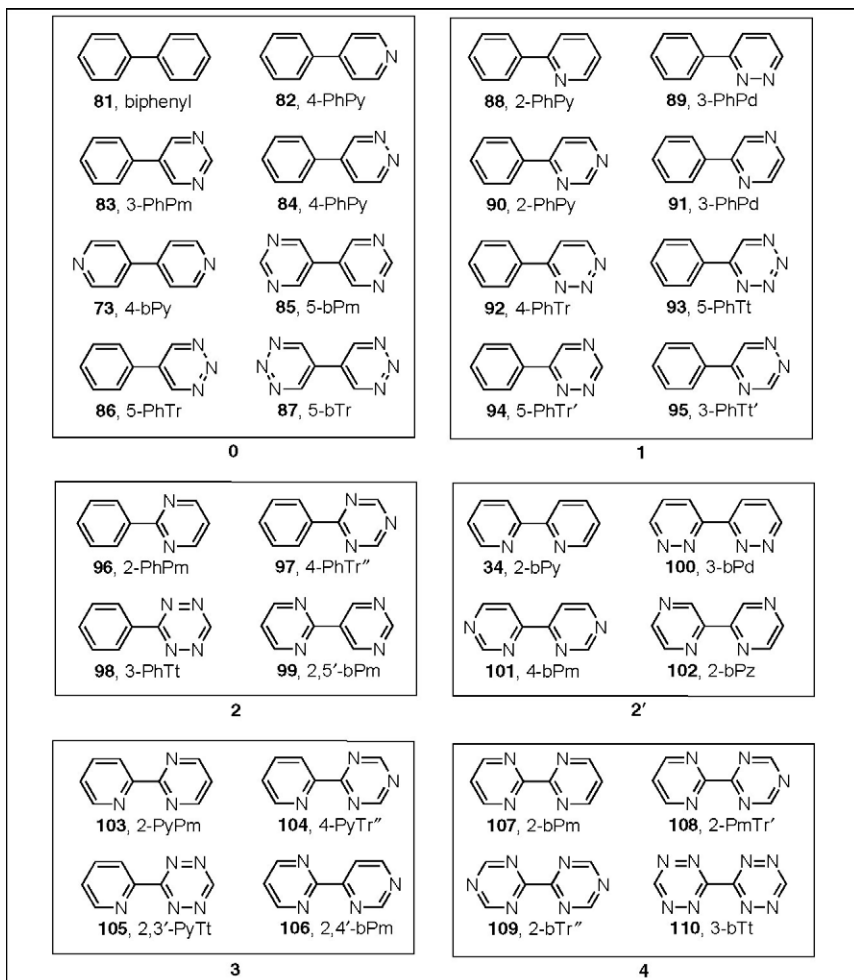
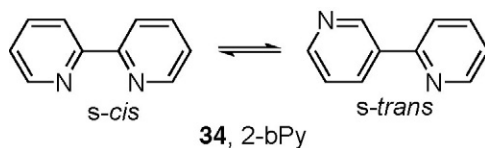


Figure 7. Structure of azabiphenyls. The number of N:/N: (lone pair, LP) interactions range from 0 to 4.

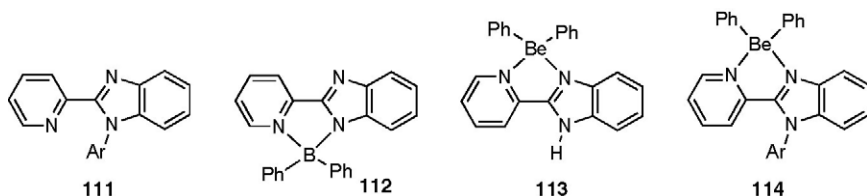
(that represented in Figure 2) (07THE(811)169). The experimental UV spectra were well reproduced using TD-DFT (time-dependent DFT) calculations.



These studies were extended to ELF and NBO analysis of **34** and substituted 2,2'-bipyridines related to allosteric receptors (09CEJ2572). The DFT study of cycloparaphenylenes and heteroatom-substituted nanohoops involves B3LYP/6-31G(d) calculations of chains formed by *p*-substituted **33** motives (10JOC6595). Recently, the minimum energy conformations and the rotational barriers of 2,2'-bipyridine (**34**), 3,3'-bipyridine, and 4,4'-bipyridine (**73**) as well as their conjugated acids were calculated (11CTC(966)334); the conclusion was that MCD conclusions (84BCSJ341) were right save for **34aH⁺** that must have the **34bH⁺** structure.

2.14.2 C–C, 5-6 Derivatives

Very few theoretical studies concern these systems. An example using TD-DFT and the localized density matrix (LDM) method approaches to calculate the electronic spectra of 2-(2'-pyridyl)benzimidazole (**111**) and its boron and beryllium derivatives **112–114** has been reported recently (10THE(955)7).



2.14.3 C–C, 5-5 Derivatives

The importance and simplicity of furans, thiophenes, and pyrroles has resulted in a series of studies concerning these nuclei linked through C–C bonds (**115–128**, Figure 8).

Compounds **124** and **127** were studied at the lowest ab initio level (STO-3G) to conclude that the structures correspond to fully planar *s-cis* (both heteroatoms on the same side, *sZ*) and *s-trans* forms (*sE*), the former being the most stable (81JCS(P2)127). STO-3G and 4-31G calculations were carried out on bifurans **115**, **116**, and **117** by Ortí and Tomás (84THE(108) 199), the authors conclude that the *sE/sZ* preferences depend on the position of the oxygen atoms: in the case of **115** the preferred conformation is the *sE*. A similar conclusion (STO-3G calculations) was reached for bithienyls **119** and **120** where for **118** the most stable conformation is the *sE* (86JCS(P2)907); in this case the rotational barrier was calculated (25.1 kJ mol^{−1}) and it agrees with that determined by DNMR (21 ± 8 kJ mol^{−1}, see Section 2.9). Compounds **115**, **118**, the Se and Te analogues as well as mixed derivatives were studied at the B3LYP/6-311 + +G(d,p) and

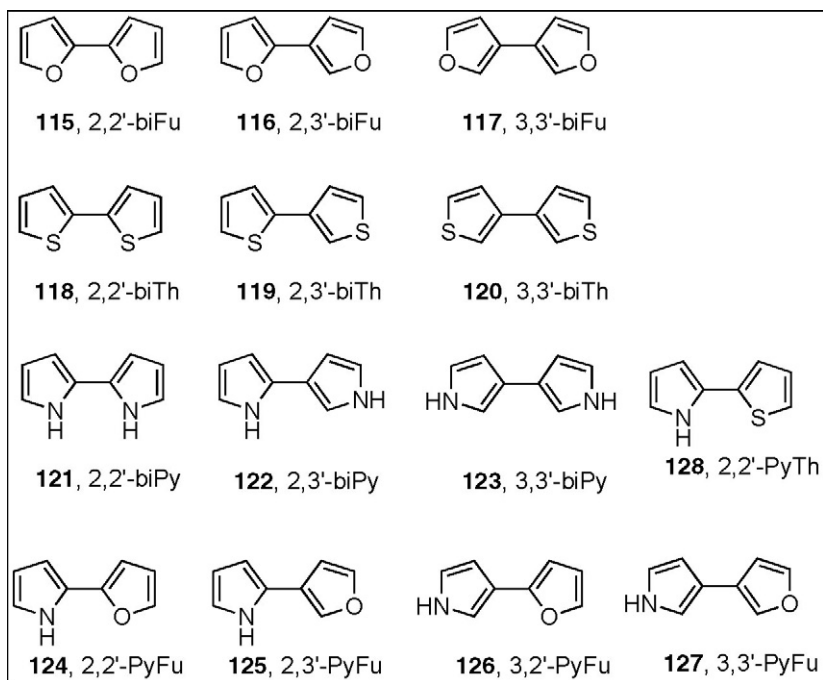


Figure 8. Structures of bifurans, bithienyls, bipyrrroles, furylpyrroles, and thienylpyrroles.

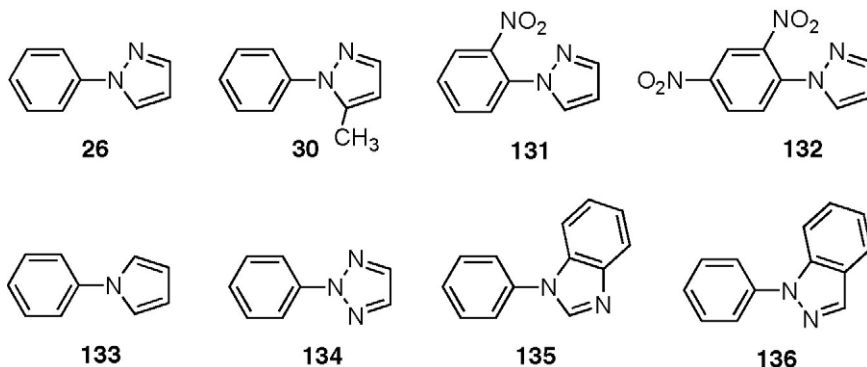
MP2/6-311++G(d,p) levels searching for chalcogen interactions (11CTC 974)37).

The internal torsional potential for the three structural isomers of bifuran 115–117 and the four furylpyrroles 124–127 have been derived from standard SCF STO-3G and 4-31G calculations. Important differences in the potential shapes arise from the two basis sets mainly concerning the planar or out-of-planar structure of equilibrium conformations and the torsional barrier heights. The more relevant results are as follows: (i) 2,2'-Isomers show twofold potentials and planar equilibrium conformations. (ii) For the rest of the isomers, STO-3G predicts twofold potentials in all cases, whereas 4-31G potentials are found to be greatly dependent on the structure of the interannular region. In particular, fourfold potentials implying “gauche” out-of-plane equilibrium conformations and strong decreasing barrier heights are found whenever four hydrogen atoms are present in that region. Furthermore, the *s-cis* conformer of 2,2'-furylpyrrole (117) is stabilized by an intramolecular hydrogen bond. A similar conformational behavior could be expected for 2,2'-thienylpyrrole (128) (87JPC545).



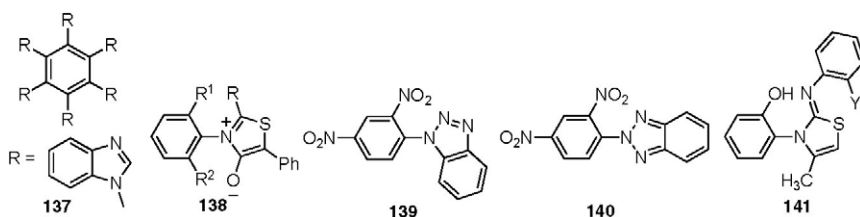
2.14.4 N-C, 6-6 Derivatives

Two papers deserve to be reported here. The absence of excited-state intramolecular proton-transfer (ESIPT) in 3-hydroxy-2-methyl-phenyl-4-pyridinone (**129**) was explained by the twist (48°) of the dihedral angle (AM1 calculations) (94CPL(220)229). The trimethyl derivative of *N*-(1-naphthyl)-pyridinium **130** shows temperature dependent multiple fluorescence. B3LYP/6-31G(d) calculations indicate that several minima on the S1-hypersurface are responsible for this behavior (01MI127).



2.14.5 N-C, 5-6 derivatives

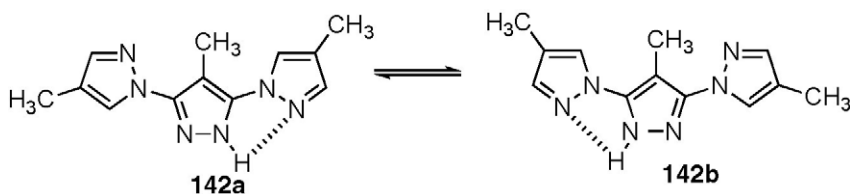
N-Arylazoles is much explored field and several papers are worth mentioning. A systematic exploration of the potential surface of several *N*-arylpyrazoles (**26**, **30**, **131**, **132**) and *N*-phenylpyrrole (**133**), 2*H*-1,2,3-triazole (**134**), benzimidazole (**135**), and indazole (**136**) was reported using the EHT methodology (78T1139). The dihedral angle in the *N*-phenyl compounds increases in the order (only the heterocycle atoms): NN (**134**) < NCH (**25**) < CHCH (**133**) < PhN (**136**) < PhCH (**135**) < NMe (**30**). The *o*-NO₂ groups prefer to be on the side of the N₂ atoms (as represented for **131** and **132**) than on the side of the CHs (see **48**).



Aromatic propellenes, poly-*N*-azolylbenzenes present an interesting problem of atropisomerism. For instance, hexakis(benzimidazol-1-yl)benzene (**137**) presents eight possible conformations that were calculated at the AM1 level (98MC(ACH)475). Other molecules belonging to this section and calculated at different levels are thioisomünchnones (**138**) at B3LYP/6-31G(d) (04EJOC2805), *N*-(2',4'-dinitrophenyl)benzotriazoles (**139** and **140**, the nitro group near the sp^2 N atom, see Section 2.8.5) at B3LYP/6-31G(d,p) (07T3737), and 2-aryl-imino-*N*-(2-hydroxyphenyl)thiazolines (**141**) at B3LYP/6-31G(d) (08JOC403).

2.14.6 N-C, 5-5 derivatives

Although the calculations are semiempirical (AM1) it is the only example of a two five-membered rings linked by an N-C bond (93CJC1443). 3,5-Bis(4-methylpyrazol-1-yl)-4-methylpyrazole present annular tautomerism **142a**/**142b** besides rotational isomerism. Intramolecular HBs stabilizes one of the conformations.



2.14.7 N-N, 6-6, 5-6, and 5-5 derivatives

These compounds were the least studied theoretically. In 1984, Olivella et al. published an MNDO study of 14 *N,N*-biazoles including quaternary salts (84CJC687). The most important conclusions are summarized in Figure 9. Averaged values (depending on the β atoms) show the nature of the interactions.

The X-ray structure of 1,1'-bipyrrole (**143**) was determined by Dey and Lightner (07JOC9395). The dihedral angle was found to be near 80° ; MM calculations were carried out but they afford nearly sp^3 N atoms that are totally unrealistic. Therefore, we decided to study the compounds of

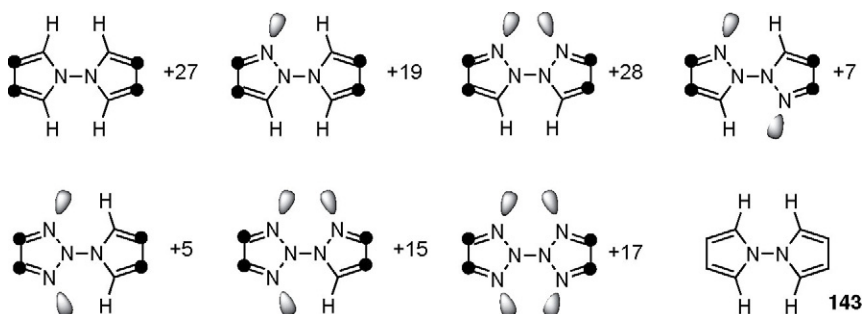


Figure 9. Contribution of different interactions to TS_0 in kJ mol^{-1} . = CR or N.

Figure 10 plus biphenyl (**14**) at the B3LYP/6-31G(d) level of the theory (11CTC(964)25).

The minimum energy conformation of most of these compounds corresponds either to the perpendicular conformation ($\theta = 90^\circ$) or to a twisted conformation ($\theta \approx 70^\circ$) very close in energy (less than 1 kJ mol^{-1}) to the perpendicular one. The only exception is 1,1'-bipyrazole (**146**) with a minimum for $\theta = 138^\circ$ close to the 180° conformation (see as represented in **Figure 4**). The barriers through the planar conformation (TS_0 , $\theta = 0^\circ$) have values between 22 (**147**) and 67 kJ mol^{-1} (**151**). The very hindered 9,9'-bicarbazyl (**144**) has a very high TS_0 , 172 kJ mol^{-1} that results in a very distorted geometry of the central pyrrole rings.

3. ROTATION ABOUT A C–C BOND

3.1 5-5 rings

The conformations of unsubstituted 2,2'-, 3,3'-, and 2,3'-bithienyls were derived from SCF MO calculations (70JA1453, 72T4419). The calculated

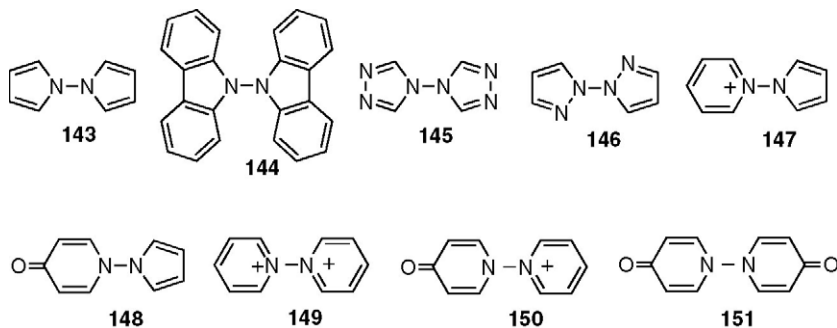


Figure 10. Conformational study of N,N' -linked heterocycles.

resonance energies being about double of that of thiophene, it was inferred that there should be very little interaction between the rings with a preference for the *trans* form. More recently *ab initio* STO-3G calculations were performed on the same compounds. The energy difference between *cis* and *trans* conformers were very low except in the case of 2,2'-bithienyl (86JCS(P2)907).

The structure of 2,2'-bithienyl was deduced from electron diffraction studies. Steric interaction between the sulfur and the opposite hydrogen was at the origin of the observed inter-ring angle of 34° excluding a rigid planar model. Such an angle accommodated the sum of the VDW radii of sulfur and hydrogen (58ACSI671). As stated by the authors "it is not unlikely that there exist two minima on the energy curve at approximately 34° and 85° with a flat minima in between." PPP calculations of 2,2'-dithienyl did not reproduce the angle of twist and resulted in a planar conformation while an angle of twist equal to 30° was calculated for the 3,3'-analogue (70ACSI389).

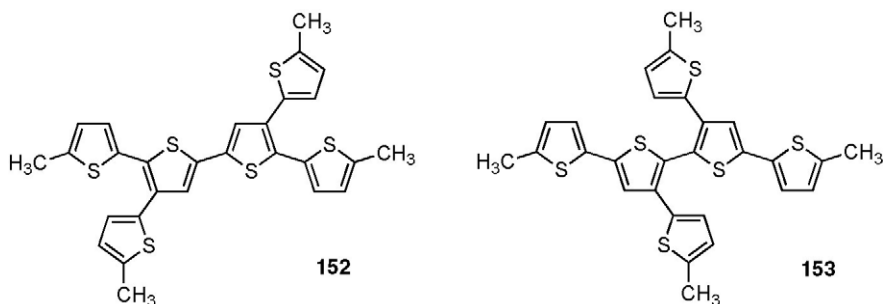
A mixture of *S-trans* and *S-cis* forms in 5,5'-disubstituted 2,2'-bithienyls accounted for the experimental liquid crystal NMR data (73JCS(P2)751, 74JA1305, 74MP(28)441).

Galasso et al. concluded from dipole moment data and theoretical calculations of conformational energies at the STO-3G level that 2-(2-furyl)pyrrole and 2-(2-thienyl)pyrrole are fully planar with *cis* and *trans* conformations, the *cis* form being favored (81JCS(P2)127, 87JPC545).

Ab initio (STO-3G) internal rotation barriers and preferred planar conformations in bifurans linked through 2,3'- 2,2'-, or 3,3'-positions were reported (87JPC545, 84THE(108)199).

The X-ray of 2,2'-bibenzoxazole showed that the two rings are coplanar with an *anti* conformation (98AX(C)668): planar conformation and disorder resulting from the occurrence of *cis* and *trans* orientation were observed by X-ray of 1*H*-3-trifluoromethyl-5-(2-thienyl)-pyrazole (00JMS (526)59). 1,1'-Disubstituted 4,4'-bi-1*H*-1,2,3-triazols have been prepared by a "click" reaction. X-rays showed that the two triazole rings are perfectly coplanar (07EJIC4597). As expected, substitution in *ortho* positions of the pivot bond drastically changed the stereochemistry in this bi-heterocyclic series.

A recent example illustrates the drastic difference in the conformation of bithienyl in the presence or the absence of a substituent in the vicinity of the pivot bond. In tetrameric-thienyl **152**, the two central rings are coplanar whereas the peripheral thiophenes are twisted; in **153** the two central rings are almost perpendicular and the peripheral thiophenes are conjugated. It results in very different UV properties (10TL2956).



The Swedish school paved the way for stereochemical studies in atropisomeric bithienyls ([94KGS1445](#)). Gronowitz *et al.* described the first synthesis and resolution of 4,4'-dibromo-2,2'-dicarboxy-5,5'-dimethyl-3,3'-bithienyl with cinchonine. Interestingly, the sign of the optical rotation is opposite in acetone and chloroform ([61TL604](#)). 2,2'-Dinitro-4,4'-dicarbomethoxy-3,3'-bithienyl ([63AK201](#)) was resolved with brucine. The mixed melting point diagrams of D- and L-atropisomer with L-dimethyl 2,2'-dinitro-6,6'-diphenate allowed the assignment of the absolute configuration. The optical rotatory dispersion curves were recorded ([63AK289](#)).

4,4'-Dicarboxy-2,2',5,5'-tetraethyl-3,3'-bithienyl (**70**) was resolved into enantiomers ([67AK115](#)). The dextrorotatory form was obtained through fractional crystallization of the cinchonidine salt from ethanol. Some remarkable features were associated to the optically active forms. The melting behavior favors the existence of liquid crystals.

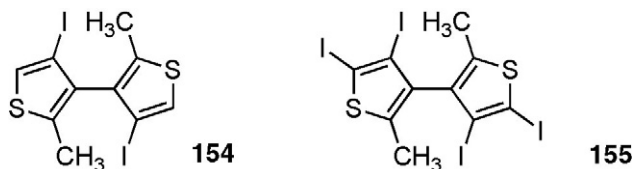
The isolated forms presented strongly solvent and concentration dependent optical rotations. The racemization barriers of the tetramethyl **69** and tetraethyl **70** analogues were determined in 0.1 N NaOH solution by polarimetry. The resulting barriers were equal to 115.8 and 133.3 kJ mol⁻¹, respectively. The origin of the barrier difference is enthalpy driven and results from the larger steric size of the ethyl group compare to the methyl group.

The determination of the (S) configuration to (+)-5,5'-dicarboxy-2,2',4,4'-tetramethyl-3,3'-bithienyl allowed the assignment of the (S) configuration to (+)-2,2',4,4'-tetramethyl-3,3'-bithienyl, (+)-5,5'-dibromo-2,2',4,4'-tetramethyl-3,3'-bithienyl, (-)-hexamethyl-3,3'-bithienyl, and (+)-2,2'-bis(bromomethyl)-4,4',5,5'-tetramethyl-3,3'-bithienyl ([73CS220](#)). The (S) absolute configuration of (+)-4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl was determined by the chemical correlation method to the known absolute configuration of (-)-S-hexamethyl-3,3'-bithienyl. During the chemical correlation the absolute configurations of (-)-4,4'-bis(hydroxymethyl)-2,2',5,5'-tetramethyl-3,3'-bithienyl and (-)-4,4'-bis(bromomethyl)-2,2',5,5'-tetramethyl-3,3'-bithienyl were established as (S). The (S) absolute configuration of (+)-4,4'-dicarboxy-2,2',5,5'-tetraethyl-3,3'-bithienyl (dioxane) was

established by the quasi racemate method on the amide derivatives (75CS131). CD spectra were recorded (74ACS(B)695, 75CS173).

The (*R*) absolute configuration was assigned by X-ray to (+)-4,4'-dibromo-2,2'-dicarbomethoxy-3,3'-bithienyl (71ACS2109, 75CS204) and (–)-2,2'-dibromo-4,4'-dicarbomethoxy-3,3'-bithienyl (76CS66).

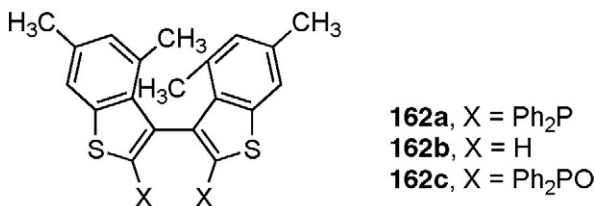
4,4'-Dicarboxy-2,2'-dimethyl-3,3'-bithienyl was prepared by the same group (67AK153). The resolution was not reported. However, some iodinated precursors that were described are prone to give rather high barriers and their resolution could be envisioned with modern chiral liquid chromatography.



The determination of the barriers to rotation in iodinated bithienyls **154** and **155** would bring information on the size of iodine in buttressing conditions in five-membered rings. However, it was shown that buttressing was hardly detectable in a five-membered ring during a series of barrier determinations which confirmed the smaller steric requirement in the transition state for a 3,3'-bithienyl ring compare to the biphenyl analogues (74CS226).

A series of atropisomeric 3,3'-bibenzothiophenyls was prepared by the Ullmann reaction of 3-halo-1-benzothiophene precursors (Figure 11). 3,3'-Bi(1-benzothiophene)-2,2'-dicarboxylic acid (**161**) was resolved with quinine. The absolute configuration of levogyre diacid is (*R*) according to CD spectrum and X-ray analysis. Reduction of the optically pure diacid gave the corresponding alcohol that reacted with AlCl_3 EtOH to yield optically pure aluminium hydride. Reduction of acetophenone resulted in modest *ees* of the 1-phenylethan-1-ol (03CCC1020).

In 1995, 2,2'-bis(diphenylphosphino)-4,4',6,6'-tetramethyl-3,3'-bibenzo [*b*]-thiophene (**162**) was the first example of a very rich family of biheteroaryl systems showing hindered rotation at the interannular bond and equipped with phosphorus atoms able to chelate transition metals (95JCS (CC)685, 95PCT2647, 96WO1831).



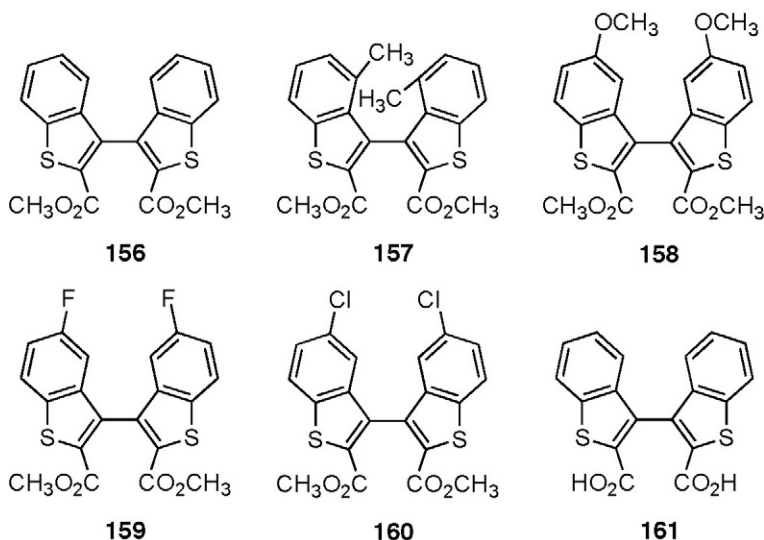
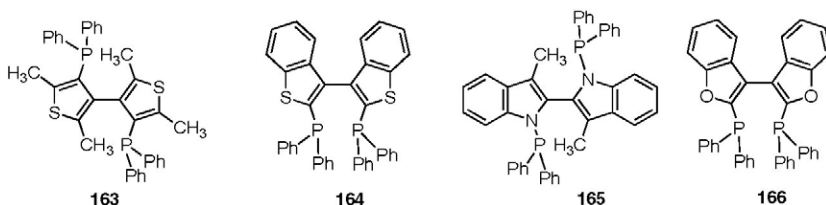


Figure 11. Bisbenzothiophenes.

The enantiomers of **162c** were resolved with (–) or (+)-2,3-O,O'-dibenzoyl-L-tartaric acid and the less soluble diastereomer was collected affording optically pure (–)-**162c** and (+)-**162c**, respectively. Reduction of (+)- and (–)-**162c** afforded (+)-**162a** and (–)-**162a**. It is worth noting that the reduction was performed on pure enantiomers in refluxing xylene for 10 h; such a procedure required a very high configurational stability in both starting and final material. Ru(II) complexes of (+)- or (–)-**162a** gave outstanding *ees* in the enantioselective hydrogenation of beta-ketoesters and opened the way to a very rich and diverse field in enantioselective catalysis, which has been recently reviewed (10AHC(99)33).

In addition to **162a**, the synthesis and resolution of three other atropisomeric biheteroaryl diphosphines **163**, **164**, **165** were reported (95PCT2647, 96WO1831).



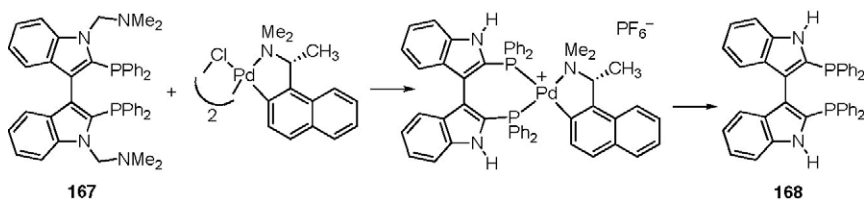
The synthesis, thermal stability of optically pure **163** and **164** and their use as ligand in Ru(II) catalyzed hydrogenation of α - and β -oxoesters was reported. 2,2'-Bis(diphenylphosphinyl)-3,3'-bibenzo[*b*]furan **166** was

found to be configurationally unstable at room temperature. The very large difference in the C–S and C–O bond is at the origin of the observed drastic difference in barriers in **164** and **166** (96JOC6244). A similar effect of the internal bond lengths and angles on the barrier was already exemplified in *N*-aryl-oxazoline-2-thione and *N*-aryl-thiazoline-2-thione derivatives (85JCS(P)273).

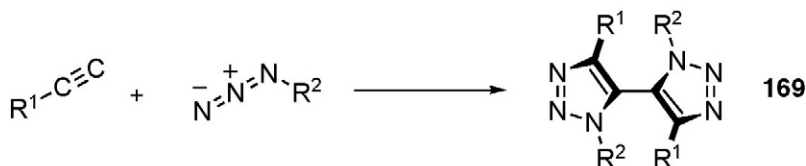
Atropisomers of 1,1'-bis(diphenylphosphanyl)-3,3'-dimethyl-1*H*, 1'*H*-2,2'-biindole (BISCAP, **165**) and 1,1'-bis(diphenylphosphoryl)-3,3'-dimethyl-1*H*,1'*H*-2,2'-biindole (BISCAPO) were prepared and resolved to participate in a study of the electronic influence of the biheteroaryl groups on the liganding properties in metal assisted enantioselective catalysis ([97JOM\(529\)445](#)).

Several chiral columns and elution conditions were screened to find the best column to determine the optical purity of nine of the underivatized diphenylphosphine and diphosphine oxide ligands describe above. Supelcosil LC-(*R*)-phenyl and (*R*)-naphthyl urea based columns and cellulose tris(4-methyl-phenylcarbamate) coated on silica (Chiralcel OG) were very efficient in these separations. All the atropisomers could be analyzed using these three columns (98JC(A795)289, 02CHR25).

Independently ([96TA285](#)), atropisomers of **167** were resolved by chiral chromatography. Resolution using a chiral palladium complex resulted in the loss of the dimethylaminomethylene group and yielded the unsubstituted biindole derivative **168**. The configurational stability of the atropisomeric form was not reported.

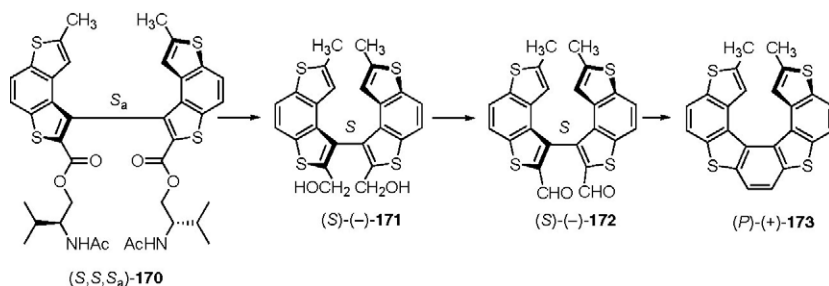


Angell and Burgess showed that “click” chemistry of copper-catalyzed Huisgen reaction between alkynes and azides in the presence of a base resulted in the formation of C–C linked bitriazole atropisomers (**169**) (07AG3723). Several examples were reported but the barriers were not determined.

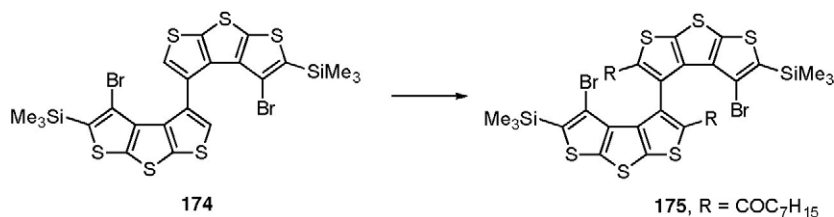


The use of an optically pure alkyne resulted in the formation of diastereomers that were separated by chromatography and analyzed by CD spectroscopy.

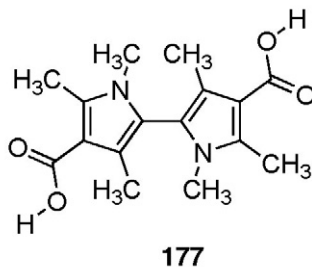
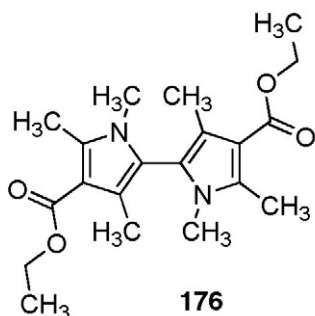
Tanaka *et al.* showed that axial chirality in bibenzodithiophenes (**170**)–(**172**) was completely transferred into helicity of the thiaheterohelicene (**173**). The key step to obtain the starting optically pure material was the metal-mediated biaryl coupling between two benzodithiophene units equipped with optically pure oxazoline moieties followed by diastereomer separation ([97JOC4465](#)).



Racemic atropisomeric diketone **175** was prepared by diacylation of the precursor **174** ([04CEJ6531](#)). The interplanar angle was 96° between the dithienothiophene units. Kinetic resolution was performed by diastereoselective reduction of one ketone by optically pure (–)- β -chloro-diisopinocampheylborane that left optically pure (–)-**175** unchanged. Oxidation of the resulting alcohol afforded optically pure (+)-**175**. Interestingly, an X-ray of (+)-**175** showed that five independent molecules that present interplanar angles 100.4 , 100.3 , 99.3 , 88.9 , and 85.9° are located in the asymmetric unit. It indicates a significant flexibility between the transoid and cisoid forms. The absolute configuration R was associated to (+)-**175**. Analysis of **175** can be performed on a Chiralpak AD column. Pure enantiomers of **175** were cyclized into the corresponding optically pure helicene by an intramolecular McMurry reaction.



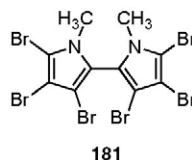
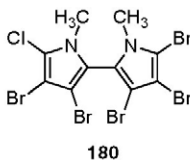
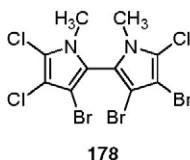
4,4'-Dicarbethoxy-1,1',3,3',5,5'-hexamethyl-2,2'-bipyrryl (**176**) opened the way to the stereochemistry in 2,2'-bipyrryl ([53JOC1413](#)). The diacid analogue **177** was partially resolved into enantiomers with brucine.



Interestingly, it is reported that the scalemic samples melted with sublimation. These compounds could be good candidates for the ongoing interest on self-disproportionation during sublimation.

A 1,1'-dimethyl-2,2'-bipyrrole with four bromines and two chlorines has been isolated and identified in various seabird egg samples from Canada. The precise substitution pattern was not established (99EST26). 5,5'-dichloro-1,1'-dimethyl-3,3',4,4'-tetrabromo-2,2'-bipyrrole (Br_4Cl_2 -DBP) was prepared and identified in Tiger Sharks (09EST2288), in various whale products in Japan (06MI135) and California sea lions (06MI522).

The following four hexahalogenated 1,1'-dimethyl-2,2'-bipyrroles, **178–181**, have been detected in marine mammal blubber (02MI244).

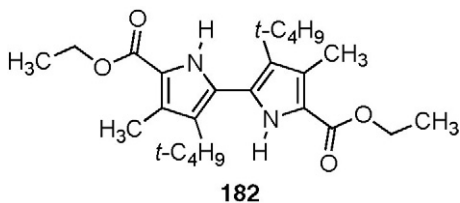


5,5'-Dichloro-1,1'-dimethyl-3,3',4,4'-tetrabromo-2,2'-bipyrrole (**179**) was recently separated into enantiomers by HPLC on cellulose tris(3,5-dimethylphenylcarbamate) in a mixture of hexane/2-PrOH (95:5) (10JC (A1217)2050). The first eluted enantiomer was the (+) form. X-ray analysis was performed on the second eluted (–) form. The inter-ring angle was 66.1° . Absolute configuration determination associated the (–) enantiomer to the (*S*) form. Efforts were conducted to analyze the enantiomers by chiral GC analysis using a permethylated cyclodextrin CP-Chirasil-DEX CB (β -PMCD). The (–)-*S* form was eluted first. The run time was particularly long on a short (8.5 m) capillary column (115–130 min). GC should not be recommended for analysis. However, an interesting result gained from GC analysis was the observation of partial racemization, which depended on the injector temperature. At 140°C no racemization occurred whereas at 220°C 9% of the (–) enantiomer was observed when a pure (+)

sample was injected. If one considers the very short transit time in the injector oven, the barrier should be easily determined.

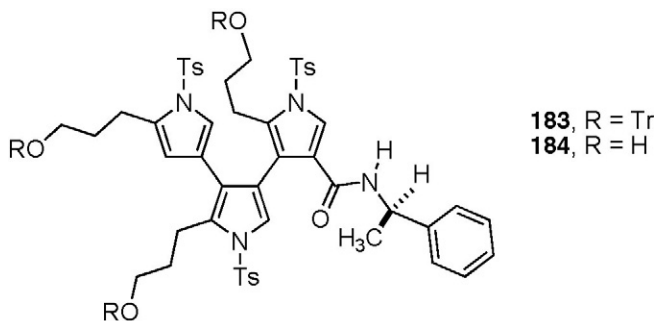
Analysis of a sample of melon-headed whale extract and pygmy sperm whale extract revealed an excess in favor of the (–)-*S* form, the origin of which is still unknown.

2,2'-Bipyrrole **182** bearing two *t*-butyl groups in the blocking positions has been reported (03MC889). Stable atropisomeric forms were detected by NMR from the diastereotopic methylene groups of the ethyl ester.



X-ray data showed that the two pyrrole rings are nearly orthogonal with an inter-ring angle equal to 84.5°. Diastereomers were formed by transesterification with optically pure 2-(*S*)-methylbutyl alcohol. Unfortunately classical crystallization or GC did not separate the diastereomers. Resolution into enantiomers should be attempted by liquid chromatography on a chiral support.

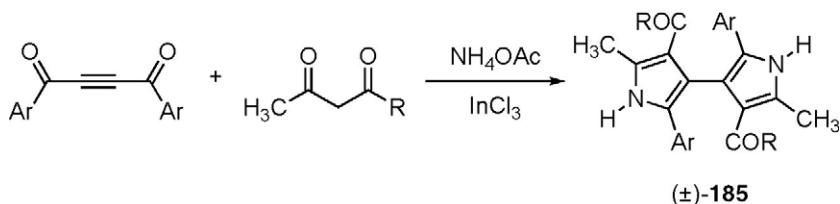
Magnus *et al.* (90JA2465) reported on multiple atropisomerisms resulting in helical enantiomeric conformations.



Three consecutive 3,3'-linked pyrroles were designed in **183** and **184**. These compounds presented two chirality axes and a fixed chirality center. If the barriers about the axes were high enough, four diastereomers should be observed by NMR. The two axes are not equivalent in terms of rotational barriers since in one case one finds two flanking substituents and in the other case one finds three flanking substituents. Obviously in the case of the axis with only two flanking substituents, the barrier is too low to be

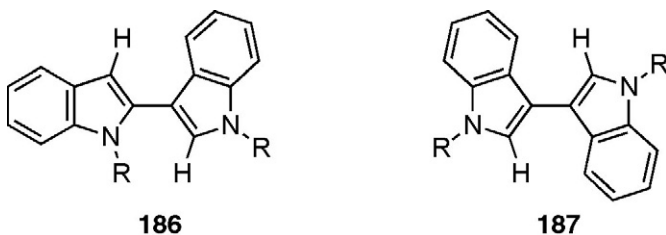
observed by NMR. Only two diastereomers resulting from one chirality axis and a fixed chirality center were observed between 0 and 100 °C. The conclusion that the observation was due to the occurrence of a *P* and *M* helix is not sound. Accordingly the reported scheme in (90JA2465) is misleading.

A series of 3,3'-bipyrroles **185** was prepared according to the following procedure (08OL1373).



Two examples **185a** (R = OEt, Ar = Ph) and **185b** (R = Me, Ar = Ph) were nicely separated into enantiomers on a Chiralcel OD-H column. The absolute configurations of (+)-**185a** (first eluted) and (–)-**185a** were found to be *R* and *S*, respectively, by comparing the experimental CD spectra with the calculated one (ZINDO method). The activation energy for the racemization of **185b** (111.6 kJ mol^{–1}) was estimated by a DFT calculation. The experimental barriers were not measured. An X-ray of **185a** showed two noncomplementary dihedral angles (82.7 and 87.9) for the inter-ring torsion indicating that the pyrrole rings deviated from planarity.

Homocoupling of various indole derivatives was recently described using Pd(OTFA)₂ and Ag(NO₃). Biindole **186** (R = Me) presented in the solid state a twisted structure (inter-ring angle 30°) whereas **187** is perfectly planar. A low barrier is expected in **186** (10CC4553).

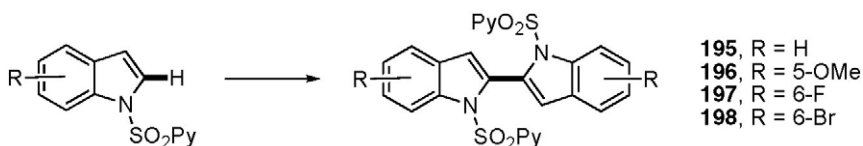


Atropisomeric brominated C–C linked biindoles have been isolated from Australian algae.

2,2',5,5'-Tetrabromo-3,3'-bi-1*H*-indole **188** and the corresponding diacetyl derivative **189** did not present optical rotation. The barrier to racemization in these 5,5'-ring connections might be not high enough to preserve a possible optical activity during isolation. It would be

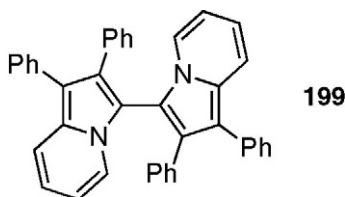
interesting to determine these barriers. The substitution pattern in 2,3',5,5'-tetrabromo-7'-methoxy-3,4'-bi-1*H*-indole **190** (5-6 rings) and the acetylated analogues **191** and **192** is much more favorable to produce a high barrier to rotation. Natural compound **190** presented a high optical rotation $[\alpha]_{20}^D = +71^\circ$ in CHCl_3 . Room temperature monoacetylation and diacetylation preserved the optical activity (+99 and $+71^\circ$ in CHCl_3). Natural biindoles **193** and **194** are also optically active ([82JA3628](#)). 2,2',6,6'-Tetrabromo-3,3'-bi-1*H*-indole that presents also a chirality axis has been described without mention of its chirality ([91JNP1661](#)). These data should be revisited using chiral chromatography to determine *ees* and barrier to rotation.

N-(2-Pyridyl)-sulfonyl protected indole underwent dehydrogenative 2,2'-homocoupling catalyzed by $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OTf})_2$. Four examples, **195**–**198**, were reported with 60–70% yields ([10CEJ9676](#)).



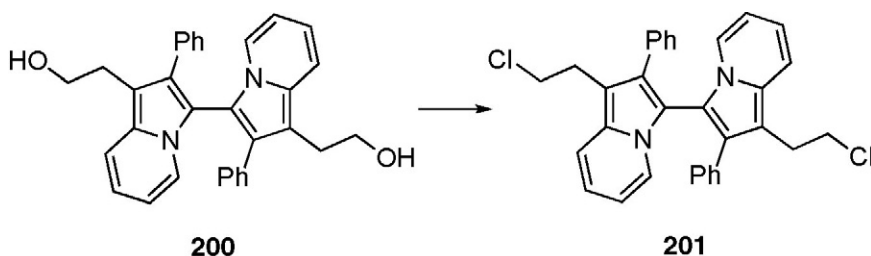
An X-ray of **195** showed that the two indole rings are nearly perpendicular, giving rise to atropisomerism. Chirality issues were not addressed.

Upon oxidation, indolizines easily undergo dimerization by C–C bond formation at their 3-position. 1,1',2,2'-Tetraphenyl-3,3'-biindolizine (**199**) and 2,2'-dimethyl-1,1'-diphenyl-3,3'-biindolizine prepared in that way have been resolved into atropisomers by means of chiral HPLC ([96JOC710](#)).



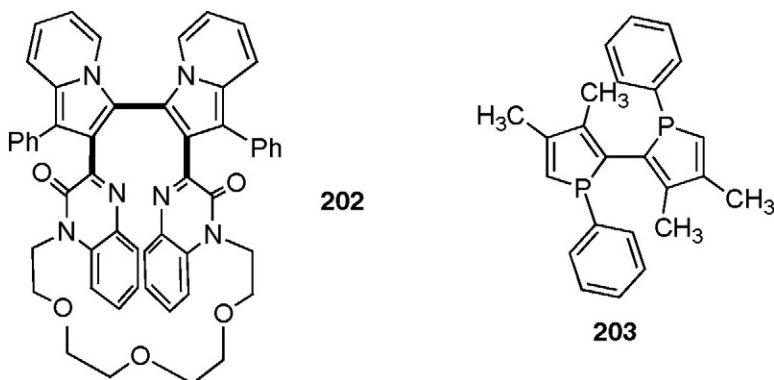
Atropisomers of 1,1'-bis(hydroxyalkyl)-3,3'-biindolizines (**200**) were obtained in enantiomerically pure forms by selective transesterification by vinyl acetate catalyzed by *Candida Antartica* (Novozym 435). They could be obtained as well by chiral liquid chromatography on Chiralpak AD ([96TA3365](#)). An unexpected racemization occurred at room temperature during the reaction with tetrachloromethane–triphenylphosphine to yield the corresponding dichloro **201**. The chirality is preserved at higher reaction temperatures. A cyclic “ansa” intermediate

resulting from the reaction of $(\text{Ph})_3\text{P}^+-\text{C}(\text{Cl}_2)-\text{P}^+(\text{Ph})_3$ with the diol would be formed at room temperature leading to these unexpected results (97JCS(CC)551).



Curiously “ansa” compounds that were prepared with different bridge lengths and characterized by X-rays did not show fast racemization. They were resolved by chiral chromatography (96JOC710).

Another 3,3'-bindolizine presenting three chirality axes in **202** has been reported (08JMS(889)89). The barrier to rotation about the indolizine–quinazoline axis was determined by DNMR and confirmed by HF/6-31G calculations. The barrier for that process is low (53 kJ mol^{-1}).



Chirality issues arising from the hindered rotation about the indolizine–indolizine bond were not addressed (08JMS(889)89).

BIPHOS (**203**) is an interesting example of stereolabile axial and center chirality. The stereolability is overcome during crystallization as a conglomerate composed of the *S*[*RR*] and *R*[*SS*] forms. Racemization occurred at -60°C in solution. The formation of a dichloropalladium complex led to spontaneous resolution affording a single enantiopure form from the racemate (94JA3306, 96CC2287, 01AG(IE)1076). Several examples in which the two phosphorous atoms were linked have been recently reported (09DT6528).

3.2 5-6 rings

α -Furyl and α -thienyl hydroquinones were prepared. The absence of splitting of diastereotopic methyl group in the NMR study of the suitable *i*Pr substituted furanes ruled out detectable hindered rotation (66HCA1794).

Solvent and steric effects on UV and ^1H NMR spectra were addressed in 4-phenylpyrazoles (67RTC1249) and 5-phenyltetrazoles (68CJC2855). Introduction of methyl groups in *ortho* positions of the pyrazole decreased the conjugation with the phenyl. Experimental and calculated dipole moments of 3(5)-phenylpyrazoles revealed the inter-ring twist (95BSB383). MO calculations (Hückel and CNDO/2) on the preferred conformation and electronic structure of phenylpyrrole, phenylfuran, and phenylthiophene showed significant twisting depending on the heterocycle. The two rings in 2-phenyl-pyrrole and 3-phenyl-pyrrole are almost coplanar with a low energy oscillation range. In *N*-phenylpyrrole, the N-phenyl bond is shorter than C-phenyl bond in 2- and 3-phenylanalogues and four hydrogens are in interaction in the coplanar conformation. The coplanar conformation is thus unfavorable (71T4947). The most probable conformation in 2-, 4-, and 5-phenylthiazole has been studied (72T2799, 76JMS(30)169, 78MI1). The X-ray structure of 1-methyl-2-phenylimidazole and 1-methyl-4-phenylimidazole revealed that the twist angle is 32.3° in the former and 7.3° in the latter for the solid state (94JHC899).

2-(1'-Pyridin-2'-one)benzimidazole was found to be planar by X-ray analysis (01JPC(B)12759). 3-Phenyl-1*H*-pyrazole and 5-phenyl-1*H*-pyrazole presented interesting cases of desmotropy. An X-ray of 5-phenyl-1*H*-pyrazole showed an inter-ring angle equal to 18° and a racemic arrangement in two adjacent helices. 3-Phenylindazole presented polymorphism and a nonplanar conformation (02HCA2763).

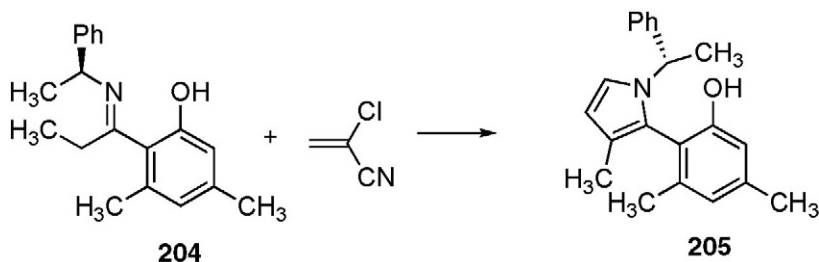
The influence of an *o*-substituent on the dihedral angle between the aryl group and the imidazole was clearly shown in the crystal structures of 2-(2'-hydroxyphenyl)imidazole and 1-methyl-2-(2'-hydroxyphenyl)imidazole. The former is planar with a strong intermolecular hydrogen bond (IMHB) while the latter presented a 116° angle (98JMS(440)193). 3(5)-Ethyl-5(3)-phenyl-1*H*-pyrazole formed a tetramer in the solid state (06SC349).

2-Phenylbenzimidazole exhibits a one-dimensional incommensurate structure related to the angle of twist between the phenyl and the benzimidazole rings, which is modulated with a $\pm 5^\circ$ and $\pm 3^\circ$ variation yielding an average almost flat structure (06ZK281). 2-(2'-Hydroxyphenyl)benzimidazole and 2-(1'-hydroxy-2'-naphthyl)benzimidazole are planar with a strong hydrogen bond between the nitrogen and the phenol. These compounds presented excited-state proton transfer processes (09JCP(A)56, 10JPC(A)4065).

The 3(5)-(1'-hydroxy-2'-naphthyl)pyrazole and the 3(5)-(2'-hydroxy-1'-naphthyl)pyrazoles have been synthesized and fully characterized (95JOC3427). NMR (^1H and ^{13}C) and UV (absorption and emission) spectroscopies in different solvents were used to determine the major tautomers, the coplanarity of both rings (naphthyl and pyrazolyl) and the existence of hydrogen bonds. The photostability of the compounds was addressed. In 3(5)-(2'-hydroxy-1'-naphthyl)pyrazole, the peri interaction between the naphthalene proton and the pyrazole yielded nonplanar structures.

In a study of the tautomerism of 3-(5)-phenylpyrazoles, the X-ray structure of 4-bromo-3-phenylpyrazole showed that a trimeric structure bonded through an H-bond was formed with a considerable twist of the phenyl group about the pyrazole-phenyl bond (92JCS(P2)1737).

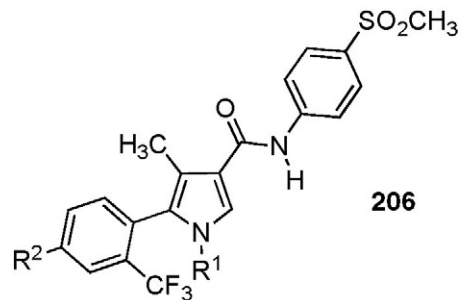
Atropisomeric 2-aryl pyrroles (**205**) have been prepared from *N*-(*S*)-phenylethyl imines (**204**) through an efficient tandem Michael reaction-azacyclization. Diastereomers were obtained in moderate or high *de*, they were separated into optically pure compounds. These compounds showed high rotational barriers since no diastereomerization was observed at 110 °C (04TA139).



Examples of atropisomers of 2-arylpyrrole derivatives have been patented for their excellent mineral-corticoid receptor antagonistic activity and high plasma concentration and blood retention by two pharmaceutical groups. Interestingly, the chirality issues in a previous patent that comprised a large series of 2-aryl-pyrrole derivatives that presented a suitable substitution pattern to give rise to stable atropisomers were not addressed (06WO12642).

The Daiichi Sankyo Company reported three examples of 2-arylpyrroles **206** that have been resolved into enantiomers by chiral chromatography (09EPP2133330). The enantiomers did not racemize standing at room temperature for 7 days in methanol or at 60 °C in an acetonitrile-phthalic acid buffer for 4 h (Table 3).

Drastic differences in activity were recorded for the two enantiomers. It is interesting to note that the activity is not correlated with the order of

Table 3. Examples of resolution of 2-arylpyrroles **206**

R ¹	R ²	CSP-(EtOH)	Elution order and R _t (min)	R _t (min)	IC _{max50} ^a (nM)	IC _{max50} ^a (nM)
Me	H	Chiralpak AD-H	(-) 4.1	(+) 6.3	(-) Form: >1000	(+) form: 2.6
CH ₂ CH ₂ OH	H	Chiralpak AD-H	(+) 4	(-) 4.5	(+) Form: >1000	(-) Form: 2.4
CH ₂ CH ₂ OH	OMe	Chiralpak AD-H	(-) 4.1	(+) 4.7	(-) Form: 1.8	(+) Form: >1000

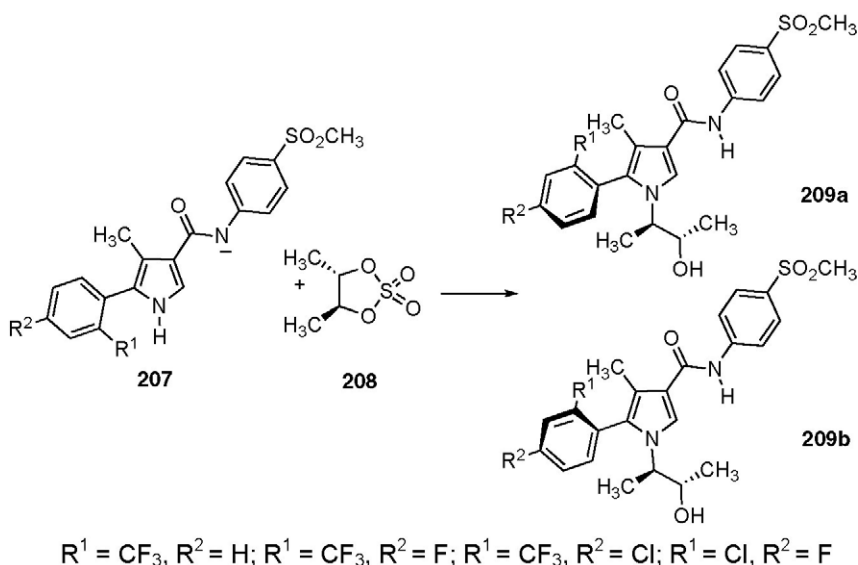
^aScreened for mineral-corticoid receptor antagonistic activity.

elution or the sign of the optical rotation. It would be quite informative to determine the absolute configuration of the more active forms.

The *N*-unsubstituted precursors presented a barrier too low for the separation of the atropisomers.

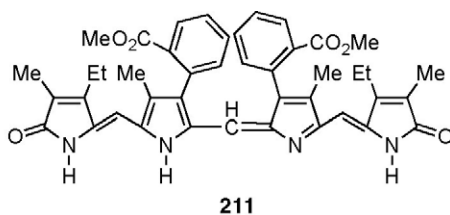
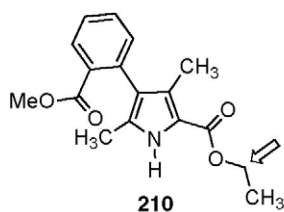
Ex-Elixis Inc. and Daiichi Sankyo Company reported on optically pure diastereomers **209** that resulted from predetermined central-central chirality on the nitrogen of the pyrrole and a variable axial chirality in the *ortho* position ([10WO42622](#)). The diastereomers were nicely separated on Chiralpak AD-H or on silica-gel column. The mineral-corticoid receptor antagonistic activity is exclusively located in the first eluted diastereomer on Chiralpak AD-H using 70:30 hexane/EtOH. Unfortunately, the optical rotation and the absolute configuration at the chiral axis were not reported. We may guess that these informations will be soon available for modeling purposes.

The diastereomers were obtained by reacting optically pure (4*S*,5*S*)-4,5-dimethyl-1,3,2-dioxathiolane-2,2-dioxide **208** with **207** in which the rotation about the C2-aryl group is probably frequent. One might expect a diastereoselectivity that has not been addressed.



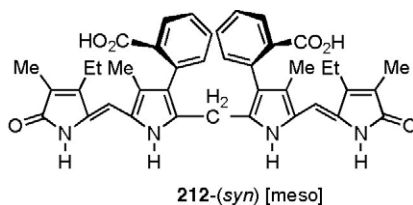
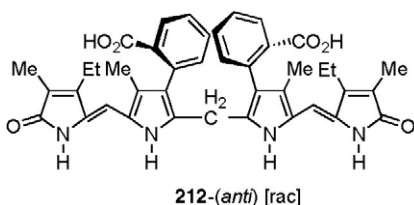
C-Phenylpyrroles that interact with tubulin have been reported as well as their *ortho-ortho'* linked derivatives (see Section 6) ([93BSF779](#)).

Axial chirality was detected in a 3-arylpyrrole **210** derivative through the occurrence of a ABX₃ system for the diastereotopic CH₂ group ([02T7411](#)).



Attempts to resolve the atropisomers of the free acid form were unsuccessful probably due to a too low barrier. 3-Arylpyrrole **210** was used to construct the verdin derivative **211** that showed *syn* (*meso*) and *anti* (*D,L*) forms in their NMR. The ratio was strongly dependent on the solvent. Variable temperature ^1H NMR experiments of verdin **211** showed coalescence at 413K; the barrier to interconversion was equal to 89.5 kJ mol^{-1} (02T7411).

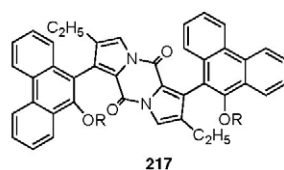
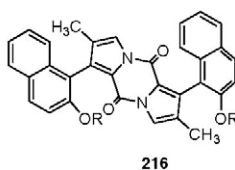
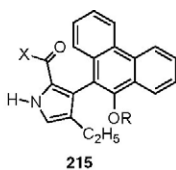
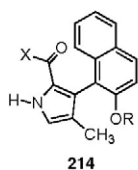
Interestingly, rubin **212** showed an induced CD signal in the presence of cinchona alkaloids in CHCl_3 .



Dynamic chiral HPLC would be quite useful to address the dynamics of these compounds.

Furusho *et al.* reported on a series of atropisomeric 4-methyl-3-(2'-methoxy-1'-naphthyl)pyrrole-2-carboxylates. The enantiomers were obtained by crystallization of the diastereoisomers of the (*R*)-phenethyl ester and further hydrogenolysis. An X-ray of the isolated diastereomer allowed the determination of the absolute configuration. The (*S*) antipode of the free acid presented a positive CD curve at 231 nm. The acid was applied in the "predetermined" synthesis of a chiral atropisomeric porphyrin **213** (Figure 12) (94JCS(CC)653).

The study was extended to the synthesis, resolution, and CD studies of a series of 3-naphthyl-pyrrole-2-carboxylates and 3-phenanthryl-pyrrole-2-carboxylates **214–217** (96JCS(P1)183).



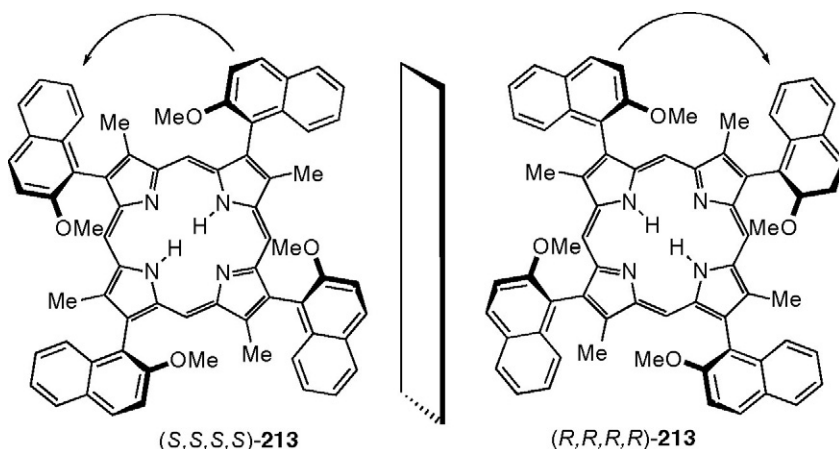
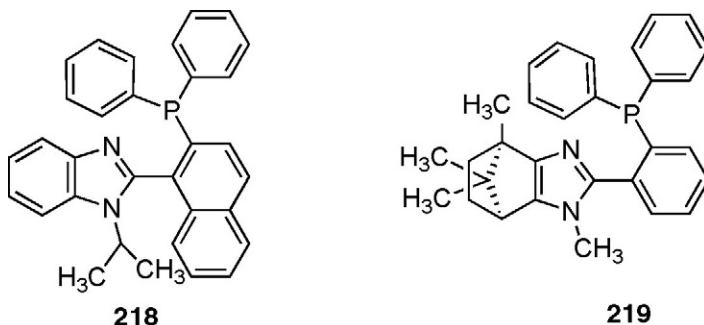


Figure 12. A chiral atropisomeric porphyrin.

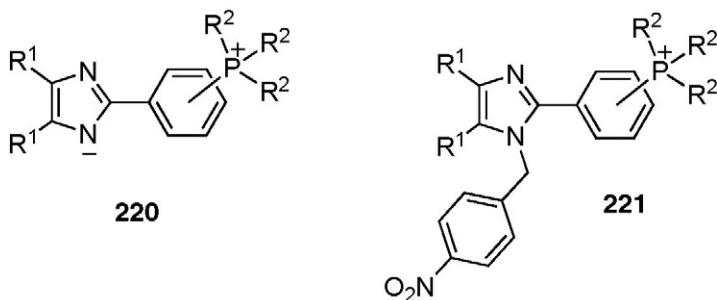
The barrier in phenanthrene **215** (160 kJ mol^{-1}) ($X = \text{OEt}$, $R = \text{Me}$) was 30 kJ mol^{-1} higher than in the naphthalene analogue **214**. Interestingly, the phenanthrene compound underwent spontaneous resolution. Lactonization resulted in racemization. Optically pure atropisomers were employed to prepare optically pure (*S,S*)- and (*R,R*)-pyrocoll derivatives **216** and **217**. All these atropisomers were screened with success as catalysts in the ethylation of aldehydes by diethylzinc.

Atropisomers of 2-[2-(diphenylphosphanyl)naphthalen-1-yl]-1-(propan-2-yl)-1*H*-benzimidazole (**218**) were separated using *ortho*-palladated derivatives of (*S*)-dimethyl(1-phenylethyl)amine as resolving agent. The resulting diastereomers were separated by fractional crystallization. X-ray analysis allowed the determination of their absolute configuration. The pure enantiomers were generated by displacement. The (*S*)-form is levogyre with a specific rotation equal to -75 (**02TA137**).



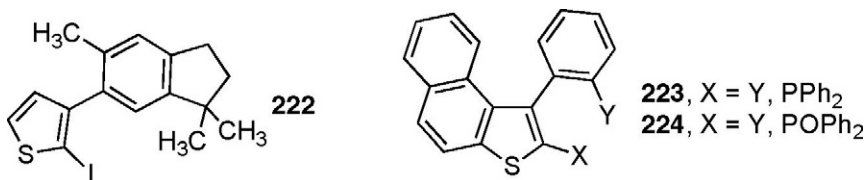
Kulhanek et al. have prepared optically pure (1*R*,7*S*)-4-[2-(diphenylphosphanyl)phenyl]-1,10,10-trimethyl-3,5-diazatricyclo [5.2.1.0^{2,6}] deca-2(6),3-diene (**219**). The barrier to rotation around the C2-aryl bond is probably smaller than in **218** and the occurrence of diastereomeric forms was not mentioned (08TA2462). **219** was used as a ligand in a Henry reaction and led to moderate *ee*.

Allen et al. prepared a series of 2-(phosphonioaryl)(benz)imidazolidine betaines and phosphonium salts **220** and **221** (95JCS(P1)2789, 98JCS(P1)335).



When the phosphonium group bearing three butyl or phenyl groups is situated in position 2 of the phenyl, the phosphonium salt should give rise to atropisomerism. Unfortunately, the NMR data, which would have revealed an AB pattern for methylene proton, were not reported.

A rationally designed system for the study of the steric effects of flanking substituents on the rotational barriers in biphenyl was introduced by Bott et al. (80JA5618). The barriers were determined by DNMR. These barriers allowed the definition of “interference values” that can be used to predict the rotational barriers in 2,2'-biphenyls. These parameters were used to estimate the barrier in a 2-iodo-3-(2-methylphenyl)thiophene derivative **222**.



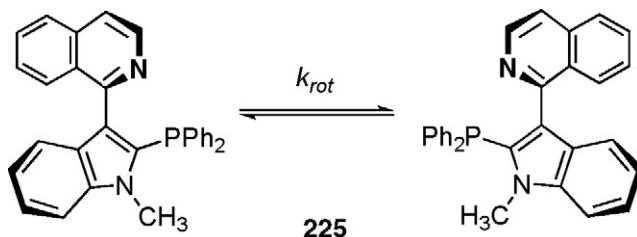
The estimated value was 69 kJ mol⁻¹ whereas the experimental value was 62.5 kJ mol⁻¹ at 340K that probably comes from the difference in the geometry of the two models, the strain being less in five-membered rings than in six-membered rings.

Sanniccolo et al. provided the synthesis and resolution of *rac*-3-[2-(diphenylphosphinyl)phenyl]-2-(diphenylphosphinyl)naphtho[2,1-*b*]

thiophene that was resolved with (–)-O,O'-dibenzoyl-L-tartaric acid or its enantiomer.

Reduction of the separated enantiomer of the phosphine oxides **224** provided optically pure (+)- and (–)-3-[2-(diphenylphosphino)phenyl]-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene **223** that were engaged as Ru, Rh, or Pd ligands (01JOC5940).

Brown et al. prepared an atropisomeric P-N ligand **225** (97T4035). The blocking positions were not large enough to prevent fast exchange at room temperature.



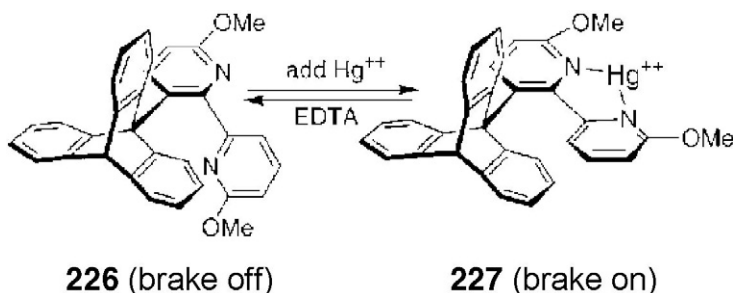
3.3 6-6 rings

In the 1950s and 1960s, the conformation of 2,2′-, 3,3′-, and 4,4′-bipyridyl derivatives in solution attracted a lot of interest using the newly available NMR technology. An NMR study showed that 2,2′-bipyridyl adopts a *trans*-planar conformation in an inert solvent while the monoprotonated and diprotonated forms adopt *transoid* skew conformations with inter-ring angles equal to 25–30° and 55–72°, respectively, in strong acids. In methanol, a large deviation from planarity was advocated (65JPC4166). Some of these results are doubtful (see Section 4.12, 11CTC(966)334). The monoprotonated 6,6′-diamino-2,2′-bipyridine was found to be *syn*-coplanar while the dication was twisted (84BCJ2121). NMR studies were also performed to address the difference in size between a C–H and a nitrogen lone pair. Biaryls having two *o*-nitrogen atoms (2,2′-bipyridyl, 2-phenyl-pyrimidine) are nearly more planar than those possessing only one *o*-nitrogen atom (2-phenylpyridine, 4-phenylpyrimidine). The latter are, in turn, more planar than biphenyl. In these models the size of the nitrogen lone pair is smaller than a C–H (65RTC1399). 3-Phenylpyridazines are planar (66ACS258). The NMR data indicated essentially *trans* coplanar conformations for 2,2′-bipyridyl, 4,4′-dimethyl-, and 5,5′-dimethyl-2,2′-bipyridyl in both inert and hydrogen bonding solvents. 3,3′-Dimethyl-2,2′-bipyridyl was estimated to have an interplanar angle of approximately 60° or 123° attributed to the interaction of the flanking methyl groups (67AJC1227). MO calculations addressed the conformations and properties of phenylpyridine, bipyridyls (71T991, 85CP(96)435, 86JQC541), 2,3′-bipyridyl

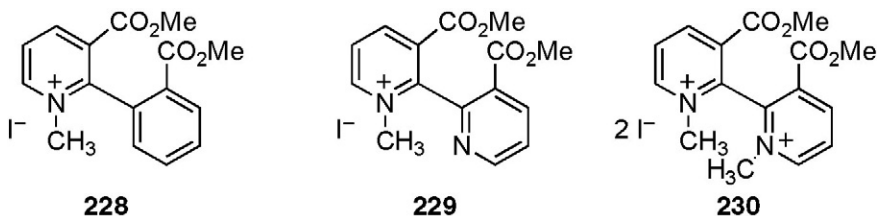
(83ZPC(134)163), phenylpyrimidines (85T1915), and 9-methyl-8-phenyl-6-thiopurine (30°) (74TCA339). A conformational study of 2,2'-bipyrimidyl by *ab initio* and semiempirical methods showed that the inter-ring angle was equal to 40° (80CPL(69)530). Magnetic circular dichroism and calculated absorption indicate a 30–40° twist in the 2,2'-bipyridyl dication (84BCJ341). 6,6'-Dimethyl-2,2'-bipyryl was found to be planar centrosymmetric with a *transoid* arrangement by X-ray crystallography (98AX(C)661).

In summary, the reported conformations show that repulsive interactions decrease in the order hydrogen–hydrogen > lone pair–lone pair > hydrogen–lone pair (86IJQC541).

A vivid example of the application of conformational analysis for unsubstituted 2,2'-bipyryl was reported by Kelly (01ACR514). In the free bipyridyl, the pyridine rings adopted a twisted conformation with a large flexibility around the pivot bond, “brake off” in **226**. Upon complexation the system adopted a much more rigid *syn*-planar conformation that blocked the triptycyl rotation at low temperature, “brake on” **227**.



Breckenridge *et al.* (50CJC26) studied the synthesis and thermal stability of the resolved enantiomers of **228**, **229**, and **230**.



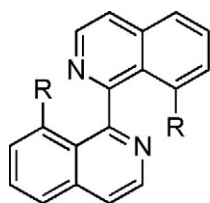
From the reported racemization data for **228** at 125 °C, we calculated a barrier to enantiomerization equal to 135.2 kJ mol⁻¹. Compound **229** racemized faster pointing out a smaller steric requirement of the nitrogen compared to the C–H in the blocking position ($\Delta G^\ddagger = 112.5$ kJ mol⁻¹ at 65 °C) (52CJC725). The double quaternary salt **230** was quite stable to racemization.

Crawford and Smyth succeeded in the resolution of 4,4'-biquinolyl and 5,5'-biquinolyl enantiomers with (+)-tartaric acid. These atropisomers

racemized rapidly at room temperature with half-lives of about 2.5 and 1.3 h, respectively (52JCS4133). The method was extended to the resolution of 1,1'-biisoquinolyl, 4,4'-biisoquinolyl, 5,5'-biisoquinolyl, and 8,8'-biisoquinolyl. In the former case mutarotation was observed in the salt due to a too low barrier (54JCS3464). These atropisomers present barriers ($\Delta G^\ddagger = 91\text{--}93\text{ kJ mol}^{-1}$) suitable for modern DHPLC, the barriers were nicely reproduced by the apparent overlap method developed by Bott et al. (80JA5618).

Oxidation of 1,1'-biisoquinoline led to 1,1'-biisoquinoline *N,N'*-dioxide. The resulting stable atropisomers were baseline separated on a Chiralcel OD chiral column (70:30 hexane/EtOH), the dextrogyre form appeared first. CD spectra were recorded (92JHC931). 1,1'-Biisoquinolines having methyl or methoxy groups in the 8,8' positions were prepared. The former was resolved into enantiomers on a Ceramospher Ru chiral column while the latter was oxidized to the corresponding *N,N'*-dioxide to achieve resolution on the same column (96H415). 7,7'-Dimethoxy-8,8'-biisoquinoline was resolved on Chiralcel OD and employed as chiral ligand for rhodium (87JCS(CC)807).

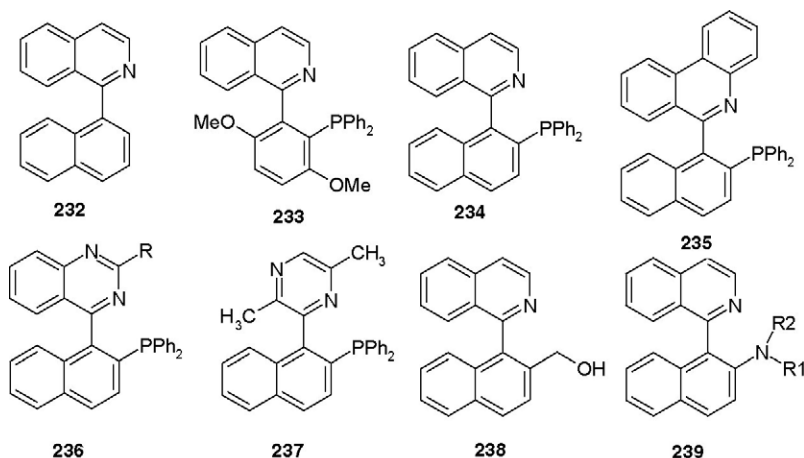
6,6'-Dihydroxy-5,5'-biquinoline enantiomers were applied in the asymmetric addition of diethylzinc to aldehydes. The resolution was performed on the corresponding triflate by chiral HPLC (00CHI510). Interestingly, 8,8'-dialkyl-1,1'-biisoquinolines **231** presented unexpected racemization barriers. The barriers *decreased* when the steric size of the alkyl group *increased* in the series R = Me, Et, and *i*Pr. The strain in the ground state accounting for the observed behavior. AM1 and PM3 calculations confirmed the hypothesis (99TA2975). The exciton chirality method was applied to assign the (*R*) absolute configuration to all the (+)-forms (99CL17, 99JCS(P1)3677).

**231**

R	Me	Et	<i>i</i> Pr
ΔG^\ddagger (kJ mol ⁻¹)	105	101	99
(303 K)			

The same absolute configuration was assigned independently by Chelucci et al. for the methyl derivative that was resolved with an optically pure dipalladium complex. They reported a barrier to enantiomerization equal to 97.2 kJ mol⁻¹ at 40 °C in CHCl₃ (96TA1027).

1-(1-Naphthyl)isoquinoline **232** was resolved with α -bromocamphor- π -sulfonate. A diastereoisomerization depending on the medium acidity was observed during the process; it was accounted for by a rather fast racemization of the free base. (–)-1-(1-Naphthyl)isoquinoline was obtained at –20 °C with a half-life equal to 13 min. The corresponding barrier is 77.5 kJ mol⁻¹ in MeOH (72ACS929).



Alcock *et al.* attempted to prepare an atropisomeric P, N ligand based on 1-aryl-isoquinoline. Derivative **233** was prepared and resolved with optically pure palladium complexes. Diastereomerization was observed in the Pd complexes. It turned out surprisingly that the free ligand racemized rapidly at room temperature ($\Delta G^\ddagger = 93 \text{ kJ mol}^{-1}$) ([92TA17](#)). The dramatic change in the steric requirement of an MeO group compared to a benzo group was illustrated by the successful preparation of QUINAP **234**, the enantiomers of which were stable for 24 h at 65 °C ([93TA743](#)). QUINAP **234** had attracted a lot of interest since it was proven to be an excellent ligand to Pd, Ag, Cu, Ru, Rh, and Ir. QUINAP was employed in a large number of asymmetric reactions ([94T4493](#), [95TA2593](#), [99CEJ1320](#), [03T9471](#)). A series of QUINAP **234** analogues differing by the aryl substituent on the phosphine has been prepared and resolved with chiral palladium complexes ([97TA3775](#)). (*R*) and (*S*)-6-(2'-Diphenylphosphino-1'-naphthyl)phenanthridine **235** were obtained by palladium complex resolution ([95TA2597](#)).

An enantioselective synthesis of chiral QUINAP **234** was reported by Knochel *et al.* ([07SL2655](#)). The organolithium species obtained from 1-(2-bromo-1-naphthyl)isoquinoline by treatment with *t*-BuLi reacted with (–)-menthyl (*S*)-*p*-toluene-sulfinate at –78 °C. The resulting diastereomers were separated via column chromatography. One pot sulfoxide lithium exchange at low temperature, Ph_2PCl reaction, sulfur protection with S_8 and a Raney-Ni desulfurization step afforded optically pure QUINAP (99% *ee*) in 60% yield. The synthetic route avoided the use of Pd complexes for the resolution. The *ees* were determined after resulfurization on Chiralcel OD-H.

A series of optically pure atropisomeric N–P ligands based on quinazoline **236** ($\text{R} = \text{H, Me, Ph, Bn, } i\text{Pr, } t\text{-Bu}$) was developed by Guiry *et al.* ([99TA2797](#), [00TL2475](#), [04JOC6572](#), [10TA1458](#)). They were applied in

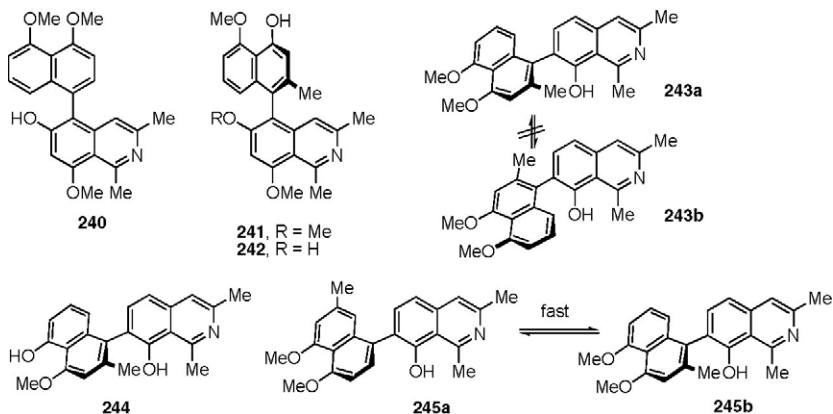
asymmetric rhodium-catalyzed olefin hydroboration. The triflate route was employed to introduce the PPh_2 group and the resolution was performed by the formation of diastereomers with optically pure palladium complexes. The main advantage of the palladium complex is the determination of the absolute configuration of the atropisomers from X-ray analysis.

[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine **237** racemized readily at room temperature and was not suitable as a ligand in asymmetric synthesis (99T3061).

Rac-1-(1-Isoquinolinyl)-2-naphthalenemethanol **238** was prepared by coupling *rac*-1-(*t*-butylsulfinyl)isoquinoline with the appropriate 1-naphthyl Grignard reagent. The enantiomers were resolved by reacting the alcohol with Noe-lactol[®] and further chromatographic separation. The (*S*) configuration was assigned to the (+) enantiomer by X-ray analysis of the *p*-bromobenzoate. The optically pure forms were stable at reflux in benzene for 24 h and they were screened in the enantioselective Et_2Zn alkylation of benzaldehyde (94TA45).

A series of 1-(isoquinolin-1-yl)naphthalen-2-amines **239** was prepared. The atropisomers of the NH_2 , *N*-Me and *N,N*-diMe₂ derivatives were separated on various CSPs and the barriers to racemization in toluene were experimentally determined: $\Delta G^\ddagger = 125.4$, 130.8, and 124.5 kJ mol⁻¹ respectively. Molecular mechanics calculation showed that the most favorable transition state is the *anti* one in which the amino group is opposite to the isoquinoline nitrogen (04H223). When racemic **239** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) and zirconium tetrakis(dimethylamide) were combined in a 2:1 ratio, X-ray data of the complex showed that a selection of identical ligand antipodes by the metal had occurred (homochiral complex) (02AG(IE)345).

Interestingly, atropisomers of fully aromatic naphthylisoquinoline alkaloids from natural sources have been isolated and characterized. Ancistrocladeine **240** was first isolated from *Ancistrocladus tectorius* and *Ancistrocladus ealaensis* (75P2699). It was optically inactive in MeOH.

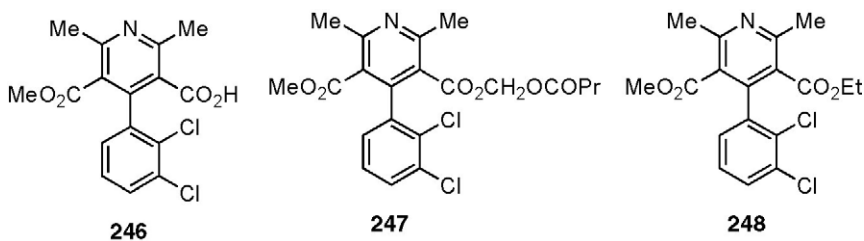


Ancistrobenomine A (**241**) and its desmethyl analogue **242** gave stable atropisomers due to the presence of four flanking groups around the pivot bond. Configurationally stable enantiomers were also reported for dioncophylleine **243b** and *ent*-dioncophylleine **243a**. Near optically pure **243a** and **243b** were isolated from different natural sources. They gave mirrored image CD spectra. Optically pure 5'-*O*-demethyl-*ent*-dioncophylleine **244** was also characterized. **245a** and **245b** that present two flanking groups about the single bond were exchanging rapidly (04JNP2058, 05JNP686).

Slany and Stang (96S1019) reported the synthesis of a series of optically pure 3,3,-disubstituted-4,4,-biquinoline derivatives. The resolution was nicely performed by formation of diastereomeric esters or amides. The absolute configurations were assigned and the configurational stability was found quite high. The substituents in position 3 and 3' were CO₂Et, CO₂H, COCl, and CN.

Streptonigrin (**72**), produced by *Streptomyces flocculus* is an interesting example in which two axes of rotation are possible. It crystallized in a chiral space group and it was shown that the B and C rings are coplanar and the D ring is twisted, accounting for the chirality of the product. From the CD spectra in solution the (*S*) configuration was assigned to the natural product. Streptonigrin monoxime, which is prepared by reaction of Streptonigrin with hydroxylamine at reflux in pyridine for 3 h, is still optically active, demonstrating a very high barrier around the C/D rings (81T2929).

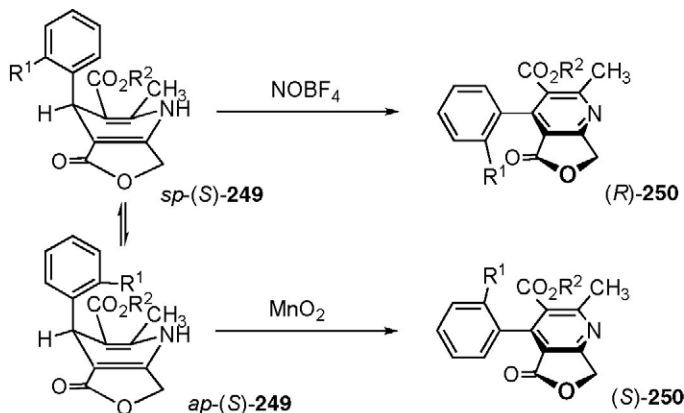
Two 4-(2',4'-dichlorophenyl)pyridine derivatives **246** and **247** were nicely separated into enantiomers on a Chiral-AGP chiral column (97JC (A763)115). These compounds are examples of oxidation products of the large family of 1,4-dihydropyridines that are important active drugs.



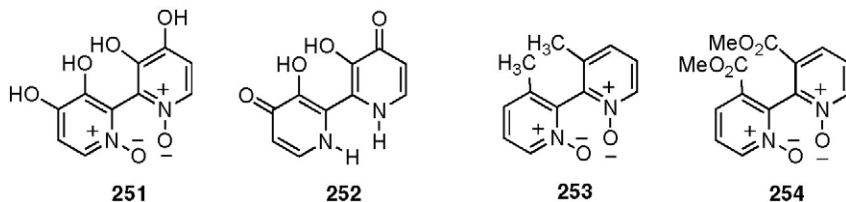
The X-ray structure of 3-ethyl-5-methyl-4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**248**), an oxidation product of felodipine showed that the inter-ring angle is 75.3° (10AX(E)o538).

The stereoselective oxidation of optically pure dihydropyridines was addressed by Schäfer et al. (01TA341). Optically pure 1,4-dihydropyridines with an *ortho*-substituted phenyl group in the 4 position present two fast equilibrating conformers (*sp* or *ap*) that are roughly bisecting the dihydropyridine along the C-4, N-1 axis, **249** and **250**. Considering that the 4-hydrogen is more hindered in the *sp* than in the *ap* form, the bulkiness of the

oxidizing agent has a dramatic effect on the absolute configuration of the resulting dihydropyridine. Bulky $\text{TEMPO}^+ \text{BF}_4^-$ reacted much faster with the *ap* form to yield optically pure dihydropyridine with *ees* > 93% while NOBF_4 yielded the opposite absolute configuration with moderate *ees*.



The reaction could be extended to *N*-Me substituted dihydropyridines. The highly toxic Orellanine, *rac*-3,3',4,4'-tetrahydroxy-2,2'-bipyridine-*N,N'*-dioxide (251) (89AQ(C)69) was isolated and identified from the mushroom *Cortinarius orellanus* Fries (79TL1931). There was no mention of optical activity. X-ray analysis of orellanine hydrate showed an inter-ring angle equal to 90.2° (91JCSR401). Orellanine was transformed into a 2,2'-bi(4-pyridone) 252 by reduction on $\text{Pt}(\text{O}_2)$ (85E769). The barrier in Orelline (252) should be much lower than Orellanine. Spectral nonequivalence of atropisomers of tetra-*O*-methyl-orellanine was induced by chiral solvating agents (02H137). Orellanine was claimed recently for the treatment of renal cell carcinoma (10USP15224). The X-ray of 2-(2-hydroxyphenyl)pyridine-1-oxide revealed a strong H-bond between the oxide and the OH, which led to a rather small inter-ring angle (38.2°) (90JCSR381). Hydrogen bonding provided the clue for abnormal deoxidation of the pyridine oxide in Orellanine to yield first orellanine and then orelline (84TL4045).

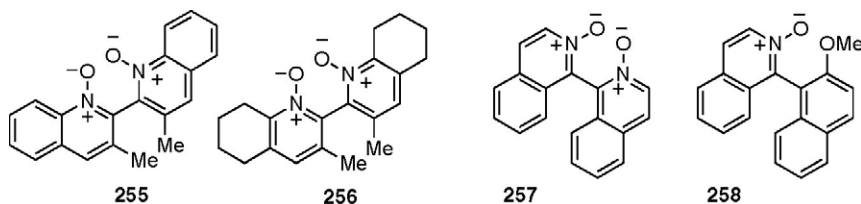


The enantiomers of 3,3'-dimethyl-2,2'-bipyridyl *N,N'*-dioxide, mbdo (253) reacted with $[\text{Cr}(\text{H}_2\text{O})_6]^{3+}$ in water to yield three diastereomers of

$[\text{Cr}(\text{mbdo})_3]^{3+}$. The diastereomers were absorbed on an SP-Sephadex column and selectively displaced with sodium (+)-tartratoantimonate. Luckily, the two first eluted complexes corresponded to the two enantiomeric homochiral complexes as checked by optical rotation and CD spectra. Treatment of the isolated complexes with $\text{Na}_2\text{H}_2\text{edta} \cdot 2\text{H}_2\text{O}$ for 10 h at 70 °C yielded the pure enantiomers of the ligand. The (*S*) absolute configuration was assigned to the dextrogyre enantiomer on the basis of CD spectra. The configuration was stable in boiling water (79BCJ1408). Mbdo enantiomers were much more efficiently resolved using optically pure binaphthol enantiomers. They also can be obtained on a Chiralcel OD-H column (99SL783).

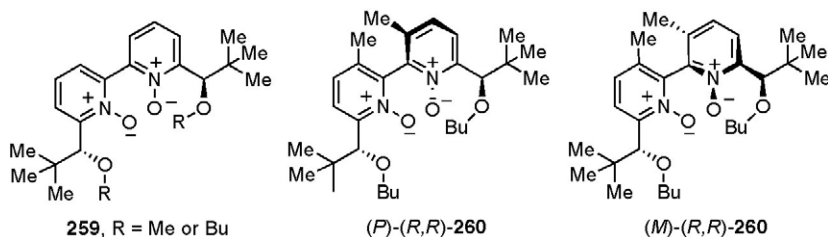
rac-2,2'-Bipyridyl-3,3'-dicarboxylic acid 1,1'-dioxide was resolved with brucine. The (*S*) configuration was assigned to the (+)-enantiomer by Bijvoet's anomalous dispersion method of the barium salt. The barrier was equal to 132.8 kJ mol⁻¹ at 93.3 °C in 0.1 M NaOH. The diester **254** was resolved by chiral HPLC on cellulose triacetate and a barrier equal to 106.5 kJ mol⁻¹ at 50 °C was determined in dioxane. There is an inversion of the sign of the optical rotation on going from the diester to the diacid for the same configuration (95TA1279).

(*R*)-(+ and (*S*)-(–) 3,3'-dimethyl-2,2'-biquinoline *N,N'*-dioxides **255** were obtained by resolution of the racemate via complexation with (*R*) or (*S*)-binaphthol. An X-ray of the complex allowed the assignment of the absolute configuration (97TA341, 98JA6419, 00CPB306, 02JA4233).



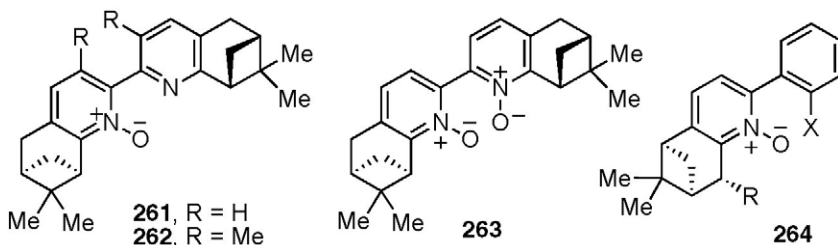
1,1'-Biisoquinoline dioxide **257** and 5,5',6,6',7,7',8,8'-octahydro-3,3'-dimethyl-2,2'-biquinoline *N,N'*-dioxide **256** have been resolved and engaged in enantioselective reactions and compared with QUINOX **258** (98JA6419, 01SL1551, 02JA4233).

Denmark *et al.* (02JA4233) reported the synthesis of optically pure 2,2'-bipyridyl-*N,N'*-dioxides **259** that have a low barrier around the pivot bond.



The stable diastereomers (*P*)-(*R,R*) and (*M*)-(*R,R*)-**260** were prepared by coupling the pyridine oxide precursor or by coupling the pyridine precursor followed by oxidation. Chromatography afforded the pure diastereomers. These optically pure compounds promoted enantioselective addition of the trichlorosilyl enolate of methyl acetate to prochiral ketones (02JA4233, 05JOC5235). The coupling process was optimized and eleven new optically pure (*P*)-(*R,R*)-**260** analogues have been described. The diastereoselectivity was excellent in the (*P*) form (06TA687).

Malkov et al. reported on the synthesis of chiral 2,2'-bipyridine *N*-monoxide and *N,N'*-dioxide derivatives whose chirality originated from a terpene unit.

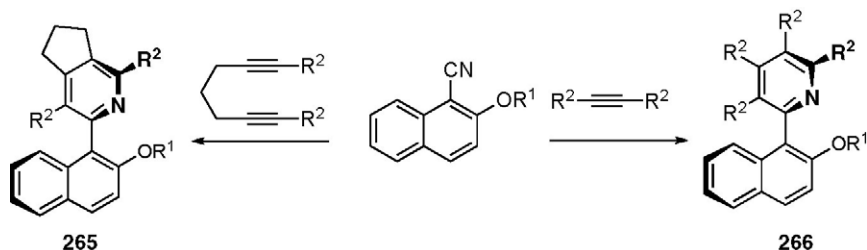


The rotation barriers around the linking bond were too low in **261** and **263** to permit separation of the atropisomers. Compound **262** that presented three groups in blocking positions gave rise to two optically pure diastereomers that could be separated by conventional HPLC. These two diastereomers slowly interconverted at room temperature to reach thermodynamic equilibrium after 1 week. Compound **261** and atropisomers of **262** were engaged as organocatalysts in the enantioselective allylation of aldehydes with allyltrichlorosilane (02OL1047). A series of optically pure pyridine oxides **264** was prepared (*X* = F, Br, MeO *R* = Me or *i*Pr). The barriers are too low to detect atropisomerism according to the reported NMR data at rt. Low-temperature study will be worthwhile to determine the barrier by DNMR (03JMOC(A)179).

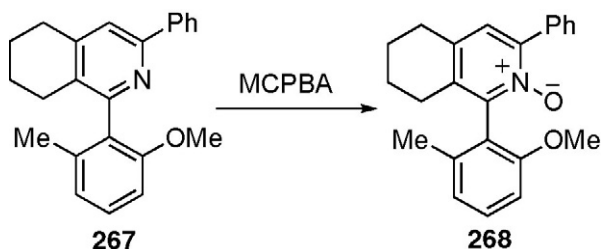
Rac-1-(2-Methoxy-1-naphthyl)-isoquinoline-*N*-oxide QUINOX **258** was prepared in two steps and resolved with optically pure (*S*)-(-)-BINOL to give the (*R*)-(+)-atropisomer. The atropisomers were also nicely separated by HPLC on Chiralpak AD-H column. The atropisomer was engaged in the asymmetric addition of allyltrichlorosilane to benzaldehyde derivatives yielding moderate to good *ees* (03AG(IE)3674, 08JA5341). The analogue in which the methoxy group has been replaced by a methyl was prepared and resolved in a similar manner. It presented lower reactivity and gave poorer *ees* than QUINOX in allylation of benzaldehyde (08JA5341).

Gutnov et al. gave the first report on the Co(I)-catalyzed asymmetric [2+2+2] cycloaddition of alkynes and nitriles leading to enantiomerically

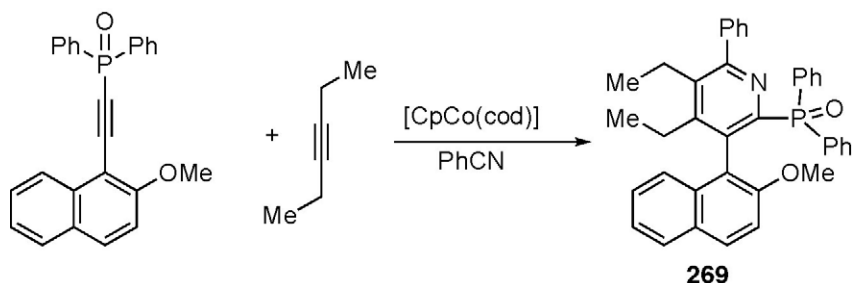
enriched atropisomers of 2-arylpyridines **265** or **266** (04AG(IE)3795, 08T11335). The enantiomeric excesses are moderate to good and the enantiomers can be nicely separated by chiral chromatography. The barriers were estimated to be larger than 110 kJ mol⁻¹.



Kotora *et al.* extended the scope of the reaction and showed that cobalt-catalyzed [2+2+2] cyclootrimerization of diynes with benzonitrile is a convenient method to prepare bis-*ortho*-substituted arylpyridines (06T968). Pyridine **267** was oxidized to give **268**.



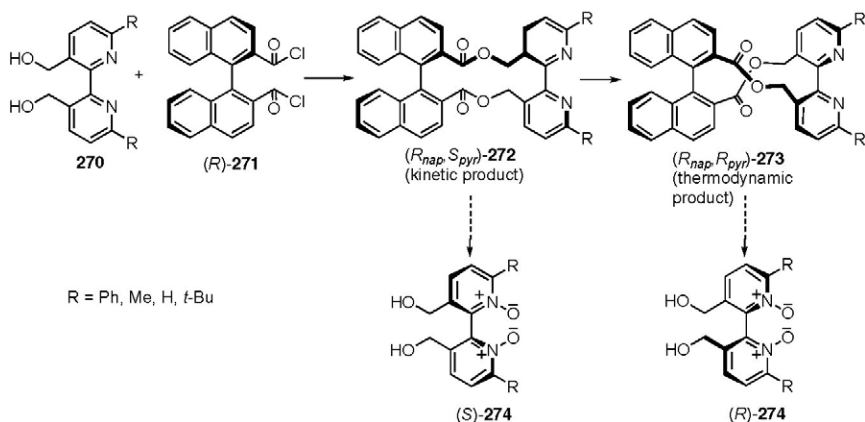
Pyridine-oxide **268** was resolved with (*S*)-(-)-BINOL into enantiomers. X-ray analysis of the crystallized diastereomer allowed the assignment of the absolute configuration (*R*) to (+)-**268**.



In a study of catalytic asymmetric cross-cyclootrimerization leading to axially chiral biaryls, one example was reported for 3-(1-naphthyl)pyridine derivative **269**, without mentioning the chirality of the obtained compound (07CEJ1117).

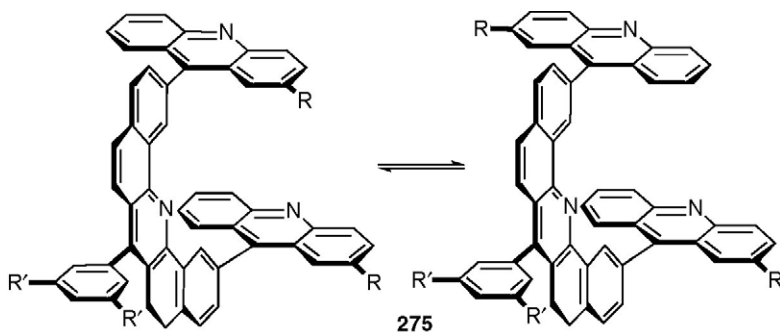
Both enantiomers of a series of 2,2'-bipyridyl-*N,N'*-dioxide (**274**) were prepared in a very elegant fashion described in the following sequence. Bipyridyls **270** reacted with optically pure binaphthyl diacylchloride (*R*)-**271** to give the kinetic diesters **272** that were oxidized followed by a further hydrolysis yielding optically pure (*S*)-**274**.

The kinetic esters **272** were transformed under reflux in toluene or by acid catalysis into the thermodynamic isomeric esters **273** that were then oxidized and the resulting bipyridyl dioxides were hydrolyzed to yield optically pure (*R*)-**274**. (*R*) and (*S*)-**274** were highly efficient catalysts for the asymmetric allylation of aldehydes with allyl(trichloro)silanes (03JOC6329).



The enantiomers of **274** (*R* = H) were also independently obtained by a rare example of enzymatic enantioselective esterification in alcohol/vinyl acetate (06TA12).

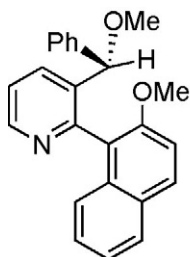
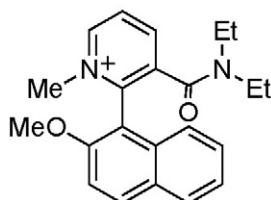
Zimmerman et al. (89JA1373) have prepared a series of rigid molecular tweezers **275** to form inclusion complexes with 2,4,7-trinitrofluorenone.



Two forms corresponding to the *meso* and *D,L* stereoisomers were observed by NMR in a 1:1 ratio (*R* = *t*-Bu). DNMR using the coalescence

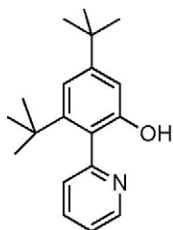
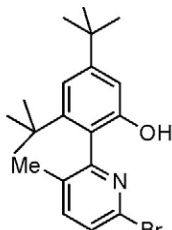
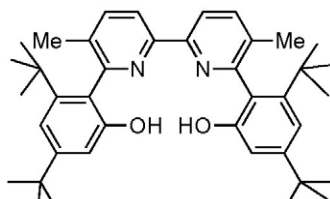
temperature equation provided the barrier to diastereomerization. The barrier range 78.8–91.5 kJ mol⁻¹ showed a low sensitivity to substitution on the acridine ring (89JA1373). The reported values correspond to observed exchange. The actual exchange processes, which should be used to interpret the origin of the barrier, are more complicated. The *meso* form is in equilibrium with a D,L pair of enantiomers leading to several routes in competition to obtain the observed exchange. The discussion on the possible interactions in the TSs should be based on the actual value of the barrier produced by each TS and not on the averaged value.

Furukawa et al. prepared arylpyridyl diastereoisomers via cross-coupling reactions of aryl 2-(3-substituted)pyridyl sulfoxides with Grignard or organolithium reagents. The barriers to atropisomerization were determined by DNMR and ranged between 62.8 and 79.5 kJ mol⁻¹ when the aryl group is singly substituted in the *o*-position. Compound **276** forms stable atropisomers at room temperature (91TL2943).

**276****277**

Fujii et al. separated the atropisomers of **277** on Chiralcel OD-H at the preparative scale. CD spectra were recorded but the absolute configuration was not established. Reduction of each atropisomer afforded axially chiral NAD(P)H models that were engaged in the enantioselective reduction of methyl benzoylformate (95% *ee*) (92JCS(CC)905).

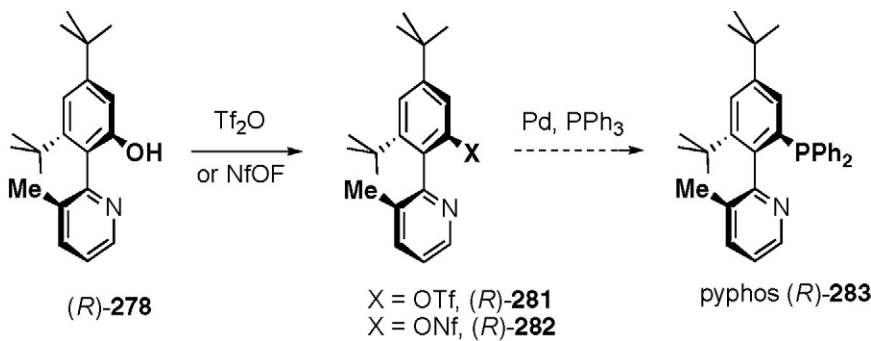
Chan et al. have reported the synthesis of highly strained 2-arylpyridine derivatives **278**. The atropisomers were resolved through the formation of diastereomers with (*S*)-(+)-camphorsulfonyl chloride. X-ray analysis of the pure diastereomer allowed the assignment of the absolute configuration (*S*) to the (–) form.

**278****279****280**

Chiralcel OD is suitable to nicely separate the enantiomers. The pure enantiomers of **278** were used as a chiral ligand in the Et₂Zn addition to benzaldehyde. The ees increased for electron attracting groups on the aldehyde (96JOC8002).

A larger series of strained 2-pyridyl phenol was prepared providing a reservoir of potential stable atropisomers (98JOC6886). Coupling of the (*S*)-(+)-bromo pyridine **279** that has been obtained by chiral HPLC led to an (*S,S*) tetradentate ligand **280** of known configuration (00TL7723).

New atropisomeric P,N ligands for rhodium catalyzed asymmetric hydroboration were designed starting from optically pure **278** through **281** and **282** intermediates.



However, the phosphination step required too high temperatures and **283** was obtained as a racemic mixture. Resolution of phosphine **283** was achieved with an optically pure palladium complex. X-ray data on the complex allowed the absolute configuration assignment. Alternatively an efficient chiral HPLC method (Chiralpak AD) was developed from the corresponding phosphine-oxide followed by a non-racemizing reduction to give (*S*) and (*R*)-**283**. **283** racemized at 130° C in dodecane (02JOC2769). A large series of **283** analogues in their racemic version was prepared during the optimization of the phosphination step (00OM2058, 01OM2570).

Chan et al. reported the preparation and resolution of closely related 3,3'-bipyridyl diphosphine atropisomers that differed by the aryl group on the phosphorous. The synthetic route which was used for Ar = Ph (99USP5886182, 00JA11513), R = *p*-tolyl (01SL1050) and R = 3,5-dimethylphenyl (02TL1539) is reported in Figure 13.

These atropisomers were engaged as ligands in asymmetric reduction reactions.

The conformational behavior of pyridone **285** provided an interesting example of several exchange processes within the same framework.

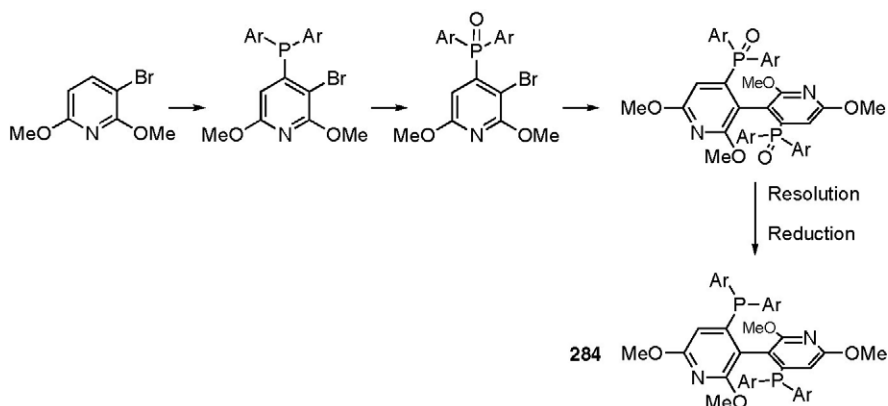
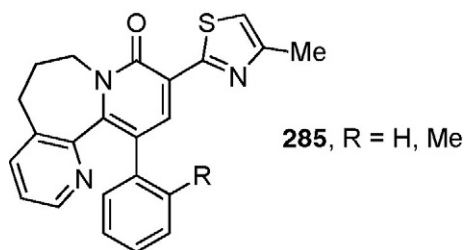
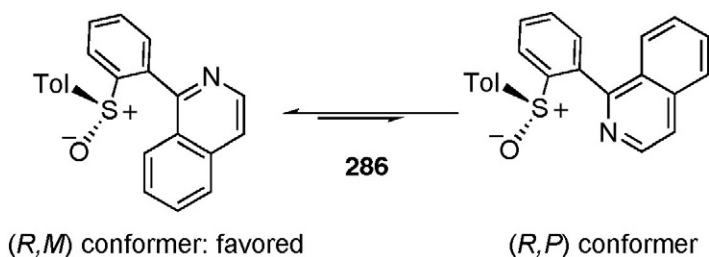


Figure 13. The synthetic sequence to prepare **284**.



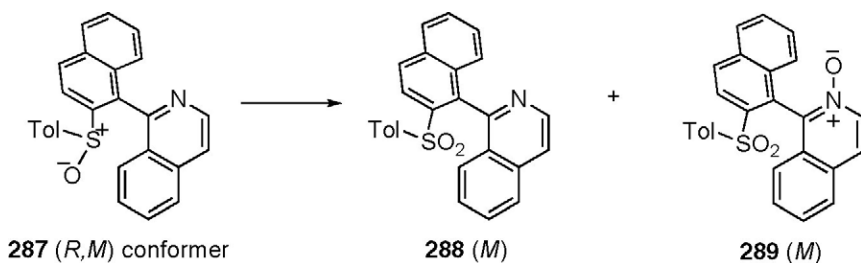
The thiazole ring is almost coplanar with the pyridone according to an X-ray of a model compound. Chiral HPLC revealed the occurrence of a plateau between two well-separated peaks when R = H. An off-line racemization study yielded an atropisomerization barrier equal to 92.7 kJ mol^{-1} corresponding to the rotation about the pyridine–pyridone bond. When R = Me, diastereomers were observed by NMR, chromatography on an achiral column gave a single peak while chiral chromatography yielded two peaks with a barrier equal to 91 kJ mol^{-1} . DNMR allowed the determination of the barrier for the rotation about the tolyl–pyridone bond: 79.2 kJ mol^{-1} at 300K. Thus, the compound with R = Me presented two pairs of enantiomers that collapsed to a single detectable pair by chiral HPLC at room temperature (02JOC9354).

Clayden *et al.* have shown recently that 2-arylpyridines and 1-arylisoquinolines **286** can adopt one of two axial conformations when they are substituted in the 2-position of the aryl by a chiral sulfinyl substituent. The preferred conformer is the one in which the nitrogen of the heterocycle is opposite to the sulfoxide S–O bond in order to minimize the dipole repulsion (09JA5331).

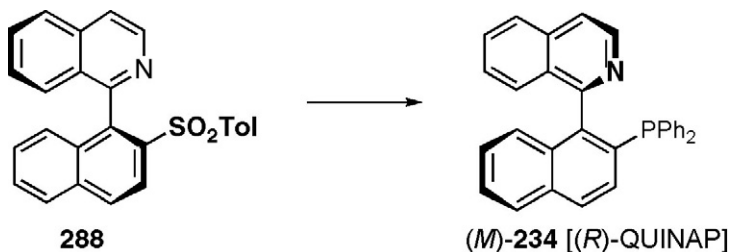


Protonation at the nitrogen increased the barriers (ca. 63 kJ mol^{-1}) and modified the diastereoisomer ratio, probably through a change in the dipole interaction. *N*-Methylation with methyltriflate led to stable atropisomeric diastereoisomers at room temperature. The observed ratio is consistent with a faster methylation of the *P* form (Curtin–Hammett principle) and could be considered as an additional proof of the preferred *M* conformation in the starting heterocycle.

When the aryl group in position 2 of the heterocycle is a 1-naphthyl, optically pure diastereoisomers can be separated by chromatography or crystallization. Oxidation of **287** readily yielded optically pure atropisomeric sulfone derivative **288** and the corresponding optically pure *N*-oxide **289**.



Optically pure **288** led to optically pure QUINAP **234** according to Thaler et al. (07SL2655).



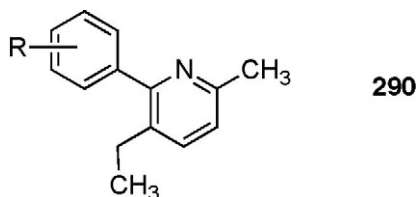
The barriers to rotation of a series of 2-(2'-substituted-aryl)-pyridines **290** were also determined by DNMR (Table 4). All fell within the range 57–68 kJ mol⁻¹, and the authors claimed that a clear dependence on the steric bulk of the *ortho*-substituents was observed. Interestingly, the barrier for 2-(2-iodophenyl)-3-ethyl-6-methylpyridine was reported lower than the barrier for the 2-bromo analogue.

Spivey *et al.* tailored a series of DMAP atropisomeric analogues for enantioselective kinetic resolution during acylation of alcohols (98TL8919, 99JOC9430, 00JOC3154, 01JOC7394, 01JCS(P1)1785) (Figure 14). The enantiomerization energies were determined by DHPLC on a chiral support or thermal racemization of the pure enantiomers that were available from chiral HPLC.

The barriers were higher for the DMAP than for the *N*-methyl-5-azaindoline derivatives due to better conjugation of the dimethylamino group with the ring in the former. The barriers were calculated using PM3 or STO-3G methods. The *ab initio* RHF/STO-3G methods gave a better fit with the experimental data (03THE(623)263).

A short three-step synthesis has been developed for the -N(Et)₂ derivative **291**. (–)-N-Boc-O-benzyl (*S*) tyrosine among 63 optically pure resolving agents was found suitable for a large-scale resolution via diastereomeric salt formation. The (*S*) configuration was assigned to the (–) form by X-ray of the diastereomeric complex (03JOC7379).

Table 4. Activation parameters for arylpyridines bearing two *o*-substituents



R	<i>T_c</i> (°C) ^a	Δ <i>G</i> [‡] (kJ mol ⁻¹) ^b	<i>t</i> _{1/2} (s) ^c
2-CH ₃	~0	58.0	0.003
2-C ₂ H ₅	~10	60.2	0.006
2-OCH ₃	~20	61.5	0.010
2-I	~40	62.2	0.014
2,3-Benzo	~30	63.0	0.020
2-Br	~50	65.7	0.060
2-C(CH ₃) ₂ OH	~65	66.6	0.086
2-SO ₂ Tol	~90	67.7	0.131

^aCoalescence temperature.

^bΔ*G*[‡] calculated at 298K.

^cHalf-life for enantiomerization calculated at 298K.

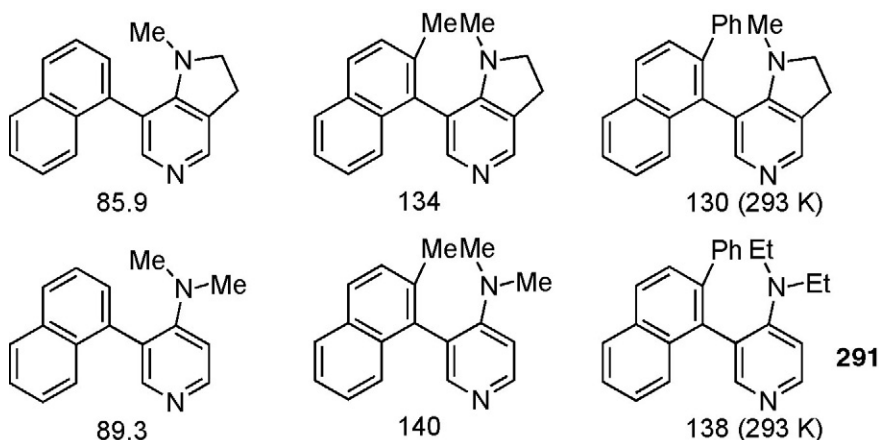
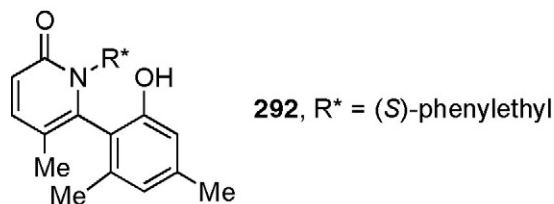


Figure 14. Experimental barriers in kJ mol^{-1} .

A series of analogues of **291** that differ by the alkyl groups on the nitrogen have been prepared ($-\text{N}(\text{CH}_2)_4$, $-\text{N}(\text{Et})_2$, $-\text{N}(\text{Me})_2$, $-\text{N}(\text{Pr})_2$, $-\text{N}(\text{iPr})_2$, $-\text{N}(\text{Bu})_2$, $-\text{N}(\text{pentyl})_2$, $-\text{N}(\text{hexyl})_2$). They were resolved on a Chiralcel OD column, the (–) forms were eluted first in all the series. The absolute configurations were assigned by comparing the sign of the Cotton-effect peaks in their CD spectra at ca 320 nm with that of (S)-(–)-**291** (04T4513). Further substitution in the 3,5-positions of the phenyl group in **291** gave hindered atropisomers that were excellent catalysts for acylation of secondary alcohols in terms of enantioselectivity but were not active enough for KR at ambient temperature (06T295).

Kakiuchi et al. succeeded in the atroposelective alkylation of the 2-(1-naphthyl)-3-methylpyridine with ethylene catalyzed by $[\text{RhCl}(\text{coe})_2]_2$ and a chiral ferrocenyl phosphine (*R*) or (*S*)-PPFOMe (Figure 15). This is a kind of dynamic kinetic resolution. The yields were moderate with fair to good *ees* (00TA2647).

Diastereomeric 2-aryl pyridone **292** has been prepared from *N*-(*S*)-phenylethyl imines through an efficient tandem Michael reaction-azacyclization followed by oxidation. No diastereomerization was observed on heating (04TA139).



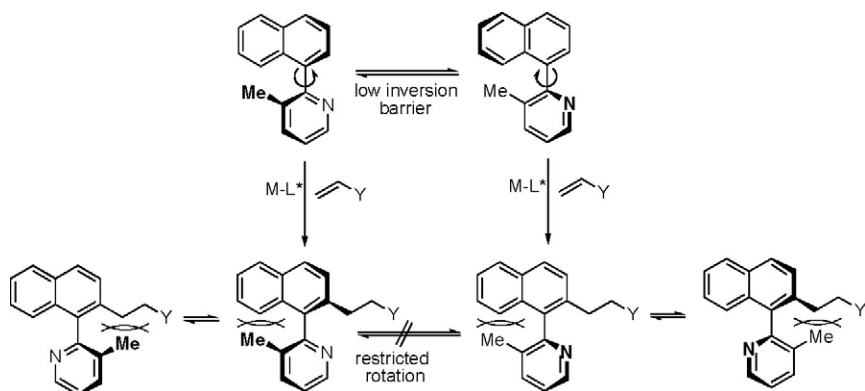
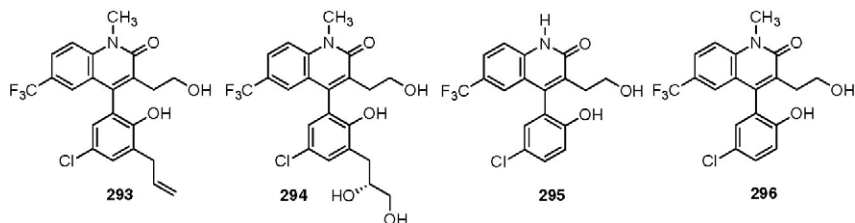


Figure 15. Kakiuchi *et al.* experiments (00TA2647).

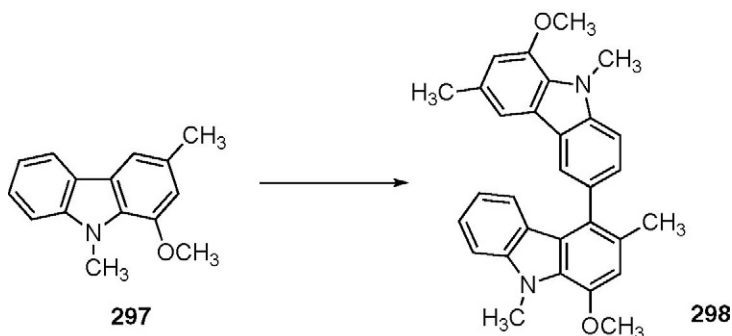
The Bristol-Myers Squibb pharmaceutical research institute has been developing a huge series of quinolinones **293**–**296** as potent maxi-K potassium channel opener (00WO34244, 01USP6184231, 03JMC2819, 04BMCL5089, 05BMCL4286). Most of these quinolinones present a suitable substitution pattern in the vicinity of the quinolinone-4-aryl bond to give rise to stable atropisomers. The chirality issues were first addressed in a patent (04WO5826). Examples that have been separated on a chiral support are given below (07JMC1050).



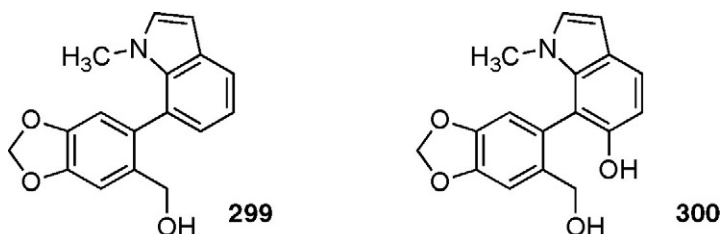
The X-ray structures of **293** and **295** were reported. The barrier to rotation in **295** can be estimated from the reported chromatograms recorded after heating at 80 °C in butanol, $\Delta G^\ddagger = 127.7 \text{ kJ mol}^{-1}$. The individual enantiomers of **295** were highly stable at physiologically relevant conditions and they showed differential activity as maxi-K channel openers. The authors stated: “This study with a quinolinone series emphasizes the relevance of atropisomerism in the context of drug development.”

The chromatographic separation of the enantiomers was revisited using analytical and preparatory SFC on several chiral columns. Baseline separations were achieved in reasonable run times (08JPBA1120).

Bicarbazole **298** was prepared by coupling of *N*-methyl protected carbazole **297** with Pd(OAc)₄, BF₃ etherate in CH₃CN at room temperature (01JA2703). The stereodynamics of **298** had not been addressed.

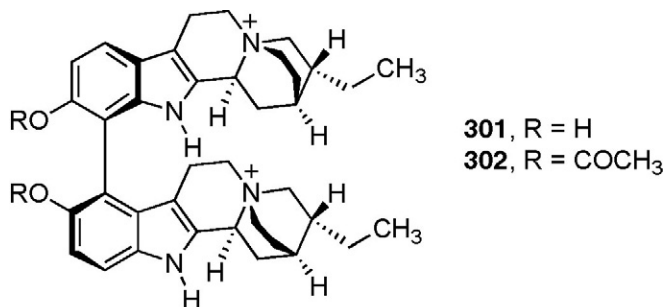


Galanthindole (**299**) was isolated from *Galanthus plicatus* ssp. *Byzantinus* (03PM869). Unver et al. states that “steric factors force the indole and benzodioxole rings out of coplanarity,” the resulting chirality could be proven by the splitting of the methylene protons of the dioxolane ring whereas the CH_2OH did not showed AB splitting.

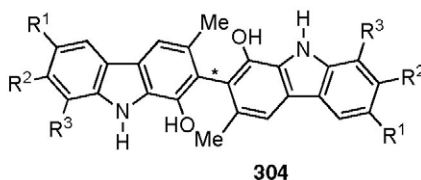
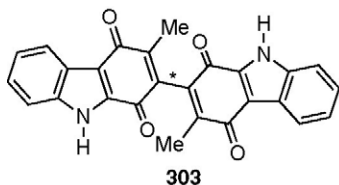


6-Hydroxy-galanthindole (**300**) presenting optical activity ($\alpha_{23}^D = +174$) was isolated from *Narcissus* cultivar “Dutch Master” (10P301). The computed rotational barrier (B3LYP functional and 6-31G* basis set) was 260 kJ mol^{-1} . The absolute configuration was shown to be *R* by comparison of the experimental and calculated CD spectra. Glycosides of 6-hydroxy-galanthindole were also isolated and characterized.

A 9,12-linked biindole derivative was isolated from *Ophiorrhiza blumeana* Korth and received the name “blumeanine” (**301**). The CD spectrum of blumeanine diacetate (**302**) suggested that it is one atropenantiomer (98JCS(P1)2537).

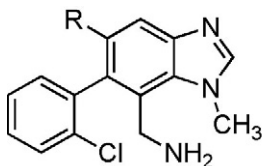


Axially chiral bicarbazolyl alkaloids **303** (bismurrayaquinone-A) and **304** (R^1 , R^2 , R^3 , H, OH, OMe, isoprenyl, geranyl) that are at the borderline of that review have been reported ([01CC761](#)).



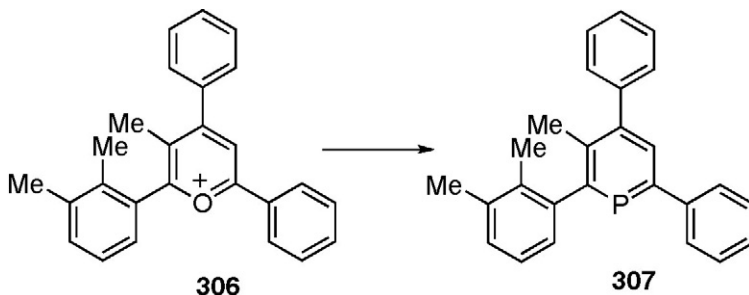
* Configurationally stable

Mixtures of atropisomers were reported among a large series of aryl benzimidazole derivatives **305** that presented dipeptidyl peptidase IV inhibitor activities ([08BMCL2362](#)). They were wrongly called diastereomer mixtures and their separation by chiral SFC is probably reported in ([07JC\(A1169\)193](#)) under sample codes.

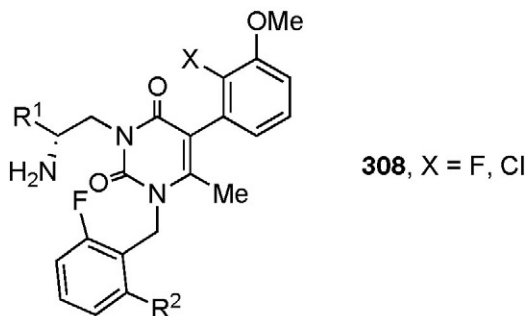


305, R = Br, CN, CONH₂

A class of atropisomeric phosphinines **307** has been prepared from the corresponding pyrylium precursors **306** ([07DT5372](#)). The enantiomers were baseline separated on a Chiralcel OD-H column. The barrier to enantiomerization was 109.5 kJ mol⁻¹ from thermal racemization in hexane at 298K ([08CEJ4899](#)). Comparison of experimental and calculated [TD-B3LYP/6-31G (d,p) level] CD spectra allowed the assignment of the (*S*) configuration to the first eluted enantiomer on a Chiralcel OD-H column. Interestingly, the pyrylium salt precursors of the phosphinine presented atropisomerism in the solid state. A pair of enantiomers was observed, the inter-ring angle being 72°. The separation of the enantiomers of the pyrylium salt **306** would be worth trying by chiral HPLC in order to detect a possible plateau.



A series of 5-aryluracils **308** were optimized as a potent GnRH antagonist. They presented a fixed chirality center and a chirality axis. The occurrence of two stable diastereomers depends on the barrier to rotation of the exchanging atropisomers.



When X = Cl diastereomers could be separated on Chirex 3020AL and are stable. A remarkable difference in activity was observed for the two atropisomers ([08BMCL3344](#)). When X = F, the rate constant for the interconversion ($k = 5.07 \times 10^{-5} \text{ s}^{-1}$) of these two atropisomers was determined by proton NMR analysis of a diastereoisomer-enriched sample in aqueous solution at 25 °C, and the corresponding barrier to rotation (97.4 kJ mol^{-1}) was calculated using the Eyring equation. The diastereoisomer half-life at physiological temperature (37 °C) in aqueous media was estimated to be about 46 min ([05CHI559](#)).

A series of axially chiral 4-aryl-2-pyridones **309** ([Figure 16](#)) was prepared in high yields and high *ee* values by enantioselective cycloisomerizations of *N*-alkenyl arylethynylamides catalyzed by a cationic palladium (II)/(*S*)-xyl-Segphos complex ([09OL1805](#)).

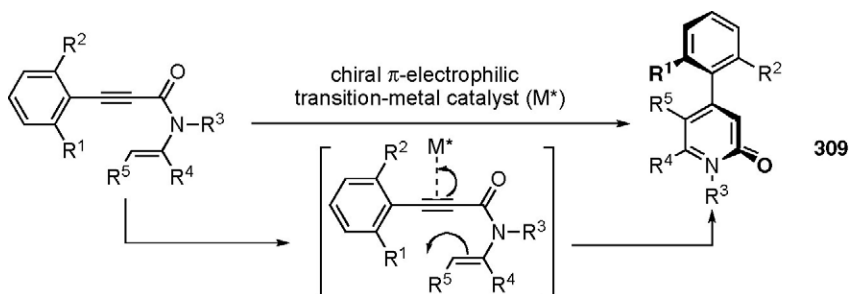


Figure 16. Synthesis of chiral arylpyridones **309**.

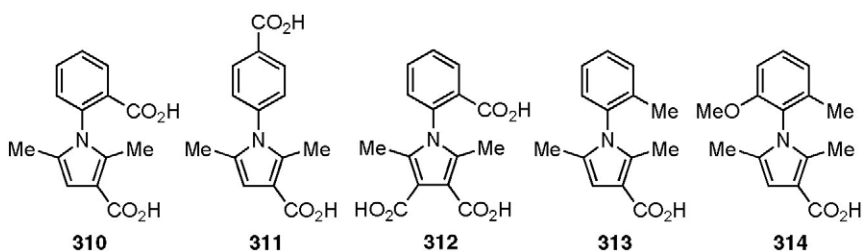
4. ROTATION ABOUT A C–N BOND

4.1 Five-membered heterocycles (azoles)

4.1.1 Pyrroles, indoles, and carbazoles

The geometry of an aromatic five-membered ring leads to smaller steric interaction than the corresponding aromatic six-membered ring (52JCS1467, 53JCS3802, 67T4469, 67T745). However, 1-arylpyrrole derivatives with different substituents at the C(1), C(3), and α positions in the phenyl and the pyrrole rings, respectively, may exist in two atropisomeric forms.

The seminal work of Adams at Illinois University around 1930 paved the way to atropisomerism in *N*-aryl compounds. 1-(2-Carboxyphenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid **310** was prepared. It was resolved by formation of diastereomers with brucine. Racemization experiments were performed on the L-form. No change in optical rotation was observed on boiling EtOH for 8 h. Boiling in acetic acid resulted in total decomposition. In 0.1 N NaOH solution, no change occurred at room temperature for 18 h and a full racemization was observed after 24 h. It is particularly interesting to recall that some doubt persisted on the origin of the chirality in these compounds: “However, the possibility must not be overlooked that in this molecule the optical activity may be dependent, not upon the restricted rotation but upon the (pyramidal) character of the nitrogen atom or it may be dependent on a combination of the two” (31JA374).

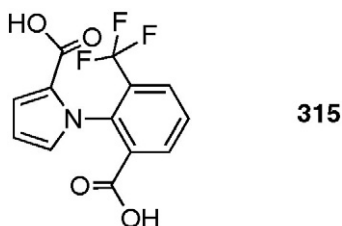


The doubt on the origin of chirality was still perceptible in (31JA3519). Achiral *N*-arylpyrroles **311** and **312**, as we can say now, were submitted to brucine resolution, an attempt affording optically inactive acids. Resolution of chiral *N*-arylpyrroles **313** and **314** failed due to the weakness of the carboxylic acid on the pyrrole ring. Nevertheless, it was stated that “the optical isomerism in phenyl pyrroles probably resembles closely that in the diphenyl series.”

Note what Adams pointed out (31JA3519, 49MI91): “If the nitrogen atoms were rigidly tetrahedral in character optical isomerism should be

possible even with symmetrical substitution of the rings.” Chirality resulting from a rigid pyramidalization of the nitrogen atom would require the pyrrole ring to be dissymmetrically substituted whereas such a dissymmetry is not required on the *N*-aryl group. Symmetrical substitution on the pyrrole ring would lead to achiral objects.

1-[2-(Trifluoromethyl)phenyl]-1*H*-pyrrole was treated with butyllithium or with BuLi-TMEDA at 0 °C in Et₂O and the resulting regioselectively α ,2-dimetalated compound was treated with CO₂ to give 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid (**315**) (99T7881).



X-ray analysis of **315** showed that the inter-ring angle was 77.5°. Two enantiomers strongly connected by H-bonding formed the unit cell. Interestingly, the frontal interaction between the CF₃ and the pyrrole induced a deformation of the pyrrole ring. The diacid was resolved by diastereoselective crystallization with α -phenethylamine and the enantiomeric excess was monitored by ¹⁹F NMR in the presence of β -cyclodextrin (00TA4771). X-ray analysis of the resulting diastereomeric salt allowed the assignment of the absolute configuration *R* and *S* to the (+) and (–) forms, respectively. CD spectra in ethanol solution (Figure 17) were recently reported (09TA98).

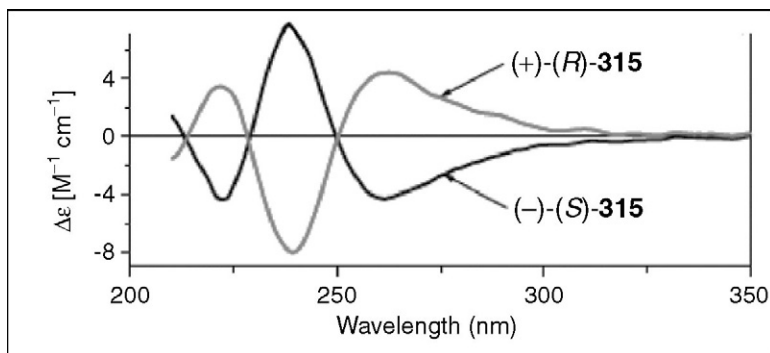
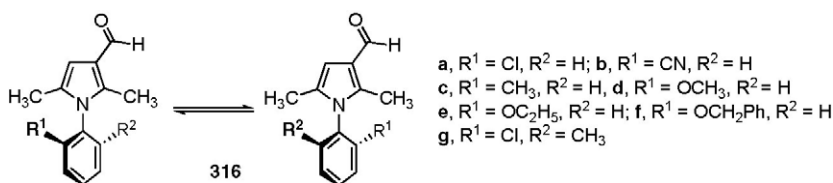


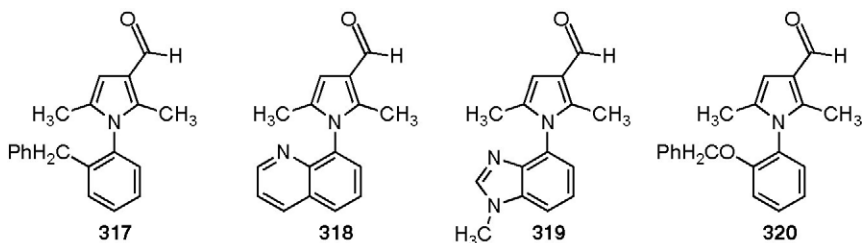
Figure 17. CD spectra of compound **315**.

(\pm)-1-(2-Carboxymethyl-6-ethylphenyl)-1*H*-pyrrole-2-carboxylic acid has been prepared recently by consecutive dilithiation and carboxylation of *N*-(2-ethyl-6-methyl phenyl) pyrrole. It was resolved into pure enantiomers by diastereomer formation with (*R*)- α -phenethyl amine. The absolute configuration was determined from an X-ray structure of the diastereomer and confirmed by comparison of experimental and calculated CD spectra (09TA98).

N-Aryl-2,5-dimethylpyrrole-3-carbaldehydes **316** were prepared by Vilsmeier–Haack formylation of the corresponding achiral *N*-aryl-2,5-dimethylpyrroles.

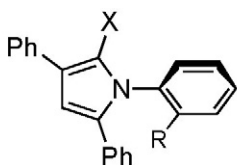


Diastereotopic association with (+)-tris[3-heptafluoropropylhydroxymethylene] camphorato]europium(III) was observed for all the compounds. The chemical shift difference for **316b** and **316d** which presents smaller hindering groups decreased when increasing the temperature. From these data the lower limit of the barriers was estimated: 98 kJ mol^{-1} . Obviously all these compounds present suitable barriers for chiral separation by chromatography on a chiral support provided the right column is found. From the successful separation of the enantiomers of **316f** on MCTA a barrier equal to 125 kJ mol^{-1} was determined (89JCS(P2)713). The study was extended to a series of *N*-heteroaryl pyrrole derivatives; the enantiomers were obtained by chiral chromatography on cellulose tribenzoate or (+)-poly(triphenyl-methacrylate) coated on silica. The ΔG^\ddagger barriers (in kJ mol^{-1}) were **317** > 128 (diglyme, $T_c = 150^\circ\text{C}$); **318** 130 ± 2 (diglyme, $T_c = 134^\circ\text{C}$); **319** 52 (CD_2Cl_2 , $T_c = -29^\circ\text{C}$); **320** 125 ± 0.2 (diglyme, $T_c = 108^\circ\text{C}$).



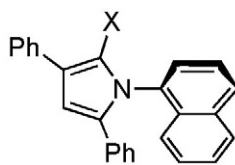
These data showed once again the dramatic influence of flanking substituents and ring size on the barriers (92JHC327).

(3,5-Diphenyl-1-*o*-tolyl-1*H*-pyrrol-2-yl)phenylmethanone **321a** and (1-naphthalen-1-yl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanone **322a** were prepared by oxidation of the corresponding quaternary pyridinium salts. Racemic forms due to atropisomerism around the *N*-aryl bond was demonstrated by ^1H NMR in the presence of chiral shift reagent $\text{Eu}(\text{hfc})_3$ as predicted from semiempirical PM3 calculations. Reduction of ketones **321a** and **322a** yielded diastereomers **321b** and **322b** presenting axial and central chirality with *de* = 40% and 10%, respectively (99MC74).



321a, X = PhCO, R = Me

321b, X = PhC*H(OH), R = Me



322a, X = PhCO, R = Me

322b, X = PhC*H(OH), R = Me

The study extended to a larger series of R groups (Figure 18) (00CCC651).

The racemic acid **324f** was transformed into diastereomeric (*R*)-1-phenylethylamides from which the absolute configuration at the chiral axis was determined by X-ray analysis.

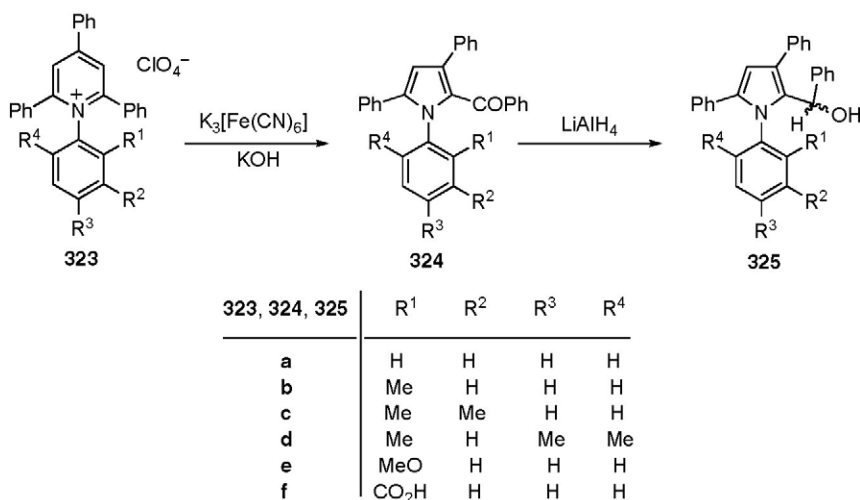
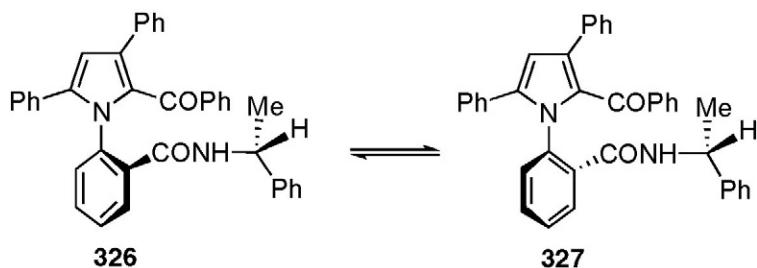
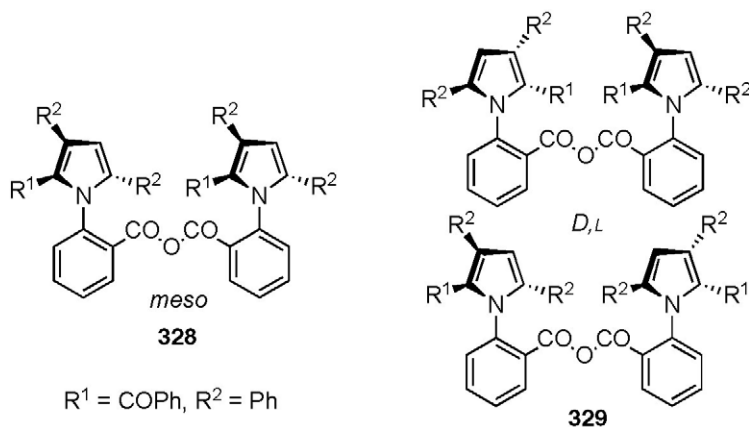


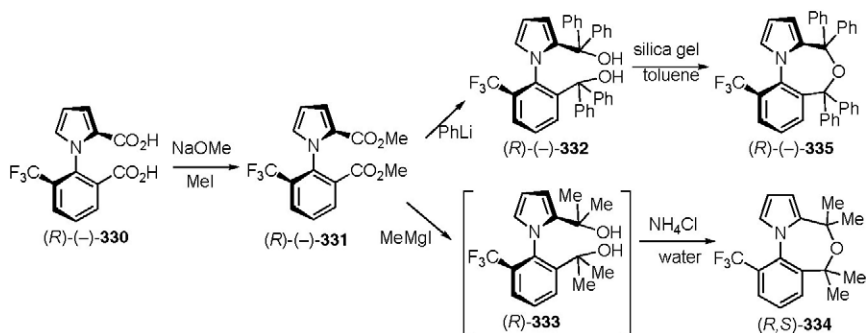
Figure 18. Structures of the compounds 323–325.



The experimental barrier to diastereoisomerization **326** to **327** was determined in DMSO-*d*₆. *Meso* and *D,L* bis-*N*-aryl anhydride derivatives have been isolated as **328** and **329**. The more soluble and lower melting compound was the *D,L* form.



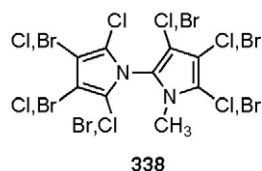
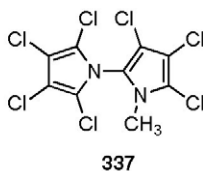
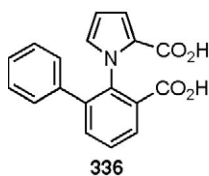
Optically pure 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid was used as a starting material for a series of reactions that maintained the initial absolute configuration or led to full racemization (08T1371).



The enantiomeric excess of **330** and **331** was determined by ^{19}F NMR in the presence of 2-hydroxypropyl- β -cyclodextrin that is more soluble than native β -cyclodextrin in water. That method did not split the signal for the atropisomers of **332**, **334**, and **335** that were analyzed by the $\text{Yb}(\text{TFC})_3$ shift reagent in an apolar solvent.

The barriers to racemization were estimated by AM1 calculations. Comparison with the experimental barrier determined for **330** in DMSO showed that the calculation overestimated the barriers. The measured barriers for **330** (off-line racemization) and the analogue of **334** (DNMR) without the CF_3 group were equal to 132.1 and 58.1 kJ mol^{-1} , respectively. The calculated barrier for **332** (476 kJ mol^{-1}) is probably not realistic but it explained the formation of **335** in optically pure state even though cyclization dramatically reduced the barrier.

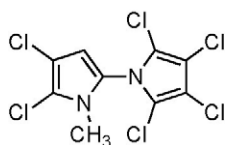
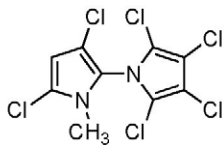
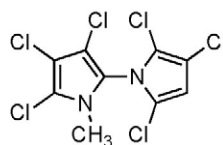
Atropisomeric 1-[(3-carboxy-1,10-biphenyl)-2-yl]pyrrole-2-carboxylic acid (**336**) was prepared by double carbonylation of the regioselectively dilithiated 1-[(1,1'-biphenyl)-2-yl]pyrrole (**09CHI905**).



The atropisomers of **336** were resolved by diastereomer crystallization with (*S*)- α -phenethylamine. The *ee* of the process can be monitored by chiral HPLC after methylation of the acids. X-ray structure analysis allowed the assignment the *R* configuration to the (+) enantiomer. The absolute configuration was also confirmed by comparison of the experimental CD spectra using ethanol with the ZINDO calculated one.

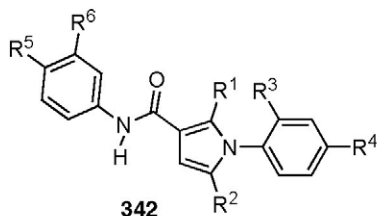
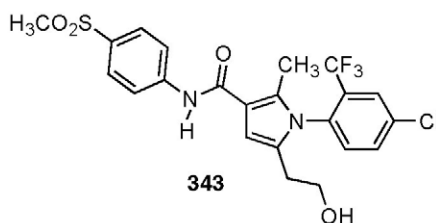
In the past 10 years halogenated 1'-methyl-1,2'-bipyrroles (MBPs) **337** and **338** emerged as a class of naturally occurring compounds that have been isolated from marine samples. Their distribution pattern suggests biomagnification (**09EST122**). Achiral GC analysis was performed on various polyhalogenated samples (bromine and chlorine).

The achiral heptachloroderivative **337** was prepared and an X-ray analysis showed that the inter-ring angle is 71.5° (**02AG(IE)1740**; **09EST2288**). It can be inferred that samples properly substituted by three halogens in flanking positions of the N-C pivot bond should present high enough barriers to give rise to stable atropisomers. Chirality issues: resolution by chiral HPLC, chiroptical properties including barriers and desymmetrization have not yet been addressed in that very interesting series.

**339****340****341**

Vetter and Jun have elucidated the structure of an hexachlorinated by-product obtained during the synthesis of the heptachloro 1'-methyl-1,2'-bipyrrole **337**. Among the three possible structures, **341** may give atropenantiomers, whereas **339** and **340** are achiral. The GC analysis on 10% permethyl- β -cyclodextrin (Chirasil-Dex, Chrompack) chemically bonded to a dimethyl polysiloxane backbone (CB- β -PMCD) coupled with EI-MS revealed two peaks that confirm the chirality of the product (02AC4287).

A very large series of *N*-aryl pyrroles **342** presenting an axial chirality has been patented recently as mineral-corticoid receptor antagonists (10WO42622). Interestingly, the chirality issues in a previous patent that comprised a large series of *N*-aryl pyrrole derivatives that presented a suitable substitution pattern that could give rise to stable atropisomers were not addressed (06WO12642).

**342****343**

More than 60 examples of diversely substituted atropisomeric scaffolds were fully described. When R^2 presented a fixed chirality, the blocked rotation around the *N*-aryl bond yielded diastereomers. Table 5 reports selected examples of all the combinations of blocking substituents in R^1 , R^2 , and R^3 .

The resolution of the enantiomers or the separation of the diastereomers was described under different elution conditions on several chiral columns (analytical and semipreparative conditions). The activity is located in a single enantiomer. We have selected a single example **343** for illustration among the 60 reported. The two enantiomers of the 1-(4-chloro-2-(trifluoromethyl)phenyl)-5-(2-hydroxyethyl)-2-methyl-*N*-(4-(methanesulfonyl)-phenyl)-1*H*-pyrrole-3-carboxamide (**343**) were

Table 5. Selected examples of a reported combination of substituents situated in blocking positions in atropisomeric *N*-aryl pyrroles (10WO42622)

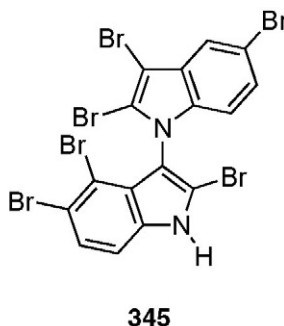
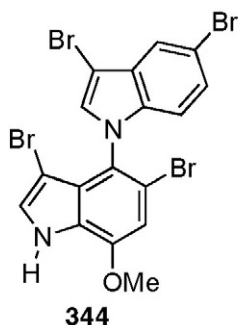
Compound	R ^{1a}	R ^{2a}	R ^{3a}	R ⁴	R ⁵	R ⁶	Chirality type
343	CH ₃	CH ₂ CH ₂ OH	CF ₃	Cl	SO ₂ Me	H	E
342a	CH ₃	CH ₂ CH ₂ OH	Cl	F	SO ₂ Me	H	E
342b	CH ₃	(S)-CH ₂ CH(OH)CH ₃	CF ₃	F	SO ₂ Me	H	D
342c	CH ₃	(S)-CH ₂ CH(OH)CH ₃	CH ₃	F	SO ₂ Me	H	D
342d	CH ₃	(S)-CH ₂ CH(OH)CH ₃	OCHF ₂	F	SO ₂ Me	H	D
342e	CH ₃	(S)-CH ₂ CH(OH)CH ₃	CF ₃	F	SO ₂ NH ₂	CH ₃	D
342f	CH ₃	(S)-CH ₂ CH(OH)CH ₃	OCF ₃	Cl	SO ₂ NH ₂	CH ₃	D
342g	CH ₃	(S)-CH ₂ CH(OH)CH ₃	Cl	Me	SO ₂ Me	H	D
342h	CH ₃	(S)-CH ₂ CH(OH)CH ₃	CHF ₂	Cl	SO ₂ Me	H	D
342i	Et	(S)-CH ₂ CH(OH)CH ₃	Cl	F	SO ₂ Me	H	D
342j	CH ₃	(S)-CH ₂ CH(OH)CH ₃	O(<i>p</i> -FPh)	Cl	SO ₂ Me	H	D
342k	Et	(S)-CH ₂ CH(OH)CH ₃	CF ₃	Cl	SO ₂ Me	H	D
342l	CH ₃	(S)-CH ₂ CH(OH)CH ₃	<i>p</i> -FPh	Cl	SO ₂ Me	H	D
342m	CH ₃	CH ₂ CH ₂ F	Me	Cl	SO ₂ Me	H	E
342n	CH ₃	CH ₂ CH ₂ F	CF ₃	F	SO ₂ NH ₂	H	E
342o	CH ₃	CH ₂ CH ₂ F	OCHF ₂	F	SO ₂ Me	H	E
342p	CH ₃	(<i>R</i>)-CH ₂ CH(F)CH ₃	CF ₃	Cl	SO ₂ Me	H	D
342q	CH ₃	(<i>R</i>)-CH ₂ CH(F)CH ₃	OCHF ₂	F	SO ₂ Me	H	D
342r	CH ₃	CH ₂ CH ₂ F	Cl	F	SO ₂ Me	H	E
342s	CH ₃	CH ₂ C(O)NMe ₂	CF ₃	Cl	SO ₂ Me	H	E
342t	CH ₃	CH ₂ CH ₂ OBn	CF ₃	F	SO ₂ Me	H	E
342u	CH ₃	CH ₃	CF ₃	H	SO ₂ Me	H	E

Chirality type: E = enantiomers, D = diastereomers.

^aBlocking positions.

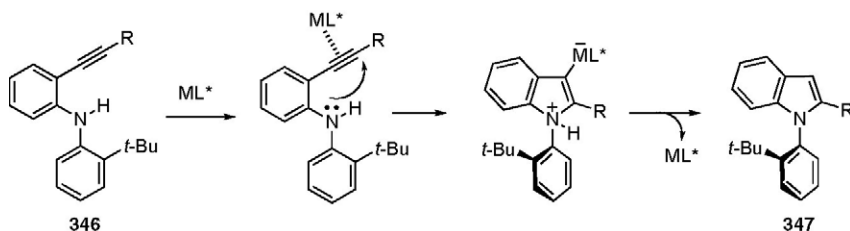
eluted at 9 and 12.5 min, respectively, on analytical Chiralpak AS-H with a mobile phase composed of hexane/EtOH/MeOH 80:16:4 (flow rate 1 mL, *T* 40 °C, UV 254 nm). The semipreparative resolution was performed in the same mobile phase on the same chiral support (250 × 20 mm column) at room temperature and a flow-rate of 20 mL/min. The first eluted enantiomer [(+) in EtOH] showed a mineral-corticoid receptor antagonistic action more than 300 times better than the second eluted enantiomer (IC_{max50} = 3.7 nM for the (+) atropisomer and >1000 nM for the (−) atropisomer). Furthermore, the atropisomer having high activity showed considerably improved concentration in plasma compared to the previously described reference compounds (06WO12642).

Optically active polybrominated biindoles **344** and **345** presenting a hindered rotation about the N–C bond have been isolated from *Rivularia firma* algae collected in Westernport Bay (Australia). They were fully characterized by ¹³C spin-lattice relaxation data.



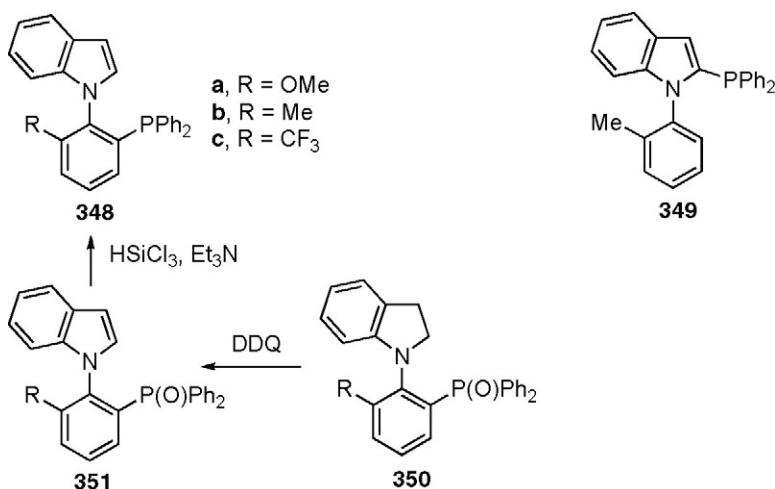
Compound **344** is levogyre in CH_3CN $[\alpha]_{\text{D}}^{26} = -6$ whereas **345** is dextrogyre $[\alpha]_{\text{D}}^{26} = +18.7$. The absolute configurations and the thermal stabilities have not been determined (82JA3628). Other C–C linked polyhalogenated biindoles also have been characterized; they are being reported in corresponding section.

A catalytic enantioselective synthesis of chiral *N*-(*o*-*t*-butylphenyl)indoles **347** has been reported (10CEJ6752). It involved a chiral Pd^{II} -catalyzed 5-*endo*-hydroaminocyclization of *N*-(*o*-*tert*-butylphenyl)alkynylanilines **346**.



A series of diphosphine ligand has been screened for $\text{R} = \text{Ph}$, the best *ees* (55–60% *ee*) were obtained using (*R*)-SYNPHOS ([[(5,6),(5',6')-bis(ethylene-dioxy)biphenyl-2,2'-diyl]bis(diphenylphosphine)] or SEGPHOS (5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole). The scope of the reaction was extended to various R aryl groups, the higher *ee* (>80%) being obtained for an aryl group bearing bulky alkyl groups, nitro, chlorine or bromine in the *ortho* position. The (*S*)-absolute configuration of the major enantiomer of 2-nitro- and 2-bromophenyl derivatives has been assigned (10CEJ6752).

Mino et al. recently reported the synthesis of optically pure phosphine ligands **348** and **349** based on atropisomeric *N*-arylindoles and demonstrated their potency as ligands for palladium-catalyzed asymmetric allylic alkylation (up to 99% *ee*) (10TA711).



The racemic forms of **348a–c** were obtained by a DDQ oxidation of the corresponding indoline phosphine oxides **350** followed by an HSiCl₃ reduction of the phosphine oxide to **351** (06JOC7346). Phosphine **349** was obtained by lithiation of the corresponding indole and reaction with ClPPh₂. X-ray data of racemic **349**, **348a**, and **348c** were reported.

Resolution of (±)-**348a–c** and (±)-**349** was achieved using a semipreparative HPLC on Chiralcel OJ and a mobile phase composed of a mixture of hexane–ethanol. The enantiomeric purities of both **348a–c** and **349** were more than 99% *ee* from chiral HPLC analyses. The enantiomers were fully characterized.

The barriers to racemization were experimentally determined in nonane at different temperatures. The calculated barriers at 25 °C were 113.3 (OMe), 138.4 (Me), 154.2 (CF₃), and 128.7 kJ mol^{−1} for **348a**, **348b**, **348c**, and **349**, respectively. The outstanding high barrier in **348c** allowed the determination of the absolute configuration by the chemical correlation method according to Figure 19.

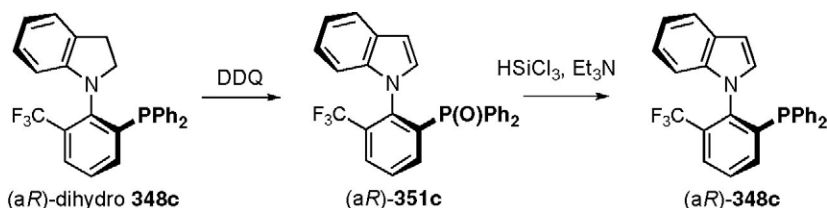


Figure 19. Determination of the absolute configuration of **348c**.

Starting from (a*R*)-dihydro **348c** (06JOC7346, 08TA2711), (a*R*)-**348c** was obtained in a two-step process. These steps required prolonged heating at 120 °C in *m*-xylene and thus very high barriers all along the process were required.

Interestingly, the X-ray analysis of suitable crystals of the π -allyl-Pd complex containing the racemic ligand (\pm)-**348a** that was synthesized upon the successive treatment of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ with ligand **348a** (Pd:**348a** = 1:1) provided information on the monodendate character of the ligand.

Kamikawa *et al.* reacted optically pure (+)-tricarbonyl{2-(1,3-dioxolanyl)-6-methyl-1-fluorobenzene} chromium (**352**) with indoles **353** (Figure 20) (06OL1097). The corresponding axially chiral *N*-arylindole chromium complexes **354** were obtained with a *de* > 96%. X-ray analysis of the major diastereomer showed that the chromium tricarbonyl group and the benzene ring of the indole were in opposite directions with respect to the N–C bond. Surprisingly the opposite configuration was obtained with 2-methylindole with a *de* > 96% confirmed by X-ray analysis. The reason for such a complete inversion of the diastereoselectivity is not clear since one should have expected a ratio governed by the difference in size between the 2-methyl and the benzo in favor of the methyl.

The rotational barrier of the chromium free derivative **355** was shown very high since no change in optical purity was noted after 4 h refluxing in toluene.

The scope of the reaction was extended to the coupling of several tricarbonyl{2-methyl-1-fluorobenzene} or tricarbonyl{2,6-disubstituted-1-fluorobenzene} chromium derivatives with a series of 2-substituted indoles. The chromium tricarbonyl group and the benzene ring of the indole were in the same direction in the major diastereomer. The opposite configuration at the chiral axis was confirmed for the 2-unsubstituted indoles (07JOC3394).

A very elegant synthetic scheme provided both optically pure enantiomers of 1-(2-ethyl-6-methylphenyl)-2-methyl-1*H*-indole (Figure 21).

Chromium migration **356** to **357** was observed on heating the 2-methylindole in which R^3 = dioxolanyl. Stereoselectivity was assisted by the

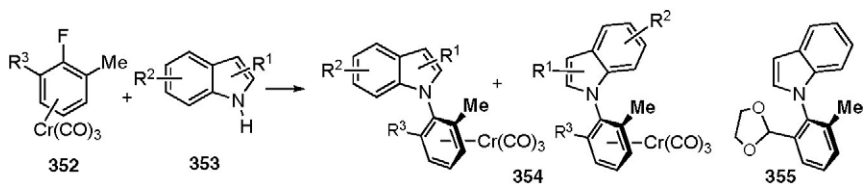


Figure 20. Structure of the compounds **352**–**355** (R^3 = 1,3-dioxolanyl).

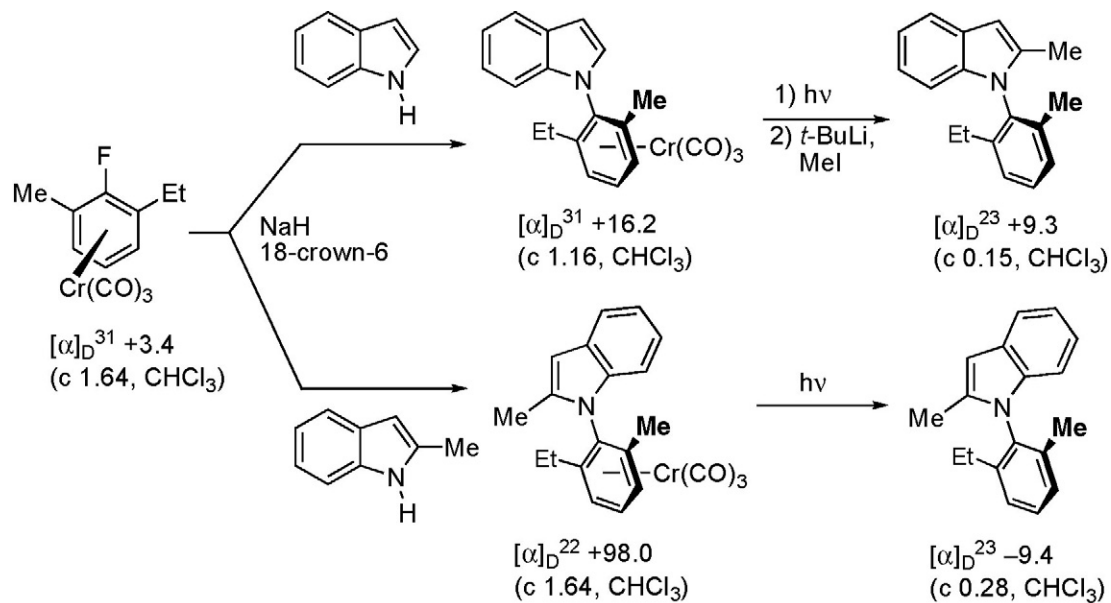
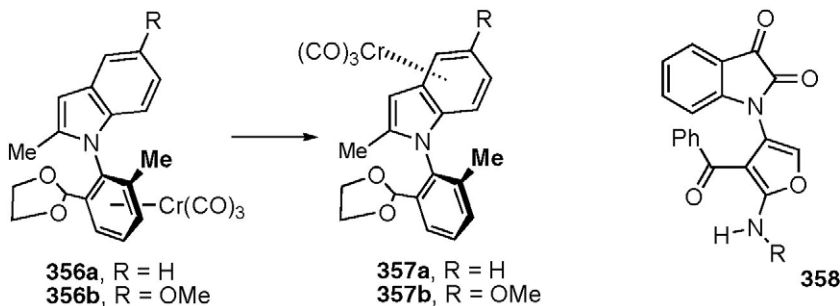
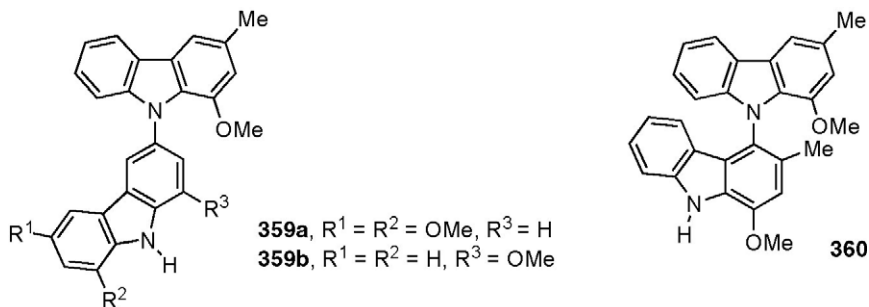


Figure 21. Synthesis of 1-(2-ethyl-6-methylphenyl)-2-methyl-1H-indoles.

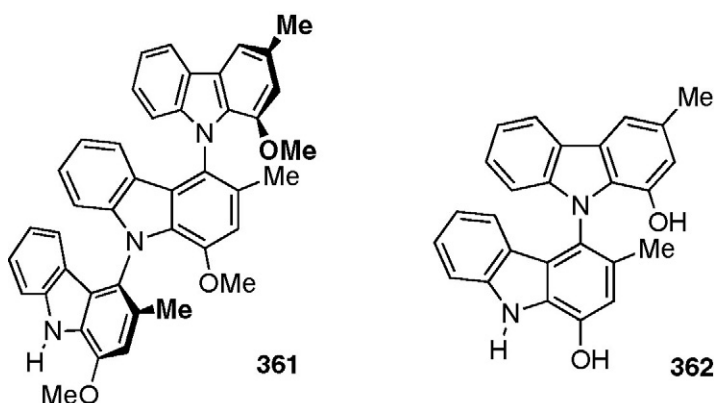
dioxolanyl substituent. Replacement of the dioxolanyl substituent by a methyl stopped the migration (07JOC3394).



A synthesis and DNMR study of functionalized 1-(3-furyl)-1H-indole-2,3-diones **358** has been reported (07MC107). A free energy of activation (ΔG^\ddagger) of 71.2 kJ mol^{-1} for the rotation about the *N*-furyl bond in **358** (R = 1,1,3,3 tetramethylbutyl) was determined. The others in the series also presented atropisomerism.



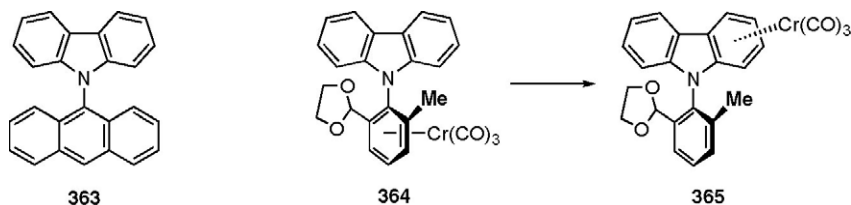
Murrastifolines A (**359a**), B (**359b**) and F (**360**) are examples of N-C linked bicarbazoles (01JA2703). The atropisomers of Murrastifolines A, B are presumably configurationally unstable. However, a study of the atropisomerization could be envisioned by cryo-chromatography on a chiral support. Murrastifoline-F presented a suitable substitution pattern to give rise to room temperature stable atropisomers. Synthesis, chiral resolution and CD analysis of the enantiomers of Murrastifoline F have been reported (01JA2703). Comparison of the experimental CD trace with the calculated one allowed the determination of the absolute configuration of the enantiomers. The barrier was not experimentally determined but AM1 calculations predicted a barrier larger than 160 kJ mol^{-1} with considerable pyramidalization in the transition state.



Several other original atropisomeric forms have been characterized in that study. Trimeric by-product **361** was obtained during the synthesis. Demethylated Murrastifoline F **362** was prepared and characterized as a starting material for the formation of a diastereomer with camphorsulfonyl chloride or Mosher's chloride. A limited number of chiral columns were screened; they gave partial separations. A good chiral separation by HPLC scalable to semipreparative separation will save a lot of effort in the determination of absolute configuration. Samples carefully extracted from *Murraya koenigii* showed a positive CD peak at 254 nm by LC-CD analysis on an ODS column indicating an excess of the *M* form in the natural sample ($10\% < ee < 16\%$).

Boyer et al. reported the NMR study and the X-ray structure of a symmetrical 9-(9'-bromo-10'-anthryl)carbazole (**363**). The inter-ring angle was 82.9° (93JCS(P2)757). Hu et al. described atropisomerism in 5,11-dihydro-5,11-di-1-naphthylindolo[3,2-b]carbazole (**25**). The *cis-meso* and *anti-D,L* form were detected by NMR. Diastereomerization occurred at the melting temperature 390°C (99JA5097).

Kamishawa et al. studied the migration of a tricarbonyl chromium from a *N*-aryl group to a carbazole. The migration is controlled by the dioxolane group.



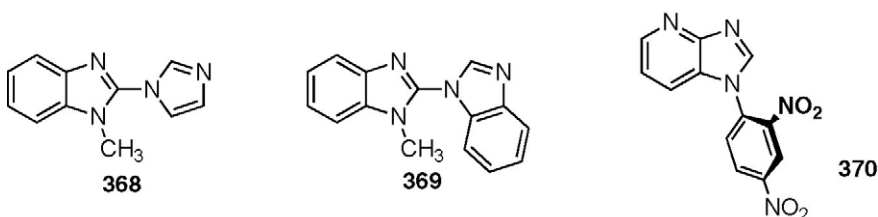
Optically pure *N*-aryl carbazole **364** with a planar chirality was transformed into **365** presenting axial and planar chirality by a totally diastereoselective migration of the tricarbonyl chromium. Interestingly, the enantiomeric excess in **365** was high at the beginning of the transfer and decreased after 2 h in refluxing toluene. A slow racemization stemmed from a slippage of the tricarbonyl chromium from one phenyl of the carbazole to the other.

The induction of axial chirality was successfully proven in several *N*-aryl acridane and related chromium complexes in which slippage was not observed (Figure 22). The data collected in Table 6 show the decisive role of the dioxolane moiety for the successful migration. The diastereoselectivity is smaller when the methyl in an *ortho* position is suppressed (10CC6846).

4.1.2 Imidazoles and benzimidazoles

The conjugation of the coplanar rings in *N*-arylimidazoles and *N*-arylbenzimidazoles was addressed by UV spectroscopy (64ZOK632), ionization constants and a Menshutkin reaction (68CHC373). The interaction between the imidazole ring and substituents in the benzene ring in some *N*-arylimidazoles was examined with the aid of dipole moments, UV spectra, ionization constants, and rate constants for the Menshutkin reaction (70CHC194). The atropisomers of *N*-naphthyl benzimidazoles bearing a diphenylphosphosphinyl group at the 2-position of the naphthalene were resolved by enantiospecific cleavage of the N2C–P bond (11CEJ5110).

Noncoplanar structures were advocated on the basis of dipole moments on introduction of a methyl group on the benzimidazole of *N*-(2-benzimidazolyl)imidazole (**368**) and benzimidazole (**369**) (70CHC515).



Dipole moments militated in favor of nonplanar structures in *N*-(*o,m,p*-nitrophenyl)(benz)imidazole (70CHC759). The X-ray structure of 1-(2,4-dinitrophenyl)-1*H*-imidazo[4,5-*b*]pyridine (**370**) shows that the dihedral angle was 56.2° in the solid state (72BSF2916, 80AX(B)1217).

In pentapeptide **371**, a twisted conformation was shown for the *N*-arylimidazole motif (09JOC8212).

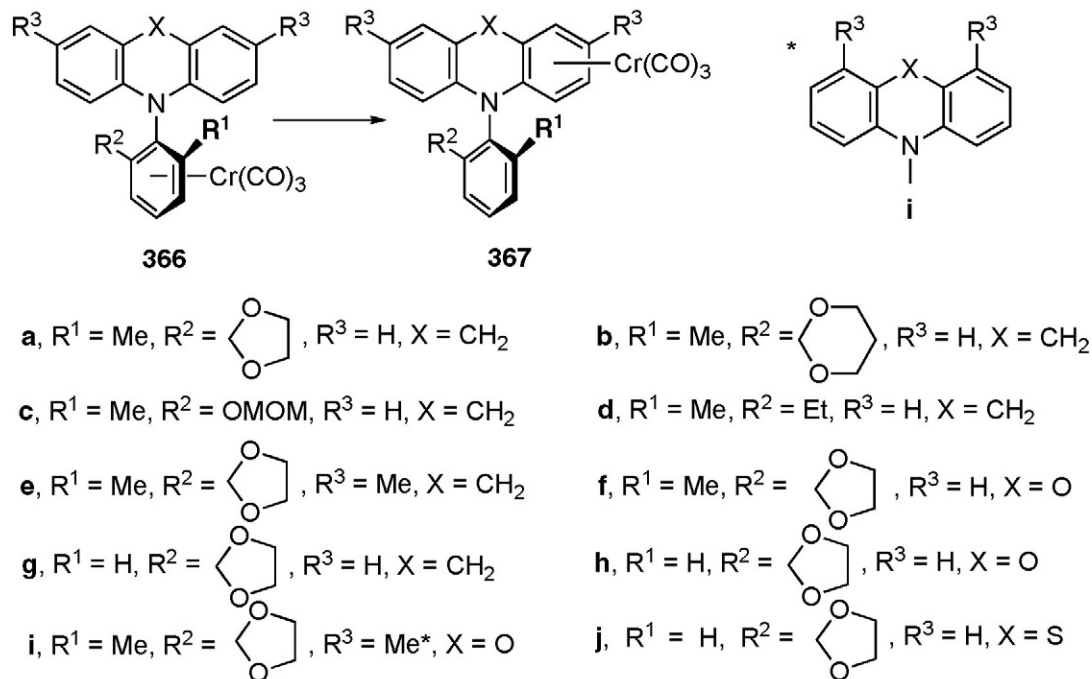
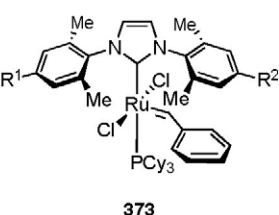
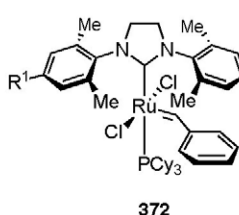
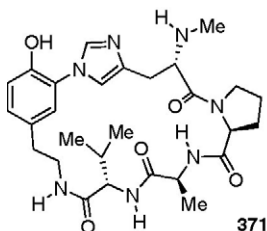


Figure 22. *N*-Aryl acridane and related O and S derivatives.

Table 6. Kamikawa *et al.* experiments (10CC6846)

Substrate	Product	Yield	dr	ee (%)
366a	367a	78	>99:<1	99
366b	367b	70	>99:<1	89
366c	367c	– ^a	–	–
366d	367d	– ^a	–	–
366e	367e	42	>99:<1	98
366f	367f	60	>99:<1	94
366g	367g	61	87:13	99
366h	367h	73	85:15	95
366i	367i	60	>99:<1	95
366j	367j	71	>99:<1	85

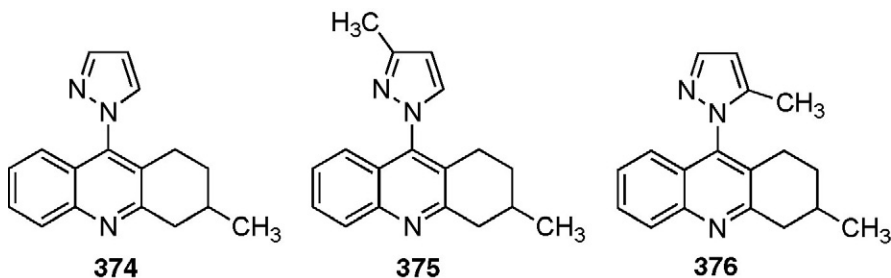
^aStarting material was recovered.

Atropisomerism in Grubbs II complexes based on imidazoline **372** and imidazole **373** has been addressed. Chiral compounds are obtained when the rotation around the C–Ru bond is slow and the R¹ and R² groups are different. Barriers equal to 64 kJ mol^{−1} about the N-aryl bonds have been measured by DNMR whereas the atropisomeric barrier about the C–Ru equals 87 kJ mol^{−1} (08CEJ5465).

4.1.3 Pyrazoles and indazoles

Steric inhibition of resonance in 5-alkyl-1-*p*-nitrophenylpyrazoles is shown by a marked hypsochromic shift of λ_{max} in their ultraviolet spectra, whereas an alkyl group in the 4-position of the pyrazole ring has the expected mildly bathochromic effect (56JOC97, 59JA5637, 65CHC613, 66T2703). The angles of twist in sterically hindered 1-arylpyrazoles were addressed by LCAO-MO calculation of UV spectra (68JCS(B)725). 1-(2',4'-dinitrophenyl)-3-phenyl-5-pyrazolone was studied by NMR and UV. *Syn* and *anti* forms were advocated (60JOC1355). The study was extended recently to a large series of 1-(2,4-dinitrophenyl)pyrazoles by ¹³C and ¹⁵N NMR chemical shifts in solution and in the solid state (08MRC697). A series of *N*-phenylpyrazoles was studied

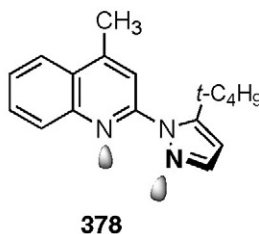
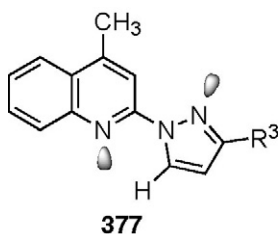
by UV, IR, and NMR (64CJC1605, 68JCS(B)211, 92MRC455). Chemical shift data were used to distinguish relative coplanarity of the phenyl and pyrazole rings (66JOC1878). NMR was employed for 1-arylindazole (67SA(A)2243). An X-ray of 1-(2',4'-dinitrophenyl)-4-chloro pyrazole revealed an inter-ring angle equal to ca. 22° (70AX(B)380). A similar angle was reported for the 4-bromo analogue (69AX(B)1637). The fluxional behavior of the (π -allyl)palladium complexes of pyrazolylpyrimidines are accompanied by rotations about the N–C bond (96CB589, 01NJC1050).



The 9-pyrazolyl-3-methyl-1,2,3,4-tetrahydroacridines show in ^1H NMR a shielding of the protons of the CH_2 group at position 1 due to the anisotropy of the 9-aromatic residue (thus proving this substituent is out of plane). According to AM1 calculations, the dihedral angle is $\varphi = 60^\circ$ for 374 and 375 and $\varphi = 75^\circ$ for 376 (always with the lone pair pointing toward the saturated ring). For the first two compounds, the barrier was too low about the C9–N1' bond to observe NMR splitting but for the last, the planar transition state ($\varphi = 0^\circ$) is hindered by the 5'-methyl group and both atropisomers (diastereoisomers due to the 3-methyl group) were observed in some ^1H and most ^{13}C NMR signals (04EJMC37). The diastereomerization barrier was not determined.

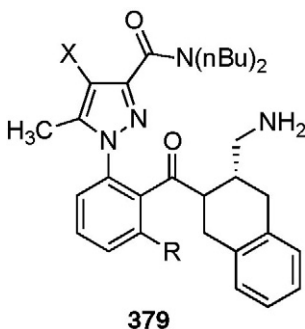
The full energetic profile according to an AM1 calculation for the rotation around the pivot bond in *N*-(2'-pyridyl)pyrazole was reported. As expected the planar diastereomer in which the two nitrogens are in opposition was the more stable with a flat profile. The *syn* diastereomer is less stable and gives rise to two enantiomeric twisted forms (30°) to accommodate the N–N repulsion (93JHC865).

The conformation and *ortho* steric effect were addressed in a series of 2-(3' or 5'-alkylpyrazol-1-yl)quinolines. For 5'-unsubstituted derivatives 377, the conformation is almost planar and the lone pairs are in an *anti* position. The introduction of substituents in position 5' increases the inter-ring dihedral angle according to the steric size of the alkyl groups in the series Me to *t*-Bu 378 (96JHC323).



Planar 1-(2-hydroxyphenyl)pyrazole derivatives presented a strong hydrogen bond between the OH group and the nitrogen. The 2-methoxy analogue was twisted ([92JA5039](#)). The importance of an intramolecular hydrogen bond was also revealed in 1-pyridyl-5-aminopyrazoles. 1-pyridylpyrazole and 1-(3' or 4'-pyridyl)-5-aminopyrazoles were nonplanar while in 1-(2'-pyridyl)-5-aminopyrazole intramolecular hydrogen bonding forced a *trans* planar conformation according to dipole moments ([70CHC45](#)). Intramolecular hydrogen bonding leading to coplanarity was observed by X-ray analysis in 5-hydroxy-3-phenyl-1-(3-methyl-1-isoquinolyl)pyrazole ([71CB2694](#)).

A dihedral angle close to 60° was reported for the solid state of 1-phenyl-3-dimethylamino-4-cyano-5-pyrazole ([77AX\(B\)413](#)). The inter-ring angle was 19.6° in 1-(4-nitrophenyl)-3-methyl-4-bromopyrazole ([72AX\(B\)791](#)).

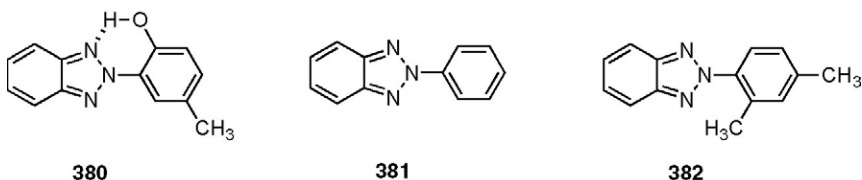


Atropisomerism was demonstrated in **379**. It arose from aryl-C=O and amide rotations. The rotation about the *N*-pyrazolyl-aryl bond was not blocked ([09BMCL1767](#)).

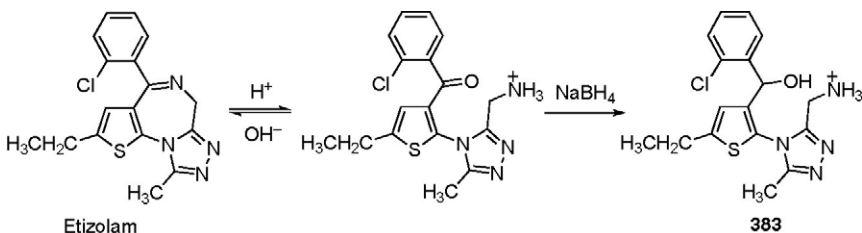
The conformation about the C-N bonds of **16** was modified by coordination with Ru-bipyridyl ([07POL4373](#)). When there is an *ortho*-nitro group adjacent to an azole with an N atom at position 2 (pyrazoles, indazoles, triazoles, and tetrazoles) the preferred conformation has the nitro group close to the N atom (**48**, X = Y = Z = CH, R⁴ = R⁵ = H, see also **26**): this is the so-called orthogonal effect (Section 2.8.5) ([05AG\(IE\)1788](#), [06ARK\(ii\)136](#)).

4.1.4 Triazoles and benzotriazoles

N-aryl-1,2,4-triazoles, *N*-aryl-1,2,3-triazoles, and *N*-aryl-benzotriazole have been studied by UV spectroscopy (54JCS4256, 58G977, 58G1035) and as new class of UV/blue light-emitting fluorophores (11CEJ5011). In 1-(2',4'-dinitrophenyl) and 1-(2',4',6'-trinitrophenyl) triazoles and benzotriazoles, the predominant conformations result from the orthogonal effect (05AJC817, 07T3737). The structure of compounds related to Tinuvin P (380) was studied by crystallography, NMR (solution and solid state), and B3LYP/6-31G(d,p) calculations (07MI2201). The suppression of the IMHB has a profound influence on the dihedral angle about the N–C bond (381 and 382). A *t*-butyl group next to the OH group drastically modified the behavior of the H-bond in a solvent such as DMSO. A shielding of the IMHB was demonstrated (92JA964).



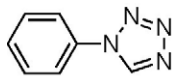
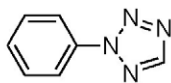
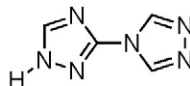
Compound **383** that resulted from the ring opening of etizolam and reduction of the carbonyl into a secondary alcohol gave two diastereomers. These atropisomers resulted from the slow rotation around the *N*-thiophene bond. The diastereomerization was monitored in methanol and chloroform at room temperature. Interestingly, the final equilibrium position was strongly dependent on the solvent and was reached in ca. 14 h. The barriers were not evaluated (92CPB220).



X-ray data showed that the molecular arrangement in the crystal is drastically different for 2-(3,5-dimethyl-1*H*-1,2,4-triazolyl)-5-nitropyridine and 3,5-dimethyl-1-(4-nitrophenyl)-1*H*-1,2,4-triazole despite the same crystal space group. The difference in molecular arrangement influences the nonlinear optical coefficients for a blue light second-harmonic generation device (94BCJ1936).

4.1.5 Tetrazoles

N-aryltetrazoles have been studied by ^1H and ^{13}C NMR by Lippmann *et al.* (76T499, 77T1399). 2-Substituted isomers **384** are more planar and consequently more conjugated than 1-substituted **385** due to steric effects.

**384****385****386**

4.1.6 Several azoles

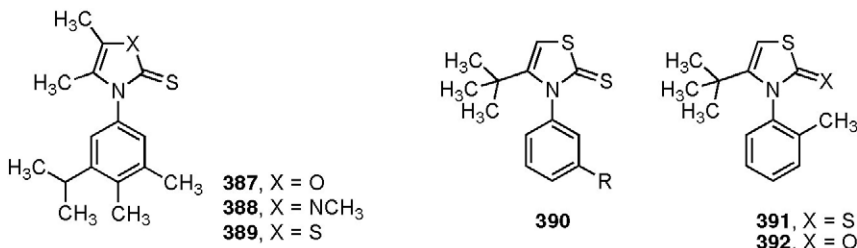
Recently, it was shown that 4-(1*H*-1,2,4-triazol-3-yl)-4*H*-1,2,4-triazole (**386**) that is almost planar in the isolated state, gave twisted structures in acentric and homochiral coordination compounds obtained by a hydrothermal reaction with CdI_2 or CdBr_2 , respectively (08CC4159). The inorganic anions Br^- and I^- induced the coordination mode of the organic ligand and thus controlled the assembled structure. With I^- the complex crystallized in an acentric space group in which the inter-ring angle between the two triazole rings was 10.78° . With Br^- the complex crystallized in a chiral space group with a 33.72° inter-ring angle. Interestingly, seven single crystals randomly picked for X-ray analysis presented the same absolute structure and the authors state that “the bulk samples consist predominantly of the same enantiomorph, and that they are probably chirally pure.” This could be considered as an example of deracemization during crystallization. It is highly probable that both enantiomorphs could be obtained randomly if different crystallization batches were considered. The chiral bromine complex gave the achiral one by hydrothermal reaction of KI.

4.2 Oxo- and thiooxo-five-membered rings

4.2.1 Thiazoline-2-one, thione, and imino

DNMR of *N*-(3'-isopropylphenyl)-4,5-dimethyl-azoline-2-thiones **387**, **388**, and **389** pointed out the dramatic effect of the ring element X on the barrier to rotation around the *N*-aryl bond. The barriers of the labile atropisomers were 38.8 kJ mol^{-1} (182K), 51.4 kJ mol^{-1} (230K), and 73.9 kJ mol^{-1} (318K) for X = O (oxazoline-2-thione), *N*-Me (imidazoline-2-thione), and S (thiazoline-2-thione), respectively. The origin of such a large barrier for the thiazoline-2-thione came from the long intracyclic C–S bonds which push the 4-methyl group and the thiocarbonyl group toward the rotating aryl group (85JCS(P2)273). The thiazoline-2-thione framework equipped with suitable substituents in position 4 and on the *N*-aryl ring lead to room

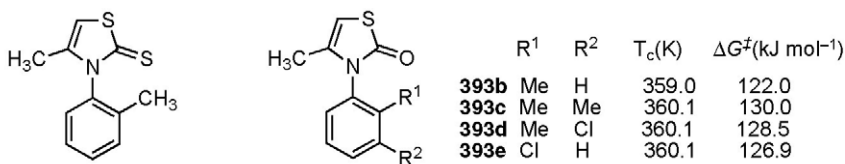
temperature stable atropisomers. *N*-(3'-*R*-phenyl)-4-*t*-Bu-thiazoline-2-thiones **390** were separated on cellulose triacetate and the barriers to rotation were determined by thermal racemization. The barriers that were in the range 103.3–105.5 kJ mol⁻¹ (298K) slightly decreased for electron attracting *R* groups in a *meta*-position and in apolar solvents (86NJC399).



3-(*o*-Tolyl)-4-*t*-butyl-thiazoline-2-thione **391** was resolved on cellulose triacetate and the absolute configuration *S* was assigned to the (+) enantiomer from X-ray analysis of the quaternary salt obtained by reaction at the sulfur with (–)-2-bromo-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl acetate. Treatment of **391** with MeI/NaOMe afforded thiazolin-2-one **392**.

Compound **393a** presented some interesting properties: it can be resolved on most available chiral stationary phases and the barrier to rotation of the enantiomers is so high that decomposition occurred before racemization starts. An estimate of barrier indicated that it should be larger than 134 kJ mol⁻¹. Enantiomers of **393a** were quantitatively transformed without racemization into the thiazolin-2-one analogue **393b** through methylation at sulfur and treatment with NaOMe at room temperature. (+)-**393a** gave (+)-**393b**. The very mild conditions to transform C=S into C=O are particularly suitable for the determination of absolute configuration by the chemical correlation method.

Derivatives **393a** and **393b** as well as a series of *N*-aryl-thiazolin-2-ones **393c–e** substituted on the phenyl by methyl or chlorine group in an *ortho* position have been resolved on MCTA and their barriers to rotation in diglyme were determined (88JOC5076).



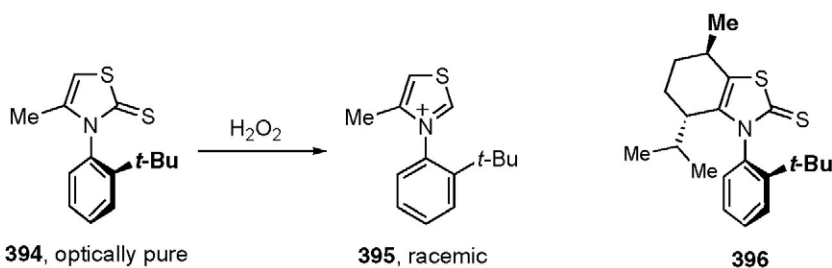
393a, Δ*G*[‡] > 134 kJ mol⁻¹

The barriers are much lower in thiazolin-2-one than in thiazoline-2-thione due to the large difference in steric requirement between C=O and C=S groups. They were as expected sensitive to buttressing of the *meta* substituent on the phenyl. The barrier was higher for chlorine (**393e**) than for a methyl (**393b**) in the blocking position. The buttressing effect of a methyl group in position 5 of the thiazoline-2-one was not operating in the five-membered ring (**90NJC169**).

When the aryl group is a phenyl bearing alkyl substituents, atropisomers of *N*-aryl-thiazolin-2-ones and thiazoline-2-thiones are composed of a very polar heterocycle and an apolar aryl group that are situated in two perpendicular planes. This is a particularly favorable combination to address chiral recognition on various chiral stationary phases or chiral additives in the mobile phase (**89JC(462)95**, **93CHI207**, **93CHI471**, **93JIP283**, **94CHI251**, **96JC(A722)177**, **97EN449**, **97JC(A761)129**, **01CHI56**). They were used as model compounds to evaluate new chiral columns (**92CHI36**, **94TA777**, **96JC(A753)109**) and new supports for electrochromatography (**00EL917**).

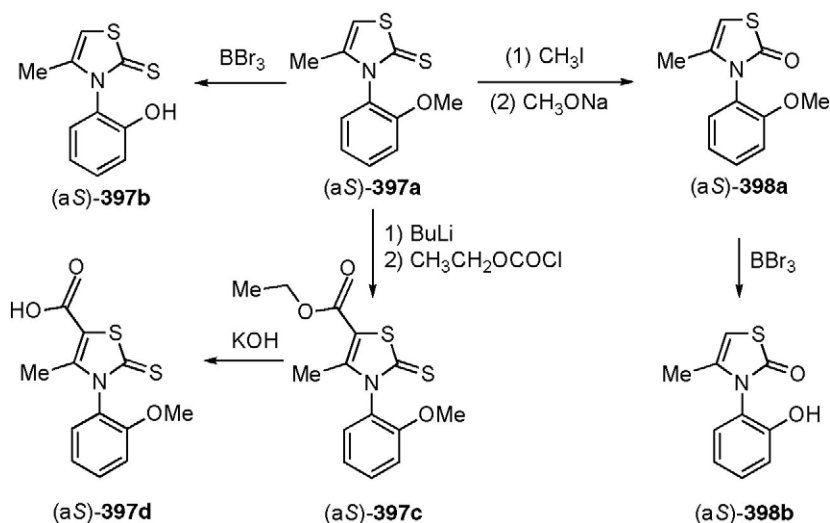
Pirkle *et al.* prepared an extensive series of atropisomeric *N*-aryl-thiazoline-2-(thi)ones to evaluate the recognition mechanism on a so-called (*S,S*)-Whelk-O1 column. In accordance with the postulated recognition mechanism the (*S*) form always eluted before the (*R*) form on that column (**96JC(A726)91**).

Bach *et al.* (**04EJOC2025**) wanted to take advantage of the very high barrier in optically pure **394** to prepare the corresponding optically pure thiazolium salt **395** through oxidation at sulfur.



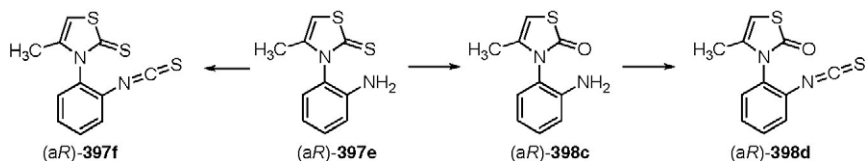
The oxidation proceeded smoothly but the salt **395** was racemized. X-ray data of **395** showed a disorder in the structure arising from the presence of the two enantiomers; the two rings are perpendicular. The axial chirality could be controlled by the central chirality at C-4 of the thiazoline thione **396** and the resulting salt could be used to produce a carbene employed in a benzoin condensation.

N-(*o*-Functionalized-aryl)-4-alkyl-thiazolin-2-one and thiazoline-2-thione atropisomers were nicely resolved by chiral chromatography (**05LOC433**).



The absolute configuration of the series was determined by X-ray analysis of the cinchonine salt with **397d** and a chemical correlation method. The thiazolinone **398b** derived from **398a** presented a plateau during chiral HPLC. The barrier in **398b** was much lower than in **398a** due to the stabilization of the TS by an intramolecular hydrogen bond.

3-(2-Aminophenyl)-4-methyl-thiazoline-2-thione (**397e**) was the lead in series of functionalized atropisomers, **398b**, **398c**, and **398d**. The configurations were determined ([04JC\(A1037\)311](#), [05LOC433](#)).



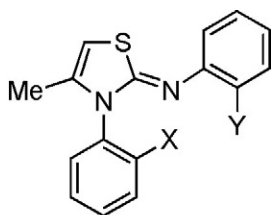
The isothiocyanates **397f** and **398d** could not be analyzed by chiral chromatography with a mobile phase containing an alcoholic modifier since thiocarbamates were readily formed. A successful separation was performed on a Chiralpak IA column with an alcohol free mobile phase.

A series of atropisomeric thioureas was prepared from optically pure isothiocyanates **397f** and **398d** with primary amines. Atropisomeric ureas were prepared by reacting **397e** or **398c** with various isocyanates. The resulting ureas and thioureas were used as neutral enantioselective anion receptors for *N*-protected amino acid tetrabutylammonium salts ([06CHI762](#)).

Contrary to what was expected on the basis of the difference in NH acidity in thiourea and urea groups, the association constants were smaller

with the thiourea than with the corresponding urea. X-ray data, DFT calculations, and NMR provided the explanation of the unexpected behavior (Figure 23): urea **399** presents a preorganized (*Z,Z*) conformation suitable for a double hydrogen bond with the carboxylate anion, while thiourea **400** presents a (*Z,E*) conformation, which must be reorganized in a constrained (*Z,Z*) conformation in the complex (06CHI762, 08CSR151).

Atropisomeric thioureas were assayed in organocatalyzed enantioselective cyanosilylation of aldehydes (06TA999). 3-(2-Aminophenyl)-4-methyl-thiazoline-2-thione (**397e**) was the starting material to prepare a series of bis-(*N*-aryl) atropisomeric triads such as 1,2-bis-[4-methyl-2-(thio)oxo-2,3-dihydrothiazol-3-yl]-benzene (09CHI160). 2-Arylimino-3-arylthiazoline derivatives showed atropisomerism (02ARK(x)72, 08JOC403).

**401**

A series of original atropisomeric iminothiazolines **401** in which X = OH or (and) Y = OH were prepared from the corresponding methoxy precursors. The resolution of the atropisomeric enantiomers on chiral support was reported, and the barriers to enantiomerization were given. These barriers were determined either by off-line racemization studies or by treatment of the plateau-shape chromatogram during chromatography on a chiral support. When X = OH, the barriers are quite low due to the hydrogen bond between the proton of the OH group and the nitrogen of the imino group. For these compounds, plateau shaped chromatograms were obtained during HPLC on a chiral support. DFT calculations

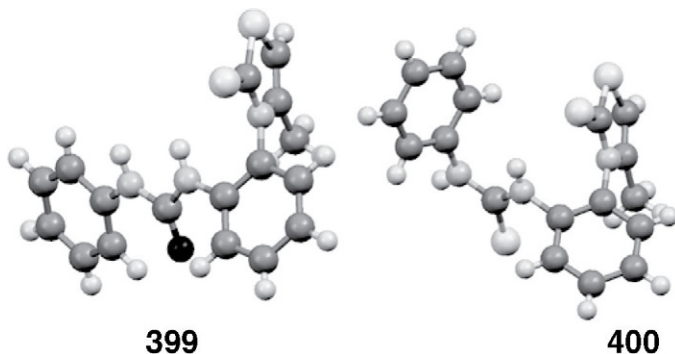


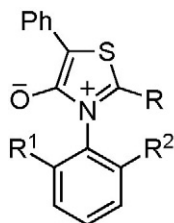
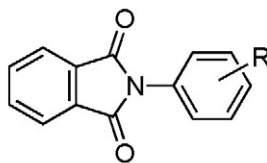
Figure 23. X-ray structures of the urea **399** (left) and of the thiourea **400** (right).

confirmed hydrogen bonding all along the rotation process and produced calculated barriers in close agreement with the experimental data (08JOC403). An atropisomeric bridged macrocycle was prepared from the dihydroxy $X = Y = \text{OH}$ derivative (08ARK(viii)28).

4.2.2 Other five-membered heterocycles

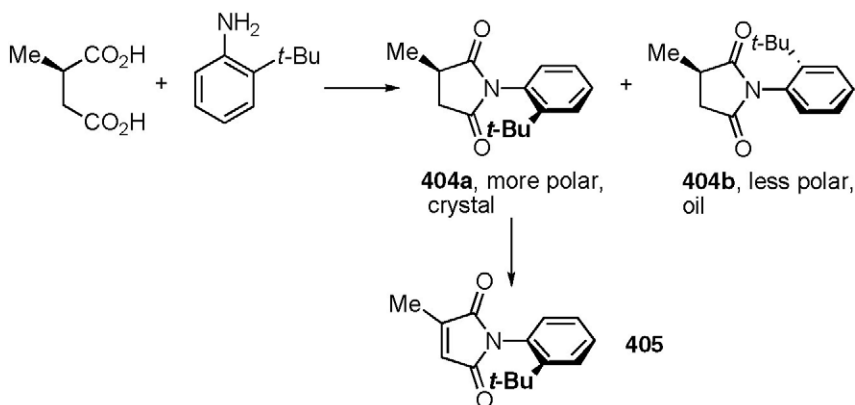
X-ray data showed that in *N*-(*p*-bromophenyl)sydnone the phenyl and the sydnone ring are not coplanar (63AX471). The observed dihedral angle 27.6° was confirmed by EHT-MO calculation (67TL1233).

Computational results (at PM3 and B3LYP/6-31G(d) levels) showed that the *N*-aryl moiety is invariably orthogonal to the heterocyclic ring while the phenyl group at C-5 adopts a coplanar arrangement in mesoionics **402** (04EJOC2805).

**402****403**

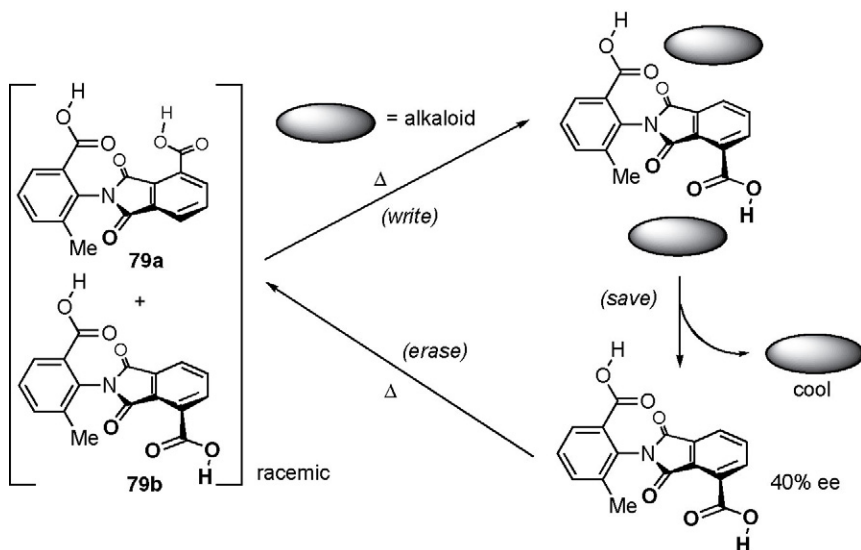
^{13}C NMR was employed to detect nonplanarity in 2-aryl-1*H*-isoindole-1,3(2*H*)-dione (**403**) (85OMR259).

(+)-*N*-(*o*-*t*-butylphenyl)-2-methylmaleimide (**405**) was prepared by an asymmetric synthesis from (*R*)-2-methylsuccinic acid in two steps and 96% *ee*. The optical purity decreased from 96% to 82% after 4 weeks at room temperature and the enantiomers were analyzed on a Chiralpak AD column.

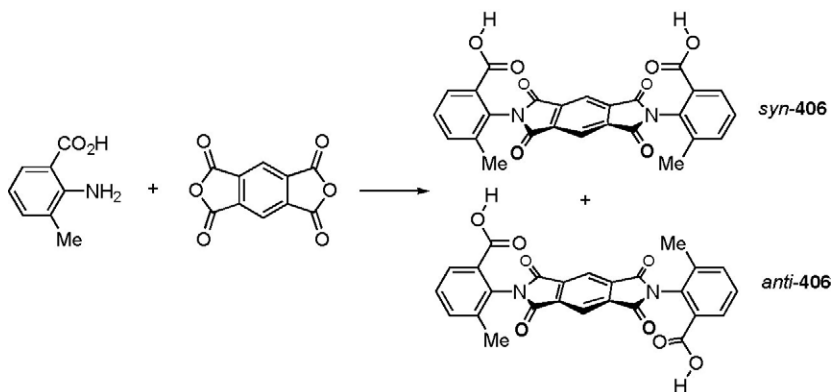


The barrier to rotation around the *N*-aryl bond was higher in **404a** than in the maleimide (**98JOC2634**). Compound **404a** was oxidized to **405** ($[\alpha]_{\text{D}}^{28} = +1.3$, $c = 1.1$, CHCl_3) without loss of *ee*.

Racemic diacid **79** was imprinted at an elevated temperature with an alkaloid. Quinine and quinidine that are “*pseudo*” enantiomers led to opposite enantiomers. The guest-induced chirality was preserved on cooling to rt, which was maintained even in the absence of a guest ($t_{1/2} = 14$ years). The chiral enrichment process was also reversible, allowing the diacid to be used as a chiral switch (**09OL2599**).



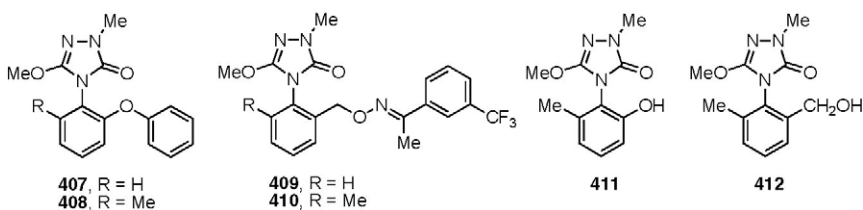
Stable achiral *syn* and *anti* atropisomeric forms were obtained in bis diimides **406**.



A recent review covers the design and applications of these atropisomeric “malleable” molecular frameworks (09OBC3899).

The barriers to rotation in *N*-aryl-oxazoline-2-thione **53** and *N*-aryl-imidazoline-2-thione **54** were evaluated by DNMR. The barrier was strongly dependent on the intracyclic heteroatom (85JCS(P2)273). Despite the relatively low barrier one should expect in *N*-aryl-oxazoline-2-ones and *N*-aryl-oxazoline-2-thiones, several examples of atropisomer separation were reported on the Whelk O1 column (96JC(A726) 91, 96JC(A753)109).

N-(2,6-Disubstituted)phenyl-triazolones constitute a very interesting class of atropisomeric compounds (04T4361). They are inhibitors of mitochondrial respiration and it was shown that the biological activity was related to the presence of a substituent in the blocking position of the *N*-aryl group.



Small quantities of atropisomers of **407** were separated by preparative chromatography on a chiral support. Racemization occurred within hours. In **408**, the atropisomers are particularly stable at ambient temperature (calculated barrier $>160 \text{ kJ mol}^{-1}$) and the activity is significantly located in the (+) enantiomer of **408** and **410**.

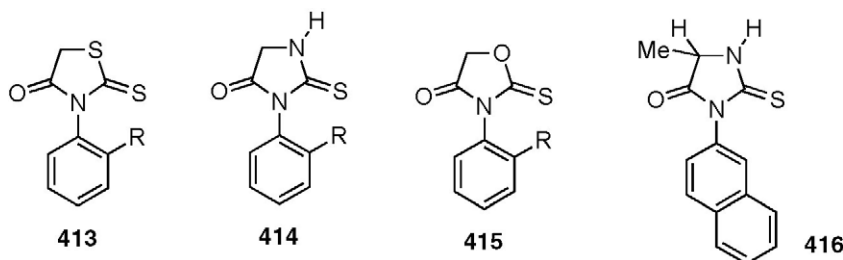
Compounds **411** and **412** that are the precursors of **408** and **410** were submitted to various resolutions methods amenable at the large scale. The formation of diastereomeric esters of **411** with optically pure naproxen or chlorocamphorsulfonate allowed the determination of the absolute configuration by X-ray analysis proving that (+) and (–) **411** are (*S*) and (*R*) respectively. A correlation method showed that (+) **408** is (*S*). The diastereomers of **412** camphorsulfonate were separated by fractional crystallization and scaled up to several hundreds of grams. The unwanted diastereomer can be equilibrated into a mixture of the two diastereomers upon heating in toluene for 48 h.

Racemic phenolic triazolones **411** form dimers, while the corresponding enantiomerically enriched compounds form extended chains. These differences in aggregation behavior were observed in crystalline states and in aprotic solvents.

Barriers and ground state conformations were addressed by calculation at three different levels of theory including the DFT [B3LYP/6–31G(d)] level on **411** and model analogues. Four substituents in blocking

positions yielded barriers larger than 115 kJ mol^{-1} ; much lower barriers were obtained when the aryl group is substituted by a single substituent in an *ortho* position (05THE(719)69).

Atropisomerism in 3-aryl-2-thioxo-1,3-thiazolidin-4-ones **413**, 3-aryl-2-thioxoimidazolidin-4-one **414**, 3-aryl-2-thioxo-1,3-oxazolidin-4-one **415** have attracted much interest. Atropisomerism was monitored by ^1H NMR of the AB spectra of the hydrogen in position 5. 5-Substituted derivatives yielded diastereomers. In the case of a high barrier, separation was performed by chromatography on a chiral support.



The first example was reported by Colebrook for 3-(2'-naphthyl)-2-thioxoimidazolidin-4-one (**416**) (72TL5239). It proved that the steric requirements of thiocarbonyl and carbonyl groups on the heterocycle were sufficient to produce a high barrier to rotation despite the absence of any *ortho* substituent on the *beta*-naphthyl group. The barrier was 90.7 kJ mol^{-1} in DMSO at 97.5°C . Curiously this is the sole example that has been described in the 3-aryl-2-thioxoimidazolidin-4-one **414** series.

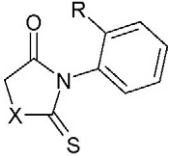
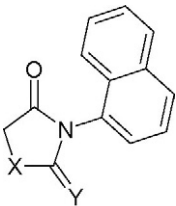
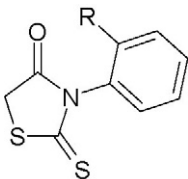
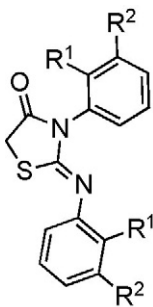
Dogan *et al.* have reported extensive studies on series **413** and **415**. Table 7 reports the barrier determination for compounds unsubstituted in position 5. Examples with one or two methyls in position 5 can be found in the references of Table 7.

Compounds **413a,b** and **415a,b** were conveniently resolved on cellulose triacetate and CD spectra were recorded. A calculation provided the absolute configuration of the isolated atropisomers. Thermal racemizations were performed in diglyme; they showed a higher steric requirement in 3-aryl-2-thioxo-1,3-thiazolidin-4-ones **413** than in 3-aryl-2-thioxo-1,3-oxazolidin-4-ones **415**. A chlorine in an *ortho* position of the phenyl group afforded a higher barrier than a methyl group (93JCS(P2)1557).

A series of *N*-(1-naphthyl) derivatives **417**, **418**, and **413c** were resolved on a Chiralpak AD column and the barriers to interconversion were determined by thermal racemization. The barriers were higher for compounds having an intracyclic sulfur atom or a sulfur atom as a flanking substituent (05TA3752).

An interesting series of *N*-(2-halogenophenyl) 2-thioxo-1,3-thiazolidin-4-ones **413d**, **413b**, **413e**, and **413f** was separated into enantiomers on

Table 7. Dogan *et al.* experiments

Samples		Solvent	$\Delta G^\ddagger / \text{kJ mol}^{-1}$ (K) (rotation barriers)	Reference
	415a , X = O, R = Me	Diglyme	103.8 (328.8)	(93JCS(P2) 1557)
	415b , X = O, R = Cl	Diglyme	110.3 (340.2)	
	413a , X = S, R = Me	Diglyme	114.4 (348.5)	
	413b , X = S, R = Cl	Diglyme	121.2 (387.6)	
	417 , X = Y = O	EtOH/Hex 60/40	103.8 (313K)	(05TA3752)
	418c , X = Y = S	EtOH/Hex 50/50	111.3 (351K)	
	418c , X = S, Y = O	EtOH/Hex 70/30	105.9 (323K)	
	413d , R = F	EtOH	91.0 (280K)	(08TA2184)
	413b , R = Cl	EtOH	119.5 (348K)	
	413e , R = Br	2-PrOH	123.6 (351K)	
	413f , R = I	Toluene	129.0 (383K)	
	419a , R ¹ = Me R ² = H	EtOH	106.2 (333K)	(07JOC2494)
	419b , R ¹ , R ² = Benzo	EtOH	111.2 (333K)	
	419c , R ¹ = OMe, R ² = H	EtOH	98.1 (308K)	
	419d , R ¹ = Cl, R ² = H	EtOH	110.7 (343K)	

Chiralpak AD-H. The barriers to rotation nicely correlated with the Van der Waals radii of the halogens (08TA2184). Determination of absolute configurations by NMR during interaction with $\text{Rh}_2^{(\text{II})}[(R)\text{-}(+)\text{-Mosher's acid}]_4$ failed (08CHI344).

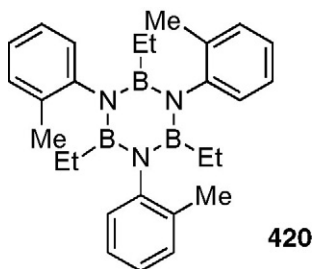
2-Arylimino-3-aryl-thiazolidine-4-ones **419a–d** with a suitable substituent on the 3-aryl groups were separated into enantiomers on several chiral columns and the barriers to interconversion were measured (see Table 7).

Here again the barrier is higher for the chloro than for the methyl derivative (07JOC2494). *Note:* we have not included in that survey in a rather arbitrary manner the derivatives with two methyl groups in position 5. Examples can be found in the references quoted in Table 7 and in (04TA925) and (03CHI242).

4.3 Six-membered heterocycles (azines)

4.3.1 Boron and pyridinium derivatives

The B–N bond is a C–C substitute in an aromatic system (09CJC8). B-triethyl-*N*-*o*-tolylborazin (420) was among the first examples of atropisomerism in *N*-aryl six-membered heterocycles. Two diastereomers were observed by NMR, one having the three methyl groups of the *o*-tolyl on the same face (*cis* form) and the other having two tolyls up and one down (*trans* form).



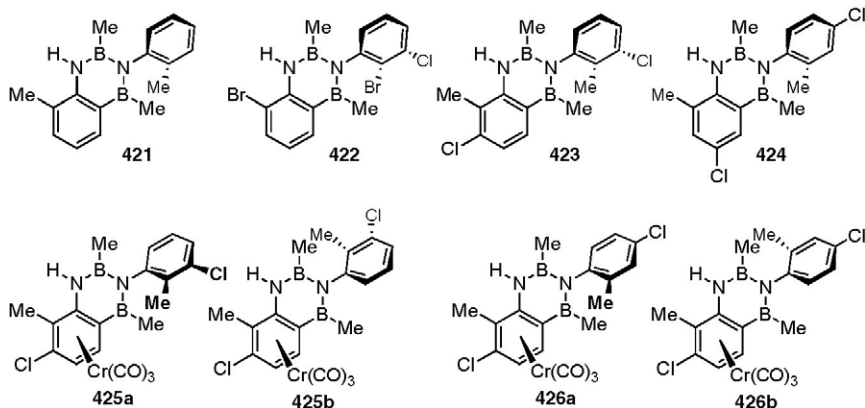
The occurrence of these two forms is an indication of the high barrier around the Aryl–N bond. The B-trichloro analogue did not display diastereoisomerism in the condition of the study (90 MHz NMR and 0 °C). The isomeric B-tri-*o*-tolyl-*N*-triethylborazin showed atropisomerism and the interconversion barrier was determined at 50 °C: $\Delta G^\ddagger_{cis \rightarrow trans} = 107 \text{ kJ mol}^{-1}$, $\Delta G^\ddagger_{trans \rightarrow cis} = 107.7 \text{ kJ mol}^{-1}$ (74IC2769).

These results have been questioned since the three methyl-B analogues were found to exist as a single all-*cis* diastereomer together with the B–OH hydrolysis by-product (85IC2520). The occurrence of the all-*cis* form might result from steric hindrance during the reaction of the methyl-Grignard reagent on the trichloro precursor. The all-*cis* trimethyl compound was heated above its melting point without forming the *cis*–*trans* form. Above 350 °C decomposition started.

The occurrence of a mixture of *cis*–*trans* isomers depends on the nature of the *o*-substituent on the aryl group and the halogen on the starting borazine (90IC1447).

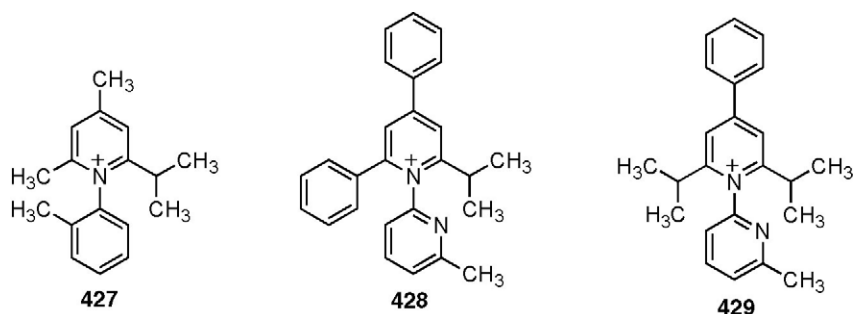
^1H , ^{13}C NMR, and crystallographic studies of η^6 -benzo-bonded (boron–nitrogen heteroarene) tricarbonylchromium complexes and

related η^6 -phenyl-bonded (B,B',B''-trimethyl-N,N',N''-triarylborazine)-tricarbonylchromium complexes of **421**–**424** have been reported (94JOM(469)59). A 1:1 mixture of diastereomers resulting from planar and axial chirality was observed in **425** and **426**. It showed that the interaction between tricarbonylchromium and the *ortho*-substituent on the phenyl ring was very weak.



The X-ray structure of *o*-tolyl-2,4-dibora-1,3-diazaronaphthalene shows the inter-ring angle between the diboradiazaronaphthalene and the tolyl is 89.7° (91JOM(406)269). Note that a boat type conformation exists for the N-B-N-B part of the diboradiazaronaphthalene.

Uncuta and Balaban described (76RRC251) the first example of atropisomerism in *N*-(2-methylphenyl)-2,4-dimethyl-6-*i*Pr-pyridinium perchlorate (**427**), which was easily prepared from a pyrylium precursor.

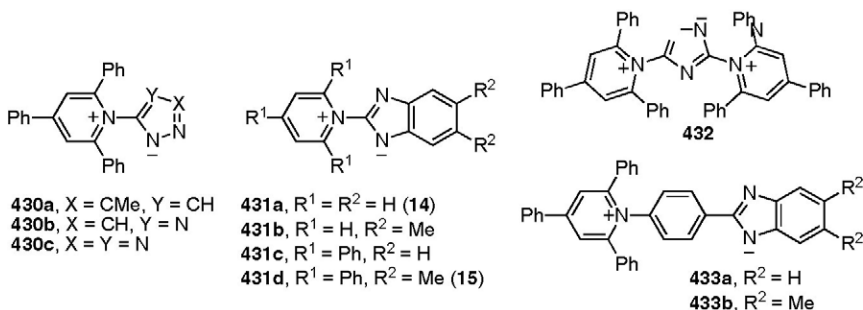


The methyl groups of the 2-isopropyl group were diastereotopic, giving rise to two doublets easily distinguishable even at 60 or 80 MHz. The barrier was not reported.

The rotational barriers for coalescence data (DMSO) in 1-(3'-methylpyridin-2-yl)pyridinium salts **428** and **429** (83OMR587) are 77.3 kJ mol^{-1}

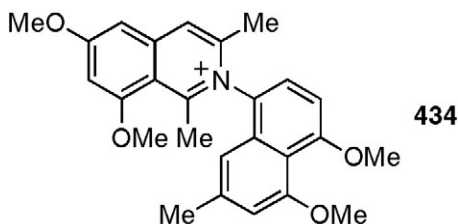
when the flanking substituents were phenyl and *i*Pr **428** and larger than 83 kJ mol⁻¹ for the prochiral 2,6 di-*i*Pr derivative **429**.

Ten mesomeric betaines, **430–432**, of pyridinium azolates have been prepared from the corresponding pyridinium azole salts. Dipole moments, ¹H and ¹³C NMR spectra, X-ray structures and theoretical calculations (MNDO) have been used to determine their molecular and electronic structures (87JOC5009).



When positions 2 and 6 of the pyridinium were unsubstituted, the structure was planar. The planar mesomeric betaines **431a** and **431b** were strongly associated when the weight fraction was greater than 0.0002, and their dipole moments tend to zero when concentrations increase, indicating a head-to-tail orientation to form a nonplanar dimer. The planar structure of **431a** was confirmed by X-ray analysis. Substitution in positions 2,6 of the pyridinium led to perpendicular structures as confirmed by the X-ray analysis of **431d** in which the inter-ring dihedral angle was 84.4° in accordance to MNDO calculations. The hindered perpendicular mesomeric betaines **431c** and **431d** did not associate. Desymmetrization of the pyridinium or the azole ring would lead to atropisomerism.

Ancisheynine (**434**) was the first characterized atropisomeric N–C linked naphthylisoquinolinium alkaloid (03TL5827). It was isolated from *Ancistrocladus heyneanus*. The extract presented no optical rotation. The nature of counter anion was not determined.



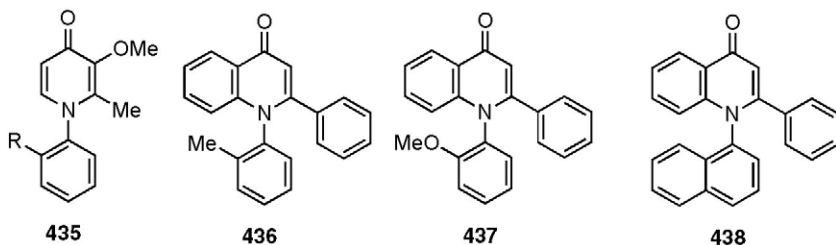
The synthesis was performed classically by reacting the properly substituted benzoisopyrylium with the properly substituted

naphthylamine (06OL1037). The enantiomers were separated under reverse phase conditions on Chiralcel OD-RH coupled with CD detection. The first eluted enantiomer gave a (–) signal at 240 nm and was identified as the *M* form by comparison of the experimental CD spectrum with the calculated one (OM2 and TD-DFT). The optical rotation of the isolated enantiomers was not reported.

4.3.2 *N*-Aryl pyridones and derivatives

4.3.2.1 *N*-Aryl-4-pyridones

A series of *N*-aryl-3-methoxy-2-methyl-4-pyridones **435** were prepared by reacting the corresponding 4-pyrones with 2-chloro-, 2-methyl-, 2-cyano-, 2-methoxy-, 2-chloro, 6-methyl-, or 2,6-dimethyl-anilines (85T229). Liquid chromatography on MCTA at the semipreparative scale resulted in a partial enrichment in enantiomers of the 2-methyl and 2-chloro derivatives that were submitted to off-line thermal racemization in order to determine the barriers to rotation in diglyme. In this model, the barrier is smaller for the chloro- than for the methyl derivative ($\Delta G^\ddagger = 109.6 \text{ kJ mol}^{-1}$ at 65.7 °C and 111.2 kJ mol^{–1} at 71.6 °C). The X-ray structure of the 2-chloro compound revealed that the dihedral angle between the two aromatic rings is 91.3° (89AX(C)126).



The barriers are higher than those obtained in the Sternhell (87JA341) biphenyl model with similar interacting groups due to the shorter bond of the rotating bond (N–C versus C–C bond) and a buttressing effect produced by the methoxy group on the blocking methyl. That pioneering study would benefit greatly from modern column developments and plateau shape treatment.

The barriers for 2-cyano and 2-methoxy compounds were too low to allow collection of the enantiomers. They were determined on line in the elution solvent (EtOH:H₂O 96:4) monitoring the decay of the optical rotation of the enriched enantiomer trapped in the polarimeter cell during the chromatographic separation (stopped flow method). The method is very convenient since the concentration in the starting material is not required for first-order kinetics. The barrier values were 93.2 and 98.3 kJ mol^{–1} for the 2-cyano and 2-methoxy derivatives, respectively. The lower limit of the

barrier for the 2-chloro-6-methyl disubstituted compound was estimated to be larger than 134 kJ mol^{-1} . In the prochiral 2,6-dimethyl derivative no coalescence of the *ortho* methyl groups was detected at 140°C in the presence of Pirkle's alcohol yielding a barrier larger than 100 kJ mol^{-1} .

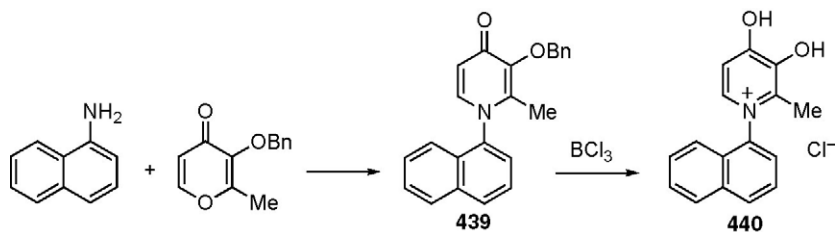
The experimental barrier for the *N*-(1-naphthyl) analogue ($121.0 \text{ kJ mol}^{-1}$) was quoted in a contribution dealing with molecular-mechanics calculations (91MI207). An X-ray structure determination indicated that the inter-ring angle is 85.5° (89AX(C)126). Molecular-mechanics calculations reproduce the experimental barriers (91MI207).

The pioneering work of Mannschreck *et al.* on 4-pyridone atropisomers should benefit greatly on going to chiral column developments and plateau shape treatment for the experimental determination of the barriers as well as by modern DFT calculations.

Recently, several examples of *N*-arylpyridones and *N*-aryl-4-quinolones equipped with a suitable substitution pattern to produce stable atropisomers have been reported, 436–438 (10OL212).

A large series of fungicidal *N*-aryl-4-pyridones has been described in patents (87EPP239391). Atropisomers were claimed without reported examples (10USP160385). At the time of this review, the chirality issues in these compounds, with possible interesting applications, have not yet been addressed.

As a typical example, the fluorescent ion sensor reported by Silva *et al.* (10T8544) could be developed in an enantiomerically pure form to produce chiral sensors.



The barrier in neutral 439 is expected to be high enough to perform the separation of enantiomers. Under treatment of the pure enantiomers with BCl_3 , optically pure 440 enantiomers would be obtained without racemization since the barrier is expected to be larger in the charged species than in the neutral precursor. X-ray data of hydrochloride 440 shows that the planes containing the two aromatic rings formed a dihedral angle equal to 77.98° . 440 possesses two dissociable protons corresponding to the two hydroxyl groups. It can be ionized to neutral and a negatively charged forms. All these forms will be configurationally stable at room temperature.

10-(3-Chlorophenyl)-6,8,9,10-tetrahydrobenzo[*b*]-[1,8]-naphthyridin-5 (7*H*)-one, Sch 40120 (441), is an antipsoriatic agent (96CHI364).

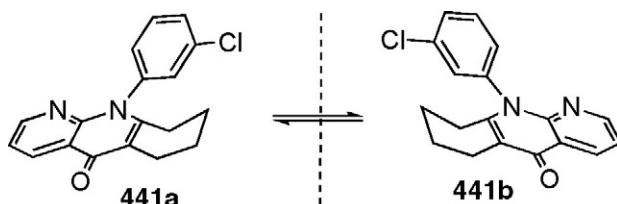
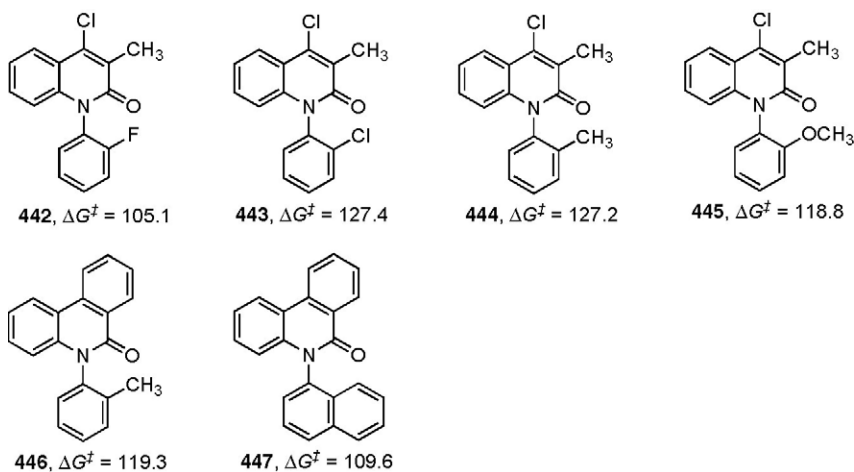


Figure 24. Interconverting enantiomeric atropisomers of *rac*-Sch 40120 (**441**) in a half-chair conformation.

Atropisomerism was detected by NMR using Pirkle's alcohol. Separation of the enantiomers by chromatography on an ovomucoid chiral column revealed the occurrence of a plateau between the enantiomers depending on the temperature. The barrier determined by DHPLC was 90.3 kJ mol^{-1} at 37°C ($t_{1/2} = 1.6 \text{ min}$). Such a low barrier at physiological temperature justified that the drug candidate will be developed as a racemate. Note that in a recent review on atropisomerism in drug discovery, Sch 40120 (**441**) was wrongly reported with the chlorine in 2 position instead of 3 position (09AG (IE)6398). A chlorine in position 2 will produce a much higher barrier yielding stable atropisomers at room temperature (Figure 24).

4.3.2.2 *N*-Aryl-2-pyridones

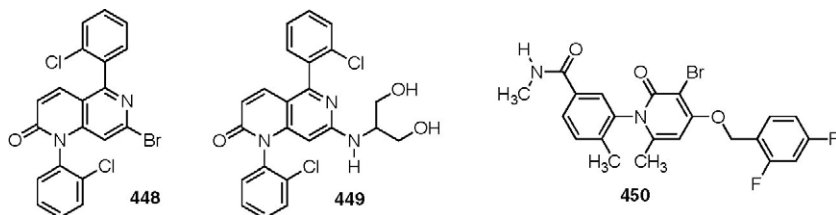
The first direct observation of atropisomers in this series was reported by NMR on 5-(2-methylphenyl)phenanthridin-6(5*H*)-one (**446**) in the presence of tris-[3-trifluoromethylhydroxymethylene-(+)-camphorato]europium(III) (73JCS(CC)537).



Later, the atropisomers of four *N*-aryl-4-chloro-3-methyl-2(1*H*)-quinolones (**442–445**) and two *N*-aryl-6(5*H*)-phenanthridinones (**446, 447**) were separated on MCTA and the barriers (values in kJ mol⁻¹) were determined by thermal racemization (90JCS(P2)619).

Remarkably, the barrier is slightly higher for the 2-chlorophenyl than for the 2-methylphenyl and may be attributed to a dipolar interaction between the carbonyl group and the chlorine in the preferred transition state. In the series 2(1*H*)-quinolones and 6(5*H*)-phenanthridinones, a *N*-(1-naphthyl) gave a larger barrier than the corresponding *N*-(2-methylphenyl) in accordance with the higher steric demand during methylation of quinoline, compared to 2-methylpyridine (83T4209). For the same *N*-aryl group the barrier is ca. 8 kJ mol⁻¹ lower in phenanthridinones.

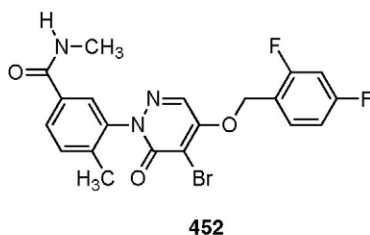
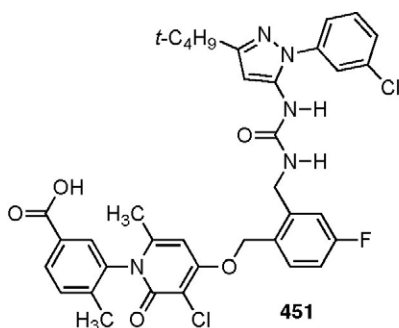
A patent (04WO73628) described a large series of 1,5,7-trisubstituted quinoline-2(1*H*)-ones, for instance **448** and **449**, which presented suitable flanking groups to produce stable atropisomers, although there is no mention of atropisomers.



A very large series of *N*-aryl pyridin-2-ones have been reported in the patent literature (03WO68230, 05WO18557). Among hundreds of perfectly described structures that should give stable atropisomers, PH 797804 (**450**) emerged as very active in inhibiting p38 α (08WO72079). The enantiomers were separated by chiral chromatography (Chiralcel OJ or Chiralpak AD) using MeOH or EtOH and the aS enantiomer alone is responsible for potency ($K_i = 5.8$ nM). The X-ray structure of the PH 797804/p38 α complex has been determined (09B6402, 10JMC2345), including the outstanding properties of PH 797804, in terms of selectivity and potential uses (09B6402, 09JPET882).

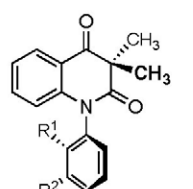
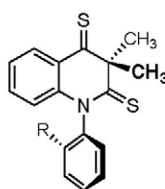
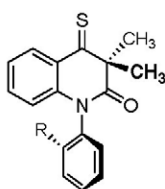
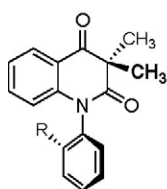
A patent (08WO72079) reported the preparation of optically pure PH 797804 at the kg scale by Novozyme Savinase enzymatic resolution of a precursor at 30 °C at pH 9.1. The unwanted enantiomer was thermally racemized.

Curiously, chirality issues arising from atropisomerism have not yet been addressed by Pfizer Products Inc. (07WO91176) that displayed a large series of analogues to **451**. The carboxy group served as precursor of amides.



Replacing the C-6-methyl of the pyridinone series by a nitrogen gives more flexible atropisomers around the *N*-aryl bond (10BMCL3146). This led to a large series of pyridazinones such **452** that have been evaluated as p38 α inhibitors. The flexibility around the *N*-aryl bond and the lower hydrogen bonding ability of the 2-carbonyl were not favorable to produce similar activities as those observed in the analogous 2-pyridones series. The pyridazinone analogue of PH 797804 (**452**) is 200 times less potent against p38 α . The barriers have not been yet reported.

Mintas et al. prepared a series of *N*-aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones and their mono and dithio derivatives, **453–456** (94MC457). The atropisomers were conveniently separated by liquid chromatography on triacetyl or tribenzoyl cellulose.



In all cases, the first eluted enantiomer was levogyre (546 nm) in the mobile phase composed of ethanol or methanol and water. The barriers (Table 8) to rotation were determined by monitoring the decay of the optical rotation for an enriched sample trapped in the polarimeter cell during chromatographic separation (on-line procedure in the mobile phase for **453a** and **454a**) or by thermal racemization of collected enantiomer in diglyme (**455a**, **453b**, and **453c**). Compound **455c** bearing a chlorine in the *ortho* position decomposed on heating and thus the barrier was not determined.

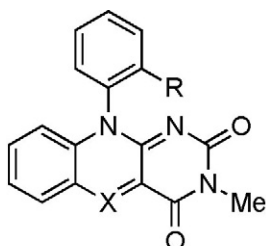
Table 8. Barriers to rotation about the C–N bond

Compound	Solvent	<i>T</i> (°C)	$10^5 k$ (s ⁻¹)	λ (nm)	ΔG^\ddagger (kJ mol ⁻¹)
(MP)- 453a	EtOH:H ₂ O (96:4)	27	10.0	365	97.4 ± 0.2
(MP)- 454a	MeOH	30	9.8	546	97.6 ± 0.2
(MP)- 455a	Diglyme	59	11.8	546	106.7 ± 0.2
(MP)- 453b	Diglyme	74	60	436	106.9 ± 0.7
(MP)- 453c	Diglyme	59	14.4	436	106.2 ± 0.2

The barrier is larger when a thiocarbonyl replaces a carbonyl in a flanking position in accordance with the size of sulfur compare to oxygen. The relative size for *R-ortho* groups is MeO < Me ~ Cl.

4.3.2.3 (5-Carba)isoalloxazines

Shinkai *et al.* reported the synthesis of a series of (5-carba)isoalloxazines bearing diversely substituted aryl groups at N-10, **457** and **458** (85TL5183,88JCS(P1)313).

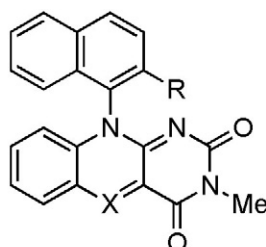


457a, X = N, R = CO₂Me

457b, X = N, R = Et

457c, X = N, R = Ph

457d, X = CH, R = Ph



458a, X = N, R = H

458b, X = N, R = OMe

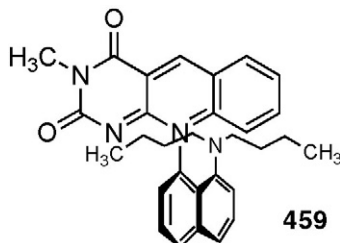
458c, X = CH, R = OMe

The enantiomers were successfully separated on Sumipax OA-2000 eluted with a mixture hexane/1,2-dichloroethane/EtOH (4:2:1). In all the series the (+) enantiomer was eluted first. These compounds are fluorescent except for the 2-MeO derivatives **458b** and **458c**. The optical rotation range in MeOH is 154–470. Compound **457a** racemized very slowly in butan-1-ol at 70 °C: k (first-order rate constant) = $1.35 \cdot 10^{-6} \text{ s}^{-1}$, $\Delta G^\ddagger = 125 \text{ kJ mol}^{-1}$. The other atropisomers did not racemize at that temperature.

Racemization of the enantiomer bearing three flanking groups around the rotating *N*-aryl bond can be promoted readily at 30 °C using different reduction methods (**457a–d**) followed by oxidation. The racemization rates were very similar to the pseudo first-order reduction rates. Reduction could not promote racemization in the two compounds presenting four interacting groups.

Conceptually these findings are particularly interesting. They point out that the formation of a racemate from optically pure atropisomers may follow another route than the simple rotation around the pivot bond.

The absolute configuration of the dextrogyre atropisomer of **459** was determined: (+)-*S* ([94TL8631](#)) during the study of the stereochemistry of asymmetric “(Net) Hydride Transfer” in an intercoenzyme model reaction system.



4.3.2.4 1-Aryl-4,6-dimethyl-2(1*H*)pyrimidones and thiones

1-Aryl-4,6-dimethyl-2(1*H*)-pyrimidones are easily prepared from *N*-aryl urea and acetylacetone. Kashima et al. were the first to isolate enantiomers resulting from atropisomerism in 1-aryl-4,6-dimethyl-2(1*H*)-pyrimidone. 2'-methyl, 2'-chloro, 2'-methoxy, 2'-ethoxy, and 2'-ethyl derivatives were resolved using D-camphor sulfonic acid. The barrier in MeOH for the 2'-Me derivative was 128.8 kJ mol⁻¹ ([78H469](#)). The barriers in the *meta* substituted derivatives were too low to allow resolution.

The barriers for 1-aryl-4,6-dimethylpyrimidin-2(1*H*)-ones **460** were compared to those obtained for the 2(1*H*)-thione analogues **461** ([Table 9](#)) ([80JCS\(P1\)1599](#)).

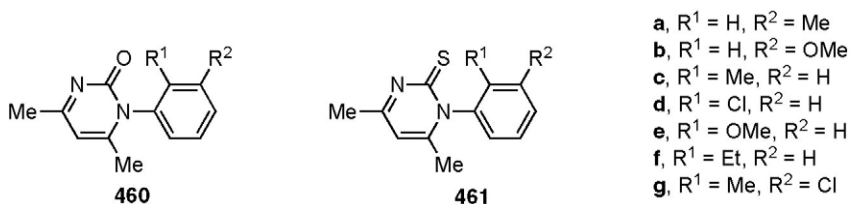


Table 9. Activation parameters of **460** and **461**

Compound	E_a	ΔG^\ddagger (kJ mol ⁻¹)	ΔH^\ddagger (kJ mol ⁻¹)	ΔS^\ddagger (J K ⁻¹ mol ⁻¹)
460c	133.1	126.8	130.5	12.1
460f	142.3	126.4	139.3	33.5
461c	131.8	115.9	128.9	36.8
461d	125.9	112.3	123.0	33.1
461g	130.1	113.0	127.2	39.7

The authors stated that “the rotational barrier was expected to increase when sulfur replaced oxygen; however, the rotational barrier of **461c** was found to be nearly equal that of **460c**.” That abnormal behavior was accounted for by “the greater single bond character (of the C=S bond) would probably promote bond bending, which will cause a decrease of the interatomic repulsion between the sulfur atom and the *ortho*-methyl group of the aryl group.” The occurrence of a lower barrier for the sulfur compound than for the oxygen one was not the only remarkable issue: the barriers were almost the same for the 2-methyl and the 2-ethyl 2(1*H*)-pyrimidones and above all there was no noticeable barrier change on the introduction of a chlorine in a buttressing position on going from **461c** to **461g**.

Sakamoto *et al.* have recently reported the barrier to racemization in different solvents for the 1-(2-methylphenyl)-4,6-dimethylpyrimidin-2(1*H*)-one (**03AG(IE)4360**) and for the 1-(1-naphthyl) analogue (**100BC5418**) after separation of the enantiomers on Chiralcel OD. The barriers were strongly solvent dependent but noteworthy in the same solvent the barriers were almost identical for the 2-methylphenyl and 1-naphthyl analogues (Table 10).

These new data bring additional evidence that the racemization barrier is independent of the steric contribution of the *ortho* substituent in the series: free methyl, buttressed methyl and locked methyl (1-naphthyl). Such a behavior cannot account for a racemization process involving a simple rotation around the pivot bond.

Roussel *et al.* have determined the barriers to atropisomerization in diglyme for 1-(2-methylphenyl)-4,6-dimethylpyrimidin-2(1*H*)-one (**460c**) and 1-(2-methylphenyl)-4,6-dimethylpyrimidin-2(1*H*)-thione (**461c**) (**88JOC5076**). After separation of the enantiomers on MCTA, the values were 118.2 and 107.7 kJ mol⁻¹, respectively, confirming a lower barrier for the sulfur derivative.

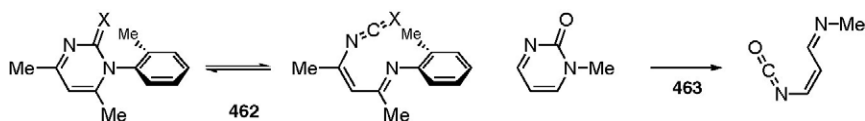
The barriers for 1-(1-naphthyl)-4,6-dimethylpyrimidin-2(1*H*)-one and 1-(1-naphthyl)-4,6-dimethylpyrimidin-2(1*H*)-thione recently have been reported after separation of the enantiomers on Chiralcel OD. Here again the barrier was lower in the thione analogue in three solvents (**100BC5418**).

Interestingly, the barriers in the 1-(2-methylphenyl) (**88JOC5076**) and 1-(1-naphthyl)thione (**100BC5418**) derivatives are similar and do not reveal the difference in steric requirements for these two groups.

To account for the insensitivity of the barriers to the variable steric requirement on the aryl group and smaller apparent size of the thiocarbonyl group in comparison with the carbonyl group, Roussel *et al.* have suggested an electrocyclic ring-opening/ring-closure reaction **462** instead of the classical rotation through a bent transition state (**88JOC5076**).

Table 10. Racemization barriers in kJ mol^{-1} determined by Sakamoto *et al.*

Compound	Solvent	ΔG^\ddagger	Reference
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	Xylene	116.62	(03AG(IE)4360)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	Diglyme	118.2	(88JOC5076)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	DMF	121.63	(03AG(IE)4360)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	1-PrOH	126.23	(03AG(IE)4360)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	MeOH	128.8	(78H469)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-one	Not reported	126.6	(80JCS(P1)1599)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-thione	Diglyme	107.7	(88JOC5076)
1-(2-Methylphenyl)-4,6-dimethylpyrimidin-2(1H)-thione	Not reported	115.8	(80JCS(P1)1599)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-one	Xylene	114.95	(10OBC5418)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-one	DMF	123.31	(10OBC5418)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-one	1-PrOH	127.49	(10OBC5418)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-thione	Xylene	96.56	(10OBC5418)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-thione	DMF	107.84	(10OBC5418)
1-(1-Naphthyl)-4,6-dimethylpyrimidin-2(1H)-thione	1-PrOH	109.10	(10OBC5418)
1-(2-Methyl-4-chloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	Xylene	115.36	(03AG(IE)4360)
1-(2-Methyl-4-chloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	DMF	120.38	(03AG(IE)4360)
1-(2-Methyl-4-chloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	1-PrOH	125.4	(03AG(IE)4360)
1-(2,4-Dichloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	Xylene	114.5	(03AG(IE)4360)
1-(2,4-Dichloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	DMF	119.1	(03AG(IE)4360)
1-(2,4-Dichloro-phenyl)-4,6-dimethylpyrimidin-2(1H)-one	1-PrOH	124.14	(03AG(IE)4360)

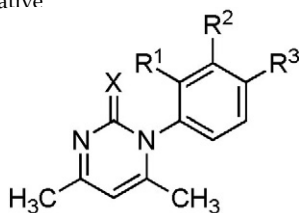


In that model the rotation around the *N*-aryl bond is not the rate determining process and the observed barrier is the energy associated with ring opening. A support for that hypothesis is the reported MP2/6-31++G(d,p) calculated potential energy curve for the conversion from the open-ring form to the close-ring structure of 1-methyl-2(1*H*)-pyrimidinone **463** independently performed by Novak *et al.* ([03JPC\(A\)5913](#)). These calculations yielded a barrier equal to ca. 100 kJ mol⁻¹.

Since the time of the suggestion of a ring-opening process, 1988, computational chemistry has reached a good level of prediction and further theoretical work is in progress.

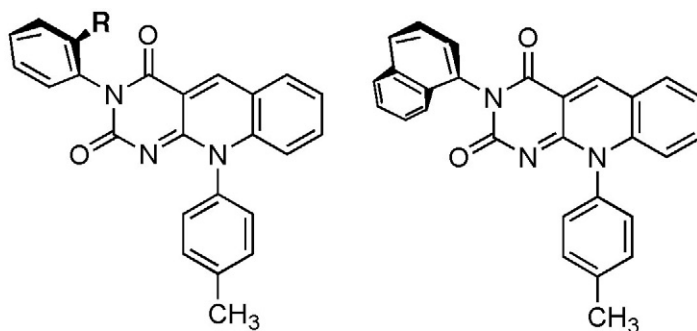
The barriers in pyrimidin-2(1*H*)-(thi)ones are not the sole domain of interest. The X-ray structures of several compounds have been reported ([Table 11](#)). They gave the inter-ring angle in the atropisomeric forms and revealed the occurrence of a conglomerate. Conglomerates were detected by chromatography on a chiral support by injection of a solution prepared from a single crystal ([03AG\(IE\)4360](#)). When two peaks are observed the crystal is composed of a racemate, when a single enantiomer is observed both on UV and chiroptical detections the compound exists as a conglomerate and several injections should give statistically the occurrence of the two enantiomers with opposite sign in the chiroptical detection ([07CHI497](#)). The occurrence of a conglomerate can be confirmed by a chiral space group for the crystal.

Sakamoto *et al.* reported the first example of chiral symmetry breaking of C–N axial chirality for *N*-aryl-2(1*H*)-pyrimidinones giving rise to a conglomerate by crystallization and induced enantiomer transformation without any outside chiral source ([03AG\(IE\)4360](#)). This work was extended recently to 1-(1-naphthyl)-4,6-dimethylpyrimidin-2(1*H*)-thione that also forms a conglomerate. Eighty-nine to ninety-one percent enantiomeric excesses were obtained by crystallization with seeding and stirring. Stirring alone yielded 41–88% *ees* with a random preference for one enantiomeric form, while seeding alone resulted in 8–37% in the same enantiomeric form as the seeding crystals ([10OBC5418](#)). An example of spontaneous symmetry breaking during interrupted crystallization of an axially chiral amino acid derivative has been reported recently ([10CC2094](#)).

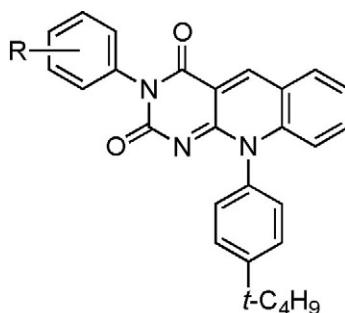
Table 11. Crystal systems obtained by X-ray structural analysis and inter-ring dihedral angle in pyrimidin-2(1*H*)-one derivative

X	R ¹	R ²	R ³	Space Group	Inter-ring angle	Reference
O	Me	H	H	<i>P</i> 2 ₁ Chiral	83.4	(03AG(IE)4360)
O	Me	H	Cl	<i>P</i> 2 ₁ Chiral	80.9	(03AG(IE)4360)
O	Cl	H	Cl	<i>P</i> 2 ₁ Chiral	81.2	(03AG(IE)4360)
O	Benzo	Benzo	H	<i>P</i> 2 ₁ / <i>n</i> Achiral	70.27	(10OBC5418)
S	Benzo	Benzo	H	<i>P</i> 4 ₃ Chiral	89.14	(10OBC5418)
S	Me	H	H	<i>P</i> 2 ₁ / <i>c</i> Achiral	81.5	(88JOC5076)

Yoneda et al. have prepared a series of atropisomeric 5-deazaflavins, **464** and **465**, with axial chirality at the pyrimidine scaffold (92TL3169, 92TL7173).

**464**, R = CH₃, C₂H₅, CH(CH₃)₂, C(CH₃)₃**465**

The atropisomers have been separated by chiral chromatography (Chiralcel OD) or by diastereomer formation in the case of a *t*-butyl substituent. The optical rotation of the enantiomers was reported. The chiral recognition ability of the 5-deazaflavin enantiomers was investigated in a model reaction of asymmetric intercoenzyme “(net) hydride transfer” reactions.

Table 12. Rotational barriers of 5-deazaflavins in kJ mol^{-1} 

R	ΔG^\ddagger (25 °C) ^a	Sign/absolute configuration	Solvent	Reference
2-Me	108.8	(+)R	DMF	(96JOC9344)
2-Et	113.3	(+)R ^b	DMF	(97T4601)
2- <i>i</i> Pr	121.2	(+)R ^b	DMF	(97T4601)
2- <i>t</i> Bu	145.04	(+)R ^b	DMF	(97T4601)
2-CF ₃	125	(+)S ^b	DMF	(97T4601)
2-HOCH ₂	108.4	(+)S ^b	DMF	(94TL9729, 96JOC9344, 97T4601)
2-TBDMSOCH ₂		(+)S ^c		(97T4601)
2,4-Br ₂ ,6-Me		(-)S ^d		(96JOC9344, 98AX(C)77)
2-HO ₂ C		X-Ray		(97AX(C)513)

^aEnantiomerization.^bCD analogy.^cChemical correlation.^dX-ray.

The barriers to rotation were determined by thermal racemization in DMF or dibutylformamide for several 4-*t*-Bu analogues (Table 12) (96JOC9344, 97T4601).

A crystalline inclusion complex of 10-(4-*t*-butylphenyl)-3-(2-ethylphenyl)-pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione/urea/EtOH obtained. X-ray analysis showed that the urea is doubly H-bonded to the pyrimidinone (96TL8905). The proximity of the chiral axis might give interesting applications in chiral recognition. The enantiomers were involved in an enantioselective hydride transfer reaction (Figure 25).

The recently prepared pyrimidones 466–468 are prone to yield stable atropisomers (10MI8843).

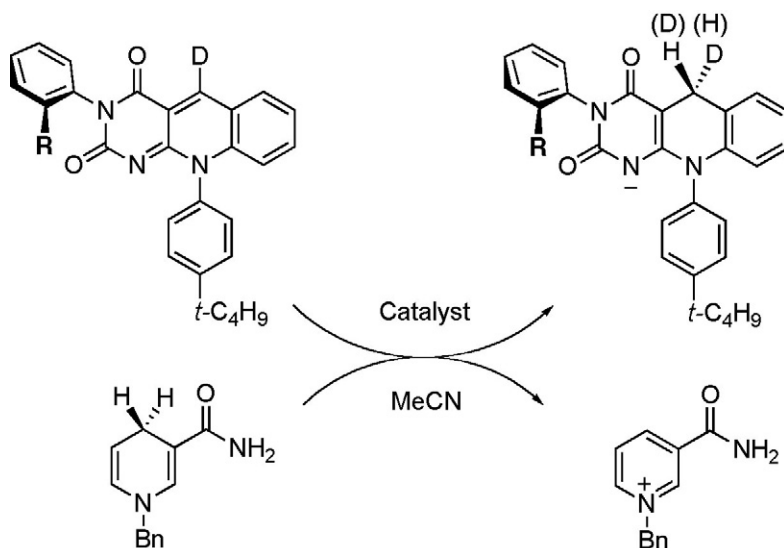
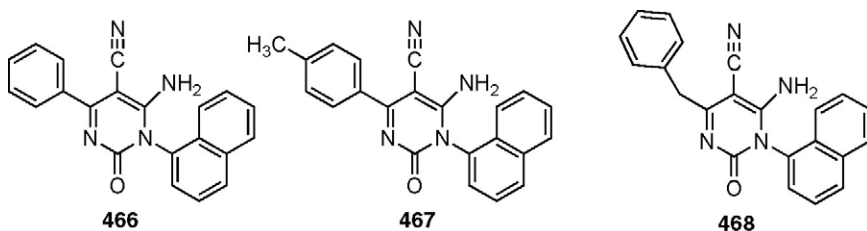
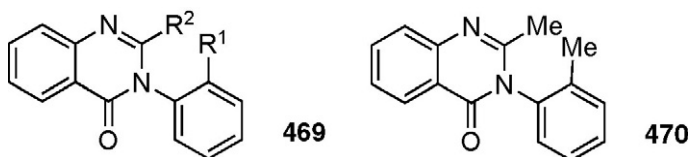


Figure 25. Enantioselective transfer reaction.



4.3.2.5 3-Aryl-4(3H)-quinazolinones

These compounds when substituted in position 2, **469**, give rise to atropisomerism around the *N*-aryl bond when the aryl group is not symmetrically substituted. Simultaneous substitution in position 2 of the 4(3H)-quinazolinone and in an *ortho* position of the aryl group leads to stable atropisomers. If one of the blocking groups either in position 2 or in an *ortho* position of the aryl is missing, the barrier is generally too low to permit isolation of the enantiomers at room temperature. However, a single particularly large group in position 2 or in an *ortho* position of the aryl might increase the barrier to produce isolable enantiomers.



Atropisomerism in 3-aryl-2-benzyl-4(3H)-quinazolinones was first described by Colebrook et al. The benzyl group at 2 acted as a blocking substituent and as a probe for DNMR study. When the 3-aryl group was a *beta*-naphthyl, a 3-bromo-phenyl or a 3-acetylphenyl the DNMR barriers in nitrobenzene were 82.8, 79.1, and 80.3 kJ mol⁻¹, respectively (72TL5239, 75CJC3431).

Analogues with an *ortho*-substituted aryl group in 2-chloro-6-methylphenyl, 2-bromophenyl, 2-chlorophenyl, 2-tolyl, 2-fluorophenyl did not show any coalescence of the methylene AB signal at high temperature. Colebrook et al. rightly concluded that "compounds of this type should be resolvable and have substantial optical stability at normal temperatures" (75CJC3431).

The quinazolinone structure is found in many biologically active compounds: methaqualone, mecloqualone, piriqualone, afloqualone, and so on. Methaqualone (MQ, 470), 2-methyl-3-(2-methylphenyl)quinazolin-4(3H)-one, an hypnotic and anticonvulsive drug, is one of the leading examples of atropisomeric six-membered *N*-aryl heterocycles. Methaqualone gives stable atropisomers at room temperature due to the three substituents in *ortho* positions of the *N*-aryl rotating bond.

In the 1980s, the enantiomers of MQ were separated by liquid chromatography on microcrystalline cellulose triacetate (MCTA) (83JC(282)89, 84EJMC381, 85JC(329)307, 85MI3, 86JC(351)346, 90JC(A498)257, 90JC(A513)195), the (+)*P* form being eluted first (96PHA379). The (–) form is first eluted on microcrystalline cellulose tribenzoate (86JC(351)346, 90MI2) and Chiralcel OB-H (96PHA379).

The chiral analysis of MQ was also conducted on a polymeric chiral support composed of poly(*N*-acryloyl-*S*-phenylalanine ethyl ester) immobilized in macroporous polymer particles (91JC(A585)145). Separations on other chiral supports have been exemplified: BSA (89CHI154, 92JC(A591)65), Chiralcel OJ (93JLC859), Chiralcel OJ-R (01JC(A906)127), Chiralcel OD-R (93JLC859), Chiralpak AD-H (06MI1), and RegisPack. Vancomycin immobilized on silica in a packed capillary column was used to separate MQ in supercritical fluid chromatography with MeOH as a modifier (99MI521). Chiralpak AS was successful for a semipreparative separation of MQ enantiomers with a mobile phase composed of isohexane, 2-PrOH and CH₃CN 99/0.5/0.5. The retention factors were 4.36 and 7.47 for the (+) and (–) enantiomer, respectively ($\alpha = 1.84$) (02JPBA431). Separation on Chiralpak IA (05JC(A1075)65), a new immobilized CSP based on a 3,5-dimethyl-phenylcarbamate of amylose was successful under various eluting conditions consisting of mixtures of hexane/THF, hexane/acetone, hexane/IPA, hexane/toluene/EtOH, TBME/EtOH, or hexane/CH₂Cl₂. The separation factors and resolutions were good, unfortunately the orders of elution were not given.

The CD spectra of the MQ enantiomers collected after chromatography on Chiraspher or (*S,S*)-Whelk-O1 columns have been reported (98CHI253). The (–) enantiomer shows a strong positive CD band around 215 nm and three negative bands at 231, 265, and 305 nm. The CNDO/S calculated oscillator strengths obtained for an AM1 optimized (*M*) configuration are in good agreement with experimental results, allowing the assignment of the absolute configuration.

The experimental barrier to racemization ($131.6 \text{ kJ mol}^{-1}$) of MQ in diphenylether at 135°C (84EJMC381) has been determined. The value of the Hartree–Fock 6-31G* calculated barrier was $136.9 \text{ kJ mol}^{-1}$. Extensive deformations in its TS were observed (02MI257).

The barrier to rotation of 2-methyl-3-(1-naphthyl)quinazolin-4(3*H*)-one in diglyme was $137.7 \pm 0.1 \text{ kJ mol}^{-1}$ at 129.2°C pointing out the steric differences between a methyl group and a more rigid benzo group (90JCS(P2)619).

For methaqualone, capillary electrophoretic methods were developed to quantify the stereoselectivity of the MQ metabolism. Five major hydroxylated metabolites are formed (Figure 26) that present three substituents in *ortho* positions of the *N*-aryl rotating bond, giving rise to stable atropisomers at room temperature.

Methaqualone enantiomers were separated by capillary electrophoresis using (–)-*N*-dodecyl-*N*-methylephedrinium bromide as chiral selector and surfactant (97PHA762).

The enantiomers of MQ and its five major monohydroxylated metabolites were analyzed by chiral capillary electrophoresis using acidic conditions and hydroxypropyl- β -cyclodextrin as buffer additive (01EL3270, 01MI96, 03EL2598, 03EL4078).

The ^1H NMR spectra of 2-methyl-3-(2'-hydroxymethylphenyl)-4(3*H*)-quinazolinone (see Figure 26), a major metabolite of methaqualone, was

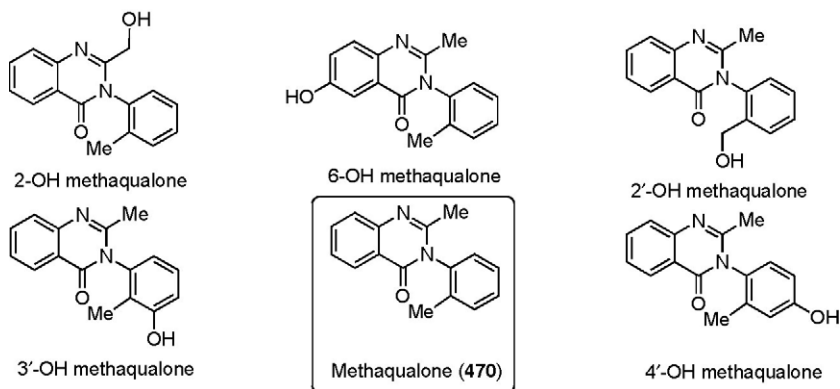
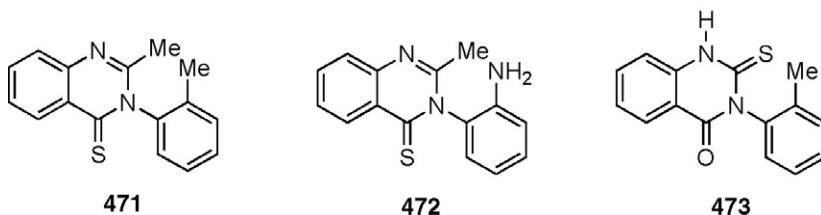


Figure 26. Metabolites of methaqualone (MQ, 470).

recorded in the presence of the chiral reagent tris[3-(heptafluoro-propyl)-hydroxy-methylene]-D-camphorato]europium. Significant induced shift differences between the enantiomers were used for a direct enantiomeric purity determination (90MI29).



2-Methyl-3-(2-methylphenyl)quinazoline-4(3H)-thione (**471**), the sulfur analogue of MQ, and 2-methyl-3-(2-aminophenyl)quinazoline-4(3H)-thione (**472**) were baseline separated into enantiomers on various chiral supports opening a way to barrier and chiroptical property determinations. Figure 27 reports the excellent baseline separation obtained on a Chiralpak AD column. Polarimetry indicates the sign of the optical rotation of the first and second eluted enantiomer in the mobile phase (11UP1).

Jira *et al.* (98CHI253) have separated the enantiomers of 3-(2-methylphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**473**) by chromatography on a chiral support. The CD spectra of both enantiomers were reported, the sign of the Cotton effect of the π - π^* transition of the

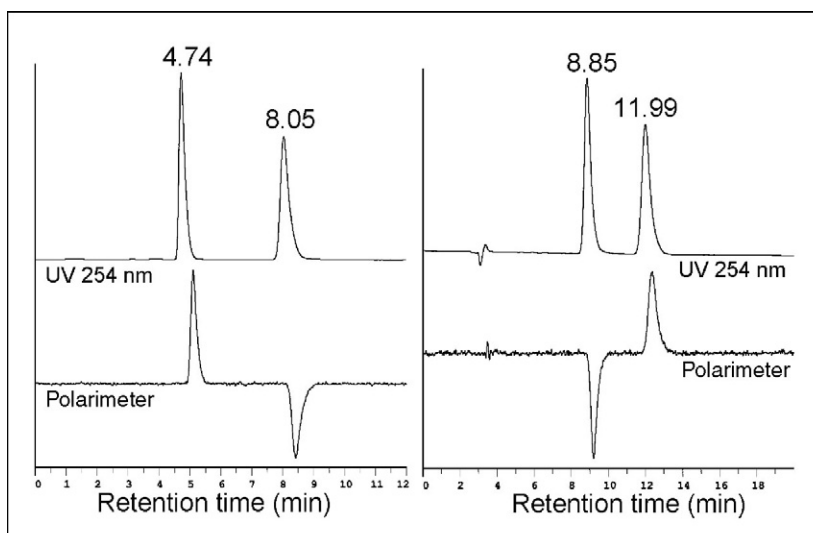
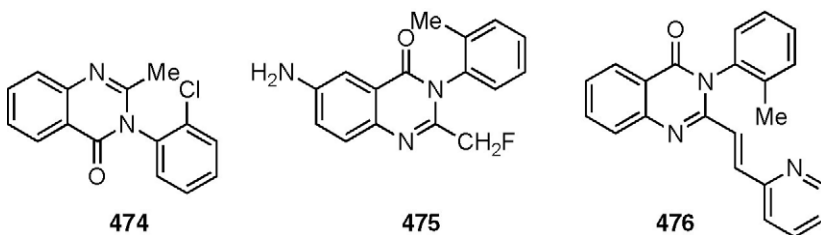


Figure 27. Resolution of **471** (left Chiralpak AD, hexane/isopropanol 6/4, α = 3.03 and R_s = 7.96) and **472** (right Chiralpak AD, ethanol, α = 1.55 and R_s = 4.34).

thiocarbonyl chromophore of 3-aryl-2-mercapto-4(3*H*)-quinazolinones is suitable for a successful stereochemical correlation. However, the assignment of the *M* or *P* configuration to the (–) or (+) enantiomers should be revisited using more recent theoretical calculations. Alkylation at sulfur with ethyl iodide led to 4-ethylthio-*N*-arylquinazolin-4(1*H*)-one that was separated by chiral chromatography into stable enantiomers (98CHI253). Jira et al. first reported the synthesis of a large series of atropisomeric 3-aryl-2-mercapto- and 3-aryl-2-alkylthio-4(3*H*)-quinazolinone derivatives (96PHA273), later separated into enantiomers on various chiral columns and eluting conditions (96PHA379).



Apparently Mecloqualone, (3-(2-chlorophenyl)-2-methylquinazolin-4(3*H*)-one, **474**), has not yet been separated into enantiomers despite a large body of reports. The value of the Hartree–Fock 6-31G* calculated barrier was 131.7 kJ mol^{–1} (02MI257). The use of chiral LSR, tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorato]europium-(III) was suitable for a direct determination of the enantiomeric excess for Mecloqualone (98MI419).

Afloqualone (**475**), 6-amino-2-(fluoromethyl)-3-(2-methylphenyl)-quinazolin-4(3*H*)-one is one of the centrally acting muscle relaxants.

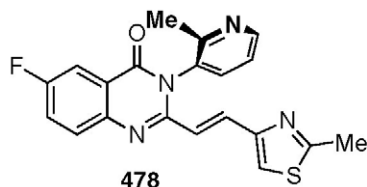
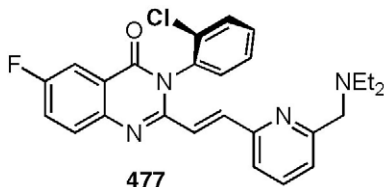
X-rays of the racemate showed that the 3-aryl group is nearly perpendicular to the quinazoline ring [dihedral angle = 87.60 (12)°] (07AX(E) o3109). Hindered rotation around the *N*-Aryl bond was confirmed by NMR in the presence of an added chiral [Eu(hfc)₃] lanthanide shift reagent (94MI225).

Afloqualone enantiomers were resolved on CSP composed of an immobilized (+)-18-crown-6 tetracarboxylic acid on 3-aminopropylsilanized silica-gel (98JC(A805)85) and on a Chiralpak AS column (see chromatograms in Application Guide for Chiral Column Selection, Daicel Internet Home Page <http://www.daicel.co.jp/chiral/>)

Despite a large body of reports on Afloqualone metabolism and Afloqualone metabolites, the enantioselectivity of the metabolism has not yet been addressed.

Piriqualone (**476**) was prepared by reacting methaqualone with 2-pyridinecarboxaldehyde in the presence of ZnCl₂, Ac₂O at reflux in dioxane. Piriqualone, which showed activity as an antagonist of AMPA receptors,

was taken by Pfizer as a lead for structure optimization (01BMCL177, 02MI113). The SAR optimization of the structure resulted in the racemates composed of the enantiomeric pairs CP-465,022 (477)/CP-465,021 and CP-471,236 (478)/CP-471,237, which were separated on Chiralcel OD.

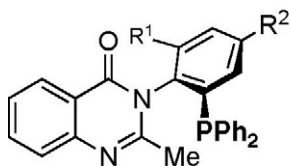


Its activity is strictly associated with the *S* enantiomer, the *R* enantiomer being more than 100 times less effective (00MI1310, 01JMC1710). CP-465,022 [(*S*)-3-(2-chlorophenyl)-2-[2-(6-diethylaminomethyl-pyridin-2-yl)-vinyl]-6-fluoro-3*H*-quinazolin-4-one] (477), optical rotation ($[\alpha]^D = +43.5^\circ$) is a selective, noncompetitive AMPA receptor antagonist (02MI143, 08MI1062) and presents anticonvulsant activity (02NPR597).

Most of the structures prepared during the SAR optimization could give stable atropisomers at room temperature. As usual in high-throughput screening, the racemate is first tested and the compounds presenting the highest activity are resolved into enantiomers for further evaluation.

The barriers to enantiomerization of CP-465,022 (477) were determined in decane and 3-methyl-butan-1-ol. In decane, the activation enthalpy and activation entropy were $\Delta H^\ddagger = 111.6 \pm 0.3 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -25.7 \pm 0.9 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively, leading to $\Delta G^\ddagger = 119.3 \pm 0.3 \text{ kJ mol}^{-1}$ at 25°C . The barrier was slightly higher in the more polar 3-methyl-butan-1-ol suggesting that the rotation occurred via a planar nonionic transition state in which the carbonyl group and the chlorine are coplanar (01JCS(P2)961).

Dai *et al.* took advantage of the very high barrier to rotation in *N*-aryl quinazolones to prepare a series of 2-methyl-3-(2'-diphenylphosphino)phenyl-4(3*H*)-quinazolinones 479 that were separated into enantiomers at the multigram scale (98JOC2597). 479b was resolved with (–)-di- μ -chlorobis-[(*S*)-dimethyl-(1-phenylethyl)aminato- C^2,N]dipalladium(II), the crystalline complex allowed the assignment of the absolute configuration *R* to (–)-479b.



479a, $R^1 = R^2 = \text{H}$

479b, $R^1 = \text{Me}$, $R^2 = \text{H}$

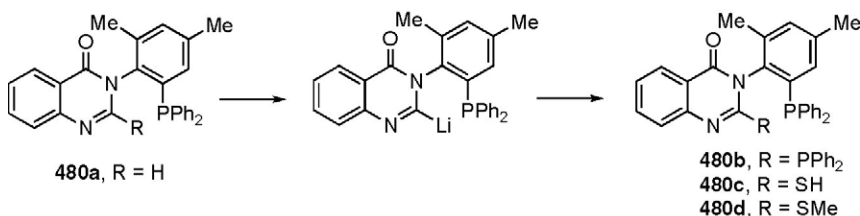
479c, $R^1 = R^2 = \text{Me}$

A more practical method for the resolution of 479a, 479b, and 479c was developed using the (benzenesulfonyl)hydrazone derivative of

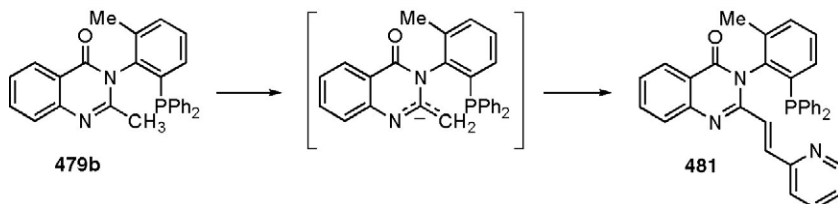
camphor-sulfonic acid as a resolving agent. The reported HPLC analytical data on chiral columns reveal that the chiral HPLC resolution method would be fast and efficient to deliver both enantiomers in high yield and high enantiopurity under semipreparative conditions.

The racemization of **479a–c** was studied in refluxing toluene under argon. **479a** that presents three substituents around the pivot bond racemized slowly ($t_{1/2} = 40$ h at 110°C , $\Delta G^\ddagger = 133.7$ kJ mol $^{-1}$) whereas the tetrasubstituted analogues **479b,c** showed no detectable racemization after more than 96 h at 110°C .

A series of tetrasubstituted analogues **480** was prepared in high yields by lithiation at low temperature of **480a** (99TA25).



Quinazolone **480a** was resolved by (–)-di- μ -chlorobis[(*S*)-dimethyl-(1-naphthylethyl)-aminato- C^2,N]dipalladium(II) into enantiomers. The chemical steps leading to **480b–d** being performed at -78°C , the enantiomers of **480a** may serve as starting material for the preparation of optically pure **480b–d**. The reaction could be used for a chemical correlation method for the determination of the absolute configuration in the series **480a** \rightarrow **480b–d**. Here again the reported chromatographic data for **480a** on Chiralcel OD column eluted by a mixture 98:2 Hexane/2-PrOH ((+)-**480a**: 17.8 min and (–)-*R*-**480a**: 32.4 min) could be easily scaled-up for preparative separation.



The optically pure quinazolones (–)*R*-**479b** and *R*-**481** ($R^1 = \text{Me}$, $R^2 = \text{H}$) in a palladium catalyzed allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate gave asymmetric inductions up to 52% *ee* and 87% *ee*, respectively. The yields were modest with monodentate ligand **479b** and interestingly the configuration of the resulting 1,3-diphenenyl propenyl malonate was strongly depending on the experimental conditions. The bidentate ligand (*R*)-**481** consistently

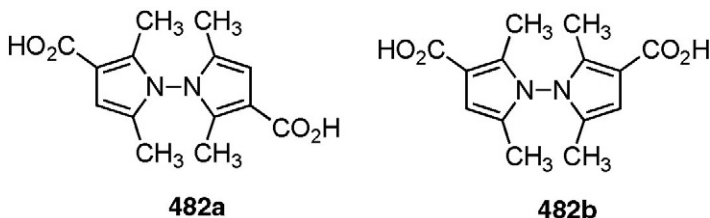
gave higher yields and higher *ee* in the *R* configuration. The reduction of the exocyclic double bond in **481** resulted in a bidentate ligand, which afforded similar yields but slightly lower *ee* than those obtained with **481** (99TL1245).

A paper has been devoted to the relationship between atropisomer axial chirality and drug discovery that contains many examples related to this section (11CMC505).

5. ROTATION ABOUT AN N–N BOND

5.1 5-5 Rings

In an epochal contribution, Chang and Adams in 1931 published a paper entitled “Stereochemistry of *N,N'*-dipyrrolys. Resolution of *N,N'*-2,5,2',5'-tetramethyl-3,3'-dicarboxydipyrrolys” (31JA2353, 49MI91). This compound presents atropisomerism and both enantiomers, **482a** and **482b**, were separated by making the brucine salt. The enantiomers proved to be very resistant to racemization under ordinary conditions. The D-acid has $\alpha_D = +0.40$ and $[\alpha]^{20}_D = +27.5$ and the L-acid has $\alpha_D = -0.31$ and $[\alpha]^{20}_D = -25.1$.



A systematic study of 1-pyrrolyl- and 1,2,4-triazol-4-yl-linked biazoles (Figure 28) afforded interesting conclusions on these, at that time, rather neglected compounds (80JCR(S)50).

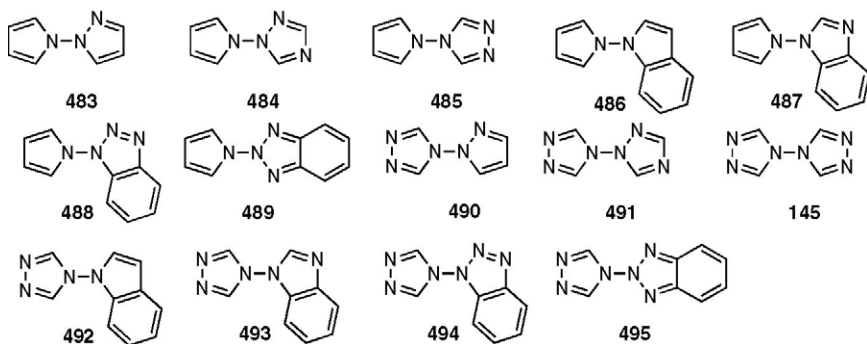
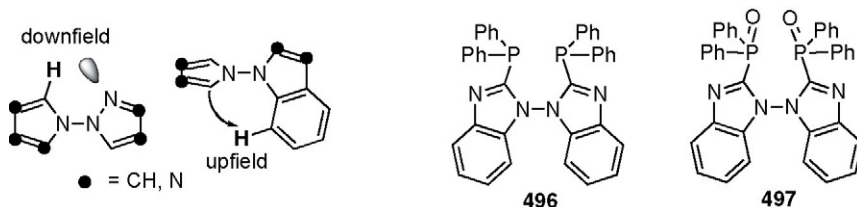


Figure 28. *N,N'*-Linked biazoles (145 has been discussed in Section 2.14.7).

From dipole moments and ^1H NMR measurements it was concluded that these compounds are twisted, producing significant induced shifts:

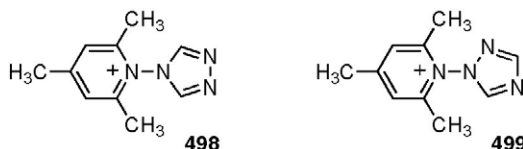


The X-ray structure of 9,9'-bicarbazyl (**144**) indicated that the dihedral angle between the planes of both rings is $72.5 \pm 2.8^\circ$ (two independent molecules) (93JCS(P2)757). High-performance liquid chromatography was employed for the determination of the optical purity of diphosphine (like **496**) and diphosphine oxide ligands (such as **497**) of transition metals used in stereoselective reactions. The separation of the enantiomers was accomplished, without any derivatization, on chiral columns containing, as chiral selectors, urea derivatives [Supelcosil LC-(*R*)-phenyl urea and (*R*)-naphthyl urea] and cellulose carbamate derivative (Chiralcel OG) (97JOM(529)445, 98JC(A795)289, 10AHC(99)33).

Several *N,N'*-bibenzotriazoles were prepared by Castle (67JA2643) and one of them, the 1,1', was used by Steel to prepare organometallic compounds (03DT992). The X-ray structure of 1,1'-bipyrrole (**143**) was determined by Dey and Lightner (07JOC9395). Mendoza et al. reported the allosteric effects in *N,N'*-bonded-2*H*-indazoles (88JOC2055).

5.2 5-6 Rings

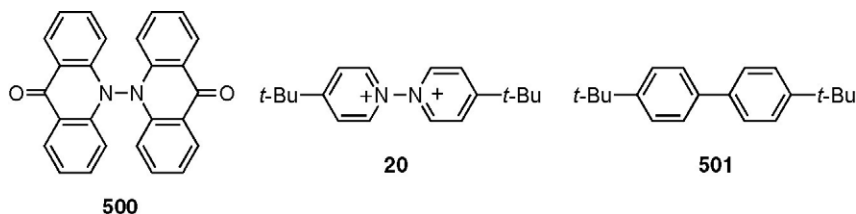
The thermolysis and photolysis of **498** and **499** (related to **147**) were studied both experimentally and theoretically but the torsion angles were not determined or calculated (01JOC1242).



5.3 6-6 Rings

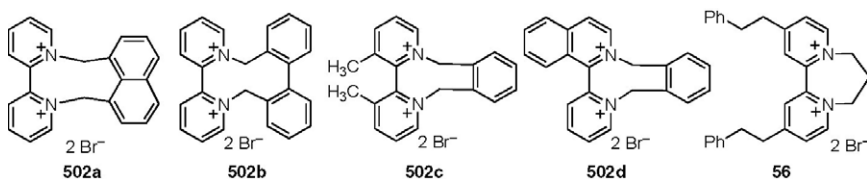
The structure of 10,10'-biacridinyl-9,9'-diones (**500**, $\theta = 85.3^\circ$), related to **149**, has been determined (93JCS(P2)757). Bock et al. prepared 4,4'-di(*t*-butyl)-*N,N'*-bipyridinium diperchlorate (**20**) (95CEJ557). The experimental

dihedral angle is 84° and that calculated at the AM1 level is 90° , larger than those of 4,4'-di(*t*-butyl)biphenyl (**501**) (exp. 40° , calcd. 42°).



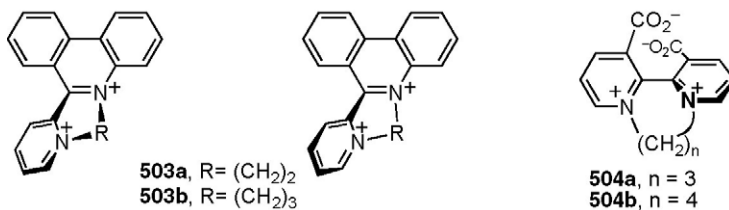
6. ROTATION ABOUT A C–C BOND *ORTHO*–*ORTHO'*-LINKED

Quaternization at nitrogen is a convenient way to prepare an *ortho*–*ortho'* linked atropisomeric framework (72JHC1165).



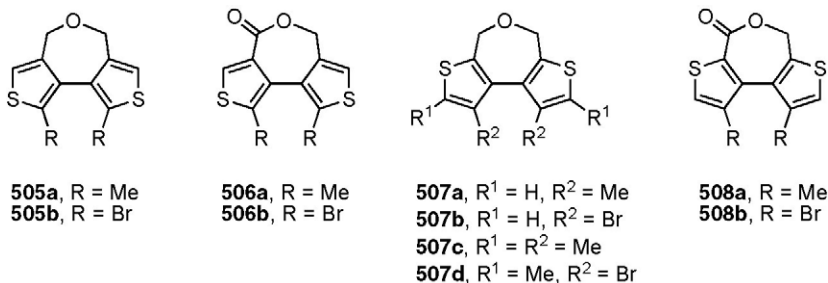
Diquaternary salts of 2,2'-bipyridine and analogues **502a–d** have been prepared leading to a large series of *ortho*–*ortho'*-linked derivatives. The AB spectra of the methylene groups indicate a large barrier to rotation. Ring topomerization is not observed by NMR even at high temperature (75CB1682). The study of these compounds would greatly benefit from modern chiral HPLC in order to separate the atropisomers.

Campa *et al.* studied several 4,4'-disubstituted 2,2'-bipyridinium bridged quaternary salts (87JOC521). Some were sulfonated to give bridged 2,2'-bipyridines with zwitterionic character. In all the 1,1'-ethano-bridged salts a sharp singlet was observed for the methylene protons indicating a quasi-planar conformation. The 4,4'-dimethyl analogue of **502a** showed an AB spectrum that persists without modification up to 100°C . The barrier to interconversion in **56** was determined by DNMR (69 kJ mol^{-1} at 335K).

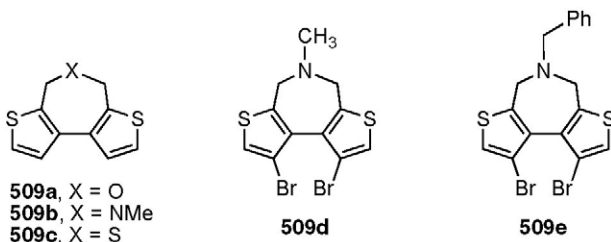


Photoactive viologens **503a,b** based on the 6-(2-pyridinium) phenanthridinium structure constitute another class of interesting *ortho-ortho'*-linked bis-salts that present atropisomerism. They display a significant visible absorption (up to 490 nm) and an intense luminescence, which is efficiently quenched by DNA ([95MI827](#)). The occurrence of blocked forms for **503b** was detected by NMR while coalescence was observed for **503a**. The enantiomers of **503b** were resolved by dialysis and DNA–cellulose affinity chromatography. The *R* enantiomer of **503b** is less bound to DNA and is eluted first. CD spectra of both enantiomers were recorded ([95BBR\(214\)716](#)).

1,1'-Trimethylene-2,2'-bipyridine-3,3'-dicarboxylic acid **504a** and 1,1'-tetramethylene-2,2'-bipyridine-3,3'-dicarboxylic acid **504b** were separated into enantiomers by chromatography on starch. NMR of the dimethylene analogue showed an AB spectrum for the methylene groups but the barrier is probably insufficient to allow a resolution into enantiomers. Zwitterionic enantiomers of **504b** when associated with a chiral Ru complex give asymmetric light-induced electron transfer ([95JPC14161](#)).



The configurational inversion of some 3,3'-bithienyls with ether (**505**, **507**) or lactone bridges (**506**, **508**) at the 2,2'- or 4,4'-positions have been investigated by ¹H-NMR in DMSO-*d*₆. Here again the occurrence of diastereotopic protons of the methylene group in the bridge is a decisive advantage to determine the barrier by NMR at elevated temperature. The barriers fall in the range 72–94.5 kJ mol^{−1} that for some is at the upper limit for high-temperature NMR experiments. Whatever the bridge, the barriers are higher for compounds with a bromine instead of a methyl group in blocking positions. Here again, modern dynamic chromatography on chiral support (DHPLC) would be efficient to revisit these barriers ([74CS226](#)).



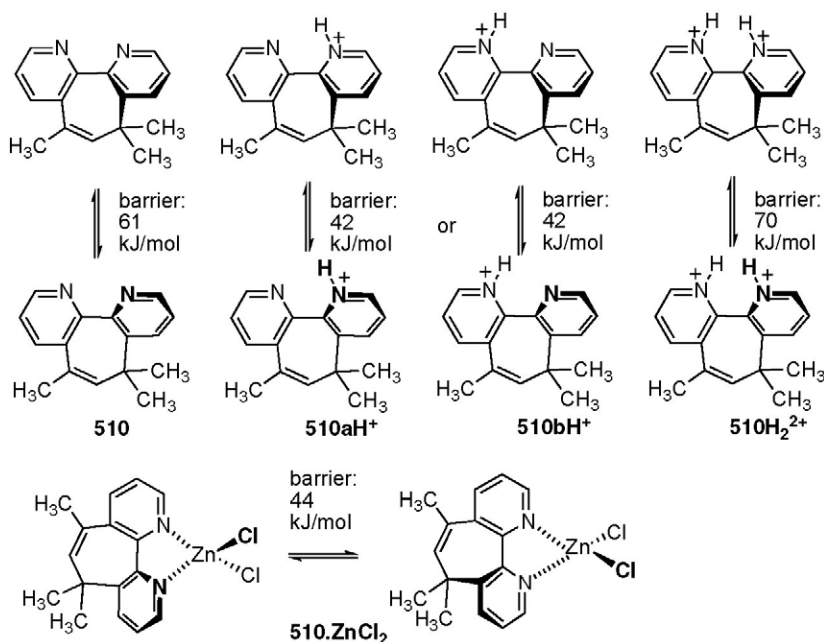
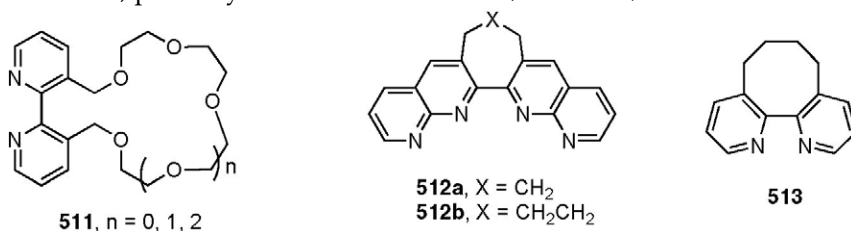


Figure 29. Rebek and Trend's results.

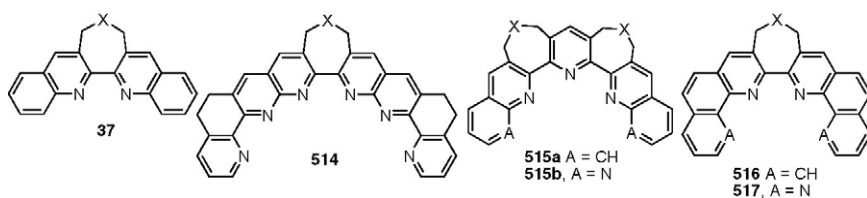
In the absence of a substituent in blocking positions in **509a–c** the barriers are very low (less than 33 kJ mol^{−1}) and no splitting of the diastereotopic protons was observed down to −100 °C (**76CS120**). When the blocking positions are occupied by bromine the barriers in DMSO-*d*₆ are 93.7 and 91.2 kJ mol^{−1} for **509d** and **509e**, respectively (**76CS117**). These values fall in the range of barriers suitable for DHPLC or on line racemization using a chiral column.

In 1978, Rebek and Trend published a fundamental paper entitled “On Binding to Transition States and Ground States: Remote Catalysis” that had a large influence on topics such as the “allosteric effect” and “molecular rotors” (**78JA4315**). They reported several racemization barriers (Figure 29) for compound **510**, its mono and diprotonated cations as well as for a Zn complex. Theoretical calculations [B3LYP/6-311++G(d,p)] are able to reproduce accurately the barriers but that of **510H⁺** higher than calculated, probably due to solvent effects (**11TA1180**).



Rebek et al. presented evidence that binding of alkali metals occurs at the crown ether cavity while binding of transition metals occurs at the bipyridyl function in crown ethers **511** (79JA4333). It was shown later that the racemization rate in chiral bipyridyl crown ethers **511** can be increased by more than 60-fold through binding to PdCl_2 . The binding with PdCl_2 occurs with the nitrogen of the pyridines. In the absence of PdCl_2 no exchange between the atropisomeric forms can be observed by high-temperature NMR in the macrocyclic compound indicating that a lower limit of the barriers is 100 kJ mol^{-1} . The barriers in complexed **511** are slightly dependent on the macrocycle size: 61 kJ mol^{-1} for $n = 0$, 58.2 kJ mol^{-1} for $n = 1$, and 58 kJ mol^{-1} for $n = 2$ (80TL2379, 83JA6668, 85JA7487). The binding with a metal at the nitrogen of the pyridines favoured the formation of *ortho-ortho'*-linked derivatives of suitably designed examples (85JA7487).

Thummel et al. have prepared a series of annulated derivatives of 2-(2'-pyridyl)-1,8-naphthyridine and 2,2'-bi-1,8-naphthyridine. Among the large list, the stereochemistry was addressed experimentally for two of them. In **512a**, a fast exchange between atropisomers is advocated while in **512b** the structure is more rigid at room temperature ($\Delta G^\ddagger = 73.5 \text{ kJ mol}^{-1}$) (84JOC2208). The study was extended to the bipyridyl derivative **513** that showed a rigid structure at room temperature while the dimethylene and trimethylene analogues undergo rapid conformational inversion (85JOC3824). These observations were confirmed by empirical force field calculations (90JOC2637). Photophysical properties of annulated bipyridines **513** were addressed (95MI58). Annulated bi-1,8-naphthyridines **512** were engaged as ligands to form ruthenium complexes (04IC6195).



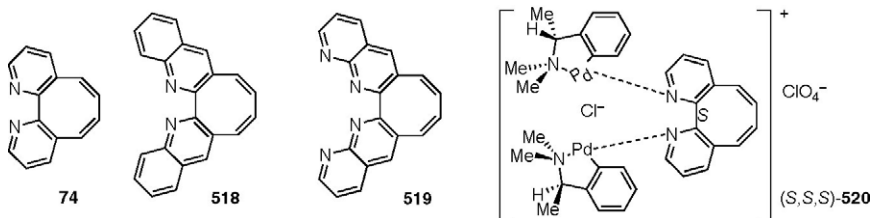
Stereochemical issues in connection with bridge length are valid for the biquinoline analogues **37** in which the dimethylene and trimethylene bridged systems present low barriers while the tetramethylene bridged one is conformationally rigid. The di-*N*-oxide of the trimethylene-bridged biquinoline was found conformationally stable by NMR (85JOC666). Annulated biquinolines **37** present a triplet-state photoexcitation confined to a single quinoline moiety without delocalization over the entire double molecule (90JPC8506). Palladium complexes of **513** and **37** were prepared (97CCC238). Copper(I) complexes of **37** were characterized by X-ray analysis, electronic spectra, and oxidation potential (97IC5390).

Bridged trimethylene and tetramethylene 2,2'-quinoline di-*N*-oxides of **37** were revisited by Jiang et al. The enantiomers were obtained through resolution of the racemates with optically pure dibenzoyltartaric acid. The absolute configuration of the trimethylene enantiomers was determined by X-ray analysis on the resulting diastereomeric complex. The enantiomers were assayed as chiral promoters in the enantioselective Strecker reaction between benzaldehyde *N*-benzhydrylimine and HCN ([01SL1551](#), [03EJOC3818](#)).

Large polyaza cavity-shaped ligands **514** were designed by Thummel et al. One or two ruthenium or osmium metal complexes were liganded by **514**. In the case of bimetallic complexation, limited communication between the two halves of the bridging ligand was observed ([93IC1587](#)).

Bridged bi-heteroaryl **515a** and **515b** in which X represents 0, 1, or 2 methylene groups were prepared. Analyses by NMR showed that when the bridges contain four methylene groups diastereomeric *meso* and *D,L* forms coexist at room temperature ([85JOC2407](#)).

The inter-ring angle in annulated derivatives **516** was estimated with PCModel and MMX calculations: 14°, 44°, and 50° for di-, tri-, and tetramethylene bridges, respectively ([94T10685](#)). Europium(III) complexes of 3,3'-di, tri, and tetramethylene 2,2'-bi-1,10-phenanthroline **516** were prepared. The complex having the most distorted tetramethylene-bridged ligand exhibits a weak, high energy $\pi \rightarrow \pi^*$ absorption and low sensitization efficiency ([10IC4657](#)). In dinuclear copper(I) complexes of **516** the distance between the two copper atoms varies from 2.92 Å for the dimethylene bridged system to 3.59 Å for the tetramethylene bridge ([03IC6648](#)). Mononuclear Copper(I) complexes were obtained with **517** ([01IC3413](#)).

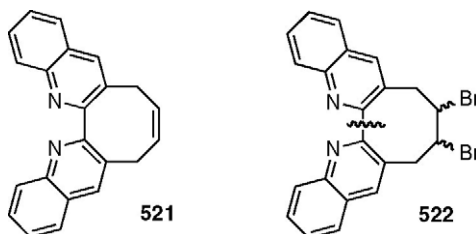


Bridge bipyrindyl derivative **74** merits a particular attention because it exists as a pair of atropisomers that were separated on microcrystalline cellulose triacetate using ethanol as eluent when the injection solution was treated with 1% (v/v) concentrate ammonia. In the absence of ammonia the separation was very poor and the collected enriched enantiomers racemized readily. The authors suspected that traces of acid might strongly catalyze the racemization process. The thermal racemization was studied in EtOH in the presence of ammonia yielding a barrier to inversion in the range 104.00–104.33 kJ mol⁻¹ (307.7–341.2K). The catalysis

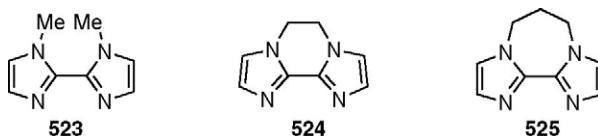
of the inversion with traces of acid probably results from a stabilization of the transition state in which the proton is shared between the two nitrogens. The influence of traces of acid leading to lower barriers may have been encountered in **511**–**513** in which the two nitrogen atoms are passing in front of each other in the transition state to inversion. Experimental and CNDO/S calculated CD spectra were compared to assign the absolute configuration of the isolated enantiomers (92JCS(P2)1625).

Wang and Wong prepared the quinoline and 1,8-naphthyridine analogues, **518** and **519** of **74**. The barriers in **518** and **519** are 109 and 108 kJ mol⁻¹, respectively. All barriers are suitable for separation of enantiomers by chiral HPLC (95T6941). Several transition metals complexes of **74**, **518**, and **519** were reported as well as their X-ray data.

The resolution of **74** using an optically pure di-Pd complex was achieved (90JCS(CC)167). The complex **520** is configurationally stable around its axis since no change in the NMR spectra occurred after the sample was heated to 100 °C (95T6941).

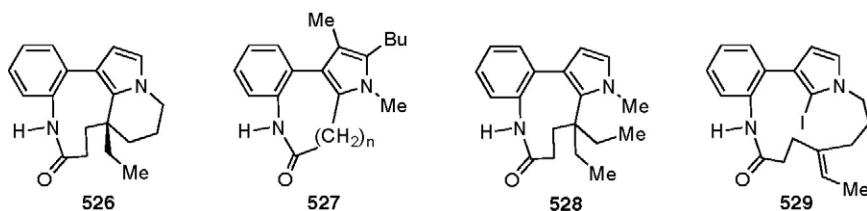


Trans-dibromination of **521** afforded two pairs of enantiomers of **522**. The diastereomerization barrier was 93 kJ mol⁻¹ at 110° C (DNMR) (95T6941).



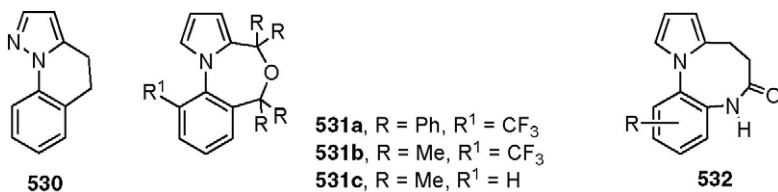
An interesting observation was reported by Deady who advocated a lone-pair cooperativity in the *N*-alkylation of some *N,N'*-bridged 2,2'-biimidazoles. The second order rate constants of alkylation are in the order **525** > **524** > **523**. Bridging has a considerable effect on the reactivity of the nitrogen atom (81AJC2569). Such a quantitative study would be interesting on other *ortho*–*ortho'*-linked azaheterocycles.

Goulle and Thummel revisited the bridged 2,2'-biimidazole series including **524** and **525** and described their ruthenium complexes (89JOC3057, 90IC1767). Derivative **524** was involved as a ligand in mixed ruthenium complexes (91IC652).



The biological interest of naturally occurring Rhazinilam **526** resides in its interaction with tubulin. The inter-ring angle in **526** is 96° according to an X-ray. Annulated analogues **527** ($n = 0-3$) were prepared and submitted to an antitubulin test. An X-ray of **527** ($n = 3$) yielded an inter-ring angle equal to 97.8° . The barriers were not determined in **527**, however, the analogue **528** has been separated into stable enantiomers. The activity of **528** is strictly located in the levogyre form (**96BSF251**). Conformational analysis of Rhazinilam and three-dimensional quantitative structure–activity relationships of Rhazinilam analogues have been performed (**05BMCL1045**). A recent total synthesis of the two enantiomers of Rhazinilam involves the chromatographic chiral resolution of an annulated precursor **529**. Optically pure atropisomers undergo axial to point chirality transfer in an enantiospecific Pd-catalyzed transannular cyclization (**10OL4224**).

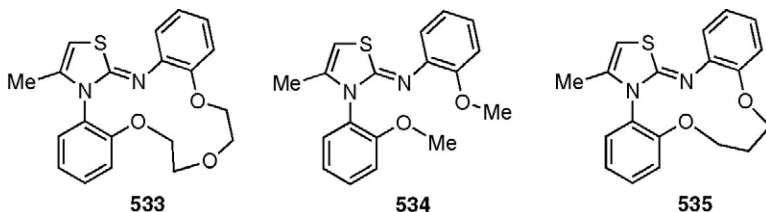
7. ROTATION ABOUT A C–N BOND *ORTHO*–*ORTHO'*-LINKED



In **530**, the *N*-phenyl group and the pyrazole ring were linked to address NMR chemical shift assignments in the open form. Raleigh diffusion studies yielded a smaller inter-ring angle in the linked form than in the unlinked analogue (**70BSF1345**).

Using the AM1 method, Faigl *et al.* calculated the barriers of atropisomerization in **531a–c**. According to the calculations, the barriers in **531a** and **531b** should be high enough to permit resolution by chiral chromatography. The experimental barrier in **531c** was determined by DNMR (58.1 kJ mol^{-1}) (**08T1371**).

For a series of pyrrolobenzodiazocines **532** atropisomerism is highly probable however the barriers were not addressed.



An atropisomeric tetradecyl-macrocyclic ether **533** was separated into enantiomers on several chiral columns. An X-ray of the racemate indicates that the inter-ring angle is 86.2° . The barrier to enantiomerization in EtOH was determined ($\Delta G^\ddagger_{\text{rot}} = 121.4 \text{ kJ mol}^{-1}$, $t_{1/2} = 15.2 \text{ h}$ at 78°C). The barrier to rotation in the open bis-ether **534** derivative was $107.2 \text{ kJ mol}^{-1}$ in EtOH at 58°C corresponding to a $t_{1/2} = 68 \text{ min}$. The 14.2 kJ mol^{-1} gap that separated the barriers in macrocycle **533** and in open bis-ether **534** might come from a contribution of the eclipsing strain of the diethylene chains during rotation (08ARK(viii)28). The barrier is also higher in the cyclic ether **535** ($119.5 \text{ kJ mol}^{-1}$, $t_{1/2} = 7.5 \text{ h}$ at 78°C in EtOH) than in **534** (08JOC403).

Lee et al. separated the atropisomers of the pyrimido[1,2-*a*] [1,4]benzodiazepines (**536a**, **536b**, and **537a**) and the eight-membered analogues (diazocines **536c** and **537b**) with HPLC on a Chiralpak AD chiral columns (Figure 30). The separations were excellent (except for **536c**) in a mixture hexane/EtOH (50:50). An X-ray of (*R*)-**536a** and *rac*-**536c** and CD spectra of all the enantiomers were reported. The barriers to rotation were determined for **536a** (108 kJ mol^{-1}), **536b** (102 kJ mol^{-1}), and **537a** (108 kJ mol^{-1}) at the physiological temperature in EtOH. The lower barrier in **536b** may be caused by the ground-state destabilization. The barriers were not reported for diazocines **536c** and **537b** but no racemization occurred at 60°C for 22 h.

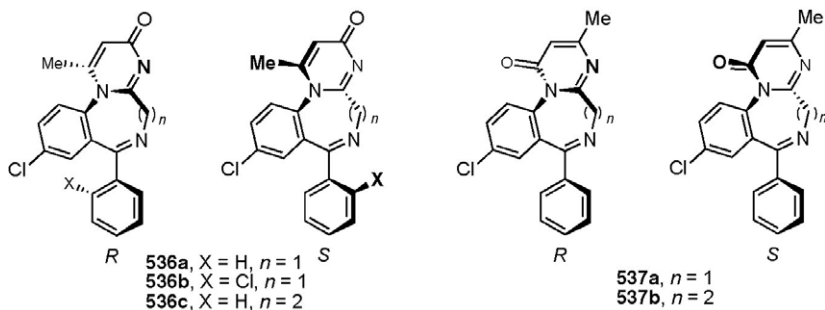
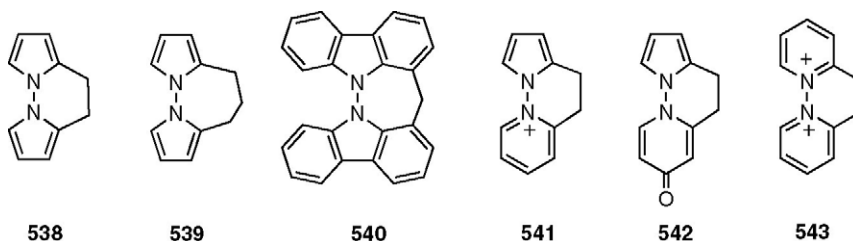


Figure 30. Atropisomers **536a–c** and **537a,b**.

The atropisomers of **536a** exhibit about a 50-fold difference in this binding affinities at the GABA_A receptor. The (*R*)-**536a** enantiomer has a strong potency with an IC₅₀ value of 46 nM while the (*S*) enantiomer has an IC₅₀ value of 2320 nM (08BMC9519).

8. ROTATION ABOUT A N–N BOND *ORTHO*–*ORTHO*'-LINKED

There are no experimental results covering this section but B3LYP/6-31G(d) calculations have been carried out on **108**–**113**.



Since in the absence of the 2,2'-bridge these compounds tend to be orthogonal or close to it, the bridge produces a mechanical effect depending on its length. Comparison of **538** and **539** shows that the longer trimethylene bridge of **539** allows for a larger dihedral angle ($\theta_b = 50.0^\circ$ vs. $\theta_b = 19.4^\circ$). Except heavily distorted **540** the remaining dimethylene compounds have dihedral angles of $\theta_b = 19.4^\circ$ (**538**), 29.1° (**541**), 28.6° (**542**), and 36.6° (**543**) (11CTC(964)25).

9. ROTATION ABOUT N–METAL BONDS

The presence of a metal linking two aromatic heterocycles (Figure 31) can be considered as an extension to classical atropisomerism, in the same way that tolane (Ph–C≡C–Ph) is a kind of extended biphenyl, with a considerable lower barrier to rotation (01JPC(A)6711).

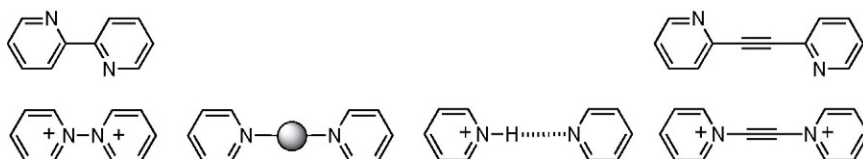


Figure 31. Possible atropisomers linked by metals.

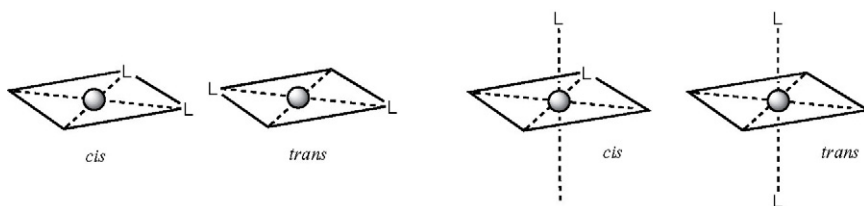


Figure 32. *Cis* and *trans* isomers in square planar and octahedral complexes.

However, if the metal, due to its geometry, resemble an sp^3 carbon atom, then the complex will be similar to biphenyl (or triphenyl) methane, lying outside this review. We consider two main situations of coordination: square planar, and octahedral (Figure 32).

Utsuno described the CD spectrum of *trans*-dichlorotetrakis(pyridine) cobalt(III) cation, an octahedral complex with four pyridine ligands in the plane (Figure 33). According to the CD measurements of nujol mulls, the hydrogen dibenzoyltartate salt shows a negative band at 630 nm that, according to Utsuno, belongs to the *P* atropisomer (82JA5846).

Lippard et al. determined the X-ray structure of bis(2-hydroxypyridine) diammineplatinum(II) (Figure 34). It corresponds to the *anti*

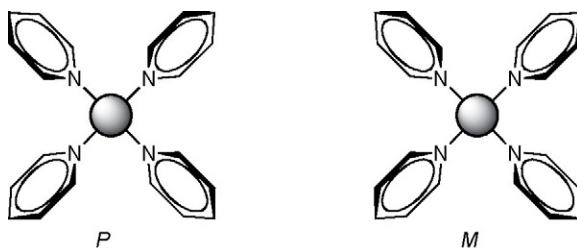


Figure 33. The *P* and *M* enantiomers of *trans*-dichlorotetrakis(pyridine) cobalt(III) cation.

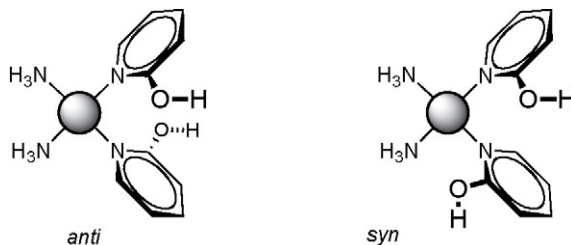


Figure 34. Bis(2-hydroxypyridine)diammineplatinum(II) *anti* and *syn* atropisomers.

rotational conformation but the authors hypothesize that the *syn* atropisomer should occur in solution (83IC2708).

Marzilli et al. published on the atropisomerism of Pt(II) nucleotide complexes (90JA8177), on Ru(II) 1,5,6-trimethylbenzimidazole complexes (94JA815), on Ru(II) 1,2-dimethylimidazole complexes (96IC2384), and the rate of atropisomerization in Pt(II) guanine compounds (98IC5260). In the last paper, the authors discuss head-to-tail (HT) versus head-to-head (HH) atropisomerism. Other HH Pt/Pd complexes of 4,7-dihydro-5-methyl-7-oxo-[1,2,4]-triazolo-[1,5-*a*]pyrimidine (HmtpO) were reported by Salas et al. (97IC3277, 99CCR(193-195)1119) and by Ruiz et al. (08IC4490). Marzilli's studies have been used to justify that guanine (dipole)–guanine(dipole) interactions favor the less tilted HT atropisomer as this orientation places the H(8) end of the dipole closer to the negative six-membered ring of the *cis*-guanine base than in the more tilted form (04IC2087).

According to Velders et al. in a *cis* bifunctional octahedrally coordinated complex, 16 possible atropisomers can be drawn (03EJC713). In the case of Ru(II) and 1-methylimidazole (MeIm) or 1-methylbenzimidazole (MeBim) as ligands, there are only eight theoretically possible rotameric structures represented in Figure 35 (azpy = 2-phenylazopyridine) because a bridge is present in an azpy complex. The rotation about the ligand–Ru bond was studied by ^1H NMR (seven atropisomers at -95°C for MeBim) (05CEJ1325). X-ray structures and molecular mechanics calculations were reported for the Ru(II) polypyridyl complexes (98IC4120).

Cis and *trans* octahedral Ru(III) complexes of 1*H*-1,2,4-triazole (Htrz) have been reported with torsion angles considerably larger in the *cis* than in the *trans* isomer due to steric effects (Figure 36). Note that the triazole exists in its minor tautomeric form, the 4*H* (03IC6024).

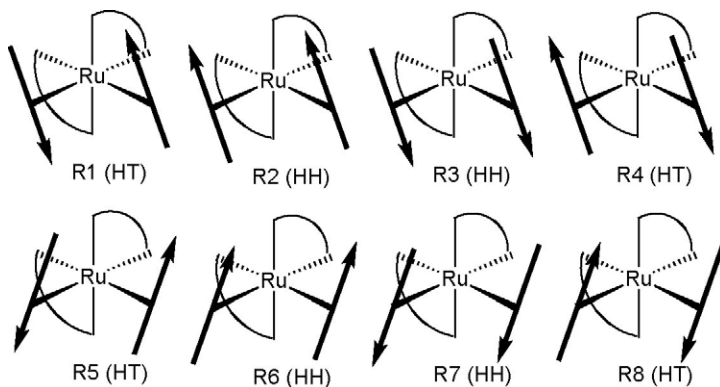


Figure 35. Schematic representation of rotameric structures of $\beta\text{-Ru}(\text{azpy})_2(\text{MeBim})_2(\text{PF}_6)_2$.

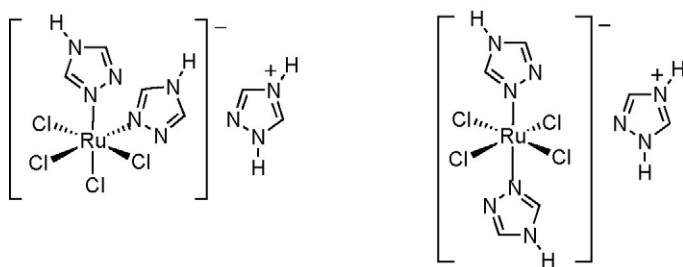


Figure 36. $(\text{H}_2\text{trz})^+[\text{RuCl}_4(\text{Htrz})_2]^-$.

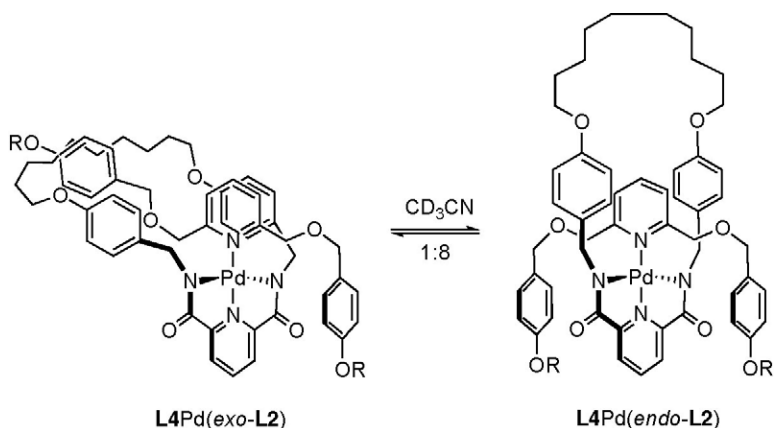


Figure 37. Macrocyclic complex **L4PdL2**.

Leigh et al. explain that the term “atropisomerism” technically refers to conformers that can be isolated as separate chemical species as a result of restricted rotation about a single bond (05JA12612). They stretch this definition slightly in applying it to **L4Pd(endo-L2)** and **L4Pd(exo-L2)** (Figure 37), which are isolable as a result of restricted rotation about various single bonds in particular ligand orientations.

10. ROTATION ABOUT N–METAL BONDS *ORTHO*–*ORTHO*'-LINKED

With multidentate ligands such as terpyridine where the octahedral structure has restricted rotation due to the bonds between nitrogen heterocycles, atropisomerism involves axial chirality. Thus, Constable, Lacour et al. prepared an iron terpyridine cation (Figure 38) that exists as two enantiomers (09NJC376). In the presence of a chiral anion and in low

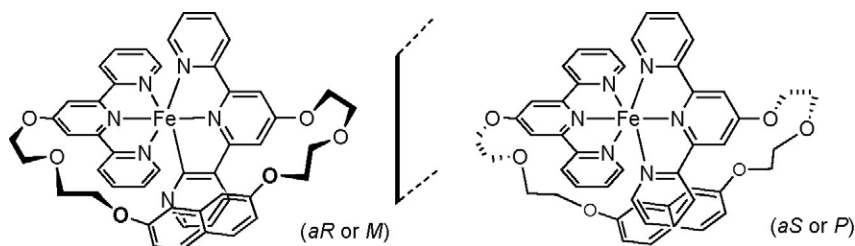


Figure 38. A conformationally locked metallomacrocycle with axial chirality.

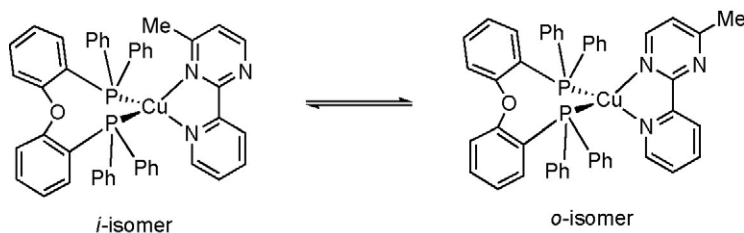


Figure 39. Mepypm copper(I) complex.

polarity solvents, the ratio of two salts is no longer 1:1; one atropisomeric cation becomes predominant and the compound presents a CD spectrum that was simulated using time-dependent DFT (TDDFT) calculations.

The last example (Figure 39) of this fascinating field concerns the ligand 4-methyl-2-pyridyl-pyrimidine (Mepypm) (10JA9579). The tetrahedral Cu (I) complex represented in Figure 39 exists in two isomers, the inner (*i*-) and the outer (*o*-) that are in dynamic equilibrium via ring inversion. Using VT ^1H NMR, the inversion rates were determined, 20 s^{-1} in CDCl_3 , 70 s^{-1} in acetone- d_6 and 120 s^{-1} in CD_3CN . These important differences are associated with a solvent molecule promoting ring inversion by assisting dissociation of the pyrimidine N atoms from the copper center.

11. MULTIPLE ROTATIONS (TRIADES)

11.1 Propellenes and related compounds

Claramunt *et al.* devoted several papers to hexa(pyrazol-1-yl)benzenes, such as 16, 58, and related compounds. These compounds can exist in a number of conformations (Figure 40). The graph becomes more complex if there are two kinds of pyrazoles, for instance pyrazole and 3,5-dimethylpyrazole (96POC717, 99JIPMC169).

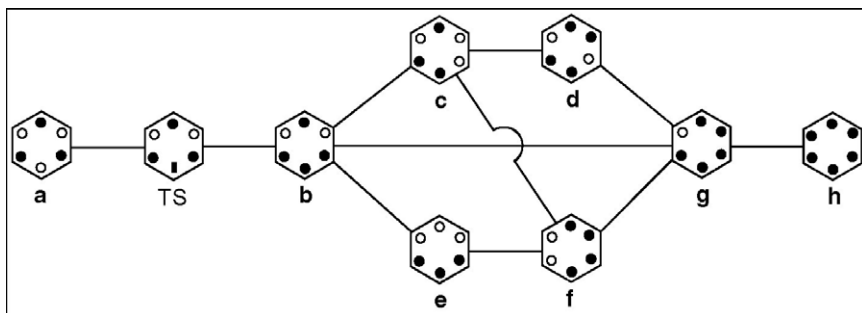
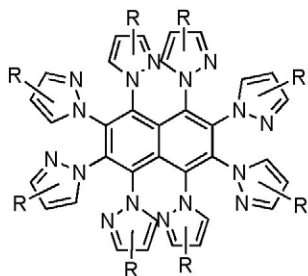
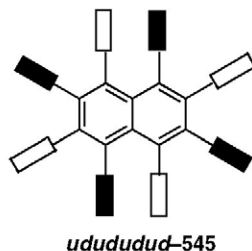


Figure 40. Hexa(pyrazol-1-yl)benzenes, black N atom up, white N atom down, line orthogonal conformations; note that isomer **c** is a mixture of two enantiomers.

When there are C-substituents on the pyrazole ring, the rotations should be geared (76JA2847) that should be possible since the number of substituents is even. We can classify these papers according to the number of azol-1-yl substituents on the benzene ring: 2 or 3 pyrazoles and 2 OH groups (92JOC1873); 2 pyrazoles and 2 OH groups (01ARK(i)172, 01ARK(i)183) as well as Rh and Ir complexes (94JOM(467)293); 2 imidazoles or 2 benzimidazoles and 2 OH groups (94T12489); 2 pyrazoles and 4 F substituents, like in **18** and **19** (97NJC195); six pyrazoles (95JCS(P2)1359, 96JPOC137, 97BSB387, 97JCS(P2)2173) as well as Pd, Pt, Cu, and Ru complexes (02EJC3178, 03ICA(347)168, 07POL4373); 6 imidazoles (99JMS(478)285), 6 benzimidazoles (98MC(ACH)475). Other poly(pyrazol-1-yl)benzenes have been reported (08NJC2225, 09LOC57, 09T4652). The results we obtained until 1997 were summarized in a review (97THS1). An interesting extension concerns octakis(pyrazol-1-yl)naphthalene (**544**) and octakis (3,5-dimethylpyrazol-1-yl)naphthalene (**545**). The simplicity of the NMR spectra led to assume that **545** adopt an *udududud* conformation (up N atom up, white N atom down) (00ARK(iv)612).



544, R = H
545, R = 3,5-dimethyl



Two papers are especially relevant in the context of the present review. The first concerns the use of dynamic HPLC to study hexapyrazolylbenzenes by Lavandera *et al.* The use of HPLC at different temperatures (DHPLC) allows determination of the rotational barrier of the 3,5-dimethylpyrazol-1-yl residue in hexakis(3',5'-dimethylpyrazol-1-yl)benzene (**58**), $\Delta G^\ddagger = 109 \pm 4 \text{ kJ mol}^{-1}$ in MeOH/water) ([97BSB387](#)). In the second, the same group determined by classical kinetics using NMR the barriers to rotation of 1,4-di(pyrazol-1-yl)-2,3,5,6-tetrakis(3',5'-dimethylpyrazol-1-yl)-benzene to be 93.7 kJ mol^{-1} ([97JCS\(P2\)2173](#)).

11.2 Polyazolylazines

Related to the preceding section are polyazolylazines, for instance penta (pyrazol-1-yl) pyridines **17**, with pyrazole ($R = H$), 3,5-dimethylpyrazole ($R = R = Me$) and a combination of both ([96T11075](#)). Important ligands in coordination chemistry are the pyrazolylpyrimidines, **59**, **62**, and **63** used to coordinate Pd **59** and **62** ([00IC1152](#)), Cu **63** ([08IC413](#)) and Ag ([Figure 41](#)) ([11CGD1766](#)) and mainly the 2,4,6-pyrazolyl-1,3,5-triazines. These ligands ([01H905](#), [01T4397](#), [03IC885](#), [03KGS1584](#)) have been used in complexes with Pd **61** and **64** ([98IC6606](#)).

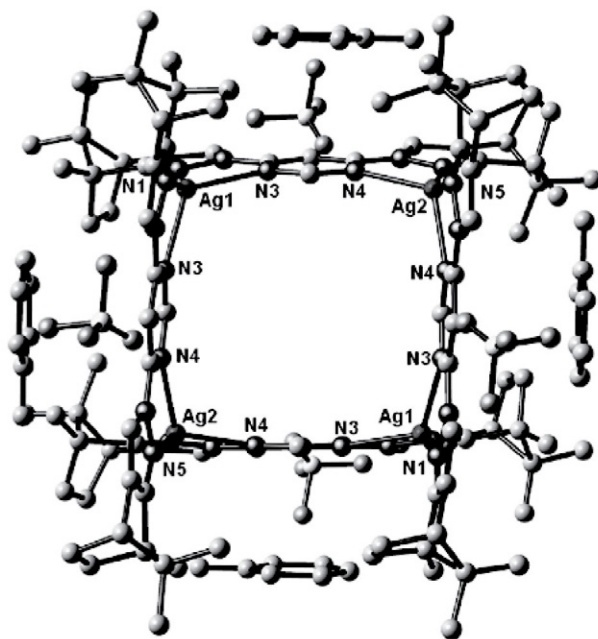
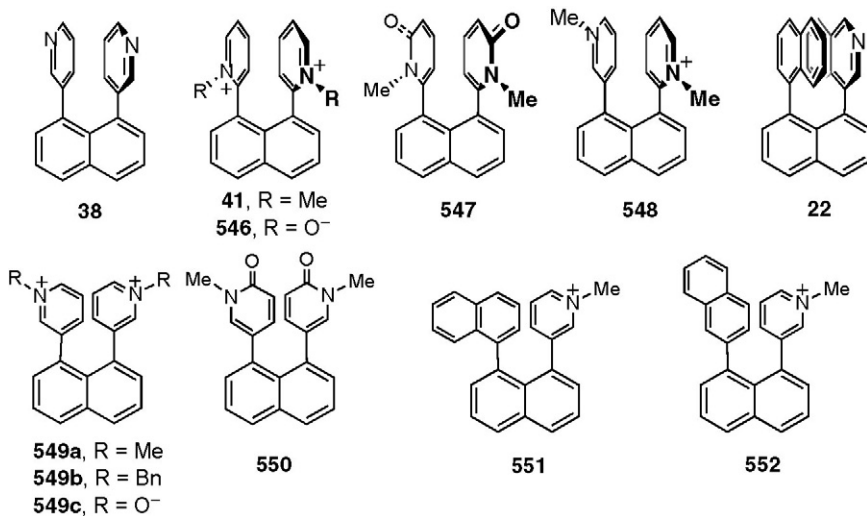


Figure 41. Complex of 4,6-bis[(4*S*,7*R*)-7,8,8'-trimethyl-4,5,6,7-tetrahydro-4,7-methane-indazol-2-yl]-pyrimidine with AgBF₄ and toluene.

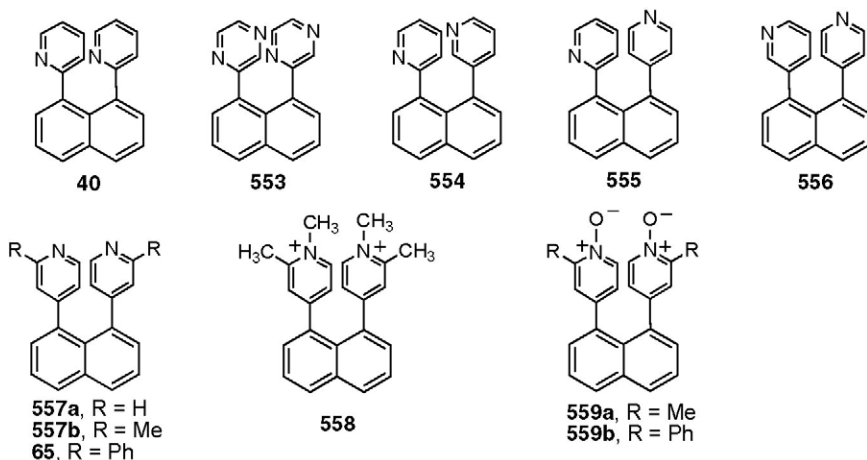
11.3 1,8-Dipyridylnaphthalenes and related compounds

Metal catalyzed cross-coupling reactions between heteroaryl compounds and 1,8-dihalogenonaphthalene opened the way to the design and stereochemical studies of a large series of 1,8-bis-hetaryl naphthalenes. Maier and Zoltewicz demonstrated by NMR the exchange of *syn* and *anti* forms in solution for 3,3'-naphthalene-1,8-diylidipyridine **38** (96T8703). Signals corresponding to the occurrence of diastereomeric species were observed by NMR in the presence of (*R*)-camphorsulfonic acid (97T465).



In compounds **41**, **546**, and **547**, which are substituted in the blocking positions, a single diastereomer was observed by NMR confirming PM3 and AM1 calculations that predicted that the *anti* form is largely favored. The ditosylate of **548** presents a *syn/anti* ratio equal to 1:2 that equilibrates to a ratio 1:1.7 at 40 °C in the NMR probe (97JOC2763). A barrier for the *anti-syn* interconversion in **22** was determined at 75 °C: $\Delta G^\ddagger = 117 \text{ kJ mol}^{-1}$. The *anti* form is favored. The barrier is very similar to the one obtained in the dinaphthyl analogue (97T5379).

The two nitrogen atoms in 1,8-di(3'-pyridyl)naphthalene **38** were quaternized by the addition of either benzyl or methyl groups to give the corresponding dication **549a** and **549b**; **549a** was oxidatively converted to the di(6'-pyridone) **550**. *N*-Oxidation of **38** gave the mono-oxide and the di-*N*-oxide **549c**. All these compounds in DMSO-*d*₆ show *anti-syn* atropisomerism at ambient temperature by ¹H NMR analysis; similar amounts of both diastereomers are present. The barriers were not addressed (96JOC7018). The *syn* form is slightly favored in the charged compounds **551** (98JOC4985) and **552** (01JOC7227).



A series of 1,8-dihetarylnaphthalenes **40**, **553**–**556** were prepared by Pd(0)-catalyzed coupling reactions. Variable-temperature proton NMR spectra show that the rotational barriers in **38** and **40**, **553**–**556** are much smaller when a nitrogen atom is located at an *ortho* site as in **40**, **553**–**555** than when a nitrogen atom is situated in 3' or 4' positions as in **556** and **38**. Coalescence temperatures may differ by as much as 100 °C. In **40**, a barrier of diastereomerization *anti*–*syn* equal to 46 kJ mol^{−1} was determined by DNMR at −55 °C. The barrier is higher in the 3' or 4' derivatives **38** and **556**: 66 kJ mol^{−1}. The results of AM1 and PM3 computations indicate the preferred transition state for sigma-bond rotation places the annular nitrogen atom in the 2' or *ortho* position toward the face of the second hetaryl ring and not toward the naphthalene ring (97JOC3215).

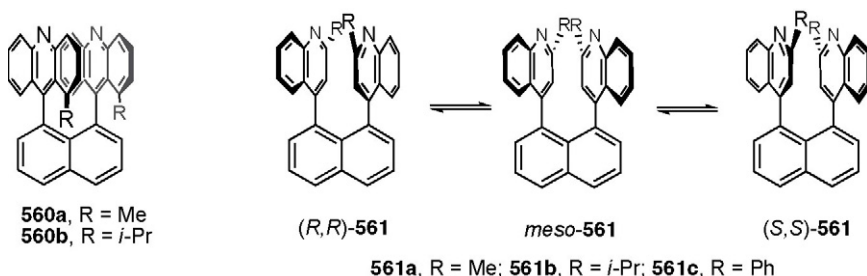
Katoh *et al.* reported an NMR study of the conformation of **38**. At 253K the NMR spectra showed two sets of distinct signals for the pyridine ring suggesting a mixture of *syn*–*anti* stereomers in solution. The equilibrium is solvent dependent and the *syn* form, which has the larger dipole moment, is favored in polar solvents. The barrier to diastereomerization was determined by total line shape analysis at 300K (*anti*–*syn*: $\Delta G^\ddagger = 65$ kJ mol^{−1}). A large positive entropy was observed. In the crystal state the *anti* form in which the dipolar interactions are minimized is observed (97T3557). 4,4'-Naphthalene-1,8-diylbis(2-methylpyridine) **557b** exists in solution as a mixture of *anti* and *syn* forms, the equilibrium is not sensitive to the solvent polarity. The barriers in three solvents were coincidentally similar (*anti*–*syn*: $\Delta G^\ddagger = 64$ kJ mol^{−1}) to the one observed in **38**. The barrier in DMF is 65 kJ mol^{−1} for **558** (97T3557).

Wolf *et al.* revisited the series **557a**, **557b**, and **65**, fast exchange of the *anti*–*syn* diastereomers was mentioned for **557b** and **65** (02S749).

Crystallization of conformationally flexible **557a** under various conditions resulted in conformational polymorphism. Crystallization in water encapsulated fused cyclic water pentamers (**06CEC377**) and HPLC on an achiral column under cryogenic conditions ($-70\text{ }^{\circ}\text{C}$) led to a baseline separation of the diastereomers of **65**. The barriers to diastereomerization were determined by DNMR and DHPLC with an excellent agreement utilizing the two methods. A single barrier equal to $68\text{--}73\text{ kJ mol}^{-1}$, depending on the temperature, was reported since the two diastereomeric forms were equally populated. The rate constants obtained from DHPLC and DNMR in different temperature ranges and in different solvents were mixed to determine the large negative entropy ($-43.4\text{ J K}^{-1}\text{ mol}^{-1}$) of the diastereomerization process (**03JPC(A)815**). The N,N' -dioxide analogues **559a** and **559b** exhibit rotational barriers equal to 65 and 69 kJ mol^{-1} at $27.5\text{ }^{\circ}\text{C}$, respectively (**02TA1153**).

Highly strained 1,8-diacridylnaphthalenes **560a,b** were prepared in moderate yields by two consecutive CuO-promoted Stille cross-couplings. The *syn-anti* diastereomers did not show any sign of interconversion after heating to $180\text{ }^{\circ}\text{C}$ for 24 h. They were separated by chromatography on an *S*-phenylglycine column. However, the enantiomers of the *anti* form were not separated. Fluorescent titration with *syn***560a** showed highly efficient selective quenching by Cu(II) ions (**03JA10651**). *Syn***560b** undergoes Fe(III)-selective fluorescence quenching in water/ CH_3CN even in the presence of other metal ions (**04TL7867**).

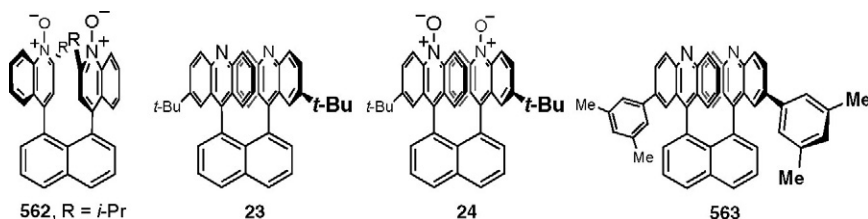
Tumambac and Wolf prepared highly constrained 1,8-bis(2,2'-dialkyl-4,4'-quinolyl)naphthalenes **561a,b** via Pd-catalyzed Stille coupling of 1,8-dibromonaphthalene and 2-alkyl-4-trimethylstannylquinolines. The *D*, *L*anti isomers were more stable than the *meso syn* isomers. The three stereoisomers of **561a** were conveniently separated on Chiralpak AD, being stable at room temperature.



The diastereoisomerization and enantiomerization processes in hexanes at $71\text{ }^{\circ}\text{C}$ were monitored by HPLC and NMR. Starting from one pure *anti* enantiomer of **561a**, one observes a fast initial increase of the *syn* form followed by a slow increase to its final concentration indicating

consecutive, reversible first order reactions. Barriers for the diastereomerization of **561a** were, respectively, 116 and 112.1 kJ mol⁻¹ for the *anti-syn* and *syn-anti* conversion. The interconversion of stereomers in **561b** was studied by NMR resulting in very similar barriers. Ground state strain in **561b** was advocated to account for the very similar barriers observed in **561a** and **561b** (04JOC2048). **561b** was used for metal ion-selective fluorescence recognition (04T11293). The *syn-anti* equilibrium **561b** was modified in the presence of 1,2-diaminocyclohexane. *Trans*-diaminocyclohexane favored the *anti* form of **561b** while *cis*-diaminocyclohexane stabilized the *syn* form (04EJOC3850). The stereomers of **561c** were separated on a Whelk-O1 column. They are stable for months at room temperature. The diastereomerization barriers in hexanes/EtOH (85:15) at 97.8 °C were 122.4 and 121.8 kJ mol⁻¹ for the *anti-syn* and *syn-anti* exchanges, respectively (05JOC2930).

The *N,N'*-dioxide **562** gave a slightly smaller barrier (115.2 kJ mol⁻¹ at 56.9 °C) than **561b** (05JOC2930). **562** was resolved on Chiralpak AD column and the enantiomers have been employed in enantioselective fluorescence analysis of the enzymatic kinetic resolution of *trans*-1,2-diaminocyclohexane (05OL4045).



The enantiomers of 1,8-diacridylnaphthalene derivative **23** were obtained by separation on Chiralpak AD. They were employed as a practical fluorosensor for the determination of concentration and enantiomeric composition of carboxylic acids and amino acid derivatives (06CC4242).

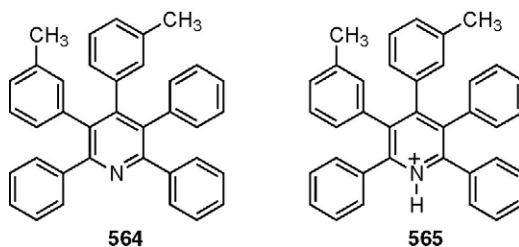
Compound **24**, the corresponding *N,N'*-dioxide of **23**, presents enhanced fluorescence when complexed with Sc(OTf)₃. **24** forms a strong Sc[(±)-**24**]₂ complex whose fluorescence disappears upon addition of amino alcohols. Optically pure scandium complex formed with optically pure **24**, Sc[(+)-**24**]₂ generates diastereomeric complexes with a racemic aminoalcohol such as alaninol. The fluorescence signal could be switched off enantioselectively and it was exploited for sensing purpose. The enantiomers of **24** were obtained by chromatography on (*R,R*)-Whelk-O1 (08JOC4267).

The enantiomers of **563** were obtained by chromatography on (*R,R*)-Whelk O1 and employed in enantioselective fluorosensing of *N*-*t*-Boc-protected amino acids (06JOC2854) and chiral carboxylic acids

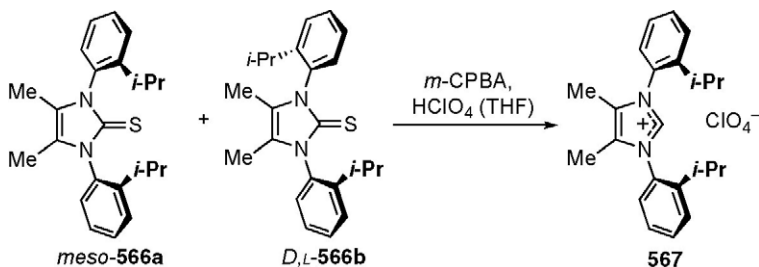
(04JA14736). The enantiomers of the N,N' -dioxide analogue of **563**, **564**, were available by chromatography on Chiralpak AD and were employed as fluorosensors for enantioselective recognition of a hydrogen bond donor such as amines and amino acids (04CC2078). X-ray of *trans*-**563** and the N,N' -dioxide analogue **564** were reported (05JOC2299). Sc [(+)-**564**]₂ was used for the determination of the enantiomeric excess and concentration of unprotected amino acids, amines, amino alcohols, and carboxylic acids by competitive binding assays (06JA13326, 06TL7901).

11.4 Other examples

Gust and Fagan prepared pentaarylpyridine **564** and the corresponding pyridinium **565**.

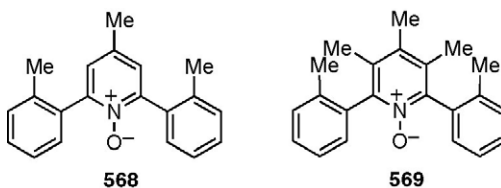


Low-temperature NMR showed four methyl signals equally populated which are consistent with the occurrence of two *D,L* diastereomeric pairs. Coalescence upon warming afforded a 61.45 kJ mol⁻¹ barrier for **564**. A higher barrier 64.35 kJ mol⁻¹ was obtained for the pyridinium **565**. The higher barrier in the pyridinium salt than in the neutral pyridine pointed out once again that the lone pair on the nitrogen has a lower steric requirement than the hydrogen (80JOC2511).



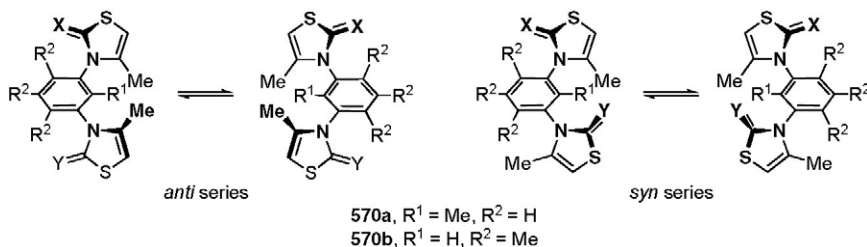
4,5-Dimethyl-1,3-bis[2-(propan-2-yl)phenyl]-1,3-dihydro-2*H*-imidazole-2-thione **566** was obtained as a pair of diastereomers (**566a**_{meso} and **566b**_{*D,L*}) that were separated by chromatography. The interconversion was not addressed. Oxidation afforded salt **567** that was obtained as a pair of diastereomers with a marked preference (90%) for the *meso* form

independently of the starting material **566a** or **566b** (04EJOC2025). Due to the substitution pattern in blocking positions, it is surprising that *meso* and D,L forms could be observed in salt **567** at room temperature by NMR. Further studies including DNMR of **567** and thermal diastereomerization in **566** would be worthwhile.



Uncuta et al. studied 2,6-di-*O*-tolylpyridine-1-oxides **568** and **569** obtained by treatment of the corresponding pyrylium salts with hydroxylamine. Diastereomers corresponding to the *syn* and *anti* forms were observed at low temperature for **568** and room temperature for **569**. The diastereomerization barriers were determined by DNMR giving $\Delta G^\ddagger_{\text{major/minor}}$ 61.9 kJ mol⁻¹ and $\Delta G^\ddagger_{\text{minor/major}}$ 59.8 kJ mol⁻¹ in **568**. The barriers are much larger in **569** due to the three groups in blocking positions. The *syn* and *anti* forms were separated by achiral HPLC and the enantiomers of the *anti* form were separated on a (S,S)-Whelk-O1 column. The *meso* form is more retained than the two enantiomers of the *anti* form on the chiral column. Diastereomer interconversion was monitored by achiral HPLC. The resulting barriers in diglyme at 403K were 134.7 kJ mol⁻¹ for the *syn-anti* exchange and 133.8 kJ mol⁻¹ for the reverse transformation. Exchange at different temperatures afforded $\Delta H^\ddagger_{\text{syn/anti}} = 118.3$ kJ mol⁻¹ and $\Delta S^\ddagger_{\text{syn/anti}} = -40$ J mol⁻¹ K⁻¹ (08Mlip).

Hirtopeanu et al. have studied the equilibrium compositions and the barriers to rotation in 1,3-bis[oxo/thioxothiazolynyl]toluene derivatives **570** (00H1669).



In **570**, X and Y are oxygen or sulfur. When X ≠ Y, both *syn-570* and *anti-570* are chiral resulting in two pairs of enantiomers; when X = Y the *syn*-form is *meso*. The rotation around the axis is not observed for the thiazoline-2-thione fragment ($\Delta G^\ddagger > 134$ kJ mol⁻¹) while the barrier for the oxygen analogue is lower ($\Delta G^\ddagger = 122$ –129 kJ mol⁻¹ depending on the

substitution). Equilibration of *syn-anti* forms occurs by rotation of the thiazolinone fragment; the *anti* form in which the dipolar interactions are minimized is always favored. When $X = Y = S$ equilibration is not observed; the ratio of the two diastereomers is established during the synthesis. HPLC on a chiral support and polarimetric detection were combined to determine the absolute configurations of **570a**.

The $C=S/C=O$ transformation proceeded without rotation about the axis (Figure 42). The absolute configuration *P,P* of the (+)-form of the (*anti*)-**570a**/*(syn)*-**570a** pair was determined by X-ray structures, and chemical correlation according to a scheme that allowed the determination of the absolute configuration of all the stereomers (**02CHI665**).

A series of 1,2-bis-[4-methyl-2-(thi)oxo-2,3-dihydrothiazol-3-yl]-benzenes has been prepared from (+)-*aS*-(**574**). These atropisomeric molecular triads **571**, **572**, and **573** were exclusively found to exist in the *anti*-form. They were separated into enantiomers by liquid chromatography on a chiral support. The absolute configuration of the enantiomers were determined using a chemical correlation method according to the following scheme, together with chiral chromatography (**09CHI160**).

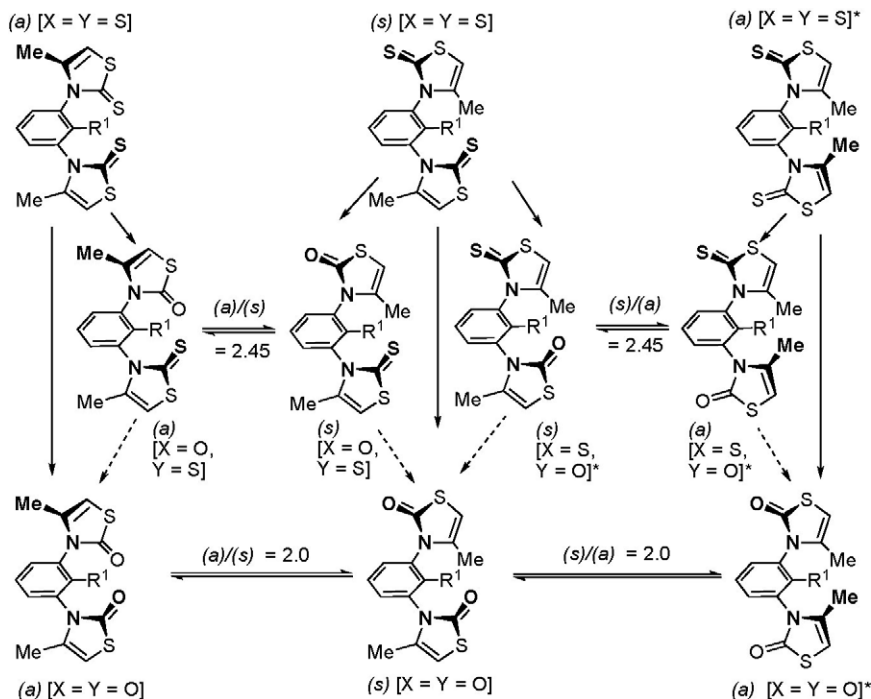
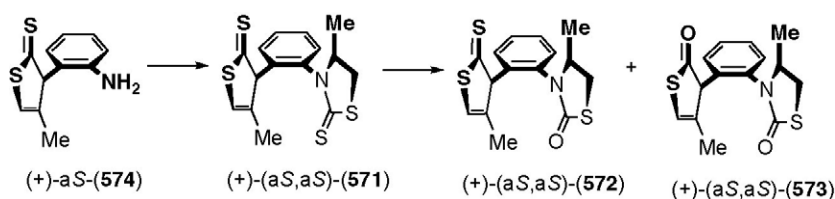
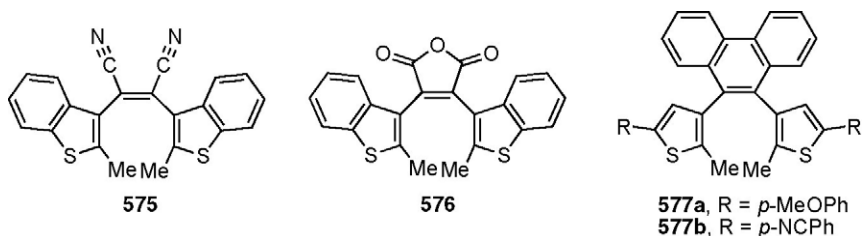


Figure 42. Chemical correlation method in the **570a** series: *a* = *anti*; *s* = *syn*; an (*) means the enantiomer.



The barrier to enantiomerization in the dioxo derivative was determined by thermal racemization ($\Delta G^\ddagger = 113.4 \text{ kJ mol}^{-1}$ in EtOH, 78°C).



1,2-Bis(benzo[b]thiophen-3-yl)ethene derivatives **575** and **576** present parallel and *anti*-parallel conformations that can be observed by NMR. The interconversion barriers obtained by DNMR are 67 kJ mol^{-1} in **575** and 71 kJ mol^{-1} in **576**, respectively. These compounds undergo reversible photocyclization (90BCJ1311).

Walko and Feringa designed strained photochromic diarylethenes **577a,b** (Figure 43) that present parallel and *anti*-parallel forms, which were separated. The enantiomers of *anti* **577a,b** were separated on a Chiralpak AD column, the meso forms were eluted later. The barriers of enantiomerization were 109.6 and $111.5 \text{ kJ mol}^{-1}$, respectively.

A stereospecific photochemical switching process provided a useful basis for chiroptical molecular switches and molecular memory elements (07CC1745).

A conformational analysis of *N,N'*-dinaphthyl heterocyclic carbenes (imidazol-2-ylidenes and imidazolin-2-ylidenes **578a–h'**) has been carried out at the B3LYP/6-31G(d) level (11SC1087). The potential hypersurface is complex (Figure 44) since the 16 minima are connected by 32 transition states. The calculated values agree with the experimental results of Dorta *et al.* (09EJIC1861).

12. AXIAL CHIRAL SYNTHESIS

Cyclization of α [(1-phenylethyl)amino]- α -(2-iodophenyl)acetonitrile (**579**) with $(\text{COCl})_2$ in toluene or chlorobenzene afforded the atropisomeric pyrazinones **580** (95TL2017). Stereochemical assignments were made by X-Ray and NOE experiments.

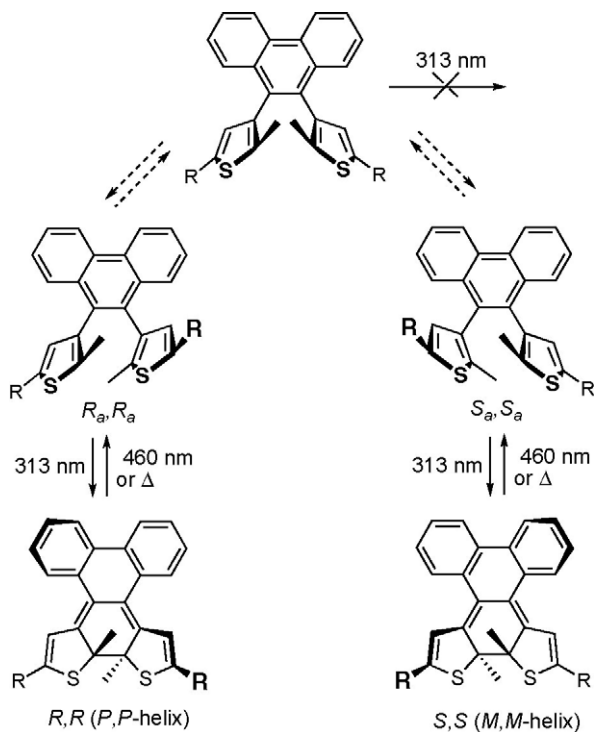


Figure 43. Photochromic diarylethenes (Me groups not represented).

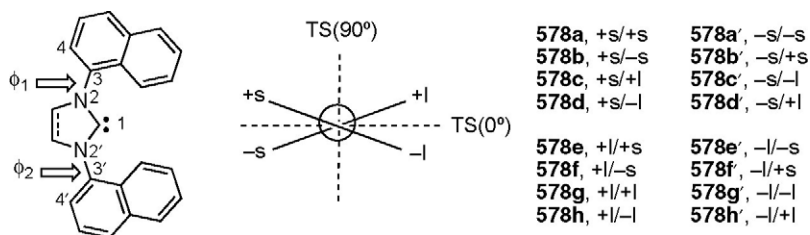
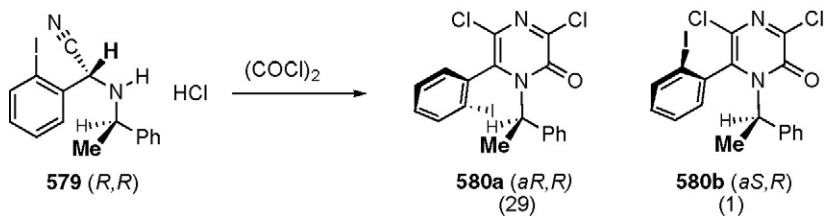
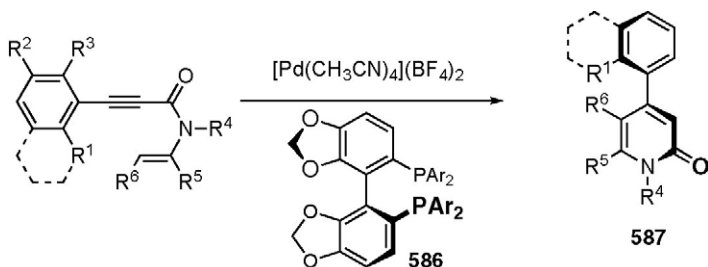


Figure 44. Geometrical definition of the 16 structures.



A remarkable series of successes were reported by Gutnov and co-workers (04AG(IE)3795) in their synthesis of enriched atropisomers of 2-arylpyridines, **581**–**585** (Figure 45).

Related to Gutnov's procedure is the highly enantioselective construction of 4-arylpyridones by Tanaka *et al.* (09OL1805). The reaction is catalyzed by a cationic palladium(II)/(*S*)-xyl-Segphos complex **586** (Ar = 3,5-Me₂-C₆H₃) and 2-pyridones **587** are obtained in up to 96% yield and up to 97% *ee*.



A review by Bringmann, Breuning *et al.* (05AG(IE)5384) entitled “Atroposelective synthesis of axially chiral biaryl compounds” contains a few examples of heteroaromatic compounds but methodologically it is of

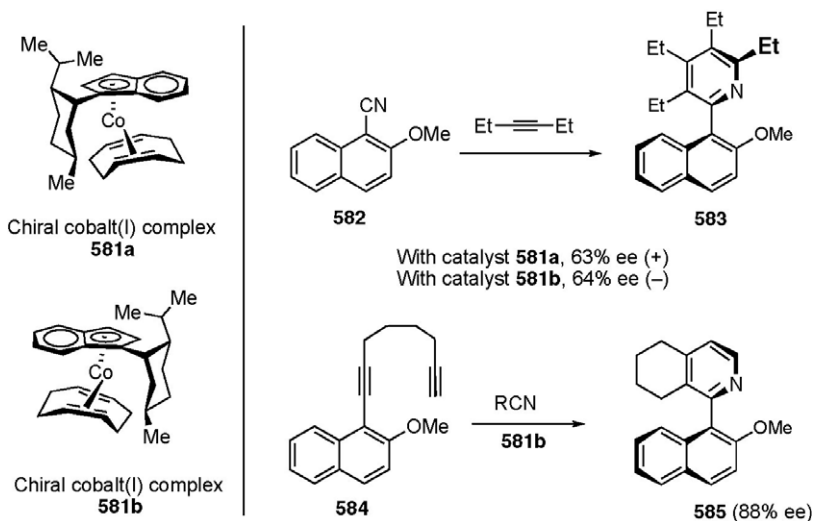
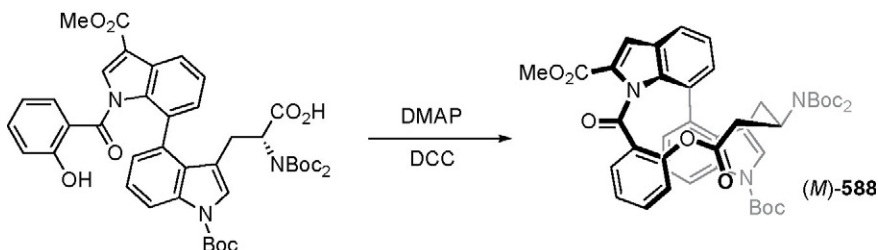


Figure 45. Synthesis of enriched atropisomers of 2-arylpyridines.

great importance. One is that from (04AG(IE)3795) and another concerns the atropodiastereoselective synthesis of the diazonamide A model (*M*)-588 by macrolactonization.



Denmark and Fan (06TA687) reported that the oxidative dimerization of chiral pyridine *N*-oxides was highly diastereoselective for the formation of the *P*-configuration, (*P*)-(*R,R*)-260, of the chiral axis.

Kitagawa et al. (10CEJ6752) have described the catalytic enantioselective synthesis of atropisomeric indoles with an N–C chiral axis that we reported as 346 and 347. Similarly, we have described the Carretero et al. results (10CEJ9676) (195–198).

13. CONCLUSIONS

Atropisomerism was discovered in 1922 (22JCS614) in diphenic acids and extended to heterocycles in 1931 by Adams et al. (31JA2353, 31JA374, 31JA3519). Eighty years later the field continues to be very active (Figure 46) and it is expected to grow in importance because atropisomerism is related to asymmetric synthesis, to materials and to biological properties and because new techniques are available such as low temperature HPLC, high field and solid-state NMR.

The development of liquid chromatography on a chiral support gave a decisive impulse to the study of atropisomerism since resolution can be quantitatively performed under very mild conditions without derivatization. The analytical methods can be easily extrapolated to preparative scale. Several atropisomeric systems, which do not present suitable functional groups to perform classical resolution through diastereomer resolution, can be readily separated into optically pure enantiomers. Dynamic chiral HPLC fills the gap between barriers attainable by DNMR and by thermal racemization of pure enantiomers. Chiral HPLC opens the way to several unexplored domains in the field of atropisomerism. We have

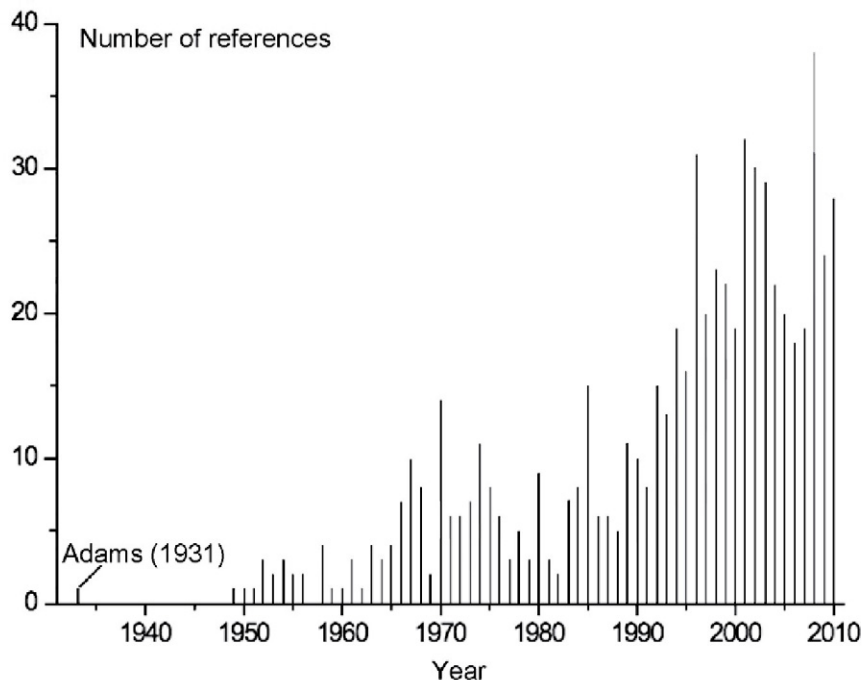


Figure 46. Plot of the number of references per year between 1930 and 2010.

shown that many very interesting “old” atropisomeric frameworks should be revisited with modern chiral HPLC techniques.

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49MI91
49MI313
50CJC26
51ZFK897
52CJC725
52JCS1467
52JCS4133
53JCS3802
53JOC1413
54JCS3464
54JCS4256
54NAT117
55JCS3773
55LA(591)200
56G797
56JOC97
58ACS1671
58G977
58G1035
58MI89
59JA5637
60JOC1355
61CCC67
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63AK289
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CHAPTER 2

Anomeric Effect in Saturated Heterocyclic Ring Systems

Eusebio Juaristi^a and Yamir Bandala^{a,b}

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1. INTRODUCTION

Since its first recognition, the anomeric effect has become one of the most important factors influencing the conformational behavior and even the reactivity of saturated heterocyclic systems. In this respect, several reviews have been dedicated to discuss the origin, magnitude, and scope of this important phenomenon in cyclic and acyclic derivatives (71PAC527, 71RCR315, 79MI1, 83MI2, 83MI3, 89ACC45, 90H1157, 92T5019, 93MI4, 95MI5, 95T11901, 99RHC35, 05AV37, 09CC13, 11WCMS109). The present contribution describes some salient observations in the topic of the anomeric effect in saturated heterocyclic compounds reported in the 1992–2011 period.

2. CLASSICAL INTERPRETATION OF THE ANOMERIC EFFECT

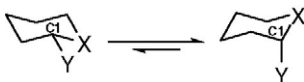
Several explanations have been presented to understand the origin of the anomeric effect, and over the years these proposals have been the cause of intense debate. Two rationalizations are generally accepted: (1) an unfavorable dipole–dipole interaction between the carbon–heteroatom bond on the ring and the bond from C(1) to the equatorial, electronegative substituent (55CIL1102), and (2) a favorable interaction of the ring heteroatom lone pair with the antibonding σ^* -orbital of the ligand bond, which stabilizes the axial orientation of the anomeric substituent (59JCS2954, 69TS39).

From the accumulated experimental and theoretical observations it is evident that *both* factors contribute to the anomeric effect. Nevertheless, alternative theories have been advanced recently to account for the origin of the anomeric effect, and some of them will be discussed in Section 4.

2.1 Anomeric effect: a brief description

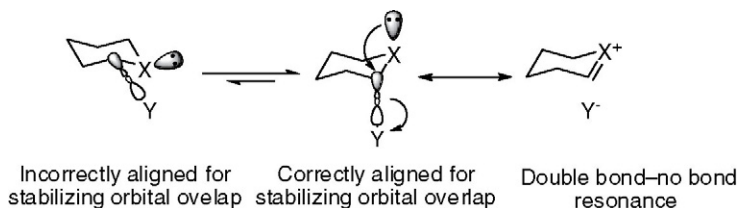
In principle, the preferred conformation of substituted saturated heterocycles should follow the basic principles that dictate the conformational behavior of cycloalkane derivatives. Nevertheless, the presence of non-carbon atoms in the ring induces significant structural changes such as variations in bond lengths and angles; thus, nonbonded interactions between substituent groups in heterocyclic systems cannot be of the same magnitude. In this regard, the presence of lone electron pairs in heterocyclic compounds can have pronounced effects on the conformation of these systems. For example, the interaction of electron-

withdrawing anomeric substituents (electronegative groups localized at C1) with endocyclic lone electron pairs induces these substituents to *preferentially adopt the axial rather than the equatorial orientation*. This conformational effect was initially described by Edward (55CIL1102) and later by Lemieux and Chü (58MI6), in what became to be known as the *anomeric effect* (Scheme 1).



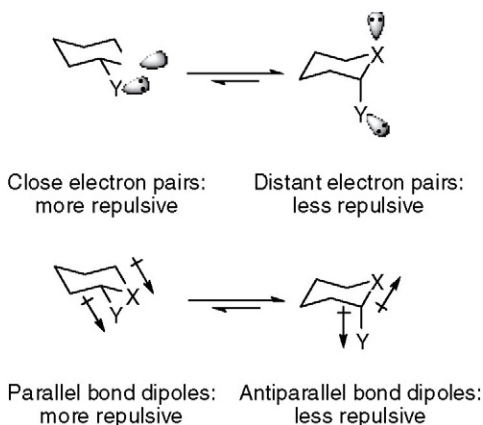
Scheme 1

Although the origin of the anomeric effect has been a matter of controversy for many years, two major conceptual interpretations are generally accepted. Furthermore, the collected information suggests that *both* factors contribute to the anomeric effect (92T5019). In one explanation, it is proposed that the existence of a stabilizing interaction between a lone electron pair on the ring heteroatom “X” and the anti-periplanar antibonding σ^* orbital of the bond connecting the axial substituent “Y” at the anomeric carbon ($n_X \rightarrow \sigma^*_{C-Y}$), results in a reinforcement of the endocyclic C–X bond and a weakening of the exocyclic C–Y bond. This interaction produces a lengthening of the C–Y bond by electron transfer to its σ^* orbital, as well as the contraction of the C–X bond as a consequence of its increased double bond character. Additionally, a significant opening of the X–C–Y angle relative to the normal tetrahedral value is usually observed because of the partial sp^2 character developed at the anomeric carbon (Scheme 2) (59TL16, 69TS39, 93MI4, 95MI5, 95MI7, 99MI8, 11OBC5321, 11WCMS109).



Scheme 2

A second major rationalization of the anomeric effect is based on anticipated dipole–dipole repulsion between the two electronegative atoms (one part of the ring, the other exocyclic) and their associated lone electron pairs in the equatorial isomer, with the consequent preference for the axial conformation with the smallest dipole moment (Scheme 3) (55CIL1102, 93MI4, 95MI5, 95MI7, 99MI8).

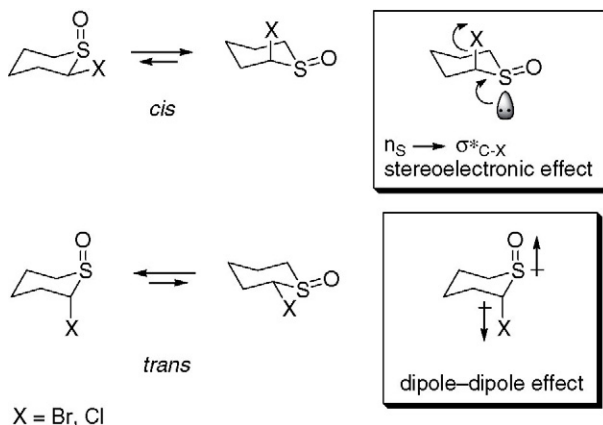


Scheme 3

A vast number of researchers have found supporting experimental and/or computational evidence for either one or both interpretations, corroborating the existence of the anomeric effect in many heterocyclic compounds. For example, X-ray diffraction has shown the anticipated reduction of endocyclic X–C bond lengths and the stretching of axial and exocyclic C–Y bond in several heterocyclic systems containing the R–X–C–Y segment (97JOM355, 02T2621, 03AX(E)o1070, 03OBC2527, 05AX(E)o910, 06JHC1695, 07AX(E)o3558, 09AX(C)o115, 09AX(C)o558).

In an illustrative report, Juaristi and Ordóñez (94T4937) proposed that the conformational preference of *cis* and *trans* isomers of 2-halotetrahydrothiopyran *S*-oxide might have different origin. Indeed, following determination of the conformational equilibrium constants by ^1H and ^{13}C NMR in the two diastereomeric isomers, it was concluded that in *cis*-2-halotetrahydrothiopyran *S*-oxide the isomer with axial C–Br or C–Cl bond predominates. This is in line with the existence of a $n_{\text{S(O)}} \rightarrow \sigma_{\text{C-X}}^*$ stereo-electronic interaction, which is nevertheless less important than the corresponding $n_{\text{S}} \rightarrow \sigma_{\text{C-X}}^*$ interaction in 2-halotetrahydrothiopyrans. By

contrast, the preference of *trans*-2-halotetrahydrothiopyran *S*-oxide to adopt the diaxial conformation was taken as consequence of the manifestation of repulsive electrostatic interactions in the equatorial conformer (Scheme 4) (94T4937). Similar conclusions are arrived by Aggarwal et al. in a related conformational analysis of 2-bromo- and 2-chloro-1,3-dithiane *trans*-1,3-dioxides (97JCS(P1)21).



Scheme 4

In the computational arena, Salzner and Schleyer reported a theoretical study (NBO method) of several tetrahydropyran derivatives, confirming that the observed anomeric effect is due to hyperconjugation (94JOC2138, 95JOC986). More recently, Migda and Rys (06JOC5498) using DFT calculations and NBO analysis concluded that the observed stabilization energy in nine-membered 2,4- and 3,5-benzodioxonine derivatives is associated with stereoelectronic $n_O \rightarrow \sigma^*_{C-O}$ interactions. By the same token, Ganguly et al. (10JPC(A)10684) used DFT and NBO methods in the study of several 1,3-diazacyclohexane derivatives and confirmed the importance of $n_N \rightarrow \sigma^*_{C-N}$ stereoelectronic interactions.

By contrast, Benn and collaborators have presented crystallographic and computational evidence that does not support $n_S \rightarrow \sigma^*_{C-CN}$ stabilization as the reason for the axial preference of the cyano substituent in 2-cyanothiane (10CJC831). In particular, comparison of bond lengths between axial and equatorial C–CN bonds showed that, contrary to expectation, the axial bond is *shorter* than the equatorial one. For relevant precedent from the X-ray diffraction study of 2-diphenylphosphinoyl-1,3-

dithiane, see: (82JOC5038) and (84JOC3026). See, also: (95JOC2734) and (99AX(C)2179).

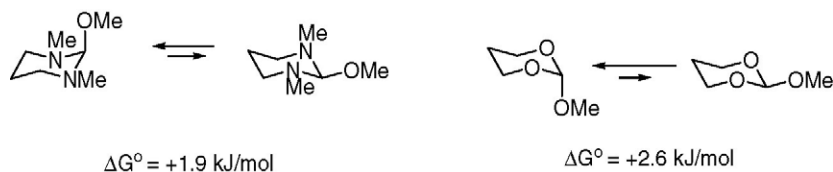
The difference in internal X–C and external C–Y *bond strengths* in axial and equatorial anomeric segments, which is in line with the stereoelectronic origin of the anomeric effect, can also be established by NMR spectroscopy. For example, double bond–no bond resonance weakens the C–H_{ax} bond in anomeric segments and attenuates the one-bond ¹³C–¹H coupling constant; thus, ¹J_{C–Heq} > ¹J_{C–Hax}, the so-called Perlin effect (69TL2921, 07ACR961). For other salient NMR studies in this topic, see: (92CJC2650, 92T4209, 94CAR141, 97MRC721, 04T10927, 08CAR404, 09JOC4740, 09TJC607, 10EJO6331).

Support for the n_X → σ*_{C–Y} stereoelectronic origin of the anomeric effect can also be gathered by infrared spectroscopy. Analysis of the so-called Bohlmann bands shows that C–H_{antiperiplanar} bonds to a vicinal nitrogen lone electron pair are longer and weaker than the C–H_{gauche} bonds, resulting in a shift of the stretching C–H_{antiperiplanar} frequency to lower wave numbers (red shift) (57AG641, 84JST313). For other relevant IR-spectroscopic studies, see: (93JA12132, 94JCP2740, 04PCCP5469, 10CPL109, 11CHS1128).

On the other hand, the application of several computational strategies (94JA2199, 95JCC188, 96JA2078, 96JST(T)135, 98BI435, 98H2389, 99CAR264, 00CAR305, 00JCA1115, 00JCC1204, 03JCC1473, 03JPC(B)2394, 06CPL600, 09PCCP8689) has provided data that are generally in agreement with the stereoelectronic nature of the anomeric effect. This is the case of particular theoretical studies in heterocycles containing oxygen (95JST(T)25, 97JPC(A)9756, 01JPC(A)9188, 05BKC1229, 08JPC(A)7072, 09JST(T)57, 10JST(T)58), sulfur (92STC155, 95PS111, 97AGE868, 98HAC537, 98JOC9490, 08CHJ471), and nitrogen or phosphorus (94HI473, 97JOC6144, 00JPC(A)11644, 11JSTC257).

As an illustrative example, Perrin and co-workers carried out a conformational study of 2-methoxy-1,3-dimethyldiazane (1,3-dimethyl-hexahydropyrimidine) and its oxygen analog, 2-methoxy-1,3-dioxane. It was found that both heterocyclic compounds present a favorable conformational free energy difference, ΔG° value, for its axial conformers (0.45 kcal/mol on average for diazane and 0.62 kcal/mol on average for the 1,3-dioxane analog), indicating that substitution of N for O did not result in a substantial increase in the proportion of the axial conformer. Perrin et al. concluded that this observation is contrary to expectation based on the hyperconjugative interaction model because the lone pair in nitrogen is higher in energy relative to a lone pair in oxygen and should lead to a stronger n_N → σ*_{C-OMe} interaction, suggesting that electrostatic forces predominate over the n → σ* orbital delocalization (Scheme 5) (94JA715). Theoretical support for this conclusion was subsequently reported by Wiberg and Marquez (94JA2197). Nevertheless, it

is important to point out that nitrogen lone pairs are sp^n hybrids ($n \sim 5$), whereas the relevant oxygen lone pair is a pure p-orbital. Based on electronegativity effects one would expect that nitrogen lone pairs are better acceptors but hybridization effects mask it (03JA14014).



Scheme 5

In a recent theoretical study, Mo used extended block-localized wave function (BLW) calculations in order to derive the appropriate wave function for the electron-localized reference molecules that would then permit evaluation of the stabilization energy due to electron delocalization (hyperconjugation). Application of the BLW method to dimethoxymethane and several substituted tetrahydropyrans led to the conclusion that classical steric and electrostatic interactions best account for the observed anomeric effect in these systems (10NAT(C)666). A similar suggestion was advanced recently by Huang and associates, who sought to establish the origin of the anomeric effect by DFT methods and concluded that the axial–equatorial energy difference in α -D-glucopyranose is dictated by classical steric hindrance and electrostatic interactions working together (11JCP84103). Nevertheless, Alabugin has pointed out the difficulty in the partitioning of repulsion versus stabilization contributions in these theoretical methods. As the result, it arbitrarily overestimates electrostatics and underestimates hyperconjugation (11WCMS109).

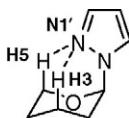
In principle, the examples illustrated above seem contradictory, suggesting that the origin of the anomeric effect in heterocycles is not a consequence of an effect alone, but is the result of several factors working together (95MI5, 11CAR1047).

2.2 Intramolecular hydrogen bonding reinforcing the anomeric effect

In addition to the classical stabilizing factors that have been proposed to explain the anomeric effect, evidence for the participation of interactions involving hydrogen bond formation has been recently reported. Interestingly, analogously to the anomeric effect, hydrogen bonding is a complex phenomenon that in the present context helps stabilize the axial

orientation of the electronegative anomeric substituent *via* C–H···Y bonding.

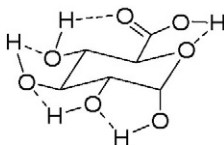
For example, in 1997, Ciunik demonstrated *via* experimental and theoretical analysis that the preferred axial conformation in iminopyranosyl pyrazoles **1** is influenced by intramolecular hydrogen bonds. Thus, the H3···N1' and H5···N1' distances are in the range 2.43–2.84 and 2.38–2.69 Å, respectively, which suggests the existence of C–H···N hydrogen bonds that contribute to the axial preference in these kinds of heterocyclic compounds (Scheme 6) (97JST173, See, also 99JCS(P2)589).



1

Scheme 6

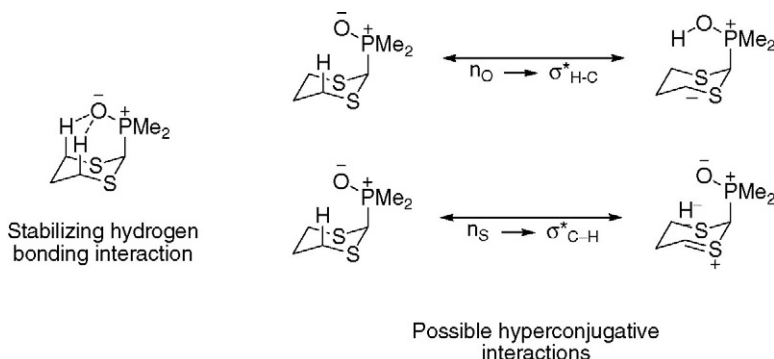
In this regard, Allinger and co-workers, employing quantum mechanical and molecular mechanical calculations examined the potential energy surfaces in a series of hexoses, confirming the axial preference of the anomeric OH substituent. In addition to the well-established major contribution from hyperconjugation and dipole–dipole interactions, intramolecular hydrogen bonding dominate the conformational energy of these sugar derivatives (98JA3411). Nyerges and Kovács arrived at a similar conclusion from their high-level DFT examination of glucuronic acid, concluding that in addition to a large *endo*-anomeric hyperconjugation effect in these structures, intramolecular hydrogen bonding plays a relevant role in the axial stability of the OH anomeric substituent (Scheme 7) (05JPC(A)892).

 α -D-Glucuronic acid

Scheme 7

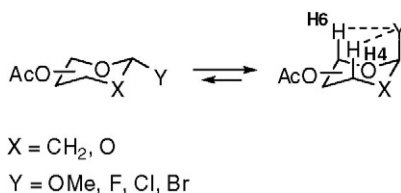
A significant contribution in this area was presented by Cuevas from his theoretical analysis of the anomeric effect in S–C–P units. Thus, using computational resources and 2-dimethylphosphinoyl-1,3-dithiane as a model system the author argues that the polar nature of the P–O bond

promotes a high charge concentration at the oxygen atom, which is then able to interact with the 1,3-*syn*-diaxial hydrogen atoms, resulting in a stabilizing contribution. Furthermore, this research shows that one of the hydrogen bridges is stronger than the other, which might imply an additional through-space hyperconjugative interaction (Scheme 8) (00JA692).



Scheme 8

Additional relevant work was presented in 2007 by Takahashi et al. using computational methods in the modeling of substituted oxanes and 1,3-dioxanes. These researchers found that the interatomic distances between axial H4 and axial H6 and the anomeric substituent (OMe, F, Cl, Br) are shorter than the sum of their van der Waals radii, which suggests that the magnitude of the anomeric effect in these heterocycles is due in part to the stabilization provided by C–H–Y hydrogen bonding (Scheme 9) (07CAR1202).



Scheme 9

3. CONSEQUENCES OF THE ANOMERIC EFFECT IN SATURATED HETEROCYCLES

The interactions involved in the anomeric effect generate a series of structural modifications, which determine the stability, the reactivity, and/or the reaction selectivity of the heterocyclic compounds.

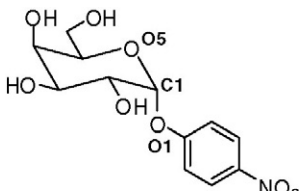
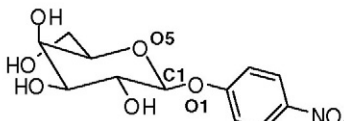
3.1 Structural changes

The orientation of the atoms that define the anomeric effect in X–C–Y segments, provided that the orbital containing the lone electron pair (n_X) in the X donor overlaps with the antibonding σ^* orbital of the acceptor C–Y bond (σ^*_{C-Y}), results in the reduction of X–C bond lengths (the bond is *strengthened*) and the stretching of C–Y bond (the bond is *weakened*) (85MI9, 11OBC5321, 11WCMS109). Additionally, when Y is a heteroatom containing lone electron pairs such as oxygen or nitrogen, the anomeric effect can operate in both directions, so that a flexible heterocyclic ring adjusts to a preferred conformation in order to maximize the overlap of the best lone electron pair donor and the best σ^* orbital acceptor (05CRV4406).

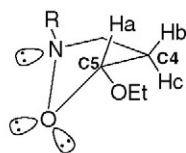
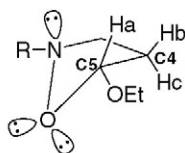
In this context, Gubica et al. recently carried out an illustrative evaluation of the structural changes induced by the anomeric effect in α - and β -galactopyranosides. In particular, these compounds showed pronounced differences in the structural parameters around the anomeric carbon atom, such as C1–O5 and C1–O1 bond lengths and O1–C1–O5 bond angles (Table 1). Giubica et al. concluded that the characteristic shortening in C1–O5 bond and lengthening of C1–O1 bond in **2** in comparison to **3** are the result of an $n_O \rightarrow \sigma^*_{C-O}$ stereoelectronic effect (09CAR1734).

On the other hand, Ali and co-workers reported that the anomeric effect dictates the solution conformational behavior of several isoxazolidines, which exist in several envelope and half-chair puckered conformations (95SA(A)2279). As evidenced by NMR, nitrogen inversion converts the *cis* isomer (*cis*-**4**) into the *trans* isomer (*trans*-**4**), and the small coupling constants (0–1.5 Hz) between the C5–H proton and the C4–H protons suggest a dihedral angle near 90°, which indicates that *cis*- and *trans*-**4** adopt a conformation with a pseudoaxially oriented ethoxy group as a

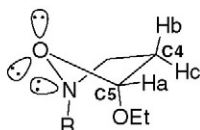
Table 1. Structural differences of selected bond lengths and bond angles in pyranosides **2** and **3**

			
2		3	
α -Galactopyranoside (2)		β -Galactopyranoside (3)	
C1O5 (Å)	1.39	C1O5 (Å)	1.41
C1O1 (Å)	1.42	C1O1 (Å)	1.40
O1C1O5 (°)	113.6	O1C1O5 (°)	106.6

Less stable isoxazolidines,
no anomeric effect present

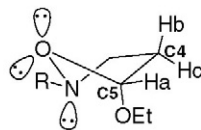


More stable isoxazolidines,
anomeric effect present



cis-4

Preferred conformation



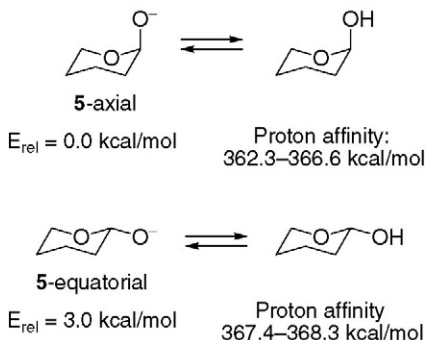
trans-4

Scheme 10

result of the anomeric effect (Scheme 10). (For other interesting examples see: 93JOC6235, 97T2551, 99SA(A)1445, 02T4439, 06HCA1351.)

3.2 Reactivity changes as a consequence of the anomeric effect

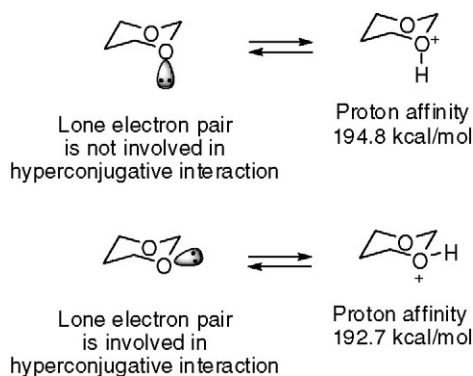
In a relevant computational *ab initio* study (MP2/6-31 + G*), Ganguly and Fuchs examined the conformationally dependent proton affinities of several acyclic and cyclic acetals, and compared them with the corresponding proton affinities of their simple ether analogs. The anomeric O–C–O containing molecular systems were estimated to be weaker bases than the corresponding simple ethers. Furthermore, tetrahydropyran 2-oxide **5** exhibits a strong anomeric effect so that **5**-axial is estimated to be more stable than **5**-equatorial by 3.0 kcal/mol. Ganguly and Fuchs also notice that the calculated proton affinity of **5**-equatorial is higher than that in **5**-axial because the former does not participate in $n_O \rightarrow \sigma^*_{C-O}$ electron transfer with the endocyclic oxygen (Scheme 11, note that the



Scheme 11

deprotonation enthalpy of the protonated forms is taken as the proton affinity of the negatively charged species) (97JOC8892).

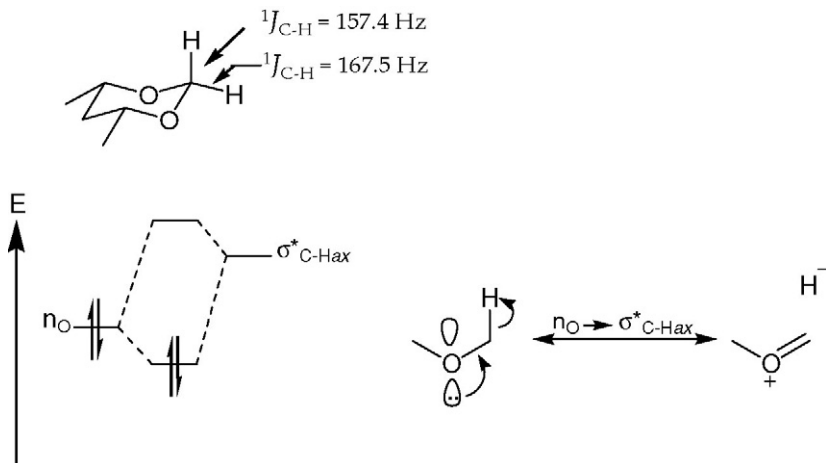
Additionally, Ganguly and Fuchs (97JOC8892) established that the computed proton affinity for axial protonation of 1,3-dioxane is ~ 2.0 kcal/mol higher than that of the equatorial conformer, reflecting the fact that the axial lone electron pair, which does not take part in $n_O \rightarrow \sigma^*_{C-O}$ electron transfer, is more available for protonation than the equatorial one (Scheme 12). (For other interesting examples see: 97JCS (P2)2621, 99IC5453, 01JA3974, 09JOC197, 10JPC(B)11196.)



Scheme 12

One of the reasons stereoelectronic effects are not yet fully accepted as a “proven” concept is the indirect nature of the evidence that is usually advanced to support its relevance. Nevertheless, *various studies during the last 20 years have provided strong evidence that empirical and theoretical analysis of one-bond C–H coupling constants is a powerful tool for the identification of stereoelectronic interactions.* In particular, coupling trends can be rationalized in terms of stereospecific interactions involving $\sigma \rightarrow \sigma^*$, $\sigma \rightarrow \pi^*$, and $n \rightarrow \sigma^*$ electron delocalization. Furthermore, the relative magnitude of the coupling constants usually correlates as well with structural parameters such as bond length and reactivity (07ACR961).

In this regard, Perlin and Casu (69TL2921) observed that the magnitude of the one-bond coupling constant for an axial C–H bond adjacent to oxygen or nitrogen in a six-membered ring is smaller by 8–10 Hz than $^1J_{C-H}$ for an equatorial C–H bond; that is, $^1J_{C-Heq} > ^1J_{C-Hax}$. This finding has been interpreted in terms of an $n_X \rightarrow \sigma^*_{C-H_{app}}$ interaction between a pair of nonbonded electrons on oxygen or nitrogen and the axial (antiperiplanar) adjacent C–H bond; that is, double bond-no bond resonance weakens the C–H_{ax} bond and attenuates the one-bond ^{13}C – 1H coupling constant (Scheme 13).



Scheme 13

3.3 Electronic density changes

Changes originated by electronic density redistribution provide valuable information about the electronic structure of heterocyclic molecules. As the electronegative group attracts electron density from the atom to which it is attached, the atom that loses electron density increases its effective nuclear charge contracting its corresponding occupied orbitals, which results in bond shortening. If an electronegative atom is attached to a bond formed by two atoms that are less electronegative (e.g., a C–C bond), this pulls electrons toward it and leaves more p character in the bond to the electronegative atom, simultaneously leaving more s character in the remaining bond. Thus, the remaining bonds undergo changes in their lengths and angles according to their increased s character; that is, they become shorter and the bond angles between them become larger. When two electronegative atoms are attached to a less electronegative central atom and one of them has a lone electron pair oriented antiperiplanar to the bond of the second electronegative atom, this results in a decrease on the force constant, that is, a weaker bond (longer bond), and a redistribution of electron density (increased negative charge) around the second electronegative atom (94JA5887).

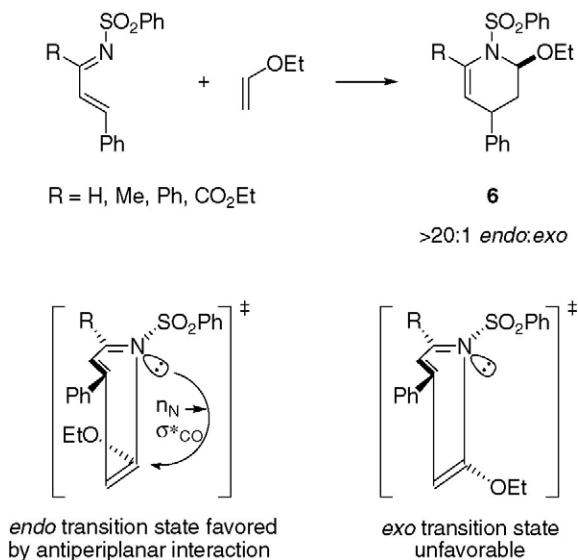
For example, from X-ray data Luger and co-workers determined that the geometry of *trans*-2,5-dichloro-1,4-dioxane is in accord with the predictions of the anomeric effect, in particular with operation of $n_O \rightarrow \sigma^*_{C-Cl}$ hyperconjugation (91JA9148, 93ZN(A)51). See, also: (10CAR1469).

In similar manner, the magnitude of $^1J_{C-H}$ coupling constants varies inversely to the length of C–H bond; that is, the magnitude of $^1J_{C-Haxial}$ adjacent to oxygen or nitrogen in a six-membered ring is smaller than

$^1J_{\text{C-Hequatorial}}$, and the corresponding bond lengths are inversely proportionally longer (90CJC1051, 92TL6927, 94JA5796, 99JPC(A)932, 00JOC3910, 02JA13088, 02MP705, 07ACR961).

3.4 Changes in reaction selectivity as consequence of the anomeric effect

Boger and coworkers analyzed the Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes with electron-rich olefins containing an ethoxy substituent, observing that product **6** is formed as a single diastereomeric cycloadduct arising from an *endo* approach at the transition state. These researchers suggest that the selectivity is a consequence of a conformationally well-defined transition state in the [4 + 2] cycloaddition reaction: the lone electron pair on nitrogen and the σ C–O bond of the dienophile lie antiperiplanar to each other in the preferred *endo* transition state, suggesting $n \rightarrow \sigma^*$ stabilization. A similar stabilizing $n \rightarrow \sigma^*$ interaction is not present in the *exo* [4 + 2] transition state for cycloaddition, and this difference helps explain the unusually large >20:1 *endo* diastereoselectivity found in this reaction (Scheme 14) (91JA1713, 93JOC2068. See also: 98JCS (P2)2699, 00JA9575, 02CAR765).

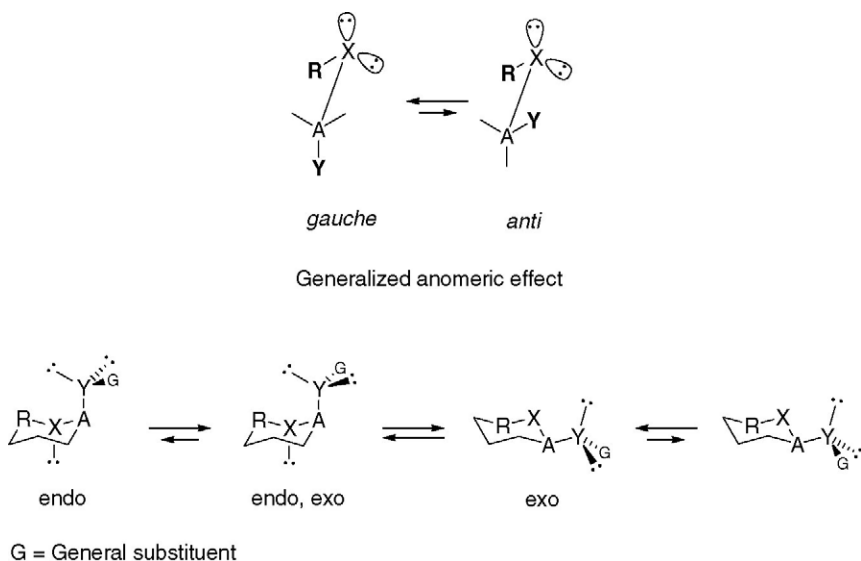


Scheme 14

3.5 The *exo*-anomeric effect

The concept of the *generalized anomeric effect* results from an extension of the original Edward–Lemieux effect to account for the *gauche* over *anti*

orientation preference of R–X with respect to A–Y in an R–X–A–Y system, where R–X–A–Y may be either acyclic or part of a heterocyclic ring. X designates an element with at least one pair of nonbonding electrons (typically O, N, or S), R and A have intermediate electronegativities (R stands for C or H atoms and A is generally a tetrahedral center such as C or Si), and Y is more electronegative than A (Y usually designates halogen, O, N, or P atoms). When the R–X–A–Y system is part of a heterocycle and both X and Y possess lone electron pairs, the conformation of the heterocyclic compound is influenced by an additional effect: the *exo*-anomeric effect in which one of the lone electron pairs of the exocyclic Y atom adopts an *antiperiplanar* orientation with respect to the endocyclic X–A bond, and is the driving force for a polar aglycon (part of the structure that is not a “sugar”) to adopt the axial orientation (Scheme 15) (92T5019, 95MI5).



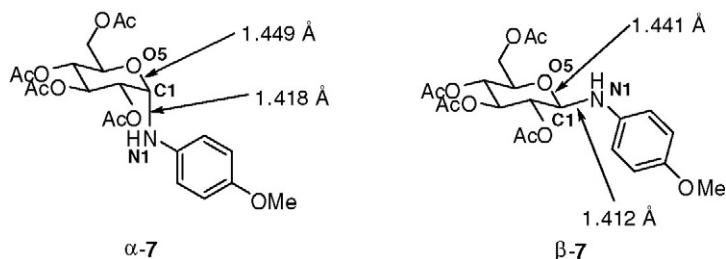
Endo- and exo-anomeric effects

Scheme 15

The conformational properties of substituted heterocycles are considerably affected by the *exo*-anomeric effect, as has been demonstrated by considerable experimental evidence in sugars and sugar derivatives (X-ray diffraction: 92CAR33, 99T2419, 01TA731, 05AX(E)o860, 07AX(C)o578, 07AX(E)o498, 07CAR1210, 10JCA299; NMR spectroscopy: 92T6151, 00CEJ1035, 00EJO1805, 05JPC(B)17320, 09CEJ8886, 09S4143; circular dichroism: 95JOC2537, 97CH626, 98JOC8247, 99TA901, 03TA2793, 04TA2385; and computational studies: 92CAR223, 92JCC102, 00JCA1319, 00JST303, 03JCA407, 08CAR1463, 10CAR2048).

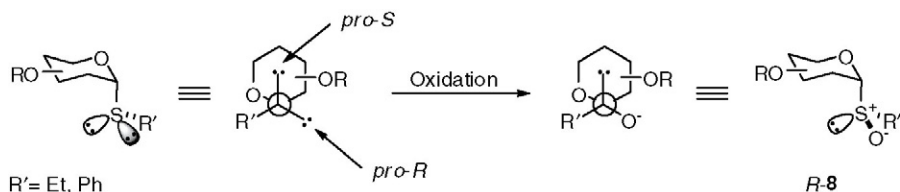
In cases of dominant *exo*-anomeric interactions in R–X–A–Y segments, there exists a contraction of A–Y bond length and a stretching of A–X bond length that stabilizes the axial or equatorial conformation where it takes place (97CAR1).

A relevant example was presented by Pinto and collaborators who carried out a complete comparative analysis between α - and β -pyranosylamine derivatives **7** in solid state and solution. The crystal structure of axial α -**7** indicates a conformational preference about the C1–N bond in which $n_N \rightarrow \sigma^*_{C-O}$ *exo*-anomeric interactions may be expressed, although this conformation is not displayed in solution. For equatorial β -**7** the observed conformation permits $n_N \rightarrow \sigma^*_{C-O}$ *exo*-anomeric interactions both in solid state and solution (01CAR421). These observations are in agreement with a dominant $n_N \rightarrow \sigma^*_{C-O}$ *exo*-anomeric effect (Scheme 16).



Scheme 16

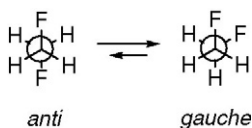
On the other hand, taking advantage of the conformational restrictions imposed by the *exo*-anomeric effect, Crich and co-workers have performed the stereoselective sulfoxidation of α -thioglycosides to obtain (*R*)-sulfoxides **8**. Thus, independently of the oxidant agent (MMPP, MCPBA, NaIO_4) the oxidation path is dictated by the imposed *exo*-anomeric effect aided by steric effects; that is, the predominant conformation induced by these interactions exposes the *pro-R* lone electron pair of the α -thioglycosides to attack by the oxidant agent, whereas the *pro-S* lone electron pair is hindered by the heterocyclic ring (Scheme 17). (98CHC2763. See also: 93T8977, 00T9059, 04CHC714.)



Scheme 17

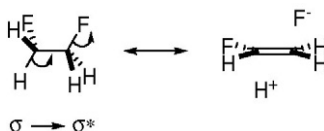
3.6 The attractive *gauche* effect

A conformational effect related to the anomeric effect takes place in X–C–C–Y segments, where X and Y are electronegative groups. In particular, it has been found that molecules such as 1,2-difluoroethane, hydrogen peroxide, and others exhibit a preference for the *gauche* arrangement over the *anti* (Scheme 18).



Scheme 18

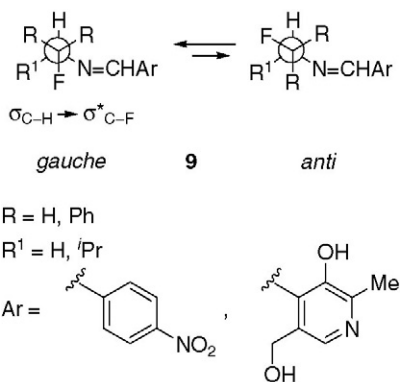
The origin of this *gauche* attractive effect, which overcomes unfavorable steric and/or dipolar interactions, can be rationalized in terms of $\sigma \rightarrow \sigma^*$ (or $n \rightarrow \sigma^*$) energy-lowering orbital interactions between the best combinations of donor and acceptor bonds (or lone pairs of electrons) in an *antiperiplanar* orientation (Scheme 19) (73TL1645, 77JA8379, 79JA1700).



Scheme 19

Recently, the *gauche* effect has been found to dictate the preferred conformation of large, biologically relevant molecules such as 4-fluoroproline, 4-azidoproline, and 9,10-difluorostearic acid (02CHC1226, 02JA2497, 05OL2397, 06JA14697). The *gauche* effect has been also used recently to control conformations of reactants without introducing strain in the first example of a 5-*endo*-dig cyclizations of carbon-centered radicals (08JA10984).

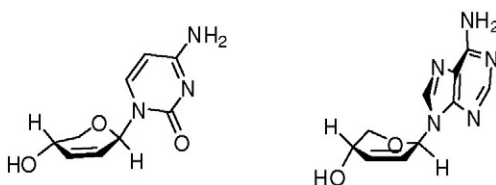
Most recently, Gilmour and coworkers reported theoretical (DFT) and X-ray crystallographic evidence of a fluoroimine *gauche* effect around the C=N–CH₂–CH₂–F segment. The preference of the *gauche* over the *anti* conformation in β -fluoroimines **9** was explained in terms of a hyperconjugative $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-F}}$ stereoelectronic interaction (Scheme 20) (11CEJ8850).



Scheme 20

4. ALTERNATIVE RATIONALIZATIONS OF THE ANOMERIC EFFECT

The complex nature of the anomeric effect has motivated researchers to propose alternative models to explain it. Thus, Doboszewski et al. justify the pseudoaxial conformational preference of purine and pyrimidinic bases in analogs of nucleotides as the result of a combination of axial-stabilizing $\pi \rightarrow \sigma_{\text{C-N}}^*$ interaction originated by the presence of a double bond in the tetrahydropyran ring, and steric repulsions present in the equatorial conformers (Scheme 21) (95JOC7909).



Scheme 21

Very recently, Benn and collaborators explained the experimentally observed axial conformational preferences of 2-cyano derivatives of oxane, thiane, and selenane in terms of an attractive *through-space* $n \rightarrow \pi^*$ interaction between the nonbonded lone electron pair of the endocyclic heteroatom and the π^* orbital of the axial cyano group. This proposal was supported with computational (NBO) analysis (Scheme 22) (10CJC831).

Another interesting theory was proposed by Vila and Mosquera within the framework of the Quantum Theory of Atoms in Molecules (QTAIM) procedure. In particular, computational studies on 2-methoxyoxane and 2,2-dimethoxypropane as model systems, led to the conclusion that the



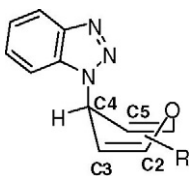
X = O, S, Se

Scheme 22

anomeric stabilization is due to the flow of electron density from the central hydrogens to adjacent carbons and oxygens, which releases electron–electron repulsions between lone electron pairs and central hydrogens (07CPL22). Mosquera and co-workers also evaluated the conformational preferences of model compounds containing the N–C–N segment and their results indicate that in contrast with molecules containing the O–C–O anomeric unit, the calculated variations of electron population due to conformational changes are not in keeping with the stereoelectronic model of the anomeric effect. Again, it is suggested that minimization of the electron–electron repulsion in lp–N–C–N segments is achieved by depletion of electron density from the central hydrogens when they display more *gauche* arrangements to nitrogen lone pairs (07JPC(A)8491).

In this regard, Cortés-Guzmán and colleagues present a computational procedure that takes advantage on the principle of additivity and transferability of functional group energies as defined by the gradient of electron density. In particular, the heterocyclic systems were divided and analyzed as ring and substituent groups, leading to the conclusion that the conformational preference is the result of an energetic balance between those groups, owing to electron transfer between the two groups. The increase in stability of the axial substituent is caused by charge transfer from the heterocyclic ring toward the axial substituent. It is proposed that the role of the heteroatom in the anomeric effect is to compensate the destabilization of the anomeric CH group linked to the substituent at the axial conformation (10PCCP13261).

Minimization of the *exo*-anomeric effect by the presence of anomeric substituents that are good acceptors but poor donors may lead to interesting manifestation of anomeric effects in heterocyclic derivatives. For example, Katritzky and co-workers reported evidence for the existence of a “vinylogous” anomeric effect in a group of benzotriazole-substituted heterocycles, presenting a lengthening of the C4–N pseudoaxial bond (by an average of 0.029 Å), a shortening of the endocyclic C4–C5 bond (by an average of 0.023 Å), an increase in C3–C4–C5 bond angle (to a value higher than the standard tetrahedral value), and a decrease in C2–C3–C4–N dihedral angle (to less than 125°), which reveal a

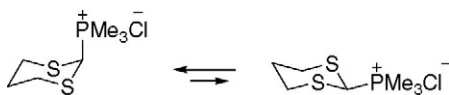


Scheme 23

stereoelectronic interaction between the ring and the $\sigma^*_{\text{C4-N}}$ orbital consistent with a “vinylogous” anomeric effect (Scheme 23) (01T3309).

On the other hand, Anderson and co-workers (97JCS(P2)2633), Alabugin and co-workers (03JA14014), and Juaristi and co-workers (07ACR961) studied the structural and energetic consequences of the homoanomeric effect (when a saturated center intervenes between a donor and an acceptor σ^* orbital). These interactions can control conformational equilibria, are responsible for characteristic spectroscopic behavior, and may increase reaction rates by preorganization of substrates into a suitable geometry for the lone electron pair assisted intramolecular rearrangements.

With regard to the “reverse anomeric effect” (the preference for the equatorial conformation exhibited by anomeric substituents bearing positive charge), much recent experimental and theoretical work argues against the generality and even the very existence of this effect. For example, in the conformational analysis of 1,3-dithian-2-yltrimethylphosphonium chloride Juaristi and Cuevas found a definite preference for the axial orientation, $\Delta G^\circ_{300\text{K}} = 0.36$ kcal/mol, which reflects a substantial $\text{S}-\text{C}-\text{PMe}_3$ anomeric effect, worth at least 2.2 kcal/mol, therefore violating expectations in terms of the so-called “reverse anomeric effect” (Scheme 24) (93JA1313).



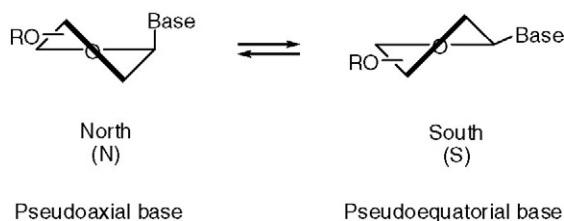
Scheme 24

Perrin and collaborators determined by ^1H NMR the proportions of axial anomers of various glucosylamines and their conjugate acids to reinvestigate this controversial effect. The observed change upon *N*-protonation was small and could be accounted for by steric effects and an enhanced anomeric effect, without any reverse anomeric effect. (94JA8398, 95T11901, 03JA8846). A similar conclusion was derived by Graczyk and Mikołajczyk (93PS313), Chan et al. (95JCS(P2)45), Kirby and co-workers (98CHC1695), and Pinto and co-workers (00JOC220), and others (01JOC1097, 06JOC5892).

5. PHYSICAL SENSING AND “TUNING” OF THE ANOMERIC EFFECT

The well-established solvent effect on the magnitude of the anomeric effect (when the difference in electrostatic interactions between axial and equatorial conformers suggests that polar solvents stabilize the more polar equatorial conformation; that the axial preference of the polar, electronegative anomeric substituent decreases with increasing solvent dielectric constant) has been amply reconfirmed (91JA1553, 94JPC6452, 94JPC9477, 94TS159, 95CAR129, 95MI5, 96JA541, 96JCC1068, 98CAR1, 98JA2168, 98JPC(B)4089, 04TAC196). Therefore, the solvent effect is one of the factors that “modulates” the conformational preference in heterocycles containing an anomeric segment X–C–Y. Nevertheless, there exist additional factors that can influence the magnitude of the anomeric effect, such as the influence of the entropic thermodynamic parameter (92T6161, 92TL2271).

On the other hand, heterocyclic bases present in nucleosides and nucleotides are involved in the anomeric effect, which results in the energetic preference of N-type (pseudoaxial nucleobase) conformation over S-type (pseudoequatorial nucleobase) conformation by interaction of a lone electron pair at the endocyclic oxygen and the antibonding σ^* orbital of the glycosyl bond (Scheme 25). Protonation of the nucleobase enhances the



Scheme 25

endo stereoelectronic interaction resulting in the increased population of N-type conformations (93JA9734, 02BMC2723).

Based in this observation, Chattopadhyaya et al. suggest that the strength of the anomeric effect can be “tuned” in nucleosides by modifying the electronic character of the purine base as the pH of the medium changes, going from neutral to protonated species (97JOC8800). In the same context, Polak and Plavec showed that, as anticipated, interaction of Zn^{2+} and Hg^{2+} ions with N7 in deoxyguanosines strengthens the anomeric effect, which is evident from the increase in the population of N-type pseudoaxial isomers (99EJI547). (See also: 01JCS(P2)1433.)

Recently, Cocinero et al. reported that *N*-acetyl-*L*-phenylalanine can bind to methyl D -galactose, and claimed that the anomeric effect can be

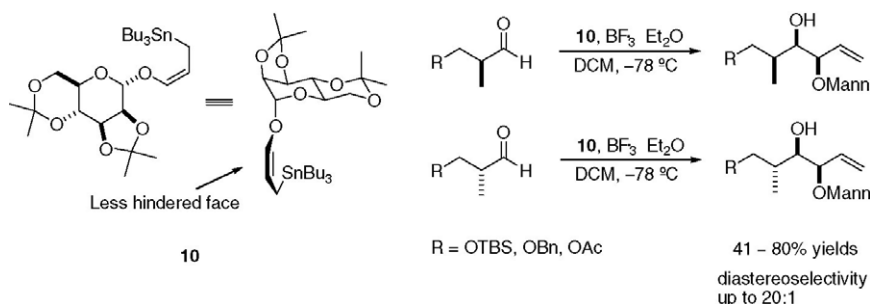
sensed by IR stretching frequency changes when comparing the β - with the α -complex. This spectroscopic behavior was attributed to the lone pair electron density change on the endocyclic oxygen atom (11NAT76). Nevertheless, Mo and co-workers have provided computational evidence that the sensor cannot sense the anomeric effect as claimed. In particular, replacement of the endocyclic oxygen in the carbohydrate with a methylene group, which disables the anomeric effect, results in similar spectroscopic shifts (11JA13731).

Two-electron/two-orbital hyperconjugative interactions of the type responsible for the anomeric effect depend on the relative orientation of bonds and lone pairs in a molecule and are also inversely proportional to the energy difference between the interacting orbitals. Spectroscopic manifestations of stereoelectronic interactions are particularly useful experimental signatures of these effects, which can be utilized for testing molecular models. Empirical observations together with theoretical interpretations in cyclohexane and six-membered heterocycles confirm the relevance of $\sigma_{C-H_{ax}} \rightarrow \sigma^*_{C-H_{ax}}$, $n_X \rightarrow \sigma^*_{C-H_{ax}}$ ($X = O$ or N), $\sigma_{C-S} \rightarrow \sigma^*_{C-Heq}$, $\beta-n_O \rightarrow \sigma^*_{C-Heq}$, $\sigma_{C2-H_{ax}} \rightarrow \pi^*_{C=Y}$ ($Y = O, S, CH_2$) and $\sigma_{C2-H_{ax}} \rightarrow \sigma^*_{S-O_{ax}}$ two-electron/two-orbital stereoelectronic interactions that weaken the acceptor (or donor) C–H bonds and attenuate the Fermi contribution to the one-bond ^{13}C – 1H coupling constants (90CJC1051, 92CHC1689, 92TL1847, 92TL6927, 93JCS(P2)601, 94JA5796, 97JA7545, 99JPC(A)932, 00JOC3910, 02JA13088, 03JA14014, 04JOC7266, 05T7349, 06JPC(A)7703, 06MRC178. For a review, see: 07ACR961).

6. APPLICATIONS OF THE ANOMERIC EFFECT IN ORGANIC SYNTHESIS

One purpose when evaluating the anomeric effect in model compounds is to understand it and eventually to apply it in anomerically driven stereospecific and/or stereoselective transformations. In effect, the systematic study of the anomeric effect in model compounds, in particular the available quantitative or semiquantitative information related to the magnitude of anomeric interactions in O–C–O, O–C–S, S–C–S, N–C–O, N–C–N, and other segments, allows for the design of synthetic strategies based on anomerically driven stereoselective reactions, or highly biased equilibria among isomeric products. In this section, a few selected examples of the application of anomeric interactions in stereoselective organic transformations are presented.

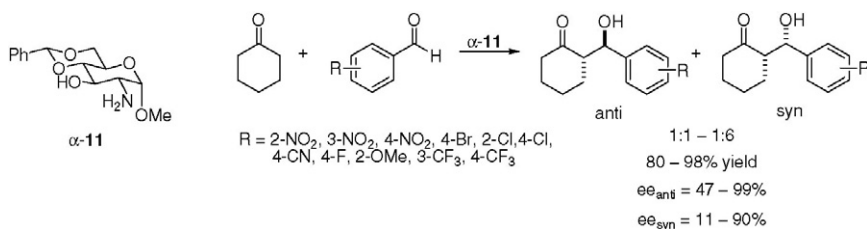
From a meticulous analysis, Roush and VanNieuwenhze developed novel sugar-based chiral reagent **10** for the asymmetric alkylation of aldehydes. Catalyst **10** was designed in the expectation that significant diastereofacial bias would be exerted as a consequence of the conformational



Scheme 26

restrictions imposed by the anomeric effect. Indeed, application of catalyst **10** in the asymmetric diastereoselective synthesis of *syn*-diols, proceeded with stereoselectivities as high as 20:1 (Scheme 26) (94JA8536).

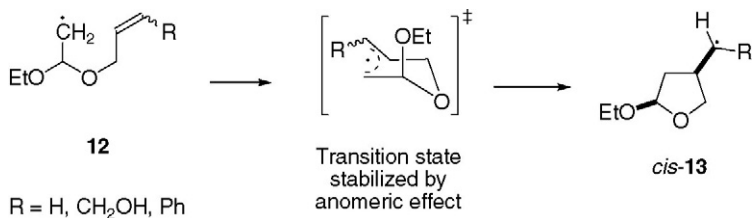
In this context, Agarwal and Peddinti synthesized novel α - and β -glucosamine organocatalyst **11**, which was employed in the asymmetric aldol reaction between cyclohexanone and aryl-substituted aldehydes. These researchers observed that the α -anomer catalyzes the reaction more efficiently than the β -anomer, affording the desired products in high enantioselectivities (Scheme 27) (11JOC3502).



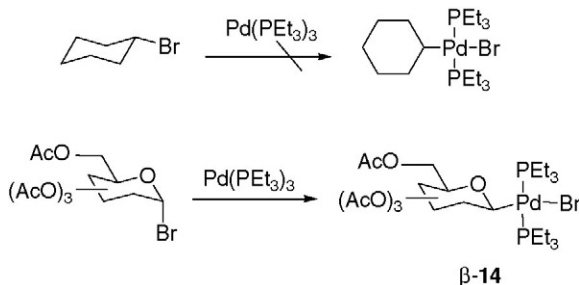
Scheme 27

Interestingly, the anomeric effect has led to high selectivity in synthetically useful reactions where free radicals are involved (95JOC3871, 98T6919, 99T3245, 01JA11870, 03JOC7439). In this regard, Beckwith and Page reported the synthesis of substituted tetrahydrofurans by stereocontrolled radical cyclization, where the anomeric effect stabilizes pseudoaxial anomeric radicals in the transition state. In this manner, compounds **12** undergo 1,5-*exo*-cyclization to afford *cis*-2,4-disubstituted tetrahydrofurans **13** (Scheme 28) (98JOC5144).

In a recent publication, Gagné and co-workers showed that the oxidative addition of bromo- α -glucose derivative to Pd(PET)₃ is significantly accelerated by the anomeric effect to obtain selectively the β -glucosyl isomer **14**. In contrast, with cyclohexyl bromide as substrate, no reaction takes place (Scheme 29) (11OM2646).

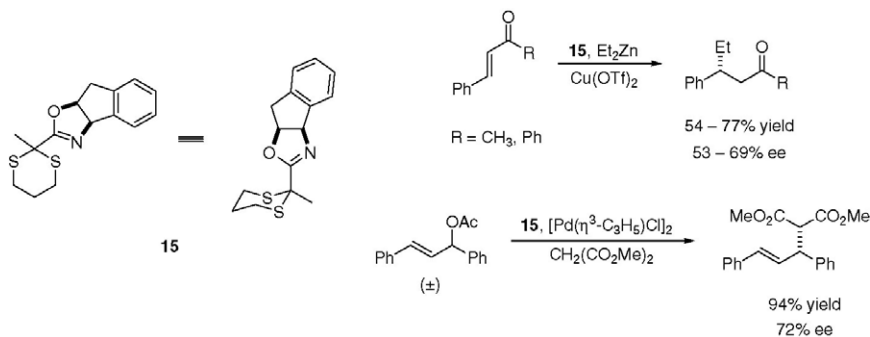


Scheme 28



Scheme 29

In this context, Capitò et al. determined the axial conformational preference of oxazoline-1,3-dithiane **15** by means of NMR and X-ray analysis, demonstrating that its conformation is driven by the anomeric effect. Furthermore, **15** was evaluated as ligand for asymmetric catalysis in the addition of Et_2Zn to enones affording enantiomeric excesses up to 69% ee. Similarly good enantioselectivity was obtained in Pd-catalyzed allylic alkylation using catalyst **15** (Scheme 30) (05TA3232).



Scheme 30

For other interesting applications of the anomeric effect in synthetic organic chemistry, see: (94JOC6404, 97T3417, 97TL7379, 98JA8328, 99TL3209, 02CEJ1336, 03JOC8142, 05EJO2903, 05JA8260, 05TA3232, 06JMC5750, 06TL3665, 07JST118, 07TL5683, 08JOC6970, 08JOC7266, 08T2042, 10EJO5263, 10H1891).

7. CLOSING REMARKS

The nature of anomeric effect is still a matter of controversy, and it is interesting to note that this challenging situation has attracted the attention of chemists and physicists for over half a century. It has been shown that steric, electrostatic, and stereoelectronic factors are *all* important forces that influence the anomeric effect, and therefore the conformational arrangement of heterocycles. It is evident that further investigation of this important effect, with the use of new model compounds and application of novel and insightful experimental and computational strategies will lead to progress in the understanding of the fundamental nature of the anomeric effect. Of course, it is possible to anticipate and/or verify the existence of the anomeric effect, especially in heterocyclic systems. Furthermore, through proper design it is possible to use the anomeric effect in our favor, especially as its application can afford highly valuable stereoselective synthetic reactions.

LIST OF ABBREVIATIONS, SYMBOLS, AND ACRONYMS

π	pi orbital
π^*	antibonding pi orbital
σ	sigma orbital
σ^*	antibonding sigma orbital
B3LYP	Becke 3-Lee, Yang, Parr functional
BLW	block-localized wave function
DCM	dichloromethane
DFT	density functional theory
CD	circular dichroism
ee	enantiomeric excess
IR	infrared
J	coupling constant
MCPBA	<i>meta</i> -chloroperbenzoic acid
MMPP	magnesium monoperoxyphthalate
MP2	perturbation theory of Møller–Plesset of order two
n	lone electron pairs

NBO	natural bond orbital
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
OTBS	<i>O</i> - <i>tert</i> -butyldimethylsilyl
pD	deuterium ion potential
QTAM	Quantum Theory of Atoms in Molecules

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CHAPTER 3

Biginelli Condensation: Synthesis and Structure Diversification of 3,4-Dihydropyrimidin-2(1*H*)-one Derivatives

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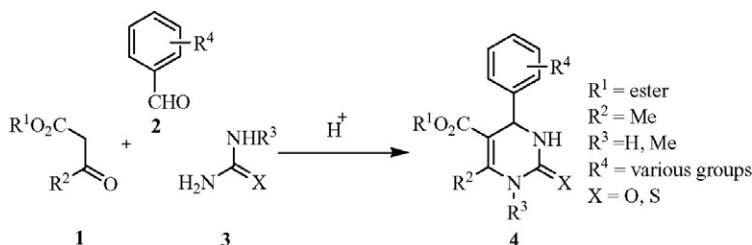
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¹Dedicated to Professor Harjit Singh on the occasion of his 73rd birthday.

1. INTRODUCTION

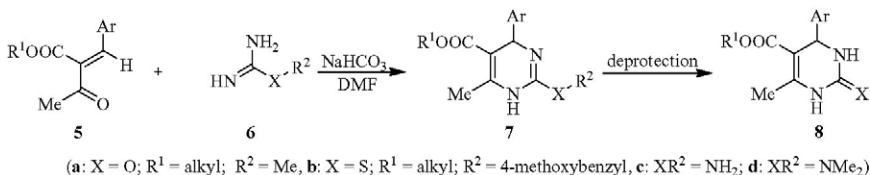
Since the first review by Kappe (93T6937), which appeared exactly 100 years after the seminal report by Pietro Biginelli on the condensation of ethyl acetoacetate **1**, an aromatic aldehyde **2** and urea **3**, using protic conditions, leading to the synthesis of reduced pyrimidines **4** (Scheme 1) (93G360), there has been an unprecedented research activity on the chemistry and biology of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) termed Biginelli compounds. The review commemorating “100 years of the Biginelli dihydropyrimidine synthesis” presented an overview on the chemistry of Biginelli compounds as well as their structural variants. Apart from fundamental oxidation and reduction reactions, this period also saw exploration of reactions on the C-5 and the C-6 substituents of the dihydropyrimidinone core.



Scheme 1

The inherently asymmetric DHPMs are structural analogs (aza analogs) of the well-established 4-aryl-1,4-dihydropyridines (DHPs) of nifedipine type (98MI1). Interest shifted not only to explore their pharmacological profile similar to clinical DHP-type calcium channel modulators, but also to get further insight into molecular interactions at the receptor level. Such work was first initiated by Khanina et al. in 1978 (78KFZ72) and more systematically explored by Atwal et al. (90JMC1510, 90JMC2629, 91JMC806, 92JMC3254).

Atwal's synthetic approach relied on what later became known as the Atwal modification, reported in 1987 (87H1185, 87H1189). This approach involved an initial Michael addition of an unsaturated ketoester **5** to a suitably protected urea, thiourea, or guanidine derivatives **6** in the presence of sodium bicarbonate, furnishing dihydropyrimidine derivatives **7**, which upon deprotection using either HCl (in case of pyrimidinones) or trifluoroacetic acid/ethanethiol (thione analogs) furnished Biginelli DHPMs **8** (Scheme 2), expeditiously. Atwal's approach provided further impetus in



Scheme 2

exploring their cardiovascular activity with special emphasis on understanding their structure–activity relationships. He undertook both *in vitro* and *in vivo* studies (90JMC1510, 90JMC2629, 91JMC806, 92JMC3254). This aspect was further reviewed by Kappe in 2000 (00MI2) and later by us in 2009, by including activities other than calcium channel blocking (09MMCIAE95).

In 2000 and in 2003, Kappe compiled the work on various solid-phase modifications suitable for combinatorial chemistry (00ACR879, 03MI12). This period also witnessed an unambiguous evaluation of the mechanism of the classical three-component Biginelli condensation involving the formation of an *N*-acyliminium ion intermediate (97JOC7201), ruling out the earlier suggestions of Folkers and Johnson of the formation of an *N,N'*-benzylidene bis-urea intermediate from an aldehyde and urea (33JA3781) or a carbenium ion (through acid-catalyzed aldol reaction of aldehyde and ethyl acetoacetate), suggested by Sweet and Fissekis (73JA8741).

Structure–activity profiles for a series of DHPM calcium channel modulators were first reported in 1995 by Rovnyak et al. using a set of enantiomerically pure DHPMs (95JMC119). Calcium channel modulation (antagonist versus agonist) activity is dependent on the absolute configuration at C-4 of DHPMs and a new binding-site model proposed that the orientation (*R*- or *S*-configuration) of the C-4 aryl group acts as a “molecular switch” between antagonist (aryl-group up) and agonist (aryl-group down) activity. Further, a substituent on the axially oriented C-4 aryl group preferred the synperiplanar (relative to C4–H) orientation in the receptor-bound conformation and bisects the boat-like dihydropyrimidine ring. With respect to the C5–C6 double bond of the dihydropyrimidine ring, a *cis* carbonyl ester was found mandatory for optimum calcium channel modulating activity.

Interestingly, only the left-hand side (enamino ester) of the DHPM molecule has been proposed to be essential for activity. Detailed pharmacological investigations by Rovnyak et al. using a large set of DHPM derivatives have led to the identification of N-3 functionalized DHPM calcium channel blockers (92JMC3254).

DHPMs hold the potential diversity-oriented centers around the scaffold (05PAC155), which leads to a renaissance in the structural elaboration of the DHPM scaffold (93T6937, 05PAC155).

2. GENERAL SYNTHETIC ROUTES TO 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES

A number of high-yielding variants of the traditional three-component Biginelli condensation employing a variety of catalysts, reagents, and reaction conditions/techniques have been developed (09MI15) these are beyond the scope of this review. Reference is made to some excellent reviews (Tables 1–4). However, scaffold decoration of Biginelli DHPMs is presented by us.

Table 1. Different synthetic methods for DHPM synthesis (up to 2003)

2002 and before 2002	H ₂ SO ₄ (00JOC6777, 06BMC4479, 33JA3361)	MWI/sf (02JCS(P1)1845)
Amberlyst-15/AcOH/MWI (00JCR(S)354)	InBr ₃ (02MI2, 02T4801, 03MI6)	2003
Nafion-H/AcOH/MWI (00JCR(S)354)	La(OTf) ₃ /100 °C/sf (02MI4, 03SC1459)	H ₃ PW ₁₂ O ₄₀ (03CJOC93, 04JCR(S)190, 05JMCCF2 (242)173, 06BMC2463)
CdCl ₂ /MeCN (04S1253)	Montmorillonite KSF-clay (99TL3465, 00MI5, 03SL1509)	Bi(OTf) ₃ /MeCN/rt (03SL67)
CoCl ₂ × 6H ₂ O/HCl/EtOH (02MI5)	AcOH (69CHE261, 74MI, 76CHE191, 02CHE1000)	CeCl ₃ /THF (03MI1)
FeCl ₃ × 6H ₂ O/HCl/MWI/sf (02MI3)	FeCl ₃ × 6H ₂ O/EtOH (00CJOC815, 02S466, 05MI11, 07MI20)	Al ₂ O ₃ (acidic)/MWI/sf (03MI13, 04IJC(B)2485)
CuCl ₂ × 2H ₂ O/HCl/MWI/sf (02MI3)	HCl/EtOH (88USP4675321, 88USP4738965, 91MI, 91MI135, 93G360, 00JFC1701MI5, 05PS1713, 08PS1911)	CeCl ₃ × 7H ₂ O/sf (03JOC587)
SnCl ₂ /HCl/MWI/sf (02MI3)	TsOH/THF (01MI5)	Cu(OTf) ₂ (03TL3305)
ZnCl ₂ /HCl/MWI/sf (02MI3)	HCl/MeOH (99JCS(P1)307, 07JHC669, 07JHC745)	H ₃ BO ₃ (03TL6153, 04MI2, 06H925, 06MI5)
HCl/MWI (95IJC(B)151, 98JFC17, 00JCS(P1)1363, 06PS2653)	I ₂ /solvent (04S2091, 04TL9111)	In(OTf) ₃ /MWI/Na ₂ SO ₄ (03JHC879)
HCl/H ₂ O/20 °C (67PJS83, 04SL279)	InCl ₃ /THF (00JOC6270, 03MI1)	NH ₂ SO ₃ H (03MI14, 05MI1, 06CJOC975)
LaCl ₃ × 7H ₂ O/HCl/EtOH (00TL9075, 02MI1)	LiBr (02CL1038, 03TL2757, 08AXC(E)0929)	PhCH(Me)N ⁺ Me ₂ Bu Br ⁻ (03TL8173)
LiClO ₄ /MeCN (01S1341)	TFA (03TL2757, 08AXC(E)0929)	Ph ₃ PH ⁺ ClO ₄ ⁻ /MeCN (03MI7)

LiOTf/MeCN (01S1341)	4-MeC ₆ H ₄ SO ₂ H (98CHE848)	Si-MCM-41 supported metal halides/MWI/sf (03CCAOAC449)
Mn(OAc) ₃ × 2H ₂ O (01TL7873)	PPE/MWI (99S1799, 03PS1241, 03PS1269)	Silica/Fe (03T1553)
Montmorillonite K10 clay/sf (99MI2157, 04IJC(B)2485)	TMSCl (92KFZ116, 04SC3167, 05EJO2354, 05H133, 06MI3, 08JFC625)	SmCl ₃ × 6H ₂ O/Montmorillonite/sf/MWI (03MI3)
NH ₄ Cl (03TL857, 06MI8)	TAFF/neat/IR-light (01MI4, 03MI2)	THF/ <i>hν</i> (03PS495)
AcOH/EtOH (03MI11, 06IJC(B)2091)	ZrCl ₄ (02TL2657, 07TL5777)	TsOH/AcOH/MWI (03MI5)
BiCl ₃ /MeCN (01SL863)	Ytterbium(III)-resin (01TL7975)	Yb(OTf) ₃ /4 mol sieves/THF (03JOC6172)
Bi(NO ₃) ₃ × 5H ₂ O/sf (04SC1551)	NiCl ₂ × 6H ₂ O (02CJOC788, 02S466, 07MI20)	Silica-SO ₃ H (03H2435, 03TL2889, 07SC47)
CAN/MeOH/sonication (01JCS(P1) 1939)	PPE/THF (98SL718, 00JCS(P1)4382)	TMSI/MeCN/rt (03SL858, 05HCA2996)
Oxone/MeOH/sonication (01JCS(P1) 1939)	TsOH (02SC1847, 07JHC455)	VCl ₃ /MeCN (03TL6497, 07JHC483)
CuCl/BF ₃ × Et ₂ O/AcOH (98JOC3454, 01TL4495)	Zeolites/toluene (01MI2)	PPA/PEG400-linked acetoacetate/sf/MWI (03S262)
FeCl ₃ × 6H ₂ O/MWI/sf (02SC147, 04SC3335)	Yb(OTf) ₃ (00JOC3864, 02TL5913, 03SC1459)	Zn(OTf) ₂ /100 °C/sf (03MI4)
FeCl ₃ × 6H ₂ O/HCl/EtOH (00SL63)	ILs (01TL5917, 05HCA986, 05MI12, 06MI15, 06SC1503, 07JICS393, 07JMCCF2 (274)208, 07MI21)	BF ₃ ·OEt ₂ /CuCl/AcOH/THF (03MI9)
HCl/AcOH (32JA3751, 07PS1589)	PPE/MWI/sf (00T1859)	ZnBr ₂ /DCM/reflux (03S2358)

Table 2. Different synthetic methods for DHPM synthesis (from 2004 to 2006)

2004	2005	Ce(NO ₃) ₃ × 6H ₂ O/sf/80 °C (06MI11)
Ag ₃ PW ₁₂ O ₄₀ /H ₂ O (04EJO552)	Bi(NO ₃) ₃ /MeCN (05MI2, 07MI14)	Cl ₃ CCO ₂ H/EtOH (06MI17)
Al(HSO ₄) ₃ /MeOH (04PJC385)	Hydroxyapatite/metal halides (05LOCEC7 561)	CuBr ₂ /EtOH (06MI14)
Al(HSO ₄) ₃ /sf (04PJC385)	CaAl ₂ Si ₇ O ₁₈ × 6H ₂ O/AcOH (05JMCCF2(236) 216)	Cu(NTf ₂) ₂ /H ₂ O/rt (06TL7861)
BiONO ₃ /MeCN (04SC3821)	CoCl ₂ × 6H ₂ O/MWI/sf (05IJC(B)762)	Yb(NTf ₂) ₃ /H ₂ O/rt (06TL7861)
Bu ₄ NHSO ₄ /80 °C/sf (04PS2169)	MnCl ₂ × 4H ₂ O/MWI/sf (05IJC(B)762)	Ni(NTf ₂) ₂ /H ₂ O/rt (06TL7861)
CuCl ₂ × 2H ₂ O/CuSO ₄ × 5H ₂ O/MWI (04SL235)	SnCl ₂ × 2H ₂ O/MWI/sf (05IJC(B)762)	Dowex50W/H ₂ O/70 °C (06H181)
FeCl ₃ × 6H ₂ O/TMSCl (04HCA2608)	Graphite (05CJOC1265)	Dowex50W/130 °C/sf (06TL4205)
In(OTf) ₃ /EtOH (04JMCCF2(217)47)	I ₂ /Al ₂ O ₃ /MWI/sf (05TL1159)	H ₃ PMo ₁₂ O ₄₀ /MeCN (06BMC2463)
IL/ultrasound/30 °C (04MI3)	In(OTf) ₃ /MeCN (05MI13)	H ₄ SiW ₁₂ O ₄₀ /MeCN (06BMC2463)
MgBr ₂ /sf (04SC171)	MgCl ₂ × 6H ₂ O/80 °C/sf (05SC829)	H ₃ PW ₁₂ O ₄₀ /sulfated ZrO ₂ /MWI/sf (06IJC(B) 2325)
NbCl ₅ /rt (04CL926)	BiOClO ₄ × <i>n</i> H ₂ O/MeCN (05IJC(B)1304)	I ₂ /ultrasound (06LOCEC7 523)
HCl/MeCN/MWI (04IJC(B)135)	Ca ₁₀ (PO ₄) ₆ F ₂ /metal halides (05CCAOAC455)	KAl(SO ₄) ₂ × 12H ₂ O/SiO ₂ /sf (06MI1)
KHSO ₄ /glycol (04JHC253, 04SL537, 05MI7, 07S2278)	Polyaniline salts and complexes (05JMCCF2 (233)9, 06JAPNAB1741)	Mg(ClO ₄) ₂ /ultrasound/EtOH (06JMCCF2(253) 207)
Mg(ClO ₄) ₂ /MeCN (04CJOC1111)	PVP-DVB/CeO ₂ /H ₂ O (05TL8221)	Nafion NR-50/MeCN (06JMCCF2(247)99)
CaCl ₂ /MWI/sf (04IJC(B)2018)	RuCl ₃ (05S1748, 06JHC777)	(NH ₄) ₂ HPO ₄ /sf (06JICS98)
NaHSO ₄ /SiO ₂ (04JMCCF2(221)137)	SrCl ₂ × 6H ₂ O/HCl/sf (05MI4)	ClSO ₃ H /60 °C/sf (06MI18)
Nd(CH ₃ SO ₃) ₃ /EtOH (04MI5)	TiCl ₄ (05MC150, 08PS1552)	H ₃ PW ₁₂ O ₄₀ /MWI/sf (06CCAOAC457)
(L)-Proline/sf (04CL1168)	Uronium hydrogen sulfates (05H1177)	H ₃ PW ₁₂ O ₄₀ /SiO ₂ /MeCN (06JMCCF2(250)57)

SnCl₂ × 2H₂O/MeCN (04IJC(B)1485, 04MI4)
ZnCl₂/80 °C/sf (04S1047)

PVP-DVB/CuSO₄/MeOH (04CCAOAC511)
ZnI₂/MeCN/300 MPa (04TL6195)
Envirocat EPZ10/toluene (04MI1)
Polyaniline/bismoclite complex (04SL1285)
SnCl₂ × 2H₂O/LiCl (04SC1559)
TMSOTf/MeCN/rt (04SL279)
NBS/EtOH/MWI (04S1239)
Yb(OTf)₃/MeCN/MWI (04OL771)
80 °C/sf (02MI7, 04MI7)
MeSO₃H/EtOH (04SC3009)
CuCl₂/LiCl (04SC2665)

Natural phosphate/metal halides (05SC2561)
Sc(OTf)₃/MeCN (05SC2645)

Si(OEt)₄/FeCl₃ (05T4275)
SmI₂ (05EJO1500, 07MI17)
Sulfated SnO₂/sf (05HEC399)
TEBA/sf/100 °C (05MI3, 07JHC697)
Yb(OTf)₃/chiral ligand/THF/rt (05JA16386)
n-Bu₂SnO/sf/100 °C (05CRE171)
Sr(OTf)₂/sf (05TL6037)
ZnCl₂/MWI/sf (05IJC(B)823)
TsOH/H₂O (05TL1901)

2006
Ultrasonication/HCl/TFA
(06LOCEC7 201)

K₅CoW₁₂O₄₀ × 3H₂O/sf (06H1217)
Binol-based phosphoric acids/CH₂Cl₂/rt
(06JA14802)
β-Cyclodextrin/HCl/EtOH (06MI9)
Supported H₃PMo₁₂O₄₀/MeCN (06MI2)
H₃PMo₁₂O₄₀/AcOH (06CCAOAC373)
H₃PW₁₂O₄₀/heat/sf (06CCAOAC843, 08MI1)
H₃PW₁₂O₄₀/SiO₂/80 °C/sf (06CCAOAC843)
H₂SO₄/sf/MWI (06MI6)
Zeolite E4a/EtOH (06SC129)
Zn(NH₂SO₃)₂/EtOH (06SC835)
Zn(NO₃)₂/EtOH (06CJOC333)
PEG-SO₃H/MWI/sf (06SC451)
(L)-Pro-OMe × HCl (06TL55)

Table 3. Different synthetic methods for DHPM synthesis (from 2006 to 2009)

2006	CoCl ₂ × 6H ₂ O/EtOH (07MI20)	Al ₂ O ₃ –SO ₃ H (08JICS26)
SbCl ₃ –Al ₂ O ₃ /MWI/sf (06CJC433)	Cu(BF ₄) ₂ /neat (07CCAOAC1929)	CuCl ₂ × 2H ₂ O/HCl/grinding (08IJC(B)434)
Sr(NO ₃) ₂ /AcOH (06JMCCF2(258)367)	CuCl ₂ × 2H ₂ O/MWI (07MI1)	Fe(HSO ₄) ₃ (08JICS96)
Zn(NH ₂ SO ₃) ₂ /MWI (06MI7)	CuI (07CCAOAC179)	HClO ₄ –SiO ₂ (08MI2)
PhB(OH) ₂ /MeCN (06TL5697)	DSA/H ₂ O/rt (07MI9)	LaCl ₃ /graphite (08BMC278)
Two-phase conditions (06CRE377)	FeCl ₃ × 6H ₂ O/EtOH/MWI (07CJOC1034)	LnCl ₃ × 7H ₂ O (08SL105)
Sulfated ZrO ₂ /MWI (06CL1074, 06MI12)	H ₄ PMo ₁₁ VO ₄₀ /EtOH (07CCAOAC279)	Scolecite/MeCN (08MI3)
ZrOCl ₂ × 8H ₂ O/sf (06SC2307, 07TL5777)	H ₄ SiW ₁₂ O ₄₀ × xH ₂ O/AcOH (07H373)	Sulfonic salicilic acid (08MI8)
TsOH/MWI/sf (06TL2423)	KH ₂ PO ₄ /glycol (07MI5)	ZrO ₂ -nanopowder/MWI/sf (08LOCEC7142)
2007	MgSO ₄ /sf/rt (07AJC435)	Pb(NO ₃) ₂ /MeCN (08MI9)
Baker's yeast (07TL4569)	Nafion-H resin/EtOH (07JMCCF2(268)221, 07MI6)	Ph ₃ P/sf/100 °C (08TL6119)
Ca(HSO ₄) ₂ /90 °C/sf (07MI8)	NH ₂ SO ₃ H/sf (07SC47)	Pr(MeSO ₃) ₃ /EtOH (08MI11)
Zn(HSO ₄) ₂ /90 °C/sf (07MI8)	PEG-400/100 °C/sf (07MI10)	Pyrazolidine dihydrochloride (08TL3238)
Oxone/90 °C/sf (07MI8)	Silica sulfuric acid/[Bmim]Br/100 °C (07LOCEC768)	SiCl ₄ /DMF/MeCN/rt (08T5023)
CuSO ₄ × 5H ₂ O/EtOH (07MI20)	SiO ₂ /ZnCl ₂ (07CJC197)	MoO ₃ /Al ₂ O ₃ /sf (08CCAOAC499)
Fe(CF ₃ CO ₂) ₃ or Fe(OTf) ₃ /sf (07CCAOAC2119)	ZnI ₂ /MWI/sf (07T1981)	Ca(NO ₃) ₂ ·4H ₂ O/80 °C/sf (08MI6)
GaCl ₃ /MWI/sf (07IJC(B)1886)	PhCO ₂ H (07CRE181)	Fe(ClO ₄) ₃ /MeCN/reflux (08MI7)
GaBr ₃ /MWI/sf (07IJC(B)1886)	P ₂ O ₅ /EtOH (07IJC(B)1545)	DDQ/MeCN/reflux (08JHC1225)
HBF ₄ /45 °C/sf (07CCAOAC123)	TaBr ₅ /75 °C/sf (07TL5407)	Chiral IL/THF/rt (08T1420)
HClO ₄ (07CRE175)	TiCl ₄ /MgCl ₂ /4CH ₃ OH (07JMCCF2(272)53)	ZnCl ₄ /ultrasound/EtOH (08MI12)

$\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \times 24\text{H}_2\text{O}$ /sf (07SC3907)
 $\text{KHSO}_4/\text{AcOH}$ (07S2782)
 $\text{AlBr}_3/\text{MeCN}$ (07IJC(B)1690)
 $(n\text{-C}_3\text{H}_7\text{PO}_2)_3/\text{AcOEt}$ (07TL1421)
 $\text{Cu}(\text{OAc})_2 \times 2\text{H}_2\text{O}/\text{EtOH}$ (07MI20)
 $\text{Cu}/\text{silica xerogel composite}$ (07LOCEC739)
 $\text{HClO}_4/\text{sf}/\text{MWI}$ (07JHC979)
 $\text{HCO}_2\text{H}/\text{sf}/\text{MWI}$ (07MI7)

Metallophthalocyanines (07JMCCF2(268)134)
 NaBF_4 (07MI11)

AlCl_3 (07CRE251, 10IJC(B)360)
 Amino acetic acid (07MI15)
 $\text{Bi}(\text{NO}_3)_3/\text{MWI}/\text{sf}$ (07TL7392)
 $\text{ClCH}_2\text{CO}_2\text{H}$ (07BMC3508)

Trichloroisocyanuric acid (07CCAOAC1641)
 ZnBr_2/sf (07MI19)
 $\text{Zn}(\text{ClO}_4)_2 \times 6\text{H}_2\text{O}/80^\circ\text{C}$ (07JHC211)
 $\text{PSSA}/\text{H}_2\text{O}/\text{MWI}$ (07TL7343)
 $\text{SbCl}_3/\text{MeCN}$ (07T11822)
 Silica-chloride/sf (07MI18)
 Silica-triflate/sf (07MI3)
 $\text{SiO}_2\text{-Si}(\text{CH}_2)_3\text{SO}_3\text{H}/\text{MeCN}$ (07JMCCF2(266)50)
 TiCl_3/THF (07MI16)
 $\text{TMSCl}/\text{MeCN}/\text{MWI}$ (07SL43)

$\text{Y}(\text{NO}_3)_3 \times 6\text{H}_2\text{O}/\text{sf}$ (07JMCCF2(271)14)
 $\text{STO}/\text{Al-P}/\text{MWI}/\text{sf}$ (07MI2)
2008
 $\text{CuCl}_2 \times 2\text{H}_2\text{O}/\text{C}_{12}\text{H}_{25}\text{SO}_3\text{Na}/\text{H}_2\text{O}$ (08SC1299)

2009

TBAB (09TL2889)
 $\gamma\text{-Fe}_2\text{O}_3/\text{CuO}$ (09MI13)
 $\text{CaF}_2/\text{ethanol}$ (09TL2222)
 $\text{P}_2\text{O}_5/\text{SiO}_2/\text{sf}$ (09MI9)
 Amberlyst-70 (09MI4)
 NaCl (09MI1)
 $\text{Cu}(\text{NH}_2\text{SO}_3)_2$ (09MI14)

1,3-Dibromo-5,5-dimethylhydantoin/sf (09MI5)
 Polymer-supported 4-diphenylaminoformoyldiphenylammonium triflate (09SC475)
 Yttria-zirconia lewis acid (09SC1299)
 $\text{Al}_2\text{O}_3/\text{MeSO}_3\text{H}$ (09SC958)
 $\text{Al}(\text{H}_2\text{PO}_4)_3$ (09PS126)
 $\text{NBS}/\text{H}_2\text{SO}_4/\text{SiO}_2/\mu\text{-wave}/\text{sf}$ (09MI17)

Table 4. Different synthetic methods for DHPM synthesis (from 2009 to 2011)

2009	2010	1,3-Dichloro-5,5-dimethylhydantoin/sf (10MI4)
Al ₂ O ₃ /SiO ₂ (09PS197)	[Et ₃ NH][HSO ₄]/100 °C/sf (10MI1)	ClSO ₃ H/ultrasound/sf (10MI11)
Cellulose/H ₂ SO ₄ (09SC1257)	HBf ₄ -SiO ₂ /EtOH/rt (10MI6)	P ₂ O ₅ /MWI (10ASJC283)
CsF-Celite (09SC880)	GaI ₃ /100 °C/sf (10MI7)	FeCl ₃ ·6H ₂ O/MWI/sf (10PS325)
Chiral bifunctional primary amine-thiourea/ <i>t</i> -BuNH ₂ .TFA/DCM/25 °C (09MI1)	SiO ₂ -MCl _{4-n} (M = Sn, Ti)/90 °C/sf (10MI5)	5-Sulfosalicyclic acid/MWI (10MI8)
I ₂ /EtOH/rt (09MI2)	Chiral primary amines (QN-NH ₂)/THF/ HCl/0 °C (10EJO3802)	AlCl ₃ ·6H ₂ O/MWI/sf (10JC(B)360)
Polymer supportea-PEG-SO ₃ H/dioxane/ <i>iso</i> -propanol/80 °C (09CCAOAC1146)	QN-NH ₂ /NbCl ₅ /dioxane/rt (10EJO4986)	Nickel nanoparticles/MWI (10MI3)
Yb(pic)/LIG (cat.)/THF/25 °C (09CL56)	TiO ₂ /70 °C/sf (10HCA261)	Al ₂ (SO ₄) ₃ ·18H ₂ O/AcOH (10MI15)
Proline ester salt/THF/70 °C (09EJO3858)	CAN/MeOH/25 °C (10JHC284)	Zeolite/MWI/sf (10ASJC5784)
Imidazolium-based phosphinite IL/100 °C (09HAC284)	Bronsted acidic IL/MWI/sf (10JHC1230)	Nafion-H/ultrasound/sf (10JICS318)
RE(NPf ₂) ₃ /C ₁₀ F ₁₈ /90 °C (09JHC1430)	<i>t</i> -BuOK/EtOH/70 °C (10JOC1162)	Ce(SO ₄) ₂ -SiO ₂ /100 °C/sf (10SC1209)
SnCl ₂ /100 °C/sf (09JOC3141)	Vitamin B ₁ /EtOH/70 °C (10MI1005)	H ₂ O/MWI or ultrasound/sf (10MI10)
Al(HSO ₄) ₃ /Al ₂ O ₃ -SO ₃ H/100 °C/sf (09PS2333)	Al-MCM41 (mesoporous silica material)/ octane/100 °C (10MI14)	Citric acid/sf (10ASJC2518)
NaHSO ₄ ·H ₂ O/hexane/reflux (09PS2465)	Na ₂ B ₄ O ₇ ·10H ₂ O/H ₂ SO ₄ / 80 °C/sf (10SC2976)	Et ₃ N/sf (10LOCEC7272)
ZnO/80 °C/sf (09SC1801)	Cu(NO ₃) ₂ ·3H ₂ O/70 °C/sf (10SC1115)	Sm(ClO ₄) ₃ /ultrasound (10MI13)

Mesoporous aluminosilicate nanocage/
MeCN/reflux (09T10608)
YbCl₃/90 °C/sf (09TL1622)
Cu(NO₃)₂/EtOH/reflux (09MI16)
NaIO₄/rt/sf (09JICS514)

Cation exchange resin (Indion 130)
(09LOCEC7619)
TMSCl/DMF/60 °C (09SC2205)

IL-tris-(2-hydroxyethyl)ammonium acetate/
MWI (09MI12)
Aq. Zn[Bf₄]₂/rt (09IJC(B)408)

Lactic acid/sf (09MI12)
Silica gel or alumina-supported H₂SO₄/
hexane/reflux (09PS1722)
Acidic IL/75 °C (09SC3436)

[Al(H₂O)₆](BF₄)₃/MeCN/reflux (10T3463)
TsOH.H₂O/DCM/rt (10T4040)
(NH₄)₂CO₃/H₂O/55–60 °C (10TL1187)
Thiamine hydrochloride/H₂O/ultrasound
(10TL3138)
[Hmim]HSO₄–NaNO₃/80 °C (10TL6436)

PEG–TUD (polyethylene glycol/thiourea
dioxide)/50 °C/sf (10TL6897)
Zr(H₂PO₄)₂/sf (10MI16)

Polyoxomethalates(POMs)/MeCN
(10ASJC877)
Dodecylphosphonic acid/sf (10JICS237)
ZrCl₄/MWI/sf (10JCSI485)

[bmim]H₂SO₄/MWI/sf (10IJC(B)611)

Tributyl borate/MWI/sf (10BCJ288)

Piperidinium triflate/MeCN/70 °C (10T2987)
Metal acetate/EtOH/reflux (10MI12)
2011

N,N'-Dichlorobis(2,4,6-trichlorophenyl)urea/
EtOH/reflux (11TL809)
Cu(OTf)₂/EtOH/100 °C /MWI (11TL80)

β-Cyclodextrin-SO₃H/100 °C/sf (11MI1)

Sulfate tungstate/80 °C/sf (11CCAOAC1153)

Gypsum/100 °C/sf (11MI2)

3. SCAFFOLD DECORATION OF DHPMs

Although a large number of DHPM derivatives can be prepared in a one-pot Biginelli condensation, systematically designed analogs of DHPMs can be obtained only through chemical functionalization of the desired center around the DHPM core. There are six possible sites (Figure 1) around the DHPM core where modification/functionalization has been achieved. Examples of some rational designs, leading to decoration of each of the six diversity-oriented centers around the heterocyclic ring are presented and their general applicability is demonstrated.

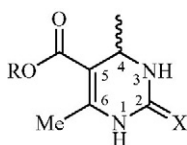
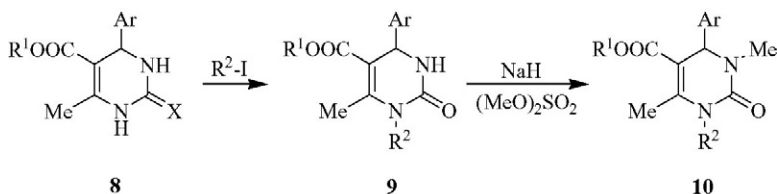


Figure 1 Diversity-oriented centers (N-1, C-2, N-3, C-4, C-5, and C-6) around the DHPM core.

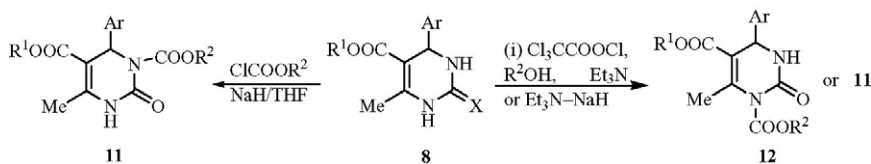
3.1 Synthesis of N-1 substituted DHPM derivatives

N1-H of the DHPM core is acidic, due to the conjugated enamino ester moiety ($\text{ROOC}-\text{C}=\text{C}(\text{R})-\text{NH}-$) and can be deprotonated upon treatment with a base. DHPM derivative **8** ($\text{X} = \text{O}$, $\text{R}^1 = \text{Et}$) has been alkylated regio-specifically at N-1 with alkyl halides (Scheme 3) (75S405, 78MI). On incorporating halide atom(s) at the C-6 position to obtain C-6 bromomethyl and C-6 dibromomethyl derivatives, the acidity of N1-H is significantly increased as compared to **8**, which furnished N-1 methylated derivatives upon treatment with dimethyl sulfate (66M1408). Similarly, trimethylphosphate provided N-1 alkylated DHPM derivatives, where the N-3 position is protected by an acetyl group (89JHC55). Under harsh conditions (e.g., dimethyl sulfate/NaH), N-1 alkylated derivatives **9** are further alkylated at N-3 to dialkyl derivatives **10** (75S405, 92T5473).



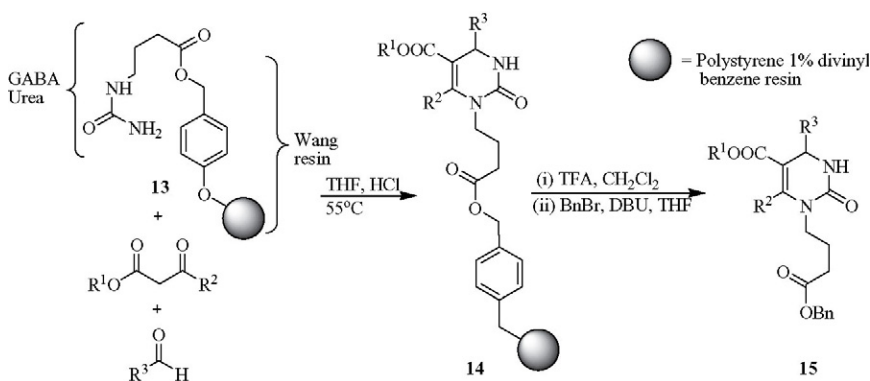
Scheme 3

Cho et al. have reported on the regioselectivity of the N-substitution process and observed that alkoxycarbonylation of DHPM **8** ($X = O$) with alkyl chloroformate in the presence of NaH occurred exclusively at N-3 to furnish **11**, whereas **8** with trichloromethyl chloroformate in the presence of Et_3N alone or in combination with NaH afforded N-1 substituted DHPM **12** or N-3 substituted derivative **11**, regioselectively depending upon the substitution on the C-4 aryl ring; *ortho*-substitution usually led to N-1 substituted DHPM **12** (Scheme 4) (88TL5405).



Scheme 4

Wipf and Cunningham have reported a polymer-supported synthesis of N-1 substituted DHPM derivatives **15** using Wang resin linked GABA urea **13** for condensation with β -ketoester and an aldehyde in acidic conditions (Scheme 5). This methodology offered an alternative to the standard solution-phase Biginelli condensation with 10–20% higher yields and without the need of crystallization and/or chromatographic purification (95TL7819).

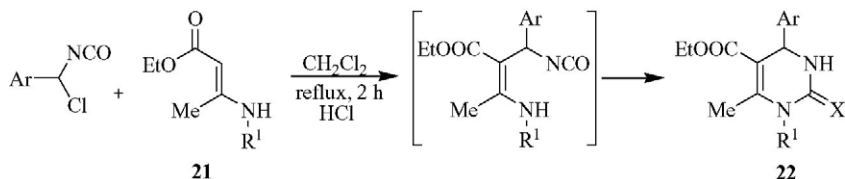


Scheme 5

Choosing fluorinated substrates, soluble in fluorinated solvents, Curran et al. have used fluorous-phase chemistry toward the synthesis of DHPMs. The reaction mixture was purified by a liquid–liquid extraction method because by-products were not soluble in fluorinated solvents. Reaction of fluorinated urea **16** with alkyl acetoacetate and an aldehyde,

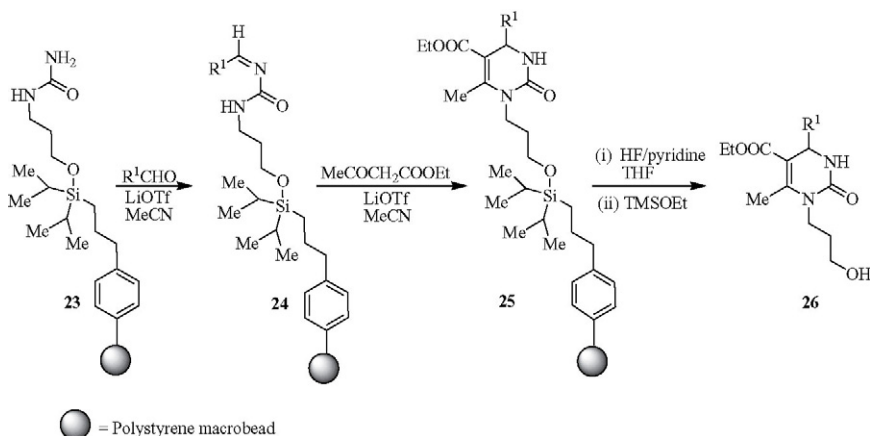
Scheme 8

N-1 Substituted DHPMs **22** (Scheme 9) have also been obtained through a two-step regioselective cyclocondensation of α -chlorobenzyl isocyanates with ethyl N-substituted- β -aminocrotonates **21** (R^1 = alkyl/aryl) (06SL375, 07S835). This methodology is further extended to synthesize N1–C6 linked bicyclic DHPM derivatives (07S835).



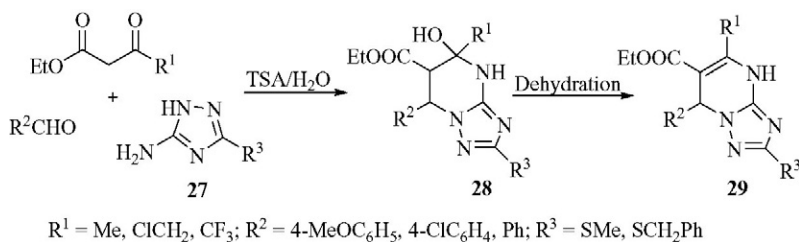
Scheme 9

In a solid-phase split-pool Biginelli synthesis of DHPMs, a urea derivative **23** studded with polystyrene macrobeads was condensed with an aldehyde to obtain a stable acylimine **24** intermediate on the bead, which upon reaction with β -ketoesters furnished **25**. Upon cleavage of the resin, **25** yielded N-1 functionalized DHPM derivatives **26** (Scheme 10) (04OL3237).



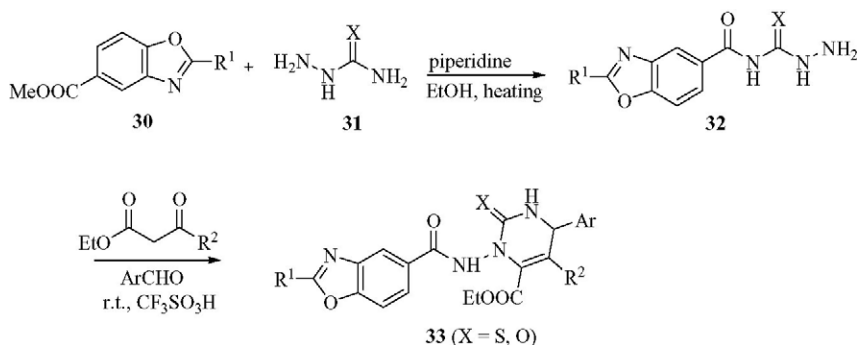
Scheme 10

On replacing the urea component with 5-amino-1,2,4-triazole **27**, **28** was obtained, which on subsequent dehydration afforded N1–C2 linked **29** (Scheme 11) (09JHC139).



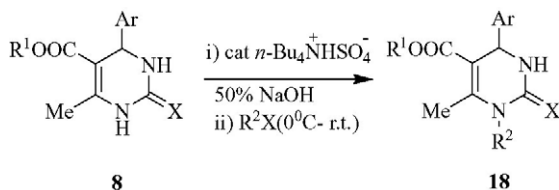
Scheme 11

N-1 benzoxazolyl 3,4-dihydropyrimidinones/thiones **33** have been obtained by reacting carbomethoxy benzoxazole **30** with semicarbazide/thiosemicarbazide **31** ($X = \text{O, S}$) in refluxing ethanol using a catalytic amount of piperidine to obtain intermediate 2-(2-alkylbenzoxazole-5-carbonyl)hydrazine carboxo/thioamide **32** ($R^1 = \text{H, Me; } X = \text{O, S}$), which upon cyclocondensation with an aromatic aldehyde and β -ketoester in the presence of trifluoromethane sulfonic acid at room temperature afforded benzoxazolyl 3,4-dihydropyrimidin-2(1H)-ones/thiones **33** ($R^1 = \text{H, Me; } R^2 = \text{Me, CF}_3$), in excellent yield (Scheme 12) (09MI6).



Scheme 12

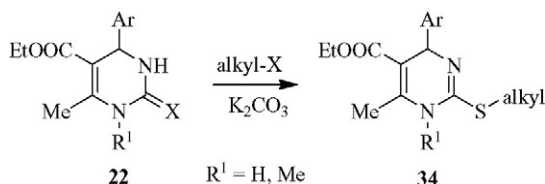
Singh et al. have developed an efficient protocol for the selective N-1 alkylation of DHPMs **8** using tetrabutylammonium hydrogen sulfate and 50% aqueous NaOH as the phase transfer catalyst and base, respectively, under mild solvent-free conditions (Scheme 13). This protocol of N-1 alkylation not only preserves the simplicity of the synthetic operation but also furnished remarkable selectivity (over N-3), giving **18** in moderate-to-high yields (09MI10).



Scheme 13

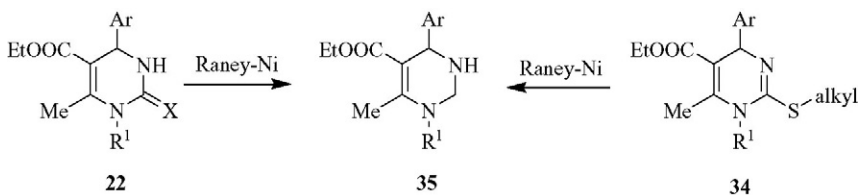
3.2 Synthesis of C-2 substituted DHPM derivatives

The C-2 position of 3,4-dihydropyrimidin-2(1*H*)-thiones **22** ($X = S$) derivatives has been alkylated with an alkyl halide in the presence of a mild base to the corresponding S-alkylated 1,4-dihydropyrimidines **34** (Scheme 14), in excellent yields (87H1185, 87IJC(B)556, 89KGS1076, 90JMC1510).



Scheme 14

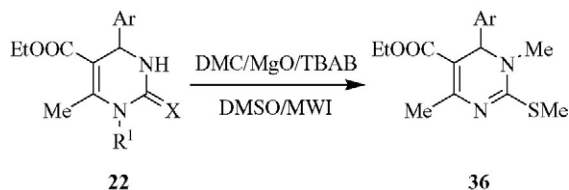
S-Alkylated DHPM derivatives **34** ($R^1 = \text{H}$) have been prepared by condensation of S-alkylthiourea derivatives with α,β -unsaturated ketoesters (87H1185, 87H1189, 89JOC5898). C-2 unsubstituted 1,4-dihydropyrimidines **35** were obtained by reductive desulfurization of **22** (86KGS1223) ($X = S$, $R^1 = \text{Me, Ph}$) or from S-methylated 1,4-dihydropyrimidine derivative **34** ($R^1 = \text{H, Me}$; alkyl = Me) with Raney-Ni (89KGS1076) (Scheme 15).



Scheme 15

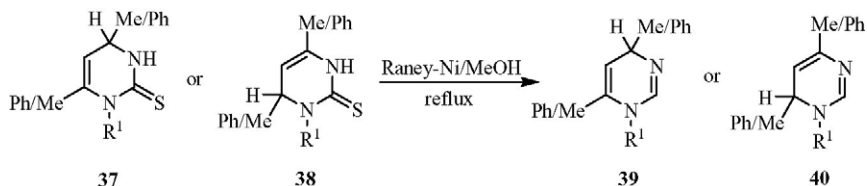
An efficient procedure for the dimethylated DHPM derivatives **36** from DHPM and dimethyl carbonate (DMC) in the presence of MgO as a base

and TBAB as a promotor under microwave irradiation has been reported (Scheme 16) (08MI5).



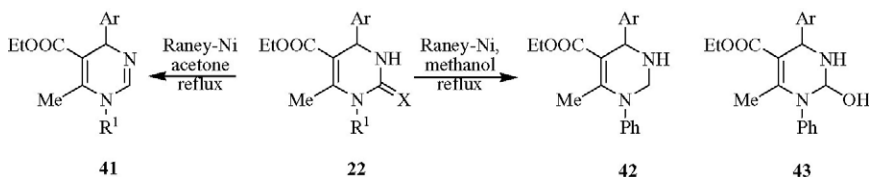
Scheme 16

Kashima et al. have explored the synthesis of N-1 substituted, C-2 unsubstituted dihydropyrimidines **39** and **40** through Raney-Ni induced desulfurization of N-1 derivatives **37** and **38** (Scheme 17) (83JCS(P1)1799). However, the 4,6-dimethyl-1-phenylpyrimidin-2(1H)-thione required an H₂ atmosphere at room temperature. The higher oxidation potential of these products than 1-benzyl 1,4-dihydronicotinamide (Ep = 0.700 V), showed their propensity to transfer hydride. Thus, the desulfurized DHPMs **39** as well as **40**, reduced malachite green to its leuco derivative (83TL209).



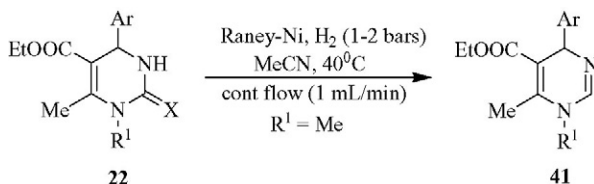
Scheme 17

To study the effect of a solvent on the reductive dethiation, when N-substituted 2-thioxo DHPM derivative **22** (X = S, R¹ = Ph) was treated with Raney-Ni in refluxing acetone, 1,4-dihydropyrimidin-5-carboxylic acid **41** (R¹ = Ph) was obtained, while in methanol, 1,2,3,4-tetrahydropyrimidin-5-carboxylic acid **42** was formed. In one case, 2-hydroxy-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid **43** was obtained (Scheme 18) (86KGS1223).



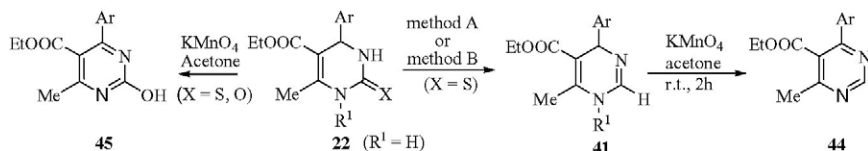
Scheme 18

Kappe et al. used a Raney-Ni catalyzed continuous flow reduction protocol for reductive dethionation of 2-thioxo DHPM **22** ($X = S$) and obtained C-2 unsubstituted **41** (Scheme 19) (05MI9).



Scheme 19

Shin et al. have used a two-step route to obtain 2-unsubstituted pyrimidines from 2-thioxo DHPM derivatives. Oxidation of **22** using Oxone on wet alumina (method A) or hydrogen peroxide in the presence of a catalytic amount of vanadyl sulfate (method B) provided 1,4-dihydropyrimidines **41**, which were oxidized to 2-unsubstituted pyrimidines **44** by $KMnO_4$. However, **22** ($X = S, O$) with $KMnO_4$ furnished 2-hydroxypyrimidine **45** (Scheme 20) (09SL599).

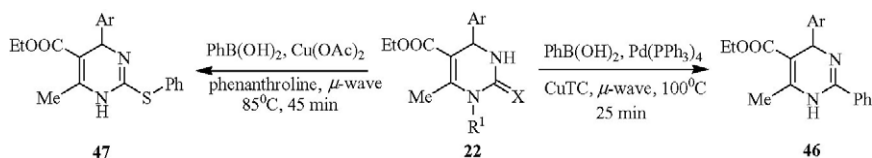


Method A: Oxone[®] (3.2-3.7 equiv), wet Al_2O_3 , $CHCl_3$, r.t., 5-8 h

Method B: 30% H_2O_2 (3.7 equiv), $VOSO_4 \cdot xH_2O$ (0.002 equiv), H_2O -EtOH, $50^\circ C$, 8-12 h

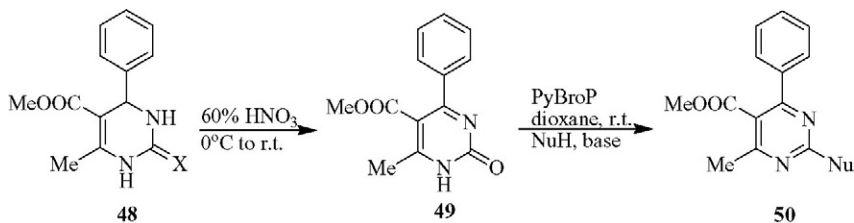
Scheme 20

Microwave-aided Pd(0)-catalyzed/Cu(I)-mediated carbon-carbon cross-coupling of **22** ($X = S, R^1 = H$) with boronic acid under Liebeskind-Srogl (00JA11260) conditions gave 2-phenyl-1,4-dihydropyrimidines **46** (Scheme 21) under an inert atmosphere, to prevent oxidation of the Cu (I) co-factor. In contrast, Cu (II)-mediated reaction of **22** yielded 2-phenylthio-1,4-dihydropyrimidine **47** (Scheme 21), through carbon-sulfur cross-coupling (04OL771).



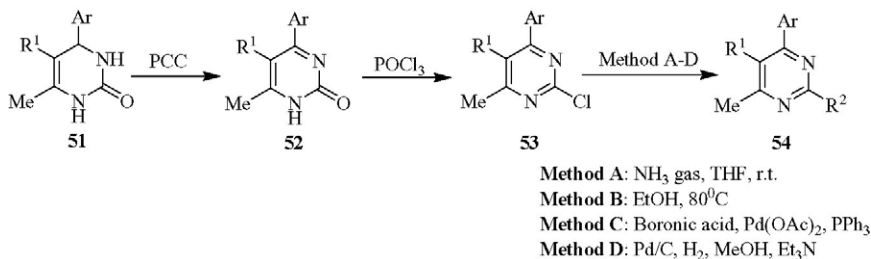
Scheme 21

DHPM **48** was converted to multifunctionalized pyrimidines **50** through initial dehydrogenation to **49** followed by coupling with various C, N, O, and S nucleophiles (Scheme 22) mediated by peptide coupling reagent PyBroP in the presence of a weak base in the case of strong nucleophiles and a strong base in the case of weak nucleophiles (05JOC1957).



Scheme 22

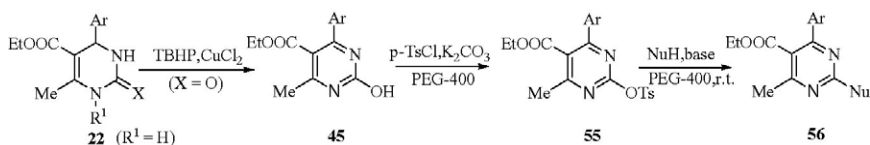
Singh et al. synthesized tetrasubstituted pyrimidines **54** through sequential functionalization of **51** ($R^1 = \text{COOEt}$, COOMe ; $\text{Ar} = \text{Ph}$) via oxidation with pyridinium chlorochromate (PCC) under neutral conditions to pyrimidin-2(1H)-ones **52** (08AJC910), subsequent chlorination with POCl_3 to 2-chloro derivatives **53** ($R^1 = \text{COOEt}$, COOMe ; $\text{Ar} = \text{Ph}$) and displacement of the chloro group with N and O nucleophiles, furnished C-2 elaborated pyrimidines **54** (Scheme 23). **54** ($R^1 = \text{COOEt}$, $R^2 = \text{NH}_2$, $\text{Ar} = \text{Ph}$) was obtained when **53** was treated with ammonia gas dissolved in THF (Method A). **54** ($R^1 = \text{COOEt}$, COOMe ; $\text{Ar} = \text{Ph}$; $R^2 = \text{NHCH}_2\text{Ph}$, $n\text{-C}_4\text{H}_9$, 2-OHPh , $3\text{-NH}_2\text{Ph}$, $-(\text{CH}_2)_5-$ etc.) were obtained upon refluxing **53** with primary or secondary amines in absolute ethanol (Method B) (Scheme 23). The methodology demonstrated ample potential for the introduction of substituents at the C-2 position in a synthetically useful manner. The nature of the C-2 substituent was found to modulate the cytostatic activity in cell culture (11MI3).



Scheme 23

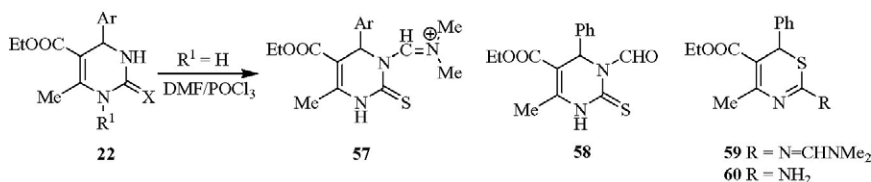
In yet another C-2 modification, pyrimidines **53** upon Suzuki/Sonogashira coupling with boronic acid, $\text{Pd}(\text{OAc})_2$ and triphenyl phosphine in the presence of saturated Na_2CO_3 -dioxane (4:6 v/v) furnished C-2 elaborated **54** ($\text{R}^1 = \text{COPh}$, COOEt ; $\text{R}^2 = \text{aryl}$, alkyl, alkenyl; $\text{Ar} = \text{Ph}$, 4- CH_3Ph , 3- NO_2Ph , 4- OCH_3Ph , etc.) (Method C) (08T10214). Catalytic reduction of **52** using Pd/C , furnished C-2 unsubstituted **53** ($\text{R}^1 = \text{CN}$, $\text{R}^2 = \text{H}$, $\text{Ar} = \text{Ph}$) (Method D, Scheme 23) (89JHC55).

Wang et al. efficiently synthesized pyrimidines **56** from **22**, followed by cross-coupling of the pyrimidin-2-yl sulfonates **55** with N, S, and O nucleophiles in PEG-400 as a green reaction medium at room temperature (Scheme 24) (10SL1657). Direct replacement of the OH group of **45** with N and O nucleophiles to gave **56** was also achieved using amines, alcohols (or phenols), and carboxylic acids *via* the Mitsunobu reaction (11T3267).



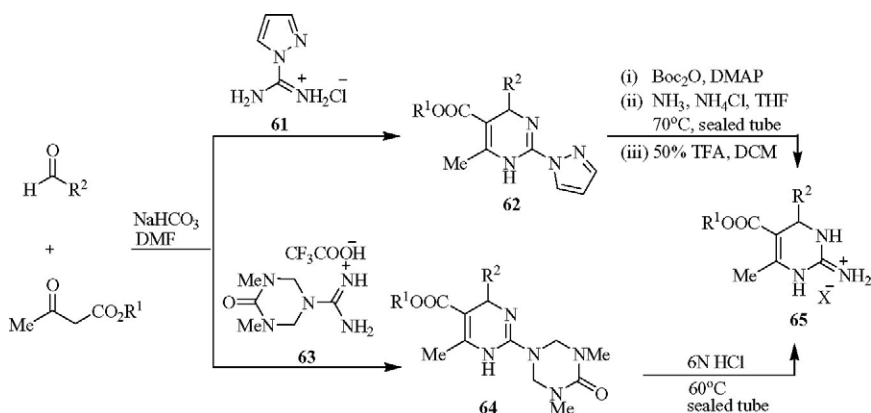
Scheme 24

Vilsmeier formylation of **22** with DMF/POCl_3 at room temperature furnished **58** through **57** (Scheme 25). At elevated temperatures (85°C), Dimroth-like rearrangement of **57** gave thiazinyl-2-formamidine **59**, which under strongly acidic conditions was hydrolyzed to 2-amino-(6*H*)-1,3-thiazine **60** (89JHC55).



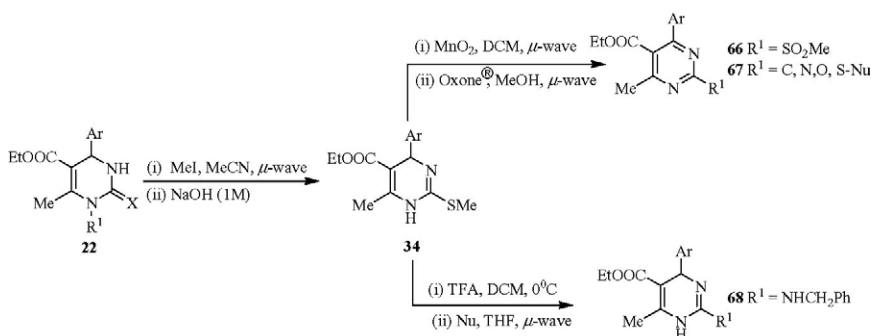
Scheme 25

In a multistep synthesis of 2-imino-DHPM **65** using pyrazole carboxamidine hydrochloride **61** (Scheme 26) as guanylated agent, the sequence: condensation to obtain 1,4-dihydropyrimidine **62**, protection of N-3, nucleophilic reaction at C-2, followed by deprotection, furnished **65**. Using 3,5-dimethyl-4-oxo-(1,3,5)-triazine-1-carboxamidine **63** as guanylated agent, **64** was obtained, which upon deprotection furnished **65** (Scheme 26) (06JOC7706).



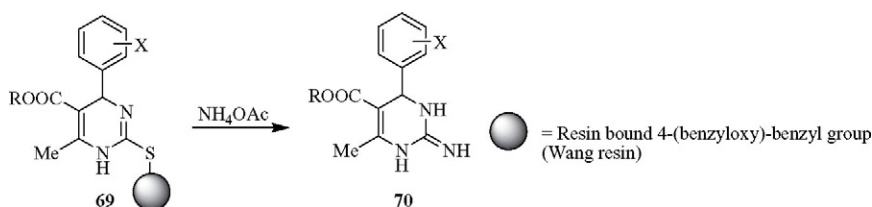
Scheme 26

In an efficient microwave-assisted solution or solid-phase protocol (07MI12) for 2-amino-4-arylpyrimidine-5-carboxylate derivatives (Scheme 27), **22** ($\text{X} = \text{S}$, $\text{R}^1 = \text{H}$) was S-alkylated with methyl iodide to 2-methylthiodihydropyrimidines **34**, which was sequentially oxidized first with manganese dioxide and then with Oxone to 2-methylsulfonyl-pyrimidines **66** as precursors of 2-substituted pyrimidines **67** *via* displacement of the reactive sulfonyl group with N, O, S, and C nucleophiles (Scheme 27). However, direct displacement of the S-methyl group of **34** with nitrogen nucleophiles provided 2-amino-1,4-dihydropyrimidines **68**.



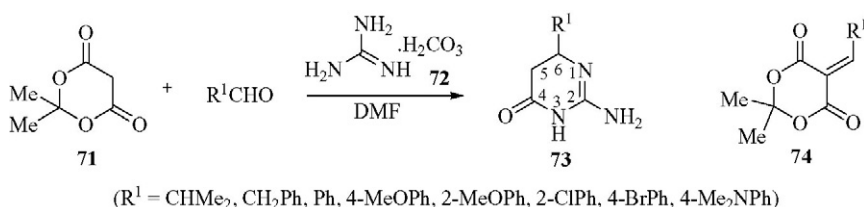
Scheme 27

Using a solid-phase strategy, the anchored 1,4-dihydropyrimidine **69** upon treatment with NH_4OAc yielded 2-imino-3,4-dihydro-2(1*H*)-pyrimidine **70** (Scheme 28) (00BMC49), an important structural feature of many marine alkaloids (00CSR57).



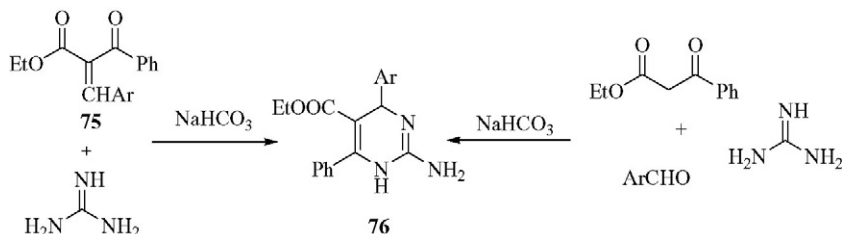
Scheme 28

2-Amino-5,6-dihydropyrimidin-4(3*H*)-one **73** was obtained in a multi-component reaction between Meldrum's acid **71**, an aldehyde (aliphatic or aromatic) and guanidine carbonate **72** in a small amount of DMF at 120–130 °C. However, 4-methoxyphenyl derivative **73** ($\text{R}^1 = 4\text{-MeOPh}$) was also obtained in two steps by condensation of arylidene Meldrum's acid **74** with guanidine carbonate (Scheme 29) (06MI10).



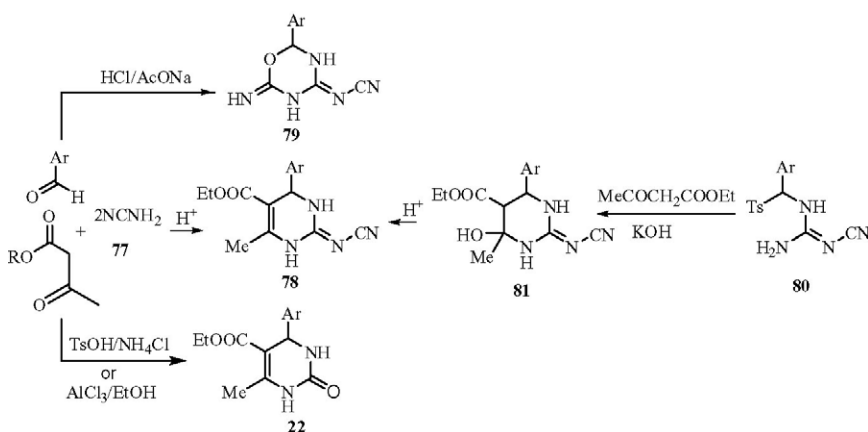
Scheme 29

2-Amino-1,4-dihydropyrimidines **76** can be synthesized from ethyl 3-aryl-2-benzoyl-propenoate **75** and guanidine in DMF in the presence of sodium hydrogen carbonate (Scheme 30) (97JHC329). Similarly, an aromatic aldehyde, ethyl benzoylacetate, guanidine hydrochloride, and sodium hydrogen carbonate in DMF also furnished **76** (Scheme 30) (01T1785).



Scheme 30

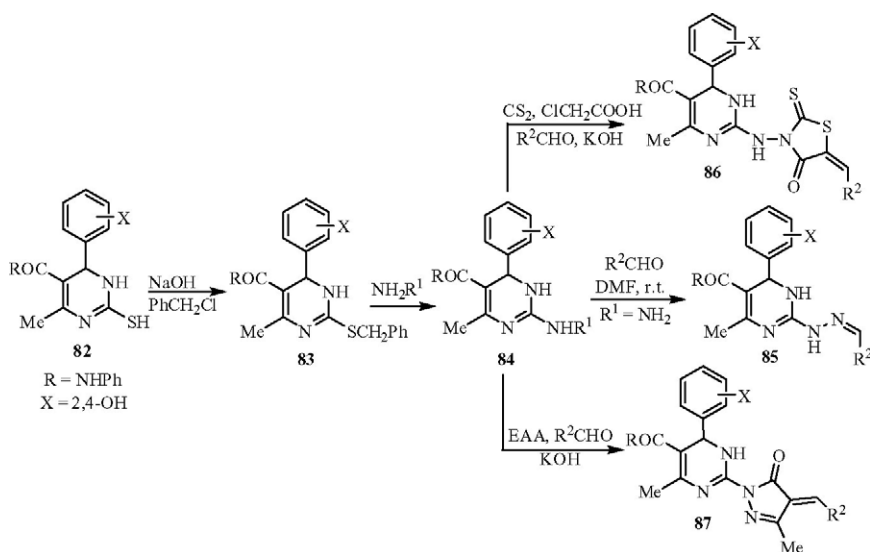
4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidines **78** have been prepared from an aldehyde, ethyl acetoacetate, and cyanamide **77** under acidic conditions (Scheme 31). However, *N*-(6-imino-2-phenyl-1,3,5-oxadiazinan-4-ylidene) cyanamide **79** was isolated when conc. HCl/AcONa were used under solventless condition. The use of TsOH/NH₄Cl or AlCl₃ as catalyst under solventless conditions in the presence of conc. HCl and AcONa furnished **22** (R¹ = H, X = O) (Scheme 31) (08T3372). **78** was also synthesized through the initial condensation of α -tosyl-substituted *N*-cyanoguanidines **80** with potassium enolates of ethyl acetoacetate to afford 5-ethoxycarbonyl-2-cyanimino-4-hydroxyhexahydropyrimidines **81**, which on acid catalyzed dehydration yielded **78** (Scheme 31) (00MI1).



Scheme 31

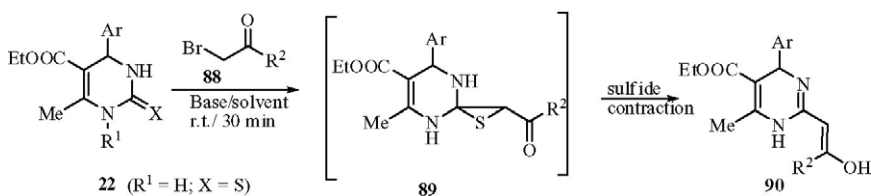
2-Mercapto pyrimidines **82** were synthesized from acetoacetanilide, dihydroxybenzaldehyde, and thiourea, which were readily alkylated with benzyl chloride to afford 2-benzylthio derivatives **83** (Scheme 32). **83** when reacted with different amines in acetic acid furnished 2-amino derivatives **84** (R¹ = Ar), whereas upon reaction with hydrazine hydrate **83** afforded 2-hydrazinyl derivative **84** (R¹ = NH₂), which with different aldehydes gave hydrazones **85** (R² = 2-furyl, 2-thienyl). Arylidene thiazolidinone **86** was obtained from **84** with carbon disulfide, monochloroacetic acid, and aryl aldehydes, while **84** with ethyl acetoacetate and different aromatic aldehydes provided pyrazoles **87** (Scheme 32) (10MI9). Such tetrasubstituted pyrimidines act as cyclin-dependent kinase (CDK2) inhibitors.

DHPM **22** has been transformed to 2-(2-hydroxy-2-arylvinyl) dihydropyrimidine derivatives **90** via Eschenmoser sulfide contraction through the selective alkylation of **22** at C-2 with α -bromoketone **88** under basic conditions and subsequent elimination of the bridged sulfur by the thiophilic



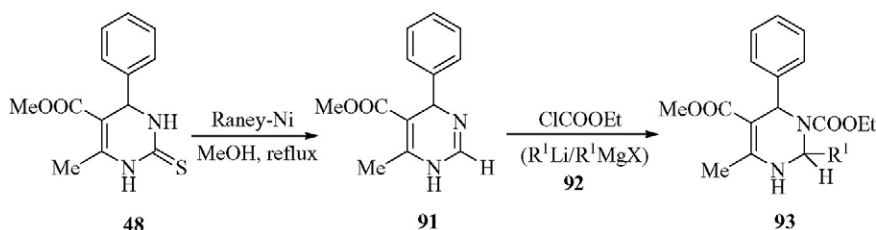
Scheme 32

triphenylphosphine. The intermediate **89** upon extrusion of sulfur allowed carbon–carbon bond formation at C-2 (Scheme 33) (09TL1838). Alternatively, the use of solid-supported triphenylphosphine simplified the work-up and enhanced the yield of **90**.



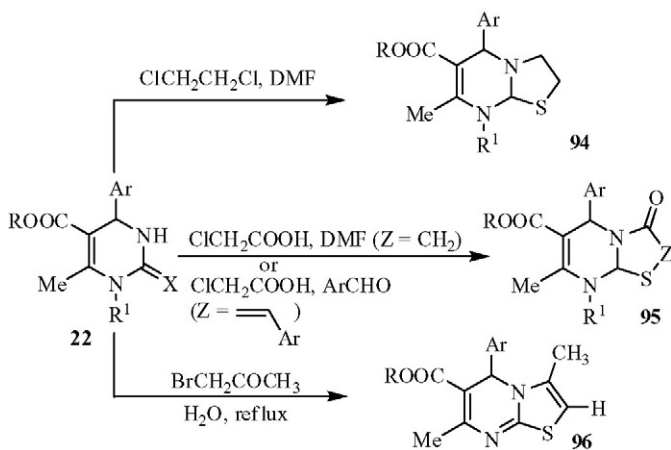
Scheme 33

Singh et al. have devised the synthesis of novel multifunctionalized tetrahydropyrimidines **93** from **48** (Scheme 34). The methodology holds potential for the introduction of a number of tailor-made nucleophilic fragments at the C-2 position of DHPMs in a synthetically useful manner. Desulfurization of **48** with Raney-Ni under hydrogen gas furnished C-2 unsubstituted **91**, which with the carbanion of acetone, thiophene, Grignard reagents of alkyl ($\text{C}_1\text{--C}_{11}$), allyl and phenyl groups **92**, proceeded smoothly and exclusively at C-2 in the presence of ethyl chloroformate to furnish **93** (Scheme 34) (10T8175).



Scheme 34

DHPM **22** ($X = S$, $R = Et$, $R^1 = H$) has been transformed to fused thiazolo[3,2-*a*] pyrimidines with halogen derivatives (Scheme 35). **94** was obtained from **22** with 1,2-dichloroethane and **95** ($Z = CH_2$) from **22** with chloroacetic acid. Similarly, **22** ($X = S$, $R = Me$, $R^1 = H$) with chloroacetic acid and an aldehyde in the presence of acetic acid and acetic anhydride gave **95** ($Z = CH = CH-Ar$) and **22** with α -bromoacetone in refluxing water formed pyrimidines **96** (Scheme 35) (06MI16, 99FA588, 08HAC149).

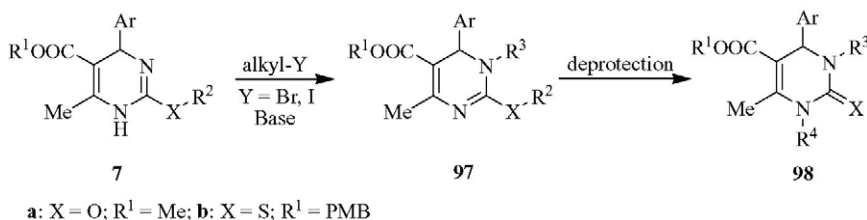


Scheme 35

3.3 Synthesis of N-3 substituted DHPM derivatives: alkylation/acylation reactions

N-3 Alkylated Biginelli DHPMs can be obtained neither by alkylation of unsubstituted derivatives nor by using alkylurea through the classical Biginelli condensation (Scheme 1) (04OR1), which furnish only N-1 alkylated products (75S405). Dihydropyrimidines **7a,b** (87H1185, 87H1189) have been alkylated to N-3 substituted **97a,b** and deprotected to N-3 alkylated DHPM **98a,b** ($R^3 = alkyl$, $R^4 = H$) (Scheme 36) (87H1185,

89JOC5898, 90JMC1510, 92JMC3254). The regioselectivity of N-3 alkylation was plagued by the formation of N1,N3-dialkylated products **98a**, **b** ($R^3 = R^4 = \text{alkyl}$) and was dependant both on the nature of the alkylating reagent and the substrate. Alkylation of **7a** (Ar = *meta*-substituted aromatic ring) with a strong electrophile followed by deprotection gave exclusively the N-3 alkylated **98** ($R^3 = \text{alkyl}$, $R^4 = \text{H}$). A less reactive electrophile gave a 5:1 mixture of N-3 ($R^3 = \text{alkyl}$, $R^4 = \text{H}$) and N-1 alkylated **98** ($R^3 = \text{H}$, $R^4 = \text{alkyl}$). Similarly, **7b** (Ar = *ortho*-substituted aromatic ring) with an electrophile, gave a 1:1 mixture of the N-3 ($R^3 = \text{alkyl}$, $R^4 = \text{H}$) and N-1 ($R^3 = \text{H}$, $R^4 = \text{alkyl}$) **98**. The latter was the result of steric hindrance at N-3 by the *ortho*-substituted aromatic ring (87H1185, 87H1189, 89JOC5898, 92JMC3254).

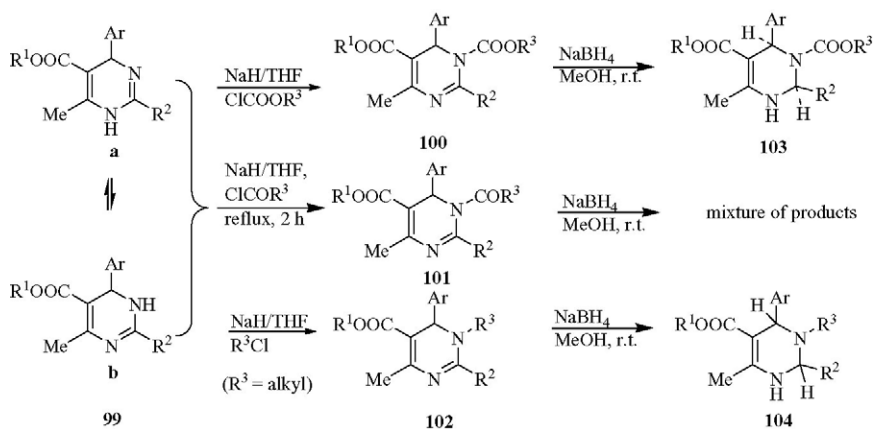


Scheme 36

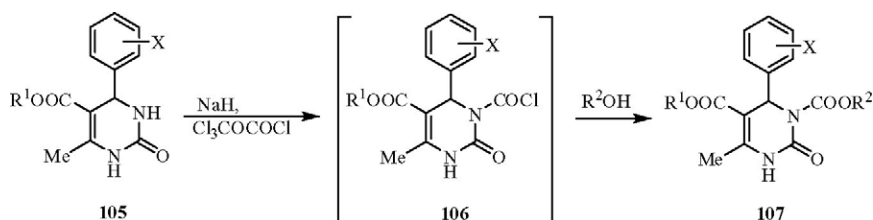
The regioselective N-3 alkoxy carbonylation of the isomeric 1,4-/3,4-dihydropyrimidine **99** by treatment of **99** with NaH and alkyl chloroformate furnished **100**. To obtain N-3 acylated **101** and N-3 alkylated **102**, an acyl chloride and an alkyl halide, respectively, were used (Scheme 37). The regioselectivity is attributed to the conformational preferences of the dihydropyrimidine ring, owing to steric hindrance between the C-4 aryl ring and the N-3 substituents. Secondly, the resonance structures resulting from the removal of proton from **99a** would increase the electron density more at N-3 than at N-1, rendering it more nucleophilic. NaBH₄ reductions of **100** furnished a single stereoisomer **103**, while similar treatment of **101** yielded a mixture, owing to the competing reductive deacylation at N-3. Similar reductive treatment of **102** furnished a diastereomeric (4:1) mixture of tetrahydropyrimidines **104** (Scheme 37) (85JOC4227).

The sodium salt of **105** with trichloromethyl chloroformate and an alcohol, in sequence, furnished N-3 alkoxy carbonylated **107**, through unstable intermediate **106** (Scheme 38). However, an *ortho* substituent on the C-4 aryl group decreased the yield of the N-3 product (88TL5405).

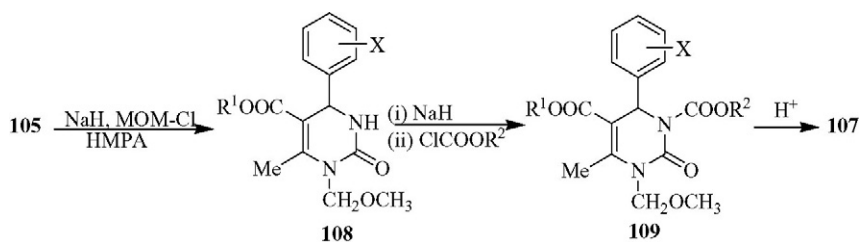
N-3 substituted **107** (X = 2-NO₂) was synthesized through alkoxy carbonylation of the N-3 sodium salt of **108** to afford **109**, which further hydrolyzed to **107**. Alkylation of **105** (X = 2-NO₂) with methoxymethyl chloride (MOM-Cl) gave N-1 substituted **108** instead (88TL5405) (Scheme 39).



Scheme 37

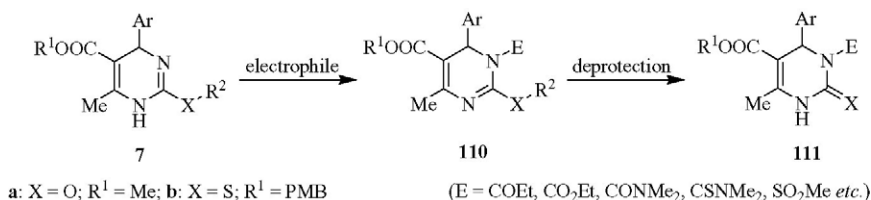


Scheme 38



Scheme 39

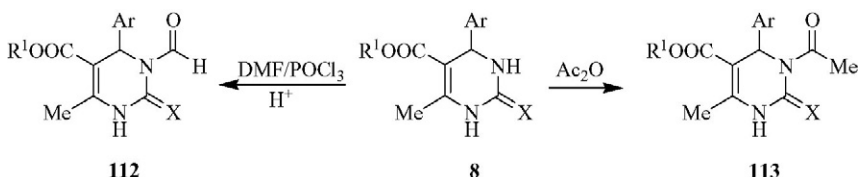
Pyrimidines **7a,b** have been used for the regioselective synthesis of N-3 acylated dihydropyrimidines **111** through deprotection of **110** (Scheme 40). Electrophiles include acyl chloride, alkoxy- and aryloxycarbonyl chloride, sulfonyl chloride, phosgene, and thiophosgene. In the latter two cases, the resulting intermediates were treated *in situ* with amines to obtain



Scheme 40

carbamoyldihydropyrimidines **110** (E = CONMe₂, CSNMe₂) (87H1185, 87H1189, 89JOC5898, 90JMC1510, 90JMC2629, 92JMC3254).

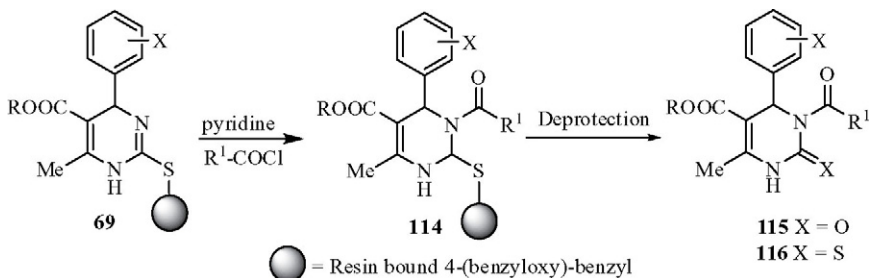
The formylation of **8** by DMF/POCl₃ furnished **112** with complete regioselectivity in favor of N-3 (Scheme 41) (89JHC55). Only N-3 acetylated **113** were formed in the acylation of **8** or its N-1 protected derivative with acetic anhydride (82KGS535, 89KGS1076). N1,N3-Diacetyl derivatives have been obtained by similar acetylation of C-4 unsubstituted DHPM derivatives (64CPB804).



Scheme 41

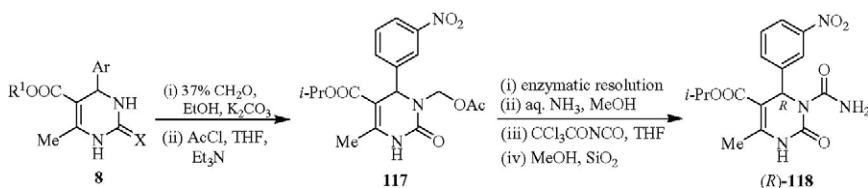
Resin-bound 1,4-dihydropyrimidine **69** with acid chlorides in a basic medium furnished N-3 acylated **114** (Scheme 42). Removal of the polymer support from **114**, using acetic acid/H₂O or TFA/EtSH, furnished **115** and **116**, respectively (Scheme 42) (00BMC49).

Enzymatic resolution of racemic DHPM **117** was achieved through N-3 acetoxy methylation of **8** (X = O, Ar = 3-NO₂Ph, R¹ = *i*-Pr) with



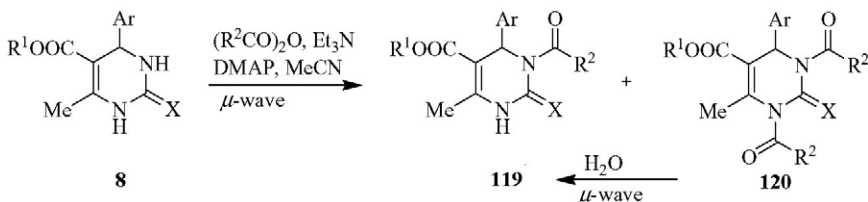
Scheme 42

formaldehyde and acetyl chloride followed by resolution using *Thermomyces lanuginosus*. Subsequent transformations formed potent calcium channel blocker (*R*)-SQ 32926 **118** (Scheme 43) (98SL718, 00TA1449).



Scheme 43

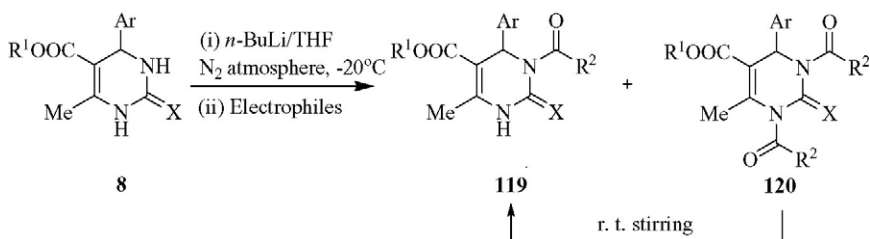
N-3 acylated DHPMs **119** were synthesized through microwave assistance using water sequestering agent coupled with an efficient solid-phase extractive work-up (Scheme 44) (03OL1205). Aliphatic ($\text{R}^2 = \text{Me}$) as well as aromatic ($\text{R}^2 = \text{Ph}$) anhydrides were acylating agents. Along with **119**, the N1,N3-diacylated **120** were also formed in minor amounts with aromatic anhydrides. Removal of excess unreacted anhydride using solid-supported nucleophilic amine or water converted undesired **120** to desired **119** (03OL1205). Acid chlorides and isocyanates served as electrophiles, in addition to acid anhydrides (03MI8). Selective N-3 acylation was also achieved using a carboxylic acid R^2COOH and thionyl chloride (05CHE260).



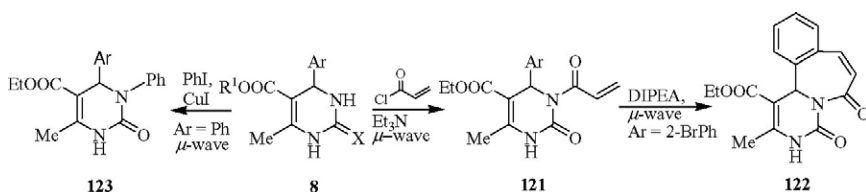
Scheme 44

Singh et al. have reported an efficient synthesis of N-3 acylated **119** (06TL8143). The treatment of **8** ($\text{R}^1 = \text{Et}$, $\text{X} = \text{S}$, O) with *n*-BuLi at -20°C , followed by quenching with various electrophiles furnished N-3 substituted **119** along with N1,N3-diacylated **120** (09T10395) (Scheme 45). Using optically pure amino acid chlorides as electrophiles gave optically pure DHPMs (09T4106). Readily available **120** efficiently acylates ammonia, primary and secondary amines to the corresponding primary, secondary and tertiary amides in good-to-excellent yields (09T10395).

Kappe et al. have developed a transition-metal-aided decoration of **8** ($\text{X} = \text{O}$, $\text{R}^1 = \text{Et}$) using controlled microwave heating as the energy source



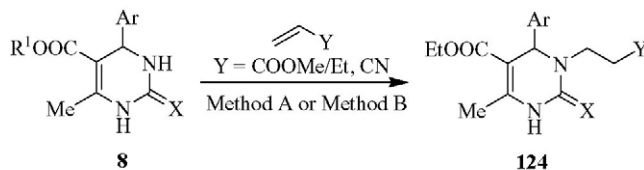
Scheme 45



Scheme 46

(Scheme 46) (05MI8). 4-(2-Bromophenyl)-3-acryloyl DHPM **121** ($\text{Ar} = 2\text{-BrC}_6\text{H}_4$) was synthesized from **8** ($\text{R}^1 = \text{Et}$, $\text{Ar} = 2\text{-BrC}_6\text{H}_4$) through N-3 acylation using acryloyl chloride and Et_3N in MeCN. An intramolecular cyclization of **121** using Heck-coupling conditions, 5 mol% of Herrmann's palladacycle ($\text{Pd}_2(\text{OAc})_2[\text{P}(o\text{-tolyl})_3]_2$) and DIPEA in DMF/ H_2O or MeCN/ H_2O , yielded tricyclic DHPM **122**. Using a copper-catalyzed Goldberg arylation gave N-3 arylated **123** not accessible through the classical Biginelli condensation (04OR1).

Regioselective N-3 alkylation of **8** ($\text{X} = \text{S}, \text{O}$, $\text{R}^1 = \text{Et}$) furnished **124** with α,β -ethylenic compounds through an Aza-Michael addition using $\text{KF}/\text{Al}_2\text{O}_3$ in DMF (06BMC4592) or K_2CO_3 in polyethylene glycol (PEG-400) (07T8227) (Scheme 47). Further, the former catalyst was reusable without any appreciable loss in its activity or regioselectivity.

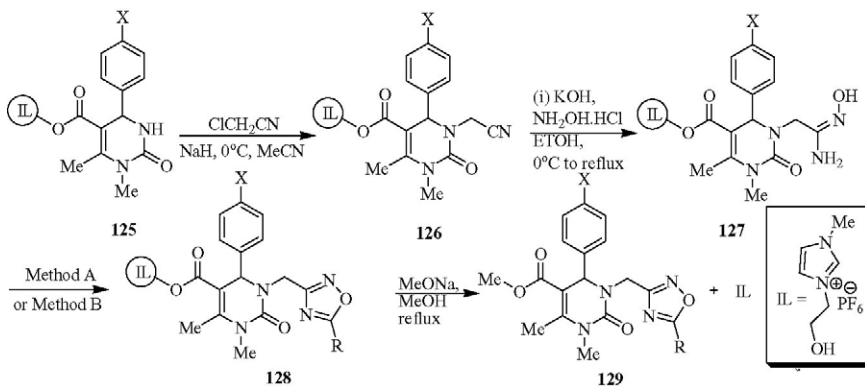


Method A: $\text{KF}/\text{Al}_2\text{O}_3$ (10 mol%), DMF, r.t., overnight

Method B: K_2CO_3 (20 mol%), PEG-400, r.t., 18 h or 50°C , 4 h

Scheme 47

Regioselective functionalization of the N-3 of **125** with 1,2,4-oxadiazole as amide isostere using an IL-bound **125** with chloroacetonitrile afforded N-3 substituted **126** (Scheme 48). The nitrile group of **126** was transformed into amidoxime **127** with hydroxylamine hydrochloride. Addition of aliphatic carboxylic anhydrides or aromatic carboxylic acid to **127** furnished **129** via the *O*-acylamidoxime intermediate **128**, after cleavage from the IL (07TL1063) (Scheme 48).

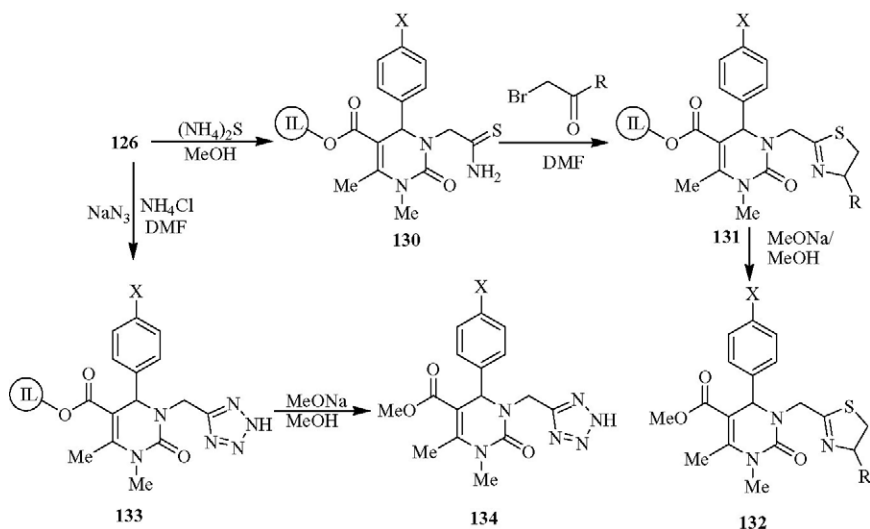


Scheme 48

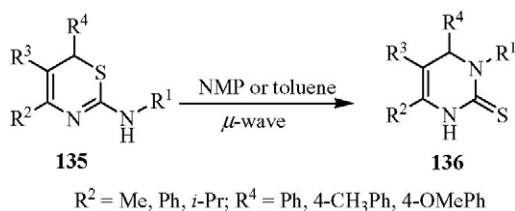
IL-bound thioamide **130** was obtained from **126** with ammonium sulfide, which react with α -bromoketone in DMF to afford thiazole derivative **131**. Cleavage of **131** from the IL furnished N-3 functionalized **132**. Similarly **126** with sodium azide and ammonium chloride in DMF and subsequently with sodium methoxide in refluxing methanol yielded tetrazole **134** (Scheme 49) (08T5328).

Kappe et al. have reported a microwave-assisted Dimorth rearrangement of a substituted 2-amino-6*H*-1,3-thiazines **135** to N-3 substituted **136** in sealed vessels (Scheme 50). Thiazines **135** with an ester functionality at C5 ($\text{R}^3 = \text{COOEt}$), required higher temperatures for rearrangement than **135** ($\text{R}^3 = \text{H}$). **135** ($\text{R}^1 = \text{H}$) was transformed into **136** ($\text{R}^1 = \text{H}$) in toluene and for the transformation of N-substituted **135** ($\text{R}^1 = \text{alkyl or aryl}$) to N-3 substituted **136** ($\text{R}^1 = \text{alkyl or aryl}$), *N*-methyl pyrrolidine was the solvent (06MI13).

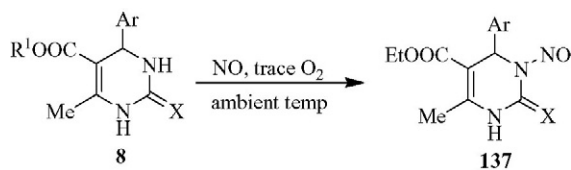
The N-3 nitrosation of **8** ($\text{X} = \text{O}$, $\text{R}^1 = \text{Et}$) with nitric oxide regioselectively furnished N-3 nitrosamides **137** by nucleophilic attack of N-3 of **8** on N_2O_3 (formed *in situ* from oxidation of NO by O_2) in the presence of aprotic and polar solvents (Scheme 51) (08TL1220).



Scheme 49

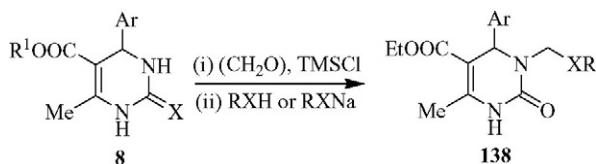


Scheme 50



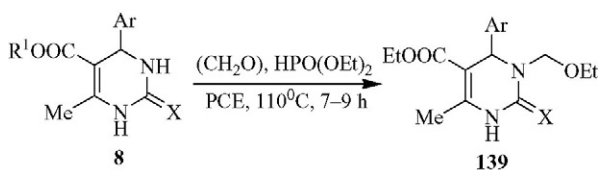
Scheme 51

N-3 substituted **138** bearing N-3 alkyloxymethyl, aminomethyl, arylsulfonylmethyl, and azidomethyl groups was regioselectively obtained in preference to the N-1 isomer from **8** ($\text{R}^1 = \text{Et}$, $\text{X} = \text{O}$) with paraformaldehyde and chlorotrimethylsilane followed by an alcohol, amine, sodium benzenesulfonate, and sodium azide, respectively, in a one-pot, method (Scheme 52) (10H1827).



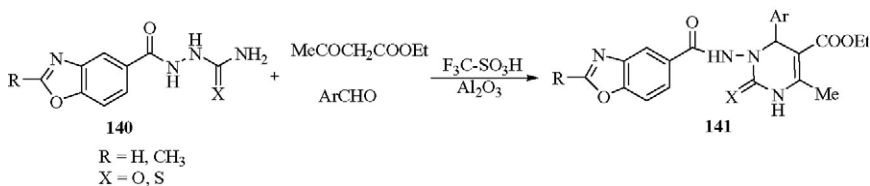
Scheme 52

The synthesis of N-3-ethoxymethylated **139** was achieved through a three-component reaction between **8** ($R^1 = Et$), paraformaldehyde and diethyl phosphate *via* P–O bond cleavage of diethyl phosphate that served as an alcohol equivalent (Scheme 53) (11T2462).



Scheme 53

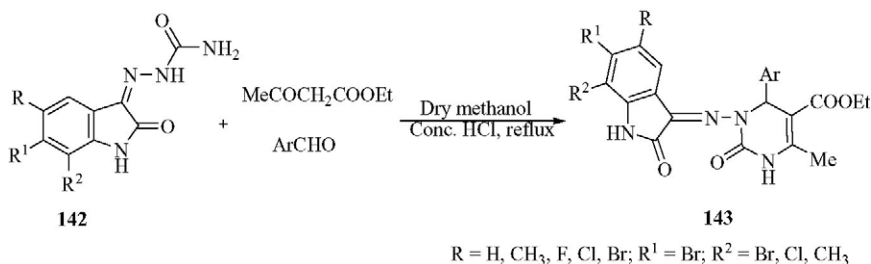
When benzoxazole-substituted urea/thiourea **140** was used in a Biginelli condensation with an aldehyde and a β -ketoester in the presence of alumina-supported trifluoromethane sulfonic acid as a heterogenous catalyst under solvent-free reaction conditions, N-3 benzoxazole-substituted **141** ($X = S, O$) was obtained in good yield (Scheme 54) (09JHC119, 09MI7).



Scheme 54

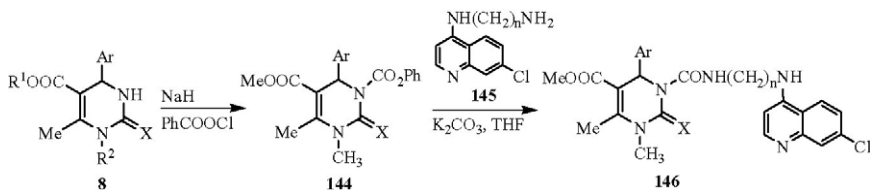
Isatin semicarbazone **142**, an aldehyde and a β -ketoester in a Biginelli condensation gave N-3 substituted **143** (Scheme 55) (09ASJC4635).

4-Aminochloroquinones **145** ($n = 2-4$) were appended to the N-3 position of DHPMs. The N-1 methylated **8** ($R^1 = R^2 = Me$) with phenyl



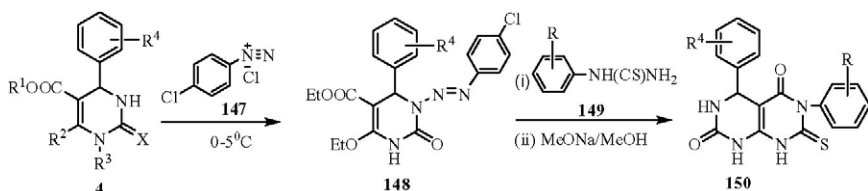
Scheme 55

chloroformate were transformed into carbamate **144**, which were subsequently transformed into N-3 substituted **146** (Scheme 56) (08MI4). DHPM–chloroquine conjugates **146** were found to exhibit antimalarial activity.



Scheme 56

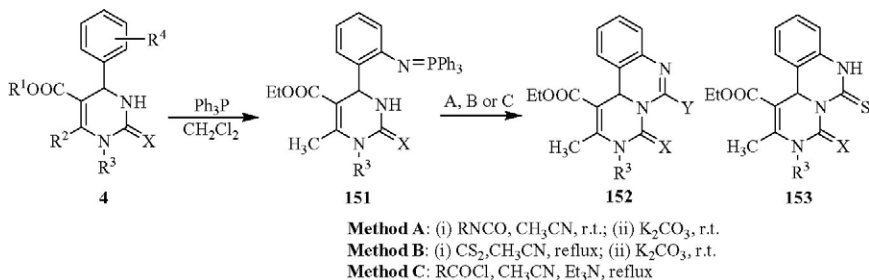
Pyrimido [4,5-*d*] pyrimidin-2,5-dione **150** were synthesized from DHPMs through a protocol, which involved the synthesis of N-3 substituted derivatives (Scheme 57). When **4** ($\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{OEt}$, $\text{R}^3 = \text{H}$, $\text{X} = \text{O}$, $\text{R}^4 = 2\text{-Cl}$) was reacted with freshly prepared 4-chlorophenyldiazonium chloride **147** in conc. HCl, N-3 **148** was obtained. Refluxing with various arylthioureas **149** and subsequently reaction with sodium methoxide in methanol at 0°C gave **150** (04BMC4185).



Scheme 57

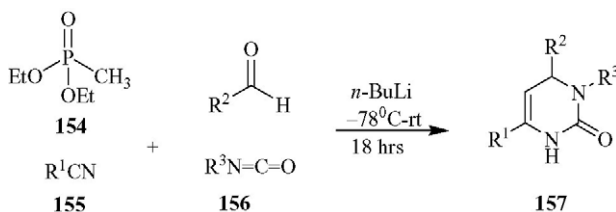
DHPM **4** ($\text{R}^1 = \text{Et}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = 2\text{-N}_3$; $\text{X} = \text{O, S}$) with triphenylphosphine in dichloromethane at room temperature provided

iminophosphorane **151** *via* a Staudinger reaction. Aza-Witting reaction of **151** with an isocyanate following method A furnished pyrimido[1,6-*c*]quinazolin-4-ones **152** ($Y = \text{NHR}$, where $R = \text{alkyl or aryl}$). Reaction of **151** with CS_2 (Method B) afforded **153** and acyl chlorides (RCOCl , Method C), in the presence of triethylamine furnished **152** ($Y = R$ where $R = \text{alkyl or aryl}$) (Scheme 58) (10T8151).



Scheme 58

A multicomponent reaction of phosphonate **154**, nitriles **155**, aldehydes, and isocyanates **156** with base afforded N-3 functionalized DHPMs **157** *via* a Horner–Emmons/aza Diels–Alder pathway (Scheme 59) (03JCS(CC)2594).



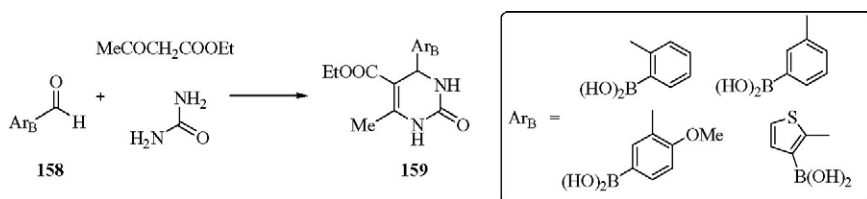
Scheme 59

3.4 Synthesis of C-4 elaborated DHPM derivatives

Of the three building blocks in the traditional Biginelli condensation, the aldehyde component has been widely varied to obtain DHPMs elaborated at C-4. Higher yields are obtained with aromatic aldehydes bearing electron-withdrawing substituents at the 3- or 4-position, the 2-substituted counterparts furnish lower yields. Heterocyclic aldehydes derived from furan, thiophene, and pyridine rings also generally furnish acceptable yields of DHPMs (04OR1). Additionally, aldehydes derived from carbohydrates (03JOC6172, 06ACR451) as well as bisaldehydes (01MI3) have

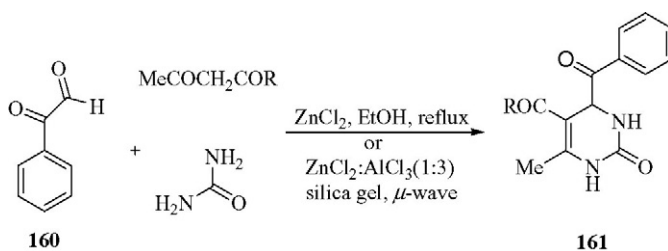
been used. Direct condensation of aliphatic aldehydes is not encouraged, due to low yields as well as the number of side products, unless special conditions are employed. The use of Lewis acid catalysts (00SL63, 02T4801, 03TL3305)/solvent-free methods (02MI7), or aldehydes in their protected form (99T12873) gave DHPM derivatives unsubstituted at C-4 as well as with aliphatic substituents at C-4.

Novel boron-containing dihydropyrimidinones **159** are synthesized using boronic acid substituted aldehydes **158**, a ketoester and a urea in the traditional three-component Biginelli reaction in the absence of an additional Lewis acid, as the boronic acid group itself acts as a Lewis acid (Scheme 60) (05CJC2052).



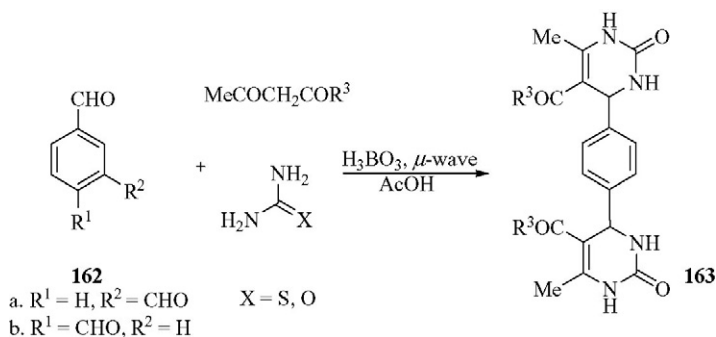
Scheme 60

Phenylglyoxal monohydrate **160**, ketoesters and urea in three-component Biginelli reaction furnished DHPMs **161** (R = Me, OMe or OEt) (Scheme 61). The ketone of **161** provided a potential site for further transformations (05JICS319).



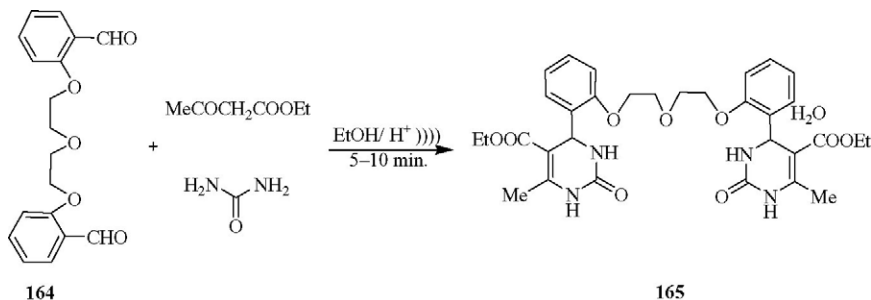
Scheme 61

Microwave-aided boric acid-catalyzed condensation of isophthalic aldehyde **162a** or terephthalic aldehydes **162b** with 1,3-dicarbonyl compounds and urea/thiourea, furnished *p*-[bis(dihydropyrimidin-2(1*H*)-one-4-yl)] benzene **163** containing two dihydropyrimidinone units linked through their C-4 position (Scheme 62) (05MI5). Solid-supported tin chloride and titanium tetrachloride were used as catalysts under solvent-free conditions (10MI5).



Scheme 62

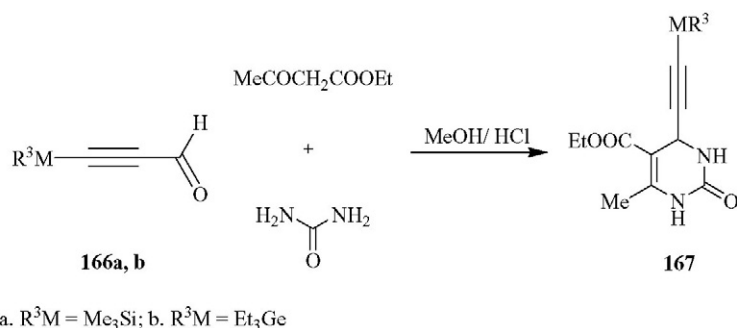
The synthesis of DHPMs linked through C-4 is precursor for supramolecular applications. DHPM-based podand **165** was synthesized from *di*-formyl precursor **164**, in a three-component Biginelli condensation in ethanol aided with ultrasonication (Scheme 63) (03MI8).



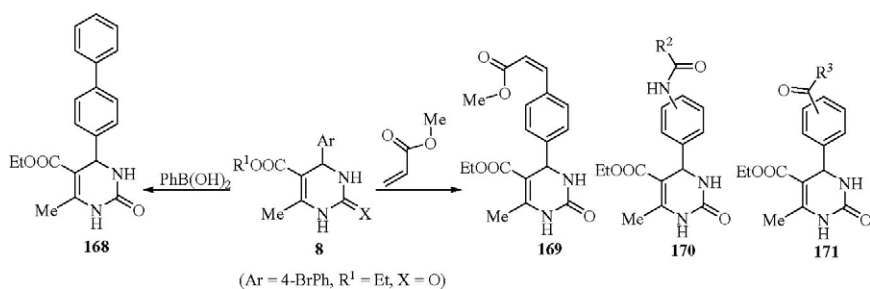
Scheme 63

DHPM derivatives **167** containing a propynyl moiety at C-4 were synthesized from propynals **166** with urea and a ketoester (Scheme 64) (06CHE1492).

The palladium-catalyzed Suzuki coupling allowed transformation of 4-bromoaryl DHPMs **8** by coupling with phenylboronic acid using heterogeneous catalyst Pd/C, Na_2CO_3 in NMP/ H_2O to obtain biphenyls **168**. Intramolecular Heck reaction of **8** with methyl acrylate afforded **169** using $\text{Pd}(\text{OAc})_2$ as the Pd source (Scheme 65) (05MI8). Palladium-catalyzed N-amidation of **8** yielded the corresponding C-4 aryl functionalized amides **170** ($R^2 = \text{CH}_3, \text{Ph}$). Aminocarbonylation of **8** with amines using $\text{Mo}(\text{CO})_6$ yielded amides **171** ($R^3 = \text{NHZ}$; $Z = \text{C}_4\text{H}_9, \text{CH}_2\text{Ph}, \text{Ph}$, etc.) and esters **171** ($R^3 = \text{OCH}_2\text{Ph}, \text{OPh}$), upon alkoxy carbonylation with alcohols. An allyl



Scheme 64



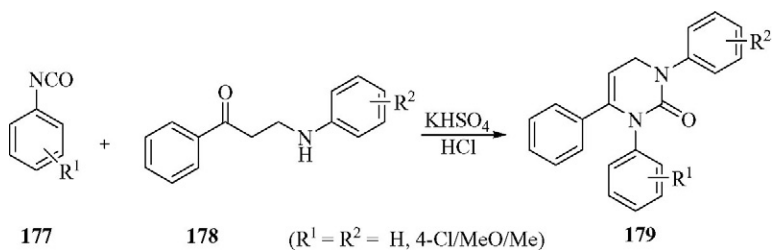
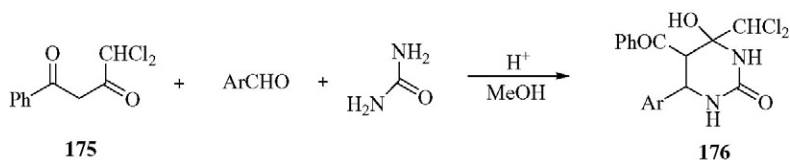
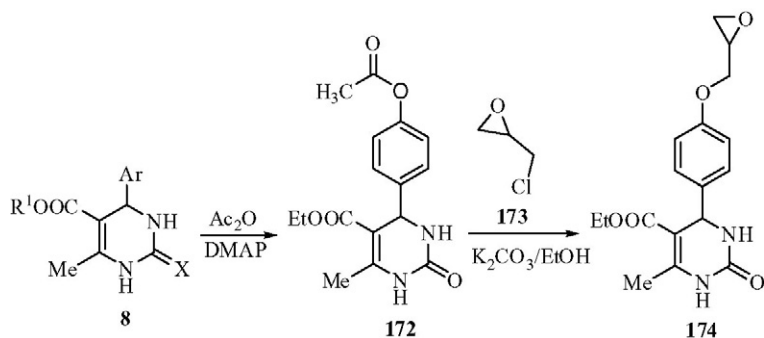
Scheme 65

tether was also introduced at C-4 of an aryl ring ($2\text{-Br} \rightarrow \text{CH}_2 = \text{CH}-\text{CH}_2-\text{SnBu}_3$) *via* a Stille reaction using allyltributylstannane ([00MI4](#)). Modifications (e.g., $\text{NO}_2 \rightarrow \text{NH}_2$, etc.) of the substituents on the C-4 aryl ring have been accomplished through a hydrogenation protocol ([06SL375](#), [07S835](#)).

DHPM **8** (Ar = 4-OHPh, $\text{R}^1 = \text{Et}$, X = O) was acetylated using acetic anhydride-pyridine and a catalytic amount of DMAP to afford **172** ([Scheme 66](#)). Epoxymethylation of **172** by refluxing with epichlorohydrin **173** in dry ethanol and K_2CO_3 provided **174** ([06MI4](#)).

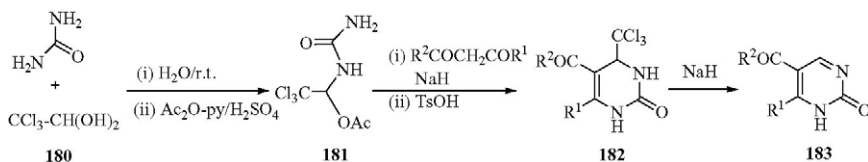
When dichloromethylaroylmethane **175** was used in place of a ketoester as the synthetic equivalent of a two-carbon synthon, perhydropyrimidines **176** bearing dichloromethyl and benzoyl groups on C-4 and C-5, respectively, capable of various transformations were obtained ([Scheme 67](#)) ([06CHE1229](#)).

Synthesis of C-4 unsubstituted 1,3,6-triaryl-3,4-dihydropyrimidin-2(1H)-ones **179**, through aromatic isocyanates **177** with β -aryl-amino-1-phenylpropan-1-ones **178** in refluxing toluene has been achieved ([Scheme 68](#)) ([08JHC1095](#)).

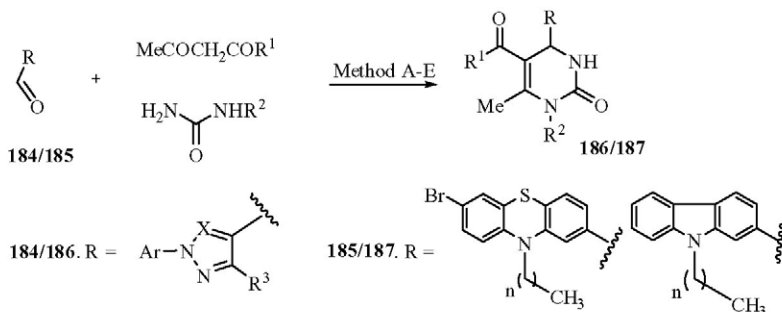


N-(1-Acetoxy-2,2,2-trichloro)ethyl]urea **181** readily available from **180** and urea with Na-enolates of ketoesters followed by heterocyclization-dehydration gave 5-acyl-4-trichloromethyl-1,2,3,4-tetrahydropyrimidinones **182**, which then in the presence of NaH eliminates CHCl_3 to give C-4 unsubstituted **183** (Scheme 69) (10T940).

The three-component Biginelli condensation of pyrazole aldehyde **185** ($\text{Ar} = \text{C}_6\text{H}_5$; $\text{X} = \text{CH}$ or CCl ; $\text{R}^3 = \text{Me}$, Et), β -ketoesters and urea catalyzed by phosphotungstic acid in methanol (Scheme 70, Method A) (05JHC863)



Scheme 69



Method A: Phosphotungstic acid, MeOH, reflux, 7 h; **Method B:** $\text{BF}_3 \cdot \text{OEt}_2$, CuCl_2 , AcOH, THF, reflux; **Method C:** 10 mol% $\text{Sm}(\text{ClO}_4)_3$, EtOH, ultrasound irradiation; **Method D:** 10 mol% $\text{Mg}(\text{NO}_3)_2$, CH_3CN , reflux; **Method E:** Piperidinium triflate catalyst, CH_3CN , 70°C , 24 h

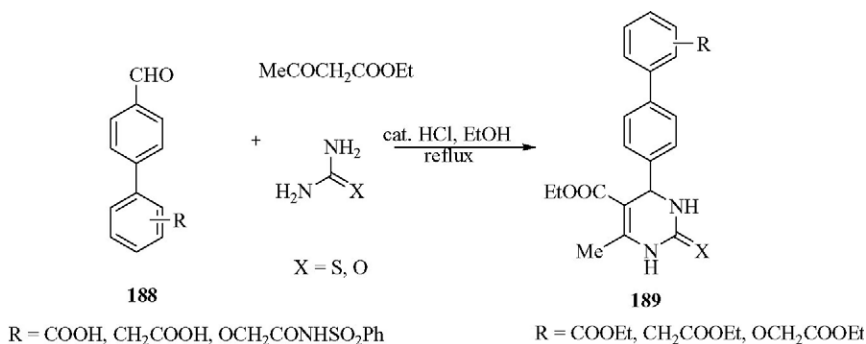
Scheme 70

or by CuCl_2 /acetic acid/ $\text{BF}_3 \cdot \text{OEt}_2$ in THF (Method B) (09IJC(B)718) yielded pyrazoles **186** ($\text{Ar} = \text{C}_6\text{H}_5$; $\text{X} = \text{CH}$ or CCl ; $\text{R} = \text{OEt}$, OMe , Me ; $\text{R}^2 = \text{H}$, Me , Ph). 1,2,3-Triazoles **186** ($\text{Ar} = \text{C}_6\text{H}_5$ or $4\text{-BrC}_6\text{H}_4$; $\text{X} = \text{N}$; $\text{R} = \text{OEt}$, OMe , Me ; $\text{R}^3 = \text{H}$; $\text{R}^2 = \text{H}$) were synthesized from 1,2,3-triazole aldehyde **184** ($\text{Ar} = \text{C}_6\text{H}_5$ or $4\text{-BrC}_6\text{H}_4$; $\text{X} = \text{N}$; $\text{R}^3 = \text{H}$) in the presence of $\text{Sm}(\text{ClO}_4)_3$ (Method C) (10MI3) or $\text{Mg}(\text{NO}_3)_2$ in acetonitrile (Method D) (11JHC92). **187** ($\text{R} = \text{Me}$, $n = 5$) were synthesized when 10-hexyl-10H-phenothiazine-3-carbaldehydes **185** were used in Method E (10T2987).

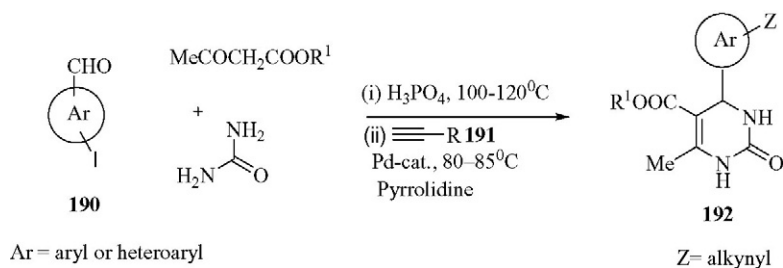
The synthesis of **189** containing substituted biphenyl substituents at C-4 has been reported through a three-component one-pot condensation of biaryl aldehydes **188**, β -ketoester and urea/thiourea (Scheme 71) (10JHC33).

DHPMs **192** containing substituted aryl or heteroaryl groups at C-4 have been achieved through a phosphorous acid-mediated solvent-free Biginelli reaction of iodobenzaldehyde **190** with urea and a β -ketoester, followed by copper-free Sonogashira coupling with terminal alkyne **191** (Scheme 72). Under suitable conditions, Biginelli–Heck ($\text{Z} = \text{alkenyl}$) and Biginelli–Suzuki ($\text{Z} = \text{aryl}$) products were also obtained (11TL1187).

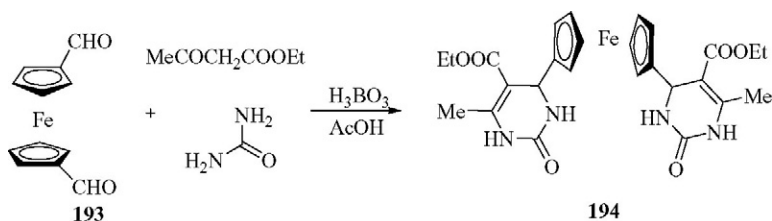
A series of ferrocenes containing *mono*- and *bis*-DHPMs **194** (Scheme 73) was prepared by boric acid-mediated three-component



Scheme 71



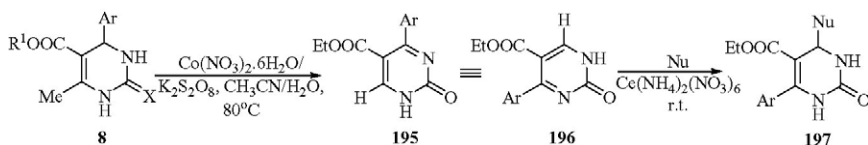
Scheme 72



Scheme 73

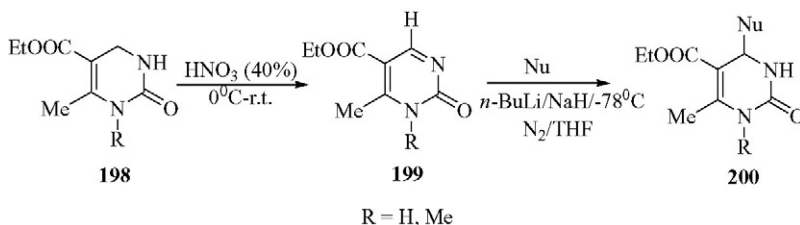
Biginelli reaction of formyl- and 1,1'-diformylferrocene **193**, β -ketoesters and urea (09JOM(694)3667).

Very limited work appears on the postcondensation derivatization of C-4 DHPMs. On oxidation with $\text{Co(II)/S}_2\text{O}_8^{2-}$, **8** ($\text{Ar} = \text{Ph, 2-ClPh, 4-ClPh, 3-NO}_2\text{Ph, 4-OMePh}$; $\text{R}^1 = \text{Et}$; $\text{X} = \text{O}$) afforded C-6 unsubstituted **195**. Elaboration of C-4 of the tautomeric mixture (**195**, **196**) through a 1,4-nucleophilic addition furnished **197** (Scheme 74) (07T12215).



Scheme 74

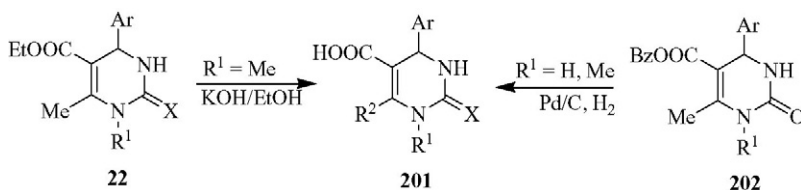
Singh et al. have demonstrated that C-4 unsubstituted **199**, obtained through oxidation (01JHC1345) of **198** by HNO_3 , undergoes regio- and chemoselective nucleophilic addition at C-4 to furnish C-4 elaborated **200** (07TL1349), including enantiomerically pure DHPMs, when optically pure sulfoxide carbanions (Scheme 75) (09EJO3258) were used.



Scheme 75

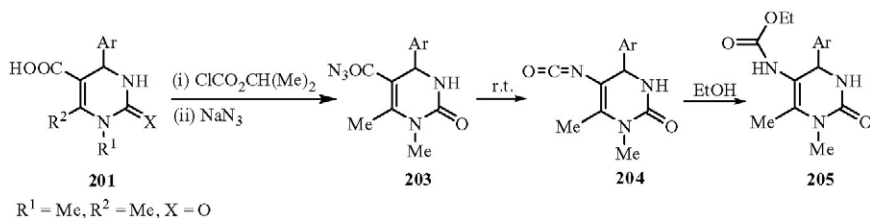
3.5 Synthesis of C-5 functionalized DHPM derivatives

The C-5 ester of DHPM does not respond to hydrolysis (33JA3781, 93G360) or attack by nucleophiles (07TL1349, 07T12215, 09EJO3258). Hydrogenolysis of benzyl ester **202** furnished N-1 unsubstituted carboxylic acid **201** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{X} = \text{O}$), which on decarboxylation yielded C-5 unsubstituted derivatives (76M587). While N-1 unsubstituted **22** ($\text{R}^1 = \text{H}$, $\text{X} = \text{O}$) are inert toward acid or base hydrolysis, N-1 methyl **22** ($\text{R}^1 = \text{Me}$, $\text{X} = \text{O}$) was saponified using 5% alcoholic KOH to carboxylic acid **201** ($\text{R}^2 = \text{Me}$) (Scheme 76). The unreactivity of the ester may be attributed to strong conjugation with the adjacent vinylic alkene, supported by the fact that the hexahydropyrimidine carboxylic ester is readily hydrolyzed (33JA3781).



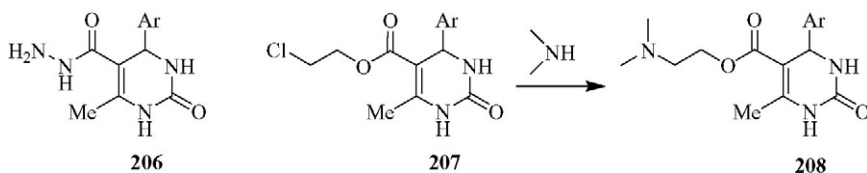
Scheme 76

N-1 substituted carboxylic acids **201** ($R^1 = \text{Me}$, $R^2 = \text{Me}$, $X = \text{O}$) are transformed into carboxylic azides **203** with 1-methylethyl chloroformate and sodium azide in DMSO (Scheme 77). Curtius rearrangement of **203** at room temperature yields isocyanates **204** that further react with nucleophiles such as ethanol to furnish urethanes **205** (75S405, 92T5473).



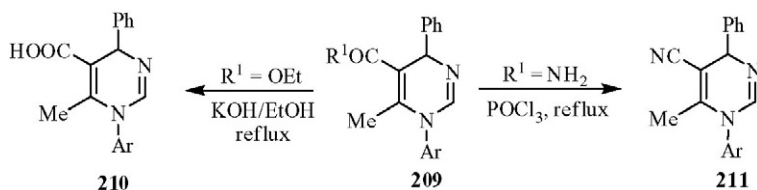
Scheme 77

Treatment of **22** ($R^1 = \text{Me}$, $X = \text{O}$) with hydrazine furnished hydrazides **206**. Nucleophilic substitution on the alkyl chain of the C-5 substituent of **207** with dialkylamine gave **208** (Scheme 78) (78KFZ72).



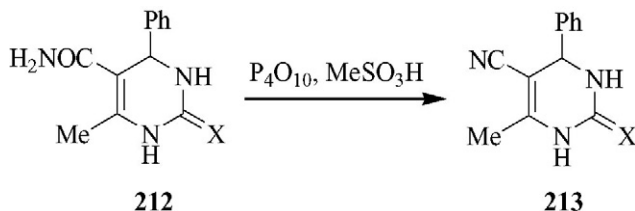
Scheme 78

Khanina et al. have described the saponification (refluxing ethanolic KOH) of the C-5 ethoxycarbonyl group of **209** ($R^1 = \text{OEt}$) to acid **210**. The transformation of **209** ($R^1 = \text{NH}_2$) to the C-5 cyano derivative **211** on refluxing in POCl_3 has also been achieved (Scheme 79) (82KGS535).



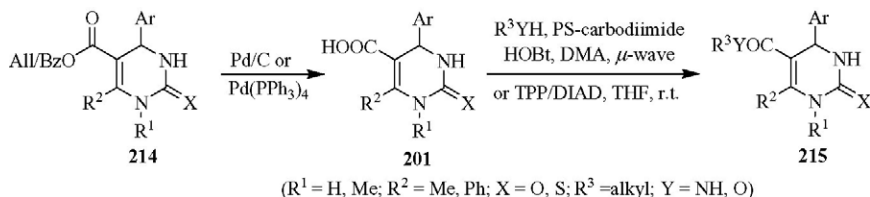
Scheme 79

Dihydropyrimidin-5-carbonitrile **213**, not obtained by direct Biginelli condensation owing to the instability of the precursor cyanoacetone, was made through the dehydration of carboxamide **212** ($X = O, S$) using P_4O_{10} in methanesulfonic acid (Scheme 80) (89JHC55). The C-5 cyano derivative **213** was obtained from **212** ($X = O$) on heating with polyphosphate ester in a sealed tube (08TL3009).



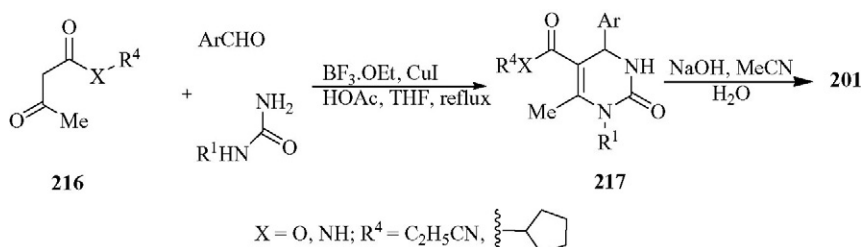
Scheme 80

Hydrogenation using Pd/C and $Pd(PPh_3)_4$ removes the C-5 benzylic and allylic ester of **214**, respectively, to furnish acid **201**, which with amines using polymer-supported coupling reagents gave C-5 amide substituted **215** ($Y = NH$) (Scheme 81) (04OL771). Further functionalization of **201** with alcohols utilizing Mitsunobu conditions provided C-5 ester **215** ($Y = O$) (06T4651).



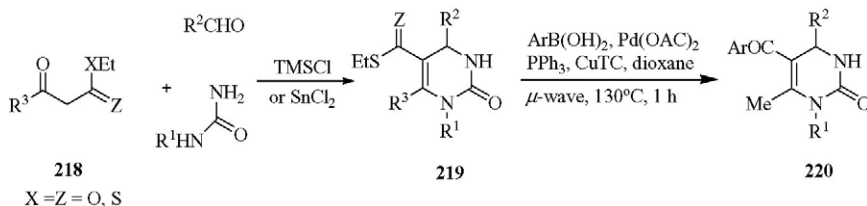
Scheme 81

To investigate structure–activity relationships at C-5 of DHPMs without the need to prepare individual β -ketoesters, the condensation of β -ketoesters **216** with aldehydes and urea in the presence of boron trifluoride afforded **217**, bearing amides and esters ($R^1 = Ph, CH_2Ph, n-Bu$; $R^4 = C_2H_5CN, C_5H_9$; $X = O, NH$), at C-5 (Scheme 82) (06BMC3504). C-5 ester **217** ($X = O, R^4 = C_2H_5CN$) afforded **201** ($R^2 = Me, X = O$), on hydrolysis under basic conditions. Esterification of **201** with alcohols or phenols in the presence of EDC afforded **215** ($Y = O$). A solid-phase approach for the synthesis of **201** (04PAC1017) has also been reported.



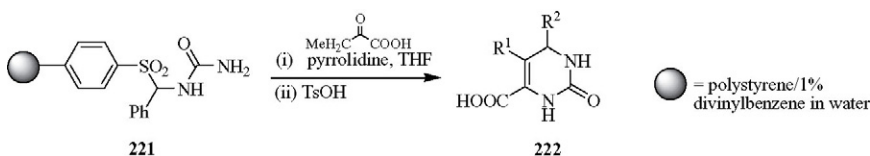
Scheme 82

Trimethylsilyl chloride-mediated Biginelli reaction of *S*-ethyl acetoacetate **218** ($\text{Z} = \text{O}; \text{X} = \text{O}, \text{S}$), aromatic aldehydes and urea furnish **219** ($\text{Z} = \text{O}; \text{R}^3 = \text{Me}$). Subsequent Pd-catalyzed Cu-mediated Liebeskind–Srogl cross-coupling with boronic acids furnishes C-5 aryl **220** (Scheme 83) (07MI13). 5-Methylmercaptothi carbonyl DHPM **219** ($\text{Z} = \text{S}$) is formed when β -oxodithioesters **218** ($\text{Z} = \text{X} = \text{S}$) replaces *S*-ethyl acetoacetate **218** ($\text{Z} = \text{O}; \text{X} = \text{S}; \text{R}^3 = \text{Me}, \text{Ph}$) (Scheme 83) (09JOC3141).



Scheme 83

Preparation of **222** ($\text{R}^1 = \text{Me}, \text{Ph}; \text{R}^2 = \text{Ph}$) bearing a methyl and a carboxylic acid group at C-5 and C-6, respectively, was achieved through a solid-phase sulfone linker strategy involving condensation of an α -keto acid with polymer-supported (benzenesulfonyl substituted)thiourea **221** (Scheme 84) (05MI10).



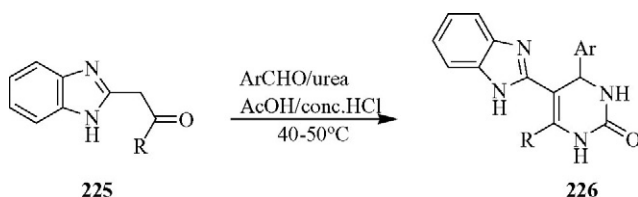
Scheme 84

In an attempt to prepare “drug-like” heterocyclic cores such as **224**, a base catalyzed reaction of *N*-methylurea with α -substituted- α,β -enone **223** has been described (Scheme 85) (03OL1551). This protocol allowed the methyl substituent to be placed at N-3 rather than at N-1 (04OR1).



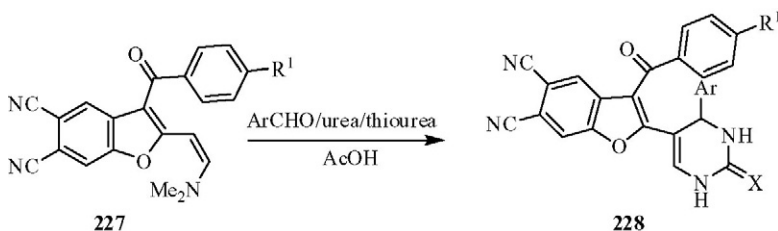
Scheme 85

Acid-catalyzed cyclocondensation of 2-acylmethyl-1*H*-benzimidazole **225** with aromatic aldehydes and urea furnished C5-benzimidazole substituted DHPM **226** (Scheme 86) (03CHE455).



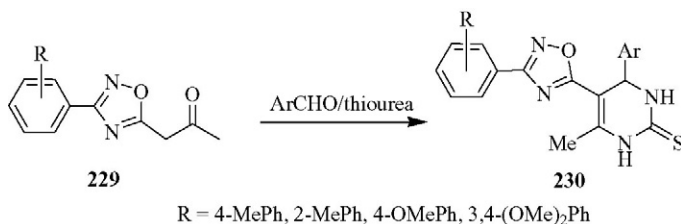
Scheme 86

Glacial acetic acid-catalyzed Biginelli condensation of 2-(2-dimethylaminovinyl)-5,6-dicyanobenzofurans **227** (*R*¹ = Me, OMe) with aldehydes and urea/thiourea furnished 5-(benzofuran-2-yl) substituted **228** (X = O, S; *R*¹ = Me, OMe) (Scheme 87) (11MC46).



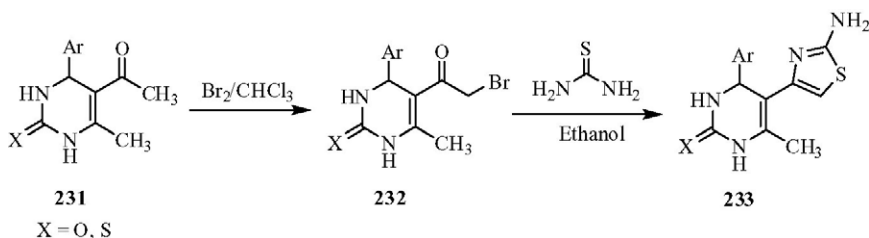
Scheme 87

One-pot three-component cyclocondensation of 1-(3-aryl-1,2,4-oxadiazol-5-yl)acetone **229**, thiourea, and aromatic aldehydes formed 5-(1,2,4-oxadiazol-5-yl) DHPM **230** (Scheme 88) (09MI8).



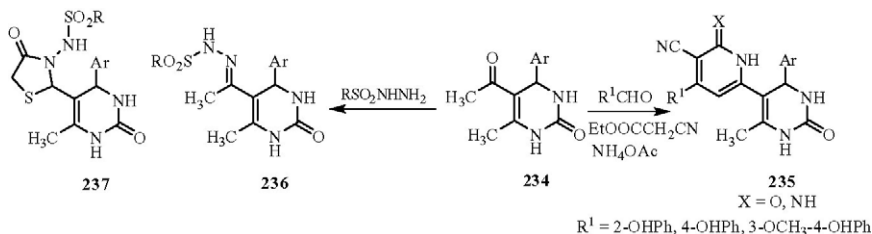
Scheme 88

Similarly, α -bromination of the 5-acetyl group of **231** with bromine afforded 5-(2-bromoacetyl) **232**, which upon cyclocondensation with thiourea yielded 5-(2-aminothiazol-4-yl)-3,4-dihydropyrimidin-2(1H)-one/thione **233** (Scheme 89) (09IJC(B)1732).



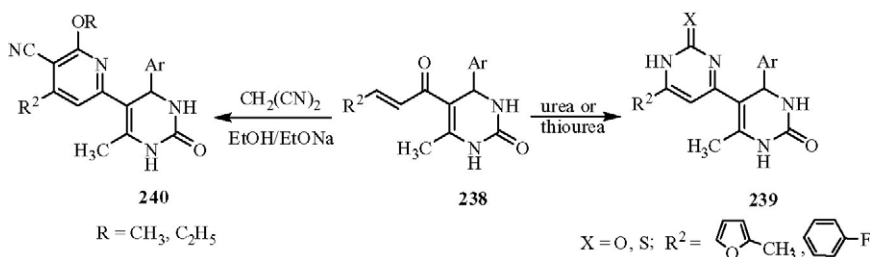
Scheme 89

Transformation of C-5 acetyl-substituted DHPM **234** (Ar = 3,4-(OMe)₂Ph) with an aldehyde and ammonium acetate and ethyl cyanoacetate in butanol afforded **235** (X = O), further transformed to **235** (X = NH) (Scheme 90). Also, **236** (R = Ph, 4-CH₃Ph) was obtained from **234** with arylsulfonylhydrazides, which following cyclocondensation with thioglycolic acid in dry benzene furnished thiazolidinone **237** (10MI2).



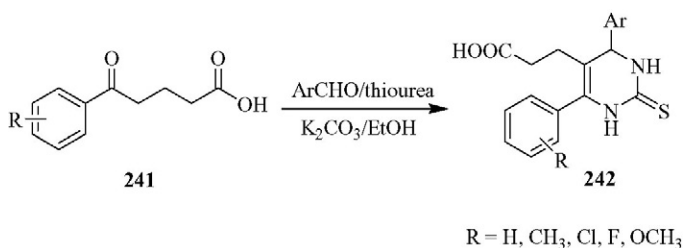
Scheme 90

5-Chalconyl derivatives **238**, obtained from **234**, react with urea in boiling ethanolic hydrochloric acid to give **239** ($X = O$) (Scheme 91). Similarly, **238** with thiourea in boiling potassium hydroxide afforded **239** ($X = S$). 2-Alkoxy pyridine derivatives **240** were obtained when **238** was condensed with malononitrile in sodium ethoxide/ethanol (10MI2).



Scheme 91

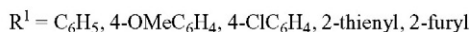
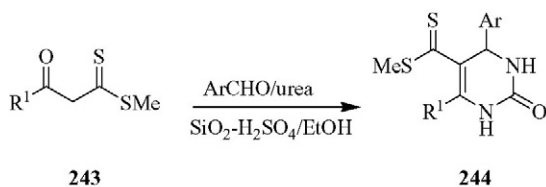
A series of 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acids **242** was synthesized by condensation of thiourea, 5-oxopentanoic acid **241** and aldehydes using K_2CO_3 in ethanol (Scheme 92) (10BMC4424).



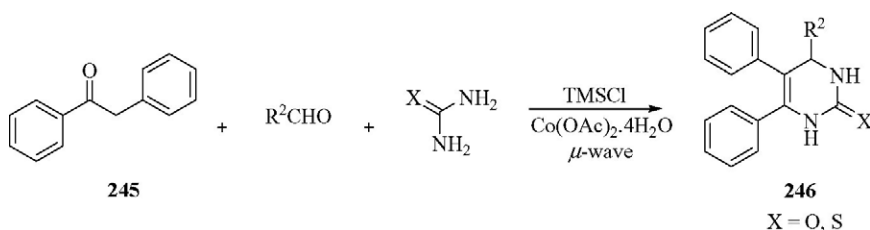
Scheme 92

Through a modified Biginelli condensation using urea, aldehydes, and β -oxodithioesters **243**, DHPM **244** have been synthesized employing a $\text{SiO}_2\text{--H}_2\text{SO}_4$ as a recyclable catalyst (Scheme 93) (10JOC7785).

DHPM derivatives **246** having phenyl moieties at C-5 and C-6 were prepared by a microwave-assisted, three-component one-pot condensation of an aromatic aldehyde, deoxybenzoin **245** and urea or thiourea, using TMSCl and $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ as Lewis acid catalyst (Scheme 94) (09PS1796).

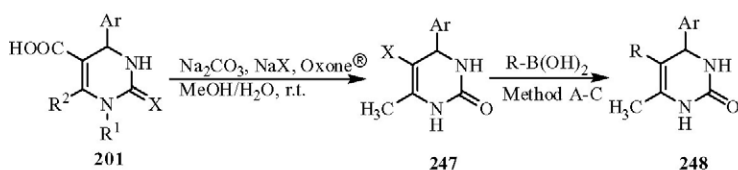


Scheme 93



Scheme 94

C5-substituted **248** were synthesized through the Suzuki–Miyaura reaction of 5-halo derivatives **247** ($X = \text{Br}, \text{I}$), prepared from carboxylic acid **201** ($R^1 = \text{H}$, $R^2 = \text{Me}$, $X = \text{O}$) through halodecarboxylation with Oxone and sodium halide in basic aqueous methanol (Scheme 95). Suzuki–Miyaura reaction of **247** with boronic acids afforded C-5 substituted derivatives, depending upon the nature of the boronic acid (10TL5103).



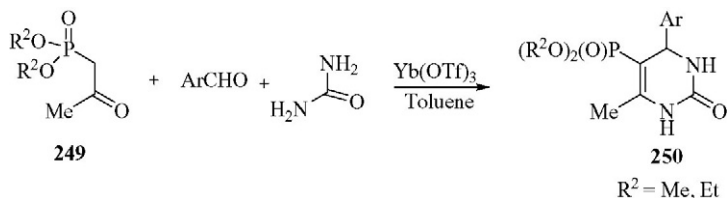
Method A: 2.0 equiv RB(OH)_2 , 5.0 equiv KF , 0.05 equiv $\text{Pd}_2(\text{dba})_3$, 0.05 equiv $\text{Pd}(\text{t-Bu}_3\text{P})_2$, THF, r.t., 18 h

Method B: same as (A), reaction conducted at 60°C , 18 h

Method C: 2.2 equiv RB(OH)_2 , 0.05 equiv $\text{PdCl}_2(\text{dppf})$, 4.0 equiv aq Na_2CO_3 , 1,4-dioxane, 70°C , 18 h

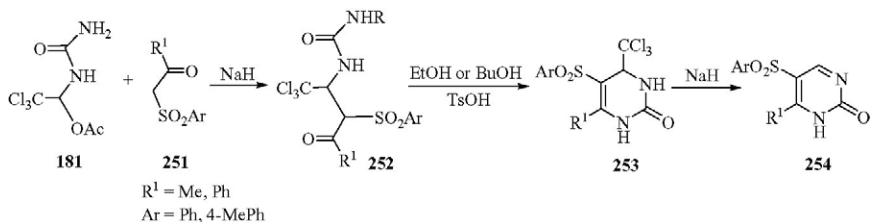
Scheme 95

DHPM derivatives **250** bearing a phosphoryl moiety at C-5 are obtained when *O,O*-dialkyl-2-oxo-propanephosphonates **249** reacts with urea and an aldehyde (Scheme 96) (03HAC13).



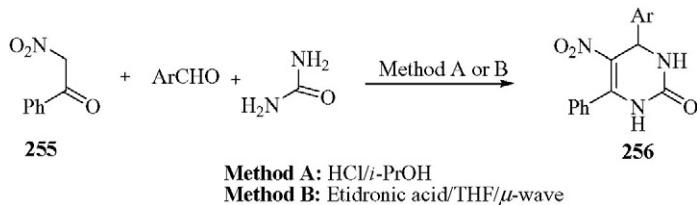
Scheme 96

253 containing an arylsulfonyl group at C-5 was obtained through heterocyclization–dehydration of trichloromethyl-substituted oxoalkylureas **252** (prepared using ureidoalkylation of a sodium enolate of α -arylsulfonyl-substituted ketones **251** with *N*[(1-acetoxy-2,2,2-trichloro)ethyl] ureas **181**) in the presence of *p*-TsOH. Elimination of CHCl_3 from **253** using a base furnishes **254** (Scheme 97) (10T7219).



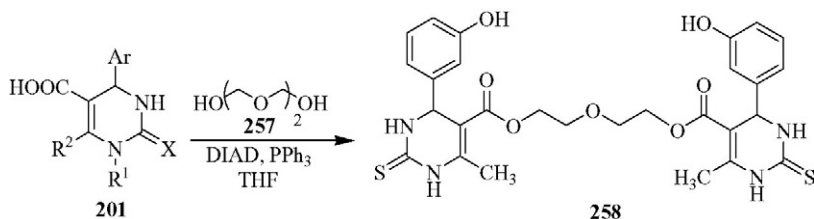
Scheme 97

5-Nitro DHPM **256** was synthesized through a modified Biginelli condensation involving cyclocondensation of α -nitro acetophenone **255** with an aldehyde and urea in the presence of conc. HCl (Scheme 98, Method A) (06BMC1418) or etidronic acid in THF under microwave irradiation (Method B, Scheme 98) (09MI3).



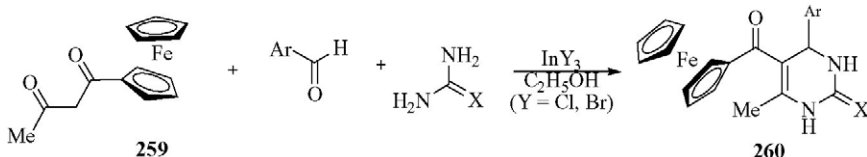
Scheme 98

When **201** ($R^1 = \text{H}$, $R^2 = \text{Me}$, $X = \text{S}$, $\text{Ar} = 3\text{-OHPh}$) reacted with diethylene glycol **257** in THF along with DIAD and PPh_3 , C-5 linked DHPM **258** was obtained (Scheme 99) (07MI4).



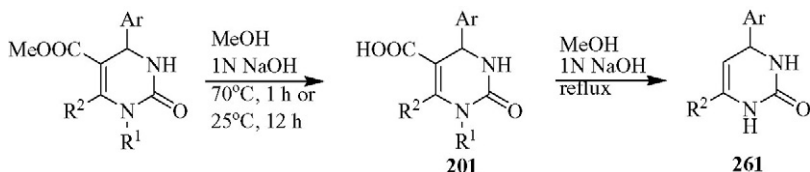
Scheme 99

Indium (III) halides catalyzed a three-component Biginelli condensation of ferrocenyl-1,3-diketones **259**, aldehydes, and urea (or thiourea) and furnished 5-ferrocenyl-DHPMs **260** ($X = \text{O}$, S) (Scheme 100) (03JOM(672)52).



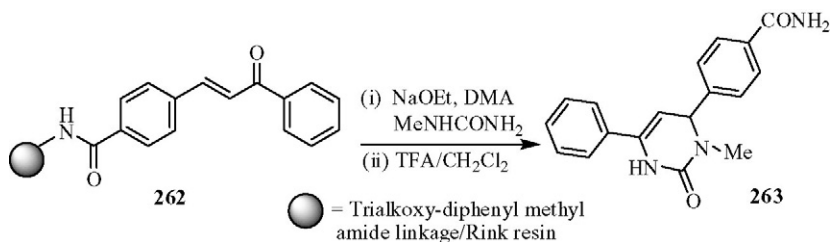
Scheme 100

C-5 unsubstituted DHPMs **261** result on refluxing a C-5 methyl ester in aqueous alkali (Scheme 101); side products were also formed (98TL9315, 05MC73).



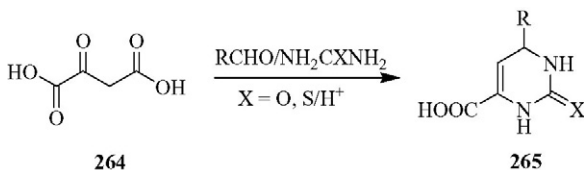
Scheme 101

Reacting polystyrene-grafted α,β -unsaturated ketones **262** with *N*-methylurea gave **263**, which was elusive in the classical Biginelli condensation using *N*-methylurea that generally furnishes N-1 substituted DHPMs (Scheme 102) (98JOC723).



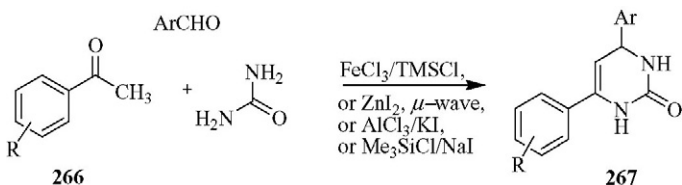
Scheme 102

Oxalacetic acid **264** in the acid-catalyzed Biginelli condensation with urea/thiourea and an aldehyde gave C-5 unsubstituted **265** bearing a carboxylic acid at C-6 (Scheme 103) (00JOC6777, 11T1294).



Scheme 103

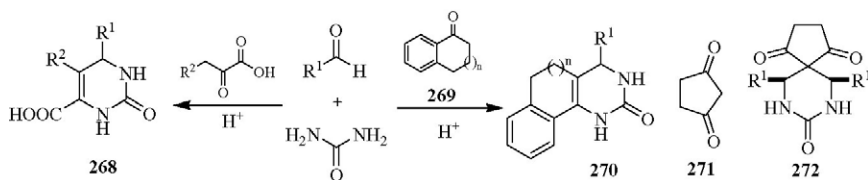
The use of ketones **266** in place of β -ketoesters in the Biginelli condensation under slightly modified conditions [$\text{FeCl}_3/\text{TMSCl}$ (04TL7951), AlCl_3 and KI , in refluxing CH_3CN (07IJC(B)1690), ZnI_2 catalyst in solvent-free cyclocondensation using microwave radiations (07T1981), and iodotrimethylsilane/ NaI in refluxing CH_3CN (05HCA2996)), furnished C-5 unsubstituted **267** (Scheme 104).



Scheme 104

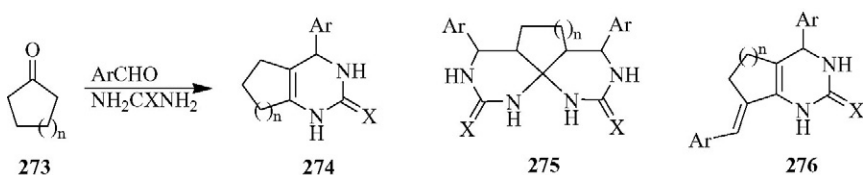
Condensation of α -keto acids, an aldehyde and urea furnished DHPMs **268** with inverted functionalities at C-5 and C-6. Cyclic ketones **269** or cyclic β -dicarbonyl derivatives **271** with acidic methylene groups provided fused **270** and spiro-fused **272**, respectively (Scheme 105) (03TL4559).

Condensation of cyclic ketones **273** with urea/thiourea and an aromatic aldehyde furnished bicyclic derivatives **274–276**, depending upon



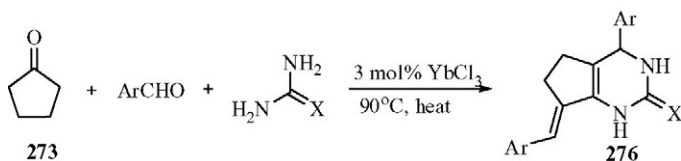
Scheme 105

the ketone in combination with the urea/thiourea and the substitution pattern of the aldehyde. Thus, while **273** ($n = 2, 4$, and 8) furnished fused heterobicyclic **274** ($X = S$ and O), **273** ($n = 1-3$) gave spiro heterotricyclic **275** ($X = O$). **276** ($X = O$) was obtained from **273** ($n = 1, 3, 4$) (Scheme 106) (05EJO2354).



Scheme 106

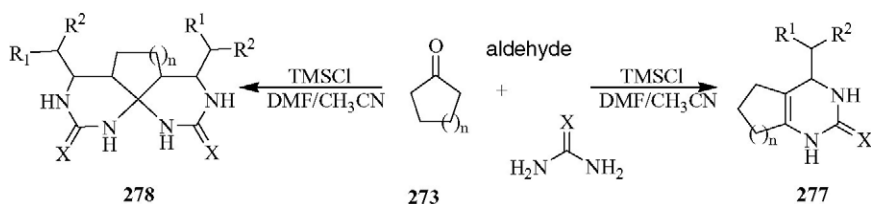
Similar condensation of cyclopentanone **273** ($n = 0$) with urea/thiourea and 3 mol% of YbCl₃ furnished **276** ($X = O, S$; $n = 1$) (Scheme 107) (09T10608).



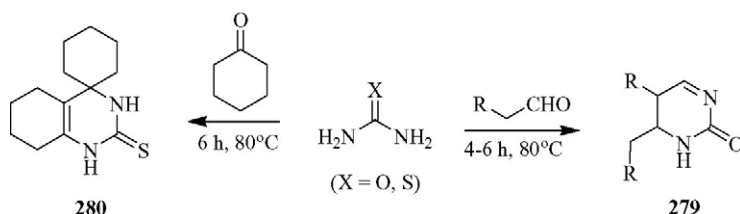
Scheme 107

Condensation of **273** with urea/thiourea and an aliphatic aldehyde provided bicyclic and tricyclic derivatives **277** and **278**. Thus, **273** ($n = 2$ and 3) with thiourea ($X = S$) and isobutyraldehyde gave **277** (Scheme 108). Similarly, **277** was derived from **273** ($n = 4$ and 8) and series of aliphatic aldehydes. **278** was obtained from **273** ($n = 1$) with thiourea ($X = S$) and isobutyraldehyde and n -heptaldehyde. Urea, **273** ($n = 8$) and isobutyraldehyde or n -heptaldehyde furnished **277** ($X = O$) (Scheme 108) (05EJO2354).

Self-condensation of an aliphatic aldehyde and urea at 80 °C (TMSCl, DMF/MeCN) provided 5,6-disubstituted-5,6-dihydro-(1*H*)-pyrimidin-2



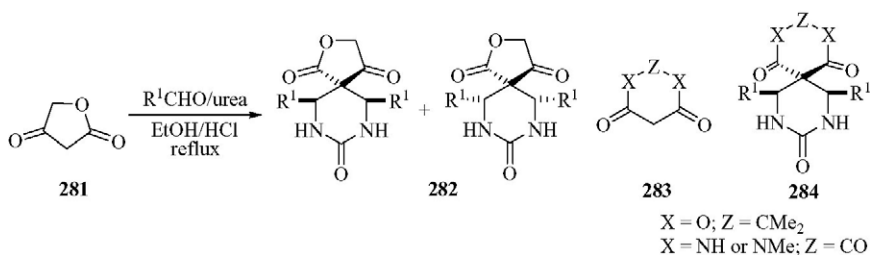
Scheme 108



Scheme 109

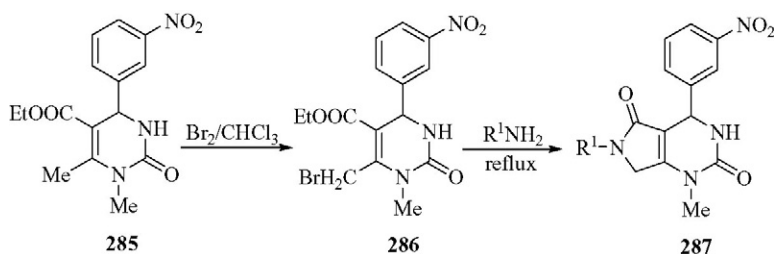
one **279** (Scheme 109). Similarly, cyclohexanone with thiourea gave spiro heterocyclic **280** (Scheme 109) (05EJO2354).

In a modified Biginelli reaction, cyclic β -keto ester **281** with urea and an aldehyde (1:2 molar ratio) gave spiro heterobicyclic aliphatic **282** (Scheme 110) (00MI3) with substituents exclusively in the *cis* configuration. Likewise, a pseudo four-component reaction of an aldehyde and urea (2:1 molar ratio) and a cyclic β -diester or β -diamide **283** (1 equiv), using microwave irradiation under solvent-free conditions, furnished spiro-fused **284** (Scheme 110) (04TL2575).



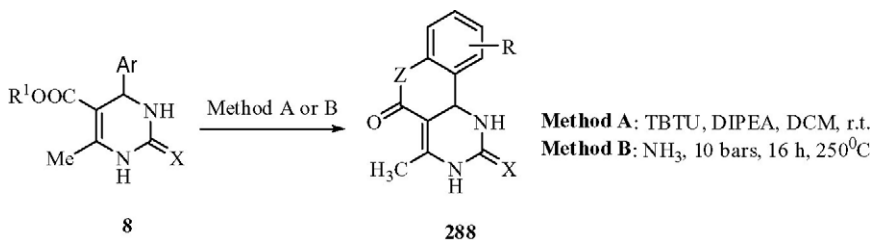
Scheme 110

Monobromination at the C-6 methyl of **285** using bromine in chloroform afforded **286**, which with methylamine and cyclohexyl amine furnished fused pyrrolo-pyrimidine **287** ($\text{R}^1 = \text{Me}, \text{Ph}$) (Scheme 111) (01JHC1051).



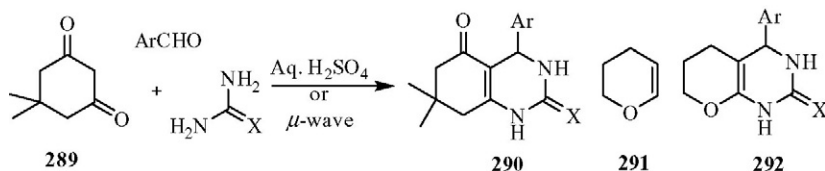
Scheme 111

Lactonization of hydroxy acids **8** (Ar = 2-OHC₆H₄, R¹ = H, X = O) to fused tricyclic benzopyrano[4,3-*d*]-pyrimidines **288** (Z = O) was achieved using 2 equiv of TBTU and 4 equiv of DIPEA in dichloromethane (Method A, Scheme 112) (09T5949). Moreover, **288** (Z = NH) was obtained from **8** (Ar = 2-ClC₆H₄; R¹ = Et; X = O, S) through cyclization with ammonia on high-temperature heating (Method B, Scheme 112) (08MI10).



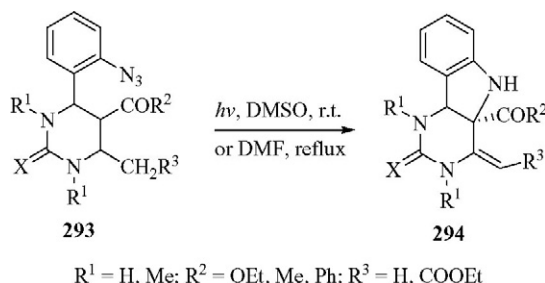
Scheme 112

Octahydroquinazolinones and their mercapto derivatives **290** (X = O and S, respectively) have been synthesized by a three-component condensation of dimedone **289**, urea/thiourea and an aldehyde in aqueous H₂SO₄ (06BMC4479) or under microwave irradiation without solvent (Scheme 113) (05MI6). Similar L-proline/TFA catalyzed reaction of **291** gave **292** (X = O, S) (Scheme 113) (09T9350).



Scheme 113

Fused indoles **294** have been synthesized by photochemical and thermal cyclization of **293** *via* electrophilic addition of a nitrene and a rearrangement (Scheme 114) (11TL192).

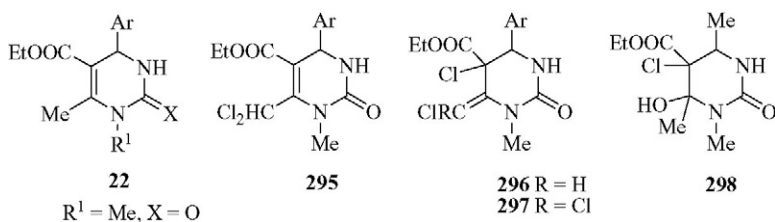


Scheme 114

3.6 Synthesis of C-6 elaborated DHPM derivatives

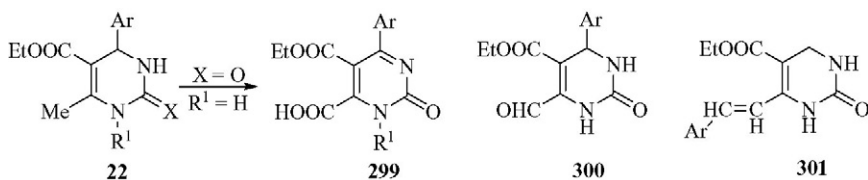
Acetoacetic esters are generally employed as one of the three components in the DHPM synthesis, which leads to an alkyl or aryl substituent at the C-6 position that is capable of further modifications.

Chlorination of DHPM **22** ($\text{X} = \text{O}$, $\text{R}^1 = \text{Me}$) with PCl_5 in refluxing phosphorous oxychloride, furnished **296** and **297**, in addition to expected dichloromethyl derivative **295** (87KGS668). However, the chlorination of C4-Me derivatives with elemental chlorine in chloroform at 4°C furnished hexahydropyrimidine **298** (66M1408).

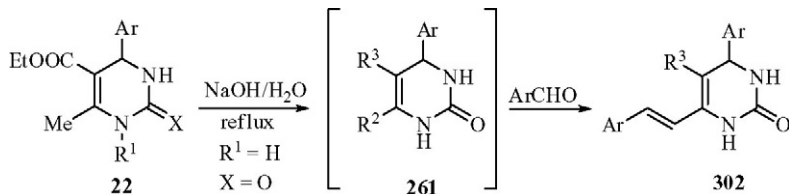


Selenium dioxide oxidation of the C-6 methyl of DHPM **22** ($\text{X} = \text{O}$, $\text{R}^1 = \text{H, Me}$) furnished acid **299** ($\text{R}^1 = \text{H, Me}$) and an aldehyde **300** (Scheme 115) (64CPB804). However, condensation of the C-6 methyl of C-4 unsubstituted DHPM with aromatic aldehydes provided styryl derivatives **301** (52ZOB1680).

DHPM derivatives **302** ($\text{R}^3 = \text{COOEt}$) having a styryl group at C-6 were obtained from **22** ($\text{X} = \text{O}$, $\text{R}^1 = \text{H}$) on alkaline hydrolysis. The C-5 unsubstituted intermediate **261** ($\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$) with aromatic aldehydes furnished **302** ($\text{R}^3 = \text{H}$) (Scheme 116) (05MC73) in refluxing xylene/*p*-TsOH (01MI1).

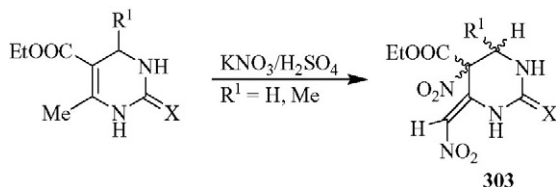


Scheme 115



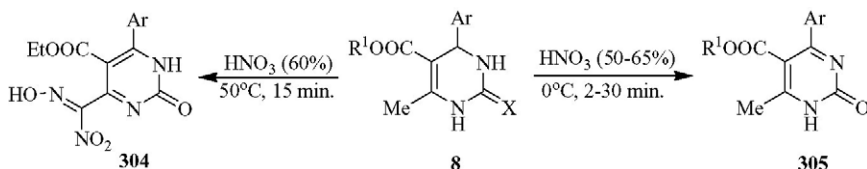
Scheme 116

Nitration of DHPM, unsubstituted as well as with a methyl group at C-4, gave *E* and *Z* isomers of C-6, namely C-5 dinitrated **303** (Scheme 117). With C-4 aryl substituted DHPM, the C-4 aryl group was additionally nitrated (89H761).



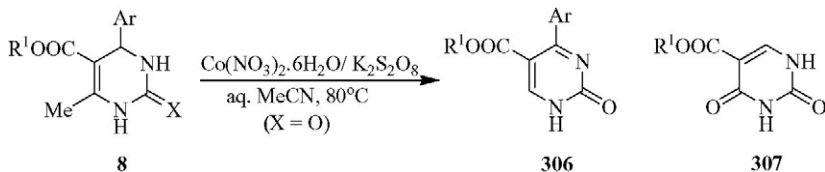
Scheme 117

Nitration of DHPM **8** (X = O) with 60% nitric acid formed C-6 functionalized nitrolic acid **304** (X = O, R¹ = Et). Depending upon the concentration of the nitric acid, temperature and the like, **305** was obtained through oxidative dehydrogenation (Scheme 118) (01JHC1345).



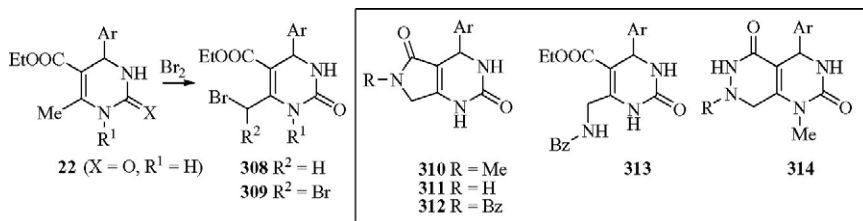
Scheme 118

Following 3,4-dehydrogenation of **8** in the presence of cobalt (II)/thio-sulfate, C-6 methyl was additionally dealkylated to furnish 1,2-dihydro **306** (Scheme 119). The aryl group at C-4 of DHPM assisted oxidative C-6 dealkylation while C-4 alkyl DHPMs gave 2,6-dioxo **307** (07T666).



Scheme 119

Stepwise substitution of the methyl group of **22** with bromine led to C-6 bromomethyl **308** ($R^1 = R^2 = H$) and dibromomethyl **309** ($R^1 = H, R^2 = Br$) (Scheme 120) (66M1408). The former with methylamine, potassium phthalimide, benzylamine provided pyrrolo[3,4-*d*]-pyrimidinone **310**, **311**, **312** (and **313**), respectively. However, **308** with an hydrazine derivative furnished pyridazino-[4,5-*d*]-pyrimidinones **314** (92JMC3254).

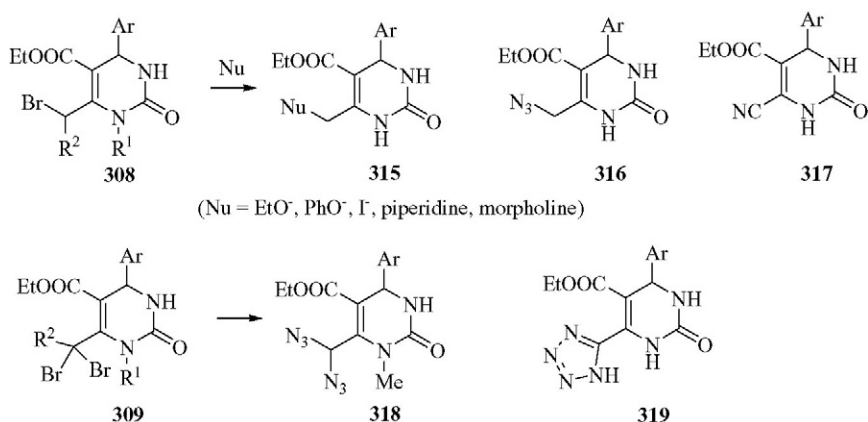


Scheme 120

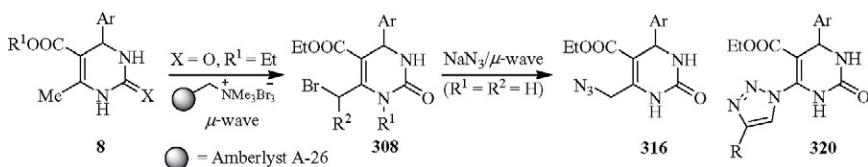
DHPM **308** ($R^1 = R^2 = H$) with nucleophiles gave C-6 substituted **315** (Scheme 121). With sodium azide, C-6 azidomethyl **316** was obtained, which with Pd(0) and a hydrogen acceptor such as diphenylacetylene furnished C-6 cyano **317**, also formed from **309** with sodium azide in HMPT. Sodium azide with **317** furnished tetrazole **319**. The N-1 methyl of **309** ($R^1 = Me, R^2 = H$) with sodium azide gave geminal diazide **318** (Scheme 121) (90LA505).

C-6 bromination of **8** using a recyclable polymer-supported brominating agent gave **308** ($R^1 = R^2 = H$), which on microwave-assisted azidation gave **316**, then treated with terminal acetylenes ("click chemistry") to furnish C-6 elaborated 6-(1,2,3-triazol-1-yl) **320** (Scheme 122) (04MI6).

In the addition reactions of organometallic reagents to pyrimidin-2-(1*H*)-one/thione **321**, Grignard reagents added regioselectively at C-6

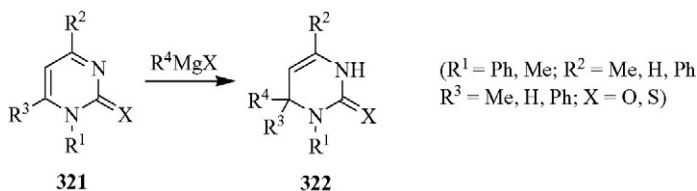


Scheme 121



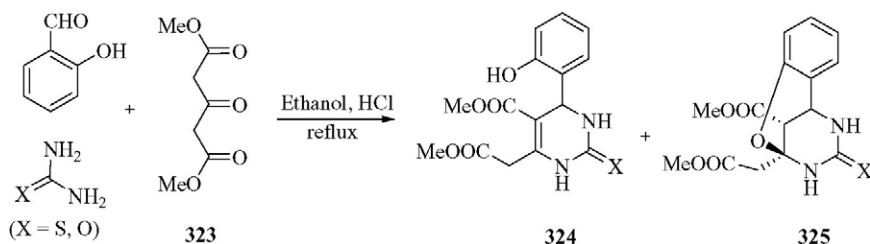
Scheme 122

(Scheme 123), but alkyllithium reagents showed a preference for C-4. Often, products from both C-4 and C-6 additions have been obtained (81JCS(P)489).



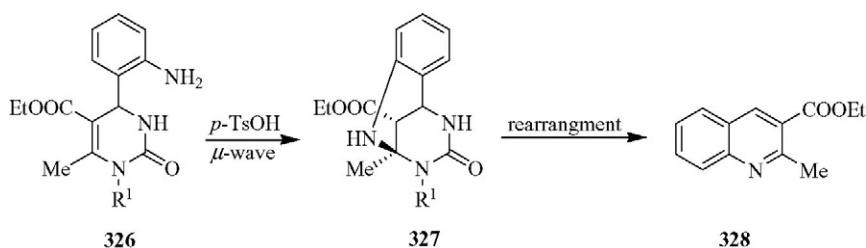
Scheme 123

Using dialkyl acetone-1,3-dicarboxylate **323** in place of the traditional β-ketoesters in a conventional Biginelli condensation (HCl or *p*-TsOH) furnished **324**, along with conformationally restricted tricyclic intramolecular Michael addition product **325** (Scheme 124) (07JHC455, 08TL3520).



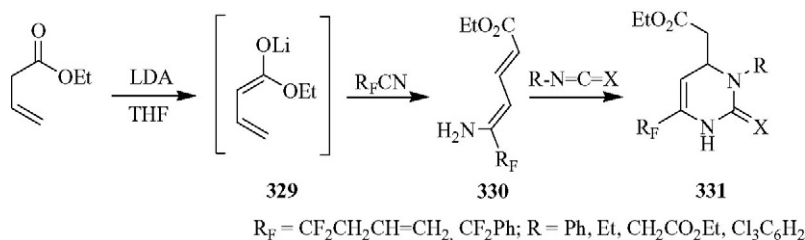
Scheme 124

Intramolecular Michael addition of the 2-amino group on a C-4 aryl ring in **326** to the C-6 position provided **327**, which further rearranged to quinoline **328** (Scheme 125) (02MI1).



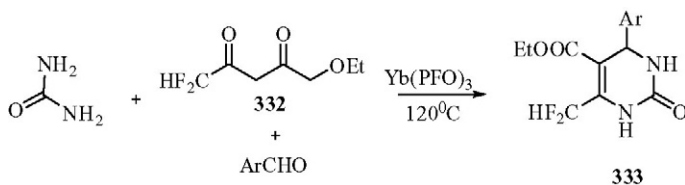
Scheme 125

Lithium enolate **329** and a nitrile-furnished enamino ester **330**, which on condensation with isocyanates/isothiocyanates gave N-3 substituted **331** (X = O, S) through a tandem nucleophilic addition–intramolecular aza-Michael reaction (Scheme 126) (09JFC1145).



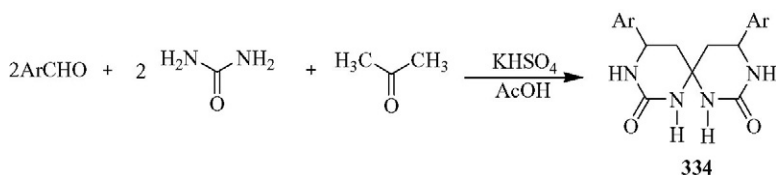
Scheme 126

Similarly, one-pot condensation of **332**, urea and an aldehyde using ytterbium perfluorooctanoate under solvent-free conditions made difluoromethyl substituted **333** (Scheme 127) (11JFC155).



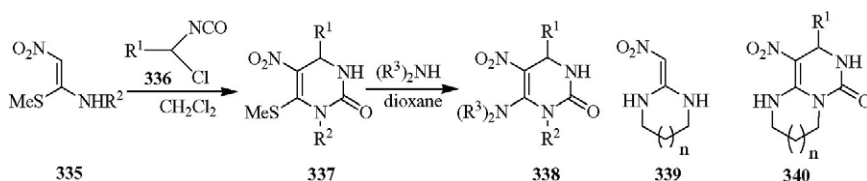
Scheme 127

An aromatic aldehyde, urea and acetone (2:2:1 molar ratio), containing potassium hydrogen sulfate in boiling acetic acid yielded 4,4'-spiro **334** (Scheme 128) (07S2782).



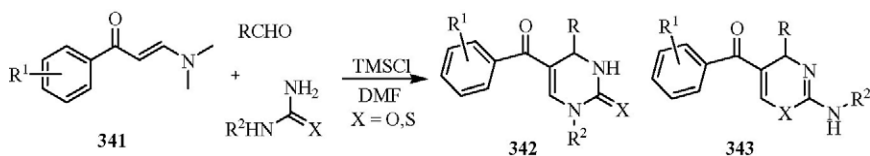
Scheme 128

The cyclocondensation of 1-chlorobenzyl isocyanate **336** with *S,N*-nitroketeneacetals **335** ($\text{R}^2 = \text{alkyl}$) furnished C-6 methylthio-5-nitro-3,4-dihydropyrimidinones **337** (Scheme 129). *N*-Aryl derivative **335** ($\text{R}^2 = \text{aryl}$) gave unidentifiable products. **337** with aliphatic primary and secondary amines as well as ammonia provided **338**. The nitro group of **338** was eliminated on heating in dioxane with a catalytic amount of a strong organic base. Bicyclic analogs **340** were synthesized from cyclic *N,N*-nitroketeneacetals **339** and isocyanates **336** in DIPEA (Scheme 129) (07S835).



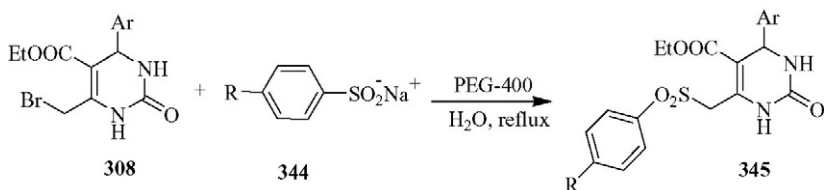
Scheme 129

A three-component reaction of enaminone **341**, aromatic/aliphatic aldehyde and urea/thiourea in DMF/TMSCl furnished C-6 unsubstituted **342**. *N*-methyl urea/thiourea furnished **342** ($\text{R}^2 = \text{Me}$) and 1,3-thiazine **343** ($\text{X} = \text{S}$), respectively (Scheme 130) (09JCS(CC)2768).



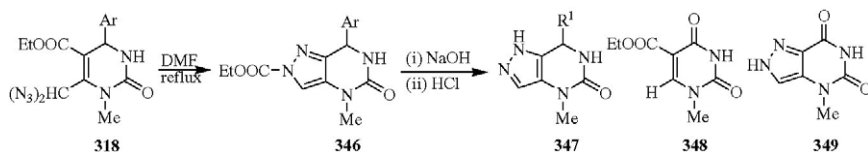
Scheme 130

A series of C-6 methyl substituted DHPMs **345** was produced through S-alkylation of **308** with sodium salt **344**, and a catalytic amount of PEG-400 in refluxing water (Scheme 131) (09SC2230).



Scheme 131

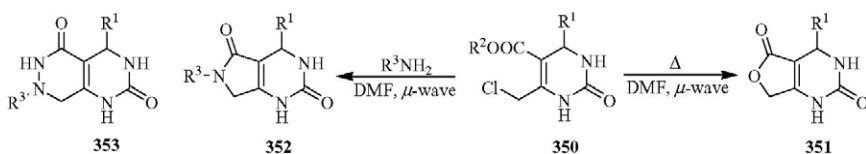
Pyrazolo[4,3-*d*]-pyrimidine **346** was prepared on refluxing diazido **318** in DMF through 1,5-electrocyclization and functional group migration. Subsequent removal of the ester led to **347** (Scheme 132). Photochemical oxidation of C-4 unsubstituted DHPM analogs, formed uracil-5-carboxylate **348** and **349**, respectively (91JCS(P1)1342).



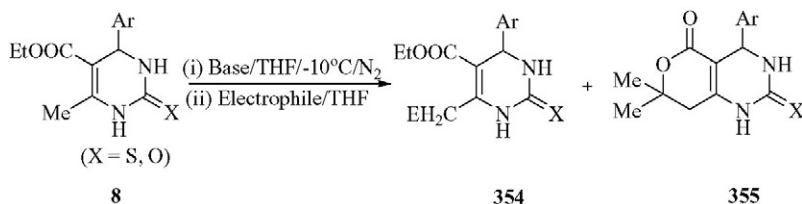
Scheme 132

Thermal cyclization of **350** produced furo[3,4-*d*]-pyrimidines **351**. Prior treatment of **350** with a variety of primary amines, followed by high-temperature microwave heating led to pyrrolo[3,4-*d*]-pyrimidine **352**. While **350** with hydrazine gave pyrimido[4,5-*d*]-pyridazines **353** (Scheme 133) (02MI6).

A highly regioselective and versatile C-6 elaboration of DHPMs was achieved through a lithiation–substitution approach and involved metalation (LDA, $-10^\circ C$) of **8** at its C-6 methyl. The resulting anion with electrophilic reagents conveniently afforded C-6 functionalized DHPMs **354** or their further transformed **355** (Scheme 134) (05JOC6114).

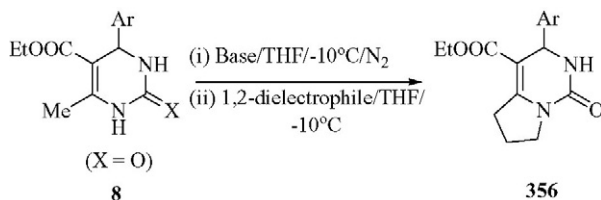


Scheme 133



Scheme 134

This approach has also been extended in the synthesis of N1–C6 linked derivatives 356 (Scheme 135) when dibromoalkanes were used as electrophiles (08T11718).



Scheme 135

4. CONCLUSIONS

We have highlighted a host of synthetic methods for obtaining DHPMs using different substrates, reagents, and/or reaction conditions. These DHPMs with their variety of substituents around the DHPM core are potentially useful in the search for drugs as they exhibit interesting biological properties.

LIST OF ABBREVIATIONS

AcOH	acetic acid
<i>n</i> -BuLi	<i>n</i> -butyllithium
Bmim	1-butyl-3-methylimidazolium
CAN	ceric ammonium nitrate
CDCl ₃	deuterated chloroform
CuTC	Cu(I)thiophene-2-carboxylate
CsF	cesium fluoride
DCC	<i>N,N'</i> -dicyclohexyl carbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyridine
DHPM	3,4-dihydropyrimidin-2-(1 <i>H</i>)-one
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -dimethylaminopyridine
DMSO- <i>d</i> ₆	deuterated dimethylsulfoxide
DMF	<i>N,N</i> -dimethylformamide
DSA	dodecyl sulfonic acid
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
Et	ethyl
EtOH	ethanol
GABA	4-aminobutyric acid
HMPT	hexamethyl phosphoramidate
IL	ionic liquid
LDA	lithium diisopropylamide
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MOM-Cl	methoxymethyl chloride
MS	mass spectrum
MWI	microwave induced
Nu	nucleophile
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methyl pyrrolidone
PCC	pyridinium chlorochromate
PEG	polyethyleneglycol
PMB	<i>p</i> -methoxy benzyl
PPE	polyphosphate ester
PPh ₃	triphenyl phosphine
PSS	physiological salt solution
PSSA	polystyrenesulfonic acid

R _f	retention factor
sf	solvent-free
TAFF	tonsil actisil FF, commercial bentonitic clay
TBAB	tetrabutyl ammonium bromide
TBP	tributylphosphine
TBTU	2-(1 <i>H</i> -benzotriazolyl)-1,1,3,3-tetramethyluronium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl iodide
TMSOEt	ethoxytrimethylsilane
<i>p</i> -TsOH	4-toluenesulfonic acid
TEBA	benzyltriethylammonium bromide
TMAD	<i>N,N,N,N</i> -tetramethylazodicarboxamide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
μ-wave	microwave

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CHAPTER 4

Recent Advances in the C2 and C3 Regioselective Direct Arylation of Indoles

Nathalie Lebrasseur and Igor Larrosa

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1. INTRODUCTION

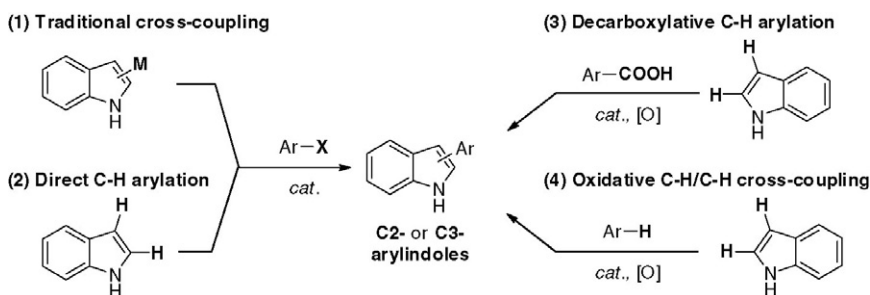
Indole is a privileged motif that enjoys widespread inclusion in molecules, both naturally occurring and designed, which find applications in pharmaceutical, agrochemical, and materials industries (70MI01, 72MI01, 96MI01, 05CRV4671). Particularly, C2- and C3-arylindoles are ubiquitous substructures that can be found in many biologically active compounds (05CRV2873). Consequently, the ability to synthesize these arylated indoles as easily, economically, and efficiently as possible is a high-priority aim, common to a range of disciplines (00MI01).

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Transition metal-mediated cross-coupling of aryl metal reagents and aryl halides or pseudohalides has become over the years the method of choice to form biaryl linkages; both academic research and industrial processes are, nowadays, heavily dependent on such reactions (Scheme 1, Eq. 1, 98T263). Numerous methodologies have been developed for the arylation of indoles that vary according to the metal employed in the organometallic unit (B, Sn, and Zn being the most commonly used). Cross-coupling reactions are often high yielding, can be carried under mild conditions, and usually tolerate a wide range of functionalities. However, they suffer from two major drawbacks: (i) they generate stoichiometric amounts of an often toxic metal halide as by-products and (ii) the installation of the metal functionality in the organometallic adds costly chemical steps to the synthesis and generates significant amounts of waste. In this context, direct C–H arylation (Scheme 1, Eq. 2), decarboxylative C–H arylation (Scheme 1, Eq. 3), and oxidative C–H/C–H cross-coupling (Scheme 2, Eq. 4) have emerged as attractive environmentally friendly alternatives for the arylation of indoles (02CRV1359, 07CRV174, 07NAT391, 09AGE9792, 10CEJ2654, 10CSR540, 11CEJ5466, 11CRV1315, 11CRV1780). These strategies prevent the need for prefunctionalization (step-economy) and metallic waste production (atom-economy, environmentally benign).



Scheme 1 Indole C2- and C3-arylation strategies: traditional versus C–H activation.

This review aims to survey the methodologies currently available to perform regioselectively the C2- and C3-arylation of indoles (09AGE9608, 09ASC673, 11PHC(22)1). Our discussion is limited to reactions that are catalyzed by transition metals. Traditional cross-coupling reactions (Scheme 1, Eq. 1) will not be discussed here as this field goes beyond the

scope of this review. Note also that our survey is restricted to intermolecular heterocoupling reactions. In addition, whenever available, mechanistic studies and discussions are presented.

2. DIRECT C–H ARYLATION REACTIONS

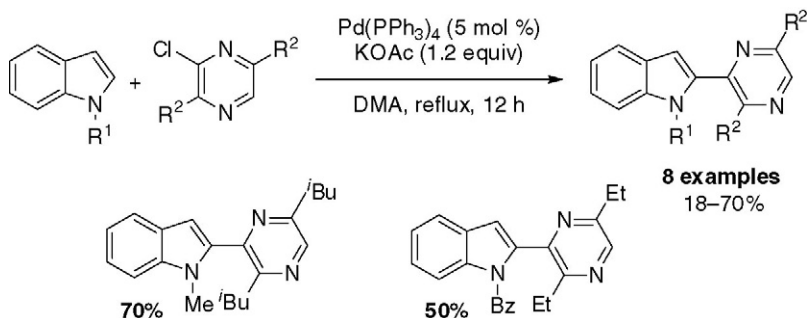
A range of methodologies for the direct C–H arylation of indoles have been developed that involve only the prefuctionalization of the aryl coupling partner, either as a (pseudo)haloarene or as an organometallic reagent. This is a challenging process, as C–H bonds are strong and ubiquitous, and therefore special attention has to be paid to chemo- and regioselectivity. The direct arylation of indoles can proceed either at the C2 or the C3 positions of the indole nucleus, this distinction being defined by a combination of various factors, including the substitution pattern on the indoles, the nature of the catalyst, solvent, ligands, additives, and base used (*vide infra*).

2.1 Palladium-catalyzed couplings

2.1.1 C2 selective couplings

2.1.1.1 Direct arylation with aryl (pseudo)halides

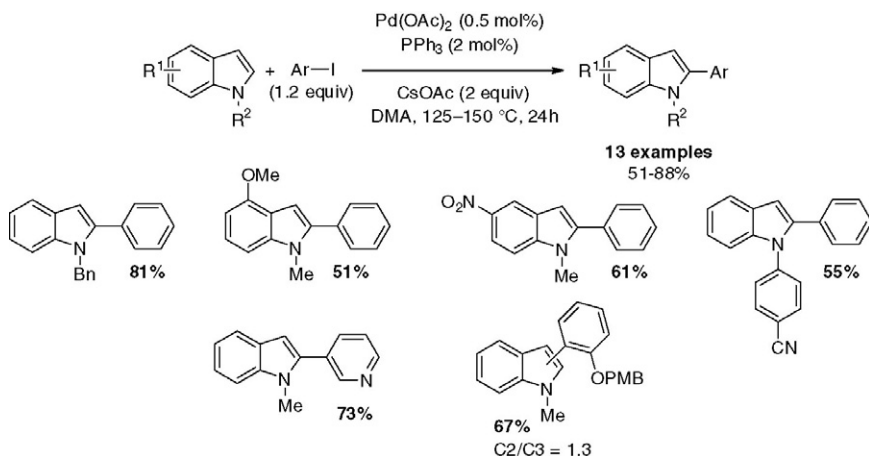
The first Pd-catalyzed direct C2-arylation of indoles was reported by Ohta and co-workers (85H2327, 89CPB1477). In the presence of $\text{Pd}(\text{PPh}_3)_4$ and KOAc indoles could be coupled with chloropyrazines in moderate-to-good yields (Scheme 2). This selectivity for the C2 position is rather intriguing because it seems, at first, to be inconsistent with a well-established electrophilic aromatic substitution mechanism. Interestingly, the authors found that when the electron-withdrawing group Ts was substituting



Scheme 2 Selective C2-arylation of indoles with chloropyrazines.

the nitrogen of the indole a reverse in the regioselectivity of the reaction was observed and C3-arylated products were obtained (*vide infra*).

Twenty years later, Sames revisited and expanded this challenging chemistry by developing a Pd-catalyzed regioselective C2-arylation of *N*-alkyl and *N*-aryl indoles (Scheme 3, 04OL2897). This methodology ben-

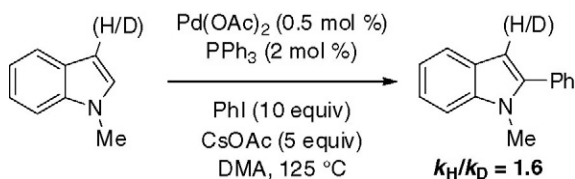


Scheme 3 Selective C2-arylation of *N*-alkyl and *N*-aryl indoles.

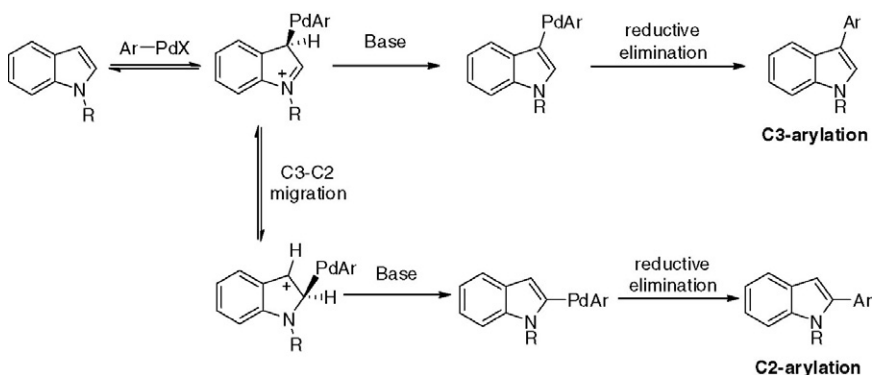
efits from fairly broad substituent compatibility and generates 2-arylin-
doles in moderate-to-good yields. Competitive homocoupling of the aryl
halide was suppressed by using low catalytic loading (0.5 mol%).
Interestingly, 2-arylin-
doles were obtained as the major product in all cases,
although when using *ortho*-substituted iodoarenes a mixture of C2- and
C3-arylin-
doles was observed.

Detailed mechanistic studies for this Pd-catalyzed direct indole aryla-
tion were reported by the same authors in 2005 (Scheme 4, 05JA8050). A
clear secondary kinetic isotope effect (KIE) at C3 was observed in the
reaction leading to the C2-arylation of *N*-methylindole (Scheme 4).

Based on this observation the authors proposed that both C2- and C3-
arylation pathways proceed *via* electrophilic addition of Pd(II) at the more
electron-rich C3 position. This C3-palladated indole may then either
undergo deprotonation and reductive elimination to give the 3-arylin-
dole, or experience a C3 to C2 Pd migration, which then would lead to the C2-



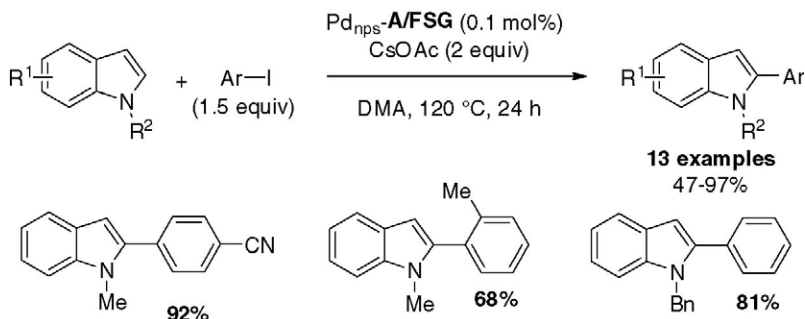
Scheme 4 KIE at C3 position of *N*-methylindole.



Scheme 5 Proposed mechanism for C2- and C3-arylation of indoles.

arylated product (Scheme 5). The driving force for the migration is proposed to be related to the stabilization of the C–Pd bond by the adjacent nitrogen atom. This proposed electrophilic aromatic substitution mechanism was supported by a Hammett plot for a variety of 6-substituted *N*-methylindoles. To rationalize the regioselectivity observed in their precedent study (*vide supra*), the authors suggested that for bulky haloarenes, the C3–C2 migration is slower and by consequence the formation of C3-arylated products becomes competitive. An alternative pathway to C2-arylation would involve nonelectrophilic addition of Pd at C2; however, the authors noted that this route is not supported by the observed KIE and that this pathway generally requires the presence of an *ortho*-directing group. Another possibility that cannot be ruled out is a Heck-type carbometallation at C3 leading to arylation at C2 (although the authors pointed out that a larger KIE is usually associated with this process).

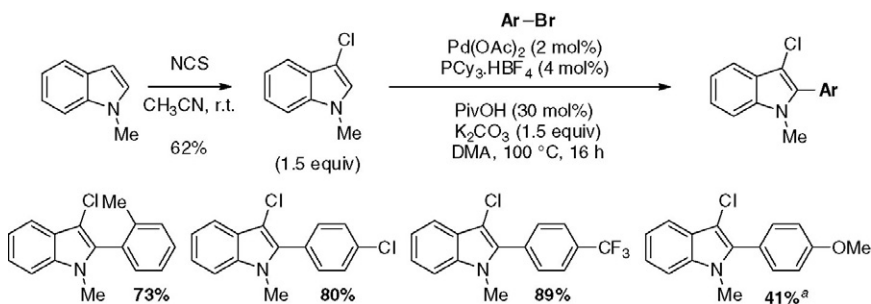
Interestingly, Cai recently reported the use of fluororous silica gel (FSG)-supported palladium nanoparticles as an efficient and recyclable catalyst for the C2-arylation of indoles in conditions similar to the ones used by Sames (Scheme 6, 11CC806). The Pd-nanoparticles were prepared by



Scheme 6 Pd-nanoparticles catalyzed C2-arylation of *N*-alkyldoles.

reduction of Na_2PdCl_4 with NaOAc in methanol in the presence of a heavily fluorinated stabilizing agent. The Pd-nanoparticles thus obtained were subsequently immobilized on FSG by fluorous–fluorous interactions. This catalyst proved to be efficient and selective for the C2-arylation of a variety of *N*-methylindoles. It could be recovered by a centrifugation/decantation process and could be reused up to six times without significant decrease in its activity.

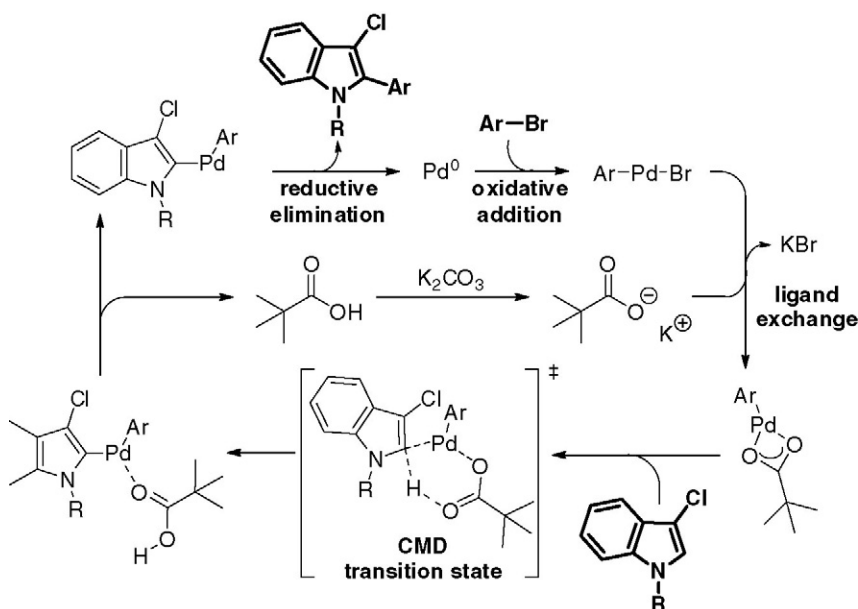
As part of a larger study into the use of chlorine substituents to induce regioselectivity in the direct arylation of heteroarenes, a clever method for obtaining C2-arylated *N*-methylindoles as single regioisomers was recently described by Fagnou and co-workers (Scheme 7, 10JOC1047). Notably this strategy gives a selective access to C2-arylated indoles with *ortho*-substituted aryl halide as coupling partner. Similarly, chlorination at C2 allowed selective access to C3-arylated indoles with very good yields (*vide infra*). The authors suggest that the Cl atom, which remains untouched under the reaction conditions, may subsequently be easily removed or used to introduce a variety of functionalities.



Scheme 7 Chlorine-induced regioselectivity for direct C–H arylation of *N*-methylindoles.

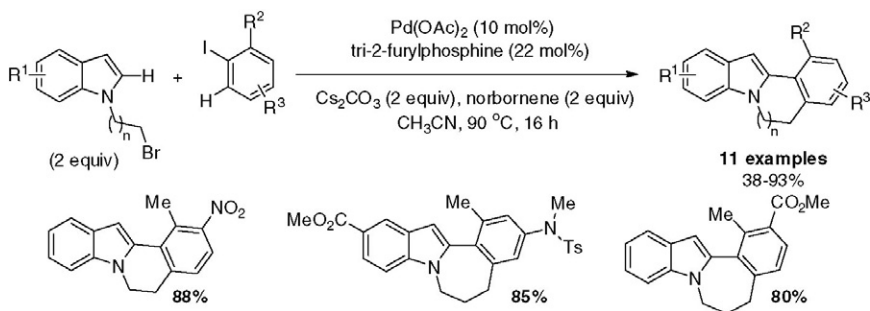
Basing their argument on extensive mechanistic studies (competition experiments and computational studies) the authors suggested a concerted metallation–deprotonation (CMD) mechanism for this reaction (Scheme 8). The catalytic cycle was proposed to commence with the oxidative addition of the bromoarene to the Pd(0) species, followed by a halide/pivalate ligand exchange (the pivalate being generated *in situ* from pivalic acid and K_2CO_3). Approach of the indole then leads to a six-membered ring CMD transition state, and subsequent reductive elimination generates the desired product.

In a methodology that takes advantage of intramolecular delivery of the arene to the C2 position of the indole, Lautens and co-workers reported the annulation of *N*-bromoalkylindoles to generate six- and seven-



Scheme 8 CMD mechanism.

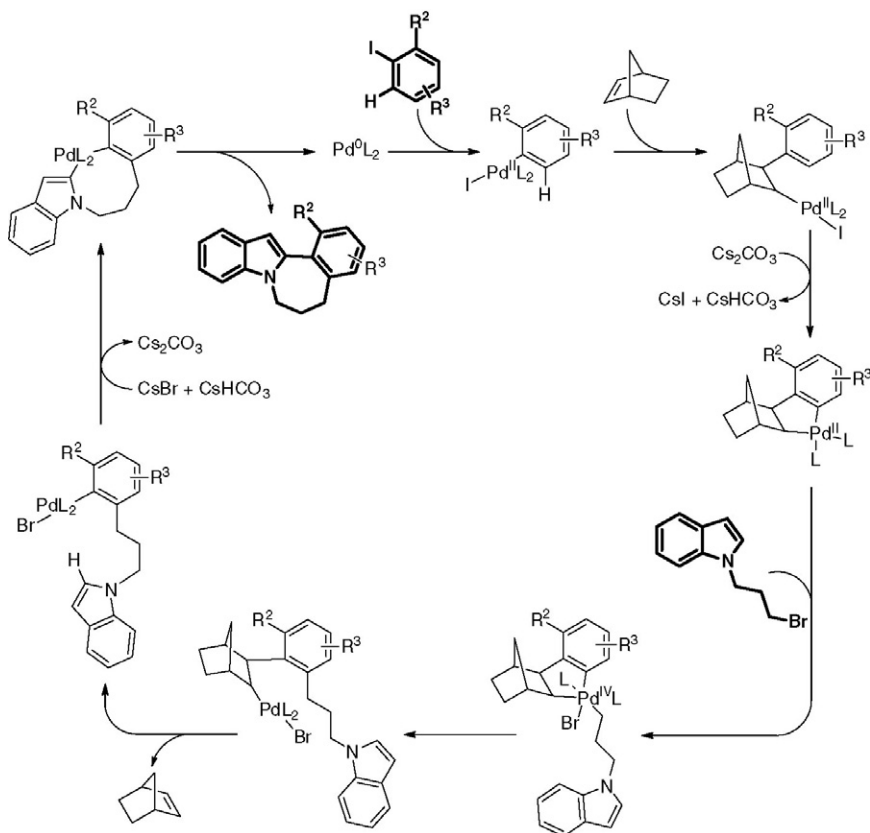
membered ring annulated indoles (**Scheme 9**, 05JA13148). This procedure is based on a modified version of the Catellani norbornene-mediated Pd-catalyzed tandem reaction (97AGE119, 02JA4336, 03SL298). Optimized conditions were applied to a number of substituted indoles and aryl iodides, with electron-donating and -withdrawing groups both well accommodated, producing consistently good-to-excellent yields.



Scheme 9 Annulated indoles *via* a tandem alkylation/direct arylation reaction.

From a mechanistic point of view, the authors proposed a tandem *ortho*-alkylation/direct C2-arylation process (**Scheme 10**), where the initial Pd(II)-aryl species undergoes norbornene-assisted *ortho*-alkylation *via* a

Pd(IV) intermediate. The alkylated Pd(II)-aryl thus generated performs an intramolecular C2-arylation on the indole. The authors suggest that this occurs *via* electrophilic addition at C3 followed by a C3–C2 Pd migration, as proposed by Sames and co-workers (05JA8050), although the possibility of a Heck-type carbopalladation cannot be excluded.



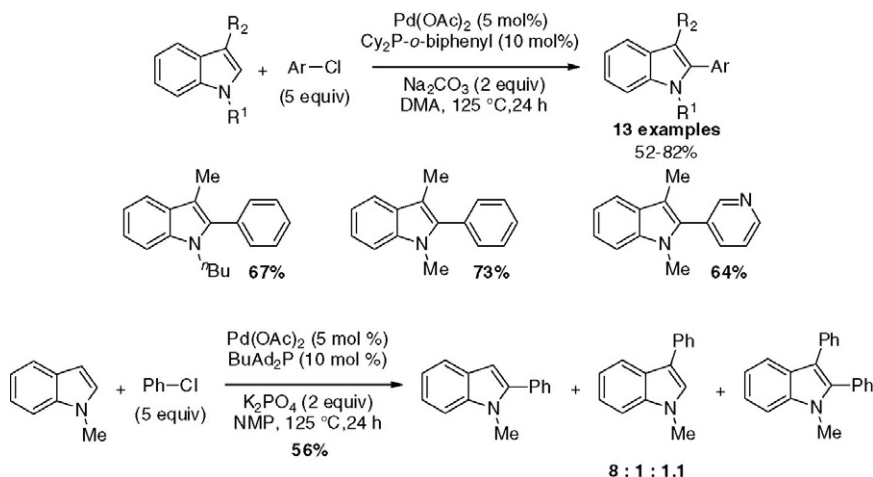
Scheme 10 Proposed reaction mechanism for the formation of annulated indoles.

Lautens and co-workers subsequently extended this methodology to the functionalization of other heteroarenes and to eight-membered ring-annulated indoles, even though with lower yields than their six- and seven-membered counterparts (08JOC1888).

Recently, Daugulis and co-workers found that chloroarenes were also suitable coupling partners for the arylation of *N*-alkylindoles (11JOC471). Chloroarenes are significantly less expensive and more readily available

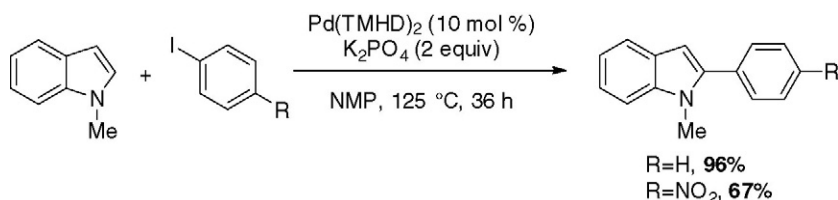
than iodoarenes, and therefore constitute valuable alternative coupling partners.

A variety of C3-substituted *N*-methylindoles were successfully C2-arylated under optimized conditions in moderate-to-good yields (Scheme 11). The authors found that under modified conditions unsubstituted *N*-methylindole could be selectively C2-arylated, although minor amounts of *N*-methyl-3-phenylindole and *N*-methyl-2,3-diphenylindole were also observed.



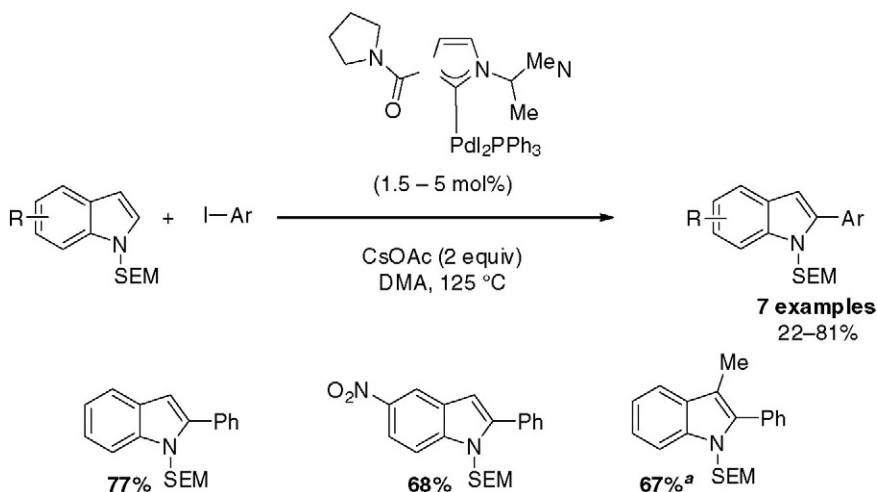
Scheme 11 Direct arylation of *N*-alkylindoles with chloroarenes.

In 2008, Bhanage and co-workers reported two examples of a phosphine-free version of the direct C2-arylation of *N*-methylindoles using Pd (TMHD)₂ as the catalyst (Scheme 12, 08TL1045). The authors noted that Pd (TMHD)₂ is very stable and not air-sensitive, in this respect, offering advantages over the phosphine-based systems.



Scheme 12 Phosphine-free direct C2-arylation of *N*-methylindoles. TMHD = 2,2,6,6-tetramethyl-3,5-heptanedioate.

In 2006, Sames demonstrated that the valuable *N*-2-(trimethylsilyl)ethoxymethyl (SEM)-indoles (that can easily be deprotected to give the *NH*-free product) could also be selectively C2-arylated (Scheme 13, 06OL1979). Optimized conditions involving the use of a bulky and electron-rich palladium complex of *N*-heterocyclic carbene and phosphine allowed the arylation of a range of functionalized SEM-protected indoles in good-to-moderate yields.



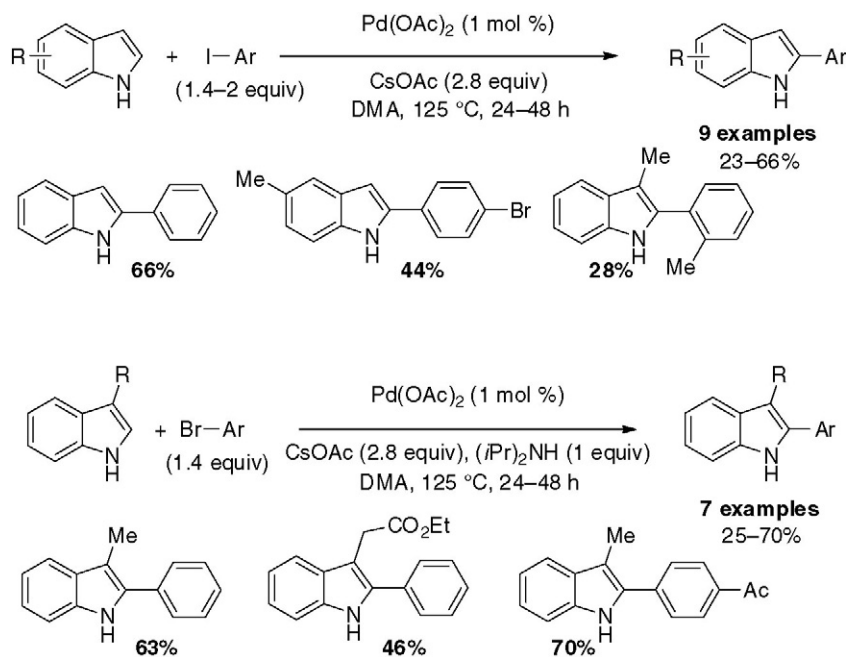
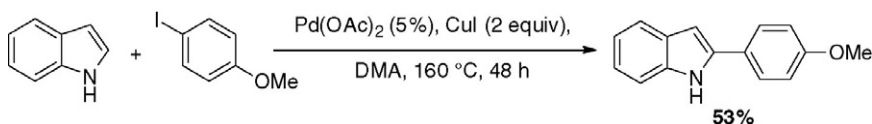
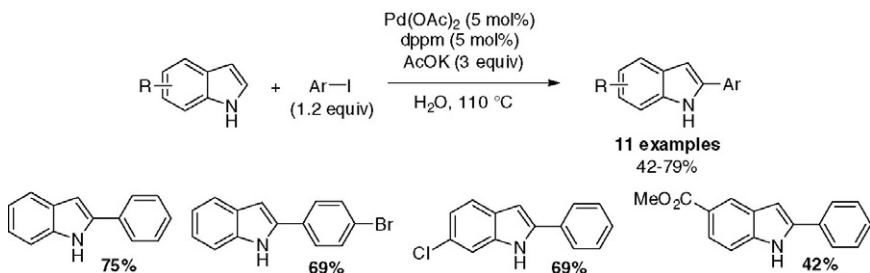
Scheme 13 C2-arylation of SEM protected indoles. SEM = 2-(trimethylsilyl)ethoxymethyl.

^aProduct was characterized after deprotection.

Subsequently, Sames reported a ligand-free method for the arylation of *NH*-free indoles with iodoarenes (Scheme 14, 07JOC1476), using otherwise identical conditions to those reported previously (e.g., $\text{Pd}(\text{OAc})_2$, CsOAc , and DMA at 125°C). This methodology permitted the successful C2-arylation of a range of functionalized *NH*-free indoles with moderate-to-good yields. By adding a stoichiometric amount of $(i\text{Pr})_2\text{NH}$ to the system, the reaction could also be carried out with bromoarenes as coupling partners; however, only examples with C3-substituted indoles were reported.

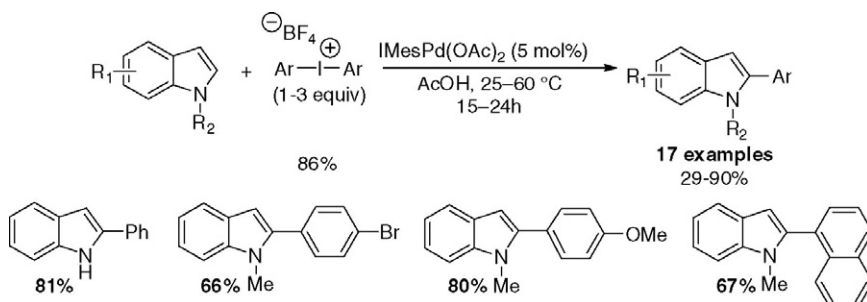
Bellina and Rossi also reported a ligand-free approach for the C2-arylation of *NH*-free indoles (Scheme 15, 06JOC1379, 07T1970). However, this Pd/Cu catalyzed reaction occurring under base-free conditions gave low yields with indoles (although this procedure was very efficient for other substrates, such as *NH*-free imidazoles).

In 2010, Djakovitch reported an attractive “on water” Pd -catalyzed C–H arylation of *NH*-free indoles (Scheme 16, 10ASC2929). Iodoarenes were successfully coupled to a variety of free indoles by using $\text{Pd}(\text{OAc})_2$ as the catalyst, bis(diphenylphosphino)methane as ligand, and AcOK as

Scheme 14 Ligand-free Pd-catalyzed arylation of *NH*-free indoles.Scheme 15 Pd and Cu-catalyzed direct C2-arylation of *NH*-free indoles.Scheme 16 “On water” C2 direct C–H arylation of *NH*-free indoles.

the base. High selectivities for the C2-arylation were observed under these conditions. While carrying out optimization studies, the authors noticed a clear base effect on regioselectivity. Remarkably, they successfully exploited this observation and showed that by using appropriate base/halide partners C3-arylation could selectively be obtained (*vide infra*).

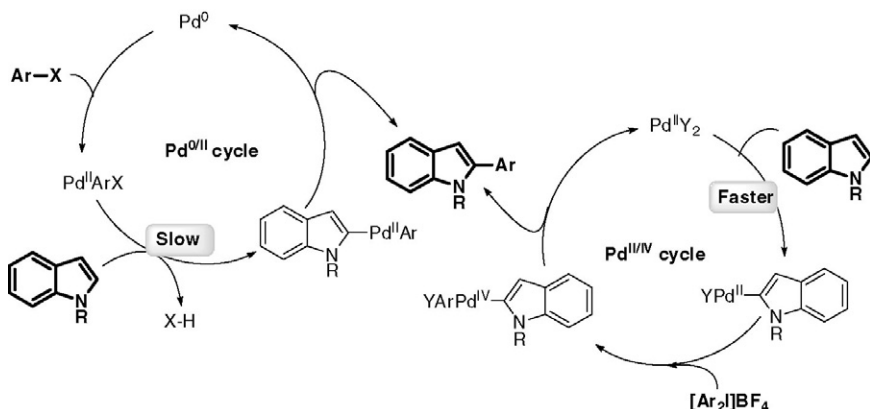
All the methodologies for C–H arylation presented so far require high temperatures and long reaction times. This, in turn, limits the substrate scope and functional group compatibility of these approaches to 2-arylindole. In 2006, Sanford reported the first indole arylation to proceed at room temperature (Scheme 17, 06JA4972). In this approach, both *N*-methylindole and *NH*-free indole were shown to react at temperatures in the range 25–60 °C in good-to-excellent yields and with high C2 regioselectivity. This method is compatible with substituted indoles bearing a range of electron-withdrawing and -donating substituents, including bromide, a potentially useful substituent for further manipulation. However, instead of a haloarene, the more oxidizing and less commercially available Ar_2IBF_4 species are required as coupling partners in this process.



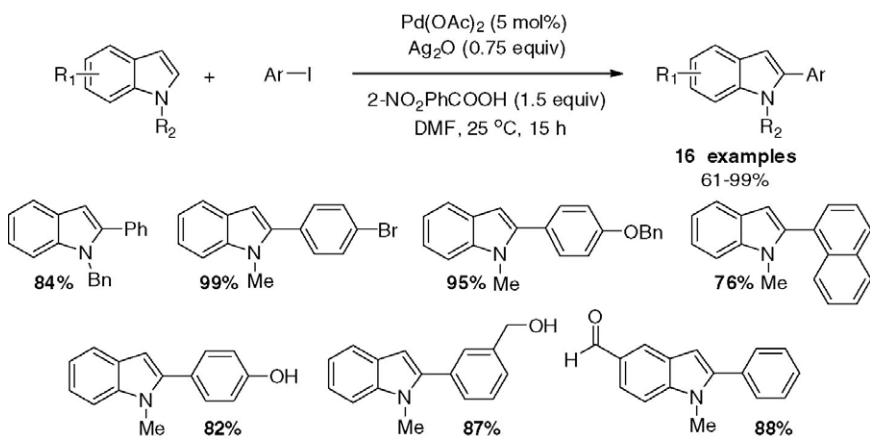
Scheme 17 Room temperature C2-arylation of indoles with Ar_2IBF_4 . IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

To rationalize the higher reactivity of this system, Sanford proposed a $\text{Pd}^{\text{II/IV}}$ catalytic cycle, bypassing the turnover-limiting electrophilic palladation step involved in a $\text{Pd}^{0/\text{II}}$ cycle, a process hindered by an already electron-rich $\text{Pd}(\text{II})$ σ -aryl species (Scheme 18, 05JA8050). The use of a comparatively electron-deficient $\text{Pd}(\text{II})$ catalyst provides faster electrophilic indole palladation, giving a $\text{Pd}(\text{II})$ σ -indole species. Oxidative addition with the diaryliodonium specie yields a $\text{Pd}(\text{IV})$ complex, which then undergoes reductive elimination to produce the C2-arylated indole.

In 2008, Lebrasseur and Larrosa reported a room temperature C–H arylation of indoles that allows the use of iodoarenes as the coupling partners (Scheme 19, 08JA2926). This methodology provides C2-arylated



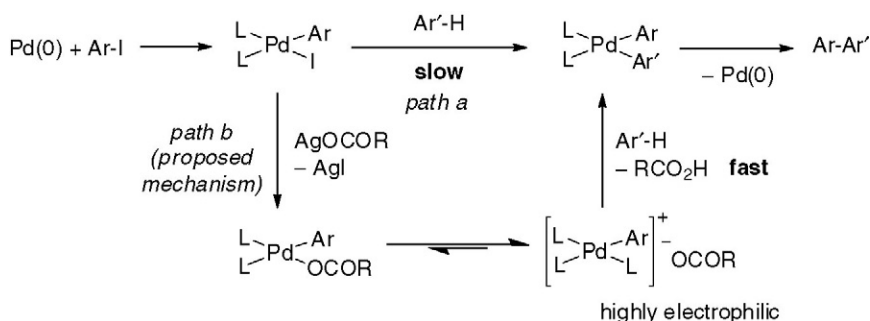
Scheme 18 Traditional $\text{Pd}^{0/\text{II}}$ catalytic cycle and proposed $\text{Pd}^{\text{II}/\text{IV}}$ cycle.



Scheme 19 Pd-catalyzed direct C2 indole arylation with ArI at room temperature.

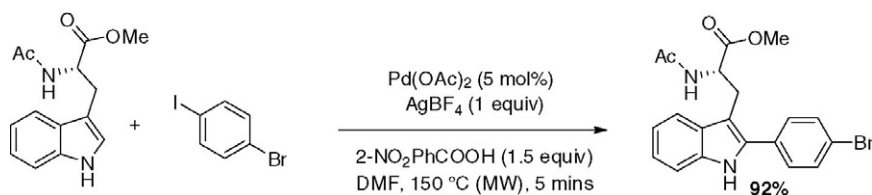
indoles with complete regioselectivity and good-to-excellent yields under remarkably mild conditions, and allows the use of sensitive functional groups such as unprotected alcohols, phenols, or aldehydes. The authors also noted that the reactions are not sensitive to air or moisture.

The authors suggested that $\text{Pd}(\text{II})$, resulting from oxidative addition with the iodoarene, can be rendered more electrophilic (Scheme 20), thus enhancing the rate of the C–H activation step, by replacing the iodine substituent with a carboxylate ligand (*path a* versus *path b*). This is accomplished by the use of an Ag-carboxylate, generated *in situ*, as the halide extractor and carboxylate donor. The $\text{Pd}(\text{II})$ carboxylate thus generated facilitates the electrophilic palladation of the indole, allowing the reaction to proceed under much milder conditions.



Scheme 20 Proposed mechanism of Pd-catalyzed room temperature C2-arylation of indole.

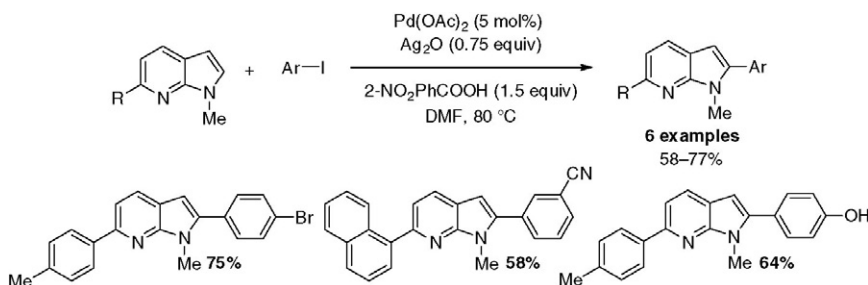
As recently reported by Lavilla and co-workers (10CEJ1124), a modification of the method developed by Lebrasseur and Larrosa (08JA2926) allowed the direct C2-arylation of *N*-acetyl-tryptophan methyl ester with a range of substituted aryl iodides, in excellent yields and selectivities (Scheme 21). In this case, higher temperatures were required, presumably due to the increased number of coordination points in tryptophan compared to indole. The use of microwave irradiation as the heat source provided the best results, permitting excellent preservation of the amino acid stereochemistry. Subsequently, this method was applied to tryptophan-containing peptide chains, which required the adjustment of the conditions to allow the increased fragility of these substrates. The same catalyst and additives in a buffered aqueous media, irradiated at 80°C for 10 min, allowed the arylation of a range of tryptophan-containing peptides in good-to-excellent yield.



Scheme 21 Pd-catalyzed direct arylation of *N*-acetyl-tryptophan methyl ester.

Azaindoles bear an obvious resemblance to indoles, sharing the same indene framework, but with one extra nitrogen. Therefore, Huestis and Fagnou turned to published methods for direct C2 indole arylation in order to develop a C2 arylation of azaindoles (09OL1357).

Having surveyed a number of methods, the authors reported that, with slight temperature modification, application of the conditions developed by Lebrasseur and Larrosa (08JA2926) generated the C2-arylated products, with high selectivity and good yields, over a range of substituted 7-azaindoles and aryl iodides (Scheme 22).

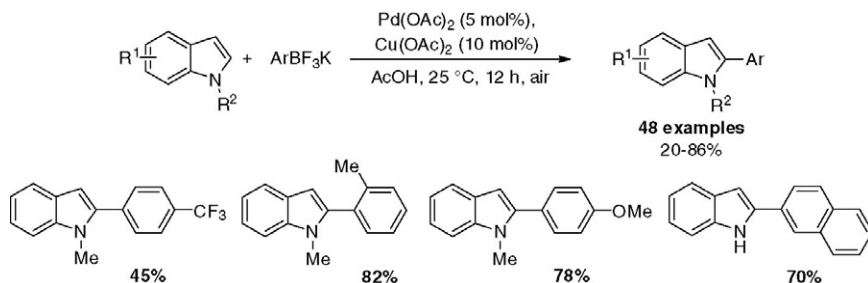


Scheme 22 Direct C2-arylation of *N*-methyl-7-azaindoles.

2.1.1.2 Direct arylation with arylboron reagents

The use of arylboron reagents for direct C–H arylation involves, conceptually, more synthetic steps for their preparation, usually from the correspond haloarene. Furthermore, in the absence of haloarene an additional stoichiometric oxidant is necessary. However, these methods tend to involve milder and lower temperature conditions.

In 2008, Zhang and co-workers explored the use of potassium aryltrifluoroborate salts as the coupling partners for the oxidative C2-arylation of free and *N*-methyl indoles (Scheme 23, 08JOC7428). The authors note that the reaction is not sensitive to air or moisture, in fact air is used as the oxidant, along with 10 mol% $\text{Cu}(\text{OAc})_2$. A wide range of substituted aryltrifluoroborate potassium salts were surveyed, giving products in moderate-to-high yields. Arenes possessing an *ortho*- or electron-withdrawing substituent produced the poorer yields, an effect far more

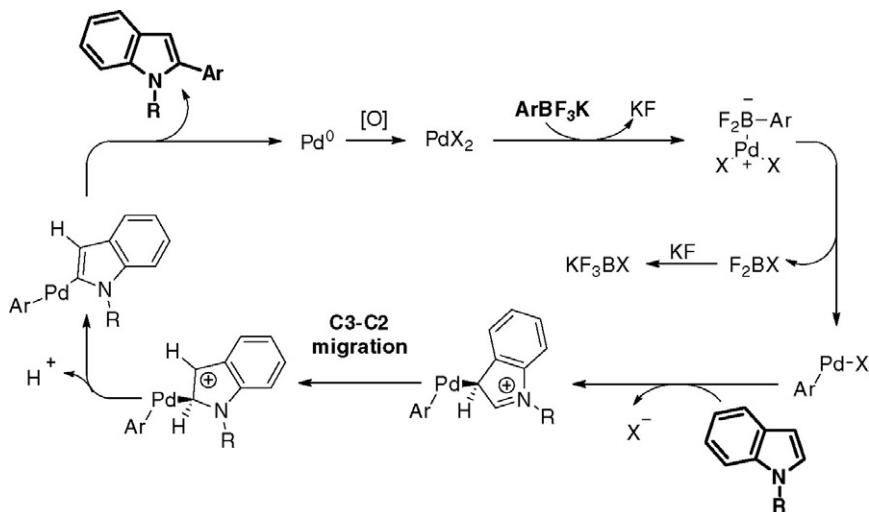


Scheme 23 Direct C2-arylation of indoles with phenyltrifluoroborate salts.

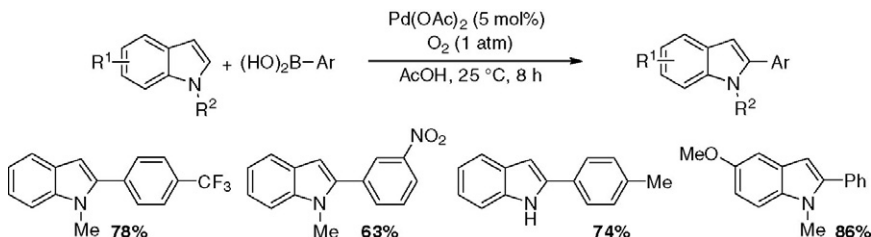
pronounced for free indole compared to *N*-methylindole, which coupled to potassium 2-methylphenyltrifluoroborate in 81% yield cf. 36% for the *NH*-free indole. A number of substituted indoles were also coupled, again with moderate-to-excellent yields with electron-withdrawing substituents leading to the lower yields.

Based on the observation that the electron-rich indoles were more reactive than the electron-deficient ones, the authors proposed a mechanism involving an electrophilic substitution–migration mechanism (Scheme 24).

Independently, Shi and co-workers developed an aerobic Pd(II)-catalyzed oxidative coupling using arylboronic acids as coupling partners (Scheme 25, 08AGE1473). Very mild conditions were reported for the arylation of a range of substituted *NH*-free indoles with high selectivity and good-to-excellent yields. The use of molecular oxygen as the terminal oxidant represents arguably a valuable feature with respect to the formation of waste by-products.

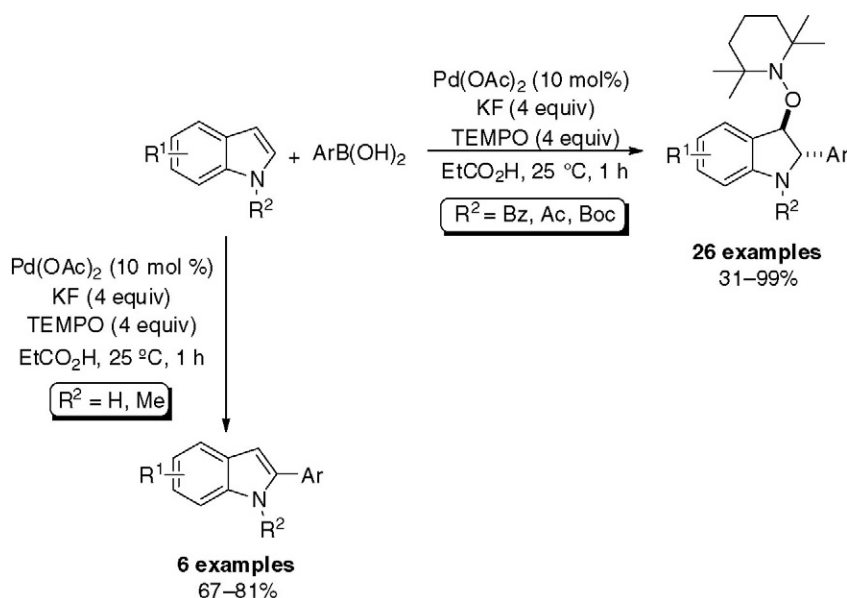


Scheme 24 Proposed mechanism for the C2-arylation of indoles with ArBF_3K .

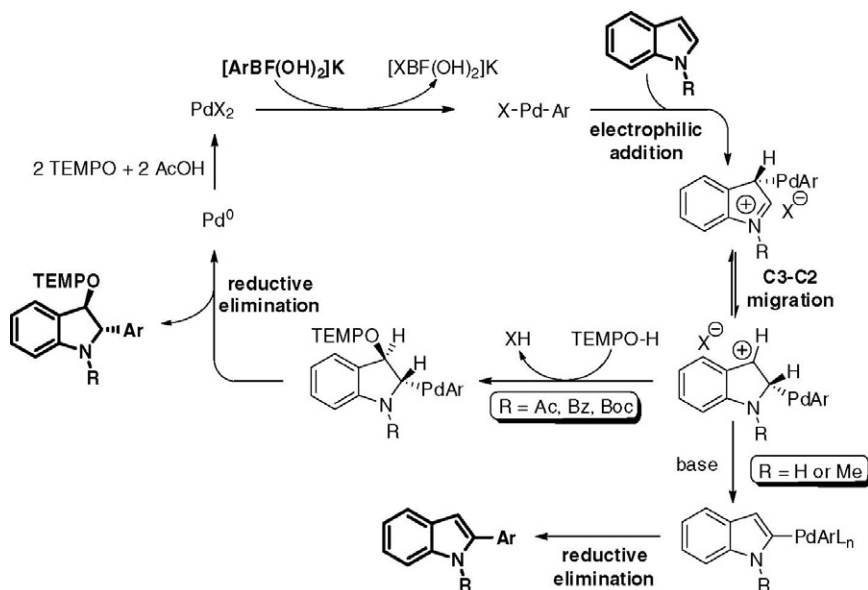


Scheme 25 Pd-catalyzed direct C2-arylation of indoles with phenylboronic acids.

Having previously investigated the use of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), as a mild terminal oxidant in the direct arylation of (hetero)arenes with arylboronic acids (08SL2841), Studer and co-workers sought to extend the substrate scope of this methodology to include indoles (Scheme 26, 09AGE4235). They did so successfully, achieving high C2 selectivity and good yields with both *N*-methyl and *NH*-free indoles. Interestingly, when the same conditions were applied to indoles *N*-protected with benzoyl or acetyl, a *trans*-2,3-disubstituted 2,3-dihydroindole was obtained. A reaction mechanism was proposed that relies on a $\text{Pd}^{0/\text{II}}$ catalytic cycle, involving electrophilic indole palladation at the C3 position and migration to C2, as suggested by Sames and co-workers (Scheme 27, 05JA8050). At this point, the *N*-methyl or *NH*-free indole intermediates are deprotonated/rearomatized and reductive elimination yields the C2-arylated product. However, the *N*-protected indoles are slower to deprotonate, as a result of increased stability arising from the protecting group, leaving the cationic intermediate highly susceptible to *trans*-trapping by TEMPO. Subsequent reductive elimination gives an arylcarboaminoxylation product in good-to-excellent yields. Furthermore, easy removal of TEMPO yields a 3-hydroxydihydroindole product.



Scheme 26 C2-arylation of indoles with arylboronic acids and TEMPO.



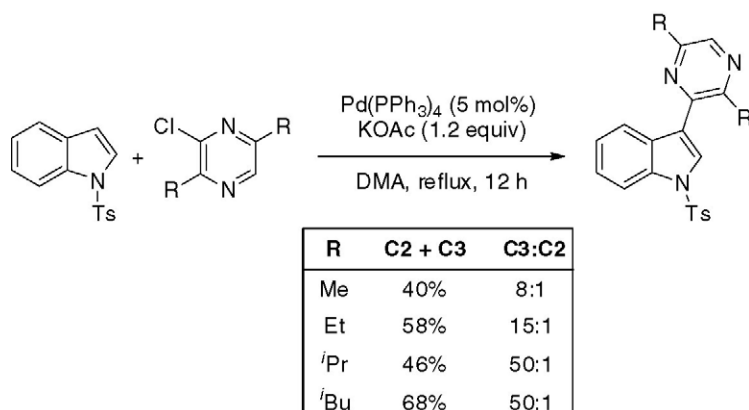
Scheme 27 C2-arylation of indoles with TEMPO: proposed mechanism.

2.1.2 C3 selective couplings

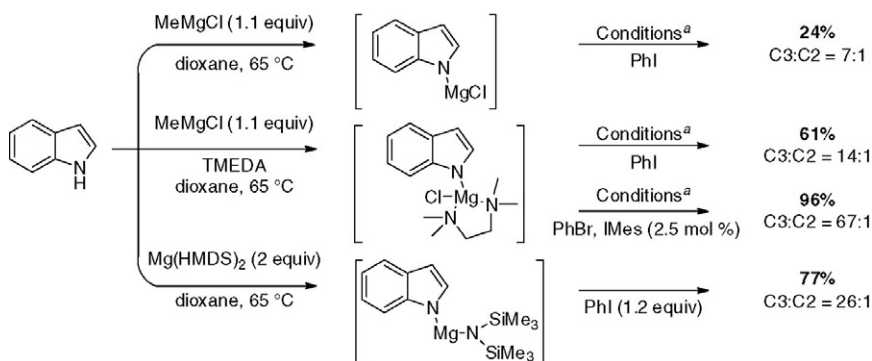
In comparison with C2-selective arylation of 2,3-unsubstituted indoles, very few protocols have been reported so far for C3-selective couplings. Moreover, these methodologies remain mainly limited to the coupling of *NH*-free indoles with bromoarenes.

While investigating the direct arylation of *N*-substituted indoles with chloropyrazines, Ohta found that using an electron-withdrawing protecting group (Ts) on the nitrogen of the indole influenced dramatically the regioselectivity of the reaction in favor of C3-arylation (Scheme 28, 85H2327, 89CPB1477). Notably, the presence of bulky substituents on the chloropyrazines leads to higher regioselectivities (up to 50:1).

Based on extensive mechanistic investigations, Sames developed in 2005 a new protocol for the selective C3-arylation of indoles (05JA8050). Relying on the observation that bulky substituents on the iodoarene lead to higher C3-regioselectivity, Sames suggested that the use of sterically hindered arylpalladium(II) intermediate should favor the C3-arylation. Following this reasoning the authors explored the use of bulky magnesium salts as bases for the reaction (Scheme 29). They found that the use of MeMgCl in conjunction with tetramethylethylenediamine (TMEDA) led to the formation of the C3-arylated product with good regioselectivity (14:1) and decent yield (61%). Interestingly, higher yield (96%) and almost



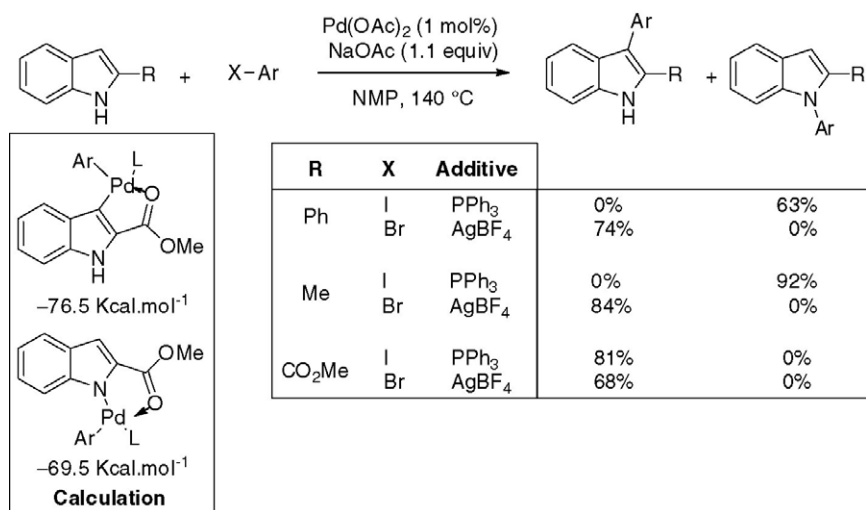
Scheme 28 Selective C3-arylation of *N*-tosylindoles with chloropyrazines.



Scheme 29 Direct C3-arylation of *N*-magnesium salts. ^aConditions: Pd(OAc)₂ (2.5 mol%), PPh₃ (10 mol%), CsOAc (2 equiv), dioxane, 125 °C, 24 h. Abbreviation: HMDS, hexamethyldisilazane.

complete selectivity (67:1) were obtained when the sterically hindered IMes ligand was used with bromoarene as coupling partner. The use of Mg(HMDS)₂ led to similar result.

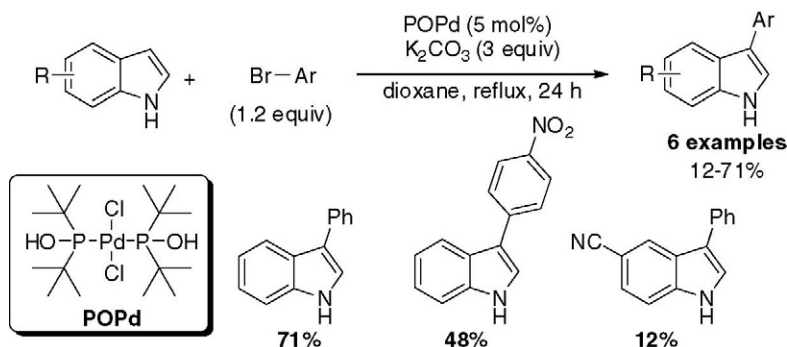
Djakovitch et al. reported the first study on intermolecular C3-arylation of *NH*-free indoles (07CCAOAC1561). Although this work was limited to C2-substituted indoles, interesting observations were made. The authors showed that in the presence of AgBF₄ the selectivity of the coupling (N versus C3) of 2-phenyl and 2-methylindoles were directly related to the nature of the haloarene coupling partner: 4-iodonitrobenzene led to *N*-arylation exclusively while 4-bromonitrobenzene gave a clean C3-arylation. On the other hand, both 4-iodo- and 4-bromonitrobenzene led to C3-arylated product when 2-(methylcarboxylate)indole was used. To explain this difference in behavior the authors proposed the existence of a



Scheme 30 C3-arylation of 2-substituted *NH*-free indoles.

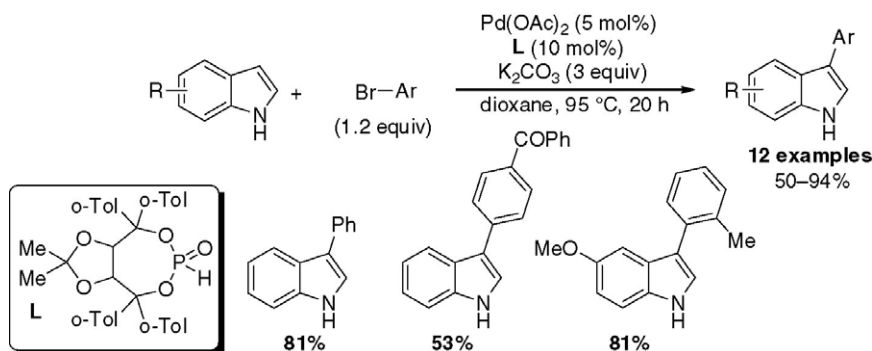
Pd(II) intermediate stabilized through coordination with the carboxylate group (Scheme 30). The authors noted that this methodology is limited to activated haloarenes.

In 2007, Zhang and co-workers reported the first protocol for the intermolecular selective direct C3-arylation of *NH*-free indoles with bromoarenes (07TL2415). The authors found that using a Pd-phosphinous acid complex as the catalyst and K₂CO₃ as the base in dioxane leads to high regioselectivity in favor of the C3-arylated products (Scheme 31). Both electron-rich and electron-poor bromoarenes were suitable coupling partners and under optimized conditions moderate-to-good yields were obtained. It is noteworthy that indoles bearing electron-withdrawing groups are rather unreactive under these conditions.



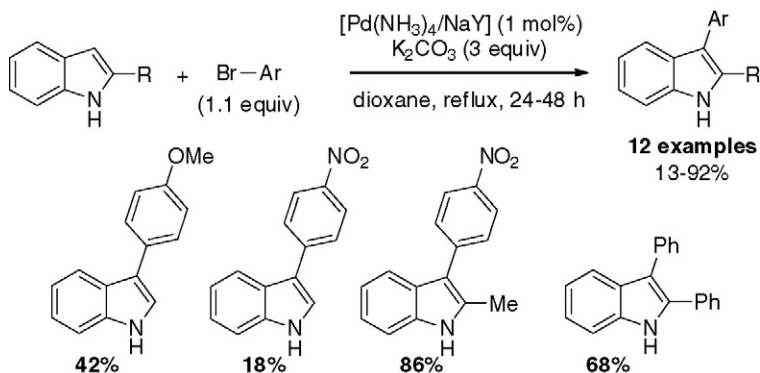
Scheme 31 Direct Pd-catalyzed C3-arylation of *NH*-free indoles.

Following Zhang and He's work, Ackermann and Barfuesser developed a protocol using a Pd-complex derived from air-stable heteroatom-substituted secondary phosphine oxides (HASPO) for the selective C3-arylation of a variety of functionalized *NH*-free indoles with bromoarenes (09SL808). Optimized conditions gave good-to-high yields and allowed the use of sterically hindered substrates (Scheme 32).



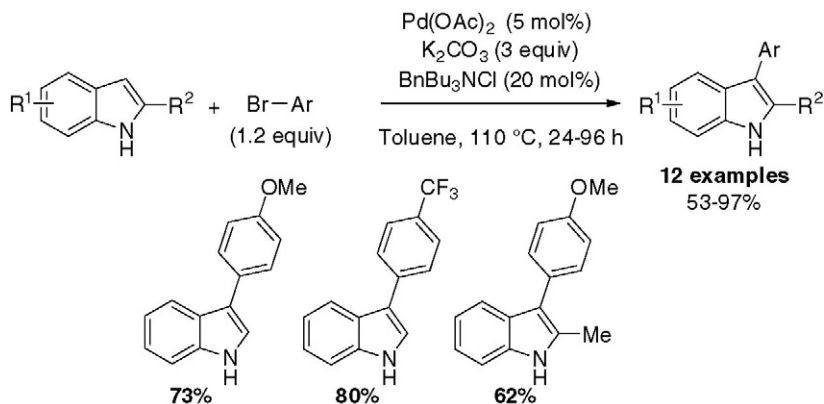
Scheme 32 Pd-catalyzed direct C3-arylation of *NH*-free indoles with an air-stable HASPO.

In 2008, Cusati and Djakovitch reported for the first time the use of a Pd heterogeneous catalyst ($[Pd(NH_3)_4/NaY]$) for the C3-arylation of *NH*-free indoles (08TL2499). The use of 1 mol% of catalyst allowed the C3-arylation of unsubstituted, 2-Me and 2-Ph indoles in moderate-to-good yields (Scheme 33).



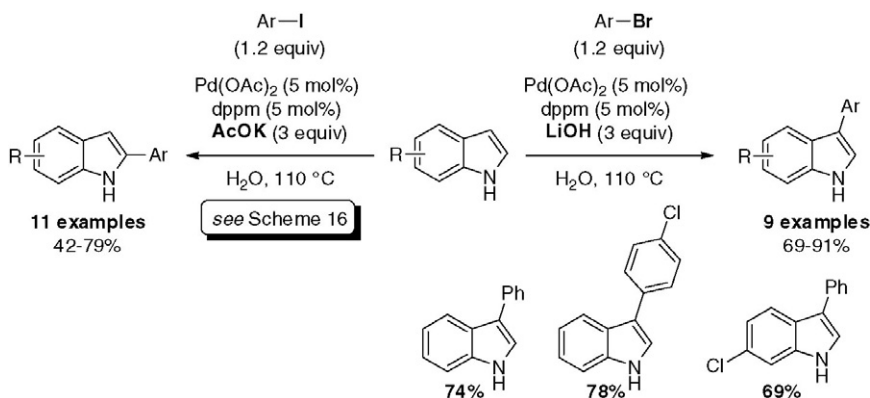
Scheme 33 Heterogeneously Pd-catalyzed C3-arylation of *NH*-free indoles.

Bellina et al. described a ligand-free version of the selective C3-arylation of *NH*-free indoles with bromoarenes (08JOC5529). The combination of $\text{Pd}(\text{OAc})_2$ and benzyl(tributyl)ammonium chloride in the presence of K_2CO_3 as the base in toluene permitted the coupling of a range of electron-poor and electron-rich bromoarenes with *NH*-free indoles leading to the C3-arylated product in decent yields (Scheme 34). *N*-Methylindoles and *NH*-free indoles bearing electron-withdrawing groups failed to react under these conditions.

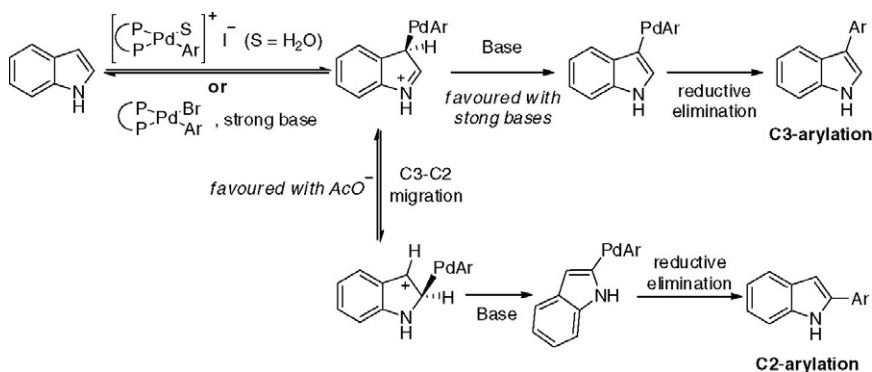


Scheme 34 Direct C3-arylation of *NH*-free indoles under ligandless conditions.

During his study on “on water” Pd-catalyzed C–H arylation of *NH*-free indoles, Djakovitch and co-workers showed that by carefully choosing the base and halide partners C3-arylation could selectively be obtained (10ASC2929). When LiOH and bromoarenes were used C3-arylated products were obtained in good-to-high yields (Scheme 35). It is noteworthy that NaOH and KOH led to almost full conversions and good C3-selectivities whether bromo- or iodoarenes were used. To account for these results, the authors proposed an electrophilic metallation mechanism (similar to the mechanism proposed by Sames and co-workers 05JA8050) and suggested that two different active species were formed depending on the nature of the haloarene used. Thus, iodoarenes would lead to the formation of highly reactive cationic Pd able to directly undergo a C3-palladation, whereas bromoarenes would give a less reactive neutral Pd complex requiring the presence of a stronger base to undergo metallation (Scheme 36). The C3-palladated intermediate may then either undergo deprotonation and reductive elimination (pathway favored when strong bases are used) to give the 3-arylindole, or experience a C3 to C2 Pd migration, which would lead to the C2-arylated product (pathway favored with weak bases such as AcOK). However, the authors note that a CMD mechanism cannot be ruled out when ArI and AcOK are used.



Scheme 35 “On water” regioselective direct C–H arylation of *NH*-free indoles.

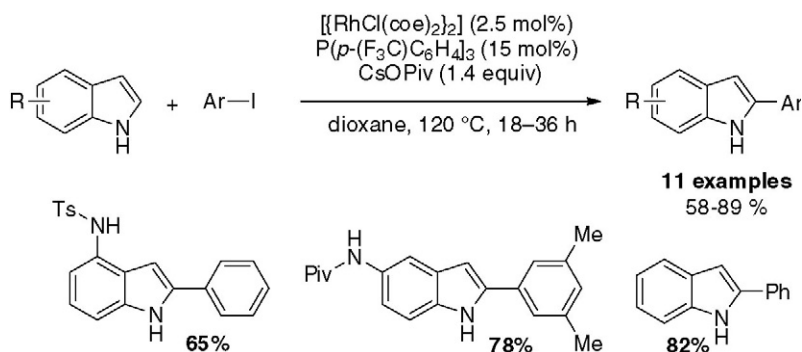


Scheme 36 Proposed mechanism for “On water” direct C–H arylation of *NH*-free indoles.

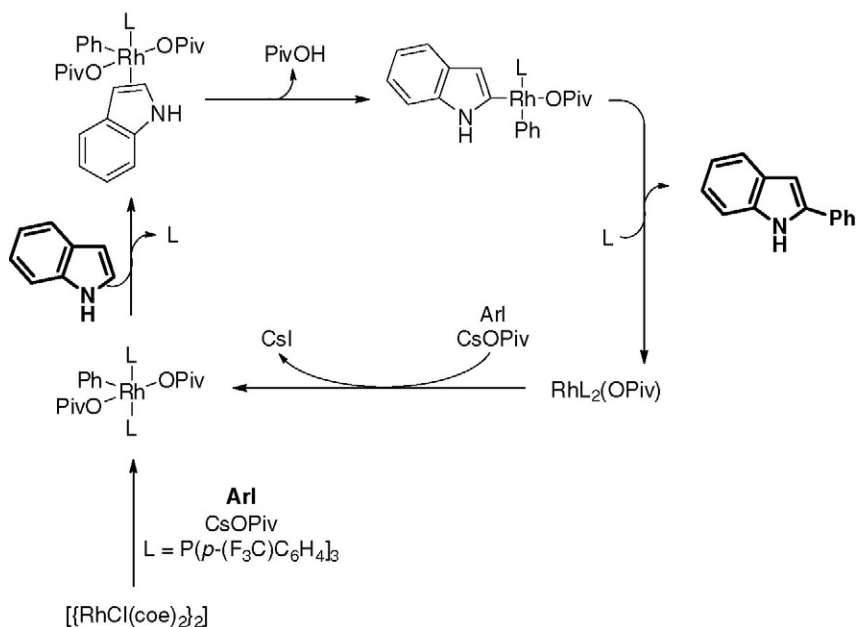
2.2. Other Metals

Despite palladium, arguably the most versatile transition metal in catalysis, dominating the field of C–H arylation, other metals have also been used to perform selective arylation of indoles.

In 2005, Sames and co-workers reported the highly selective (>50:1) C2-arylation of *NH*-free indoles using a rhodium complex derived from an electron-deficient phosphine as the catalyst, CsOPiv as a base, and iodoarenes as coupling partners (Scheme 37, 05JA4996). Mechanistic studies revealed that a highly electrophilic Ar–Rh(III) complex was formed *in situ* through the oxidative addition of aryl iodide to Rh(I) (Scheme 38). Then the displacement of the phosphine ligand by indoles takes place, followed by



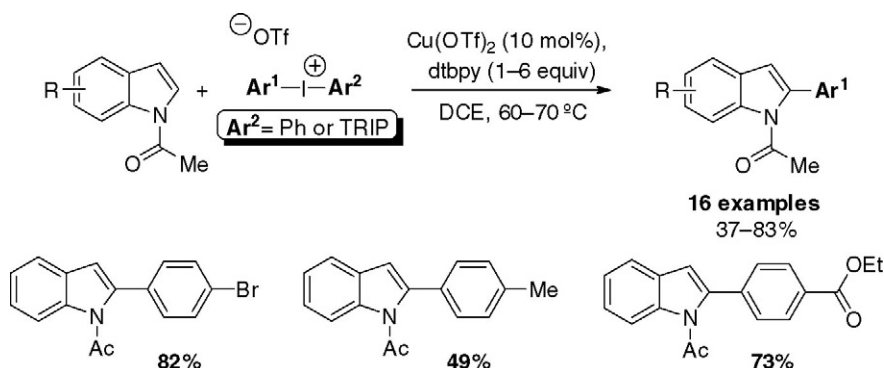
Scheme 37 Rhodium-catalyzed free indole arylation (coe = *cis*-cyclooctene).



Scheme 38 Proposed catalytic cycle for the Rh-catalyzed direct arylation of indoles.

the slow C–H bond metallation step. Subsequent reductive elimination yields the desired product. This methodology proved to be compatible with a range of substituents retaining high C2-selectivity with moderate-to-good yields. However, 7-azaindole was completely inert under these conditions.

In 2008, Gaunt and co-workers developed an elegant Cu(II)-catalyzed process that allows the regioselective couplings of indoles and diaryliodine (III) under mild conditions (08JA8172). Although this method



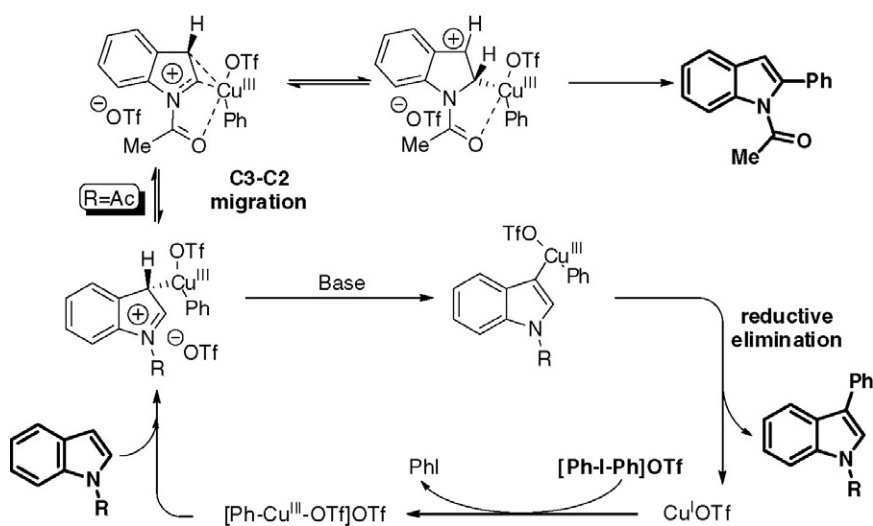
Scheme 39 Cu-catalyzed direct arylation of indoles.

requires the use of relatively expensive or commercially unavailable diaryl- λ^3 -iodane coupling partners, it provides high selectivity, good yields, and tolerates a broad range of functionalities (Scheme 39). An attractive unsymmetrical diaryl- λ^3 -iodane ([TRIP-I-Ar]OTf) has been developed to allow the transfer of complex aryl groups: the bulky 2,4,6-triisopropylphenyl (TRIP) does not transfer in this case. Interestingly, the regioselectivity can be controlled by choosing carefully the *N*-substituent on the indoles: *N*-H and *N*-alkyl indoles gave C3-arylated products, whereas *N*-acetylindoles lead to the C2-arylated indoles. The authors proposed a mechanism involving highly electrophilic Cu(III)-aryl that enable the mild arylation process (Scheme 40). To explain the switch in regioselectivity Gaunt proposed an initial functionalization at the C3 position followed by a migration to C2 and rearomatization – the migration step being favored by the presence of a chelating acetyl group on the nitrogen atom.

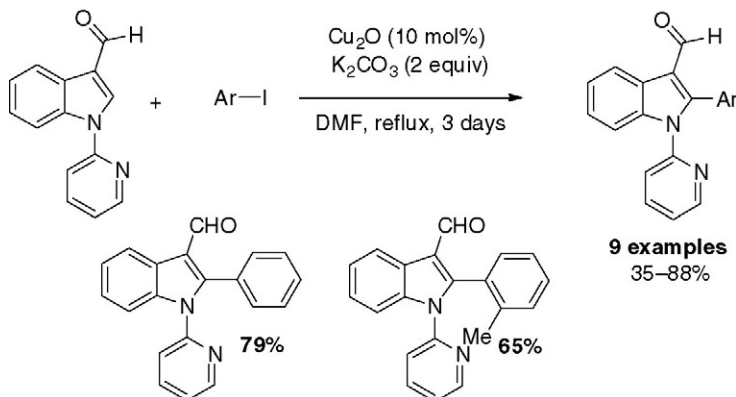
In 2009, Joseph and co-workers reported a Cu-catalyzed methodology for the arylation of *N*-pyridinylindoles with iodoarenes (Scheme 41, 09SL433). Despite this process requiring the presence of an aldehyde or nitrile group at the C3 position of the indole, high temperatures and long reaction times, good yields were generally obtained, and no protection was required for the aldehyde functionality.

Domínguez and co-workers have employed a Cu-catalyzed intramolecular indole arylation in their route to isoindolo[2,1-*a*]indoles (09TL2129). The reaction proceeds *via* initial *N*-benzylation, after which the resulting *N*-(2-halobenzyl)indole undergoes an intramolecular Cu-catalyzed C2-arylation to give isoindolo[2,1-*a*]indole (Scheme 42). This multistep procedure requires very high temperatures (180°C), and its scope and generality were not explored.

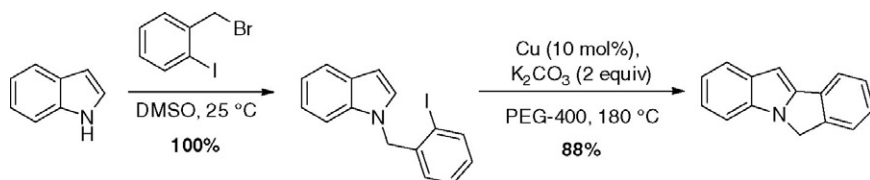
The use of a Cu catalyst in a tandem process for the preparation of indolo-[2,1-*a*]isoquinolines has been disclosed by Larock and co-workers



Scheme 40 Proposed catalytic cycle for the Cu-catalyzed direct arylation of indoles.

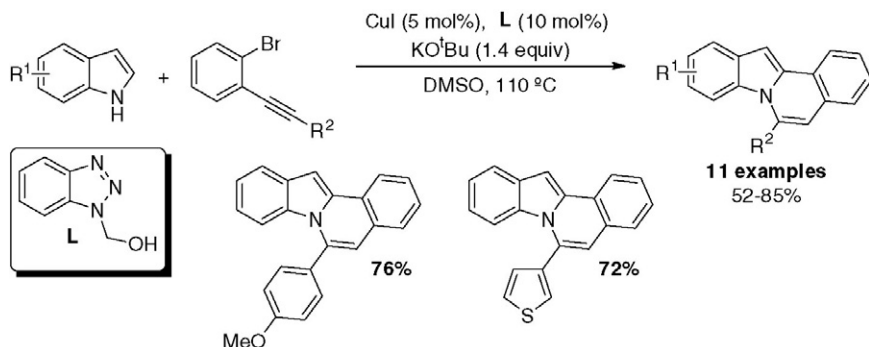


Scheme 41 Cu-mediated arylation of indole.



Scheme 42 Route to isoindolo[2,1-*a*]indole proceeding *via* direct C2-arylation.

(Scheme 43, 09AGE1138). The authors propose the initial generation of an enamine intermediate, which then undergoes intramolecular C2-arylation to give the indolo[2,1-*a*]isoquinoline. A wide range of functionalized indoles and haloarylalkynes were coupled with good-to-excellent yields. Interestingly, bromoarenes are used in this case as the aryl donor coupling partners.



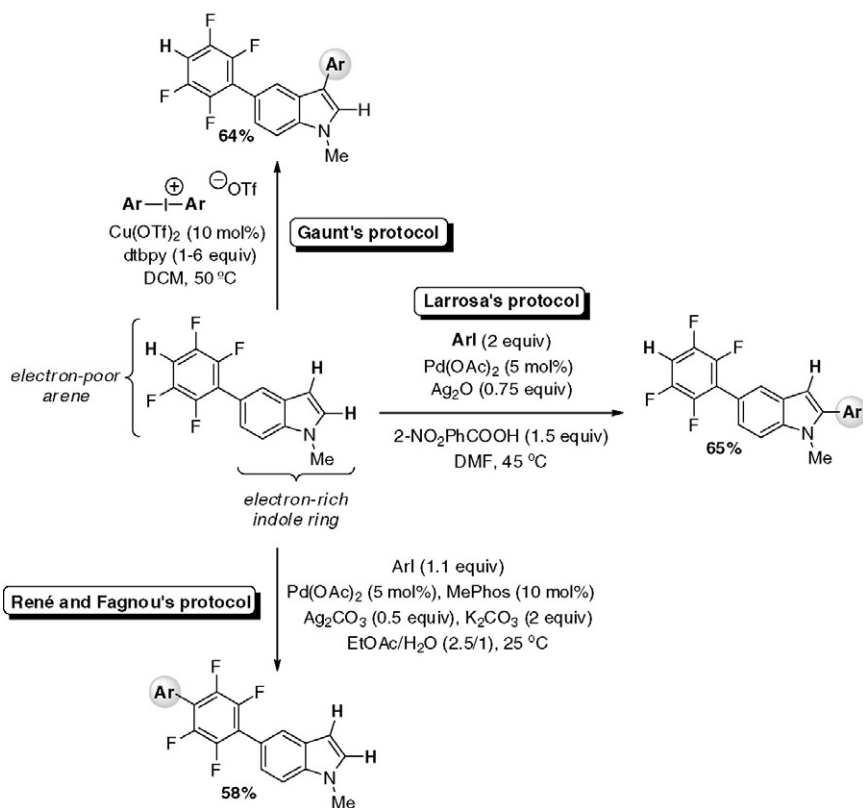
Scheme 43 Cu-catalyzed tandem synthesis of indolo[2,1-*a*]isoquinolines.

Very recently Lapointe et al. published an extensive study aimed at tackling the site-selectivity issue underlying the challenging functionalization of complex substrates containing multiple C–H bonds. The authors showed that by taking advantage of the specificities of previously published methodologies for the C–H arylation of indoles it is possible to obtain selective and predictable functionalization at various positions of substrates with multiple C–H bonds (Scheme 44, 11JOC749).

3. DECARBOXYLATIVE C–H ARYLATION

Decarboxylative functionalization has recently emerged as an appealing alternative to C–H functionalization (07AGE1374, 08AGE3100, 08AGE10022, 10S3395). In this approach the regioselectivity is easily controlled by the position of the carboxylic acid functional group and only CO₂ is produced as waste from the activation. The ready availability of carboxylic acids and their stability renders this strategy particularly attractive.

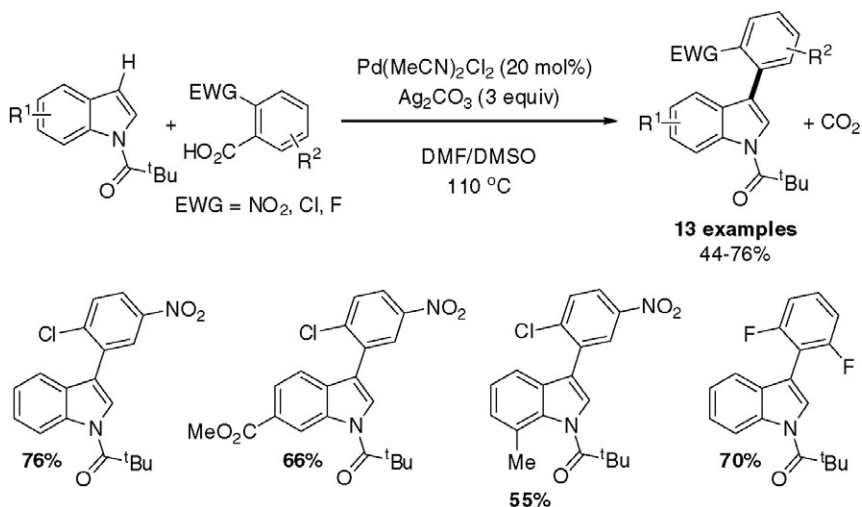
In 2009, Larrosa and co-workers developed the first decarboxylative direct C–H arylation methodology that allowed the intermolecular coupling of a variety of electron-poor benzoic acids with *N*-pivaloylindoles (09OL5506). Remarkably, this process occurs with high chemo- and regioselectivity in both coupling partners and led to the formation of C3-arylated products exclusively, with good yields (Scheme 45). The authors proposed



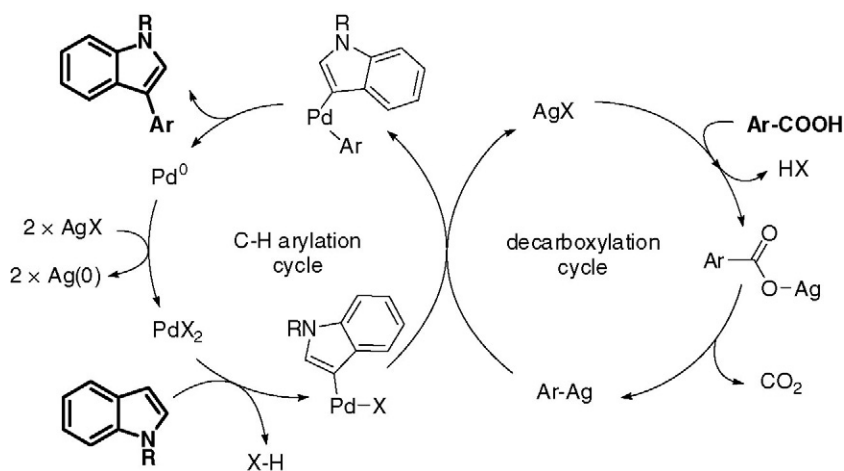
Scheme 44 Selective and predictable functionalization at various positions of substrates with multiple C–H bonds.

a mechanism based on two intertwined catalytic cycles, one involving a Pd-catalyzed C–H activation and a second one a Ag(I)-catalyzed decarboxylative activation (**Scheme 46**). In their hypothesis the Pd-catalyst is responsible for the C–H activation and reductive elimination steps, whereas the Ag-salts perform the decarboxylative activation step. Both cycles are connected through the transmetalation of the arylsilver species to palladium. An oxidant is then necessary to reoxidize Pd(0) to Pd(II), which in this case is ensured by the presence of a stoichiometric amount of Ag(I) salts.

Independently, Su and co-workers developed a catalytic system enabling the use of both electron-rich and electron-poor *o*-substituted benzoic acids (**10CEJ5876**). The authors showed that the regioselectivity is highly dependent on the nature of the benzoic acid coupling partner: C2-Arylated products were exclusively formed from electron-rich benzoic

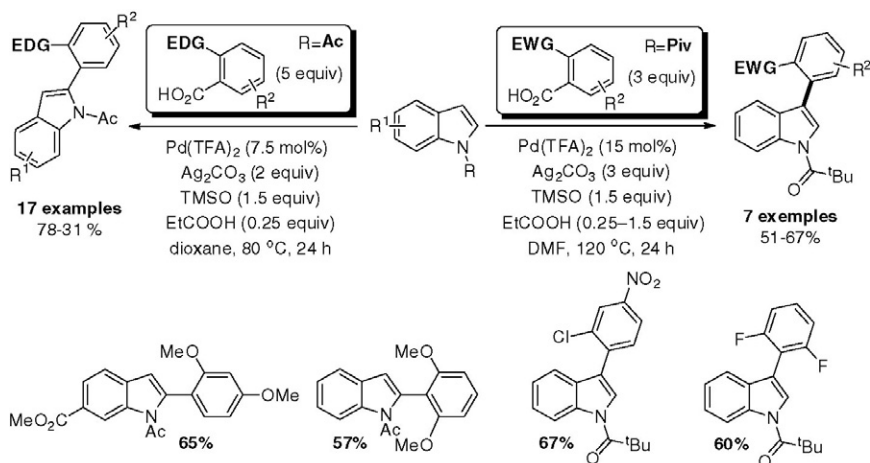


Scheme 45 Decarboxylative C3-arylation of indoles with benzoic acids.



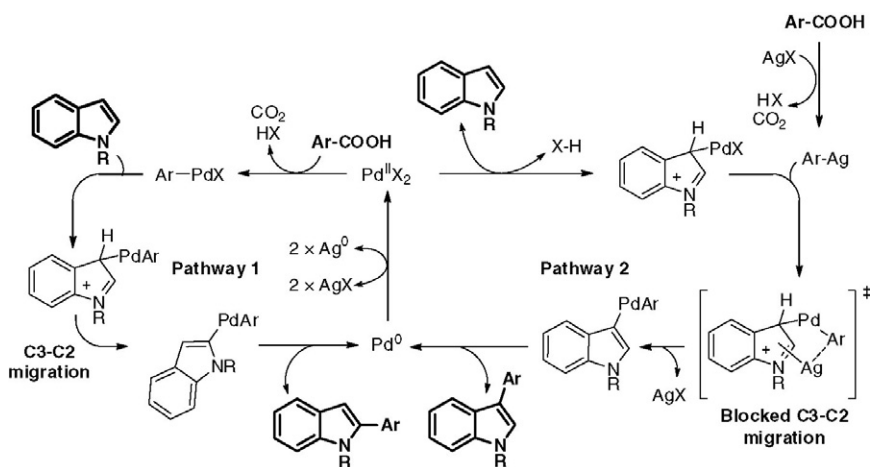
Scheme 46 Proposed mechanism for the decarboxylative C3-arylation of indoles with electron-poor benzoic acids.

acids, whereas electron-poor acids led to C3-arylated indoles (this last observation being consistent with Larrosa's results). The combination of Pd(TFA)₂, Ag₂CO₃, propionic acid, and TMSO proved to be an efficient catalytic system and allowed the coupling of a wide range of *N*-acetylindoles with electron-rich benzoic acids in good yields and high regioselectivity. A slight modification of the conditions permitted coupling



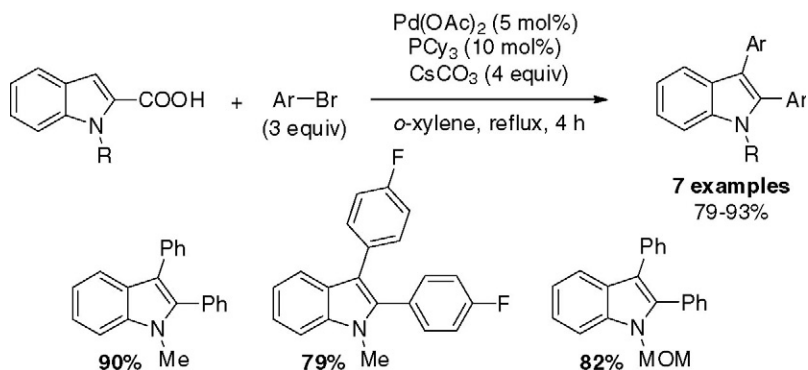
Scheme 47 C2- and C3-decarboxylative arylation of indoles.

N-pivaloylindoles with electron-poor benzoic acids in moderate-to-good yields and complete regioselectivity (**Scheme 47**). The authors carried out mechanistic investigations and confirmed that $\text{Pd}(\text{TFA})_2$ alone was able to promote the decarboxylation of electron-rich benzoic acids, but that in the case of electron-poor acids the decarboxylation was observed to arise from Ag_2CO_3 rather than $\text{Pd}(\text{TFA})_2$. Based on this observation, they proposed two different mechanisms as depicted in **Scheme 48**.

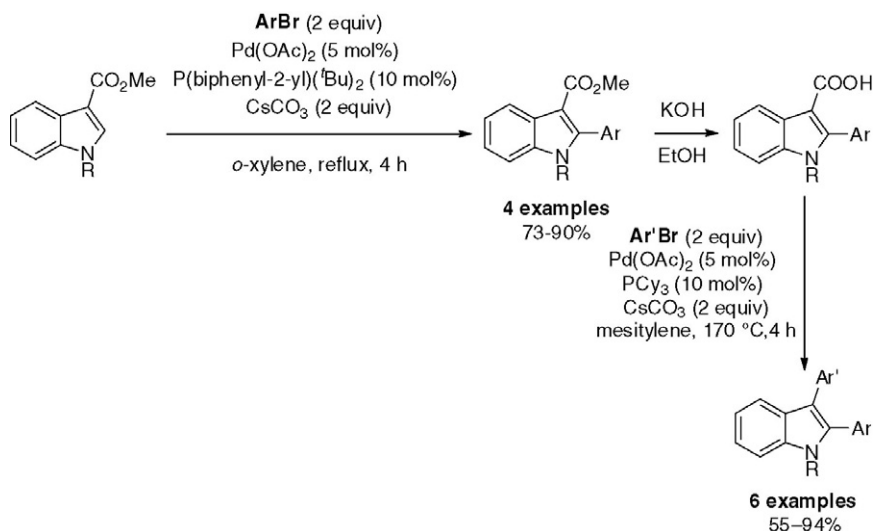


Scheme 48 Proposed mechanism for the C2- and C3-decarboxylative arylation of indoles.

In 2009, Miura and co-workers reported a Pd-catalyzed 2,3-diarylation of carboxyindoles derivatives with bromoarenes (09CEJ3674). A one-pot procedure allowed the coupling of various electron-poor and electron-rich bromoarenes with 2-carboxyindoles with excellent yields (Scheme 49). The authors also described a stepwise protocol starting from 3-(methoxycarbonyl)indoles that provide access to indoles bearing a different aryl group at the 2- and 3- positions (Scheme 50).



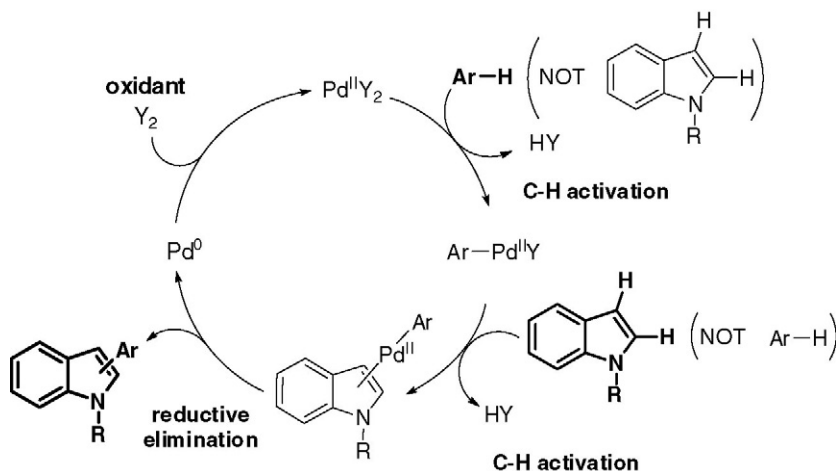
Scheme 49 Reaction of 2-carboxyindoles with bromoarenes.



Scheme 50 Stepwise diarylation of 3-(methoxycarbonyl)indoles.

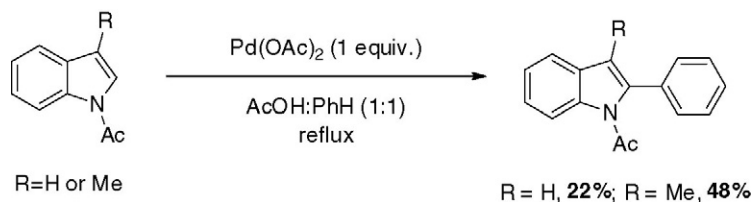
4. OXIDATIVE C–H/C–H CROSS-COUPLING

The catalytic cross-coupling of two different arenes without the need for prefunctionalization of any of the coupling partners (known as oxidative C–H/C–H cross-coupling, catalytic dehydrogenative cross-coupling or twofold oxidative C–H activation) is an appealing alternative to C–H arylation with aryl halides ([10CSR540](#), [11CRV1215](#), [11CRV1780](#)). It represents by far the most direct and efficient strategy to construct biaryl linkages. However, this approach is as attractive as it is challenging: in addition to the issues of reactivity and regioselectivity inherent in any C–H activation methodology, oxidative coupling strategies face the major challenge of having to avoid the formation of unwanted homocoupling products. The catalyst needs to perform the C–H bond activation of both substrates sequentially, while avoiding the homocoupling of each of them ([Scheme 51](#)). Furthermore, electron-rich arenes such as indoles readily undergo oxidative decomposition and are considered as particularly challenging targets for such methodologies ([77H743](#), [79S276](#), [03JA9578](#)).



Scheme 51 Pd-catalyzed oxidative coupling: general mechanism.

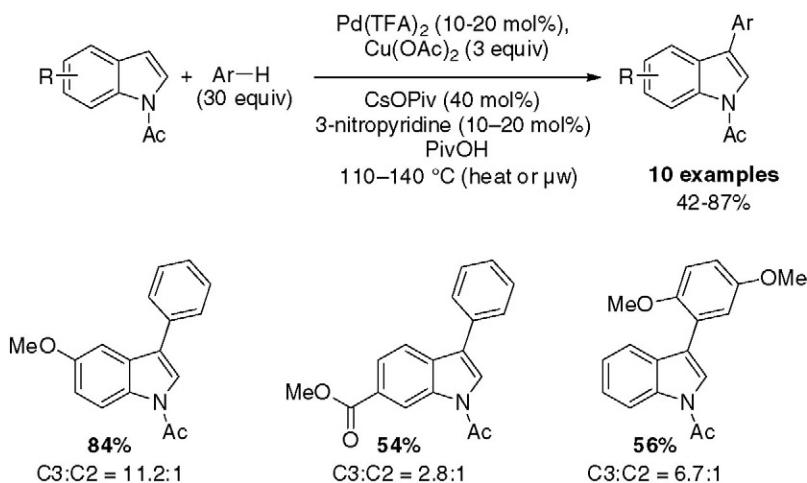
The first examples of oxidative cross-couplings with indoles were reported by Itahara and co-workers in the late 1970s ([78S607](#), [79S151](#), [81JCS\(CC\)254](#)). The intermolecular version of the coupling required the use of *N*-acetylindoles and stoichiometric amount of Pd(OAc)₂ in a refluxing mixture of AcOH and benzene ([Scheme 52](#), [81JCS\(CC\)254](#)).



Scheme 52 Itahara's first intermolecular oxidative coupling of indoles.

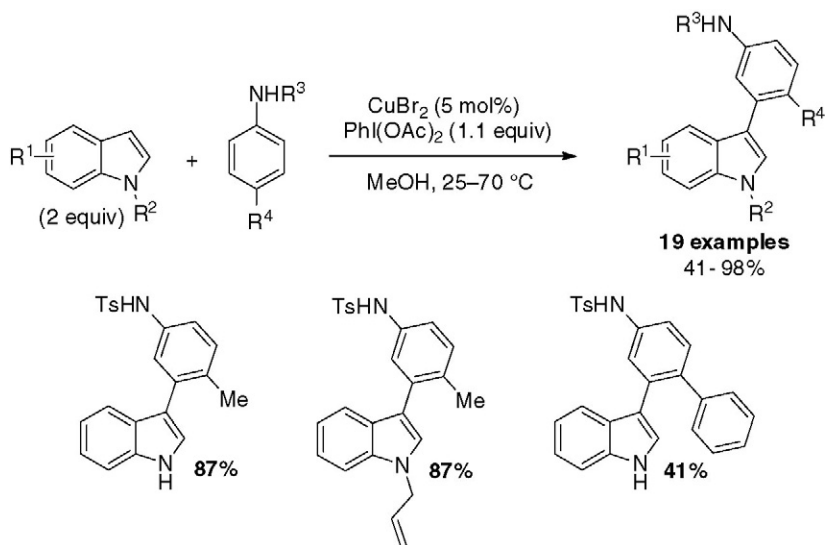
4.1 C3 selective arylation

A ground-breaking catalytic version of this reaction was reported by Fagnou and co-workers in 2007 ([Scheme 53](#), [07JA12072](#), [07SCI1172](#)). The use of Pd(TFA)_2 and Cu(OAc)_2 in combination with 3-nitropyridine and CsOPiv allowed the formation of a variety of C3-arylated indoles with high regioselectivity (C3:C2 ratio up to 11.2:1) and satisfactory yields. 3-Nitropyridine and CsOPiv do not appear to be crucial for the reactivity but lead to improved turnover and reproducibility. High chemoselectivity for the oxidative cross-coupling product was achieved by using a large excess of the arene coupling partner (30 equiv). The choice of the N-protecting group on the indole appears to be critical as unprotected indole failed to react under the reaction conditions while N-methylindole produced mainly self-dimerization. The reaction tolerates a broad range of substituents on the indole and allows the use of electron-poor and electron-rich *p*-disubstituted arenes. Remarkably, by simply changing the oxidant and the N-protecting group on the indole a reversal in regioselectivity was observed and 2-arylidindoles were obtained (*vide infra*, [07JA12072](#)).



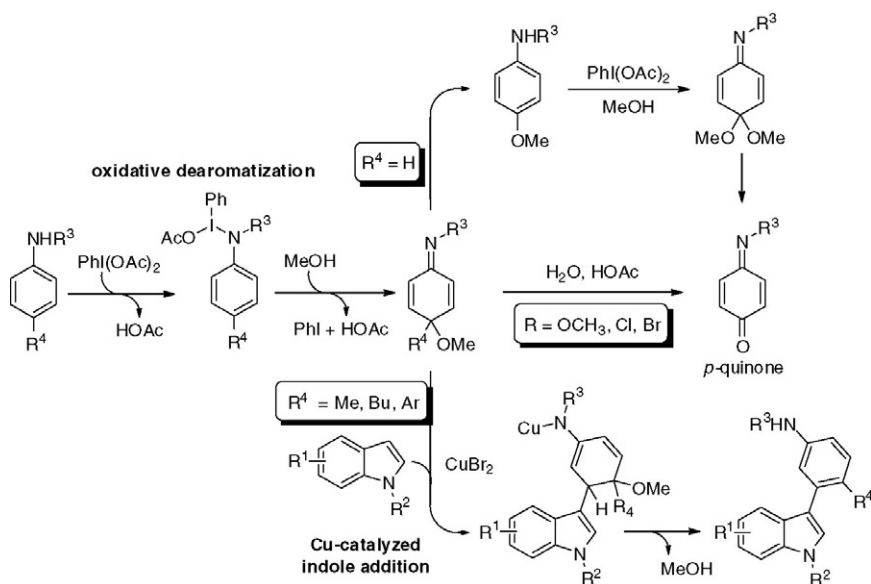
Scheme 53 Selective C3 oxidative cross-coupling of N-acetylindoles.

In 2010, Fan and co-workers described the selective C3–C3 oxidative coupling between anilines and indoles in presence of CuBr_2 (5 mol%) and $\text{PhI}(\text{OAc})_2$ as a stoichiometric oxidant (10ASC3230). In order to avoid side reactions, the coupling was carried out in a stepwise manner: the aniline and $\text{PhI}(\text{OAc})_2$ were premixed in MeOH for 15 min before adding the indole and the catalyst. These conditions proved to be compatible with a variety of substrates and coupling products were obtained in good-to-high yields and high regioselectivities (Scheme 54). Interestingly, the authors reported that the C4-substituent on the aniline played a crucial role: 4- CF_3 , 4-H, 4-OMe, 4-Cl, and 4-Br substituents failed to give coupling products and led to the formation of the *p*-quinone derivatives instead. Contrastingly, 4-alkyl and 4-aryl substituents were compatible with the conditions and led to the desired coupling products. Finally, the presence of an electron-withdrawing group on the nitrogen atom of the anilines was essential. Based on all these observations the authors proposed the mechanism depicted in Scheme 55.

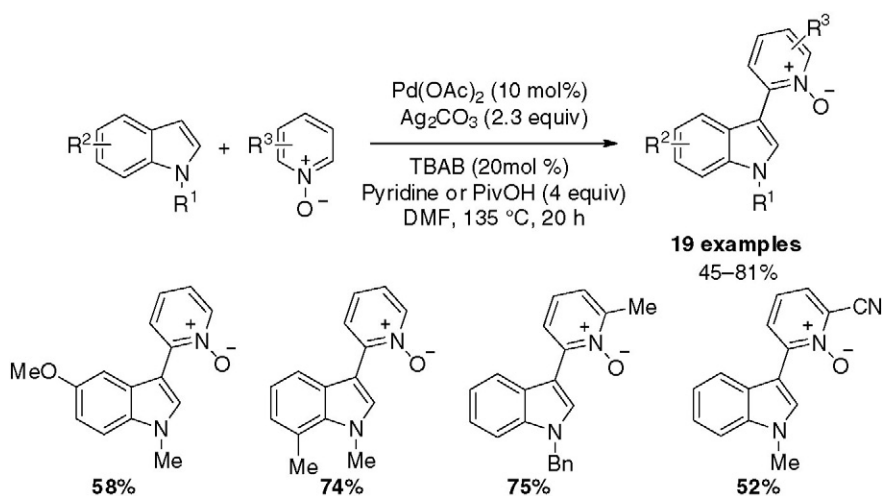


Scheme 54 Selective C3–C3 oxidative coupling of anilines and indoles.

Recently, Li and co-workers reported the C3-selective oxidative arylation of indoles with pyridine N-oxides (Scheme 56, 11OL1766). Using $\text{Pd}(\text{OAc})_2$ and Ag_2CO_3 as the oxidant, the cross-coupling of *N*-methyl, *N*-benzyl, and *N*-phenylindole derivatives with different pyridine N-oxides



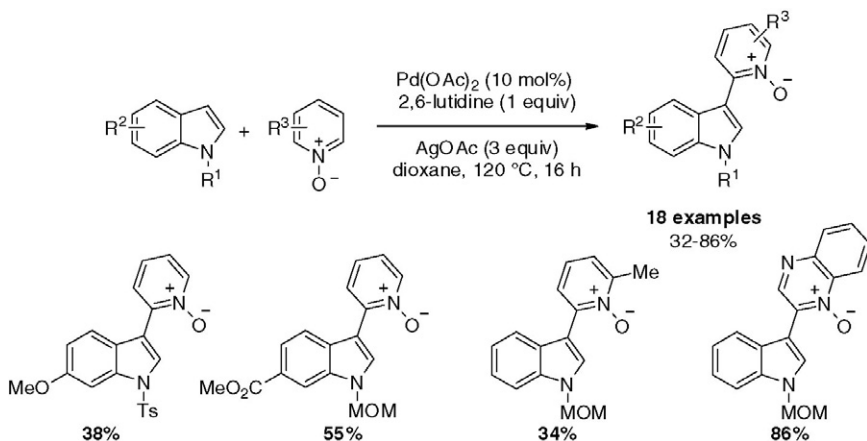
Scheme 55 Proposed mechanism for the selective C3–C3 oxidative coupling of anilines and indoles.



Scheme 56 Zhang and Li's oxidative coupling of *N*-protected indoles with pyridine *N*-oxides.

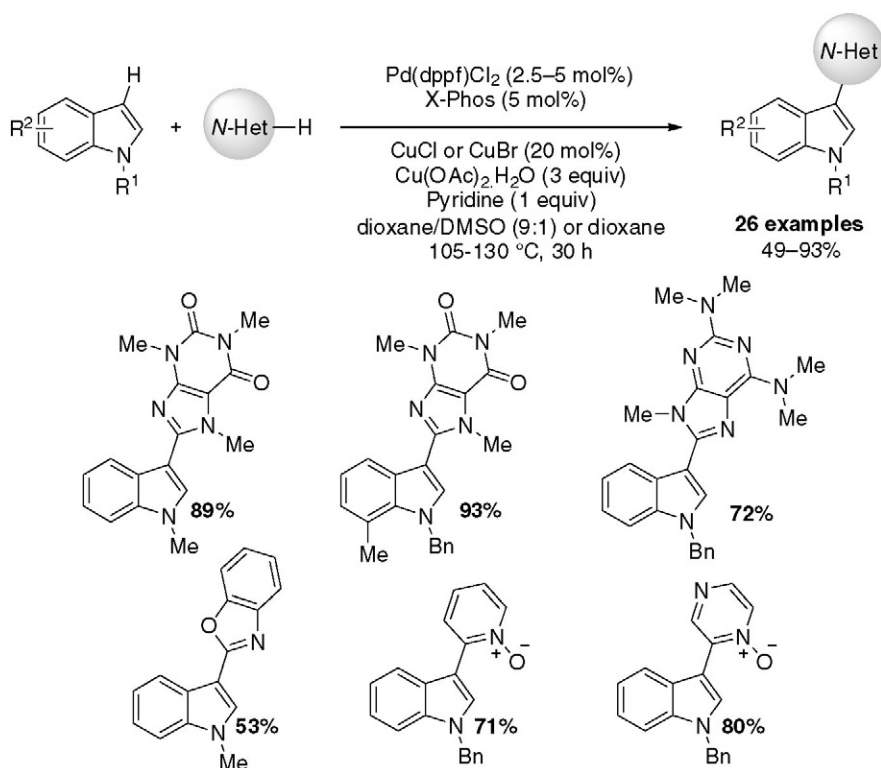
could be achieved with high regioselectivity (C2 position of the pyridine N-oxide and C3 position of the indole) and moderate-to-high yields. The authors found that the presence of pyridine (4 equiv) and TBAB (20 mol%) dramatically improved the yield. The use of other tetrabutylammonium salts (TBAF, TBAC, TBAI) leads to very low yields. Oxygen transfer to pyridine was observed when using pyridine N-oxides bearing electron-withdrawing groups and pyridine-free conditions had to be used in those cases (PivOH was used instead).

A similar methodology has been reported concurrently by Yamagushi and Itami (11CL555). Optimized conditions allowed the coupling of a variety of *N*-MOM and *N*-Ts indoles with pyridine and pyrazine N-oxides – also the latter required the use of AcOH instead of 2,6-lutidine (Scheme 57). Notably the authors applied their methodology to the synthesis of eudistomin U, a marine alkaloid with DNA-binding activity.



Scheme 57 Yamagushi and Itami's oxidative coupling of *N*-protected indoles with azine N-oxides.

Independently, You and co-workers developed a robust Pd/Cu bimetallic catalytic system allowing the highly regioselective C3 coupling of indoles with a large variety of *N*-heteroarenes (Scheme 58, 11AGE5365). Under optimized conditions xanthines, purines, azoles, pyridine N-oxides, quinolone N-oxides, quinoxaline N-oxides, and pyrazine N-oxides were successfully coupled with different *N*-protected indoles. X-Phos appeared to be a critical additive and allowed high-yielding couplings by significantly decreasing the decomposition of starting material and product.

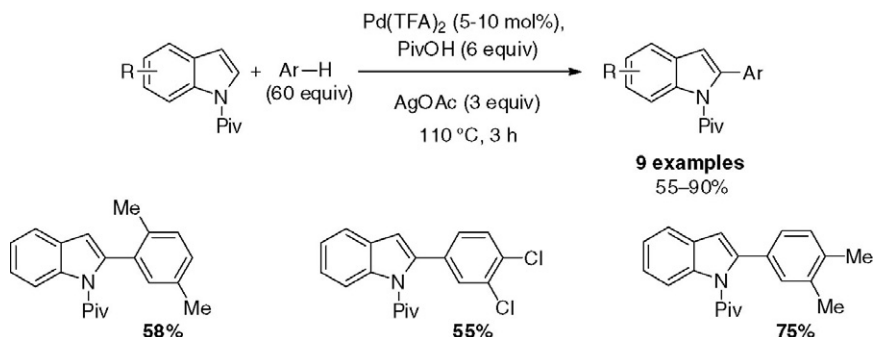


Scheme 58 Oxidative cross-coupling of *N*-protected indoles with *N*-heteroarenes.

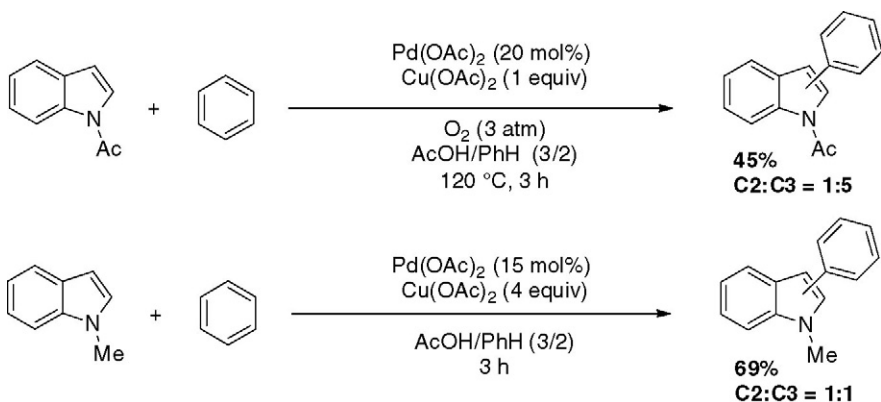
4.2 C2 selective arylation

Following his seminal work on C3-arylation of indoles (*vide supra*, 07SCI1172) Fagnou and co-workers showed that high regioselectivity for C2-arylation could be achieved from *N*-pivaloyl protected indoles when using AgOAc instead of Cu(OAc)_2 as the stoichiometric oxidant (Scheme 59, 07JA12072). A range of substituents were examined in both the indole and the benzene moieties, observing generally good yields and regioselectivities. Remarkably, despite the important excesses used for the benzene coupling partner (60 equiv), homocoupling was not observed for either arene, indicating that a complete reversal in catalyst selectivity is achieved.

Concurrently, DeBoef and co-workers reported two examples of the oxidative arylation of indoles (Scheme 60, 07OL3137). Similarly to Fagnou's report this process requires high catalyst loadings (15–20 mol%)



Scheme 59 Oxidative C2-arylation of *N*-pivaloylindoles.

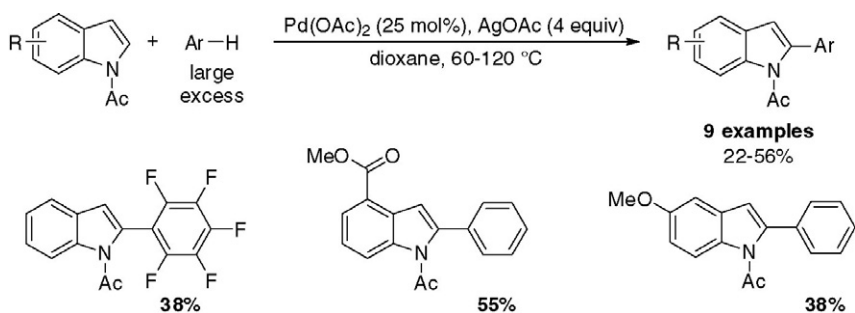


Scheme 60 Oxidative arylation of *N*-acetyl and *N*-methylindole.

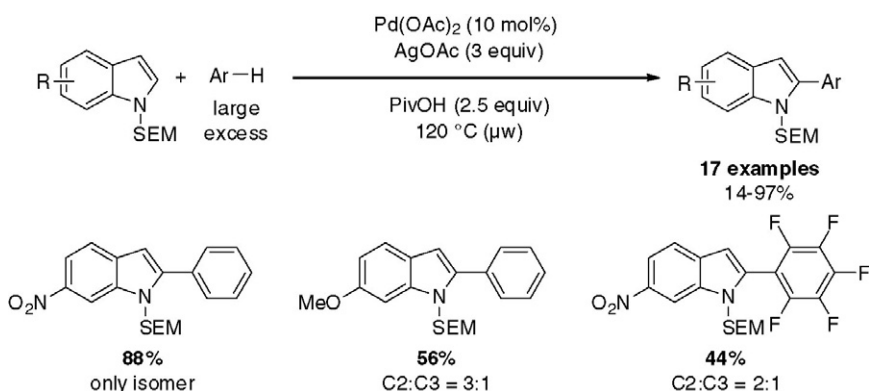
and a stoichiometric amount of Cu oxidant (1–4 equiv). In contrast to Fagnou's results, C2-arylated *N*-methylindole could be obtained with a decent yield but low C2/C3 regioselectivity was achieved.

In agreement with the work of Fagnou, DeBoef later described that high regioselectivity for the C2-arylation of *N*-acetylindoles could be obtained by using AgOAc as the oxidant (Scheme 61, 08TL4050). Low-to-moderate yields were obtained for a broad range of indoles, whereas electron-rich arenes failed to react.

In 2010, DeBoef published a complementary study showing that these conditions were compatible with *N*-alkylindoles when the coupling reactions were performed in the presence of nearly equal amounts of pivalic acid and AgOAc (Scheme 62, 10JA14676). Optimized conditions allow *N*-SEM, *N*-Bn, and *N*-MOM protected indoles to be coupled with benzene

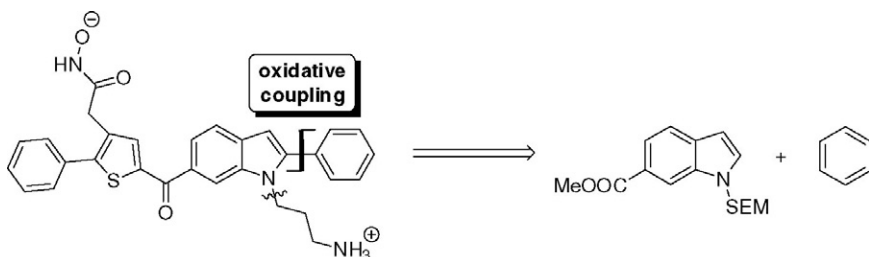


Scheme 61 Oxidative C2-arylation of *N*-acetylindoles.



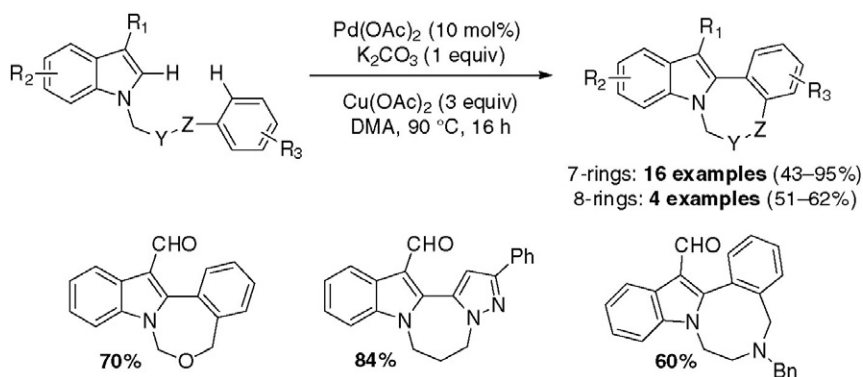
Scheme 62 Oxidative C2-arylation of *N*-alkylindoles.

with moderate-to-good yields. A large range of *N*-SEM indoles and arenes were examined and found to lead to moderate-to-high yields and generally satisfactory regioselectivities. Subsequently, DeBoef reported the use of this approach to achieve a formal synthesis of an inhibitor of botulinum neurotoxin serotype A ([Scheme 63](#), 11CC4679).

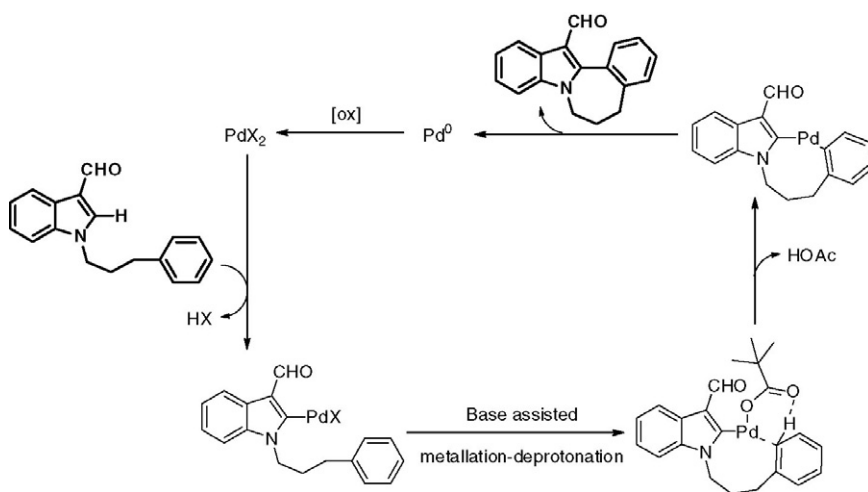


Scheme 63 Formal synthesis of an inhibitor of BoNTA using an oxidative cross-coupling.

Recently, Greaney and co-workers developed an efficient strategy to prepare medium-ring compounds based on an intramolecular oxidative cross-coupling between indoles and arenes (Scheme 64, 11JA1209). The conditions allow the preparation of a variety of 6-, 7-, and 8-membered ring annulated indoles in good-to-high yields. An electron-withdrawing group is required at the indole C3 position and optimized conditions involved the use of $\text{Pd}(\text{OAc})_2$ as the Pd source, $\text{Cu}(\text{OAc})_2$ as an oxidant and K_2CO_3 in DMA. Based on some preliminary mechanistic studies the authors proposed the mechanism depicted in Scheme 65.



Scheme 64 Intramolecular oxidative cross-coupling for medium-ring synthesis.



Scheme 65 Proposed mechanism for the intramolecular oxidative cross-coupling for medium-ring synthesis.

5. CONCLUSION

Transition metal-catalyzed direct and site-selective C2- and C3-arylations of the indole core represent an attractive strategy for the development of more efficient and “greener” chemical synthesis. The last few years have seen tremendous progress in this field, particularly with the development of catalytic systems able to perform under very mild conditions, and the application of these methodologies to the synthesis of indole-based complex targets. Many of the strategies described in this review present very high selectivities for either C2- or C3-arylation. However, our mechanistic understanding behind these selectivities is still lacking a refined model, as seemingly small changes in conditions can lead to the predominance of one regioisomer over the other. Surely, over the next decade the field will deliver even more impressive advances, with methodologies providing access to a variety of substituted indoles under very mild conditions, using lower catalyst loadings, and starting from readily available nonprefunctionalized arenes.

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