

Chiral Fullerenes from Asymmetric Catalysis

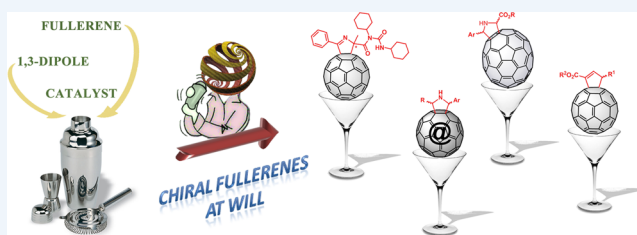
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CONSPECTUS: Fullerenes are among the most studied molecules during the last three decades, and therefore, a huge number of chemical reactions have been tested on these new carbon allotropes. However, the aim of most of the reactions carried out on fullerenes has been to afford chemically modified fullerenes that are soluble in organic solvents or even water in the search for different mechanical, optical, or electronic properties. Therefore, although a lot of effort has been devoted to the chemical functionalization of these

molecular allotropes of carbon, important aspects in the chemistry of fullerenes have not been properly addressed. In particular, the synthesis of chiral fullerenes at will in an efficient manner using asymmetric catalysis has not been previously addressed in fullerene science. Thus, despite the fact that the chirality of fullerenes has always been considered a fundamental issue, the lack of a general stereoselective synthetic methodology has restricted the use of enantiopure fullerene derivatives, which have usually been obtained only after highly expensive HPLC isolation on specific chiral columns or prepared from a pool of chiral starting materials. In this Account, we describe the first stereodivergent catalytic enantioselective syntheses in fullerene science, which have allowed the highly efficient synthesis of enantiomerically pure derivatives with total control of the stereochemical result using metallic catalysts and/or organocatalysts under very mild conditions. Density functional theory calculations strongly support the experimental findings for the assignment of the absolute configuration of the new stereocenters, which has also been ascertained by application of the sector rule and single-crystal X-ray diffraction. The use of the curved double bond of fullerene cages as a two- π -electron component in a variety of stereoselective cycloaddition reactions represents a challenging goal considering that, in contrast to most of the substituted olefins used in these reactions, pristine fullerene is a noncoordinating dipolarophile. The aforementioned features make the study of stereoselective 1,3-dipolar cycloadditions onto fullerenes a unique scenario to shed light onto important mechanistic aspects. On the other hand, the availability of achiral starting materials as well as the use of nonexpensive asymmetric catalysts should provide access to chiral fullerenes and their further application in a variety of different fields. In this regard, in addition to biomedical applications, chiral fullerenes are of interest in less-studied areas such as materials science, organic electronics, and nanoscience, where control of the order and morphology at the nanometer scale are critical issues for achieving better device efficiencies.



1. INTRODUCTION

Fullerenes represent the only molecular allotropic form of carbon that, in contrast to the other well-known reticular allotropes of carbon, diamond and graphite, is constituted by a defined number of carbon atoms forming highly symmetric closed cages. Since the discovery of the soccer-ball-shaped C_{60} molecule by Robert F. Curl, Sir Harold W. Kroto, and Richard E. Smalley in 1985,¹ fullerenes have stimulated the creativity of the scientific community because of their singular round shape, physicochemical properties, and unexpected high reactivity.²

The chirality of fullerenes can stem from an asymmetric arrangement of carbon atoms to afford chiral cages. Since the isolation of D_2 - C_{76} (Figure 1) from fullerene soot extract,³ a variety of such inherently chiral fullerenes have been reported.⁴ In addition to these pristine chiral cages, inherently chiral fullerene derivatives can be obtained from the geometric arrangement of the same achiral addends on the surface of an achiral cage. The addition patterns of [60]fullerene, namely, *cis*-3,

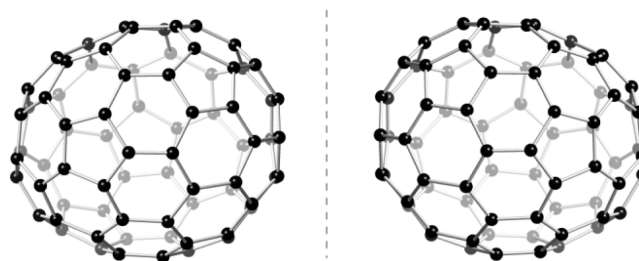
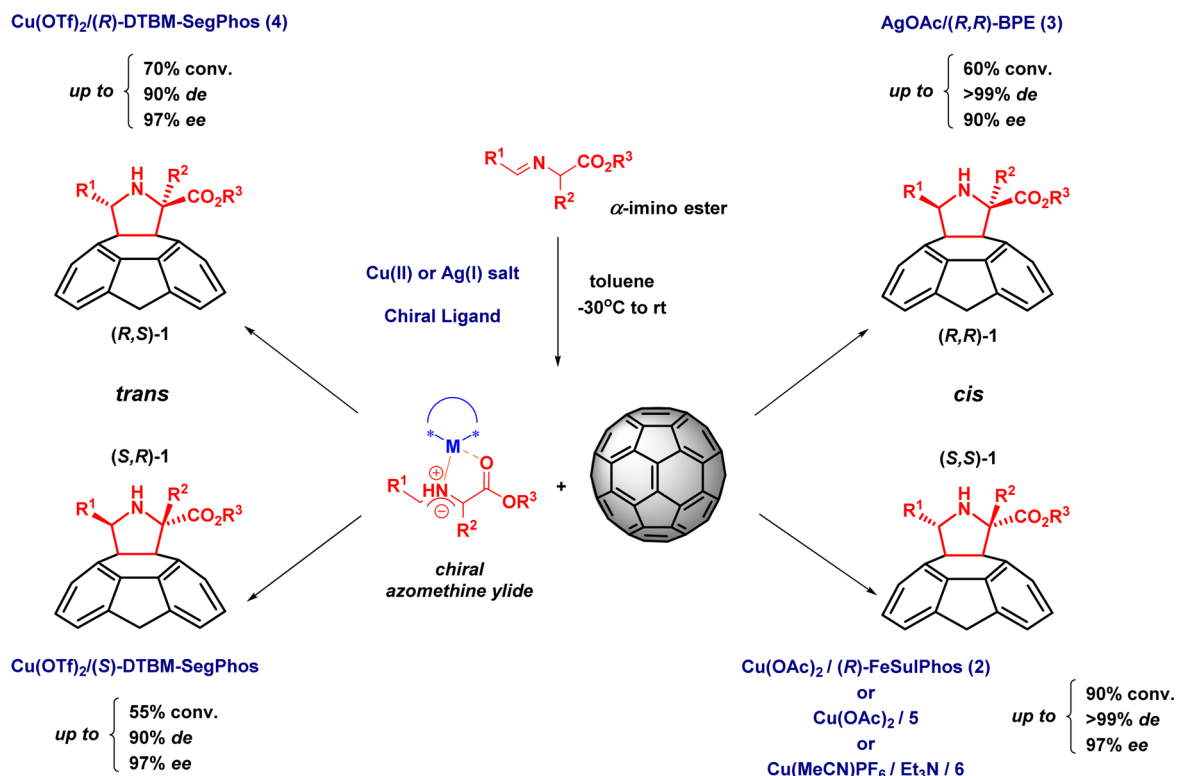


Figure 1. Structures of the two enantiomers of the inherently chiral fullerene D_2 - C_{76} .

trans-3, and *trans*-2, result in chiral products when the addends are identical and exhibit C_{2v} symmetry. Bisadducts (*cis*-1, *cis*-2,

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Scheme 1. Stereodivergent [3 + 2] Cycloaddition of N-Metalated Azomethine Ylides onto C₆₀

and *trans*-4) do not present inherently chiral addition patterns, but they can be chiral when the addends are not identical.⁴ Finally, chiral fullerene derivatives can also be prepared when the attached organic addends contain chiral elements.⁵

Nowadays, there is a complete understanding of the chemical reactivity of fullerenes. However, the control of some fundamental chemical aspects such as stereoselectivity and chirality are issues of paramount importance that have not been properly addressed to date. Actually, only relatively few examples based on the use of chiral starting materials^{6–9} or on expensive and highly time-consuming HPLC separations¹⁰ have been reported. Furthermore, how chirality modifies the electronic properties of the carbon-based nanostructures is still an open question. In particular, chiral fullerene derivatives have been shown to be important motifs in materials science¹¹ and medicinal chemistry.^{12,13}

In the past decade, the catalytic asymmetric version of 1,3-dipolar cycloaddition of azomethine ylides to alkenes has emerged as an atom-economical and powerful reaction for the synthesis of optically active pyrrolidines.^{14,15} In particular, the 1,3-dipolar cycloaddition of azomethine ylides formed by thermal treatment from aldehydes and amino acids^{16,17} or from imino esters¹⁸ onto C₆₀ affords pyrrolidino[3,4:1,2][60]fullerenes, which are probably the most widely used fullerene derivatives because of their versatility and stability and the availability of the starting materials. In addition, these heterocyclic-fused compounds constitute valuable building blocks for the formation of fulleropeptides.¹⁹

In this context, our group's introduction of asymmetric metal catalysis for the synthesis of pyrrolidinofullerenes with control of the absolute configuration of the created stereogenic centers has been a first and significant breakthrough. This Account summarizes the current status of the preparation of chiral fullerene derivatives by enantioselective catalytic 1,3-dipolar

cycloadditions of several dipoles onto C₆₀. Moreover, because of the growing interest in less-known higher fullerenes (more than 60 carbon atoms) and endohedral fullerenes (those bearing an atom, molecule, or cluster in the inner cavity), this methodology has also been successfully extended to C₇₀ as well as to metallofullerenes (La@C₇₂) and H₂-containing endofullerenes (H₂@C₆₀). Furthermore, the most recent highly enantioselective organocatalytic protocols that have also been successfully applied on fullerenes in our group are also discussed.

2. METAL-CATALYZED ASYMMETRIC [3 + 2] CYCLOADDITIONS ONTO FULLERENES

2.1. Metal-Catalyzed Asymmetric [3 + 2] Cycloadditions onto [60]Fullerene

Despite the noncoordinating nature of [60]fullerene, the presence of curved double bonds and its poor electron character stemming from the presence of only sp²-hybridized carbon atoms make this spherical carbon cage a challenging scenario for the reaction with 1,3-dipoles such as α -imino esters^{20–22} or azlactones.²³ In the reaction, catalyzed by metals, [60]fullerene acts as the dipolarophile, giving rise to N-containing five-membered-ring structures with total stereocontrol of the new stereocenters.

2.1.1. α -Imino Esters as 1,3-Dipoles: Enantiomeric Synthesis of Pyrrolidinofullerenes. When an α -imino ester reacts under thermal conditions in the presence of [60]fullerene, a mixture of two isomers (*cis* and *trans*) of the 2-alkoxycarbonyl-5-arylpyrrolidino[3,4:1,2][60]fullerene (**1**) is obtained. The lack of stereoselectivity in the final products disrupts the challenging synthesis of their four enantiomeric forms. For this reason, a deeper study employing metal–ligand complexes was required in order to induce the stereoselective formation of the 1,3-dipole, thereby carrying out the process under milder conditions and

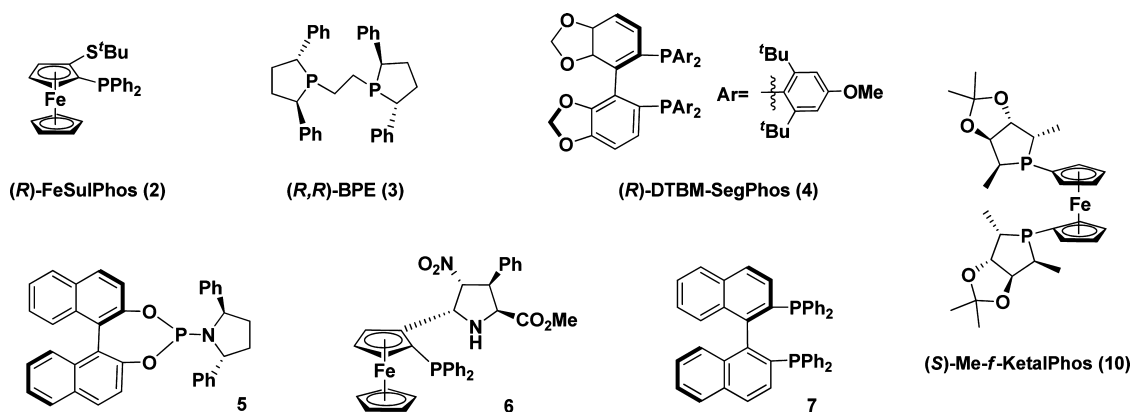


Figure 2. Chiral phosphines tested in the preparation of fulleropyrrolidines and fulleropyrrolines.

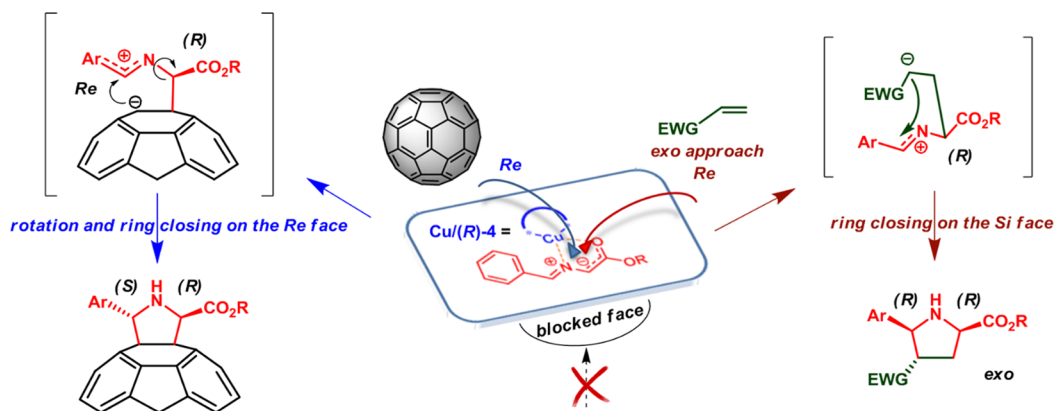


Figure 3. Plausible mechanism of the stereodivergent [3 + 2] cycloaddition of α -imino esters with C_{60} and conventional olefins.

controlling the stereochemical outcome in terms of diastereo- and enantioselectivity. Thus, screening of different metal–ligand pairs revealed the feasibility of the metal-mediated azomethine ylide cycloaddition onto the fullerene sphere, and even with catalytic amounts, the reactions take place quickly at room temperature, leading to the final pyrrolidinofullerenes in high conversions and excellent diastereo- and enantiomeric excesses.

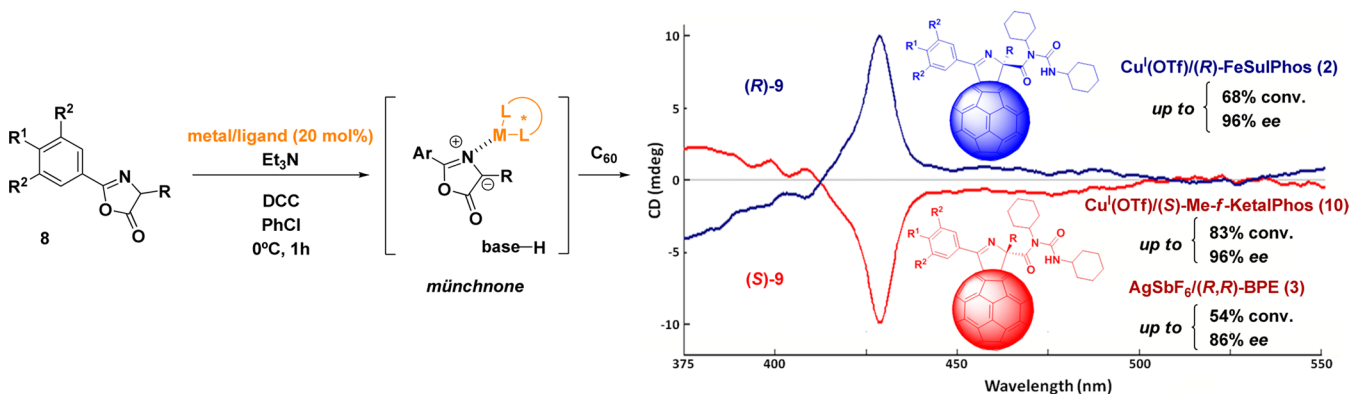
As shown in Scheme 1, depending on the metal, counterion, and chiral ligand (Figure 2) employed, a stereodivergent synthesis of fulleropyrrolidines a la carte can be achieved. Thus, for instance, when $Cu(OAc)_2/(R)$ -FeSulPhos (2) or phosphoramidite 5 catalytic pairs are used, (*S,S*)-*cis*-1 is obtained, in contrast to the system formed by $AgOAc/(R,R)$ -BPE (3), which affords the opposite enantiomer, (*R,R*)-*cis*-1. However, the enantiomeric excesses observed in the reactions are slightly lower than those reported for other non-fullerene dipolarophiles.¹⁴ This behavior is probably due to the nonligand features of the [60]fullerene, which does not coordinate with the metal, in sharp contrast to most dipolarophiles used to date (typically α,β -unsaturated carbonyl compounds). In this regard, it is worth mentioning that the presence of acetate as counterion in the reaction mixture could play a leading role in both the formation of the azomethine ylide and the high enantioselectivities achieved.

In addition, other chiral ligands such as 6, which features the chirality of unnatural prolines and the planar chirality of the ferrocene skeleton, also afford the (*S,S*)-*cis*-1 enantiomer with excellent ee values at lower catalyst loadings (5 mol %), even with α -imino esters derived from alanine with higher steric hindrance.

On the other hand, *trans* enantiomers can also be obtained and switched by using commercially available (*R*)- or (*S*)-DTBM-SegPhos as the ligand and $Cu(OTf)_2$ as the metal source, leading to (*R,S*)-*trans*-1 or (*S,R*)-*trans*-1, respectively. Here, an additional base (Et_3N) is necessary for the optimal outcome of the process, since the triflate counterion in those cases is not able to trigger the formation of the azomethine ylide.

In general, aryl-substituted α -imino esters work well in terms of reactivity and enantioselectivity, in contrast to the less stable alkyl-substituted α -imino esters, which lead to poorer conversions due to their easier hydrolysis. Moreover, the presence of electron-releasing and/or electron-withdrawing groups in the aromatic moiety at the *ortho* or *meta* positions of the phenyl ring was also tested and resulted in different behavior in terms of stereoselectivity and reactivity. In order to extend the scope of the methodology and the effect on the stereochemistry of the final products, the use of less-explored chiral α -imino amides as starting 1,3-dipoles was also carried out. Interestingly, a double asymmetric induction resulting in a matching/mismatching effect, depending upon the absolute configuration of the stereocenter in the starting α -imino amide, was observed.

Since it was not possible to obtain suitable crystals from fullerene derivatives for X-ray diffraction, the assignment of the absolute stereochemistry of the obtained compounds was determined by circular dichroism (CD) analysis. In accordance with the sector rule,²⁴ all of the pyrrolidinofullerenes formed from the $Ag(I)/3$ catalytic complex showed in their CD spectra a positive Cotton effect (CE) in the signal at 425–430 nm, which is consistent with a (*2R,5R*) stereochemistry. Likewise, the negative CE corresponding to the $Cu(II)/2$, 4, 5, and 6 systems is in

Scheme 2. Metal-Catalyzed Enantioselective [3 + 2] Cycloaddition of Azlactones onto C₆₀

accordance with the (2*S*,5*S*) configuration. This assignment is in agreement with the stereochemical outcome obtained with the same catalytic system in the synthesis of fullerene-free pyrrolidines observed by other researchers.¹⁴ Interestingly, *trans* derivatives afford an additive contribution in the corresponding signal, leading to a higher intensity compared with their respective *cis* diastereoisomers.

In regard to the mechanism, two competitive reaction pathways are present depending on the substrate and ligand structures. First, some catalytic systems, namely, Ag(I)/(*R,R*)-BPE (3) and Cu(II)/FeSulPhos (2), allow the formation of favorable secondary interactions in the intermediate that lead to *cis*-fulleropyrrolidines or *endo* isomers when conventional olefins are employed.²⁵ On the other hand, we observed for the first time that when an *exo*-selective catalyst is employed, such as Cu(II)/DTBM-SegPhos (4) or BINAP (7), cycloaddition of *N*-metalated azomethine ylides onto the fullerene occurs in a *supra-antara* manner, giving rise efficiently to *trans*-pyrrolidine derivatives. Indeed, all of the previously reported cycloadditions of *N*-metalated azomethine ylides afforded *cis*-pyrrolidines because of the more stable w-shaped geometry of the dipole. In sharp contrast, the above-mentioned catalysts promote a rotation around the N–C2 pyrrolidine bond, affording unusual *trans* isomers. Nevertheless, when conventional olefins are used, the zwitterionic intermediate is not sufficiently stabilized to undergo a rotation, and therefore, *exo/cis* adducts are formed (Figure 3).¹⁴

2.1.2. Azlactones as 1,3-Dipoles: Enantiomeric Synthesis of Pyrrolinofullerenes. In light of the aforementioned results, we turned our attention onto oxazol-5-(4*H*)-ones (oxazolones or azlactones, 8). The versatile chemistry of this family of substrates due to their different reactive sites (acidic, electrophilic or Lewis acid active site) has already been reported in the literature.²⁶ Particularly, oxazolones are known to efficiently react as 1,3-dipoles (the so-called münchnones) with alkenes under Lewis acidic conditions. However, the only stereoselective examples reported to date for the preparation of Δ^1 -pyrrolines involve the silver-mediated reaction and the enantioselective gold-catalyzed synthesis developed by the research groups of Tepe²⁷ and Toste,²⁸ respectively. Following the same strategy used before with α -imino esters, we explored the combination of nonprecious metals with easily available chiral phosphines. Thus, (\pm)-BINAP along with AgOAc was found to efficiently afford, after dicyclohexyl carbodiimide (DCC) addition, a racemic mixture of 5-carbamoylpyrrolino-[3,4:1,2][60]fullerene derivatives 9 in moderate conversions.²³ Here those chiral metal complexes that previously gave us better

results failed in the cycloaddition of azlactones to fullerenes; however, both Ag(I) and Cu(I) proved to be suitable metals for this transformation.

Unlike α -imino esters, azlactones behave as monodentate ligands when coordinated to a metal and show a preference for less-coordinating nonbasic counterions as a result of a tighter interaction between the metal and the monodentate azlactone. Indeed, the use of SbF₆[−] as the counterion of the Ag(I)/3 complex along with Et₃N as the base afforded pyrrolinofullerene 9 with 86% ee. This behavior was also observed when the Cu(I)/2 pair was employed along with triflate instead of acetate as the counterion and Et₃N as base. As with the azomethine ylides formed from α -imino esters, this chiral copper complex directs the addition onto [60]fullerene toward the opposite enantiomer. Fortunately, the enantioselectivity was found to be higher and opposite to that for the previous Cu(I) system when other chiral phosphines such as (*S*)-Me-f-KetalPhos (10) (Figure 2) were used in combination with Cu^I(OTf)–benzene complex. Moreover, these results represented the first example of enantioselective cycloaddition of münchnones catalyzed by a copper salt.

In order to explore the scope of the reaction, different azlactones were prepared from amino acids such as glycine, alanine, and phenylalanine. In regard to the substitution on the aryl moiety, neither electron-releasing nor electron-withdrawing groups modified the behavior of these substrates. Moreover, derivatives endowed with solubilizing chains performed well in terms of conversions and ee values. In general, metal-based chiral catalysts gave rise to the desired pyrrolinofullerene derivatives 9 in moderate to good conversions with high enantiomeric excesses (Scheme 2). It is worth noting that the asymmetric induction sense is fully switched and controlled by a suitable choice of the metal complex, with little influence of the substitution pattern in the starting azlactone.

As in the case of the pyrrolidinofullerenes, the assignment of the absolute stereochemistry of the pyrrolinofullerenes was determined by CD analysis (Scheme 2).²⁴ Thus, the pair Cu^I(OTf)–benzene complex/2 leads to the (*R*)-9 products (positive CE at 425–430 nm) while the system based on Cu^I(OTf)–benzene complex/10 affords the opposite (*S*)-9 products (negative CE), thus nicely complementing each other. It is important to note, however, that in contrast to pyrrolidinofullerenes, the more stable pyrrolinofullerenes could be further functionalized on the carboxylic acid moiety by using standard esterification or amidation processes.²³

2.2. Metal-Catalyzed Asymmetric [3 + 2] Cycloadditions onto [70]Fullerene

In contrast to highly symmetric [60]fullerene, the main geometrical feature of higher fullerenes is their lower degree of symmetry, which in turn leads to a complex covalent chemistry.⁴ Furthermore, the high cost and low abundance of higher fullerenes have prevented an appropriate exploration of their properties as well as their potential applications to organic electronics and materials science. Therefore, the availability of an efficient synthetic methodology to limit a broad distribution of products constitutes a chemical challenge and an essential issue for further applications.

Encouraged by the excellent asymmetric induction achieved on C₆₀, we focused our attention on extending the scope of this methodology to higher fullerenes, particularly C₇₀ as the most abundant and available higher fullerene. However, asymmetric functionalization of [70]fullerene has to face four different levels of selectivity since different double bonds are present as a result of the loss of the spherical symmetry (Figure 4). Similar to

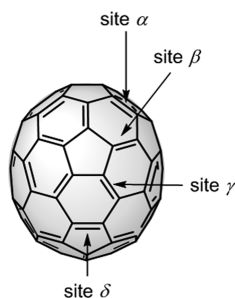


Figure 4. Possible addition sites on C₇₀.

[60]fullerene, additions to [70]fullerene are driven by the release of strain of the attacked double bond. Thus, they preferentially take place at the most strained and reactive polar zone, namely, at the α double bond [C(8)–C(25)] according to IUPAC nomenclature,²⁹ followed by the β [C(7)–C(22)] and, to a lesser extent, γ [C(1)–C(2)] sites.³⁰ Cycloadditions rarely occur at the less reactive δ site, located in the equatorial region. Although the cycloaddition of azomethine ylides onto C₆₀ is one of the most used and versatile methods for [60]fullerene functionalization, this reaction has been limited to the use of symmetrical 1,3-dipoles with C₇₀.³¹

To obtain a better understanding, we proposed to designate these isomers (α , β , γ , and δ) as *site isomers* and this selectivity as *site selectivity*, following the particular nomenclature applied to systems where a functional group is repeated³² and to distinguish them from regioisomers, which are formed as a consequence of the addition of nonsymmetrical dipoles to the C₇₀ double bond. Thus, depending on the orientation of the azomethine ylide

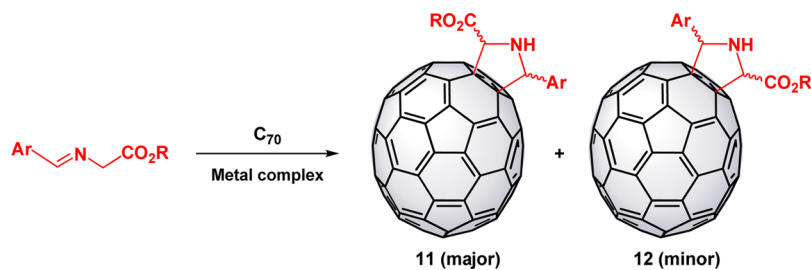
during the reaction, two possible regioisomers can be formed for each site isomer. In addition, each regioisomeric adduct can give rise to *cis* or *trans* diastereoisomers, each of them in its two possible enantiomeric forms. This scenario is significantly more complex than that for C₆₀, and its control represents a real challenge for synthetic chemists.

The chiral complexes described for C₆₀ were found to be effective in the cycloaddition of N-metalated nonsymmetric azomethine ylides onto C₇₀. Thus, the reaction occurred with very high site selectivity, affording almost exclusively the α -site isomer under mild conditions and maintaining the atom economy principle. In addition, good levels of regioselectivity were also addressed, as the reaction preferentially led to the regioisomer bearing the alkoxycarboxyl group on the polar region (**11**) regardless of the catalytic system used (Scheme 3).³³ Moreover, the synthesis of optically active [70]-pyrrolidinofullerenes was accomplished with enantioselectivities that could be completely switched by changing the chiral metal catalyst complex. In the presence of 10 mol % copper(II) acetate and 2, α -imino esters give rise to (*S,S*)-*cis*-[70]-pyrrolidinofullerenes with good regioselectivities (up to 80% for the derivative **11**) and excellent enantioselectivities of 92–99%, which are even higher than those obtained with the same catalyst onto C₆₀ (Scheme 4).²⁰ The stereocontrolled formation of the opposite (*R,R*) enantiomers was also achieved with Ag(I)/**3**, affording slightly lower enantioselectivities ranging from 80 to 90%.

A complete stereodivergence requires the efficient formation of each stereoisomer. Analogous to the cycloaddition reaction onto C₆₀, the use of 0.1 equiv of copper(II) triflate along with (*R*)- or (*S*)-DTBM-SegPhos (**4**) in the presence of Et₃N at room temperature yielded both enantiomers of *trans*-[70]-pyrrolidinofullerenes for a wide variety of α -imino esters.²¹ Thus, 1,3-dipoles undergo cycloaddition affording *trans* isomers **11** and **12** (having the ester group in the polar and equatorial zones, respectively) with good to excellent regio- and diastereoselectivities. For all of the tested α -imino esters, the enantiomeric excesses were excellent, and as expected, these values could be inverted using the opposite enantiomeric form of the catalyst. It is worth mentioning that the reaction is highly site-selective since all of the products are nearly pure α isomers (only traces of β isomers are detected).

Density functional theory (DFT) calculations strongly support the regio- and stereochemical outcome of the Ag(I)-catalyzed cycloaddition of azomethine ylides onto C₇₀ (Figure 5). In addition, the experimentally observed selectivity has been explained by a stepwise mechanism in which the first step of the cycloaddition clearly determines the subsequent site, regio-, and enantioselectivity. In regard to the enantioselectivity observed in the cycloaddition, the (*Si,Re*) attack is prevented by the steric

Scheme 3. Regioselectivity in 1,3-Dipolar Cycloaddition of Azomethine Ylides onto C₇₀



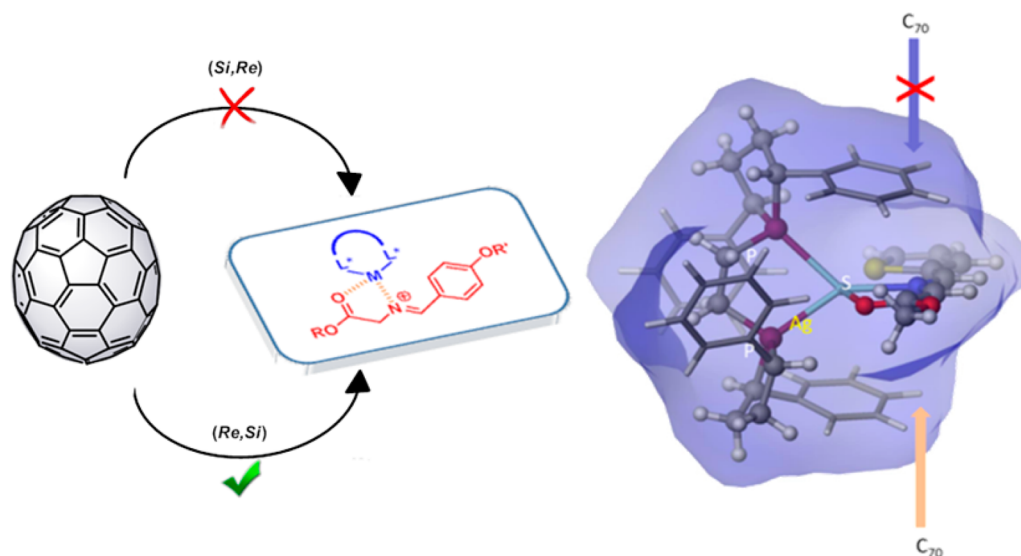
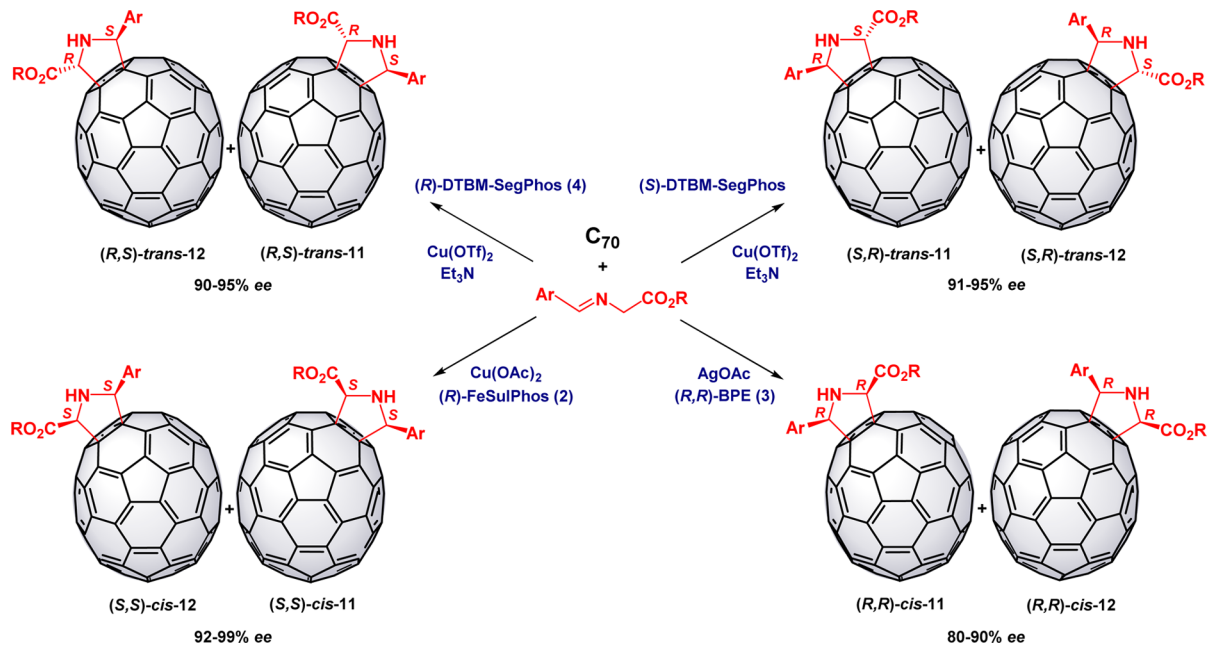
Scheme 4. Stereodivergent Asymmetric 1,3-Dipolar Cycloaddition of N-Metalated Azomethine Ylides onto C_{70} 

Figure 5. Blockage of the (Si,Re) face predicted by DFT calculations.

hindrance of the chiral ligand since it demands a larger digression of the catalyst from its optimal conformation. Thus, the (Re,Si) attack is favored (Figure 5), in good agreement with the experimental finding.

2.3. Metal-Catalyzed Asymmetric [3 + 2] Cycloadditions onto Endohedral Fullerenes

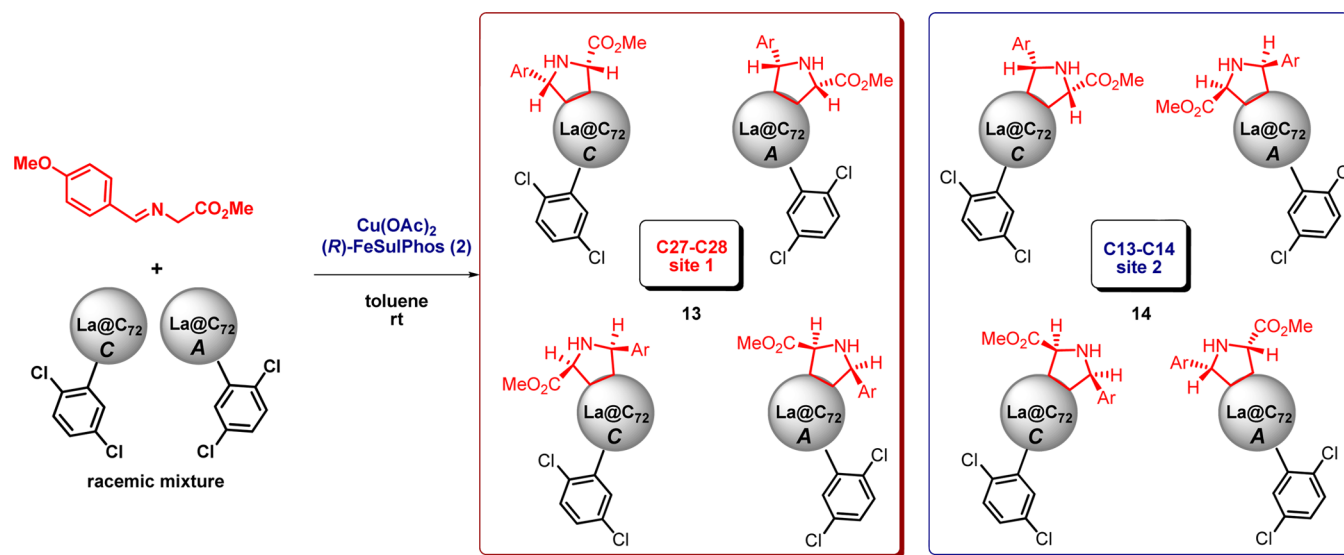
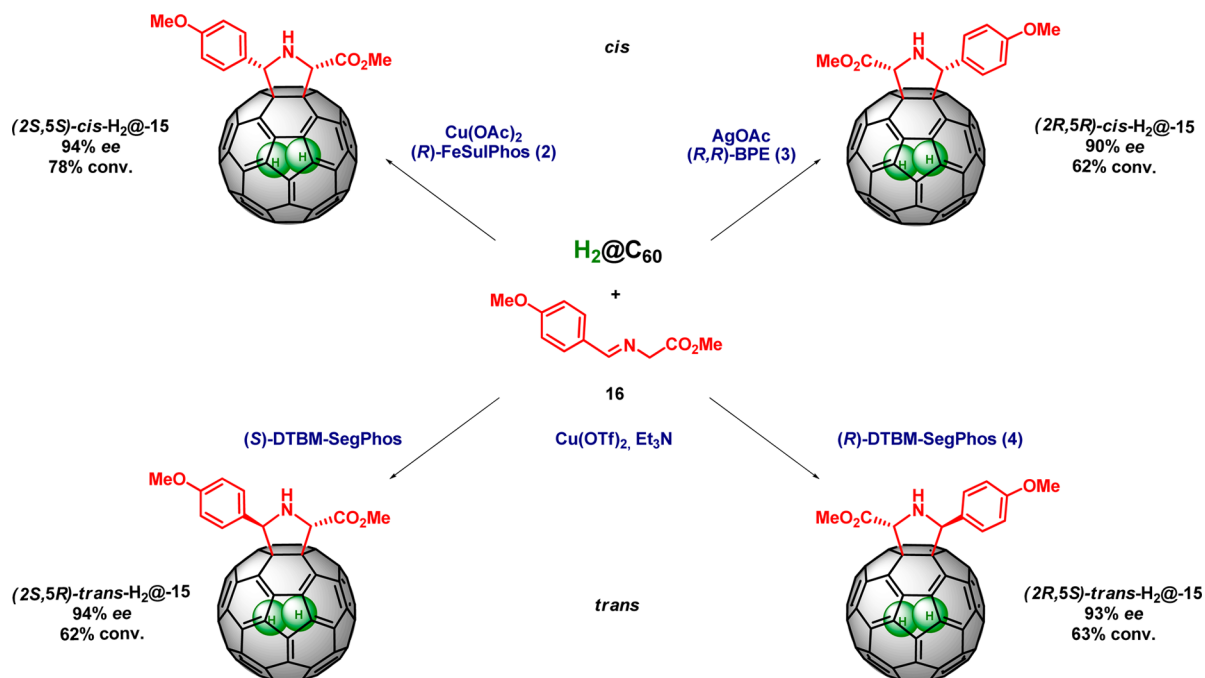
Soon after the discovery of [60]fullerene, the possibility of using these carbon cages to encapsulate different atoms, molecules, or clusters into the inner cavity and the determination of the properties of these new materials fostered the research in fullerene science. Since the isolation and characterization of the first endohedral monometallofullerene, $\text{La}@C_{82}$,³⁴ many other endohedral fullerenes of the type $\text{M}@C_{2n}$ ($\text{M} = \text{Sc}, \text{Y}, \text{La}, \text{Ce}, \text{Gd}$, etc.) have been obtained, with C_{2v} - C_{82} as the most abundant cage.³⁵

In 2011, chiral 1,3-dipolar cycloaddition of N-metalated azomethine ylides was extended to the enantio- and

regioselective synthesis of endofullerene derivatives. This process catalyzed by a copper chiral complex on a racemic mixture of non-IPR [i.e., not satisfying the isolated pentagon rule (IPR)]³⁶ $\text{La}@C_{72}(\text{C}_6\text{H}_3\text{Cl}_2)$ produced only eight enantiopure bisadducts (Scheme 5).³⁷ The products were isolated by multistep HPLC separation using nonchiral columns in the process.

The enantiomeric purity of the eight isomers was evaluated by HPLC using a REGIS Whelk-O 2 chiral column, which revealed high enantiomeric excesses (90–98%). These values are slightly higher than the ones reported for C_{60} and C_{70} because of the larger size of the cage in $\text{La}@C_{72}(\text{C}_6\text{H}_3\text{Cl}_2)$, which presents a better facial discrimination.

Recently, the scope of the enantioselective 1,3-dipolar cycloaddition of N-metalated azomethine ylides was explored in the symmetric endohedral fullerene $\text{H}_2@\text{C}_{60}$. The reaction afforded both enantiomers of each *cis* and *trans* diastereomer

Scheme 5. Synthesis of 13 and 14, Enantiopure Derivatives of $\text{La@C}_{72}(\text{C}_6\text{H}_3\text{Cl}_2)$ ($^{f,s}\text{C}$ and $^{f,s}\text{A}$)Scheme 6. Stereodivergent Asymmetric 1,3-Dipolar Cycloaddition of N-Metalated Azomethine Ylide 16 onto $\text{H}_2@\text{C}_{60}$ 

with high enantiomeric excesses.³⁸ As mentioned before, a $\text{Cu}(\text{II})/2$ complex directs the cycloaddition toward (2*S*,5*S*)-*cis* fulleropyrrolidine. The opposite (2*R*,5*R*) enantiomer was achieved using the $\text{Ag}(\text{I})/3$ catalytic system (Scheme 6). Moreover, the treatment with $\text{Cu}(\text{II})/(S)$ -DTBM-SegPhos in the presence of Et_3N as the base afforded (2*S*,5*R*)-*trans*-15, and as expected, the use of the opposite chiral ligand (R)-DTBM-SegPhos (4) yielded the opposite enantiomer, (2*R*,5*S*)-*trans*-15 (Scheme 6). Figure 6 shows the CD spectra of the four enantiomers, in which the typical CE for a [6,6] fullerene monoadduct at around 430 nm and the opposite signs for each enantiomeric pair are clearly observed.

The aforementioned experimental results found in the enantiomeric synthesis carried out on $\text{H}_2@\text{C}_{60}$ reveal that the chemical behavior of this endohedral fullerene is the same as that observed for pristine C_{60} , and therefore, in contrast to the

previously mentioned metallofullerene $\text{La@C}_{72}(\text{C}_6\text{H}_3\text{Cl}_2)$, the presence of the H_2 molecule in the inner cavity of the C_{60} cage does not modify the chemical reactivity of the carbon cage.

3. ASYMMETRIC ORGANOCATALYSIS IN [3 + 2] CYCLOADDITIONS ONTO [60]FULLERENE

The concept of *organocatalysis* has become a recurring topic in the literature over the last decades.³⁹ Its roots are known to be situated in the beginning of 20th century; however, it was not until the year 2000 that this field proved to be a very useful and competitive area in the asymmetric synthesis compared with its "competitors", metal catalysis and enzymatic catalysis. A variety of advantages are known to date, namely, the robustness of the catalysts due to their inertness toward moisture and oxygen, their ready availability linked to their low price, and their obvious lower toxicity. These features make this eco-friendly method-

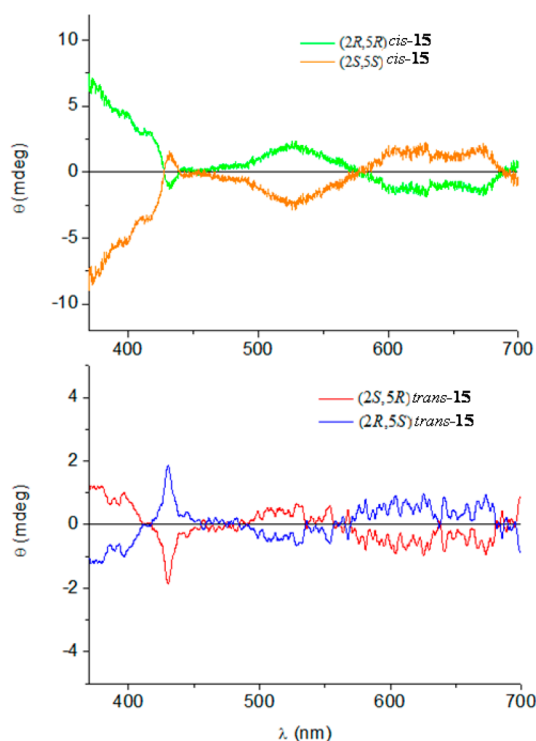


Figure 6. CD spectra of the four enantiomers of **15** (2×10^{-6} M in toluene): (top) *cis*-**15** enantiomers; (bottom) *trans*-**15** enantiomers.

ology highly attractive for industrial processes, where the scaling issue is no longer present.

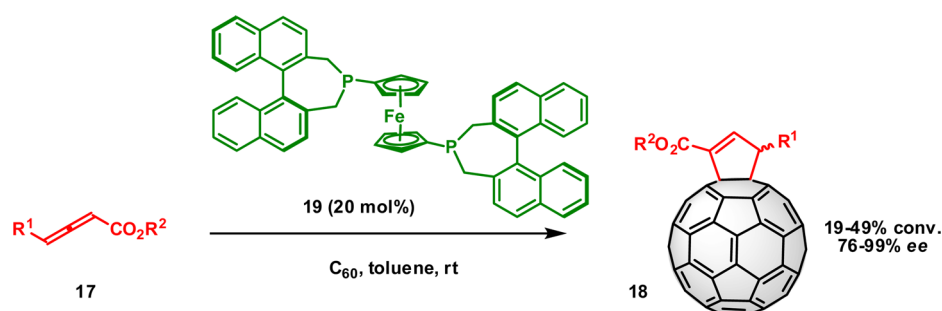
Taking into account the curved and highly reactive nature of fullerene double bonds, among all of the described organocatalytic methods we decided to investigate the use of nucleophilic phosphines as covalent organocatalysts.⁴⁰ These Lewis bases are highly versatile reagents as a consequence of the ability to vary their nucleophilic nature by modifying the steric and electronic features of their substituents as well as their commercial availability and efficiency in the synthesis of a wide range of cyclic and acyclic compounds. In particular, we focused on Lu's cycloaddition reaction,⁴¹ an interesting method for the preparation of unsaturated five-membered rings (Scheme 7). When these phosphines activate α -allenic esters (**17**) by nucleophilic attack on the central *sp*-hybridized carbon atom, these allenates are able to react with electron-deficient double bonds. The attractiveness of this reaction, reported in its racemic version on [60]fullerene by Kroto and co-workers,⁴² and the commercial availability of mono- and bidentate phosphines as organocatalysts encouraged us to investigate the enantioselective

version of the process. Several phosphines were evaluated according to their nucleophilicity and steric hindrance in the reaction of ethyl 2,3-pentadienoate with [60]fullerene. Those bearing aliphatic chains turned out to be better in terms of conversion efficiency than their aromatic analogues. In particular, those being part of a P-containing heterocycle yielded the corresponding cycloadducts **18** in good conversions and with promising enantiomeric excesses when they were part of a seven-membered ring instead of a five-membered ring. Indeed, the ferrocenyl-based phosphine (*S,S*)-*f*-binaphane (**19**) was selected as the chiral organocatalyst for its latter deeper evaluation (Scheme 7). Its higher nucleophilicity and its flexibility due to the low rotation barrier of the ferrocene backbone make this phosphine able to perform the reaction in a very good conversion of 49% (taking into account the typical conversions for fullerene functionalization) and an enantiomeric ratio of 94:6. The reaction setup was lately evaluated on several allenates endowed with alkyl or aromatic groups and yielded the corresponding cyclopenteno-fused derivatives in good conversions with excellent enantioselectivities.

The definition of the absolute configuration via X-ray analysis, together with the CD data, helped us to redefine the sector rule employed up to this date for the assignment of the configuration of fullerene derivatives. All cyclopenteno[4,5:1,2][60]fullerene derivatives **18** obtained under these reaction conditions featured a negative CE, which is in agreement with an *S* configuration on the C3 carbon atom of the cyclopentene ring (Figure 7).

Going one step further in the use of organocatalytic methods for the preparation of chiral fullerene derivatives, we turned our attention to a different type of 1,3-dipole, azlactones **8**, which afforded excellent results in the metallic version of the reaction.²³ The presence of a highly acidic proton in these heterocyclic structures led us to think about a base-catalyzed process in which a chiral catalyst could trigger the cycloaddition of the azlactone onto the fullerene. Starting with Et_3N and azlactone **8a** (Scheme 8), we realized that the reaction actually took place, albeit in low conversion. Then we focused on the use of non-covalent catalysis, particularly with cinchona alkaloid derivatives, which were able to yield the corresponding pyrrolino[60]fullerenes but in a racemic way. Several thioureas,⁴³ squaramides,⁴⁴ and bifunctional catalysts⁴⁵ were also evaluated; however, the achieved enantiomeric excesses were poor because of the impossibility of LUMO activation via hydrogen bonding in fullerenes. Phase-transfer catalysts (PTCs) working in mixtures of toluene and basic water yielded the cycloadducts, but no enantioselectivity was observed. We finally evaluated chiral N-heterocyclic carbenes, which have been widely employed as ligands in metal catalysis and more recently in organocatalysis.⁴⁶ Their ability to behave as Brønsted base catalysts allowed the

Scheme 7. (*S,S*)-*f*-Binaphane-Catalyzed [3 + 2] Cycloaddition of Allenates onto C_{60}



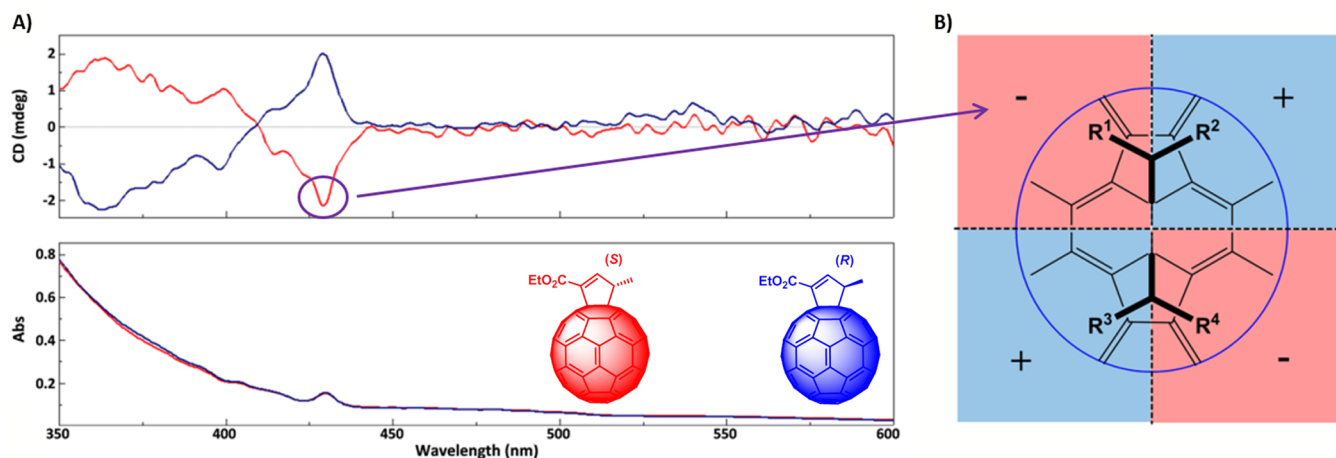
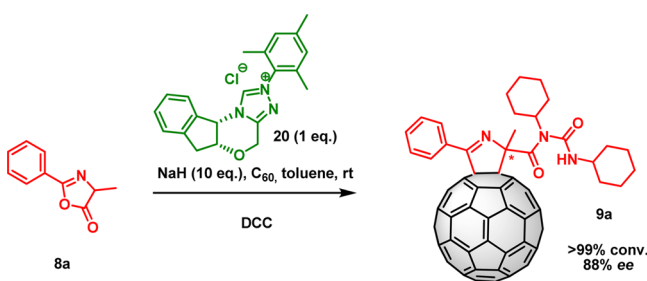


Figure 7. (A) CD and UV-vis spectra for both enantiomers of (3*S*)-1-ethoxycarbonyl-3-methyl-1-cyclopenteno[4,5,1,2][60]fullerene (4×10^{-4} M in dichloromethane). (B) Corrected sector rule.

Scheme 8. Organocatalytic Enantioselective [3 + 2] Cycloaddition of Azlactones onto C_{60}



formation of the adducts not only in good conversion but also with very interesting enantioselectivities. The reaction between azlactone **8a**, [60]fullerene, NaH, and Bode catalyst (**20**) in anhydrous toluene gave rise to an enantioselective cycloaddition (88% ee) in excellent conversion (>99%), and it was even possible to obtain the opposite enantiomer by using the commercially available opposite enantiomer of the NHC (Scheme 8).

As a whole, the methodology is tolerant of the introduction of substituents on the aromatic ring, with variable results depending on the employed substrate (23–99% conversion). In this regard, the best enantiomeric excesses were obtained from the use of less-hindered azlactones (28–88% ee).

4. CONCLUSIONS

The great development undergone by the variety of known low-dimensional carbon nanoforms started with the discovery of zero-dimensional (0D) fullerenes almost three decades ago. Actually, most of the reactions carried out on the pristine C_{60} molecule have later been tested on 1D carbon nanotubes as well as 2D graphene. Thus, fullerenes have been used as a benchmark for the study of further carbon nanostructures. However, from our point of view, the chemistry of fullerenes has not been properly addressed, since frequently the ultimate goal of chemical modification of fullerenes has been directed to their solubilization/functionalization under different conditions in the search for practical applications. In particular, the ease of access to enantiomerically pure fullerenes has almost been neglected by the chemical community. In this Account, we have described the first asymmetric catalysis carried out on fullerenes involving one of the most versatile and used chemical functionalizations of

fullerenes, namely, the 1,3-dipolar cycloaddition of azomethine ylides to C_{60} . This reaction has been widely studied, and Cu and Ag together with the appropriate chiral ligand have afforded enantiomerically pure fullerenes with excellent ee values surpassing 90%. The reaction has also been extended to larger fullerenes such as C_{70} , where site isomers, regioisomers, diastereomers, and enantiomers are formed. Furthermore, this reaction has also been tested on endofullerenes, where either the reactivity is controlled by the inner metal, as with the metallofullerene $La@C_{72}(C_6H_3Cl_2)$, or the encapsulated molecule does not influence the reactivity of the outer sphere, as with the endofullerene $H_2@C_{60}$. In all cases, the chiral fullerenes have been produced at will with excellent enantioselectivities, depending upon the metal used as the catalyst and the chiral ligands and experimental conditions used in the reaction.

Organocatalysis has also been used for the first time in the preparation of chiral fullerenes with total control of the stereochemical outcome of the reaction. In particular, the use of readily available chiral phosphines has allowed the synthesis of carbocyclic-fused fullerenes to be carried out with excellent ee values. Furthermore, we have also proven the complementarity of metal catalysis and organocatalysis in the 1,3-dipolar cycloaddition of münchnones on [60]fullerene.

The results of these catalytic processes have been underpinned by DFT calculations as well as X-ray diffraction analysis and the use of the sector rule. Interestingly, the plausible mechanisms reveal that the noncoordinating fullerene molecule attacks the respective activated 1,3-dipole through the less-hindered face of the catalytic complex, thus accounting for the stereochemical outcome in the above-mentioned reactions.

The aforementioned results pave the way to the large-scale preparation of enantiomerically pure fullerenes and therefore to their use not only in biomedical applications, where chirality is an important issue, but also in materials science, where fullerenes find their main applications.

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Notes

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Nazario Martín has research interests spanning a range of targets with emphasis on the molecular and supramolecular chemistry of carbon nanostructures. He is a fellow of the Royal Society of Chemistry and a member of the Editorial Advisory Board of *Accounts of Chemical Research*. He is a recipient of an Advanced Grant from the European Research Council (Chirallcarbon).

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