ENANTIOSELECTIVE SYNTHESIS OF FULLERENES

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Fullerene

- Among the most studied molecules
- Benchmark for other carbon nanoforms
- Potential applications in different fields
Fullerenes for Mimicking Photosynthesis

Energy Environ. Sci., 2011, 4, 604

Chem. Sci., 2011, 2, 1677

Chem. Rev. 1998, 98, 2527

Angew. Chem. Int. Ed. 2006, 45, 4637
Fullerenes for Organic Photovoltaics

Energy Conversion Efficiency of ~3 %

With J. Bisquert et al., J. Phys. Chem. Lett. 2010, 1, 2566
STM images (taken at 170 K) in UHV with the surface held at 300 K.

Preferential nucleation at the elbow of the “herringbone” reconstruction.

This supramolecular ordering is the result of two combined effects:
1) The interaction of the molecular tail with the surface
2) The $\pi-\pi$-interactions among the C$_{60}$ cages
Unambiguous One-Molecule Conductance Measurements under Ambient Conditions

Fullerenes for Biomedical Applications

Hexaadducts of $C_{60}$: a highly versatile multivalent scaffold

Glycofullerenes Inhibit Viral Infection

Representative examples of covalently connected exTTFs
Strategies for Concave-Convex Supramolecular Ensembles

J. Am. Chem. Soc. 2006, 128, 7172

J. Am. Chem. Soc. 2010, 132, 1772
J. Am. Chem. Soc. 2011, 133, 3184

J. Am. Chem. Soc. 2010, 132, 5351

J. Am. Chem. Soc., 2010, 132, 17387


Chem. Sci., 2011, 2, 1384

Angew. Chem. Int. Ed. 2008, 47, 1094
Angew. Chem. Int. Ed. 2010, 49, 9876 –9880

Submitted for publication
Chirality in Fullerenes:

- Is an important but undeveloped issue of interest in fields such as materials science and medicinal chemistry (racemic mixtures are typically used).
- Enantiopure fullerenes have been made from chiral starting materials or by separating racemic mixtures.
- The lack of a general enantioselective synthetic methodology has limited the use of enantiopure fullerene derivatives.
- Well-defined chiral carbon atoms linked to the fullerene sphere are able to perturb the inherent symmetry of the fullerene π-system.
- It would be highly desirable to have an enantioselective catalytic synthesis of chiral fullerene derivatives.

*Nature Chem., 2009, 1, 578-582*
Most of the catalytic asymmetric versions are based on α-iminoesters as dipoles. The great effectiveness of this ylide precursor is due:

a) to the acidity of the enolizable Cα position
b) to the formation of a rigid five membered N,O-bidentate metalated azomethine ylide

Both aspects facilitate the asymmetric induction from the chiral ligand.

Generation of the chiral metal complex

Chiral Ligand
(Differentiate the two faces of the dipole)

Metal
(Ag\textsuperscript{I}, Zn\textsuperscript{II}, Cu\textsuperscript{I/II}, Ni\textsuperscript{II}, Ca\textsuperscript{II})

1,3-Dipole
Chiral Catalysis in Fullerene chemistry

Dipolarophile

Chiral metal complex

Dipolarophiles
(The heteroatom coordinates to the metal)

Non-coordinating Dipolarophile
Fully Stereodivergent Synthesis of Fullerenes

$\text{(2S,5R)-trans}$

$\text{(2R,5S)-trans}$

$\text{up to 99\% of er}$

$\text{(S)-DTBM SegPhos}$

$\text{Cu(O Tf$_2$)}$

$\text{Et$_3$N}$

$\text{Ar = p-MeO-Ph; R = Me}$

$\text{Ar = 2-thiophenyl; R = Me}$

$\text{(R)-DTBM SegPhos}$

$\text{(S)-DTBM SegPhos}$

$\text{Cu(AcO)$_2$}$

$\text{AgAcO}$

$\text{(2S,5S)-cis}$

$\text{(2R,5R)-cis}$

$\text{up to 96\% of er}$

$\text{J. Am. Chem. Soc., 2012, 134, 12936}$

$\text{Nature Chem., 2009, 1, 578-582}$
Stereodifferentiation of the two faces of the azomethine ylide

Unpublished results
Stereodivergent Synthesis of Pyrrolidines

**trans** (up to 97 % ee) vs. **cis** (up to 89 % ee)

**cis/trans diastereoselectivity in fullerene**

**endo/exo diastereoselectivity in conventional olefins**

Hierarchical Selectivity in Fullerenes: Site-, Regio-, Diastereo-, and Enantiocontrol of the 1,3-Dipolar Cycloaddition to C$_{70}$

Selectivity is still a major challenge in fullerene research. The careful choice of the experimental conditions affords chiral [70]fullerene derivatives with unusually high site- and regioselectivity.

Selectivity Levels in the Asymmetric [3+2] Cycloaddition to C\textsubscript{70}

\[
\text{Ar} = \text{N} - \text{C} = \text{O} + \text{OR} \rightarrow \alpha: \text{C}(8) - \text{C}(25) \quad \beta: \text{C}(7) - \text{C}(22) \quad \gamma: \text{C}(1) - \text{C}(2)
\]

\text{Site-selectivity}

\[94-99\%\]

\text{Regio-selectivity}

\text{Diastereo-selectivity}

\[\text{Angew. Chem. Int. Ed. 2011, 50, 6060 – 6064}\]
Asymmetric [3+2] Cycloadditions on C\textsubscript{70}: REGIOSELECTIVITY

Two approximations depending upon the thienyl group is oriented in eq or ax on the C\textsubscript{70}

Theoretical study carried out using dppe/Ag(I)

Equatorial aproximation

Equatorial aproximation is favoured

TSeq1
(0.0)

TSax1
(+2.1)
Site- and Regioselectivity. Fukui indexes at the α-γ sites
(The different values for the atoms predict an asynchronous reaction and a regioselectivity)

Fukui nucleophilic function on the carbon atoms of the dipole show an enolate-like nucleophilicity of the azomethine

Figure 2. a) Electrostatic potential projected on the electron density of C_{70} (B3LYP/LANL2DZ level of theory). Given numbers are the electrophilic Fukui indexes at the α-γ sites in arbitrary units. The higher the number, the higher the local electrophilicity. b) Fully optimized silver azomethine ylide (B3LYP/LANL2DZ:PM6 level of theory) derived from imine 1b and diphosphine 7. B3LYP and PM6 layers are represented in ball and stick and tube modes, respectively. The blockage of the (re, re) face is readily appreciated. Numbers correspond to the nucleophilic Fukui indices in arbitrary units.

Figure. Chemical shifts of the regioisomers formed for the cis products a-f. The assignment has been made taking into account the strong deshielding effect characteristic for the polar region of C$_{70}$.
**Asymmetric [3+2] Cycloadditions on C\textsubscript{70}: DIASTEREOSELECTIVITY**

*Cis* azomethine ylides cycloadd preferentially to *trans*. We suppose that *cis-trans* equilibrium in the initial azomethine ylide is a low energy process. Thus, according to Curtin-Hammet, we only need to compare the high of both processes.
Asymmetric [3+2] Cycloadditions on C\textsubscript{70}: ENANTIOSELECTIVITY

The attack on the \textit{si, re} face is not favoured. Therefore, \textbf{Peq1} is the final product.
Diastereo and Enantioselectivity (similar to C$_{60}$)

\[ \text{de} = 94-99\% \quad \text{ee} = 86-99\% \]

1a Ar = p-MeO-Ph; R = Me

b Ar = 2-thiophenyl; R = Me

\[ \text{de} = 94-99\% \quad \text{ee} = 86-99\% \]
Endohedral Fullerenes

Are cages of Fullerenes able to encapsulate atoms, clusters or small molecules?

Rodríguez-Forteza, Balch, Poblet, *Chem. Soc. Rev.* 2011, 40, 3551
Endohedral fullerenes

- Is the reactivity of the fullerene affected by the entrapped species?

- What kind of atom(s)/molecule(s) are placed inside the fullerene cage?

- Is the fullerene actually a cage or there is an interaction between the atom(s)/molecule(s) and the carbon sphere?

- The atom(s)/molecule(s) inside the sphere are static, in motion?
Endohedral Fullerenes

Is its chemical reactivity affected?
What kind of chemical compound? It is a hydrocarbon?

H₂@C₆₀
Enantiomeric synthesis of fulleropyrrolidine-$\text{H}_2\text{@C}_{60}$

$\text{H}_2\text{@C}_{60}$ shows the same reactivity than hollow $\text{C}_{60}$

In collaboration with Murata’s group
Enantiomeric synthesis of fulleropyrrololidine-H$_2$@C$_{60}$

$^1$H-RMN (500MHz, 298K, CDCl$_3$)
Circular Dichroism spectra

solvent: CS$_2$/CDCl$_3$ (1:3)

430nm

face (Re,Si)

face (Si,Re)

MeO

(R,R)-cis 34

(COOME)

MeO

(S,S)-cis 35

(COOME)
The H$_2$ molecule is not active in the IR since the dipolar moment is not modified during the vibration. On the contrary it is active in Raman spectroscopy. The asymmetry of the fullerene sphere should be responsible for this experimental finding under routine conditions.
The translation–rotation coupling is measured as a splitting of absorption lines in the IR spectrum.

The strength vibration of the $\text{H}_2$ molecule is active in IR !!!

Unpublished results In collaboration with Navarrete group

IR Spectrum of fulleropyrrolidine-$\text{H}_2@\text{C}_{60}$
Organocatalysis in Fullerenes Chemistry:

Phosphine-catalyzed Cycloaddition of Allenoates onto [60]fullerene

Non-activated Dipolarophile

HOMO Activation or nucleophilic activation

We have described the first enantiomeric synthesis of fullerenes by using asymmetric catalysis. The use of a suitable chiral catalyst controls the addition of fullerenes to both faces of a 1,3-dipole, thus determining the stereochemical outcome. Organocatalysis has been successfully used in fullerene chemistry affording cyclopentenofullerenes with high ee values. This methodology is currently being extended to other systems, namely endohedral fullerenes, other dipoles (münchnones).
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# Metal catalysis vs Organocatalysis

<table>
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<td>Work up simplicity</td>
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<tr>
<td>Field of application</td>
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</tbody>
</table>

![Chemical reaction image]
Asymmetric Organocatalysis

![Graph showing the number of publications per year in different types of catalysis.](image-url)
Catalytic enantioselective [3+2] cycloaddition

Año

nº de publicaciones

Organocatálisis
Catálisis metálica

1,3-DIPOlar CYCLOADICIÓN WITH AZOMETHINE YLIDES

Cicloadición (3+2) catalítica enantioselectiva
HOMO Activation vs nucleophilic activation

\textit{ad metallis}

\textbf{Chiral N-metallated AMY}
(Transition metal and base)

\textbf{Non-coordinating Dipolarophile}

\textit{ad organicam, catalysem}

\textbf{Chiral metal free nucleophile}
(Chiral phosphine)

Phosphine-catalyzed Cycloaddition of Allenoates onto [60]fullerene

Allenoate Activation by Phosphines

Aromatic phosphines do not activate efficiently!!!
Allenoate Activation by Phosphines

Aliphatic phosphines do activate but are not always selective

P-containing heterocycles
Phosphine-catalyzed Cycloaddition of Allenoates onto [60]fullerene

\[
\text{CO}_2\text{Et}
\]

Chiral ligand
toluene, rt

57%
66 ee (R)

40%
60 ee (S)

48%
82 ee (S)
Phosphine-catalyzed Cycloaddition of Allenoates onto [60]fullerene

Extension of methodology

\[
\text{Conversion: 49\%  \hspace{1cm} ee: 88\%}
\]

\[
\text{Conversion: 36\%  \hspace{1cm} ee: 92\%}
\]

\[
\text{Conversion: 19\%  \hspace{1cm} ee: >99\%}
\]

\[
\text{Conversion: 28\%  \hspace{1cm} ee: 80\%}
\]

\[
\text{Conversion: 57\%  \hspace{1cm} ee: 74\%}
\]
[3+2] Cycloaddition with allenoates

Assignment of the new created stereocenter
[3+2] Cycloaddition with allenoates

Assignment of the new created stereocenter
[3+2] Cycloaddition with allenoates

Assignment of the new created stereocenter
[3+2] Cycloadition with allenoates

Assignment of the new created stereocenter

![Graph showing CD and UV spectra with molecular structure](image)
Sector Rule for the assignment of the configuration
Chemical Structure of Cyclopenteno[4,5:1,2][60]fullerene
Cycloadition with allenoates
Stereoconvergent cycloaddition

\[ \text{Stereoconvergent cycloaddition} \]

\[ \text{R}^1\text{C}_2\text{R}^2 + \]
\[ \text{tolueno seco, Ar, rt} \]

(10 mol%)
Stereoconvergent cycloaddition

\[
\text{R}^1\text{C}≡\text{C}\text{CO}_2\text{R}^2 + \text{R}^1\text{C}≡\text{C}\text{CO}_2\text{R}^2 + \text{Chiral Base} \to \text{H-\text{COOEt}} + \text{N}_2
\]
De Fullerenorum Catalyse

Usque ad metalla
Usque ad organocatalysem

ad metallin, ad organicam (nucleoflicitam) activationem
Other Asymmetric Functionalizations in Fullerenes

Azalactone

\[
\begin{align*}
\text{M-L} & \quad \text{C}_{60} \\
\text{base} & \quad \text{solvent: Toluene or CIPh or o-DCB} \\
& \quad 30-40\% \\
\end{align*}
\]

Münchnone

\[
\text{Ar-} + \text{NH}_2 \rightarrow \text{Ar-} + \text{H} \\
\text{EDC.HCl, CH}_2\text{C}_2 \text{anh} \rightarrow \text{Ar-} + \text{H} \\
\text{NaOH} 16h \rightarrow 75-86\% \\
0^\circ\text{C}, 40\text{min} \rightarrow 37-50\% 
\]
• Ligandless conditions
• Stereoselective
• Only exo-adduct

Chiral ligands
Preformed chiral catalyst
Enantioselective
Only exo-adduct

Enantioselective synthesis of pyrrolinefullerenes

Metal-catalysis

azlactone

[M]-L*

C₆₀

base

Solvent

Pyrrolino[3,4:1,2][60]fullerenes

Alternative to the pyrrolidinefullerenes
- More stable at high temperatures
- Potential further functionalization
Enantioselective synthesis of \textit{pyrrolinefullerenes}

- Development of new chiral catalytic systems
- Based on non-precious metals (Cu)
- Apply novel systems outside of the fullerene chemistry
- $\Delta^1$-Pyrrolines allow accessing to biologically active molecules

Use of $C_{60}$ as benchmark for...
Enantioselective synthesis of **pyrrolinefullerenes**

![Chemical structure and reaction scheme](image-url)

- **Azlactone**
- **[M]·L*\(^*\)**
- **C\(_{60}\)**
- **Base**
- **Solvent** (toluene, PhCl, \(\alpha\)-DCB)
- **Yield**: 30-40%
Enantioselective synthesis of pyrrolinefullerenes

Mechanistic pathway

soluble in organic solvent
Enantioselective synthesis of pyrrolinefullerenes

Mechanistic pathway
Enantioselective synthesis of **pyrrolinefullerenes**

Mechanistic pathway

Enzyme (M) catalyzes the reaction between arylhydrazones (Ar=N=N) and a base, forming pyrrolinefullerenes.
Enantioselective synthesis of pyrrolinefullerenes

Mechanistic pathway

Find the best [M]-L* pair in order to discriminate one of the dipole faces
1,3 dipolar cycloaddition of Munchrones: FulleroPyrrolines

\[
\begin{align*}
\text{Cu}^I(\text{OTf})_{\text{complex}} / \text{NEt}_3 & \quad \text{YIELD} \quad \text{ee} \\
\text{AgSbF}_6 / \text{NEt}_3 & \quad 33\% \quad 86 \quad 93 \quad 7 \\
\text{Cu}^I(\text{OTf})_{\text{complex}} / \text{NEt}_3 & \quad 61\% \quad 88 \quad 94 \quad 6
\end{align*}
\]
Enantioselective synthesis of pyrrolinefullerenes

Further functionalization

Isolated by column chromatography
Enantioselective synthesis of pyrrolinefullerenes

Organocatalysis

Organocatalyst (X mol%) + Base (Y eq.) → toluene, T

PTC quinine

PTC quinidine

PTC cinchonine

PTC cinchonidine

Phase Organique

Phase Aquéreuse
Complementary methodology: with or without metal

\[
\text{Cu}^1(\text{OTf})^{\text{complex}} (20 \text{ mol%})
\]
\[
(S)-\text{Me-}\text{f-KetalPhos} (20 \text{ mol%})
\]
\[
\text{PhCl, 1h Et}_3\text{N DCC}
\]

C_{60} \quad \text{C}_{6H_{13}O-}\quad 25\% \text{ yield} \quad 90\% \text{ ee} \\
\text{N} \quad \text{Me} \quad \text{CODCC} \\
\quad \quad C_{60} \quad 14\% \text{ yield} \quad 70\% \text{ ee}

C_{6H_{13}O-}\quad 10\% \text{ yield} \quad 62\% \text{ ee} \\
\text{N} \quad \text{H} \quad \text{CODCC} \\
\quad \quad C_{60} \quad 12\% \text{ yield} \quad 96\% \text{ ee}

C_{12H_{25}O} \quad 14\% \text{ yield} \quad 68\% \text{ ee} \\
\text{N} \quad \text{Me} \quad \text{CODCC} \\
\quad \quad C_{60} \quad 40\% \text{ yield} \quad 84\% \text{ ee}

C_{12H_{25}O} \quad 50\% \text{ yield} \quad 96\% \text{ ee} \\
\text{N} \quad \text{Me} \quad \text{CODCC} \\
\quad \quad C_{60} \quad 43\% \text{ yield} \quad 84\% \text{ ee}
Enantioselective synthesis of pyrrolinefullerenes

Sector rule: stereocenter assignment by CD

Stereodivergent Synthesis of Pyrrolidines

cis/ trans diastereoselectivity in fullerene

endo/exo diastereoselectivity in conventional olefins

*J. Am. Chem. Soc., 2012, 134, 12936*
Stereodivergent Synthesis of Pyrrolidines

cis

(2R,5R)-cis

(2S,5S)-cis

trans

(2R,5S)-trans

(2S,5R)-trans

endo

(2R)-BPE

(2S)-BPE

R-DTBM

S-DTBM

AgAcO

Cu(O Tf)2

Et3N

C60 or C70


exO

Plausible mechanism of the AMY cycloaddition onto different double bonds

Intermediate stabilized by a benzylic cation and a fullerene anion, where the stereochemistry $(R)$ of the C-2 is yet defined.

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Calculations
Prof. F. P. Cossío
Dr. Abel de Cózar

Prof. T. Akasaka and his group
N-Metalated Azomethine Ylides

\[
\begin{align*}
\text{Ar} & \equiv \text{N} - \text{C(\text{O})} - \text{OR} + \text{Ph} &=& \text{H} \quad \text{end} \quad \text{CO}_2\text{R} \\
\text{M}^{n+} & \text{L} & \text{Base(B)} & \text{exo}
\end{align*}
\]
Asymmetric [3+2] Cycloadditions on C\textsubscript{60}: Mechanism

\[
\text{MeOOC} \begin{array}{c} \text{N} \\ \text{Ar} \end{array} \xrightarrow{\text{L}^* + \text{NEt}_3 + \text{MX}} \text{INT1} \xrightarrow{\text{C}_{60}} \quad \text{INT2} \xrightarrow{\text{TS2cis}} \text{Pcis}
\]

\[
\text{TScon} \quad \text{L}^* + \text{NEt}_3 + \text{MX} \quad \text{X} \text{HNET}_3 \quad \text{L}^* + \text{NEt}_3 + \text{MX}
\]

L\textsuperscript{*} = \text{Me-BPE}
MX = \text{AgOAc}
Ar = p-\text{NC-Ph}
Stereodifferentiation of the two faces of the azomethine ylide

Unpublished results
Geometries for the TSs in the first step for the [3+2] cycloaddition. In both cases is a non-concerted reaction.

TS1(major) (0.0) (+2.8 kcal/mol) TS1(minor)
INT2 rapidly form the final cycloadduct INT3 through TS2. Therefore, Ptrans cannot be the result of rotation of INT2. It results from the ylide isomerization previous to the cycloaddition process. The stereochemistry of all new centres is defined in the first step!!!
Asymmetric [3+2] Cycloadditions on C\textsubscript{70}: REGIOSELECTIVITY

Two approximations depending upon the thienyl group is oriented in eq or ax on the C\textsubscript{70}.

Equatorial aproximation is favoured

Theoretical study carried out using dppe/ Ag(I)

TSeq1
(0.0)

TSax1
(+2.1)

ONIOM(B3LYP/LANL2DZ:PM6)
Ball&stick:tube
Regioselectivity. Fukui indexes at the $\alpha$-$\gamma$ sites
(The different values for the atoms predict an asynchronous reaction and a regioselectivity)

Fukui nucleophilic function on the carbon atoms of the dipole show an enolate-like nucleophilicity of the azomethine

*Figure 2.* a) Electrostatic potential projected on the electron density of $C_{70}$ (B3LYP/LANL2DZ level of theory). Given numbers are the electrophilic Fukui indexes at the $\alpha$–$\gamma$ sites in arbitrary units. The higher the number, the higher the local electrophilicity. b) Fully optimized silver azomethine ylide (B3LYP/LANL2DZ:PM6 level of theory) derived from imine 1b and diphosphine 7. B3LYP and PM6 layers are represented in ball and stick and tube modes, respectively. The blockage of the (re,re) face is readily appreciated. Numbers correspond to the nucleophilic Fukui indices in arbitrary units.

Asymmetric [3+2] Cycloadditions on $C_{70}$: DIASTEREOSELECTIVITY

Cis azomethine ylides cycloadd preferentially to trans. We suppose that cis-trans equilibrium in the initial azomethine ylide is a low energy process. Thus, according to Curtin-Hammet, we only need to compare the high of both processes.

TSeq1 (0.0) TSeq1-trans (+6.7)
Asymmetric [3+2] Cycloadditions on $C_{70}$: ENANTIOSELECTIVITY

The attack on the $si,re$ face is not favoured. Therefore, Peq1 is the final product.
Asymmetric [3+2] Cycloadditions on C$_{70}$: CATALYTIC CYCLE

L* + NEt$_3$ + MX
X HNEt$_3$ + C$_{70}$

L* = Me-BPE
MX = AgOAc
Ar = 2-thienyl

1.9 kcal/mol

13.19 kcal/mol

2.1 kcal/mol

ONIOM(B3LYP/LANL2DZ:PM6)
ball&stick: tube
Figure. Chemical shifts of the regioisomers formed for the cis products a-f. The assignment has been made taking into account the strong deshielding effect characteristic for the polar region of C$_{70}$.

Catalytic 1,3 dipolar cycloaddition onto C₆₀

\[
\begin{align*}
\text{Ar} &= \text{p-MeO-Ph; } R = \text{Me} \\
\text{Cu(ACN)}₄\text{ClO}_4 / (\text{Et}_3\text{N}) &\text{ Yield } d.e \text{ (2S,5S)-2a} \\
\text{Toluene } -15^\circ\text{C} &\text{ (2R,5R)-2a}
\end{align*}
\]

Carretero et al., JACS, 2005, 127, 16394

Nature Chem., 2009, 1, 578-582
Thermal 1,3-dipolar cycloaddition onto $\text{C}_{60}$

$$\text{Ar} = \text{p-MeO-Ph}; \quad R = \text{Me}$$

Low yield, mixture of products.
Catalytic 1,3 dipolar cycloaddition onto $C_{60}$

1a $Ar = p$-MeO-Ph; $R = Me$

Copper or Silver acetates

cis diastereoselectivity
Catalytic 1,3 dipolar cycloaddition onto C\textsubscript{60}

\[
\begin{align*}
\text{Ar} & \equiv \text{N} - \text{C} - \text{OR} \\
1a \text{ Ar} & = \text{p-MeO-Ph}; \text{ R} = \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Mn}^+ / \text{Ligand} & \quad \text{Base (10\%)} \\
\text{Toluene} & \quad -15^\circ \text{C}
\end{align*}
\]

\[
\begin{align*}
(2S,5S)-2a \\
(2R,5R)-2a
\end{align*}
\]

\textit{Nature Chem., 2009, 1, 578-582}
Catalytic 1,3 dipolar cycloaddition onto C$_{60}$

$$\text{Ar} = p\text{-MeO-Ph}; \ R = \text{Me}$$

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield</th>
<th>d.e</th>
<th>$d(2S,5S)$-2a</th>
<th>$d(2R,5R)$-2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(ACN)$_4$ClO$_4$ / (Et$_3$N)</td>
<td>45%</td>
<td>94%</td>
<td>82%</td>
<td>18%</td>
</tr>
<tr>
<td>Cu(AcO)$_2$</td>
<td>88%</td>
<td>&gt;99%</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>Fesulphos Cu(ACN)$_4$PF$_6$ / (Bu$_4$NACO)</td>
<td>60%</td>
<td>&gt;99%</td>
<td>96%</td>
<td>4%</td>
</tr>
<tr>
<td>AgAcO</td>
<td>60%</td>
<td>&gt;99%</td>
<td>5%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Nature Chem., 2009, 1, 578-582
Switchable enantioselective cycloaddition onto C$_{60}$

\[
\text{de} \quad \text{ee} \\
>99 \quad 81 \ (2R,5R)-2b \\
>99 \quad 85 \ (2R,5R)-2c \\
>99 \quad 86 \ (2R,5R)-2d \\
80 \quad 70 \ (2R,5R)-2e \\
\]

1. Ar = 2-thiophenyl; R1 = COOMe; R2 = H
2. Ar = pF-Ph; R1 = COOMe; R2 = H
3. Ar = pCN-Ph; R1 = COOMe; R2 = H
4. Ar = pMeO-Ph; R1 = COOMe; R2 = Me
5. Ar = Ph; R1 = P(O)(OEt)$_2$; R2 = H
6. Ar = 2-thiophenyl; R1 = COOMe; R2 = H
7. Ar = pF-Ph; R1 = COOMe; R2 = H
8. Ar = pCN-Ph; R1 = COOMe; R2 = H
9. Ar = pMeO-Ph; R1 = COOMe; R2 = Me
10. Ar = Ph; R1 = P(O)(OEt)$_2$; R2 = H

*Nature Chem.*, 2009, 1, 578-582
Stereodifferentiation of the two faces of the azomethine ylide

Unpublished results

Blockage of the (si,re) face
Geometries for the TSs in the first step for the [3+2] cycloaddition. In both cases is a non-concerted reaction.

**TS1(major)**

- Energy: 0.0 kcal/mol
- Energy relative to TS1(minor): +2.8 kcal/mol
- Geometry: (re,si) attack

**TS1(minor)**

- Geometry: (si,re) attack

- Calculated distances:
  - 2.031 Å
  - 2.823 Å
  - 2.055 Å
  - 2.813 Å
The scope of our methodology has been expanded to enable a complete switch in the diastereoselectivity!

first experimental evidence of a stepwise mechanism

Nature Chem., 2009, 1, 578-582
Stepwise or Concerted?

“supra antara” not allowed [4+2] cycloadditions
Switching the Stereoselectivity: Fulleropyrrolidines “a la Carte”

\[
\begin{align*}
\ce{RO2C-N-H-Ar} & \quad \text{(2S,5R)-trans} \\
\ce{Ar-N-CO2R} & \quad \text{(2R,5S)-trans} \\
\ce{RO2C-N-H-Ar} & \quad \text{(2S,5S)-cis} \\
\ce{Ar-N-CO2R} & \quad \text{(2R,5R)-cis}
\end{align*}
\]

\(1a \text{ Ar} = \text{p-MeO-Ph; } R = \text{Me}
\)

\(\text{b Ar} = \text{2-thiophenyl; } R = \text{Me}
\)


up to 99% of er

Nature Chem., 2009, 1, 578-582

up to 96% of er
Asymmetric [3+2] Cycloadditions on C\textsubscript{60}: Mechanism
Stepwise or Concerted?

“supra antara” not allowed [4+2] cycloadditions
Stereodivergent Synthesis of Pyrrolidines

(2R,5R)-cis

(2S,5S)-cis

(2R,5S)-trans

(2S,5R)-trans

\[ \text{AgAcO} \quad \text{Cu(OTf)}_2 \quad \text{Et}_3\text{N} \]

\[ \text{C}_{60} \text{ or } \text{C}_{70} \]

\[ \text{Ph} \quad \text{N} \quad \text{COOMe} \]

\[ R, R_1 \]

\[ R, R_1 \]

\[ R, R_1 \]

\[ R, R_1 \]

\[ \text{J. Am. Chem. Soc., 2012, 134, 12936} \]
[3+2] Cycloaddition with allenoates

Optimización de condiciones