

Hierarchical Selectivity in Fullerenes: Site-, Regio-, Diastereo-, and Enantiocontrol of the 1,3-Dipolar Cycloaddition to C₇₀**

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Dedicated to Professor Luis Echegoyen on the occasion of his 60th birthday

Since the discovery of fullerenes^[1] and their further preparation on a multigram scale,^[2] these molecular carbon allotropes have been thoroughly investigated from the chemical viewpoint in the search for new modified fullerenes that are able to exhibit unconventional properties for practical applications.^[3] Furthermore, this knowledge has allowed a faster and better understanding of the chemical reactivity of the related carbon nanostructures, in particular of the promising carbon nanotubes, endohedral fullerenes, and the most recent graphenes.^[4] However, the number of studies on the reactivity of higher fullerenes is comparatively scarce and the use of asymmetric catalysis in these systems has been neglected so far.^[5]

Higher fullerenes include a great diversity of molecules with different structures and chemical behavior that, because of the minor degree of symmetry, give rise to a complex

covalent chemistry, in which chirality is an important and fascinating aspect.^[6] The preparation of chiral fullerenes has been based on chiral starting materials or, alternatively, on the most common racemic syntheses followed by complex, expensive, and highly time-consuming chromatographic isolation and purification processes.^[7] However, even when the isolation of the different isomers is feasible, the high costs and low abundance of higher fullerenes make necessary the availability of an efficient synthetic methodology to limit a broad distribution of products.

Recently, we reported a straightforward procedure catalyzed by silver or copper acetate to efficiently obtain pyrrolidino[60]fullerenes with stereochemical control by enantioselective cycloaddition of azomethine ylides to the C₆₀ molecule.^[8] However, the extension of the scope of such a methodology to higher fullerenes, namely C₇₀, is not a trivial process because C₇₀ has to face many distinct levels of selectivity.

Unlike C₆₀, C₇₀ lacks a spherical symmetry and has four different types of double bonds on the cage. The most common additions to [70]fullerene proceed in a 1,2 manner with a regioselectivity driven by the release of the strain of the double bond. Accordingly, additions occur preferentially at the most strained fullerene double bonds, namely those located at the polar zone (α site followed by β and γ sites).

The flatter equatorial region is less reactive and the addition only rarely takes place at the double bond of the δ site.^[9] Particularly, cycloadditions of azomethine ylides typically give rise to the α , followed by the β , and a small amount of the γ regioisomers (C(8)–C(25), C(7)–C(22), C(1)–C(2) according to the systematic numbering; Figure 1).^[10]

We propose to refer to these isomers (α , β , etc.) and to this form of selectivity as “site isomers” and site selectivity, respectively,^[11] to distinguish them from the regioisomers that result from the addition of nonsymmetric 1,3-dipoles to a double bond of the fullerene sphere. Indeed, depending on the orientation of the asymmetric azomethine ylide addition to the fullerene double bond, two regioisomers are, in turn, possible for each of the formed cycloadducts (see Figure 1). Furthermore, each of these regioisomeric pyrrolidines could be formed in a *cis* or *trans* configuration (diastereomers) and, in turn, in both of the enantiomeric forms.

Herein we describe an efficient catalytic site-, regio-, diastereo-, and enantioselective cycloaddition of N-metalated azomethine ylides to C₇₀ at low temperatures and while maintaining the atom economy principle. This methodology

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[**] Financial support by the Ministerio de Ciencia e Innovación (MICINN) of Spain (projects CTQ2010-16959, CTQ2008-00795/BQU; Consolider-Ingenio CSD2007-00010, CSD2007-00006; research grant, E.E.M.; R y C grant; S.F.), the Basque Government (IT-324-07) and the CAM (MADRISOLAR-2 project S2009/PPQ-1533) is acknowledged. The authors also thank the SGI/IZO-SGiker UPV/EHU for generous allocation of computational resources.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201101246>.

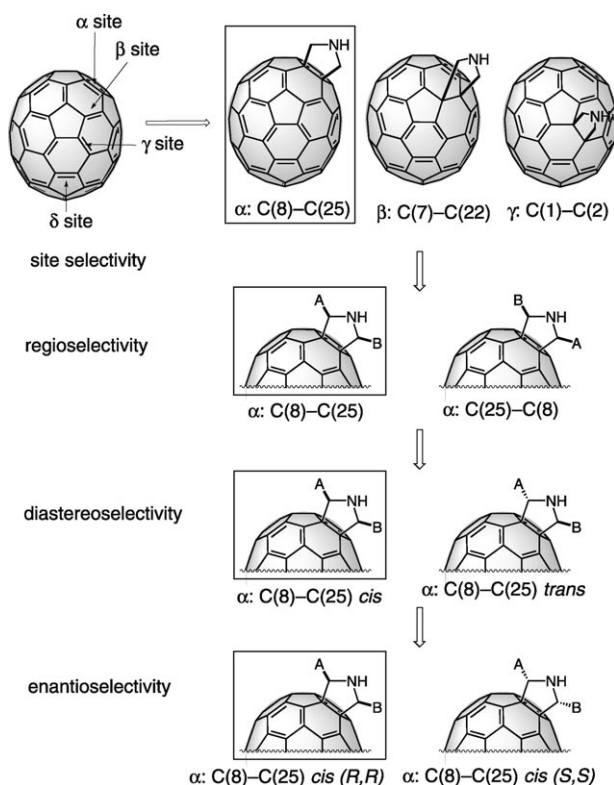
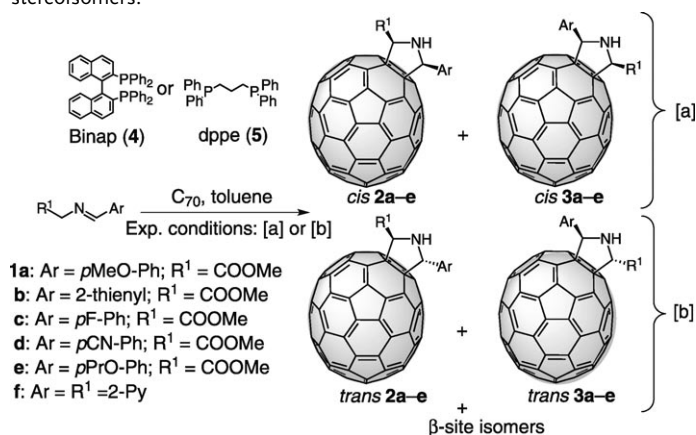


Figure 1. Different levels of selectivity for a cycloaddition reaction with the C_{70} molecule (site-, regio-, diastereo-, and enantioselectivity). Each highlighted molecule gives rise to the following level of selectivity.

allows the synthesis of chiral pyrrolidino[70]fullerenes with a controlled stereochemistry that depends on the metal complexes used. The azomethine ylide cycloaddition to [60]fullerenes is one of the most employed and versatile methods for the functionalization of C_{60} .^[12] However, it has been mainly limited to symmetric 1,3-dipoles for [70]fullerene. Indeed, for the most simple example reported, the thermal cycloaddition of *N*-methylazomethine ylide to C_{70} gave a mixture of the three site isomers C(8)–C(25), C(7)–C(22), and C(1)–C(2) (α : β : γ) in a 46:41:13 ratio.^[13] As a first step in our present study, we investigated the cycloaddition of iminoesters (**1a–f**) as stabilized 1,3-dipoles to [70]fullerene (Table 1).

By thermal treatment in refluxing toluene, the addition to C_{70} occurs with a good α -site selectivity. β -Site isomers are formed only in low yield (from 4% to 10%, see the Supporting Information) and no trace of the γ isomer was detected. However, such α -site isomers are formed as a 1:1 regioisomeric mixture of 2-methoxycarbonyl-5-aryl pyrrolidino[3,4:25',8'] [70]fullerene (**2**) and 2-methoxycarbonyl-5-aryl pyrrolidino[3,4:8':25'] [70]fullerene (**3**).^[14] Each regioisomer is formed in turn in a diastereomeric ratio (*cis*/*trans*) of around 60:40 (Table S1 in the Supporting Information, entries 1–5). The symmetric 1,3-dipole **1f** cannot form regioisomers and therefore only one product is obtained as previously reported (Table S1, entry 6).^[15] Despite this increase of site selectivity, the thermal treatment is not a suitable method to obtain efficiently chiral pyrrolidinofullerenes because a broad product distribution of stereoisomers

Table 1: The cycloaddition reaction of iminoesters (**1a–f**) to [70]fullerene selectively affords compounds **2** and **3** (α -site isomer), which are formed as a mixture of two regioisomers constituted in turn by *cis* and *trans* stereoisomers.



Entry	Iminoester (T [°C])	t [h] (Yield [%]) ^[c]	Selectivity		
			Site- (α : β)	Regio- (2:3) ^[d]	Diastereo- (<i>cis</i> : <i>trans</i>) ^[e]
1	1a (–30) ^[a]	12 (47)	97:3	82:18	97:3
2	1b (–45) ^[a]	15 (40)	99:1	90:10	97:3
3	1c (–40) ^[a]	15 (41)	94:6	85:15	99:1
4	1d (–40) ^[a]	15 (41)	94:6	88:12	99:1
5	1e (–39) ^[a]	15 (41)	94:6	83:17	96:4
6	1a (25) ^[b]	0.3 (77)	97:3	80:20	15:85
7	1b (25) ^[b]	0.3 (77)	95:5	85:15	11:89
8	1c (25) ^[b]	0.3 (75)	95:5	91:9	9:91
9	1d (25) ^[b]	0.3 (72)	95:5	97:3	11:89
10	1e (25) ^[b]	0.3 (72)	94:6	82:18	15:85

[a] Experimental conditions: dppe (**5**), AgAcO; [b] Experimental conditions: binap (**4**), [Cu(TfO)₂]/Et₃N; [c] Determined by HPLC, with respect to the sum of monoadduct isomers; [d] Determined by ¹H NMR spectroscopy and HPLC (see the Supporting Information and Ref. [14]); [e] Compound **2**.

would produce very low yields, even after chromatographic separation using chiral stationary phases.

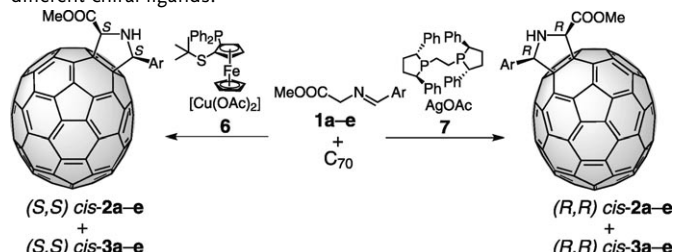
To address this issue, we have carried out the cycloaddition to C_{70} by using copper or silver catalysts (experimental conditions [a] and [b] in Table 1). In the presence of 20% of silver acetate and [1,2-bis(diphenylphosphino)ethane] (dppe, **5**), imino esters **1a–f** undergo cycloaddition in toluene at low temperatures to form the *cis* pyrrolidino[70]fullerenes **2a–e** in relatively good yields (up to 40%). The good values of site selectivity shown in the previous thermal addition are improved and, therefore, the amount of the minor β -site isomers formed at higher temperatures decreased to 1–6% (Table 1, entries 1–5). More important, however, was the effect on the regioselectivity; the regioisomers with the ester moiety on the polar region and the aromatic ring on the equatorial region were formed preferentially with a ratio ranging from 8:2 to 9:1, as in the case of dipole **1b** (Table 1, entry 2).

Copper triflate along with racemic Binap (**4**) and triethylamine as a base were found to be a complementary catalyst system for the preparation of pyrrolidinofullerenes with a 2,5 *trans* configuration (Table 1, entries 6–10). At room temper-

ature, this complex prompts the cycloaddition on the α site of the C_{70} within 15 minutes and with yields over 70%. The regioselectivity observed is similar to that obtained with the silver complex, and the 2-methoxycarbonyl-5-aryl pyrrolidino[3,4:25',8'] [70]fullerene regioisomer that bears the ester group on the polar zone is formed in a 80–97% ratio. The copper complex at room temperature is able to invert the diastereoselectivity to form *trans* pyrrolidinofullerene with a ratio that ranges from 85:15 to 91:9. The obtained results clearly showed the ability of the metal catalyst to control the cycloaddition process of azomethine ylides, thus avoiding the undesired broad product distribution.

Therefore, we looked for a broadening of the scope of such a methodology towards the synthesis of optically active pyrrolidino[70]fullerenes through chiral induction. To this end, we used the chiral metal complex **7**, based on the pair silver acetate and (–)-1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane, and the Fesulphos-copper(II) acetate **6** (Table 2).

Table 2: Asymmetric Ag^I and Cu^{II} -catalyzed 1,3-dipolar cycloadditions of azomethine ylides derived from imines **1a–e** to [70]fullerene using different chiral ligands.



Imine	Ligand (T [°C])	Yield [%] ^[a]	regioselectivity 2:3	de 2	ee 2 (ee 3)
1a	7 (–30)	20	81:19	94	89 (90)
1a	6 (–35)	23	82:18	94	–93 (–93)
1b ^[b]	7 (–43)	24	90:10	94	80 (80)
1b ^[b]	6 (–45)	31	90:10	94	–99 (–99)
1c	7 (–40)	23	85:15	98	88 (88)
1c	6 (–45)	30	85:15	99	–95 (–94)
1d	7 (–40)	22	87:13	98	87 (87)
1d	6 (–48)	24	88:12	99	–92 (–92)
1e	7 (–30)	20	83:17	93	86 (86)
1e	6 (–35)	24	83:17	94	–92 (–93)

[a] With respect to the product isolated after column chromatography on silica gel and HPLC purification and with the *ee* indicated. [b] The presence of the thienyl changes the priority on the C5 chiral carbon atoms.

These complexes showed a very similar behavior in obtaining almost the same level of site- and regioselectivity that was obtained when no chiral complexes were used. Indeed, both **6** and **7** direct the cycloaddition of iminoester **1a** towards the α site with a 98% selectivity, whereas the regioisomeric ratio between **2** and **3** ranged from 4:1 to 9:1 (Table 2). The stereoselectivity values determined with these chiral complexes were similar to those obtained for the related C_{60} .^[8]

Finally, metal complexes formed by silver-phosphine **7** and copper-Fesulphos **6** presented a high and opposite chiral

induction between them for both the major (**2a**) and the minor (**3a**) regioisomers (see Table 2 and the Supporting Information).

In particular, it is worth mentioning that the metal complex formed by copper acetate and Fesulphos **6** gives rise to an even better chiral induction than the related [60]pyrrolidines with *ee* ranging from 92% to 99% as in the case of pyrrolidines **2b** and **3b** (Table 2). These selectivity levels allow, for the first time, to gain control over the enantiomeric outcome of the cycloaddition process on [70]fullerene, and they allow to obtain a single stereoisomer (with the indicated *ee*) in relatively good yield (20–30%) after purification by column chromatography.^[16] As expected, the two metal complexes **6** and **7** give rise to enantiomers with the same UV/Vis spectra but with opposite Cotton effects in circular dichroism (CD) spectroscopy (see Figures S31–S37).

Since in these reactions the fullerene acts as an electrophilic dipolarophile, we performed DFT calculations^[17–20] (B3LYP/LANL2DZ level of theory) on C_{70} (Figure 2A) to

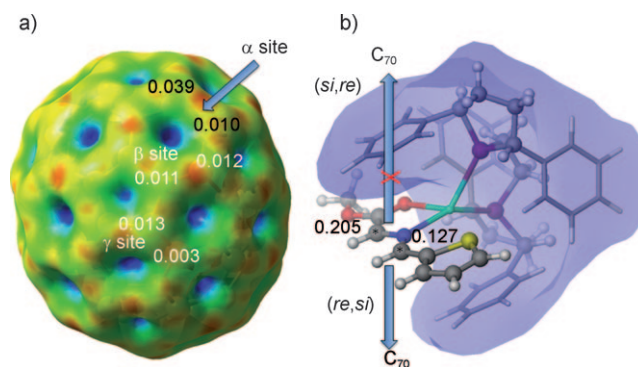


Figure 2. a) Electrostatic potential projected on the electron density of C_{70} (B3LYP/LANL2DZ level of theory). Given numbers are the electrophilic Fukui indexes at the α – γ sites in arbitrary units. The higher the number, the higher the local electrophilicity. b) Fully optimized silver azomethine 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.

assess the local electrophilicity of the different sites by means of the electrophilic Fukui functions f_k^+ of different atoms.^[21] Our results are compatible with the site selectivity observed. Thus, the α site is the most electrophilic one (highest f_k^+ values), followed by the β and γ sites.

These reactive sites exhibit different values for the individual atoms, thus predicting asynchronous reaction paths and regioselectivity issues. Geometry optimization (B3LYP/LANL2DZ:PM6 level of theory) of the azomethine ylide derived from imine **1b**, silver acetate, and diphosphine **7** (Figure 2B) shows an efficient blockage of the (*si, re*) face induced by a phenyl group.

In addition, the f^- Fukui nucleophilic functions localized on the carbon atoms of the dipole show an enolate-like nucleophilicity of the azomethine moiety, since the f^- value for the α carbon atom of the dipole is larger than that

corresponding to the other carbon terminus of the dipole (Figure 2B).

Figure 3 shows the geometries and energies of the possible transition structures associated with the different processes gathered in Figure 1. The outcome is consistent with the

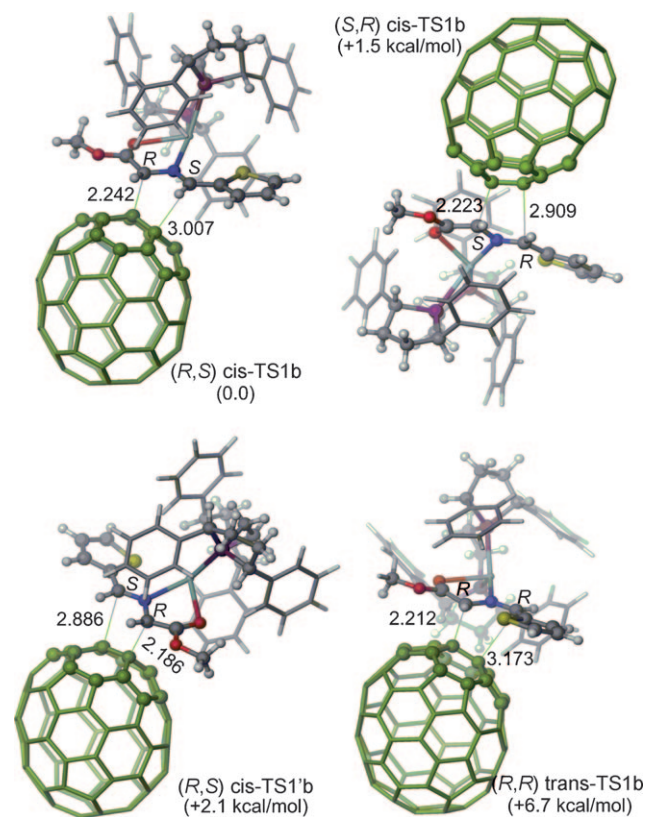


Figure 3. Fully optimized first transition structures (B3LYP/LANL2DZ//B3LYP/LANL2DZ:HF/PM6 + Δ ZPVE) associated with the formation of (*R,S*) and (*S,R*) *cis*-**2b** by reaction between imine **1b** and [70]fullerene catalyzed by diphosphine **7**. High and low computational levels in the ONIOM partition are represented in ball and stick and tube modes, respectively. Bond lengths are given in Å.

predictions made on the basis of the previous DFT analysis. Thus, saddle points associated with nucleophilic attacks on the α site of C_{70} reported in Figure 3 show that (*R,S*) *cis*-TS1b is approximately 1.5 kcal mol⁻¹ lower in energy than its (*S,R*) analogue. The calculated deformation energy for the dipole catalyst moiety in (*R,S*) *cis*-TS1b is 4.5 kcal mol⁻¹, whereas the corresponding value for (*S,R*) *cis*-TS1b is 5.7 kcal mol⁻¹. This result indicates that the (*si, re*) attack requires a larger deviation of the catalyst conformation from its optimum conformation shown in Figure 2A, thus favoring the (*re, si*) attack, which is consistent with the experimentally observed enantioselectivity.

As far as the regioselectivity of the reaction is concerned, transition structure (*R,S*) *cis*-TS1'b is calculated to be approximately 2 kcal mol⁻¹ higher in energy than that ((*R,S*) *cis*-TS1b) associated with the formation of the saddle point and leading to the predominant regioisomer that bears the methoxycarbonyl substituent above the polar region. This

result is indicative of the appropriate coupling between the centres that possess the largest nucleophilic and electrophilic Fukui indexes (see above). This factor is also responsible for the large asynchrony of the computed transition structures that actually correspond to stepwise mechanisms (see the Supporting Information).

The diastereoselectivity observed is also compatible with the higher stability of the *cis* dipoles, which favors formation of the corresponding *cis* cycloadducts (Figure 3). However, the stepwise nature of the cycloaddition results in zwitterionic intermediates that cyclize to give the corresponding pyrrolidines with quite low activation barriers. Therefore, our calculations indicate that the origins of the observed selectivity are determined by the first step of the cycloaddition at the site-, regio-, and enantio- levels, although a small loss of diastereocontrol cannot be ruled out during the second step of the reaction. It is interesting to note that our calculations also indicate that the metal-catalyst complex shows a lower affinity for the cycloadduct than for the starting azomethine ylide, thus allowing the completion of the catalytic cycle (see Figure S38).

In summary, we describe the first enantioselective cycloaddition of N-metalated azomethine ylides with the C_{70} molecule that affords the respective enantiomers, with *ee* values higher than 90%, depending on the chiral metal complex used. Furthermore, the highly regioselective process observed for the formation of the regioisomers that results from the cycloaddition of the 1,3-dipole to the α -site double bond of the C_{70} (up to 9:1) has been accounted for by the nucleophilic and electrophilic Fukui indexes determined by theoretical calculations (B3LYP/LANL2DZ). This work paves the way to the selective control (site-, regio-, diastereo-, enantiocontrol) in the functionalization of higher fullerenes, as well as endohedral fullerenes, which still represents a challenge in fullerene research.

Received: February 18, 2011

Published online: May 9, 2011

Keywords: asymmetric catalysis · computational chemistry · 1,3-dipolar cycloaddition · fullerenes · stereoselectivity

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