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Switching the Stereoselectivity: (Fullero)Pyrrolidines "a la Carte"

Enrique E. Maroto, Salvatore Filippone, Angel Martín-Domenech, Margarita Suarez,[‡] and Nazario Martín*,[§]

[†]Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, E-28040 Madrid, Spain
[‡]Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, 10400 La Habana, Cuba
[§]IMDEA–Nanoscience, Campus de Cantoblanco, E-28049 Madrid, Spain

Supporting Information

ABSTRACT: Stereodivergent syntheses of *cis*/*trans* pyrrolidino[3,4:1,2]fullerenes and *endo*/*exo* pyrrolidines are reported with high enantioselectivity levels. Fullerenes are revealed as a useful benchmark to develop suitable catalysts to control the stereochemical outcome and to shed light on the mechanism involved in the related 1,3-dipolar cycloaddition.

Carbon nanostructures have received the attention of the scientific community due to their interest in biomedical and materials science applications.[1] Among them, fullerenes (the only molecular allotrope of carbon)[2] have been used as a benchmark for further chemical studies on the less-known carbon nanotubes (single wall and multiwall)[3] and graphenes.[4] However, despite the interest in preparing chiral carbon nanoforms,[5] the synthesis of enantiomerically pure fullerene derivatives has almost been neglected in the literature and still remains a major scientific challenge.[6] Actually, the chiral starting materials used in the previous asymmetric inductions significantly reduce the nature and number of chiral fullerene derivatives and make the synthesis dependent on their availability, structures, and specific configuration.[7]

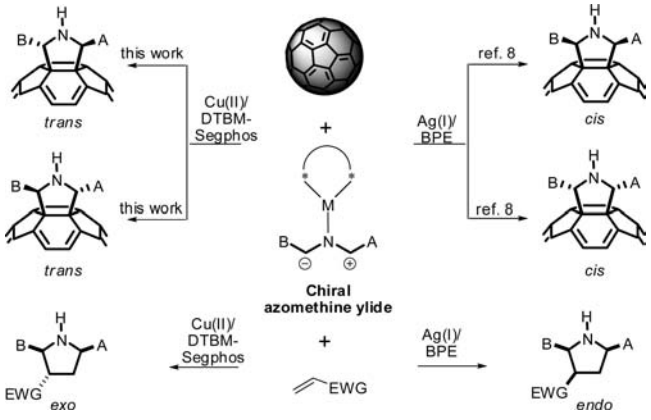
A recent major breakthrough has been, however, the introduction of chiral metal catalysis for the stereoselective synthesis of optically active [60], [70] and metallo-fullerene derivatives.[8−10] Thus, the suitable combination of metal salts and chiral ligands allowed the diasteroselective cycloaddition of *N*-metalated azomethine ylides (AMY) toward the *trans* or *cis* 5-aryl-2-alkyloxycarbonyl pyrrolidino[3,4:1,2][60]fullerene. Furthermore, the (*R*)-Fesulphos chiral ligand along with $Cu(AcO)_2$ directed the enantioselectivity to the (2*S*,5*S*)-*cis* adduct, whereas the (−)-1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane silver acetate complex (Ag(I)/(−)BPE) switched the cycloaddition toward the opposite (2*R*,5*R*)-*cis* enantiomer.[8] However, attempts to achieve an enantiodivergent synthesis for the *trans* diastereoisomer failed since low *ee* values were obtained.[8]

At any rate, the search for full control of the cycloaddition of AMY goes beyond the fullerene chemistry.[11] The great importance of preparing at will highly functionalized pyrrolidines[12,13] with precise stereochemical control has fueled the search for versatile chiral catalysts[14] as well as theoretical and empirical mechanistic studies related to this cycloaddition process.[15]

In this regard, the *trans* diastereoselectivity displayed by the Cu(II)/Binap complex in the AMY cycloaddition onto fullerenes[8] represents the first experimental evidence of a *supra-antara* stepwise mechanism, and it demonstrated the usefulness of fullerene cages as a suitable benchmark for testing new or classical reactions. Soon afterward, other chiral complexes with an *exo* and *trans* diastereoselectivity have been reported for this 1,3-dipolar cycloaddition onto related highly electron-poor nitro olefins.[16]

Here, we report the stereodivergent asymmetric AMY cycloaddition onto fullerenes affording to all the four possible isomeric pyrrolidino[3,4:1,2][60] and [70]fullerenes with high levels of enantioselectivity (Scheme 1). Furthermore, the

Scheme 1. Stereodivergent Synthesis of Chiral Pyrrolidines



diastereoselective chiral complexes used to afford *trans* pyrrolidinofullerenes, such as Cu(II)/DTBM-Segphos-**3**, also efficiently catalyze the AMY cycloaddition onto activated olefins with high enantioselectivity and complete *exo* and *cis* selectivity, whereas the *cis* selective catalyst Ag(I)/BPE affords *endo*-*cis* pyrrolidines also with high *ee*. This finding paves the way to a stereodivergent synthesis of pyrrolidines "a la carte" and sheds light on the AMY cycloaddition mechanism.

Thus, the complex Cu(II)/(*R*)-DTBM-Segphos-**3** directs the AMY cycloaddition of iminoesters **1a−c** onto C_{60}, at rt, toward the formation of *trans*-(2*R*,5*S*)-pyrrolidinofullerenes **2a−c** with *ee* ranging from 90 to 97% (Table 1, entries 1−3). With the

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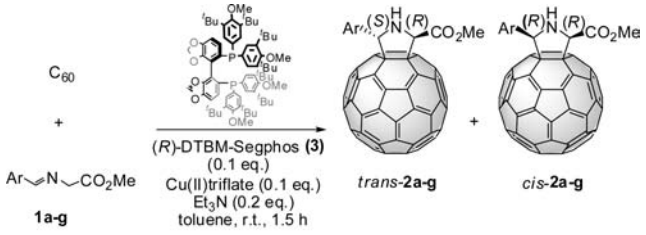
Table 1. Stereoselective Cycloaddition of *N*-Metalated Azomethine Ylides onto [60]Fullerene



a Ar= 4-MeO-Ph; **b** Ar= 2-thienyl; **c** Ar= 4-PrO-Ph; **d** Ar= Ph; **e** Ar= 4-TMSC≡C-Ph; **f** Ar= 4-F-Ph; **g** Ar= 4-CN-Ph

entry	imino-ester	yield[a] (%)	*trans*/*cis*	*ee trans*[b] (%)	*ee cis*[b] (%)
1	**1a**	55	95/5	97 (2*R*,5*S*)-**2a**	n.d.
2	**1b**	70	90/10	90 (2*R*,5*R*)-**2b**[c]	n.d.
3	**1c**	55	95/5	91 (2*R*,5*S*)-**2c**	n.d.
4	**1d**	50	75/25	93 (2*R*,5*S*)-**2d**	93 (2*R*,5*R*)-**2d**
5	**1e**	57	72/28	96 (2*R*,5*S*)-**2e**	91 (2*R*,5*R*)-**2e**
6	**1f**	61	50/50	95 (2*R*,5*S*)-**2f**	95 (2*R*,5*R*)-**2f**
7	**1g**	70	30/70	91 (2*R*,5*S*)-**2g**	93 (2*R*,5*R*)-**2g**
8[d]	**1a**	55	95/5	95 (2*S*,5*R*)-**2a**	n.d.

[a]The yield is calculated on the basis of the total amount of monoadduct. [b]Determined by HPLC. [c]The apparent change of configuration is due to the different priority of the substituents. [d](*S*)-**3** has been used. n.d.: not determined.

increase of electron-poor character of the aromatic ring of the iminoesters **1d−g**, the cycloaddition undergoes a switch toward the *cis* diastereoisomers **2d−g** (Table 1, entries 4−7), where pyrrolidinofullerenes with a (2*R*,5*R*) configuration are obtained with high enantioselectivity.

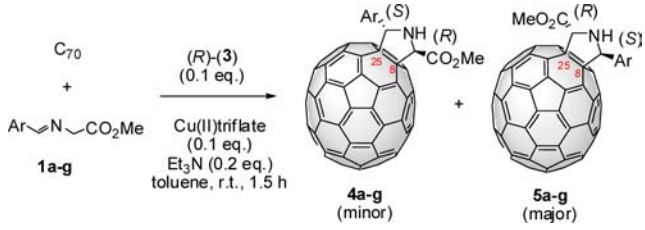
It is worth noting that the configuration of the pyrrolidine carbon atom C-2 is maintained, in both *trans* and *cis* diastereoisomers, as a result of the addition to the same enantioface (C-2 *Re* face). Finally, as expected, the enantioselectivity could be inverted by using the opposite chiral ligand (*S*)-DTBM-Segphos-**3** (entry 8; for other related examples, see Supporting Information (SI)).

The cycloaddition reaction on [70]fullerene occurs with an even higher selectivity. The reaction is clearly site-selective because all the products formed are α isomers, and only traces of β isomers are found (between 1 and 3% depending on the dipole; see SI).[17]

Except for the dipole derived from **1b** (Table 2, entry 2), isomer **5**, bearing a carboxylate group on the polar region, is formed with good to excellent regioselectivity.[9] Furthermore, the Cu(II)-**3** complex enables the formation of the *trans* diastereoisomer even when iminoesters bearing electron-poor aromatic groups are employed (entries 6, 7). Finally, for all the iminoesters the *ee* values are higher than 90% and enantioselectivity could be inverted by the use of the opposite enantiomeric catalyst (Table 2, entry 8; see SI).

Circular dichroism (CD) analysis confirmed the optical activity of the compounds obtained. Interestingly, the *trans* derivatives **2a−g** exhibited a signal at 425−430 nm in the CD of higher intensity when compared with their respective *cis* diastereoisomers (see SI). Indeed, with the sector rule for chiral fullerene derivatives taken into account,[7a,18] a *trans* substitution on the fullerene cycloadduct affords an additive contribution in the corresponding signal.

Table 2. *Trans*-Selective Cycloaddition of *N*-Metalated Azomethine Ylides onto [70]Fullerene

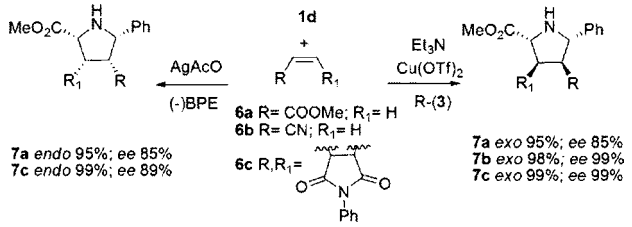


entry	iminoester	yield[a] (%)	**5**/**4**[b]	*de*[b] (%)	*ee trans*[b] (%)
1	**1a**	60	82:18	80	94
2	**1b**	55	65:35	94	95
3	**1c**	55	85:15	82	95
4	**1d**	58	82:18	80	91
5	**1e**	57	91:9	84	93
6	**1f**	61	97:3	94	92
7	**1g**	63	95:5	92	90
8[c]	**1a**	60	82:18	80	−95

[a]The yield is calculated on the basis of the total amount of monoadduct. [b]Determined by HPLC. [c](*S*)-**3** has been used.

When we carry out the AMY cycloaddition onto suitably functionalized olefins, the stereodivergency of these catalysts has to be intended as *exo*/*endo* stereodivergency since only *cis*-pyrrolidines are obtained. Thus, Cu(II) triflate along with DTBM-Segphos **3** affords the *exo* adducts in both enantiomeric forms and good *ee*, maintaining the same configuration onto C-2—bearing the ester group—pyrrolidine carbon as in the case of fullerene. On the other hand, chiral metal complexes [AgAcO/(−)BPE] that direct the cycloaddition onto fullerene toward the diastereoisomer *cis* afford *endo*-pyrrolidines with high optical purity for both enantiomers (Scheme 2 and SI).

Scheme 2. *Endo*/*Exo* Stereodivergent Synthesis of Chiral Pyrrolidines



These findings can be rationalized by the competitive presence of two reaction paths depending on the substrate and ligand structures. Thus, the bulky (*R*)-**3** Segphos ligand/Cu(II) complex allows the dipolarophiles to attack by an *exo* approach, similarly to that reported by using the BINAP ligand.[19] Probably, the lack of secondary interactions between the dipole/dipolarophiles FMOs promotes a stepwise (Michael-like addition) mechanism that occurs onto the *Re* face of the iminoester (Figure 1). This path leads to an intermediate, stabilized by a benzylic cation and a fullerene anion, where the stereochemistry (*R*) of the C-2 is yet defined. The fate of this species depends on the stability of the zwitterionic intermediate. Thus, when very stable fullerene anions and electron-rich benzylic cations are involved, the intermediate undergoes rotation around the N−C2 pyrrolidine bond affording the more stable *trans* isomers. It is worthy to note that the anion formed onto the C-8 position of the C_{70} is more

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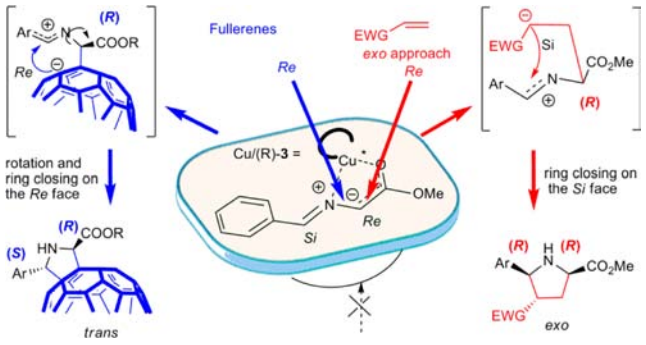

Figure 1. Plausible mechanism of the AMY cycloaddition onto different double bonds.

stable than the relevant C_{60} anion due to the more planar geometry.[9] Thus, all the regioisomers **5a−e** present a *trans* conformation regardless of the type of aromatic substitution (Table 2). In sharp contrast, when conventional olefins are used (right part of Figure 1), the zwitterionic intermediate is not sufficiently stabilized to allow a rotation and, therefore, *exo-cis* adducts are formed. Finally, other chiral complexes, namely Ag(I)/(−)BPE or Cu(II)/Fesulphos, allow the formation of favorable secondary interactions leading to *cis* (fullero)-pyrrolidines, and *endo* isomers when conventional olefins are employed.[20]

In conclusion, we report a set of chiral metal complexes able to afford a stereodivergent synthesis of (fullero)pyrrolidines with complete control of the diastereo- and enantioselective outcome. Particularly, the Cu(II)/Segphos complex directs the AMY cycloaddition toward the 2,5-*trans* disubstituted pyrrolidinofullerenes or to the *exo* diastereomer when conventional olefins are used. These results pave the way to the synthesis of very useful fulleropyrrolidines with complete control of their stereochemistry, thus broadening the scope of their use for biomedical and materials science applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Other data, experimental procedures, and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

nazmar@quim.ucm.es

Notes

The authors declare no competing financial interest.

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