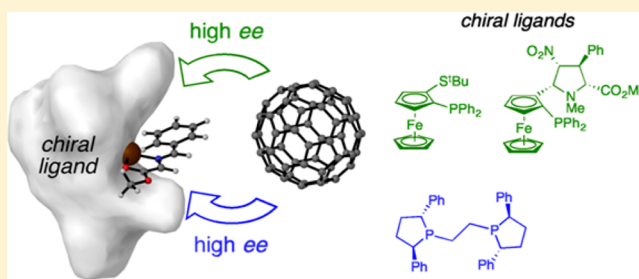


Stereodivergent Synthesis of Chiral Fullerenes by [3 + 2] Cycloadditions to C₆₀Enrique E. Maroto,[§] Salvatore Filippone,[§] Margarita Suárez,^{§,#} Roberto Martínez-Álvarez,[§] Abel de Cózar,^{||,‡} Fernando P. Cossío,^{*,||} and Nazario Martín^{*,§}[§]Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, E-28040 Madrid, Spain[#]Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, 10400 La Habana, Cuba[‡]IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain^{||}Departamento de Química Orgánica I, Universidad del País Vasco, 20018, San Sebastián-Donostia, Spain

S Supporting Information

ABSTRACT: A wide range of new dipoles and catalysts have been used in 1,3-dipolar cycloadditions of N-metalated azomethine ylides onto C₆₀ yielding a full stereodivergent synthesis of pyrrolidino[60]fullerenes with complete diastereoselectivities and very high enantioselectivities. The use of less-explored chiral α -iminoamides as starting 1,3-dipoles leads to an interesting double asymmetric induction resulting in a matching/mismatching effect depending upon the absolute configuration of the stereo-center in the starting α -iminoamide. An enantioselective process was also found in the retrocycloaddition reaction as revealed by mass spectrometry analysis on quasi-enantiomeric pyrrolidino[60]fullerenes. Theoretical DFT calculations are in very good agreement with the experimental data. On the basis of this agreement, a plausible reaction mechanism is proposed.



■ INTRODUCTION

During the last two decades, new carbon forms have been discovered by the scientific community with a sensational pace. First, fullerenes as carbon molecular allotropes, then carbon nanotubes and, more recently, graphene have emerged as suitable materials with promising and outstanding properties.¹ Simultaneously, the chemical modification of these new carbon nanoforms has been developed to process and make these materials available for different applications. However, despite the high level of knowledge reached specially in the molecular chemistry of fullerenes, a fundamental issue of chirality control has been scarcely addressed so far. Indeed, the unavailability of most of the known asymmetric induction methods for the activation of fullerene double bonds hampered the direct synthesis of optically active fullerene derivatives and has limited their preparation and their use to just a few examples.²

On the other hand, fullerene chirality, far from being something purely exotic, has proven to exert a profound influence on some electronic properties.³ Thus, control of fullerene derivative chirality is critical to many fields including biomedical devices, molecular electronics and nanoscience where fullerenes find their main potential applications.⁴

The direct synthesis of optically active [60]fullerene derivatives by using chiral metal catalysis constituted a very important milestone.⁵ Shortly after, optically pure [70]fullerene derivatives⁶ and endofullerenes⁷ were prepared with a complete stereocontrol by the use of copper or silver chiral complexes. Organocatalytic cycloaddition of allenates triggered by chiral phosphines has been

another important step toward the direct preparation of chiral carbon nanostructures.⁸

Particularly, chiral metal complexes described proved to be versatile catalysts affording optically pure pyrrolidino[60]fullerenes by a fully stereodivergent cycloaddition of azomethine ylides.⁹

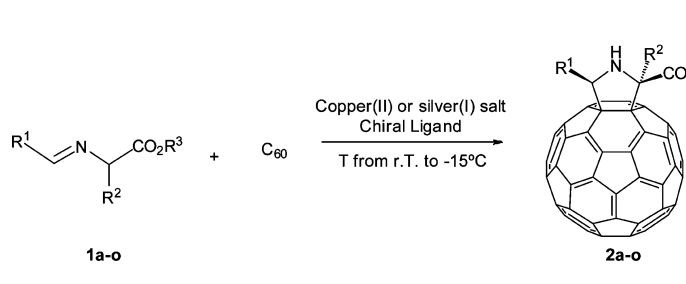
Herein, we have carried out a thorough and systematic study to expand the scope of this highly versatile stereoselective catalytic cycloaddition onto C₆₀ to other catalysts and dipoles, using also complementary mass spectrometry (MS) methodologies. Theoretical calculations at the DFT level by using the two-layered ONIOM (ONIOM: our own *n*-layered integrated molecular orbital and molecular mechanics) have been used to propose a plausible mechanism by which these reactions occur with such a high level of stereocontrol.

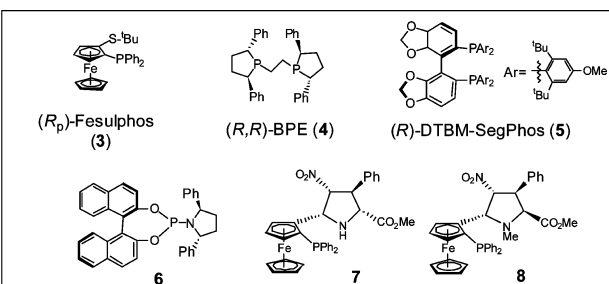
■ RESULTS AND DISCUSSION

New Catalysts for the Synthesis of Chiral Pyrrolidino[60]Fullerenes. The set of four chiral metal complexes, previously described by us, directs the cycloaddition of N-metalated azomethine ylides onto fullerenes with a completely stereodivergent control onto the two new formed stereocenters. Thus, the formed 2-alkoxycarbonyl-5-aryl disubstituted pyrrolidino[60] and [70]fullerenes were obtained in all the possible stereoisomeric forms: copper(II) acetate/**3** and silver acetate/**4** displayed a *cis* diastereoselectivity affording enantiomers **2S,5S**

Received: October 10, 2013

Table 1. 1,3-Dipolar Cycloaddition of Different N-Metalated Azomethine Ylides onto C₆₀ with Different Catalytic Systems





entry	α -iminoester	R ¹	R ²	R ³	chiral complex	T (yield %)	cis:trans ^a	ee trans (%) ^[b]	ee cis (%) ^b
1	1a	4-MeO-Ph	H	Me	Cu(OAc) ₂ / 6	-15 °C (55)	>99:<1	—	90 (2 <i>S</i> ,5 <i>S</i>)
2	1b	2-thienyl	H	Me	Cu(OAc) ₂ / 6	-15 °C (60)	>99:<1	—	88 (2 <i>S</i> ,5 <i>R</i>) ^d
3	1c	4-F-Ph	H	Me	Cu(OAc) ₂ / 6	-15 °C (51)	>99:<1	—	91 (2 <i>S</i> ,5 <i>S</i>)
4	1d	4-CN-Ph	H	Me	Cu(OAc) ₂ / 6	-15 °C (54)	>99:<1	—	90 (2 <i>S</i> ,5 <i>S</i>)
5	1e	4-MeO-Ph	Me	Et	Cu(OAc) ₂ / 6	-15 °C (33)	>99:<1	—	80 (2 <i>S</i> ,5 <i>S</i>)
6 ^c	1a	4-MeO-Ph	H	Me	Cu(OAc) ₂ / 6	-15 °C (51)	>99:<1	—	89 (2 <i>S</i> ,5 <i>S</i>)
7	1a	4-MeO-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 7	-20 °C (80)	>99:<1	—	61 (2 <i>S</i> ,5 <i>S</i>)
8	1a	4-MeO-Ph	H	Me	Cu(OTf) ₂ /Et ₃ N/ 7	25 °C (91)	>99:<1	—	53 (2 <i>S</i> ,5 <i>S</i>)
9	1e	4-MeO-Ph	Me	Et	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 7	-25 °C (70)	>99:<1	—	10 (2 <i>R</i> ,5 <i>R</i>)
10	1a	4-MeO-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (71)	>99:<1	—	96 (2 <i>S</i> ,5 <i>S</i>)
11	1c	4-F-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (69)	>99:<1	—	95 (2 <i>S</i> ,5 <i>S</i>)
12	1d	4-CN-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (70)	>99:<1	—	95 (2 <i>S</i> ,5 <i>S</i>)
13	1e	4-MeO-Ph	Me	Et	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (65)	>99:<1	—	80 (2 <i>S</i> ,5 <i>S</i>)
14	1j	Cy	H	Me	Cu(OAc) ₂ / 3	25 °C (39)	70:30	—	33 (2 <i>S</i> ,5 <i>S</i>)
15	1j	Cy	H	Me	AgOAc/ 4	25 °C (25)	71:29	—	42 (2 <i>R</i> ,5 <i>R</i>)
16	1k	CO ₂ Et	H	Et	Cu(OAc) ₂ / 3	25 °C (0)	—	—	—
17	1f	4-PrO-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (70)	>99:<1	—	90 (2 <i>S</i> ,5 <i>S</i>)
18	1f	4-PrO-Ph	H	Me	AgOAc/ 4	-15 °C (56)	>99:<1	—	84 (2 <i>R</i> ,5 <i>R</i>)
19	1f	4-PrO-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (69)	>99:<1	—	94 (2 <i>S</i> ,5 <i>S</i>)
20	1g	Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (63)	>99:<1	—	90 (2 <i>S</i> ,5 <i>S</i>)
21	1g	Ph	H	Me	AgOAc/ 4	-15 °C (60)	>99:<1	—	85 (2 <i>R</i> ,5 <i>R</i>)
22	1h	4-(C≡C)TMS-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (55)	>99:<1	—	93 (2 <i>S</i> ,5 <i>S</i>)
23	1h	4-(C≡C)TMS-Ph	H	Me	AgOAc/ 4	-15 °C (50)	>99:<1	—	85 (2 <i>R</i> ,5 <i>R</i>)
24	1h	4-(C≡C)TMS-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (71)	>99:<1	—	97 (2 <i>S</i> ,5 <i>S</i>)
25	1i	4-MeO-Ph	H	^t Bu	Cu(OAc) ₂ / 3	-15 °C (64)	>99:<1	—	93 (2 <i>S</i> ,5 <i>S</i>)
26	1i	4-MeO-Ph	H	^t Bu	AgOAc/ 4	-15 °C (60)	>99:<1	—	86 (2 <i>R</i> ,5 <i>R</i>)
27	1l	2-Cl-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (90)	>99:<1	—	95 (2 <i>S</i> ,5 <i>R</i>) ^d
28	1l	2-Cl-Ph	H	Me	AgOAc/ 4	-15 °C (66)	>99:<1	—	85 (2 <i>R</i> ,5 <i>S</i>) ^d
29	1l	2-Cl-Ph	H	Me	Cu(OTf) ₂ /Et ₃ N/ 5	25 °C (86)	>99:<1	—	88 (2 <i>R</i> ,5 <i>S</i>) ^d
30	1m	2-MeO-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (63)	99:1	—	66 (2 <i>S</i> ,5 <i>R</i>) ^d
31	1m	2-MeO-Ph	H	Me	AgOAc/ 4	-15 °C (66)	99:1	—	83 (2 <i>R</i> ,5 <i>S</i>) ^d
32	1m	2-MeO-Ph	H	Me	Cu(OTf) ₂ /Et ₃ N/ 5	25 °C (71)	70:30	74 (2 <i>R</i> ,5 <i>R</i>) ^d	70 (2 <i>R</i> ,5 <i>S</i>) ^d
33	1m	2-MeO-Ph	H	Me	Cu(ACN) ₄ PF ₆ /Et ₃ N/ 8	-30 °C (72)	>99:<1	—	87 (2 <i>S</i> ,5 <i>R</i>) ^d
34	1n	3-Cl-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (75)	98:2	—	11 (2 <i>S</i> ,5 <i>S</i>)
35	1n	3-Cl-Ph	H	Me	AgOAc/ 4	-15 °C (47)	>99:<1	—	87 (2 <i>R</i> ,5 <i>R</i>)
36	1n	3-Cl-Ph	H	Me	Cu(OTf) ₂ /Et ₃ N/ 5	25 °C (75)	50:50	86 (2 <i>R</i> ,5 <i>S</i>)	77 (2 <i>R</i> ,5 <i>R</i>)
37	1o	3-MeO-Ph	H	Me	Cu(OAc) ₂ / 3	-15 °C (50)	99:1	—	90 (2 <i>S</i> ,5 <i>S</i>)
38	1o	3-MeO-Ph	H	Me	AgOAc/ 4	-15 °C (77)	99:1	—	86 (2 <i>R</i> ,5 <i>R</i>)
39	1o	3-MeO-Ph	H	Me	Cu(OTf) ₂ /Et ₃ N/ 5	25 °C (55)	1:99	95 (2 <i>R</i> ,5 <i>S</i>)	—

^aDetermined by ¹H NMR. ^bDetermined by chiral HPLC. The absolute configuration is indicated in brackets. ^c5% mol load of catalyst. ^dFor compounds **2b**, **2l**, and **2m** the configurations shown represent the change in priority of the substituent at position 5 of the newly created pyrrolidine ring relative to the other entries of this table.

and 2*R*,5*R* respectively,⁵ whereas copper(II) triflate/TEA and (*R*) or (*S*)-DTBM Segphos (**5**) led, respectively, to the two *trans* 2*R*,5*S* and 2*S*,5*R* stereoisomers in high optical purity.⁹ In the search for other even more efficient chiral complexes, we have found in phosphoramidite **6** a suitable ligand, along with copper(II) acetate, able to direct the cycloaddition of fullerenes—in the same way as copper(II) acetate/Fesulphos **3**—onto the 2*Si*,5*Re* face of

the N-metalated azomethine ylide affording (2*S*,5*S*) pyrrolidino-[3,4:1,2][60]fullerenes **2a–e** (2 and 5 are also used for numbering the two prochiral centers in the iminoesters **1**, see also below). The enantioselectivity was found to be very similar to copper(II) acetate/**3** (Table 1, entries 1–5), and the *cis* diastereoselectivity was also complete for the more hindered iminoester **1e** derived from alanine (entry 5). Remarkably, the cycloaddition occurs also by

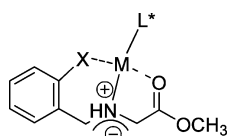


Figure 1. W conformation of the N-metalated azomethine ylide with α -iminoester 2-methoxy (X = OMe) or 2-chloro (X = Cl) aryl substituted.

using a lower catalyst loading (5% mol) while maintaining a high value of reactivity and enantioselectivity (entry 6).

We have also tested noncommercially available chiral complexes, recently reported by some of us, featuring both the adjustable chirality of unnatural prolines and planar chirality of the ferrocenyl skeleton such as catalysts **7** and **8**.¹⁰ Thus, chiral ligand based on N-unsubstituted D-proline **7**—that gave rise to an *exo* diastereoselectivity when used with olefins—neither induce high values of enantioselectivity (entries 7–9) nor showed a *trans* diastereoselectivity when used with copper triflate on fullerene at room temperature.¹¹ However, in sharp contrast, the configuration of ligand **8** afforded an enantioselectivity that was found to be more favorable. Indeed, the chiral complex formed from the salt $\text{Cu}(\text{ACN})_4\text{PF}_6$ and **8** directs the cycloaddition toward the enantiomers 2*S*,*5S* with enantioselectivities over 95% and with good yields (entries 10–12 and see below). For the more substituted iminoester **1e**, derived from alanine, the system Cu/**8** allowed a complete *cis* diastereoselectivity and a significant yield improvement, although we failed to pass the 80% of enantioselectivity showed with other ligands (entry 13).

Influence of the α -Iminoester Nature and Substitution Pattern. In order to evaluate the effect of the nature and substitution pattern on the stereochemical outcome, a variety of

α -iminoesters have been prepared from different aldehydes and aminoesters.

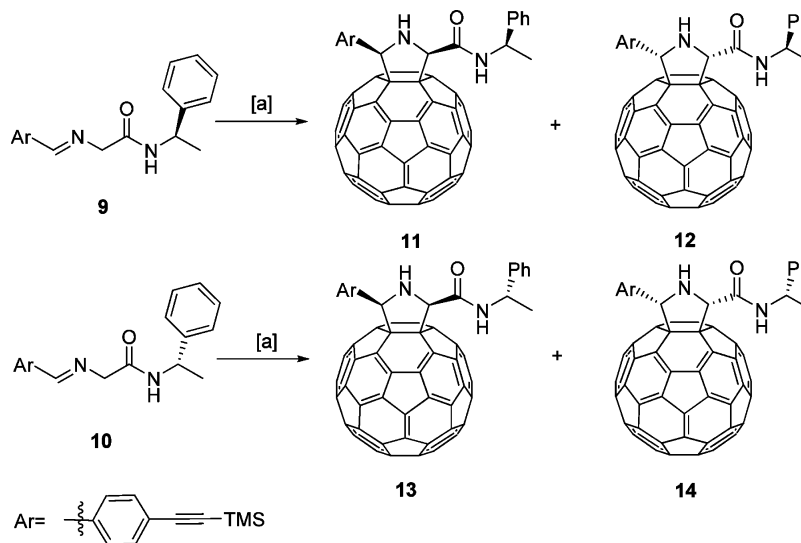
The reaction does not reach a good stereocontrol with aliphatic dipoles such as α -iminoesters **1j** and **1k** (aliphatic iminoesters are often unstable and typically they undergo hydrolysis) affording poor selectivities (entries 14–15) and reactivities (entry 16).

On the other hand, phenyl iminoesters or four-substituted phenyl iminoesters cycloadd to C_{60} maintaining very high values of *cis* diastereoselectivity. Both enantiomers have been obtained in high optical purity depending on the catalyst used (entries 17–26). Particularly, pyrrolidino[60]fullerenes **2h,i**, featuring a *tert*-butyl ester or a 4-trimethylsilylphenyl group, were obtained with 93% of enantiomeric excess (ee) (2*S*,*5S* enantiomers) with the ligand **3** (entries 22 and 25) and 85–86% (2*R*,*5R* enantiomers) with the complex silver-BPE **4** (entries 23 and 26). Once more, the new chiral complex copper/**8** was found to be the best performer with enantioselectivities as high as 97% (entry 24).

All the aforementioned aromatic α -iminoesters tested so far as dipoles precursors have different substituents in *para* position. In this context, we decided to synthesize other aromatic α -iminoesters bearing different electron-releasing and electron-withdrawing substituents in *ortho* and *meta* positions of the phenyl ring to evaluate their potential influence on the stereoselectivity of the reaction. As summarized in Table 1, the reaction worked with all these new α -iminoesters when applying the respective catalysts to obtain either the *cis* or *trans* adduct but with remarkable differences, depending upon the substituent nature and position.

Ortho-methoxy substituted aryl iminoester, **1m**, gave rise to slightly lower diastereoselectivity and moderate enantioselectivity as a result of a higher steric demand, affording better ee values with the system Ag/**4** (83% versus 66%, entries 30–31).

Table 2. Influence of an Additional Stereocenter in the Selectivity of the 1,3-Dipolar Cycloaddition of Chiral α -Iminoamides and C_{60}



entry ^a	α -iminoamide	chiral catalyst	de (%) ^b	yield (%)
1	9	$\text{Cu}(\text{OAc})_2$ / 3	92 (12)	70
2	9	AgOAc / 4	20 (11)	66
3	10	$\text{Cu}(\text{OAc})_2$ / 3	17 (14)	63
4	10	AgOAc / 4	90 (13)	64

^aConditions (cycloaddition): metal salt (10% mol), chiral ligand (10% mol), anhydrous toluene, -15°C , 3 h. ^bDetermined by HPLC; indicating in brackets the major product.

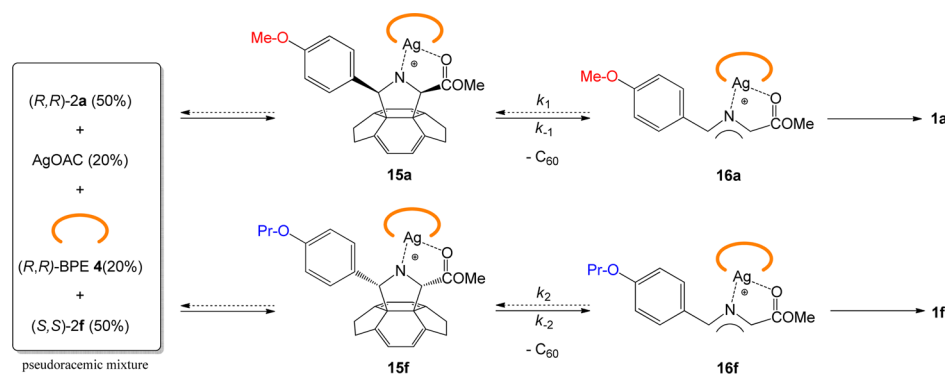


Figure 2. Retrocycloaddition of the pseudoracemic mixture formed by equimolecular amount of (*R,R*)-**2a** and (*S,S*)-**2f**. ESI/MS analysis revealed a faster formation of species derived from (*R,R*)-**2a** ($k_{-1} > k_{-2}$) as a result of the silver/(*R,R*)-BPE **4** catalysis, analogously to that found for the direct reaction.

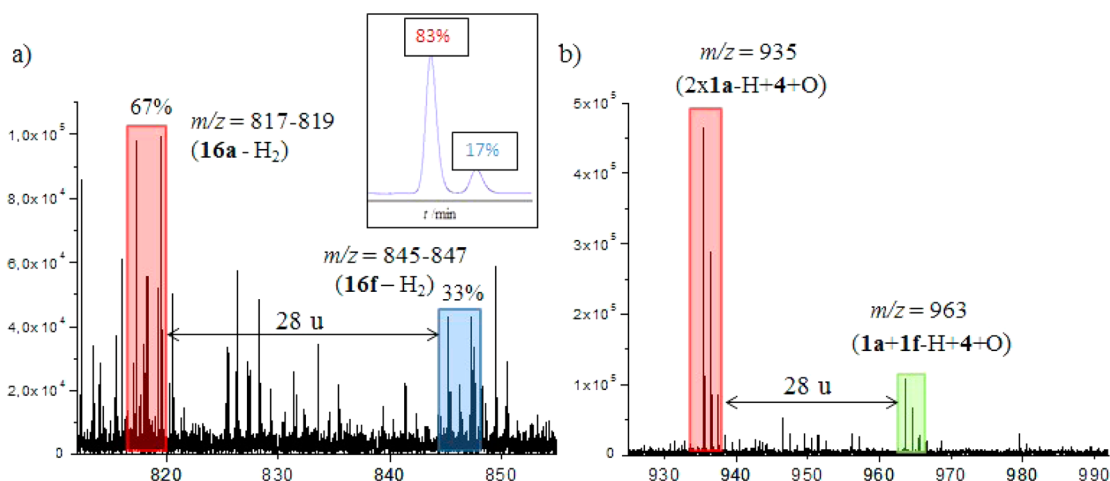


Figure 3. Products derived from catalyzed retrocycloaddition revealed by ESI/MS with their relative intensities. (a) Peaks derived from the loss of C_{60} . Inset: enantiomeric ratio determined by HPLC for the direct addition of **1a** (first peak refers to the (*R,R*) stereoisomer) catalyzed by Ag/**4** at room temperature. (b) Clusters of the homodimer of **1a** (red) and heterodimer of **1a** and **1f** (green) along with catalyst **4**.

Furthermore, in sharp contrast to the other iminoesters,⁹ catalyst Cu/**5** is not able to switch the diastereoselectivity toward the *trans* adduct, probably as a result of the metal coordination with three anchor groups in the dipole that yields a *cis* stereoisomer (entry 32, see Figure 1). Nevertheless, chiral ligand **8** along with Cu(ACN)₄PF₆ proved to be very effective also with this substrate affording *cis* pyrrolidine (**2S,5R**)-**2m** with 87% of ee (entry 33). Interestingly, the cycloaddition of 2-chlorophenyl α -iminoester **1l** occurs with a complete *cis* selectivity and good enantioselectivity regardless the catalytic system used (entries 27–29). Thus, Cu/**3** catalyzed cycloaddition of **1l** onto C_{60} occurs with excellent selectivity and yield (entry 27). Finally, *meta* substituted aryl iminoesters **1n,o** showed an intermediate behavior between *ortho* and *para* substituted analogues (entries 34–39). Along with nitrogen atom and ester moiety, chlorine leads to a stronger binding of the dipole to the metals with respect to the more hindered methoxy group (Figure 1). The same reason could explain the lack of selectivity when the chlorine atom is located in the *meta* position (dipole **1n**) because it is too far to coordinate the metal but can hinder the stereodifferentiation (11% ee). The different electronic nature of the methoxy group does not have any significant impact on the selectivity when located in the *meta* position affording the same ee than that obtained in the *para* position (dipole **1a**).

Double Chiral Induction. The majority of 1,3-dipolar cycloaddition reactions imply the use of α -iminoesters, providing

pyrrolidines with 2-carboxylate substitution. The use of α -iminoamides as azomethine ylides precursors has been considerably less explored.¹² Taking this into account and with the aim of exploring the interplay of the chirality of the catalytic system described and the chirality of a substrate, we have carried out some experiments of double asymmetric induction with chiral α -iminoamides as dipoles. Thus, iminoamides **9** and **10** were prepared from commercially available (*R*) and (*S*)- α -methylbenzylamine respectively by reaction of the primary amine with Boc-glycine, subsequent deprotection with HCl, and finally dehydration with the corresponding aldehyde. All the reactions are nearly quantitative and the overall yield is 88% (see SI).

Iminoamides **9** and **10** could be used as substrates for a metal catalyzed 1,3-dipolar cycloaddition over C_{60} , and two diastereoisomers bearing three different chiral centers were synthesized in good yield and in different ratios, depending upon the catalytic system used (Table 2). In fact, when the reaction with **9** was catalyzed by copper(II) acetate and Fesulphos **3** as chiral ligand at $-15\text{ }^{\circ}\text{C}$, pyrrolidine **12**, featuring a **2S,5S** configuration [and obviously (*R*) in the benzylic carbon atom of the amide], was obtained with a 92% of diastereomeric excess (de). This product is consistent with a coherent effect of the chirality of the catalyst with the chirality of the substrate that directs the cycloaddition on the **2Si,5Re** face of the dipole derived from **9** (Table 2, entry 1). On the other hand, despite the sense of asymmetric induction

of silver(I) acetate/[*(R,R)*-BPE] **4** as catalyst was found to be predominant (compound **11** with a configuration *2R,5R* as main product). A mismatched effect of the chirality of **9** led to a mixture of both diastereoisomers **11** and **12** with only a 60:40 of diastereomeric ratio. Analogously, carrying out the reaction with the opposite enantiomer of the α -iminoamide (**10**) a mismatched effect was found with the complex Cu/**3** (entry 3). These experimental findings clearly indicate that the asymmetric induction sense of the chiral N-metale azomethine ylides is not strong enough to overcome the effect of substrate chirality and to give rise to high levels of enantioselectivity, regardless of the effect of the iminoamide stereocenter. Thus, the metal-chelated dipole (whether it be copper/**3** or silver/**4**) in its predictable secondary amide conformation - with the chiral methine hydrogen eclipsing the carbonyl group - slightly prefers approaching of C₆₀ from the side of the methyl group rather than the side of the phenyl group.

Mass Spectrometry Studies. Along with its classical use for the characterization of organic compounds, electrospray ionization mass spectrometry (ESI/MS) has proven to be a very useful tool for mechanistic investigations due to its ability to detect ions and also transient intermediates involved in different reactions.¹³ ESI/MS technique has also been successfully used for the analysis, detection, and investigation of reactions involving fullerenes highlighting its usefulness to develop a procedure to modulate the 1,3-dipolar retrocycloaddition of pyrrolidinofullerenes.^{14–16} Furthermore, ESI/MS has also proven to be a very useful tool for fast screening of asymmetric reactions by using mass labeled enantiomers.¹⁷

In this context and to gain some insight into the reaction mechanism, MS experiments were first conducted on the reaction mixtures of the different catalytic systems employed. All of them showed the peaks corresponding to the respective catalytic systems (metal + ligand in different oxidation state) and the reactive chiral complex (metal + dipole + ligand in different oxidation state), but none of them showed the presence of acetate anion in the complex as previously postulated (the absence of anion acetate in the reactive complex was also confirmed by theoretical calculations, see below).⁵

Furthermore, we have also evaluated the intrinsic enantioselectivity of one of our systems (Ag/**4**) by ESI/MS analysis of the corresponding back reaction. The reversibility of the 1,3-dipolar cycloaddition of azomethine ylides (retro-Prato reaction)^{18–20} and the usefulness of ESI/MS in the study of the retrocycloaddition reactions of fullerene derivatives enable the use of reverse reaction screening by following the recent methodology reported by Pfaltz for the related retro-Diels–Alder reactions.²¹ This approach is based on the use of “an artificial racemate” formed by two mass labeled (pseudo)enantiomers with opposite absolute configuration and a slight mass difference in such a way that they behave as real enantiomers. Thus, the capacity to be transferred to the gas phase and the peak intensities for all the pseudo-enantiomeric species are assumed to be the same.^{17,21}

Thus, we have prepared a pseudoracemic mixture using equimolar amounts of 2-methoxycarbonyl-5-(4-methoxyphenyl)-pyrrolidino[60]fullerene **2a** with a *2R,5R* configuration (obtained with the complex *(R,R)*-BPE **4** and silver acetate) and its pseudoenantiomer 2-methoxycarbonyl-5-(4-propoxyphenyl)-pyrrolidino[60]fullerene **2f** with the opposite *2S,5S* configuration (this compound was prepared using copper-Fesulphos **3** as catalyst). Since the different substituents of **2a** and **2f** (the difference in the mass is 28 units) are located in a far *para* position, the same behavior is expected for both pseudo-enantiomers.

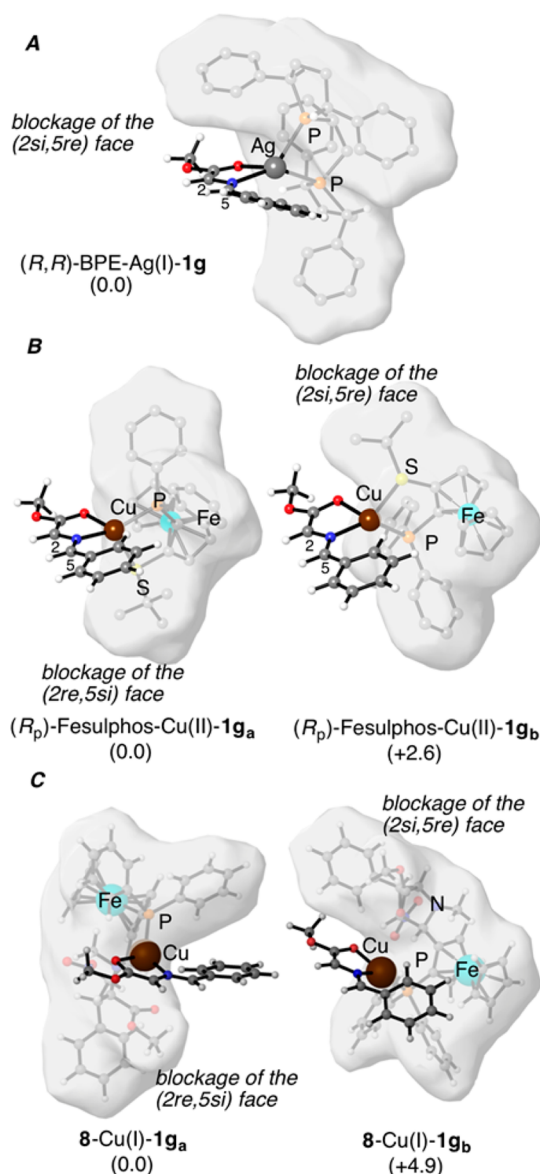


Figure 4. Main geometric features and relative energies (in kcal mol^{−1}) of azomethine ylides derived from imine **1g** and (A) *(R,R)*-BPE-Ag(I), (B) *(R_p)*-Fesulphos-Cu(II), or (C) **8**-Cu(I) catalytic systems computed at (A,C) M06/LANL2DZ//B3LYP/LANL2DZ + ZPVE or (B) UM06/LANL2DZ//UB3LYP/LANL2DZ + ZPVE. White surfaces represent the corresponding solvent accessible surface areas.

Thus, the pseudoracemic mixture, dissolved in toluene/ acetonitrile along with 20% of chiral ligand *(R,R)*-BPE **4** and silver acetate, was submitted to ESI-MS experiments at room temperature (Figure 2). This mass spectrum displayed peaks of low intensity both for the clusters at *m/z* 1556 and 1572 of different oxidized forms of **15a** ([**2a**+ (*R,R*)-BPE **4** + Ag + *nO*]⁺ and at *m/z* 1584 and 1600 for **15f** ([**2f**+ (*R,R*)-BPE **4** + Ag + *nO*]⁺), being these latter present in double amounts (see also SI).

The presence of two clusters, at *m/z* 817–819 and at *m/z* 845–847 corresponding to the loss of C₆₀ from **15a** and **15f**, respectively, could be justified only through a silver catalyzed retrocycloaddition process (the isotopic pattern also confirms the presence of silver in the cluster, see Figure 3).

Taking into account that the transition states for the forward and backward reactions are identical (principle of microscopic reversibility), the peaks intensity ratio encountered during the

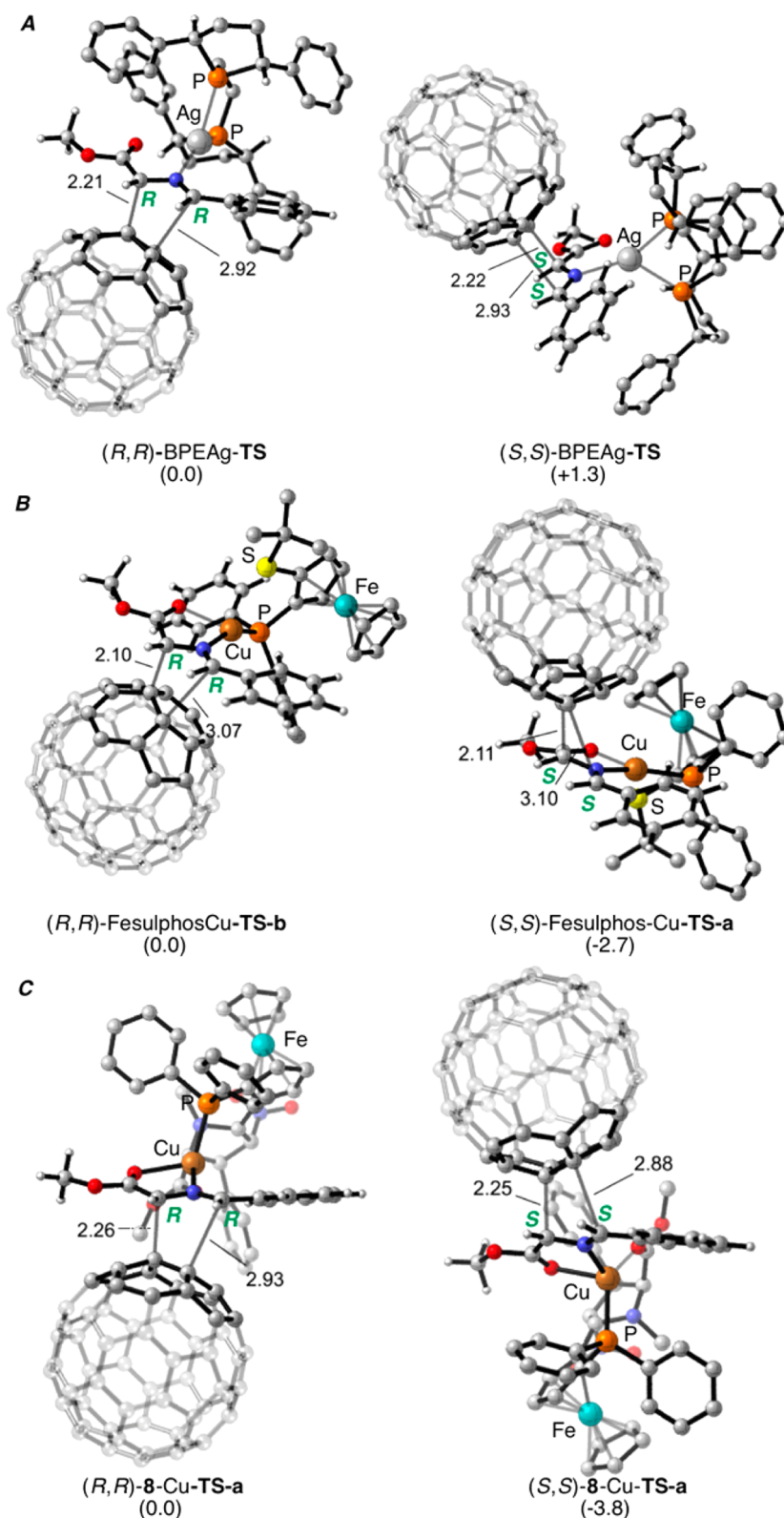


Figure 5. Main geometrical features and relative energies (in kcal mol⁻¹) of the transition structures associated with the first step of the reaction between C₆₀ and (A) (*R,R*)-BPE-Ag(I)-**1g**, (B) (*Rp*)-Fesulphos-Cu(II)-**1g**, or (C) **8-Cu**(I) metallic azomethine ylides computed at (A,C) M06/LANL2DZ//ONIOM(B3LYP/LANL2DZ:PM6) + ZPVE or (B) UM06/LANL2DZ//ONIOM(UB3LYP/LANL2DZ:UFF) + ZPVE levels of theory. Low-level atoms in the ONIOM partitions are shown as transparent ball and sticks representations. Bond lengths are given in Å. Selected hydrogen atoms of the ligands are omitted for clarity.

retrocycloaddition reflects the enantioselectivity of the catalyst (indeed we assume the same chemical behavior for **1a,f** and **2a,f** that differ only in the methoxy or propoxy *para* substituent).

Thus, as expected, silver/(*R,R*)-BPE **4** chiral complex that affords (*R,R*)-**2a** in the direct reaction with a enantiomeric ratio of 83:17 at room temperature (Figure 3 inset), displays the same

direction of enantioselectivity also for the back reaction. Thus, as appears in the different intensity of the peaks derived by loss of C_{60} (**16a** and **16f**, Figure 3a), silver/(*R,R*)-BPE **4** promotes a faster retrocycloaddition of **15a** (*R,R*) with respect to **15f** (*S,S*), albeit with a lower enantioselectivity (ESI/MS detects a 67/33 ratio for the peaks at 817 (**16a-H₂**) and 845 (**16f-H₂**)).

The same sense of enantioselectivity of the chiral complex $Ag^+/4$ in the retrocycloaddition reactions was confirmed also by the prevalent formation of **1a** with respect to **1f** in a ratio similar to that of the direct reaction. Indeed, the final products of the retrocycloadditions **1a** and **1f** have been found as homodimer and heterodimer along with catalyst **4** at m/z 935 ($2 \times 1a-H + (R,R)-4 + O$) and at m/z 963 ($1a + 1f-H + (R,R)-4 + O$), while the corresponding **1f** homodimer (m/z 991) is not observed. It is worthy to note that such retrocycloaddition products are not observed in the absence of silver, and therefore, they could only be formed through a metal catalyzed process.

Theoretical Calculations. In order to shed some light on the origins of the high stereocontrol obtained in the synthesis of pyrrolidino[60]fullerenes employing the aforementioned catalytic systems, DFT calculations have been performed on selected systems. Initially, geometry optimizations of the metalated azomethine ylides derived from imine **1g** and (*R,R*)-BPE **4**- $Ag(I)$, (*Rp*)-Fesulphos **3**- $Cu(II)$, or **8**- $Cu(I)$ catalytic systems were carried out (Figure 4).

Our calculations predict that only one conformation of the complexed azomethine ylide (*R,R*)-BPE- $Ag(I)$ -**1g** is energetically available. In this 1,3-dipole, the preferred tetrahedral environment around the silver atom generates an effective blockage of the (*2Si,5Re*) prochiral face. On the other hand, when a less constrained chiral ligand is employed, two possible azomethine ylides conformations are accessible (Figure 4B,C). Using both ligands (*Rp*)-Fesulphos **3**- $Cu(II)$ or **8**- $Cu(I)$, the **1g_a** conformation was found to be the most stable as a result of the stabilizing interaction between the carboxy group of the α -iminoester moiety and the Fe atom.²² The energy differences with respect to the alternative **1g_b** conformation are large enough (2.6 and 4.9 kcal mol⁻¹, respectively) to ensure that only **1g_a** conformations are relevant in the catalytic cycles associated with both catalytic systems. In the **1g_a** conformation, the catalytic system promotes the effective blockage of the (*2Re,5Si*) prochiral face (Figure 4B,C). As a consequence, (*R,R*)-BPE **4** catalytic system induces an opposite stereochemical outcome with respect to those obtained when (*Rp*)-Fesulphos- $Cu(II)$ or **8**- $Cu(I)$ were used.²³

We have also located all the stationary points associated with the 1,3-dipolar cycloaddition of the previously described metalated ylides and C_{60} by means of two layer ONIOM calculations (See SI). It is known that the reaction of the metal catalyzed 1,3-dipolar cycloaddition presents a stepwise mechanism, in which the first step is the responsible for the observed stereocontrol (see also Figures S26–28).²⁴ The main geometrical features and relative energies of the least energetic transition structures associated with the first step in the formation of pyrrolidino[60]fullerenes **2g** are gathered in Figure 5.

Our results show that (*R,R*)-BPE- $Ag(I)$, (*Rp*)-Fesulphos- $Cu(II)$ or **8**- $Cu(I)$ catalysts induce a critical effect on the stereochemical outcome of the obtained pyrrolidino[60]-fullerenes **2g**. When (*R,R*)-BPE- $Ag(I)$ is used as catalyst, (*R,R*)-BPE- Ag -TS is 1.3 kcal mol⁻¹ more stable than (*S,S*)-BPE- Ag -TS. This energy difference stems from in the effective blockage of the (*2Si,5Re*) prochiral face of the reactive metalated azomethine (*R,R*)-BPE- $Ag(I)$ -**1g** which results in a longer distortion

of (*S,S*)-BPE- Ag -TS (Figure 4). On the other hand, the stereocontrol observed when (*Rp*)-Fesulphos- $Cu(II)$ system is employed is the opposite one. In fact, (*R,R*)-Fesulphos- Cu -TS-**b** was found to be 2.7 kcal mol⁻¹ less stable than (*S,S*)-Fesulphos- Cu -TS-**a**. The same stereochemical outcome was obtained when **8**- $Cu(I)$ catalytic system was considered. In this latter case (*R,R*)-**8**- Cu -TS-**a** was found to be 2.6 kcal mol⁻¹ less stable than (*S,S*)-**8**- Cu -TS-**a**. Both results are consistent with the stereochemical outcome experimentally observed and predicted from the geometry of the respective starting azomethine ylide complexes.

It is interesting to note that in the case of densely functionalized ligand **8** the coordination patterns of $Cu(I)$ are quite different on going from the azomethine ylides to the possible transition structures. Thus, in the case of **8**- $Cu(I)$ -**1g_a** the $Cu(I)$ center interacts with the PPh₂ and N-Me groups of the chiral ligand as well as with the nitrogen atom and the carboxy group of the azomethine ylide. This structure is distorted in (*S,S*)-**8**- Cu -TS-**a**, for which the $Cu-N(Me)$ interaction is lost as a consequence of the approach of C_{60} along the less hindered (*2Si,5Re*) face. In addition, in this latter TS, the ferrocenyl moiety lies away from the methoxycarbonyl group in contrast with the geometry computed for **8**- $Cu(I)$ -**1g_b** (*vide supra*). These results indicate that the geometries of the transition structures of these catalyzed cycloadditions cannot be anticipated from the geometric features of the N-metalated azomethine ylides.

CONCLUSIONS

In summary, we report a fully stereodivergent methodology for the synthesis of chiral pyrrolidinofullerenes by the correct choice of a wide and easily available arsenal of chiral ligands, metals, and iminoesters or iminoamides. The complete control of the stereochemical outcome could be affected by the chirality of the dipole as revealed by experiments of double induction. ESI/MS experiments on a quasiracemic mixture showed a similar value of enantioselectivity and proved to be a suitable methodology for the screening of chiral catalysts for the azomethine cycloaddition onto fullerenes. Finally, DFT calculations shed light on the origin of the stereoselectivity displayed by the catalysts copper/**3**, silver/**4**, and copper/**8**. The experimental findings have been accounted for by the preferential attack of the fullerene as dienophile from the less hindered face of the previously formed metal complex.

ASSOCIATED CONTENT

Supporting Information

General methods, synthesis of starting materials, spectroscopical data and computational methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

nazmar@quim.ucm.es

fp.cossio@ehu.es

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is dedicated to Prof. Maurizio Prato on the occasion of his 60th birthday. Financial support by the Ministerio de Economía y Competitividad (MINECO) of Spain (projects CTQ2010-16959; Consolider-Ingenio CSD2007-00010), the CAM (MADRISOLAR-2 project S2009/PPQ-1533), and the

European Research Council ERC-2012-ADG_20120216 (Chirallcarbon) is acknowledged. The DIPC and the SGI/IZO-SGIker UPV/EHU are gratefully acknowledged for generous allocation of computational resources.

REFERENCES

- (1) (a) Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162. (b) Iijima, S. *Nature* **1991**, *354*, 56. (c) Novoselov, K. S.; Geim, A. K.; Morozov, S. V.; Jiang, D.; Zhang, Y.; Dubonos, S. V.; Grigorieva, I. V.; Firsov, A. A. *Science* **2004**, *306*, 666. (d) For a recent general review, see: Dirian, K.; Herranz, M. A.; Katsukis, G.; Malig, J.; Rodríguez-Pérez, L.; Romero-Nieto, C.; Strauss, V.; Martín, N.; Guldi, D. M. *Chem. Sci.* **2013**, *4*, 4335.
- (2) (a) Novello, F.; Prato, M.; Da Ros, T.; De Amici, M.; Bianco, A.; Toniolo, C.; Maggini, M. *Chem. Commun.* **1996**, 903. (b) Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villanai, C.; Prato, M. *J. Am. Chem. Soc.* **1996**, *118*, 4072. (c) Thilgen, C.; Gosse, I.; Diederich, F. *Top. Stereochem.* **2003**, *23*, 1. (d) Nishimura, T.; Tsuchiya, K.; Ohsawa, S.; Maeda, K.; Yashima, E.; Nakamura, Y.; Nishimura, J. *J. Am. Chem. Soc.* **2004**, *126*, 11711. (e) Thilgen, C.; Diederich, F. *Chem. Rev.* **2006**, *106*, 5049.
- (3) Hizume, Y.; Tashiro, K.; Charvet, R.; Yamamoto, Y.; Saeki, A.; Seki, S.; Aida, T. *J. Am. Chem. Soc.* **2010**, *132*, 6628.
- (4) Wang, Y.; Xu, J.; Wang, Y.; Chen, H. *Chem. Soc. Rev.* **2013**, *42*, 2930.
- (5) (a) Filippone, S.; Maroto, E. E.; Martín-Domenech, A.; Suárez, M.; Martín, N. *Nat. Chem.* **2009**, *1*, 578. (b) Nambo, M.; Wakamiya, A.; Itami, K. *Chem. Sci.* **2012**, *3*, 3474.
- (6) Maroto, E. E.; de Cózar, A.; Filippone, S.; Martín-Domenech, Á.; Suárez, M.; Cossio, F. P.; Martín, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6060.
- (7) Sawai, K.; Takano, Y.; Izquierdo, M.; Filippone, S.; Martín, N.; Slanina, Z.; Mizorogi, N.; Waelchli, M.; Tsuchiya, T.; Akasaka, T.; Nagase, S. *J. Am. Chem. Soc.* **2011**, *133*, 17746.
- (8) Marco-Martínez, J.; Marcos, V.; Reboredo, S.; Filippone, S.; Martín, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5115.
- (9) Maroto, E. E.; Filippone, S.; Martín-Domenech, A.; Suárez, M.; Martín, N. *J. Am. Chem. Soc.* **2012**, *134*, 12936.
- (10) Conde, E.; Bello, D.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossio, F. P. *Chem. Sci.* **2012**, *3*, 1486.
- (11) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.
- (12) (a) Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2012**, 48, 2149. (b) For a recent review, see: Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, 47, 6784.
- (13) (a) Eberlin, M. *Eur. J. Mass Spectrom.* **2007**, *13*, 19. (b) Schröder, D. *Acc. Chem. Res.* **2012**, *45*, 1521.
- (14) Delgado, J. L.; Filippone, S.; Martín-Domenech, Á.; Altable, M.; Maroto, E.; Langa, F.; Martín, N.; Martínez-Álvarez, R. *J. Am. Soc. Mass Spectrom.* **2011**, *22*, 557.
- (15) Maroto, E.; Filippone, S.; Martín-Domenech, Á.; Suárez, M.; Martín, N.; Martínez-Álvarez, R. *J. Mass Spectrom.* **2011**, *46*, 1016.
- (16) Martín, N.; Altable, M.; Filippone, S.; Martín-Domenech, Á.; Martínez-Álvarez, R.; Suárez, M.; Plonska-Brzezinska, M. E.; Lukoyanova, O.; Echegoyen, L. *J. Org. Chem.* **2007**, *72*, 3840.
- (17) Muller, C. A.; Markert, C.; Teichert, A. M.; Pfaltz, A. *Chem. Commun.* **2009**, 45, 1607.
- (18) Martín, N.; Altable, M.; Filippone, S.; Martín-Domenech, Á.; Echegoyen, L.; Cardona, C. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 110.
- (19) Lukoyanova, O.; Cardona, C. M.; Altable, M.; Filippone, S.; Martín Domenech, Á.; Martín, N.; Echegoyen, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7430.
- (20) Filippone, S.; Barroso, M. I.; Martín-Domenech, Á.; Osuna, S.; Solà, M.; Martín, N. *Chem.—Eur. J.* **2008**, *14*, 5198.
- (21) Teichert, A.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3360.
- (22) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossio, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587.
- (23) de Cózar, A.; Cossio, F. P. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858.
- (24) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2903.