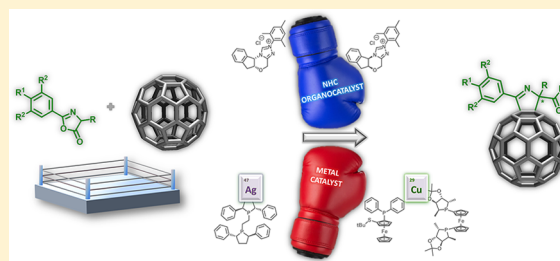


Enantioselective Cycloaddition of Münchnones onto [60]Fullerene: Organocatalysis versus Metal Catalysis

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S Supporting Information

ABSTRACT: Novel chiral catalytic systems based on both organic compounds and metal salts have been developed for the enantioselective [3 + 2] cycloaddition of münchnones onto fullerenes and olefins. These two different approaches proved to be efficient and complementary in the synthesis of optically active pyrrolino[3,4:1,2][60]fullerenes with high levels of enantiomeric excess and moderate to good conversions. Further functionalization of the pyrrolinofullerene carboxylic acid derivatives has been carried out by esterification and amidation reactions.



INTRODUCTION

Chirality in fullerenes and related carbon nanostructures is currently a challenging topic of interest for the design and application of these new optically active compounds in fields such as medicinal chemistry or materials science.¹ Particularly, in the latter field, where fullerenes find the most promising applications, chirality has recently proved to play a critical role in the control of some physical properties.² On the other hand, the unavailability of asymmetric synthesis in fullerene science has strongly limited the use of chiral fullerene derivatives and, therefore, the development of chiral carbon nanostructures with enhanced properties. A major breakthrough has been the introduction of asymmetric metal-catalyzed processes to prepare optically pure [60] and [70]fullerene derivatives by cycloaddition reaction of azomethine ylides onto hollow fullerenes^{3,4} as well as onto metallofullerenes⁵ with a full control of the stereochemical outcome. Furthermore, more recently, organocatalytic methods have been applied for the first time in fullerene science affording chiral [60]fullerene derivatives by a convergent cycloaddition of allenates onto C₆₀.⁶

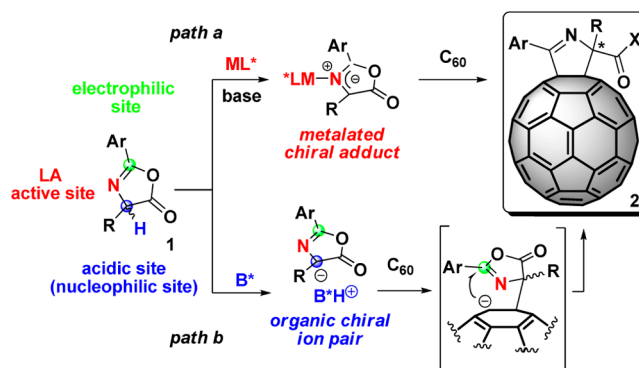
Despite the aforementioned achievements, the difficult activation and the even more difficult asymmetric induction of all-carbon cages make the introduction of chirality onto fullerenes still a challenging and profitable task. Indeed, the absence of functional groups and the non-coordinating polyolefin nature of fullerenes prevent both the use of metal-mediated processes and the employ of chiral organic molecules to activate the fullerene double bonds.

On the other hand, what is a drawback in the chiral functionalization of fullerenes turns into a very useful setting for the evaluation “*a priori*” of the employed catalyst, regardless of the olefin system used. Thus, the efficiency, the sense of the asymmetric induction, or, in general, the stereochemical outcome for a chiral metal- or organocatalyst could be benchmarked

by fullerenes thanks to their neutral behavior toward the catalyst in nucleophilic addition reactions. An illustrative example of this use of fullerenes has recently been reported by our group.^{3b}

Thus, in the search for new optically active fullerene derivatives as well as for new chiral induction modes onto non-activated double bonds such as those of fullerenes, we turned our attention onto oxazol-5-(4H)-ones (oxazolones or azlactones). These substrates featuring different reactive sites (acidic, electrophilic, or Lewis acid active site) allow a versatile chemistry⁷ and a potentially diverse chiral induction using both metal catalysts⁸ and organocatalysts (Scheme 1).⁹

Scheme 1. General Strategies for the Catalytic Asymmetric Synthesis of Pyrrolino[3,4:1,2][60]fullerenes



Particularly, oxazolones are known to efficiently react as 1,3-dipoles (the so-called münchnones) with alkenes under Lewis acidic conditions. A diastereoselective silver-mediated reaction

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and an enantioselective gold-catalyzed synthesis, reported by Tepe¹⁰ and Toste,¹¹ respectively, are the sole stereoselective examples reported so far for the preparation of Δ^1 -pyrrolines. These nitrogen-containing heterocyclic systems are extensively found in nature as biosynthetic intermediates and as part of pheromones, alkaloids, steroids, hemes, and chlorophylls.¹²

Recently, the first organocatalytic [3 + 2] cycloaddition of münchnones to a double bond was achieved by the employment of a bifunctional catalyst endowed with a basic site (chiral amine) and thiourea moiety able to activate the double bond. However, these results were limited to the highly activated dipolarophiles methyleneindolinones.¹³

Herein, we report two different asymmetric activations of azlactones (Scheme 1), able to induce a cycloaddition to the “singular” fullerene dipolarophile affording optically active pyrrolino[3,4:1,2][60]fullerenes, a new class of chiral fullerene derivatives. For the first time, catalysts based on nonprecious metals¹⁴ and on an organocatalytic methodology are described and evaluated onto fullerenes as well as conventional double bonds.

RESULTS AND DISCUSSION

Screening of Chiral Organic Catalysts. As none of the organocatalytic activation modes known so far¹⁵ enable the asymmetric activation of fullerenes double bonds, the organocatalytic chiral induction on these all-carbon compounds has to be necessarily introduced through the partner starting material. Thus, thanks to the presence of a highly acidic proton in the oxazolone ring, we guessed the use of a chiral base could be a suitable method to trigger the enantioselective cycloaddition onto [60]fullerene.

On the other hand, since base-catalyzed reactions of azlactones with electron-poor olefins give rise to nucleophilic addition with different regioselectivity at C-2 or C-4 carbon atom,¹⁶ we started to verify the feasibility of the [3 + 2] cycloaddition onto [60]fullerene by the use of a common base. Thus, Et₃N promoted the [3 + 2] cycloaddition of azlactone **1a** to [60]fullerene affording a 5-carboxypyrroline (26% conversion). The different chemoselectivity with respect to other olefins, and therefore the pyrroline formation, is probably due to the high electron-withdrawing nature of fullerene. Thus, after the nucleophilic addition of the azlactone, the stability of the fullerene anion allows the further cyclization by nucleophilic attack on the C-2 followed by ring-opening of the oxazolone ring (Scheme 1, path b). The efficiency of this reaction as well as the stereoselectivity of the chiral catalysts screened were evaluated through the easily isolated and stable *N*-acyl urea derivative **2a** that results from a typical rearrangement of carbodiimides.¹⁷

Based on the previous organocatalytic reports of [3 + 2] cycloaddition of iminoesters onto different activated double bonds,¹⁸ we decided to start our screening focusing on the noncovalent catalysis, in particular, in cinchona alkaloid derivatives¹⁶ for their easy availability and their excellent results in a large number of stereoselective nucleophilic additions to activated double bonds.

Despite the ability of organic bases to promote such cycloaddition was confirmed, catalysts **3a–d** and **4a,b**, featuring one or two quinuclidine skeletons, respectively, were unable to afford any significant enantiomeric excesses of pyrrolino[60]-fullerene **2a** (Figure 1).

The thioureas **5a–c** and squaramide **6** are also bifunctional catalysts featuring a chiral base and a thiourea moiety very similar to the catalysts used for the cycloaddition of azlactones

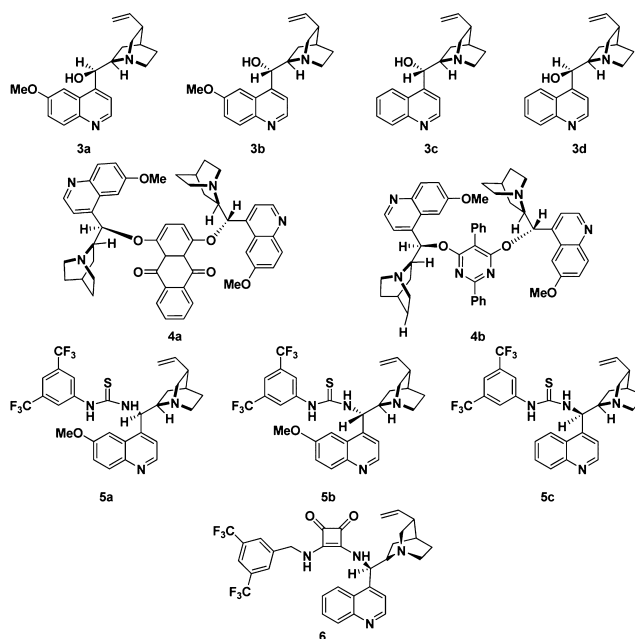


Figure 1. Cinchona-type catalysts tested for the organocatalytic [3 + 2]-cycloaddition of münchnones onto [60]fullerene.

onto methyleneindolinone (Figure 1).¹³ However, and not surprisingly, they did not display any enantioselectivity. Indeed, these catalysts can only activate azlactones by means of the nitrogen base, while the LUMO activation by hydrogen bond with thiourea does not take place in fullerenes.

The use of phase transfer catalysts **7a–h** (PTC, Figure 2) in toluene/basic water achieved the formation of no racemic

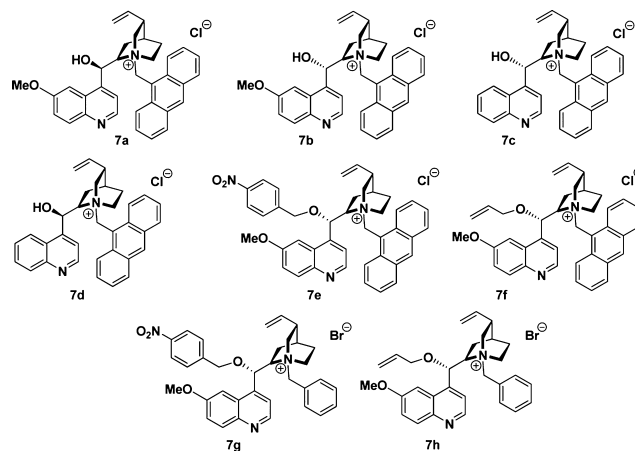


Figure 2. PTCs tested for the organocatalytic [3 + 2] cycloaddition of münchnones onto [60]fullerene.

mixtures of **2a**. However, the enantioselectivities obtained were poor even at low temperature, once again in contrast to that previously reported in the literature.¹⁹

Finally, we turn our attention into chiral *N*-heterocyclic carbenes (NHCs). These compounds have been widely employed as ligands in metal catalysis,²⁰ while more recently have experienced a great interest in organocatalysis.²¹ In this regard, NHCs have been used as Brønsted base catalysts capable to generate alkoxides and enolates in transesterification reactions²² or Claisen condensations,²³ respectively. With this in mind, we tested several commercially available chiral

triazolium salts (8–11) as NHC precursors by reaction with 10 equiv of NaH in anhydrous toluene (Figure 3 and Table 1).

Under these reaction conditions, we were able to isolate the desirable adduct **2a** in variable conversions (Table 1, entries 1–4) but in excellent enantiomeric excess (ee) when 1 equiv of the triazolium salt **8a** was used (entry 1). Several bases with variable

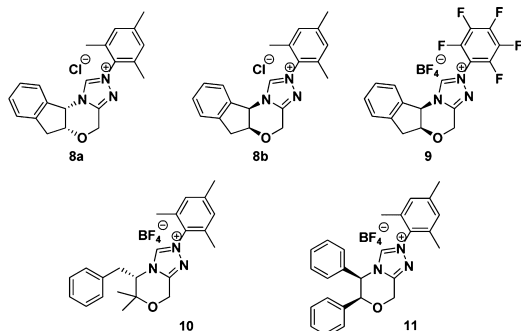


Figure 3. NHCs tested for the organocatalytic [3 + 2] cycloaddition of münchnones onto [60]fullerene.

Table 1. Screening of NHCs in the Cycloaddition of Azlactone **1a** with [60]Fullerene^a

entry	NHC	base (equiv)	solvent	T (°C)	conv. ^b (%)	ee ^b (%) product ^c
1	8a	NaH (10)	toluene	rt	>99	88 (S)- 2a
2	9	NaH (10)	toluene	rt	10	16 (S)- 2a
3	10	NaH (10)	toluene	rt	98	16 (R)- 2a
4	11	NaH (10)	toluene	rt	11	22 (R)- 2a
5	8a	KI (10)	toluene	rt	4	0
6	8a	Na ₂ CO ₃ (10)	toluene	rt	33	34 (S)- 2a
7	8a	NaHCO ₃ (10)	toluene	rt	37	4 (S)- 2a
8	8a	KHDMS (10)	toluene	rt	—	—
9	8a	DBU (10)	toluene	rt	—	—
10	8a	KOH (10)	toluene	rt	96	74 (S)- 2a
11	8a	NaH (1)	toluene	rt	98	72 (S)- 2a
12	8a	NaH (5)	toluene	rt	45	72 (S)- 2a
13	8a	NaH (100)	toluene	rt	78	76 (S)- 2a
14	8a	NaH (1000)	toluene	rt	37	80 (S)- 2a
15	8a	NaH (10)	CS ₂	rt	—	—
16	8a	NaH (10)	CH ₃ CN	rt	—	—
17	8a	NaH (10)	<i>o</i> -DCB	rt	89	68 (S)- 2a
18	8a	NaH (10)	PhCl	rt	85	36 (S)- 2a
19	8a	NaH (10)	toluene	0	8	84 (S)- 2a
20	8a	NaH (10)	toluene	−30	10	34 (S)- 2a
21	8a	NaH (10)	toluene	50	>99	54 (S)- 2a
22	8b	NaH (10)	toluene	rt	99	84 (R)- 2a
23 ^d	8a	NaH (10)	toluene	rt	28	64 (S)- 2a

^aGeneral reaction conditions: A mixture of the triazolium salt (NHC, 1 equiv), [60]fullerene (1 equiv), and the base (10 equiv) in 1 mL of solvent is stirred for 10 min at rt, then 0.016 mmol of azlactone **1a** (2 equiv) is added. After 30 min of reaction, excess of DCC is added.
^bConversion and ee have been determined by HPLC analysis.
^cAbsolute configuration has been assigned on the base of CD measurements.
^d10 mol % of **8a** is used.

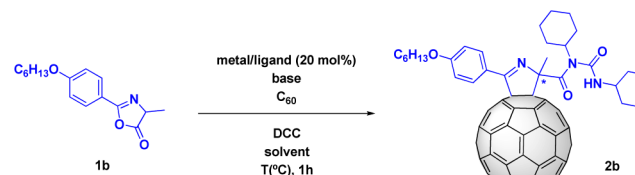
basicity were evaluated (entries 5–10) demonstrating that stronger bases such as KOH (entry 10) worked better in terms of conversion and enantioselectivity than weaker ones like Na₂CO₃ (entry 6). However, when DBU, widely used with this type of NHCs, was employed, the reaction did not take place (entry 9). The quantity of base was also studied in the reaction (entries 11–14), and we could observe that the optimal enantioselectivity was achieved with 10 equiv of NaH. Afterward, the solvent study revealed a preference for toluene (entries 15–18). In addition, and with the aim of finding the better conditions for an efficient enantioselective cycloaddition, we also screened the temperature of the process; nevertheless, neither the lower temperatures (entries 19–20) nor the higher ones (entry 21) improved the previous obtained results. Fortunately, we were also able to isolate the corresponding enantiomer of pyrrolinofullerene **2a** by using the commercially available NHC opposite enantiomer **8b** with also high ee and conversion values (entry 22). Finally, the catalytic version of the process has also been tested (10 mol %), giving rise to a decrease in the conversion as well as in the enantioselectivity (entry 23).

Therefore, after many attempts, we eventually succeeded in inducing and controlling the chirality on [60]fullerene derivatives by using an NHC-organocatalyst. It is worth noting that the process takes place without the previous activation of the dipolarophile under mild reaction conditions and with moderate to good levels of conversion and enantioselectivity.

Screening of Chiral Metal–Ligand Complexes. In the search for an alternative methodology for the asymmetric synthesis of pyrrolinofullerenes, we explored the combination of non precious metals with easily available chiral phosphines.

Racemic (±)-BINAP along with silver acetate salt was found efficient to afford, after *N,N'*-dicyclohexylcarbodiimide (DCC) addition, the racemic mixture of 5-carbamoyl pyrrolino[3,4:1,2] [60]fullerene derivative **2b** in moderate conversion (45%) (entry 1, Table 2). As (*R*)-BINAP afforded poor ee values (20%) (see Supporting Information), we decided to use those chiral metal complexes that previously gave us better results in the cycloaddition of iminoesters to fullerenes.³ Thus, chiral complex AgOAc/(*R,R*)-BPE (**12**) induced the cycloaddition of the azlactone **1b** with good conversion but with a modest 50% ee (entry 2, Table 2). On the other hand, Cu(OAc)₂, while gave rise to poor conversion and ee with (*R*)-FeSulPhos (**13**), proved to be a suitable metal for this transformation (entry 3, Table 2). Neither the complex (*R*)-DTBM-SegPhos-gold benzoate was able to reproduce the same high enantioselective level reported previously.¹¹ Thus, the cycloaddition occurs in high conversion though only 40% of ee was achieved (entry 4, Table 2). This result is probably due to the no coordinating nature of [60]fullerene that needs different conditions to those used for typical electron poor coordinating olefins. However, it is noteworthy that the absolute configuration of the new chiral center (*S*) in **2b**, inferred by CD spectra, is the same as the nonfullerene analogue obtained with the same catalyst,¹¹ and it is consistent with an electrophilic attack of the [60]fullerene to the *Re* face of the münchnone.

The next step was to skip from the acetate to a less coordinating no basic counterion in an attempt to obtain a tighter interaction between metals and the monodentate azlactone. In sharp contrast to what happened in the cycloaddition of the iminoesters,³ the use of SbF₆[−] as counterion of the complex silver-(*R,R*)-BPE (**12**) along with Et₃N as a base, afforded pyrroline **2a** with 87% ee (entry 5, Table 2). This behavior was also observed when we employed the pair (*R*)-FeSulPhos (**13**)-Cu(I) but using

Table 2. Metal-Catalyzed 1,3-Dipolar Cycloaddition of Azlactone **1b** with [60]Fullerene^a


entry	metal salt/ligand	solvent (base)	T (°C)	conv. ^b (%)	ee ^b (%) product ^c
1	AgOAc/(±)-BINAP	toluene (/)	25	45	—
2	AgOAc/(<i>R,R</i>)-BPE	toluene (/)	0	88	50 (<i>S</i>)- 2b
3	Cu(OAc) ₂ /(<i>R</i>)-FeSulPhos	toluene (/)	25	23	5 (<i>R</i>)- 2b
4	(<i>R</i>)-DTBM-SegPhos(AuOBz) ₂	PhF/THF (/)	−30	95	40 (<i>S</i>)- 2b
5	AgSbF ₆ /(<i>R,R</i>)-BPE	PhF (Et ₃ N)	0	33	87 (<i>S</i>)- 2b
6	Cu ^I (OTf) ^d /(<i>R</i>)-FeSulPhos	PhCl (Et ₃ N)	25	25	70 (<i>R</i>)- 2b
7	Cu ^I (OTf) ^d /(<i>S</i>)-Me- <i>f</i> -KetalPhos	PhCl (Et ₃ N)	0	25	90 (<i>S</i>)- 2b

^aGeneral reaction conditions: A mixture of 0.01 mmol azlactone **1b**, [60]fullerene (1 equiv), metal salt (20 mol%), ligand (20 mol%), and base (1 equiv) in 1.5–2 mL of indicated solvent is stirred for one hour at indicated temperature, then excess of DCC is added. ^bConversion and ee have been determined by HPLC analysis. ^cAbsolute configuration has been assigned on the base of CD measurements. ^dCu^I(OTf)-benzene complex.

triflate instead of acetate and Et₃N as base. Similarly to the azomethine ylides addition onto [60]fullerene, this chiral ligand gave rise to the opposite pyrroline enantiomer with 25% conversion and −70% ee (entry 6, Table 2). The enantioselectivity was found higher by using (*S*)-Me-*f*-KetalPhos (**14**) as chiral ligand of Cu(I)triflate-benzene complex since the pyrroline **2b** is formed with 25% conversion and 90% ee (entry 7, Table 2). It is worthy to note that these results represent the first example of enantioselective cycloaddition of münchnones catalyzed by a copper salt (Figure 4).

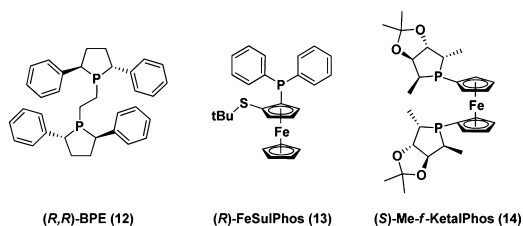


Figure 4. Chiral ligands: (*R,R*)-BPE ((−)-1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane), (**12**), (*R*)-FeSulPhos ((*R*)-2-(*tert*-butylthio)-1-(diphenylphosphino)ferrocene), (**13**), (*S*)-Me-*f*-KetalPhos (1,1-bis[(2*S*,3*S*,4*S*,5*S*)-2,5-dimethyl-3,4-*O*-isopropylidene-3,4-dihydroxyphosphanyl]-ferrocene), (**14**).

Scope of the Catalytic Processes with Different Oxazolones. Once optimized the conditions for the organocatalytic and for the metal-catalyzed [3 + 2] cycloaddition of oxazolones onto [60]fullerene, we studied the scope of the reaction. The different oxazolones used were prepared from amino acids such as glycine, alanine, and phenylalanine and benzoic acid or derivatives endowed with one or three hydrocarbon chains. The results obtained for both methodologies, using different azlactones **1a–j** as 1,3-dipoles are shown in Table 3.

In general, metal-based chiral catalysts gave rise to the desired pyrrolinofullerene derivatives **2a–j** with moderate to good conversions and high enantiomeric excesses. The asymmetric induction sense is fully controlled by suitable choice of the metal complex, and enantioselectivity is unaffected, or little influenced, by the substitution of the starting oxazolone.

Thus, azlactones **1a**, **1b**, or **1i** lead to the formation of **2a**, **2b**, and **2i** with high enantioselectivities both with silver or copper

chiral complexes (entries 1, 2, and 9, Table 3). Furthermore, excellent enantiomeric excesses were observed for the pyrrolinofullerenes **2b** and **2c** (90% and 96%, entries 2 and 3, Table 3) with Cu^I(OTf)-benzene complex/(*S*)-Me-*f*-KetalPhos (**14**)/Et₃N for the (*S*)-**2** products. It is worth mentioning that in the latter case, the presence of three large alkoxy chains in the aromatic moiety of **2c** provided enough solubility to allow the direct isolation of the free carboxylic acid pyrrolinofullerene derivative without the need of using DCC for the further esterification (see SI).

When Cu^I(OTf)-benzene complex/(*S*)-Me-*f*-KetalPhos (**14**)/Et₃N system is employed, the enantioselectivity of cycloaddition of azlactone **1d**, endowed with a more hindered benzyl group, onto [60]fullerene is still high with 88% of ee (entry 4, Table 3). The complex silver-(*R,R*)-BPE (**12**) gave rise to slightly lower enantioselectivity (68%). Interestingly, its chiral induction sense resulted substrate dependent, and it reverted when the phenylalanine-substituted azlactone **1d** was used (entry 4, Table 3). Thus, such cycloaddition afforded the opposite enantiomer of pyrroline **2d**.

Azlactones based on glycine, **1e,f**, showed moderate conversions probably due to a less stability of the final products (also the trapping of the more acidic second proton affords side products and/or racemization processes).

Moreover, the pair Cu^I(OTf)-benzene complex/(*R*)-FeSulPhos (**13**) leads always to the (*R*)-**2** products. In the case of pyrrolinofullerene **2g**, this copper system with (*R*)-FeSulPhos (**13**) performed even better in terms of ee than (*S*)-Me-*f*-KetalPhos (**14**), 96% (*R*-**2g**) vs 90% (*S*-**2g**), respectively (entry 7, Table 3). Therefore, copper chiral systems allow the efficient switching on the enantioselectivity of the formed pyrrolino[3,4:1,2][60]fullerenes and with better conversion and ee values than the silver chiral system.

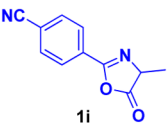
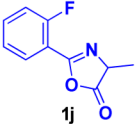
Finally, different substitution on the aryl ring of the oxazolone with donating or electron-withdrawing groups did not modify the behavior of these substrates. Thus, products **2h–j** were obtained with excellent ee values (82–94%) when Cu^I(OTf)-benzene complex/(*S*)-Me-*f*-KetalPhos (**14**)/Et₃N system was employed (entries 8–10, Table 3).

On the other hand, organocatalysis also provides good to excellent conversion and enantiomeric excesses. However, better results on enantioselectivity were obtained for less hindered

Table 3. Scope of the Enantioselective 1,3-Dipolar Cycloaddition of Azlactones 1a–j with [60]Fullerene

Entry	Oxazolone	Organocatalysis ^a			Product ^d	Metal-catalysis ^b			Product ^d
		Triazolium salt NHC	conv. ^c (%)	ee ^c (%)		Metal salt/ligand	conv. ^c (%)	ee ^c (%)	
1		8a	99	88	(S)-2a	Cu ^I (OTf) ^e /(13)	54	80	(R)-2a
		8b	99	84	(R)-2a	Cu ^I (OTf) ^e /(14)	70	88	(S)-2a
						AgSbF ₆ /(12)	17	84	
2		8a	63	53	(S)-2b	Cu ^I (OTf) ^e /(14)	25	90	(S)-2b
						AgSbF ₆ /(12)	33	86	
3		8a	-	-	(S)-2c	Cu ^I (OTf) ^e /(14)	50	96	(S)-2c
4		8a	23	46	(S)-2d	Cu ^I (OTf) ^e /(14)	68	88	(S)-2d
						Cu ^I (OTf) ^e /(13)	68	74	(R)-2d
						AgSbF ₆ /(12)	48	68	
5		8a	-	-	(S)-2e	Cu ^I (OTf) ^e /(14)	10	62	(S)-2e
6		8a	-	-	(S)-2f	Cu ^I (OTf) ^e /(14)	14	88	(S)-2f
7		8a	96	28	(S)-2g	Cu ^I (OTf) ^e /(13)	57	96	(R)-2g
						Cu ^I (OTf) ^e /(14)	75	90	(S)-2g
						AgSbF ₆ /(12)	29	66	
8		8a	>99	84	(S)-2h	Cu ^I (OTf) ^e /(13)	23	60	(R)-2h
		8b	93	74	(R)-2h	Cu ^I (OTf) ^e /(14)	20	82	(S)-2h
						AgSbF ₆ /(12)	46	70	

Table 3. continued

9		8a	69	66	(S)-2i	Cu ^I (OTf) ^c /(13)	39	86	(R)-2i
		8b	81	44	(R)-2i	Cu ^I (OTf) ^c /(14)	25	88	(S)-2i
						AgSbF ₆ /(12)	27	82	
10		8a	>99	88	(S)-2j	Cu ^I (OTf) ^c /(13)	28	16	(R)-2j
		8b	96	78	(R)-2j	Cu ^I (OTf) ^c /(14)	83	94	(S)-2j
						AgSbF ₆ /(12)	54	66	

^aGeneral reaction conditions: A mixture of the triazolium salt (1 equiv), [60]fullerene (1 equiv), and the base (10 equiv) in 1 mL of solvent is stirred for 10 min at rt, then 0.016 mmol of azlactone **1a–j** (2 equiv) is added. After 30 min reaction, excess of DCC is added. ^bGeneral reaction conditions: A mixture of 0.01 mmol azlactone **1a–j**, [60]fullerene (1 equiv), metal salt (20 mol%), ligand (20 mol%), and Et₃N (1 equiv) in 1.5 mL of chlorobenzene is stirred for 1 h at 0 °C, then excess of DCC is added. ^cConversion and ee have been determined by HPLC analysis. Isolated yields have only been determined for the racemic mixture (see SI). As a general trend, higher conversions correspond to higher yields. ^dAbsolute configuration has been assigned on the base of CD measurements. ^eCu^I(OTf)-benzene complex.

oxazolones such as **1a**, **1h**, or **1j**, in which also an efficient switching on the enantioselectivity is achieved depending on the triazolium salt-NHC used (84–88% ee with **8a** and 74–84% ee with **8b**; entries 1, 8 and 10, Table 3). Unfortunately, this methodology seems to be much more substrate dependent than the metallic one (see, for instance, entries 4 or 7, Table 3). All in all, milder reaction conditions and higher conversion values make the organocatalytic methodology an efficient tool for the synthesis of this kind of fullerene derivatives in larger amounts.

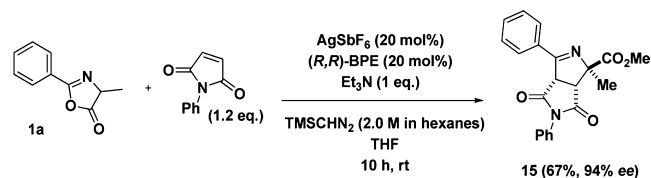
In summary, the aforementioned results reveal that the metal-catalyzed and the organocatalytic procedures have a different behavior depending upon the substitution pattern. Thus, whereas the metal-catalyzed procedure afforded better enantioselectivities with a larger scope of oxazolones, the organocatalytic methodology showed the best enantiocontrol with less hindered oxazolones and with better conversion values. Therefore, we can conclude that both methodologies nicely complement to each other in the synthesis of new enantiopure pyrrolinofullerene derivatives.

[3 + 2] Cycloaddition onto *N*-phenylmaleimide. The efforts to promote the 1,3-dipolar cycloaddition reaction onto nonfullerene olefins by using NHC methodology were unsuccessful. Thus, analogously to other previous described organic catalyst,^{7b,24} it promoted a Michael addition but with poor or no stereoselectivity.

On the other hand, we have demonstrated that silver-based chiral catalyst is able to trigger efficiently the cycloaddition onto nonfullerene alkenes. Thus, catalytic system AgSbF₆/(*R,R*)-BPE (12)/Et₃N induced the addition of the azlactone **1a** onto *N*-phenylmaleimide as dipolarophile with high ee (94%, 97:3) for the *exo* adduct (**15**) after 10 h at rt and treatment with (trimethylsilyl)diazomethane solution (TMSCHN₂, 2.0 M in hexanes) with 67% yield (Scheme 2).

Moreover, controlled formation of pyrrolino[3,4:1,2][60]-fullerene carboxylic acid derivatives allows new and straightforward ways for the further functionalization of the [60]fullerene. In contrast to the pyrrolidino[3,4:1,2][60]fullerenes, which undergo retrocycloaddition processes, pyrrolino[3,4:1,2][60]-fullerenes are more stable and could be functionalized either on the imino double bond or the carboxylic acid moiety. Thus,

Scheme 2. Silver-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition of Azlactone **1a** with Nonfullerene Alkenes



when the reaction crude from azlactone **1b** (entry 1, Table 2) is reacted with MeOH (under acidic conditions), resulting pyrrolinofullerene is esterified affording **16**. In the same way, treatment with glycine methyl ester hydrochloride leads to **17** in an amidation reaction (Figure 5, for experimental details see SI).

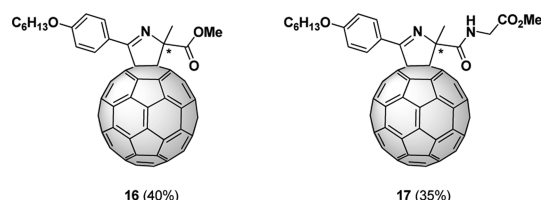


Figure 5. Ester (**16**) and amido (**17**) functionalized pyrrolino[3,4:1,2]-[60]fullerenes.

As expected, both enantiomers of all pyrrolinofullerenes gave rise to mirror pairs of circular dichroism (CD) spectra characterized by a strong Cotton effect at around 430 nm (Figure 6). This peak, which is associated to the UV–vis band typical of all fullerene monoadducts, has been used as an empirical way to assign the absolute configuration of chiral fullerene derivatives.²⁵ According to the corrected sector rule,⁶ since all pyrrolinofullerenes formed by Cu^I(OTf)-benzene complex/(14) and AgSbF₆/(12) (except **2d**) feature a negative Cotton effect (red line, Figure 6 and SI), an *S* configuration in the C-5 of the heterocyclic ring is assigned. Instead an *R* configuration could be assigned to the derivative stemming from the use of Cu^I(OTf)-benzene complex/(13) catalyst (see SI).

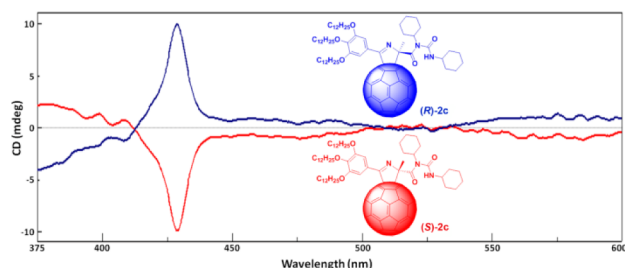


Figure 6. CD spectra for both enantiomers of **2c** (concentration, 4×10^{-4} M in dichloromethane).²⁶

CONCLUSIONS

In summary, we describe two complementary enantioselective synthetic methods to obtain new, stable, and versatile pyrrolino[60]fullerene derivatives with good enantiomeric excesses. For the first time, and in sharp contrast to conventional olefins, we have described an organocatalytic methodology able to promote [3 + 2]cycloaddition of azlactones onto [60]fullerene. This represents the first organocatalytic example where the oxazolones are used as 1,3-dipoles with fullerenes.

[60]Fullerene has also been successfully used as a benchmark to develop novel chiral catalytic systems based, for the first time, on silver and copper salts able to promote the enantioselective cycloaddition of münchnones both on [60]fullerene and *N*-phenylmaleimide. Furthermore, this new synthetic approach to enantiomerically pure fullerene derivatives affords *in situ* preparation of compounds endowed with different chemical functionality, thus enhancing the scope and versatility of these new compounds.

The aforementioned results pave the way for the application of fullerenes in fields where chirality is a key issue such as in biomedical applications as well as in the thus far less explored materials science, where chirality has recently been shown to impact some physical properties.²

ASSOCIATED CONTENT

Supporting Information

Experimental details for the preparation of the azlactones, pyrrolino[3,4:1,2][60]fullerenes, and functionalized derivatives; spectroscopic and chromatographic data for characterization of compounds and CD measurements. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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