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Double Transfer of Chirality in Organocopper-Mediated bis(Alkylating) Cycloisomerization of Enediynes**

Damien Campolo, Tanzeel Arif, Cyril Borie, Dominique Mouysset, Nicolas Vanthuyne, Jean-Valère Naubron, Michèle P. Bertrand, and Malek Nechab**

Dedicated to Prof. Max Malacria on the occasion of his 65th birthday

Abstract: *An original synthesis of chiral benzofulvenes triggered by organocopper reagents is reported. These enantiopure products are available through a highly chemo-, regio-, diastereo-, and enantioselective bis(alkylating) cycloisomerization process. A double chirality transfer (central-to-axial-to-central) is observed.*

The ever-growing interest in atom-economical reactions explains the popularity of cycloisomerization reactions. This generic term embraces a large variety of rearrangements of polyunsaturated substrates leading to cyclic or polycyclic frameworks.[1] The literature bears witness to the tremendous advances made in this field. More and more complex building blocks are now available from such processes. These reactions can be promoted by electrophilic activation by a wide range of π-philic transition-metal complexes which can be used either as catalytic or as stoichiometric reagents. Despite the prolific literature dedicated to this topic, there are very few reports where an organocopper reagent was used as reagent to trigger a cycloisomerization process.[2,3] Moreover, no example involving chirality transfer in copper-triggered cycloisomerizations has ever been reported so far.

An organocopper-mediated bis(alkylating) cycloisomerization of chiral enediynes, which proceeds with double chirality transfer from central-to-axial-to-central, is disclosed herein. Chirality transfer from one site to another refers to a process in which a new chiral element is created while the original chiral element is destroyed.[4,5]

[*] Dr. D. Campolo, Dr. T. Arif, C. Borie, Dr. D. Mouysset, Prof. M. P. Bertrand, Dr. M. Nechab
Aix-Marseille Université, CNRS, Institut de Chimie Radicalaire UMR7273, 13390 Marseille (France)
E-mail: michele.bertrand@univ-amu.fr
malek.nechab@univ-amu.fr
Dr. N. Vanthuyne
Aix-Marseille Université, CNRS, Institut des Sciences Moléculaires de Marseille UMR 7313, 13390 Marseille (France)
Dr. J.-V. Naubron
Spectropole
Fédération de Chimie Marseille (France)

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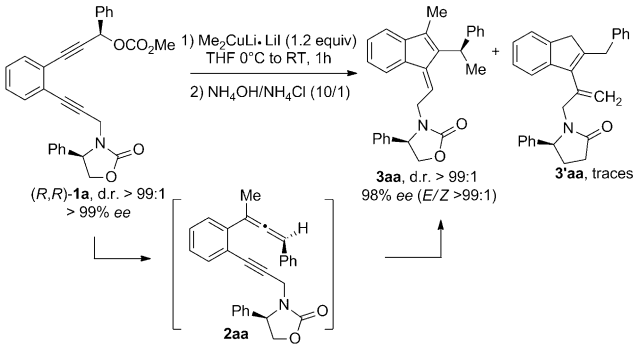
We have recently investigated memory of chirality in cascade rearrangements of chiral enediynes.[6] These reactions proceed with central-to-central chirality transfer. They are based on the multistep combination of in situ allene moiety formation, Saito–Myers cyclization, 1,5-hydrogen atom transfer, and radical recombination, which leads to polycyclic derivatives bearing one or two contiguous stereogenic centers. During the course of these rearrangements, the initial stereogenic center is trigonalized, but the key radical intermediate is generated in a transiently chiral conformation and is long-lived to ensure the memory of chirality during the transformation. The continuation of this work was to extend the process to axially chiral enyne-allenes (generated in situ from suitable enediynes) with the prospect of promoting axial-to-central chirality transfer in this polar/radical crossover cascade.

Among the methodologies available to prepare enantioenriched allenes, the standard laboratory methodology developed by Crabbé 45 years ago has seen a rapid expansion.[7] The S_N2' displacement of enantiopure propargyl carbonate (of type **1**; for structure see Scheme 1) by organocopper reagents offers numerous advantages such as high yields, efficient central-to-axial chirality transfer, and use of inexpensive and easily accessible starting materials.[8] The envisaged substrates were thus synthesized in three to four steps using Sonogashira coupling reactions from commercially available compounds.



Scheme 1. Cycloisomerization of (*R*,*R*)-**1a**.

When the enediyne (*R*,*R*)-**1a** was reacted with lithium dimethylcuprate,[9] the enyne-allene **2aa** was not isolated (Scheme 1). In the preliminary experiments, we were sur-

prised to not detect any of the products which would have resulted from **2aa** undergoing Saito–Myers or Schmittel cyclization.[10] Instead, the benzofulvene (*R*,*R*)-**3aa**, where two methyl groups were incorporated, was isolated together with trace amounts of **3′aa**. Much to our delight, (*R*,*R*)-**3aa** was formed as a single diastereomer, thus showing that a highly regio- and stereoselective bis(alkylating) cycloisomerization had been achieved. The *R*,*R* absolute configuration of **3aa** was demonstrated by VCD and ECD spectroscopies combined with DFT calculations (see the Supporting Information). The 98% *ee* of the product gave evidence that the tandem process occurred with a highly efficient transmission of the initial chiral information.[11] It is to be noted that, under optimized experimental conditions, (*S*,*S*)-**3aa** was isolated with 97% *ee* in 55% yield when starting from the enantiomeric *S*,*S* substrate. During the optimization studies it was observed that performing the reaction at room temperature in ether (or THF) gave the optimal yield. The screening of different experimental conditions is detailed in the Supporting Information.

Product (*R*,*R*)-**3aa** belongs to the class of fulvene derivatives, which constitute an important family of cross-conjugated olefins. The latter are attractive because their properties have found applications in important fields.[12–14] The availability of chiral fulvenes will open new prospects. The most common method used to access these frameworks is the condensation of cyclopentadienes onto carbonyl groups.[15] Other strategies, based on the above-cited Schmittel cyclization of hindered enediynes[16,17] or more recent metal-catalyzed procedures, have been developed.[18] No example of chiral fulvene formation through a cycloisomerization reaction has been reported to date.

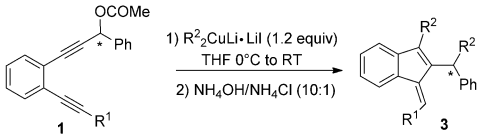
We then considered the incorporation of other alkyl groups as a variable in this cyclization. Dibutyl-, diisobutyl-, and dihexylcuprates were found to be efficient in triggering the cycloizomerization. The benzofulvenes **3ab**, **3ac**, and **3ad** were isolated in 51, 48, and 57% yield, respectively (entries 1-3, Table 1). A high level of diastereoselectivity (>95:5) was observed for each case. The applied bis(alkylating) cycloisomerization also proceeded with the organocuprate prepared from $TMSCH_2Li$. The diastereomeric ratio of the product was only 85:15 in this case (entry 4).

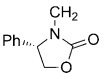
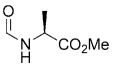
Because of its remoteness, the chiral auxiliary was unlikely to participate in the control of the chirality transfer. To confirm this assumption, we investigated the reactivity of the Gilman's reagent prepared from *n*-butyl lithium with respect to the carbonate **1b**, bearing only one stereocenter in the propargylic position, so that the formation of a transient chiral allene could be controlled by chirality transfer without any suspicion of a possible diastereoselective process.

The cycloisomerization of **1b** (entry 5, Table 1) led to **3bb** with both efficient chirality transfer and *Z*/*E* control. The level of chirality transfer (product *ee* divided by substrate *ee*) was close to 98% since **3bb** was isolated with 96% *ee* when starting from **1b** (98% *ee*). This indicated that a double transfer of chirality was operative: the first transfer occurring from the stereogenic center to the axis of chirality of the transient allene, and the second one from this axis to the new stereogenic center. It can be noted that the allene **4bb** was also isolated. It is likely to result from the elimination of a [Cu]N(Ts)Me species from a vinyl copper intermediate.[19] This side-product was less abundant in THF (this explains why THF was selected as solvent rather than Et_2O). Again, isobutyl and *n*-hexyl groups were efficiently transferred (97% and 91% level of chirality transfer, respectively; entries 6 and 7). The reaction of $(TMSCH_2)_2CuLi{\cdot}LiI$ with **1b** afforded the desired product in moderate yield and 93% *ee* (entry 8).

Interestingly, when di-*tert*-butylcuprate was used, the allene **2bf** (Figure 1) was the only product (45% yield) and no further cyclization was observed (entry 9, Table 1). In all likelihood, the subsequent alkylating cyclization suffers from steric impediment in this case. This assertion is consistent with the proposed mechanism (see below). The conversion of **2bf** into benzofulvene by addition of $nBu_2CuLi{\cdot}LiI$ or $MeCu^{I}$ was not successful, and the starting material was recovered unreacted.

Table 1: Transfer of chirality in the cycloisomerization of the enediynes **1a–d**.[a]



Entry	R^1	R^2	**1**	**3**[b]	Yield [%]
1		*n*Bu	(*S*,*S*)-**1a** (d.r.>95:5)	(*S*,*S*)-**3ab** (d.r.>95:5)	51
2		*i*Bu	(*R*,*S*)-**1a** (d.r.>95:5)	(*R*,*S*)-**3ac** (d.r.>95:5)	48
3		*n*Hex	(*R*,*S*)-**1a** (d.r.>95:5)	(*R*,*S*)-**3ad** (d.r.>95:5)	57
4		CH_2TMS	(*R*,*S*)-**1a** (d.r.>95:5)	(*R*,*S*)-**3ae** (d.r.=85:15)	55
5		*n*Bu	(*R*)-**1b** (98% *ee*)	(*R*)-**3bb** (96% *ee*)	42[c]
6		*i*Bu	(*R*)-**1b** (98% *ee*)	(*R*)-**3bc** (95% *ee*)	51
7		*n*Hex	(*R*)-**1b** (98% *ee*)	(*R*)-**3bd** (90% *ee*)	48
8		CH_2TMS	(*R*)-**1b** (98% *ee*)	(*R*)-**3be** (93% *ee*)	43
9		*t*Bu	(*rac*)-**1b**	**2bf**[d]	45
10		*n*Bu	(*R*)-**1c** (90% *ee*)	(*R*)-**3cb** (86% *ee*)	62
11		*n*Bu	(*S*,*S*)-**1d** (d.r.>95:5)	(*S*,*S*)-**3db** (d.r.>95:5)	48

[a] Reaction conditions: a solution of $R^2_2CuLi{\cdot}LiI$ in THF was added dropwise to a solution of the enediyne **1** in THF at 0°C. The reaction mixture was warmed to RT for 1 h and quenched with NH_4OH/NH_4Cl (10:1). Complete conversion was observed in all experiments. [b] The configurations were assumed by analogy with the structures of **3aa** and **3bb** established by VCD and ECD, and XRD, respectively (see the Supporting Information). [c] The allene **4bb** (4%) was also isolated (see Ref. [19]). [d] The allene **2bf** was the only product. THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

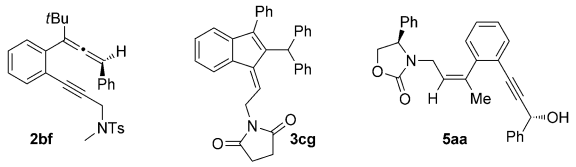
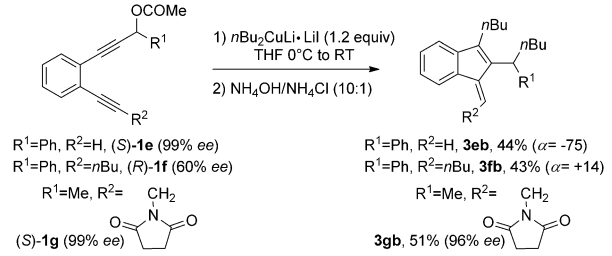


Figure 1. Structures of **2b**, **3cg**, and **5aa**.

The scope of the transformation was further illustrated by varying the nature of the R^1 group. Extension to the propargyl succinimide **1c** led to the highest yield of isolated product. The product **3cb** was isolated in 62% yield with overall 95% of chirality transfer (entry 10, Table 1). The incorporation of two phenyl groups from two equivalents of lithium diphenylcuprate afforded the achiral fulvene **3cg** (Figure 1) in acceptable yield (52%). The enantiopure amide **1d**, derived from alanine methyl ester, was also efficiently converted into **3db** (entry 11). It is interesting to mention that no competitive conjugate addition of the organocuprate to the conjugated triple bond was observed. The S_N2' substitution of the propargylic carbonate proceeded much faster. The product was isolated as a single *Z* diastereomer in 48% yield (diastereomeric ratio superior to 95:5).

To exclude the assistance of any chelating atom in this process, we investigated the cyclization of the enediynes **1e** and **1f** (R^2 = H and *n*Bu, respectively; Scheme 2). These



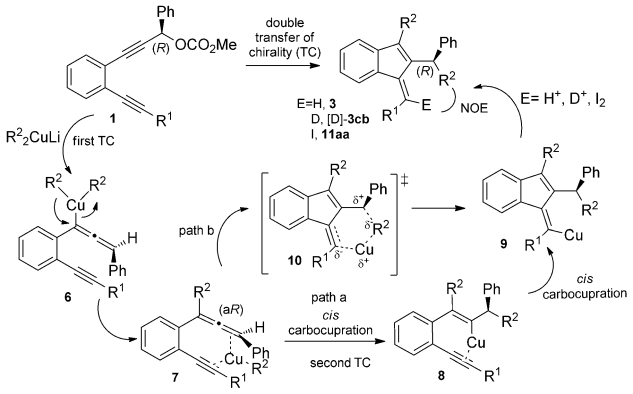
Scheme 2. Cycloisomerization of (*S*)-**1e**, (*R*)-**1f**, and (*S*)-**1g**.

enediynes cyclized with moderate yields (43 and 44%).[20] The *ee* values of the products **3eb** and **3fb** could not be determined because of their low polarity, however, their $[\alpha]_D^{25}$ values [−75 (0.1, $CDCl_3$) and +14 (0.9, $CDCl_3$)] are indicative of chirality transfer.

To further evaluate the versatility of the reaction, we explored the reactivity of the substrate (*S*)-**1g** where a methyl substituent replaced the phenyl group at the propargylic carbon atom. Under similar experimental conditions, the fulvene (*R*)-**3gb** was isolated in 51% yield (Scheme 2). The *R* absolute configuration was assumed by analogy with the mechanism evidenced for **1b**. NOESY 2D NMR spectroscopy confirmed the stereochemistry of the alkene moiety. The presence of the phenyl group is not compulsory for the alkylating cycloisomerization to proceed.

Conversely, the presence of the leaving group is crucial for the cyclization to proceed. A completely different outcome was observed when the reaction was performed on the alcohol precursor of (*R*,*R*)-**1a** in the presence of an excess of dimethylcuprate. Carbocupration of the triple bond bearing the oxazolidinone ring leading to (*R*,*R*)-**5aa** was observed in 79% yield [this experiment was performed on (*R*,*R*)-**1a**; Figure 1]. This result supports the hypothesis that the cyclization only proceeds after the S_N2' displacement of the propargylic carbonate has occurred.

A tentative mechanism is proposed in Scheme 3 to rationalize the experimental data. According to the well-



Scheme 3. Mechanistic rationale.

documented anti S_N2' displacement of propargylic carbonates, the reaction should proceed with central-to-axial chirality transfer via the Cu^{III}-allenic intermediate **6**, which should evolve through reductive elimination to afford the transient allene **7**.[7,21] In the S_N2' process, the Gilman's reagent ($R^2_2CuLi{\cdot}LiI$) releases the monoorganocopper species, R^2Cu, which is reported to be much less reactive than its precursor.[22] This issue was initially considered as the main drawback to the use of organocuprate in nucleophilic substitutions. Remarkably, the two alkyl groups were transferred in the process leading to the product **3** and thereby the initial limitation was overcome.

In the present study, the reactivity of the released $MeCu^I$ species might be enhanced through the template effect of the enyne-allene moiety by the formation of **7**. The stereoselective carbocupration of methoxyallene in Et_2O, reported by Normant and Alexakis, was shown to be controlled by the coordination of the methoxy group with copper.[23] Similarly, the coordination of the metal to the triple bond would govern the stereochemical outcome of the cycloizomerization. Subsequent *cis* carbocupration of the terminal allene π bond would lead to the vinyl organocopper **8**.[24] A second intramolecular *cis* carbocupration of the triple bond, proceeding according to the 5-*exo*-mode, would produce the vinyl copper **9** as a precursor of **3** (path a, Scheme 3).[25] The *Z* stereochemistry of the exocyclic double bond was unambiguously assigned from NOESY 2D NMR spectroscopy and is in good agreement with the proposed sequence.

Masked zwitterions can be involved in transition-metal-promoted rearrangement of enediynes and enyne-allenes.[26,27] The metal coordination would facilitate zwitterionic pathways. Gold-catalyzed Schmittel cyclization pro-

ceeds at low temperature.[27b] Thus, alternatively, the concerted cyclization of **7** might be viewed as the equivalent to a zwitterionic Schmittel rearrangement leading directly to **9** through the transition state **10** (path b, Scheme 3). It is difficult to choose between the stepwise and concerted metal-promoted pathways, which are both consistent with the observed axial-to-central chirality transfer. The development of a positive charge on the carbon atom, in a zwitterionic-like cyclization, might explain why the second methyl group could be so easily transferred from the R^2Cu^I species released in the S_N2' step.

When deuteriolysis of the vinyl copper **9cb** was achieved during work-up, the product [D]-**3cb** was completely and stereoselectively labeled at the exocyclic double bond. Similarly, the iodination of **9aa** leading to **11aa** confirmed the mechanistic hypothesis according to which a stoichiometric amount of copper reagent is needed. It is worth mentioning that the iodide **11aa** offers opportunity for further transformations through cross-coupling or radical reactions.

It must be emphasized that in all cases a total conversion was observed, thus demonstrating that the two alkyl groups of the organocuprate reagent are actually transferred. Competitive side-polymerization of the product could explain why the overall reaction yield did not exceed 62%.[20]

The mechanism was ascertained by the determination of the absolute configurations (AC) assigned by VCD and ECD spectroscopies for (*R*,*R*)-**3aa** and by the X-ray data for (*R*)-**3bb** (Figure 2).[28] This data supports the regio- and stereoselectivity of the proposed mechanism, and implies that when starting from (*R*)-**1b**, the allene **7bb** should be formed in its (*aR*) configuration (Scheme 3). The tandem *cis*-carbocupration steps (or their metal-triggered polar alternative) would then control the absolute configuration of the newly created stereogenic center, that is, this axial-to-central chirality transfer which induces the *R* configuration of the sp^3-carbon atom and the *Z* stereochemistry of the exocyclic double bond.

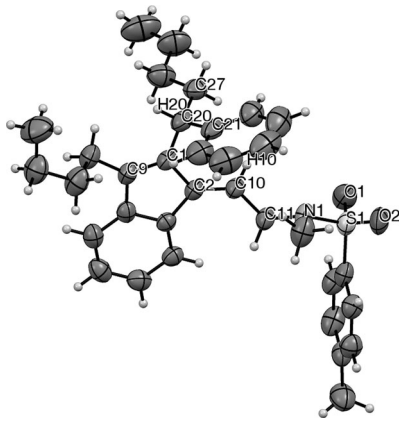


Figure 2. ORTEP diagram of (*R*)-**3bb**.

In conclusion, dialkylcuprates were used as stoichiometric reagents (1.2 equiv) to mediate the enantiospecific bis(alkylating) cycloisomerization of enediynes into benzofulvene derivatives in yields varying from 42 to 62%. The cascade process is likely to involve S_N2' displacement, two stepwise intramolecular carbocupration steps, and electrophilic trapping of the resulting fulvenyl copper species, and proceeds with high diastereo- and enantioselectivity. As expected from the well-documented *anti*-S_N2' and *cis* carbocupration, the stereochemical outcome of the reaction is controlled by a double transfer of chirality from central-to-axial-to-central. A concerted metal-promoted zwitterionic-like Schmittel cyclization might be proposed as an alternative pathway. It is worth mentioning that in this process the two alkyl groups of the dialkylcuprate reagent were transferred, a process which has never been observed before in the presence of only 1.2 equivalents of reagent. Theoretical calculations are underway, and they will probably help to determine the lowest energy pathway involved.

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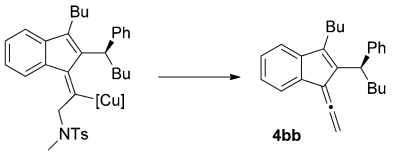

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[28] The *R* absolute configuration was determined by anomalous scattering effect measured with 1023 Bijvoet pairs. Flack parameter: −0.02 (5). CCDC 969656 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For more details see the Supporting Information.

