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The winding road towards an atropo-enantioselective 'ARYNE coupling'

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David Augros was born in Châteauroux (France) in 1993. He obtained a Master degree in Molecular and Supramolecular Chemistry at the University of Strasbourg (France), where he also graduated from the European School of Chemistry, Polymers and Materials Science with a specialisation in organic chemistry. He obtained his Ph.D. in 2018 under the supervision of Dr. Frédéric R. Leroux and Dr. Armen Panossian, working on the "aryne coupling" reaction to access atropisomerically enriched biaryls and on the synthesis of biphenylenes. He is now working as a radiochemist at Selcia in Ongar (United Kingdom).



Corinne Comoy studied chemistry at the University of Orléans (France), where she received her Ph.D in Organic and Bioorganic Chemistry in 1996. After postdoctoral research positions at the University of Göttingen (Germany, 1996-1997) with Professor A. de Meijere and then with Professor François Huet at the University of Le Mans (France, 1997-1998), she has been appointed as assistant professor at University of Lorraine in 1998. Her research fields include organic synthesis, polar and transition metal organometallic chemistry as well as heterocyclic chemistry. Since 2003, she has joined the research group of Professor Yves Fort, where her current research interests concern the development of new methodologies for the regio- and stereoselective functionalization of heterocycles and for cascade reactions.



Yves Fort received his Ph.D. in 1983 under the supervision of Prof. J.-P. Pete (Reims University). He successively held a postdoctoral and a CNRS researcher positions in Nancy (France), where he obtained his Doctorat d'Etat des sciences physiques in 1987 under the supervision of Prof. P. Caubère. In 1998, he has been appointed as Professor at Nancy. His current research interests are focused on polar (Li, Na) and transition metal (Ni, Pd ...) organometallic chemistry directed towards organic synthesis and new nanomaterials for catalysis or electronics.



Frederic Leroux obtained a Ph.D. from the University of Konstanz (Germany) in 1997. After a postdoctoral stay with Prof. M. Schlosser at the University of Lausanne (Switzerland) he became Assistant Professor in 1998. In 2001 he moved then to the Swiss Federal Institute of Technology in Lausanne (EPFL). He joined in 2003 the CNRS as Research Associate and was promoted CNRS Research Director in 2009. The philosophy of his research is based on a fruitful interplay of several objectives (a) the synthesis of biologically relevant molecules, (b) asymmetric methodologies using organic and organometallic chemistry, (c) organofluorine chemistry and (d) application of the objectives to industrial problems, which led to strong industrial collaborations.



Armen Panossian carried out his PhD studies under the supervision of Dr. Angela Marinetti at the ICSN (Gif-sur-Yvette, France). In 2009, he moved to the ICIQ (Tarragona, Spain) for a postdoctoral position in the group of Dr. Anton Vidal-Ferran. After one year as temporary assistant professor at the Université Pierre et Marie Curie (Paris, France), he became in 2011 CNRS Research Associate (Chargé de Recherche). He obtained his habilitation in 2019. His research interests focus on the control of chirality, heavy metal-free methods, the organic chemistry of heteroelements of the main group.



Abstract: For the first time, the challenging atropo-enantioselective coupling of *in-situ* generated arynes and aryllithiums in the presence of a chiral ligand of lithium was investigated. This preliminary study demonstrates the feasibility of this concept, by affording enantioenriched axially chiral biaryls even in the case of products showing a high degree of steric congestion around the newly created aryl-aryl bond.

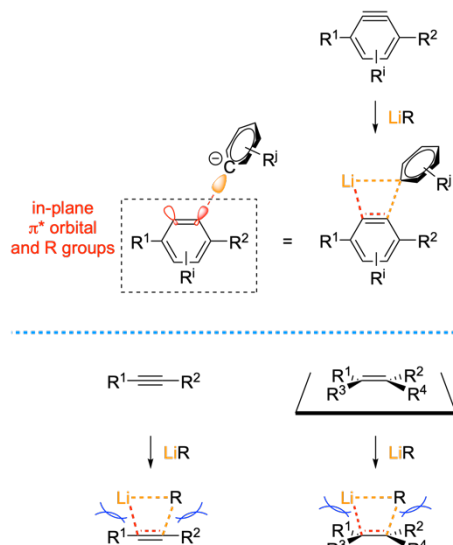
Introduction

In contrast to the well-studied and successful enantioselective trapping of organolithiums with various activated electrophiles, enantioselective carbolithiations have been less studied.^[1] In the latter reactions, the electrophilic partner is a non-activated prochiral olefin and the nucleophilic one is most often an aryllithium. Yet, aryllithium nucleophiles have also been studied in this reaction, leading to a broad range of enantioselectivity, usually with sparteine employed as the chiral ligand for lithium.^[2] Concerning the electrophile, however, apart from olefins, there are only a few reports on alkynes as reaction partners for enantio-retentive carbolithiations, although some of the latter involve an enantioselective lithiation as the first step, rendering the whole sequence enantioselective.^[3]

Formally, *ortho*-arynes^[4] could be seen as a peculiar case of reaction partner for carbolithiation, with the π system of the transient arynes being much more reactive than in standard inactivated alkenes or alkynes. However, unlike alkenes whose π system is orthogonal to the atomic plane, thus allowing *re/si* face differentiation, the electrophilic π system of an *ortho*-aryne is coplanar with the arene ring. Hence, steric distinction in the course of the enantioselective carbolithiation step would be much more challenging with arynes, especially since the triple bond is strongly bent, thus moving away substituents from the incoming nucleophile (Scheme 1).

For some years now, we have been interested in the access to biaryls from *ortho*-arynes,^[5] more exactly in the reaction of

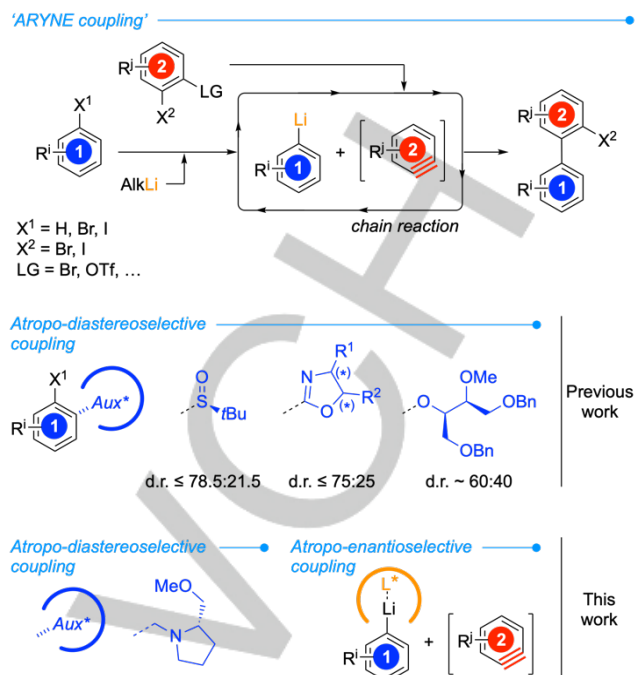
aryllithiums and *ortho*-arynes generated *in situ* upon halogen/lithium exchange, a chain process that was termed the 'ARYNE coupling', which is in fact a specific case of carbolithiation.^[6] We were particularly interested in the development of atroposelective versions of this coupling, in order to access axially chiral biaryls; so far, we have explored the post-coupling deracemization or desymmetrization^[7] or the atropo-diastereoselective coupling (Scheme 2).^[8] In the present paper, we will describe our preliminary attempts towards the atropo-enantioselective version of the reaction (Scheme 2), which is highly challenging on several aspects: 1) As mentioned above, enantioselective carbolithiations have not been studied intensely, in particular on alkynes as electrophiles, and are unknown for arynes and 2) The control of selectivity would be more difficult with arynes than with alkenes or linear alkynes, as stated earlier; 3) Enantioselective reactions of arynes are scarce;^[9] 4) Atropo-enantioselective creation of a biaryl bond from an aryllithium as precursor has also been scarcely reported.^[10]



Scheme 1. Schematic comparison of the carbolithiation of arynes with aryllithiums, of alkynes and of alkenes.

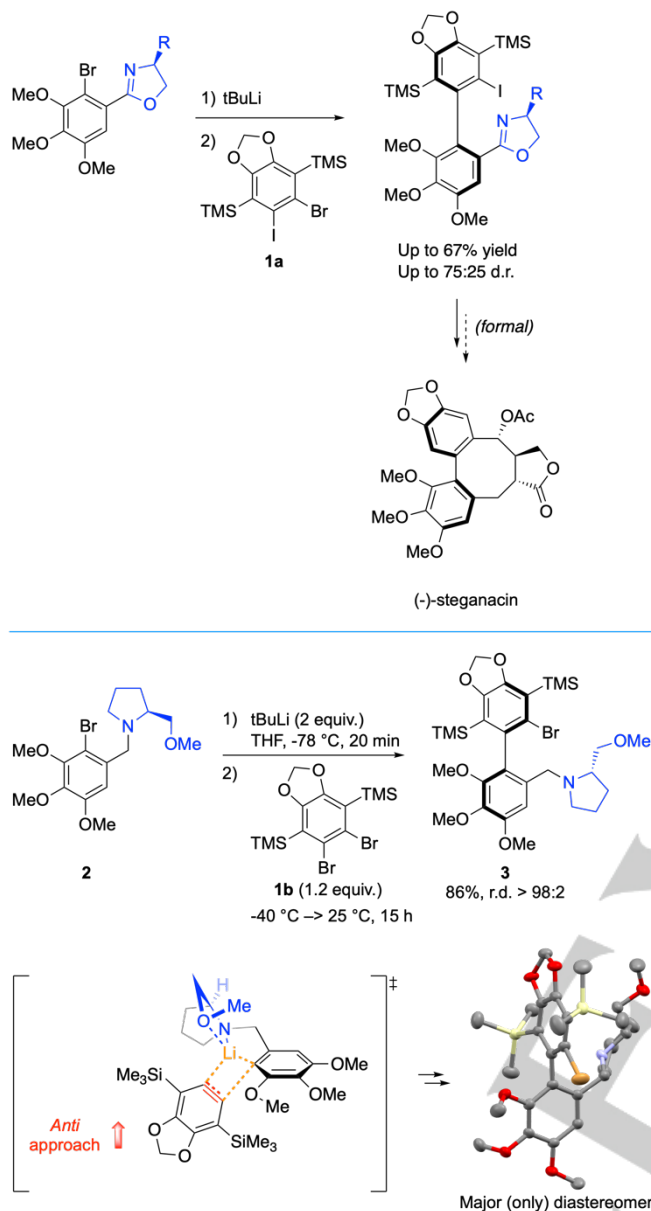
Results and Discussion

In our previous efforts for the development of an atropo-stereoselective ARYNE coupling by means of chiral sulfoxides, oxazolines or diether auxiliaries attached to the aryllithium nucleophile, we were unable to achieve concomitantly high yields and high diastereoselectivities.^[8] The most efficient approach appeared to be the use of a chiral oxazoline as chiral auxiliary, leading to moderate diastereoselectivity but satisfying yield, and allowing efficient separation of atropodiastereomers as well as post-functionalization of the biaryl moiety, as demonstrated in the formal synthesis of each enantiomer of natural product steganacin with high enantiopurity.^[8b-d] As a new attempt for stereocontrol of the organolithium species, we decided to assess the L-proline-derived (*S*)-[(2-methoxymethyl)pyrrolidine-1-yl]methyl auxiliary (SMP-methyl), which had successfully been used in the diastereoselective derivation of ferrocene.^[11] In this case, when targeting the biaryl core of (-)-steganacin, we gratifyingly obtained both a high yield (86%) and an optimal atroposelectivity, with only one detectable atropo-diastereomer; furthermore, the product could be analyzed by X-ray diffraction crystallography, allowing determination of the configuration of the newly created chiral axis and proposition of a stereochemical rationale (Scheme 3).^[12] Unfortunately, all our attempts to remove efficiently the chiral auxiliary by quaternarization, oxidation or coordination of nitrogen followed by benzylic substitution or oxidation proved fruitless.



Scheme 2. The ARYNE coupling and its atroposelective versions.

Considering the additional steps required for installation and transformation of a covalently bound chiral auxiliary and the difficulties we encountered, an enantioselective process involving a chiral ligand of lithium seemed much more appealing. Towards this end, a few solvents were assessed as a replacement for THF, which is usually employed in this reaction. The aim was to use a less coordinating solvent, to favor complexation of lithium by the potentially chiral ligand. As reaction partners, we selected **1a** as aryne precursor and achiral 2-aryloxazoline **4a** as pronucleophile so as to mimic the conditions of a working atropo-diastereoselective ARYNE coupling. As a slight difference, the pronucleophile was iodinated to ensure efficient formation of the aryllithium in other solvents than THF, by iodine/lithium exchange instead of bromine/lithium exchange or direct lithiation. With these partners in hand, the coupling promoted by butyllithium was shown to proceed in all solvents tested, namely THF, toluene, diethyl ether and even dichloromethane, although with modest yields in the latter two solvents. Interestingly, toluene afforded formation of the product in a very good 91% yield, which is in line with our previous studies,^[8c,6f,6g] and even in higher yield than in THF in this case. When *tert*-BuLi was used in place of BuLi in toluene, a much lower 34% conversion was observed by ¹H NMR (Table 1).



Scheme 3. Atropo-diastereoselective coupling with the SMP-methyl auxiliary and comparison with previous work with oxazolines.

We then evaluated a small series of bidentate ligands, achiral or chiral, nitrogen- or oxygen-based (Table 2). It was shown indeed in our previous work on the coupling of 3-thienyllithium and 1,2-benzyne that some ligands could have a dramatic accelerating effect in toluene as solvent.^[6f,g] The ligand was added to the reaction mixture after the full formation of the aryllithium nucleophile, the resulting mixture was stirred for 5 minutes and the aryne precursor **1a** was finally introduced. While in the absence of ligand, 91% yield of the coupling product **5a** were achieved, employing 0.2 equiv. of TMEDA (**L1**) led to 76% yield, and a full equivalent of **L1** afforded a complex mixture, in which only traces of **5a** were detected (entries 1–3). The racemic analogue **L2** based on *trans*-cyclohexane-1,2-diamine similarly furnished a low yield of **5a** under either substoichiometric or stoichiometric conditions (entries 4–5). The BINAM-derived analogue **L3** unfortunately proved insoluble under the reaction

conditions. We were hopeful concerning the well-known ligand sparteine,^[13] which proved efficient in enantioselective carbolithiations by aryllithiums.^[2] Disappointingly, its (+)-enantiomer **L4** also led to a complex mixture and only traces of **5a**. Moving to oxygen-based ligands, we assessed the lithium salt of (*S*)-BINOL **L5**, obtained by reaction of 2 equiv. of BuLi with (*S*)-BINOL. Similarly to the case of **L3**, we encountered solubility issues and had to add some THF during the formation of **L5**; this allowed us to obtain the coupling product **5a** with 71% yield, albeit in racemic form. Tomioka's diether ligand **L6**, which was successful in other strategies to access axially chiral biaryls via organolithiums,^[10a,10b,14,10c] gave a racemic product under substoichiometric conditions (0.2 equiv.), but, gratifyingly, 11% ee of **5a** under stoichiometric conditions with an honorable 60% yield, thus proving the concept of the atropo-enantioselective ARYNE coupling mediated by a chiral external ligand of lithium (entries 9–10). The structurally related ligand **L7**,^[10c,2k] which is also a diether analogue of **L2**, afforded a much lower yield of **5a**, which was contaminated with an unidentified side-product in small amounts preventing accurate determination of the enantiomeric excess, although the latter remains low ($\leq 19\%$, entry 11).

Table 1. Assessment of solvents in a model ARYNE coupling

Entry	Solvent	AlkLi (nb equiv.)	Yield or (conversion) ^[a]
1	THF	BuLi (1 equiv.)	59%
2	Et ₂ O	BuLi (1 equiv.)	34%
3	DCM	BuLi (1 equiv.)	36%
4	Toluene	BuLi (1 equiv.)	91%
5	Toluene	<i>t</i> BuLi (2 equiv.)	(34%)
6	Toluene	<i>t</i> BuLi (2 equiv.) ^[b]	Traces ^[c]

[a] Isolated yield, or conversion into the product estimated by ¹H NMR given in parentheses. [b] Pronucleophile **4a** was added onto a -78 °C solution of *t*BuLi in toluene. [c] Degradation of the reaction mixture.

Following this first hit in terms of enantioselectivity, we tackled the variation of reaction conditions for the atropo-enantioselective coupling. We had to target coupling partners leading to biaryls that would be at least trisubstituted in *ortho* positions of the biaryl junction, in order to ensure, as much as possible, their configurational stability.^[15,16] Initially, we selected sesamol-derived pronucleophile **4b**, displaying two different oxygen-based substituents, inert towards organolithiums, in *ortho* positions of the masked carbanion, which would stabilize the latter without internal coordination of the lithium cation,^[17] but could allow intermolecular coordination. Considering the

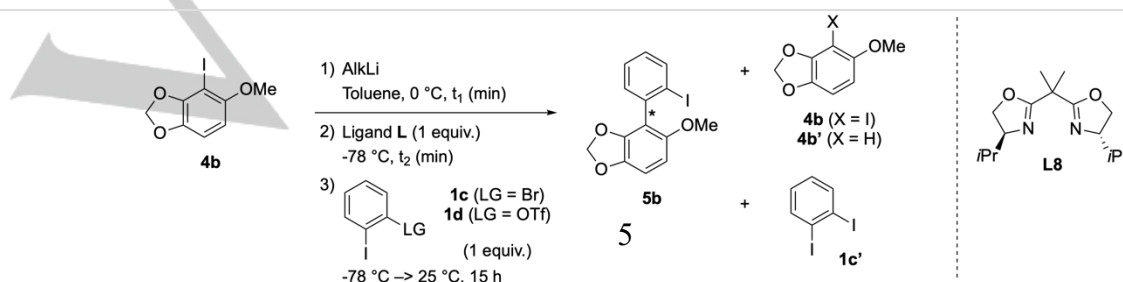
unknown degree of aggregation of the chiral aryllithium, we wished indeed to depart from the case of the coordinating oxazolanyl group, presumably leading to smaller and more rigid aggregates, which would have a different impact on enantioselectivity. As reaction partners, we chose **1c–d**, which were shown to be the most efficient benzyne precursors for ARYNE couplings taking place in toluene as solvent^[6g] (Table 3). In this series of experiments, the time required for full formation of the aryllithium nucleophile had been ascertained by separate tests. In the absence of added ligand, the coupling showed low efficiency, with at best 26% conversion into the desired biaryl **5b** (entries 1–3). The main products observed were **4b** and **4b'**, resulting respectively from re-iodination (by iodine/lithium exchange on **1c–d**) and hydrolysis (either by the *n*- or *sec*-butyl iodide generated in the first stage of the reaction or during the final aqueous quench) of the aryllithium. We then assessed a few chiral ligands in this reaction, namely (+)-sparteine **L4**, Tomioka's diether **L6** and bis-oxazoline **L8**. In all cases, the yield of **5b** remained quite low due to the formation of side-products **4b** and **4b'** mentioned above, as well as of the rather unexpected 1,2-diiodobenzene **1c'**, which we never observed in coupling experiments carried out in THF as solvent. Disappointingly, **L4** repeatedly afforded a racemic product (entries 4–7), whereas, on the contrary, **L6** repeatedly gave 10% ee (entries 9–13). Ligand **L8**, which had not been tested yet, was unable to produce the biaryl (entry 8). These modest yields and low enantioselectivities could not be improved by changing the nature of the aryllithium base (entries 4–5 and 9, 12–13), the order of addition of reactants for the formation of the chiral aryllithium (entries 5–7), the nature of the benzyne precursor and the length of the mixing time in the presence of the ligand (entries 10–11). Note that, upon addition of a ligand, the yield of **5b** tends to increase, as well as those of iodinated side-products **4b** and **1c'**, whereas the yield of the protonated nucleophile **4b'** tends to decrease.

Table 2. Evaluation of ligands in the ARYNE coupling

Entry	Ligand	x equiv.	Yield (conversion) ^[a]	or ee ^[b]
1	-	-	91%	-
2	L1	0.2	76%	-
3	L1	1	(Traces) ^[c]	-
4	L2	0.2	24%	-
5	L2	1	18%	-
6	L3	0.2	n.d. ^[d]	-
7	L4	1	(Traces) ^[c]	-
8	L5	0.2	71% ^[e]	0%
9	L6	0.2	67%	0%
10	L6	1	60%	11%
11	L7	1	12%	≤19% ^[f]

n.d. = not determined. [a] Isolated yield, or conversion into the product estimated by ¹H NMR given in parentheses. [b] Enantiomeric excess determined by chiral phase HPLC. [c] Complex mixture. [d] The ligand proved insoluble under the reaction conditions. [e] THF (0.125 mL/mL toluene) was added to help solubilize **L5**. [f] The product could not be perfectly purified from traces of an unidentified side-product.

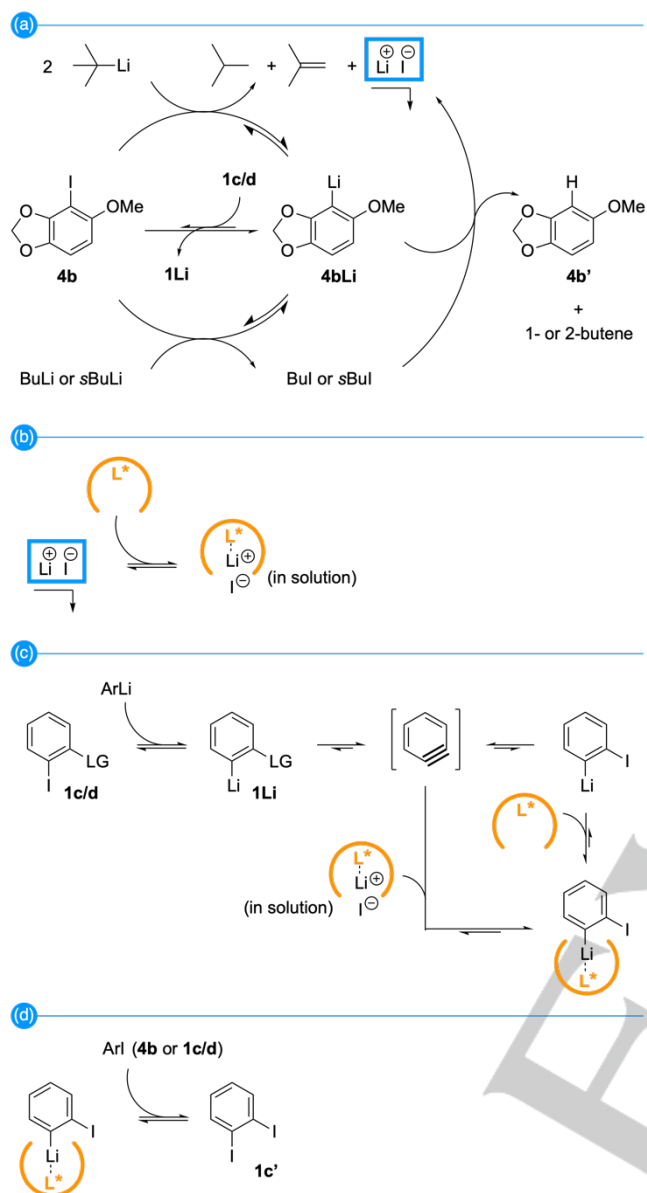
Table 3. Variation of parameters in the atropo-enantioselective ARYNE coupling of **4b** with benzyne



Entry	1	AlkLi (nb. equiv.)	t ₁ (min)	t ₂ (min)	Ligand	Yield or (conv.) ^[a]	ee ^[b]	Side-products/ Yields or (conv.) ^[a]
1	1c	BuLi (1)	30	-	-	(26%)	-	4b /(11%), 4b' /(56%)
2	1c	sBuLi (1)	60	-	-	(18%)	-	4b /(13%), 4b' /(64%)
3	1c	<i>t</i> BuLi (2)	15	-	-	(11%)	-	4b' /(89%)
4	1c	BuLi (1)	30	60	L4	2%	n.d.	4b /(32%), 4b' /(52%)
5	1c	<i>t</i> BuLi (2)	15	60	L4	27%	0%	4b /(12%), 4b' /(51%), 1c' /19%
6	1c	<i>t</i> BuLi (2)	60 ^[c]		L4	32%	0%	4b /(21%), 4b' /(28%), 1c' /18%
7	1c	<i>t</i> BuLi (2)	60 ^[d]		L4	28%	0%	4b /(18%), 4b' /(34%), 1c' /20%
8	1c	<i>t</i> BuLi (2)	15	60	L8	(Traces)	0%	4b /(13%), 4b' /(79%), 1c' /36%
9	1c	<i>t</i> BuLi (2)	15	60	L6	11%	10%	4b /13%, 4b' /59%, 1c' /50%
10	1d	<i>t</i> BuLi (2)	15 ^[e]		L6	30%	10%	4b /(34%), 4b' /(23%), 1c' /42%
11	1d	<i>t</i> BuLi (2)	120 ^[e]		L6	14%	10%	4b /(43%), 4b' /(22%), 1c' /40%
12	1c	BuLi (1)	30	60	L6	32%	10%	4b /(14%), 4b' /(33%), 1c' /3%
13	1c	sBuLi (1)	60	60	L6	36%	10%	4b /(24%), 4b' /(23%), 1c' /14%

n.d. = not determined. [a] Isolated yield, or conversion into the product estimated by ¹H NMR given in parentheses. [b] Enantiomeric excess determined by chiral phase HPLC. [c] *t*BuLi was added to a mixture of **4b** and **L4**. [d] **4b** was added to a mixture of *t*BuLi and **L4**. [e] *t*BuLi was added to a mixture of **4b** and **L6**.

The formation of product **1c'** from benzyne had already been documented under different reaction conditions, either *via* a postulated radical mechanism^[18] or by attack of iodide on benzyne followed by trapping of the 2-iodoaryl carbanion by an electrophilic iodine source (I₂ or IF).^[19] In our case, we presume that a mechanism similar to the latter one accounts for the formation of **1c'**, with the nucleophilic iodide being lithium iodide, generated upon iodine/lithium exchange on **4b** by *t*BuLi or protonation of the aryllithium with *n*- or sBuLi; and the electrophilic iodine source being **1c-d** or the re-iodinated **4b**. The fact that **1c'** is formed only in the presence of a ligand would then be explained by the complexation of LiI or of the resulting 2-iodophenyllithium, respectively solubilizing the former in toluene and stabilizing the latter, overall favoring their availability for further reactions (Scheme 4). Interestingly, an additional experiment involving **4b**, BuLi and **1c** in the absence of ligand but in the presence of added lithium iodide (1 equiv.) gave 31% of **5b** but no diiodo compound **1c'**.

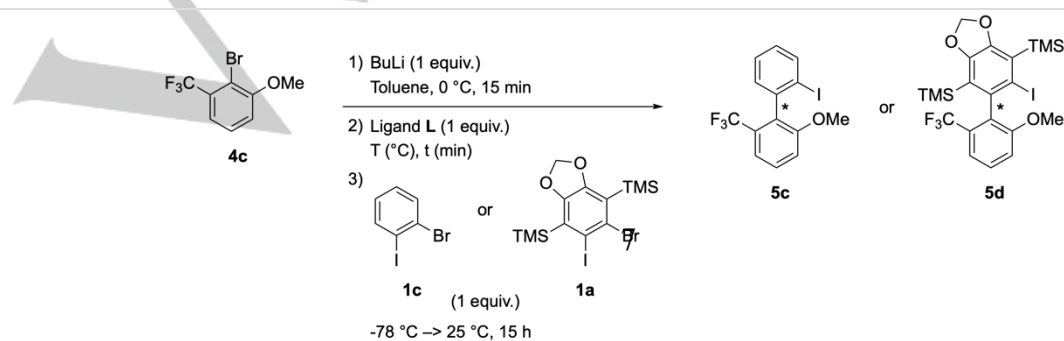


Scheme 4. Tentative rationale for the formation of **4b'** and **1c'**.

The low enantioselectivities obtained in the coupling of **4b** and **1c-d** led us to reconsider the structure of the aryllithium nucleophile. Whereas **4b** shows little steric distinction between the methoxy group and the dioxole ring, the latter being moreover quite flat, we were hoping that **4c**, bearing on either side of the masked carbanion a small methoxy group and a large and spherical trifluoromethyl substituent, would allow a better differentiation in the stereoselective course of the

nucleophilic attack onto the aryne. Additionally, the presence of the bulky CF_3 group would impede a dynamic interconversion of atropo-diastereomeric biaryllithium/chiral ligand complexes by axial epimerization, leading to dynamic thermodynamic or kinetic resolutions as potential alternative scenarios for the enantioselection of the process. Thus, **4c** was opposed to aryne precursors **1c** and **1a** (Table 4). Interestingly, although the aryllithium resulting from bromine/lithium exchange on **4c** was not fully soluble in toluene, the reaction in absence of ligand still managed to produce the desired biaryls **5c** and **5d** (entries 1 and 4 respectively). The yield was moderate for **5c**, the main side-product being 3-trifluoromethylanisole formed by protonation of the aryllithium derived from **4c**. Some other side-products were detected in small amounts in ^{19}F NMR with chemical shifts close to the one of the desired biaryl **5c**, suggesting the formation of isomers arising from equilibration of the 2-lithio-2'-methoxy-6'-trifluoromethylbiphenyl intermediate towards more stable biphenyllithium isomers—with lithium *ortho* to OMe or CF_3 — caused by a too long residence time before trapping by iodine from **1c**. On the other hand, biaryl **5d** was obtained in a very good 89% yield (entry 4), especially when considering the very high steric congestion around the aryl-aryl bond due to the bulky iodo, trifluoromethyl and trimethylsilyl *ortho* substituents.^[16] Chiral ligands were then assessed in these reactions. (+)-Sparteine **L4** failed to afford the expected coupling products (entries 2 and 5). Tomioka's diether **L6** proved more successful, with similar 59% and 55% yields of **5c** and **5d** (entries 3 and 6 respectively). In the reaction of entry 3, **5c** was formed in very low ee, while side-product **6**, whose structure was confirmed by X-ray diffraction crystallography (Figure 1), was isolated in 13% yield and presumably formed by an unexpected homocoupling of **4c** upon loss of CF_3^- to generate an aryne.^[20] This side-product was not detected when using **1a**, which gratifyingly led to 17% ee of **5d** when using ligand **L6** (entry 6). When 2 equiv. of **L6** were employed instead of one (entry 7), the ee remained sensibly the same, but the yield was twice lower, presumably due to the enhancement of the nucleophilicity or basicity of lithium-based intermediates upon coordination, leading to side-reactions as in the formation of **1c'** (*vide supra*). We also varied the temperature in the complexation stage of the aryllithium nucleophile with **L6** and observed a small decrease in ee when their mixing temperature was lowered (entries 6, 8–9), possibly implying a less efficient complexation; indeed, the reaction proceeds already well in the absence of ligand (entry 4). Finally, employing diether **L7** gave almost identical results in terms of yield and ee of **5d** than when using the structurally related **L6** (entries 10 vs 6). One would thus favor the use of **L6** since it is much more easily accessible and is moreover UV-active, allowing a better tracking and recovery of the ligand at the end of the reaction.

Table 4. Variation of parameters in the atropo-enantioselective ARYNE coupling of **4c**



Entry	Aryne precursor	Ligand	T (°C)	t (min)	Product	Yield or (conv.) ^[a]	ee ^[b]
1	1c	-	-	-	5c	46%	-
2	1c	L4	-78	60	5c	n.d. (traces)	n.d.
3	1c	L6	0	30	5c	59%	<5%
4	1a	-	-	-	5d	89%	-
5	1a	L4	0	60	5d	n.d. (traces)	n.d.
6	1a	L6	0	60	5d	55%	17%
7	1a	L6 ^[c]	0	60	5d	26%	14%
8	1a	L6	0/-78 ^[d]	60	5d	32%	13%
9	1a	L6	-78 ^[e]	60	5d	68%	10%
10	1a	L7	0	60	5d	54%	16%

n.d. = not determined. [a] Isolated yield, or conversion into the product estimated by ¹H NMR given in parentheses. [b] Enantiomeric excess determined by chiral phase HPLC. [c] 2 equivalents of **L6** were used. [d] The temperature of the reaction medium was decreased from 0 °C to -78 °C as soon as the ligand had been added to the mixture, which was then stirred for 60 min at -78 °C before addition of **1a**. [e] The temperature of the reaction medium was decreased from 0 °C to -78 °C prior to the addition of the ligand, and only then the resulting mixture was stirred for 60 min at -78 °C before addition of **1a**.

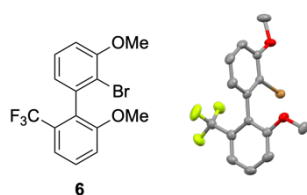


Figure 1. Structure of side-product **6** and X-ray diffraction crystallographic picture (ellipsoids at the 50% probability level).

Considering the specific increments for *ortho* substituents MeO, F₃C and TMS (respectively 4.6, 9.5 and 9.4 kcal/mol)^[16] one could estimate, by coarse but erroneous additivity, a rotational barrier of at least 23.5 kcal/mol for the key biaryllithium intermediate leading to **5d**. The actual value, which should be even higher, would render axial epimerization extremely slow in the temperature range of the reaction. Hence, a dynamic resolution as mentioned earlier seems improbable. Accordingly, the enantioselectivity of the reaction would either arise from a selective attack of the aryllithium/chiral ligand complex onto the aryne, or by a non-selective attack onto the aryne followed by a non-dynamic kinetic resolution in the trapping of the biaryllithium/chiral ligand complex by an iodine atom provided by the aryne precursor. Finally, a combination of both scenarios, operating at the same time, is also possible.

Conclusion

In summary, we have engaged in the development of an atropo-enantioselective version of the so-called ARYNE coupling, which would lead to axially chiral biaryls starting from haloarenes, halogenated *ortho*-aryne precursors, alkyllithiums and chiral ligands for lithium. This targeted process was expected to be highly challenging due to the lack of precedents in enantioselective carbolithiations of alkynes in general, and of

arynes in particular, and to the very little number of reports on enantioselective reactions of arynes and on the atropo-enantioselective construction of a biaryl bond from an aryllithium. And indeed, the task proved difficult. Gratifyingly, we were able to obtain a proof of concept, with a handful of reactions affording the desired atropo-enantioenriched products with up to 17% ee. Among the few ligands screened, Tomioka's diether based on a hydrobenzoin core offered the best compromise in terms of synthetic access, enantioselectivity, efficiency and practicality. Yet, the scope of the reaction and enantioselectivity remain to be improved, and the mechanism for enantioselectivity remains to be elucidated. Corresponding efforts are underway in our laboratories.

Experimental Section

General procedure for the ARYNE coupling

BuLi (1 equiv.) or *tert*-BuLi (2 equiv.) was added dropwise to a stirred solution of the pronucleophile **4a**, **4b** or **4c** (1 equiv.) in the desired anhydrous solvent (0.25 M) at the specified temperature. The mixture was stirred for a known time and was then cooled down to -78 °C. A precooled -78 °C solution of the aryne precursor **1a**, **1c** or **1d** (1 equiv.) in the same solvent (0.25 M) was then cannulated into the first one. The mixture was stirred overnight (ca. 15 h) from -78 °C to r.t. and then quenched with water and extracted thrice with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness to give the crude material, which was then purified by flash chromatography on silica gel to afford the pure biaryl product.

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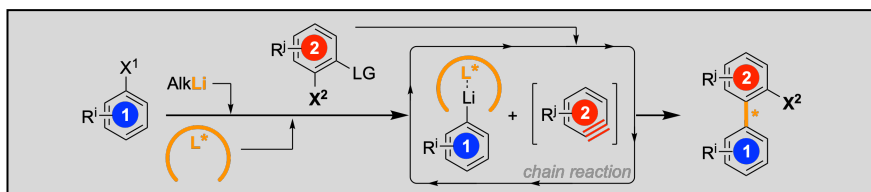
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Keywords: Arynes • Aryllithiums • Biaryls • Axial chirality • Ligand effects

- [1] a) J. F. Normant, in *Topics Organomet. Chem.*, Vol. 5, **2003**, pp. 287–310; b) A. Gomez-Sanjuan, N. Sotomayor, E. Lete, *Beilstein J. Org. Chem.* **2013**, 9, 313–322; c) G. Marsico, P. Scafato, S. Belviso, S. Superchi, *RSC Adv.* **2020**, 10, 32581–32601.
- [2] a) W. F. Bailey, M. J. Mealy, *J. Am. Chem. Soc.* **2000**, 122, 6787–6788; b) G. S. Gil, U. M. Groth, *J. Am. Chem. Soc.* **2000**, 122, 6789–6790; c) T. Suzuka, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2002**, 67, 3355–3359; d) J. Barluenga, F. J. Fananas, R. Sanz, C. Marcos, *Org. Lett.* **2002**, 4, 2225–2228; e) M. J. Mealy, M. R. Luderer, W. F. Bailey, M. B. Sommer, *J. Org. Chem.* **2004**, 69, 6042–6049; f) J. Barluenga, F. J. Fananas, R. Sanz, C. Marcos, *Chem. Eur. J.* **2005**, 11, 5397–5407; g) P. O'Brien, *Chem. Commun.* **2008**, 655–667; h) U. Groth, P. Köttgen, P. Langenbach, A. Lindenmaier, T. Schütz, M. Wiegand, *Synlett* **2008**, 1301–1304; i) U. Martinez-Estibalez, N. Sotomayor, E. Lete, *Org. Lett.* **2009**, 11, 1237–1240; j) H. Guyon, A. Boussonniere, A. S. Castanet, *J. Org. Chem.* **2017**, 82, 4949–4957; k) H. Guyon, A. S. Castanet, A. Boussonniere, *J. Org. Chem.* **2020**, 85, 8933–8943.
- [3] a) M. Oestreich, R. Fröhlich, D. Hoppe, *Tetrahedron Lett.* **1998**, 39, 1745–1748; b) G. Gralla, B. Wibbeling, D. Hoppe, *Org. Lett.* **2002**, 4, 2193–2195; c) G. Gralla, B. Wibbeling, D. Hoppe, *Tetrahedron Lett.* **2003**, 44, 8979–8982; d) M. Simon, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, 20, 3518–3521.
- [4] For some selected reviews, see: a) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem. Int. Ed.* **2003**, 42, 502–528; b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, 59, 701–730; c) R. Sanz, *Org. Prep. Proc. Int.* **2008**, 40, 215–291; d) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, 112, 3550–3577.
- [5] J. A. Garcia-Lopez, M. F. Greaney, *Chem. Soc. Rev.* **2016**, 45, 6766–6798.
- [6] a) F. Leroux, M. Schlosser, *Angew. Chem. Int. Ed.* **2002**, 41, 4272–4274; b) F. R. Leroux, L. Bonnafoux, C. Heiss, F. Colobert, D. A. Lanfranchi, *Adv. Synth. Cat.* **2007**, 349, 2705–2713; c) F. R. Leroux, L. Bonnafoux, F. Colobert, *Synlett* **2010**, 2953–2955; d) L. Bonnafoux, R. Gramage-Doria, F. Colobert, F. R. Leroux, *Chem. Eur. J.* **2011**, 17, 11008–11016; e) V. Diemer, M. Begaud, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2011**, 341–354; f) C. Demangeat, T. Saied, R. Ramozzi, F. Ingrosso, M. Ruiz-Lopez, A. Panossian, F. R. Leroux, Y. Fort, C. Comoy, *Eur. J. Org. Chem.* **2019**, 547–556; g) T. Saied, C. Demangeat, A. Panossian, F. R. Leroux, Y. Fort, C. Comoy, *Eur. J. Org. Chem.* **2019**, 5275–5284.
- [7] a) F. R. Leroux, A. Berthelot, L. Bonnafoux, A. Panossian, F. Colobert, *Chem. Eur. J.* **2012**, 18, 14232–14236; b) M. J. Fer, J. Cinqualbre, J. Bortoluzzi, M. Chessé, F. R. Leroux, A. Panossian, *Eur. J. Org. Chem.* **2016**, 4545–4553; c) J. Bortoluzzi, V. Jha, G. Levitre, M. J. Fer, J. Berreur, G. Masson, A. Panossian, F. R. Leroux, *J. Org. Chem.* **2018**, 83, 7751–7761.
- [8] a) A. Berthelot-Bréhier, A. Panossian, F. Colobert, F. R. Leroux, *Org. Chem. Front.* **2015**, 2, 634–644; b) B. Yalcouye, A. Berthelot-Bréhier, D. Augros, A. Panossian, S. Choppin, M. Chessé, F. Colobert, F. R. Leroux, *Eur. J. Org. Chem.* **2016**, 725–732; c) D. Augros, B. Yalcouye, A. Berthelot-Bréhier, M. Chessé, S. Choppin, A. Panossian, F. R. Leroux, *Tetrahedron* **2016**, 72, 5208–5220; d) D. Augros, B. Yalcouye, S. Choppin, M. Chessé, A. Panossian, F. R. Leroux, *Eur. J. Org. Chem.* **2017**, 497–503.
- [9] a) J. Caeiro, D. Peña, A. Cobas, D. Pérez, E. Guitián, *Adv. Synth. Cat.* **2006**, 348, 2466–2474; b) K. Mohanan, Y. Coquerel, J. Rodriguez, *Org. Lett.* **2012**, 14, 4686–4689; c) H. Jia, Z. Guo, H. Liu, B. Mao, X. Shi, H. Guo, *Chem. Commun.* **2018**, 54, 7050–7053.
- [10] a) M. Shindo, K. Koga, K. Tomioka, *J. Am. Chem. Soc.* **1992**, 114, 8732–8733; b) M. Shindo, Y. Yamamoto, K. Yamada, K. Tomioka, *Chem. Pharm. Bull.* **2009**, 57, 752–754; c) T. T. T. Nguyen, H. Guyon, K. P. P. Nguyen, A. Boussonniere, J. Mortier, A.-S. Castanet, *Eur. J. Org. Chem.* **2020**, 3829–3833.
- [11] a) C. Ganter, T. Wagner, *Chem. Ber.* **1995**, 128, 1157–1161; b) L. Xiao, K. Mereiter, W. Weissensteiner, M. Widhalm, *Synthesis* **1999**, 1354–1362; c) B. Pugin, X. D. Feng, M. Thommen, *PCT Int. Appl. WO/2006/003195*, **2006**; d) M. Steurer, Y. Wang, K. Mereiter, W. Weissensteiner, *Organometallics* **2007**, 26, 3850–3859; e) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, 130, 14030–14031; f) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *Adv. Synth. Cat.* **2009**, 351, 1968–1976; g) M. Neel, A. Panossian, A. Voituriez, A. Marinetti, *J. Organomet. Chem.* **2012**, 716, 187–192.
- [12] Deposition Number 2053140 contains the supplementary crystallographic data of compound **3** for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
- [13] D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, 36, 2282–2316.
- [14] a) Q. Perron, A. Alexakis, *Adv. Synth. Catal.* **2010**, 352, 2611–2620; b) J. Graff, T. Debande, J. Praz, L. Guénée, A. Alexakis, *Org. Lett.* **2013**, 15, 4270–4273; c) J. Graff, E. Lastawiecka, L. Guénée, F. Leroux, A. Alexakis, *Adv. Synth. Catal.* **2015**, 357, 2833–2839; d) J. Praz, J. Graff, L. Egger, L. Guénée, S. Wagschal, E. P. Kündig, A. Alexakis, *Chem. Commun.* **2015**, 51, 16912–16915.
- [15] For a reference review, see: G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, 44, 5384–5427.
- [16] For a selected approach to determine the relative size of *ortho*-substituents of a biphenyl, see: a) A. Mazzanti, L. Lunazzi, M. Minzoni, J. E. Anderson, *J. Org. Chem.* **2006**, 71, 5474–5481; b) R. Ruzziconi, S. Spizzichino, L. Lunazzi, A. Mazzanti, M. Schlosser, *Chem. Eur. J.* **2009**, 15, 2645–2652; c) A. Mazzanti, L. Lunazzi, R. Ruzziconi, S. Spizzichino, M. Schlosser, *Chem. Eur. J.* **2010**, 16, 9186–9192; d) R. Ruzziconi, S. Spizzichino, A. Mazzanti, L. Lunazzi, M. Schlosser, *Org. Biomol. Chem.* **2010**, 8, 4463–4471; e) L. Lunazzi, M. Mancinelli, A. Mazzanti, S. Lepri, R. Ruzziconi, M. Schlosser, *Org. Biomol. Chem.* **2012**, 10, 1847–1855.
- [17] a) J. Gorecka-Kobylnska, M. Schlosser, *J. Org. Chem.* **2009**, 74, 222–229; b) F. Mongin, C. Curty, E. Marzi, F. R. Leroux, M. Schlosser, *Arkivoc* **2015**, 2015, 48–65.
- [18] Y. Zeng, G. Li, J. Hu, *Angew. Chem. Int. Ed.* **2015**, 54, 10773–10777.
- [19] D. Rodriguez-Lojo, A. Cobas, D. Peña, D. Pérez, E. Guitián, *Org. Lett.* **2012**, 14, 1363–1365.
- [20] Deposition Number 2053141 contains the supplementary crystallographic data of compound **6** for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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The enantioselective addition of aryllithiums onto arynes, leading to axially chiral biaryls in the absence of transition metals, was investigated by means of chiral ligands of lithium. Biaryls with a high degree of steric congestion around the aryl-aryl bond could be obtained.