



Transition-Metal-Free Approach for the Direct Arylation of Thiophene: Experimental and Theoretical Investigations towards the (Het)-Aryne route

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Abstract: This paper presents the results of our investigations on the arylation of thiophene using the transition metal-free "Aryne coupling" methodology. The reaction was studied by both experiment and computation (density functional theory) and comparison with phenyllithium was established. In parallel, the effect of ligand and salt on the coupling reaction was examined. The results underline the remarkable effect of such additives on the coupling reaction and the potency of the method to construct hetaryl-aryl backbones which open up a promising access to a wide range of heterobiaryl structures using the novel "Het-Aryne" route.



Introduction

Biaryls and heterobiaryls are ubiquitous in pharmaceuticals, natural products as well as organic functional materials.^[1] The classical transition-metal-catalyzed cross-coupling reactions remain the most reliable and powerful tool to connect the two aromatic partners. The well-established Suzuki-Miyaura cross-coupling reaction - and its related processes - has been largely overviewed to this aim.^[2,3] Besides this conventional method, the direct arylation of heteroarenes in which the C-H bond is used as the reaction center, has recently emerged as a valuable

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alternative^[4] since it can skip the key preactivation steps of the coupling partners required in the traditional method. Among others,^[5] Itami and co-workers^[6] reported significant advances in this area. Yet, the regioselectivity of the arylation remains an important limitation, especially in the oxidative variant of the coupling. Additionally, heavy-metal contamination of the products has become subject of a serious demand for their complete removal in view of biological applications in the pharmaceutical industry.^[7] Consequently, several recent reports have described the development of transition-metal-free "greener" synthetic routes to access bi(het)-aryl backbones.^[8] The use of such methods in the direct arylation of heteroarenes has been entirely reviewed recently.^[9]

Not so long ago, some alternative strategies based on aryne chemistry have emerged.^[10] Leroux and co-workers extensively investigated on an efficient transition metal free aryl-aryl coupling protocol, the so-called "Aryne coupling" reaction.[11] This methodology relies on the subsequent generation and trapping of a key aryne intermediate with an aryllithium derivative, proceeding as a chain reaction mechanism through the subtle interplay of several halogen-lithium exchanges (Scheme 1). The reaction is initiated by the lithiation of an orthodihalogenobenzene aryne precursor (2) with a small amount of a thermodynamically stable organolithium intermediate generated in the former step of the reaction (1), affording the in situ formation of some aryne traces (3). Then, the key step of this protocol is the nucleophilic addition of the aryllithium previously prepared, onto the transient aryne (4) allowing both the biaryl axis formation and the subsequent aryne regeneration by the in situ bromine or iodine transfer from the starting material to the resulting 2biaryllithium intermediate (5).[12a] This "aryne coupling" has become a robust method for the synthesis of various polyhalogenated biaryls that could be easily further functionalized. Among other advantages, the use of cheap and easily accessible coupling partners is worthy to note. Remarkably, this coupling method was successfully applied to the synthesis of axially chiral and the recent development biarvls latelv. of an atropodiastereoselective version of this reaction has well complemented this work.^[12]

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Scheme 1. Mechanism of the Aryne Coupling as proposed by F.R. Leroux. $^{\left[12h\right] }$

Until now, the use of a heterocyclic coupling partner in this procedure has never been explored. To the best of our knowledge, the addition of (hetero)aryllithiums to arynes has only been sporadically described in the literature.^[13-15] However, these methodologies required the introduction of a third electrophilic partner since they are not chain procedures.

We report here results on the arylation of thiophene using the transition metal free "aryne coupling" methodology. To achieve this goal, a three-fold study has been conducted, including in parallel: i) extension of the scope of the aryne coupling reaction to the construction of hetaryl-aryl backbones, ii) observations regarding the effect of ligand as well as LiBr salt on the reaction, and iii) mechanistic insight of the coupling reaction using theoretical calculations.

Results and Discussion

Experimental results:

The main purpose of this work was first to adapt the aryne coupling procedure^[11] developed for the synthesis of biaryl compounds to a new one in adequacy with the heterocyclic lithiated partner. To this end, we investigated the reaction of 3bromothiophene 1a and 1,2-dibromobenzene 2 as a model. In this preliminary work, the use of 1,2-dibromobenzene as aryne precursor seems reasonable with regard to its ubiquity in several previous reports, attesting the appreciable versatility of this precursor towards diverse aromatic lithiated partners. Thus, in a first set of experiments, we performed addition of 1,2dibromobenzene 2 to the 3-lithiated thiophene 1a under the variation of classical reaction parameters - such as temperature, time of condensation, equivalent and solvent, using reaction conditions derived from those originally developed. bromine/lithium exchange allowed preparation of the lithiated partners using t-butyllithium (t-BuLi, 2.0 equiv.) as the base. The most significant results are reported in Table 1.

First in tetrahydrofuran (THF), we examined the influence of temperature on the coupling step when 1,2-dibromobenzene (1.2

equiv.) was added to the 3-lithiothiophene (entries 1-3). To be noted that total consumption of starting material 1a was observed when THF was used as solvent (entries 1-5). Whether precursor 2 was added at lower or at higher temperature did not seem to sensibly affect the reaction, since the expected product 3a was obtained in a yield ranging from 54 to 60% after 2h reaction time. Interestingly, the side product 4, 2,2'-dibromo-biphenyl, resulting from the homo-coupling of the lithiated aryne precursor, was observed at -80 °C in 21% yield without sensible decrease of 3a yield. Additionally, prolonging the reaction time of the aryne coupling to 6h, or varying the amount of aryne precursor used (from 1.2 to 1.0 equiv.) have only minor influences on the reaction (entries 4 and 5). In contrast, moving from THF to a noncoordinating apolar solvent critically affected the reaction since no product was observed when performing the reaction in toluene or hexane, even when the system was warmed up to higher temperatures.





	(Het)ArBr	Solvent	2	t (b)	T (°C)	Yield ^{[i}	^{a]} (%)
			eq	(1)	(0)	3a-b	4
1		THF	1.2	2	-80	54	21
2		THF	1.2	2	-50	60	traces
3	Pr	THF	1.2	2	-30	59	-
4		THF	1.2	6	-50	60	traces
5	5 1a	THF	1.0	2	-50	57	-
6		hexane	1.2	2	-50	0 ^[b]	-
7		toluene	1.2	2	-50	0 ^[c]	-
8		toluene/DME ^[d]	1.2	2	-50	45 ^[e]	-
9		THF	1.2	2	-50	44 ^[f]	9
10	Br	toluene	1.2	2	-50	O [a]	-
11	1b	toluene/DME ^[d]	1.2	2	-50	36 ^[h]	5

^[a] Isolated yields after centrifugal thin-layer chromatography purification. ^[b] 3-Bromothiophene **1a** was recovered unchanged in 85% yield when hexane was used as solvent. ^[c] 3-Bromothiophene **1a** was recovered unchanged in 82% yield when toluene was used as solvent. ^[d] DME (1.0 equiv.) was added at -80 °C; temperature was allowed to reach -50 °C for 45 min. ^[e] 97% conversion rate for the reaction when toluene/DME was used as solvent. Observed conversion rates were ^[I]100% in THF, ^[g]25% in toluene and ^[h]98% in toluene/DME

The reactivity of organolithiums is indeed strongly altered in hydrocarbon solvents and halogen-metal exchange is usually

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very slow in such media.^[17] Also, chelating ligands as well as lithium salts are commonly employed to modify the properties of organolithiums, since they demonstrated high influence on the nature and reactivity of organometallics aggregates.^[16,17,18] Therefore we envisioned that such additives could allow the reaction to occur or could improve it when it furnished improvable yields.

Interestingly, whereas only low conversion rates were observed when hexane or toluene was used as solvent (15 and 18 % respectively, entries 6 and 7), the use of dimethoxyethane (DME, 1.0 equiv.) as co-solvent proved to be effective, since it allowed recovering of **3a** in 45 % yield (almost quantitative conversion rate, entry 8, Table 1). A similar trend was observed for the carbocyclic analog bromobenzene **1b**, although lower yields were generally obtained.

Subsequently, to acquire further insight on the effect of the chelating DME on the coupling reaction, we decided to examine the influence of the ligand stoichiometry on the reaction developed in toluene (Table 2).



^[a] Isolated yields after centrifugal thin-layer chromatography purification.

The obtained results clearly showed that the use of an increased amount of ligand had a beneficial effect on the yield. While the use of a substoichiometric amount of ligand seemed to dramatically affect the reaction (entry 2), better yields were not achieved when increasing the amount of ligand to 10.0 equiv. (entry 7) and it appeared overall that 4.0 equiv. of ligand proved to be optimal (entry 6), results remaining pretty close to those initially obtained in THF (see Table 1, entry 2). On the other hand, it has been reported previously^[18h,19] that the use of 2.0 equiv. of *t*·BuLi in the reaction conditions could potentially "remove" a full equivalent of ligand by preferential complexation of the latter with the lithium bromide salt generated by elimination reaction starting from the *t*-BuBr formed and the excess of base (*t*·BuLi). To address this problem, one solution is to increase the [ligand:*t*·BuLi] ratio, either by increasing the amount of ligand used or by decreasing the stoichiometry of the base. Attempts to use a [ligand:*t*-BuLi] ratio of [1:1] in the reaction performed with DME had a deleterious effect on the yield (29%, entry 4, Table 2). This result naturally led us to question on the actual effect of LiBr on the coupling reaction.

Subsequently, to acquire further insight regarding the influence of lithium bromide, inevitably generated along with benzyne, as well as in the first stage of the reaction when using 2.0 equiv. of *t*-BuLi, we investigated the effect of this salt when added to the reaction in toluene during the metalation step, with and without DME (Table 3). Importantly, in addition to the classical metalation route employed until now with *t*-BuLi for **1a** (Metalation A), a second metalation protocol (Metalation B) using *n*-BuLi (1.0 equiv.) as the base was developed to avoid the initial formation of LiBr in the reaction medium, making this metalation pathway the "salt-free reference method".

Considering first attempts performed with DME, it is clear that the salt positively affected the reaction: up to 69% yield was indeed achieved when an excess of LiBr was added to the reaction using the usual metalation path A (entry 7, metalation A) overtaking the previous results obtained without further introduction of salt by approximately 10 points (58%, entry 3, metalation A). Interestingly, whether metalation path A or B was used for the metalation of 3bromothiophene, similar results were obtained when a comparable amount of salt was added to the reaction (entries 3-7). Especially an appreciable increase was reported when more than 3.0 equiv. of salt were added to the reaction. The LiBr effect is actually demonstrated by the considerable drop in yield observed without any salt in the reaction mixture apart from the one formed concomitantly with benzyne (40%, entry 2 -salt-free metalation B without LiBr addition). Nevertheless, addition of the ligand remains essential to the reaction since all experiments failed to occur when performed without DME, whatever the amount of LiBr used or the metalation path followed (entry 1). It appeared overall that the previous hypothesis on the possible trapping of the ligand by the salt generated in the metalation step improvement of the yield observed when using an increased amount of ligand- is not consistent with these observations, and that the combination of both salt and ligand seemed favorable to the reaction.

Table 3: Influence of LiBr addition on the optimized reaction using metalation A or B.

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i) RLi (p equiv.), toluene.



LiBr A : 1 + x equiv. B:0+x equiv.

iv) 2 (1.2 equiv.),

v) H₂O, -50 °C

toluene, -50

°C, 2h

entry	Metalation A (t-BuLi) ^[b]			Metalation B (n-BuLi) ^[b]			
	DME	LiBr ^[c]	Yield ^[a] (%)	DME	LiBr ^[c]	Yield ^[a] (%)	
	(m eq)	(1 + x eq)	3a	(m eq)	(0 + x eq.)	3a	
1	0	0 + (1 to 4)	0	0	1 + (1 to 4)	0	
2	-	-	-	4.0	0+0	40	
3	4.0	1 + 0	58	4.0	0 + 1	56	
4	4.0	1 + 1	58	4.0	0 + 2	58	
5	4.0	1 + 2	60	4.0	0 + 3	59	
6	4.0	1 + 4	67	4.0	0 + 5	65	
7	4.0	1 + 9	69	4.0	0 + 10	67	

^[a] Isolated yields after centrifugal thin-layer chromatography purification.^[b] Metalation A: + BuLi (2.0 equiv.) toluene, -80 °C, 1h; Metalation B: n-BuLi (1.0 equiv) toluene, -40 °C, 1h. [c] Note that LiBr (1.0 equiv.) is also generated during the formation of the aryne intermediate (step 3, scheme 1)

Guided by the experimental results above, we decided to carry out a theoretical study trying to shed new light on the main factors that affect the reaction mechanism. Below, we report an interpretation scheme according to which different factors that might influence the reaction are considered separately. Since coordinating ligands (DME) were found to be necessary for the reaction to proceed, we assumed that the reactions would take place with the aryl lithium compounds as monomers.

Computational modeling and mechanism interpretation:

In our computational analysis, we investigated the reaction path, with a particular attention to the formation of the aryne intermediate and to the influence of the presence of a salt and of a coordinating ligand on the overall reaction mechanism. To match with the experimental procedure, our model system was thiophene-Li in toluene, although complementary calculations were performed on the reaction involving PhLi in tetrahydrofuran for comparison purposes (see below), as this is a model for the aryl-aryl coupling reaction reported by Leroux et al.[11] The preliminary formation of thiophene-lithium from bromothiophene and t-BuLi was not investigated here but it is worth noting that the lithiation of 2-bromothiophene has already been studied at a theoretical level.[20]

Before presenting our results, it is worth mentioning other theoretical investigations in the literature related to these systems. It has been pointed out that thiophene displays similar capacities compared to benzene, in particular with respect to the formation of aryne intermediates.^[21] The reactivity of 3-substituted and 3,6-

substituted benzynes from 2-haloaryllithium compounds has been extensively studied at a theoretical level by Riggs et al.[22] In that work, the role of the coordinating solvent THF was explicitly taken into account and the authors suggested that a different dissociation mechanism was found for the elimination step leading to the benzyne when LiF and LiCl were considered. Density Functional Theory (DFT) computations were carried out for the carbolithiation of olefinic aryllithiums (ArLi), showing that the role of a coordinating solvent, such as THF, would affect rather the aggregation state of the ArLi intermediates than the overall reaction mechanism.^[23] Indeed, several theoretical studies have reported the importance of the role of coordinating solvents such as THF and/or of Lewis bases in the association/dissociation equilibria involving organolithium compounds that leads in some cases to strong regio- or chemo-selectivity effects. [24,25,26,27]

In the following, we compare the different reaction steps for the two systems considered, namely thiophene-Li and PhLi reacting with dibromobenzene, in toluene and THF, respectively (Figures 1-3). The role of explicit consideration of LiBr (Figure 4) or DME (Figure 5) will be analyzed afterwards. We note that in all Figures the reported values are relative values, calculated with respect to the reference given by the initial reactant (dibromobenzene). Both electronic energies corrected for the zero-point energy (ZPE) and free energies were computed and are reported in the Figures. Activation energies given with respect to the energy minimum preceding the transition state are reported in blue italics. For the sake of simplicity, in the discussion below, only the values of the ZPE-corrected energies, defining the potential energy surface (PES) of the reaction, will be considered. We refer to the Figures for the naming of the stationary points and their optimized structures are reported as Supporting Information.

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Figure 1. Theoretical calculation of the potential energy surface describing the formation of the first reaction intermediate when a) thiophene-Li in toluene and b) PhLi in THF are studied. The reported values are not in scale and the energy barriers are reported in blue italics.

As shown in Figure 1, the overall barrier to give the required intermediate for the coupling reaction (3-Thio or Int3-Ph) is significantly smaller in the case of the reaction of dibromobenzene with PhLi. We note that two minima were found for the 1-Thio intermediate (namely, 1a-Thio and 1b-Thio), differing with respect to the mutual orientation of the two rings. Figure 2 displays the energy profile for the aryne mechanism and C-C bond formation step. The computed PES illustrates, on one hand, that the formation of an aryne intermediate by direct elimination of LiBr is thermodynamically unfavorable in both reactions. Instead, the process proceeds through reaction with another monomer of the organolithium compound, thiophene-Li or PhLi. In the case of the process involving PhLi, our calculations reveal the formation of an aryne intermediate (Int5A-Ph). Noteworthy, this intermediate lies in an extremely flat potential energy surface; as shown in Figure 2b, the zero-point corrected energy is very close to the values for the two adjacent transition states TS5A-Ph and TS5B-Ph (actually, the corrected energy of the intermediate is even slightly above that of the transition states). The presence of

this extremely flat region on the PES is consistent with the results provided by Riggs et al.^[22] for reactions involving aryne species. In contrast, in the case of the reaction with thiophene-Li, no such an intermediate could be found and the process goes directly from the intermediate 4-thio to the aryl-aryl 6-thio compound. Considering the flatness of the surface in the case of the PhLi process, we cannot definitively exclude that a similar aryne intermediate structure actually exists in the case of the thiophene-Li reaction but several attempts to locate an energy minimum were unsuccessful. As a matter of fact, the geometrical structure of the TS5-thio transition state is quite similar to that of the intermediate Int5A-Ph, and in particular, analysis of the C-C distances show that an aryne-like ring is formed (one C-C bond length is close to 1.25 Å, the other C-C bond lengths are in the range 1.38-1.41 Å, see supporting information). We can therefore conclude that the formation of a transient aryne structure postulated by some experiments in the aryl-aryl coupling reaction mechanism^[11] is supported by our theoretical study.

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Figure 2. Theoretical calculation of the potential energy surface describing the aryne mechanism and C-C bond formation step when a) thiophene-Li in toluene and b) PhLi in THF are studied. The reported values are not in scale and the energy barriers are reported in blue italics. In b), for the reaction starting from PhLi, the Int6-Ph structure was optimized using a larger basis set (see text for details) and the reported values (in red) were thus evaluated differently with respect to the overall PES.

The energy barrier for the process giving rise to **6-Thio** (13.5 kcal/mol) is comparable to the barrier leading to **Int6-Ph** (in this case, the effective barrier can be estimated to 12.7 kcal/mol, considering that the intermediate **Int5A-Ph** is the highest energy point separating **Int4-Ph** and **Int6-Ph**). The stabilization energy computed for **6-Thio** with respect to **4-Thio** amounts to 67.9 kcal/mol, while the stabilization energy of **Int6-Ph** with respect to **Int4-Ph** was estimated to 88.0 kcal/mol. Note that in the latter

case, the stabilization energy was evaluated at a different theoretical level because the optimization (started from the final structure in the Intrinsic Reaction Coordinate calculation, see experimental section) did not converge at the M062X/6-31G(d,p) level of theory. Hence, additional calculations were carried out at the higher level M062X/6-311+G(d,p) (the stationary point found in this case has a very small imaginary frequency, with absolute value 6 cm-1).



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Figure 3. Theoretical calculation of the potential energy surface describing the regeneration and final reaction steps when a) thiophene-Li in toluene and b) PhLi in THF are studied. The reported values are not in scale and the energy barriers are reported in blue italics. The values in red for Int6-Ph represent an estimate, as explained in the main text (see also Figure 2).

At this stage, the biaryl-Li compounds are formed but the process must proceed through reaction with dibromobenzene for the regeneration of 2-bromophenyllithium, which is necessary to complete the chain reaction (see Scheme 1). If this is accompanied by elimination of LiBr, the formation of the corresponding reaction intermediates **7C-Thio** and **Int7-Ph** is energetically very disfavored in both cases, as illustrated in Figure 3. In addition, from these intermediates the activation energy toward the final products amounts to 15.5 kcal/mol (thio-derivative in toluene) or 12.3 kcal/mol (2-bromobiphenyl in THF).

For comparison with the results above, we explored the effect of explicitly including LiBr in the reaction mechanism. For simplicity, we only considered the case of the reaction between the heterobiaryl-Li compound (6-Thio) and dibromobenzene in toluene. The results are reported in Figure 4. By doing so, we

expect our computational results to provide an explanation of the experimental finding according to which the use of this salt has a favorable effect on the process (even though it is poorly soluble in the reaction medium). As a matter of fact, our computations show that, globally, the incorporation of a lithium bromide monomer into the process leads to the formation of much more stable species. Indeed, in the presence of LiBr, the favorable formation of a complex between **6-Thio** and dibromobenzene is obtained (compare **10-Thio** and **7C-Thio**). Likewise, the final products are stabilized with respect to the reactants (**6-Thio** and dibromobenzene) by 11.0 kcal/mol (compare **12-Thio** and **9C-Thio**). The energy barrier to obtain the corresponding final product and to regenerate 2-bromophenyllithium is quite similar to that obtained in the absence of LiBr, though slightly higher (17.9 kcal/mol, to be compared with 15.5 kcal/mol).



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Figure 4. Theoretical calculation of the potential energy surface describing the effect of the explicit presence of LiBr on the PES in the case of thiophene-Li in toluene and comparison with the PES obtained in the absence of LiBr. The reported values are not in scale and the energy barriers are reported in blue italics.

We turn now to examine the effect of explicit consideration of a chelating ligand in the calculations. As we have mentioned before, experiments showed that the presence of DME in the medium is necessary for the reaction to proceed and in the results reported thus far, we implicitly accounted for this finding by considering organolithium monomers in the theoretical model. However, it is interesting to reveal whether the inclusion of explicit ligand molecules influences the position of the relevant stationary points along the reaction path. Results for the reaction involving thiophene-Li in toluene when one DME molecule is present are shown in Figure 5. As illustrated by comparing the energies in Figure 5 with those reported in Figures 1-3a, all the structures are strongly stabilized by the interaction with the DME molecule, as expected. There are, however, significant differences between the different stabilization energies, and this fact implies that the individual reaction steps can display important changes under DME addition. Let us briefly comment some specific values for the activation barriers. The activation energy for the first reaction step in the presence of DME 1-ThioDME -> 3-ThioDME amounts 10.9 kcal/mol, which is much lower than the 16.7 kcal/mol that are necessary for the equivalent step in the absence of DME, i. e. for the process 1a-Thio -> 3-Thio (Figure 1). The next step that requires a substantial activation energy concerns the process 4-ThioDME -> 6-ThioDME, or equivalently 4-Thio -> 6-Thio in the absence of DME (Figure 2). This elementary step involves the transient aryne formation and the associated activation energies are not quite different, independently of the presence or absence of DME (14.5 kcal/mol vs 13.5 kcal/mol, respectively).

Finally, the last part of the reaction connecting 6-ThioDME to 9-ThioDME deserves some special remarks. In the DME assisted process (Figure 5), 6-ThioDME first forms a complex with dibromobenzene liberating LiBr, 7-ThioDME. This is a favorable process with negative reaction energy -6.4 kcal/mol. In contrast, as noted before, in the absence of DME (Figure 3), this process (6-Thio to 7C-Thio) is guite unfavorable involving a positive reaction energy as large as 16.8 kcal/mol. Hence, despite a larger barrier for the elementary step 7-ThioDME -> 9-ThioDME, compared to the barrier for the 7-Thio -> 9-Thio process (24.4 kcal/mol vs 15.5 kcal/mol, respectively), the overall kinetics of the reaction step leading from 6-ThioDME to 9-ThioDME is expected to be much faster than the one for the non-assisted process 6-Thio to 9-Thio and this seems to be one of the important effects of the DME ligand. It is worth to note, in addition, that in this reaction step LiBr is assumed to be liberated, a process that can

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be enhanced by interaction of the salt monomer with DME molecules; the number of DME equivalents in the experiments is then expected to affect very especially the energetics and even the mechanism of this reaction step. The supporting information provides other complementary results obtained for the reaction, in particular the energetics for the process when both lithium bromide and DME are explicitly considered. Further confirmation of the stabilizing effect achieved by using DME and LiBr is found by considering the lowering in energy of the **7-ThioDME** intermediate (Figure 4), obtained in the presence of LiBr, in the

corresponding PESs in the presence of DME (**7-ThioDME**, Figure 5) and of both DME and LiBr (**10-ThioDME**, in the SI). The same trend is observed for the products (12-Thio in Figure 4, **9-ThioDME** in Figure 5 and **12-ThioDME** in the SI).

All in all, our results hint at the fact that both LiBr and the chelating ligand concur to the optimization of the overall reactivity, in agreement with the experimental observations. Despite the inevitable simplifications of the computational models, this finding supports the reaction mechanism described above for the direct arylation of thiophene via the aryne route.



Figure 5. Theoretical calculation of the potential energy surface describing the effect of the chelating ligand DME on the PES in the case of thiophene-Li in toluene. The reported values are not in scale and the energy barriers are reported in blue italics.

Conclusions

In this work, we have demonstrated that the "Aryne coupling" methodology —which focused so far (exclusively) on carbocyclic biaryl compounds— can be efficiently applied to the construction of hetaryl-aryl backbones by the use of a heterocyclic coupling partner in the reaction, resulting in a promising transition metal-free "Het-Aryne coupling" methodology. In our experiments, we performed regioselective β -arylation of thiophene in good yields in both coordinating and non-coordinating solvent with the aid of

chelating ligand DME and LiBr salt; we thus showed that the use of such additives could sensibly improve the yield of the reaction. Theoretical modeling has allowed us to propose a mechanistic scheme for the reactions. According to the computational study, the postulated aryne intermediate is indeed formed along the processes; it appears as a short-lived species in all cases. However, though it is produced as a labile reaction intermediate in the reaction path of bromobenzene, in the "Het-Aryne" route it forms upon activation to the transition state preceding the arylaryl bond formation. An interpretation of the positive effect of adding LiBr and a ligand on the reaction was provided too.

Currently, a further analysis of the role of the *O*-, *N*- or *S*-based heterocyclic partner as well as of ligand and salt additives through this strategy is being developed.

Experimental Section

Computational details: All calculations were performed using the Gaussian09 package.^[28] The M06-2X/6-31G(d,p) level was chosen to optimize all geometries.^[29,30] It is worth mentioning that this choice was made based on the extensive benchmark studies by Pratt's group.^[31] Transition state structures were located using the string method as implemented in the freely available Opt'n Path software.^[32] Such structures were confirmed by performing IRC (Intrinsic Reaction Coordinate) calculations.^[33] Single point calculations of the electronic energies were performed with the 6-311++G(d,p) basis set. The zero-point energy correction was included based on the geometry optimization level at 1 bar and 298 K. An implicit solvation model (IEF-PCM) was considered in all calculations.^[34] The reaction path for thiophen-Li was performed in toluene and the one for PhLi in THF.

General Methods. All reactions were performed under argon atmosphere in oven and flame-dried, argon-cooled glassware. All air- and moisturesensitive compounds were introduced via syringes through a rubber septum. ¹H and ¹³C NMR spectra were recorded on a Bruker 200- or 400 MHz spectrometer with CDCl₃ as solvent. Chemical shifts are reported in δ units (parts per million, ppm) and were measured relative to the signals for residual chloroform (7.26 ppm for ¹H NMR and 77.00 ppm for ¹³C NMR). Coupling constants J are given in Hz. Coupling patterns are abbreviated as s (singlet), d (doublet), td (triplet of doublets), m (multiplet). MS experiments were recorded on a GCMS-QP 2010 spectrometer. Thin-layer chromatography (TLC) was carried out using 0.25 mm Merck silica-gel (60-F254) plates and visualized under UV light. Centrifugal thin-layer chromatography purifications were performed on silica gel (silica gel 60 PF254 containing gypsum).

Reagents. All reagents were commercially available and used as received after adequate checks/without further purifications unless otherwise stated. *n*-BuLi (1.6 M in hexane) and *t*-BuLi (1.7 M in pentane) were titrated prior to use against diphenylacetic acid in dry THF. Commercial grade anhydrous LiBr was dried on a MB25 ohaus thermobalance before use. DME and hexane were stored over sodium wire before use. THF and toluene were freshly distilled and stored under argon before use.

3-(2-Bromophenyl)thiophene (3a).[35]

Procedure in THF. At -80 °C, a solution of 3-bromothiophene (**1a**; 0.326 g, 2.0 mmol) in THF (3 mL) was added dropwise to a solution of *t*-BuLi (4.0 mmol, 2.0 equiv.) in THF (5 mL). After stirring for 1h, the reaction mixture was allowed to reach -50 °C and 1,2-dibromobenzene (**2**; 0.566 g, 2.4 mmol, 1.2 equiv.) in THF (4 mL) was added. After 2h of stirring at -50 °C, the reaction mixture was hydrolyzed with water (15 mL) and was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over MgSO₄, and solvents were removed under reduced pressure. The crude product was purified by centrifugal chromatography using hexane to afford 0.287 g (60%) of compound **3a** as a colorless oil.

General procedure in Toluene/DME with the addition of LiBr.

Metalation (A) To a solution of *t*-BuLi (2.0 equiv., 1.7M in pentane) at -80 °C in toluene (5 mL) was added a solution of 3-bromothiophene (1.0 equiv.). After stirring for 1h, dried LiBr (x equiv.) was added to the mixture

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at -80 °C, followed by the addition of DME (m equiv.) after stirring for 5 min. at the same temperature. The temperature was allowed to rise until -50 °C for 45 min. and 1,2-dibromobenzene (1.2 equiv.) was added. After 2h of stirring at -50 °C, the reaction mixture was hydrolyzed with water (15 mL) and was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over MgSO₄, and solvents were removed under reduced pressure.

Metalation (B) To a solution of 3-bromothiophene (1.0 equiv.) at -40 °C was added a solution of *n*-BuLi (1.0 equiv., 1.6M in hexane). After stirring for 30 min., dried LiBr (x equiv.) was added to the mixture at the same temperature followed by the addition of DME (m equiv.) at -40 °C after stirring for 5 min. The temperature was lowered to -50 °C after stirring for 45 min, and 1,2-dibromobenzene (1.2 equiv.) was added. After 2h of stirring at -50 °C, the reaction mixture was hydrolyzed with water (15 mL) and was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over MgSO₄, and solvents were removed under reduced pressure.

¹H NMR (CDCl₃) δ 7.18 (td, J = 8.0 Hz, J = 0.4 Hz, 1H), 7.30-7.42 (m, 5H), 7.67 (d, J = 8.0 Hz, 1H); 13 C NMR (CDCl₃) δ 122.6, 124.0, 124.8, 127.4, 128.7, 128.9, 131.3, 133.4, 137.5, 141.1; MS (EI): m/z 238 ([M]+,18); 115 (53); 89 (20); 63 (40); 45 (100); 39 (45); HRMS m/z 237.9455 (calcd for C10H7BrS, m/z 237.9452).

2-Bromobiphenyl (3b) (Procedure in THF).[36]

At -80 °C, a solution of bromobenzene (**1b**; 0.314 g, 2.0 mmol) in THF (3 mL) was added dropwise to a solution of *tert*-butyllithium (4.0 mmol, 2 equiv.) in THF (5 mL). After stirring for 1h, the reaction mixture was allowed to reach -50 °C and 1,2-dibromobenzene (**2**; 0.566 g, 2.4 mmol, 1.2 equiv.) in THF (4 mL) was added. After 2h of stirring at -50 °C, the reaction mixture was hydrolyzed with water (15 mL) and was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over MgSO₄, and solvents were removed under reduced pressure. The crude product was purified by centrifugal chromatography using hexane to afford 0.205 g (44%) of compound **3b** as a colorless oil. ¹H NMR (CDCl₃) δ 7.08-7.37 (m, 5H), 7.42-7.79 (m, 4H). ¹³C NMR (CDCl₃) δ 122.2, 127.1, 127.4, 127.7, 128.9, 129.3, 131.2, 133.1, 141.0, 142.1. MS (EI): *m/z* 234 (33); 152 (65); 126 (11); 87 (14); 74 (56); 63 (52); 50 (87); 39 (100).

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Keywords: reaction mechanisms • aryne • salt effect • ligand effect • density functional calculation

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Abstract: This paper presents the results of our investigations on the arylation of thiophene using the transition metal-free "Aryne coupling" methodology. The reaction was studied by both experiment and computation (density functional theory) and comparison with phenyllithium was established. In parallel, the effect of ligand and salt on the coupling reaction was examined. The results underline the remarkable effect of such additives on the coupling reaction and the potency of the method to construct hetaryl-aryl backbones which open up a promising access to a wide range of heterobiaryl structures using the novel "Het-Aryne" route.



Reaction mechanisms • density functional calculation*

Catherine Demangeat, Tarak Saied, Romain Ramozzi, Francesca Ingrosso,* Manuel Ruiz-Lopez, Armen Panossian, Frédéric R. Leroux, Yves Fort, Corinne Comoy.*

Page 1. – Page 12. Transition-Metal-Free Approach for the Direct Arylation of Thiophene: Experimental and Theoretical Investigations towards the (Het)-Aryne route