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Lithium/Element Exchange as an Efficient Tool for Accessing Atropo-enriched Biaryls *via* Arynes

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Dedicated to Professor Manfred Schlosser

Abstract: This account documents the development of transition metal-free, aryne-mediated aryl-aryl coupling, the 'ARYNE coupling', which began in 2001 in Lausanne. *ortho,ortho'*-Di-, tri- and even tetrasubstituted biphenyls have now become accessible on a multi-gram scale. The reaction is perfectly regioselective and the obtained polybromobiphenyls can be submitted to regioselective bromine/lithium interconversions. The access to enantiopure biphenyls is now possible using enantiopure sulfoxides as chiral auxiliaries, which allow for subsequent chemoselective sulfoxide/metal exchange on each atropo-diastereoisomer with configurational stability of the intermediate biaryllithiums. Direct atropo-diastereoselective ARYNE coupling has been reported more recently.

Keywords: Aryllithium · Aryne · Biaryl · Bromine/lithium interconversion · Coupling · Stereoselectivity

1. Introduction

The presence of biaryls in numerous drugs, natural products, catalysts, and organic materials stresses the importance of these structural motifs. Accordingly, various strategies were explored for their synthesis. Particularly, the control of axial chirality is a stimulating and challenging research field. Several excellent review articles have tackled this aspect in the past years.[1–8] In the present account, we will describe the developments, carried out in our laboratory, relating to the transition metal-free access to biaryls, the so-called 'ARYNE coupling', which started during a Lausanne visit. We started to investigate there the potential of a known reaction of a 2-bromo- or 2-iodo-halobenzene and an aryllithium, leading to biaryls bearing a functionalizable halogen in position 2.[9–12] After studying its regioselectivity,[9,11–14] we applied it to the synthesis of various phosphorus ligands bearing C_1-symmetry.[15–18] Next, we accessed highly atropo-enriched biphenyls in a highly modular manner by means of the ARYNE coupling.[19] The latter was used to prepare achiral or racemic polyhalobiphenyls, which were then desymmetrized or deracemized. In particular, we used 2,2',6-tribromo-1,1'-biphenyl as a platform for sequential, regio- and stereoselective derivatizations to access atropo-enriched biphenyls. More recently, our attention has focused on an alternative method, where a chiral auxiliary is already present on one of the coupling partners, leading to an atropo-diastereoselective ARYNE coupling.[20]

2. Transition-metal Free Construction of Biphenyls

2.1 *The ARYNE Coupling*

ortho-Dihaloarenes can serve as efficient sources of transient *ortho*-arynes, which can be trapped *in situ* with aryllithium compounds, allowing the preparation of *ortho*-halobiaryls. This 'ARYNE coupling' has become a robust method for biaryl synthesis, and presents several advantages when compared to other aryl–aryl coupling methods: cheap and/or easily accessible halogeno-aromatic starting materials; possibility to produce, highly selectively, dissymmetric biaryl units and – further functionalizable – poly-halogenated biaryls (which are difficult to prepare selectively with the usual methods); no transition metals required, but only organolithium or -magnesium bases; and multi-gram reaction scales.[12]

The mechanism proceeds as a chain reaction,[12] (Fig. 1) and involves several organometallic species, whose relative basicities are critical for the course of the reaction: 1) By lithiation or halogen/lithium exchange and possible equili-

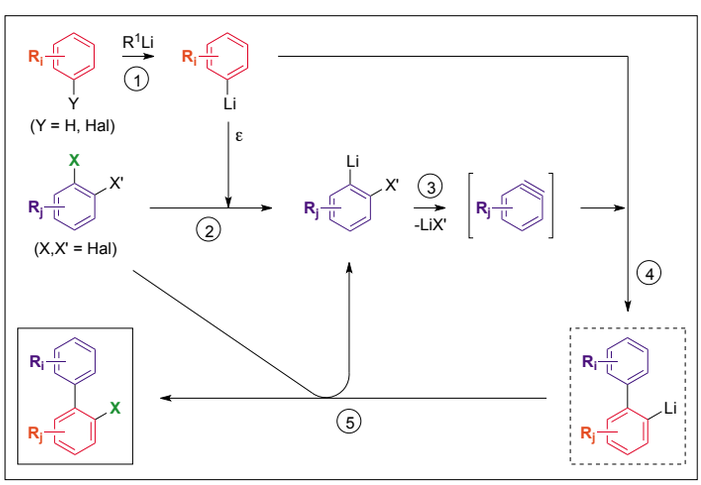

Fig. 1. Mechanism of the ARYNE coupling.

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bration, a thermodynamically stable organolithium intermediate is formed; of which 2) a small amount reacts with the *ortho*-dihalobenzene *via* halogen/metal exchange, generating a thermodynamically unstable *ortho*-halophenyllithium intermediate (*Initiation*). 3) The latter collapses into the key aryne intermediate by spontaneous elimination of lithium halide, then 4) undergoes nucleophilic addition of the organolithium precursor to produce a 2-biaryl lithium intermediate, which 5) is quenched *in situ* by transfer of bromine or iodine from the aryne precursor, thus generating again some *ortho*-halophenyllithium to pursue the chain reaction (*Propagation*). The *Termination* of the chain reaction is believed to occur *via* trapping of the aryllithium species by protons or by di- or trimerization of the aryne, since the corresponding products were observed by GCMS analysis. The ARYNE coupling can be carried out on gram-scale to afford bromo- or iodobiaryls that are mono-, di- or even tetra-substituted in positions *ortho* to the aryl–aryl bond. S. L. Buchwald *et al.* actually reported on an impressive application of this methodology in the preparation of one of the most versatile ligands for the Suzuki-Miyaura coupling (S-Phos) .[21]

A key point of the reaction was to be able to determine which would be the major biaryl product, *i.e.* what would be the regio- and/or chemoselectivity of the reaction. This implies predicting the nature of the aryllithium nucleophile (obtained in stage 1 of the mechanism in Fig. 1), as well as the one of the aryne intermediate, and the regioselectivity of the addition onto the latter (stage 4).

First, the selectivity of the formation of the aryllithium nucleophile could be conveniently anticipated, since the monolithiation of substituted benzene rings is under thermodynamic control – provided that enough equilibration time is ensured. Indeed, relative basicities of aryllithiums can be predicted thanks to $\Delta\Delta G$ increments calculated from equilibrium constants by Schlosser *et al.* for each methoxy, chlorine, fluorine, trifluoromethyl and trifluoromethoxy substituent, in positions *ortho*, *meta*, and *para* to lithium.[22]

Second, while no regioselectivity issue was expected when 1,2-dibromobenzene or 1-bromo-2-iodobenzene were used as benzyne source, one major challenge was to find an efficient access to suitable and decorated aryne precursors. Indeed, only few functionalized 1,2-dibromobenzenes were accessible or had been described in the literature. To overcome these restrictions, our group developed straightforward syntheses of numerous 1,2-dibromobenzenes with various substitution patterns.[14] Furthermore, we studied then the regioselectivity of the addition of aryllithiums onto these dissymmetrical benzynes (Fig. 2) in order to find reaction conditions allowing the ARYNE coupling with complete control of the regioselectivity.

We showed that the ARYNE coupling becomes fully regioselective using various dissymmetric benzynes when a trimethylsilyl group is located in *ortho* position to the triple bond, which orients the addition of the nucleophile during the coupling. Moreover, the silyl group can be afterwards either removed by protodesilylation or converted *via* halo-, borodesilylations, *etc*.[13]

2.2 *Regioselective Bromine/Lithium Interconversions on Polybromobiphenyls*

As polyhalobiaryls can be obtained by ARYNE coupling, we then had to determine whether one Br atom among others would undergo selective exchange on compounds where those bromine atoms are not activated by adjacent, but rather remote heteroatoms or groups. Only occasional examples were reported where the chemical environment of two bromine atoms allows for such an effective discrimination.[23–27] Luckily, systematic studies on the bromine/lithium permutation on doubly brominated aromatic substrates enabled us to demonstrate reactivity differences.[24,25] The presence of a remote, additional halogen substituent was enough to provide an activating effect, as we demonstrated in intramolecular competition experiments on 1,3-dibromo-5-(((3-bromobenzyl)oxy)methyl)benzene or 2,2',6-tribromobiphenyl (Scheme 1).[24] In both cases, we exclusively observed bromine/metal interchange at the ring bearing the additional halogen, whether aromatic rings are directly connected or not.[24]

As we emphasized above, in the polybrominated aromatic substrates of Scheme 1, no vicinal group is present to effect a kinetic discrimination between bromine atoms by pre-coordination of the lithium base. Consequently, the selectivity of these reactions is only under thermodynamic control. Here again, the relative basicities of substituted aryllithiums and the corresponding $\Delta\Delta G$ increments reported by Schlosser *et al.* account for the regioselectivity.

Similarly, when a broader range of 6-substituted 2,2'-dibromobiphenyls were exposed to 1 equiv. of butyllithium in tetrahydrofuran at –78 °C, the bromine/lithium exchange took place regioselectively on the more functionalized ring (Scheme 2). The resulting biphenyllithiums could be trapped with various electrophiles to access selectively diversely functionalized biphenyls in high yield.[17]

2.3 *Desymmetrization of Achiral Biphenyls*

We had now in hand an efficient protocol affording biphenyls rapidly and on multi-gram scale with access to even tri- and tetra-substituted congeners, but in racemic form. We wondered how to ac-

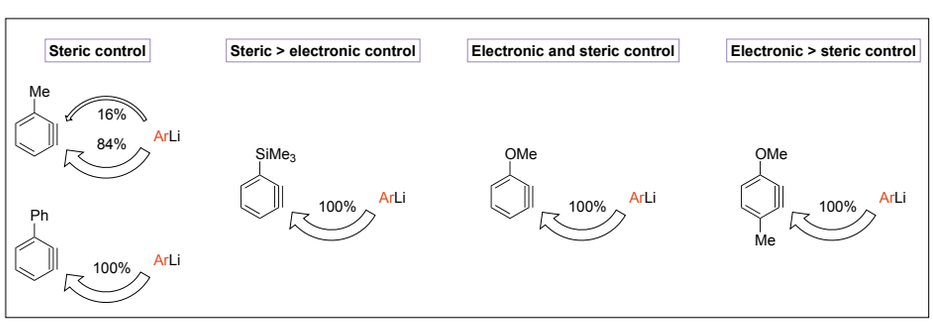
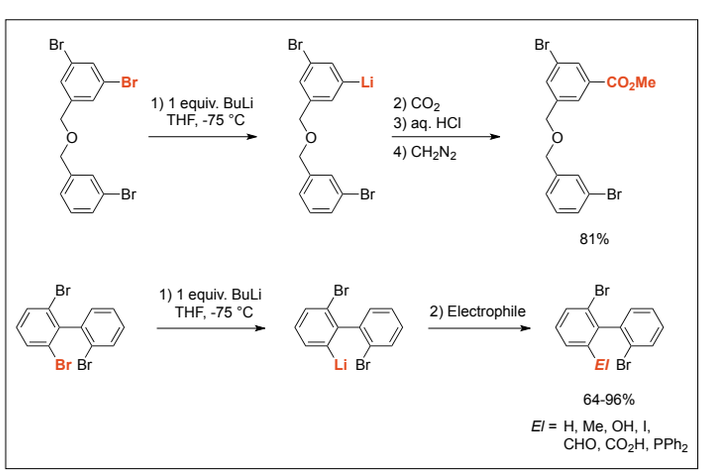
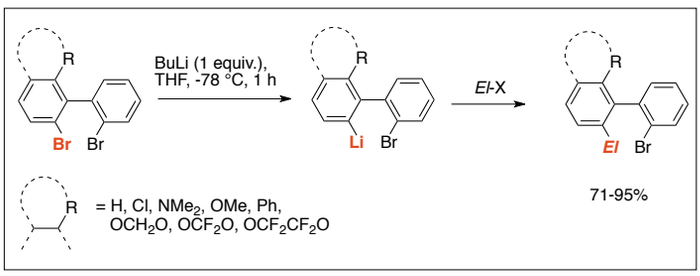


Fig. 2. Parameters influencing the regioselectivity of the addition of aryllithiums onto arynes.



Scheme 1. Regioselective bromine/lithium permutation on seemingly equivalent positions.



Scheme 2. Regioselective bromine/lithium interconversions on various 2,2-dibromobiphenyls.

cess enantiopure compounds. The first approach relied on a desymmetrization strategy employing suitable chiral auxiliaries which should be introduced by means of the regioselective bromine/lithium interconversions described above. The sulfinyl group became our auxiliary of choice as it outcompetes many other chiral auxiliaries, thanks to several advantages:[28–30] i) its high racemization barrier; ii) the availability, in both enantiomeric forms, of several sulfinylating agents, iii) its recognized efficiency as *ortho* directing group, iv) its ability to efficiently transfer the chiral information, v) its dipole moment, which is the preponderant reason for the increased contrast between the physical properties of two stereoisomers bearing the sulfinyl group,[28] and building on this, vi) in the case of the *para*-toluenesulfinyl group, their efficiency as traceless resolving agents, since they can be converted by sulfoxide/lithium permutation[25] and trapping by electrophiles into various functional groups.[31–38]

We applied the latter strategy to 2,2',6-tribromobiphenyl and the related 2,2'-dibromo-6-chloro-analogue, which, after regioselective bromine/lithium exchange,[17,24] were treated with enantiomerically pure (1*R*,2*S*,5*R*)-(–)-menthyl-(*S*)-*p*-toluenesulfinate.[39,40] The expected biarylsulfoxides were obtained in excellent yields as pairs of (*S*,a*R*)- and (*S*,a*S*)-atropodiastereomers, which could be easily separated by simple crystallization (Scheme 3).

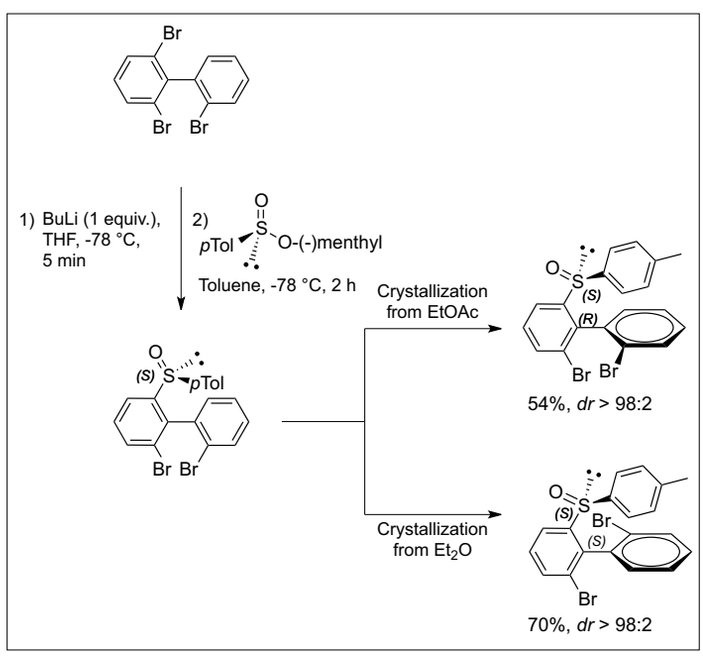
The most challenging part was then to see if a chemoselective functionalization of the resulting isomerically pure biaryls was possible, moreover without loss of axial stereo-enrichment. Indeed, permutational reactions with organolithium reagents are possible on both the sulfinyl group and bromine atoms; additionally, the configurational stability of 2-lithiobiphenyls prior to trapping was critical for this strategy. When the 2-bromo-2'-sulfinylbiphenyls were treated at –78 °C with the usual organolithium reagents butyllithium and *tert*-butyllithium then trapped with electrophiles after 5–10 min., a complete absence of chemoselectivity was observed. On the other hand, P. Knochel's *i*PrMgCl·LiCl reagent afforded a clean sulfoxide/magnesium interchange at –50 °C. However, the trapping of the biarylmagnesium intermediate with an electrophile required a high temperature (0 °C) for complete conversion, leading to partial racemization of the chiral axis.

Thus, the required exchange reagent had to i) be able to discriminate between the bromine atom(s) and the sulfinyl group and ii) produce a biaryllithium intermediate which is reactive enough to be trapped at low temperature. PhLi afforded the best results, by enabling a clean sulfoxide/Li interconversion within a few minutes at –78 °C, and giving, after subsequent trapping with various electrophiles, the desired enantioenriched biaryls with excellent *er*'s (≥ 96:4; Scheme 4).

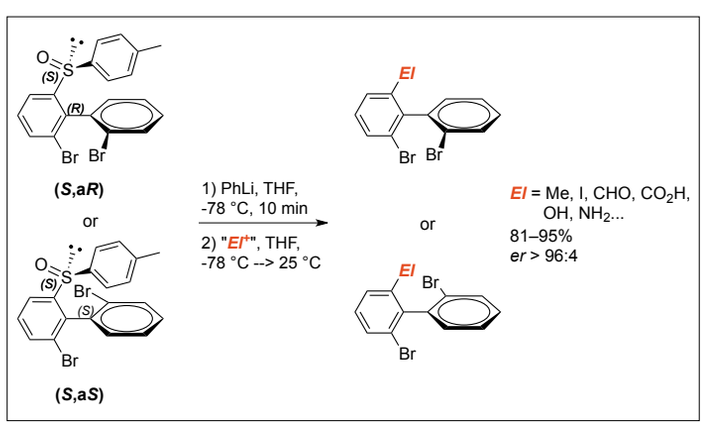
We exemplified the scope of this approach in the complete functionalization of 2,2',6-tribromobiphenyl into an enantioenriched trisubstituted biphenyl bearing three different substituents. First the (*S*,*aR*) atropo-diastereoisomer was transformed into the methoxy derivative. The second functionalization was carried out by regioselective bromine/lithium interchange then trapping with iodomethane. Finally, the third substituent was introduced by a last bromine/lithium exchange followed by quenching with freshly crushed dry ice (Scheme 5). The slight loss of enantioenrichment in the last step of the sequence was expected, even at low temperature, since the intermediate biaryllithium is only substituted by small groups (Me, MeO and Li), as explained by their respective *B* values.[41,42] Additionally, an internal coordination of lithium by the methoxy group could also be envisaged and would facilitate rotation around the aryl–aryl bond.

2.4 *Atropo-diastereoselective ARYNE Coupling*

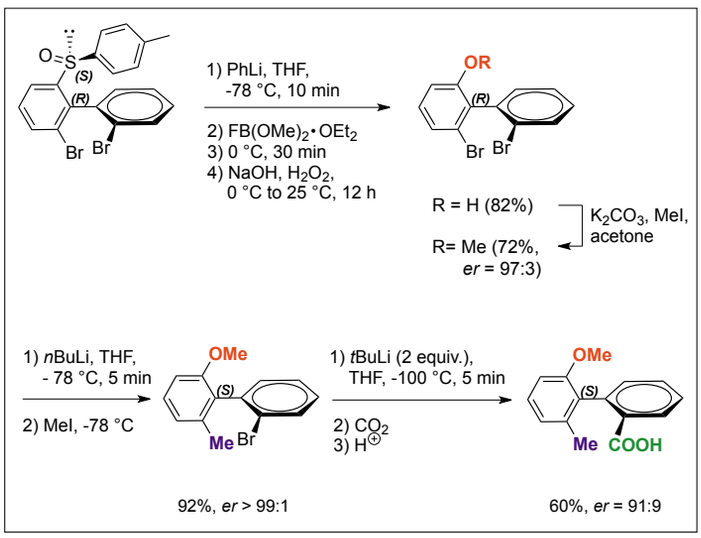
As a logical extension of the previous results, we then envisaged an alternative strategy, where axial stereo-enrichment is



Scheme 3. The enantiopure *p*-tolylsulfinyl group as the key for the desymmetrization of achiral 2,2',6-tribromobiphenyl.



Scheme 4. Chemoselective and stereospecific functionalization of atropo-isomerically pure biaryl sulfoxides.



Scheme 5. Example for a modular biaryl construction.

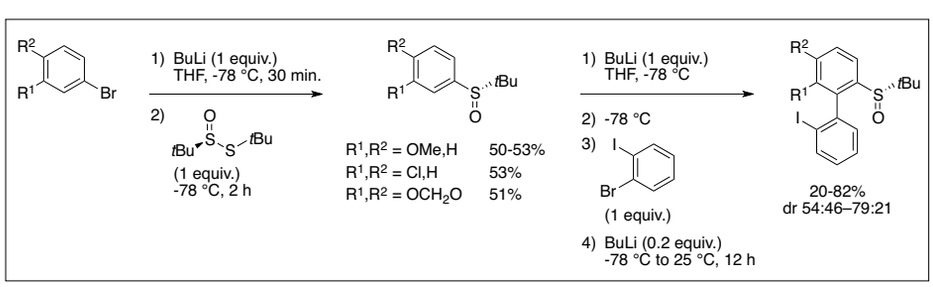
not created after, but in the course of the aryl–aryl coupling step. Therefore, we chose to use a covalently attached chiral auxiliary, namely a chiral sulfinyl group, to mediate this atropo-diastereoselective ARYNE coupling.

The desired aryl *tert*-butyl sulfoxide coupling partners were readily prepared following Ellman's method,[43,44] and submitted to the ARYNE coupling. After several unsuccessful attempts we found an improved reaction protocol, which led to the coupling products in moderate to good yields and atropo-selectivities (Scheme 6).[20] We were able to separate the atropo-diastereoisomers, crystallize them and perform X-ray diffraction crystallography and propose a mechanism for the coupling reaction.

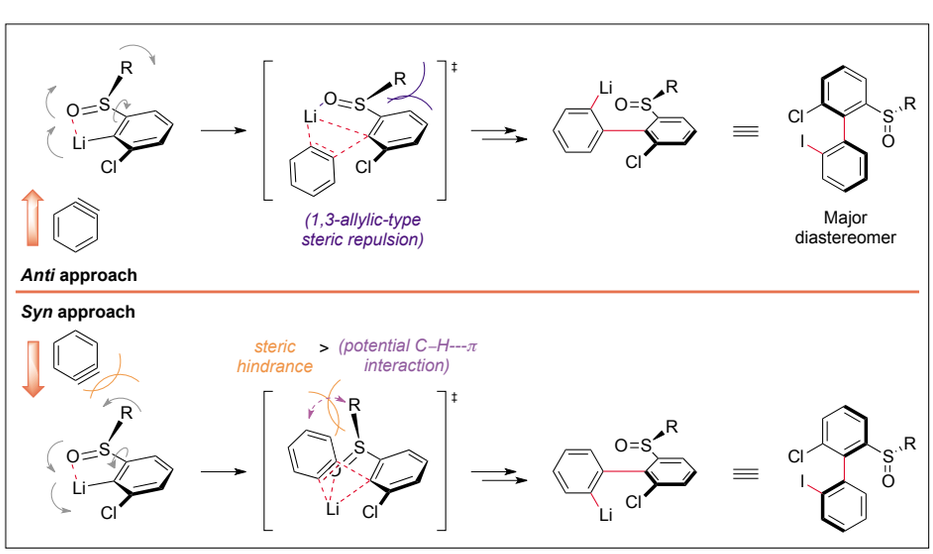
In fact, the stereochemical course of this atropo-diastereoselective ARYNE coupling could be explained by the following rationale (Scheme 7). To ensure the creation of the aryl–aryl bond, the aryllithium and the aryne should approach almost perpendicularly to minimize steric interactions. Since *ortho*-located sulfinyl groups strongly coordinate to lithium, the aryllithium intermediate is presumed to form a metallacycle, with the non-bonding electron pair and the *tert*-butyl substituent pointing away from each side of the arene ring. Two pathways could then compete to determine stereoselectivity. In the first one, the approach of the aryne towards the carbon–lithium bond would take place *anti* to the *t*Bu group; the sulfoxide would be forced to undergo a 'clockwise' rotation in the transition state, thus placing the *tert*-butyl close to the *ortho*-proton. This *anti* transition state would thus be disfavored by an 1,3-allylic-type repulsion. In contrast, in the second scenario, if the aryne approaches the carbon–lithium bond *syn* to the *t*Bu group, the sulfinyl moiety would rotate 'counter-clockwise', forcing the *t*Bu group to become pseudo-axial. Consequently, although the flat aryne approaches perpendicularly to the aryllithium, it would face a significant repulsion by the *t*Bu group, thus dramatically disfavoring the *syn* transition state. On the other hand, due to electron depletion by the electron-withdrawing sulfinyl group, one could expect the C–H bonds of *t*Bu to interact with the π cloud of the aryne *via* a weak electrostatic attraction.[45] Given the absolute configuration of the major atropo-diastereoisomer confirmed by X-ray diffraction crystallography, it appears that the *anti* approach is favored. The steric congestion generated by the *t*Bu group with regard to the *syn* approaching aryne seems therefore to overpower any other stabilizing or destabilizing effects and to determine the stereochemical outcome of the reaction.

3. Conclusion

The ARYNE coupling, a transition metal-free aryl–aryl coupling, has become a powerful tool in organic chemistry allowing the modular construction of *ortho,ortho'*-di-, tri- and even tetrasubstituted biphenyls on multi-gram scale. The reaction involves various aryllthium coupling partners and aryne precursors under perfect regioselectivity of the addition. Subsequent functionalization becomes possible by means of regioselective bromine/lithium interconversions. The access to enantiopure biphenyls has been guaranteed by a desymmetrization protocol using enantiopure sulfoxides as chiral auxiliaries, which allow subsequent chemoselective sulfoxide/metal exchange on each atropo-diastereoisomer with configurational stability of the intermediate biaryllithiums. More recently, a direct atropo-diastereoselective ARYNE coupling has been developed. The concept has found a successful



Scheme 6. Atropo-diastereoselective ARYNE coupling mediated by the *tert*-butyl sulfinyl group.



Scheme 7. Proposed atropo-diastereoselectivity rationale in the ARYNE coupling of aryl *tert*-butyl sulfoxides.

application in the synthesis of monophosphine ligands for C–C and C–N coupling reactions,[17,20,46] diphosphines for asymmetric hydrogenation,[16,26] *P*-chirogenic derivatives,[15,18] phospholes[47] for hydroformylation as well as natural products like (–)-steganacin.[48,49] Actually, our group is now working on an enantioselective version. This approach is highly challenging, in particular if one realizes that only a handful of enantioselective Suzuki-Miyaura coupling reactions – the best potential alternative for a general, user-friendly atropo-enantioselective aryl–aryl coupling leading to unsymmetrical biaryls – on specific substrates have been reported so far.

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