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Atropo-diastereoselective coupling of aryllithiums and arynes — variations around the chiral auxiliary

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ABSTRACT

The atropo-selective coupling of in situ generated arynes and aryllithiums bearing various chiral auxiliaries *ortho* to lithium (*tert*-butylsulfoxide, *para*-tolylsulfoxide, tartrate-derived chiral diethers and oxazolines) is described. Chiral oxazolines showed the best results in terms of yields of coupling products. Different reaction parameters like the nature of the aryne precursor, the oxazoline, the alkyllithium base or the solvent revealed to be crucial for obtaining good yields and for diastereoselection.

1. Introduction

Among the methods allowing access to the biphenyl backbone, the addition of an aromatic carbanion onto a 1,2-didehydroarene, i.e., an *ortho*-aryne, was postulated by Gilman in the late 1950s in the reaction of *ortho*-dihalobenzenes with butyllithium.[1] However, this halogen/lithium interconversion-based method remained rather dormant for several decades while the magnesium-based counterpart was intensively studied by Hart.[2] We started reinvestigating the former in 2001 and then extended its scope to access various biaryls, which could be derivatized to prepare phosphorous ligands, and we clarified the mechanism of the reaction (Scheme 1).[3] This 'ARYNE coupling' is actually a chain reaction, proceeding via sequential halogen/lithium exchanges, and finally yields 2-halobiphenyls that can be functionalized further. Once having developed efficient conditions for the ARYNE coupling, we became interested in its application to the preparation of axially chiral biaryls. Indeed, the synthesis of axially stereoenriched biaryls remains an active research field motivated by their presence in natural products or their use as biologically active compounds, chiral ligands for catalysis, chiral auxiliaries for asymmetric synthesis or optically active organic materials. The most widespread strategies are the resolution of pre-constructed biaryls and the atropo-selective coupling of two aromatic partners.[4] We first tackled the resolution strategy by taking advantage of a specificity of the ARYNE coupling, namely the regeneration of a carbon-exchangeable halogen bond in position 2 of the biaryl product, to introduce a chiral sulfinyl auxiliary enabling desymmetrization or deracemization of the biaryl, separation of atropo-diastereomers, and lastly functionalization by sulfoxide/lithium exchange.[3g] We then investigated the atropo-diastereoselective ARYNE coupling, where a coupling partner bears a chiral auxiliary prior to the coupling, so as to yield atropo-diastereomers of the desired biaryl.[5,3i] We wish, in the present paper, to describe our efforts towards this aim.

2. Results and discussion

In the development of the atropo-diastereoselective version of the ARYNE coupling, the choice of the chiral auxiliary and its location onto the coupling partners were critical. First, the auxiliary should be able to bind to lithium, in order to produce more rigid

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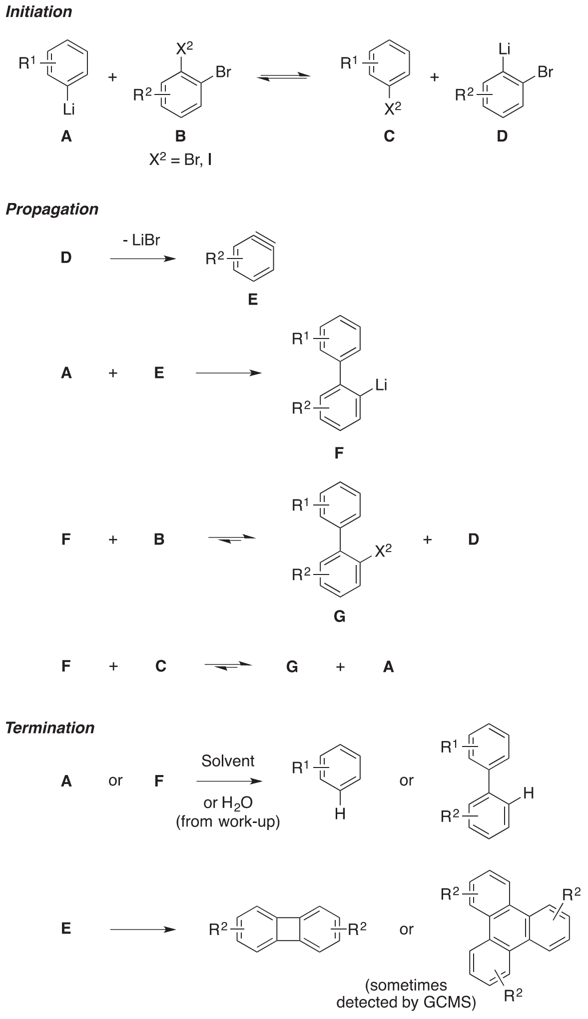


Scheme 1. Mechanism of the ARYNE coupling.

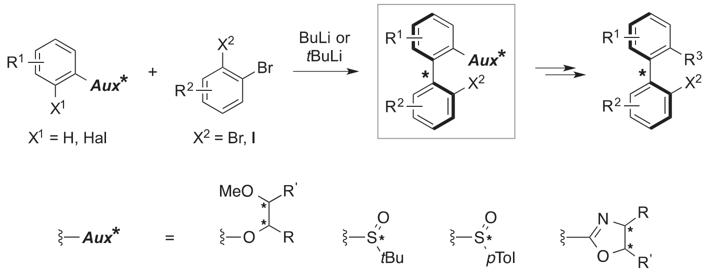
transition states and, consequently, lead to higher stereoselectivity. Therefore, an oxygen- and/or nitrogen-bearing auxiliary was needed. Second, to avoid regioselectivity issues during the addition of the aryllithium nucleophile onto the aryne, the auxiliary should be located on the former, not on the latter. Indeed, as shown by Meyers, a competition between kinetic and thermodynamic additions onto the aryne can take place when an oxazoline is placed *ortho* to the triple bond.[6] Last, we chose to investigate several chiral auxiliaries, bound to the arene ring through sulfur, oxygen and carbon, so as to access a variety of 2-substituted biphenyls after transformation of the auxiliary (Scheme 2). The results obtained with the different kinds of auxiliaries are summarized hereafter.

2.1. Aryl *tert*-butyl sulfoxides

In our first attempt towards the atropo-diastereoselective ARYNE coupling, we chose aryl *tert*-butyl sulfoxides as pronucleophiles.[3i] The known chemical stability of the *tert*-butyl sulfinyl group towards lithium or magnesium bases, as well as its efficient stereoinductive power in directed lithiation– diastereoselective trapping sequences on aromatic compounds,[7] were solid advantages for the potential success of the ARYNE coupling. After a preliminary study with aryl *tert*-butyl sulfoxides **1a**–**d**, prepared by trapping of the corresponding aryllithiums with (*S*)-di-*tert*-butyl thiosulfinate, we soon realized that the usual ARYNE coupling conditions (1 equiv of BuLi to generate the aryllithium nucleophile, followed by addition of 1 equiv of a 1,2-dibromobenzene as aryne precursor) were ineffective to produce the expected biaryls (Table 1).[3i] We assumed a low reactivity of the 2-lithioaryl sulfoxide and/or of the 2-lithio-2′-(*tert*-butyl sulfinyl)-1,1′-biphenyl in the halogen/lithium exchange reaction with the brominated aryne precursor, thus blocking respectively the initiation and/or the propagation of the chain reaction (Scheme 1). We solved this problem by concomitantly replacing the dibrominated aryne precursors by the corresponding 1-bromo-2-iodobenzenes and adding a small amount of additional BuLi after introduction of the aryne precursor so as to trigger the generation of the aryne (Table 1).[3i] Interestingly, in the case of *tert*-butyl 2-lithiophenyl sulfoxide, lacking a substituent in position 3 of the aromatic ring, the coupling could take place even with a less-reactive *ortho*-dibromobenzene aryne precursor, although with complete absence of atropo-stereoselectivity (Table 1, entry 9). The 3-substituent is therefore a critical parameter in the chain reaction.

2.2. Aryl *para*-tolyl sulfoxides

Aryl *para*-tolyl sulfoxides were then considered as appealing alternative substrates in the atropo-diastereoselective ARYNE coupling. Indeed, unlike the corresponding *tert*-butyl sulfoxides, aryl *p*-tolyl sulfoxides can be easily converted into diversely functionalized arenes by sulfoxide/metal exchange using lithium or magnesium bases[8]—a valuable asset for the derivatization of biaryls, as others and ourselves already demonstrated.[9,3g] Yet, for this very same reason, an iodine substituent had to be introduced in position 2 of aryl *para*-tolyl sulfoxides to allow their use as substrates in the ARYNE coupling. Indeed, one could generate the aryllithium nucleophile in situ by direct lithiation either with a lithium amide (lithium di-*iso*-propylamide or lithium 2,2,6,6-tetramethylpiperidide) or an alkyllithium. But the first strategy produces 1 equiv of secondary amine, which can then add onto the aryne,[10] and the second strategy leads to competitive desulfinylation by BuLi. Therefore, the best way to generate the desired 2-lithioaryl *p*-tolyl sulfoxide was via iodine/lithium exchange on substrates **6a**–**b**, as the exchange was reported to be selective for iodine on 2-iodophenyl *p*-tolyl sulfoxide.[11] Thus, substrates **6a**–**b**



Scheme 2. Chiral auxiliaries for the atropo-diastereoselective ARYNE coupling.

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