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Aryne-mediated fluorination: Synthesis of fluorinated biaryls *via* a sequential desilylation–halide elimination–fluoride addition process

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ABSTRACT

An unusual aryne-mediated fluorination of aromatic ring systems during the desilylation of *ortho*-bromo-biphenyl-trimethylsilanes with tetrabutylammonium fluoride (TBAF) is described. *In* situ formation of an aryne and addition of fluoride affords fluorinated biphenyls. The structures have been undoubtfully confirmed by synthesis of authentic samples *via* Suzuki–Miyaura cross-coupling and X-ray analysis. *In situ* trapping experiments with furan proved the transient formation of aryne by fluoride-induced displacement of the TMS group and subsequent bromide elimination.

The "Laboratoire de stéréochimie" belongs to a mixed CNRS-University of Strasbourg research group (UMR CNRS 7509) implemented at the European School of Chemistry, Polymers and Material Sciences (ECPM) in Strasbourg. Our research focuses on the development of new organic and organometallic methodologies and find their application in the synthesis of biologically active compounds, new ligands for asymmetric catalysis and pharmacophores as well as agrochemical targets. One of the principal research activities of the group lies in the total synthesis of natural products. The second research topic focuses on the control of axial chirality in biaryls employing atropo-diastereo- and enantioselective Suzuki–Miyaura cross-coupling reactions, C–H activation or transition-metal free aryl–aryl ARYNE coupling reactions. This expertise has been successfully applied in the synthesis of biaryl-based ligands for C–C, C–N, C–O and, more recently, C–F coupling protocols. The use of fluorinated ligands being intensively studied in this field. The third research area concerns the development of new fluorination methodologies with application in the synthesis of uncommon heterocycles bearing fluorinated substituents like α-fluoroethers with application in Life Science oriented research. The group succeeded recently in the first modular synthesis of trifluoromethoxy pyridine building-blocks.

1. Introduction

Arynes (1,2-dehydrobenzenes) and their heterocyclic analogues (heteroarynes) are highly reactive intermediates in organic chemistry and have attracted in recent years increasing interest due to their wide synthetic applications [1,2]. They react with a variety of *N*-, *S*-, *O*-, *Se*- [3–11], and *P*-nucleophiles [12] as well as with carbanions [13–19]. With alkenes they undergo Diels–Alder-type cycloaddition reactions [20–22], [2 + 2] cycloaddition [23,24], 1,3-dipolar cycloaddition [25,26] and transition-metal catalyzed reactions making them powerful tools in organic synthesis [27–31]. Note that aryl–aryl couplings using arynes as key intermediates have been described in the literature in some cases [14,32–35]. In this research area, our group made intensive researches and reported very recently on the efficient synthesis of *ortho*,*ortho′*-tri- and tetrasubstituted bromobiphenyls *via* a transition metal free cross-coupling procedure. This so-called "ARYNE coupling" methodology is based on the reaction of thermodynam-

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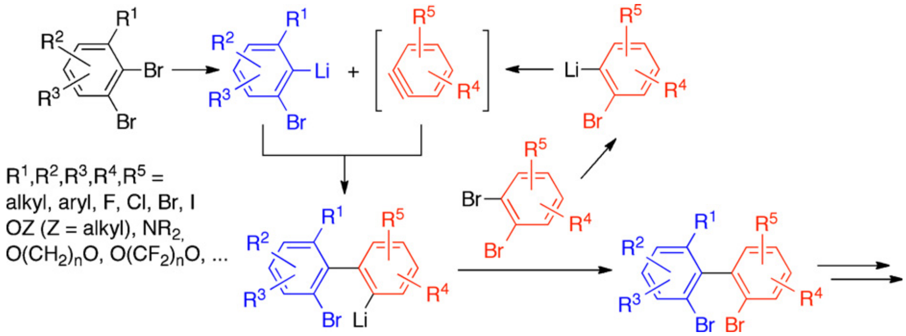


Fig. 1. ARYNE coupling methodology.

ically stable organolithium intermediates with arynes [13,14] generated *in situ* by reaction with symmetrical [13], and more recently, unsymmetrical 1,2-dibromobenzenes (Fig. 1) [36]. The latter became accessible due to highly complementary transition-metal catalyzed and polar organometallic protocols [37]. We could show that unsymmetrical arynes undergo with perfect regioselectivity the ARYNE coupling by using sterically demanding silyl-groups in the *ortho*-position of the aryne functionality [36]. The advantage of trialkylsilyl groups is, beside their sterical crowding, that they can be easily displaced by protodesilylation [38,39], bromodesilylation [38,40], or iododesilylation [38,41–43].

In the ARYNE cross coupling, 1,2-dibromobenzenes are used as aryne precursors, but various other methods for the *in situ* generation of an aryne are known. They imply most oftenly the elimination of a leaving group such as halide, tosylate, triflate, diazonium, trialkyl-ammonium, etc. from the *ortho*-position of a metalated aromatic ring [44–50].

For example, *ortho*-metalations on aromatic triflates [51] as well as halogen/metal permutations on *ortho*-halotriflates [52] or 1,2-dibromobenzenes (as shown in Fig. 1 in the mechanism of the ARYNE cross-coupling) have been successfully applied to produce arynes. Beside these well-established organometallic methods, an alternative strategy has emerged starting from trimethylsilyl triflate precursors (Kobayashi reagent). In that case, the elimination of the leaving group is induced under mild conditions by displacement of the trimethylsilyl group with fluoride anions [53]. This approach requires, however, the synthesis of aryl trimethylsilyl triflates [54].

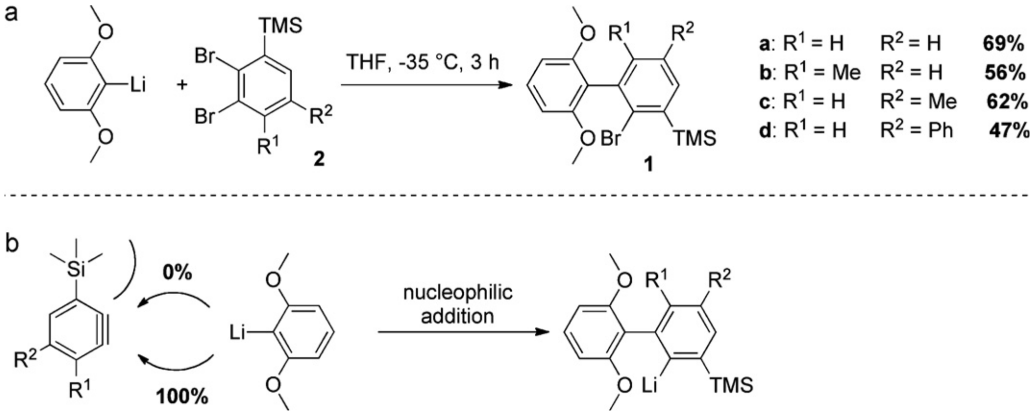
In the context of our researches dedicated to the removal of the directing silyl-group in the ARYNE coupling methodology, we describe now the generation of aryne by fluoride induced elimination of bromide on *ortho*-trimethylsilyl-bromoarenes. It will be shown that the combination of this new desilylation–halide elimination process with subsequent fluoride addition allows the access to fluorinated aromatic scaffolds.

2. Results and discussion

2.1. Desilylation of biaryls **1a–d** with TBAF

The *ortho*-bromobiaryls **1a–d** were prepared by applying the ARYNE cross-coupling methodology [13,36] starting from 2,6-dimethoxy aryllithium and functionalized 1,2-dibromobenzenes **2a–d** (Scheme 1a). As outlined previously, the trimethylsilyl group (TMS) has been chosen in order to guarantee a perfect control of the regioselectivity during the addition of the aryllithium nucleophile onto the aryne by virtue of its steric hindrance (Scheme 1b). Moreover, the TMS group can be easily introduced on the starting material by means of selective *ortho*-metalation reactions [37].

Classically, the TMS group can be removed with tetrabutylammonium fluoride (TBAF) in THF at 25 °C. However, in case of the *ortho*-bromobiaryls **1a–d**, the expected desilylated biaryls **3a–d** were obtained in mixture with the fluorinated derivatives **4a–d** (Scheme 2). The isolated yields as well as the ratio of desilylated and fluorinated products depended on the substitution pattern of the aryl silane moiety. Starting from the non-substituted compound **1a**, a mixture that mainly contained the fluorinated derivative **4a** (70%) was isolated in 49% yield. When a phenyl group was present in *meta*-position of the silane, the yield of the reaction was increased to 72% and the ratio between fluoro and bromobiaryls increased in favor of the latter one (**3d**/**4d** = 74:26). Crystallization from MeOH provided the analytically pure terphenyl **3d** in 40% yield. An intermediate situation was observed with biaryls **1b–c** substituted with a methyl group either at the 5′- or 6′-position of the biaryl ring system.



Scheme 1. Synthesis of biaryls **1a–d** by ARYNE cross-coupling. (a) Experimental results. (b) Regioselectivity of the addition.