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Control of axial chirality in absence of transition metals based on arynes

Contrôle de la chiralité axiale à l'aide d'arynes et en absence de métaux de transition

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ABSTRACT

The modular construction of enantioenriched biaryl derivatives is presented. This approach is based on (1) an almost quantitative access to polybrominated precursors via a transition metal-free aryl–aryl coupling, the ARYNE coupling, (2) the regioselective introduction of a traceless chiral auxiliary (an enantiopure *para*-tolylsulfinyl group), (3) the chemoselective functionalization of this auxiliary, and (4) subsequent regioselective functionalization of the remaining bromine atoms without any racemization during these steps. Next, the atroposelective coupling of in situ generated arynes and aryllithiums bearing various chiral auxiliaries (*tert*-butyl sulfoxide, *para*-tolyl sulfoxide, and tartrate-derived chiral diethers and oxazolines) is described and applied to the formal synthesis of (−)-steganacin.

RÉSUMÉ

La construction modulaire de dérivés biaryliques énantioenrichis est présentée. Cette approche est basée sur (a) un accès quasi quantitatif aux précurseurs polybromés *via* un couplage aryle–aryle sans métaux de transition, le couplage ARYNE, (b) l'introduction régiosélective d'un auxiliaire chiral (un groupe *para*-tolylsulfinyl énantiopur), (c) la fonctionnalisation chimiosélective de cet auxiliaire et (d) la fonctionnalisation régiosélective subséquente des atomes de brome restants sans racémisation au cours de ces étapes. Ensuite, le couplage atropo-sélectif à l'aide d'arynes générés in situ et d'aryllithiums portant divers auxiliaires chiraux (*tert*-butyl sulfoxyde, *para*-tolyl sulfoxide, diéthers dérivés du tartrate et des oxazolines chirales) est décrit et appliqué à la synthèse formelle de la (−)-stéganacine.

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1. Introduction

Biaryls are a key structural feature of numerous natural products, biologically active molecules, tools for asymmetric synthesis, pharmaceuticals, agrochemicals, and other materials (Fig. 1). Various approaches have been developed toward efficient methods for their atroposelective synthesis [1]. Three important issues have to be addressed for their synthesis, namely, the regio- and stereoselective control in biaryl synthesis and the minimization of metal amounts in these processes.

In recent years, classical methods for creating aryl–aryl bonds [2] have been complemented by direct arylation with the carbon–hydrogen bond used as a functional group (Fig. 2) [3]. The major drawback in these approaches is the use of heavy metals, which may cause contamination of the products, requiring purification for biological applications. Because of potentially toxic contamination of pharmaceutical products, effective removal of the metal (Pt, Pd, Ir, Rh, Ru, or Os) in active pharmaceutical ingredients causes acute problems for pharmaceutical companies [4].

In the present work, we report on our contributions in this field. The transition metal-free ARYNE coupling will be presented toward first racemic biaryl scaffolds and then our developments for the synthesis of enantiopure or -enriched biaryls.

2. Results and discussion

2.1. Aryne route to access biaryls

The use of arynes to access biaryls or polyaryls has been nicely reviewed recently [5]. The first example of such a process was described by Wittig et al. [6] in 1940 using phenyllithium and fluorobenzene. Later, Gilman and colleagues [7] in 1950s reported on the reaction of *ortho*-dihalobenzenes with butyllithium leading to a biphenyl backbone, presumably via a 1,2-didehydroarene, that is, an *ortho*-aryne (Scheme 1). This halogen/lithium interconversion-based approach remained dormant for several decades except for a procedure improvement [8].

We started reinvestigating this reaction in 2001 and then extended its scope to access various biaryls, and we clarified the mechanism of the reaction. The reaction of aryllithium compounds with *ortho*-dihaloarenes, proceeding via the in situ formation of arynes allows the preparation of *ortho*-halobiaryls. This "ARYNE coupling" has become a robust method for aryl–aryl coupling and combines several advantages, as the use of cheap and/or easily accessible halogen aromatic compounds, the access to biaryls bearing two distinct aromatic units and to polyhalogenated biaryls that can be functionalized further, the use of lithium reagents (i.e., in the absence of transition metals), and multigram reaction scales (Fig. 3) [9].

The mechanism is based on a subtle interplay of several organometallic species and their relative basicities (Fig. 4). The chain reaction proceeds as follows: (1) A thermodynamically stable organolithium intermediate is formed, of which (2) a small amount performs a halogen/metal exchange on the coupling partner via an ate complex, generating a thermodynamically unstable *ortho*-halophenyllithium intermediate (*initiation*). The latter (3) eliminates spontaneously lithium halide affording an aryne; then, (4) the transient aryne species undergoes nucleophilic addition of the organolithium precursor; and (5) the resulting 2-biaryllithium intermediate is finally

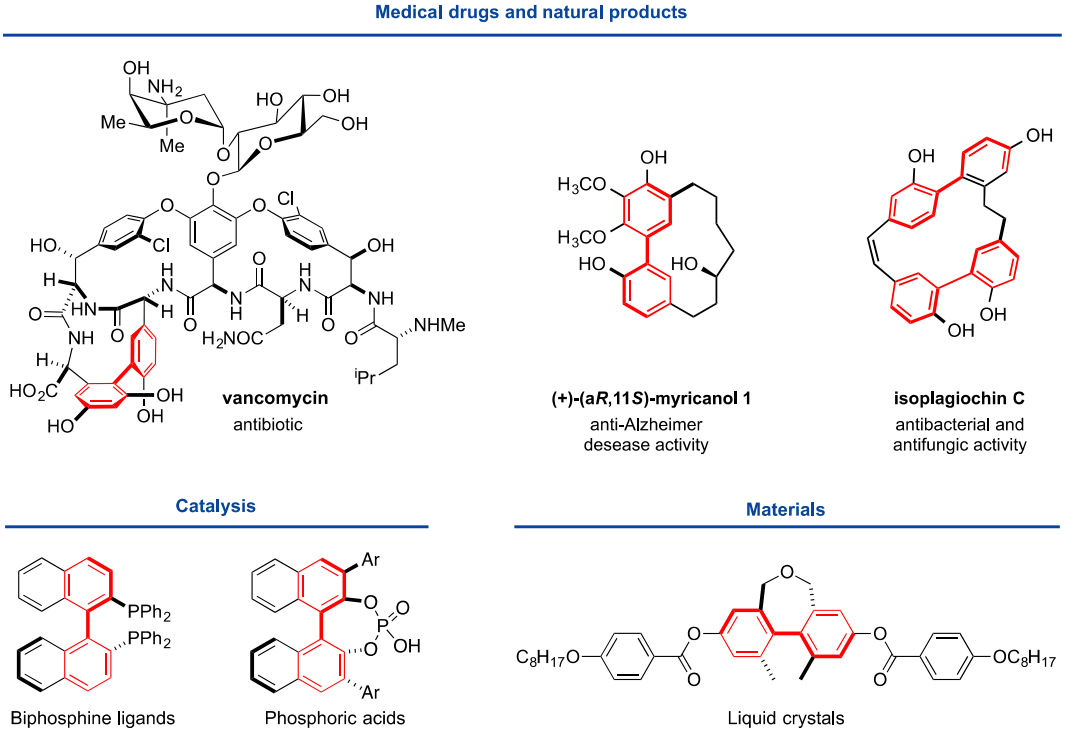

Fig. 1. Biaryls as important structural motifs.