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Transition-Metal-Free Atropo-Selective Synthesis of Biaryl Compounds Based on Arynes

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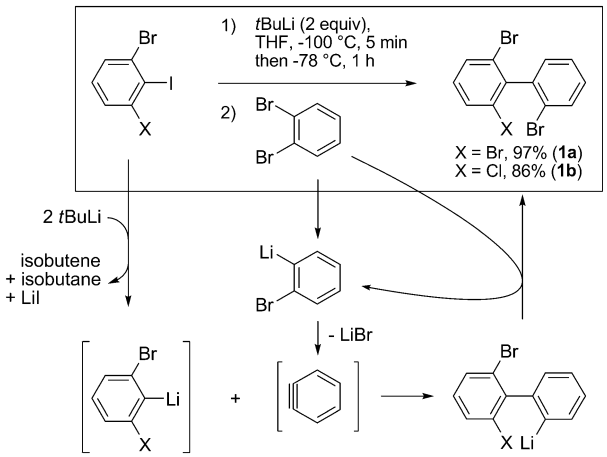
The biaryl motif occupies an iconic role in chemistry, being a key structural feature of natural products, biologically active molecules, drugs, agrochemicals, and other novel optical and mechanical materials.[1] Furthermore, the stereogenic axes provide rigid molecular frameworks for highly efficient tools in asymmetric synthesis.[2] With the continuously increasing importance of axially chiral biaryl compounds as chiral auxiliaries and ligands for asymmetric synthesis and as a structurally decisive element in bioactive natural products, considerable efforts have been undertaken to develop efficient methods for their atropo-selective synthesis.[3] Thus, three issues are currently being addressed, namely the regio- and stereoselective control in biaryl synthesis, as well as the minimization of the amounts of metal used in these processes.

In recent years, classical methods for creating aryl–aryl bonds[3b] have been supplanted by direct arylation methodologies in which the carbon–hydrogen bond is used as a functional group.[4] However, in all these approaches the employment of heavy metals often causes contamination of the products, which require purification for biological applications. Indeed, due to potentially toxic contamination of pharmaceutical products, effective removal of the metal (Pt, Pd, Ir, Rh, Ru, Os) in active pharmaceutical ingredients (API) causes acute problems for pharmaceutical companies.[5]

We recently reported on an efficient transition-metal-free aryl–aryl coupling protocol, the aryne coupling.[6] Starting from haloarenes and alkyllithium reagents, it consists of the reaction of in situ formed aryllithiums and arynes, with concomitant regeneration of a carbon–halogen bond. The aryne coupling gives rise to a large number of diversely substituted coupling products, which can easily be functionalized further on both phenyl rings.[7] Yet this approach represents an attractive alternative to the important transition-metal-catalyzed coupling reactions for different reasons: 1) no need for transition metals; 2) no need for expensive ligands; 3) the possibility to couple polybrominated aryls, difficult to realize by Suzuki–Miyaura coupling; and 4) access to product families through subsequent functionalization. This methodology has become a mature method for the synthesis of biaryls, and has been applied successfully to the preparation of phosphorus ligands for catalysis.[8]

For instance, 2,2′,6-tribromobiphenyl (**1a**) and 2,2′-dibromo-6-chlorobiphenyl (**1b**) can be obtained on multigram scale through aryne coupling in almost quantitative yield (Scheme 1).[9] We showed that the polybrominated scaffold allows for regioselective, successive bromine/lithium interconversions, which opens a route to a vast library of biaryls.[10]



Scheme 1. Synthesis of 2,2′,6-tribromo- and 2,2′-dibromo-6-chlorobiphenyls (**1**) as common building-blocks by aryne coupling.

We disclose here an efficient route to the modular construction of enantiopure biaryls based on the deracemization or desymmetrization and subsequent regio- and chemoselective functionalization of some common building blocks.

In order to control the axial chirality, we decided to introduce a traceless chiral auxiliary after the first bromine/lithium exchange. The sulfinyl group has advantages that can

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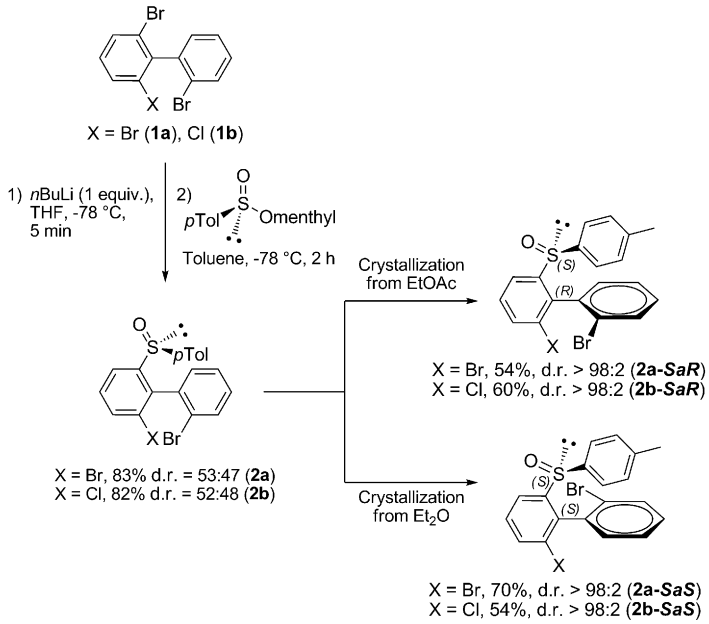
hardly be improved by other chiral auxiliaries:[11] 1) its high optical stability; 2) the existence of a large number of sulfinylating agents in both enantiomeric forms; 3) the known *ortho*-directing ability of the sulfinyl group and its efficiency as a carrier of chiral information; 4) electronic properties, which enhance the contrast between the physical properties of the two stereoisomers, mainly because of dipole orientation;[11c] and 5) they are very useful as traceless resolving agents, as they may undergo sulfoxide/lithium exchange[10c] affording new organometallic intermediates, which can subsequently be trapped by various electrophiles.[12]

When 2,2′,6-tribromobiphenyl (**1a**) or the analogous 2,2′-dibromo-6-chlorobiphenyl (**1b**) were submitted to the regioselective bromine/lithium interconversion[10a,b] followed by trapping with enantiomerically pure (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate,[13] the atropo-diastereomeric biarylsulfoxides **2** were obtained in excellent yields. Simple crystallization allowed for the separation of both atropo-diastereoisomers affording **2a-*SaR*** and **2a-*SaS*** in 54 and 70% yield, respectively, based on the theoretically possible yield of each diastereoisomer (Scheme 2).



Scheme 2. Desymmetrization of achiral **1a** and deracemization of racemic **1b** by means of enantiomerically pure *p*-tolylsulfoxide as chiral auxiliary.

The chlorobiphenyl **1b** gave the corresponding diastereoisomers in 60 and 54% yield, respectively. The structures of these compounds and the absolute configuration of **2a-*SaR*, 2a-*SaS***, and **2b-*SaR*** were determined by single-crystal X-ray diffraction analysis (Figure 1).[14]

The most challenging part is now the chemoselective functionalization of the atropo-diastereomerically pure biaryls without racemization. Both substitutents, the sulfoxide group as well as the bromine atoms, may undergo exchange reactions. When standard organolithium reagents (*n*-butyllithium or *tert*-butyllithium) were employed, no chemoselectivity between both types of substituents was observed. In contrast, when employing Knochel's *i*PrMgCl·LiCl reagent, a clean sulfoxide/magnesium interconversion was observed at −50 °C. However, when the intermediate biaryl Grignard reagent was treated with iodomethane as the electrophile, the temperature had to be raised to 0 °C, which caused partial racemization of the biaryl axis. Thus, we had to find an exchange reagent 1) which allows the discrimination between the sulfoxide group and the bromine atom(s) and 2) which leads to an intermediate which is reactive enough for trapping at lower temperature. PhLi appeared to be the reagent of choice fulfilling all these requirements. It has been rarely employed in this kind of exchange reaction.[15]

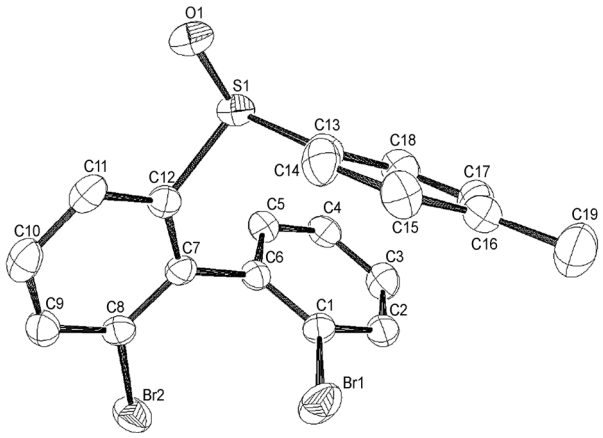
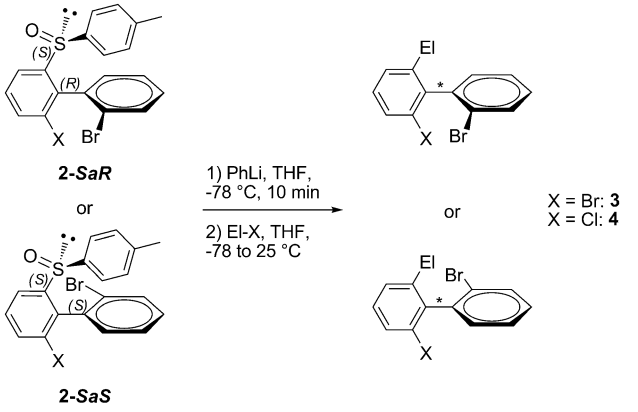


Figure 1. ORTEP representation of the structure of **2a-*SaR*** (for **2a-*SaS*** see reference [14]); thermal ellipsoids at the 50% probability level.

When the atropo-diastereomeric biaryl sulfoxides **2** were treated with PhLi at −78 °C, a clean sulfoxide/Li interconversion occurred within 10 min. Subsequent trapping with various electrophiles afforded enantioenriched biaryls with excellent e.r.'s (≥96:4, Table 1). For example, starting from biaryl **2a-*SaR***, the methyl derivative **3a-*aR*** was obtained upon treatment with iodomethane (Table 1, entry 1), the aldehyde **3b-*aR*** was obtained after trapping of the lithiated intermediate with *N*,*N*-dimethylformamide (Table 1, entry 3), and the acid **3c-*aR*** was obtained after pouring onto freshly crushed dry ice (Table 1, entry 4). The iodo derivative **3d-*aS*** was obtained in a similar way after addition of iodine (Table 1, entry 5). After treatment of the lithiated intermediate with fluorodimethoxyborane diethyl etherate and oxidative treatment, the phenol was obtained and immediately converted into the methyl ether **3e-*aR*** (Table 1, entry 6).

Similarly, when performing the reaction with the other atropoisomer **2a-*SaS***, as exemplified in entry 2 of Table 1, the enantiomer **3a-*aS*** was obtained in excellent yield and e.r. after trapping with iodomethane. The chlorobiphenyl **2b** was functionalized in a similar way as shown in entries 7–10 of Table 1. The absolute configuration of the biaryl axes in **3a-*aR***, **3b-*aR***, **3d-*aS***, **4a-*aR*** and **4d-*aS*** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).[14]

Table 1. Chemoselective sulfoxide/lithium interconversion towards enantiopure biaryls **3**.[a]



	Precursor	X	Product	X	EI	Yield [%]	e.r.
1	**2a-*SaR***	Br	**3a-*aR***	Br	Me	95	98:2
2	**2a-*SaS***	Br	**3a-*aS***	Br	Me	96	98:2
3	**2a-*SaR***	Br	**3b-*aR***	Br	CHO	81	99:1
4	**2a-*SaR***	Br	**3c-*aR***	Br	COOH	86	>99:1
5	**2a-*SaR***	Br	**3d-*aS***	Br	I	92	>99:1
6	**2a-*SaR***	Br	**3e-*aR***	Br	OMe	72	97:3
7	**2b-*SaR***	Cl	**4a-*aR***	Cl	Me	95	96:4
8	**2b-*SaR***	Cl	**4b-*aR***	Cl	CHO	69	99:1
9	**2b-*SaR***	Cl	**4c-*aR***	Cl	COOH	84	>99:1
10	**2b-*SaR***	Cl	**4d-*aS***	Cl	I	90	97:3

[a] * in the structures of the products indicates the element of chirality.

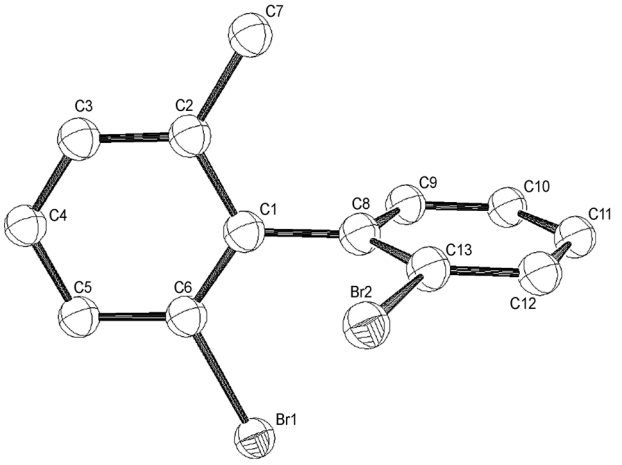
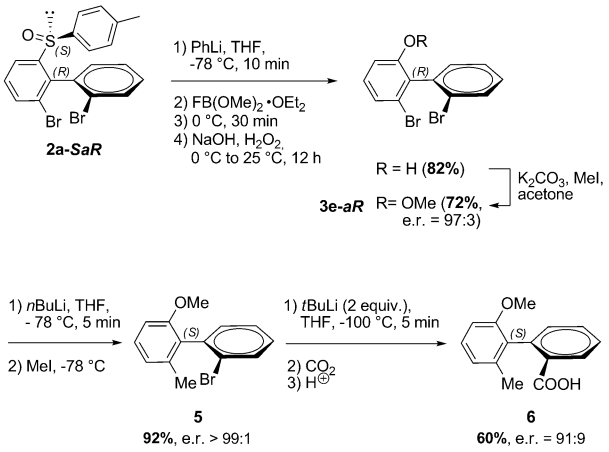


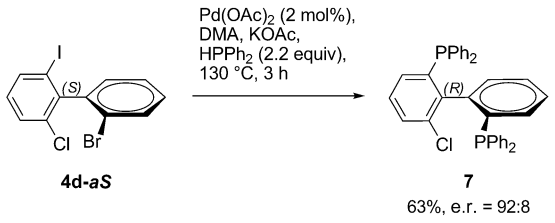
Figure 2. ORTEP representation of the structure of **3a-*aR*** (for **3b-*aR***, **3d-*aR***, **4a-*aR***, **4d-*aS*** see reference [14]); thermal ellipsoids at the 50% probability level.



Scheme 3. Example for a modular biaryl construction.

position. The biphenyl **5** was obtained in 92% yield and e.r. >99:1 (Scheme 3). The third substituent, a carboxylic group, was then introduced after another bromine/lithium interconversion followed by pouring onto freshly crushed dry ice. When the bromine/lithium exchange was performed at −78°C during 5 min, the carboxylic acid **6** was obtained in 60% yield and 85:15 e.r. When the biaryl lithium intermediate was kept for 45 min at −78°C before trapping, a 70:30 e.r. was obtained (85:15 e.r. after 5 min). In contrast, when performing the exchange at −100°C for 5 min, a 91:9 e.r. was achieved. These results underline the configurational stability of the intermediate biaryl lithium.

In another model reaction, we decided to apply our recently developed catalytic phosphination[16] on the enantiomerically pure biphenyl **4d-*aS*** (Table 1, entry 10). Although this trisubstituted biphenyl had to be heated at 130°C for 3 h, the diphosphine **7** was obtained with an e.r. of 92:8 (Scheme 4). The absolute configuration of the biaryl axes



Scheme 4. Example for a Pd-catalyzed phosphination on enantiopure biphenyl **4d-*aS***.

In order to show the scope of this approach, we decided to perform a complete functionalization of the biaryl through subsequent sulfoxide- and bromine/lithium interconversions. First the atropo-diastereoisomer **2a-*SaR*** was converted into the methoxy derivative as already shown in Table 1, entry 6. In the next step, a regioselective bromine/lithium interconversion followed by trapping with iodomethane allowed the introduction of a methyl group at the 2′-position. The biphenyl **5** was obtained in 92% yield and e.r. >99:1 (Scheme 3). The third substituent, a carboxylic group, was then introduced after another bromine/lithium interconversion followed by pouring onto freshly crushed dry ice. When the bromine/lithium exchange was performed at −78°C during 5 min, the carboxylic acid **6** was obtained in 60% yield and 85:15 e.r. When the biaryl lithium intermediate was kept for 45 min at −78°C before trapping, a 70:30 e.r. was obtained (85:15 e.r. after 5 min). In contrast, when performing the exchange at −100°C for 5 min, a 91:9 e.r. was achieved. These results underline the configurational stability of the intermediate biaryl lithium.

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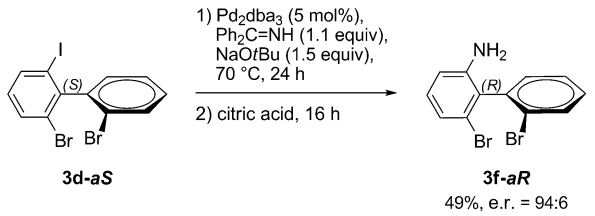
Similarly, we could show that iodobiaryl **3d-*aS*** can be efficiently submitted to a catalytic amination in order to introduce an NH_2 substituent (Scheme 5). The aminobiphenyl **3f-*aR*** was obtained in 49% yield and with 94:6 e.r.

In conclusion, we have developed an efficient protocol for the modular construction of enantioenriched biphenyl derivatives based on 1) an almost quantitative access to polybro-



3d-*aS* **3f-*aR***
49%, e.r. = 94:6

Scheme 5. Example for a catalytic amination on enantiopure biphenyl **3d-*aS***.

minated precursors by means of a transition-metal-free aryl–aryl coupling, 2) the regioselective introduction of a traceless chiral auxiliary (an enantiopure *p*-tolylsulfinyl group) allowing the separation of atropo-diastereoisomers by simple crystallization, 3) the chemoselective functionalization of this auxiliary, and 4) subsequent regioselective functionalization of the remaining bromine atoms. During all these transformations, the configuration of the biaryl axes is maintained and no racemization occurs.

Experimental Section

At −78 °C, *n*-butyllithium (1 equiv) was added dropwise to a solution of the substrate (1 equiv) in THF (2 mL mmol^{-1} substrate). At 0 °C, this solution was added through a cannula to a stirred solution of (−)-(*S*)-menthyl-*p*-toluenesulfinate (1 equiv) in toluene (6.7 mL mmol^{-1} (−)-(*S*)-menthyl-*p*-toluenesulfinate). The reaction mixture was allowed to reach RT over 12 h. Water (4 mL mmol^{-1} substrate) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 4 mL mmol^{-1} substrate). The combined organic layers were dried, filtered and evaporated. The crude material was purified by column chromatography to yield the desired compound.

General procedure for sulfoxide/lithium exchange and trapping with an electrophile (iodomethane or iodine): A pre-cooled solution of the substrate (1 equiv) in THF (10 mL mmol^{-1} substrate) was added to a solution of PhLi (2 equiv; prepared by adding *t*BuLi (2.0 equiv) to idobenzene (1 equiv) in diethyl ether (4 mL mmol^{-1} iodobenzene) and stirring for 30 min at 0 °C) at −78 °C. After 10 min, the electrophile (3 equiv) was added and the mixture was warmed to r.t. Water (4 mL mmol^{-1} substrate) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 4 mL mmol^{-1} substrate). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by column chromatography to yield the desired compound.

Acknowledgements

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Keywords: biaryls · chirality · selectivity · sulfoxide · synthetic methods

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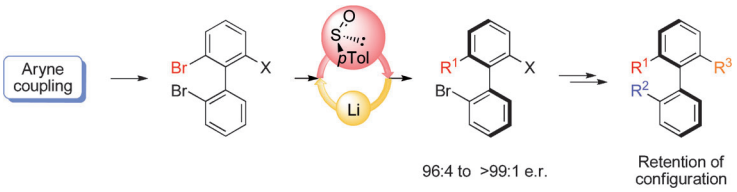
Coupling Reactions

F. R. Leroux, A. Berthelot, L. Bonnafoux, A. Panossian, F. Colobert** ..... ▮▮▮▮–▮▮▮▮

Transition-Metal-Free Atropo-Selective Synthesis of Biaryl Compounds Based on Arynes



A modular way towards biaryls: Highly enantioenriched biphenyls can be prepared based on a transition-metal-free aryl–aryl coupling followed by efficient desymmetrization or deracemization and chemoselective functionalization (see scheme).

