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Chiral Ligand-Mediated Nucleophilic Aromatic Substitution of Naphthoic Acids: A Fast and Efficient Access to Axially Chiral Biaryls

Thi Thanh Thuy Nguyen ,[a] Hélène Guyon,[a] Kim Phi Phung Nguyen,[b] Anne Boussonnière,[a] Jacques Mortier,[a] and Anne-Sophie Castanet*[a]

Abstract: A transition metal-free synthesis of enantioenriched biaryls from aryllithiums has been developed. This approach relies on atropoenantioselective nucleophilic aromatic substitution (S_NAr) reaction of unprotected naphthoic acids. The ability of a diverse set of chiral ligands to mediate this transformation has been investigated. 1,2-diether ligands outperform their diamine counterparts and the best enantiocontrol was obtained with readily accessible enantiopure *trans*-1,2-dimethoxycyclohexane. This S_NAr reaction offers an efficient and rapid access to enantioenriched binaphthalenes, phenylnaphthalene and phenanthrylnaphthalenes (up to 94:6 er).

Axially chiral biaryls are a family of privileged structural motifs that are commonly found in natural products,[1] pharmaceuticals,[2] chiral ligands,[3] and optically active organic materials.[4] To satisfy the continuously increasing demand for these valuable scaffolds, considerable synthetic efforts have been devoted to their atroposelective construction. The most widespread strategies rely on transition-metal-catalyzed asymmetric reactions.[5] However, these reactions have major shortcomings for the pharmaceutical industry, as removing transition-metal residues from active pharmaceutical ingredients requires costly and time-consuming purifications.[6,7] On the other hand, biaryls can be efficiently synthesized, under transition metal-free conditions, by nucleophilic aromatic substitution (S_NAr) reactions, using organolithium or Grignard reagents as nucleophiles. We previously demonstrated that subjecting *o*-fluoro or methoxynaphthoic acids to organolithiums results in fluoride or methoxide displacement.[8] This process, which doesn't require protection of the carboxyl group, provides a straightforward and convenient access to *racemic* biaryls. In pursuit of our contribution to the development of the CO_2Li-mediated S_NAr reaction,[9] we report herein an efficient atropo-enantioselective synthesis of *axially chiral* biaryls through the chiral diether-mediated S_NAr reaction on naphthoic acids.

Various strategies to access enantioenriched chiral biaryls through asymmetric S_NAr have been documented.[10] The most investigated so far has been the use of chiral aryloxazolines (the Meyers reaction).[11] Alternatively, stereocontrol can result from a chiral alkoxide leaving group located *ortho* to an achiral oxazoline or ester.[12] A major limitation of these approaches relies in the additional steps required for the prior introduction and later removal of the covalently bound stereodirecting auxiliary. These tedious protection-deprotection steps can in principle be circumvented by the use of external chiral ligands chelating the aryllithium nucleophiles. However, despite impressive progress in enantioselective organolithium reactions, the chiral ligand-controlled S_NAr reaction has been scarcely investigated. This strategy was pioneered in 1992 by Tomioka who reported on high atroposelectivity (up to 95:5 er) in the reaction of 1-naphthyllithium with hindered 1-fluoro-2-naphthimine in the presence of a chiral 1,2-diether ligand.[13] However the tedious preparation of LiBr-free naphthyllithium (crucial to attain high enantioselectivity), and the harsh reaction conditions required to deprotect the bulky imino group (stoichiometric amounts of TFA) greatly reduce the attractiveness of this method and have hampered its further application. To face this issue, hindered naphthoates were investigated in chiral ligand-mediated S_NAr reaction but led to modest stereoselectivities (up to 76:24 e.r).[14] As a consequence, further developments on chiral-ligand mediated S_NAr are still needed.

Our first investigations focused on the reaction of 1-fluoro-2-naphthoic acid (**1a**) with 1-naphthyllithium (**2**) (Table 1). (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane **L1,** which was the sole ligand investigated so far in enantioselective S_NAr reaction,[13, 14] was selected as chiral inducer. Initially, a solvent screening was carried out at –20 °C with 1.1 equiv. of **L1** against naphthyllithium **2.** This aryllithium derivative was prepared by bromine-lithium exchange from equimolar amount of *t*-BuLi and 1-bromonaphthalene. No enantioenrichment was observed when the S_NAr reaction was carried out in THF, as the coordinating ability of THF toward lithium presumably competes with that of ligand **L1** (Table 1, entry 1). We thus switched to less coordinating solvents. Diethyl ether induced a modest stereoselectivity (70:30 er) (Table 1, entry 2). Reaction in n-hexane yielded only trace quantities of the product, arguably due to the reduced solubility of the lithium carboxylate arising from the deprotonation of **1a** by aryllithium **2** (Table 1, entry 3). Toluene was identified as the most suitable solvent, demonstrating acceptable yield (60%) and atroposelectivity (85:15 er) (Table 1, entry 4). To improve the reaction, the effect of temperature on the enantiocontrol was next studied (Table 1, entries 5–9). Increasing the temperature over –20 °C resulted in side reactions, likely due to competitive lithiation at the benzylic positions of toluene and **L1**,[15] and led to diminished yields and enantioselectivities. While decreasing the temperature enhanced the stereoselectivity, the yield was extremely low (7%) at –85 °C. Hence, we selected –65 °C as the reaction temperature for further investigation on the influence of

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Supporting information for this article is given via a link at the end of the document. It contains experimental protocols, characterization data and copies of ^1H and ^{13}C NMR spectra for all new compounds; copies of HPLC spectra proving the enantiomeric purity of compounds.

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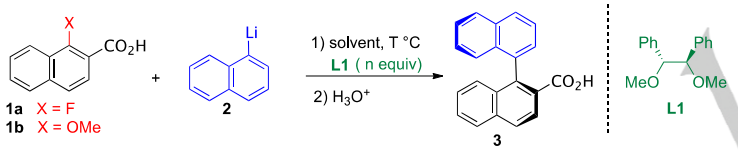
LiBr on the reaction course. It is well known that inorganic lithium salts may have a dramatic effect on the aggregation state of organolithiums,[16] and thus affect the yield and/or enantioselectivity of asymmetric reactions.[17] However, in contrast to the previously reported **L1**-mediated S_NAr reaction on naphthylimines,[13] using LiBr-free naphthyllithium **2** (prepared by tellurium-lithium exchange, see SI) or adding LiBr (2 equiv) to the reaction mixture did not appreciably alter the atroposelectivity (Table 1, entries 10 and 11). In addition, further optimization showed that increasing reaction's concentration positively impacted the yield (70%) while not hampering the selectivity (91:9 er) (Table 1, entry 12). The influence of the chiral ligand stoichiometry on the reaction outcome was then studied. When the reaction was performed under ligand-free conditions in toluene at –65 °C, less than 5% of racemic **3** was produced after 24 h (Table 1, entry 13). Thus the chiral ligand not only controls the stereoselectivity of the S_NAr reaction but also enhances the reaction rate, presumably through deaggregation of the organolithium.[18] The catalytic use of diether **L1** was therefore evaluated. Employing substoichiometric amounts of **L1** (0.25 equiv/ArLi**)** drastically slowed down the reaction whereas the enantioselectivity diminished only slightly (80:20 er) (Table 1, entry 14). Consequently, a stoichiometric amount of ligand **L1** (1.1 equiv/ArLi) is required to achieve synthetically useful yields. It is nevertheless worthy of note that the chiral ligand can be recovered from the reaction mixture by column chromatography and reused with maintained levels of yield and stereoselectivity. Finally, the impact of the leaving group on the reaction course was investigated. Although the reaction of 1-methoxy-2-naphthoic acid (**1b**) with **2** proceeded smoothly in THF under ligand-free conditions,[8a] poor yield (46%) and modest enantioselectivity (67:33 er) were obtained when **1b** was reacted with **2** in toluene in presence of diether **L1,** (Table 1, entry 15).

Table 1. Optimization of atropo-enantioselective **L1**-mediated S_NAr reaction



Entry[a]	Substrate	Preparation of **2**[b]	Temperature (°C)	Ratio **L1**/**2**	Solvent	Additive	Yield (%)[c]	(R_a-**3** : S_a-**3**) er[d]
1	**1a**	Method A	–20	1.1	THF	_	55	49.5 : 50.5
2	**1a**	Method A	–20	1.1	Et_2O	_	60	70:30
3	**1a**	Method A	–20	1.1	hexane	_	< 5	86:14
4	**1a**	Method A	–20	1	toluene	_	41	85:15
5	**1a**	Method A	20	1.1	toluene	_	38	74:26
6	**1a**	Method A	0	1.1	toluene	_	35	83:17
7	**1a**	Method A	–45	1.1	toluene	_	57	87:13
8	**1a**	Method A	–65	1.1	toluene	_	61	91:9
9	**1a**	Method A	–85	1.1	toluene	_	7	92:8
10	**1a**	Method B	–65	1.1	toluene	_	48	90:10
11[e]	**1a**	Method A	–65	1.1	toluene	LiBr	59	91:9
12[f]	**1a**	Method A	–65	1.1	toluene	_	70	91:9
13[g]	**1a**	Method A	–65	_	toluene	_	< 5	n.d
14	**1a**	Method A	–65	0.25	toluene	_	27	80:20
15	**1b**	Method A	–65	1.1	toluene	_	46 (25*)	67:33

[a] Unless otherwise noted, reactions were carried out under the following conditions : **1** (1.0 mmol), **2** (2.2 mmol.), ligand **L1** (2.4 mmol), solvent (48 mL), 24 h. [b] Method A: **2** is prepared by Br-Li exchange; Method B : **2** is prepared by Te-Li exchange. [c] Yield estimated by ^1H NMR spectroscopy on fractions from silica-gel chromatography containing a mixture of **1** and **3.** Isolated yields of pure **3** are followed by an asterisk [d] er measured by HPLC analysis (Chiralcel OD column). The absolute configuration of **3** was determined on the basis of $[\alpha]_D$ comparison with previously reported data. [e] 2 equiv. of LiBr was used. [f] **1** (1.0 mmol), **2** (2.2 mmol.), ligand **L1** (2.4 mmol), toluene (23 mL), 24 h. [g] reaction run without **L1**.

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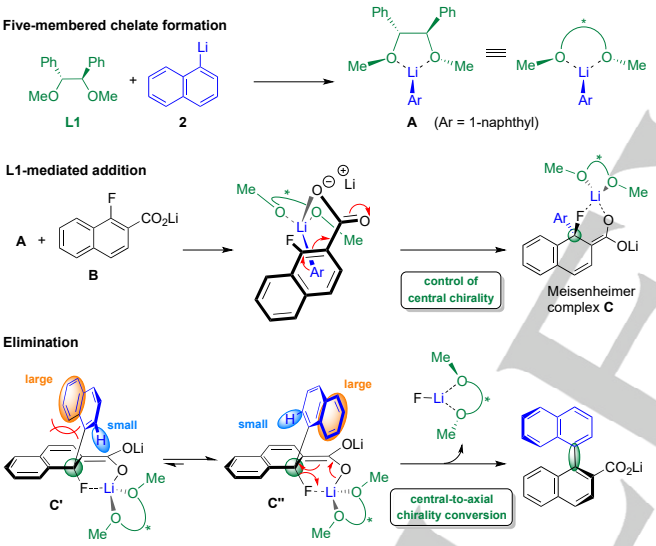
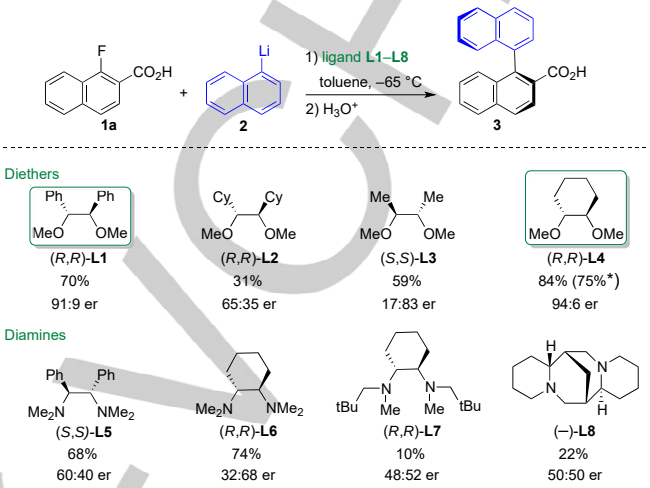
The absolute configuration of **3** was assigned by comparing its specific rotation ([α]D) with that reported in the literature.[19] The sense of enantioselection is consistent with the model proposed by Tomioka for the **L1**-promoted S_NAr reaction of fluoronaphthylimines.[13] It is assumed that the S_NAr reaction proceeds by an addition-elimination mechanism, with the overall stereoselectivity determined by the two steps (Scheme 1). Initial complexation of naphthyllithium **2** with diether **L1** would result in the formation of chelate **A,** in which the two Me groups on the ether oxygens are in a locked *trans* relationship to avoid steric repulsion with the phenyl groups.[20] This chelation creates a chiral environment around the lithium that would govern the facial selectivity of the subsequent addition step. Thus, complex **A** would add stereoselectively to the lithium 1-fluoro-2-naphthoate **B** to give the Meisenheimer intermediate **C**.[21] Of the two possible resulting conformers **C'** and **C'', C'** would be disfavored owing to the steric interactions between the peri hydrogen atom and the naphthalene ring undergoing the substitution. Subsequent elimination of LiF with central-to-axial chirality conversion would afford the R_a-**3** lithium salt.



Scheme 1. Postulated mechanism for the chiral diether **L1**-mediated atropo-enantioselective S_NAr reaction.

Prior to the present work, the effect of ligand structure on the atropoenantioselective S_NAr reaction had not been studied in the literature. In an attempt to further increase the enantiocontrol of this reaction, we then investigated the efficiency of a diverse set of chiral ligands in the reaction of naphthoic acid **1a** with naphthyllithium **2** (scheme 2). These exploratory reactions were conducted under the optimized conditions (Toluene, –65°C, 2.2 equiv. of **2**, 2.4 equiv. of **L**). Diether ligands were first investigated. Replacing the phenyl substituents of **L1** with cyclohexyl or methyl moieties (ligands **L2** and **L3**) resulted in decreased yield and enantioselectivity. Gratifyingly, diether **L4**, which exhibits a rigid *trans*-cyclohexane backbone, proved to be an excellent chiral promoter as it delivered the binaphthyl **3** with improved yield (84%) and enantioselectivity (94 :6 er). This level of atroposelectivity equals or exceeds the stereoselectivities previously reported for enantio- or diastereoselective S_NAr reactions using 1-naphthyllithium or 1-naphthyl Grignard reagent.[22]



Scheme 2. Survey of ligand effects in atropoenantioselective S_NAr reaction. **1a** (1 equiv.), **2** (2.2 equiv., prepared by Br-Li exchange), ligand **L1**-**L8** (2.4 equiv.), toluene, –65 °C. Yields estimated by ^1H NMR spectroscopy on fractions from silica-gel chromatography containing a mixture of **1a** and **3.** Isolated yields of pure **3** are followed by an asterisk (*). (R_a-**3** : S_a-**3**) er measured by HPLC analysis (Chiralcel OD column).

We then switched to chiral tertiary diamine ligands as these compounds have been frequently used as chiral inducers in organolithium chemistry.[23] To gain insight about the influence of the chelating function of the ligand on the stereoselectivity of the S_NAr reaction, 1,2-diamines featuring the same carbon skeleton as diether ligands **L1** and **L4** were first investigated. Results displayed in scheme 2 reveal that none of the evaluated diamines surpasses the stereocontrol imparted by **L1** and **L4.** *N,N,N',N'*-tetramethyldiamines **L5** and **L6** afforded biaryl **3** in correct yields but in modest stereoselectivities. Remarkably, switching from diether (*R*,*R*)-**L4** to diamine (*R*,*R*)-**L6** led to an unexpected reversal of the enantioselectivity. Results obtained with 1,2-diphenylethane-based ligands **L1** and **L5** suggest that this enantioreversal would be rather general for this enantioselective S_NAr reaction. Although it has been demonstrated that tertiary diamines in which the nitrogen atoms bear two different substituents impart better stereoselectivities than their tetramethylated analogs in diverse organolithium transformations,[24] disappointing results were obtained with ligand **L7**. Indeed, this sterically hindered diamine produced an aryllithium complex that was unreactive (low yield with significant amounts of recovered starting materials) and gave almost a racemic product. The widely used (–)-sparteine **L8** similarly proved ineffective at promoting the S_NAr reaction. Noteworthy, none of the chiral controllers evaluated in our ligand survey led to the formation of detectable amounts of the ketone resulting from the nucleophilic 1,2-addition of the 1-naphthyllithium to the carboxylate.[25]

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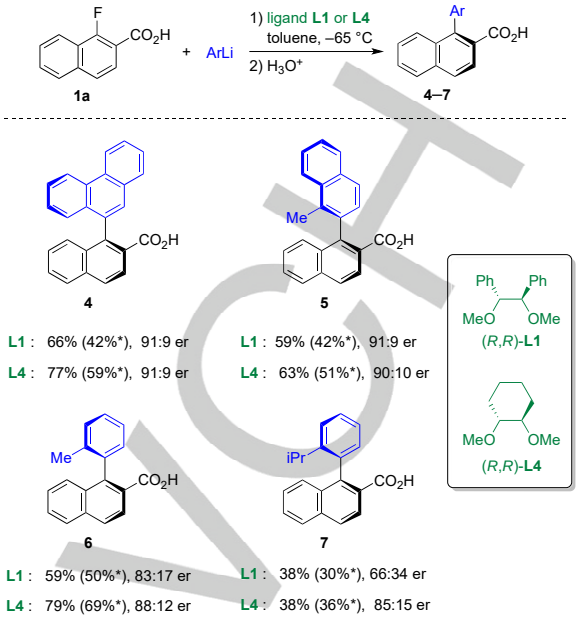
As previous studies on enantioselective S_NAr reactions were restricted to the use of 1-naphthyllithium, it was also of interest to briefly probe the scope of the aryllithiums (Scheme 3). Both diethers **L1** and **L4** were investigated in this study. Phenanthren-9-yllithium successfully participated in the S_NAr reaction and afforded phenanthrylnaphthalene **4** in good yields (up to 77%) with high enantiocontrol (91:9 er). 2-naphthyllithium also proved suitable and the corresponding 1,2'-binaphthalene **5** was obtained with acceptable yields (63%) and good enantioselectivities (up to 91:9). Additionally, the enantiocontrol was efficient in the benzene series as 2-methylphenyllithium smoothly displaced the fluoride leaving group of **1a**, delivering the phenylnaphthalene **6** with up to 88:12 er. Increasing the steric hindrance further, using 2-isopropylphenyllithium as nucleophile, had a slight impact on the enantioselectivity (85:15 er) but drastically decreased the conversion (38%). Importantly, in all these transformations, cyclohexyl-based diether **L4** compares favorably with the Tomioka's diether **L1**. To the best of our knowledge**,** the use of **L4** as stereocontroller in asymmetric reactions is unprecedented. This compound can be synthesized from the corresponding enantiopure diol, which is commercially available or can be readily obtained by chemical resolution.[26]

In conclusion, we have successfully developed an atropoenantioselective nucleophilic aromatic substitution on naphthoic acids. Enantioenriched biaryls are thus available from unprotected precursors without recourse to tedious chemical manipulations of chiral auxiliaries or protecting groups. The enantiocontrol relied on the use of a chiral bidentate ligand chelating the aryllithium nucleophile. A ligand survey revealed the superiority of the diether ligands over their diamine counterparts and the best enantiocontrol was obtained with the previously unknown (1*R*,2*R*)-dimethoxycyclohexane. This enantioselective S_NAr reaction provides an efficient and direct approach to highly valuable axially chiral carboxylic acids. These compounds have found useful applications as chiral ligands in their own right.[28] Alternatively, the carboxyl group can serve as a versatile handle for further transformation into various functional groups and heterocyclic compounds. Evaluation of (1*R*,2*R*)-dimethoxycyclohexane in other stereoselective organolithium reactions as well as extension of the atropoenantioselective S_NAr reaction to Grignard reagents are currently ongoing in our laboratory.



Scheme 3. Atropoenantioselective S_NAr reaction of **1a** with various aryllithiums. **1a** (1 equiv.), **ArLi** (2.2 equiv., prepared by Br-Li exchange), ligand **L1** or **L4** (2.4 equiv.), toluene, –65 °C. Yields estimated by ^1H NMR spectroscopy on fractions from silica-gel chromatography containing a mixture of **1a** and **4-7.** Isolated yields of pure **4-7** are followed by an asterisk (*). Enantiomeric ratios were determined by chiral HPLC.[27]

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Keywords: organolithium • chiral ligand • biaryl • axial chirality • nucleophilic aromatic substitution

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[27] The absolute configuration of **4** was assigned by $[\alpha]_D$ comparison with reported data. The absolute configuration of **6** was determined by conversion to (1-(*o*-tolyl)naphthalen-2-yl)methanol and comparison of its optical rotation to reported data. The absolute configuration of biaryls **5** and **7** are tentatively assigned as shown in scheme 3 on the assumption that the S_NAr reaction with (1-methylnaphthalen-2-yl)lithium and (2-isopropylphenyl)lithium proceeds with the same sense of stereoinduction as does the S_NAr reaction with 1-naphthyllithium **2,** phenanthren-9-yllithium and *o*-tolyllithium.

[28] L. Lin, S. Fukagawa, D. Sekine, E. Tomita, T. Yoshino, S. Matsunaga, *Angew. Chem., Int. Ed. Engl.* **2018**, *57*, 12048-12052.