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Remote Central-to-Axial Chirality Conversion: Direct Atroposelective Ester to Biaryl Transformation

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Dedicated to Professor Andreas Pfaltz on the occasion of his 70th birthday

Abstract: A strategy for the remote central-to-axial chirality conversion by simultaneous planarization of an encoding and a transient stereocenter is presented. Based on a diastereoselective double addition of a chiral 1,5-bifunctional organomagnesium alkoxide reagent to a broad range of aryl ester substrates, axially chiral biaryls are directly obtained upon in situ reduction. Various structurally distinct atropisomeric biaryl silanes that serve as valuable chiral biaryl anion surrogates are accessible in one step with up to e.r. 98:2.
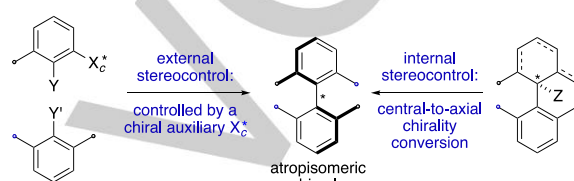
Unique molecular topology is regularly characterized by chirality elements of different nature. However, the realms of stereochemical diversity are unmet by current synthetic methodology to control their configuration. While stereocenter configuration is governed by numerous seminal methods, stereocontrol over other chirality elements is often limited. The selective interconversion of compounds with different chirality elements is thus fundamental to advance stereochemistry.[1]
Grounded in the findings on external stereocontrol over stereogenic axes using chiral auxiliaries,[2] several innovative approaches for the conversion of central to axial chirality were established by virtue of planarization of a proximal stereocenter (Scheme 1a).[3] While these methods reliably provide atropisomers with high levels of stereospecificity, the steric bulk of the *ortho*-substituents required for configurational stability of atropisomers hampers the accessibility of the substrates in enantiomerically enriched form. A remote central-to-axial chirality conversion would therefore be of particular value to render these strategies generally applicable.[4]
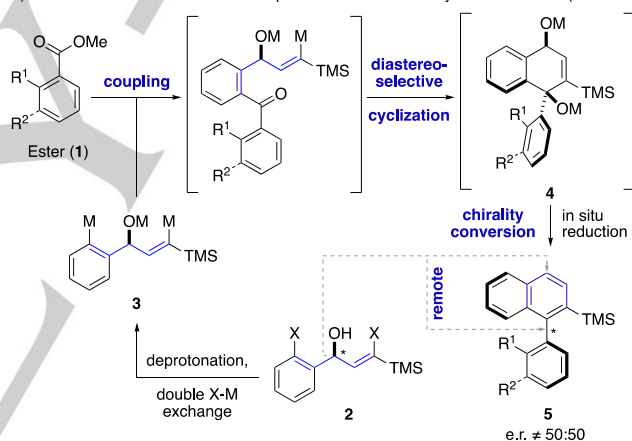We hence considered a stereochemical relay by 1,4-stereoinduction of an encoding to a proximal stereocenter that controls the chirality conversion by the simultaneous planarization of both stereocenters. In particular, we envisaged an atroposelective one-step synthesis of biaryls from simple aryl esters (1) with a chiral 1,5-bifunctional[5] organomagnesium alkoxide (3) reagent (1, Scheme 1b). The coupling of the ester with reagent 3, prepared by deprotonation and double halogen-metal (X-M) exchange from readily accessible precursor 2, would induce a diastereoselective cyclization[6] and provide bisalkoxide 4, which upon in situ reduction directly delivers enantioenriched axially chiral biaryls 5. Fascinated by the possibility to convert *ortho*-substituted esters directly into various atropisomeric biaryls in

enantioenriched form, we selected to study a silyl-stabilized reagent that would allow a versatile subsequent functionalization of the chiral biaryl silane products 5 at the *ortho*-position.
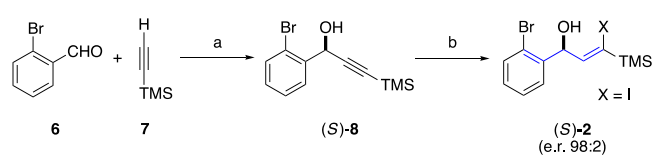

Scheme 1. a) Strategies for the atroposelective biaryl synthesis by external or internal stereocontrol.[2,3] b) Remote internal stereocontrol in the direct atroposelective transformation of esters into biaryls: coupling of the ester (1) with chiral 1,5-bifunctional magnesium alkoxide reagent (3) triggers a diastereoselective cyclization controlling the configuration of a transient stereocenter in 4. Upon in situ reduction, a central-to-axial chirality conversion leads to the atroposelective formation of biaryls by simultaneous planarization of the encoding and transient stereocenters. M: metal; TMS: trimethylsilyl.

The assets of the stereochemical relay of a remote to a transient stereocenter were instantly perceived by the simplicity and scalability of the synthesis of precursor (S)-2 in enantioenriched form (Scheme 2). Embracing stereoselective transfer hydrogenation or the Midland reduction,[7] several stereoselective methods for the reduction of the 2-bromobenzaldehyde derived arylalkynyl ketone provided the chiral propargylic alcohol (S)-8 with an e.r. of 98:2 in 91% yield over three steps. A subsequent *trans*-selective hydroalumination with Red-Al (E:Z > 1:99)[8] and ensuing addition of iodine gave the chiral precursor (S)-2 in 77% yield and an e.r. of 98:2 on a 45 mmol scale.

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Scheme 2. Synthesis of (*S*)-**2**: a) 1. **7**, *i*-PrMgCl, THF, then **6**, RT; 2. MnO₂, EtOAc, 75°C; 3. (*R*)-Alpine-Borane, neat, RT; 91% yield over three steps, e.r. 98:2; b) *i*-PrMgCl, Red-Al, THF, 0°C, then −35°C, EtOAc, I₂, 77% yield.

With chiral precursor (*S*)-**2** in hand, we investigated the double X-M exchange of the corresponding alkoxide by a deprotonation-magnesiation sequence.[9] Initially, the addition to a mixture of *i*-PrMgCl in a slurry of fine magnesium powder in THF only afforded mono-metalation at the alkenyl position (Table 1, entry 1). We therefore activated the magnesium with LiCl at 40°C[10] to reach full metalation within 45 min in THF, Et₂O or 2-MTHF (Table 1, entries 2–5). These solutions of stable reagent (*S*)-**3** were directly used to convert methyl 1-naphthoate **1a** (1 h at RT) into intermediary 1,4-bisalkoxide **4**.[11] We next

Table 1. Optimization of the atroposelective ester to biaryl transformation with remote central-to-axial chirality conversion.
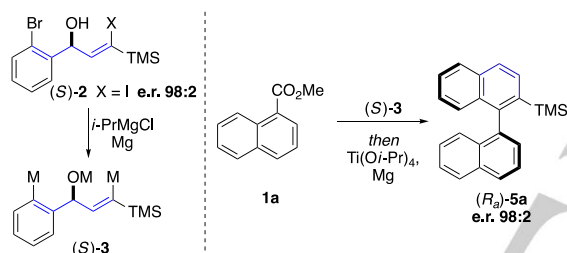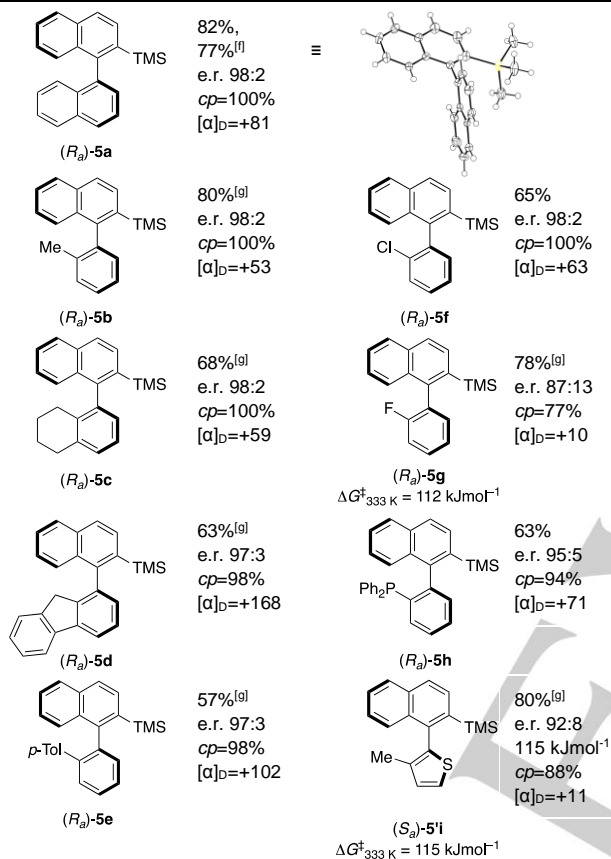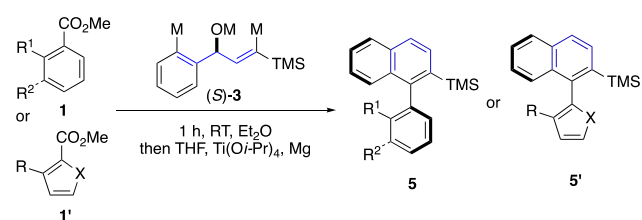

Entry	Metalation[a]	Addition[b]	Reduction[c]	Yield[d]
1	THF, RT[e]	–	–	–
2	THF, **LiCl, 40°C**	1.50 eq. **3**	THF, RT	–
3	**Et₂O**, LiCl, 40°C	1.50 eq. **3**	Et₂O, RT	16%[f]
4	2-MTHF, LiCl, 40°C	1.50 eq. **3**	2-MTHF, RT	–
5	MTBE, LiCl, 40°C[e]	1.50 eq. **3**		–
6	Et₂O, LiCl, 40°C	1.50 eq. **3**	**THF**, RT	80%[f]
7	Et₂O, LiCl, 40°C	**1.25 eq. 3**	THF, RT	**82%[f]**
8	Et₂O, LiCl, 40°C	1.10 eq. **3**	THF, RT	79%
9	Et₂O, LiCl, RT	1.10 eq. **3**	THF, RT	58%
10	Et₂O, LiCl, 40°C	1.10 eq. **3**[g]	THF, 40°C	73%

[a] Mg powder (3.00 mmol), LiCl (640 µmol), *i*-PrMgCl (220–300 µmol) and (*S*)-**2** (220–300 µmol) in 2.0 mL solvent for 45 min. [b] **1a** (200 µmol) in the identical solvent (2.0 mL) at RT for 1 h. [c] Specified solvent (4.0 mL) and Ti(O*i*-Pr)₄ (600 µmol) for 1 h at RT. [d] Yield of the isolated product. [e] Incomplete metalation. [f] An e.r. of 98:2 was determined by HPLC. Conversion percentage (*cp*) = 100.[13] [g] At 40°C.

investigated the in situ reduction by adding Ti(O*i*-Pr)₄, that forms a black slurry with the residual elemental magnesium indicating the formation of low-valent titanium species.[12] Gratifyingly, the formation of the desired product was observed in Et₂O and the axially chiral biaryl (*Rₐ*)-**5a** was isolated in 16% yield with an excellent e.r. of 98:2 (conversion percentage (*cp*)=100). Considering that the heterogeneous nature of the reaction mixture retards the reduction step, a solvent mixture with THF was evaluated, which ultimately delivered the product in high yield (80%, Table 1, 6). We next determined that 1.25 eq. of (*S*)-**3** are required as an optimal amount of reagent (*S*)-**3**, providing 82% of the binaphthyl product (*Rₐ*)-**5a** (Table 1, entry 7). Variation of the reaction conditions with 1.1 eq. of (*S*)-**2** indicated that the yield is only slightly compromised and that metalation at RT or performing the entire reaction sequence at 40°C leads to lower overall efficiency (58% and 73%, Table 1, entries 8–10). The degree of the central-to-axial chirality transfer in the formation of product (*Rₐ*)-**5a** was not affected by changing the solvent and an excellent stereoselectivity was observed in all cases (entries 3, 6 and 7, (*cp*)=100).[13]

Having defined an optimal reaction protocol, we next tested the scalability and the scope of the atroposelective ester to biaryl transformation. With a ten-fold increase of the reaction scale, a similar yield and equal selectivity was observed for the formation of product (*Rₐ*)-**5a** (2.00 mmol, 77% yield, e.r. 98:2, table 2, the absolute configuration of the product was assigned by X-ray crystallographic analysis).[14] We then explored the substrate scope by examining various *ortho*-substituted benzoic acid esters. Methyl *o*-toluate was converted with similar efficiency and selectivity after increasing the reduction time to 3 h (80% of (*Rₐ*)-**5b**, e.r. 98:2) and also the annulated tetrahydro-naphthalene- and 9*H*-fluorene ester was transformed with nearly complete stereoselectivity ((*Rₐ*)-**5c** and (*Rₐ*)-**5d**, e.r. 98:2 and 97:3). Even an *ortho*-arylated methyl benzoate gave the desired product (*Rₐ*)-**5e** with an e.r. of 97:3 (*cp* = 98). Due to the mild reaction conditions and short reaction times, we investigated the limitations of the configurational stability of biaryl products with small *ortho*-substituents.[11,15] Methyl 2-chloro- and fluorobenzoate led to a 65% and 78% yield for the axially chiral biaryls (*Rₐ*)-**5f** and (*Rₐ*)-**5g** with a remarkable e.r. of 98:2 and 87:13, respectively (Table 2, entries 6 and 7). A notably low rotational barrier was measured for the 2-fluorobiaryl (*Rₐ*)-**5g** ($\Delta G^{\ddagger}_{333\,K}$ = 112 kJmol⁻¹) underlining the mild nature of the method that allows to stereoselectively provide products with reduced configurational stability. Having established the efficiency of the one-step transformation of esters into atrop-isomeric biaryls, we became interested by the possibility to expeditiously prepare an axially chiral phosphine in enantio-enriched form.[16] Interestingly, when methyl 2-(diphenyl-phosphino)benzoate was treated with (*S*)-**3**, the desired mono-phosphine (*Rₐ*)-**5h** was obtained in 63% yield with an e.r. of 95:5 (Table 2, entry 8). Furthermore, to investigate the atroposelective synthesis for non-biaryl atropisomers,[17] we prepared the methylthiophene derivative (*Sₐ*)-**5'j**, which was obtained in 80% yield (Table 2, entry 10). Despite the low rotational barrier of $\Delta G^{\ddagger}_{333\,K}$ = 115 kJmol⁻¹, a high enantioenrichment of e.r. of 92:8 was attained, thus validating the scope of the remote central-to-axial chirality conversion beyond atropisomeric biphenyls.

**Table 2.** Scope of the atroposelective esters to biaryl transformation.[a-e]

(Ra)-5a
82%, 77%[f]
cp=100%
[α]D=+81

(Ra)-5b
80%[g]
e.r. 98:2
cp=100%
[α]D=+53

(Ra)-5f
65%
e.r. 98:2
cp=100%
[α]D=+63

(Ra)-5c
68%[g]
e.r. 98:2
cp=100%
[α]D=+59

(Ra)-5g
78%[g]
e.r. 87:13
cp=77%
[α]D=+10
$\Delta G^{\ddagger}_{333\ K}$ = 112 kJmol⁻¹

(Ra)-5d
63%[g]
e.r. 97:3
cp=98%
[α]D=+168

(Ra)-5h
63%
e.r. 95:5
cp=94%
[α]D=+71

(Ra)-5e
57%[g]
e.r. 97:3
cp=98%
[α]D=+102

(Sa)-5'i
80%[g]
e.r. 92:8
115 kJmol⁻¹
cp=88%
[α]D=+11
$\Delta G^{\ddagger}_{333\ K}$ = 115 kJmol⁻¹

[a] Mg powder (3.00 mmol), LiCl (640 μmol), *i*-PrMgCl (250 μmol) and (*S*)-**2** (250 μmol) in 2.0 mL Et₂O at 40°C for 45 min. [b] **1a** (200 μmol) in Et₂O (2.0 mL) at RT for 1 h. [c] THF (4.0 mL) and Ti(O*i*-Pr)₄ (600 μmol) for 1 h at RT. [d] Yield of isolated product. [e] Enantiomeric ratio determined by HPLC. [f] 2.00 mmol scale. [g] Reduction with Ti(O*i*-Pr)₄ for 3 h.

We next evaluated the transformation of a protic ester substrate after initial deprotonation. Notably, the anion of 1*H*-indole-ester **1j** was selectively transformed into the corresponding biaryl with complete selectivity inversion,[6] giving aryl indole (*Sa*)-**5j** with an e.r. of 98:2 (Scheme 3, 70%, *cp*=100%).[14]
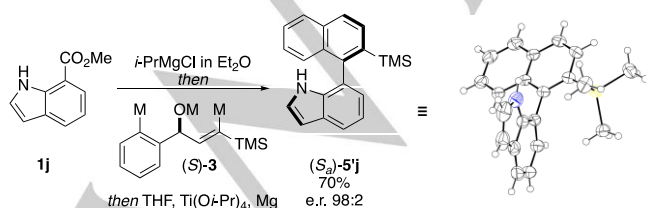
Scheme 3. Inversion of selectivity with protic substrate **1j**. Double addition for 1 h at RT, reduction for 3 h at RT, *cp* = 100, [α]D=−42.[14]

To gain insight into the mechanism and the reactivity of the chiral 1,5-bifunctional organomagnesium alkoxide reagent, (*S*)-**3** was treated with an equimolar amount of benzophenone, showing a higher reactivity at the aryl over the vinylsilane position (Scheme 4). Moreover, an excellent level of diastereoselectivity[6] for *cis*-diol (*S,S*)-**10** was confirmed by hydrolysis of bisalkoxide intermediate **4**,[11] while the naphthyl *endo* conformation observed in the solid state emphasizes the preorganization of the precursor poised for a stereoselective arene formation.[14]
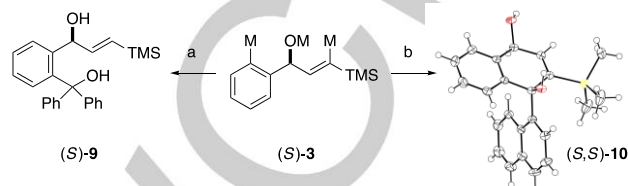
Scheme 4. Reactivity of (*S*)-**3** and diastereoselectivity of the cyclization step. a) (*S*)-**3**, Ph₂CO, Et₂O, −78°C to RT, 65%; b) (*S*)-**3**, 1-naphth-CO₂Me, Et₂O, RT, 64%.[14] Diastereoisomer (*S,R*)-**10** was not observed in the reaction crude.

To assess the synthetic utility of the axially chiral biaryl silanes,[18] (*Ra*)-**5a** was treated with NBS and ICl to straightforwardly provide the analogous bromide (*Ra*)-**11** and iodide (*Ra*)-**12** (80%, 77%, e.r. 98:2, Scheme 5).[19] Furthermore, a versatile diversification was achieved by combining a mild iodination with an in situ Negishi cross-coupling[19] using *p*-tolylzinc chloride, directly providing the arylated product (*Ra*)-**13** in 72% yield and an e.r. of 98:2.

X=Br: (*Ra*)-**11**
80%, e.r. 98:2
X=I: (*Ra*)-**12**
77%, e.r. 98:2

(*Ra*)-**5a**

(*Ra*)-**13**
72%, e.r. 98:2
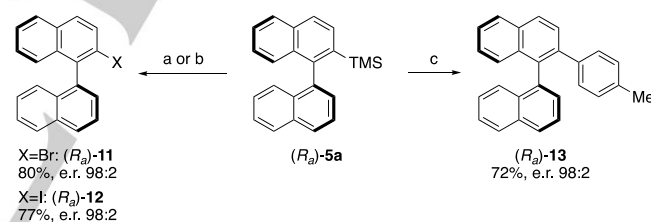
Scheme 5. Diversification of the atropisomeric biarylsilane (*Ra*)-**5a**. a) NBS, MeCN, 60°C, 80%; b) ICl, CH₂Cl₂, RT, 77%; c) ICl, *n*-heptane, 0°C, then *p*-tolylzinc chloride, THF, Pd(PPh₃)₄, RT, 72%.

In conclusion, a stereochemical relay strategy for the remote central-to-axial chirality conversion was established. Simple aryl esters were converted into axially chiral biaryl silanes with excellent atroposelectivity by using a chiral 1,5-bifunctional organomagnesium alkoxide reagent. The remote, encoding stereocenter is readily installed during the synthesis of highly enantioenriched reagent on scale. The diastereoselective double addition to esters controls the configuration of a transient stereocenter that guides the central-to-axial chirality conversion upon in situ reduction. Simultaneous planarization of the encoding and the transient stereocenter thus results in the formation of a new aromatic ring with up to 98:2 enantiocontrol. The scope of this mild reaction comprises axially chiral products with low configurational stability, biaryl phosphines, and anionic substrates, hence providing versatile chiral biaryl carbanion surrogates from ester precursors within one step. Ongoing studies in our group focus on the diastereoselective synthesis of atropisomeric scaffolds with multiple stereogenic axes.

Conflict of interest

The authors declare no conflict of interest.

Keywords: arylsilanes • atropisomerism • carboxylic acid esters • organomagnesium reagents • stereoselectivity

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[11]   See the Supporting Information for details.

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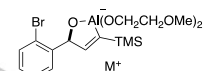
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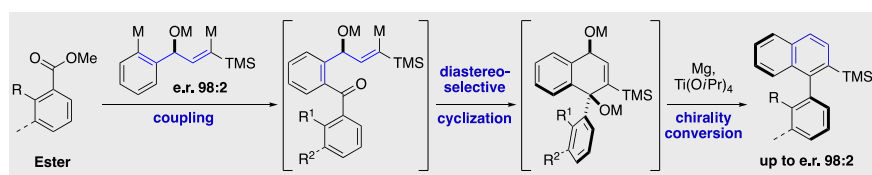
A. Link, C. Sparr*

Atroposelective Ester to Biaryl Transformation by Remote Central-to-Axial Chirality Conversion

Relay to Control: A versatile atroposelective synthesis of biaryl silanes from simple aryl esters was developed. A stereochemical relay featuring a diastereoselective double addition of a chiral 1,5-bifunctional organomagnesium alkoxide reagent and in situ reduction with simultaneous planarization of the encoding and transient stereocenters allows a remote central-to-axial chirality conversion. Various atropisomeric biaryls are accessible from esters in one step with up to e.r. 98:2.