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Chirality Exchange from sp³ Central Chirality to Axial Chirality: Benzannulation of Optically Active Diaryl-2,2-dichlorocyclopropylmethanols to Axially Chiral α-Arylnaphthalenes

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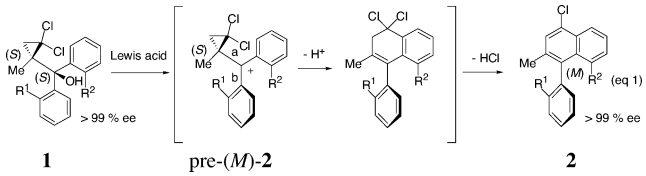
Axially chiral biaryls are well recognized as a characteristic chemical class in organic synthesis due to their utility as efficient chiral ligands and key intermediates of biologically active compounds.[1] Various synthetic methods have been exploited to produce chiral biaryls.[2] Chirality transfer protocols from stereogenic axes to the sp³ centers have also attracted much attention for studies of asymmetric reactions.[3] In addition, opposite methodologies for chirality transfer from a stereogenic sp³ center to axial chirality have moved into the spotlight.[2c−h,4,5] This transformation requires more than two steps to obtain atropenantiomers: the initial chirality transfer to construct chiral atropdiastereomers, followed by removal of the sp³ central chirality to produce atropenantiomers. Recently, Shair and co-workers achieved an elegant biomimetic synthesis of (−)-longithorone A using a chirality transfer as the key step.[5]

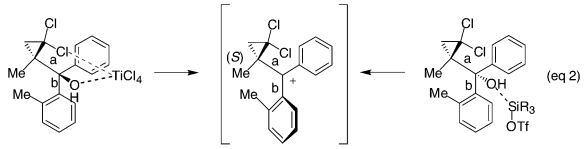
Here we disclose a novel efficient *chirality exchange*, single-step chirality transformation from sp³ central to axial; benzannulation of optically active aryl(aryl′)-2,2-dichlorocyclopropylmethanols (AACMs) **1** afforded chiral biaryls **2** with excellent level of stereo induction (eq 1).



1 pre-(*M*)-**2** **2**

As part of the program of synthetic studies on the transformation of *gem*-dihalocyclopropropanes,[6] we reported the Lewis acid-promoted regiocontrolled benzannulation of some racemic AACMs **1** lacking ortho substituents (R^1 or R^2) to afford achiral α-arylnaphthalenes.[6d] The choice of Lewis acids determined the cyclization regioselectivity of the benzannulation: $TiCl_4$ and $SnCl_4$ utilized the chelation pathway, while silyl triflates utilized a nonchelation one eventually to give regioisomeric α-arylnaphthalenes. The present plan is based on the hypothesis that the incorporation of an ortho substituent (R^1 and/or R^2) into chiral AACMs **1** would rationally control the orientation of the benzannulation by fixing the conformation around bonds *a* and *b* of the cationic intermediate pre-(*M*)-**2**. Thus, (*M*)-α-arylnaphthalenes **2** would be produced by the chirality exchange (a type of memory effect[7]).

A couple of chiral diastereomeric AACM substrates, **1a** and **1a′**, were conveniently prepared to verify our hypothesis (eq 2) (Supporting Information describes the preparation and characterization of **1a** and **1a′**). Both (*S*)- and (*R*)-cyclopropanecarboxylic acids, the precursors of chiral AACMs **1**, were obtained; in this context we used the (*S*)-form. On the basis of previous studies,[6d] $TiCl_4$ and $SnCl_4$ were employed for the reaction of AACM **1a** and silyl triflates for diastereomer **1a′** to obtain the chiral biaryl product **2a**.



1a_$TiCl_4$ pre-(*M*)-**2a** **1a'**_R_3SiOTf

Table 1 lists the results of the chirality exchange. The benzannulation of AACM **1a** using $TiCl_4$ at 0 °C gave the chiral naphthalene **2a** (55% yield, 97% ee) along with 20% of the achiral α-phenylnaphthalene **3a** (entry 1). The reaction at −78 °C successfully proceeded in excellent yield (96%) and with both excellent regio- (>99:1) and enantioselectivities (>99% ee) (entry 2). Excellent selectivities were also achieved by the use of $SnCl_4$ (entry 3). In the case of AACM **1a′**, the use of $TiCl_4$ resulted in a switch of the regioselectivity to give achiral naphthalene **3a** exclusively (entry 4). This finding is consistent with the reported benzannulation.[6d] In contrast to the reaction of **1a′** with $TiCl_4$, the use of silyl triflates gave mainly **2a**, and the yield and enantiomeric excess were moderate (entries 5−7). Absolute configurations of **1a** and **2a** were unambiguously determined by X-ray crystallographic analysis.[8]

The excellent result using $TiCl_4$ encouraged us to investigate the chirality exchange of other AACMs **1b**−**1f** (Table 2). Similar to **1a**, Cl (R^1) analogue AACM **1b** also exhibited an excellent result (entry 1). A notable aspect of the present method lies in its generality; when R^2 substituents were introduced into AACMs **1c**−**1f**, an excellent level of chirality exchange (>99% ee's) was achieved in every case examined to give the desired (*M*)-α-naphthalenes **2c**−**2f** (entries 2−5). The absolute configurations of naphthalenes **2b**−**2f** were determined by analogy with **2a**.

The proposed mechanism of the chirality transfer mediated by $TiCl_4$ is as follows (Scheme 1). First, $TiCl_4$ chelates with the oxygen and chlorine of AACMs **1** to give a rigid intermediate **A**. Due to steric repulsion, the ortho substituent (R^1) orients itself at the backside of the chelation face. Successive $TiCl_4$-promoted elimination of the OH group gives the cationic intermediate pre-(*M*)-**2** while sufficiently maintaining the conformation by freezing the free rotation of bonds *a* and *b*. The conjugation between the cyclopropylmethyl cation and benzene ring system should contribute to prevent the free rotation of bond *b* bearing an accessory R^1-phenyl in pre-(*M*)-**2**.[9] Then, highly regioselective ring-opening of bond *c* and Friedel−Crafts-type cyclization sequentially occur to give α-arylnaphthalene (*M*)-**2** exclusively. In contrast, because silyl triflates cannot coordinate with Cl, nonchelation intermediate **B** is presumably produced. Thus, bonds *a* and *b* rotate to some extent to generate pre-(*P*)-**2** in the cation-formation step.

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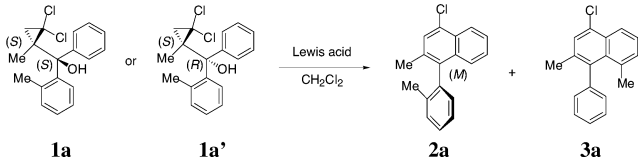
Table 1. Chirality Exchange Benzannulation of AACM **1a** and **1a′**

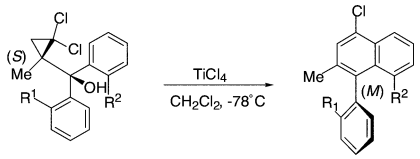


1a **1a'** **2a** **3a**

entry	substrate[a]	Lewis acid[b]	*T* (°C)	yield (%)[c]	ratio[d] (**2a**:**3a**)	ee of **2a** (%)[e]
1	**1a**	$TiCl_4$	0	75	(74:26)	97
2	**1a**	$TiCl_4$	−78	96	(>99:1)	>99
3	**1a**	$SnCl_4$	−78	72	(>99:1)	>99
4	**1a′**	$TiCl_4$	−78	89	(>1:99)	−
5	**1a′**	TBDMSOTf	0	41	(97:3)	45
6	**1a′**	TMSOTf	0	54	(77:23)	55
7	**1a′**	TBDMSOTf	−78	trace	−	−

[a] Optical purities: >99% ee. [b] 1.0 equiv of Lewis acid was used. [c] Isolated yields. [d] Determined by ^{1}H NMR. [e] Determined by HPLC with a Chiralcel OD column.

Table 2. Chirality Exchange Benzannulation of AACMs **1b**−**f** Using $TiCl_4$ [a]

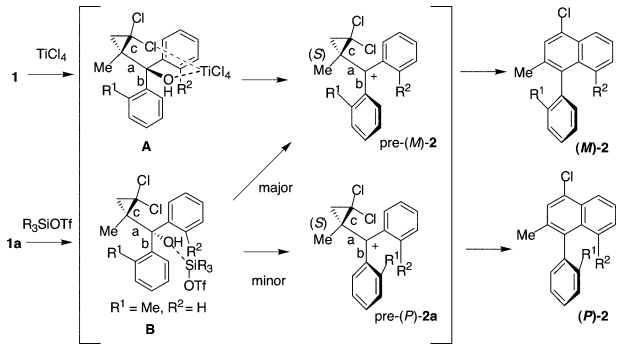


1b-f **2b-f**

entry	substrate[b]	R^1	R^2	product	yield (%)[c]	ee (%)[d]
1	**1b**	Cl	H	**2b**	97	>99
2	**1c**	Cl	Cl	**2c**	70	>99
3	**1d**	MeO	Me	**2d**	71	>99
4	**1e**	MeO	Cl	**2e**	65	>99
5	**1f**	Me	Cl	**2f**	47	>99

[a] 1.0 equiv of $TiCl_4$ was used. [b] Optical purity of each AACM was >99% ee. [c] Isolated yields. [d] Determined by HPLC with a Chiralcel OD column.

Scheme 1



In summary, we achieved the first chirality exchange benzannulation from sp^3 central chirality to axial chirality using optically active *o*-R^1-substituted AACMs **1** and obtained axially chiral α-arylnaphthalenes **2** with excellent enantioselectivity. The present method is a new avenue for the synthesis of axially chiral biaryls.

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Supporting Information Available: Experimental details, analytical and crystallographic data and characterization for reactions in Tables 1 and 2 (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The absolute configuration of **1a** was deduced as follows. The stereogenic center of the cyclopropane moiety was determined as (*S*) using a derivative, *N*-(1*S*)-1-phenylethyldichlorocyclopropylcarboxamide. That of the tertiary carbon-bearing OH group was determined as (*S*) using AACM **1a**. The absolute configuration of **2a** was determined as (*M*) using a derivative, (−)-(*P*)-2-bromomethyl-1-(2-bromomethylphenyl)-4-chloronaphthalene. (The reverse stereodescriptor (*P*) is a consequence of the sequence rule of the CIP nomenclature.)

(9) Both the σ-orbital of the cyclopropyl group and the π-orbital of the *o*-R^2-aryl group can stabilize the π-orbital of the adjacent carbocation with a maximum overlap, in which the bisected conformation of the cyclopropylmethyl cation is the most stable system. For discussion of cyclopropylmethyl cation, see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; pp 222−223, p 416−418.

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