ORGANIC LETTERS

2008
Vol. 10, No. 6
1243−1246

An Efficient and Versatile Approach for Optical Resolution of C_2-Symmetric Axially Chiral Biaryl Dials. Synthesis of Enantiopure Biaryl-Derived Cyclic *trans*-1,2-Diols

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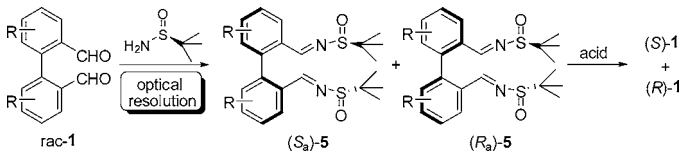
Received January 18, 2008

ABSTRACT



An efficient and practical method for optical resolution of axially chiral biaryl dials using enantiomeric *tert*-butanesulfinamide as resolving agent was developed. The approach offers a very convenient and straightforward access to versatile enantiomerically pure C_2-symmetric biaryl dials in good yields. With the obtained axially chiral dials, stereoselective synthesis of a series of cyclic *trans*-1,2-diols in optically pure form was investigated.

Axially chiral biaryl frameworks are found in a large number of natural products as well as pharmaceutical molecules.[1] Atropisomerically enriched biaryl compounds with C_1- or C_2-symmetry are also widely used as efficient chiral ligands or auxiliaries in asymmetric synthesis.[2] Over the last two decades, development of methods for constructing axial chirality including resolution of racemic biaryls and atropselective synthesis has been actively investigated.[3] Axially chiral biaryl dials with two carbaldehyde functionalities are extremely useful precursors to a range of important biaryl compounds (Scheme 1). Although several procedures for the preparation of optically pure biaryl dicarboxylic acids were reported,[4] the straightforward achievement of axially chiral

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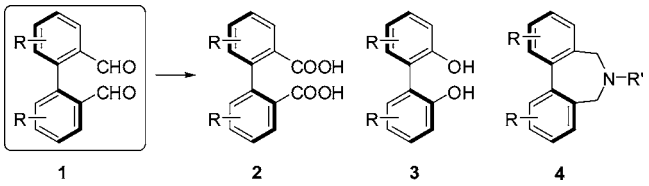
10.1021/ol800122x CCC: $40.75 © 2008 American Chemical Society
Published on Web 02/28/2008

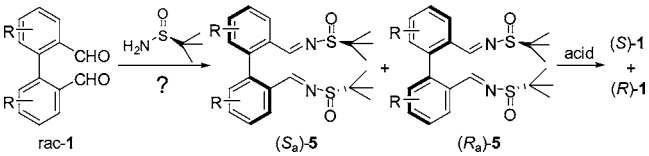
Scheme 1



biaryl dials remains a significant challenge.[5] To our knowledge, the only direct example documented in the literature is the kinetic resolution of racemic 1,1′-binaphthyl-2,2′-dicarbaldehyde with (*R*,*R*)-1,2-diphenylethylenediamine; however, the result was far from ideal (15% yield, 92% ee).[6] In this paper, we present our studies regarding a solution to this subject and provide an efficient and practical approach for optical resolution of C_2-symmetric axially chiral biaryl dials.

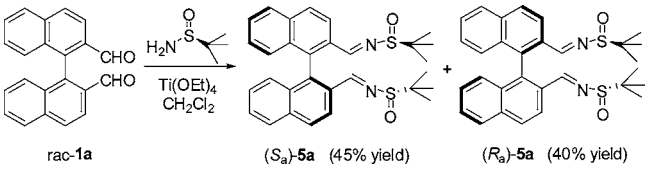
Recently, we have been successfully using enantiomerically pure *N*-*tert*-butanesulfinyl imines[7] as exceedingly versatile intermediates in asymmetric synthesis for the preparation of chiral amines[8a−c] and amino alcohols.[8d] In most cases, the *tert*-butanesulfinyl group serves as a powerful chiral discriminating group. On the other hand, *N*-*tert*-butanesulfinyl imines are easily hydrolyzed in acidic conditions. Inspired by these two facts, we envisioned an optical resolution process of racemic biaryl dials (**1**) using the atropisomeric *tert*-butanesulfinyl bis-imine (**5**) formation approach. Hydrolysis of each imine isomer would afford the expected axially chiral biaryl dicarbaldehyde compounds (*S*)-**1** and (*R*)-**1** (Scheme 2).

Scheme 2



Initial attempts were carried out by using racemic 1,1′-binaphthyl-2,2′-dicarbaldehyde (**1a**) as substrate. Upon treatment of **1a** with (*S*)-*tert*-butanesulfinamide in CH_2Cl_2 in the presence of $Ti(OEt)_4$, we observed significant formation of two major products with an approximate ratio of 1:1 on TLC plate. After the completion of the reaction, the two products were readily separated by flash column chromatography on silica gel. As expected, NMR spectra proved that they were diastereomerically pure binaphthyl *N*-sulfinyl bis-imines (S_a)-**5a** and (R_a)-**5a** (Scheme 3). It is notable that chromatographical resolution of diastereomeric bis-imines prepared by the condensation of rac-**1a** with other potential resolving agents such as (*R*)-α-methylbenzylamine or (*R*)-2-phenylglycine methyl ester is unsuccessful. The absolute configuration of the chiral axis of less polar isomer **5a** was determined as *S* by X-ray crystallography (Figure 1). It was

Scheme 3



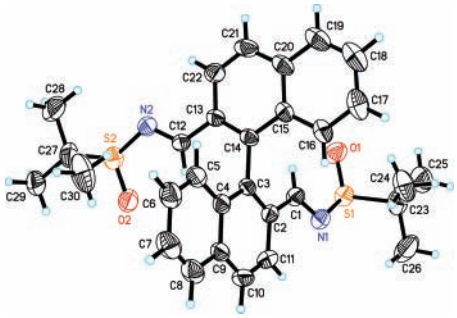


Figure 1. X-ray crystal structure of (S_a)-**5a**.

also found that the molecule in solid state exhibits a significant transoid conformation. Two bulky *tert*-butanesulfinyl imine units on the naphthyl ring were far away to avoid the steric repulsion.[9] To obtain the enantiopure 1,1′-binaphthyl-2,2′-dicarbaldehydes, two binaphthyl imine products were subsequently treated with 6 N HCl in MeOH. Gratifyingly, the hydrolysis went smoothly at room temperature to give the desired enantiomers (*S*)-**1a** and (*R*)-**1a**, respectively, in high yield without any racemization.[10]

Encouraged by the above results, we decided to apply the new strategy to the resolution of a range of synthetically useful biaryl dials carrying axial chirality. Typically, binaphthyl and biphenyl dials were examined as substrates, and the results are summarized in Table 1. With (*S*)-*tert*-butanesulfinamide, all biaryl dials were successfully converted into the corresponding bis-imines in good yields

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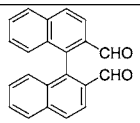
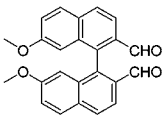
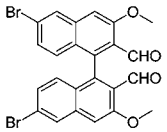
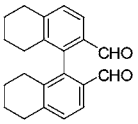
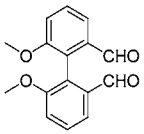
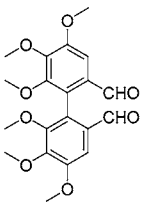
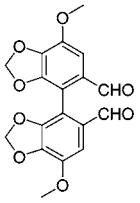
(9) The dihedral angle C2−C3-C14−C13 is 100.6°, and C4−C3-C14−C15 is 93.1°.

(10) Determined by HPLC analysis on a Chiralpak AD-H column.

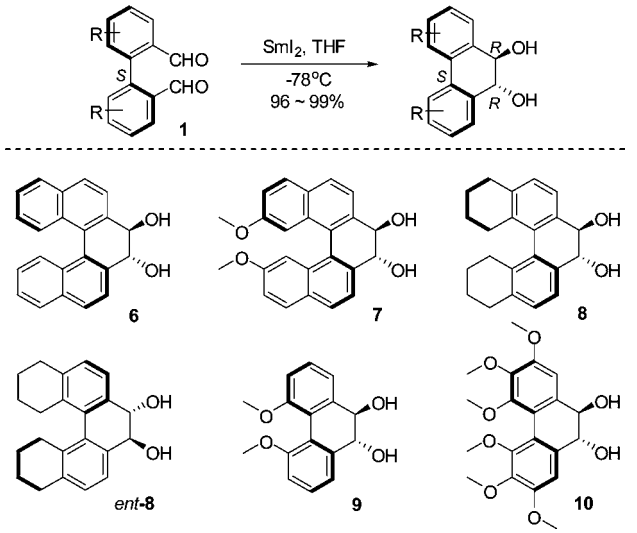
Table 1. Optical Resolution of Racemic Biaryl Dials via (*S*)-*tert*-Butanesulfinyl Imine Formation

entry	substrate **1**[a]	bis-imines			enantiopure dials		
		5	R_f	yield (%)[b]	**1**	$[\alpha]_D$[c]	yield (%)[b]
1	 **1a**	(S_a)-**5a**	0.30[d]	45	(*S*)-**1a**	-2.8 (c 0.30)[i]	90
		(R_a)-**5a**	0.23[d]	40	(*R*)-**1a**	+2.7 (c 0.35)[j]	91
2	 **1b**	(S_a)-**5b**	0.34[e]	47	(*S*)-**1b**	+77.8 (c 1.10)	94
		(R_a)-**5b**	0.28[e]	41	(*R*)-**1b**	-77.0 (c 0.62)	92
3	 **1c**	(S_a)-**5c**	0.28[d]	40	(*S*)-**1c**	-18.6 (c 0.40)	92
		(R_a)-**5c**	0.22[d]	32	(*R*)-**1c**	+18.4 (c 0.33)	91
4	 **1d**	(S_a)-**5d**	0.34[f]	44	(*S*)-**1d**	-81.0 (c 0.52)	92
		(R_a)-**5d**	0.28[f]	40	(*R*)-**1d**	+79.1 (c 0.83)	92
5	 **1e**	(S_a)-**5e**	0.32[e]	45	(*S*)-**1e**	-287 (c 0.72)[k]	94
		(R_a)-**5e**	0.25[e]	45	(*R*)-**1e**	+289 (c 0.51)	91
6	 **1f**	(S_a)-**5f**	0.24[g]	45	(*S*)-**1f**	-80.9 (c 0.88)[l]	95
		(R_a)-**5f**	0.18[g]	40	(*R*)-**1f**	+81.4 (c 0.62)	93
7	 **1g**	(S_a)-**5g**	0.44[h]	47	-	-	93
		(R_a)-**5g**	0.32[h]	47	-	-	94

[a] Racemate. [b] Isolated yield. [c] Performed in $CHCl_3$ at 20 °C. [d] Eluted with hexane/ethyl acetate = 3:1. [e] Eluted with hexane/ethyl acetate = 2:1. [f] Eluted with hexane/ether = 3:1. [g] Eluted with hexane/ethyl acetate = 4:1. [h] Eluted with hexane/ethyl acetate = 1:1. [i] $[\alpha]_D = -3.1$ (*c* 1.01, $CHCl_3$) in ref 4b. [j] $[\alpha]_D = +3.2$ (*c* 1.04, $CHCl_3$) in ref 4b. [k] $[\alpha]_D = -291$ (*c* 1.30, $CHCl_3$) in ref 12. [l] $[\alpha]_D = -81.7$ (*c* 1.17, $CHCl_3$) in ref 12.

regardless of the substituents on naphthalene or benzene ring. To our delight, these imine diastereomers are all physically stable and chromatographically separable. It seems that the electronic nature of the aryl ring has no influence on the resolution efficiency. After hydrolysis, various C_2-symmetric enantiomerically pure biaryl dials with both (*R*) and (*S*) configurations were accessed in high yields (entries 1−6). By comparing the first Cotton effect pattern of (*S*)-**1a** and others in CD spectra, the absolute configurations of more polar (slower eluting) isomers were assigned to have (*R*)-configurations.[11] It is noteworthy that the preparation of these optically pure dials by direct optical resolution has not been

Scheme 4



cyclization. In all cases, the reactions took place smoothly and gave quantitatively a single product. ^{1}H- and ^{13}C NMR spectroscopies of these products were consistent with cyclic diols bearing *trans* configuration (Scheme 4). The stereochemistry was further assigned on the basis of the X-ray crystal structure of **7** (Figure 2). Thus, upon employment of

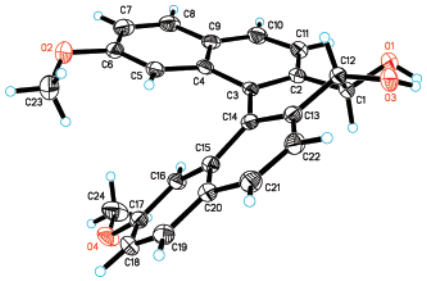


Figure 2. X-ray crystal structure of diol **7**.

successfully achieved before. For dials (*S*)-**1e** and (*S*)-**1f**, Meyers and co-workers have reported an asymmetric synthetic approach via magnesium- and copper-mediated coupling reactions,[12] while it requires many steps and needs to use chiral aryl oxazoline substrates. With our resolution method, these dial enantiomers are readily accessed. Using substrate **1b**, the resolution was found equally successful on a gram scale. In the case of entry 7, the rotation barrier at the biphenyl axis of dial **1g** was low so that rapid racemization was observed upon removal of the bulky *tert*-butanesulfinyl groups in (S_a)-**5g** and (R_a)-**5g**.

With a series of enantiopure biaryl dials in hand, we are interested in exploring their intramolecular pinacol couplings using SmI_2[13] to produce cyclic 1,2-diols containing both axial chirality and central chiralities. Previously, pinacol cyclization of biaryl dials has been reported to proceed by the synclinal mode and give only *trans*-diols;[14] however, very few examples of using optically pure biaryl dials have been investigated.[15] Under the conditions of SmI_2 at −78 °C, dials (*S*)-**1a**,**b**, **1d**−**f** as well as (*R*)-**1d** were examined for pinacol dial (*S*)-**1** in reaction, the sole formation of the corresponding helix-like *trans*-(*S*,*S*)-diols in excellent yields were determined. Notably, these novel C_2-symmetric biaryl-derived cyclic *trans*-1,2-diols would be expected to be useful chiral ligands in asymmetric synthesis.

In summary, we have developed an efficient and practical method for optical resolution of axially chiral biaryl dials via *tert*-butanesulfinyl bis-imines. Enantiomeric *tert*-butanesulfinamide was used as the resolving agent. The current approach offers a very convenient and straightforward access to versatile enantiomerically pure C_2-symmetric biaryl dials in good yields. With the obtained axially chiral dials, stereoselective synthesis of a series of cyclic *trans*-1,2-diols in optically pure form was investigated. It is believed that both the resolution strategy and the attained chiral biaryl dials as well as biaryl-derived cyclic diols would find wide application in asymmetric synthesis.

Acknowledgment. Financial support from the NSF of China (20672123, 20721003), the Chinese Academy of Sciences, and the Major State Basic Research Development Program (2006CB806106) is acknowledged.

Supporting Information Available: Experimental procedures, characterization data, copies of CD, NMR spectra, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (*S*)-**1a** gave a negative first Cotton effect at 360−380 nm, while all positive first Cotton effects were observed for other slower-eluting isomers; see Supporting Information for CD spectra. The absolute configurations of (*S*)-**1e** and (*S*)-**1f** were further confirmed by comparing the optical rotation $[\alpha]_D$ with known data.

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