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A Novel Axially Chiral 2,2′-Bipyridine *N,N′*-Dioxide. Its Preparation and Use for Asymmetric Allylation of Aldehydes with Allyl(trichloro)silane as a Highly Efficient Catalyst

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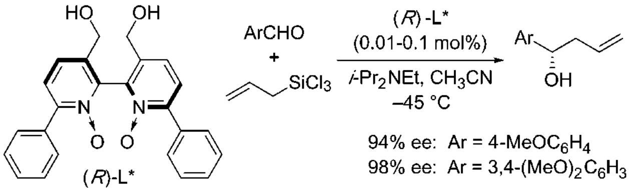
ABSTRACT



New axially chiral 2,2′-bipyridine *N,N′*-dioxides were obtained by a new method that does not involve any procedures for the separation of enantiomers. One of the dioxides, (*R*)-3,3′-bis(hydroxymethyl)-6,6′-diphenyl-2,2′-bipyridine *N,N′*-dioxide, exhibited extremely high catalytic activity for the asymmetric allylation of aldehydes with allyl(trichloro)silane. The allylation of aromatic aldehydes proceeded in the presence of 0.01 or 0.1 mol % of the dioxide catalyst to give the corresponding homoallyl alcohols of up to 98% ee.

Among the useful methods for allylation of carbonyl compounds is the use of hypervalent allylsiliconates as the allylating reagents,[1] the reaction of which with aldehydes proceeds by way of six-membered cyclic transition states.[2] Kobayashi[3] and Denmark[4] found that the hypervalent siliconates can be conveniently generated by addition of DMF or HMPA to allylic trichlorosilanes to give homoallylic alcohols in high yield on reaction with aldehydes. On the basis of these findings, Denmark reported, in 1994, the first example of asymmetric allylation by use of chiral phosphoramides as chiral Lewis base ligands.[4] After this report, a variety of chiral Lewis bases have been designed and used for the asymmetric allylation with allylic trichlorosilanes.[5−9] One big problem in the Lewis base-catalyzed asymmetric allylation is that a large amount (5−10 mol %) of the catalyst is required for a reasonable reaction rate, as has been observed also in most of the Lewis acid-catalyzed asym-

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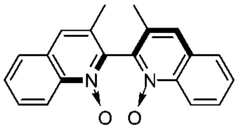
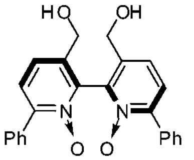
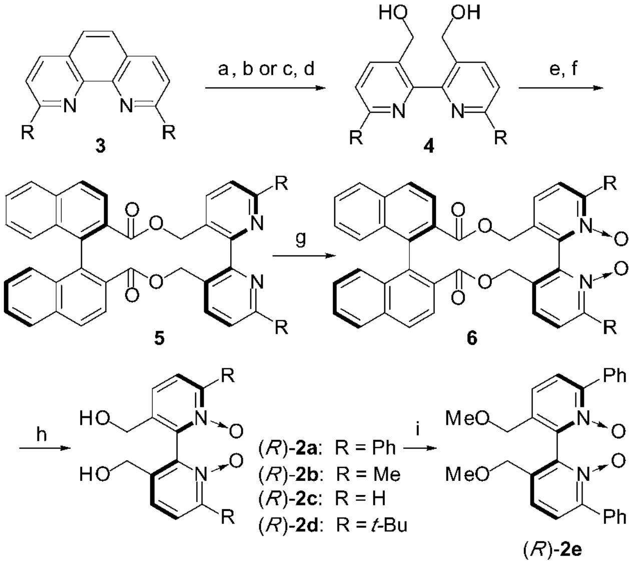
metric reactions.[10] The axially chiral biquinoline *N*,*N*′-dioxide (*S*)-**1** reported by Nakajima[8] attracted our attention because of its highly skewed chiral environment capable of bringing about high enantioselectivity in the asymmetric allylation of aldehydes, and we have looked for a new type of axially chiral bipyridine *N*,*N*′-dioxides whose catalytic activity for the asymmetric allylation is higher than others and a new general method for their synthesis where the optical resolution is not involved. Here we report our recent result that a new 2,2′-bipyridine *N*,*N*′-dioxide (*R*)-**2a** prepared without optical resolution has high catalytic activity as well as high enantioselectivity for the asymmetric allylation.[11]


(*S*)-**1**


(*R*)-**2a**

For the preparation of enantiomerically pure 2,2′-bipyridine *N*,*N*′-dioxide **2a**, whose chirality is based on the biaryl axial chirality, we developed a new method of introducing and fixing the axial chirality by oxidation of the cyclic diester **5a**, which consists of (*R*)-1,1′-binaphthalene-2,2′-dicarboxylic acid and 3,3′-bis(hydroxymethyl)-6,6′-diphenyl-2,2′-bipyridine (**4a**) (Scheme 1). Thus, bipyridine-diol **4a**, which is readily accessible from 2,9-diphenylphenanthroline (**3a**)[12] by oxidation with potassium permanganate and sodium periodate followed by esterification of the dicarboxylic acid and reduction with lithium aluminum hydride, was coupled with (*R*)-2,2′-bis(chlorocarbonyl)-1,1′-binaphthalene in the presence of triethylamine to give a high yield of the cyclic diester. On heating the diester in refluxing toluene, thermodynamically more stable diastereoisomer **5a** was obtained as a single isomer,[13] whose axial chirality of bipyridine moiety is (*R*).[14] Oxidation of the bipyridine in **5a** with *m*-chloroperbenzoic acid followed by alkaline hydrolysis gave enantiomerically pure (*R*)-3,3′-bis(hydroxymethyl)-6,6′-diphenyl-2,2′-bipyridine *N*,*N*′-dioxide (**2a**), whose axial chirality is now fixed by the formation of *N*,*N*′-dioxide. In a similar manner, (*R*)-2,2′-bipyridine *N*,*N*′-dioxides **2b**, **2c**, and **2d**, which are substituted with methyl, hydrogen, and *tert*-butyl, respectively, at the 6 and 6′ positions, were prepared starting from the corresponding phenanthroline derivatives **3**.

Scheme 1[a]



[a] Reaction conditions: (a) $KMnO_4$, $NaIO_4$; (b) CH_2N_2; (c) (i) $SOCl_2$, (ii) MeOH, Et_3N; (d) $LiAlH_4$, THF; (e) (*R*)-2,2′-bis(chlorocarbonyl)-1,1′-binaphthalene, Et_3N, $CHCl_3$; (f) PhMe, reflux; (g) *m*CPBA, CH_2Cl_2; (h) 6 N NaOH, MeOH; (i) NaH, MeI.

The 2,2′-bipyridine *N*,*N*′-dioxide (*R*)-**2a** was found to possess high catalytic activity as well as high enantioselectivity for the asymmetric allylation of aldehydes with allyl(trichloro)silane (Scheme 2 and Table 1). Thus, the reaction of 4-methoxybenzaldehyde (**7a**) with allyl(trichloro)silane (1.2 equiv) in the presence of 0.1 mol % of (*R*)-**2a** and diisopropylethylamine (3 equiv) in acetonitrile at −45 °C was completed within 2.5 h to give 96% isolated yield of homoallyl alcohol **8a**, which is an (*S*) isomer of 94% ee (entry 2). The amount of the catalyst can be reduced to 0.01 mol % without loss of the enantioselectivity, though the reaction is somewhat slower (entry 3). The high catalytic activity of (*R*)-**2a** observed here makes a remarkable contrast to the much lower catalytic activity of other chiral Lewis

Scheme 2

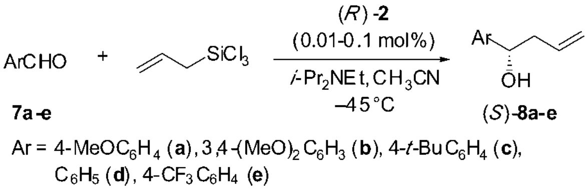


Table 1. Asymmetric Allylation of 4-Methoxybenzaldehyde (**7a**) with Allyl(trichloro)silane Catalyzed by (*R*)-Bipyridine Dioxides **2**[a]

entry	catalyst **2** (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)	% ee[c] (config)[d]
1	**2a** (1)	CH_3CN	−45	0.25	96	94 (*S*)
2	**2a** (0.1)	CH_3CN	−45	2.5	96	94 (*S*)
3	**2a** (0.01)	CH_3CN	−45	12	68	94 (*S*)
4	**2a** (0.5)	CH_2Cl_2	−78	2.5	90	78 (*S*)
5	**2a** (0.1)	CH_2Cl_2	−45	2.5	91	76 (*S*)
6	**2b** (0.1)	CH_3CN	−45	2.5	22	85 (*S*)
7	**2c** (0.1)	CH_3CN	−45	2.5	20	75 (*S*)
8	**2d** (0.1)	CH_3CN	−45	2.5	0	
9	**2e** (0.1)	CH_3CN	−45	2.5	95	92 (*S*)

[a] The allylation was carried out with allyl(trichloro)silane (1.2 equiv) and diisopropylethylamine (3 equiv) in 1.0 M (aldehyde) solution. [b] Isolated yields. [c] Determined by GLC analysis with CP-Chiralsil-Dex. [d] Determined by the optical rotation of alcohol **8a**.

base catalysts used so far in the asymmetric allylation of aldehydes, where 5−10 mol % of the catalyst is usually required for a reasonable reaction rate.[5−9] The allylation also proceeded smoothly in dichloromethane with the low amount loading of (*R*)-**2a**,[15] which is reported to be the solvent of choice with most of the Lewis base catalysts, though the enantioselectivity was lower than in acetonitrile (entries 4 and 5). The high catalytic activity of (*R*)-**2a** is ascribed mainly to the phenyl substituents at the 6 and 6′ positions. The allylation was much slower with the bipyridine dioxides (*R*)-**2b** and (*R*)-**2c** where the phenyl group in (*R*)-**2a** was replaced by methyl and hydrogen, respectively (entries 6 and 7). No allylation took place with (*R*)-**2d**, which is the bipyridine dioxide substituted with *tert*-butyl groups at the 6 and 6′ positions (entry 8). The $\pi-\pi$ stacking between the phenyl group on (*R*)-**2a** and the aromatic ring in aldehyde **7a** in the transition state probably enhances the catalytic activity as well as the enantioselectivity. The hydroxymethyl groups at 3 and 3′ positions do not play an important role in catalyzing the reaction, which was demonstrated by essentially the same catalytic activity and enantioselectivity observed with the methyl ether (*R*)-**2e** (entry 9).

The catalytic activity of bipyridine dioxides (*R*)-**2a** was also very high for other aldehydes. The allylation of aromatic aldehydes **7b**−**e** substituted with electron-donating and -withdrawing groups proceeded in high yields in the presence of 0.1 mol % of the catalyst (Table 2). The enantioselectivity was strongly dependent on the substituents on the phenyl ring, being higher with more electron-donating groups. The highest enantioselectivity (98% ee) was observed in the reaction of 3,4-dimethoxybenzaldehyde (**7b**) (entry 2).

Table 2. Asymmetric Allylation of Aldehydes **7** with Allyl(trichloro)silane Catalyzed by 0.1 mol % of (*R*)-**2a**[a]

entry	aldehyde **7** Ar in ArCHO	yield[b] (%) of **8**	% ee[c] of **8** (config)	$[\alpha]^{20}_{D}$ of **8** (*c* in C_6H_6)
1	4-$MeOC_6H_4$ (**7a**)	96 (**8a**)	94 (*S*)	−32.7 (1.0)
2	3,4-$(MeO)_2C_6H_3$ (**7b**)	95 (**8b**)	98 (*S*)	−37.8 (1.9)
3	4-*t*-BuC_6H_4 (**7c**)	93 (**8c**)	89 (*S*)	−24.1 (1.0)[d]
4	Ph (**7d**)	95 (**8d**)	84 (*S*)	−48.9 (1.0)
5	4-$CF_3C_6H_4$ (**7e**)	83 (**8e**)	56 (*S*)	−18.1 (1.9)

[a] The allylation was carried out with (*R*)-**2a** (0.1 mol %), allyl(trichloro)silane (1.2 equiv), and diisopropylethylamine (3 equiv) in 1.0 M acetonitrile solution at −45 °C for 2.5 h. [b] Isolated yields. [c] Determined by GLC analysis with CP-Chiralsil-Dex for **8a**, **8b**, **8c**, and **8e**, and by HPLC analysis with Chiralcel OD-H (hexane/2-propanol = 95/5) for **8d**. [d] Specific rotation in Et_2O.

To summarize, new axially chiral 2,2′-bipyridine *N*,*N*′-dioxides (*R*)-**2** were obtained by a new method that does not involve any procedures for the separation of enantiomers. One of the dioxides, **2a**, exhibited extremely high catalytic activity for the asymmetric allylation of aldehydes with allyl(trichloro)silane giving homoallyl alcohols. Such a low catalyst loading (0.01−0.1 mol %) is unprecedented for the Lewis base-catalyzed asymmetric allylation.[4−9,16] Further studies are in progress to rationalize the high catalytic activity caused by the phenyl groups at the 6 and 6′ positions as well as the solvent effects of acetonitrile on the enantioselectivity.

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Supporting Information Available: Full experimental and spectroscopic details for the compounds reported and X-ray crystallographic data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For books containing Lewis acid-catalyzed asymmetric reactions: (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, Germany, 1999. (c) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley: New York, 2001.

(11) Very recently, new chiral bipyridine *N*,*N*′-dioxides have been prepared and used for Lewis base-catalyzed asymmetric addition to carbonyl compounds: (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1047. (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc*. **2002**, *124*, 4233.

(12) Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291.

(13) The diester formation reaction at a low temperature gave the other diastereoisomer as a kinetic product with high selectivity (over 95% selectivity), which is isomerized into the thermodynamic isomer by heating. These phenomena will be described in detail elsewhere.

(14) The absolute configuration was determined by X-ray structure analysis of the cyclic diester **5a** (see Supporting Information).

(15) The allylation with 0.1 mol % of (*R*)-**2a** at −45 °C did not proceed in toluene, diethyl ether, or THF.

(16) A few examples of this level of low catalyst loading have been reported in the Lewis acid-catalyzed Hetero-Diels−Alder reactions: (a) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599, where 0.05 mol % of catalyst was used. (b) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc*. **2001**, *123*, 5366, where 0.01 mol % of catalyst was used. (c) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10, where 0.005 mol % of catalyst was used.