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# Simple and Fast Synthesis of New Axially Chiral Bipyridine *N,N′*-Dioxides for Highly Enantioselective Allylation of Aldehydes

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**Abstract:** Unsymmetrically 3,3′-substituted axially chiral bis(tetrahydroisoquinoline) *N,N′*-dioxides can be prepared in just three steps. They exhibit unique catalytic activity (turnover frequency, enantioselectivity, substrate scope) in the asymmetric allylation of aromatic aldehydes (up to 96% *ee*). The product of the enantioselective allylation of benzaldehyde served as a building block for the preparation of an intermediate useful in the enantioselective synthesis of diospongines.

**Keywords:** asymmetric catalysis; cobalt; cyclotrimerization; microwave heating; organic catalysis

There is no doubt that the development of organocatalysis in the last decade has provided organic chemists with a number of useful synthetic methods, especially in the area of asymmetric reactions.[1] One of the fast growing areas is catalysis by Lewis bases, among which a prominent role is played by pyridine *N*-oxides. Their popularity stems from the fact that due to the strong donating ability they activate the C–Si bond of halosilanes to such an extent that it reacts with various functional groups.[2] The area of catalytically active *N*-oxides for the allylation of aldehydes[3] spans from monodentate pyridine *N*-oxides with additional chelating functional groups such as OMe,[4–7] nitrogen-containing functionalities,[8–10] bipyridine *N,N′*-dioxides,[11,12] to terpyridine *N,N′,N″*-trioxides.[13] All of these catalysts have pros and cons with respect to substrate specifity, enantioselectivity, catalytic activity, preparation, etc. Notwithstanding, the obtained homoallylic alcohols could serve as important building blocks for the synthesis of various compounds such as fluoxetine[14a] and (−)-diospongines A and B.[14b] Thus the present situation creates an ideal environment for further activities regarding the synthesis of new and potentially generally applicable catalysts.

In this regard we have found that axially chiral pyridine and bipyridine *N*-oxides could be easily accessed by using the cyclotrimerization of diynes with nitriles catalyzed by $CpCo(CO)_2$. Microwave irradiation significantly improved the course of the reaction resulting in higher product yields and shorter reaction times in comparison with the thermal variant or even made it to take place in cases where the thermal initiation totally fails.[15] The prepared axially chiral pyridine *N*-oxides had aryltetrahydroisoquinoline,[15a] pyridyl-tetrahydroisoquinoline,[15b,c] isoquinolinyltetrahydroisoquinoline,[15c] and bis(tetrahydroisoquinoline)[15d] frameworks. All of these compounds were tested as chiral catalysts for the asymmetric allylation of aldehydes. Although the last group of catalysts[15d] proved to have interesting features (they possess high catalytic activity and the enantiodiscrimination is profoundly dependent on the reaction solvent used), the enantioselectivity stayed below 90% *ee*.

Our next effort was focused on the increase of enantioselectivity to an acceptable level as well as the simplicity of bipyridine *N,N*-dioxides resolution into enantiomerically pure compounds, which has usually been carried out by crystallization or by HPLC. Since the previously prepared catalysts ***A*** and catalyst ***B*** (Figure 1) showed generally good catalytic activity and reasonable enantioselectivity, we presumed that the synthesis of a compound bearing both functional groups, that is, phenyl and tetrahydrofuranyl, would afford a catalyst with better properties (Figure 1).

We expected that the presence of an additional center of chirality on the tetrahydrofuranyl moiety would result in an easier separation of diasteroisom-

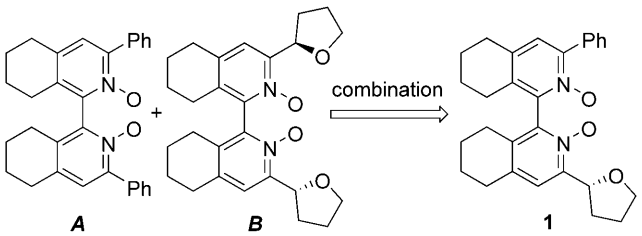



**Figure 1.** Design of bipyridine *N,N′*-dioxide **1**.

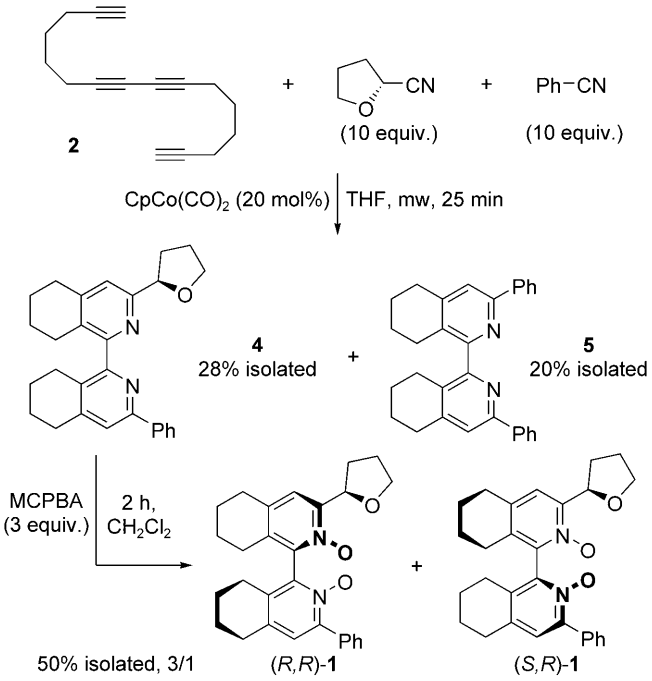
ers in comparison to the tedious HPLC resolution of enantiomers.[16]

It was initially envisioned that a stepwise synthesis of the pyridine ring could provide a suitable method for its preparation. Once again, as in our previous work, tetrayne **2** was chosen as a starting material. Attempts to selectively monocyclotrimerize **2** with benzonitrile using Okamoto conditions ($CoCl_2 \cdot 6H_2O$, Zn, dppe, NMP or DMF)[17] were met only with partial success. Disappointingly, the reaction proceeded with low selectivity giving the expected 1-diynyltetrahydroisoquinoline **3** only in 10% isolated yield.[15d] Varying the reaction conditions or molar ratios of starting compounds did not change the situation. Also the second step, the catalytic cyclotrimerization [$CpCo(CO)_2$] of **3** with (*R*)-tetrahydrofurannitrile under microwave irradiation yielded the desired bipyridine **4** in just 28% isolated yield. Again, the change of the reaction conditions or the catalytic system did not lead to any improvement. An attempt to use (*R*)-tetrahydrofurannitrile for the first cyclotrimerization failed: no product was isolated.

Therefore we chose the one-pot cyclotrimerization of tetrayne **2** with benzonitrile and (*R*)-tetrahydrofurannitrile, which could provide a straightforward route to the unsymmetrically substituted bipyridine **4**. Against all odds, the one-pot cyclotrimerization of all three components in the presence of $CpCo(CO)_2$ (20 mol%) under microwave irradiation yielded the desired bipyridine **4** in a reasonable 28% isolated yield along with the Ph-substituted symmetrical bipyridine **5** (20%) (Scheme 1).[18,19] (The combined yield of the cyclotrimerization products was 48%, which is almost the same as in the previous synthesis of symmetrically substituted bis(tetrahydroisoquinolines).

Oxidation of **4** by MCPBA (3 equiv.) in dichloromethane proceeded uneventfully to give a 3/1 mixture of diastereoisomeric bipyridine *N,N*-dioxides (*R,R*)-**1** and (*S,R*)-**1** in 50% isolated yield (Scheme 1). Both diastereoisomers were readily separated by a column chromatography on silica gel.

Having thus secured the preparation of (*R,R*)-**1** and (*S,R*)-**1** in three steps (including the preparation of **2**), we set out to explore their catalytic activity and enantioselectivity in the allylation of variously substituted benzaldehydes with allyltrichlorosilane (Table 1). The



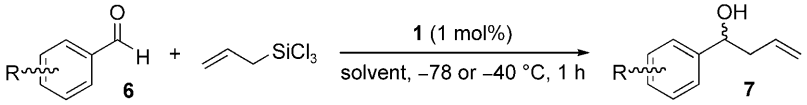

**Scheme 1.** Synthesis of (*R,R*)-**1** and (*S,R*)-**1**.

reactions were carried out in the presence of 1 mol% of **1** at −40 °C ($CH_2Cl_2$ and PhCl) or at −78 °C (THF). Initially, the reactions catalyzed by the more abundant bipyridine *N,N′*-dioxide (*R,R*)-**1** were examined. The allylation of benzaldehyde **6a** to homoallylic alcohol **7a** proceeded with full conversion in all solvents within 1 hour. The lowest asymmetric induction, 53% *ee* (entry 1), was observed in MeCN. On the other hand, in PhCl and THF the *ee*s were as high as 93% (entries 2 and 3).

As in our previous reports, the same solvent effect was observed: the catalyst with *R*-axial chirality gave the *S*-product in MeCN, but the *R*-product was obtained in PhCl and THF (and *vice versa*). Comparison of allylations of 4-methoxybenzaldehyde **6b** and 4-trifluoromethylbenzaldehyde **6f** to the corresponding homoallylic alcohols in PhCl (**7b**, 55% *ee*, entry 4; **7f**, 67% *ee*, entry 9) and THF (**7b**, 86% *ee*, entry 5; **7f**, 95% *ee*, entry 10) revealed THF as the superior solvent to achieve high enantioselectivity. The reactions with 4-methyl-, 4-fluoro, 4-chloro-, and 4-cyanobenzaldehydes **6c–6e** and **6g** proceeded with good enantioselectivities: **7c** (85% *ee*), **7d** (84% *ee*), **7e** (89% *ee*), and **7g** (83% *ee*) (entries 6–8, and 11). Good enantioselectivity (**7h**, 87% *ee*) was also observed in the allylation of 3-chlorobenzaldehyde **6h** (entry 12). However, a sharp decrease in asymmetric induction to 46% *ee* was observed for 2-chlorobenzaldehyde (entry 13). Next, a set of experiments was performed with (*S,R*)-**1** under identical conditions. The allylation of benzaldehyde **6a** in MeCN proceeded again with a low enantioselectivity of 44% *ee* (entry 1), but in

**Table 1.** Allylations of substituted benzaldehydes **6** to homoallylic alcohols **7** catalyzed by **1**.

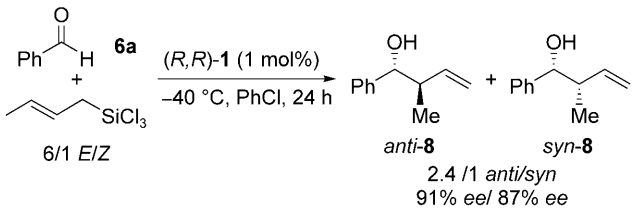



| Entry | R | Solvent | *T* [°C] | (*R,R*)-**2**[a] Yield [%][b] | (*R,R*)-**2**[a] *ee* [%][c] | (*S,R*)-**2**[a] Yield [%][b] | (*S,R*)-**2**[a] *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **6a**, H | MeCN | –40 | **7a**, 100 | 53 (*S*) | 100 | 44 (*R*) |
| 2 | **6a**, H | PhCl | –40 | **7a**, 100 | 93 (*R*) | 100 | 94 (*S*) |
| 3 | **6a**, H | THF | –78 | **7a**, 100 | 93 (*R*) | 98 | 96 (*S*) |
| 4 | **6b**, 4-MeO | PhCl | –40 | **7b**, 93 | 55 (*R*) | – | – |
| 5 | **6b**, 4-MeO | THF | –78 | **7b**, 100 | 86 (*R*) | 90 | 91 (*S*) |
| 6 | **6c**, 4-Me | THF | –78 | **7c**, 99 | 85 (*R*) | 99 | 94 (*S*) |
| 7 | **6d**, 4-F | THF | –78 | **7d**, 81 | 84 (*R*) | 99 | 95 (*S*) |
| 8 | **6e**, 4-Cl | THF | –78 | **7e**, 89 | 89 (*R*) | 91 | 93 (*S*) |
| 9 | **6f**, 4-$CF_3$ | PhCl | –40 | **7f**, 76 | 67 (*R*) | – | – |
| 10 | **6f**, 4-$CF_3$ | THF | –78 | **7f**, 76 | 95 (*R*) | 91 | 87 (*S*) |
| 11 | **6g**, 4-CN | THF | –78 | **7g**, 55 | 83 (*R*) | 93 | 88 (*S*) |
| 12 | **6h**, 3-Cl | THF | –78 | **7h**, 75 | 87 (*R*) | 78 | 92 (*S*) |
| 13 | **6i**, 2-Cl | THF | –78 | **7i**, 45 | 46 (*R*) | 42 | 14 (*S*) |

[a] 1 mol%, unless otherwise noted.
[b] GC yields.
[c] Determined by GC.

PhCl the corresponding homoallylic alcohol was obtained with 94% *ee* (entry 2) and it rose to 96% (entry 3) when the solvent was switched to THF. The allylations of 4-methoxy-, 4-methyl-, 4-fluoro-, 4-chloro-, and 4-trifluoromethylbenzaldehydes **6b–6f** proceeded mostly in very good enantioselectivities: **7b** (91% *ee*), **7c** (94% *ee*), **7d** (95% *ee*), **7e** (93% *ee*), **7f** (87% *ee*), and **7g** (88% *ee*) (entries 3, 5–8, and 11). It is also worth of mentioning that unusually high *ee* (92%) was obtained for the *meta*-substituted substrate (entry 12). A surprising drop in asymmetric induction (14% *ee*) was again observed for 2-chlorobenzaldehyde.

The allylation of benzaldehyde **6a** with *E*-crotyltrichlorosilane, prepared as a 6:1 *E*/*Z* mixture by the CuCl-catalyzed reaction of crotyl chloride with $HSiCl_3$,[20] was briefly explored to assess the scope of the reaction (Scheme 2). The reaction carried out in PhCl afforded a 2.4/1 mixture of *anti*/*syn* diastereoisomers with good enantioselectivity (91 and 87% *ee*) in 82% yield.




**Scheme 2.** Crotylation of benzaldehyde **6a** catalyzed by (*R,R*)-**1**.

In an attempt to assess the scope of the catalytic reaction with respect to other aldehydes, the allylations of *n*-octanal **9a** and cyclohexylcarbaldehyde **9b** were carried out in $CHCl_3$ (it was shown that chloroform is the solvent of choice for the allylation of aliphatic aldehydes[21]). Thus, the allylations of **9a** and **9b** catalyzed by (*R,R*)-**1** provided products **10a** and **10b** with higher enantioselectivity (Table 2, entries 1 and 2) in comparison with the catalysis by (*S,R*)-**1** (Table 2, entries 3 and 4).

From a general point of view, (*S,R*)-**1** is the better catalyst for highly enantioselective allylation of benzaldehydes bearing electron-withdrawing as well as electron-donating groups. On the other hand in some specific cases, the superior enantioselection was achieved with (*R,R*)-**1**, for example, the allylation of 4-trifluoromethylbenzaldehyde **6f** gave **7f** with 95% *ee* (entry 10).

Regarding the high asymmetric induction, the crucial role is played by THF, which enables the reaction mechanism to proceed through the sterically more crowded neutral six-coordinate silicon species leading to higher selectivities.[22] The comparison of catalysts **1** with the 3-tetrahydrofuranyl-3′-unsubstituted derivative[15d] (allylation proceeded with 49% *ee*) clearly indicates that the simultaneous substitution in positions 3 and 3′ is essential for high enantioselectivity. In addition, the comparison with symmetrically substituted 3,3′-diphenyl-bis(tetrahydroisoquinoline) *N,N′*-dioxide[15d] seems to confirm that an unsymmetrical environment may favour non-equivalent coordination of the N–O moieties to the silicon atom, as indicated

**Table 2.** Allylations of aliphatic aldehydes (RCHO) **9** to homoallylic alcohols **10** catalyzed by **1**.

| Entry | R | Catalyst | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | **9a**, *n*-$C_7H_{15}$ | (*R,R*)-**1** | **10a**, 90 | 60 (*S*) |
| 2 | **9b**, *c*-$C_6H_{11}$ | (*R,R*)-**1** | **10b**, 95 | 67 (*R*) |
| 3 | **9a**, *n*-$C_7H_{15}$ | (*S,R*)-**1** | **10a**, 88 | 43 (*S*) |
| 4 | **9b**, *c*-$C_6H_{11}$ | (*S,R*)-**1** | **10b**, 94 | 38 (*R*) |

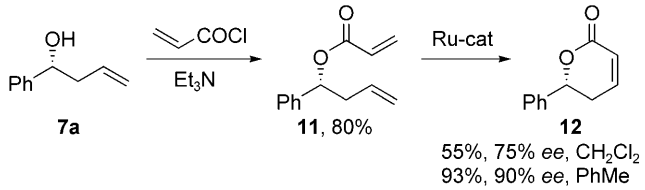
[a] GC yields.
[b] Determined by GC.

by previous calculations.[22] This may thus enhance the preferential dissociation of a more weakly bound N–O moiety to allow coordination of the incoming carbonyl group while keeping the rigid transtion state necessary for the high asymmetric induction.

Although the enantiodiscriminating properties of both catalysts are comparable with other ones such as those prepared by Kočovský et al.[4] (long reaction times and high catalyst loadingd), Hayashi[12] (low *ee*s in the allylation of substrates with electron-withdrawing groups), Andrus[10] (long reaction times), their use has several considerable advantages: i) it is easier to prepare them from a simple starting material (just three steps, no special resolution techniques are required, just simple column chromatography), ii) short reaction times (the reaction is usually finished with 1 h even at −78 °C, iii) low catalyst loads (usually 1 mol%).

In order to verify the synthetic application of the prepared homoallylic alcohols, we decided to prepare lactone **12**, which is a known intermediate used in the synthesis of diospongines.[14b] Esterification of (*R*)-**7a**, prepared by the allylation of benzaldehyde **6a** catalyzed by (*R,R*)-**1** (Table 1, entry 3), with acryloyl chloride afforded ester **11** in good 80% isolated yield (Scheme 3). Then **11** was subjected to a ring-closing metathesis reaction catalyzed by Grubbs 2nd generation catalysts,[23] $(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh$, (5 mol%), affording the known intermediate **12**. The RCM carried out in toluene yielded **12** in 93% yield (~90% *ee*).[24] Interestingly, the use of $CH_2Cl_2$ as the solvent resulted in a lower yield (75%) and in a loss of enantiopurity (75% *ee*).[25]

In summary, we have presented a new class of axially chiral bipyridine *N,N′*-dioxides – 3,3′-unsymmetrically substituted bis(tetrahydroisoquinoline) *N,N′*-dioxides – that exhibit unique catalytic activity (turnover frequency, enantioselectivity, substrate scope) in the enantioselective allylation of aromatic aldehydes (up to 96% *ee*). The efficiency (just three steps from commercially available material) and potentially modular nature of the synthesis should allow for further tuning of the catalyst properties. Further studies aimed at diversifying the structure of the catalysts and their applications in other reactions are under way.




**Scheme 3.** Synthesis of the diospongine intermediate **12**.

Experimental procedures, analytical and spectral data, and copies of the NMR spectra for the key compounds are available in the Supporting Information.

## Experimental Section

### General Procedure for Allylation of Aromatic Aldehydes 6

To a solution of bipyridine-*N,N′*-dioxides (*R,R*)-**1** or (*S,R*)-**1** (0.004 mmol, 2 mg) in THF, PhCl or MeCN (1 mL), aldehyde (0.4 mmol), diisopropylethylamine (0.6 mmol, 104 μL, 77 mg) and allyltrichlorosilane (0.6 mmol, 85 μL, 51 mg) were added at −78 or −40 °C and the reaction mixture was stirred for 1 hour. The reaction was quenched with brine (4 mL), organic layer was separated, dried over $MgSO_4$ and filtrated on silica gel. Yields and *ee*s were determinated by GC (HP-Chiral ß column, 30 m × 0.25 mm, oven: 80 °C for 1 min, then 1 °C min$^{-1}$ to 160 °C, 5 min).

## Acknowledgements

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[25] The origin of this observation is not currently clear and will be subject of further investigation.

  