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A Simple Approach to Unsymmetric Atropoisomeric Bipyridine *N,N′*-Dioxides and Their Application in Enantioselective Allylation of Aldehydes

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Abstract: The [2+2+2] cyclotrimerization of 1-isoquinolinyl-1,7-octadiyne with benzonitrile catalyzed by $CpCo(CO)_2$ opened a new pathway for a synthesis of unsymmetrical axially chiral bipyridine *N,N′*-dioxides. The *N,N′*-dioxide **3a** was found to be highly catalytically active and enantioselective for the asymmetric allylation of aldehydes with allyltrichlorosilane. The allylation took place with even 1% of the catalyst with an enantioselectivity up to 87% *ee*.

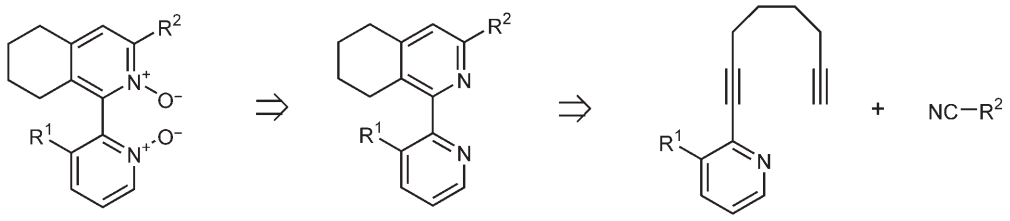
Keywords: allylation; asymmetric catalysis; Lewis bases; microwave heating; organic catalysis

Recently, asymmetric organocatalysis based either on Lewis acid or base interactions has been recognized as an efficient method for obtaining chiral compounds with high enantioselectivity.[1] Among the numerous examples of such molecules considerable attention has been attracted by amine *N*-oxides as powerful electron-pair donors. In this context, pyridine *N*-oxides and bipyridine *N,N′*-dioxides are of special interest in cases where the pyridine moiety is a part of a chiral scaffold. The electron-donating properties of pyridine *N*-oxides make them rather strong Lewis bases that are able to activate a number of reactants for a plethora of reactions such as allylation and alkylation of carbonyl compounds, conjugated addition, aldol reaction, desymmetrization of epoxides, epoxidation, etc.[2] Although a number of various pyridine-,[3–8] bipyridine-,[9–11] and terpyridine-based ligands[12] has been introduced into organic synthesis, there is a considerable synthetic demand for the development of new bipyridine-based organocatalysts. In this regard it would be attractive to develop a methodology that would allow the simple and fast synthesis of bipyridine *N,N′*-dioxides bearing various substituents in a close vicinity to the chiral scaffold.

Recently, we have reported that the cobalt-catalyzed [2+2+2] cyclotrimerization of diynes with nitriles is a suitable method for the preparation of potential pyridine-based organocatalysts with axial chirality. Unfortunately, the catalytic activity and enantioselectivity of the corresponding chiral pyridine *N*-oxides was low: catalysis of the reaction of allyltrichlorosilane or diethylzinc with benzaldehyde afforded after 3 days at 20 °C the corresponding products in 50% (20% *ee*) and 72% (17% *ee*), respectively.[13]

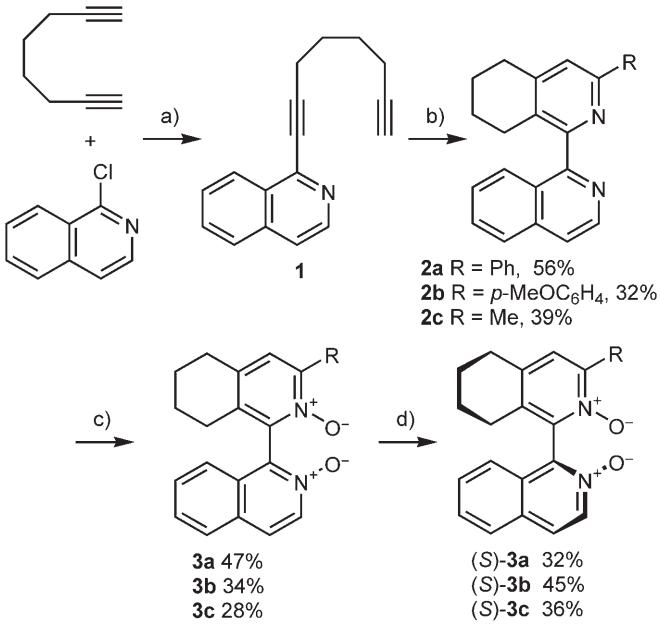
In the course of this cyclotrimerization research project aiming at the preparation of various heterocycles, we realized that [2+2+2] cyclotrimerization could be used for a modular synthesis of potentially atropoisomeric bipyridines from suitably substituted α-heteroaryl-α,ω-diynes and nitriles (Scheme 1).[14] In this context, a plethora of unsymmetrically substituted bipyridines could be prepared by varying the substituents R^1 and R^2 in the reactants. Such bipyridines would constitute an ideal starting material for the preparation of chiral bipyridine *N,N′*-dioxides, because they could, besides having axial chirality, also exert additional steric and electronic effects caused by the unsymmetrical substitution pattern.

In this work we focused on varying the substituent R^2 in the target compounds. As a starting compound for the cyclotrimerization reaction diyne **1** was chosen. It was prepared in 56% yield by Sonogashira coupling of 1-chloroisoquinoline with 1,7-octadiyne



Scheme 1. Retrosynthetic analysis of unsymmetrical bipyridine synthesis.

under standard conditions (Scheme 2).[15] In order to obtain variously substituted bipyridines, the $CpCo(CO)_2$-catalyzed cyclotrimerization of **1** was carried out in an excess of the respective nitrile. The reaction with benzonitrile proceeded uneventfully at 140 °C and afforded the corresponding bipyridine **2a** in 46% isolated yield. Surprisingly, the reaction with 4-methoxybenzonitrile under the same reaction conditions proceeded in very low yield ($\leq$5%) and with acetonitrile it did not give any product at all. To enhance the course of the reaction we carried out the cyclotrimerizations with both nitriles in a microwave reactor. In both cases we obtained the desired products **2b** and **2c** in 32 and 39% isolated yields, respectively. To the best of our knowledge, this is the first successful example of a microwave-induced transition metal-catalyzed cyclotrimerization. Their oxidation with *m*-CPBA furnished racemic bipyridine *N,N′*-dioxides **3a** (47%), **3b** (34%), and **3c** (28%). Bipyridine *N,N′*-dioxides **3a** and **3c** were resolved by standard co-crystallization with (*S*)-(−)-BINOL (BINOL = 2,2′-dihydroxy-1,1′-binaphthyl) in a mixture of CH_2Cl_2/MeCN. The crystalline material contained (*S*)-(−)-BINOL and (−)-**3a** (in 1:1 ratio), while (+)-**3a** remained in the solution. This co-crystallization, followed by a chromatographic separation of (−)-**3a** from (*S*)-(−)-BINOL, furnished pure (−)-**3a** of 95% *ee* (as detected by chiral HPLC, Chiracel OD-H) in 32% yield. The mother liquor containing excess of (+)-**3a** was co-crystallized under similar conditions with (*R*)-(+)-BINOL to get pure (+)-**3a**. The absolute configuration was found to be (*R*)-(+)-**3a** by X-ray crystallographic analysis of the molecular crystal of (*R*)-(+)-**3a** with (*R*)-(+)-BINOL (Figure 1) of known absolute configuration. The pairing in the crystal structure mentioned above is in sharp contrast to the previously observed pairing of symmetrical bipyridine *N,N′*-dioxides with BINOL. For example, (*S*)-(−)-3,3′-dimethyl-2,2′-biquinoline *N,N′*-dioxide and (*S*)-1,1′-biisoquinoline *N,N′*-dioxide make co-crystals with (*R*)-(+)-BINOL and these crystal structures consist of



Scheme 2. Preparation of the chiral bipyridine *N,N′*-dioxide (***R***)-(+)-**3** and (***S***)-(−)-**3**. a) $Pd(OAc)_2$ (0.05 equivs.), PPh_3 (0.1 equiv.), CuI (0.1 equiv.), *i*-Pr_2NH/THF (solvent). b) Nitrile (in excess), $CpCo(CO)_2$ (0.2 equivs.), 140 °C or mω. c) *m*-CPBA (2.2 equivs.), CH_2Cl_2, room temperature. d) Co-crystallization with (*S*)- or (*R*)-BINOL, CH_2Cl_2/MeCN or chiral HPLC.

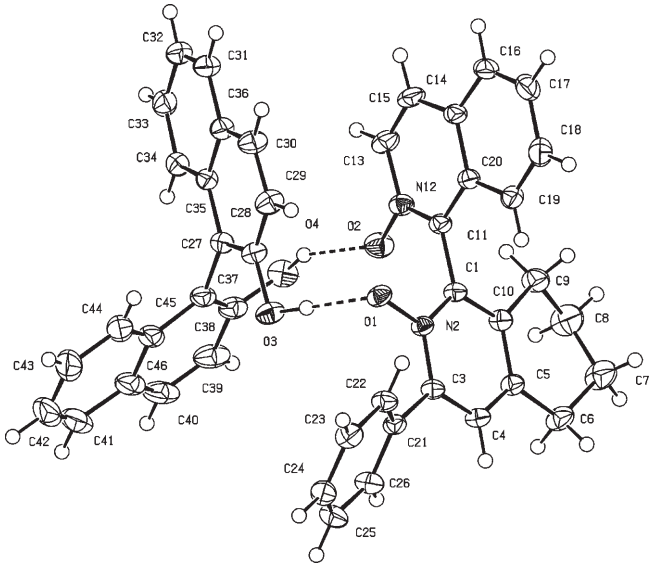
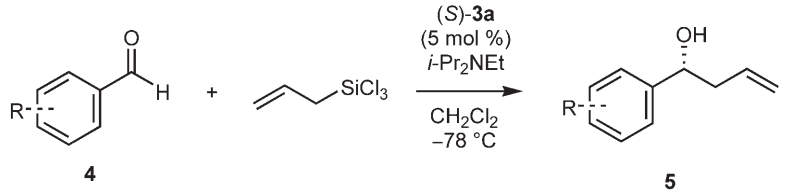


Figure 1. An ORTEP diagram illustrating the interaction of (*R*)-(+)-BINOL (*left*) and (*R*)-(+)-**3a** (*right*), in particular the hydrogen bonding N−O···H−O. Displacement parameters are shown at the 50% probability level.



Scheme 3. Enantioselective allylation of *para*-, *meta*-, and *ortho*-substituted benzaldehydes **4** to (*R*)-**5** catalyzed by (*S*)-**3a**.

continuous chains of tightly hydrogen-bonded species aligned along the axis of the crystal,[9a,16] whereas in our case each molecule of the *N,N′*-dioxide makes two hydrogen bonds with a molecule of BINOL. (*S*)-(−)-**3c** was obtained in 36% yield by the same procedure and assignment of its absolute configuration was based on the fact that (*S*)-bipyridine *N,N′*-dioxides preferentially co-crystallize with (*S*)-(−)-BINOL. Bipyridine *N,N′*-dioxide **3b** was separated by HPLC on a column with a chiral phase and both enantiomers (+)-**3b** and (−)-**3b** were obtained in 48% and 45% yields, respectively. Although we were not able to achieve selective formation of co-crystals of **3b** with BINOL, enantiomers of **3b** form with (*S*)- or (*R*)-BINOL in solution distinct molecular pairs through the hydrogen bonding that can be readily observed by NMR. This and a comparison of CD spectra with those of (*S*)-(−)-**3a** enabled us to assign the absolute configurations as (*R*)-(+)-**3b** and (*S*)-(−)-**3b**.

Thus having both enantiomers (*R*)-(+)- and (*S*)-(−)-**3** in pure form in our hands the catalytic activity and enantioselectivity was tested in the addition of allyltrichlorosilane to various aldehydes (Sakurai–Hosomi reaction). Initially, the reaction catalyzed by (*S*)-(−)-**3a** was carried out with benzaldehyde **4d** to assess the influence of reaction temperature on enantioselectivity. The catalytic activity was high at all temperatures and total conversion of the starting material (benzaldehyde) to the product, (*R*)-(+)-1-phenyl-3-buten-1-ol, (*R*)-**5d**, was observed within 3 h. As far as the enantioselectivity was concerned, it rose steadily as the reaction temperature decreased: 20 °C, 38% *ee*; 0 °C, 40% *ee*; −40 °C, 73% *ee*; −78 °C, 80% *ee*.

In the next step catalytic activity and enantioselectivity of the prepared (*S*)-(−)-**3a–3c** (5 mol%) were tested in the addition of allyltrichlorosilane to variously substituted benzaldehydes **4** (Scheme 3, Table 1). Representatives of benzaldehydes bearing electron-withdrawing and -donating substituents were chosen: *p*-trifluoromethylbenzaldehyde **4a**, benzaldehyde **4d**, and *p*-methoxybenzaldehyde **4e**. For aldehyde **4a** the best, albeit mediocre, enantioselectivity (64% *ee*) was achieved by (*S*)-(−)-**3b** (entry 1). A sharp increase in enantioselectivity (80% *ee*) was observed in the reaction with simple benzaldehyde **4d** (entry 2). In this case, the best enantioselectivity was obtained with (*S*)-(−)-**3a**. This reaction was also carried out in the presence of 1 mol% of the catalyst with the same results. The highest enantioselectivity was obtained with aldehyde **4e** (87% *ee*) for catalysis

Table 1. Enantioselective addition of allyltrichlorosilane to aromatic aldehydes catalyzed by (−)-(***S***)-**3**.[a]

Entry	Catalyst	Aldehyde **4**	Alcohol **5**	Yield [%][b]	*ee* [%][c]
1	(*S*)-(−)-**3a**	**4a**, R = *p*-CF_3	**5a**	60	54
	(*S*)-(−)-**3b**	**4a**, R = *p*-CF_3	**5a**	64	58
	(*S*)-(−)-**3c**	**4a**, R = *p*-CF_3	**5a**	55	21
2	(*S*)-(−)-**3a**	**4b**, R = *p*-F	**5b**	48	78
3	(*S*)-(−)-**3a**	**4c**, R = *p*-Cl	**5c**	88	71
4	(*S*)-(−)-**3a**	**4d**, R = H	**5d**	95	80
	(*S*)-(−)-**3b**	**4d**, R = H	**5d**	61	76
	(*S*)-(−)-**3c**	**4d**, R = H	**5d**	64	61
5	(*S*)-(−)-**3a**	**4e**, R = *p*-MeO	**5e**	62	87
	(*S*)-(−)-**3b**	**4e**, R = *p*-MeO	**5e**	72	70
	(*S*)-(−)-**3c**	**4e**, R = *p*-MeO	**5e**	78	0
6	(*S*)-(−)-**3a**	**4f**, R = *m*-Cl	**5f**	46	70
7	(*S*)-(−)-**3a**	**4g**, R = *m*-MeO	**5g**	53	80
8	(*S*)-(−)-**3a**	**4h**, R = *o*-Cl	**5h**	66	65
9	(*S*)-(−)-**3a**	**4i**, R = *o*-MeO	**5i**	61	67

[a] The reactions were run with 5 mol% of the catalyst in CH_2Cl_2, −78 °C, 3 h (**3a**), 1 h (**3b**), and 24 h (**3c**).
[b] GC yields.
[c] The *ee* was determined by GC (HP-Chiral β).

with (*S*)-(−)-**3a**. Interestingly, in this instance the use of the methyl-substituted bipyridine *N,N′*-dioxide (*S*)-(−)-**3c** was totally ineffective – no asymmetric induction was observed.

Further additions to other aldehydes bearing electron-withdrawing and -donating substituents in the *para*, *meta*, and *ortho* positions, **4b**, **4c**, **4f–4i**, were carried out with (*S*)-(−)-**3a** since it proved to induce the highest asymmetric inductions. Thus, electron-poor benzaldehydes **4b** and **4c** gave products **5b** and **5c** with enantioselectivities of 78 and 71% *ee* (entries 2 and 3). Allylation of *meta*-substituted benzaldehydes **4f** and **4g** gave products **5f** and **5g** with 70% and 80% *ee*, respectively, following the trend observed in the *para*-substituted series (entries 6 and 7). The reactions of *ortho*-substituted benzaldehydes **4h** and **4i** proceeded with the lowest enantioselectivity affording products **5h** (65% *ee*) and **5i** (67% *ee*). In view of the foregoing it is clear, that enantioselectivity declined (87→80→65%) as the substituent moved closer to the carbonyl group (entries 5, 7 and 9).

In conclusion, we have demonstrated that the cobalt-catalyzed [2+2+2] cyclotrimerization of diynes with nitriles represents a simple and easy pathway to unsymmetrically substituted bipyridine *N,N′*-dioxides. It is also noteworthy that microwave irradiation had a positive effect on the course of the cyclotrimerization. The whole synthetic procedure takes just three simple steps from commercially available starting materials. Resolution of the racemic bipyridine *N,N′*-dioxides with BINOL, that can be easily recycled, or HPLC afforded both enantiomers in high optical purity. These compounds were effective catalysts for the enantioselective allylation of benzaldehydes with a selectivity comparable to that of other chiral bipyridine *N,N′*-dioxides.

Experimental Section

1-(5,6,7,8-Tetrahydro-3-phenylisoquinolin-1-yl)isoquinoline (2a)

1-(Octa-1,7-diynyl)isoquinoline (1 g, 4.2 mmol) was dissolved in dry benzonitrile (15 mL) in a microwave vial, $CpCo(CO)_2$ (151 mg, 0.84 mmol) was added, and the vial was placed into the microwave oven. The reaction mixture was irradiated for 30 min (180 °C, 20 bar), then was quenched with water, extracted by diethyl ether, and volatiles were removed under reduced pressure. Column chromatography on silica gel (1/1 hexane/EtOAc) afforded the title compound as a pale yellow solid; yield: 677 mg (48%); mp 154 °C (hexane); ^{1}H NMR (400 MHz, C_6D_6): δ = 1.36–1.46 (m, 4H), 2.47–2.49 (m, 2H), 2.59–2.63 (m, 2H), 7.06-7.28 (m, 6H), 7.35 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 8.00 (dd, J = 8.5, 0.8 Hz, 1H), 8.15–8.18 (m, 2H), 8. 64 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 23.1, 23.8, 26.9, 30.4, 120.9, 121.1, 127.7, 127.9 (2C), 128.5, 128.9, 129.0, 129.4, 129.5 (2C), 130.5, 132.1, 137.7, 140.6, 143.1, 148.4, 153.7, 157.7, 160.8; IR ($CHCl_3$): ν = 2944, 1589, 1440, 1319, 1146, 1120, 1030 cm^{-1} ; EI-MS: *m/z* (% relative intensity) = 336 (M^+, 61), 335 (100), 308 (40), 168 (6), 154 (6); HR-MS: *m/z* = 336.161153, calcd. for $C_{24}H_{20}N_2$: 336.162649.

1-(5,6,7,8-Tetrahydro-3-phenylisoquinolin-1-yl)isoquinoline *N,N′*-Dioxide (3a)

Compound **2a** (0.6 g, 1.8 mmol) was dissolved in dry dichloromethane (7 mL) cooled to 0 °C and *m*-CPBA (0.87 g, 3.9 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for one hour. Then it was quenched by brine (7 mL), extracted by dichloromethane (7 mL), the organic layer was dried over $MgSO_4$, and volatiles were removed under reduced pressure. Column chromatography on silica gel (9/1 $CHCl_3$/2-propanol) afforded the title compound as a white solid; yield: 313 mg (47%); mp 220 °C (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.81 (m, 4H), 2.13–2.18 (m, 1H), 2.55–2.61 (m, 1H), 2.86–2.88 (m, 2H), 7.34–7.42 (m, 4H), 7.52–7.57 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.82–7.88 (m, 2H), 8.31 (d, J = 7.2, Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 21.8, 25.0, 28.7, 124.3, 125.4, 127.9, 128.6 (2C), 128.7, 129.0, 129.8, 129.9, 130.0, 130.3 (2C), 131.0, 132.8, 136.5, 137.5, 138.8, 140.4, 141.1, 147.6; IR ($CHCl_3$): ν = 2978, 2947, 1725, 161, 1600, 1563, 1471, 1395, 1327, 1267, 1228, 1145, 820 cm^{-1}; EI-MS: *m/z* (% relative intensity) = 368 (M^+, 10), 351 (9), 335 (48), 286 (100), 268 (10), 257 (18), 239 (18), 226 (10), 189 (12), 149 (28), 134 (9), 119 (18); HR-MS: *m/z* = 368.152922, calcd. for $C_{24}H_{20}N_2O_2$: 368.152478.

(*S*)-(−)-1-(5,6,7,8-Tetrahydro-3-phenylisoquinolin-1-yl)isoquinoline *N,N′*-Dioxide [(*S*)-(−)-3a]

To a solution of (*S*)-(−)-BINOL **4** (97 mg, 0.34 mmol) and (±)-1-(5,6,7,8-tetrahydro-3-phenylisoquinolin-1-yl)isoquinoline *N,N′*-dioxide **3a** (124 mg, 0.34 mmol) in dichloromethane (2 mL), acetonitrile (1 mL) was added, the flask was closed with a septum pierced with a needle and set aside to allow slow evaporation of dichloromethane through the needle. The molecular complex (*S*)-(−)-**3a**-(*S*)-(−)-**4** crystallized within 2 days as colourless crystals that were collected by suction filtration. Individual components were collected by column chromatography on silica gel (9/1 $CHCl_3$/2-propanol), which afforded (*S*)-(−)-**3a**; yield: 31 mg (32%). Chiral HPLC (Chiralcel OD-H, 0.46 cm × 25 cm, 2/1 heptane/2-propanol, 1.2 mL min^{-1}) showed 95% *ee* depending on the batch (t_S = 13 min, t_R = 23 min); $[\alpha]_D$: −309.5 (*c* 0.01, $CHCl_3$).

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