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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 3185–3191

An easy route to atropoisomeric bipyridine *N*,*N*′-dioxides and allylation of aldehydes

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Received 7 November 2006; accepted 13 November 2006
Available online 12 December 2006

Abstract—Axially chiral bipyridine *N*,*N*′-dioxides (Lewis basic organocatalysts) are easily accessible in three steps from commercially available material. The key step of this reaction sequence is cobalt-catalyzed heterocyclotrimerization of 1-pyridyl-1,7-octadiynes with nitriles. Our effort was focused on the synthesis of unsymmetrically substituted bipyridines. The scope of the cyclotrimerization reaction was tested under thermal and microwave conditions. Two of the synthesized bipyridine *N*,*N*′-dioxides were successfully resolved into enantiomers and tested in enantioselective allylation of aldehydes.

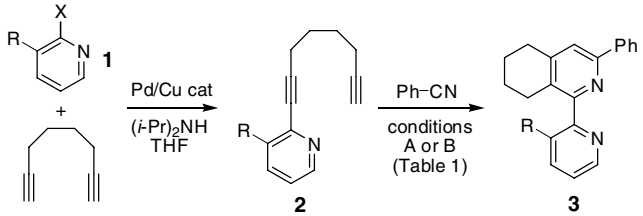
1. Introduction

Organocatalysis is one of the rapidly developing fields of organic synthesis and involves the acceleration of chemical reactions with a catalytic or a substoichiometric amount of an organic compound, which does not contain a metal atom. Recently, the scope of organocatalytic reactions has been expanded upon considerably from aldol condensation to Ullmann coupling, which is usually considered to be a transition-metal-mediated reaction.[1] Nevertheless, there is still demand for developing new inexpensive and more efficient organocatalysts. Our attention was focused on the activation of Lewis acids by Lewis bases. Typical representatives of Lewis bases are bipyridine *N*,*N*′-dioxides, which are able to activate trichlorosilanes and catalyze a number of various reactions (allylation, propargylation, aldol condensation, ring opening of epoxides, etc.).[2] The allylation of aldehydes is usually a first choice reaction to test the catalytic properties and enantioselectivity of a new organocatalyst.[3–9] Herein, we report a new and simple route to a variety of axially chiral bipyridine *N*,*N*′-dioxides using a sequence of three steps: (i) [2+2+2]-cocyclotrimerization of 2-pyridyl-octadiynes with benzonitrile to provide unsymmetrical bipyridines, (ii) oxidation, and finally (iii) resolution into enantiomers.

2. Results and discussion

The starting *ortho*-substituted 1-pyridyl-1,7-octadiynes were prepared by Krause modification of the Sonogashira coupling of 1,7-octadiyne with halopyridines **1** (Scheme 1).[10] The coupling proceeded smoothly to afford the desired pyridyldiynes **2** in moderate to good isolated yields (22–73%) (Scheme 1). [2+2+2]-Cyclotrimerization of nitriles with alkynes (diynes) catalyzed by $CpCo(L)_n$ (L = CO, ethane, etc.) under thermal conditions[11] is known to be one of the most straightforward methods for the synthesis of bipyridines.[12] Thus, this protocol was used for assembling the desired bipyridine framework.

At the outset, the reaction of pyridyldiynes **2** with benzonitrile was carried out under standard conditions:



Scheme 1. Preparation of diynes **2** and their cocyclotrimerization with benzonitrile to bipyridines **3**.

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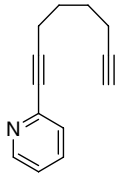
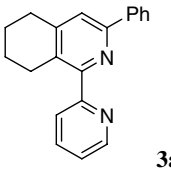
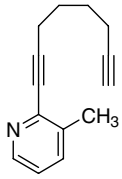
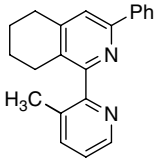
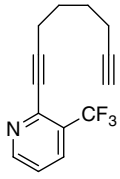
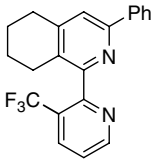
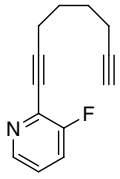
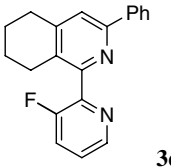
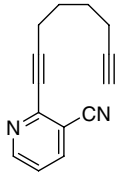
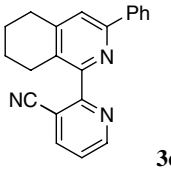
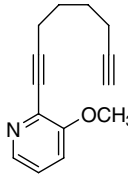
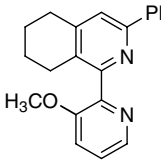
doi:10.1016/j.tetasy.2006.11.025

20 mol % of $CpCo(CO)_2$, 140 °C, 24 h (Scheme 1). Typical examples of thermal cyclotrimerizations are presented in Table 1 (conditions A). The reaction with unsubstituted 2-pyridyl-1,7-octadiyne **2a** gave the corresponding product **3a** in a rather mediocre isolated yield of 30% (entry 1). The cyclotrimerizations of diynes bearing various substituents in position 3 **2b**–**2e** afforded bipyridines in even lower yields (9–27%) (entries 2–5). Surprisingly, the reaction of benzonitrile with diyne **2f** did not yield any product (entry 6). Moreover, in all cases we observed the formation of tar-like products that indicated polymerization of the starting material.

Table 1. Cyclotrimerization of diynes **2** with benzonitrile to bipyridines **3**

Entry	Diyne	Product	R.C.[a]	Yield[b] (%)
1	 **2a**	 **3a**	A B	30 43
2	 **2b**	 **3b**	A B	27 84
3	 **2c**	 **3c**	A B	24 35
4	 **2d**	 **3d**	A B	9 65
5	 **2e**	 **3e**	A B	18 30
6	 **2f**	 **3f**	A B	0 72

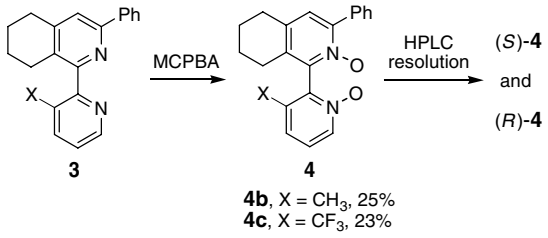
[a] Reaction conditions: A = $CpCo(CO)_2$ (20 mol %), 140 °C, 24 h; B = $CpCo(CO)_2$ (20 mol %), MW irradiation, 20 min.
[b] Isolated yields.

To overcome the side reactions caused by the prolonged heating of the reactants and to attempt to increase the yields of the desired reaction, we decided to carry out the cyclotrimerization under microwave irradiation. The positive effect of microwave irradiation on the course of the reaction has been noticed for a number of various processes.[13]

Thus, cyclotrimerizations were run in closed vessels in a microwave reactor and irradiated for 20 min (during this time, the internal temperature and pressure rose to 200 °C and 5 bar, respectively) (Table 1, conditions B). Gratifyingly, in all cases the bipyridines were isolated in improved yields. Unsubstituted bipyridine **3a** was formed in 43% yield. Methyl-substituted bipyridine **3b** was obtained in high 84% yield. Bipyridines **3c**–**3e** bearing electron-accepting groups such as F, CF_3, and CN were isolated in 35%, 65%, and 30% yields, respectively. Microwave irradiation also proved to be very effective for the cyclotrimerization of 3-methoxypyridyl-diyne **2f** that yielded the corresponding bipyridine **3f** in very good yield (72%) (entry 6).

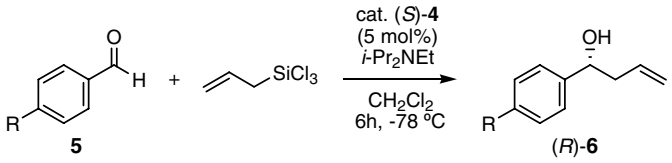
Out of the series of the bipyridines prepared, compounds **3b** and **3c** bearing CH_3 and CF_3 groups at the 3-position were chosen for further transformations. Their oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) proceeded smoothly to give the corresponding bipyridine *N*,*N*′-dioxides **4b** and **4c** in 25% and 23% isolated yields, respectively (Scheme 2). These racemic compounds **4b** and **4c** were resolved into enantiomers by using semipreparative chiral HPLC (Chiracel OD-H column) in 90% and 85% combined yields. The absolute configuration was estimated from absolute configuration of the allylation products obtained.[14]

The axially chiral bipyridine *N*,*N*′-dioxides (*S*)-(−)-**4b** and (*S*)-(+)-**4c** obtained here were examined for their catalytic activity and enantioselectivity in the asymmetric addition of allyltrichlorosilane to benzaldehyde **5a**, 4-trifluoromethylbenzaldehyde **5b**, and 4-methoxybenzaldehyde **5c** in dichloromethane (Table 2). The allylation catalyzed by methyl-substituted bipyridine (*S*)-(−)-**4b** proceeded in all cases with very good yields of the corresponding (*R*)-homoallylic alcohols **6** within 6 h with rather average ees. The highest ee was obtained in the reaction with benzaldehyde (74%). The reaction with **5c** gave product **6c** with lower enantioselectivity then expected. This observation is surprising, because it has previously been observed that the



Scheme 2. Oxidation of the bipyridines **3b** and **3c** to their resolution.

Table 2. Enantioselective allylation of *para*-substituted benzaldehydes



a, R = C_6H_5; **b**, R = 4-$CF_3C_6H_4$; **c**, R = 4-$CH_3OC_6H_4$

Entry	Aldehyde **5**	Alcohol **6**	Yield,[a] ee[b] (%)	
			(*S*)-(−) **4b**	(*S*)-(+) **4c**
1	**5a**	**6a**	87 (74)	53 (72)
2	**5b**	**6b**	82 (63)	36 (27)
4	**5c**	**6c**	79 (41)	30 (68)

[a] GC yields.

[b] Ee was determined by GC (HP-Chiral β, details are given in Experimental Section).

introduction of electron-donating groups (Me, OMe, etc.) onto the aromatic ring of benzaldehyde usually leads to increase in enantioselectivity. On the other hand, the observed decrease in asymmetric induction in the reaction with **5b** is not surprising and it has been observed with benzaldehydes bearing electron-withdrawing groups.[3a,4] Allylations of benzaldehydes **5a**–**5c** catalyzed by trifluoromethyl-substituted bipyridine *N*,*N*′-dioxides (*S*)-(+)-**4c** under the same conditions gave the corresponding (*R*)-homoallylic alcohols **6** in lower yields (30–53%). However, the enantioselectivity trend was quite different. Thus the enantioselectivity of the allylation was similar for benzaldehyde **5a** (72%), but a lower ee of 27% was observed for 4-trifluoromethylbenzaldehyde **5b**, while 68% was observed in the reaction with 4-methoxybenzaldehyde.

3. Conclusion

In conclusion, this work has shown that cobalt-catalyzed [2+2+2]-cocyclotrimerization of pyridyl-diynes with benzonitrile under microwave irradiation is a convenient and straightforward method for the preparation of axially chiral unsymmetric bipyridines. Comparison of catalytic activity and enantioselectivity of methyl- and trifluoromethyl-substituted *N*,*N*′-oxides clearly indicates that the control of the catalyst properties is likely more complicated than it has been so far assumed. These results may thus provide impetus for further development of more selective catalysts.

4. Experimental

4.1. General methods

All solvents, unless otherwise stated, were used as obtained. THF was distilled from sodium and benzophenone, and dichloromethane from CaH_2 under Ar. All other reagents were obtained from commercial sources.

^1H and ^{13}C NMR spectra were recorded on a Varian AVANCE 400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) as solutions in C_6D_6 or $CDCl_3$ with Me_4Si as an internal standard referenced to the residual solvent signal. Chemical shifts are given in δ-scale, coupling constants J are given in Hertz. Melting points (uncorrected) were determined using a Kofler apparatus. Mass spectra were recorded on a ZAB-SEQ (VG-Analytical) instrument. Infrared spectra were recorded on a Bruker IFS 55 spectrometer as $CHCl_3$ solutions and are reported in wave numbers (cm^{-1}). Fluka 60 silica gel was used for flash chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets (Merck). All reactions were carried out under an argon atmosphere using the Schlenk-tube technique or in a microwave reactor Biotage Initiator.

4.2. Preparation of diynes 2

4.2.1. General procedure for preparation of pyridyl-substituted 1,7-octadiynes. CuI (0.5 mmol), $PdCl_2(MeCN)_2$ (0.25 mmol), PPh_3 (0.5 mmol) were suspended in dry, degassed THF (10 mL) under an argon atmosphere. Aryliodide (10 mmol), 1,7-octadiyne (10 mmol), and $(^iPr)_2NH$ (10 mL) were added to the suspension and the reaction was left stirring at 50 °C temperature overnight. The solution was extracted with water (20 mL) and diethylether (2×15 mL) and the organic layer dried over $MgSO_4$ before being evaporated under reduced pressure. Purification of the residue on silica gel provided the corresponding compounds.

4.2.2. 2-(Octa-1,7-diynyl)pyridine 2a. 2-Iodopyridine (1 g, 4.9 mmol), PPh_3 (127 mg, 0.48 mmol), CuI (46 mg, 0.24 mmol), $PdCl_2(MeCN)_2$ (31 mg, 0.12 mmol), THF (5 mL), 1,7-octadiyne (1.3 mL, 9.7 mmol), *i*-Pr_2NH (5 mL). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 600 mg (67%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.38–1.42 (m, 4H), 1.75 (t, $J = 2.3$ Hz, 1H), 1.80–1.92 (m, 2H), 2.03–2.07 (m, 2H), 6.49–6.52 (m, 1H), 6.86–6.90 (m, 1H), 7.12–7.16 (m, 1H), 8.40 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.7, 19.6, 28.2, 28.4, 69.7, 82.7, 84.6, 90.7, 122.7, 127.5, 136.1, 145.5, 150.9; IR ($CHCl_3$) ν 3307, 2949, 2867, 2231, 2116, 1585, 1563, 1465, 1429, 1329, 1271, 1150, 1048, 992 cm^{-1}; EI-MS *m*/*z* (% relative intensity) 183 (M^+, 41), 182 (100), 167 (39), 154 (42), 143 (7), 130 (25), 117 (19), 89 (17), 78 (11), 63 (11), 51 (10), 39 (11); HR-MS calcd for $C_{13}H_{13}N$ 183.10480, found 183.10396.

4.2.3. 3-Methyl-2-(octa-1,7-diynyl)pyridine 2b. 2-Bromo-3-methyl-pyridine (1 g, 5.8 mmol), PPh_3 (87 mg, 0.3 mmol), CuI (63 mg, 0.3 mmol), $PdCl_2(MeCN)_2$ (43 mg, 0.16 mmol), THF (6.5 mL), 1,7-octadiyne (1.5 mL, 11.6 mmol), *i*-Pr_2NH (6.5 mL). Column chromatography on silica gel (1.5/1 hexane/EtOAc) afforded 837 mg (73%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.40–1.44 (m, 4H), 1.76 (t, $J = 2.8$ Hz, 1H), 1.85–1.89 (m, 2H), 2.09–2.12 (m, 2H), 2.19 (s, 3H), 6.54–6.57 (m, 1H), 6.89 (dd, $J = 7.8$, 1.0 Hz, 1H), 8.34 (dd, $J = 4.7$, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.7, 19.7, 20.2, 28.3, 28.4, 69.8, 81.5, 84.6, 94.5, 122.7, 135.8, 137.0, 145.2, 148.3; IR ($CHCl_3$) ν 3307, 3056, 3015, 2949, 2867, 2227, 2115, 1581, 1426, 1386, 1327, 1289, 1226, 1137, 1114, 1079 cm^{-1}; EI-MS *m*/*z* (% relative intensity) 196 (M^+, 100), 182 (40), 168

(94), 154 (20), 144 (36), 130 (41), 117 (23), 103 (16), 89 (7); HR-MS calcd for $C_{14}H_{15}N$ 197.12045, found 197.12105.

4.2.4. 3-(Trifluoromethy)-2-(octa-1,7-diynyl)pyridine 2c. 2-Chloro-3-(trifluoromethyl)pyridine (10 g, 55 mmol), PPh_3(1.44 g, 5.5 mmol), CuI (524 mg, 2.8 mmol), $PdCl_2(MeCN)_2$ (358 mg, 1.39 mmol), 1,7-octadiyne (14.6 mL, 112 mmol), THF (60 mL), *i*-Pr_2NH (60 mL). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 4 g (30%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.38–1.43 (m, 4H), 1.78 (t, $J = 2.75$ Hz, 1H), 1.85–1.89 (m, 2H), 2.04–2.07 (m, 2H), 6.34–6.38 (m, 1H), 7.23–7.25 (m, 1H), 8.26 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.7, 19.7, 27.9, 28.4, 70.2, 79.5, 85.0, 98.2, 122.7, 123.9, 126.6, 134.6, 143.6, 154.0; IR ($CHCl_3$) ν 3308, 2996, 2950, 2867, 2236, 2117, 1588, 1568, 1440, 1279, 1166, 1147, 1077, 1030, 1021, 984, 810 cm^1; EI-MS *m*/*z* (% relative intensity) 250 (M^+, 100), 236 (52), 222 (43), 212 (9), 198 (34), 185 (19), 154 (12), 105 (9); HR-MS calcd for $C_{14}H_{11}F_3N$ 250.09218, found 250.08413.

4.2.5. 3-Fluoro-2-(octa-1,7-diynyl)pyridine 2d. 3-Fluoro-2-chloro-pyridine (1 g, 7.6 mmol), PPh_3 (119 mg, 0.4 mmol), CuI (72 mg, 0.4 mmol), $PdCl_2(MeCN)_2$ (50 mg, 0.2 mmol), 1,7-octadiyne (2 mL, 15.2 mmol), THF (8 mL), *i*-Pr_2NH (8 mL). Column chromatography on silica gel (2/1 hexane/EtOAc) afforded 962 mg (62%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.36–1.40 (m, 4H), 1.75 (t, $J = 2.8$ Hz, 1H), 1.82–1.86 (m, 2H), 2.04–2.07 (m, 2H), 6.30–6.34 (m, 1H), 6.58–6.63 (m, 1H), 8.06–8.08 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.8, 19.8, 28.2, 28.5, 70.1, 77.0, 85.0, 98.0, 123.6, 124.7, 147.2, 160.7, 163.3; IR ($CHCl_3$) ν 3308, 2991, 2950, 2866, 2837, 2236, 2117, 1594, 1563, 1449, 1329, 1264, 1236, 1182, 1101 cm^{-1}; EI-MS *m*/*z* (% relative intensity) 200 ($M-H^+$, 100), 185 (41), 172 (42), 159 (8), 148 (28), 135 (22), 122 (6); HR-MS calcd for $C_{13}H_{12}FN$ 201.09538, found 201.09638.

4.2.6. 2-(Octa-1,7-diynyl)pyridine-3-carbonitrile 2e. 2-Chloro-3-pyridinecarbonitrile (1 g, 7.2 mmol), PPh_3 (108 mg, 0.4 mmol), CuI (78 mg, 0.4 mmol), $PdCl_2(MeCN)_2$ (54 mg, 0.2 mmol), 1,7-octadiyne (1.87 mL, 14.4 mmol), THF (8 mL), *i*-Pr_2NH (8 mL). Column chromatography on silica gel (dichloromethane) afforded 330 mg (22%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.40–1.43 (m, 4H), 1.75 (t, $J = 2.7$ Hz, 1H), 1.86–1.88 (m, 2H), 2.00–2.03 (m, 2H), 6.04 (dd, $J = 7.9$, 4.9 Hz, 1H), 6.72 (dd, $J = 7.9$, 1.8 Hz, 1H), 8.07 (dd, $J = 4.9$, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.7, 19.7, 27.9, 28.5, 70.2, 80.2, 84.9, 99.1, 114.3, 117.9, 122.5, 130.0, 140.5, 153.9; IR ($CHCl_3$) ν 3308, 3013, 2950, 2234, 2116, 1558, 1430, 1329, 1227, 1178, 1101 cm^{-1}, EI-MS *m*/*z* (% relative intensity) 207 ($M-H^+$, 100), 193 (38), 179 (28), 168 (8), 155 (17), 142 (13), 129 (6), 114 (15); HR-MS calcd for $C_{14}H_{12}N_2$ 208.10005, found 208.10000.

4.2.7. 3-Methoxy-2-(octa-1,7-diynyl)pyridine 2f. 2-Bromo-3-methoxypyridine (1 g, 5.32 mmol), PPh_3 (86 mg, 0.3 mmol), CuI (52 mg, 0.3 mmol), $PdCl_2(MeCN)_2$ (35 mg, 0.1 mmol), 1,7-octadiyne (1.4 mL, 11 mmol), THF (5.6 mL), *i*-Pr_2NH (5.6 mL). Column chromatography on silica gel (2/1 hexane/EtOAc) afforded 600 mg (53%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.43–1.46 (m, 4H), 1.80 (t, $J = 2.4$ Hz, 1H), 1.86–1.90 (m, 2H), 2.14–2.17 (m, 2H), 6.45 (d, $J = 9.0$ Hz, 1H), 6.62–6.65 (m, 1H), 8.12 (d, $J = 4.6$ Hz, 1H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 18.8, 20.1, 28.4, 28.6, 55.9, 70.0, 79.8, 85.3, 95.9, 118.3, 124.2, 136.5, 143.3, 158.6; IR ($CHCl_3$) ν 3672, 3308, 3063, 3013, 2943, 2866, 2838, 2231, 2117, 1929, 1871, 1818, 1727, 1579, 1567, 1285, 1254, 1193, 1124, 1070, 1018 cm^{-1}; EI-MS *m*/*z* (% relative intensity) 212 ($M-H^+$, 100), 198 (77), 184 (73), 170 (26), 160 (22), 146 (22), 133 (21), 117 (22), 104 (10), 89 (27); HR-MS calcd for $C_{14}H_{15}NO$ 213.11536, found 213.11571.

4.3. Preparation of bipyridines 3

4.3.1. General procedure for catalytic cyclotrimerization of pyridyl-substituted 1,7-octadiynes with benzonitrile under thermal conditions. Pyridyloctadiyne (0.4 mmol) was dissolved in dry benzonitrile (16 mmol) under an argon atmosphere. Then the cobalt catalyst $CpCo(CO)_2$ (11.3 μL, 0.08 mmol) was added and the reaction mixture was heated at 140 °C for 24 h. Then the reaction was quenched with water (1 mL) and benzonitrile was evaporated under reduced pressure. Purification of the residue on silica gel provided the corresponding compounds.

4.3.2. General procedure for catalytic cyclotrimerization of pyridyl-substituted 1,7-octadiynes with benzonitrile under microwave conditions. Pyridyloctadiyne (0.4 mmol) was put to a vial filled with argon. Then benzonitrile (16 mmol) and the cobalt catalyst $CpCo(CO)_2$ (11.3 μL, 0.08 mmol) were added to a starting material under an argon atmosphere. The vial was then placed into the microwave reactor and irradiated for 20 min. (Internal temperature and pressure in the vial rose to 200 °C and 5 bar within 5 min and they stayed constant.) The reaction mixture was quenched with water (1 mL) and benzonitrile was evaporated under reduced pressure. Purification of the residue on silica gel provided the corresponding compounds.

4.3.3. 5,6,7,8-Tetrahydro-3-phenyl-1-(pyridin-2-yl)isoquinoline 3a. Diyne **2a** (62 mg, 0.3 mmol), benzonitrile (1.6 mL, 16 mmol), $CpCo(CO)_2$ (11.3 μL, 0.08 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 49 mg (43%) of a viscous liquid. ^1H NMR (400 MHz, C_6D_6) δ 1.47–1.54 (m, 4H), 2.44–2.47 (m, 2H), 3.20–3.25 (m, 2H), 6.73–6.76 (m, 1H), 7.20–7.34 (m, 5H), 8.07–8.10 (m, 1H), 8.19–8.22 (m, 2H), 8.58 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.2, 24.2, 28.3, 30.8, 121.9, 123.7, 126.6, 128.6 (2C), 130.1, 130.2 (2C), 132.9, 137.5, 141.6, 149.3, 149.4, 154.6, 157.6, 162.2; IR ($CHCl_3$) ν 3724, 3688, 3305, 3063, 3020, 2947, 2883, 2851, 2223, 1595, 1562, 1460, 1423, 1389, 1327, 1219, 1168, 1139, 1080, 851 cm^{-1}; EI-MS *m*/*z* (% relative intensity) 286 (M^+, 100), 271 (16), 258 (36), 250 (16), 236 (7), 198 (7), 167 (6), 142 (10); HR-MS calcd for $C_{20}H_{18}N_2$ 286.14700, found 286.14671.

4.3.4. 5,6,7,8,-Tetrahydro-1-(3-methylpyridin-2-yl)-3-phenylisoquinoline 3b. Diyne **2b** (79 mg, 0.4 mmol), benzonitrile (1.6 mL, 16 mmol), $CpCo(CO)_2$ (11.3 μL, 0.08 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc)

afforded 103 mg (86%) of a viscous liquid. ^{1}H NMR (400 MHz, C_6D_6) δ 1.44–1.47 (m, 4H), 2.45 (s, 3H), 2.42–2.48 (m, 2H), 2.62–2.66 (m, 2H), 6.75–6.78 (m, 1H), 7.13–7.20 (m, 2H), 7.25–7.29 (m, 3H), 8.14–8.16 (m, 2H), 8.51 (d, $J = 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 19.8, 23.2, 23.9, 27.0, 30.4, 120.6, 123.3, 127.8 (2C), 129.3, 129.4 (2C), 131.1, 132.8, 138.7, 140.8, 147.2, 148.2, 153.7, 158.6, 159.6; IR ($CHCl_3$) ν 3062, 2942, 2864, 2837, 1589, 1555, 1498, 1450, 1432, 1420, 1384, 1348, 1313, 1249, 1208, 1163, 1110, 1026, 956, 911, 871, 825 cm^{-1}; EI-MS m/z (% relative intensity) 300 (M^+, 100), 285 (55), 272 (75), 258 (17); HR-MS calcd for $C_{21}H_{20}N_2$ 300.16264, found 300.16187.

4.3.5. 1-(3-(Trifluoromethyl)pyridin-2-yl)-5,6,7,8-tetrahydro-3-phenylisoquinoline 3c. Diyne **2c** (1.67 g, 6.6 mmol), benzonitrile (26 mL, 262 mmol), $CpCo(CO)_2$ (138 μL, 0.98 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 830 mg (35%) of a white solid. Mp 112 °C (heptane); ^{1}H NMR (400 MHz, C_6D_6) δ 1.40–1.46 (m, 4H), 2.37–2.38 (m, 2H), 2.50–2.54 (m, 2H), 6.50–6.54 (m, 1H), 7.14–7.18 (m, 2H), 7.24–7.27 (m, 2H), 7.50 (dd, $J = 7.9$, 1.2 Hz, 1H), 8.17–8.19 (m, 2H), 8.40 (d, $J = 3.8$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.2, 23.7, 26.9, 30.3, 122.1, 123.5, 126.7, 127.1, 128.5 (2C), 130.1, 130.2 (2C), 131.4, 136.1, 141.2, 148.9, 153.1, 154.6, 157.7, 159.7; IR ($CHCl_3$) ν 3308, 2926, 2855, 2236, 1600, 1569, 1440, 1321, 1147, 1121, 1030, 811 cm^{-1}; EI-MS m/z (% relative intensity) 354 (M^+, 100), 333 (20), 326 (74), 306 (16), 285 (41), 177 (6), 153 (6); HR-MS calcd for $C_{21}H_{17}N_2F_3$ 354.13438, found 354.13296.

4.3.6. 1-(3-Fluoropyridin-2yl)-5,6,7,8-tetrahydro-3-phenylisoquinoline 3d. Diyne **2d** (120 mg, 0.6 mmol), benzonitrile (1.6 mL, 16 mmol), $CpCo(CO)_2$ (11.3 μL, 0.08 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 79 mg (65%) of a white solid. Mp 126 °C (heptane); ^{1}H NMR (400 MHz, C_6D_6) δ 1.39–1.43 (m, 4H), 2.38–2.39 (m, 2H), 2.63–2.66 (m, 2H), 6.57–6.60 (m, 1H), 7.17–7.19 (m, 3H), 7.23–7.28 (m, 2H), 8.17–8.19 (m, 2H), 8.28 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.1, 23.8, 26.8, 30.4, 122.2, 124.7, 124.9, 125.4 (d, $J = 3.4$ Hz), 128.7 (2C), 130.1, 130.2 (2C), 132.4, 141.4, 146.2 (d, $J = 5.3$ Hz), 149.1, 155.2, 158.2, 160.8; IR ($CHCl_3$) ν 3605, 2931, 2859, 1724, 1690, 1592, 1553, 1449, 1433, 1384, 1350, 1312, 1237, 1180, 1161, 1136, 1101, 1028, 1001, 870, 802 cm^{-1}; EI-MS m/z (% relative intensity) 304 (M^+, 100), 285 (38), 276 (65), 250 (6), 152 (8); HR-MS calcd for $C_{20}H_{17}N_2F$304.13757 found 304.13883.

4.3.7. 2-(5,6,7,8-Tetrahydro-3-phenylisoquinolin-1-yl)pyridine-3-carbonitrile 3e. Diyne **2e** (247 mg, 1.2 mmol), benzonitrile (4.6 mL, 48 mmol), $CpCo(CO)_2$ (83.5 μL, 0.59 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 109 mg (30%) of a white solid. Mp 129 °C (heptane); ^{1}H NMR (400 MHz, C_6D_6) δ 1.41–1.44 (m, 4H), 2.35–2.38 (m, 2H), 2.78–2.81 (m, 2H), 7.17–7.21 (m, 4H), 7.31–7.35 (m, 2H), 8.23 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.33–8.36 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.0, 23.8, 27.3, 30.5, 111.9, 119.0, 123.2, 123.3, 128.8 (2C), 129.9, 130.3 (2C), 132.5, 141.2, 142.7, 149.9, 152.0, 155.1, 155.2, 163.5; IR ($CHCl_3$) ν 2938, 2865, 2234, 1593, 1580, 1563, 1498, 1457, 1429, 1422, 1386, 1359, 1315, 1233, 1095 cm^{-1}; EI-MS m/z (% relative intensity) 310 ($M-H^+$, 100), 296 (12), 283 (46), 250 (10), 235 (7), 147 (8); HR-MS calcd for $C_{21}H_{17}N_3$ 311.14224, found 311.14349.

4.3.8. 5,6,7,8-Tetrahydro-1-(3-methoxypyridin-2-yl)-3-phenylisoquinoline 3f. Diyne **2f** (85 mg, 0.4 mmol), benzonitrile (1.6 mL, 16 mmol), $CpCo(CO)_2$ (11.3 μL, 0.08 mmol). Column chromatography on silica gel (3/1 hexane/EtOAc) afforded 91 mg (72%) of a white solid. Mp 121 °C (heptane); ^{1}H NMR (400 MHz, C_6D_6) δ 1.44–1.46 (m, 4H), 2.41–2.43 (m, 2H), 2.58–2.60 (m, 2H), 3.10 (s, 3H), 6.65 (d, $J = 8.4$ Hz, 1H), 6.82–6.85 (m, 1H), 7.15–7.17 (m, 1H), 7.22–7.26 (m, 3H), 8.17–8.19 (m, 2H), 8.37 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.3, 23.9, 26.7, 30.4, 56.2, 119.7, 121.6, 124.8, 128.7 (2C), 129.8 (2C), 130.0, 131.9, 141.8, 142.7, 148.4, 151.8, 155.1, 155.6, 158.1; IR ($CHCl_3$) ν 3623, 3060, 3012, 2936, 2860, 2832, 1711, 1587, 1448, 1420, 1280, 1207, 1112, 1014, 774, 701, 574 cm^{-1}; EI-MS m/z (% relative intensity) 316 (M^+, 100), 301 (55), 288 (45), 273 (15) 158 (10), 149 (12); HR-MS calcd for $C_{21}H_{20}N_2O$ 316.15756, found 316.15756.

4.4. Preparation of bipyridine *N,N′*-dioxides

4.4.1. General procedure for oxidation of bipyridines. A solution of bipyridine (1.66 mmol) in dichloromethane (11 mL) was cooled to 0 °C. Then MCPBA (630 mg, 3.65 mmol) was added, the reaction mixture was allowed to reach room temperature and stirred for 1 h. Then the reaction mixture was quenched with brine (10 mL), extracted with dichloromethane (10 mL), the organic layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Purification of the residue on silica gel provided the corresponding bis-*N*-oxides.

4.4.2. 5,6,7,8,-Tetrahydro-1-(3-methylpyridin-2-yl)-3-phenylisoquinoline *N,N*-dioxide 4b. Bipyridine **3b** (500 mg, 1.66 mmol), dichloromethane (11 mL), *m*-chloroperoxybenzoic acid (630 mg, 3.65 mmol). Column chromatography on silica gel (9/1 MeOH/$CHCl_3$) afforded 160 mg (25%) of a white solid. Mp decomposition >100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.88 (m, 4H), 2.15 (s, 1H), 2.19–2.27 (m, 1H), 2.60–2.68 (m, 1H), 2.80–2.83 (m, 2H), 7.16–7.28 (m, 5H), 7.38–7.43 (m, 3H), 7.84–7.87 (m, 2H), 8.2 (d, $J = 6.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.6, 21.7, 24.5, 28.3, 125.1, 126.9, 127.4, 127.8 (2C), 129.1, 129.4 (2C), 132.5, 134.7, 136.4, 137.3, 137.3, 141.5, 142.8, 146.1; IR ($CHCl_3$) ν 3663, 3383, 3062, 2988, 2946, 2866, 1596, 1473, 1456, 1449, 1425, 1394, 1355, 1343, 1278, 1262, 1249, 1135, 1086, 1044, 964, 914, 885, 851, 817 cm^{-1}; EI-MS m/z (% relative intensity) 332 (M^+, 6), 315 (42), 299 (34), 285 (17), 272 (18), 259 (16), 236 (7), 212 (7), 185 (7), 157 (7), 141 (8), 129 (16); HR-MS calcd for $C_{21}H_{20}N_2O_2$ 332.15240, found 332.15309.

4.4.3. 1-(3-(Trifluoromethyl)pyridin-2-yl)-5,6,7,8-tetrahydro-3-phenylisoquinoline *N,N*-dioxide 4c. Bipyridine **3c** (957 mg, 2.5 mmol), dichloromethane (16 mL), *m*-chloroperoxybenzoic acid (695 mg, 5.5 mmol). Column chromatography on silica gel (9/1 MeOH/$CHCl_3$), afforded 220 mg

(23%) of a white solid. Mp decomposition >100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74–1.90 (m, 4H), 2.38–2.43 (m, 2H), 2.82–2.86 (m, 2H), 7.30–7.48 (m, 5H), 7.6 (d, $J = 7.8$ Hz, 1H), 7.79–7.83 (m, 2H), 8.47 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR δ (75 MHz, $CDCl_3$) δ 21.5, 21.8, 24.9, 28.3, 122.4, 125.7, 128.0 (2C), 128.1, 129.3, 129.4 (2C), 129.9, 131.9, 132.7, 135.3, 136.8, 139.3, 142.4, 142.5, 146.3; IR ($CHCl_3$) ν 3085, 3061, 3033, 2931, 2858, 1599, 1477, 1451, 1420, 1392, 1321, 1257, 1217, 1203, 1175, 1140, 1118, 1081, 1033, 1015, 964, 911, 884, 870, 823, 779, 758, 738, 699, 672, 619, 562 cm^{-1}; EI-MS m/z (% relative intensity) 386 (M^+, 9), 369 (50), 354 (65), 341 (35), 326 (45), 314 (30), 301 (100), 285 (30), 273 (10); HR-MS calcd for $C_{21}H_{17}N_2F_3$ 386.12421, found 386.12537.

4.5. Resolution of bipyridine *N*,*N*′-dioxides into enantiomers

4.5.1. (*S*)-(−)-5,6,7,8,-Tetrahydro-1-(3-methylpyridin-2-yl)-3-phenylisoquinoline *N*,*N*-dioxide (*S*)-4b. Separation of racemic **4b** carried out on HPLC with a column with a chiral phase (Chiralcel OD-H, 0.46 × 25 cm, 3/1 heptane/2-propanol, 0.7 mL/min), afforded (*S*)-(−)-**4b** and (*R*)-(+)-**4b**. Each enantiomer was obtained in >98% ee ($t_S =$ 20 min, $t_R = 37$ min). The separated enantiomers were purified by column chromatography on silica gel (9/1 $CHCl_3$/2-propanol) prior to the use. $[\alpha]_D = -350$ (*c* 0.01, $CHCl_3$).

4.5.2. (*S*)-(+)-1-(3-(Trifluoromethyl)pyridin-2-yl)-5,6,7,8-tetrahydro-3-phenylisoquinoline *N*,*N*-dioxide (*S*)-(+)-4c. Separation of racemic **4c** carried out by HPLC with a column with a chiral phase (Chiralcel OD-H, 0.46 × 25 cm, 3/1 heptane/2-propanol, 0.7 mL/min), afforded (*S*)-(+)-**4b** and (*R*)-(−)-**4b**. Each enantiomer was obtained in >98% ee ($t_S = 24$ min, $t_R = 35$ min). The separated enantiomers were purified by column chromatography on silica gel (9/1 $CHCl_3$/2-propanol) prior to the use. $[\alpha]_D = +39$ (*c* 0.01, $CHCl_3$).

4.6. Enantioselective allylation

4.6.1. General procedure for the enantioselective allylation of benzaldehydes with allyltrichlorosilane catalyzed by 4. To a solution of **4b** (**4c**) (0.0125 mmol) in dichloromethane (0.8 mL), aldehyde (0.25 mmol), diisopropylethylamine (54 μL, 0.31 mmol), and allyltrichlorosilane (46 μL, 0.31 mmol) were added at −78 °C and the reaction mixture was stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), the organic layer was separated and dried over $MgSO_4$. Yields and ees were determined by GC (HP-Chiral β, 30 m × 0.25 mm, oven: 80 °C for 15 min, then 1 °C/min to 150 °C, 5 min at that temperature).

4.6.1.1. (*R*)-(+)-1-(4-Trifluoromethylphenyl)-but-3-en-1-ol 6b. ($t_R = 59.58$ min, $t_S = 61.09$ min).

4.6.1.2. (*R*)-(+)-1-Phenyl-but-3-en-1-ol 6a. ($t_R = 57.90$ min, $t_S = 58.33$ min).

4.6.1.3. (*R*)-(+)-1-(4-Methoxyphenyl)-but-3-en-1-ol 6c. ($t_R = 83.64$ min, $t_S = 84.26$ min).

Acknowledgments

We gratefully acknowledge financial support from the Czech Science Foundation (Grant No. 203/05/0102) and Ministry of Education of the Czech Republic to the Center for Structural and Synthetic Application of Transition Metal Complexes (Project No. LC06070).

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