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Diastereomeric Atropisomers from a Chiral Diyne by Cobalt(I)-Catalyzed Cyclotrimerization

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The reaction of new, chiral, proline-based naphthyl diynes with different nitriles through a key [2+2+2] cycloaddition reaction step catalyzed by Co^{I}–olefin complexes under thermal and photochemical conditions gave diastereomeric atropisomers in good yield and nearly 1:1 ratios. Facile chromatographic separation of the naphthyl tetrahydroisoquinolines gave access to both pure and stable diastereomeric atropisomers. The deprotection and direct functionalization of the methyl- or methoxymethyl-protected 2-naphthyl position of the atropisomers were investigated. The configuration of the formed atropisomers was assigned from results of X-ray studies and circular dichroism spectroscopy.

Introduction

The large body of experimental work on synthetic approaches to chiral biaryls highlights their importance in many fields of organic chemistry and especially in catalysis today.[1] Biaryls are a widespread structural element in natural products,[2] and recently their role in pharmacological ingredients was also discussed.[3] Within the array of different methods, the [2+2+2] cycloaddition reaction has developed into a mature methodology for this purpose in recent years.[4] The construction of heterocyclic ring systems by cross-cyclotrimerization has also been established for the synthesis of pyridine and related systems.[5] However, the use of cobalt-catalyzed cycloaddition reactions as a key step in the construction of natural products has been applied in numerous examples.[6] A highly interesting example is the preparation of Steganone analogues by Motherwell et al., notably because of the very interesting and intriguing structure of the molecule.[7] Beside the axis of a atropisomeric biaryl moiety two more stereogenic elements are derived from a *trans*-fused γ-lactone ring. The synthetic approach featured the preparation of the chiral diyne and the final elaboration of the second aromatic ring providing the biaryl axis by application of a [2+2+2] cycloaddition reaction.

We are interested in the synthesis of chiral biaryl systems containing pyridine fragments.[8] For potential applications, for example, as ligands in stereoselective catalysis, however, it might also be very interesting to gain access to biaryl systems with more than one stereogenic element, that is to introduce a different stereochemical element into the precursor that is not meant to act as an auxiliary and be cleaved from the final product in a later step, but rather stays in it. In this way one can gain access to a pair of diastereomeric atropisomers with different properties and that might even be easily separated. Classes of different diastereomeric atropisomers have been described and their properties towards asymmetric synthesis and stability of the stereoisomers, as well as their use in chiral separations, have been studied.[9] The approach presented herein was aimed at the synthesis of diastereomeric aryl pyridines, containing two different stereochemical elements, by different achiral Co^{I}–olefin catalysts, and their synthetic potential was investigated.

Results and Discussion

The use of a cheap and synthetically versatile chiral group in diyne substrate **2** and the application of an achiral Co^{I}-catalyzed [2+2+2] cycloaddition with nitriles should result in the formation of both diastereomeric atropisomers, which, after separation, should provide access to both diastereomerically pure stereoisomers (**1**, Scheme 1).[10]

These diastereomeric atropisomers should be a highly useful platform for further introduction of functionalities, especially regarding the preparation of new ligand systems. Before the start of the synthetic sequence with the chiral diyne substrate, the choice of the chiral group was essential (Scheme 2). It was required that it (a) provided a configurationally stable chiral center and (b) could be incorporated into the backbone of the diyne moiety in a synthetically straightforward fashion. Initially, we considered proline (**3**)

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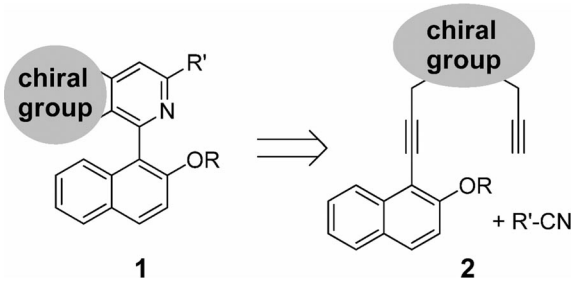
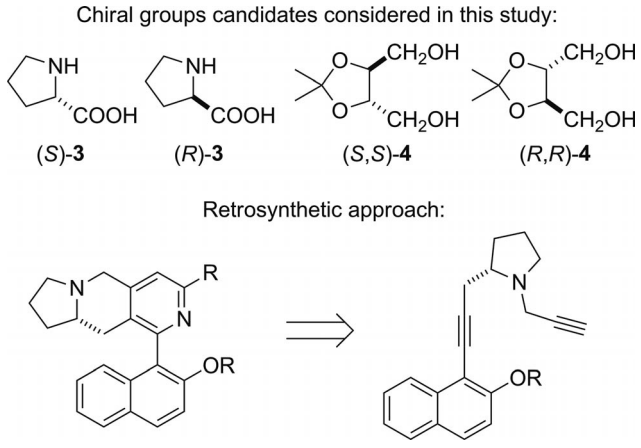


Scheme 1. Approach for the synthesis of diastereomeric biaryls **1** containing two chiral elements.

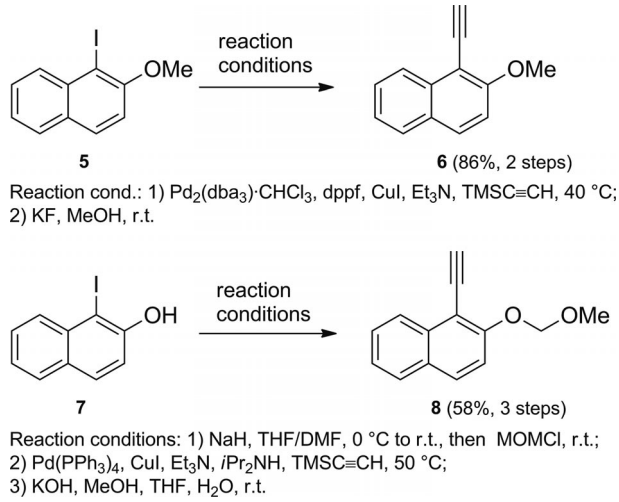
and tartaric acid derived 2,3-*O*-isopropylidenethreitol (**4**) as suitable chiral precursor compounds (Scheme 2). For the latter, the preparation of alkynylated derivatives was not very convenient and low yielding, making it an unattractive approach.[11] Therefore, we chose (*S*)-proline [(*S*)-**3**] as the chiral group.



Scheme 2. Chiral groups investigated and the retrosynthetic approach for the proline-based chiral diyne.

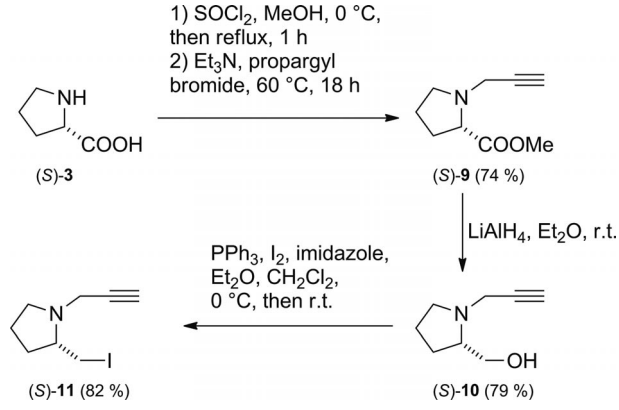
The convergent synthesis of the chiral diyne cycloaddition substrate started with the preparation of the appropriate methoxy-protected naphthalene derivative **6** from **5** as well as the MOM-protected (MOM = $-CH_2OCH_3$) naphthalene **8** from **7** (Scheme 3).[12] While the methoxy group proved to be very useful in cycloaddition reactions with related naphthyl derivatives,[8] the use of the MOM group should be beneficial for the ease of cleavage to provide a free hydroxy group. The synthesis of compound **8** has been described before,[13] but we used a modified procedure: deprotonation of **7** with NaH in DMF/THF and quenching with MOMCl gave the protected naphthole, which was then subjected to a Sonogashira reaction and deprotection to give arylacetylene **8**.

The synthesis of the required chiral proline coupling component, (*S*)-**11**, started from enantiomerically pure (*S*)-proline [(*S*)-**3**] (Scheme 4). The one-pot esterification/propargylation sequence gave ester (*S*)-**9**, which could easily be reduced to the corresponding alcohol (*S*)-**10** by using $LiAlH_4$ in ethyl ether, with good yields in both cases. The final iodination, involving a substitution reaction in the



Scheme 3. Synthesis of the alkynylated naphthalene derivatives **6** and **8** (TMS = trimethylsilyl, dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene).

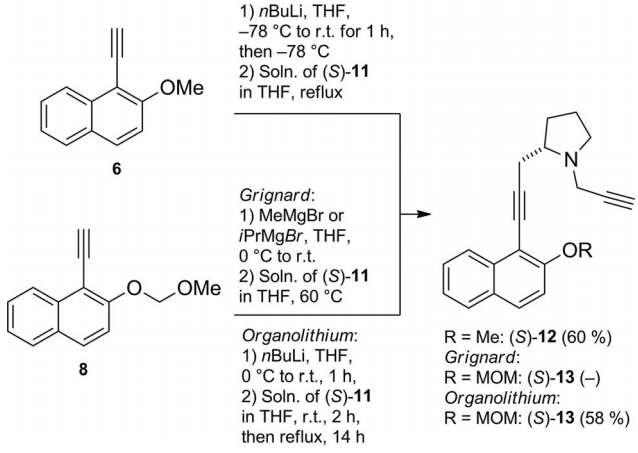
presence of PPh_3 and elemental iodine, turned out to be a very smooth reaction with up to an excellent yield of 82%, providing pure (*S*)-**11** as a dark oil after chromatographic purification.



Scheme 4. Synthesis of (*S*)-proline derivative (*S*)-**11**.

Finally, the complete chiral diyne precursors needed to be assembled (Scheme 5). After testing the reaction with different additives, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), the simple reaction of lithiated acetylene **6** with (*S*)-**11** under reflux was the best coupling protocol. However, the maximum isolated yield for (*S*)-**12** was 60%, but some unreacted starting material could be recovered from the reaction mixture after workup and purification. For the reaction with MOM-protected alkyne **8**, we initially applied Grignard reagents for the deprotonation of the terminal alkyne to circumvent possible deprotonation in the 3-position of the naphthyl ring by the use of *n*BuLi, which would possibly be alleviated by the MOM group. However, deprotonation seemed to proceed smoothly as expected, and subsequently, reaction with iodide (*S*)-**11** occurred. Usual workup yielded a product that showed the expected resonances for (*S*)-**13** in the ^1H NMR spectrum, comparable to the resonances of (*S*)-**12** for iden-

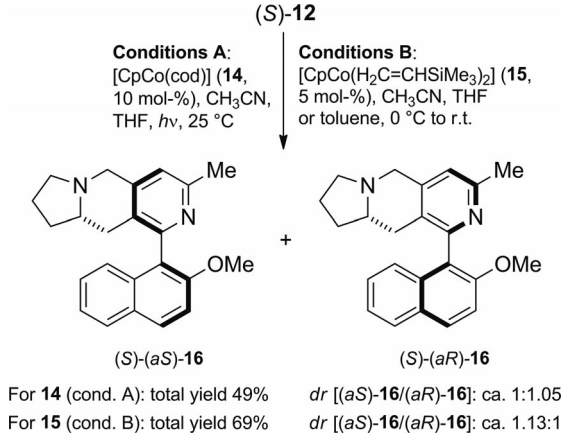
tical parts of the molecule. Unfortunately, a side reaction seemed to have occurred because additional signals were identified to indicate that the isolated coupling product was not the expected product (*S*)-**13**.[14] For comparison, we then utilized the same conditions with *n*BuLi as those used for the preparation of (*S*)-**12**. Coupling product (*S*)-**13** was isolated in a yield of 58% (Scheme 5). The use of lithium diisopropylamide (LDA) as the deprotonating base did not give any advantages.



Scheme 5. Successful synthesis of the chiral diynes (*S*)-**12** and (*S*)-**13**.

With chiral diynes (*S*)-**12** and (*S*)-**13** in hand, we set out to investigate the Co^I-catalyzed [2+2+2] cycloaddition reaction with nitriles as the key step.[15] The cycloaddition reaction with substrates possessing a methoxy group in the 2-position of the naphthalene system, such as (*S*)-**12**, was known to be more successful than that of substrates with other groups; therefore, we first investigated this substrate.[8] Two different Co^I catalyst systems were evaluated towards their usefulness in the assembly of the chiral diyne substrates (*S*)-**12** and (*S*)-**13**. The complex [CpCo(cod)] (**14**; cod = 1,5-cyclooctadiene, Cp = cyclopentadiene) is a well-known catalyst with a long history as a catalyst in cyclotrimerization reactions.[4] Whereas this complex requires rather high temperatures under thermal reaction conditions, significantly milder conditions are possible with a photochemical setup, which is especially useful for reactions with chiral substrates.[16] Recently, we reported the synthesis and catalytic features of the new Co^I complex, [CpCo(H_2C=$CHSiMe_3$)$_2$] (**15**), which showed extraordinary reactivity in cycloaddition reactions, even at low temperatures.[17] Even though both precatalyst complexes deliver the "CpCo"-fragment as a catalytically active species,[18] the reactivity differences should be investigated.

The results for the cycloaddition reaction of (*S*)-**12** with acetonitrile and either **14** or **15** as the catalysts nicely display the excellent reactivity of precatalyst **15** (Scheme 6). Although in both cases the products **16** were formed, the overall yield for catalyst **15** (69%) is significantly higher than the yield observed for the use of **14** (49%). In both cases, no large selectivity effects were observed by ^{1}H NMR spectroscopy of the crude product or in the isolated amounts of the products, regardless of whether THF or toluene was used as the solvent. This observation was unsurprising because the chiral proline moiety was too far from the reaction center to induce significant selectivity; therefore, both atropisomers could be concurrently constructed. This finding was complemented by the ease of separation of both diastereomeric atropisomers, which could be separated by simple column chromatography on silica gel, yielding the pure individual diastereomers (*S*)-(*aS*)-**16** and (*S*)-(*aR*)-**16**.



Scheme 6. Cobalt-catalyzed [2+2+2] cycloaddition reaction of (*S*)-**12** with acetonitrile, using different catalysts systems, to provide the diastereomeric atropisomers **16**. The stereochemistry of (*S*)-(*aS*)-**16** was determined by X-ray crystallography; see below.

To gain insight into the stability of the diastereomers (*S*)-(*aS*)-**16** and (*S*)-(*aR*)-**16**, we heated solutions of the biaryls in [D_8]toluene in Young NMR tubes and monitored the appearance and disappearance of significant resonances such as the methoxy group of the respective diastereomers by ^{1}H NMR spectroscopy. The experiments showed that the half-life time was about 7.5 h at 100 °C for both diastereomers, which were converted into the opposite stereoisomer. Finally, 1:1 mixtures of both diastereomers were obtained after heating for 15 h. Therefore, it can be concluded that the formation of neither of the investigated diastereomers were thermodynamically favored over the other.

Having isolated each diastereomeric atropisomer as a pure solid, we decided to determine the absolute configuration of the biaryl axis. CD spectroscopic investigation of the diastereomers clearly showed the opposite configuration of the chromophore.[19] We were able to obtain single crystals of (*S*)-(*aS*)-**16** suitable for X-ray analysis, and thus, were able to assign the (*aS*)-configuration to the biaryl moiety (Figure 1).[20] As a result, the opposite (*aR*)-configuration was assigned for the second atropisomer.

We also investigated the reaction with aromatic nitriles, specifically benzonitrile and 2-fluorobenzonitrile, to evaluate the versatility of the method (Scheme 7). The fluorinated nitrile should later provide the potential opportunity for further functionalization by nucleophilic aromatic substitution.[21] For the reaction with benzonitrile using [Cp-

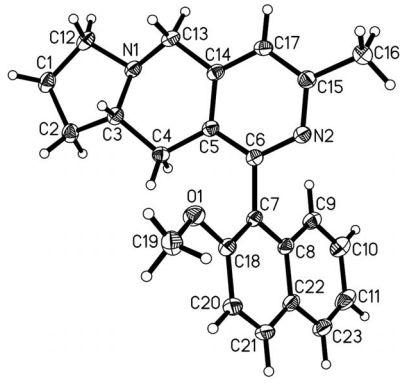
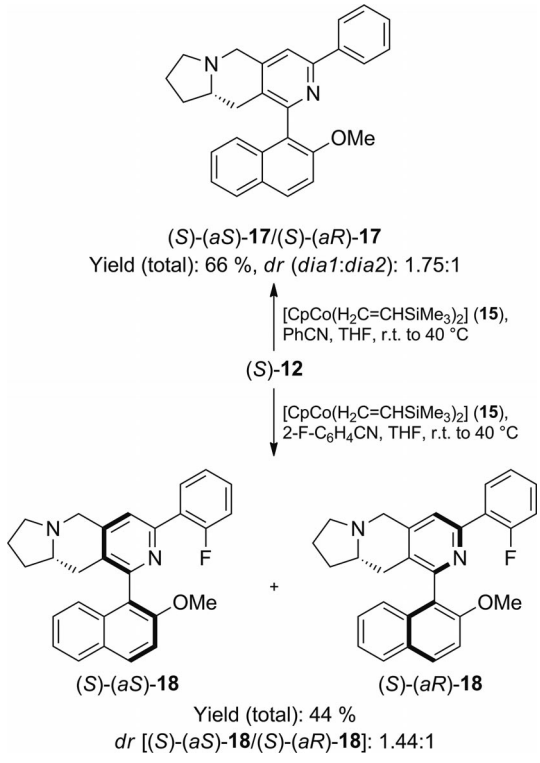


Figure 1. ORTEP plot of the molecular structure of (*S*)-(*aS*)-**16** (the naphthyl ring points in the opposite direction than that shown in Figure 2). Ellipsoids are drawn at the 30% probability level.

Co(cod)] (**14**) under photochemical conditions, again a much lower total yield (38%) of **17** was obtained. The estimation of the diastereomeric ratio (*dr*) from the crude NMR spectrum was 1.22:1; a slight excess of the first diastereomer was collected by column chromatography. The application of optimized conditions with catalyst **15** provided much higher total yields (66%) and also with a slightly higher *dr* (1.75:1) for the isolated atropisomers **17**. The use of 2-fluorobenzonitrile for cycloaddition with (*S*)-**12** using **15** as the catalyst led to the isolation of the two atropisomers **18** in a total yield of 44%.



Scheme 7. Cobalt-catalyzed [2+2+2] cycloaddition reactions of (*S*)-**12** with benzonitrile and 2-fluorobenzonitrile [the stereochemistry of (*S*)-(*aR*)-**18** was determined by X-ray crystallography; see below].

We were able to determine the absolute configuration of one of the diastereomers of **18** by obtaining a single crystal that was suitable for X-ray analysis (Figure 2).[22,23] It turned out that the atropisomer isolated second by column chromatography had an (*aR*)-configured biaryl axis. Therefore, the *dr* value was determined from the isolated products to be slightly in excess for (*S*)-(*aS*)-**18**. However, both atropisomers are accessible.

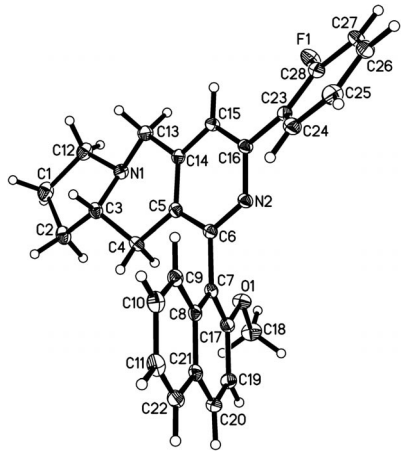
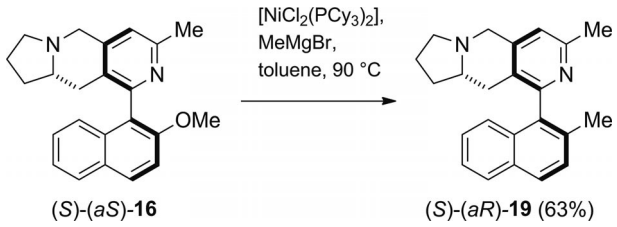


Figure 2. ORTEP plot of the molecular structure of (*S*)-(*aR*)-**18** (the naphthyl ring points in the opposite direction than that shown in Figure 1). Ellipsoids are drawn at the 30% probability level.

The atropisomers **16** appeared to be a useful chiral platform for the preparation of chiral derivatives and potential ligands. While the methyl group at the pyridine moiety and the methoxy group in the 2-position of the naphthyl ring can be regarded as potential targets for further functionalization, the substitution of the methoxy group for a PPh_2 group is well documented for the synthesis for P,N ligands.[24] Interestingly, our experiments with conventional systems for the demethylation of the methoxy group showed that the methyl group of **16** was very difficult to cleave and largely resisted most conditions investigated. All attempts to cleave the methoxy functional group by using standard strong Lewis acid reagents, such as BBr_3, $BBr_3{\cdot}SMe_2$, or Me_3SiI, did not provide the OH-unprotected biaryl in useful amounts.[25] It should be noted that **16** could be easily protonated by HCl and became soluble in the aqueous phase, from which it could be extracted with organic solvents upon the addition of base.

We sought to investigate other direct functionalization possibilities for the methoxy group in **16**. For example, we examined the nickel-catalyzed methylation of the methoxy group, which has emerged as a new and highly interesting arene functionalization methodology only very recently.[26] We expected this substitution to proceed without any epimerization concerning the biaryl axis; this would immediately be seen by the formation of two diastereomeric atropisomers, which could therefore act as a chemical probe for epimerization. Initial experiments provided the information that $[NiCl_2(PCy_3)_2]$ (Cy = cyclohexyl) together with MeMgBr was the most suitable methylation system and the reaction proceeded smoothly at 90 °C in toluene. Both

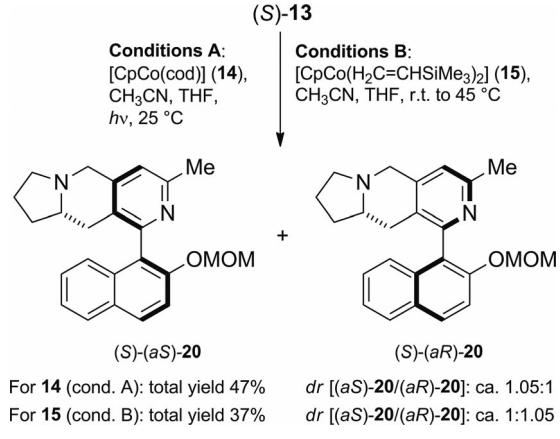
atropisomers (*S*)-(*aS*)-**16** and (*S*)-(*aR*)-**16** can be reacted under these conditions, which is exemplified in Scheme 8 for the methylation of (*S*)-(*aS*)-**16**, providing (*S*)-(*aR*)-**19** in 63% yield. Although the absolute configuration of the axial bond is the same, the stereochemical assignment changes due to interchanged priority of the substituents, according to Cahn–Ingold–Prelog (CIP) nomenclature. No epimerization was observed, demonstrating the stability of the chiral axis of this heterobiaryl for transition-metal-catalyzed substitution reactions in the *ortho* position. The introduction of the methyl group in the *ortho* position seems to contribute to a higher stability of the biaryl axis, as can be concluded in the light of the epimerization experiments discussed above.



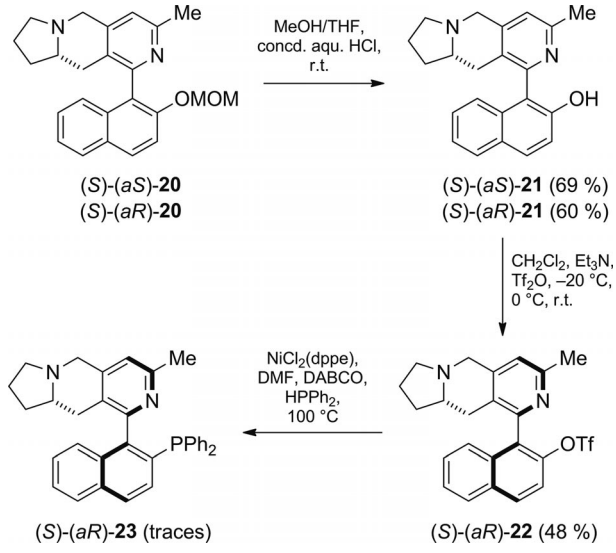
Scheme 8. Nickel-catalyzed coupling reaction with (*S*)-(*aS*)-**16**, leading to the methylated product (*S*)-(*aR*)-**19**.

The problematic demethylation step for **16** turned our attention again to the use of a different protecting group, which is easier to cleave, allowing further functionalization. However, the 2-position of the naphthyl system was found to have a significant influence on the outcome of the cobalt-catalyzed cycloaddition reaction under photochemical conditions.[8] We therefore investigated the use of (*S*)-**13** for our purpose because of the ease of cleavage of the MOM group under mild acidic conditions. Application of the cycloaddition conditions used for the cyclization of (*S*)-**12** with acetonitrile gave both diastereomers of **20**, although lower overall yields were encountered (Scheme 9). Interestingly, here the photochemically activated catalyst system was superior to catalyst **15**, where in addition slightly higher temperatures were applied. The reason is certainly the presence of the larger group in the 2-position, leading to a lower reaction rate and catalyst deactivation over time. The stereochemistry of the products could be assigned by comparison of the CD spectra with those measured for **16**.[19]

With the diastereomers of **20** in hand, we investigated the functionalization of the 2-naphthyl position again. In the first step, and in contrast to 2-methoxy-substituted **16**, the MOM group of **20** could easily be cleaved off with HCl in good yields (Scheme 10). Further transformation into a P,N ligand was investigated for the pure 2-naphthol derivative (*S*)-(*aR*)-**21**. The biaryl was converted into the triflate by using Tf_2O in the presence of amine under standard reaction conditions, yielding (*S*)-(*aR*)-**22**. Finally, nickel-catalyzed coupling with $HPPh_2$ was attempted for the preparation of the P,N ligand (*S*)-(*aR*)-**23**, following a reported procedure for related P,N ligands.[24d] This method is advantageous to other methods, applying the oxide $HP(O)Ph_2$ as coupling partner, but requires subsequent reduction of the resulting phosphane oxide. Unfortunately, after purification by column chromatography, only traces of product were identified by NMR spectroscopy and MS.[27] We turned our attention to another functionalization, using compound (*S*)-(*aR*)-**21** directly for the preparation of a chiral phosphite with 1,1′-bi-2,2′-naphthol (BINOL), as reported by Brown et al.[28] However, also in this case, the conditions provided in the literature were largely unsuccessful to provide the expected product in preparative yields. No further optimization of reaction conditions was attempted, but compounds **19**, **21**, and **22** are certainly interesting starting materials for further derivatization studies.



Scheme 9. Cobalt-catalyzed [2+2+2] cycloaddition reaction of (*S*)-**13** with acetonitrile, using different catalyst systems, to provide the diastereomeric atropisomers **20** [the stereochemistry of (*S*)-(*aS*)-**20** and (*S*)-(*aR*)-**20** was assigned by CD spectroscopy].



Scheme 10. Conversion of MOM-protected biaryls **20** into the OH-free compounds and attempted transformation into the P,N ligand **23**.

Conclusions

We demonstrated the use of two chiral diynes for the concurrent preparation of diastereomeric atropisomers containing two different stereochemical elements. The study was initiated to make both stereoisomers accessible in one step combined with an easy chromatographic separation procedure. The key step is the [2+2+2] cycloaddition reaction between the chiral diyne and nitriles, catalyzed by achiral cobalt(I) complexes. The choice of the reaction conditions was crucial for the [2+2+2] cycloaddition between the chiral diyne and nitriles and the highly reactive precatalyst complex [CpCo(H_2C=CHSiMe_3)$_2$] (**15**) was superior to the application of [CpCo(cod)] (**14**) under photochemical conditions for small groups in the 2-naphthyl position of the biaryl. In all cases, nearly equal amounts (*dr* ca. 1:1–1:2) of both pure diastereomeric atropisomers were isolated after facile separation by column chromatography. The stereochemistry of the biaryl atropisomers was elucidated by X-ray analysis and CD spectroscopy. The use of the MOM group in the 2-naphthol position was superior to the methyl group for subsequent cleavage to supply the OH-free compound. This strategy provides access to both diastereomeric atropisomers without the need for chiral catalysts, offering a chiral platform for further manipulations towards ligands and chiral backbones for synthetic purposes.

Experimental Section

General Methods: NMR spectra were, in general, recorded at 298 K and the individual measurement conditions are given with the data. Chemical shifts are reported in ppm relative to the ^{1}H and ^{13}C residual signals of the deuterated solvent (deuteriochloroform: δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C). Mass spectra were obtained at an ionizing voltage of 70 eV for EI. Only characteristic fragments containing the isotopes of highest abundance are listed. Relative intensities in percentages are given in parentheses. In all cases, the enantiomeric excesses of pyridines were analyzed by HPLC using appropriate chiral columns. For photochemistry, two metal halogen lamps (460 W each) were used for irradiation of thermostated Schlenk-type reaction vessels.

All reactions including transition metal catalysts were carried out in an argon atmosphere, using standard techniques in dry, oxygen-free solvents. All liquid reagents were distilled under argon prior to use. The liquid starting materials were dried with and distilled from molecular sieves under argon before use. Chromatographic purifications were done with 240–400 mesh silica gel or an automated flash chromatography system (Biotage SP1). THF used as eluent for chromatographic separations was distilled before use to remove the added stabilizer (BHT) or unstabilized THF was used. 1-Iodo-2-methoxynaphthalene (**5**),[29] 1-iodonaphthalen-2-ol (**7**),[29] [CpCo(cod)] (**14**),[30] [CpCo(H_2C=CHSiMe_3)$_2$] (**15**),[17] and [$NiCl_2$(PCy_3)$_2$],[31] were synthesized according to known procedures. A modified procedure was applied for 1-ethynyl-2-(methoxymethoxy) naphthalene (**8**) and is given in the Supporting Information. All other compounds and reagents not referenced were commercially available and have been purchased.

(*S*)-Methyl 1-(Prop-2-ynyl)pyrrolidine-2-carboxylate [(*S*)-9]:[32] (*S*)-Proline [(*S*)-**3**, 10.0 g, 86.9 mmol] was suspended in dry methanol (100 mL) under argon and cooled to 0 °C, afterwards $SOCl_2$ (7.0 mL, 95.6 mmol) was added dropwise. The reaction mixture was heated for 1 h under reflux and allowed to cool to room temp. All volatile compounds were removed in vacuo through a cool trap. The residue together with Et_3N (26.7 mL, 191.2 mmol), toluene (100 mL), and propargyl bromide (11.2 mL, 100.4 mmol) were heated to 60 °C for 18 h. After cooling, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted with toluene after separation. The combined phases were washed with H_2O twice (50 mL each) and brine (50 mL) and dried with Na_2SO_4. After evaporation of the solvent, the oily residue was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate, 4:1 (v/v + 1% Et_3N) as the eluent and compound (*S*)-**9** was obtained as colorless oil (10.63 g, 74%). Further purification could be executed by bulb-to-bulb (Kugelrohr) distillation (50–60 °C/ 5×10^{-3} mbar). $[\alpha]_D^{22}$ = –148.7 (*c* = 1.168, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 3.54 (t, *J* = 2.5 Hz, 2 H), 3.38 (dd, *J* = 9.0, 6.6 Hz, 1 H), 2.99 (ddd, *J* = 8.7, 7.8, 2.7 Hz, 1 H), 2.66 (td, *J* = 9.0, 7.6 Hz, 1 H), 2.16 (t, *J* = 2.4 Hz, 1 H), 2.12–2.05 (m, 1 H), 1.97–1.71 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 78.2, 73.2, 62.3, 52.1, 51.8, 41.1, 29.5, 23.2 ppm. MS (ESI^+): *m*/*z* (%) = 168 (100) $[M + H]^+$, 108 (69). HRMS (ESI): calcd. for $C_9H_{14}NO_2$ $[M + H]^+$ 168.1019; found 168.1020.

(*S*)-[1-(Prop-2-ynyl)pyrrolidin-2-yl]methanol [(*S*)-10]:[32] Lithium aluminum hydride (100 mL, 100 mmol, 1 M in Et_2O) was diluted with dry Et_2O (200 mL) in a 500 mL flask fitted with a dropping funnel and argon inlet. The ester (*S*)-**9** (8.3 g, 50 mmol) was added dropwise over about 2.5 h and the reaction mixture was stirred for additional 4 h. TLC control [eluent: *n*-hexane/ethyl acetate, 1:1 (v/v) + 1% Et_3N] indicated complete conversion and the reaction was quenched with a mixture of NH_4Cl/aq. NH_3 in water, the solution was buffered to pH 8 and a saturated aqueous solution of Na_2SO_4 was added to enhance precipitation of the metal salts. The suspension was filtered through Celite and the solid residue was washed with ethyl ether. The filtrate was separated from the aqueous phase and dried with Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by Kugelrohr distillation (80–90 °C/ 5×10^{-3} mbar). The pure product was obtained in 79% yield (5.44 g). $[\alpha]_D^{23}$ = –47.0 (*c* = 0.961, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (dd, *J* = 11.1, 3.6 Hz, 1 H), 3.55–3.38 (m, 2 H), 3.41 (dd, *J* = 11.1, 2.9 Hz, 1 H), 3.04–2.97 (m, 1 H), 2.86–2.78 (m, 1 H), 2.65 (q, *J* = 8.5 Hz, 2 H), 2.18 (t, *J* = 2.4 Hz, 1 H), 1.92–1.82 (m, 1 H), 1.79–1.69 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.4, 72.7, 62.3, 61.9, 53.4, 41.1, 27.8, 23.5 ppm. MS (ESI^+): *m*/*z* (%) = 140 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_8H_{14}NO$ $[M + H]^+$ 140.1070; found 140.1074.

(*S*)-2-(Iodomethyl)-1-(prop-2-ynyl)pyrrolidine [(*S*)-11]: A solution of imidazole (1.95 g, 28.7 mmol) and PPh_3 (5.64 g, 21.45 mmol) in Et_2O (40 mL) was cooled to 0 °C and iodine (5.44 g, 21.45 mmol) was added in three portions within 30 min. The mixture was warmed to room temp. and stirred for an additional 10 min, followed by the addition of a solution of alcohol (*S*)-**10** in CH_2Cl_2 (30 mL), and the precipitation of a white solid was observed. After stirring for 15 h, a thick suspension was obtained. The suspension was filtered and the solids were washed with *n*-hexane. The precipitation of more white solid (PPh_3) was observed with increasing amounts of *n*-hexane and when the filtrate was evaporated. The precipitate was removed by additional filtration. After evaporation, the product was isolated from the residue by column chromatography (*n*-hexane/ethyl acetate, 1:1 v/v + 1% Et_3N) and obtained as a dark oil (2.92 g, 82%). $[\alpha]_D^{22}$ = +34.3 (*c* = 1.047, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29–4.19 (m, 1 H), 3.31 (dd, *J* = 2.4, 0.9 Hz, 2 H), 3.09 (d, *J* = 11.0 Hz, 1 H), 2.79 (dd, *J* = 11.0,

4.0 Hz, 1 H), 2.65 (dd, *J* = 11.0, 4.0 Hz, 1 H), 2.34 (ddd, *J* = 11.0, 9.9, 3.8 Hz, 1 H), 2.25 (t, *J* = 2.4 Hz, 1 H), 2.22–2.15 (m, 1 H), 1.89–1.79 (m, 1 H), 1.74–1.61 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.4, 73.6, 62.5, 51.7, 46.7, 37.0, 27.2, 26.1 ppm. MS (ESI$^+$): *m*/*z* (%) = 250 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_8H_{13}IN$ [M + H]$^+$ 250.0087; found 250.0088.

(*S*)-2-[3-(2-Methoxynaphthalen-1-yl)prop-2-ynyl]-1-(prop-2-ynyl)pyrrolidine [(*S*)-12]: Compound **6** (2.72 g, 14.9 mmol) was dissolved in THF (ca. 150 mL) and cooled to –78 °C. Then *n*BuLi (9.8 mL, 15.6 mmol, 1.6*M*) was added dropwise and after complete addition the reaction mixture was stirred for a further 30 min at 0 °C, resulting in the formation of a beige suspension. Subsequently, a solution of iodide (*S*)-**11** (3.37 g, 13.5 mmol) in THF (30 mL) was added and the reaction mixture heated under reflux for 16 h, resulting in the formation of a dark-brown solution and TLC control predominantly showed consumption of **11**. After cooling, the reaction was quenched with water and Et_2O was added. The aqueous phase was separated and repeatedly extracted with Et_2O. The combined organic phases were washed with brine and dried with Na_2SO_4. After evaporation of the solvent, a black oily crude product was obtained and purified by flash chromatography on silica gel, using *n*-hexane/ethyl acetate (2:1 v/v) as the eluent. In addition to the recovery of unreacted **6** (900 mg, 33% recovered), the product (*S*)-**12** was isolated as a dark viscous oil [2.25 g, 60% with respect to (*S*)-**11**]. The product was stored under argon in the fridge (4 °C). $[\alpha]_D^{22}$ = –69.6 (*c* = 1.250, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.77 (d, *J* = 9.1 Hz, 1 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.52 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1 H), 7.36 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1 H), 7.23 (d, *J* = 9.1 Hz, 1 H), 4.01 (s, 3 H), 3.66 (t, *J* = 2.4 Hz, 2 H), 3.13–3.00 (m, 2 H), 2.88 (dd, *J* = –16.7, 4.9 Hz, 1 H), 2.73–2.69 (m, 1 H), 2.65 (dd, *J* = –16.7, 7.6 Hz, 1 H), 2.13 (t, *J* = 2.4 Hz, 1 H), 1.95–1.74 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 135.0, 129.5, 128.7, 128.1, 127.2, 125.6, 124.2, 112.8, 107.1, 97.8, 79.5, 75.8, 72.7, 60.5, 56.7, 53.4, 41.3, 31.4, 25.9, 22.6 ppm. MS (ESI$^+$): *m*/*z* (%) = 304 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{22}NO$ [M + H]$^+$ 304.1700; found 304.1700. $C_{21}H_{21}NO$ (303.40): calcd. C 83.13, H 6.98, N 4.62; found C 83.41, H 7.20, N 4.25.

(*S*)-2-{3-[2-(Methoxymethoxy)naphthalen-1-yl]prop-2-ynyl}-1-(prop-2-ynyl)pyrrolidine [(*S*)-13]: Compound **8** (2.5 g, 11.8 mmol) was dissolved in THF (ca. 35 mL) and cooled to 0 °C. Then *n*BuLi (7.3 mL, 12.4 mmol, 1.6*M*) was added dropwise and, after complete addition, the reaction mixture was stirred for a further 60 min at 0 °C, resulting in the formation of a beige suspension. Subsequently, a solution of iodide (*S*)-**11** (2.67 g, 10.7 mmol) in THF (35 mL) was added and the reaction mixture was heated under reflux for 14 h, resulting in a dark-brown solution and TLC control predominantly showed consumption of **11**. After cooling, the reaction was quenched with a saturated aqueous solution of NH_4Cl and Et_2O was added. The aqueous phase was separated and repeatedly extracted with diethyl ether. The combined organic phases were washed with water and brine and dried with Na_2SO_4. After evaporation of the solvent, a black oily crude product was obtained and purified by flash chromatography on silica gel, using *n*-hexane/ethyl acetate (1:1 v/v) as the eluent. Unreacted **8** was recovered (500 mg, 20% recovered) and the product (*S*)-**13** was isolated as a dark viscous oil [2.04 g, 58% with respect to (*S*)-**11**]. The product was stored under argon in the fridge (4 °C). $[\alpha]_D^{22}$ = –63.1 (*c* = 0.809, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.53 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.42–7.36 (m, 1 H), 7.38 (d, *J* = 8.9 Hz, 1 H), 5.36 (s, 2 H), 3.68 (t, *J* = 2.0 Hz, 2 H), 3.57 (s, 3 H), 3.14–2.99 (m, 2 H), 2.86 (dd, *J* = –16.7, 5.0 Hz, 1 H), 2.76–2.68 (m, 1 H), 2.65 (dd, *J* = –16.7, 5.0 Hz, 1 H), 2.23 (t, *J* = 2.4 Hz, 1 H), 2.21–2.11 (m, 1 H), 1.95–1.76 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 134.8, 129.5, 129.3, 128.1, 127.1, 125.8, 124.7, 116.8, 109.3, 97.7, 95.7, 79.5, 75.8, 72.7, 60.4, 56.5, 53.4, 41.2, 31.4, 25.9, 22.6 ppm. MS (ESI+): *m*/*z* (%) = 334 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{22}H_{24}NO_2$ [M + H]$^+$ 334.1802; found 334.1804.

General Procedures for the [2+2+2] Cycloaddition Reaction of (*S*)-8 with Nitriles under Photochemical Conditions (Catalyst 14) or under Thermal Conditions (Catalyst 15): Note for the following examples using acetonitrile as the substrate: During the separation process, using the general solvent mixture THF/*n*-hexane as the eluent, the first diastereomer (*dia1*) with R_f = 0.80 and the second diastereomer (*dia2*) with R_f = 0.78 (R_f's for the eluent THF/*n*-hexane, 6:1 v/v) were obtained. Investigation into the stereochemistry provided the information that *dia1* could be assigned as (*S*)-(*aS*)-**16** and *dia2* as (*S*)-(*aR*)-**16**.

General Procedure 1: Photochemical Conditions (Catalyst 14) with Acetonitrile: In a typical experiment, the chiral diyne (*S*)-**12** (890 mg, 2.93 mmol) was secured in a Schlenk flask under argon and dissolved in THF (20 mL). The yellow–brownish solution was transferred to a secured and thermostated (25 °C) Schlenk reactor containing **14** (69 mg, 0.294 mmol). Finally, acetonitrile (0.78 mL, 14.7 mmol, 5 equiv.) was added by syringe. The reactor was radiated for 48 h, after which time the starting material had disappeared. After switching off the lamps, the reaction vessel was opened to air, the reaction mixture was transferred to a round-bottomed flask, and the reaction mixture was evaporated to dryness. The residue was dissolved in a mixture of THF/Et_2O (1:1) and filtered through Celite. The solution was evaporated to dryness and purified by column chromatography (eluent: THF/*n*-hexane, 6:1 v/v) on silica gel. The two diastereomers were obtained separately; however, sometimes a second chromatography step was necessary for complete separation. Isolation of the diastereomeric atropisomers gave *dia1* (243 mg, 24%) and *dia2* (255 mg, 25%) in a combined overall yield of 49%. The diastereomeric ratio was estimated from the ^{1}H NMR spectra: 1:1.05 (*dia1*:*dia2*).

General Procedure 2: Thermal Conditions (Catalyst 15) with Acetonitrile in THF or Toluene: In a typical experiment, the diyne (*S*)-**12** (380 mg, 1.25 mmol) was dissolved in THF or toluene and acetonitrile (0.33 mL, 6.32 mmol, 5 equiv.) was added by syringe. The solution was cooled to 0 °C and then a solution of **15**[17] (0.063 mmol in 0.57 mL Et_2O) was added. The reaction mixture was warmed to room temp. with stirring and TLC control showed complete conversion after a couple of hours, while the reaction mixture became dark. After the reaction was complete, the solvent was evaporated and the dark residue was charged to silica gel and then purified by repeated flash column chromatography (eluent: THF/*n*-hexane, 6:1, v/v) or by using an automated chromatography system. Isolation of the diastereomeric atropisomers gave *dia1* (154 mg, 36%) and *dia2* (140 mg, 33%) in a combined overall yield of 69%. The diastereomeric ratio was estimated from the crude ^{1}H NMR spectra: 1.13:1 (*dia1*:*dia2*). The yields of optimized reactions using THF were in the same range and differences in the ratio of isolated atropisomers were due to the purification process.

(*S*)-(*aS*)-1-(2-Methoxynaphthalen-1-yl)-3-methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-16 (*dia1*)]: M.p. 105–107 °C. $[\alpha]_D^{22}$ = +113.1 (*c* = 0.273, $CHCl_3$). ^{1}H NMR (400 MHz, 318 K, $CDCl_3$): δ = 7.87 (d, *J* = 9.0 Hz, 1 H), 7.79–7.76 (m, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 7.30–7.24 (m, 2 H), 7.09 (br. d, *J* = 7.4 Hz, 1 H), 6.93 (s, 1 H), 4.16 (d, *J* = –15.5 Hz, 1 H), 3.83 (s, 3 H, -OC*H*$_3$), 3.53 (br. d, *J* = –15.5 Hz, 1 H), 3.29–3.20 (m, 1 H),

2.61–2.53 (m, 1 H), 2.56 (s, 3 H, -CH_3), 2.44–2.24 (m, 2 H), 2.18–2.07 (m, 1 H), 1.94–1.71 (m, 3 H), 1.37–1.25 (m, 1 H) ppm. ^{13}C NMR (100 MHz, 318 K, $CDCl_3$): δ = 155.5, 155.3, 153.8, 144.3, 133.3, 129.9, 129.6, 128.0, 127.9, 126.8, 124.9, 123.8, 123.6, 120.2, 114.1, 61.0, 57.0 (-OCH_3), 55.3, 54.7, 32.1, 30.9, 24.3 (-CH_3), 21.6 ppm. MS (ESI$^+$): *m*/*z* (%) = 345 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{25}N_2O$ [M + H]$^+$ 345.1961; found 345.1967. $C_{23}H_{24}N_2O$ (344.45): calcd. C 80.20, H 7.02, N 8.13; found C 80.57, H 7.18, N 8.27.

(*S*)-(*aR*)-1-(2-Methoxynaphthalen-1-yl)-3-methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aR*)-16 (*dia2*)]: M.p. 118–121 °C. $[\alpha]_D^{22}$ = +150.4 (*c* = 0.195, $CHCl_3$). ^{1}H NMR (300 MHz, 295 K, $CDCl_3$): δ = 7.89 (d, *J* = 9.0 Hz, 1 H), 7.82–7.77 (m, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.18–7.14 (m, 1 H), 6.92 (s, 1 H), 4.19 (d, *J* = –15.7 Hz, 1 H), 3.79 (s, 3 H, -OCH_3), 3.44 (d, *J* = –15.7 Hz, 1 H), 3.29 (ddd, *J* = 8.6, 8.5, 2.1 Hz, 1 H), 2.56 (s, 3 H, -CH_3), 2.39–2.31 (m, 2 H), 2.24–2.13 (m, 2 H), 1.90–1.78 (m, 2 H), 1.77–1.68 (m, 1 H), 1.44–1.31 (m, 1 H) ppm. ^{13}C NMR (75 MHz, 295 K, $CDCl_3$): δ = 155.3, 155.0, 154.3, 144.5, 133.2, 129.8, 129.2, 128.2, 128.0, 126.7, 124.6, 123.5, 122.9, 120.0, 113.6, 60.9, 56.5 (-OCH_3), 55.6, 54.8, 32.3, 30.8, 24.4 (-CH_3), 21.5 ppm. MS (ESI$^+$): *m*/*z* (%) = 345 (100) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{23}H_{25}N_2O$ [M + H]$^+$ 345.1961; found 348.1966. $C_{23}H_{24}N_2O$ (344.45): calcd. C 80.20, H 7.02, N 8.13; found C 80.45, H 7.07, N 7.89.

(*S*)-(*aS*)/(*aR*)-3-Phenyl-1-(2-methylnaphthalen-1-yl)-5,7,8,9,9a,10-hexahydro-pyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-17/(*S*)-(*aR*)-17]: The reaction of the chiral diyne (*S*)-**12** with benzonitrile was performed according to General Procedure 2. Compound (*S*)-**12** (400 mg, 1.32 mmol) and benzonitrile (0.68 mL, 6.6 mmol, 5 equiv.), together with THF (10 mL), were cooled to 0 °C in a Schlenk flask, then a solution of **15** (0.066 mmol in 0.4 mL Et_2O, concentration of the catalyst stock solution: 0.122 mmol mL^{-1}) was added. The reaction mixture was warmed to room temp. and stirring was continued for an additional 15 h. TLC control showed complete conversion. The dark reaction mixture was then evaporated to dryness and chromatographic separation (THF/*n*-hexane, 3:1 v/v) gave both diastereomeric atropisomers (description in the succession of their elution from the chromatography column). Diastereomer 1 was obtained in 42% (223 mg) yield and diastereomer 2 was obtained in 24% (131 mg) yield, providing a total yield of 66% (354 mg).

Diastereomer 1: M.p. 135–137 °C. $[\alpha]_D^{23}$ = –26.2 (*c* = 1.324, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.97 (m, 2 H), 7.94 (d, *J* = 9.0 Hz, 1 H), 7.84 (dd, *J* = 7.0, 2.0 Hz, 1 H), 7.53 (s, 1 H), 7.45–7.29 (m, 6 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 4.31 (d, *J* = –15.6 Hz, 1 H), 3.88 (s, 3 H, -OCH_3), 3.60 (d, *J* = –15.6 Hz, 1 H), 3.37–3.28 (m, 1 H), 2.68 (dd, *J* = –16.4 Hz, 1 H, 3.6 Hz), 2.45–2.13 (m, 3 H), 2.01–1.74 (m, 3 H), 1.42–1.27 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1, 154.8, 153.7, 144.8, 139.9, 133.2, 129.9, 129.8, 129.4, 128.6, 128.5, 127.9, 127.2, 126.8, 124.9, 123.8, 123.6, 117.7, 114.0, 60.8, 57.0, 55.8, 54.7, 32.5, 30.9, 21.5 ppm. MS (EI, GC–MS): *m*/*z* (%) = 406 (100) [M]$^+$, 405 (81), 363 (17), 336 (23), 322 (87), 306 (32). HRMS (ESI): calcd. for $C_{28}H_{27}N_2O$ [M + H]$^+$ 407.2118; found 407.2123.

Diastereomer 2: M.p. 99–102 °C. $[\alpha]_D^{23}$ = +162.8 (*c* = 0.458, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.90 (m, 2 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.80–7.76 (m, 1 H), 7.43 (s, 1 H), 7.36–7.24 (m, 6 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 4.26 (d, *J* = –15.6 Hz, 1 H), 3.76 (s, 3 H, -OCH_3), 3.51 (d, *J* = –15.6 Hz, 1 H), 3.30–3.24 (m, 1 H), 2.44 (dd, *J* = –16.5, 10.8 Hz, 1 H), 2.34 (dd, *J* = –16.5, 3.6 Hz, 1 H), 2.26–2.14 (m, 2 H), 1.89–1.66 (m, 3 H), 1.43–1.32 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 154.6, 154.5, 144.7, 139.9, 133.4, 130.1, 130.0, 129.3, 128.6, 128.5, 128.1, 127.2, 126.7, 124.8, 123.6, 123.1, 117.5, 113.8, 60.9, 56.6, 55.7, 54.8, 32.4, 30.9, 21.6 ppm. MS (EI, GC–MS): *m*/*z* (%) = 406 (100) [M]$^+$, 405 (77), 363 (15), 336 (20), 322 (86), 306 (33). HRMS (ESI): calcd. for $C_{28}H_{27}N_2O$ [M + H]$^+$ 407.2118; found 407.2116.

(*S*)-(*aS*)/(*aR*)-3-(2-Fluorophenyl)-1-(2-methylnaphthalen-1-yl)-5,7,8,9,9a,10-hexahydro-pyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-18/(*S*)-(*aR*)-18]: The reaction of the chiral diyne (*S*)-**12** with 2-fluorobenzonitrile was performed according to General Procedure 2. Compound (*S*)-**12** (600 mg, 1.98 mmol) and 2-fluorobenzonitrile (1.07 mL, 10.89 mmol, 5.5 equiv.), together with THF (15 mL), were cooled to 0 °C in a Schlenk flask and a solution of **15** (0.099 mmol in 0.6 mL Et_2O, concentration of the catalyst stock solution: 0.165 mmol mL^{-1}) was added. The reaction mixture was warmed to room temp. and stirring was continued for an additional 15 h. TLC control showed complete conversion. The dark reaction mixture was then evaporated to dryness and chromatographic separation (THF/*n*-hexane, 3:1 v/v) gave both diastereomeric atropisomers (separated by chromatography column). Diastereomer 1 was obtained in 26% (215 mg) yield and diastereomer 2 was obtained in 18% (148 mg) yield, providing a total yield of 44% (363 mg). Later crystals of diastereomer 2 were obtained from evaporation of a solution in $CDCl_3$ and the absolute configuration of the biaryl axis was determined to be (*aR*). Therefore, diastereomer 1 was defined as (*S*)-(*aS*)-**18** and diastereomer 2 was (*S*)-(*aR*)-**18**.

(*S*)-(*aS*)-3-(2-Fluorophenyl)-1-(2-methylnaphthalen-1-yl)-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-18]: M.p. 111–112 °C. $[\alpha]_D^{22}$ = –20.9 (*c* = 0.546, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.91 (m, 1 H), 7.93 (d, *J* = 9.0 Hz, 1 H), 7.84–7.81 (m, 1 H), 7.60 (d, *J* = 2.1 Hz, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H), 7.34–7.27 (m, 3 H), 7.20–7.09 (m, 3 H), 4.30 (d, *J* = –15.6 Hz, 1 H), 3.87 (s, 3 H, -OCH_3), 3.65 (d, *J* = –15.6 Hz, 1 H), 3.30 (t, *J* = 8.5 Hz, 1 H), 2.69 (dd, *J* = –16.4, 3.8 Hz, 1 H), 2.54–2.30 (m, 2 H), 2.21 (dd, *J* = –16.4, 10.4 Hz, 1 H), 2.02–1.74 (m, 3 H), 1.42–1.29 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 153.7, 150.6, 144.2, 133.2, 131.7, 130.1 (d, *J* = 3.2 Hz), 130.0, 129.9, 129.4, 128.0, 126.9, 124.8, 124.5 (d, *J* = 3.7 Hz), 123.8, 123.2, 121.6 (d, *J* = 8.5 Hz), 116.2, 115.9, 113.8, 60.8, 56.9, 55.5, 54.7, 32.3, 30.9, 21.6 ppm (not all carbon resonances detected). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.7 ppm. MS (EI, GC–MS): *m*/*z* (%) = 424 (100) [M]$^+$, 423 (89), 381 (22), 354 (23), 340 (83), 324 (33). HRMS (ESI): calcd. for $C_{28}H_{26}FN_2O$ [M + H]$^+$ 425.2024; found 425.2029.

(*S*)-(*aR*)-3-(2-Fluorophenyl)-1-(2-methylnaphthalen-1-yl)-5,7,8,9,9a,10-hexahydro-pyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aR*)-18]: M.p. 117–118 °C. $[\alpha]_D^{24}$ = +161.0 (*c* = 0.436, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 8.0, 2.1 Hz, 1 H), 7.93 (d, *J* = 9.1 Hz, 1 H), 7.86–7.81 (m, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 7.37 (d, *J* = 9.1 Hz, 1 H), 7.37–7.27 (m, 4 H), 7.18–7.09 (m, 2 H), 4.33 (d, *J* = –15.7 Hz, 1 H), 3.83 (s, 3 H, -OCH_3), 3.59 (d, *J* = –15.7 Hz, 1 H), 3.33 (t, *J* = 7.6 Hz, 1 H), 2.59–2.19 (m, 4 H), 1.98–1.74 (m, 3 H), 1.53–1.37 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 154.4, 150.3, 133.2, 131.9, 131.6 (d, *J* = 3.0 Hz), 130.4, 130.0, 129.8 (d, *J* = 8.7 Hz), 129.2, 128.0, 126.7, 124.6, 124.4 (d, *J* = 3.2 Hz), 123.6, 122.7, 121.4, 121.3 (d, *J* = 8.5 Hz), 116.1, 115.8, 113.6, 60.7, 56.5, 55.5, 54.7, 32.2, 30.7, 21.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.9 ppm. MS (EI, GC–MS): *m*/*z* (%) = 424 (100) [M]$^+$, 423 (85), 381 (20), 354 (23), 340 (80), 324 (33). HRMS (ESI): calcd. for $C_{28}H_{26}FN_2O$ [M + H]$^+$ 425.2024; found 425.2029.

(*S*)-(*aS*)-3-Methyl-1-(2-methylnaphthalen-1-yl)-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-19]: Compound (*S*)-

(*aS*)-(**16**) (100 mg, 0.29 mmol) and $[NiCl_2(PCy_3)_2]$ (20 mg, 0.029 mmol, 10 mol-%) were weighed into a secured Schlenk flask, then the air was evacuated and back-filled with argon three times. Afterwards toluene (10 mL) was added and finally a solution of methylmagnesium bromide (0.85 mL, 1.19 mmol, 1.4 M, toluene/THF, 3:1 v/v) was added by syringe. The reaction mixture became dark brown–red and was stirred for 19 h at 90 °C. After cooling to room temp., the mixture was quenched with a saturated aqueous solution of Na_2CO_3 and extracted several times with CH_2Cl_2. The combined organic phases were washed with water and brine and dried with Na_2SO_4. After removal of the solvent and all volatile compounds, the residue was purified by column chromatography on silica gel, using THF/*n*-hexane (3:1 v/v) as the eluent. One main fraction was obtained, yielding product (*S*)-(*aS*)-**18** (60 mg, 63%) as an oily solid. $[\alpha]_D^{23}$ = +48.2 (*c* = 0.437, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.78 (m, 1 H), 7.80 (d, *J* = 8.4 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.38 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1 H), 7.29 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 6.99 (br. s, 1 H), 4.24 (d, *J* = –15.7 Hz, 1 H), 3.57 (d, *J* = –15.7 Hz, 1 H), 3.35–3.25 (m, 1 H), 2.58 (s, 3 H, -CH_3), 2.48–2.37 (m, 2 H), 2.25–2.16 (m, 2 H), 2.17 (s, 3 H, -CH_3), 1.96–1.74 (m, 3 H), 1.38–1.26 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 155.7, 151.4, 144.1, 135.8, 129.1, 128.7, 128.2, 128.0, 127.9, 126.8, 126.4, 125.3, 125.0, 120.1, 60.1, 55.1, 54.6, 31.0, 30.6, 24.3 (-*C*H_3), 21.5, 20.1 (-*C*H_3) ppm. MS (EI, GC–MS): *m*/*z* (%) = 328, (97) $[M]^+$, 327 (100) $[M^+ - H]$, 285 (35), 258 (40), 244 (52). HRMS (ESI): calcd. for $C_{23}H_{25}N_2$ $[M + H]^+$ 329.2012; found 329.2008.

(*S*)-(*aS*)/(*aR*)-1-(2-Methoxymethoxynaphthalen-1-yl)-3-methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-20 (*dia1*)/(*S*)-(*aR*)-20 (*dia2*)]. Thermal Conditions: The reaction of the chiral diyne (*S*)-**13** with acetonitrile was performed according to General Procedure 2. Compound (*S*)-**13** (1.0 g, 2.99 mmol) and acetonitrile (0.79 mL, 15.0 mmol, 5 equiv.), together with THF (20 mL), were cooled to 0 °C in a Schlenk flask and a solution of **15** (0.15 mmol in 1 mL Et_2O, concentration of the catalyst stock solution: 0.153 mmol mL^{-1}) was added. The reaction mixture was warmed to room temp. and stirring was continued for a further 2 h at room temp. and then for 14 h at 45 °C. Then the reaction mixture was allowed to cool to room temp. and additional catalyst **15** (0.06 mmol in 0.4 mL Et_2O) was added. After 2 h at room temp., TLC control showed complete disappearance of (*S*)-**13**. The dark reaction mixture was then evaporated to dryness and chromatographic separation (THF/*n*-hexane, 3:1 v/v) gave both diastereomeric atropisomers (separated by chromatography column). The *dia1* was obtained in 19% (192 mg) yield and *dia2* was obtained in 18% (190 mg) yield, providing a total yield of 37% (382 mg).

Photochemical Conditions: The photochemical reaction was performed according to General Procedure 1 by reacting the chiral diyne (*S*)-**13** (500 mg, 1.50 mmol) and acetonitrile (0.4 mL, 7.45 mmol, 5 equiv.) together with **14** (17.4 mg, 0.074 mmol) in a thermostated (25 °C) Schlenk reactor. The reactor was radiated for 17 h, after which time the starting material has disappeared. Usual workup and separation by chromatography under the conditions mentioned before (eluent: THF/*n*-hexane, 3:1 v/v) yielded *dia1* (127 mg, 23%) and *dia2* (135 mg, 24%) in a combined overall yield of 47%.

The configuration of the diastereomers could be assigned by comparison of the CD spectra with those of compound **16**. Therefore, *dia1* was identified to be (*S*)-(*aS*)-**20** and *dia2* was identified as (*S*)-(*aR*)-**20**.

(*S*)-(*aS*)-1-(2-Methoxymethoxynaphthalen-1-yl)-3-methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aS*)-20 (*dia1*)]: $[\alpha]_D^{22}$ = +18.3 (*c* = 1.093, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 9.0 Hz, 1 H), 7.81 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 1 H), 7.36–7.24 (m, 2 H), 7.11 (br. d, *J* = 8.2 Hz, 1 H), 6.96 (s, 1 H), 5.22 (d, *J* = 6.7 Hz, 1 H, -OCH_2-), 5.10 (d, *J* = 6.7 Hz, 1 H, -OCH_2-), 4.21 (d, *J* = –15.7 Hz, 1 H), 3.49 (br. d, *J* = –15.7 Hz, 1 H), 3.34 (s, 3 H, -OCH_3), 3.32–3.24 (m, 1 H), 2.66–2.57 (m, 1 H), 2.56 (s, 3 H, -CH_3), 2.37–2.07 (m, 3 H), 1.97–1.69 (m, 3 H), 1.39–1.24 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 155.3, 151.3, 144.0, 133.0, 130.1, 129.9, 128.0, 127.7, 126.9, 125.0, 124.6, 124.4, 120.3, 116.9, 95.4 (-O*C*H_2-), 60.9, 56.4 (-O*C*H_3), 56.2, 54.7, 32.2, 30.8, 24.3 (-*C*H_3), 21.6 ppm. MS (EI, GC–MS): *m*/*z* (%) = 374 (61) $[M]^+$, 329 (100), 260 (31), 45 (25). HRMS (EI): calcd. for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1989; found 374.1986.

(*S*)-(*aR*)-1-(2-Methoxymethoxynaphthalen-1-yl)-3-methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]naphthyridine [(*S*)-(*aR*)-20 (*dia2*)]: $[\alpha]_D^{24}$ = +76.7 (*c* = 0.952, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.0 Hz, 1 H), 7.84–7.79 (m, 1 H), 7.50 (d, *J* = 9.0 Hz, 1 H), 7.37–7.28 (m, 2 H), 7.19–7.15 (m, 1 H), 6.94 (s, 1 H), 5.10 (s, 2 H, -OCH_2-), 4.21 (d, *J* = –15.7 Hz, 1 H), 3.47 (d, *J* = –15.7 Hz, 1 H), 3.33 (s, 3 H, -OCH_3), 3.31–3.25 (m, 1 H), 2.56 (s, 3 H, -CH_3), 2.50–2.32 (m, 2 H), 2.31–2.14 (m, 2 H), 1.94–1.70 (m, 3 H), 1.46–1.31 (m, 1 H) ppm. ^{13}C NMR (75 MHz, 295 K, $CDCl_3$): δ = 155.1, 154.9, 152.3, 144.4, 133.1, 130.1, 129.8, 128.2, 128.0, 126.6, 124.8, 124.7, 124.1, 120.0, 117.1, 95.5 (-O*C*H_2-), 60.9, 56.2 (-O*C*H_3), 55.5, 54.8, 32.3, 30.9, 24.3 (-*C*H_3), 21.5 ppm. MS (EI, GC–MS): *m*/*z* (%) = 374 (61) $[M]^+$, 329 (100), 260 (32), 45 (25). HRMS (EI): calcd. for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1989; found 374.1985.

(*S*)-(*aS*)-1-(3-Methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]-naphthyridin-1-yl)naphthalen-2-ol [(*S*)-(*aS*)-21]: For hydrolysis of the MOM groups, compound (*S*)-(*aS*)-**20** (110 mg, 0.29 mmol) was dissolved in THF (40 mL) and methanol (40 mL) and finally conc. HCl (3.7 mL) was added by pipette. The reaction mixture was stirred at room temp. for 16 h and then quenched with a saturated aqueous solution of $NaHCO_3$ until the aqueous phase was slightly basic. The mixture was extracted with CH_2Cl_2 several times and the combined organic phases were dried with Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent: THF/*n*-hexane, 3:1 v/v), yielding the product as an oily solid (66 mg, 69%). Additionally, a small amount of starting material was recovered (10 mg, 9%). $[\alpha]_D^{22}$ = +296.4 (*c* = 0.938, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 1 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 7.31–7.21 (m, 2 H, H), 7.04 (br. d, *J* = 7.4 Hz, 1 H), 6.88 (s, 1 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 4.21 (d, *J* = –16.1 Hz, 1 H), 3.43 (d, *J* = –16.1 Hz, 1 H), 3.27 (ddd, *J* = 9.6, 8.5, 2.1 Hz, 1 H), 2.54 (m, 1 H), 2.31 (s, 3 H, -CH_3), 2.25–2.09 (m, 3 H), 1.90–1.66 (m, 3 H), 1.35–1.22, (m, 1, H) (O*H* resonance was not observed) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 154.3, 152.0, 146.4, 132.5, 130.0, 129.3, 128.9, 127.9, 126.3, 124.3, 123.1, 120.5, 120.3, 119.7, 60.8, 55.7, 54.8, 32.7, 30.7, 23.1 (-*C*H_3), 21.5 ppm. MS (EI, GC–MS): *m*/*z* (%) = 330 (72) $[M]^+$, 315 (40), 287 (49), 260 (100), 232 (44). HRMS (ESI): calcd. for $C_{22}H_{23}N_2O$ $[M + H]^+$ 331.1805; found 331.1806.

(*S*)-(*aR*)-1-(3-Methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]-naphthyridin-1-yl)naphthalen-2-ol [(*S*)-(*aR*)-21]: Diastereomer (*S*)-(*aR*)-**20** was deprotected as described before: compound (*S*)-(*aR*)-**20** (85 mg, 0.23 mmol) was dissolved in THF (40 mL) and methanol (40 mL) and finally conc. HCl (3.0 mL) was added by pipette. The reaction time and workup were identical to those described for (*S*)-(*as*)-**20**. The oily product was obtained in 60% yield (45 mg). Additionally, a small amount of starting material was recovered

(17 mg, 20%). $[\alpha]_D^{22}$ = +43.5 (*c* = 0.896, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 6.2, 3.3 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.32–7.25 (m, 2 H), 7.10–7.03 (m, 1 H), 6.83 (s, 1 H), 6.44 (d, *J* = 8.8 Hz, 1 H), 4.15 (d, *J* = –15.9 Hz, 1 H), 3.41 (d, *J* = –15.9 Hz, 1 H), 3.26 (ddd, *J* = 9.5, 8.6, 2.2 Hz, 1 H), 2.51–2.30 (m, 2 H), 2.26 (s, 3 H, -C*H*$_3$), 2.21–2.11 (m, 2 H), 1.89–1.65 (m, 3 H), 1.43–1.29 (m, 1 H) (O*H* resonance was not observed) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 154.3, 152.5, 146.0, 132.9, 129.9, 129.4, 129.0, 127.9, 126.3, 124.0, 123.0, 120.6, 120.4, 120.1, 60.8, 55.5, 54.8, 31.7, 30.7, 23.1 (-*C*H$_3$), 21.4 ppm. MS (EI, GC–MS): *m*/*z* (%) = 330 (73) $[M]^+$, 315 (42), 287 (50), 260 (100), 232 (44). HRMS (ESI^+): calcd. for $C_{22}H_{23}N_2O$ $[M + H]^+$ 331.1805; found 331.1805.

(*S*)-(*aX*)-1-(3-Methyl-5,7,8,9,9a,10-hexahydropyrrolo[1,2-*b*][2,6]-naphthyridin-1-yl)naphthalen-2-yl trifluoromethanesulfonate [(*S*)-(*aR*)-22]: Diastereomer (*S*)-(*aR*)-**21** (130 mg, 0.39 mmol) was secured in a Schlenk flask and dissolved in CH_2Cl_2 (4.5 mL) and Et_3N (0.54 mL, 3.9 mmol). The solution was cooled to –20 °C and trifluromethanesulfonic anhydride (0.11 mL, 0.59 mmol) was added by syringe. The reaction mixture was stirred for 15 min at –20 °C and then for 1 h at 0 °C. Afterwards the mixture was warmed to room temp. and then quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 several times. The combined organic phases were dried with Na_2SO_4 and the solvent was evaporated. Column chromatography on silica gel (eluent: THF/ethyl acetate, 3:1 v/v + 1% Et_3N) gave the pure product as a viscous oil (87 mg, 48% yield). $[\alpha]_D^{24}$ = +12.0 (*c* = 0.915, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.0 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.54 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.50 (d, *J* = 9.0 Hz, 1 H), 7.47 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 7.01 (s, 1 H), 4.23 (d, *J* = –15.9 Hz, 1 H), 3.47 (d, *J* = –15.9 Hz, 1 H), 3.28 (dd, *J* = 8.4, 2.1 Hz, 1 H), 2.57 (s, 3 H, -C*H*$_3$), 2.36–2.31 (m, 2 H), 2.26–2.18 (m, 2 H), 1.92–1.80 (m, 2 H), 1.78–1.69 (m, 1 H), 1.41–1.32 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.4, 145.5, 144.9, 132.7, 132.4, 130.7, 130.4, 128.4, 128.2, 127.9, 127.1, 126.0, 121.2, 119.8, 118.4 (*C*F$_3$, $J_{C,F}$ = 320 Hz), 60.6, 55.5, 54.7, 32.2, 30.7, 24.0 (-*C*H$_3$), 21.4 ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –73.9 ppm. MS (ESI^+): *m*/*z* (%) = 462 (21) $[M]^+$, 329 (100), 260 (34), 243 (19). HRMS (ESI^+): calcd. for $C_{23}H_{22}F_3N_2O_3S$ $[M + H]^+$ 463.1298; found 463.1297.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization of **8**, copies of ^1H and ^{13}C spectra of all relevant compounds, and CD spectra of **16** and **20**.

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[20] CCDC-847945 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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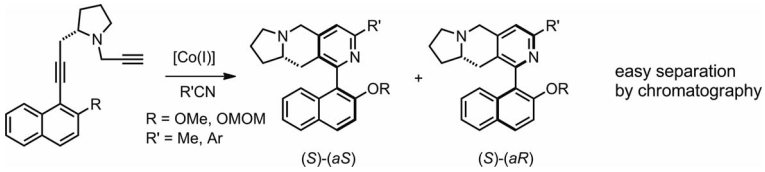
[2+2+2] Cyclotrimerization



The cobalt-catalyzed [2+2+2] cycloaddition of chiral diynes with different nitriles under very mild conditions led to the formation of pairs of diastereomeric biaryl atropisomers in one step. These diastereomers can easily be separated by column chromatography to provide the pure single atropisomers. The 2-position of the naphthyl ring can further be functionalized.

Keywords: Homogeneous catalysis / Cobalt / Cycloaddition / Cyclotrimerization / Atropisomerism / Biaryls / Alkynes

