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Synthesis of Naphthylpyridines from Unsymmetrical Naphthylheptadiynes and the Configurational Stability of the Biaryl Axis

Fabian Fischer,[†] Alexander F. Siegle,[∥] Marek Checinski,[§] Christine Fischer,[†] Karolin Kral,[†] Richard Thede,[⊥] Oliver Trapp,[∥] and Marko Hapke*[,†,‡]

[†]Leibniz-Institut für Katalyse e.V. an der Universität Rostock (LIKAT), Albert-Einstein-Straße 29a, D-18059 Rostock, Germany

[‡]Johannes Kepler Universität Linz, Institut für Katalyse, Altenberger Straße 69, A-4040 Linz, Austria

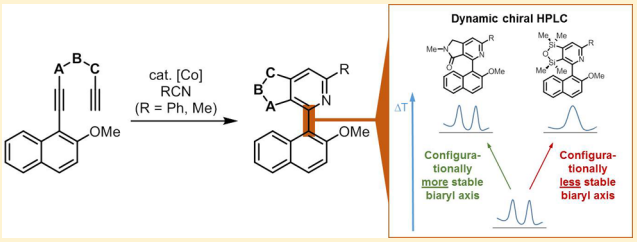
[§]CreativeQuantum GmbH (Adlershof), Wegedornstrasse 32, D-12524 Berlin, Germany

[⊥]Institut für Biochemie, Universität Greifswald, Felix-Hausdorff-Straße 4, D-17487 Greifswald, Germany

[∥]Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Supporting Information

ABSTRACT: A series of different unsymmetrically substituted naphthyl-based diynes were synthesized. These substrates formed the foundation for the assembly of novel biaryls containing pyridine moieties with differently substituted five-membered rings in the backbone of the newly formed heterobiaryl system. The key step for their efficient construction was the photo- and cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction between the corresponding naphthyldiyne and aceto- or benzonitrile. The heterobiaryl products have been isolated and investigated with respect to the configurational stability of their biaryl axis using dynamic chiral HPLC; subtle effects of the substitution pattern on the stability of the axis were observed. For several compounds the activation barriers ($\Delta G^{\ddagger}$) of racemization were determined. Suitable substitution of the five-membered ring backbone exemplarily allowed the Co-catalyzed enantioselective cyclization to yield the enantiomerically enriched heterobiaryl.



INTRODUCTION

The connecting axis between two aromatic ring systems, simply referred to as the biaryl axis, belongs to the most fascinating structural and stereochemical features of biaryl compounds.[1] The biaryls comprise a steadily expanding class of compounds and represent a structural motif found in numerous natural products[2] as well as in ligand systems used for catalysis.[3] Recently, atropisomers and the configurational stability of the chiral axes have gained increasing attention in medicinal chemistry due to the fact that atropisomers can play a significant structural role in drug potency, which might be an often overlooked phenomenon.[4] The development of efficient synthetic methodologies for the asymmetric assembly of biaryls has become a flourishing area of synthetic organic chemistry over the past decade. In addition to strategies utilizing chiral auxiliaries to induce stereoselectivity during formation of the biaryl axis, direct asymmetric coupling methodologies of two aryl fragments or the stereoselective synthesis of one moiety in the atropisomers have found great interest.[5] For the direct asymmetric coupling methods, enantioselective oxidative coupling, as well as cross-coupling reactions such as enantioselective Suzuki−Miyaura reactions are worth mentioning.[6,7] Over the past decade de novo construction of chiral arene systems by cycloaddition approaches has attained considerable interest and especially [2 + 2 + 2] cycloaddition reactions have matured from the reports of single examples with preformed stereocenters into a methodology using chiral transition metal complexes for the assembly of chiral biaryl frameworks from achiral substrates.[8]

We have investigated the use of chiral Co(I)-complexes for the photochemical, enantioselective [2 + 2 + 2] cycloaddition reaction of 1-naphthyldiynes with different nitriles, providing enantioselective access to substituted biaryls possessing a tetrahydroisoquinoline fragment.[9] During our studies it was established that the size of the spacer between the two alkyne bonds in the substrate, which later defines the size of the saturated backbone ring annulated to the newly formed pyridine ring, obviously plays a significant role in both the reactivity and selectivity of the cyclization reaction. Biaryls with newly formed six-membered rings in the backbone of the pyridine were obtained in good yields and enantioselectivities, while biaryls with five-membered ring in the backbones were only obtained as racemates. At first glance, the reason for the lack of selectivity might be assigned to obvious structural parameters of the product, such as the size of the annulated five-membered ring, providing significantly less steric hindrance compared to a six-

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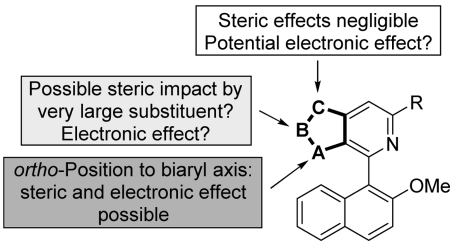
membered ring. Investigations published so far on pyridine-containing heterobiaryls most often utilize isoquinoline moieties, leading to rather stable heterobiaryls. For some of these systems, the free activation energy barrier has been determined with different methodologies.[10]

We were interested in studying the configurational stability of the biaryl axis in molecules of the general structure shown in Scheme 1 and how this stability can be influenced by substituents

Scheme 1. Effect of Backbone Substituents on the Stability of the Biaryl Axis of Naphthylpyridines



on the five-membered ring. In view of the large application of biaryl systems such a systematic examination might also be generally interesting for the conceptual design of new biaryl systems. In addition, such an investigation into the backbone modification offers a higher degree of structural variability than functionalization of the pyridine N atom in the *ortho*-position, which is usually restricted to oxidation (N-oxide) or alkylation. The dynamic stereochemical behavior of such structures can be studied with a variety of chromatographic methods, e.g., enantioselective dynamic HPLC or gas chromatography. These studies aim to reveal the impact of small structural variations in the backbone ring on the stability of the biaryl axis under mild and accessible conditions. The selection of the 2-methoxynaphthalin backbone resulted from our experience in previous studies and the easy access to key intermediates for the synthesis of the required derivatives. In addition, the naphthyl moiety is a very common component of numerous biaryl systems. We were also retaining the pyridine core due to the obvious importance of the pyridine backbone substitution for the configurational stability and therefore to elicit the impact of different structural changes for so far unknown five-membered ring derivatives in contrast to usually investigated isoquinoline derivatives.

The influence of substitution in the backbone of the pyridine ring on the configurational stability of the biaryl axis can generally be envisioned in different ways (Scheme 1). These substitution effects, however, should be clearly distinguishable. Certainly, the functionalization of the *ortho*-position (**A** in Scheme 1) has the most essential steric, and potentially electronic, impact on the stability of the biaryl axis, as it is already textbook knowledge. Even smaller substituents here should have an observable effect on the stability. Position **B** should be much less important for administering stability to the chiral axis. Finally, the introduction of substituents in position **C** will obviously have no steric influence due to its remote position in the backbone, but potentially have a possible electronic factor.

In the present study we set out to investigate the steric effect of substitution in the **A** position, neighboring the pyridine ring as well as an exemplarily look into an electronic effect of different groups in the **C** position. This synthetic endeavor requires the efficient assembly of a range of differently functionalized diynes for the first time. These diynes will be substrates for the synthesis of the corresponding heterobiaryls by applying [2 + 2 + 2] cycloadditions as the key reaction step. Subsequent studies regarding the stereochemical features of the biaryl axis will provide the required information about the configurational stability.

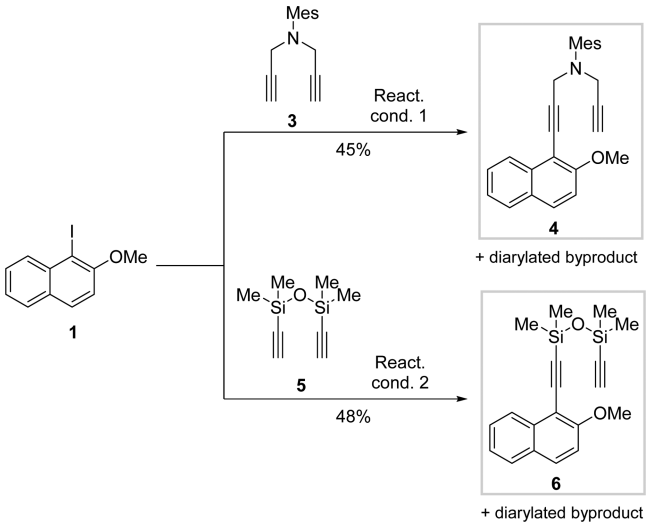
RESULTS AND DISCUSSION

Synthesis of the Substituted Unsymmetrical Diynes. To study the steric effects of potential substituents, an array of differently and unsymmetrically substituted diynes as precursor molecules for the cyclization reaction were prepared. The preparation of arylalkynes is a highly efficient synthetic methodology, usually following the Sonogashira protocol.[11] Unfortunately, when it comes to the coupling of aryl halides with diynes, selectivity issues begin to have an effect on the reaction outcome, usually leading to both mono- and bisarylation. The coupling of unsymmetrical terminal diynes also faces potential selectivity issues due to the fact that in the Sonogashira reaction more electron-rich alkyne groups are usually coupled preferentially. Therefore, the synthetic pathways for unsymmetrical diynes follow a stepwise construction approach, to allow the incorporation of a variety of various functionalities like methyl, carbonyl, malonyl or alkenyl groups, which later constitute the **A** position substituent.

Common synthethic starting materials for our purposes are 1-iodo-2-methoxynaphthalene (**1**) or the derived 1-ethinyl-2-methoxynaphthalene (**2**).[9b] The direct synthesis of monoarylated diynes using symmetrical terminal diyne precursor molecules and aromatic halides like **1** generally uses the Sonogashira protocol. The monoarylation reaction of **1** with 2,4,6-trimethyl-*N*,*N*-di(prop-2-ynyl)aniline (**3**) or 1,3-diethynyltetramethyldisiloxane (**5**) is exemplified in Scheme 2.

Compared to often high-yielding Sonogashira reactions without selectivity issues, the isolated yields for biaryls **4** and **6**

Scheme 2. Synthesis of the Monoarylated Diynes 4 and 6 by Sonogashira Reaction of 1 with Diynes 3 (Mes = 2,4,6-Trimethylphenyl) or 5[a]



[a]The isolated yields are shown. Reaction condition 1: 2,4,6-Trimethyl-*N*,*N*-di(prop-2-ynyl)aniline (**3**, 3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI (15 mol %), THF, Et_3N, 50 °C, 14 h. Reaction condition 2: 1,3-Diethynyltetramethyldisiloxane (**5**, 2.0 equiv), $Pd_2dba_3{\cdot}CHCl_3$ (6 mol %), CuI (15 mol %), dppf (1,1′-bis(diphenylphosphino)ferrocene, 6.5 mol %), THF, 45 °C, 24 h.

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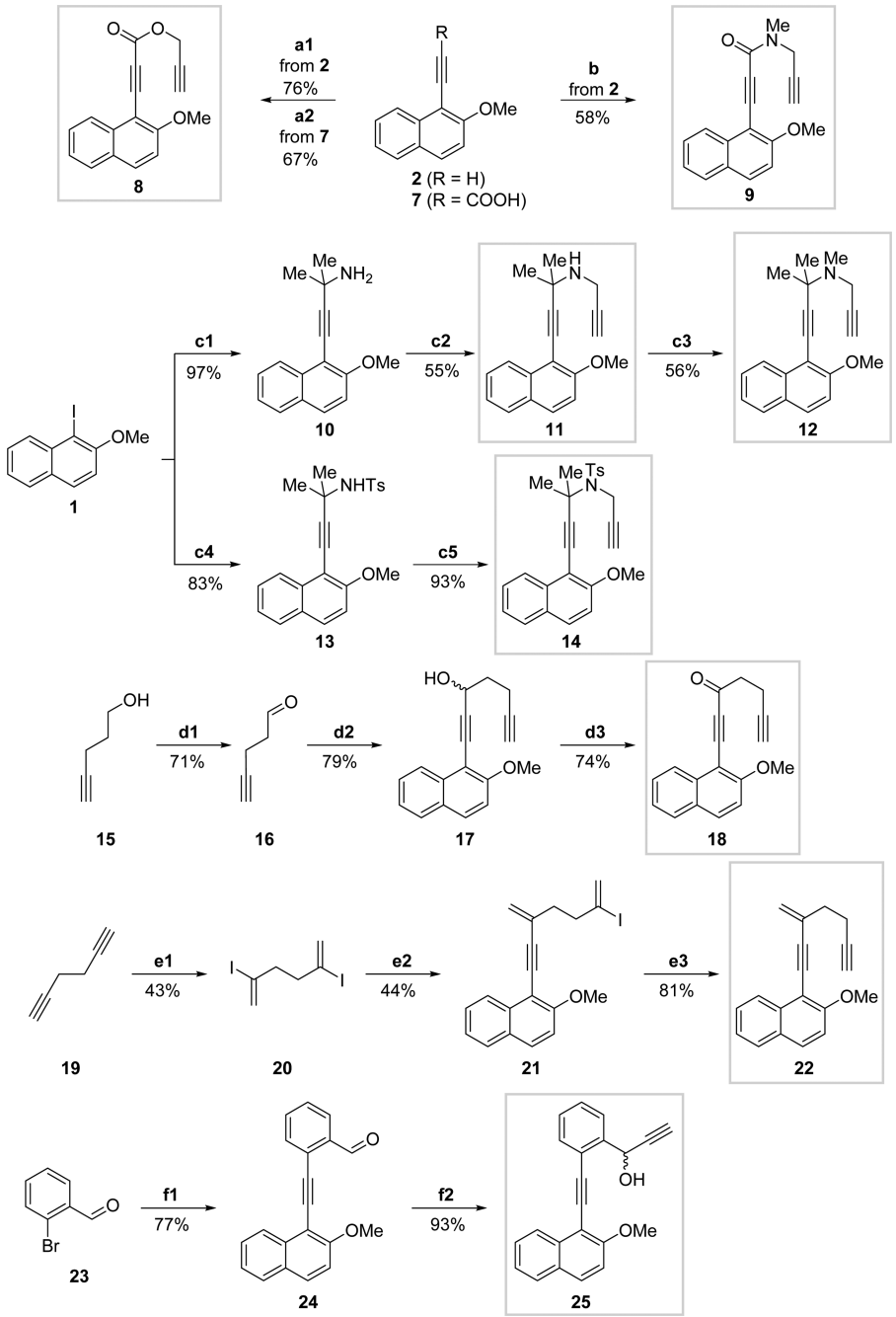
Scheme 3. Synthesis of the Diynes 8, 9, 11, 12, 14, 18, 22 and 25 with Unsymmetrical Backbones by Stepwise Construction[a]



[a]The given yields are isolated yields. Conditions and reagents: (**a1**) Alkyne **2**, *n*-BuLi, −78 °C, 0 °C, then −78 °C, addition of propargyl chloroformate, 0 °C to rt. (**a2**) Propargyl alcohol, DMAP (4-dimethylaminopyridine), DCC (*N*,*N*′-dicyclohexylcarbodiimide), CH_2Cl_2, 0 °C, then rt. (**b**) *n*-BuLi, THF, −78 °C, then rt for 30 min, then −78 °C, methyl(prop-2-ynyl)carbamic chloride, rt. (**c1**) 2-Methylbut-3-yn-2-amine, $Pd(PPh_3)_4$ (2 mol %), CuI (6 mol %), Et_3N, 55 °C, 14 h. (**c2**) K_2CO_3, DMF, propargyl bromide, 100 °C, 18 h. (**c3**) K_2CO_3, DMF, MeI, 80 °C, 24 h. (**c4**) 4-Methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide, $Pd(PPh_3)_4$ (5 mol %), $ZnCl_2$ (20 mol %), I_2 (cat.), piperidine, 65 °C, 20 h. (**c5**) NaH, DMF, rt, 1h, then propargyl bromide, rt, 16 h. (**d1**) Et_3N, DMSO, $(COCl)_2$, −78 °C, then rt. (**d2**) Alkyne **2**, *n*-BuLi, −78 °C, 0 °C, then −78 °C, addition of 16, rt. (**d3**) Dess−Martin periodinane, CH_2Cl_2, rt. (**e1**) NaI, CH_3CN, TMSCl, H_2O, rt, 15 min; 1,5-hexadiyne, CH_3CN, rt, 16 h. (**e2**) $Pd(PPh_3)_4$ (4.8 mol %), CuI (4.9 mol %), alkyne **2**, *i*-Pr_2NH, rt, 4 h. (**e3**) DMF, 0 °C, then NaHMDS soln. (0.6 M), 10 min. (**f1**) Alkyne **2**, $PdCl_2(PPh_3)_2$ (3.8 mol %), CuI (7.6 mol %), Et_3N, 50 °C, 36 h. (**f2**) Trimethylsilylacetylene, *n*-BuLi, 78 °C, rt for 75 min, then −78 °C, addition of **24**, −78 °C to rt, workup; then MeOH/THF (1:1), KF (6 equiv), rt, 16 h.

are rather low, resulting from the significant formation of the diarylated products (not shown). This problem can generally be circumvented by a protection−cross-coupling−deprotection approach, as it has been demonstrated for other symmetrical diynes.[12]

The synthesis of diynes with unsymmetrical backbones poses greater synthetic challenges caused by the need to construct the diyne backbone stepwise. Initial investigations into the possibility of the selective Sonogashira coupling of **1** with unsymmetrically substituted diynes did not prove to be a useful route to obtain

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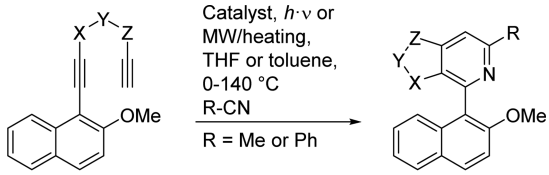
Table 1. Synthesis of the Heterobiaryls by Photo- and Co(I)-catalyzed [2 + 2 + 2] Cycloaddition Reaction of Diynes with Nitriles



4, **6**, **8**, **9**, **11**, **12**, **14**, **18**, **22**, **25** → (*rac*)-**26**-**37**

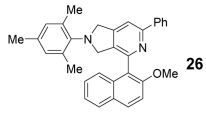
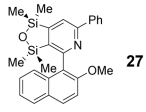
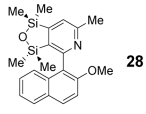
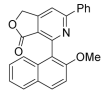
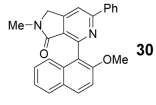
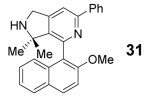
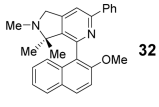
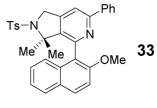
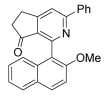
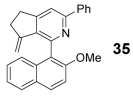
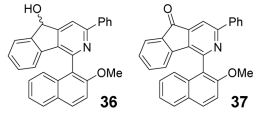
Entry	Diyne	Nitrile	Biaryl	Conditions	Yield [a]
1	**4**	PhCN	 **26**	Cat: [CpCo(COD)] THF, *h*·ν, 0 °C	43%
2	**6**	PhCN	 **27**	Cat: [CpCo(COD)] THF, *h*·ν, 0 °C	44%
3	**6**	MeCN	 **28**	Cat: [CpCo(COD)] THF, *h*·ν, 0 °C	93%
4	**8**	PhCN	 **29**	Cat: [CpCo(COD)] THF, *h*·ν, 25 °C	39% (21%[b])
5	**9**	PhCN	 **30**	Cat: [CpCo(COD)] THF, *h*·ν, 25 °C	42%
6	**11**	PhCN	 **31**	Cat: [CpCo(COD)] THF, *h*·ν, 25 °C	62%
7	**12**	PhCN	 **32**	Cat: [CpCo(COD)] THF, *h*·ν, 25 °C	35%
8	**14**	PhCN	 **33**	Cat: [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] Toluene, MW, 140 °C	71%[b]
9	**18**	PhCN	 **34**	Cat: [CpCo(COD)] THF, *h*·ν, 25 °C	70%
10	**22**[b]	PhCN	 **35**	Cat: [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] Toluene, 100 °C	56%[c]
11	**25**[b]	PhCN	 **36** **37**	Cat: [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] Toluene, MW, 140 °C	14% (**36**); 43% (**37**) [b,d]

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Table 1. continued

[a]Isolated yields. [b]The cycloaddition was performed under microwave conditions at 140 °C in toluene with [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] as catalyst. [c]The cycloaddition was performed at 100 °C in toluene with [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] as catalyst. The product contained ca. 20% of the compound with the *endo*-isomerized double bond. [d]After workup of the reaction mixture, purification by chromatography on silica gel yielded the expected **36** and ketone **37**.

products with the envisioned substitution pattern.[13] The preparative procedures for the unsymmetrical diynes **8**, **9**, **11**, **12**, **14**, **18**, **22** and **25** are detailed in Scheme 3. The synthesis of diynylester **8** was found to be feasible either from alkyne **2** or carboxylic acid **7**. Thus, using **2** as a starting material, lithiation followed by quenching with propargyl chloroformate yielded ester **8** in 76% yield. The preparation of **8** from **7** and propargyl alcohol was possible under standard coupling conditions using DMAP and DCC, however, resulting in lower yield (67%).[14] Applying identical conditions as the latter for the preparation of amide **9** from **7** and *N*-methy-*N*-propargylamine also gave the desired compound. Unfortunately the complete separation from the resulting coupling reaction byproducts proved to be very difficult. Alternatively, the synthesis of amide **9** was conducted by the reaction of the lithiated naphthylacetylene **2** with methyl-(prop-2-ynyl)carbamic chloride.[15] Furthermore, preparation of the bis-propargylated amines **11** and **12** started with the Sonogashira coupling of 2-methylbut-3-yn-2-amine with iodide **1**, providing **10** in excellent yield. The subsequent derivatization with propargyl bromide provided the desired secondary amine **11** in 55% yield, as well as the bis-propargylated tertiary amine as minor byproduct. Isolated **11** was submitted to subsequent alkylation with methyl iodide, furnishing **12** in modest yield. The more straightforward synthesis of the *N*-tosylated diyne **14** initially involved cross-coupling of the tosylated 2-methylbut-3-yn-2-amine with iodide **1** to deliver product **13** in 83% yield.[16] Subsequent propargylation of this intermediate building block proceeded in an excellent yield of 93%, allowing the isolation of the desired diyne **14**. Preparation of ketodiyne **18** started with the conversion of 4-propyn-1-ol (**15**) to the corresponding aldehyde **16** by Swern oxidation. Reaction of **16** with lithiated **2** gave the hydroxylated diyne **17**, from which **18** was easily accessible via oxidation under convenient conditions with Dess–Martin periodinane.[17]

The synthesis of enediyne **22** was initially attempted by olefination from **18** using Wittig or Tebbe reagents. Unfortunately, the reaction mostly gave a mixture **18** and **22**, which were difficult to separate. A new approach was then initiated with the double hydroiodination of 1,5-hexadiyne (**19**) affording bisolefin **20**. Interestingly, we were only able to isolate **20** despite various attempts to change the amount of hydroiodination reagent in order to obtain the corresponding monohydroiodination product.

In the following step, a Sonogashira coupling under slow addition of **2** to the reaction solution furnished **21** with 44% yield. Finally, the elimination reaction applying NaHMDS in DMF solution proceeded smoothly to give the desired enediyne **22** in high yield. The synthesis of diyne **25** possessing an annulated phenyl ring in the **A** and **B** position (Scheme 1) was envisioned to provide a compound with a large steric hindrance between these two positions. Several synthetic approaches for related diynes were investigated but the one presented starting from 2-bromobenzaldehyd (**23**) was identified as the most efficient and reliable.[18] Starting from **23** the Sonogashira reaction with **2** delivered **24** in good yield (77%). Subsequent reaction with in situ-prepared lithium trimethylsilylacetylide followed by desilylation of the crude product delivered the intended precursor diyne **25**. Having this selection of differently substituted diynes in sufficient amounts in hand, we were then able to investigate the Co(I)-catalyzed [2 + 2 + 2] cycloaddition reactions and subsequently, the configurational stability of the atropisomers' chiral axes.

[2 + 2 + 2] Cycloaddition Reactions of the Diynes with Nitriles. The [2 + 2 + 2] cycloaddition under photochemical conditions using [CpCo(COD)] (COD = 1,5-cyclooctadiene) has proven to be an excellent method for the cyclization of acetylenes or diynes with nitriles, resulting in, for example, the formation of heterobiaryls with five- and six-membered rings annulated to the newly formed pyridine.[9] Consequently, we applied [CpCo(COD)] for most syntheses of racemic mixtures of the heterobiaryls for subsequent analysis by dynamic chromatography methods. The cycloaddition reactions were performed in a photoreactor usually at temperatures between 0 and 25 °C, using either benzonitrile or in a single case acetonitrile in excess amounts.[9] The cycloaddition reactions furnished the desired heterobiaryls in moderate to good yields (Table 1). The products could easily be isolated by column chromatography and in some cases unreacted diyne was recovered and recycled. The use of MeCN instead of PhCN led to the formation of the methylated pyridine **28** in significantly higher yield (Table 1, heterobiaryls **27** and **28**, entries 2 and 3).[20]

In several cases (Entries 4, 8 and 11) the cyclization was additionally performed under thermal or microwave (MW) conditions using the novel air-stable catalyst [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}], leading to the desired products in moderate to good yields.[19] However, in the case of lactone **29**, a minor yield was observed under microwave conditions (21%), which can be attributed to the decomposition of the ester moiety under these reaction conditions. While most compounds are stable solids after isolation, the mesityl-substituted amine **24**, as well as the disiloxane-derived compounds **27** and **28** were isolated as oils. Cyclization of **14** with PhCN under microwave conditions furnished **33** in 71% yield. The cyclization of enediyne **22** indeed gave the expected product **35**, containing the exocyclic double bond and only very minor amounts of the internal isomerization product with an endocyclic double bond.

In the case of naphthyldiynol **25** the reaction delivered a mixture of products with both conventional heating or under microwave conditions. Diastereomers of the expected benzylic alcohol **36** and unexpected ketone **37** were formed. Formation of **37** is easy recognizable from the intense yellow color of the compound. This unusual direct oxidation under cycloaddition conditions was also observed when O-acetylated diynol **25** was subjected to the cycloaddition reaction under photochemical conditions.

Alcohol **36** was formed as a mixture of diastereomeric atropisomers due to the presence of the stereogenic carbon atom carrying the hydroxyl group. Accordingly, further functional group conversions were executed to eliminate this additional racemic stereo center to gain access to either ketone **37** or the reduced compound **38**. Because we had the alcohol **36**

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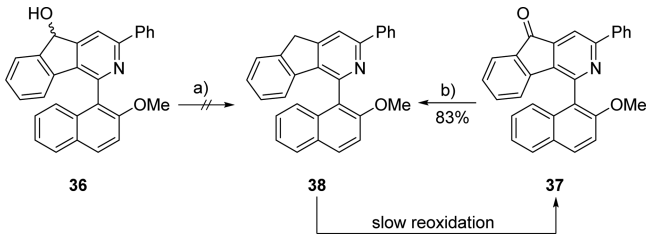
already in our hand, the derivative **38** containing a methylene group was targeted (Scheme 4). Therefore, **36** was initially

Scheme 4. Transformation of Primary Cyclization Product 36 into the Oxidized Keto-Form 37 and the Reduced Methylene-Containing Heterobiaryl 38[a]



[a]Reaction conditions: (a) TsCl, NEt_3, CH_2Cl_2, 0 °C to rt; then $LiAlH_4$, Et_2O, 0 °C to rt. (b) $N_2H_4{\cdot}H_2O$, diglyme, MW, 180 °C, 4 h (MW = microwave).

transformed into the tosylate ester with tosyl chloride. The subsequent reduction with $LiAlH_4$, however, did not work in our case to finally afford **38**. An alternative approach starting from ketone **37** via Wolff–Kishner reduction under microwave conditions initially proved to be troublesome after the successful formation of the hydrazide intermediate and subsequent reaction with aqueous KOH solution. Under the chosen conditions, a possible decomposition to undesired side-products was a major process. An alternative approach applying an excess of hydrazine hydrate without added base at 180 °C in diglyme under microwave conditions was finally successful and furnished the desired compound **38** in 83% yield.[21] As indicated in Scheme 4, compound **38** slowly reoxidizes in solution to ketone **37**, which might also explain the favored isolation of **38** from the cyclotrimerization reaction (see Table 1).[22] From these transformations we were able to obtain two heterobiaryls (**37** and **38**) possessing an annulated phenyl group in the backbone of the newly formed biaryl system and, in addition, exhibiting two electronically different substituents in the **C** position (compare Scheme 1), whose influence on the biaryl axis stability should be possible to study.

We were able to corroborate the molecular structure of compound **37** by X-ray structure analysis of suitable crystals which were obtained by recrystallization from THF (Figure 1). The structure displays the nearly perpendicular torsion of the planar naphthyl and pyridine moieties.

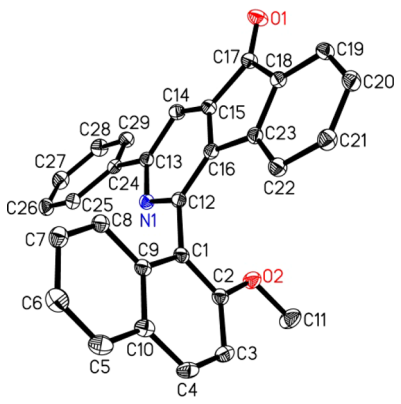


Figure 1. Molecular structure of racemic biaryl **37** (hydrogens omitted for clarity, ellipsoids with 30% probability).

Investigation of Configurational Stabilities of the Heterobiaryl Axes. Investigation of the rotational barriers of atropisomerization in biaryls can be performed using spectroscopic (e.g., dynamic NMR), chiroptical (e.g., polarimetry, circular dichroism) or chromatographic methods (enantioselective dynamic HPLC or GC).[1,23] In the case of stable isolable enantiomers, the individual stereoisomer can be heated at certain temperatures and the conversion into the opposite enantiomer is easily determined by HPLC or GC using chiral phases. From the obtained data, the half-life time and rotational barriers can be derived, as it was exemplified early on for 1,1′-binaphthyl and 1,1′-binaphthyl-2,2′-diol (BINOL) and later corroborated by theoretical calculations.[24] Especially the configurational stability of BINOL, possessing a high barrier of rotation of up to $\Delta G^{\ddagger}$ = 158 kJ mol^{-1}, caused by the tetra-*ortho*-substituted biaryl system has made it one of the most frequently utilized axially chiral structure elements for synthetic and catalytic purposes.[25]

The successful synthesis of heterobiaryls **26**–**35**, **37** and **38** (Table 1) gave us the opportunity to investigate these formally tri-*ortho*-substituted naphthylpyridines. Initial assessment of the activation barrier of interconversion of the compound containing the pure carbocyclic, unsubstituted ring (see Scheme 1, **A**, **B**, **C** = CH_2 and compound **39** in Figure 1) gave a $\Delta G^{\ddagger}$ = 89 kJ mol^{-1} (20 °C) from numerical approximation of the HPLC data.[9b,29b] This value corroborates that the component is configurationally labile at room temperature, according to a general estimate of $\Delta G^{\ddagger}$ = 96 kJ mol^{-1} necessary for biaryl configurational stability at this temperature.[26] It was expected that when introducing stabilizing structural changes in the molecule's backbone, these should be visible through corresponding changes in energetics for the biaryl axis activation barrier for racemization. The convenient tool we applied here was enantioselective dynamic HPLC analysis to determine the rate constants of interconversion *k*, the interconversion barriers $\Delta G^{\ddagger}$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ from temperature-dependent measurements.[27−29]

Initial attempts to separate the *N*-mesityl-substituted heterobiaryl **26** via HPLC on different chiral phases unfortunately did not lead to a successful separation of atropisomers, possibly pointing to a molecule with low configurational stability leading to peak coalescence or due to lack of enantioselectivity of the chiral stationary phases. Therefore, no stabilization compared to the completely unsubstituted five-membered carbocycle **39** could be accounted for. Investigations of the compounds **27** and **28** with the symmetrically substituted disiloxane backbone were more successful and a stabilizing effect of the tetramethyl-substituted disiloxane moiety was clearly visible. While in **39**, already at 20 °C, the formation of a plateau between the signals shows the increase in the number of molecules with unhindered rotation around the biaryl axis, a similar observation for **27** and **28** requires temperatures of up to 40 °C. Loss of configurational stability of the heterobiaryl's chiral axis was observed at 60 °C (Figure 2). In addition, and in accordance with the observations from **27** and **28**, a potential electronic or steric influence of the substituent on the nitrile cyclization component (either Me or Ph) for the configurational stability of the naphthylpyridine was found to be negligible. It was again possible to determine the free energy activation barrier $\Delta G^{\ddagger}$ for **27** and **28** from the obtained data as exemplified for **39**.[29b] The estimated values for **27** ($\Delta G^{\ddagger}$ = 93 kJ mol^{-1} at 22 °C) and **28** ($\Delta G^{\ddagger}$ = 97 kJ mol^{-1} at 40 °C) correspond to a slightly higher activation barrier for the interconversion of the enantiomers compared to **39**. Significant racemization occurs already at rather low temperature and the

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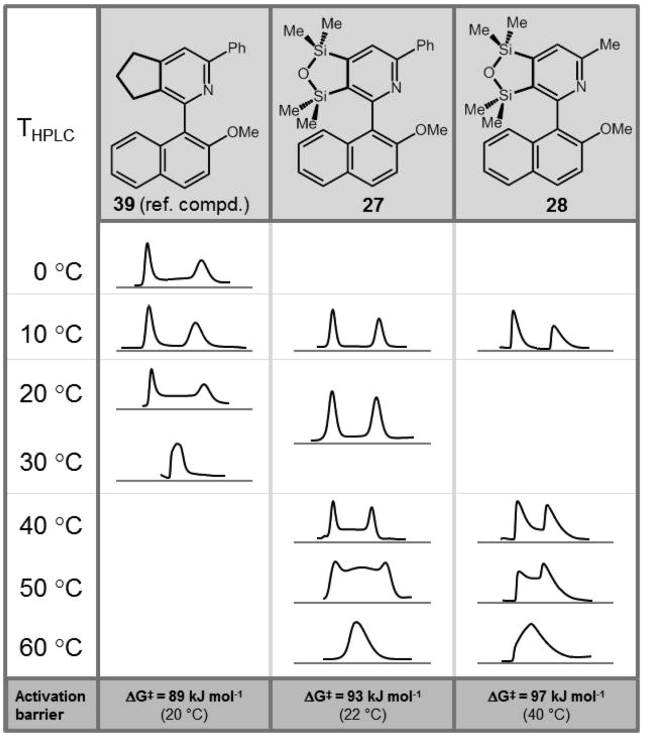

Figure 2. Effects of substituents on configurational stability of the biaryl axis in the five-membered backbone ring: reference compound **39** and the heterobiaryls **27** and **28** with tetramethyldisiloxane backbones. T_{HPLC} is the temperature of the chiral column during the dynamic HPLC analysis.

half-life time of **27** was estimated to be around 13 min at 25 °C. However, when comparing these data to those discussed in the next paragraph for the carbonyl group-containing heterobiaryls (Figure 3, **29**, **30** and **34**), these values appear to be too high in terms of the HPLC elution profiles observed (Figure 2 and 3). The latter compounds even at 80 °C do not show peak coalescence, which would indicate free rotation around the biaryl axis, while this is the case for **27** and **28**.

The next set of molecules we investigated were compounds containing a carbonyl group in the *ortho*-position including **29**, **30** and **34**. The C═O group in the five-membered ring is assumed to be coplanar to the pyridine ring, thus representing a substituent which should be able to efficiently hinder the rotation around the biaryl axis. These heterobiaryls display a highly interesting behavior (Figure 3). The lactone **29** and ketone **34** display rather similar HPLC elution profiles at different temperatures, characterized by pronounced plateau formation, which indicates the enantiomerization by rotation around the biaryl axis. In contrast, the lactam **30** shows no sign of enantiomerization even at 80 °C and therefore appears to be significantly more stable than the related compounds **29** and **34**. This can be explained by the high degree of planarity of the —(C═O)—(N-Me)—CH_2— fragment due to the partial "double-bond character" in the resonance structure between C and N, which obviously imparts the higher configurational stability compared with the carbonyl congeners. A high substantial barrier to rotation has even been observed in the acyclic form of secondary amides (typically $\Delta G^{\ddagger}$ = 62−84 kJ mol^{-1}).[30]

From the HPLC data measured at different temperatures between 35 and 80 °C, the free activation energy ($\Delta G^{\ddagger}$) values were determined from the rate constants of enantiomerization and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained from an Eyring plot by temperature-dependent dynamic HPLC measurements. The $\Delta G^{\ddagger}$ values represent the differences in stability for the various carbonyl compounds; for compound **30** a lower limit of the enantiomerization barrier has been estimated because of negligible interconversion at 80 °C. While the energetic difference between **29** and **34** is small ($\Delta\Delta G^{\ddagger}$ = 2.5 kJ mol^{-1}), the lactam **30** has an estimated $\Delta G^{\ddagger}$ value already over 100 kJ mol^{-1}. However, all investigated heterobiaryls so far have a larger activation barrier compared to 1-(1′-naphthalenyl)-isoquinoline ($\Delta G^{\ddagger}$ ~ 80 kJ mol^{-1} at −20 °C).[31] Comparable investigations with structurally related compounds have been performed with atropisomeric analogues of DMAP (4-dimethylaminopyridine).[32]

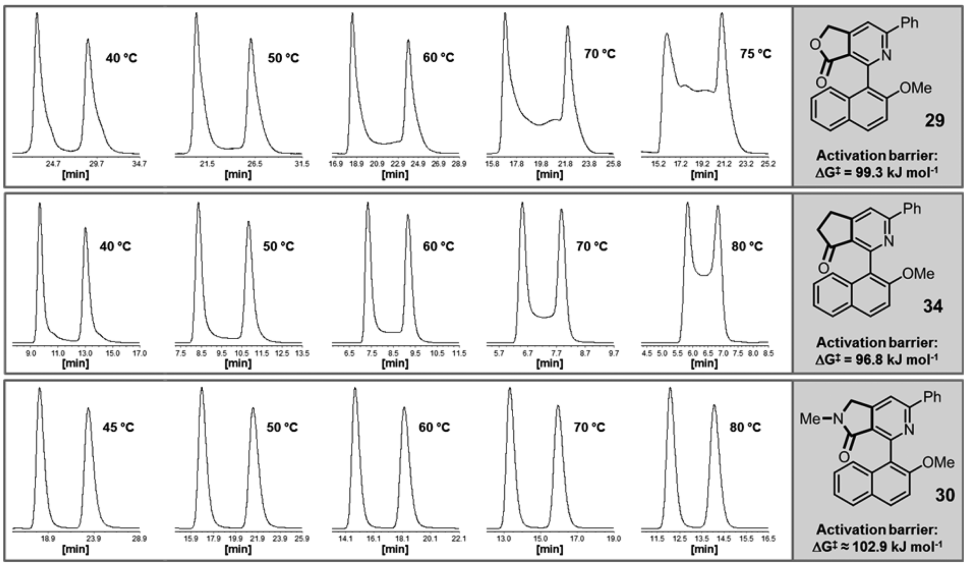

Figure 3. Effects of different neighboring groups on the configurational stability of five-membered carbonyl-containing backbone rings in heterobiaryls **29**, **30** and **34** ($\Delta G^{\ddagger}$ at 25 °C). T_{HPLC} is the temperature of the chiral column during the dynamic HPLC analysis.

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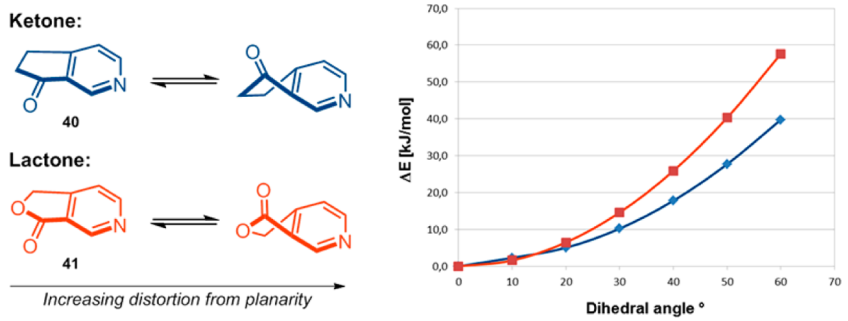

Figure 4. Computed energy profiles for the ketone **40** and lactone **41**.

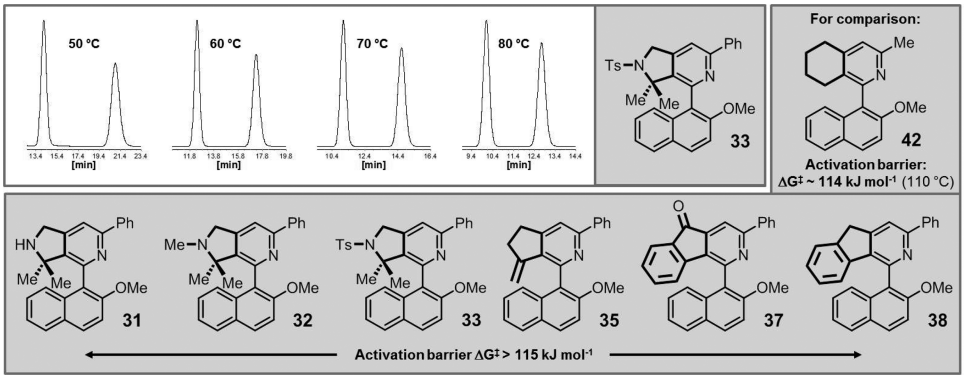

Figure 5. Exemplary dynamic chiral HPLC diagram for **33** and activation barriers of investigated compounds **31**−**33**, **35**, **37** and **38** ($\Delta G^{\ddagger}$ at 80 °C) as well as compound **42** for comparison. T_{HPLC} is the temperature of the chiral column during the dynamic HPLC analysis.

We performed calculations for two model compounds, 5*H*-cyclopenta[*c*]pyridin-7(6*H*)-one (**40**) and furo[3,4-*c*]pyridin-3(1*H*)-one (**41**), to evaluate the energetics of a possible deviation of the annulated five-membered ring, which could influence the interconversion also in **29** and **34** (Figure 4). The computed energies of the two compounds illustrate that the lactone needs slightly more energy to distort from the planarity of the five-membered ring compared to the ketone. With increasing deviation from planarity, the required amount of energy rises significantly. At a deviation of 60° from planarity, about 18 kJ mol^{-1} more energy was required for the ester **41**. This trend correlates well with the different free activation energies derived from the dynamic HPLC experiments with **29** and **34** (Figure 3) and thus illustrates the importance minor structural changes can have for the configurational stability of the biaryl axis in closely related compounds.

A possible detour for the enantiomerization by enolization of ketone **29** was excluded by treatment of the ketone under thermal conditions in deuterated solvents like CD_3OD, where no incorporation of deuterium has been observed.

Finally the other heterobiaryls were investigated, possessing either a $-CMe_2-$ group in the **A** position (compare Scheme 1) like compounds **31**−**33**, an exocyclic double bond (compound **35**) or an annulated phenyl group in position **A** and **B** (compound **37** and **38**). The investigation of these compounds by dynamic HPLC evidenced rather large activation barriers; as up to 80 °C column temperature no changes could be observed (Figure 5). Therefore, the activation barriers for all these compounds are higher than $\Delta G^{\ddagger}$ = 115 kJ mol^{-1} at 80 °C. We were able to determine the enantiomerization rate for the naphthyl-tetrahydroisoquinoline compound **42**, which can be synthesized with high enantioselectivity applying the asymmetric [2 + 2 + 2] cycloaddition, by heating the solution of one enantiomer at 110 °C and subsequently analyzing the enantiomeric ratio by chiral HPLC. We found the half-life time for racemization to be approximately 148 min corresponding to an activation barrier $\Delta G^{\ddagger}$ of approximately 114 kJ mol^{-1}. For further comparison, the structurally very similar 1-(2-methoxynaphthalen-1-yl)isoquinoline was found to possess an activation barrier of $\Delta G^{\ddagger}$ = 117 kJ mol^{-1} at 87 °C.[10b] These examples corroborate the assumption that adequate substitution of the five-membered ring backbone in the appropriate position can lead to heterobiaryls with comparable or even higher configurational stability compared to heterobiaryls possessing six-membered backbone rings. The in **A** position dimethylated amines **31**−**33** are obviously more rigid, independent from the substitution of the five-membered ring nitrogen atom. This is also obvious when comparing these with other compounds containing a dimethylated carbon atom in the **A** position like the structurally related tetramethyldisiloxane-substituted heterobiaryls **27** and **28**. The presence of a free N−H (like in **31**) proton seems to have no effect on the configurational stability as observed under HPLC conditions. The heterobiaryl **35** decorated with an exocyclic olefin bond is structurally analogous to the ketone **34**. The significantly larger stability of **35** can therefore certainly be derived from the terminal $=CH_2$ group, which is sterically more demanding compared to the carbonyl oxygen and leads to the observed stabilization against free rotation around the biaryl axis. Finally, installation of an annulated phenyl ring as for **37** and **38**, which can be considered as embedding of the double bond in position **A** in an aromatic system also provides significant stabilization, by increasing the rigidity of the newly formed five-membered ring and increasing the steric size of the backbone tremendously. A significant electronic effect of the keto group in the position **C** of **37**, which

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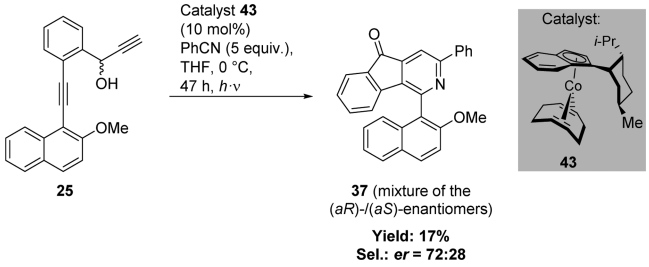
would be the only plausible influence thinkable, was not observed.

We isolated very small amounts of the heterobiaryls **33** and **37** from analytical chiral HPLC separations and heated solutions of the samples at different temperatures to check the stereochemical integrity. It was found that **37** could be heated for several hours at 120 °C without significant racemization. Unfortunately decomposition was an interfering problem at higher temperatures using NMP or toluene as solvent, preventing further studies.

For a better understanding of the experimental data from the dynamic HPLC investigations, we calculated the energy profiles of the rotation around the biaryl axis for selected molecules.[33] A number of theoretical investigations on the rotational barriers of different heterobiaryls have been reported.[32] In our approach, we computed relative energies for a complete 360° rotation around the biaryl axis, providing an energetic curve for model heterobiaryls. The results corroborated (a) the size of the backbone either of the naphthyl or the pyridine ring has a large impact of stability, (b) substitution of the pyridine nitrogen for a C−H group or methylation of the nitrogen significantly raises the activation barrier for the rotation around the biaryl axis, and (c) the substituent of the pyridine ring *ortho* to the ring nitrogen atom (Ph or Me) plays no role for the activation barrier.

Finally, we applied the conditions for the enantioselective photocatalyzed [2 + 2 + 2] cycloaddition with the chiral Co(I)-indenyl complex **43** to diyne **25** and benzonitrile,[9] to prove the higher configurational stability of the products' biaryl axis under these reaction conditions (Scheme 5). As it was mentioned in the

Scheme 5. Cocyclotrimerization of Diyne 25 with PhCN, Yielding Enantiomerically Enriched Heterobiaryl Product 37



beginning this reaction failed to deliver compound **39** with any selectivity. We investigated several conditions, also at lower reaction temperatures as low as −20 °C to maximize the enantioselectivity; however, at these low temperatures no reaction was observed. We then successfully performed the reaction at 0° under photochemical conditions.

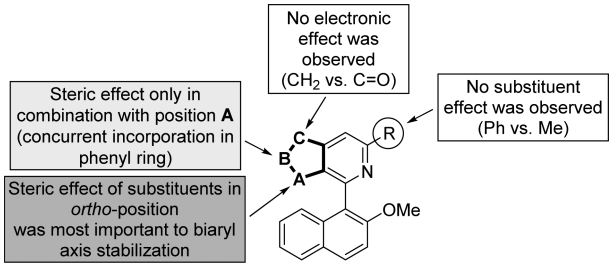
To our delight the expected heterobiaryl product **37** was formed, albeit with low yield, but much more important with an enantiomeric ratio of 72:28, demonstrating exemplarily that here the barrier of rotation was large enough to allow the enantioselective syntheses of **37**, possessing a substituted five-membered backbone ring. This also substantiates the assumption that the appropriate configuration of the backbone ring can result in a barrier of rotation large enough to be useful for further enantioselective elaborations.

CONCLUSION

The presented investigation details the systematic synthetic approach for a series of heterobiaryls containing pyridines with annulated, differently substituted five-membered ring systems by Co-catalyzed cyclotrimerization reactions of unsymmetrical diynes with aceto- or benzonitrile as the key step. Many of the unsymmetrically substituted diynes with structurally diverse connections of the two alkyne moieties were synthesized for the first time. The photochemical cycloaddition of the diynes and nitriles catalyzed by [CpCo(COD)] was found as an efficient possibility for the construction of the heterobiaryls. Application of [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] under thermal or microwave conditions proved to be even superior for certain cases. The obtained heterobiaryl racemates were investigated in terms of the configurational stability of their newly formed stereogenic biaryl axis by dynamic HPLC on different chiral phases. Some of the compounds display remarkable differences while increasing the column temperature, showing that small structural differences can play a large role for the stabilization of the biaryl axis. From these HPLC investigations it was possible to determine the free energy activation barriers ($\Delta G^{\ddagger}$) for the enantiomerization process. It was found that (A) the heterobiaryls with a tetramethyldisiloxane backbone (**27** and **28**) are configurationally more stable compared to the compound with an unsubstituted five-membered ring (**39**). (B) Introduction of a carbonyl group as a constituent of the five-membered ring attached to the pyridine ring *ortho* to the biaryl axis significantly raises the free energy activation barriers ($\Delta G^{\ddagger}$ = 96.8 to ∼103 kJ mol^{-1}), especially depending on the group adjacent to the C═O group in the five-membered ring (CH_2, O or NMe). The five-membered lactam ring provided the largest stabilization of the biaryl axis. (C) We found that the introduction of a cyclic amine possessing a "CMe_2" group *ortho* to the biaryl axis significantly raises the activation barrier over $\Delta G^{\ddagger}$ = 115 kJ mol^{-1}. (D) The same effect was found for an exocyclic C−C double bond *ortho* to the biaryl axis and also the connection of an annulated phenyl ring at the five-membered ring backbone. Comparison with biaryl **42**, possessing a six-membered ring in the backbone, yielded comparable activation enthalpies. This demonstrates the feasibility of stabilizing the configuration of the biaryl axis by appropriate substitution of the five-membered ring.

In summary, the investigations demonstrated that in addition to the novel synthetic access to this class of increasingly important unsymmetrically substituted heterobiaryls, the suitable substitution of five-membered ring backbones can significantly support the configurational stability of the biaryl axis of such systems (Scheme 6). As further evidence the

Scheme 6. Summary on the Observed Effects of Backbone Substituents on Biaryl Axis Stabilization



enantioselective photocatalyzed [2 + 2 + 2] cycloaddition of diyne **25** applying a chiral Co(I)-catalyst enabled the formation of the corresponding heterobiaryl product **37** with an *er* of 72:28.

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EXPERIMENTAL SECTION

The NMR spectra were in general recorded at 298 K and the individual measurement conditions given with the data. Chemical shifts are reported in ppm relative to the ^{1}H and ^{13}C residue signals of the deuterated solvent (deuterochloroform δ 7.26 ppm for ^{1}H and δ 77.16 ppm for ^{13}C). Mass spectra were obtained with a mass spectrometer 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. High-resolution mass spectroscopy (HRMS) analyses were performed using electrospray ionization/time-of-flight (ESI-TOF) mass spectrometry or electron ionization (EI) with a sector field mass analyzer. Melting points were not corrected. In all cases the enantiomeric excesses of pyridines were analyzed by HPLC using appropriate chiral columns. For the photochemistry two halogen lamps (460 W each) have been used for irradiation of the thermostated Schlenk-type reaction vessel (pictures of the setup are given in the Supporting Information).[40] All reactions were carried out in an argon atmosphere, using standard techniques in dry, oxygen-free solvents. The liquid reagents were distilled under argon prior to use. All solid compounds used for the photocatalyzed reactions were recrystallized from degassed solvents and the liquid starting materials were dissolved in the appropriate solvent and dried over and distilled from molecular sieves under argon before use. For microwave experimentation we used a CEM Discover SP with glass tubes. Chromatographic purifications were done with 240−400 mesh silica gel or on an automated flash-chromatography system. CpCo(COD),[34] $Pd(PPh_3)_4$,[35] $Pd_2dba_3{\cdot}CHCl_3$,[35] 1-iodo-2-methoxynaphthalene (**1**)[36] and 3-(2-methoxynaphthalen-1-yl)propiolic acid (**7**)[14] were synthesized according to known procedures. 1-Ethynyl-2-methoxynaphthalene (**2**) was prepared after either one of the published procedures.[37] The synthesis and catalytic properties of the air-stable precatalyst [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] have been reported by us recently.[19] All other starting materials and compounds were commercially available and have been purchased or were prepared by procedures described below.

Preparation of Cyclization Substrate Molecules. *N-(3-(2-Methoxynaphthalen-1-yl)prop-2-ynyl)-2,4,6-trimethyl-N-(prop-2-ynyl)aniline (**9**). 2,4,6-Trimethyl-N,N-di(prop-2-ynyl)aniline (**3**).* The synthetic procedure for 2,4,6-trimethyl-*N*,*N*-di(prop-2-ynyl)aniline (**3**) was derived according to published work.[38] In a 3-necked flask equipped with reflux condenser anhydrous K_2CO_3 (21.9 g, 159.8 mmol) was suspended in DMF (135 mL). Afterward, the 2,4,6-trimethylaniline as well as the propargyl bromide (18 mL, 159.8 mmol, 80% soln. in toluene) were added and the reaction mixture stirred at 100 °C for 18 h. Then additional propargyl bromide and K_2CO_3 (one-fifth of the original amounts each) were added and heating at 100 °C continued for another 2 h. After cooling, the reaction was quenched with water and then extracted with ethyl acetate. After drying over $MgSO_4$ and evaporation of the solvent, the oily residue can be purified either by bulb to bulb distillation (ca. 4×10^{-2} mbar, 100 °C) in high vacuum or column chromatography on silica gel with petrol ether/ethyl acetate (10:1, v/v) as the eluent. The known product was obtained as a slightly yellow liquid (yield: 10.7 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.87 (s, 2H), 3.98 (d, *J* = 2.3 Hz, 4H), 2.35 (s, 6H), 2.29 (s, 3H), 2.25 (t, *J* = 2.3 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.3, 137.5, 135.4, 129.5, 81.3, 71.8, 41.4, 20.9, 19.5. ppm. MS (EI, 70 EV): 211 (69) $[M]^+$, 172 (71), 157 (100), 91 (28), 77 (20), 39 (32).

*N-(3-(2-Methoxynaphthalen-1-yl)prop-2-ynyl)-2,4,6-trimethyl-N-(prop-2-ynyl)aniline (**4**).* The best results were obtained utilizing the Sonogashira reaction according to the following procedure: 1-Iodo-2-methoxynaphthalene (**1**, 1.83 g, 6.44 mmol), $Pd(PPh_3)_4$ (370 mg, 0.32 mmol, 5 mol %), CuI (182 mg, 0.96 mmol, 15 mol %) were secured in a Schlenk flask under argon. Et_3N (80 mL), the 2,4,6-trimethyl-*N*,*N*-di(prop-2-ynyl)aniline (**3**, 4.08 g, 19.3 mmol) and finally THF (20 mL) were added subsequently and the reaction mixture heated to 50 °C. After 60 min a thick precipitate already formed and the reaction was stopped after 15 h, when TLC showed complete consumption of iodide. The reaction mixture was quenched with sat. NH_4Cl soln. and stirred for 15 min. The phases were separated and the aqueous phase was extracted several times with ether and the combined organic phases washed with sat. $NaHCO_3$ soln. and brine. After drying over Na_2SO_4 and removal of the solvent, the dark oily residue containing large amounts of unreacted amine was charged to silica gel and purified by chromatography, using petrol ether/ethyl acetate (3:1, v/v) as the eluent. It turned out to be beneficial to remove excessive diyne **3** by bulb to bulb distillation before the chromatographic purification. The pure product is a yellow solid (1.07 g, 45%). For further purification the product can be recrystallized from Et_2O/*n*-pentane (2:1, v/v). mp 106−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 9.1 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.45 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.23 (d, *J* = 9.1 Hz, 1H), 6.90 (s, 2H), 4.42 (s, 2H), 4.11 (d, *J* = 2.4 Hz, 2H), 4.01 (s, 3H), 2.42 (s, 6H), 2.31 (s, 3H), 2.28 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9, 144.4, 137.8, 135.3, 134.8, 129.7, 129.6, 128.6, 128.0, 127.2, 125.6, 124.2, 112.9, 106.7, 96.5, 81.7, 78.3, 71.8, 56.7, 42.9, 41.9, 21.0, 19.6 ppm. MS (ESI): 366 (18) $[MH]^+$, 195 (100). Anal. Calcd for $C_{26}H_{25}NO$ (367.48): C 84.98, H 6.86, N 3.81. Found: C 84.71, H 6.88, N 3.51.

*3-(2-Methoxynaphthalen-1-yl)ethyn-2-ynyl)-tetramethyldisiloxane (**6**).* In a 250 mL Schlenk flask, $Pd_2dba_3{\cdot}CHCl_3$ (437 mg, 0.42 mmol, 6 mol %), CuI (402 mg, 2.11 mmol, 15 mol %) and dppf (505 mg, 0.92 mmol, 6.5 mol %) were evacuated and backfilled with argon three times. THF (15 mL) was added and the mixture stirred for a short period (ca. 20 min) at rt. In another Schlenk flask **1** (4.0 g, 14.1 mmol) was set up as above and dissolved in THF (9 mL). To the catalyst solution Et_3N (120 mL) as well as 1,3-diethynyltetramethyldisiloxane (**5**, 5.14 g, 28.2 mmol) were added. The solution of the naphthyl iodide **1** was then charged to a 10 mL syringe, connected to the reaction flask via a Teflon tubing and a needle and afterward the syringe was clamped into a syringe pump. The reaction mixture was heated to 45 °C and the addition of the diyne started with 1 mL of the solution immediately and then with an addition rate of 2.5 mL/h. After stirring for a total time of 22 h, the reaction was allowed to cool down and subsequently quenched with sat. NH_4Cl soln. under argon. The aqueous phase was extracted with ethyl acetate (3×), the combined organic phases washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent, a dark-brown oily residue remained and the excessive diyne was removed in high vacuum. The crude product was charged to silica gel and purified by flash-chromatography with *n*-heptane and ethyl acetate, yielding two main fractions: diarylated byproduct (903 mg, 13%) and the monoarylated product **6** (oil, 2.28 g, 48%). We later developed a modified procedure, preventing the formation of the diarylated product, however, the overall yields are lower.[12] Characterization data for compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.23 (d, *J* = 9.1 Hz, 1H), 4.03 (s, 3H), 2.46 (s, 1H), 0.48 (s, 6H), 0.41 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.8, 134.8, 130.6, 128.4, 128.0, 127.4, 125.3, 124.2, 112.7, 105.8, 103.1, 98.7, 92.2, 89.4, 56.5, 2.4, 2.0 ppm. ^{29}Si NMR (79 MHz, $CDCl_3$) δ = −16.5, −16.7 ppm. MS (EI, 70 eV), *m*/*z* (%) 338 (61) $[M^+]$, 323 (95), 308 (57), 293 (100), 283 (70), 189 (28), 165 (26). HRMS (pos. ESI) for $C_{19}H_{23}O_2Si_2$ $[MH^+]$ calcd 339.1231, found 339.1234.

*Prop-2-ynyl 3-(2-methoxynaphthalen-1-yl)propiolate (**8**).* In a 50 mL Schlenk tube 1-ethynyl-2-methoxynaphthalene (**2**, 770 mg, 4.23 mmol) was evacuated and backfilled with argon three times. Then THF (20 mL) was added and the resulting solution was cooled to −78 °C, following by the addition of *n*-BuLi (1.5 M, 3.0 mL, 4.44 mmol) at this temperature. After 10 min the reaction mixture was allowed to warm to 0 °C and stirred for additional 20 min. Afterward the mixture was cooled again down to −78 °C and propargyl chloroformate (526 mg, 0.44 mL, 4.44 mmol) was added via syringe slowly. The reaction solution was stirred for further 15 min, then stirred in an ice-bath for 3 h and finally allowed to warm to rt. The brown reaction mixture was quenched with sat. NH_4Cl soln. and extracted with Et_2O (2×). The combined organic layers were washed with washed with water (3×) and brine and dried over Na_2SO_4. The crude product charged to silica gel and purified by chromatography with petrol ether and ethyl acetate (4:1 v/v), yielding **8** as slightly yellowish solid (845 mg, 76%).

*Alternative Approach for **8**.* 3-(2-Methoxynaphthalen-1-yl)propiolic acid (**7**, 500 mg, 2.21 mmol) and 4-dimethylaminopyridine (DMAP)

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(26.9 mg, 0.22 mmol) were evacuated in a 25 mL Schlenk tube and backfilled with argon three times. Afterward CH_2Cl_2 and propargyl alcohol were added and the reaction mixture cooled to 0 °C. *N,N'*-Dicyclohexylcarbodiimide (DCC) (912 mg, 4.42 mmol) was added in portions under inert conditions and the reaction mixture stirred for 16 h. TLC control showed complete conversion and a new spot. Finally, the reaction mixture was quenched with HCl (0.25 M), the aqueous phase extracted with CH_2Cl_2 several times and then washed again with HCl (0.25 M). Afterward, the organic phase was washed with sat. $NaHCO_3$ soln., water and brine and dried over Na_2SO_4. The crude product was charged to silica gel and purified by chromatography with *n*-hexane and ethyl acetate (4:1, v/v), yielding **8** as a white-yellow solid (386 mg, 67%). mp 98−99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.59 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.41 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.24 (d, J = 9.2 Hz, 1H), 4.88 (d, J = 2.5 Hz, 2H), 4.04 (s, 3H), 2.56 (t, J = 2.5 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.1, 153.6, 135.1, 133.5, 128.5 (2×), 128.3, 124.9, 124.8, 112.3, 102.1, 89.3, 83.7, 75.7, 56.7, 53.2 ppm (one C could not be detected, presumably due signal overlap). MS (EI, 70 eV), *m/z* (%) 264 (48) [M$^+$], 220 (65), 205 (25), 191 (25), 182 (78), 163 (32), 152 (100), 139 (75). HRMS (EI) for $C_{17}H_{12}O_3$ calcd 264.0781, found 264.0781.

*3-(2-Methoxynaphthalen-1-yl)-N-methyl-N-(prop-2-ynyl)-propiolamide (**9**). Methyl(prop-2-ynyl)carbamic chloride.* The general preparation for this class of compounds was reported.[15]

In a 250 mL Schlenk flask triphosgene (2.95 g, 9.95 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to −78 °C. Dry pyridine (0.25 mL, 3.0 mmol) and a solution of *N*-methylprop-2-yn-1-amine (2.5 mL, 28.0 mmol) in CH_2Cl_2 (20 mL) were added slowly, while adjusting the pressure to the atmospheric pressure. Afterward the reaction mixture was allowed to warm to rt, continuing stirring for another 68 h. After evaporation of the solvent the crude product was distilled in vacuum at 80 °C oil-bath temperature. Methyl(prop-2-ynyl)carbamic chloride is a yellowish oily liquid, which becomes dark brown after storage for several weeks in fridge (yield: 2.22 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.23 (d, J = 2.4 Hz, 0.8H), 4.14 (d, J = 2.5 Hz, 1.2H), 3.15 (s, 1.8 H), 3.05 (s, 1.2H), 2.36 (t, J = 2.4 Hz, 0.38H), 2.33 (t, J = 2.5 Hz, 0.62H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.8/148.7, 76.7/76.6, 73.7, 42.4/39.7, 37.5/36.1 ppm (there are too many ^{13}C signal, due to the formation of rotamers; accordingly, these signals are separated with "/").

*3-(2-Methoxynaphthalen-1-yl)-N-methyl-N-(prop-2-ynyl)-propiolamide (**9**).* In a 250 mL Schlenk tube 1-ethynyl-2-methoxynaphthalene (**2**, 640 mg, 3.51 mmol) was evacuated and backfilled with argon three times. Then THF (20 mL) was added and the resulting solution was cooled to −78 °C, following by the addition of *n*-BuLi (1.6 M, 2.3 mL, 3.7 mmol) at this temperature. After 10 min the reaction mixture was allowed to warm to room-temperature and stirred for additional 30 min. Afterward the mixture was cooled again to −78 °C and methyl(prop-2-ynyl) carbamic chloride (466 mg, 3.51 mmol) was added via syringe slowly. The reaction solution was then allowed to warm to rt overnight. The mixture was quenched with water and extracted with CH_2Cl_2 (3× 20 mL each). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product charged to silica gel and purified by chromatography with *n*-hexane and ethyl acetate (1:1 v/v + 2% Et_3N), yielding **9** as an yellow-orange solid (560 mg, 58%). mp 127−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 (dd, J = 8.4, 6.4 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.56 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.39 (ddd, J = 8.0, 6.9, 1.2 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 4.66 (d, J = 2.5 Hz, 1H), 4.36 (d, J = 2.5 Hz, 1H), 4.03 (s, 1,5H), 4.01 (s, 1,5H), 3.47 (s, 1.5H), 3.13 (s, 1.5H), 2.36 (t, J = 2.5 Hz, 0.5H), 2.27 (t, J = 2.5 Hz, 0.5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.3/161.1, 154.8/154.7, 134.8/134.7, 132.62/132.57, 128.32/128.30, 128.2, 125.2/125.1, 124.7, 112.2, 103.34/103.32, 90.7/90.5, 86.3/86.1, 78.2/78.0, 73.0/72.4, 56.62/56.58, 40.8, 35.6/35.4, 31.7 ppm. (there are to many ^{13}C signal, due to the formation of rotamers; accordingly, these signals are separated with "/"). MS (EI, 70 eV), m/z (%) 277 (4) [M$^+$], 247 (100), 218 (46), 189 (21). HRMS (ESI) for $C_{18}H_{16}NO_2$ calcd 278.1176, found 278.1178.

*4-(2-Methoxynaphthalen-1-yl)-2-methylbut-3-yn-2-amine (**11**)*[5a] *and 4-(2-Methoxynaphthalen-1-yl)-N,2-dimethyl-N-(prop-2-ynyl)-but-3-yn-2-amine (**12**). 4-(2-Methoxynaphthalen-1-yl)-2-methyl-but-3-yn-2-amine (**10**).* 1-Iodo-2-methoxynaphthalene (**1**, 5.71 g, 20.1 mmol), $Pd(PPh_3)_4$ (464 mg, 0.40 mmol, 2 mol %) and CuI (230 mg, 1.21 mmol, 6 mol %) were secured in a Schlenk flask (3×). Subsequently Et_3N (100 mL) and 2-methyl-2-amino-3-butyne (2.0 g, 24.1 mmol) were added and the reaction mixture heated to 55 °C. The reaction was stopped after 14 h, when TLC showed complete consumption of **1** and the reaction mixture had become slurry. The reaction mixture was filtrated over Celite, the filter content washed with ether and the combined filtrates were subjected to the removal of the solvent in vacuum, giving roughly 6 g of crude product. The residue was plugged to silica gel and purified by column chromatography with ethyl acetate (+2% Et_3N) as the eluent. Pure **10** was isolated as a white solid (4.67 g, 97%). mp 67−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.19 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.50 (ddd, J = 8.5, 6.7, 1.3 Hz, 1H), 7.33 (ddd, J = 8.3, 6.7, 1.2 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 3.97 (s, 3H), 3.00 (bs, 2H), 1.65 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8, 134.7, 129.9, 128.6, 128.1, 127.4, 125.3 (2×), 124.2, 113.0, 106.2, 75.1, 56.8, 46.8, 31.8 ppm. MS (EI, 70 eV), *m/z* (%) 239 (19) [M$^+$], 224 (100), 208 (19), 139 (23). Anal. Calcd for $C_{16}H_{17}NO$ (239.31): C 80.30, H 7.16 N 5.85. Found: C 80.28, H 7.22 N 5.67.

*4-(2-Methoxynaphthalen-1-yl)-2-methyl-N-(prop-2-ynyl)but-3-yn-2-amine (**11**).* Potassium carbonate (1.60 g, 11.6 mmol) and **10** (2.21 g, 9.31 mmol) were secured in a Schlenk flask and anhydrous DMF (80 mL) was added. Propargyl bromide (1.29 mL, 11.6 mmol, 80 wt % in toluene) was added via syringe and the reaction mixture stirred for 18 h at 100 °C. After cooling, ca. 50 mL water were added and the mixture extracted with ethyl acetate (4×). The combined organic phases were washed with sat. $NaHCO_3$ soln. and brine and dried over Na_2SO_4. The solvents were evaporated and the residue dried in vacuum (crude product: 4.8 g of brown oil). The crude product was charged onto silica gel and purified by column chromatography, using petrol ether/ethyl acetate (3:1 v/v + 1% Et_3N). Two main fractions have been isolated: the dipropargylated side product (749 mg, 26%) and low-melting solid **11** (1.409 g, 55%). mp 48−50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.52 (ddd, J = 8.6, 6.8, 1.2 Hz, 1H), 7.35 (ddd, J = 8.3, 6.8, 1.1 Hz, 1H), 7.21 (d, J = 9.3 Hz, 1H), 3.99 (s, 3H), 3.74 (d, J = 2.6 Hz, 2H), 2.23 (t, J = 2.5 Hz, 1H), 1.77 (bs, 1H), 1.58 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.9, 134.6, 130.0, 128.6, 128.2, 127.4, 125.2, 124.2, 112.9, 106.3, 103.0, 82.8, 77.3, 71.3, 56.7, 51.3, 34.0, 29.8 ppm. MS (70 eV), *m/z* (%) 276 (100) [M$^+$], 244 (25), 220 (44), 178 (26), 162 (36), 152 (20), 56 (27). HRMS (ESI) for $C_{19}H_{19}ON$ calcd 277.1461, found 277.1460. Anal. Calcd for $C_{19}H_{19}NO$ (277.36): C 82.28, H 6.90 N 5.05. Found: C 82.12, H 7.04 N 4.91.

*4-(2-Methoxynaphthalen-1-yl)-N-(2-dimethyl-N-(prop-2-ynyl))-but-3-yn-2-amine (**12**).* Compound **11** (982 mg, 3.54 mmol) and K_2CO_3 (636 mg, 4.60 mmol) were weighted into a Schlenk flask and anhydrous DMF (30−40 mL) as well as MeI (0.29 mL, 656 mg, 4.60 mmol) were added. The reaction mixture was heated to 80 °C for 24 h. After cooling, water was added and the mixture extracted with diethyl ether (4×). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the residue dried in vacuum. The crude product was charged to silica and purified by column chromatography, using petrol ether/ethyl acetate (3:1 v/v + 1% Et_3N). The product **12** (581 mg, 56%), starting material (**11**, 194 mg, 20% recovered) and 2-methoxy-1-(3-methylbut-3-en-1-yn-1-yl)-naphthalene (235 mg) were isolated. The 2-methoxy-1-(3-methylbut-3-en-1-yn-1-yl)naphthalene was identified by NMR and is the formal result of an elimination reaction. Data for **12**: mp 50−51 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.58 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.37 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.23 (d, J = 9.1 Hz, 1H), 4.00 (s, 3H), 3.59 (d, J = 2.5 Hz, 2H), 2.64 (s, 3H), 2.28 (t, J = 2.5 Hz, 1H), 1.67 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 134.6, 129.9, 128.6, 128.2, 127.3, 125.3, 124.2, 113.0, 106.4, 100.0, 81.6, 78.9, 72.5, 56.8, 56.1, 41.9, 36.7, 28.9 ppm. MS (EI, 70 eV), *m/z* (%) 291 (3) [M$^+$], 276 (100), 244 (26), 220 (44), 178 (26), 165 (36), 152 (20), 56 (27). HRMS (ESI) for

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$C_{20}H_{21}NO$ calcd 291.1618, found 291.1625. Anal. Calcd for $C_{20}H_{21}NO$ (291.39): C 82.44, H 7.26 N 4.81. Found: C 82.65, H 7.28 N 4.72.

*N-(4-(2-Methoxynaphthalen-1-yl)-2-methylbut-3-yn-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**14**). N-(4-(2-Methoxynaphthalen-1-yl)-2-methylbut-3-yn-2-yl)-4-methylbenzenesulfonamide (**13**).* 1-Iodo-2-methoxynaphthalene (**1**, 8.64 g, 30.4 mmol), $Pd(PPh_3)_4$ (1.74 g, 1.51 mmol, 5 mol %), 4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide (7.83 g, 33.0 mmol)[16] and $ZnCl_2$ (817.5 mg, 6.0 mmol, 6 mol %) were secured in a Schlenk flask (3×). Subsequently piperidine (45 mL) and iodine (20 mg) were added and the reaction mixture stirred at 65 °C for 20 h. After this time TLC control showed complete consumption of **1** and the reaction was allowed to cool to rt. The mixture was diluted with *n*-hexane/Et_2O (5:3 v/v) and stirred for further 60 min. The precipitated solids were filtered off and washed with same solvent mixture. The solvent was removed and the residue was plugged to silica gel and purified by column chromatography with ethyl acetate/petroleum ether (1:1 v/v) as the eluent. Pure **10** was isolated as a white solid (9.92 g, 83%). mp 136−138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.82 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.47−7.41 (m, 1H), 7.38−7.33 (m, 1H), 7.18 (d, J = 9.1 Hz, 1H), 6.87 (d, J = 8.2 Hz, 2H), 5.20 (s, 1H), 3.95 (s, 3H), 1.90 (s, 3H), 1.76 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 143.0, 138.5, 134.5, 130.2, 129.2 (2×), 128.5, 128.0, 127.6 (2×), 127.3, 125.3, 124.2, 121.8, 112.9, 105.9, 100.3, 56.8, 51.4, 31.2 (2×), 21.4 ppm. MS (EI, 70 eV), m/z (%) 393 (31) [M^+], 378 (15), 298 (25), 272 (35), 222 (100), 208 (19), 182 (30), 178 (51), 171 (19), 165 (24), 155 (26), 152 (25), 139 (30), 91 (65). HRMS (ESI) for $C_{23}H_{23}NO_3S$ ([M + H]$^+$) calcd 394.1471, found 394.1474.

*N-(4-(2-Methoxynaphthalen-1-yl)-2-methylbut-3-yn-2-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**14**).* The tosylated naphthylacetylene **13** (5.0 g, 12.7 mmol) is secured in a flame-dried Schlenk flask (250 mL) three times and DMF (75 mL) was added. The solution was cooled to 0 °C and then sodium hydride (696 mg, 17.4 mmol, 60% dispersion with paraffin oil) was added under argon. The reaction mixture was allowed to warm to rt andstirred for another hour while the evolution of hydrogen gas was observed. After cooling down to 0 °C again, propargyl bromide (2.21 g, 1.41 mL, 18.6 mmol) was added via syringe and the reaction mixture allowed to warm to rt and then stirred for another 16 h. After that time the reaction was quenched with water and extracted with ethyl acetate (3×). After washing with water and brine the combined organic phases were dried over $MgSO_4$ and the solvent removed in vacuum. The crude product purified by column chromatography, using petrol ether/diethyl ether (4:5 v/v). Two fractions were isolated which both turned out to be pure product **14** (5.08 g, 93%) as a syrup, which solidifies after standing. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8. Thirty (dd, J = 8.4, 0.8 Hz, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.48 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.36 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 4.60 (d, J = 2.4 Hz, 2H), 3.98 (s, 3H), 2.34 (t, J = 2.4 Hz, 1H), 2.25 (s, 3H), 1.95 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 143.1, 139.6, 134.5, 130.4, 129.4, 128.5, 128.1, 127.4 (2×), 125.3, 124.3, 112.9, 105.8, 100.7, 81.7, 79.2, 72.3, 58.4, 56.8, 37.6, 30.7, 21.5 ppm. MS (EI, 70 eV), m/z (%) 416 (100), 276 (48), 261 (88), 246 (29), 223 (62), 220 (90), 208 (24), 181 (22), 178 (21), 169 (24), 165 (38), 91 (49), 80 (32), 70 (24). HRMS (ESI) for $C_{26}H_{26}NO_3S$ ([M + H]$^+$) calcd 432.1628, found 432.1633.

*1-(2-Methoxynaphthalen-1-yl)hepta-1,6-diyn-3-one (**18**). rac-1-(2-Methoxynaphthalen-1-yl)hepta-1,6-diyn-3-ol (**17**).* The synthesis of aldehyde **16** from pen-4-yn-1-ol (**15**) using a Swern-Oxidation has been described before and was accomplished in 71% yield (containing small amounts of NEt_3) after Kugelrohr distillation.[39] The NMR data are in agreement with the reported data.

A 100 mL Schlenk tube was charged with **2** (1.0 g, 5.49 mmol) and secured three times with vacuum and argon and dissolved in 50 mL of THF. The solution was cooled to −78 °C and *n*-BuLi solution (3.6 mL, 5.61 mmol, 1.56 M) was introduced via syringe dropwise. After stirring for additional 30 min the solution was allowed to warm to rt and after further stirring for 30 min the solution is cooled back to −78 °C again. In a second flask a solution of **16** (451 mg, 5.49 mmol) in THF (30 mL) was prepared under argon and cooled to −78 °C. The cooled solution of the organolithium reagent was transferred into that mixture slowly via cannula. An orange solution resulted which was warmed to rt and stirred for additional 12 h. The reaction was quenched with NH_4Cl soln. and the aqueous phase extracted with ethyl acetate several times. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography on silica gel first using *n*-hexane/ethyl acetate (6:1 v/v) and then pure ethyl acetate as eluent provided a main fraction, which was found to be product **17** (1.14 g, 79%) as a syrupy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.19 (dd, J = 8.5, 1.0 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.52 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.37 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 5.02−4.94 (m, 1H), 4.00 (s, 3H), 2.65 (d, J = 5.0 Hz, 1H), 2.61−2.52 (m, 2H), 2.21−2.12 (m, 2H), 2.03 (t, J = 2.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 134.6, 130.5, 128.5, 128.2, 127.6, 125.1, 124.3, 112.6, 105.4, 99.0, 83.7, 79.9, 69.2, 62.2, 56.7, 36.6, 14.8 ppm. MS (EI, 70 eV), m/z (%) 264 (100) [M^+], 233 (16), 221 (28), 208 (28), 182 (28), 178 (35), 165 (59), 152 (46), 139 (59). HRMS (EI) for $C_{18}H_{16}O_2$ calcd 264.1145, found 264.1142.

*1-(2-Methoxynaphthalen-1yl)hepta-1,6-diyn-3-one (**18**).* Dess−Martin periodinane (1.765 g, 4.16 mmol) was dissolved in CH_2Cl_2 (40 mL) in a Schlenk flask under argon and cooled to 0 °C. A solution of **17** (1.0 g, 3.78 mmol) in CH_2Cl_2 (20 mL) was added via syringe and the orange reaction mixture stirred for 16 h at rt. The reaction mixture was quenched with sat. $NaHCO_3$ soln. and the aqueous phase extracted with CH_2Cl_2 (3×). The combined organic phases were washed with sat. $Na_2S_2O_3$ soln., water and brine and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 6:1, v/v) to yield pure **18** as the single product (730 mg, 74%). mp 110−111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21 (dd, J = 8.5, 1.2 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.60 (ddd, J = 8.5, 6.9, 1.3 Hz, 1H), 7.42 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.26 (d, J = 9.1 Hz, 1H), 4.06 (s, 3H), 3.05 (dd, J = 8.1, 6.7 Hz, 2H), 2.71 (ddd, J = 8.1, 6.7, 2.7 Hz, 2H), 2.02 (t, J = 2.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.4, 162.0, 135.0, 133.7, 128.6, 128.5, 128.4, 124.9, 124.8, 112.3, 102.6, 97.2, 88.0, 82.7, 69.3, 56.7, 44.3, 13.7 ppm. MS (EI, 70 eV), m/z (%) 262 (32) [M^+], 233 (28), 219 (52), 209 (25), 203 (26), 189 (29), 182 (26), 152 (100), 138 (42). HRMS (EI) for $C_{18}H_{14}O_2$ calcd 262.0989, found 262.0992.

*2-Methoxy-1-(3-methylenehepta-1,6-diyn-1-yl)naphthalene (**22**). 2,5-Diiodohexa-1,5-diene (**20**).* In a 250 mL Schlenk flask NaI (7.67 g, 51.2 mmol) is secured three times with vacuum/argon and then dissolved in acetonitrile (100 mL) and afterward TMSCl (6.5 mL, 51.2 mmol) and distilled water (0.51 mL, 25.6 mmol) were added via syringe. The yellow-orange suspension was stirred for 15 min and a solution of 1,5-hexadiyne (**19**, 5 mL, 2.0 g, 25.6 mmol, 50% w/w in *n*-pentane) in acetonitrile (10 mL) was introduced via syringe. The reaction mixture was becoming darker upon the addition and the mixture was stirred overnight. For workup water (ca. 50 mL) was added and the mixture extracted with Et_2O (3×), washed with NaOH (5%) and brine and dried over Na_2SO_4. The reaction product was chromatographed over a short silica column with *n*-hexane/ethyl acetate (4:1, v/v), yielding **20** as an oil (3.65 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.11 (d, J = 1.5, 2H), 5.75 (d, J = 1.5 Hz, 2H), 2.60 (s, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 127.3, 108.9, 44.5 ppm. MS (GC-MS), m/z (%) 334 (17) [M^+], 207 (44), 80 (100). HRMS (EI) for $C_6H_8I_2$ calcd 333.8710, found 333.8708.

*1-(6-Iodo-3-methylenehept-6-en-1-yn-1-yl)-2-methoxynaphthalene (**21**).* For the coupling reaction $Pd(PPh_3)_4$ (165 mg, 0.143 mmol) and CuI (28 mg, 0.143 mmol) were secured in a Schlenk flask and diisopropylamine (100 mL) as well as the diiodide **20** (1.0 g, 3.0 mmol, weighted and added via argon-flushed syringe) introduced. Afterward the solution of the alkyne **2** (519 mg, 2.85 mmol, 0.95 equiv) in diisopropylamine (20 mL) was added very slowly from a dropping funnel. After completed addition the reaction mixture was stirred for another 2 h. During that time a precipitate is formed, yielding a yellow suspension and TLC control showed, that the alkyne substrate has been completely consumed. Workup was performed by addition of sat. NH_4Cl soln. and extraction by ethyl acetate (3×). The combined organic extracts were washed with water and brine and dried over Na_2SO_4. After evaporation of the solvents the crude product was

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purified chromatographically using *n*-hexane/ethyl acetate (4:1, v/v), yielding the product **21**, beside excessive **20**, as a yellowish sirup (381 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.56 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.39 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.24 (d, J = 9.2 Hz, 1H), 6.17 (d, J = 1.5 Hz, 1H), 5.77 (d, J = 1.5 Hz, 1H), 5.59 (d, J = 1.5 Hz, 1H), 5.44 (d, J = 1.5 Hz, 1H), 4.03 (s, 3H), 2.87 (t, J = 7.5 Hz, 2H), 2.59 (d, J = 7.5, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 134.5, 130.3, 129.9, 128.6, 128.2, 127.5, 126.5, 125.3, 124.3, 122.1, 112.8, 110.8, 106.3, 98.8, 84.6, 56.7, 44.0, 37.2 ppm. HRMS (EI) for $C_{19}H_{17}IO$ calcd 388.0319, found 388.0315.

*2-Methoxy-1-(3-methylenehepta-1,6-diyn-1-yl)naphthalene (**22**).* Compound **21** (400 mg, 1.03 mmol) was dissolved in DMF (10 mL) and the solution cooled to 0 °C. The NaHMDS (2 mL, 1.2 mL, 0.6 M soln. in THF) was added via syringe and the TLC control showed, that the reaction was complete after additional 10 min stirring. For workup water was added at 0 °C and the solution extracted with ethyl acetate (3×) and the combined organic phases were dried over Na_2SO_4. Evaporation of the solvent in vacuum gave the crude product, which was purified by column chromatography applying *n*-hexane/ethyl acetate (4:1, v/v) as the eluent, yielding diyne **22** as a white solid (215 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (dd, J = 8.5, 1.1 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.55 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.40 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 5.61 (d, J = 1.7 Hz, 1H), 5.44 (d, J = 1.7 Hz, 1H), 4.03 (s, 3H), 2.68−2.56 (m, 4H), 2.02 (t, J = 2.5 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 134.5, 130.3, 130.2, 128.6, 128.2, 127.5, 125.3, 124.3, 121.9, 112.8, 106.3, 98.5, 84.6, 83.8, 68.9, 56.7, 36.7, 17.9 ppm. MS (EI, 70 eV), m/z (%) 260 (100) [M^+], 245 (21), 215 (21), 202 (46). HRMS (EI) for $C_{19}H_{16}O_1$ calcd 260.1196, found 260.1190.

*rac-1-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)prop-2-yn-1-ol (**25**). 2-((2-Methoxynaphthalen-1-yl)ethynyl)benzaldehyde (**24**).* A 250 mL Schlenk flask containing 1-ethynyl-2-methoxynaphthalene (**2**, 1.635 g, 8.97 mmol, 1.05 equiv), $PdCl_2(PPh_3)_2$ (227.4 mg, 0.33 mmol, 3.8 mol %) and CuI (123.8 mg, 0.65 mmol, 7.6 mol %) was evacuated and backfilled with argon three times. Afterward triethylamine (100 mL) was added and the resulting solution was stirred for 15 min, while changing color from yellow to dark brown. Subsequently 2-bromobenzaldehyde (**23**, 1.58 g, 1.0 mL, 8.55 mmol, 1.0 equiv) was added via syringe and the reaction mixture heated to 50−55 °C. Shortly after heating started an increasingly dense precipitate formed. TLC control showed complete consumption of the starting materials after 36 h and the reaction was quenched with sat. NH_4Cl soln. after cooling to rt. Extraction with ethyl acetate (3×) and washing of the combined organic phases with water and sat. NaCl soln. was followed by drying over Na_2SO_4. The crude product (2.98 g) was charged to silica gel and purified by chromatography with cyclohexane and ethyl acetate (4:1 v/v), yielding **24** as a yellow solid (1.876 g, 77%). mp 99−100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.87 (d, J = 0.8 Hz, 1H), 8.31 (dd, J = 8.4, 1.4 Hz, 1H), 7.99 (dd, J = 7.8, 1.4 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.84−7.77 (m, 2H), 7.66−7.56 (m, 2H), 7.50−7.43 (m, 1H), 7.42 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 4.08 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.7, 159.9, 135.8, 134.4, 133.9, 133.3, 131.2, 128.6, 128.5, 128.4, 127.9, 127.8, 127.3, 125.2, 124.5, 112.5, 105.6, 94.7, 91.5, 56.7 ppm. MS (EI, 70 eV), m/z (%) 286 (86) [M^+], 271 (31), 257 (25), 255 (35), 243 (49), 226 (31), 215 (100), 213 (78), 187 (23), 139 (19). HRMS (EI) for $C_{20}H_{14}O_2$ calcd 286.0988, found 286.0985.

*rac-1-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)prop-2-yn-1-ol (**25**).* A 50 mL Schlenk flask was charged with THF (25 mL) and *n*-BuLi solution (4.5 mL, 7.0 mmol, 1.55 M, 1.1 equiv) and the solution was cooled to −78 °C. Trimethylsilylacetylene (0.99 mL, 7.0 mmol, 1.1 equiv) was introduced in portions via syringe and after completed addition the reaction mixture was stirred for further 30 min. After stirring for additional 75 min at room temperature the solution was cooled back to −78 °C again. Meanwhile in a second 250 mL Schlenk flask a solution of **24** (1.822 g, 6.36 mmol, 1.0 equiv) in THF (75 mL) was prepared under argon and cooled to −78 °C as well. The cooled solution of the organolithium reagent was transferred into that mixture in portions via syringe over 10 min. After additional stirring for 30 min at −78 °C the yellow-orange mixture was allowed to warm to room temperature and after 3h became increasingly dark. The TLC control (eluent: Et_2O) indicated complete consumption of aldehyde **24** and the reaction was quenched with NH_4Cl soln., the aqueous phase were extracted with Et_2O (2×) and the combined organic phases washed with water and brine, dried over Na_2SO_4 and concentrated and dried in vacuum (ca. 2.7 g crude product).

The crude product was directly subjected to desilylation. It was therefore dissolved in a mixture of THF and MeOH (70 mL each, 1:1 v/v) and potassium fluoride (2.20 g, 38.2 mmol, 6 equiv) added. After stirring for 18 h the desilylation was completed. The solvent was removed in vacuum and the residue charged to silica gel and purified by column chromatography over silica gel using cyclohexane/diethyl ether. The pure product **25** was obtained as solid (1.852 g, 93%). mp 83−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.37 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.81−7.74 (m, 2H), 7.73−7.68 (m, 1H), 7.60 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.44−7.36 (m, 3H), 7.22 (d, J = 9.2 Hz, 1H), 6.03 (dd, J = 6.3, 2.4 Hz, 1H), 4.53 (d, J = 6.3 Hz, 1H), 4.05 (s, 3H), 2.72 (d, J = 2.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 142.0, 133.8, 132.2, 130.7, 128.6, 128.5, 128.4, 128.2, 127.6, 127.1, 125.2, 124.4, 122.0, 112.1, 105.8, 96.6, 90.2, 82.7, 75.0, 63.6, 56.5 ppm. MS (EI, 70 eV), m/z (%) 312 (43) [M^+], 297 (58), 281 (59), 268 (33), 252 (83), 250 (46), 239 (100), 226 (27), 213 (29), 158 (54), 126 (22), 115 (29), 53 (29). HRMS (ESI) for $C_{22}H_{17}O_2$ calcd 313.1223, found 313.1220.

General Procedures for [2 + 2 + 2] Cycloaddition Reactions. *General Procedure A: Photochemical [2 + 2 + 2] Cycloaddition Reactions.*[40] An inerted and thermostated (between 0 and 25 °C) reaction vessel was loaded with either diyne **4**, **6**, **8**, **9**, **11**, **12**, **18** or **22** (1 equiv), catalyst [CpCo(COD)] (1−10 mol %), THF (10−20 mL) and nitrile (4−6 equiv) under argon atmosphere. The mixture was stirred thoroughly and irradiated by two 460 W lamps for 20−36 h. The reaction was quenched by switching off the lamps and simultaneously letting in air. The solvent was evaporated, and the oily residue was purified on silica gel, in general using either *n*-hexane, petrol ether or cyclohexane/ethyl acetate in different proportions as eluent.

General Procedure B: Microwave-Assisted [2 + 2 + 2] Cycloaddition Reactions. The diyne **4**, **14**, or **25** (1 equiv) and catalyst [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] (10 mol %) were weighted into a microwave reaction vial (10 mL) and flushed with argon. Afterward toluene (2−3 mL) and nitrile (5 equiv) were added via syringe and the tube sealed with a septum. The reaction vessel was introduced to the microwave and heated at 140 °C for 10 min. The solvent was removed under vacuum and the residue charged to silica gel. The crude product was purified on silica gel.

*2-Mesityl-4-(2-methoxynaphthalen-1-yl)-6-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**26**).* The compound was prepared from **4** (230 mg, 0.63 mmol) after the General Procedure A, yielding the pyridine **24** with 43% yield (127 mg) after chromatography (silica gel, eluent: petrol ether/ethyl acetate 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.08−8.03 (m, 2H), 7.90 (d, J = 9.0 Hz, 1H), 7.84−7.79 (m, 1H), 7.73 (s, 1H), 7.57−7.53 (m, 1H), 7.45−7.31 (m, 6H), 6.86 (s, 2H), 4.73 (dd, J = 3.9, 3.4 Hz, 2H), 4.43 (ddd, J = −13.8, 3.7, 3.4 Hz, 1H), 4.14 (ddd, J = −13.8, 3.7, 3.4 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 6H), 2.16 (s, 3H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 156.3, 154.1, 151.0, 140.1, 138.5, 136.4, 135.6, 134.8, 130.4, 129.4, 129.3, 128.9, 128.7, 128.6, 128.4, 128.0, 127.8, 127.3, 126.7, 125.4, 124.9, 123.6, 113.9, 113.3, 57.9, 56.8, 56.5, 21.1, 18.5 ppm. MS (EI, 70 eV), m/z (%) 469 (100) [M^+], 453 (21), 207 (19). HRMS (ESI-TOF) for $C_{33}H_{31}N_2O$ calcd 471.2431, found 471.2423.

*4-(2-Methoxynaphthalen-1-yl)-1,1,3,3-tetramethyl-6-phenyl-1,3-dihydro-[1,2,5]oxadisilolo-[3,4]pyridine (**27**).* Following the General Procedure A, compound **27** was prepared from diyne **6** (340 mg, 1 mmol) and benzonitrile, providing the product as a yellow oil (yield: 44%, 195 mg) after chromatography (silica gel, eluent: petrol ether/ethyl acetate 6:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.03 (ddd, J = 7.3, 5.5, 1.7 Hz, 2H), 7.93 (s, 1H), 7.89 (s, 1H), 7.80−7.77 (m, 1H), 7.44−7.35 (m, 3H), 7.33 (d, J = 9.1 Hz, 1H), 7.30−7.26 (m, 2H), 7.11−7.07 (m, 1H), 3.80 (s, 3H), 0.45 (s, 3H), 0.43 (s, 3H), 0.0 (s, 3H), −0.61 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.6, 157.4, 154.0, 140.2, 134.0, 130.1, 128.9, 128.8, 127.9, 127.7, 127.5, 126.6, 125.3, 124.3, 123.6, 121.6, 113.0, 56.1, 0.92, 0.89, 0.42, 0.31 ppm. ^{29}Si NMR (79.5

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MHz, $CDCl_3$) δ = 16.3, 14.5 ppm. MS (EI, 70 eV), m/z (%) 441 (100) [M^+], 426 (22), 410 (32). HRMS (ESI) for $C_{26}H_{28}NO_2Si_2$ calcd 442.1653, found 442.1650. HPLC conditions: Reprosil 100, *n*-heptane/ethanol 99:1, 1.0 mL/min, T_1 = 14.5 min, T_2 = 18.5 min.

*4-(2-Methoxynaphthalen-1-yl)-1,1,3,3,6-pentamethyl-1,3-dihydro-[1,2,5]oxadisilolo-[3,4]pyridine (**28**).* The substance was prepared from **6** (220 mg, 0.65 mmol) and acetonitrile after General Procedure A, yielding **28** in 93% yield (229 mg, yellow oil) after chromatography (silica gel, eluent: petrol ether/ethyl acetate 6:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.88 (d, J = 9.2 Hz, 1H), 7.78−7.75 (m, 1H), 7.37 (d, J = 0.5 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.27−7.25 (m, 3H), 7.00−6.97 (m, 1H), 3.79 (s, 3H), 2.65 (s, 3H), 0.40 (s, 3H), 0.39 (s, 3H), −0.04 (s, 3H), −0.62 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 158.2, 153.9, 140.0, 130.0, 128.7, 127.8, 126.5, 125.1, 124.8, 124.2, 123.5, 112.7, 55.9, 24.9, 0.9, 0.8 ppm. ^{29}Si NMR (79.5 MHz, $CDCl_3$) δ = 16.2, 14.3 ppm. MS (EI, 70 eV), m/z (%) 379 (100) [M^+], 364 (36), 348 (49), 245 (25). HRMS (ESI) for $C_{21}H_{26}NO_2Si_2$ calcd 380.1497, found 380.1495. HPLC conditions: Chiralcel OD-H, *n*-heptane/ethanol 99:1, 1.0 mL/min, T_1 = 9.5 min, T_2 = 12.7 min.

*4-(2-Methoxynaphthalen-1-yl)-2-phenylfuro[3,4-c]pyridin-3(1H)-one (**29**).* Following the General Procedure A, heterobiaryl **29** was synthesized from **8** (264 mg, 1 mmol). The crude product was purified via chromatography on silica gel (eluent: petrol ether/ethyl acetate 4:1 v/v), yielding the product in 39% yield (140 mg). mp 211−214 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16−8.09 (m, 2H), 8.00 (d, J = 9.1 Hz, 1H), 7.85 (s, 1H), 7.89−7.82 (m, 1H), 7.55−7.44 (m, 4H), 7.41 (d, J = 9.1 Hz, 1H), 7.38−7.31 (m, 2H), 5.36 (d, J = 16.1 Hz, 1H), 5.30 (d, J = 16.1 Hz, 1H), 3.87 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 160.8, 157.1, 156.2, 155.2, 138.2, 132.9, 131.5, 130.3, 129.3, 129.0, 128.4, 127.9, 127.0, 124.2, 123.7, 120.4, 119.1, 113.0, 112.2, 68.2, 56.6 ppm. MS (EI, 70 eV), m/z (%) 367 (100) [M^+], 338 (29), 323 (68), 308 (29), 294 (45), 280 (17), 176 (19), 133 (21). HRMS (EI) for $C_{24}H_{17}NO_3$ calc. 367.1203, found 367.1201. HPLC conditions: Chiralpak AD-H, *n*-heptane/ethanol 98:2, 1.0 mL/min, T_1 = 15.4 min, T_2 = 18.3 min.

*4-(2-Methoxynaphthalen-1-yl)-2-methyl-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one (**30**).* Preparation of **30** from **9** (400 mg, 1.44 mmol) after General Procedure A gave the product in 42% yield (230 mg). Purification was performed with chromatography on silica gel (eluent: petrol ether/ethyl acetate 1:1 v/v + 2% NEt_3). mp 160−163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.12−8.07 (m, 2H), 7.96 (d, J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.85−7.80 (m, 1H), 7.49−7.35 (m, 5H), 7.32−7.27 (m, 2H), 4.44 (d, J = 17.7 Hz, 1H), 4.36 (d, J = 17.7 Hz, 1H), 3.85 (s, 3H), 3.09 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1, 158.8, 155.1, 153.8, 151.6, 139.1, 133.3, 130.7, 129.6, 129.4, 128.9, 128.2, 127.8, 127.0, 126.6, 124.5, 123.4, 120.6, 113.6, 113.5, 56.8, 51.2, 29.5 ppm. MS (EI, 70 eV), m/z (%) 380 (100) [M^+], 351 (53), 323 (44). HRMS (ESI) for $C_{25}H_{21}N_2O_2$ calcd 381.1598, found 381.1604. HPLC conditions: Chiralcel OD-H, *n*-heptane/ethanol 98:2, 1.0 mL/min, T_1 = 15.4 min, T_2 = 56.0 min.

*4-(2-Methoxynaphthalen-1yl)-3,3-dimethyl-6-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**31**).* Diyne **11** (200 mg, 0.72 mmol) was reacted in accordance to the General Procedure A and the expected product **31** was isolated after chromatography on silica gel with CH_2Cl_2/ethanol (4:1 v/v + 1% NEt_3) as eluent in 62% yield (246 mg). mp 137−139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99−7.92 (m, 3H), 7.85−7.79 (m, 1H), 7.65 (s, 1H), 7.44−7.28 (m, 6H), 7.14−7.08 (m, 1H), 4.31 (d, J = 16.1 Hz, 1H), 4.25 (d, J = 16.1 Hz, 1H), 3.83 (s, 3H), 2.01 (broad s, NH, 1H), 1.21 (s, 3H), 0.82 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.6, 154.2, 153.2, 150.8, 143.3, 140.0, 134.1, 130.1, 129.0, 128.7, 128.6, 127.9, 127.5, 126.5, 125.5, 123.6, 123.0, 114.3, 113.3, 64.6, 56.1, 49.9, 27.7, 26.8 ppm. MS (EI, 70 eV), m/z (%) 378 (100) [M-H$^+$], 363 (67), 347 (34). HRMS (ESI) for $C_{26}H_{23}N_2O$ calcd 379.1805, found 379.1807. HPLC conditions: Lux Celullose1, *n*-heptane/ethanol 99:1, 1.0 mL/min, T_1 = 22.3 min, T_2 = 24.6 min.

*4-(2-Methoxynaphthalen-1yl)-2,3,3-trimethyl-6-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**32**).* Heterobiaryl **32** was prepared from **12** (175 mg, 0.6 mmol) following the General Procedure A, yielding the compound in 35% yield (83 mg). The crude product was purified by chromatography on silica gel with petrol ether/ethyl acetate (3:1 v/v + 1% NEt_3) as eluent. mp 88−89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99−7.94 (m, 2H), 7.94 (d, J = 9.3 Hz, 1H), 7.82 (dd, J = 6.2, 2.5 Hz, 1H), 7.67 (s, 1H), 7.43−7.25 (m, 7H), 7.14−7.10 (m, 1H), 4.05 (s, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.05 (s, 3H), 0.67 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.2, 154.2, 150.5, 149.7, 142.9 140.1, 134.2, 130.1, 129.0, 128.6 (2×), 127.8, 127.5, 126.5, 125.7, 123.6, 123.1, 114.1, 113.4, 65.3, 57.6, 56.2, 33.6, 22.1, 20.5 ppm. MS (EI, 70 eV), m/z (%) 394 (100) [M], 365 (42), 309 (98), 189 (18). HRMS (ESI) for $C_{27}H_{27}N_2O$ calcd 395.2118, found 395.2123. HPLC conditions: Lux Cellulose2, *n*-heptane/ethanol 96:4, 1.0 mL/min, T_1 = 6.5 min, T_2 = 7.4 min.

*4-(2-Methoxynaphthalen-1-yl)-6-phenyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**33**).* Heterobiaryl **33** was prepared from **14** (163 mg, 0.38 mmol) following the General Procedure B (140 °C, 10 min). The crude product was purified via chromatography on silica gel (eluent: cyclohexane/ethyl acetate 4:1 v/v), yielding the product yielding the compound in 71% yield (143 mg). mp 234−235 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, J = 9.1 Hz, 1H), 7.93−7.88 (m, 2H), 7.85−7.80 (m, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 7.42−7.26 (m, 8H), 7.04−6.99 (m, 1H), 4.76 (d, J = 14.4 Hz, 1H), 4.70 (d, J = 14.4 Hz, 1H), 3.80 (s, 3H), 2.41 (s, 3H), 1.61 (s, 3H), 1.21 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.9, 154.2, 151.3, 145.1, 143.3 140.1, 139.2, 138.0, 134.0, 130.7, 129.7 (2×), 129.0, 128.9, 128.8 (2×), 128.1, 127.5 (2×), 127.4 (2×), 126.8, 125.2, 123.7, 113.8, 113.2, 72.1, 56.1, 52.4, 27.8, 26.9, 21.6 ppm (one C atom could not be assigned). MS (EI, 70 eV), m/z (%) 534 (11) [M^+], 520 (78), 519 (100), 363 (18), 333 (19), 323 (18). HRMS (ESI) for $C_{33}H_{31}N_2O_3S$ calcd 535.2050, found 535.2050.

*1-(2-Methoxynaphthalen-1-yl)-3-phenyl-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one (**34**).* The synthesis of **34** from **18** (58 mg, 0.22 mmol) according to the General Procedure A gave the product in 70% yield (51 mg). The crude product was purified by chromatography on silica gel with petrol ether/ethyl acetate (4:1 v/v) as eluent. mp 120−123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16−8.10 (m, 2H), 7.97 (d, J = 9.3 Hz, 1H), 7.90 (s, 1H), 7.84 (dd, J = 6.0, 3.7 Hz, 1H), 7.48−7.39 (m, 3H), 7.39 (d, J = 9.3 Hz, 1H), 7.34−7.28 (m, 2H), 3.83 (s, 3H), 3.34−3.17 (m, 2H), 2.78−2.58 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 203.0, 165.1, 160.8, 155.0, 154.8, 138.8, 133.1, 131.0, 130.8, 129.9, 129.4, 128.9, 128.3, 128.0, 126.7, 124.4, 123.5, 121.0, 117.2, 113.4, 56.7, 36.5, 25.6 ppm. MS (EI, 70 eV), m/z (%) 365 (75) [M^+], 350 (100), 337 (77), 308 (55), 207 (21), 174 (22). HRMS (ESI) for $C_{25}H_{20}NO_2$ calcd 366.1489, found 366.1484. Anal. Calcd for $C_{25}H_{19}NO_2$ (365.42): C 82.17, H 5.24 N 3.83. Found: C 82.22, H 5.27 N 3.67. HPLC conditions: Chiralcel OD-H, *n*-heptane/ethanol 98:2, 0.8 mL/min, T_1 = 33.2 min, T_2 = 52.7 min.

*1-(2-Methoxynaphthalen-1-yl)-7-methylene-3-phenyl-6,7-dihydro-5H-cyclopenta[c]pyridine (**35**).* Diine **22** (100 mg, 0.384 mmol), catalyst [CpCo(*trans*-$MeO_2CHC{=}CHCO_2Me$){$P(OEt)_3$}] (9 mg, 0.019 mmol) and PhCN (0.2 mL, 1.92 mmol) were dissolved under inert conditions in dry toluene (10 mL) in a Schlenk flask. The reaction solution was heated to 100 °C for 7 h and after cooling, the solvent and all volatiles were removed and the residue on silica gel silica gel using *n*-hexane/ethyl acetate (4:1, v/v) as eluent, yielding **35** as a white solid (78 mg, 56%). According to the ^{1}H NMR contains the product ca. 20% of the compound with *endo*-isomerized double bond as byproduct [significant signals in the ^{1}H NMR spectra ($CDCl_3$): 5.75 (q, J = 1.7 Hz, 0.20 H), 3.89 (s, 0.64 H), 1.56 (d, J = 1.7 Hz, 0.60 H)]. NMR data for **35**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (dd, J = 8.1, 1.5 Hz, 2H), 7.95 (d, J = 9.0 Hz, 1H), 7.86−7.81 (m, 1H), 7.72 (dd, J = 1.0 Hz, 1H), 7.46−7.29 (m, 7H), 4.71 (dd, J = 2.4, 2.0 Hz, 1H), 4.18 (dd, J = 2.5, 2.0 Hz, 1H), 3.85 (s, 3H), 3.11 (dd, J = 7.3, 7.3 Hz, 2H), 2.88−2.75 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.2, 154.3, 151.6, 147.2, 135.1, 133.0, 130.1, 129.5, 128.9, 128.7, 128.0, 127.5, 127.4, 126.8, 124.7, 123.9, 122.8, 116.7, 114.4, 107.4, 57.3, 32.2, 30.0 ppm (1 C atom could not be asigned). MS (EI, 70 eV), m/z (%) 363 (45) [M^+], 348 (37), 332 (100). HRMS (ESI) for $C_{26}H_{22}NO$ calcd 364.1696, found 364.1701. Anal. Calcd for $C_{26}H_{21}NO$ (363.45): C 85.92, H 5.82 N 3.85. Found: C 85.38, H 5.68 N 3.76. HPLC conditions: Reprosil 100, *n*-heptane/ethanol 99.5:0.5, 1.0 mL/min, T_1 (20 °C) = 9.23 min, T_2 (20 °C) = 11.58 min.

*1-(2-Methoxynaphthalen-1-yl)-3-phenyl-5H-indeno[1,2-c]-pyridine-5-ol (**36**) and 1-(2-Methoxynaphthalen-1-yl)-3-phenyl-5H-*

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*indeno[1,2-c]pyridin-5-one (**37**).* The reaction of **25** (477 mg, 1.53 mmol) and PhCN (0.78 mL, 7.63 mmol) was accomplished following General Procedure B and furnished two products (**36** and **37**) with 14% yield of the diastereomeric alcohols **36** (88 mg) and 43% yield for **37** (271 mg) after chromatography on silica gel (eluent: cyclohexane/ethyl acetate 2:1 v/v). The spectra of **36** were complex due to several sets of signals and have not been further investigated. The reaction using conventional heating (100 °C, 15.5 h) gave nearly identical results (**36**: 12% yield and **37**: 41% yield). MS (EI, 70 eV), *m*/*z* (%) 413 (100) [M(−2H)$^+$], 398 (40), 382 (24). HRMS (ESI) for $C_{29}H_{20}NO_2$ calcd 414.1489, found 414.1496. Compound **37**: mp 239−241 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13−8.06 (m, 3H), 8.08 (s, 1H), 7.94−7.88 (m, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.51−7.32 (m, 7H), 7.20 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 7.12 (dd, *J* = 7.5, 7.4, 1.3 Hz, 1H), 6.34 (dd, *J* = 7.4, 0.9 Hz, 1H), 3.82 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.8, 159.3, 154.7, 150.3, 144.2, 142.6, 138.8, 136.0, 135.6, 134.0, 133.0, 131.1, 129.7, 129.5, 129.1, 128.9 (2 C), 128.3, 127.3 (3 C), 124.9, 124.6, 124.2, 122.7, 121.8, 113.7, 113.2, 56.8 ppm. MS (EI, 70 eV), *m*/*z* (%) 413 (100) [M$^+$], 398 (35), 382 (20), 258 (16), 170 (21). HRMS (EI) for $C_{29}H_{19}NO_2$ calcd 413.1410, found 413.1404. HPLC conditions: Chiralcel OJ-H, *n*-heptane/ethanol 95:5, 1.2 mL/min, T_1 = 14.81 min, T_2 = 23.51 min (20 °C) or Cellulose 2, *n*-heptane/isopropanol 95:5, 0.5 mL/min, T_1 = 10.41 min, T_2 = 11.43 min (20 °C).

*1-(2-Methoxynaphthalen-1-yl)-3-phenyl-5H-indeno[1,2-c]-pyridine (**38**).* For the synthesis of compound **38**, ketone **37** (100 mg, 0.242 mmol) was suspended together with the 4-fold amount of hydrazine hydrate (0.03 mL, 0.967 mmol) in diethylene glycol dimethyl ether (diglyme, 2.5 mL) in a microwave reaction vial. The vial was put in an microwave oven and heated to 180 °C for 4 h (200 W). After that reaction time the TLC control showed complete conversion of **36**. For the workup ethyl acetate was added and the mixture washed with water several times, then with brine and finally dried over anhydrous Na_2SO_4. Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate 2:1 v/v + 2% NEt_3) gave the product as syrupy solid in 83% yield (79 mg). Small impurities steaming from **37** are due to fast reoxidation of **38**. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13−8.08 (m, 2H), 8.06 (d, *J* = 9.1 Hz, 1H), 8.02 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.49−7.26 (m, 6H), 7.20 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.96 (dd, *J* = 7.7, 7.6 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 4.10 (s, 2H), 3.78 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.1, 154.7, 153.7, 149.8, 142.9, 139.9, 139.6, 136.6, 133.4, 130.6, 129.5, 128.9, 128.8 (3 C), 128.1, 127.5 (2 C), 127.3, 127.1 (2 C), 126.9, 124.9, 124.8, 123.9, 122.4, 116.5, 114.0, 56.9, 37.3 ppm. MS (EI, 70 eV), *m*/*z* (%) 399 (100) [M$^+$], 368 (23), 244 (26). HRMS (EI) for $C_{29}H_{21}NO$ calcd 399.1618, found 399.1609.

*Procedure for the Enantioselective Photocatalyzed [2 + 2 + 2] Cycloaddition of Diyne **25** with Benzonitrile Using the Chiral Co(I)-Indenyl Complex **43** as Catalyst.*[9] For performing this reaction we followed the General Procedure A, reacting diyne **25** (100 mg, 0.32 mmol) and PhCN (0.17 mL, 1.60 mmol) in the presence of chiral catalyst **43** (10 mol%) in THF (10 mL) at 0 °C for 47 h under irradiation. After workup of the reaction the crude product was purified twice by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate 2:1 v/v) and provided 22 mg (17%) of **37**. The identity of the material was confirmed by NMR and the chiral HPLC analysis gave the enantiomeric ratio of 72:28.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02190.

Additional experimental details for an attempted synthetic approach towards a precursor for compound **38**, ^{1}H and ^{13}C NMR spectra for all synthesized new compounds, data and methods for the chiral HPLC analysis, data and coordinates for the performed calculations. (PDF)

Crystallographic data for compound **37**. (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marko.hapke@catalysis.de.

Notes

The authors declare no competing financial interest.

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