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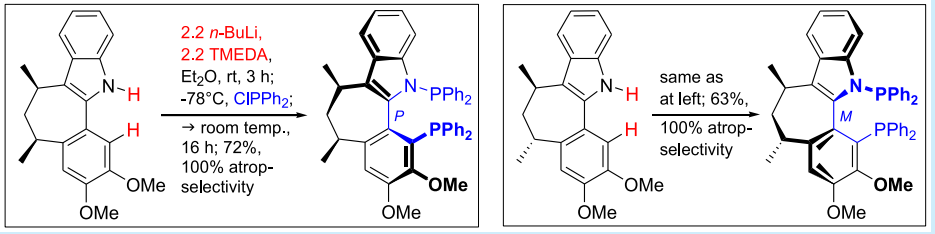
Atropselective Synthesis of *N,C*-Bis(diphenylphosphanes) from Bridged 2-Arylindoles Based on Effective Point-to-Axial Asymmetric Inductions after an Unusual Dilithiation[⊥]

Felix Bäuerle and Reinhard Brückner*

Institut für Organische Chemie, Albert-Ludwigs-Universität, Albertstr. 21, D-79104 Freiburg, Germany

Supporting Information



ABSTRACT: An asymmetric methanolysis of glutaric anhydride and 6 ensuing steps gave veratrol-annulated dimethylcycloheptenone diastereomers with 99% *ee*; ring closures occurred by Friedel−Crafts acylations of carboxylic acids obtained by stereospecific hydrogenolyses of a pair of diastereomeric *δ*-lactones. The mentioned cycloheptenones and Ph−NH−NH_2 underwent Fischer indole syntheses providing the tetracyclic indoles *cis*- and *trans*-**14a**, respectively. Double lithiations with BuLi and quenchings with $ClPPh_2$ furnished the diphosphanes *cis*- and *trans*-**15** with perfect (*P*)- and (*M*)-atropselectivity, respectively.

Enantiomerically pure diphosphanes are abundantly used ligands in asymmetric catalysis.[1] An important subclass thereof contains a diisocyclic C_2-symmetric 1,1′-biaryl-2,2′-bis(diphosphane) scaffold. The most famous diphenylphosphane of this design is BINAP.[2] Many variations thereof are known, including H_8-BINAP,[3] SEGPHOS,[4] DIFLUORPHOS,[5] SUNPHOS,[6] SYNPHOS,[7] SOLPHOS,[8] a nameless aza analog thereof,[9] and many others.[1] Related diphosphane designs are BIPHEMP,[10] MeO-BIPHEP,[11] C_nTunaPhos = TUNEPHOS,[12] Bu-PQ-PHOSPHOS,[13] Pent-PQ-PHOS-PHOS,[14] Hex-PQ-PHOSPHOS,[14] and many more.[1] Almost all diphosphanes of this kind have been synthesized atropunselectively: by resolving the racemic phosphane, the corresponding racemic bis(phosphane oxide), or a racemic precursor. The only atropselective syntheses in this series used point-to-axial asymmetric inductions which allowed Ullmann couplings (inter alia) to afford the bis(phosphane oxide) precursors of one diphosphane with *ds* = 78:22[8] and of three other diphosphanes with *de* ≥ 98%.[13,14]

Diheterocyclic C_2-symmetric 1,1′-biaryl-2,2′-bis(diphosphanes) have been reported as well.[15] Figure 1 illustrates them by the biindolyldiphosphanes **1**−**4**.[16−19] Compounds **1**−**3b**[16−18] and all respective diphosphanes based on other heterocycles[20] stem from resolving racemic mixtures, wherein the biaryl axis had been established without atropcontrol. The only atropselective diphosphane syntheses in this series exploited point-to-axial asymmetric inductions in two dibrominations of a 2,2′-biindolyl (*ds* = 95:5 and 5:95).[19]

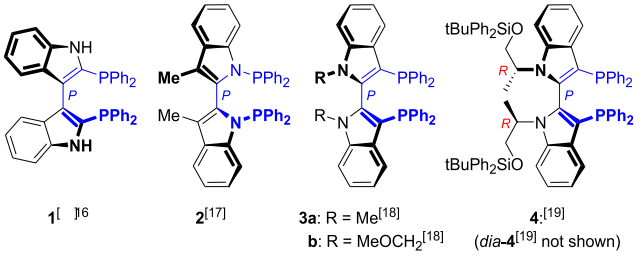


Figure 1. C_2-symmetric 3,3′-biindolyl-2,2′-bis(diphosphane) **1**,[16] 2,2′-biindolyl-1,1′-bis(diphosphane) **2**,[17] and 2,2′-biindolyl-3,3′-bis(diphosphanes) **3a,b**,[18] and **4**.[19]

Refunctionalizations afforded the diphosphanes **4** [= (*R,R,P*)-**4**] and *dia*-**4** [= (*R,R,M*)-**4**] atropisomerically pure.[19]

Monoheterocyclic and therefore only C_1-symmetric biarylbis(diphenylphosphanes) exist, too. Those with an arylindole scaffold (**5**−**9**,[21−23] Figure 2) can be regarded as hybrids of the earlier mentioned diisocyclic C_2-symmetric 1,1′-biaryl-2,2′-bis(diphosphane) scaffolds and the diphosphane motifs from Figure 1. None of them has been obtained atropisomerically pure yet. In contrast, the present study reveals perfectly atropselective syntheses of the arylindole diphosphanes *cis*-**15**, which is *P*-configured, and *trans*-**15**, which is *M*-configured (formulas: Figure 4).

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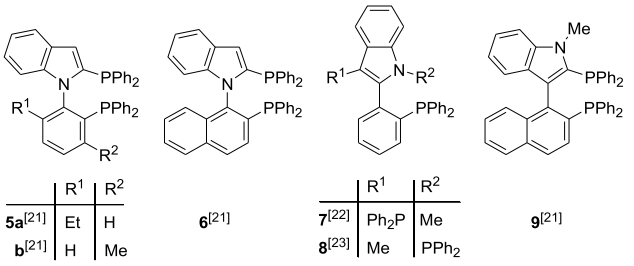

Figure 2. Arylindole-based diphosphanes known to date.

Our approach was inspired by a 60 year old observation:[24] The UV absorption of the cycloheptadieno-phenylindole **10** (Figure 3) exhibits a hypsochromic shift relative to the

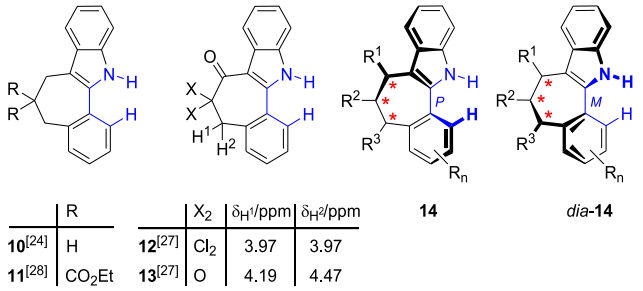

Figure 3. Cycloheptadieno-2-arylindoles: scaffolds with temporary, if not permanent twists.

analogous cyclohexadieno-phenylindole.[24] This was attributed to a decreased conjugation across the indole-phenyl bond due to "the polymethylene chain acting as a lever which turns the benzene moiety out of the indole plane".[24] The resulting twist about the phenyl-indole bond causes the formation of an (equilibrating) 50:50 mixture of an (*M*)- and a (*P*)-atropisomer.[25] We wanted to design cycloheptadieno-phenylindoles which would twist unidirectionally (with or without equilibrating with each other) and thereby result as single atropisomers in a conceptually novel manner.

The atropisomerization of a few derivatives of the unsubstituted cycloheptadieno-phenylindole **10**[26] and some related biaryls was studied by ^{1}H NMR spectroscopy: Compound **13**[27] did not atropisomerize, but compounds **11**[28] and **12**[27] did. Biphenyl—rather than 2-phenylindole—containing a $CH_2-CH_2-CH_2$ bridge ($\Delta G^{\ddagger}_{\text{atropisomerization in the }^1\text{H NMR spectrometer}}$ = 12.5 kcal/mol[29]) and their $CH_2-C(CO_2Et)_2-CH_2$- or CH_2-O-CH_2-containing analogs atropisomerize with similar rates.[30] A biphenyl with a *meso*-configured C(Me)H−NH−C(Me)H bridge atropisomerizes more slowly ($\Delta G^{\ddagger}$ = 13.6 kcal/mol[31]) and a biphenyl with a $O-CH_2-O$ bridge much faster ($\Delta G^{\ddagger} \approx 1$ kcal/mol[32]). Related biphenyls contain the chiral bridges C(Me)H−NH−C(Me)H[31] or $CH_2-NH-C(Me)H$[33] and are single atropisomers. Their stereocenter(s) differentiate(s) the stabilities of the respective (diastereomorphic!) atropisomers so much that the more stable atropisomer does not cross the atropisomerization barrier—no matter how low it might be—*because there is no driving force*.

The preceding insights and our objective of modifying the (*P*)- *and* (*M*)-twisted scaffold **10** to exclusively (*P*)- or exclusively (*M*)-twisted derivatives let us screen the atropisomerical preferences of several type-**14** and type-*dia*-**14** cycloheptadieno-arylindoles (formulas: Figure 3). Proving our concept, we synthesized their representatives *cis*- and *trans*-**14a**[34] and derived the arylindolediphosphanes *cis*- and *trans*-**15** therefrom (formulas: Figure 4).

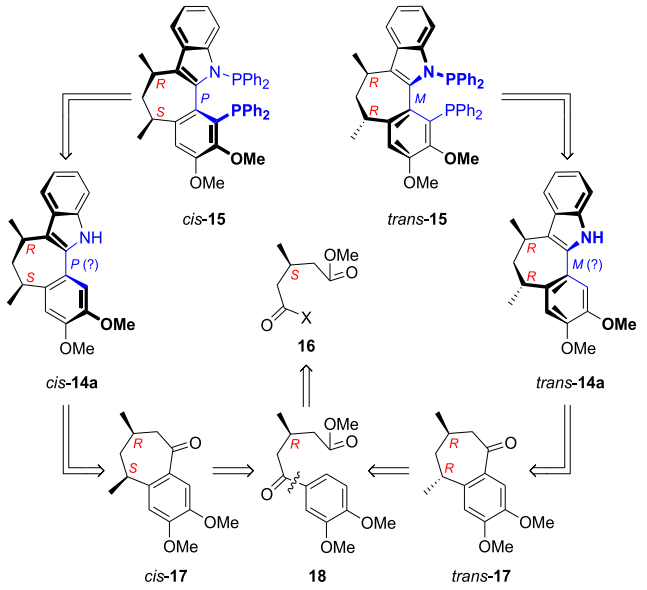

Figure 4. C_1-symmetric biarylbis(diphosphanes) *cis*-**15** and *trans*-**15**, their precursors *cis*-**14a** and *trans*-**14a** (cf. Figure 3), and their conceived origin from the enantiomerically pure *δ*-ketoester **18**.

Our retrosynthetic analyses of the cycloheptadieno-arylindoles *cis*- and *trans*-**14a** proceeded via the equally configured cyclohepteno-veratroles *cis*- and *trans*-**17**, respectively, to the veratrol-containing *δ*-ketoester **18** (Figure 4). Its aliphatic moiety should originate from an unsymmetric derivative **16** of 3-methylglutaric acid. Type-**16** compounds can be obtained by desymmetrizing 3-methylglutaric anhydride (**19**) by an asymmetric methanolysis.[35] We started synthesizing compounds *cis*- and *trans*-**14a** using Bolm's variant[36] of such a reaction[37] (Scheme 1). Methanolysis of **19** in chlorobenzene rather than in CCl_4[36,38] provided 97% of the glutaric half-ester **16a** with 70% *ee*;[39] three low-temperature recrystallizations[40a] of the salt(s)[40] formed with 1.0 equiv of (−)-cinchonidine increased the *ee*[39] of regenerated **16a** to 99%. This compound was converted into the acid chloride **16b**. Without purification, a CH_2Cl_2 solution acylated veratrol (**20**) at room temp after the addition of 1.0 equiv of either $AlCl_3$ or Me_2AlCl. To our surprise, the resulting *δ*-ketoester **18** was racemic.[41,42] We surmise that racemization occurred by the mechanism suggested in Scheme 2.

We proceeded to the (*R*)-configured *δ*-ketoester **18** rather than to *rac*-**18** after activating the glutaric half-ester **16a** as the *S*-ethyl thioester **16c**, which we isolated in 70% yield, or as the mixed anhydride **16d** (accessed with $MeO_2C-O-CO_2Me$[43] rather than with MeO_2C-Cl), which we carried on without purification (Scheme 1). The thioester **16c** and an excess of veratrylzinc halide **21a** (prepared from 4-iodoveratrol by succcessive I → Li and Li → ZnCl exchanges) coupled in a Fukuyama ketone synthesis.[44] It delivered over 60% of the *δ*-ketoester **18**. However, this compound was hard to separate from considerable amounts of accompanying 3,3′,4,4′-tetramethoxybiphenyl by flash chromatography on silica gel.[45] Coupling the mixed anhydride **16d** with the veratrolboronic acid **21b** [prepared from 4-bromoveratrol as described;[46]

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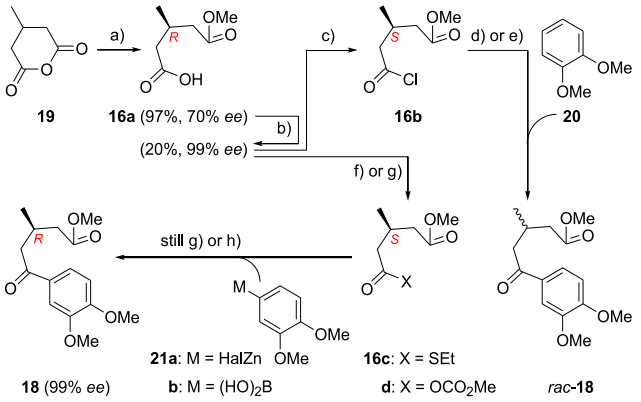
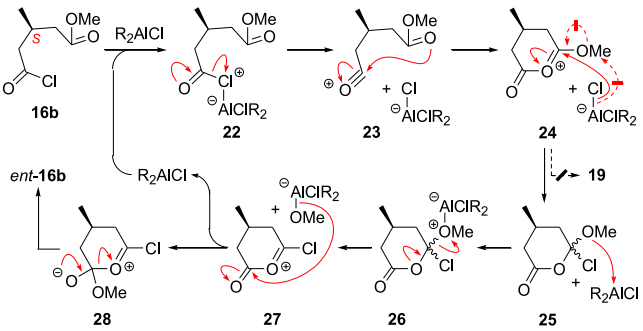
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of δ-Ketoester 18[a]



[a]Reaction conditions: (a) MeOH (3.0 equiv), (−)-quinine (1.1 equiv), chlorobenzene/toluene (1:1), −55 °C, 72 h; 97%, 70% *ee*; (b) (−)-cinchonidine (1.0 equiv), acetone/H_2O, 40 °C → 4 °C, 24 h; aq. HCl (1 M); 20%, 99% *ee*; (c) $(COCl)_2$ (1.1 equiv), DMF (cat.), CH_2Cl_2, room temp, 3 h; (d) $AlCl_3$ (1.0 equiv), **20** (1.0 equiv), CH_2Cl_2, room temp, 20 h; 97% over the 2 steps; (e) same as (d) but Me_2AlCl (1.0 equiv); 89% over the 2 steps; (f) DCC (1.0 equiv), EtSH (1.0 equiv), DMAP (20 mol %), CH_2Cl_2, room temp, 18 h; 70%; (g) $MeO_2C{-}O{-}CO_2Me$ (3.0 equiv), **21b** (1.2 equiv), $Pd(OAc)_2$ (3.0 mol %), P(*p*-anisyl)$_3$ (7.0 mol %), H_2O (17 mol %), THF, 80 °C, 16 h; 79%; (h) **21a** (3.0 equiv), $PdCl_2(PPh_3)_2$ (5.0 mol %), THF, room temp, 16 h; 60% over the 2 steps.

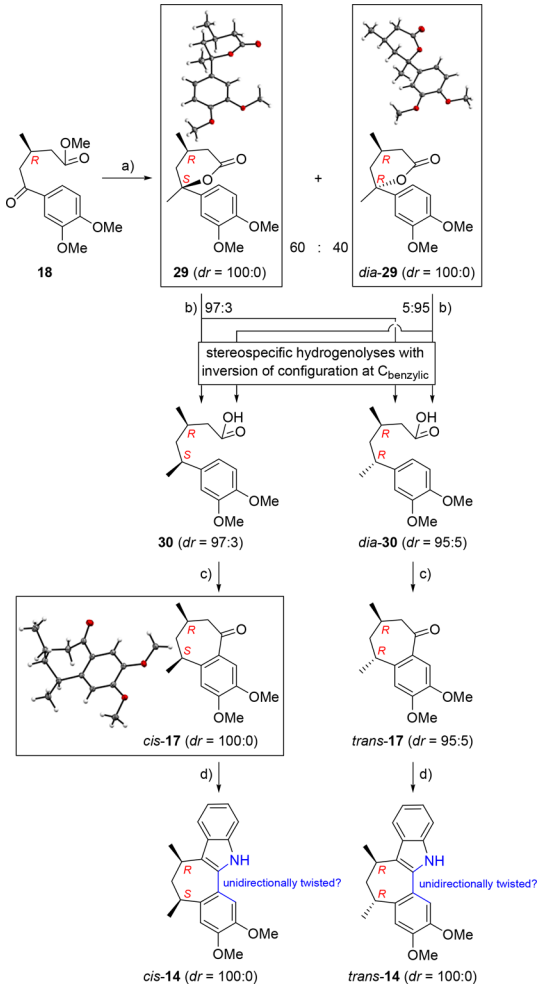
Scheme 2. Mechanism of the Enantiomerization 16b → *ent*-16b Which Causes the Racemization of the Acid Chloride 16b under both Friedel−Crafts Acylation Conditions of Scheme 1



yield: 56% (60%[46])] was a better synthesis[43a] of the desired δ-ketoester **18** because no difficult to separate 3,3′,4,4′-tetramethoxybiphenyl interfered.

Our cycloheptadieno-arylindole syntheses continued by adding MeMgCl to the carbonyl group of the δ-ketoester **18** (Scheme 3). Quenching the reaction mixture with satd. aq. $NaHCO_3$, extractive workup, and purification by flash chromatography on silica gel[45] furnished no δ-hydroxyesters but the derived valerolactones **29**[47a] and *dia*-**29**[47b] with *ds* = 60:40. Next, the benzylic C−O bonds of lactones **29** and *dia*-**29** were hydrogenolyzed in EtOH catalyzed by 15 mol % Pd/C. Under this proviso, both hydrogenolyses exhibited ≥95% inversion of configuration. This rendered the carboxylic acids **30** (whose follow-up product *cis*-**17** was X-rayed,[47c] revealing the steric course of the preceding hydrogenolysis) and *dia*-**30**, respectively. Less Pd/C, other catalysts [Pd-black, $Pd(OH)_2$], or other solvents (MeOH, AcOEt, and 2-Me-THF) gave inferior selectivities. Hydrogenolyses of tertiary $C_{benzylic}{-}O$

Scheme 3. Synthesis of the Cycloheptadieno(arylindolyls) *cis*- and *trans*-14[a]



[a]Reaction conditions: (a) MeMgCl (1.5 equiv), THF, −78 °C → room temp, 18 h; 37% **29**,[47a] 25% *dia*-**29**,[47b] 20% *de*; (b) H_2 (balloon), Pd/C (10 wt-%, 15 mol %), EtOH, room temp, 19 h; 90% **30** or 92% *dia*-**30**; (c) Polyphosphoric acid (10 times the mass of **30** or *dia*-**30**), sulfolane, 100 °C, 1 h; 90% *cis*-**17**[47c] or 88% *trans*-**17**; (d) $PhNHNH_2$ (1.0 equiv), HCl (concd, 4.0 equiv), EtOH, reflux, 24 h; 72% *cis*-**14** or 68% *trans*-**17**.

bonds akin to our examples **29** → **30** and *dia*-**29** → *dia*-**30** and proceeding with inversions of configurations, too, were first investigated by Mitsui et al.[48] One such hydrogenolysis of a tolyl-substituted δ-lactone was accomplished by Campagne et al.[49] during our own studies.

At 100 °C the carboxylic acids **30** and *dia*-**30** underwent Friedel−Crafts cyclizations in polyphosphoric acid[50] which we diluted with sulfolane[51] to improve miscibilities and thereby increase yields (Scheme 3). This led to the benzosuberone *cis*-**17**[47c] in 90% yield rather than only in 53% yield and to the benzosuberone *trans*-**17** in 88% yield. *Cis*-**17** crystallized from *n*-hexane with *dr* = 100:0 while *trans*-**17** remained an oil with *dr* = 95:5. The last steps of Scheme 3 are Fischer indole syntheses combining the Friedel−Crafts products *cis*-**17** or *trans*-**17** with phenylhydrazine in hot ethanolic HCl.[52] A 72% yield of the bridged arylindole *cis*-**14** resulted from *cis*-**17**, and a 68% yield of *trans*-**14** resulted from *trans*-**17**. *Cis*-**14** was diastereopure immediately, whereas *trans*-**14** had to be crystallized to become diastereopure.

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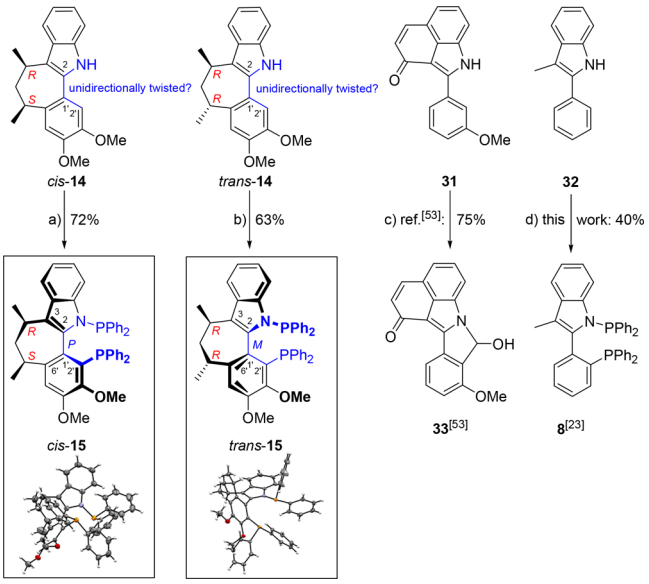
Org. Lett. XXXX, XXX, XXX−XXX

The H−N−C^2−$C^{1'}$−$C^{2'}$−H motifs of the arylindoles *cis*- and *trans*-**14** gave Li−N−C^2−$C^{1'}$−$C^{2'}$−Li motifs upon exposure to 2 equiv of *n*BuLi provided that TMEDA was present (Scheme 4, not depicted). Treatment with $ClPPh_2$

Scheme 4. *N*-Directed Lithiation/Phosphorylation of the Cycloheptadieno(indolylaryls) *cis*- and *trans*-14; Lithiation Analogies and Differences[a]



[a]Reaction conditions: (a) *n*BuLi (2.5 equiv), TMEDA (2.5 equiv), Et_2O, room temp, 3 h; $ClPPh_2$ (10 equiv), −78 °C → room temp, 18 h; 72%;[47d] (b) Same as (a); 63%;[47e] (c) Reference 53; LiTMP (5.0 equiv), THF, −10 °C, 1 h; HCO_2Et (1.0 equiv), TMSCl (10.0 equiv), −78 °C → room temp; 75%; (d) Same as (a) but using *s*BuLi instead of *n*BuLi; 40%.

established the Ph_2P−N−C^2−$C^{1'}$−$C^{2'}$−PPh_2 motifs of the diphosphane targets *cis*- and *trans*-**15**. Purification by flash chromatography on silica gel[45] rendered *cis*-**15** in 72% yield and *trans*-**15** in 63% yield.

The double C- and N-lithiation employed in the last step of our routes to the diphosphanes *cis*- and *trans*-**15** was unprecedented. The closest-related dilithiation of that kind was the transformation **31** → **33**[53] (Scheme 4; the NH group of **31** belongs to a vinylogous amide and thus should be more acidic than the NH group of the indoles *cis*- and *trans*-**14**). The feasibility of lithiating a 2-arylindole *twice* does not require the support of a MeO group: 3-Methyl-2-phenylindole (**32**) was both C- *and* N-lithiated with *s*BuLi (though not with *n*BuLi); this allowed progression to the previously described[54] diphosphane **8** in 40% yield.[55]

In the solid state, the N−C^2−$C^{1'}$−$C^{2'}$ motifs of our diphosphanes are twisted *in opposite senses*. These twists allow the following dihedral angle quantifications: +62.8° in *cis*-**15**[47d] and −67.9° in *trans*-**15**.[47e] The different signs of these angles are due to the biaryl axis being (*P*)-configured in diphosphane *cis*-**15** yet (*M*)-configured in *trans*-**15**. This contrast arises in response to the changing configurations of the stereocenter attached to $C^{6'}$ (*S*-configured in *cis*-**15**, *R*-configured in *trans*-**15**), no matter the invariant (*R*)-configuration of the stereocenter attached to C^3. Differently expressed, the diphosphane syntheses of the present study were not only atropselective but additionally atropdivergent. These findings underline the viability of a concept first laid out in the discussion of Figure 3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03896.

Experimental procedures, characterization data, NMR spectra, and details concerning the X-ray analyses. (PDF)

Accession Codes

CCDC 1533413, 1533414, 1549686, 1561798, and 1578270 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de.

ORCID

Reinhard Brückner: 0000-0002-9028-8436

Notes

The authors declare no competing financial interest.

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■ DEDICATION

[⊥]Dedicated to Professor Rolf Huisgen at the occasion of his 99th birthday.

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Org. Lett. XXXX, XXX, XXX−XXX

X-ray crystallography; the corresponding data are contained in CCDC 1533414. (d) Racemic diphosphane *cis*-**15** formed crystals whose structure was elucidated by X-ray analysis; the corresponding data are contained in CCDC 1549686. (e) Racemic diphosphane *trans*-**15** formed crystals whose structure was elucidated by X-ray analysis; the corresponding data are contained in CCDC 1561798.

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Org. Lett. XXXX, XXX, XXX−XXX