A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Enantioselective Synthesis of 1-Aryl Benzo[5]helicenes Using BINOL-Derived Cationic Phosphonites as Ancillary Ligands

Authors: Manuel Alcarazo, Pablo Redero, Thierry Hartung, Jianwei Zhang, Leo D.M. Nicholls, Guo Zichen, Martin Simon, and Christopher Golz

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202010021

Link to VoR: https://doi.org/10.1002/anie.202010021

WILEY-VCH

10.1002/anie.202010021

WILEY-VCH

COMMUNICATION

Enantioselective Synthesis of 1-Aryl Benzo[5]helicenes Using BINOL-Derived Cationic Phosphonites as Ancillary Ligands

Pablo Redero,‡ Thierry Hartung,‡ Jianwei Zhang, Leo D. M. Nicholls, Guo Zichen, Martin Simon, Christopher Golz, and Manuel Alcarazo.*

[*] P. Redero, T. Hartung, Dr. J. Zhang, Dr. L. D. M. Nicholls, G. Zichen, M. Simon, Dr. C. Golz, Prof. Dr. M. Alcarazo
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstr. 2, 37077-Göttingen, Germany
E-mail: malcara@gwdg.de
[‡] Equal contribution from both authors

Supporting information for this article is given via a link at the end of the document.

Abstract The synthesis of unprecedented BINOL-derived cationic phosphonites is described. Through the use of these phosphanes as ancillary ligands in Au(I) catalysis, a highly regio- and enantioselective assembly of appropriately designed alkynes into 1-(aryl)benzo[5]carbohelicenes is achieved. The modular synthesis of these ligands and the enhanced reactivity that they impart to Au(I)-centers after coordination have been found to be the key features that allow an optimization of the reaction conditions until the desired benzo[5]helicenes are obtained with high yield and enantioselectivity.

The unique physical and chiroptical properties of helicenes, which ultimately derive from their π-expanded *ortho*-fused architecture, and the continuously emerging number of their applications in areas as diverse as molecular machines[1] or liquid crystal technology,[2] has led to the flourishing of this chemistry.[3] A number of synthetic approaches are available for the preparation of carbo-,[4] hetero-,[5] extended,[6] expanded,[7] and even multi-helicene structures;[8] however, very often the desired helicoidally-shaped architectures are obtained as racemic mixtures, which need to be separated by high performance liquid chromatography (HPLC). The development of effective enantioselective strategies towards helicenes and helicene-like molecules is therefore desirable and challenging in equal amounts. Consider, as an illustrative example, the assembly of the [5]helicene skeleton. Many racemic and several diasteroselective syntheses have been reported in recent years,[9] but despite being a prototype scaffold in helicene chemistry, the number of highly enantioselective approaches available is still low.[10]

Being aware of the potential offered by Au-catalysed intramolecular hydroarylation reactions for the assembly of conveniently designed alkynes into condensed polyarenes;[11] we conceived the enantioselective synthesis of benzo[5]helicenes of general formula **1** from readily available [4]helicene substrates containing a pendant alkyne moiety **2**. An aryl rest was installed at the alkyne terminus to obtain configurationally stable products; otherwise, the enantiomers of unsubstituted [5]helicenes slowly interconvert at ambient temperature.[12] Building upon the experience of our laboratory in the enantioselective synthesis of other helicenes using Au-catalysts bearing TADDOL-derived cationic phosphonites as ancillary ligands, we initially screened the available set of these catalysts for the cyclisation of **2** in **1**.[13] Soon however, it was clear that the chiral environment provided by the TADDOL moiety was not able to promote acceptable levels of enantioinduction; hence, alternative chiral platforms were evaluated giving preference to those scaffolds that have already demonstrated their suitability in asymmetric Au catalysis.[14] As a result from that initial screening Au complexes **3**, containing a cationic phosphonite derived from BINOL, were identified as the most promising catalysts to promote the formation of **1** in terms of isolated yield and levels of regio- and enantioinduction (Figure 1). Herein, the synthesis and structure these new Au-catalysts, together with their catalytic performance, are reported.

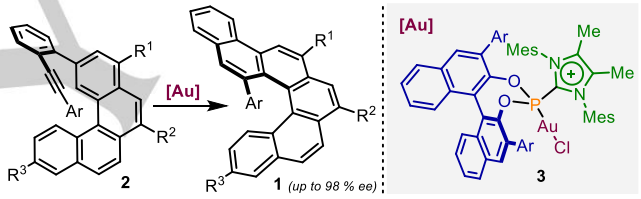


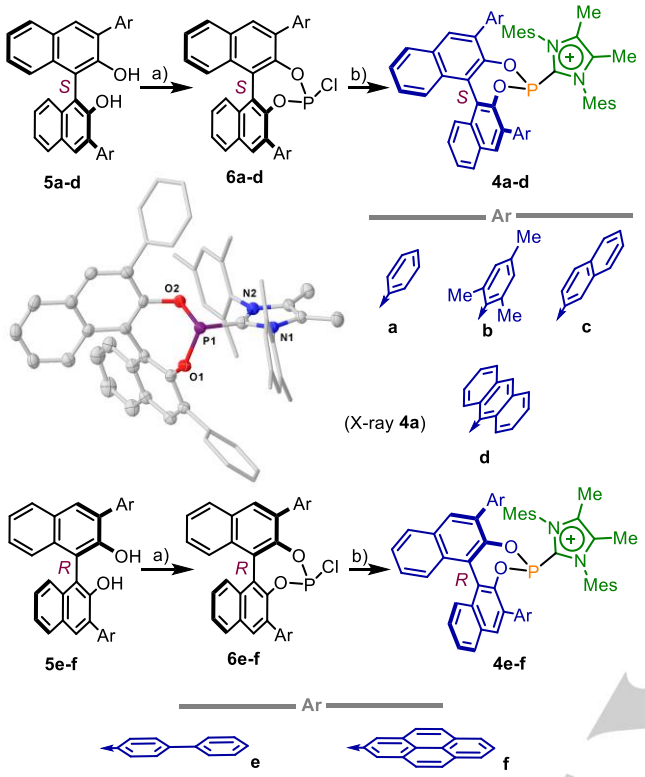
Figure 1. Au-catalysed enantioselective synthesis of benzo[5]helicenes and structure of the newly designed family of BINOL-derived catalysts.

BINOL-derived α-cationic phosphonites **4a-f** were prepared via a two-step process starting from known diols **5a-f**.[15] First, reaction of **5a-f** with PCl_3 in the presence of pyridine delivered the corresponding chlorophosphites **6a-f**, which were subsequently submitted, without further purification, to reaction with 3,4-dimethyl IMes (**7**) affording phosphonites **4a−f** in moderate to good yields. The methyl groups at the backbone of the imidazolium moiety are essential to block these positions and avoid the formation of side-adducts derived from the corresponding mesoionic carbenes. Column chromatography on silica gel of the crude reaction mixtures delivered analytically pure samples of **4a-f** in moderate yields (Scheme 1). Formation of the expected cationic phosphonites was initially suggested by ^{31}P NMR, where a distinct signal for the cationic phosphonites arises at δ = 135−155 ppm. Subsequently, monocrystals of **4a** were grown and its solid-state structure was determined by X-ray diffraction analysis (See Scheme 1 and the Supplementary Information). In this compound the phosphorus atom adopts the expected pyramidal geometry (sum of angles around P = 302.9°); therefore, retaining an electron pair available for coordination.

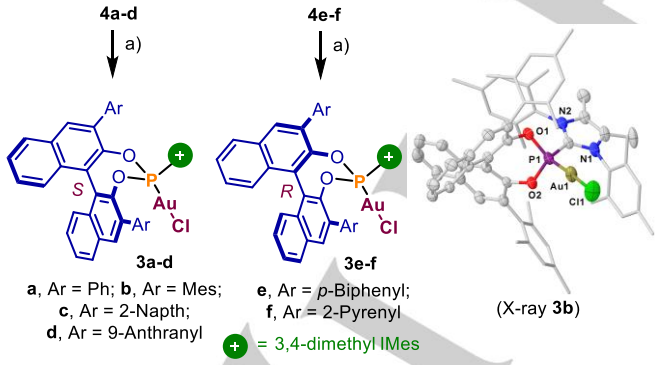
Reaction of **4a-f** with $(Me_2S)AuCl$ in CH_2Cl_2 led to the formation of the corresponding Au(I) complexes **3a−f**, which were obtained as white or light yellow solids in good to excellent isolated yields. Upon coordination of Au to the phosphonites a pronounced upfield shift of their ^{31}P-NMR signals (δ = 105−115 ppm) is observed. Previously reported cationic phosphonite-Au

10.1002/anie.202010021

complexes resonate at identical range.[13a,b] Finally, unambiguous confirmation of the expected connectivity was again obtained, in this case by X-ray diffraction of monocrystals of **4b** (See Scheme 2 and the Supplementary Information).



Scheme 1. Synthesis and structure of α-cationic phosphonites **4a-f**.[a]Reagents and conditions: a) PCl_3 (1.1 equiv.), pyridine (3 equiv.), toluene, 1h, 60°C; b) ^{Me}IMes (1 equiv.), $NaSbF_6$ (3 equiv.), Et_2O, -78°C→rt; yields over two steps: **4a**, 73%; **4b**, 16%; **4c**, 47%; **4d**, 37%; **4e**, 34%, **4f**, 18%. X-ray structure of **4a**; H atoms, solvent molecules and SbF_6 anion removed for clarity.[16]

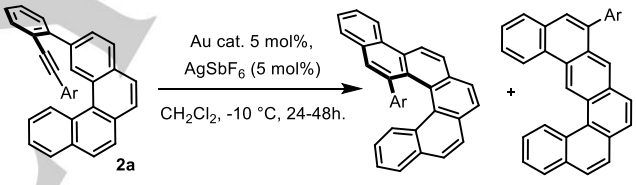


Scheme 2. Synthesis and Structure of Au-complexes **3a-f**. [a]Reagents and conditions: a) $(Me_2S)AuCl$ (1 equiv.), CH_2Cl_2, 1h, -20°C→rt; yields: **3a**, 98%; **3b**, 67%; **3c**, 78%; **3d**, 67%; **3e**, 95%, **3f**, 97%. X-ray structure of **3b**; H atoms, solvent molecules and SbF_6 anion removed for clarity.[16]

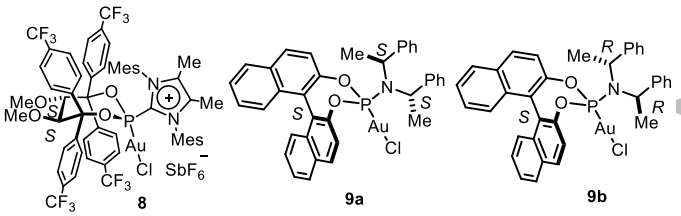
Once this initial set of Au-precatalysts was prepared, their performance on the cyclization of model alkyne **2a** into benzo[5]helicene **1a** was evaluated. This substrate, as all of general formula **2** were readily obtained in only two steps via oxidative photocyclization of conveniently substituted stilbenes, followed by Suzuki-coupling to install the pending diphenylethyne unit.[17] For details see the Supplementary Information.

Our initial explorative conditions were set up as follows: catalyst loading of 5 mol %, CH_2Cl_2 as solvent and a working temperature of -10°C. All reactions were allowed to proceed until total consumption of the starting material or stopped after 48h. As mentioned previously, TADDOL-derived catalysts are not appropriate for this cyclisation. The best result was obtained with complex **8**, which furnished **2a** with only 33% ee (Table 1, Entry 1). Classical BINOL-phosphoramidite Au complexes **9a-b** afforded low conversions at -10°C, as expected for neutral ancillary ligands; also poor enantioselectivities were observed regardless of any possible matched/mismatched effect between the chiral diol or amine fragments (Entries 2-3).[18] Gratifyingly, already the less sterically demanding catalyst of the new series, **3a**, was able to promote the desired cyclisation towards **1a** with high conversion, regio- (**1a**:**10a**; 98:2), and enantioselectivites (93 % *ee*) (Entry 4). Replacement of the phenyl rests at positions 3 and 3' of the BINOL moiety by mesityl groups was detrimental in terms of yield and *ee* (Entry 5), while introducing 2-naphthyl fragments at the same positions improved the *ee* up to 97% at the expense of a slightly lower regioselectivity (**1a**:**10a**; 95:5) (Entry 6). Installing 9-anthranyl rests at the BINOL basically cancels any catalytic activity in **3d** (Entry 7); while catalyst **3e**, decorated with biphenyl rests, afforded complete regioselectivity towards **1a** maintaining high enantioselectivity (Table 1, Entry 8). Finally, the best compromise was obtained rigidifying the catalyst periphery with 2-pyrenyl substituents; this slightly improves the enantioselectivity if compared to **3e**, without eroding the conversion or regioselectivity (Entry 9).

Table 1. Screening of Chiral Au-Phosphonite and related Complexes.



Entry	Catalyst	Conv (%)[a]	Ratio **1a:10**[a]	ee (%) **1**[b]
1	**8**	86	87:13	(+)-33
2	**9a**	11	>99:1	(-)-61
3	**9b**	35	85:15	(-)-40
4	**3a**	>98	98:2	(-)-93
5	**3b**	55	97:3	(-)-86
6	**3c**	>98	95:5	(-)-97
7	**3d**	<5	n.d.	(-)-8
8	**3e**	>98	>99:1	(+)-94
9	**3f**	>98(88)[c]	>99:1	(+)-95



Reactions were carried out at 0.1 mmol scale in CH_2Cl_2 (0.05 M). [a]Conversions and **1a:10a** ratios were determined by ^{1}H NMR of the crude reaction mixtures. [b]Determined by chiral HPLC. [c]Isolated yields in parenthesis.

With the most adequate catalyst already identified, the scope of the cyclization was evaluated. Hence, a series of alkyne substrates **2a-p**, which contain diverse substitution pattern at different positions of their structure were prepared and submitted to the optimized cyclisation conditions. We were pleased to see that the high levels of regio- and enantioinduction imparted by **3f**

10.1002/anie.202010021

were maintained for most of the substrates studied; moreover, some structure-reactivity relationships could be clearly established (Figure 2).

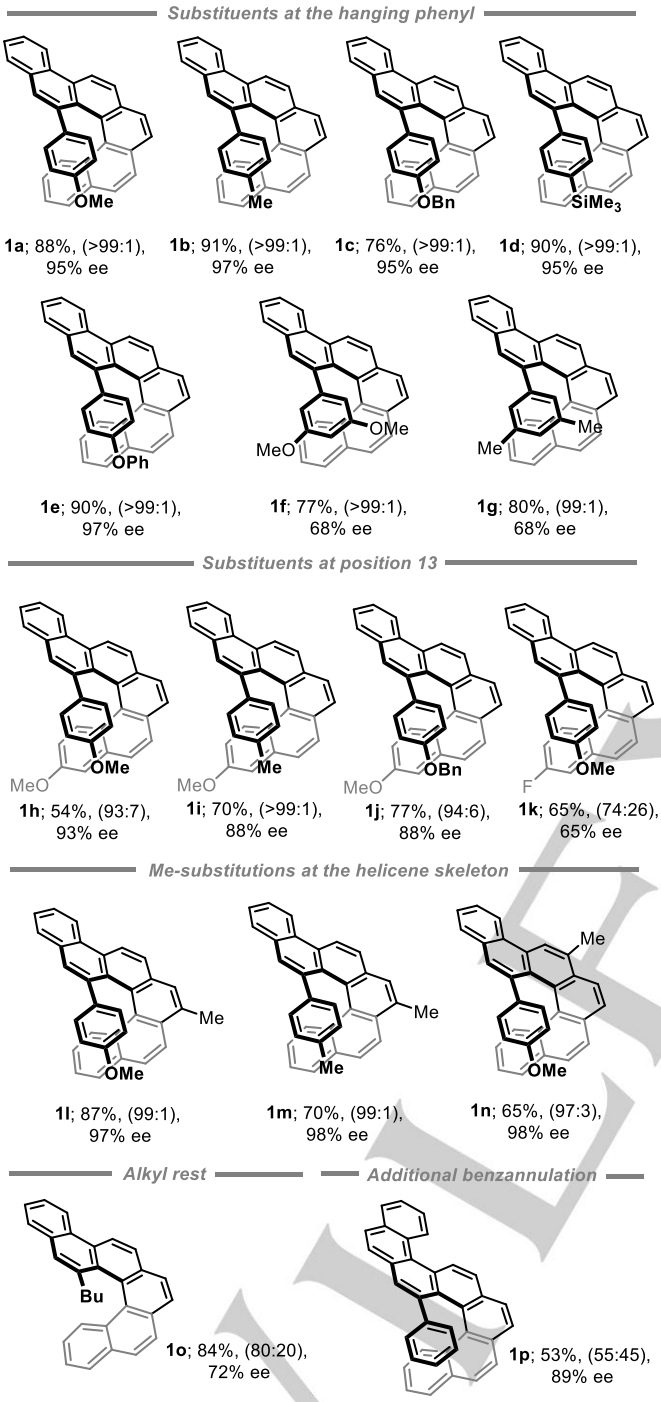


Figure 2. Substrate scope and limitations. Reaction conditions: **3f**, 5 mol%, $AgSbF_6$, 5 mol%, CH_2Cl_2, (0.05M), -10°C, 24-48h. Yields are of isolated products; in parenthesis **1**:**10** ratios determined by ^{1}H-NMR; ee values by were determined by chiral HPLC.

Electron donating groups are necessary in *p*-position of the terminal aryl rest of **2** to secure high conversions, regio-, and enantioselectivities **1a-e.** Electron withdrawing substituents in that position, or even an unsubstituted terminal phenyl rest, make the reaction extremely slow and low yielding under the conditions applied. *m*-Substituents at the same ring are also tolerated (**1f-g**), but in that case the ee's substantially decay. Me- and MeO-substituents can be incorporated at the external rim of the helicene structure keeping remarkable levels of regio- and enantioselectivity **1h-j** and **1l-n**. Remarkably, the extension of the π-system by additional benzannulation is also possible with good enantioselectivity even if an undecorated phenyl ring substitutes the alkyne terminus (**1p**). Better yields and regioselectivities are expected by introducing electron donating groups at the *p*-position of that ring. Finally, alkyl-substituted substrates undergo the desired cyclisation as well, albeit with moderate regio- and enantioselectivity (**1o**).

Colourless blocks of **1a** suitable for X-ray diffraction analysis were obtained via vapor diffusion of hexane into a dichloromethane solution of this compound. The thus obtained molecular structure reveals that the absolute configuration of **1a** to be *P* (Figure 3a). Both, the Flack and Hooft parameters (0.05(5) and 0.05(3), respectively) unambiguously support this assignment. Additionally, the circular dichroism spectrum (EDC) of **1a** was also recorded (Figure 3c); comparison of its spectrum with those reported for other 1-substituted [5]helicenes further confirms the assignment of the helicity.[12b] Finally, a pure sample of **10h** was obtained after HPLC separation and crystallized from hexane. Through this analysis the connectivity of the minor regioisomers obtained in this cyclisation could be determined; they depict a dibenzo[a,m]tetraphene structure (Figure 3b). The absorption and fluorescence spectra of **1a** are also shown in Figure 3d.

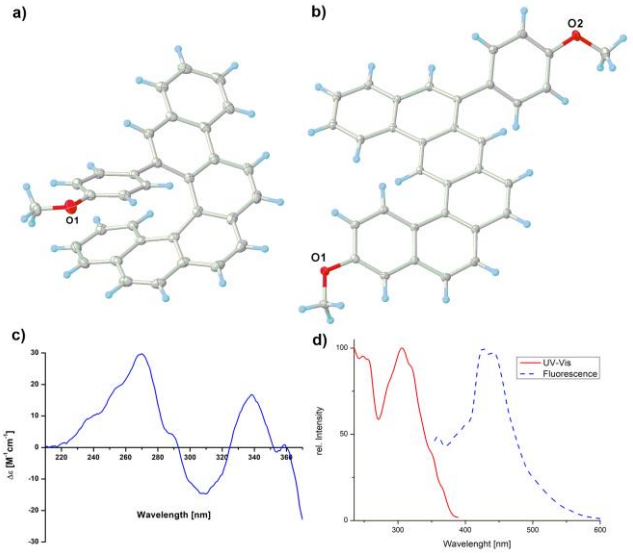


Figure 3. a) X-ray structure of **1a;** b) X-ray structure of **10h**, solvent molecules were removed for clarity;[16] c) EDC spectrum of **1a** and d) UV-Vis absorption and fluorescence spectrum of the same molecule.

In summary, we report herein the synthesis of a new family of α-cationic phosphonites derived from BINOL, and their application as ancillary ligands. Specifically, a highly enantioselective route for the synthesis of 1-aryl substituted benzo[5]carbohelicenes has been achieved via the Au-catalysed intramolecular hydroarylation of appropriate alkynes. While the chiral pocket around the Au atom should not be very different to that created by phosphoramidites of similar structure, the unique donor properties of the cationic ligands prepared render the corresponding Au-catalysts more active than those, allowing the transformation to occur under cryogenic conditions. While the substrate structure

still plays a fundamental role, this seems to be very useful to gain control over the regio- and enantioselectivity of the whole process. Single crystal X-ray analysis unambiguously determined the connectivity of the new benzo[5]helicenes obtained and established their absolute configuration. Ongoing research in our laboratory is focused on the further optimization of the catalytic system herein presented towards the enantioselective synthesis of other carbo- and heterohelicenes of higher order and multi-helicoidal architectures.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (Al 11348/4-3, INST 186/1237-1 and INST 186/1298-1) is gratefully acknowledged. We also thank Dr. R. Goddard (MPI Kohlenforschung, Mülheim/Ruhr) for the X-ray analysis of **3b**.

Conflict of Interest

The authors declare no competing financial interests.

Keywords: [5]helicenes • asymmetric catalysis • Au catalysis • ligand design • cationic phosphonites

[1] W. C. Chen, Y. W. Lee, C. T. Chen, *Org. Lett.* **2010**, *12*, 1472-1475.

[2] N. Saito, K. Kanie, M. Matsubara, A. Muramatsu, M. Yamaguchi, *J. Am. Chem. Soc.* **2015**, *137*, 6594−6601.

[3] (a) Y. Shen, C.-F.Chen, *Chem. Rev.* **2012**, *112*, 1463−1535; (b) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 968−1006; (c) M. Gingras, G. Félix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007−1050; (d) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 1051−1095; (e) C.-F. Chen, Y. Shen, *Helicene Chemistry, From Synthesis to Applications*. Springer-Verlag: Berlin, Heidelberg, Germany, **2017**.

[4] For selected examples: (a) F. Teplý, I. G. Stará, I. Starý, A. Kollárovič, D. Šaman, L. Rulíšek, P. Fiedler, *J. Am. Chem. Soc.* **2002**, *124*, 9175-9180; (b) D. C. Harrowven, I. L. Guy, L. Nanson, *Angew. Chem. Int. Ed.* **2006**, *45*, 2242-2245; (c) S. K. Collins, A. Grandbois, M. P. Vachon, J. Côté, *Angew. Chem. Int. Ed.* **2006**, *45*, 2923-2926; (d) K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi, M. Hirano, *J. Am. Chem. Soc.* **2007**, *129*, 12078-12079; (e) A. Jančařík, J. Rybáček, K. Cocq, J. V. Chocholoušová, J. Vacek, R. Pohl, L. Bednárová, P. Fiedler, I. Císařová, I. G. Stará, I. Starý, *Angew. Chem. Int. Ed.* **2013**, *52*, 9970-9975; (f) R. K. Mohamed, S. Mondal, J.V. Guerrera, T. M. Eaton, T. E. Albrecht-Schmitt, M. Shatruk, I. V. Alabugin, *Angew. Chem. Int. Ed*. **2016**, *55*, 12054-12058.

[5] Selected references for the enantioselective synthesis of heterohelicenes: (a) T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tsuchikama, K. Endo, *Chem. Commun.* **2012**, *48*, 1311-1313; (b) K. Nakamura, S. Furumi, M. Takeuchi, T. Shibuya, K. Tanaka, *J. Am. Chem. Soc.* **2014**, *136*, 5555−5558; (c) L. Kötzner, M. J. Webber, A. Martínez, C. De Fusco, B. List, *Angew. Chem., Int. Ed*. **2014**, *53*, 5202−5205; (d) Y. Kimura, N. Fukawa, Y. Miyauchi, K. Noguchi, K. Tanaka, *Angew. Chem., Int. Ed.* **2014**, *53*, 8480−8483; (e) M. Sako, Y. Takeuchi, T. Tsujihara, J. Kodera, T. Kawano, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2016**, 138, 11481−11484; (f) J. Klívar, A. Jančařik, D. Šaman, R. Pohl, P. Fiedler, L. Bednárová, I. Starý, I. G. Stará, *Chem. Eur. J.* **2016**, *22*, 14401-14405.

[6] Y. Nakakuki, T. Hirose, H. Sotome, H. Miyasaka, K. Matsuda, *J. Am. Chem. Soc.* **2018**, *140,* 4317-4326.

[7] (a) G. R. Kiel, S. C. Patel, P. W. Smith, D. S. Levine, T. D. Tilley, *J. Am. Chem. Soc.* **2017**, *139*, 18456-18459; (b) Y. Nakakuki, T. Hirose, K. Matsuda, *J. Am. Chem. Soc.* **2018**, *140,* 15461-15469.

[8] Selected reviews: (a) C. Li, Y. Yang, Q. Miao, *Chem. Asian J.* **2018**, *13*, 884-894; (b) K. Kato, Y. Segawa, K. Itami, *Synlett.* **2019,** *30,* 370-377.

[9] For selected examples: (a) M. C. Carreño, S. García-Cerrada, A. Urbano, *J. Am. Chem. Soc.* **2001**, *123*, 7929–7930; (b) M. C. Carreño, M. J. Sanz-Cuesta, S. García-Cerrada, A. Urbano, *Chem. Commun*. **2001**, 1452-1453; (c) Y. Ogawa, T. Ueno, M. Karikomi, K. Seki, K. Haga, T. Uyehara, *Tet. Lett.* **2002**, *43*, 7827–7829; (d) Y. Ogawa, M. Toyama, M. Karikomi, K. Seki, K. Haga, T. Uyehara, *Tet. Lett.* **2003**, **44**, 2167–2170; (e) M. Šámal, S. Chercheja, J. Rybáček, J. V. Chocholoušová, J. Vacek, L. Bednárová, D. Šaman, I. G. Stará, I. Starý, *J. Am. Chem. Soc.* **2015**, *137*, 8469-8474.

[10] (a) I. G. Stará, I. Starý, M. Tichý, J. Závada, V. Hanuš, *J. Am. Chem. Soc.*, **1994**, *116*, 5084-5088; (b) J. Caeiro, D. Peña, A. Cobas, D. Pérez, E. Guitián, *Adv. Synth. Catal.* **2006**, *348*, 2466-2474; (c) A. Yubuta, T. Hosokawa, M. Gon, K. Tanaka, Y. Chujo, A. Tsurusaki, K. Kamikawa, *J. Am. Chem. Soc.* **2020**. DOI: 10.1021/jacs.0c01723; (d) U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, DOI: 10.1002/anie.202003826.

[11] (a) M Alcarazo, *Chem.-Eur. J.* **2014**, *20*, 7868-7877; (b) M. Alcarazo, *Acc. Chem. Res.* **2016**, *49*, 1797-1805.

[12] (a) K. Yamamoto, M. Okazumi, H. Suemune, K. Usui, *Org. Lett.* **2013**, *15*, 1806-1809; (b) P. Ravat, R. Hinkelmann, D. Steinebrunner, A. Prescimone, I. Bodoky, M. Juríček, *Org. Lett.* **2017**, *19*, 3707-3710.

[13] (a) E. González-Fernández, L. D: M. Nicholls, L. D. Schaaf, C. Farès, C. W. Lehmann, M. Alcarazo, *J. Am. Chem. Soc.* **2017**, *139*, 1428-1431; (b) L. D. M. Nicholls, M. Marx, T. Hartung, E. González-Fernández, C. Golz, M. Alcarazo, *ACS Catal*. **2018**, *8*, 6079-6085; (c) T. Hartung, R. Machleid, M. Simon, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* **2020**, *59*, 5660-5664.

[14] For recent reviews on enantioselective Au(I) catalysis see: (a) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889–901; (b) W. Zi, F. D. Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567-4589.

[15] (a) I. Ahmed, D. K. Clark, *Org. Lett*. **2014,** *16*, 4332-4335.

[16] CCDC 2009207- 2009207, 2010180-2010182 and 2025999 contain the supplementary crystallographic data for this paper.

[17] H. R. Talele, A. R. Chaudhary, P. R. Patel, A. V. Bedekar, ARCHIVOC **2011**, *9*, 15-37.

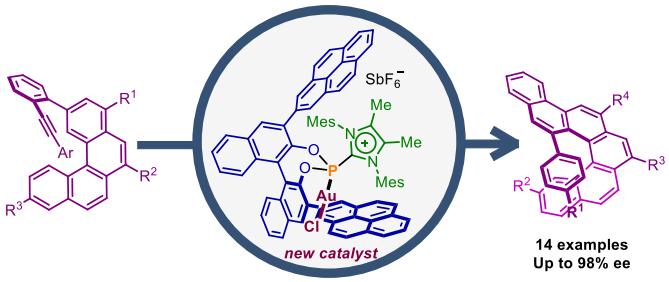
[18] J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486-2528.

10.1002/anie.202010021

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



A new family of α-cationic phosphonites derived from BINOL has been synthesized. Their use as ancillary ligands in Au(I) catalysis allows the enantioselective assembly of 1-aryl [5]helicenes with excellent yields and in up to 98% ee.