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

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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-catalyzed 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 unsubsituted [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** into **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 of these new Au catalysts, together with their catalytic performance, are reported.

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**. 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 phosphorus atom arises at $\delta = 135$–155 ppm. Subsequently, monocrystals of **4a** were grown and its solid-state structure

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Figure 1. Au-catalyzed enantioselective synthesis of benzo[5]helicenes and structure of the newly designed family of BINOL-derived catalysts.
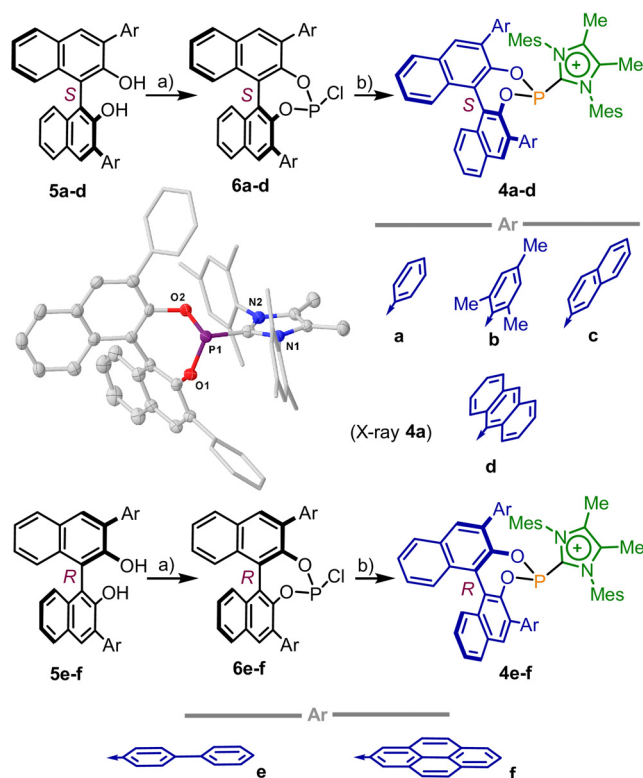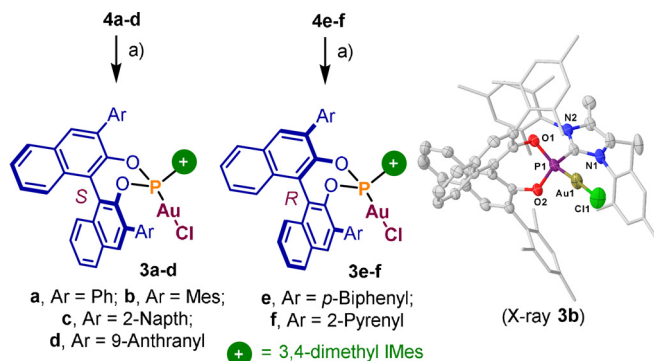
Scheme 1. Synthesis and structure of α-cationic phosphonites **4a–f**. Reagents and conditions: a) PCl₃ (1.1 equiv), pyridine (3 equiv), toluene, 1 h, 60 °C; b) MeIMes (1 equiv), NaSbF₆ (3 equiv), Et₂O, −78 °C→ rt; yields over two steps: **4a**, 73 %; **4b**, 16 %; **4c**, 47 %; **4d**, 37 %; **4e**, 34 %, **4f**, 18 %. X-ray structure of **4a**; H atoms, solvent molecules and SbF₆ anion removed for clarity.[16]

was determined by X-ray diffraction analysis (see Scheme 1 and the Supporting 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 (Me₂S)AuCl in CH₂Cl₂ 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 ³¹P NMR signals ($\delta = 105–115$ ppm) is observed. Previously reported cationic phosphonite–gold 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 **3b** (see Scheme 2 and the Supporting Information).

Once this initial set of gold precatalysts was prepared, their performance on the cyclization of model alkyne **2a** into benzo[5]helicene **1a** was evaluated. This substrate, as with 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 Supporting Information.

Our initial explorative conditions were set up as follows: catalyst loading of 5 mol %, CH₂Cl₂ as solvent, and a working

Scheme 2. Synthesis and structure of Au-complexes **3a–f**. Reagents and conditions: a) (Me₂S)AuCl (1 equiv), CH₂Cl₂, 1 h, −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 SbF₆ anion removed for clarity.[16]

temperature of −10 °C. All of the reactions were allowed to proceed until total consumption of the starting material or stopped after 48 h. 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

Table 1: Screening of chiral gold phosphonite and related complexes.[a]

Entry	Catalyst	Conv [%][c]	Ratio **1a:10**[b]	*ee* [%] **1**[c]
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)[d]	>99:1	(+)-95

[a] Reactions were carried out at 25 μm scale in CH₂Cl₂ (0.05 M).
[b] Conversions and **1a:10a** ratios were determined by ¹H NMR of the crude reaction mixtures. [c] Determined by chiral-phase HPLC. [d] Yield of isolated product in brackets.
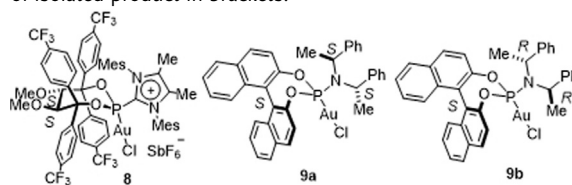
or amine fragments (entries 2,3).[18] Gratifyingly, already the less sterically demanding catalyst of the new series, **3a**, was able to promote the desired cyclisation towards **1a** with high conversion, regio- (**1a:10a**; 98:2), and enantioselectivites (93 % *ee*; entry 4). Replacement of the phenyl rests at positions 3 and 3′ of the BINOL moiety by mesitryl 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).

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

Electron-donating groups are necessary in the *p*-position of the terminal aryl rest of **2** to secure high conversions and regio- and enantioselectivities for **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 (**1 f,g**), but in that case the *ee* values 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**. Moreover, 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**).

Colorless 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 3 a). 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 3 c); 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;
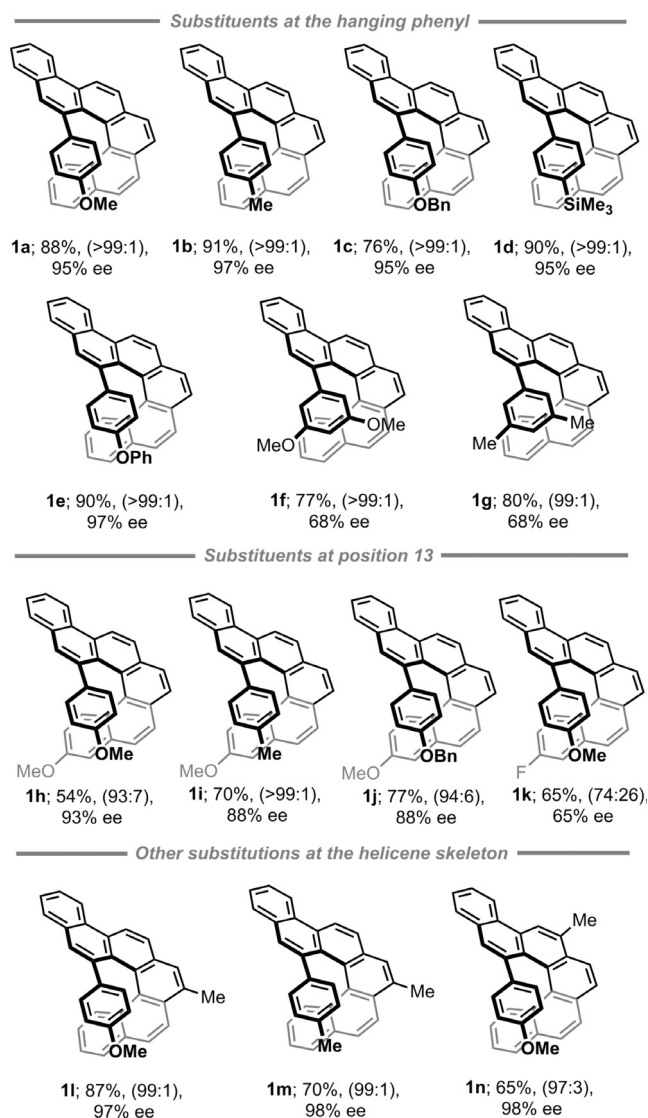

Figure 2. Substrate scope and limitations. Reaction conditions: **3 f**, 5 mol %, AgSbF$_6$, 5 mol %, CH$_2$Cl$_2$, (0.05 M), −10 °C, 24–48 h. Yields are of isolated products; in parenthesis **1**:**10** ratios determined by ^{1}H NMR; *ee* values by were determined by chiral-phase HPLC.

they depict a dibenzo[a,m]tetraphene structure (Figure 3 b). The absorption and fluorescence spectra of **1a** are also shown in Figure 3 d.

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-catalyzed 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; this seems to be very useful to gain control over the regio- and enantioselectivity of the whole process. Single-crystal X-ray analysis unambiguously deter-
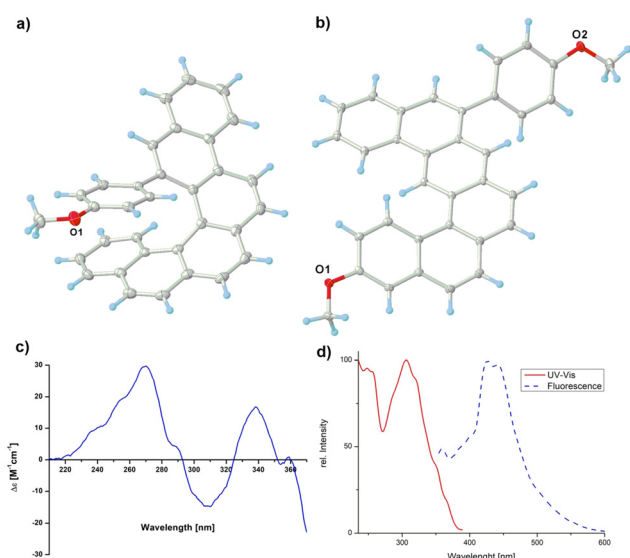
Figure 3. a) X-ray structure of **1a**. b) X-ray structure of **10h**, solvent molecules were removed for clarity.[16] c) EDC spectrum of **1a** and d) UV/Vis absorption and fluorescence spectrum of the same molecule.

mined 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

Conflict of interest

The authors declare no conflict of interest.

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