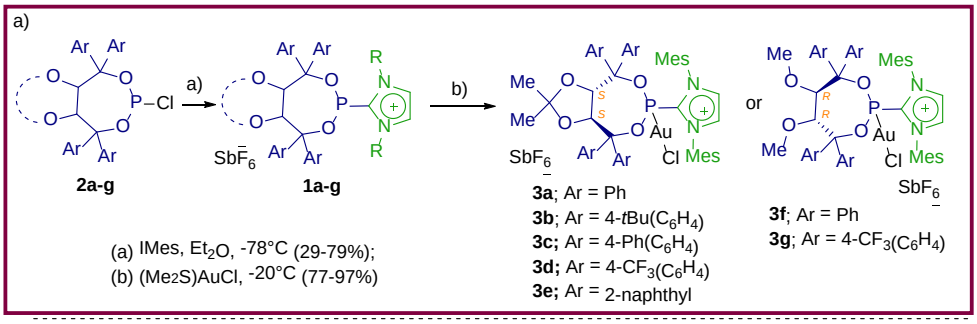
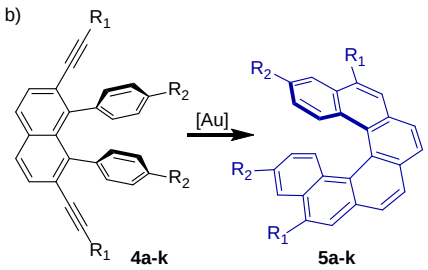
1 Chiral cationic phosphines

Encouraged by the realization that the alkyne hydroarylation already mentioned has the potential to assemble aromatic rings into helicenes if applied on suitably designed substrates,[1] we embarked on the design of an enantioselective route toward [6]carbohelicenes employing chiral cationic ancillary ligands.

The starting point for our approach was the synthesis of a library of chiral cationic phosphanes. Being aware of the difficulties inherent to asymmetric gold catalysis, which stem from its linear coordination geometry and the outer-sphere nature of Au(I)-catalysed processes, we reasoned that the new ligand structure had to be highly modular in order to tackle this challenge with any possibility of success.[2] Cationic phosphonites of general formula **1** fulfill this requirement. The chiral information is provided by well-precedented TADDOL-derived moieties **2**, which are cheap, easy to tune, and have already demonstrated their suitability in asymmetric gold catalysis.[3] In addition, the imidazolium unit introduces a positive charge which eventually will be responsible for enhanced catalyst efficiency (Figure 1a).

Once a first set of Au-precatalysts **3a-g** was made available, they all were screened on the cyclisation of diynes **4a-k** into helicenes **5a-k**. Substrates of general formula **4** were chosen as adequate starting materials for the [6]helicenes synthesis because they do not contain any interfering element of chirality, and can be assembled in gram scale through a robust and modular route. The results obtained after optimization are shown in Figure 1b, together with the X-ray structures of precatalysts **3e**, **3g** and helicene **5b** (Figure 1c). Precatalyst **3g** produced the best results in terms of yields and enantioselectivities. Gratifyingly, these high levels of enantioinduction were maintained through the series reaching up to 99% ee





Diyne	Prod.	R_1	R_2	Yield	5:6	ee
4a	**5a**	*p*-tolyl	H	88%	97:3	91
4b	**5b**	Ph	H	77%	95:5	92
4c	**5c**	*p*-F(C_6F_4)	H	90%	93:7	90
4d	**5d**	*p*-tolyl	Ph	84%	97:3	82
4e	**5e**	*p*-OBn(C_6H_4)	H	98%	95:5	99
4f	**5f**	*p*-OMe(C_6H_4)	H	90%	96:4	81
4g	**5g**	*p*-Cl(C_6H_4)	OMe	92%	87:13	95
4h	**5h**	*p*-TMS(C_6H_4)	H	76%	87:13	87
4i	**5**	*p*-TMS(C_6H_4)	OMe	64%	73:27	94
4j	**5j**	*p*-(TIPSO-CH_2)Ph	OMe	94%	80:20	82
4k	**5k**	Me	H	82%	99:1	63

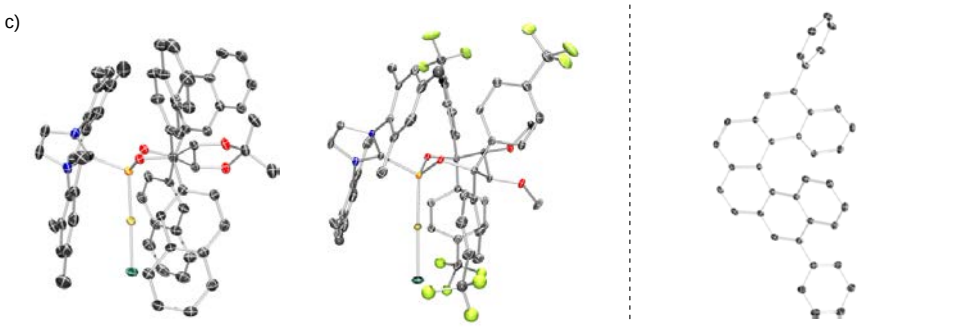


Figure 1. (a) Synthesis and structure of chiral cationic phosphonites; (b) Substrate scope of the Au(I)-catalysed hydroarylation of dienes into phenanthrenes; (c) X-ray structures of precatalysts **3e**, **3g** and helicene **5b**.

(**5e**). Only the methyl capped alkyne **5k** afforded significantly lower ee for reasons that are under study at this moment.[4]

2 Chelating cationic phosphines:

As it has been already shown, the strategic placement of one or more positively charged group(s) directly attached to the central phosphorus atom of phosphines provides an useful entry, complementary to polyfluorination, for the design of ligands of enhanced π-acceptor character. In addition, the absence of labile P-halogen bonds in these α-cationic phosphines significantly enhances their robustness and facilitates their handling.[5] Unfortunately, **the use of cationic ligands still faces important shortcomings:** (i) the strongest π-acceptor phosphines that might be conceived, namely di- and tricationic ones, show **very little propensity to form coordination complexes** and (ii) the utility of α-cationic phosphines has only been demonstrated in the area of π-acid catalysis since only Pt- and Au-derivatives have been in-deep studied.[6]

In an attempt to overcome these intrinsic disadvantages and to expand the use of (poly)cationic ligands to other transformations, which might also benefit from the unique electronic properties that they impart, we recently envisioned that an additional donating atom in the ligand architecture may serve as an anchor that should bring the cationic moiety into the vicinity of the metal, and thus induce its coordination (Figure 2). This strategy has been applied with success in the past to coordinate groups that were reluctant to do so, such as monocationic nitrenium moieties or boranes and their heavier analogues.[7,8] Hence, we decided to prepare a prototypic dicationic chelating phosphine **7** containing a neutral $–PPh_2$ group and a dicationic $[-P(H_2Im)_2]^{+2}$ moiety (H_2Im = 1,3-dimethyl-4,5-dihydroimidazol-2-ylidene) in its structure (Figure 2).[9]

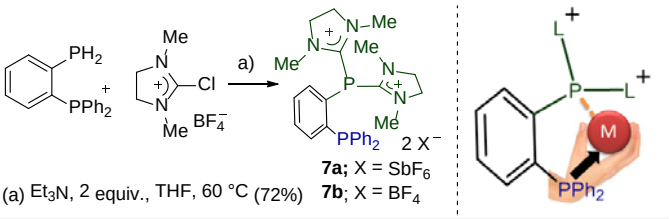


Figure 2. Structural design of dicationic chelating phosphine **7**.

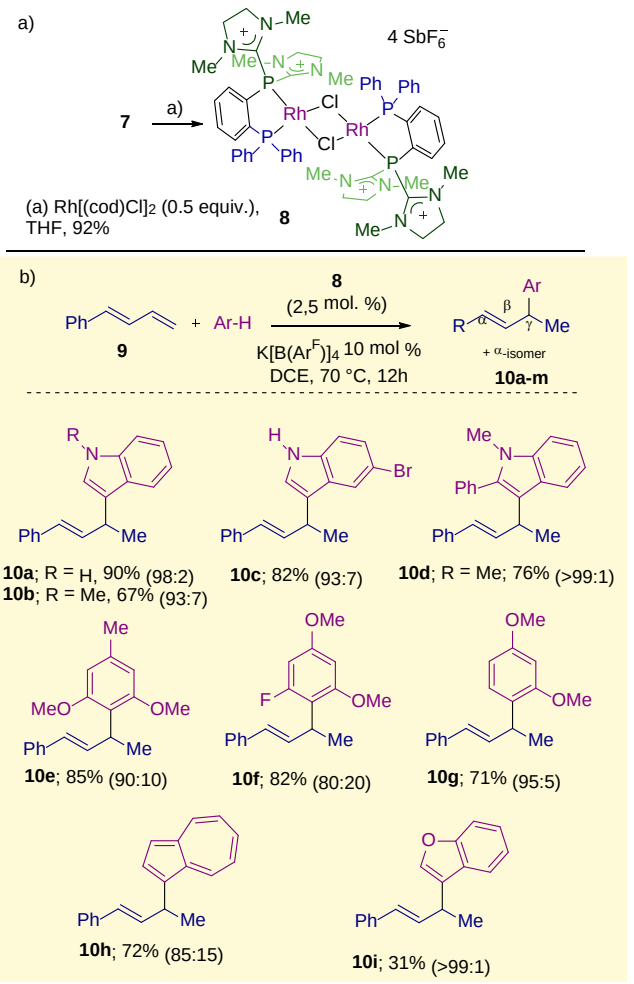


Figure 3. Synthesis of catalyst **8** and preliminary scope of its reactivity.

The global donor ability of **7** was estimated through comparative analysis of the CO stretching frequencies in $LMo(CO)_4$ complexes (L = chelating diphosphine). This analysis confirmed **7** as an exceptionally high acceptor ligand, whose π-acceptor character surpasses that of all other chelating diphosphines known by a wide margin.[10]

Interestingly, **7** was able to form coordination complexes such as **8** with Rh(I) precursors (Figure 3a). This compound

shows remarkable activity in the hydroarylation of diene **9** with electron-rich hetero- and homoarenes which surpasses that of other known catalysts. Less than 5% conversion of **9** to product **10** was observed when 1,2-bis(diphenyl-phosphanyl)benzene, or the stronger acceptors 1-(diphenylphosphanyl)-2-bis(pentafluorophenyl)phosphanylbenzene and 1-(diphenylphosphanyl)-2-di(1-pyrroyl)phosphanylbenzene were used as ancillary ligands under otherwise identical reaction conditions.[11]

The mechanistic pathway of the transformation of **9** into **10a** has been investigated using DFT calculations at the BP86-D3(CPCM)/def2-TZVP//BP86-D3/def2-SVP level. The lowest energy pathway found is shown in Figure 4. The reaction starts with the coordination of the substrate to the rhodium complex to form **INT1** or **INT2** in which the butadiene side-chain moiety adopts either a η^4 or η^2 coordination mode respectively. Both complexes are in equilibrium but it is the lower energy **INT2**, in which only the terminal π-system is coordinated to Rh that is attacked by indole at the internal carbon of the terminal olefin to form **INT3**. The free energy of activation for this step is calculated to be 14.9 kcal/mol. Subsequent rotation of the molecule around the Rh-C bond forms **INT4**, which features a weak hydrogen bonding interaction between the chloride ligand and the hydrogen at the 3-position of the indole. Proton transfer to the Rh center takes place through **TS3** to form a Rh(III) species, **INT5**, which undergoes a facile reductive elimination to afford the desired product **10a** still coordinated through the internal C=C double bond of the original butadiene moiety to Rh in **INT6**. Our calculations indicate that **TS3** leading to the formation of **INT5** is the highest-energy transition state of the complete catalytic cycle and therefore governs the kinetics of the complete process.[12] Finally, product release from **INT6** with association of new substrate is only slightly uphill by 3.4 kcal/mol.

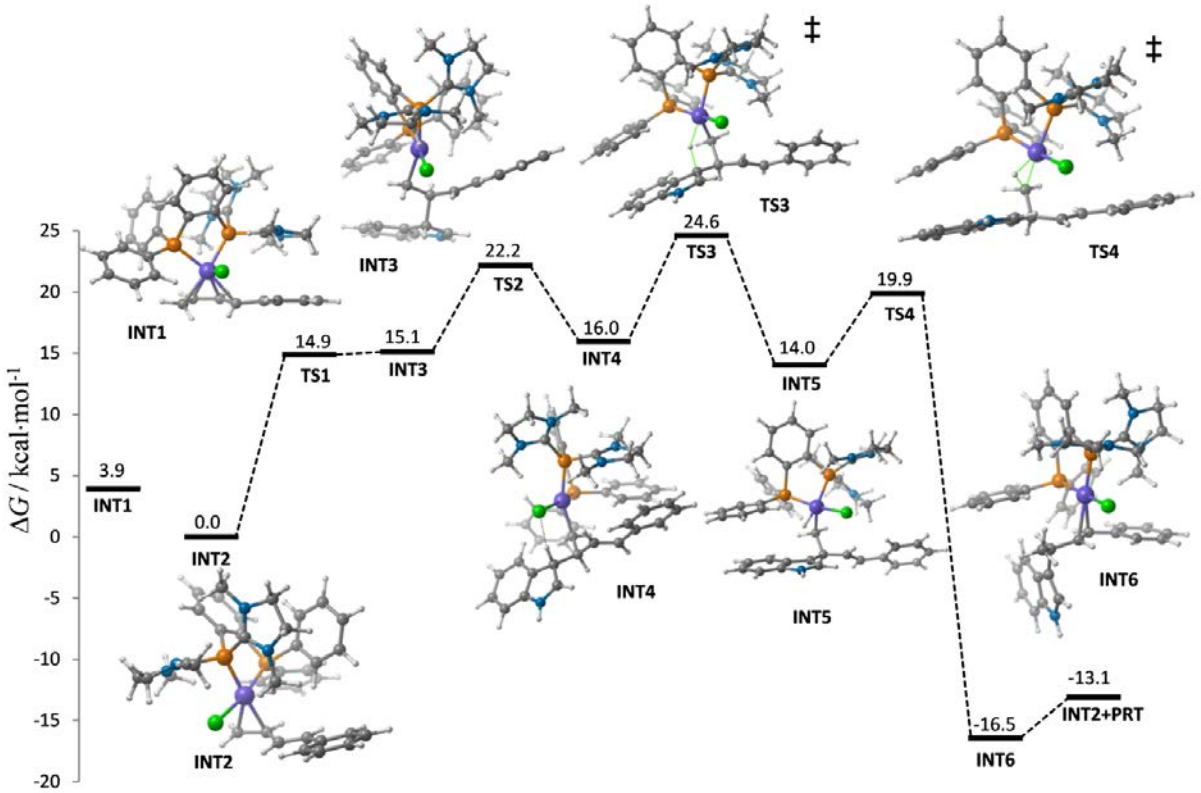


Figure 4. Gibbs free energy profile for the Rh-catalyzed hydroarylation of phenyl-1-butadiene with indole using catalyst **8**. Calculations at the BP86-D3(CPCM)/def2-TZVP//BP86-D3/def2-SVP level.

Two of these steps deserve further discussion since they are fundamental to understanding the role of the ancillary ligand **7**. The nucleophilic attack of indole to the coordinated olefin via **TS1** is not an easy step, and it can only take place because of the high acceptor strength of **7**; in fact this step is energetically prohibitive when catalysts based on neutral ligands are

employed. Also relevant is the nature of the highest-energy step, which is predicted to be the proton transfer from the substrate to Rh (via **TS3**) yielding an effective activation barrier of 24.6 kcal/mol for the whole cycle. This step involves the oxidation of the metal center from Rh(I) to Rh(III) and should thus be facilitated by a strong donor rather than an acceptor ligand; however, it still occurs smoothly. Hence, the acceptor strength of **7** is large enough to allow the attack of the nucleophile to the coordinated diene, but not excessive enough to hinder the subsequent metal protonation.

These preliminary results demonstrate that **by incorporating cationic phosphines into chelating scaffolds, their use can be further extended.** Specifically, reactions based on Rh(I)/Rh(III)catalytic cycles that do not proceed using typical neutral ancillary ligands can be promoted by these new catalytic systems. We believe that this concept could be applied to other metals and catalytic transformations. **In fact, cationic phosphines might *a priori* be the ligands of choice for any concrete process where the step determining the speed benefits from Lewis acidity at the metal,** such as coordination of the substrate, nucleophilic attacks or reductive eliminations.

[11] Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.
[12] (a) Widenhofer, R. *Chem. Eur. J.* **2008**, *14*, 5382-5391; (b) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178-2181; (c) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, *5*, 675-691; (d) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, *10*, 1501-1514; (e) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567-4589.
[13] For the use of TADDOL-derived phosphoramidites in asymmetric catalysis see: (a) Lam, H. W. *Synthesis* **2011**, 2011-2043; (b) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949-1953; (c) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331-15432.
[14] González-Fernández, E.; Nicholls, L. D. M.; Schaaf, L. D.; Farès, C.; Lehmann, C. W.; Alcarazo, M., *J. Am. Chem. Soc.* **2017**, *139*, 1428–1431.
[15] (a) Alcarazo, M. *Acc. Chem. Res.* **2016**, *49*, 1797-1805; (b) Alcarazo, M. *Chem. Eur. J.* **2014**, *20*, 7868-7877; (c) Gaillard, S.; Renaud, J. L., *Dalton Trans.* **2013**, *42*, 7255-7270; (d) Canac, Y.; Maaliki, C.; Abdellah, I.; Chauvin, R. *New J. Chem.* **2012**, *36*, 17-27.
[16] (a) Coles, M. P.; Hitchcock, P. B., *Chem. Commun.* **2007**, 5229-5231; (b) Petuškova, J.; Patil, M.; Holle, S.; Lehmann, C. W.; Thiel, W.; Alcarazo, M., *J. Am. Chem. Soc.* **2011**, *133*, 20758-20760.
[17] (a) Tulchinsky, Y.; Iron, M. A.; Botoshansky, M.; Gandelman, M., *Nat. Chem.* **2011**, *3*, 525-531; (b) Tulchinsky, Y.; Kozuch, S.; Saha, P.; Botoshansky, M.; Shimon, L. J. W.; Gandelman, M., *Chem. Sci.* **2014**, *5*, 1305-1311; (c) Bouhadir, G.; Amgoune, A.; Bourissou, D., *Adv. Org. Chem.* **2010**, *58*, 1-106; (d) Ke, I.-S.; Gabbaï; F. P., *Inorg. Chem.* **2013**, *52*, 7145-7151*; (e)* Ke, I.-S.; Jones, J. S.; Gabbaï, F. P., *Angew. Chem. Int. Ed.* **2014**, *53*, 2633-2637.
[18] Monocationic chelating ligands have been previously described; however, the cationic phosphines employed are also known to act as monodentate ligands on their own. See: (a) Abdellah, I.; Lepetit, C.; Canac, Y.; Duhayon, C.; Chauvin, R., *Chem.–Eur. J.,* **2010**,*16*, 13095–13108; (b) Canac, Y.; Debono, N.; Vendier, L.; Chauvin, R., *Inorg. Chem*. **2009**, *48*, 5562–5568; (c) Ruíz, J.; Mesa, A. F., *Chem. Eur. J.* **2012**, *18*, 4485-4488.
[19] L. Gu, L. M. Wolf, A. Zielinski, W. Thiel, M. Alcarazo., *J. Am. Chem. Soc.* **2017**, *139*, 4948-4953.
[20] Mukerjee, S. L.; Nolan, S. P.; Hoff, C. D.; López de la Vega, R., *Inorg. Chem.* **1998**, *27*, 81-85.
[21] Gu, L.; Wolf, L. M.; Zielinski, A.; Thiel, W.; Alcarazo, M., *J. Am. Chem. Soc*. **2017**, *139*, 4948-4953.
[22] Kozuch, S.; Shaik, S., *Acc. Chem. Res.* **2011**, *44*, 101-110.