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Gold Catalysis

Phosphathiahelicenes: Synthesis and Uses in Enantioselective Gold Catalysis

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Dedicated to Professor Max Malacria on the occasion of his 65th birthday

Abstract: Enantiomerically pure thiahelicenes displaying a terminal phosphole unit and a stereogenic phosphorus center have been prepared by oxidative photocyclization of a diaryl-olefin precursor. Starting from one of these phosphathiahelicene oxides, the corresponding trivalent phosphine–Au^{I} complex is obtained with complete diastereoselectivity. It affords a new, excellent precatalyst for the enantioselective cycloisomerization of N-tethered enynes (up to 96% *ee*).

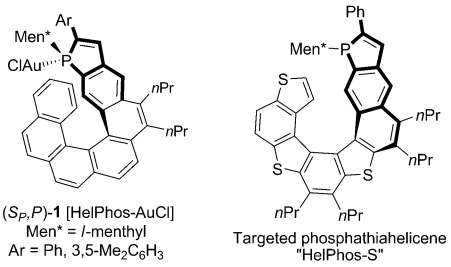

Figure 1. HelPhos gold complexes from previous studies[8] and targeted ligands.

Helically chiral structures are known to display peculiar properties with applications in many fields including asymmetric catalysis.[1] However, both the synthesis of helical phosphorus ligands[2] and their uses in enantioselective organometallic catalysis have been underdeveloped so far. Catalytic screenings in enantioselective reactions mainly include Rh-promoted hydrogenations or hydroformylations of olefins,[2e,3] palladium-promoted allylic substitutions[4] and Ir-promoted allylic aminations of cinnamyl-type substrates.[3c] The phosphines used in these processes display phosphorus functions grafted on helical scaffolds. Following to the pioneering work of Tanaka[5] and Nozaki,[6] we have introduced recently a new design for helical phosphorus ligands where a trivalent phosphorus function is embedded in the helical structure itself, as a phosphole unit.[7] In these series, the so-called HelPhos ligands (Figure 1) afforded excellent catalysts for gold-promoted enantioselective cycloisomerizations with *ee* values up to 86% for the conversion of N-tethered 1,6-enynes into 3-azabicyclo[4.1.0]heptenes.[8] These promising results are especially rewarding as enantioselectivity in gold-catalyzed processes remains to date a highly challenging target.[9]

A brief analysis of the structural features of complex **1** and comparison of its catalytic behavior with other phosphahelicenes, suggest that a key for high enantioinduction from these ligands specifically relates to the positioning of the phosphorus function in the internal rim of the helical scaffold.[10] Thus, as the next step of our work, we intend to expand the same design to phosphahelicenes combining phosphole units with different helical scaffolds, so as to finely tune their structural features and catalytic behaviors.

In this work we demonstrate that thiophene-containing helical scaffolds can be adapted suitably to the synthesis of phosphahelicenes of this class, as well as that the corresponding gold complexes afford unprecedented enantioselectivity levels in enyne cycloisomerization reactions.

Helicenes based on alternating thiophene and benzene units have been extensively developed by Licandro et al. by using the photochemical oxidative cyclization of dithienyl olefins as the preferred synthetic approach.[11] Inspired by this work and considering that heterohelicenes can be functionalized and tuned more easily than the carbon analogues,[12] joint studies have been set up with the aim of preparing thiahelicene mimics of the HelPhos ligand in **1** (Figure 1).

The synthesis of the targeted helicene (HelPhos-S), involves preparation of the diaryl olefin **7**, which combines a [5]-thiahelicene and a 1*H*-phosphindole fragments (Scheme 1), followed by a photochemical oxidative cyclization step (Scheme 2). Olefin **7** has been formed from the olefinic bis-boronate **4**[11c] by two subsequent palladium-catalyzed Suzuki couplings involving the [5]-thiahelicene bromide **3**[13] and the phosphindole triflate (R_P)-**6**,[8] respectively. The phosphindole triflate **6** is an optically pure compound which displays a chiral *l*-menthyl

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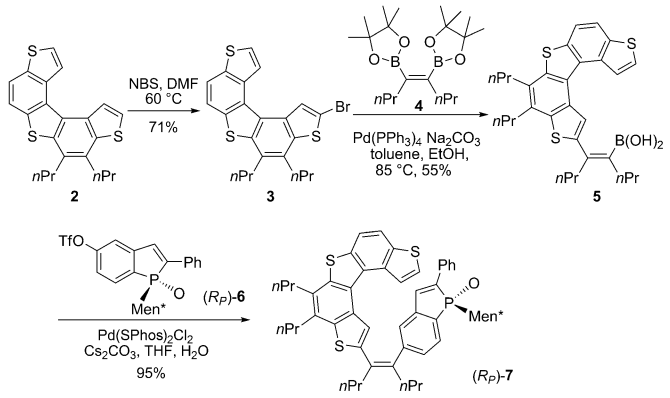
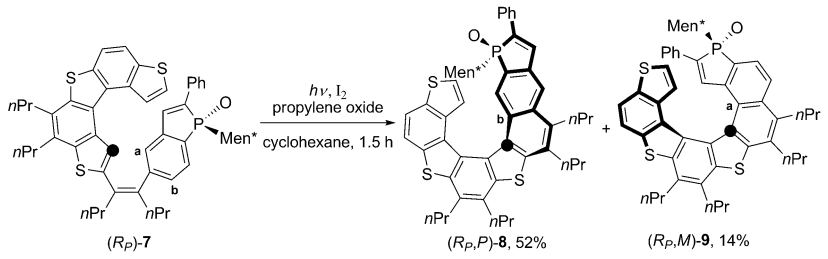


Scheme 1. Synthesis of the olefinic derivative (R_P)-**7** by Suzuki couplings.

group on phosphorus and a stereogenic phosphorus with R_P configuration ($[\alpha]_D = -150$ ($c = 0.2$, $CHCl_3$)).[14]

The coupling step between the olefinic boronate **4** and the [5]-thiahelicene bromide **3** was performed with $Pd(PPh_3)_4$ as the catalyst, while the second coupling, which involves (R_P)-**6**, requires the use of the $Pd(SPhos)_2Cl_2$ precatalyst. It takes place in almost quantitative yield, giving olefin (R_P)-**7** as a pale yellow solid ($[\alpha]_D = -187$ ($c = 1$, $CHCl_3$)).

Next, the key photocyclization step (Scheme 2) was carried out in cyclohexane in the presence of iodine and propylene oxide: irradiation of a diluted solution of (R_P)-**7** (0.3 mg mL^{-1}) for 1.5 h with a 150 W mercury lamp, afforded a mixture of the helical compounds (R_PP)-**8** and (R_PM)-**9** in 66% total yield. Structural assignments were made by NMR spectroscopy and the helical configurations were assigned based on the sign of optical rotation: $[\alpha]_D = +1358$ ($c = 1$, $CHCl_3$) for (R_PP)-**8** and $[\alpha]_D = -1366$ ($c = 1$, $CHCl_3$) for (R_PM)-**9**.

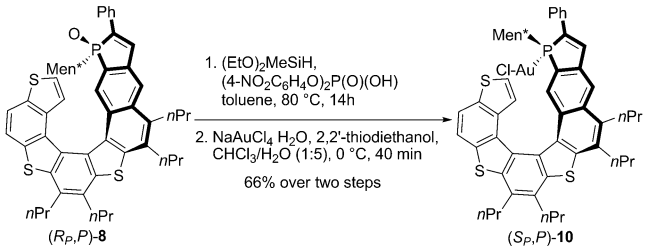


Scheme 2. Oxidative photocyclization of (R_P)-**7**.

The photocyclization reaction gives only very small amounts of side products and affords the desired [7]-helicene, **8**, as the major product in an 8:2 ratio to **9**. Overall this reaction is therefore much more efficient than the analogous photochemical generation of phosphahelicenes with all-carbon backbones.[8]

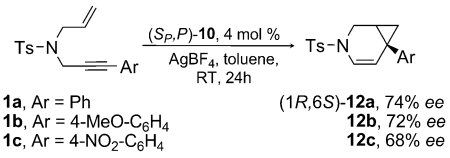
Both the [7]-helicene **8** and the [8]-helicene **9** were isolated as single epimers with defined helical configuration, meaning that the phosphorus configuration dictates the stereochemistry of the helical structures at this photocyclization step.

The synthesis of gold complexes from (R_PP)-**8** was then carried out according to Scheme 3. After reduction of the phosphine oxide (R_PP)-**8** into the corresponding trivalent phosphine, in situ complexation was performed by reaction with AuCl·thiodiethanol. This procedure affords the desired gold complex (S_PP)-**10** as a single diastereomer. We could not obtain X-ray data for complex **10**, nevertheless, based on NMR spectroscopy data (see the Supporting Information), we assume that the gold atom is oriented toward the helical structure (*endo* isomer) while the *l*-menthyl group occupies the external face of the phosphahelicene. The reaction thus involves overall inversion of the phosphorus configuration, as a result of the configurational lability of phosphorus in phosphindole-type derivatives.[15] The same reduction-complexation procedure had been applied before to the analogous all-carbon phosphahelicenes (Figure 1), but it displayed much lower diastereoselectivity, giving 1:1 mixtures of the *exo* and *endo* isomers of the gold complexes **1**.[8]



Scheme 3. Synthesis of the gold complex (S_PP)-**10**.

The helical scaffold of (S_PP)-**10** differs significantly from that of the phosphahelicene ligand in (S_PP)-**1**, as it contains seven *ortho*-condensed aromatic rings instead of six and includes five-membered heterocyclic units. These structural and geometrical modifications might result in deep changes in the catalytic behavior of the gold complex (S_PP)-**10**, with respect to **1**, that cannot be easily anticipated. Therefore, the catalytic properties of (S_PP)-**10** were investigated in a systematic way, starting from its use as precatalyst in enyne cycloisomerization reactions. In this field, a benchmark reaction is the cycloisomerization of the N-tethered 1,6-enynes **11** into aza-bicyclo-[4.1.0]heptenes **12**[16] shown in Scheme 4. Starting from **11a** (Ar = Ph), the gold complex (S_PP)-**10** displayed good catalytic activity at room temperature, after activation with $AgBF_4$. It afforded **12a** in 74% enantiomeric excess. Changing the activating agent from $AgBF_4$ to $AgNTf_2$ did not change the enantioselectivity level (*ee* = 75%), while other silver salts such as AgOTf or $AgSbF_6$ decreased the enantiomeric excess to 45 and 63%, respectively. Significant enantiomeric excesses were

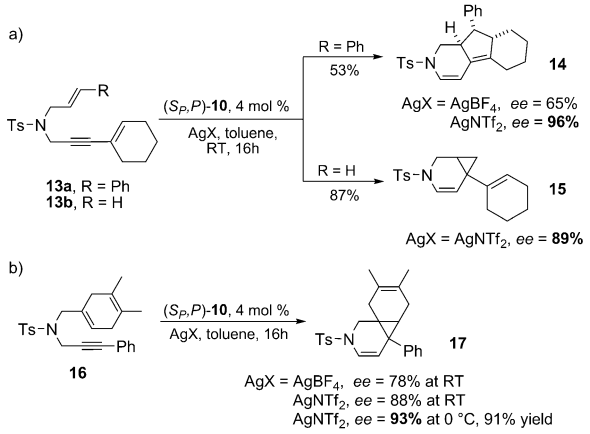


Scheme 4. Enantioselective cycloisomerization of the N-tethered enynes **11 a–c**.

obtained also in the cycloisomerization of enynes with either electron-rich (**11 b**) or electron-poor (**11 c**) aryl substituents on the alkyne unit (72 and 68% *ee*, respectively, Scheme 4).

The promising enantioselectivity levels above encouraged us to extend our investigations to the cycloisomerization of different classes of enynes. At first, dienynes **13**[17] were considered that display conjugated enyne moieties (Scheme 5 a). Depending on the nature of the R substituent, the gold-catalyzed cycloisomerization affords either the aza-bicyclo[4.1.0]heptene **15** (for R = H) or the tricyclic derivative **14** (for R = Ph), which results from a vinylcyclopropane-cyclopentene rearrangement[18] of the intermediate aza-bicyclo[4.1.0]heptene. In the cycloisomerization of **13 a** (R = Ph), the nature of the silver salt has a remarkable effect on the enantioselectivity level, going from a moderate 65% *ee* for AgX = $AgBF_4$ to an excellent 96% *ee* for AgX = $AgNTf_2$. The same catalytic system ((*S*$_P$,*P*)-**10**/$AgNTf_2$) affords the aza-bicyclo[4.1.0]heptene **15** in 89% *ee*. Thus, the thiaphosphahelicene–Au^I catalyst (*S*$_P$,*P*)-**10** gives the highest enantiomeric excesses attained so far in these cycloisomerization reactions.[19]

Finally, the same catalyst was used in the cycloisomerization of enyne **16**[20] in which the olefinic function is included into a cyclic structure (Scheme 5 b). The reaction affords the expected tricyclic derivative **17** as a single diastereomer, with high enantiomeric excess. In this reaction also, the enantioselectivity level was found to change significantly by changing the counterion in the cationic gold catalyst. So far, NTf_2^- proved to be the best counterion giving an 88% *ee* for reactions run at room temperature, compared to a 78% *ee* for BF_4^-, under the same conditions. The enantiomeric excess could be increased



Scheme 5. Enantioselective cycloisomerizations of dien-ynes promoted by (*S*$_P$,*P*)-**10**.

then up to 93% by carrying out the cycloisomerization reaction at 0 °C. As far as we know, enantioselective variants of this reaction have been reported before under platinum catalysis (92% *ee*),[16b] never under gold catalysis.

In summary, we have shown that enantiomerically pure phosphathiahelicenes are easily available by a highly regio- and diastereoselective photocyclization procedure. Overall the phosphathiahelicene oxide **8** and the corresponding gold complex **10** are obtained more efficiently than the analogous phosphacarbohelicene gold complexes described in our previous work. The new complex displays especially high enantioselectivity levels in the cycloisomerization of N-tethered dien-ynes. More extended catalytic screening is currently ongoing in our group so as to assess the potential of these helical ligands in enantioselective gold catalysis.

Acknowledgements

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Keywords: enantioselectivity · enyne cycloisomerization · gold · phosphahelicenes · thiahelicenes

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