Communication

Tunable asymmetric catalysis through ligand stacking in chiral rigid rods.

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Highly tunable asymmetric catalysis through ligand stacking in chiral rigid rods.

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Supporting Information Placeholder

ABSTRACT: Chiral benzene-1,3,5-tricarboxamide (BTA) ligands, comprising one diphenylphosphino group and one or two remote chiral octan-2-yl side chains, were evaluated in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate. Despite the fact that the rhodium atom and the chiral center(s) are separated by more than 12 covalent bonds, up to 82% ee was observed. A series of control and spectroscopic experiments confirmed that the selectivity arises from the formation of chiral helical polymers by self-association of the BTA monomers through non-covalent interactions. The addition of a phosphine-free chiral BTA, acting as a co-monomer for the chiral BTA ligands, increases the level of enantioselectivity (up to 88% ee). It highlights the subtle control that can be achieved with this class of highly tunable supramolecular catalysts. The concept was further probed by performing the same experiment with an achiral BTA ligand, *i.e.* a phosphine-functionalized BTA that contains two remote octanyl side chains. It afforded an encouraging 31% ee, thus demonstrating the catalytically relevant transfer of chirality between the self-assembled units. It constitutes a unique example of the sergeants-and-soldiers principle applied to catalysis.

In Nature, the combination of local chiral centers and recognition elements leads to the formation of supramacromolecular chiral assemblies such as the right-handed double helical structure of DNA (B-DNA) and the complex secondary structure of proteins. These highly ordered architectures furnish a well-defined chiral environment that can be used as a scaffold for the development of non-natural reactions. To this end, efficient asymmetric hybrid catalysts[1] have been constructed that combine a metal and small peptide sequences,[2] proteins[3] or DNA-scaffolds.[4]

An important challenge that remains is the design of asymmetric catalysts for which the chiral nature can be easily fine-tuned or even completely inversed without changing the overall catalyst architecture. To date, most of the existing metal catalysts based on non-natural synthons operate through the direct transfer of the chiral information located on the ligand to the metal center. Slightly more elaborated systems have recently been developed that associate a metal center and a chiral module linked by non-covalent interactions, but again the transfer of chirality is hardly controllable/tunable.[5] Two main classes of asymmetric metal catalysts based on chiral covalent polymers have been reported: (i) preferential ligands (mainly BINOL and BINAP) embedded in a polymer backbone,[6] and (ii) metal binding groups covalently attached to a chiral polymeric scaffold.[7] Only for the latter approach, some fine-tuning and control of the chiral environment have been demonstrated but the modularity of the catalytic systems remains limited because of their covalent nature. To the best of our knowledge, only one example of an asymmetric metal catalyst based on an artificial supramacromolecular scaffold has been reported. Liu and coworkers found that Cu^{2+} atoms interact with the chiral tubular self-assembly formed by a bolaamphiphile gelator in water,[8] and that the Cu^{2+} aligned at the surface of the nanotube worked as catalytic sites. The self-assembled catalyst provides 55% ee at best for a benchmark Diels–Alder cycloaddition, the sense of induction of the product being dictated by the chirality of the nanotube. Even though this catalytic system is based on non-covalent hydrophobic interactions, its modularity has not been probed yet. Clearly, the design of highly tunable asymmetric catalysts based on a chiral supra-macromolecular scaffold remains to be accomplished.

Among the large number of supramolecular polymers with a well defined helical structure,[9] we focused on the benzene-1,3,5-tricarboxamide (BTA) moiety due to its well-known ability to generate helical rods through a combination of three-fold hydrogen bonds and π-π stacking interactions.[10] Introduction of one remote chiral center as a side-chain of the BTA enables the formation of chiral helices with a single helical twist. Moreover, the chirality of the helices can be finely tuned because mixtures of BTA monomers follow the "majority rules"[11] and the "sergeants-and-soldiers" effects.[12] Herein, we demonstrate that phosphine-functionalized BTAs self-assemble into chiral helices, providing an efficient scaffold for asymmetric catalysis. It allows an unprecedented modularity in the design of artificial asymmetric catalysts by simple mixing of various self-assembling units.[13]

Our initial approach was to probe if chiral helices formed by self-assembled BTA units can be used as a catalytic platform for metal-catalyzed asymmetric reactions. Also we wondered

Chart 1. BTA derivatives used in this study and their nomenclature.

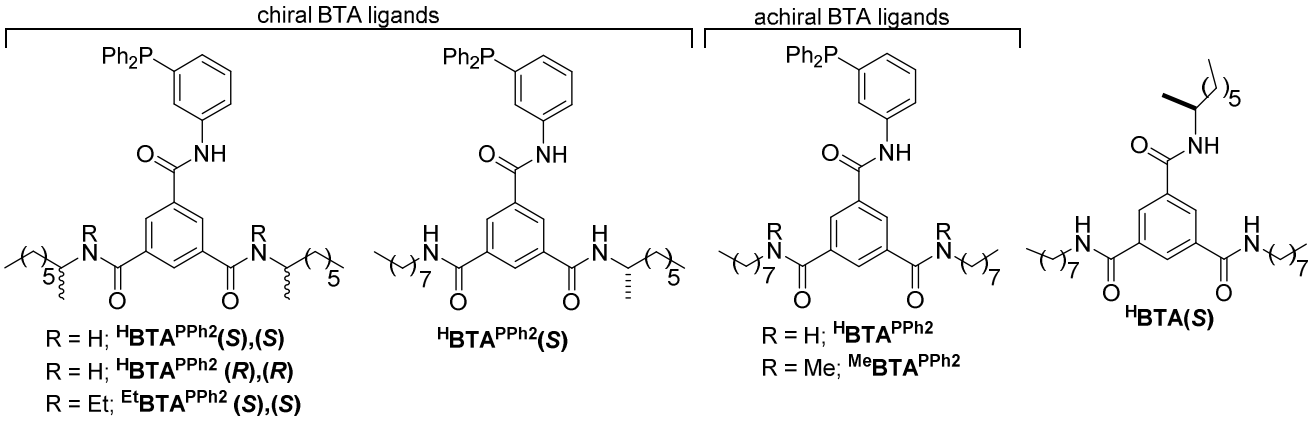
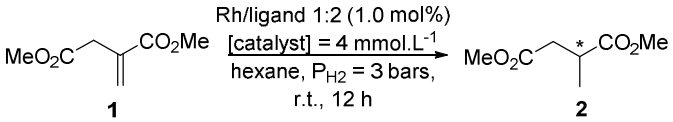


Table 1. Evaluation of the BTA ligands for the hydrogenation of 1[a]



Entry	BTA ligand	BTA addtive	Rh precursor	ee (%)
1	^{H}BTA^{PPh2}(*S*),(*S*)	–	[Rh(cod)$_2$]BAr$_F$	82
2	^{H}BTA^{PPh2}(*S*)	–	[Rh(cod)$_2$]BAr$_F$	67
3	^{H}BTA^{PPh2}(*R*),(*R*)	–	[Rh(cod)$_2$]BAr$_F$	-81
4	^{H}BTA^{PPh2}(*S*),(*S*)	–	[Rh(cod)$_2$]BF$_4$	15[b]
5	^{Et}BTA^{PPh2}(*S*),(*S*)	–	[Rh(cod)$_2$]BAr$_F$	0
6	^{Et}BTA^{PPh2}(*S*),(*S*)	^{H}BTA(*S*)[c]	[Rh(cod)$_2$]BAr$_F$	0
7	^{H}BTA^{PPh2}(*S*),(*S*)	^{H}BTA(*S*)[c]	[Rh(cod)$_2$]BAr$_F$	**88**
8	^{H}BTA^{PPh2}(*S*)	^{H}BTA(*S*)[c]	[Rh(cod)$_2$]BAr$_F$	86
9	^{H}BTA^{PPh2}	–	[Rh(cod)$_2$]BAr$_F$	0
10	^{H}BTA^{PPh2}	^{H}BTA(*S*)[c]	[Rh(cod)$_2$]BAr$_F$	31
11	^{Me}BTA^{PPh2}	^{H}BTA(*S*)[c]	[Rh(cod)$_2$]BAr$_F$	0

[a] Conversion 100%, the experiments were performed at least in triplicate (except for control experiments 4,5,6, 9,11). Standard deviation for the ee < 2% (entries 1,3,7,8), =5% (entry 10), =8% (entry 2). Positive value of ee corresponds to the (*R*) enantiomer according to reference 14 [b] Conversion 90%. [c] BTA additive (2.5 mol%). See SI for more details.

whether the sergeants-and-soldiers principle can be applied to catalysis in order to control the selectivity of the supramolecular catalysts. We chose the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate (**1**) as a reaction of reference.

A set of BTA ligands have been prepared (see the SI) that contain a central BTA ring connected to a 1,3-phenylenediphenylphosphino group and two alkyl side chains. The BTA ligands differ by the nature of the alkyl side chain (either chiral octan-2-yl or octanyl) and the degree of substitution of the two alkyl amide functions. Chiral BTA ligands contain one or two remote chiral octan-2-yl side chains while achiral BTA ligands possess two peripheral octanyl chains (see formulae and nomenclature in Chart 1). A short screening of the catalytic conditions (see the SI, Table S.1) helped us to identity the following satisfactory parameters: hexane as the solvent, a rhodium:ligand ratio of 1:2 and [Rh(cod)2]BAr$_F$ as the rhodium precursor. Because the rhodium atom and the chiral centers are separated by more than 12 covalent bonds, we were surprised to see that ^{H}**BTA**^{PPh2}(***S***),(***S***) alone provided the (*R*) enantiomer of **2** with 82% ee (Table 1, entry 1).[5] Its enantiomer, ^{H}**BTA**^{PPh2}(***R***),(***R***), yielded the (*S*) enantiomer of **2** with the same selectivity (81% ee, entry 3). ^{H}**BTA**^{PPh2}(***S***), which contains only one chiral side chain, was slightly less selective than ^{H}**BTA**^{PPh2}(***S***),(***S***) (67% ee, entry 2). As expected, the achiral phosphine ligand, ^{H}**BTA**^{PPh2}, provided no enantioselectivity for the catalytic reaction (entry 9). Consequently, additional catalytic experiments and structural studies were performed to check whether the selectivity observed arises from the formation of non-covalent interactions between the BTA monomers.

A first evidence of the key role played by non-covalent interactions on the enantioselectivity stems from the fact that ^{Et}**BTA**^{PPh2}(***S***),(***S***), for which two alkyl amide functions have been ethylated, gave no enantioselectivity for the reaction (Table 1, entry 5). The presence of a single N–H function (corresponding to the aryl amide function) instead of three N–H functions probably prevents the formation of the assemblies. Also, the enantioselectivity dropped when: (i) the solvent polarity was increased (the selectivity was low in toluene and totally lost in CH_2Cl_2, see Table S.2) and (ii) the hydrogen bond accepting ability of the rhodium counteranion was increased (compare BAr$_F$ and BF4, entry 1 and 4 respectively in Table 1). These experiments demonstrate that the observed selectivity for ^{H}**BTA**^{PPh2}(***S***),(***S***), ^{H}**BTA**^{PPh2}(***S***) and ^{H}**BTA**^{PPh2}(***R***),(***R***) is not due to isolated, dissociated chiral BTA ligands: it is related to the formation of chiral self-assemblies that results from hydrogen bonding interactions between the BTA units.

We then performed spectroscopic and scattering analyses to gain insight into the structure of the self-associated ^{H}**BTA**^{PPh2}(***S***),(***S***). We compared the spectroscopic signature of ^{H}**BTA**^{PPh2}(***S***),(***S***) and ^{H}**BTA**(***S***) since the cooperative polymerization in alkanes of the latter has been fully assessed by Meijer, Palmans and co-workers.[15] FTIR spectroscopy (Figure S.1) shows that both BTA derivatives are fully aggregated in decaline (4.0 mmol.L^{-1}), as shown by the frequency of the amide vibrations (3236 cm^{-1}, 1640 cm^{-1} and 1555 cm^{-1}). Conversely, ^{H}**BTA**^{PPh2}(***S***),(***S***) is fully dissociated in CH_2Cl_2 at the same concentration ($\nu_{free\ N\text{-}H}$ = 3430 cm^{-1}, $\nu_{free\ C=O}$ = 1665 cm^{-1}, $\nu_{free\ amideII}$ = 1519 cm^{-1}). Moreover, small angle

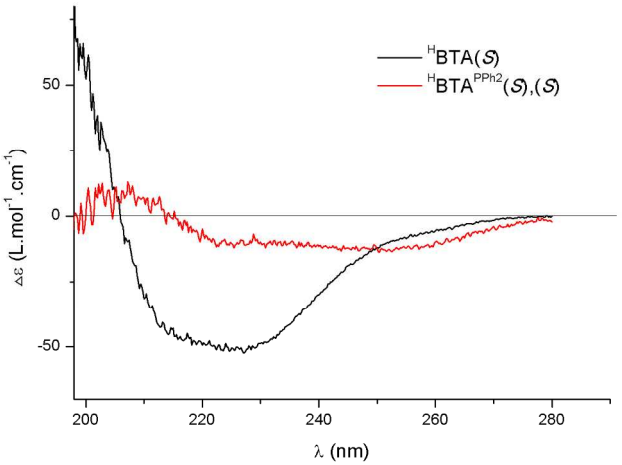


Figure 1. CD spectra of ^{H}**BTA**(***S***) and ^{H}**BTA**^{PPh_2}(***S***),(***S***) in decaline recorded at 298 K at a concentration of 30 µmol.L^{-1}.

neutron scattering (SANS) analyses prove the formation of long aggregates for both ^{H}**BTA**(***S***) and ^{H}**BTA**^{PPh_2}(***S***),(***S***) in deuterated cyclohexane (at ca. 3 mmol.L^{-1}). The scattering curves (Figure S.2) are characterized by a q^{-1} dependence at low angles representative of rigid cylindrical objects that are longer than 200 Å, i.e. at least 60 stacked BTAs. The data can be fitted[16] using the form factor for rigid rods with a circular cross-section yielding radii of 10 and 9 Å for ^{H}**BTA**(***S***) and ^{H}**BTA**^{PPh_2}(***S***),(***S***) respectively. Finally, the chiral nature of the self-assemblies was probed by circular dichroism (CD). The CD spectrum of ^{H}**BTA**^{PPh_2}(***S***),(***S***) in decaline (30 µmol.L^{-1}) shows a negative Cotton effect with two maxima at approximately 207 nm and 225 nm (Figure 1). The shape of the CD spectrum and the values of the molar ellipticity significantly differ from the one obtained with ^{H}**BTA**(***S***) as a probable result of the additional presence of aromatic chromophores located on the phosphorus atom (see the UV-Vis spectra, Figure S.3) and/or a different conformation of the monomer within the chiral nanohelices.

The above analyses clearly demonstrate that ^{H}**BTA**^{PPh_2}(***S***),(***S***) is able to form chiral helical polymers in alkanes. It proves that the presence of the phosphine does not significantly alter the formation of the self-assemblies that are typically observed with non-functionalized BTA derivatives. Investigation of the self-assembly behavior of the precatalyst, obtained by mixing two equiv. of ^{H}**BTA**^{PPh_2}(***S***),(***S***) and one equiv. of [Rh(cod)$_2$]BAr$_F$, is hampered by its very low solubility (<<30 µmol.L^{-1}) in apolar solvents. However, control experiments performed for the catalytic reactions (see Table 1) support the formation of chiral assemblies for the precatalyst and/or the catalytically active species in hexane. Accordingly, we propose a helical polymeric structure for the precatalyst (see Figure 2); the catalytically active centers formed by the rhodium atoms linked to the phosphorous atoms are distributed along the scaffold of the helices formed by association of the BTA rings.[17]

The non-covalent nature and the one-dimensional structure of the catalytic system make it particular easy to try and tune the selectivity of the reaction by adding a co-monomer. Therefore, a phosphorus-free chiral BTA, ^{H}**BTA**(***S***), was combined with the previously mentioned chiral BTA ligands to examine whether the presence of this co-monomer affects the overall catalytic performance. ^{H}**BTA**(***S***) (2.5 mol%) and

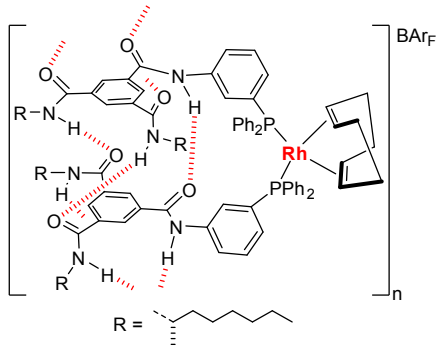


Figure 2. Proposed structure for the precatalyst derived from ^{H}**BTA**^{PPh_2}(***S***),(***S***), n is the degree of polymerization.

the chiral BTA ligands (2.0 mol%) were combined together before the addition of [Rh(cod)$_2$]BAr$_F$ (1.0 mol%). An increase of the selectivity was observed for both ^{H}**BTA**^{PPh_2}(***S***),(***S***) and ^{H}**BTA**^{PPh_2}(***S***), providing **2** with 88% ee (entry 7, Table 1) and 86% ee (entry 8) instead of 82% ee and 67% ee respectively in the absence of the additive. Such an increase in the selectivity was not observed with ^{Et}**BTA**^{PPh_2}(***S***),(***S***) (entry 6) demonstrating that the incorporation of ^{H}**BTA**(***S***) within the self-assemblies of ^{H}**BTA**^{PPh_2}(***S***),(***S***) is at the origin of the improved catalytic performance. This blank experiment also shows that fortuitous coordination of the amides moieties to the rhodium could not explain the enhanced enantioselectivity observed.

As an ultimate test of the concept, catalytic experiments were performed by mixing an achiral BTA ligand (^{H}**BTA**^{PPh_2}) and ^{H}**BTA**(***S***)**.** Although the observed selectivity was low (31% ee, entry 10) it clearly proves that ^{H}**BTA**(***S***) is able to create a chiral environment for catalysis, although it does not directly interact with the rhodium atoms. Control experiments with ^{Me}**BTA**^{PPh_2}, the analogue of ^{H}**BTA**^{PPh_2} with *N*-methylated alkyl amide functions, confirmed that the selectivity arises from the formation of a hydrogen-bonded copolymer between ^{H}**BTA**^{PPh_2} and ^{H}**BTA**(***S***) (entry 11). The exact mechanism at the origin of the enhanced enantioselectivity observed with ^{H}**BTA**(***S***) as an additive remains to be elucidated; however it can act as a co-monomer, improving the degree of the chiral amplification in a way that is reminiscent of the sergeants-and-soldiers principle occurring in both helical supramolecular[18] and covalent polymers.[19]

To conclude, the self-association of phosphine-functionalized BTA monomers that possess remote chiral groups provides supramolecular chiral helices; the chirality transfer between the helices and the catalytically active rhodium centers is sufficiently efficient to promote the asymmetric hydrogenation of dimethyl itaconate with excellent selectivity. The self-assemblies are based on non-covalent interactions (hydrogen bonding and π-π stacking) and can thus be easily modulated by incorporation of phosphorus-free monomers. Ongoing work in our laboratory encompasses a better understanding of the nature of the rhodium self-assemblies and the scope and limitations of this new class of catalysts.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and spectral data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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