ChemPubSoc Europe

DOI: 10.1002/chem.201600158

CHEMISTRY
A European Journal
Communication

Supramolecular Chemistry

A Supramolecular Chiral Auxiliary Approach: "Remote Control" of Stereochemistry at a Hierarchically Assembled Dimeric Helicate

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

Abstract: Dimeric hierarchically-assembled titanium(IV) helicates are in solvent-dependent equilibrium with the corresponding monomers. Statistically formed mixtures of such complexes bearing chiral stereocontrolling ligands and achiral diene-substituted ligands show high diastereoselectivity and reasonable enantioselectivity in the Diels–Alder reaction with maleimides if the reaction proceeds with the dimer but not with the monomer. Thus, solvent dependent switching between the monomer and dimer enables on/off switching of the enantioselectivity.

Chemo-, regio-, and stereoselectivity are of utmost importance in C–C bond-forming reactions to obtain well-defined organic products. This is not only fundamental in organic synthesis but also has some significant influence in industrial applications as well as in biochemical processes. The stereochemistry of a C–C bond-forming reaction is usually controlled either by a chiral auxiliary[1] or by a chiral catalyst.[2]

In the present study, we describe a supramolecular chiral-auxiliary approach in which the source of the chiral information and the reactive unit are separated. Incorporation of both moieties into one aggregate allows us to perform a stereoselective reaction, which affords a chiral product after disassembly. The expensive chiral stereocontrolling building block (auxiliary) is recovered. Furthermore, solvent control of the degree of the hierarchical supramolecular aggregation allows on/off switching of the enantioselectivity of the reaction.

Few examples for the "remote control" of stereoselectivity have been described.[3] Figure 1 shows the selected supramolecular chiral catalysts **A**[4] and **B**,[5] in which stereochemistry is introduced by a building block forming an aggregate with nonchiral phosphanes either by a coordination or electrostatic attraction. The obtained chelating ligands form catalytically active metal complexes. A comparable "remote control" by a long distance induction is also found in nanoparticle-catalyzed reactions.[6] For example, a chiral palladium-nanoparticle-catalyzed allylation results in over 80% *ee*.[6]

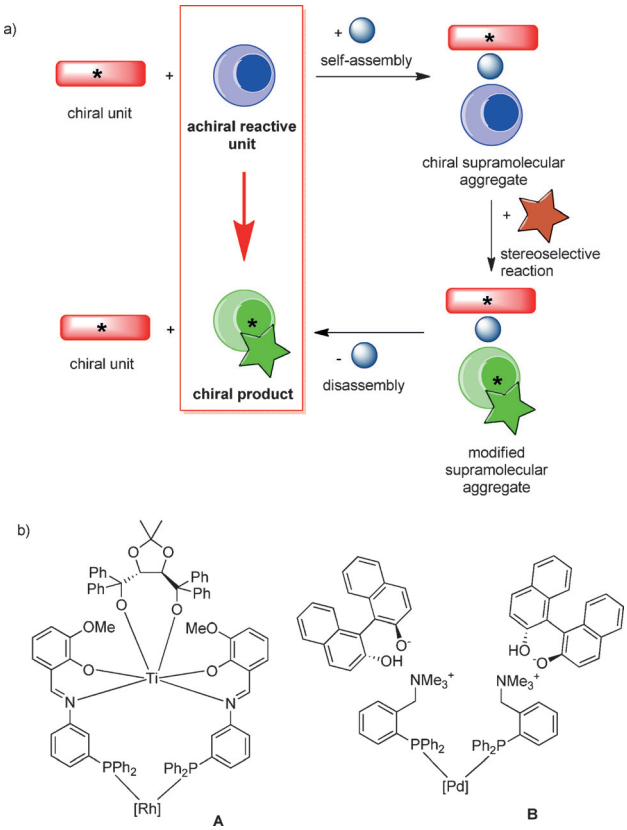

Figure 1. a) The concept of "remote control" of stereochemistry in a supramolecular chiral auxiliary approach as discussed in this study; b) two examples for "remote control" of stereoselectivity in metal catalysis.

The term "helicate" was introduced by Lehn in 1987 for intrinsically chiral oligonuclear complexes formed by self-assembly of metal ions and two or more linear ligand strands.[7] Hierarchical approaches to the self-assembly of dinuclear helicates involving imine condensation were developed by Hannon[8] and Nitschke.[9] Raymond et al.[10] described helicate-type complexes with phosphane-substituted triscatecholates bridged by three metal ions as spacers.[11] A decade ago, we found hier-

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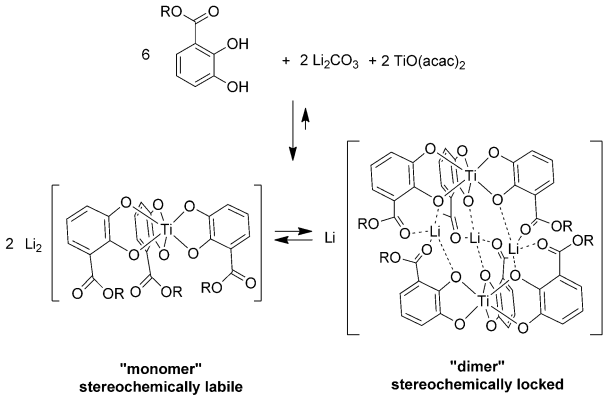
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201600158.



Scheme 1. Formation of dimeric hierarchically self-assembled lithium-bridged titanium(IV) helicates, which are in solvent dependent equilibrium with the corresponding monomers.

archically assembled lithium-bridged titanium(IV) helicates with aldehyde-, keto-, or ester-functionalized catechol ligands (Scheme 1).[12]

The use of appropriate chiral ligands affords the dimeric complexes in enantiomerically pure form.[13,14] The configuration at the homochiral metal complex units of the dimer is locked due to the interlocking of the ester side chains. Inversion of the stereochemistry at the two metal complex moieties only occurs by kinetically slow dissociation into the monomers. The monomers are labile at the metal complex units and undergo nondissociative Bailar or Ray-Dutt twist rearrangements.[15] In solvents that coordinate Li^+ well (e.g. DMF), mainly a monomer is observed, whereas less polar solvents (e.g. THF) strongly favor the dimeric helicate.

Herein, we describe the formation of triple lithium-bridged helicates from statistical mixtures of an achiral ligand that are able to undergo a post-assembly functionalization[16] by a Diels–Alder reaction, and a chiral ligand for "remote control" of the stereoselectivity at the reactive ligand (Figure 2).

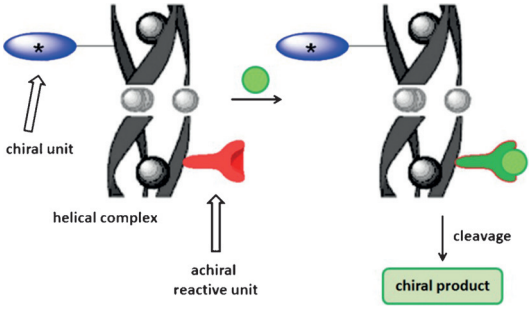
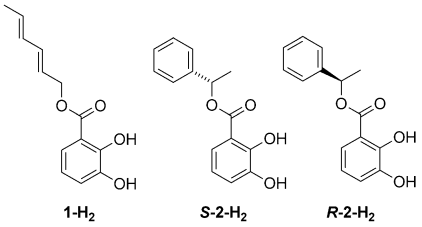


Figure 2. Schematic representation of the concept of "remote control" for stereoselective C–C bond forming reactions with helicates based on mixtures of chiral ligands and nonchiral ligands bearing a reactive unit.

The achiral diene ligand **1-H$_2$**, as well as the chiral ligands ***S*-2-H$_2$**[13] and ***R*-2-H$_2$** were reacted with $TiO(acac)_2$ and Li_2CO_3 to obtain the helicates listed in Table 1. All complexes, except $Li_4[(\mathbf{1})_6Ti_2]$, were obtained as $Li_4[(\mathbf{1})_x(\mathbf{2})_{6-x}Ti_2]$ (x = 1–6) mixtures, with a close to statistical distribution of the ligands within the

Table 1. Synthesis of mixtures of complexes from achiral reactive ligand **1-H$_2$** and the chiral ligands ***S*-2-H$_2$** and ***R*-2-H$_2$**.



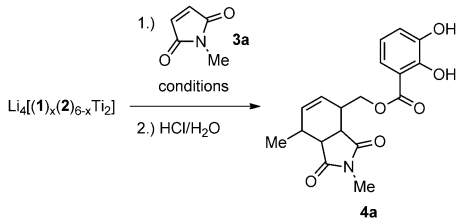
Entry	Complex	**1-H$_2$** [Equiv]	**2-H$_2$** [Equiv]	Configuration at metal[a]
1	$Li_4[(\mathbf{1})_6Ti_2]$	6	0	rac.
2	$Li_4[(\mathbf{1})_5(\mathbf{S\text{-}2})_1Ti_2]$[b]	5	1	ΔΔ
3	$Li_4[(\mathbf{1})_3(\mathbf{S\text{-}2})_3Ti_2]$[b]	3	3	ΔΔ
4	$Li_4[(\mathbf{1})_1(\mathbf{S\text{-}2})_5Ti_2]$[b]	1	5	ΔΔ
5	$Li_4[(\mathbf{1})_3(\mathbf{R\text{-}2})_3Ti_2]$[b]	3	3	ΛΛ

[a] Confirmed by CD.[19] [b] A statistical mixture of complexes based on the given ratio of ligands is present.

complexes as observed by ESI mass spectrometry. Four constitutional isomers of the monomer and thirteen constitutional isomers of the dimer (as well as corresponding stereoisomers) are possible. Twelve of the latter bear at least one of the chiral ligands **2** to control the stereochemistry of a post-assembly functionalization reaction at the coordinated ligand **1**. All Diels–Alder reactions at the helicate were performed with three equivalents of a dienophile, based on diene units. After hydrolytic work-up, the Diels–Alder product was isolated and the chiral ligand was recovered (77%).

The Diels–Alder reaction with *N*-methylmaleimide (**3a**) was first tested with racemic $Li_4[(\mathbf{1})_6Ti_2]$ (characterized by X-ray).[17] The reaction proceeded quantitatively (observed by ESI-FTMS) in THF at 70 °C in a closed tube with an isolated yield of 96% after an acidic cleavage resulting in **4a** (Table 2) with high diastereoselectivity (only one isomer observed). According to our

Table 2. Diels–Alder reactions at self-assembled helicates.

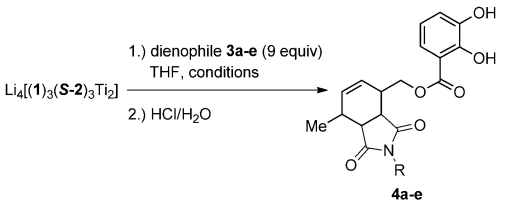


Entry	x	**2**	R	Equiv.	Solvent	*t*	*T* [°C]	Y [%]	*ee* [%]
1	6	-	Me	18	THF	2 d	70	96	rac.
2	5	***S*-2**	Me	15	THF	7 d	20	76	7
3	3	***S*-2**	Me	9	THF	42 d	−32	<1	–
4	3	***S*-2**	Me	9	THF	21 d	0	55	21
5	3	***S*-2**	Me	9	THF	7 d	20	71	25
6	3	***S*-2**	Me	9	THF	20 h	70	72	20
7	1	***S*-2**	Me	3	THF	20 h	70	45	26
8	3	***R*-2**	Me	9	THF	20 h	70	74	−23
9	3	***S*-2**	Me	9	DMF	20 h	70	30	5

assumption, Diels–Alder reactions with the helicates obtained from ligand mixtures proceed with some enantioselectivity. The dependence of the stereoselectivity on the composition of mixed complexes, temperature, and solvent are listed in Table 2. The enantiopurity of the product depends on the average number of chiral ligands in the complex. A dinuclear helicate with ligand **1** to ligand ***S*-2** ratio of 5:1 leads to 76% of the Diels–Alder product with only 7% *ee* at room temperature after 7 days. Increasing the number of chiral ligands to a ratio of 3:3 results in a similar yield of 71%. However, the *ee* increases to 25%. Further increase of the amount of **S-2** does not lead to a significant increase of the *ee*. The Diels–Alder reaction does not show dramatic changes of selectivity between 0 and 70 °C. Nevertheless, reaction times are shorter at elevated temperatures. Use of the corresponding ligand ***R*-2** leads to the Diels–Alder product preferring the other enantiomer (entry 8). In THF as solvent the titanium complexes are present as dimeric helicates. Changing the solvent to DMF, results in the monomer as predominant species. In the Diels–Alder reaction of **3a** and $Li_4[(\mathbf{1})_3(\mathbf{S}\text{-}\mathbf{2})_3Ti_2]$, this leads to product **4a** with a non-significant enantioselectivity of only 5% *ee*.

In order to show the scope of the Diels–Alder reaction, more dienophiles were tested as substrates in the reaction with $Li_4[(\mathbf{1})_3(\mathbf{S}\text{-}\mathbf{2})_3Ti_2]$ at 0 and 70 °C (Table 3). Enantioselectivities at

Table 3. Substrate scope of the "remote-controlled" Diels-Alder reaction.



			T = 70 °C		T = 0 °C	
Entry	3	R	Y [%]	*ee* [%]	Y [%]	*ee* [%]
1	3a	Me	72	20	55	21
2	3b	Et	78	19	75	20
3	3c	*t*Bu	77	15	69	15
4	3d	Cy	75	25	84	27
5	3e	Bz	77	21	75	32

0 °C and elevated temperatures (70 °C) in all cases, except for *N*-benzylmaleimide **3e**, show no significant temperature dependence. With **3e** as dienophile, the *ee* is 11% higher at 0 °C (32%) than at 70 °C (21%). With the bulky dienophile **3c**, only 15% *ee* was obtained at both temperatures.

Comparison of the NMR spectrum with data from the literature revealed that the *endo*-product was exclusively formed.[18] Circular dichroism spectroscopy in combination with computation[19] revealed the enantiomer in Figure 3 to be the major isomer of **4c**.

The Diels–Alder reaction of the 2,4-hexadienol ester of catechol with maleimides performed in the periphery of the helicate is highly diastereoselective, although enantioselectivities are significant but only moderate. However, the study shows that some enantioselectivity can be achieved by "remote control" with the chiral moiety of the auxiliary located relatively far away from the reacting unit (closest distance between the chiral center of ligand **2** to the prochiral carbon atom of **1** in the complex: 9 bonds; distance between the chiral titanium center and the prochiral carbon atom of **1**: 7 bonds). The studied system allows solvent dependent switching between the dimeric and the monomeric complex. In case of the monomer, stereoselectivity is nearly switched off. The monomer is configurationally more flexible than the dimer and no well-defined orientation of the stereocontrolling unit towards the diene is enforced.

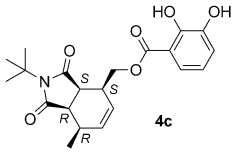


Figure 3. The major isomer of **4c**. Stereochemistry was assigned based on experimental and computed CD signals and with comparison of the literature NMR data.[18,19]

In summary, this study introduces new supramolecular concepts for the auxiliary control of C–C bond forming reactions even though the obtained enantioselectivities are only moderate. The enantioselectivity is influenced by a chiral unit, which is independent from the reactive moiety and can be easily recovered in close to 80% after reaction. A toolbox of chiral units can be developed in order to easily test different building blocks for different reactions. Furthermore, due to the solvent dependence of the monomer/dimer equilibrium, the stereoselectivity of the reaction can be turned on or off by simple solvent switching. Future work has to focus on the improvement of the enantioselectivity and catalytic systems have to be found.

Acknowledgements

We thank the international graduate school SeleCa of the DFG for support. The determination of enantioselectivities by Prof. Magnus Rueping and Cornelia Vermeeren is gratefully acknowledged.

Keywords: Diels–Alder reaction · helicates · lithium · self-assembly · titanium

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Received: January 13, 2016
Published online on February 2, 2016