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Hierarchically assembled helicates as reaction platform – From stoichiometric Diels-Alder reactions to enamine catalysis

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Dedicated to the memory of Prof. Dr. Carsten Schmuck

Abstract

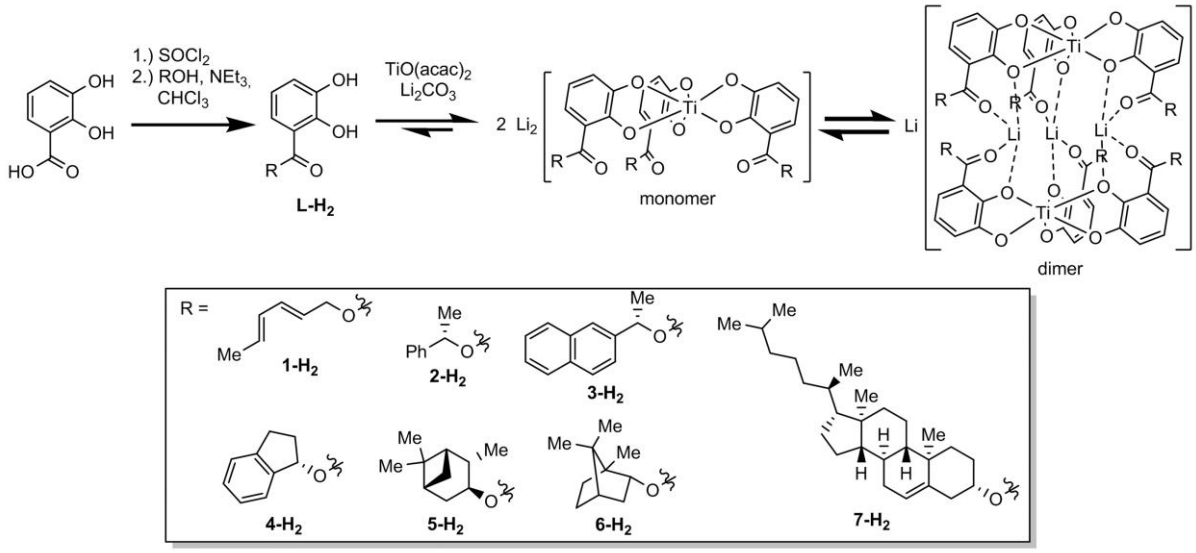
The stereoselectivity of a Diels-Alder reaction within the periphery of hierarchically assembled titanium(IV) helicates formed from mixtures of achiral, reactive and chiral, unreactive ligands is investigated in detail. Following the pathway of the chiral induction, the chiral ligands, solvents as well as substituents at the dienophile are carefully varied. Based on the results of the stoichiometric reaction a secondary amine catalyzed nitro-Michael reaction is performed as well which affords reasonable diastereoselectivities.

Keywords

hierarchical helicates; remote-control; stereoselectivity; Diels-Alder reaction; enamine catalysis

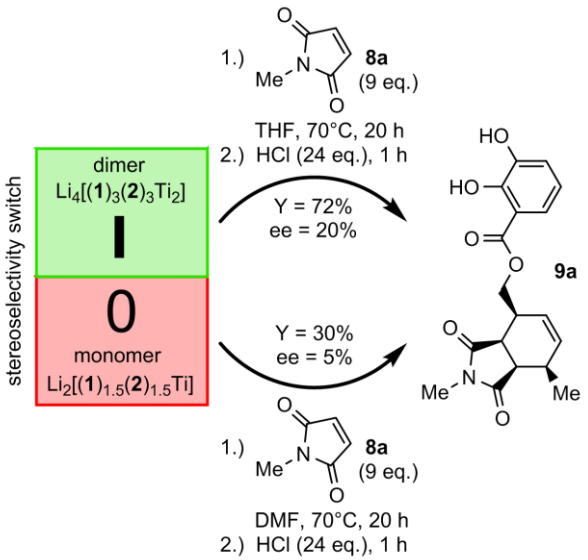
Introduction

C-C bond-forming reactions play a key role in organic chemistry. Hereby the stereoselectivity of the reaction is highly important due to the different behavior of stereoisomers in human metabolism [1,2]. Stereocontrol is achieved either via an auxiliary [3] or a catalyst [4], both providing the stereoinformation necessary for induction during the C-C bond-formation. Catalytic approaches for C-C bond-forming reactions even found their way into the relatively young field of supramolecular chemistry. E.g., regioselective Diels-Alder reactions within supramolecular hosts as described by Fujita *et al.* [5] or stereoselective nucleophilic substitutions by Raymond *et al.* [6] are important examples in this context. Recently, we described the use of hierarchically assembled helicates as templates for stereoselective Diels-Alder reactions via a post-functionalization process [7]. Catechol ligands **L-H$_2$** with an ester functionality in the 3-position are prepared via conversion of the acid chloride of 2,3-dihydroxybenzoic acid to the corresponding esters. Those ligands undergo a complexation with titanoyl(IV) bisacetylacetonate and lithium carbonate initially forming a mononuclear “Werner-type” triscatecholate titanium(IV) complex. Two of these monomers dimerize in a consecutive step to obtain a non-covalently linked helicate (scheme 1). The dimerization takes place via the coordination of three lithium cations acting as bridges between two monomeric complex units [7,8].



Scheme 1: Formation of hierarchically assembled lithium-bridged titanium(IV) helicates as well as the ligands used for the stereoselective Diels-Alder reaction.

Enantioselectivities up to 25 % *ee* at elevated temperature (32 % *ee* at 0 °C) depending on the substrate were achieved in a Diels Alder reaction by introducing two different substituted catechol ester ligands during the complex formation: (1) A diene substituted ligand **1-H$_2$** for the Diels-Alder reaction [9] and (2) a chiral ligand **2-H$_2$** for the stereocontrol [7]. Cleaving the complex under acidic conditions results in the desired enantiomerically enriched product **9** and enables the recovery of the chiral ligand **2-H$_2$** (scheme 2) [7].



Scheme 2: Previously reported on/off switch for stereoselectivity of a Diels-Alder reaction by use of different solvents. The heteroleptic complexes are mixtures with an average ligand distribution as shown [7,10].

The solvent choice allows on/off-switching of the stereoselectivity of the Diels Alder reaction. In THF the stereochemically locked dimer of the hierarchical helicate is present. Here stereoselectivity is turned on. On the other hand, the highly dynamic and fast racemizing/epimerizing monomer is the major species in DMF switching off the stereoselectivity [7].

Herein we investigate the induction pathway and significantly optimize the stereoselectivity of the reaction. Furthermore, a catalytic approach is introduced which paves the way to the final goal of supramolecular stereoselective catalysis with hierarchical helicates as homogeneous catalysts.

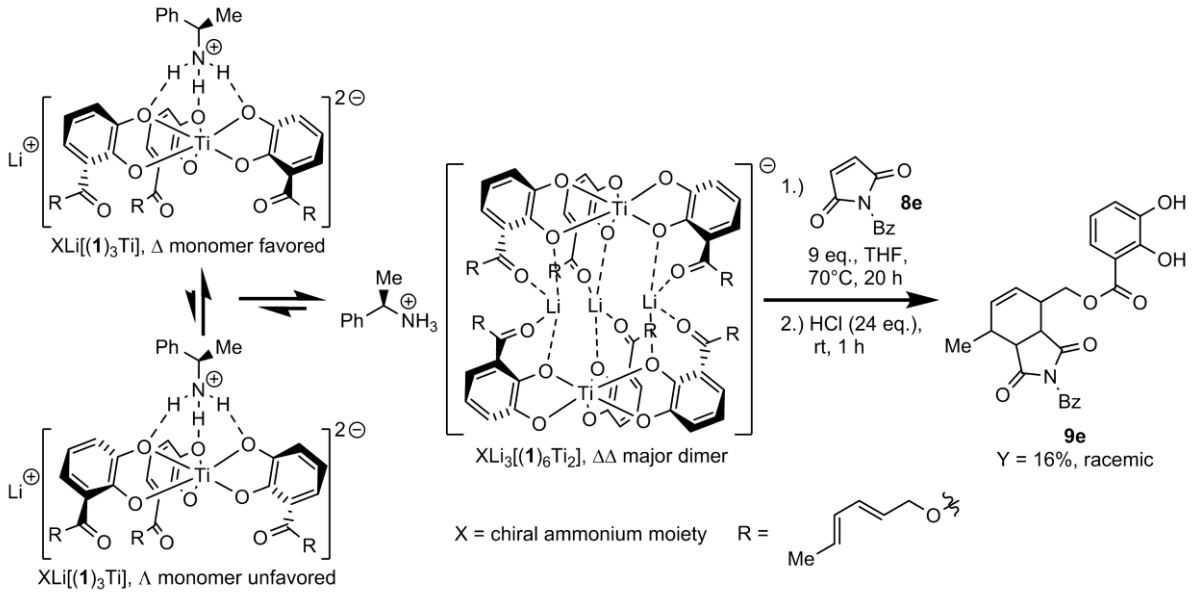
Results and Discussion

Stereoselective Diels Alder reactions in the periphery of hierarchically assembled helicates

Elucidating the induction pathway of the Diels-Alder reaction is vital for the optimization of the system described above and for the development of future processes based on the principle to use self-assembled coordination platforms (or as in the present case mixtures thereof) to control stereoselective C-C bond-forming reactions. Stereoinduction usually relies on spatial proximity of the prochiral carbon atoms and a chiral information of e.g. a chiral auxiliary, Lewis-acid or catalyst. In the previously reported system two different induction pathways are conceivable: (1) A chiral ligand is located close to the diene and controls the stereochemistry of the cycloaddition. (2) The chiral ligand controls the helicity of the helicate (ΔΔ or ΛΛ) and the helix induces the stereochemistry of the Diels-Alder reaction.

To find out which of the induction pathways takes over the control of the Diels-Alder reaction in the periphery of the helicates, a specific helicity was induced at an achiral diene bearing helicate. It has been described before that addition of chiral ammonium salts leads to the preference of a specific twist at the helicate [11]. As inductor, (*R*)-1-phenylethylammonium chloride was added to the racemic hexadiene substituted helicate $[Li_3(\mathbf{1})_6Ti_2]^-$. The chiral salt influences the helicity of the monomeric complexes and favors the right-handed (Δ) form to be present [11]. As the process is slow, the mixture of ammonium salt and complex was stirred for two weeks at room temperature in methanol. Solvent was removed and the Diels-Alder reaction with *N*-benzylmaleimide was performed at elevated temperature in THF. The reaction yields racemic product after purification (scheme 3). This shows that the induction of

stereochemistry of the Diels-Alder reaction depends on the chirality at the chiral ligand and not at the helix. This allows improvement of the stereoselectivity by using more appropriate sterically hindered or rigid chiral ligands. In addition, a solvent screening was performed in which solvents were used which favor the dimer. This is imminent for good enantioselectivities because the presence of a high amount of stereolabile monomer switches off the selectivity [7].



Scheme 3: Elucidating the pathway of the stereoinduction of the Diels-Alder reaction. Ten equivalents of chiral ammonium salt are added to the hierarchical helicate in methanol and stirred for two weeks. Afterwards methanol is removed and the residue is dissolved in THF to perform a Diels-Alder reaction at the side chain.

Solvent dependence

Initially the solvent dependence of the stereochemical induction of the Diels-Alder reaction by the phenylethyl-derived ligand **2** was studied using *N*-benzyl-maleimide **8e** as dienophile (table 1). The solvents dioxane (17 % *ee*) and acetone (14 % *ee*) show a slight decrease of the enantioselectivity compared to THF (21 % *ee*). Yields of the reactions are rather moderate. On the other hand, the use of acetonitrile has no

significant influence on the yield compared to THF while the enantioselectivity dramatically drops to 8 % *ee*. In this case the lower selectivity correlates with the increasing lithium solvating capability of the solvent resulting in a higher proportion of the monomer and thus in lower stereoselectivities. In contrast to this, less polar solvents such as dichloromethane and chloroform result in increasing stereoselectivities in the Diels-Alder reaction due to their poor ability to stabilize lithium cations. Chloroform shows the best induction with 32 % *ee* followed by dichloromethane with 25 % *ee*, both with 50 % yield (table 1).

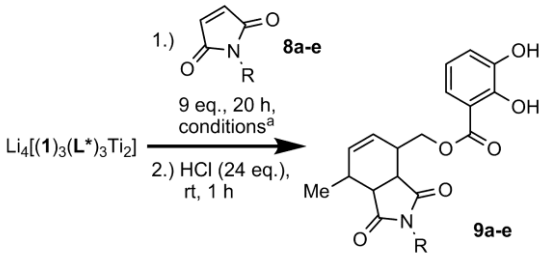
Ligand screening

In a second optimization step, the chiral ligands have been varied. An increase of stereoselectivity is achieved by using the helicates with a statistical ligand distribution $Li[Li_3(\mathbf{1})_3(\mathbf{L^*})_3Ti_2]$ (L* = **3-7**-H_2). The given formula only describes the ratio of the ligands but in fact a statistical mixture of complexes $Li[Li_3(\mathbf{L^*})_6Ti_2]$, $Li[Li_3(\mathbf{1})(\mathbf{L^*})_5Ti_2]$, $Li[Li_3(\mathbf{1})_2(\mathbf{L^*})_4Ti_2]$, $Li[Li_3(\mathbf{1})_3(\mathbf{L^*})_3Ti_2]$, $Li[Li_3(\mathbf{1})_4(\mathbf{L^*})_2Ti_2]$, $Li[Li_3(\mathbf{1})_5(\mathbf{L^*})_1Ti_2]$, and $Li[Li_3(\mathbf{1})_6Ti_2]$ is present. Expanding the aromatic unit to a naphthyl group in **3-H₂** results in an increase of the enantioselectivity to 44 % *ee*. Even better selectivities were obtained with **4-H₂** bearing an indanyl [12] substituent which combines a stereogenic center implemented in a ring system providing rigidity as well as an aromatic residue. The enantioselectivity is increasing to 58 % *ee* (table 1).

Besides the aromatic ligands, terpenyl-substituted ligands are investigated too. The biggest ligand **7-H₂** with a cholesteryl moiety favors the opposite enantiomer, however, only with –8 % *ee* in only 11 % yield. The low yield may be attributed to the poor solubility of the helicate. The other terpene [13] derived systems $Li[Li_3(\mathbf{1})_3(\mathbf{5})_3Ti_2]$ and $Li[Li_3(\mathbf{1})_3(\mathbf{6})_3Ti_2]$ show a different behavior. The (1*S*2*S*3*S*5*R*)-3-pinanyl substituted $Li[Li_3(\mathbf{1})_3(\mathbf{5})_3Ti_2]$ yields 46 % *ee* while the complex bearing a *L*(−)-borneyl residue

Li[Li_3(**1**)$_3$(**6**)$_3Ti_2$] shows only 16 % *ee*. Yields are higher than 60 %. A possible reason for the significant drop in enantioselectivity by switching from ligand **5** to **6** is the different dimerization behavior. The homoleptic helicate Li[Li_3(**6**)$_6Ti_2$] show a lower dimerization tendency compared to Li[Li_3(**5**)$_6Ti_2$] [13]. Thus, the higher amount of undesired monomer in solution of Li[Li_3(**1**)$_3$(**6**)$_3Ti_2$] results in a partial switch-off of stereoselectivity.

Table 1: Optimization of the stereoselectivity achieved of the Diels-Alder reaction at hierarchical helicates with solvent and chiral ligand screening.



#	**L***	**9**	R	solvent	T [°C]	Y [%]	ee [%]
1	**2**	**e**	Bz	THF	70	77[7]	21[7]
2	**2**	**e**	Bz	dioxane	105	53	17
3	**2**	**e**	Bz	acetone	60	50	14
4	**2**	**e**	Bz	MeCN	86	44	8
5	**2**	**e**	Bz	DCM	44	50	25
6	**2**	**e**	Bz	$CHCl_3$	65	50	32
7	**3**	**e**	Bz	$CHCl_3$	65	71	44
8	**4**	**e**	Bz	$CHCl_3$	65	64	58
9	**5**	**e**	Bz	$CHCl_3$	65	61	46
10	**6**	**e**	Bz	$CHCl_3$	65	64	16
11	**7**	**e**	Bz	$CHCl_3$	65	11	-8
12	**4**	**a**	Me	$CHCl_3$	65	76	43
13	**4**	**b**	Et	$CHCl_3$	65	79	39
14	**4**	**c**	tBu	$CHCl_3$	65	82	18
15	**4**	**d**	Cy	$CHCl_3$	65	80	49

[a]Reactions performed in closed tubes;

Screening of the dienophile

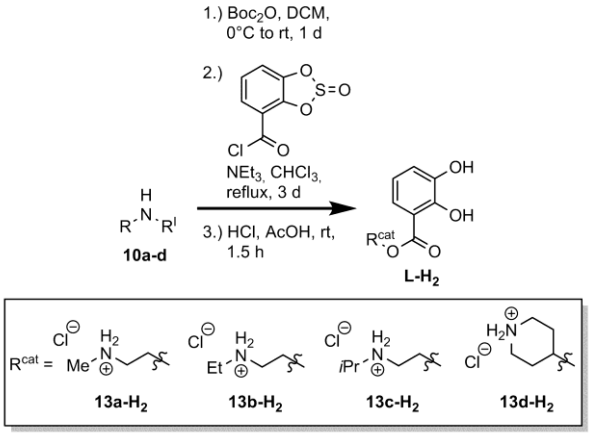
Variation of the dienophile is studied in chloroform using the helicate $Li_4[(\mathbf{1})_3(\mathbf{4})_3Ti_2]$. *N*-maleimides **8a** and **8b** with a methyl and an ethyl residue show higher yields and a lower induction in comparison to the benzyl derivative **8e** with 43 % *ee* and 39 % *ee* (table 1). The poorest result was obtained by using dienophile **8c** with a *tert*-butyl substituent (82 % yield, 18 % *ee*). This maleimide gave the lowest induction in our previous work, too [7]. Thus, no improvement is made in comparison to the 15 % *ee* [7] with chiral ligand **2-H$_2$** in THF as solvent. The cyclohexyl substituted dienophile **8d** shows a higher induction (49 % *ee* and 80 % yield) than **8a** and **8b**, but cannot reach the results of **8e**. The described optimization of reaction conditions based on solvent, chiral ligand and substituent at the dienophile results in a nearly threefold increase of the enantioselectivity compared to the earlier described results [7].

The screening shows the opportunity to use hierarchically formed helicates with mixtures of ligands as platforms to control the stereochemistry of C-C bond-forming reactions. However, it would be of big advantage to transfer the findings to catalytic C-C bond-forming reactions which are catalyzed by hierarchical helicates containing chiral ligands for stereocontrol and achiral catalytically active ligands.

Enamine catalyzed nitro-Michael reactions

The nitro-Michael reaction [14] seems to be suitable to be performed at hierarchically assembled helicates due to it's "benchmark-character" [15]. Therefore, ligands bearing secondary amine residues were introduced instead of the diene ligands. Again helicates with a statistical distribution of chiral ligands and of the new amine ligands in the complex are investigated as catalysts. The ligands with potential catalytic activity are synthesized in a three step approach (scheme 4). Initially the amino alcohols **10a-**

d are protected with a Boc group [16]. Esterification of the protected alcohols **11a-d** with 2,3-dioxosulfinylbenzoyl chloride obtained from 2,3-dihydroxybenzoic acid and thionyl chloride affords *N*-Boc substituted catechol ligands **12a-d.** They are deprotected under acidic conditions with hydrochloric acid yielding ligands **13a-d-H$_2$** as ammonium chloride salts.



Scheme 4: Synthesis of the ligands with secondary amines in the substituents.

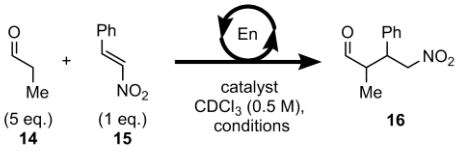
13a-d-H$_2$ are used together with the chiral ligand **2,4,5-H$_2$** for the formation of hierarchical helicates with a statistical ligand ratio. Those are formed from 1 equivalent of **13-H$_2$** and 5 equivalents of **2-H$_2$**, **4-H$_2$** and **5-H$_2$**.

The catalytic activity of the amine ligands is tested first by using the uncoordinated ligand **13a-H$_2$** substituted with a *N*-methyl-ethylamine moiety. The reaction is performed in DMSO-d_6 due to solubility limitations of the ligand. Fast and easy measurement of the yield and the diastereoselectivity is possible by NMR spectroscopy. The nitro-Michael reaction of 3 eq. propanal **14** and *β*-nitrostyrene **15** with 25 mol% of **13a-H$_2$** after 2 days at room temperature results in 45 % yield of product **16** and a nearly 1:1 diastereomeric ratio (table 2).

Catalysis at the “statistical” helicates are carried out with 5 eq. of propanal **14** in order to gain a higher conversion. 15 mol% catalyst is used in $CDCl_3$ at room temperature

and 0 °C with three or seven days reaction time. The conversion is controlled via NMR spectroscopy and TLC. The helicate $Li_4[(\mathbf{13a})_1(\mathbf{2})_5Ti_2]$ does not lead to any conversion at room temperature (table 2). The catalyst $Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$ with an ethyl substituted amine works well resulting in 88 % yield at room temperature with 66 % *de*. The diastereomeric excess increases slightly to a maximum of 74 % *de* (*dr* = 87:13) at 0 °C. A dramatic decrease is observed at 70 °C showing 30 % *de*. No enantioselectivity is observed using the helicate $Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$ as catalyst. The helicates $Li_4[(\mathbf{13c})_1(\mathbf{2})_5Ti_2]$ and $Li_4[(\mathbf{13d})_1(\mathbf{2})_5Ti_2]$ with an isopropyl substituted ethylamine and a cyclic secondary amine ligand as catalytically active unit show no conversion in the nitro-Michael reaction. Solubility problems are the supposed reason for this. Thus, the amine ligand **13b-H₂** seems to be an appropriate component to make helicates from ligand mixtures which possess catalytic activity.

Table 2: Enamine catalyzed nitro-Michael reaction with hierarchically assembled helicates.[a]



#	catalyst	mol %	T [°C]	t [d]	Y [%]	*de* *[%]*
1[b]	**13a-H₂**	25	rt	2	45[c]	52:48[c]
2	$Li_4[(\mathbf{13a})_1(\mathbf{2})_5Ti_2]$	15	rt	3	0	-
3	$Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$	15	0	7	71	87:13
4	$Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$	15	rt	3	88	83:17
5	$Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$	7.5	70	1	48	65:35
6	$Li_4[(\mathbf{13c})_1(\mathbf{2})_5Ti_2]$	15	rt	3	0	-
7	$Li_4[(\mathbf{13d})_1(\mathbf{2})_5Ti_2]$	15	rt	3	0	-
8	$Li_4[(\mathbf{13b})_1(\mathbf{4})_5Ti_2]$	15	rt	3	13	80:20
9	$Li_4[(\mathbf{13b})_1(\mathbf{5})_5Ti_2]$	15	rt	3	27	80:20

[a]No enantioselectivity is achieved. [b]Reaction was performed in DMSO-d_6 (0.26 M) due to solubility limitations of the free ligand with 3 eq. of propanal. [c]Values determined via integration of the crude NMR spectrum of the reaction.

Exchange of the chiral ligand **2** by other chiral ones results in the corresponding complexes $Li_4[(\mathbf{13b})_1(\mathbf{4})_5Ti_2]$ and $Li_4[(\mathbf{13b})_1(\mathbf{5})_5Ti_2]$, but does not lead to a control of enantioselectivity. Reasonable diastereoselectivity of 60 % *de* is observed for both catalysts. The limited solubility of those complexes causes a significant reduction of the yield at room temperature and due to this the reaction is not performed at lower temperatures.

Conclusion

An optimization of the Diels-Alder reaction taking place in the periphery of hierarchically assembled helicates is carried out. It is based on the elucidated induction pathway showing that the stereoselectivity is due to the proximity of the chiral units of ligand **2** to the diene unit. The helicity of the helicate does not have a significant influence. After optimization of solvent, chiral ligand and substituent at the dienophile stereoselectivity is nearly tripled. Up to 58 % *ee* is achieved in the Diels-Alder reaction in chloroform with the indanyl substituted chiral ligand **4-H$_2$** and *N*-benzylmaleimide **8e** as dienophile. In addition, the transition from the stoichiometric Diels-Alder reaction to a catalytic nitro-Michael reaction is described utilizing secondary amine ligands as catalysts. Only amine ligand **13b-H$_2$** seems suitable in the catalysis with the corresponding statistical helicates. With other complexes solubility problems arise. $Li_4[(\mathbf{13b})_1(\mathbf{2})_5Ti_2]$ is the most efficient catalyst discussed in this study and provides good yields up to 88 % at room temperature. Suitable diastereoselectivities are obtained with up to 74 % *de* (*dr* = 87:13) at 0 °C and 66 % *de* (*dr* = 83:17) at room temperature. Enantioselectivity is not achieved even with the chiral ligands **4-H$_2$** and **5-H$_2$**.

Nevertheless, successful implementation of diastereoselective catalysis by hierarchically assembled helicates is a big step forward and will draw our focus on the development of new systems possessing catalytic activity with improved solubility.

Supporting Information

Supporting Information File 1

File Name: supporting_information.pdf

File Format: pdf

Title: Synthetic procedures, characterization data, SFC and HPLC conditions, ^{1}H and ^{13}C NMR spectra of unknown compounds

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