Organometallic Hybrid Catalysis

DOI: 10.1002/anie.200900713

Allylic Amination by a DNA–Diene–Iridium(I) Hybrid Catalyst**

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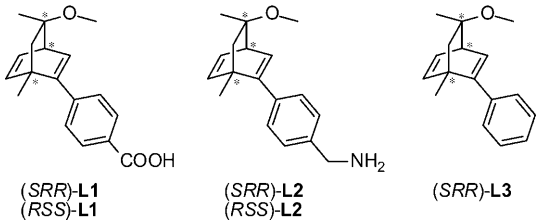
Hybrid catalysis combines homogeneous catalysts with biopolymers to develop selective catalysts for organic reactions. While proteins have been used as hosts for various transition-metal complexes,[1] there are only a few examples involving nucleic acids.[2] In these reports high stereoselectivities were obtained in Diels–Alder reactions, Michael additions and fluorinations, with DNA as sole source of chirality, but all these systems relied on Lewis acid catalysis by Cu^{II} ions. Our goal is the application of DNA-conjugated transition-metal complexes in organometallic catalysis, because organometallic complexes catalyze numerous synthetically useful reactions.

Herein we present a DNA-based system that exploits iridium(I) diene chemistry to catalyze an allylic substitution in aqueous medium. We demonstrate that catalysis occurs in the presence of DNA and its numerous functional groups, and that the structure of the DNA modulates the stereochemical outcome of the reaction.

We set out to take advantage of the three-dimensional structure of nucleic acids to create a chiral environment around an active metal catalyst. Our approach is based on a modular design in which a 19 mer oligodeoxynucleotide (ODN) carrying a diene ligand is combined with different complementary DNA (cDNA) or RNA (cRNA) strands, thereby forming perfect and imperfect duplexes that provide subtle changes in the environment of the metal center. The covalent attachment of the ligand guarantees its specific, reproducible positioning on the nucleic acid structures.

Although diene ligands have recently attracted considerable interest,[3] they have not been used as anchoring ligands in hybrid catalysis to date. We selected the bicyclo-[2.2.2]octadiene scaffold which has shown good activity in iridium(I)-catalyzed allylic substitution reactions[4] and provides convenient positions for derivatization. Both enantiomers of diene ligands **L1** and **L2** were synthesized, allowing the interaction between carrier ODN and metal complex to be modulated by varying the absolute ligand configuration and the spacer between DNA and diene. Ligand (*SRR*)-**L3** was prepared as reference. For coupling of the diene ligands



(*SRR*)-**L1**
(*RSS*)-**L1**
(*SRR*)-**L2**
(*RSS*)-**L2**
(*SRR*)-**L3**

site-specifically to DNA, the activated nucleoside 4-triazolyl-deoxyuridine[5] was incorporated into a 19 mer DNA sequence by solid-phase synthesis and the resulting ODN functionalized by reaction with primary amines[6] (Scheme 1).

To couple ligand **L1**, the DNA was first derivatized with ethylene diamine, and then the resulting aliphatic primary amine linked to the acid function of **L1**. **L2** was attached to DNA in a single step through its primary amine function. The resulting ligands were tested in the iridium-catalyzed allylic substitution[8] of phenyl allyl acetate (**1**) with morpholine in aqueous medium (Table 1).[9] 100 mM of $NaClO_4$ and 5 mM of $Mg(ClO_4)_2$ were included in the reaction mixture to ensure nucleic acid structure formation (which was verified by thermal denaturation experiments, see Supporting Information, Figure S2). While the $[\{Ir(C_2H_4)_2Cl\}_2]$ precatalyst was inactive (Table 1, entry 1), the complex formed by mixing it with ligand **L3** for 2 h in dioxane at room temperature showed excellent activity, giving 81 % yield after 13 h in spite of a low substrate concentration (50 mM) and a low catalyst loading (0.2 mol %), even compared with commercial $[\{Ir(cod)Cl\}_2]$ reference (Table 1, entry 3). $[\{Ir(coe)_2Cl\}_2]$ was less effective as a precatalyst[4] (Table 1, entry 4). The low yield observed in pure dioxane (Table 1, entry 5) illustrates the tremendous acceleration brought about by water in allylic substitution.[10]

The addition of DNA to the reaction mixture did not reduce the activity of the catalyst (Table 1, entry 6 vs. 2). Furthermore, DNA-based dienes **ODN1a** and **ODN2a** formed catalysts that showed slightly higher activities than the complex of free diene **L3** (Table 1, entries 7, 8 vs. 2). No difference in activity was observed between single- and double-stranded hybrid catalysts (Table 1, entry 9 vs. 7). These results show that in this system DNA and its numerous nitrogen-containing heterocycles do not compete with the diene ligand for iridium coordination and do not disturb the organometallic catalysis. The stability of the catalyst under these conditions is remarkable; up to 4600 turnovers were observed (entry 10, 10 μM iridium used). In the presence of an unmodified DNA strand the iridium precatalyst was inactive (Table 1, entry 11), showing that non-specific binding of iridium to DNA does not contribute to catalysis.

We evaluated the stereoselectivity of the hybrid catalysts in the kinetic resolution of acetate **1**. To modulate the shape of the environment surrounding the iridium complex the

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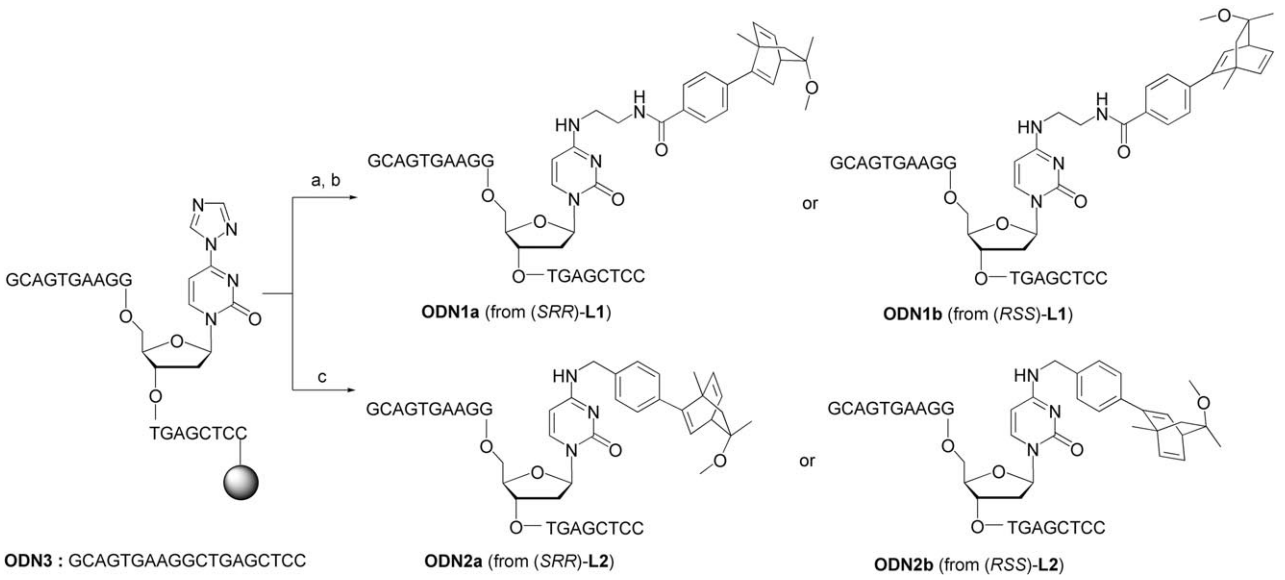
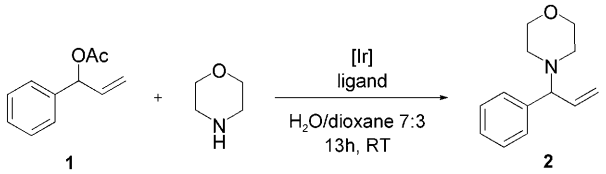
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 623) and the Fonds der Chemischen Industrie. The authors thank Dr. M. Caprioara and M. Dauner for experimental assistance and helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900713.



Scheme 1. a) ethylene diamine, H_2O, 4 h, room temperature; b) **L1**, EDC-HCl, $NaHCO_3$, H_2O/DMF, 8 h, 2 °C; c) **L2**, DMSO, 2 h, 60 °C.[7] EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMSO = dimethylsulfoxide.

Table 1: Allylic amination of phenyl allyl acetate **1**.[a]



entry	catalyst	ligand	Yield[b] [%]
1	$[\{Ir(C_2H_4)_2Cl\}_2]$	–	3
2	$[\{Ir(C_2H_4)_2Cl\}_2]$	**L3**	81
3	$[\{Ir(cod)Cl\}_2]$[c]	–	71
4	$[\{Ir(coe)_2Cl\}_2]$[c]	**L3**	72
5[d]	$[\{Ir(C_2H_4)_2Cl\}_2]$	**L3**	3
6[e]	$[\{Ir(C_2H_4)_2Cl\}_2]$	**L3**	80
7	$[\{Ir(C_2H_4)_2Cl\}_2]$	**ODN1a**	88
8	$[\{Ir(C_2H_4)_2Cl\}_2]$	**ODN2a**	85
9[f]	$[\{Ir(C_2H_4)_2Cl\}_2]$	**ODN1a**	87
10[g]	$[\{Ir(C_2H_4)_2Cl\}_2]$	**ODN1a**	92
11[e]	$[\{Ir(C_2H_4)_2Cl\}_2]$	–	2

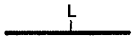
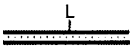
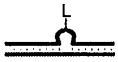
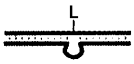
[a] Reaction conditions: 50 μM catalyst, 100 μM ligand, 50 mM **1**, 50 mM morpholine, in water/dioxane (7:3) with 100 mM $NaClO_4$, 5 mM $Mg(ClO_4)_2$, 50 μL reaction volume, 13 h, room temperature. [b] GC yield. [c] cod = 1,5-cyclooctadiene, coe = cyclooctene. [d] In 100% dioxane. [e] In the presence of 100 μM of **ODN3**. [f] In the presence of 100 μM of complementary RNA. [g] 5 μM of $[\{Ir(C_2H_4)_2Cl\}_2]$, 10 μM ligand, 50 mM **1**, 150 mM morpholine, 4 day reaction.

diene-carrying DNA oligonucleotides were allowed to hybridize with various DNA and RNA complementary strands. We chose perfectly complementary sequences (**cDNA1** and **cRNA1**), as well as sequences designed to form a bulge on the diene-carrying strand (**cDNA2** and **cRNA2**) or across from it (**cDNA3** and **cRNA3**; Table 2). 0.5 Equivalents of morpholine were used to allow the measurement of enantiomeric excesses (*ee*) at 50% conversion of **1**.[4,11] While the obtained *ee* values and stereoselectivity factors[12] remained low, a chirality transfer from the nucleic acid to the iridium complex could clearly be observed. In the absence of complementary strand, the hybrid catalysts gave rise to *ee* values similar to those obtained with the corresponding free diene **L3** (Table 2, entries 1, 2, and 4), and enantiomorphous dienes gave *ee* values opposite from each other (Table 2, entries 2, 4 vs. 3, 5): they behaved as if they experienced little influence from the DNA they were bound to. The *ee* values, however, changed if a complementary sequence was added, the most noticeable example being the addition of **cRNA1** to **ODN1a** (Table 2, entry 10), which triggered a reversal of the stereoselectivity, with an *ee* value for reaction product **2** going from +23% to −27% and the corresponding change in the stereoselectivity factor. Interestingly, the effect was much less pronounced when the complementary sequence was a DNA strand (Table 2, entry 6).

The different selectivities observed for the three constructs are most likely due to differences in their helix structures (single strand: no helix, DNA/DNA duplex: B-type helix, DNA/RNA duplex: A-type helix), which are suggested by the large variations in their circular dichroism (CD) spectra (See Supporting Information, Figure S3). As expected, the type of spacer between DNA and diene also had an influence on the stereoselectivity (Table 2, entry 6 vs. 8 and 10 vs. 12). The introduction of bulges had an unpredictable influence on the stereoselectivity (Table 2, entries 14–17), demonstrating that small structural variations may have strong effects and thereby highlighting the potential of screening large oligonucleotide libraries.

In conclusion, we report the first application of DNA hybrid catalysis to organometallic chemistry. The covalent conjugates of DNA and dienes form highly active and stable complexes with iridium(I) in aqueous medium as evidenced by turnover numbers of up to 4600 in allylic amination. As expected, the nucleic acid structure influences the stereochemical outcome of the reaction. These results pave the way

Table 2: Hybrid catalysts in the kinetic resolution of phenyl allyl acetate **1**.[a]

	catalyst design[b]	ligand	complementary strand	Yield[c] [%]	*ee*[d] **1** [%]	s[e]	*ee*[d] **2** [%]
1		**L3**	–	48	23	2.0	28
2		**ODN1a**	–	49	16	1.6	23
3		**ODN1b**	–	47	−12	*1.5*	−24
4		**ODN2a**	–	45	16	1.7	20
5		**ODN2b**	–	46	−16	*1.7*	−18
6		**ODN1a**	**cDNA1**	45	≤5	–	9
7		**ODN1b**	**cDNA1**	47	≤5	–	≤5
8		**ODN2a**	**cDNA1**	44	−7	*1.3*	−6
9		**ODN2b**	**cDNA1**	43	≤5	–	≤5
10		**ODN1a**	**cRNA1**	48	−19	*1.8*	−27
11		**ODN1b**	**cRNA1**	45	≤5	–	≤5
12		**ODN2a**	**cRNA1**	42	≤5	–	−13
13		**ODN2b**	**cRNA1**	46	≤5	–	≤5
14		**ODN1a**	**cDNA2**	49	9	1.3	15
15		**ODN1a**	**cRNA2**	46	≤5	–	≤5
16		**ODN1a**	**cDNA3**	40	≤5	–	−12
17		**ODN1a**	**cRNA3**	49	≤5	–	≤5

[a] Reaction conditions: 50 μM [{Ir(C_2H_4)$_2$Cl}$_2$], 100 μM ligand, 50 mM **1**, 25 mM morpholine, 50 μL reaction volume, in water/dioxane (7:3) with 100 mM $NaClO_4$, 5 mM $Mg(ClO_4)_2$, 40 h, room temperature. [b] Black strands: DNA, gray strands: RNA. [c] GC yield, based on **1**. [d] Enantiomeric excesses were determined by chiral HPLC, positive *ee* values were assigned for excess of the first eluting enantiomer; "≤5" indicates that the absolute *ee* value was smaller than 5%. [e] s indicates the stereoselectivity factor, see ref. [12]; values in italics correspond to negative *ee* values of **1**.

for the directed evolution of hybrid catalysts,[13] in which the unique properties of nucleic acids (i.e. their ability to be enzymatically replicated) can be utilized to isolate, from combinatorial nucleic acids libraries, catalysts with higher activities and more synthetically useful selectivities.

Experimental Section

General procedure for the allylic amination in the presence of DNA: The reactions were carried out under an atmosphere of argon. Dioxane (p.a. grade), as well as stock solutions of phenyl allyl acetate (**1**) and morpholine, were degassed prior to use. A 200 μL plastic vial was charged with an aqueous solution of diene-functionalized 19 mer and complementary strand (5 nmol each), the solution was lyophilized. The vial containing the dried oligonucleotides was introduced into a Schlenk flask filled with argon. The oligonucleotides were dissolved in an aqueous salt solution (8 μL; 143 mM $NaClO_4$, 7 mM $Mg(ClO_4)_2$), a 1 mM solution of [{Ir(C_2H_4)$_2$Cl}$_2$] in dioxane (2.5 μL; 2.5 nmol, 0.5 equivalents based on ODN) was added. The mixture was left to stir at room temperature for 2 h for complex formation, after which dioxane, the Na/Mg salt solution (amount needed to reach a final reaction volume of 50 μL, in a 7:3 water/dioxane ratio), phenyl allyl acetate (**1**), dodecane (5 μL of a dioxane solution containing 0.5 M of **1**, 0.4 M of dodecane), and finally morpholine (0.5 M solution in dioxane) were added. The reaction mixture was then stirred at room temperature (23–25 °C). At the end of the reaction, the mixture was extracted with chloroform (3 × 100 μL). The combined organic phases were passed through a short silica plug, eluted with diethyl ether (750 μL), and the resulting solution analyzed by GC and chiral HPLC. All experiments have been repeated 2 or 3 times, yields and *ee* values agreed within 3%.

Received: February 5, 2009
Revised: March 10, 2009
Published online: May 8, 2009

Keywords: allylic substitution · diene ligands · DNA · hybrid catalysis · iridium

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