Organometallic Hybrid Catalysis

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

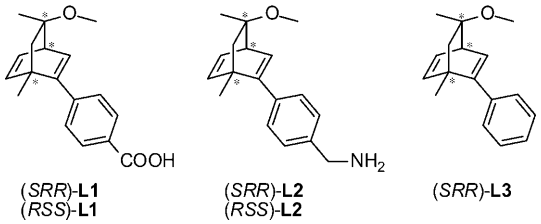
*Pierre Fournier, Roberto Fiammengo, and Andres Jäschke**

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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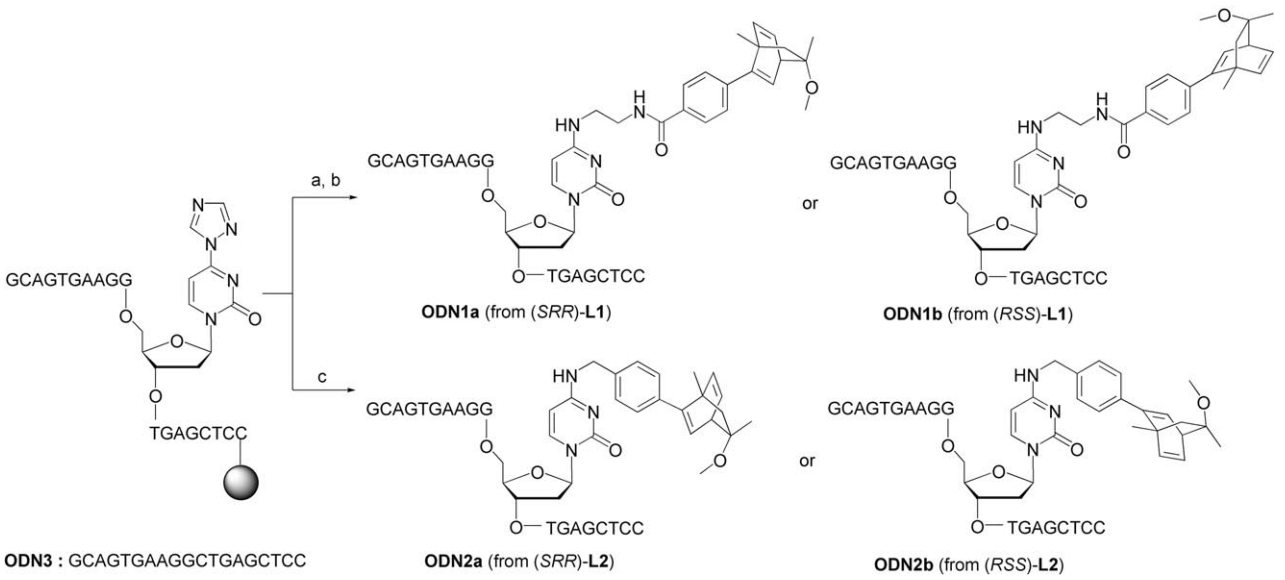
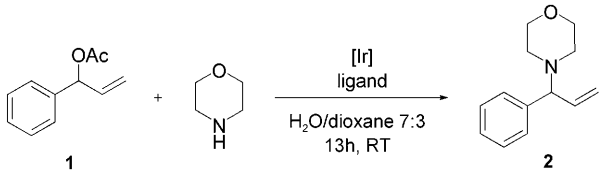


Scheme 1. a) ethylene diamine, H_2O, 4 h, room temperature; b) **L1**, EDC-HCl, $NaHCO_3$, H_2O/DMF, 8 h, 2 °C; c) **L2**, DMSO, 2 h, 60 °C.[7] EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMSO = dimethylsulfoxide.

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

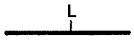
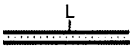
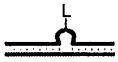
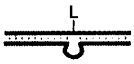
[a] Reaction conditions: 50 μM catalyst, 100 μM ligand, 50 mM **1**, 50 mM morpholine, in water/dioxane (7:3) with 100 mM $NaClO_4$, 5 mM $Mg(ClO_4)_2$, 50 μL reaction volume, 13 h, room temperature. [b] GC yield. [c] cod = 1,5-cyclooctadiene, coe = cyclooctene. [d] In 100% dioxane. [e] In the presence 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%.

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Supporting Information

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Allylic Amination by a DNA-Diene-Ir(I) Hybrid Catalyst

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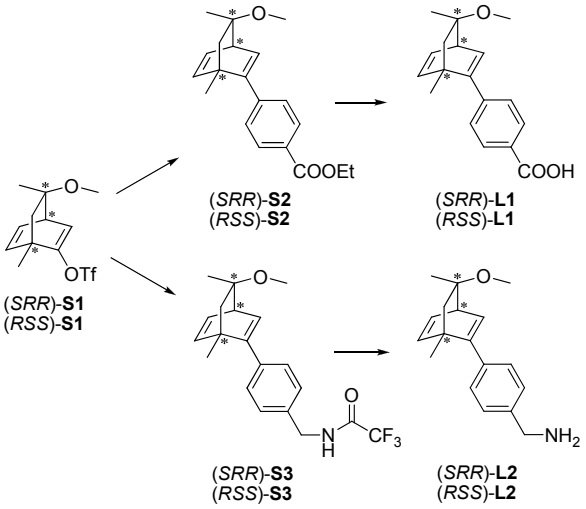
General. All reagents were purchased from Acros or Sigma-Aldrich and used without further purification, except for 4-(aminomethyl)phenylboronic acid and $[Ir(COE)_2Cl]_2$ which was from ABCR and $[Ir(COD)Cl]_2$ which was from Strem Chemicals. $[Ir(C_2H_4)_2Cl]_2$ was prepared according to literature procedures[1] from $[Ir(COE)_2Cl]_2$, kept at -20°C and used within 4 weeks. 4-((2,2,2-trifluoroacetamido)methyl)phenylboronic acid was prepared from 4-(aminomethyl)phenylboronic acid according to literature procedures. Phenyl allyl acetate **1** was prepared by acetylation of the commercially available α-vinylbenzyl alcohol. Ligand **L3** was prepared according to literature procedures.[2] Unmodified oligodeoxynucleotides **cDNA1**, **cDNA2**, **cDNA3** were purchased from IBA, unmodified oligonucleotides **cRNA1**, **cRNA2**, **cRNA3** were purchased from Dharmacon. TLC was carried out on silica gel plates Polygram Sil G/UV_{254} (40 × 80 mm) from Macherey-Nagel. Flash chromatography was carried out on silica gel 40-63 μm from J.T. Baker. HPLC analyses were performed on a Agilent 1100 Series HPLC system equipped with a diode array detector using a Phenomenex Luna C18 5μ column (4.6×250 mm) and eluting with a gradient of 100 mM triethylammonium acetate (TEAA) pH 7.0 (buffer A) and 100 mM TEAA in acetonitrile/water 80:20 (buffer B) at 1 mL/min. The *ee*'s were determined by chiral HPLC analyses carried out on an Agilent 1100 Series system equipped with a Daicel OJ-H column, elution was with hexanes/iPrOH 99:1, 1.2 mL/min. GC analyses were carried out on a Shimadzu GC-2014 gas chromatograph equipped with a FS Supreme 5 capillary column (0.25mm x 30m) using dodecane as internal standard. Thermal denaturation experiments were carried out on a Varian Cary 100 Bio Spectrophotometer. CD spectra were recorded on a Jasco J-810 Spectropolarimeter. NMR spectra were recorded on a Varian Mercury Plus 300 MHz spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectra were calibrated to TMS on the basis of the relative chemical shift of the solvent as an internal standard. FAB and EI mass spectra were recorded on a JEOL JMS-700 sector field mass spectrometer. ESI-FTICR mass spectra were recorded on a Bruker ApexQe mass spectrometer in negative mode. Reactions under microwave irradiation were carried out in a CEM Discovery microwave synthesizer.

General procedure for the synthesis of ODN1a and ODN1b. The reaction mixture containing 100 μM of ethylene diamine-functionalized 19mer DNA[3] and 100 mM $NaHCO_3$ in water/DMF 1:1 was cooled down to 2°C. Additions of a solution of **L1** (80 eq.) and EDC (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 100 eq.) in DMF were made in 2-hour intervals, and the reaction allowed to proceed at 2°C. The progress of the reaction was followed by HPLC, after 4 additions no further consumption of starting material was observed. The reaction mixture was precipitated by addition of EtOH, the obtained pellet was re-dissolved in water and purified by semi-preparative HPLC. The collected fractions were lyophilized and desalted using size exclusion cartridges (NAP, GE Healthcare) to give the pure product.

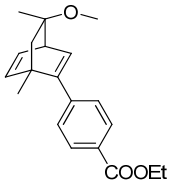
General procedure for the synthesis of ODN2a, ODN2b, ODN3a, ODN3b. Glass beads carrying the triazolyl-functionalized ODN[3] were treated with 50 μL of a 2.5 M solution of amine **L2** in DMSO for 2h at 60°C. Ammonium hydroxide (28% w/w aqueous solution, 100 μL) and AcOEt (100 μL) were added, the phases separated, and the aqueous phase washed with 2×100 μL AcOEt. To this aqueous phase was added ammonium hydroxide (28% w/w aqueous solution, 200 μL) and this mixture was allowed to stir at RT for 4h. The oligodeoxynucleotide solution was purified on a GlenPak cartridge (Glen Research) followed by a NAP desalting column. Alternatively, if necessary it was purified by semi-preparative HPLC, de-tritylated in a 2% aqueous trifluoroacetic acid solution, neutralized and desalted on a size exclusion cartridge.

Chemical Synthesis



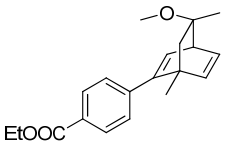
Scheme S1. Synthesis of ligands **L1** and **L2**.

(1*S*,4*R*,8*R*)-ethyl 4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)benzoate ((*SRR*)-S2)



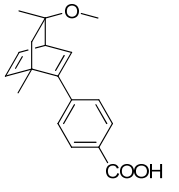
In a 12 ml vessel 100 mg of triflate (*SRR*)-**S1**[2] (0.32 mmol) and 93 mg of 4-ethoxycarbonylphenylboronic acid (0.48 mmol, 1.5 eq.) were dissolved in 2 ml THF. After addition of 0.96 ml of an aqueous 1 M K_3PO_4 solution (0.96 mmol, 3 eq.) the mixture was stirred and bubbled with argon for 10 min. 7.8 mg (9.6 µmol, 3 mol%) of $Pd(dppf)Cl_2$ were added, the reaction vessel was sealed and submitted to microwave irradiation (100 °C, 150 W, 12 min), after which no starting material could be detected. For workup, 20 ml diethyl ether and 20 ml 1 M HCl were added to the reaction mixture. The organic layer was washed with 1 M HCl (2×20 ml) and brine (3×20 ml) and dried with Na_2SO_4. The crude product was purified by flash chromatography (hexanes/AcOEt 92:8), giving (*SRR*)-**S2** as a yellow oil (137.3 mg, 0.44 mmol, 61%).
^{1}H NMR (300 MHz, $CDCl_3$, 25°c, TMS): δ=7.96 (2H, m), 7.20 (2H, m), 6.38 (1H, t, J=6.6 Hz), 6.22 (1H, d, J=5.9 Hz), 6.15 (1H, dd, J=7.2 Hz, 1.3 Hz), 4.37 (2H, q, J=7.1 Hz), 3.66 (1H, td, J=6.1 Hz, 1.3 Hz), 3.21 (3H, s), 1.63 (1H, d, J=12 Hz), 1.39 (3H, t, J=7.1 Hz), 1.32 (3H, s), 1.31 (1H, d, J=12 Hz), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$, 25°c, TMS): δ =166.9, 149.4, 141.7, 134.3, 132.9, 129.2, 128.8, 128.6, 84.4, 65.8, 61.0, 50.8, 50.2, 48.0, 45.6, 29.7, 25.0, 21.9, 14.6; HR ESI MS: m/z 335.16194 $[M+Na]^+$ (calculated for $[C_{20}H_{24}O_3Na]^+$ 335.16177).

(1*R*,4*S*,8*S*)-ethyl 4-(8-methoxy-1,8-dimethylbicyclo[2.2.2] octa-2,5-dien-2-yl)benzoate ((*RSS*)-S2)



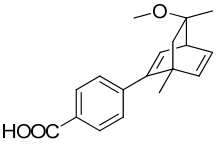
(*RSS*)-**S2** was synthesized from (*RSS*)-**S1** following the same experimental procedure as for (*SRR*)-**S2.** The title compound was obtained as a yellow oil in 61% yield.
EI MS: m/z 335.16215 $[M+Na]^+$ (calculated for $[C_{20}H_{24}O_3Na]^+$ 335.16177); NMR data was identical to that of (*SRR*)-**S2.**

(1*S*,4*R*,8*R*)-4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)benzoic acid ((*SRR*)-L1)



130 mg of (*SRR*)-**S2** (0.42 mmol) were dissolved in 5 ml MeOH. 70 mg LiOH (7 eq., 2.91 mmol), dissolved in 2 ml H_2O, were added and the reaction mixture was stirred at RT for 6 h. For workup, the mixture was acidified with 20 ml 1 M HCl and extracted with AcOEt (2×20 ml). The combined organic phases were washed with brine (2 × 20 ml) and dried over Na_2SO_4. After evaporation of the solvent (*SRR*)-**L1** was obtained as a white solid (119 mg, 0.38 mmol, 91 %).
$[\alpha]_D^{20}$ = -14.4 cm^3 g^{-1} dm^{-1} (*c* = 0.98 g cm^{-3} in $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 25°c, TMS): δ=12.84 (1H, s), 7.88 (2H, m), 7.21 (2H, m), 6.39 (1H, t, J=6.9 Hz), 6.17 (1H, d, J=6.0 Hz), 6.15 (1H, dd, J=7.3 Hz, 1.4 Hz), 3.68 (1H, td, J=6.2 Hz, 1.3 Hz), 3.10 (3H, s), 1.57 (1H, d, J=11.9 Hz), 1.29 (3H, s), 1.27 (1H, d, J=11.9 Hz), 1.22 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6, 25°c, TMS): δ=167.1, 148.1, 143.8, 141.0, 133.9, 132.9, 128.8, 128.7, 2x128.0, 83.3, 50.4, 49.3, 46.8, 44.6, 24.5, 21.3; HR FAB MS: m/z 285.1493 $[M+H]^+$ (calculated for $[C_{18}H_{21}O_3]^+$ 285.1491).

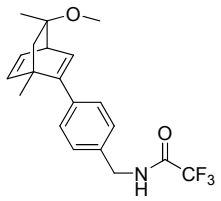
(1*R*,4*S*,8*S*)-4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)benzoic acid ((*RSS*)-L1)



(*RSS*)-**L1** was synthesized from (*RSS*)-**S2** following the same experimental procedure as for (*SRR*)-**L1.** The title compound was obtained as a white solid in 95% yield.
$[\alpha]_D^{20}$ = +14.2 cm^3 g^{-1} dm^{-1} (*c* = 0.99 g cm^{-3} in $CHCl_3$); HR FAB MS: m/z 285.1438 $[M+H]^+$ (calculated for $[C_{18}H_{21}O_3]^+$ 285.1491); NMR data was identical to that of (*SRR*)-**L1.**

(1*S*,4*R*,8*R*)-*N*-(4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)benzyl)-2,2,2-trifluoroacetamide ((*SRR*)-S3)

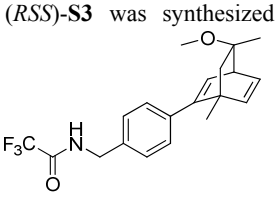
187 mg (0.60 mmol) of triflate (*SRR*)-**S1** and 190 mg of 4-((2,2,2-trifluoroacetamido)methyl)phenylboronic acid (0.77 mmol, 1.3 eq.) were dissolved in 3.5 ml THF. After addition of 1.8 ml 1 M K_3PO_4 solution (1.8 mmol, 3 eq.) the mixture was bubbled with argon for 10 min. 15 mg (0.018 mmol, 3 mol%) $Pd(dppf)Cl_2$ were added and the reaction was carried out under microwave irradiation (150 Watt, 100 °C). After 12 min the reaction mixture still contained small amounts of starting material, which could not be reduced by increasing the reaction time. For workup, the mixture was extracted with 20 ml AcOEt, washed with 1 M HCl (2 ×20 ml) and brine (2×20 ml). The organic layer was dried with Na_2SO_4 and the solvent was removed. The crude product was purified by flash chromatography (hexanes/AcOEt 9:1), yielding 145 mg (0.40 mmol, 66 %) of (*SRR*)-**S3** as a yellow oil.



^{1}H NMR (300 MHz, $CDCl_3$, 25°c, TMS): δ=7.21 (2 H, m), 7.15 (2 H, m), 6.55 (1 H, bs), 6.38 (1 H, t, J=6.9 Hz), 6.17 (1 H, d, J=5.4 Hz,), 6.15 (1 H, dd, J=7.0 Hz, 1.5 Hz), 4.51 (2 H, d, J=5.7 Hz), 3.64 (1 H, td, J=6.1 Hz, 1.3 Hz), 3.20 (3 H, s), 1.61 (1 H, d, J=11.9 Hz), 1.31 (3 H, s), 1.31 (1 H, d, J=12 Hz)1.30 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, 25°c, TMS): δ=156.3 (J_{C-F}=36 Hz), 149.3, 141.8, 140.1, 134.2, 134.0, 132.4, 129.4, 127.6, 115.9 (J_{C-F}=286 Hz), 84.4, 50.8, 50.1, 47.9, 45.6, 44.0, 24.9, 21.9; HR ESI MS: m/z 388.14992 $[M+Na]^+$ (calculated for $[C_{20}H_{22}F_3NO_2Na]^+$ 388.14948).

(1*R*,4*S*,8*S*)-*N*-(4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)benzyl)-2,2,2-trifluoroacetamide ((*RSS*)-S3)

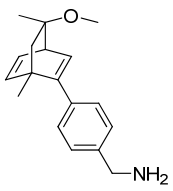
(*RSS*)-**S3** was synthesized from (*RSS*)-**S1** following the same experimental procedure as for (*SRR*)-**S3.** The title compound was obtained as a yellow oil in 55% yield.



HR ESI MS: m/z 388.14954 $[M+Na]^+$ (calculated for $[C_{20}H_{22}F_3NO_2Na]^+$ 388.14948); NMR data was identical to that of (*SRR*)-**L1.**

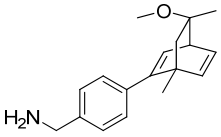
(1*S*,4*R*,8*R*)- (4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)phenyl)methanamine ((*SRR*)-L2)

144 mg (0.40 mmol) (*SRR*)-**S3** was dissolved in 4 ml MeOH. 4 ml of a 1 M NaOH solution (4 mmol, 10 eq.) was added and the reaction mixture was stirred for 30 min at RT. The product was extracted from the aqueous reaction mixture with AcOEt (3×20 ml). The combined organic phases were washed with 20 ml 1 M NaOH and brine (3×20 ml). After drying with Na_2SO_4 the



solvent was removed under reduced pressure, yielding 102 mg of (*SRR*)-**L2** as a yellow oil (0.38 mmol, 94%).
$[\alpha]_D^{20}$ = -30.6 cm^3 g^{-1} dm^{-1} (*c* = 1.14 g cm^{-3} in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°c, TMS): δ=7.25 (2H, m), 7.11 (2H, m), 6.37 (1H, t, J=6.9 Hz), 6.15 (1 H, d, J=5.9 Hz), 6.15 (1H, dd, J=7.1 Hz, 1.2 Hz), 3.87 (1H, s), 3.62 (1H, td, J=6.1 Hz, 1.3 Hz), 3.20 (3 H, s), 2.54 (2H, b), 1.61 (1H, d, J=12 Hz), 1.31 (3H, s), 1.30 (3H, s), 1.27-1.30 (1H, d); ^{13}C NMR (75 MHz, $CDCl_3$, 25°c, TMS): δ=149.4, 141.6, 138.6, 134.0, 131.6, 128.8, 126.8, 84.2, 50.5, 49.9, 47.7, 45.4, 30.9, 24.8, 21.8; HR FAB MS: m/z 270.1853 $[M+H]^+$ (calculated for $[C_{18}H_{24}NO]^+$ 270.1858).

(1*R*,4*S*,8*S*)-(4-(8-methoxy-1,8-dimethylbicyclo[2.2.2]octa-2,5-dien-2-yl)phenyl)methanamine ((*RSS*)-L2)

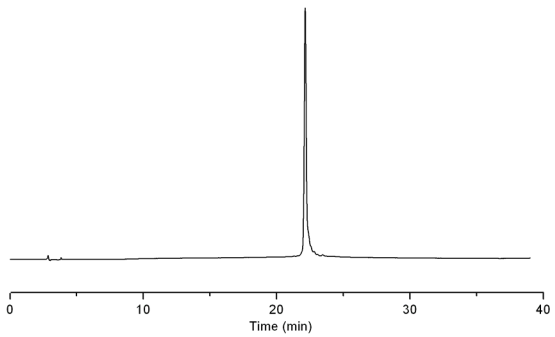


(*RSS*)-**L2** was synthesized from (*RSS*)-**S3** following the same experimental procedure as for (*SRR*)-**L2.** The title compound was obtained as a yellow oil in 98% yield.
$[\alpha]_D^{20}$ = +31.5 cm^3 g^{-1} dm^{-1} (*c* = 1.02 g cm^{-3} in $CHCl_3$); HR FAB MS: m/z 270.1844 $[M+H]^+$ (calculated for $[C_{18}H_{24}NO]^+$ 270.1858); NMR data was identical to that of (*SRR*)-**L1.**

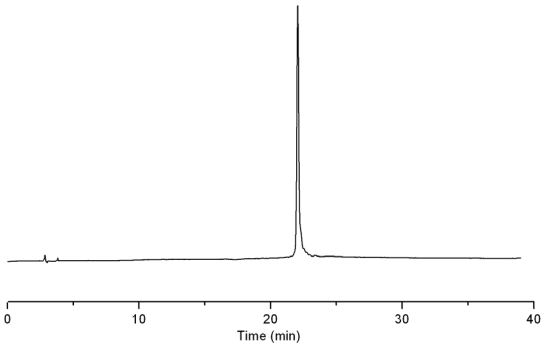
[1] A. L. Onderdelinden, A. van der Ent, *Inorg. Chim. Acta* **1972**, *6*, 420-426; M. A. Arthurs, J. Bickerton, S. R. Stobart, J. Wang, *Organometallics* **1998**, *17*, 2743-2750.
[2] C. Fischer, C. Defieber, T. Suzuki, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.
[3] M. Caprioara, R. Fiammengo, M. Engeser, A. Jäschke, *Chem. Eur. J.* **2007**, *13*, 2089-2095.

Time (min)	% buffer B
0	10
2	10
28	26
34	26
35	100
39	100

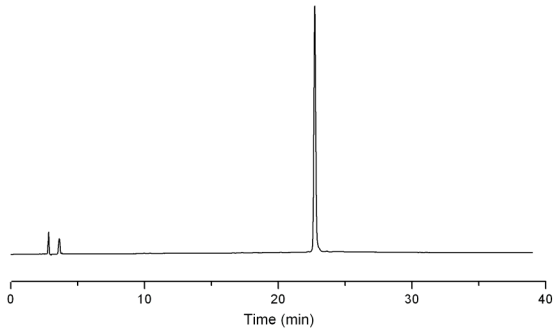
ODN1a: t_R = 22.13 min



ODN1b: t_R = 22.05 min



ODN2a: t_R = 22.73 min



ODN2b: t_R = 22.71 min

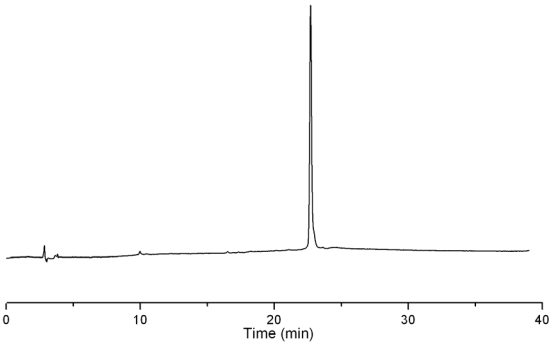


Figure S1. HPLC Chromatograms for oligonucleotides **ODN1a**, **ODN1b**, **ODN2a**, **ODN2b**.

Table S1. ESI-FTICR-MS analysis of oligonucleotides **ODN1a**, **ODN1b**, **ODN2a**, **ODN2b**.

Oligonucleotide	Found[1]	Calculated
ODN1a	6160,20594	6160,18569
ODN1b	6160,20387	6160,18569
ODN2a	6102,17021	6102,15640
ODN2b	6102,16348	6102,15640

[1] Given is the mass of the parent ion obtained by deconvolution.

Table S2. Oligonucleotide sequences.

Oligonucleotide	Sequence
cDNA1	5'-GGAGCTCAGCCTTCACTGC-3'
cDNA2	5'-GGAGCTCCTTCACTGC-3'
cDNA3	5'-GGAGCTCACAAGTCCTTCACTGC-3'
cRNA1	5'-GGAGCUCAGCCUUCACUGC-3'
cRNA2	5'-GGAGCUCCUUCACUGC-3'
cRNA3	5'-GGAGCUCACAUACCUUCACUGC-3'

Table S3. Melting temperatures for the duplexes cited in Table 2.

ODN	Complementary strand	Melting temperature (°c)
ODN3	**cDNA1**	52
ODN1a	**cDNA1**	44
ODN2a	**cDNA1**	44
ODN3	**cRNA1**	62
ODN1a	**cRNA1**	52
ODN2a	**cRNA1**	51
ODN3	**cDNA2**	39
ODN1a	**cDNA2**	38
ODN3	**cRNA2**	44
ODN1a	**cRNA2**	43
ODN3	**cDNA3**	41
ODN1a	**cDNA3**	38
ODN3	**cRNA3**	48
ODN1a	**cRNA3**	47

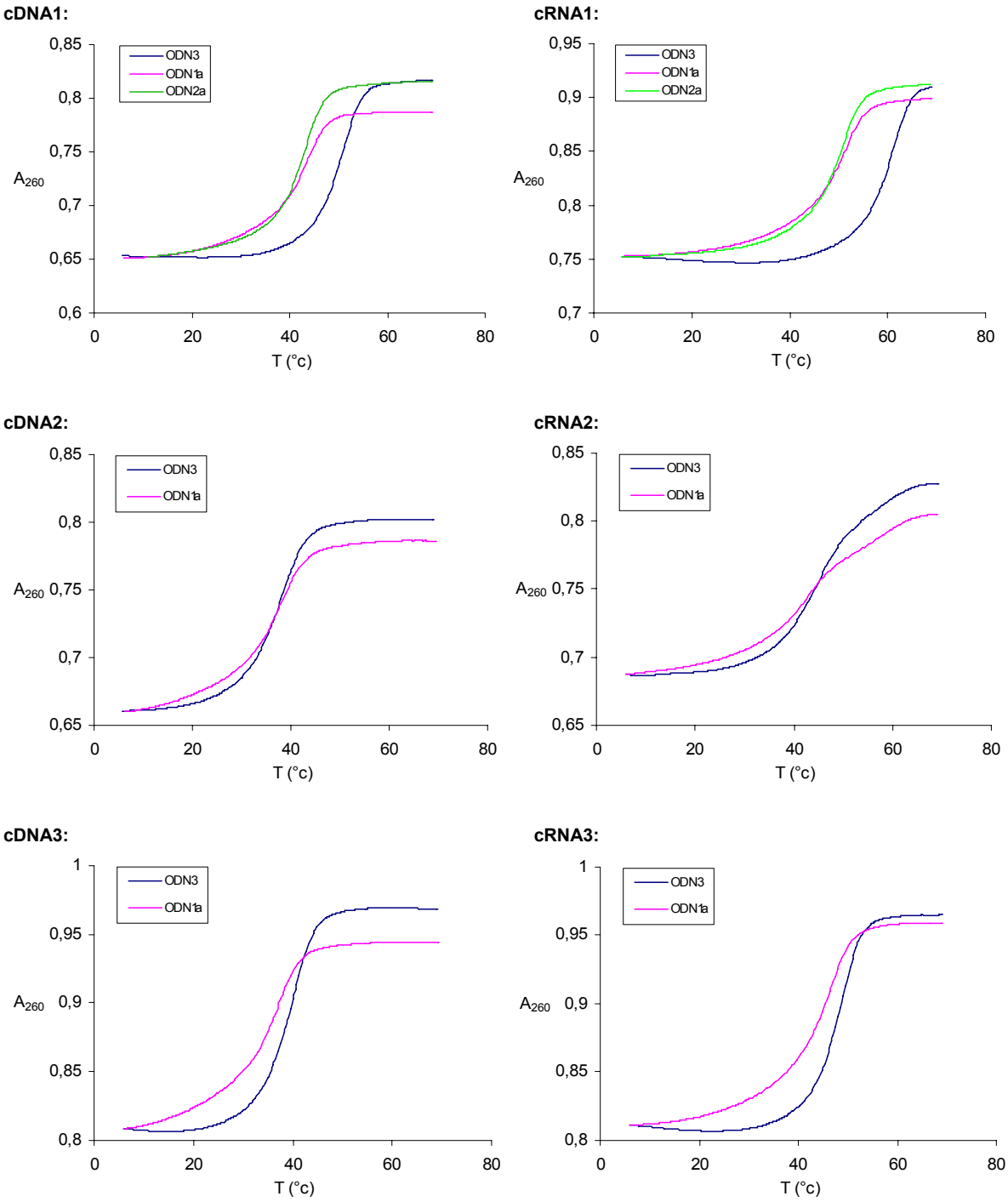
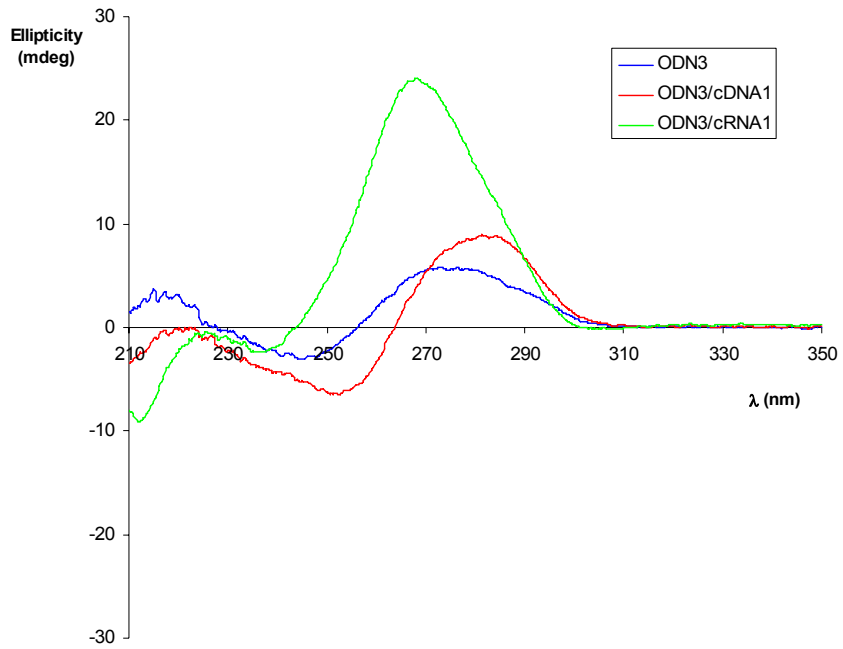


Figure S2. Normalized thermal denaturation curves for the duplexes cited in Table 2. The curves were recorded in the medium used for catalysis: 100 mM $NaClO_4$, 5 mM $Mg(ClO_4)_2$ in H_2O/dioxane 7:3. Each diagram combines the curves for one given complementary strand.

a)



b)

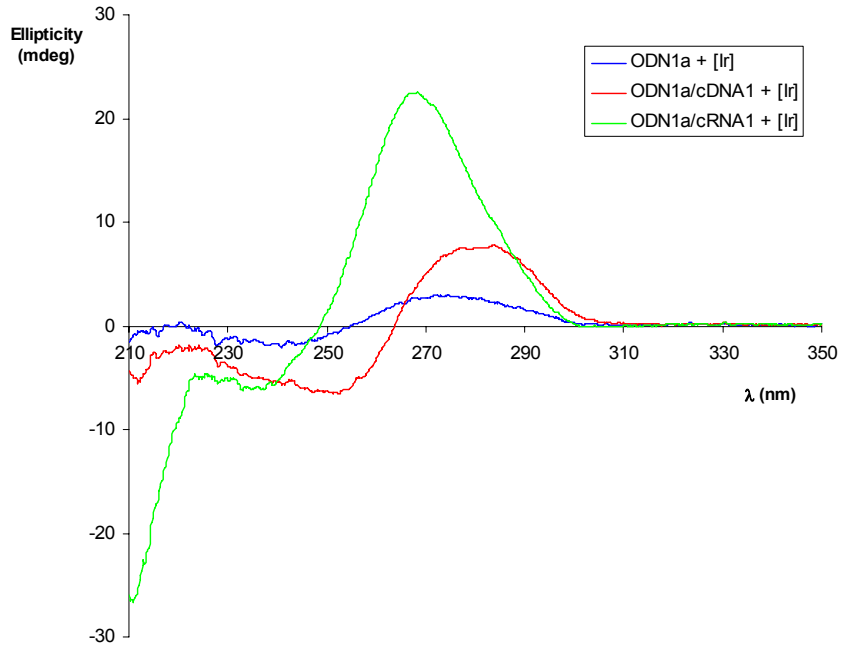


Figure S3. CD spectra for single strands and duplexes of **ODN3** and **ODN1a**. The curves of panel b correspond to entries 2, 6 and 10 of Table 2. The spectra were recorded with 10 μM solutions of nucleic acids in H_2O/dioxane 7:3 containing 100 mM $NaClO_4$ and 5 mM $Mg(ClO_4)_2$, in a 0.2 cm cuvette. Spectra of **ODN1a** were recorded after allowing complex formation in the presence of 0.5 equivalents of $[Ir(C_2H_4)_2Cl]_2$ for three hours.