Asymmetric Catalysis

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Enantioselective Friedel–Crafts Reactions in Water Using a DNA-Based Catalyst**

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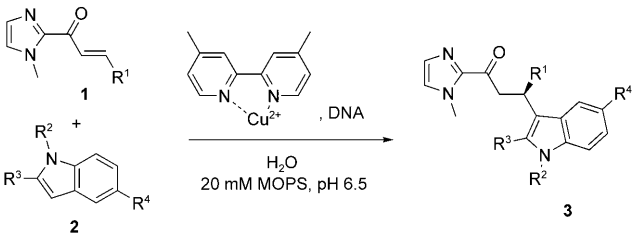
The Friedel–Crafts alkylation is one of the archetypical Lewis acid catalyzed C–C bond-forming reactions. The discovery in recent years of catalytic enantioselective variants has further increased the synthetic importance of the Friedel–Crafts reaction.[1,2] These variants involve the addition of a heteroaromatic π nucleophile, such as indole or pyrrole, to a ketone or activated alkene electrophile, resulting in useful synthons for pharmacologically interesting compounds.[2,3] Although traditionally associated with strictly anhydrous conditions, some examples of Friedel–Crafts alkylations in water, catalyzed by achiral Lewis acids, have been reported.[4] To date, the reported catalytic enantioselective versions of this reaction are, however, only tolerant to small amounts of water.[2b,f] Herein, we report the first catalytic asymmetric Friedel–Crafts alkylation reaction with olefins using water as the solvent and mediated by a DNA-based catalyst.

Polynucleotides are an attractive scaffold for catalyst design, and recently a number of catalysts based on DNA and RNA have been reported for C–C bond-forming reactions.[5] In our approach to DNA-based asymmetric catalysis,[6] a hybrid catalyst[7] is generated by noncovalent binding of a transition-metal complex to the DNA, which allows efficient transfer of the chirality of the DNA double helix to the catalyzed reaction. This strategy has been applied successfully in important C–C bond-forming reactions, such as the copper(II)-catalyzed Diels–Alder and Michael addition reactions, and *ee* values of up to 99% were obtained in several cases.[6]

The DNA-based catalytic enantioselective Friedel–Crafts alkylation reaction of indoles in water was explored using α,β-unsaturated 2-acyl imidazoles, which can bind to the Cu^{2+} ions in a bidentate fashion under aqueous conditions,[6b] as the electrophile (Scheme 1).[8] The conjugate addition reaction between **1a** and five equivalents of 5-methoxy indole (**2a**) in MOPS buffer at pH 6.5 was used to establish the optimal conditions for this reaction. The DNA-based catalyst was self-assembled by combining a copper(II) complex with salmon testes DNA (st-DNA), which is inexpensive and readily



1a: R^1=Me
1b: R^1=Ph
1c: R^1=*o*-BrC_6H_4
1d: R^1=*p*-$MeOC_6H_4$
1e: R^1=*p*-ClC_6H_4
1f: R^1=*n*-pentyl
2a: R^2=R^3=H, R^4=MeO
2b: R^2=R^3=R^4=H
2c: R^2=R^3=H, R^4=Cl
2d: R^2=Me, R^3=R^4=H
2e: R^2=H, R^3=Me, R^4=H

3a: R^1=Me, R^2=R^3=H, R^4=MeO
3b: R^1=Me, R^2=R^3=R^4=H
3c: R^1=Me, R^2=R^3=H, R^4=Cl
3d: R^1=R^2=Me, R^3=R^4=H
3e: R^1=Me, R^2=H, R^3=Me, R^4=H
3f: R^1=Ph, R^2=Me, R^3=R^4=H
3g: R^1=*o*-BrC_6H_4, R^2=Me, R^3=R^4=H
3h: R^1=*p*-$MeOC_6H_4$, R^2=R^3=H, R^4=MeO
3i: R^1=*p*-ClC_6H_4, R^2=R^3=H, R^4=MeO
3j: R^1=*n*-pentyl, R^2=Me, R^3=R^4=H

Scheme 1. Cu-dmbpy/st-DNA catalyzed Friedel–Crafts alkylation.

available. From a screening of copper(II) complexes,[9] it was evident that the best results were obtained with 4,4′-dimethyl-2,2′-bipyridine (dmbpy) as ligand, using 30 mol% (0.3 mM) of $[Cu(dmbpy)(NO_3)_2]$ (Cu-dmbpy) and 1.4 mg mL^{-1} of st-DNA (2 mM in base pairs). A full conversion was achieved in 0.5 h, and the (+)-enantiomer of **3a** was obtained with an *ee* value of 83% (Table 1, entry 1).[10]

The catalyst loading could be lowered to 0.3 mol% (3 μM) Cu-dmbpy whilst maintaining the same Cu/DNA ratio without any loss of *ee*, albeit requiring 44 h to reach full conversion (Table 1, entry 2). This loading of Cu-dmbpy is an order of magnitude lower than what is commonly used in catalytic asymmetric Friedel–Crafts alkylation reactions.[1] Particularly noteworthy is that, based on the binding affininity $K_b = (1.12 \pm 0.02) \times 10^4\,M^{-1}$ of Cu-dmbpy to DNA,[6c] only 16% of the Cu-dmbpy is bound to the DNA. This means that the effective catalyst loading is only 0.05 mol%; yet, the *ee* value is the same compared to the highest catalyst loading (Table 1, entry 1), at which concentration 95% of Cu-dmbpy is bound. This observation strongly suggests that the reaction is accelerated by DNA; this effect was also observed in the DNA-based catalytic Diels–Alder reaction.[11]

The apparent second-order rate constant k_{app} of the reaction of **1a** with **2a** catalyzed by Cu-dmbpy/st-DNA was determined to be $(1.00 \pm 0.05)\,M^{-1}s^{-1}$, whereas in the absence of st-DNA the rate was found to be $(3.35 \pm 0.03) \times 10^{-2}\,M^{-1}s^{-1}$. Thus, the presence of DNA causes a 30-fold rate acceleration of the reaction. This explains why unbound Cu-dmbpy does not contribute significantly to the enantiomeric excess obtained; the DNA-bound catalysts dominate the reaction owing to their increased reactivity. A further decrease in

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Table 1: Cu-dmbpy/DNA-catalyzed Friedel–Crafts reaction between **1a** and **2a**.[a]

Entry	DNA sequence[b]	**3a** *ee* [%]
	Double-stranded DNA:	
1[c]	st-DNA	83 (+)
2[d]	st-DNA	82 (+)
3[e]	st-DNA	23 (+)
4	$d(TCAGGGCCCTGA)_2$	93 (+)
5[f]	$d(TCAGGGCCCTGA)_2$	93 (+)
6	$d(TCGGGGCCCCGA)_2$	88 (+)
7	$d(GCGCGCGCGCGC)_2$	83 (+)
8	$d(TCGGGATCCCGA)_2$	81 (+)
9	$d(TCAGCGCGCTGA)_2$	79 (+)
10	$d(TCGGAATTCCGA)_2$	65 (+)
11	$d(TCAGAGCTCTGA)_2$	65 (+)
12	$d(TCAGTGCACTGA)_2$	63 (+)
13	$d(TCGCGATCGCGA)_2$	62 (+)
14	$d(GACTGACTAGTCAGTC)_2$	55 (+)
15	$d(ATATATATATAT)_2$	35 (+)
	Single-stranded DNA:	
16	d(AGTCCCGTGA)	12 (+)
17	d(GGG)	10 (+)
18	d(CCC	22 (+)

[a] Experiments were carried out with 1 mM **1a**, 5 mM **2a**, 2 mM base pairs DNA, 30 mol% (0.3 mM) Cu-dmbpy, at 5°C in 20 mM of MOPS (pH 6.5) for 10 h. [b] The melting temperatures and CD spectra for most of the sequences have been reported in Ref. [11]. [c] Reaction time 0.5 h. [d] 0.3 mol% (3 μM) Cu-dmbpy and 14 $\mu g\,mL^{-1}$ base pairs DNA, reaction time 44 h. [e] 0.03 mol% (0.3 μM) Cu-dmbpy and 1.4 $\mu g\,mL^{-1}$ base pairs DNA, reaction time 44 h. [f] 0.15 mol% (1.5 μM) Cu-dmbpy and 7 $\mu g\,mL^{-1}$ base pairs DNA, reaction time 44 h, 14 mg **1a**, 70% yield of isolated product after column chromatography.

catalyst loading to 0.03 mol% (0.3 μM) led to an expected decrease in the *ee* value (Table 1, entry 3), as only 2% of the Cu-dmbpy is bound to the DNA.

The DNA sequence proved to be an important variable in the optimization of the reaction. Evaluation of a series of synthetic double and single stranded DNAs showed that the best results were obtained using Cu-dmbpy in combination with the self-complementary oligonucleotide $d(TCAGGGCCCTGA)_2$ (DNA-1), with which an *ee* value of 93% (Table 1, entry 4) has been obtained. Interestingly, this sequence also provided the best results in the Diels–Alder reaction.[11] In general, similar patterns were found for the sequence dependence of the Friedel–Crafts alkylation of **1a** with **2a** compared to that of the Diels–Alder reaction. AT-rich duplexes and single stranded DNAs usually give rise to lower *ee* values, whereas the presence of G-tracts is beneficial to the reaction.

The Cu-dmbpy/DNA-1 catalyzed reaction of **1a** with **2a**, which results in the highest *ee* value, was performed on a 0.09 mmol (14 mg of **1a**) scale. Using a catalyst loading of only 0.15 mol%, an isolated yield of 70% and an *ee* value of 93% was obtained after two days (Table 1, entry 5).

A variety of indoles with different substitution patterns (**2a**–**e**, Scheme 1), reacting with 2-acyl imidazole **1** and catalyzed by Cu-dmbpy/st-DNA give full conversion in 10 h, which demonstrates the broad scope of the reaction (Table 2, entries 1–5). The *ee* values range from 72–83%, which indicates that the substitution of the indole does not have a significant influence on the *ee*. The DNA-based catalyst tolerates both aliphatic and aromatic substituents R^1 on the α,β-unsaturated 2-acyl imidazole. The *ee* values varied between 69% (**3h**) and 83% (**3a**), as indicated in Table 2 (entries 1, 6–10). However, when R^1 is an aromatic moiety, with the exception of $R^1 = p$-chlorophenyl (**1e**), the reaction was slower and 20 equivalents of indole were required to achieve full conversion in the same time. Finally, increasing the steric bulk at the imidazole nitrogen gave rise to a small decrease in the *ee* value (Supporting Information, Scheme S1).[9]

Table 2: Reaction scope.[a]

Entry	**1**	**2**	**3**	*ee* [%][b,c]	*ee* [%][d,e]	Yield [%][f] (*ee* [%])[g]
1[h]	**1a**	**2a**	**3a**	83 (+)	93	78 (82)[i]
2	**1a**	**2b**	**3b**	72 (+)-*R*	85	79 (69)[i]
3	**1a**	**2c**	**3c**	72 (+)	82	54 (69)[i]
4	**1a**	**2d**	**3d**	79 (−)-*R*	85	68 (71)[i]
5	**1a**	**2e**	**3e**	81 (−)	76	45 (77)[i]
6[j]	**1b**	**2d**	**3f**	75 (+)-*S*	74	87 (77)
7[j,k]	**1c**	**2d**	**3g**	79 (+)	79	79 (78)[l]
8[j,k]	**1d**	**2a**	**3h**	69 (+)	49	71 (64)
9	**1e**	**2a**	**3i**	79 (+)	75	77 (71)[l]
10	**1f**	**2d**	**3j**	82 (−)	84	68 (82)
11	**1b**	**4**	**5**	76 (+)	81	60 (76)

[a] All experiments were carried out with 1 mM **1**, 5 mM **2**, 2 mM base pairs DNA, 30 mol% (0.3 mM) Cu-dmbpy at 5°C, in 20 mM MOPS (pH 6.5) for 10 h, unless noted otherwise. Full conversion was obtained in all cases. [b] st-DNA. [c] 15 mL reaction volume. [d] DNA-1: $d(TCAGGGCCCTGA)_2$. [e] 0.6 mL reaction volume. [f] Preparative scale. [g] 0.086 mmol of **1**, yield of isolated product after column chromatography. [h] Reaction time 0.5 h. [i] 2 mM **1a**. [j] 20 equiv indole. [k] Reaction time 3 days. [l] 0.45 mmol of **1**.

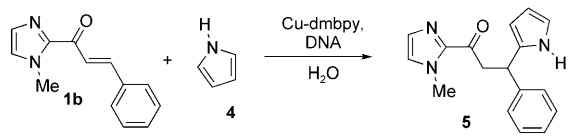
Cu-dmbpy/DNA-1 was also used as a catalyst for all the reactions mentioned above. In some cases, the use of Cu-dmbpy/DNA-1 resulted in an improved *ee* value (Table 2, entries 1–4), whereas in other reactions similar or slightly lower *ee* values were found (Table 2, entries 5–7, 9, 10). A general observation is that, in the case of $R^1 = Me$ (**1a**) or *n*-pentyl (**1f**) the *ee* values of the products improved compared to that of the Cu-dmbpy/st-DNA. A notable exception was the reaction with **1d**, where a significantly lower *ee* value was found with DNA-1 compared to that of st-DNA (Table 2, entry 8). Apparently, DNA-1 is not the optimal sequence for this substrate (**1d**). A preliminary investigation of different sequences showed that the trends observed for the sequence dependence with **1d** are clearly different compared to those for **1a** with **2a**.[9] For example, DNAs containing alternating GC and AT base pairs provide *ee* values comparable to DNA-1. These results demonstrate that different substrates have different requirements for the second coordination sphere provided by the DNA.

The reactions catalyzed by Cu-dmbpy/st-DNA were also performed on a preparative scale, that is, up to 0.45 mmol (130 mg) of **1** (Table 2). The Friedel–Crafts products were

obtained in good isolated yields after column chromatography, with no significant change in the *ee* value compared to the analytical scale. In case of the reaction between **1a** and **2a** (Table 2, entry 1), the catalyst solution was recycled twice without a decrease in yield and *ee* value. Yields of 70 and 75%, and *ee* values of 82 and 81%, were obtained in the second and the third run, respectively.

From the optical rotation measurements it was concluded that the *R* enantiomer of **3b** and **3d** and the *S* enantiomer of **3f** were obtained (Table 2, entry 2, 4, and 6).[2e] This corresponds to attack of the indole nucleophile from the same face of the enone moiety in all cases, that is, the *re*-face of **1a** and the *si*-face of **1b**.[12] Moreover, this coincides with the face selectivity in the Cu-dmbpy/DNA-catalyzed Michael and Diels–Alder reaction,[6a,b] which strongly suggests that the mechanism of asymmetric induction is similar in these reactions.

Finally, addition of pyrrole **4** to **1b** in the presence of Cu-dmbpy/st-DNA (Scheme 2) gave the corresponding product **5** in yields of 60% and an *ee* value of 76% (Table 2, entry 11). The *ee* value improved to 81% when DNA-1 was used instead of st-DNA.



Scheme 2. Asymmetric Friedel–Crafts alkylation of pyrrole.

In conclusion, using a DNA-based catalyst, we have achieved Lewis acid catalyzed asymmetric Friedel–Crafts alkylations with olefins in water for the first time. Employing catalyst loadings as low as 0.15 mol%, good yields and excellent enantioselectivities (up to 93%) were obtained in the synthetically important reaction of α,β-unsaturated 2-acyl imidazoles with heteroaromatic π nucleophiles.

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[8] The reactants were dissolved in DMSO prior to addition, giving rise to a final DMSO concentration of 0.4% v/v.
[9] See the Supporting Information.
[10] Using $Cu(NO_3)_2$/st-DNA without the dmbpy ligand gave rise to a 38% *ee* of the (−)-enantiomer.
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[12] There is a change in priority of the substituents going from **1a** to **1b**.

