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α,*β*-Unsaturated 2-Acyl Imidazoles as a Practical Class of Dienophiles for the DNA-Based Catalytic Asymmetric Diels–Alder Reaction in Water

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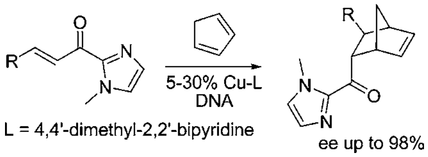
ABSTRACT



α,*β*-Unsaturated 2-acyl imidazoles are a novel and practical class of dienophiles for the DNA-based catalytic asymmetric Diels–Alder reaction in water. The Diels–Alder products are obtained with very high diastereoselectivities and enantioselectivities in the range of 83–98%. The catalytic reaction was performed on a 1.0 mmol scale, and the imidazole auxiliary was removed readily.

The combination of the catalytic power of transition metal complexes with the chiral architectures of biopolymers has given rise to a new generation of highly enantioselective hybrid catalysts.[1] In particular, artificial metalloenzymes formed by using the supramolecular approach, in which metal complexes are bound to biopolymers by noncovalent interactions,[2] have already shown effective catalysis and high enantioselectivity.[3] In addition to proteins, polynucleotides have proven to be versatile scaffolds for assembly of enantioselective catalysts.[4] We have introduced a novel DNA-based asymmetric catalysis concept based on the modular assembly of a DNA-based catalyst, using a copper complex of a nonchiral ligand that can bind to DNA.[5] As a result, the active Cu^{2+} center is brought into proximity of the DNA double helix, allowing transfer of chirality from DNA to the product of the Cu^{2+}-catalyzed Diels−Alder reaction of aza-chalcone with cyclopentadiene in water, resulting in ee values up to 99%. Here, we present α,*β*-unsaturated 2-acyl imidazoles as an alternative class of dienophiles, which greatly increases the practicality of this DNA-based catalytic concept (Scheme 1).

An investigation of the substrate scope of our reported asymmetric Diels−Alder reaction with aza-chalcone type dienophiles[5] revealed that the substituent at the alkene moiety of the dienophile was amenable to variation, but the 2-acyl pyridine moiety proved to be essential for both catalysis and

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[1] (a) Letondor, C.; Ward, T. R. *ChemBioChem* **2006**, *7*, 1845−1852. (b) Thomas, C. M.; Ward, T. R. *Chem. Soc. Rev.* **2005**, *34*, 337−346. (c) Lu, Y. *Curr. Opin. Chem. Biol.* **2005**, *9*, 118−126. (d) Reetz, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5716−5722.

[2] Ward, T. R. *Chem. Eur. J.* **2005**, *11*, 3798−3804.

[3] (a) Reetz, M. T.; Jiao, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 2416−2419. (b) Letondor, C.; Humbert, N.; Ward, T. R. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 4683−4687. (c) Mahammed, A.; Gross, Z. *J. Am. Chem. Soc.* **2005**, *127*, 2883−2887. (d) Collot, J.; Gradinaru, J.; Humbert, N.; Skander, M.; Zocchi, A.; Ward, T. R. *J. Am. Chem. Soc.* **2003**, *125*, 9030−9031. (e) Ohashi, M.; Koshiyama, T.; Ueno, T.; Yanase, M.; Fujii, H.; Watanabe, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 1005−1008. (f) Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1978**, *100*, 306−307.

[4] (a) Roelfes, G. *Mol. BioSyst.* **2007**, *3*, 126−135. (b) Caprioara, M.; Fiammengo, R.; Engeser, M.; Jäschke, A. *Chem. Eur. J.* **2007**, *13*, 2089−2095. (c) Ropartz, L.; Meeuwenoord, N. J.; van der Marel, G. A.; van Leeuwen, P. W. N. M.; Slawin, A. M. Z.; Kamer, P. C. J. *Chem. Commun.* **2007**, 1556−1558. (d) Seelig, B.; Keiper, S.; Stuhlmann, F.; Jäschke, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4576−4579.

[5] (a) Roelfes, G.; Boersma, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 635−637. (b) Roelfes, G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3230−3232.

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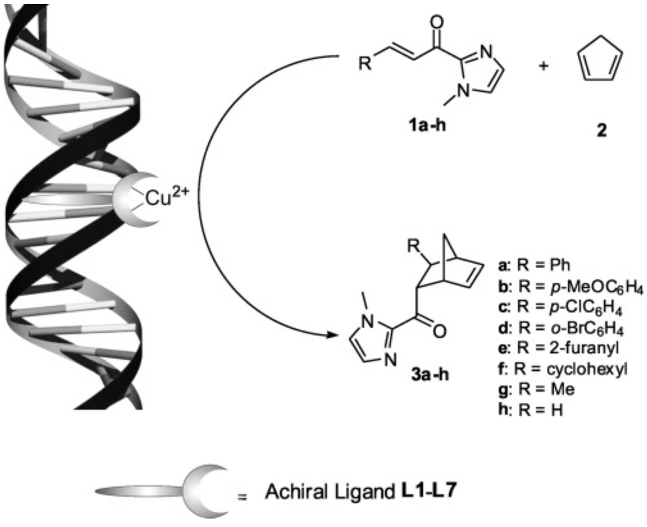
Scheme 1. Schematic Representation of the DNA-Based Copper-Catalyzed Asymmetric Diels−Alder Reaction of α,β-Unsaturated 2-Acyl Imidazoles and Cyclopentadiene



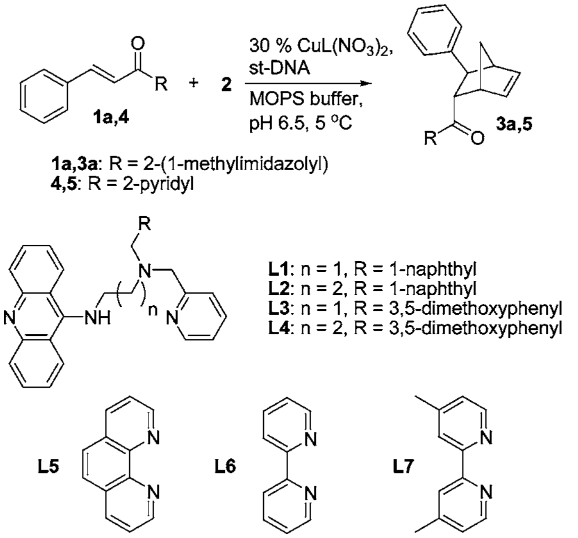
enantioselectivity. Substrates lacking the pyridyl nitrogen are less activated by Cu^{2+} in water.[3a,6] When using the well-known 3-alkenoyl-1,3-oxazolidinones,[7] which have two carbonyl oxygens available for coordination to Cu^{2+}, no catalytic effect was observed.[5a] Presumably, the dienophile cannot compete effectively with H_2O for binding to the copper, suggesting that bidentate binding to Cu^{2+} by using an N,O donor set is required. However, the 2-acyl pyridine moiety of the substrate limits the synthetic potential of the catalytic system, since the pyridyl moiety is not removed readily or transformed after the Diels−Alder reaction. Therefore, we sought to replace the 2-pyridyl moiety by an alternative, removable auxiliary, which still allows for efficient binding to Cu^{2+} under aqueous conditions.

Recently, α,β-unsaturated-1-acyl-3,5-dimethylpyrazoles were reported as substrates for the catalytic Diels−Alder reaction with use of chiral copper complexes. Although generally good yields and enantioselectivities were reported, only limited success was obtained in pure water.[8] Evans et al. have demonstrated that α,β-unsaturated 2-acyl imidazoles are good substrates in a variety of Lewis acid-catalyzed reactions,[9] e.g., Friedel−Crafts reactions[9a,b] and 1,3-dipolar cycloadditions.[9c] This substrate class was also employed in the conjugate addition of carbonyl anions under aqueous conditions, although not in pure water.[9d] Subsequently, the imidazole group has been transformed into a good leaving group by treatment with methyl triflate, allowing substitution by a nucleophile. These features make α,β-unsaturated 2-acyl imidazoles a very attractive class of substrates for DNA-based catalytic asymmetric Diels−Alder reactions.

α,β-Unsaturated 2-acyl imidazoles **1a−f** were prepared via aldol condensation of 2-acetyl-1-methylimidazole and the appropriate aldehyde, as described previously.[9d] Although cyclohexyl carboxaldehyde can, in principle, also form an enolate, dienophile **1f** was the only product observed. 1-(1-Methyl-1*H*-imidazol-2-yl)propenone (**1h**) was prepared by addition of lithiated imidazole to acrolein, followed by oxidation of the allylic alcohol with MnO_2. This dienophile is prone to polymerization, and therefore was prepared freshly prior to use.

Initially a series of DNA-based catalysts from both classes investigated to date, i.e., using ligands of the acridine[5b] (**L1−L4**) and the bipyridine type[5a] (**L5−L7**), were screened in the Diels−Alder reaction of **1a** with **2** (Scheme 1, Table 1). The DNA-based catalyst was formed through self-assembly by mixing solutions of salmon testes DNA (st-DNA), which is inexpensive and readily available, and the appropriate copper complex. For screening purposes the

Table 1. Screening of Ligands for the Copper(II)-Catalyzed Diels−Alder Reaction of α,β-Unsaturated 2-Acyl Imidazole **1a** and Cyclopentadiene **2** in the Presence of DNA[a]



entry	ligand	% conversion[b] of **1a**	% ee[c] of **3a**	% ee[c−e] of **5**
1		<5	n.d.[f]	10 (+)
2	L1	61	10 (+)	48 (+)
3	L2	83	16 (−)	49 (−)
4	L3	78	29 (+)	37 (+)
5	L4	93	68 (+)	37 (+)
6	L5	17	68 (+)	72 (+)
7	L6	25	87 (+)	90 (+)
8	L7	90	97 (+)	99 (+)

[a] All experiments were carried out with salmon testes DNA (1.3 mg mL^{-1}, 2 mM in base pairs), 0.3 mM $[Cu(L)(NO_3)_2]$ (30 mol %), 1 mM **1a** in 15 mL of MOPS buffer (20 mM, pH 6.5) for 3 days at 5 °C, unless noted otherwise. [b] Determined by ^1H NMR. [c] For the endo isomer. [d] All conversions >80%. [e] Data taken from ref 5. [f] n.d. = not determined.

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(6) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702−7707.

(7) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

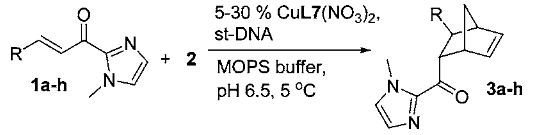
(8) Ishihara, K.; Fushimi, M. *Org. Lett.* **2006**, *8*, 1921−1924.

(9) (a) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249−2252. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. (c) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351−3354. (d) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675−14680.

catalyst loading was 30 mol % with respect to substrate, but this can be lowered to 5 mol % without a significant effect on the enantioselectivity (vide infra). The reaction was initiated by addition of 10 equiv of cyclopentadiene (**2**), and continued for 3 days at 5 °C, after which the cyclopentadiene was depleted. The catalytic reaction is ligand accelerated;[10] in the absence of a ligand, i.e., using only $Cu(NO_3)_2$, no conversion was observed (entry 1). The catalysts based on the acridine ligands (**L1**−**L4**) gave rise to good conversion and moderate ee values (entries 2−5). Although the enantiomeric preference was always the same, significant variations in the ee were observed, compared to aza-chalcone (**4**). For example, complexes based on ligands **L1** and **L2** gave a lower enantiomeric excess, whereas the copper complex based on ligand **L4** gave rise to a significantly higher enantioselectivity. In contrast, using the copper complexes of the bipyridine class ligands (**L5**−**L7**), comparable results are seen for aza-chalcone and **1a** with respect to both the enantiomeric excess, i.e., ee values up to 97%, and enantiomeric preference, albeit with low conversion in the case of ligands **L5** and **L6**. Surprisingly, by using the catalyst based on **L7** 90% conversion was obtained, indicating that this catalyst is much more reactive, with 97% ee of the (+) enantiomer. The reason for this remarkable difference in reactivity of Cu-**L7** compared to Cu-**L6** is still unclear and subject to further investigation. On the basis of these results, it was evident that the copper complex of **L7** is the catalyst of choice, and all further experiments were performed with this catalytic system.

The substrate scope of the reaction was investigated by using α,*β*-unsaturated 2-acyl imidazoles **1b**−**h** (Table 2). All substrates underwent efficient Diels−Alder reactions with cyclopentadiene, catalyzed by Cu-**L7**/salmon testes DNA. The Diels−Alder product was the sole product; no side products were detected by NMR and HPLC analysis. In all cases the endo diastereomer was obtained almost exclusively and with an excellent enantiomeric excess. The best results were obtained when the R substituent in the enone was an aromatic group, with ee values ranging from 94% to 98%. The electronic nature of the substituent on the aryl ring, i.e., electron donating or electron withdrawing, or the position on the aryl ring did not influence the ee significantly (entry 2−6). In the case of R = *p*-ClPh and *o*-BrPh (entry 4 and 5), the conversion was somewhat decreased, most likely caused by the low solubility of **1c** and **1d**. When R was a 2-furanyl group, which is a convenient handle for further functionalization,[11] an excellent ee was obtained (entry 7). Dienophiles **1f**−**h**, which contain alkyl groups or are unsubstituted, also gave rise to high enantiomeric excess, i.e., ee = 80−88%, although the enantioselectivity is somewhat lower compared to when R is an aromatic group (entries 7, 8, and 10). No conversion was obtained when cyclopentadiene was replaced by the more water soluble diene furan.

Table 2. Substrate Scope of the Diels−Alder Reaction with α,*β*-Unsaturated 2-Acyl Imidazoles Catalyzed by $Cu\mathbf{L7}(NO_3)_2$/st-DNA[a]



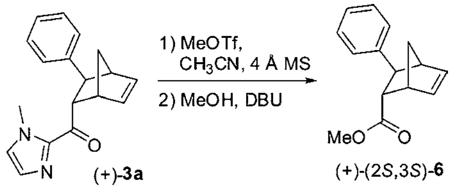
entry	R (substrate)	endo:exo	% ee[b]
1	Ph (**1a**)	99:1	97 (+) (2*S*,3*S*)
2[c]	Ph (**1a**)	99:1	98 (+) (2*S*,3*S*)
3	*p*-$MeOC_6H_4$ (**1b**)	99:1	98
4[d]	*p*-ClC_6H_4 (**1c**)	n.d.	96
5[e]	*o*-BrC_6H_4 (**1d**)	96:4	94
6	2-furanyl (**1e**)	97:4	94
7	cyclohexyl (**1f**)	94:6	88
8	Me (**1g**)	>99:1	86
9[c]	Me (**1g**)	>99:1	88
10	H (**1h**)	98:2	80
11[c]	H (**1h**)	99:1	83

[a] All experiments were carried out with st-DNA (1.3 mg mL^{-1}, 2 mM in base pairs), 0.3 mM $[Cu(\mathbf{L7})(NO_3)_2]$ (30 mol %), 2 mM **1** in 45 mL of MOPS buffer (20 mM, pH 6.5) for 3 days at 5 °C, unless noted otherwise. [b] For the endo isomer. [c] 1 mM **1**, 0.05 mM $Cu(\mathbf{L7})(NO_3)_2$ (5 mol %), 1.3 mg mL^{-1} st-DNA (2 mM in base pairs). [d] Conversion ~50%. [e] Conversion ~70%.

The loading of Cu-**L7** could be reduced to 5 mol % without affecting the endo:exo selectivity and the enantioselectivity (entries 2, 9, and 11).[12]

To demonstrate that the present reaction is practical from a synthetic point of view, we performed the DNA-based catalytic asymmetric Diels−Alder reaction of **1a** with **2** on a 1.0 mmol (210 mg) scale, with a catalyst loading of 5 mol %. Product **3a** was obtained in 70% isolated yield (85% conversion), and 96% ee after column chromatography. With use of the procedure of Evans et al.,[9c] the imidazole of **3a** was first methylated with methyl triflate, followed by treatment with methanol. Thus, we obtained the corresponding methyl ester **6** in 41% isolated yield (80% conversion of the Diels−Alder product; see Scheme 2).[13] The optical rotation of the product was $[\alpha]^{20}_D$ +126.8 (*c* 0.401, $CHCl_3$). From comparison with literature values ($[\alpha]^{20}_D$ −130.2,

Scheme 2. Synthesis of 3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Methyl Ester **6** from **3a**



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[10] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

[11] Sasaki, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 3013−3016.

[12] DNA concentration was kept at 1.3 mg/mL, which means that the Cu-**L7**/DNA base pair ratio in this case was 1:40.

[13] The same yield and purity of **6** was observed without column chromatography of Diels−Alder product **3a**.

>95% ee in the 2*R*,3*R*-enantiomer)[14] it can be concluded that the Diels−Alder product is obtained from the st-DNA-based catalytic reaction as the 2*S*,3*S*-enantiomer.

In conclusion, we have demonstrated that α,*β*-unsaturated 2-acyl imidazoles are an alternative and practical class of dienophiles for the DNA-based catalytic asymmetric Diels−Alder reaction in water. The Diels−Alder products are obtained with excellent diastereoselectivity and enantioselectivity, and the imidazole auxiliary is readily displaced. Currently, we are exploring new DNA-based catalytic reactions using this class of substrates.

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Supporting Information Available: Characterization data, NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Arai, Y.; Masuda, T.; Masaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2165−2170.