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Enantioselective Michael addition reactions in water using a DNA-based catalyst

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ABSTRACT

Enantioselective Michael addition reactions of malononitrile and cyanoesters to α,β-unsaturated 2-acylimidazoles can be achieved in water using a DNA-based catalyst consisting of double-stranded DNA and copper(II) complex. Quantitative conversions and good enantioselectivities (up to 84% ee) are obtained for a wide range of substrates. The UV–vis absorption and circular dichroism (CD) indicate that the copper(II) complex may interact with salmon testes DNA via minor groove binding.

1. Introduction

The development of catalytic enantioselective reactions in aqueous media has received a great deal of attention in recent years.[1] Water is an ideal solvent because it is not only cheap, safe and environmentally benign, but in some cases can also accelerate the reaction rate and influence the reaction selectivity. Since the water-enhanced Diels–Alder reaction pioneered by Breslow in the 1980s,[2] a series of carbon–carbon bond formation reactions and their enantioselective fashions, e.g., aldol reactions, pericyclic reactions, and Mannich reactions have been developed in aqueous media.[3] In nature, many chemical transformations with high stereoselectivities are catalyzed by enzymes in aqueous environments, which inspires chemists to develop new methodologies to create new carbon–carbon bonds and stereocentres.[4] Learning from the nature, utilizing biomolecules as sources of chiral catalysts or chiral auxiliaries is highly promising for achieving enantioselective reactions in water. Amino acids and their derivatives have been proved to be excellent organocatalysts for water-involved enantioselective reactions.[5] The unique structure of DNA has recently aroused many interests in enantioselective catalysis. A DNA-based catalyst composing of double-stranded DNA and transition metal complex has been successfully applied to a series of enantioselective reactions in water,[6] and G-quadruplex DNA (G4DNA) can proceed as well.[7] Very recently, a human telomeric G4DNA alone has been found to show enantioselective catalytic function and its copper(II) metalloenzyme can remarkably enhance the reactivity and the enantioselectivity in Diels–Alder reactions and Friedel–-Crafts reactions.[8]

As one of the important asymmetric reactions, enantioselective Michael addition reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[9] Much effort has been devoted to the development of novel chiral catalysts, such as organocatalysts[10] and Lewis acid catalysts[11] for enantioselective Michael reactions in aqueous media. Although DNA-based catalysis has been applied to an enantioselective Michael addition[6b] using nitromethane and dimethyl malonate as nucleophiles, the requirement of useful building blocks with various nucleophiles in the organic synthesis still needs further work. Herein, we report that an enantioselective Michael addition reaction in water has been achieved using a DNA-based catalyst between α,β-unsaturated 2-acylimidazoles and nucleophiles including malononitrile and cyanoacetates. We found that nearly full conversions and good enantioselectivities up to 84% ee can be obtained using DNA-based catalysts for a wide range of substrates.

2. Results and discussion

2.1. Optimization

As shown in Scheme 1, we tried to investigate whether enantioselective Michael reactions of α,β-unsaturated 2-acylimidazoles

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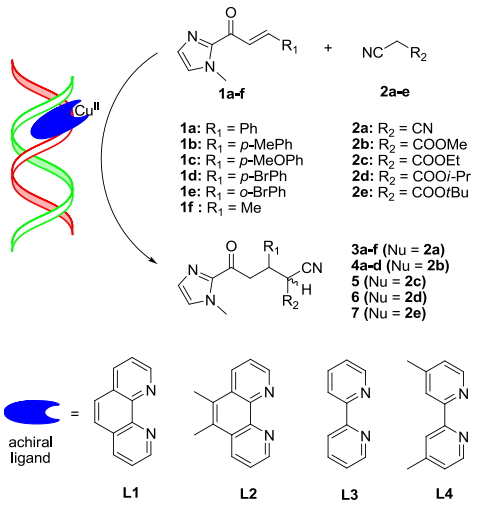
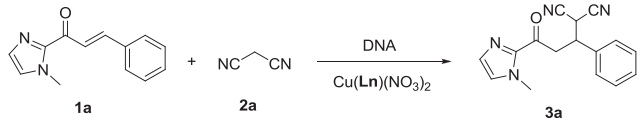


Scheme 1. Schematic representation of the enantioselective Michael addition reactions in water catalyzed by Cu(**Ln**)$(NO_3)_2$ in the presence of DNA.

(**1a**–**f**) and nucleophiles (**2a**–**e**) can be achieved using DNA-based catalysts composing of salmon testes DNA (stDNA) and achiral copper(II) complexes. For an initial attempt, a typical Michael reaction between (*E*)-1-(1-methyl-1*H*-imidazol-2-yl)-3-phenylprop-2-en-1-one (**1a**) and malononitrile (**2a**) was selected to examine the catalytic function of the DNA-based catalysts (Table 1). With only stDNA and copper(II) salt as the catalysts, the Michael reaction provides modest conversion (55%) and racemic product (Table 1, entry 1). While in the presence of 1,10-phenanthroline (**L1**) as ligand, the conversion of **1a** is improved to 78% and the enantiomeric excess (ee) of **3a** is at 17% (Table 1, entry 2), indicating that the chirality of DNA can be successfully transferred to the Michael product. When tuning the steric element of ligand to 5,6-dimethyl-1,10-phenanthroline (**L2**), a little higher conversion and enantioselectivity were obtained compared with those of ligand **L1** (Table 1, entry 3 vs entry 2). With the ligand 4,4′-dimethyl-2,2′-bipyridine (**L4**), nearly full conversion and good enantioselectivity at 68% ee are obtained (Table 1, entry 5), but lack of methyl groups of **L3** results in deceased conversion and ee value (Table 1, entry 4), which is in accordance with the trend in the previous reports.[6b,6d]

Table 1
Screening of the reaction conditions for the Michael addition reaction[a]



Entry	DNA	Cu(**Ln**)$(NO_3)_2$		Conversion[b] (%)	ee[c] (%)
		$Cu(NO_3)_2$ (mM)	**Ln**		
1	stDNA	0.30	None	55	0
2		0.30	**L1**	78	17
3		0.30	**L2**	84	31
4		0.30	**L3**	72	23
5		0.30	**L4**	>99	68
6		0.10	**L4**	>99	66
7		0.05	**L4**	88	55
8	ctDNA	0.30	**L4**	>99	62
9[d]	htDNA	0.05	**L4**	>99	2
10[d]	htDNA	0.05	None	82	4

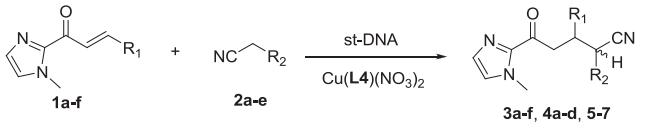
[a] Reaction conditions: **1a** (1 μmol), **2a** (0.1 mmol, 100 equiv), salmon testes DNA or calf thymus DNA (stDNA or ctDNA, 1.4 mg/mL), human telomeric DNA (htDNA, 5′-$G_3(T_2AG_3)_3$-3′, 100 μM), 3-(*N*-morpholino)propanesulfonic acid buffer (1 mL, 20 mM, pH 6.5), 24 h, 4 °C. All data are averaged by two separated experiments.
[b] Determined by ^{1}H NMR within the reproducibility of ±10%.
[c] Determined by chiral HPLC within the reproducibility of ±5%.
[d] 50 mM NaCl was added to form antiparallel G-quadruplex conformation.

Compared with the amount of copper(II) complex at 30 mol %, the conversion and the enantioselectivity cause no significant changes when the copper(II) complex loading is decreased to 10 mol % (Table 1, entry 5 vs entry 6), but further deceasing the copper(II) complex to 5 mol % leads to reduced conversion and enantioselectivity (Table 1, entry 5 vs entry 7). In order to rule out the influence of the source of double-stranded DNA, calf thymus DNA (ctDNA) was tested and similar results were obtained compared to those of stDNA (Table 1, entry 5 vs entry 8). In addition, we also investigated a guanine-rich single-stranded human telomeric DNA (htDNA, 5′-$G_3(T_2AG_3)_3$-3′), which can fold into an antiparallel G-quadruplex in Na^+-containing solution.[12] Using G-quadruplex DNA as a chiral scaffold, nearly racemic products are obtained for the corresponding Michael reactions either in the presence or absence of the ligand (Table 1, entries 9 and 10).

2.2. Substrate scope and limitations

The substrate scope of α,β-unsaturated 2-acylimidazoles (**1a**–**f**) and nucleophiles (**2a**–**e**) was investigated under optimized reaction conditions (Table 2). Quantitative conversions are obtained in the DNA-based asymmetric Michael reactions between 2-acylimidazoles (**1a**–**f**) and malononitrile (**2a**) (Table 2, entries 1–6). Compared with the Michael reaction between **1a** and **2a**, there are no significant changes for the enantioselectivities of the Michael reactions when the substrates bear with electron-donating substituents, such as *p*-methylphenyl (**1b**) and *p*-methoxyphenyl (**1c**) (Table 2, entries 2, 3 vs entry 1). However, the enantioselectivities obviously decrease when employing the substrates with electron-withdrawing groups, i.e., *p*-bromophenyl (**1d**) and *o*-bromophenyl (**1e**) (Table 2, entries 4, 5 vs entry 1). When R_1 in the 2-acylimidazole changes from an aryl (**1a**, R_1=Ph) to an alkyl group (**1f**, R_1=Me), decreased ee value is obtained (Table 2, entry 6). In the case of methyl cyanoacetate (**2b**) as nucleophile, the

Table 2
Substrate scope for the DNA-based enantioselective Michael addition reactions[a]



1a: R_1 = Ph
1b: R_1 = *p*-MePh
1c: R_1 = *p*-MeOPh
1d: R_1 = *p*-BrPh
1e: R_1 = *o*-BrPh
1f : R_1 = Me
2a: R_2 = CN
2b: R_2 = COOMe
2c: R_2 = COOEt
2d: R_2 = COO*i*-Pr
2e: R_2 = COO*t*Bu
3a-f (Nu = **2a**)
4a-d (Nu = **2b**)
5 (Nu = **2c**)
6 (Nu = **2d**)
7 (Nu = **2e**)

Entry	1	2	Product	Conversion[b] (%)	ee[c] (%)
1	**1a**	**2a**	**3a**	>99	68
2	**1b**	**2a**	**3b**	>99	72
3	**1c**	**2a**	**3c**	>99	64
4	**1d**	**2a**	**3d**	>99	57
5	**1e**	**2a**	**3e**	>99	31
6	**1f**	**2a**	**3f**	>99	36
7	**1a**	**2b**	**4a**[d]	>99	71[e]
8	**1b**	**2b**	**4b**[d]	>99	76[e]
9	**1c**	**2b**	**4c**[d]	>99	84[e]
10	**1d**	**2b**	**4d**[d]	54	67[f]
11	**1a**	**2c**	**5**[d]	95	64[f]
12	**1a**	**2d**	**6**[d]	37	63[f]
13	**1a**	**2e**	**7**[d]	<5	45[f]

[a] Reaction conditions: **1** (1 μmol), **2** (0.1 mmol, 100 equiv), Cu(**L4**)$(NO_3)_2$ (0.3 equiv), salmon testes DNA (1.4 mg/mL), 3-(*N*-morpholino)propanesulfonic acid buffer (1 mL, 20 mM, pH 6.5), 4 °C, 24 h. All data are averaged by two separated experiments.
[b] Determined by ^{1}H NMR within the reproducibility of ±10%.
[c] Determined by chiral HPLC within the reproducibility of ±5%.
[d] Products were obtained as roughly 1:1.5 mixture of two diastereoisomers.
[e] The same ee values were obtained for the two diastereoisomers of the products.
[f] The ee values were obtained for the major diastereoisomers of the products.

enantioselectivities are all good to the Michael reaction of various 2-acylimidazoles (**1a**–**d**) (Table 2, entries 7–10). In particular, the ee value is up to 84% ee when using **1c** and **2b** as substrates (Table 2, entry 9). In addition, the other substituted cyanoacetates (**2c**–**e**) were also investigated. With the ester group of nucleophiles becoming larger (methyl→ethyl→*iso*-propyl→*tert*-butyl), the reactivity and the enantioselectivities of the Michael reactions decreased obviously (Table 2, entries 7, 11–13). The above results indicate that the electronic and steric effects cause great effect on the enantioselective induction in the DNA-based catalysis.

In order to demonstrate the practicability of this DNA-based enantioselective Michael addition reaction, we carried out the reaction with the scale of **1a** and **2a** at 1 mmol (**1**a: 212 mg). The resulting product **3a** was obtained with the isolated yield 86% and 68% ee after column chromatography. Moreover, the groups that α,β-unsaturated 2-acylimidazole, nitrile, and methyl cyanoacetate in products are synthetic potential building blocks for further transformations, which might be useful in organic synthesis and medical design.[13] The above results suggest that the DNA-based enantioselective Michael reaction has the potential to be applied in organic synthesis.

2.3. Binding mode

In attempt to rationalize the catalytic model, we tried to investigate the binding mode between the copper(II) complex (Cu-**L4**) and stDNA by UV–vis absorption spectroscopy and circular dichroism spectroscopy. UV–vis absorption spectra (Fig. 1) show that, upon addition of stDNA, the characteristic band of Cu-**L4** centered at 307 nm has a larger degree of hypochromicity but no distinct shift. This is in contrast to the characteristic of intercalative binding mode, in which the hypochromicity (≥35%) and red shift (≥15 nm) are usually observed.[14] So we deduces that intercalation may not be the dominant binding mode for Cu-**L4** with stDNA, which is in agreement with previous report based on the UV melting experiment.[15]

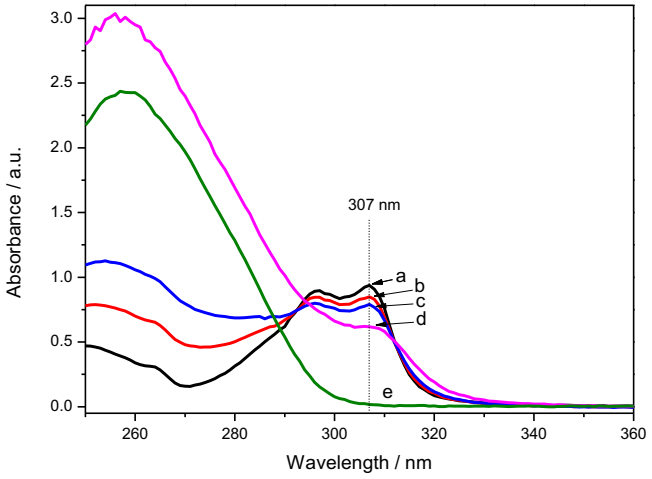


Fig. 1. UV–vis absorption spectra of (a) 65 μM Cu-**L4** and its complex with stDNA (b–d). The molar ratios of stDNA/Cu-L4 are (b) 0.5, (c) 1.0, (d) 3.0; (e) 195 μM stDNA. The concentration of stDNA is given in base pairs. All samples are in MOPS buffer (20 mM, pH=6.5).

CD spectroscopy is sensitive to characterize the asymmetric information of chiral materials. As shown in Fig. 2, the CD spectrum of free stDNA has emerging two characteristic bands, a negative band at 245 nm due to the helicity and a positive band at 276 nm due to the base stacking, which is the characteristic of DNA in the right-handed *B*-form.[16] With the addition of copper(II) complex,

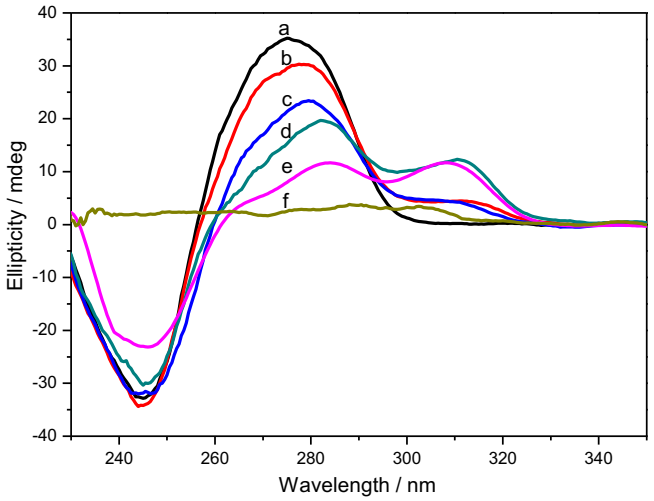


Fig. 2. CD spectra of (a) 160 μM stDNA and its complex with Cu-**L4** (b–e), the molar ratios of stDNA/Cu-L4 are (b) 10.7, (c) 5.3, (d) 2.7, (e) 1.3, (f) 120 μM Cu-**L4**. The concentration of stDNA is given in base pairs. All samples are in MOPS buffer (20 mM, pH=6.5).

there are less changes of the negative band, but larger changes of the positive band with regard to the intensity and position. This suggests that the interaction of copper(II) complex with DNA has a great influence on base pairs stacking, but little influence on the structure of chiral skeleton. For copper(II) complex, free Cu-**L4** has no intrinsic CD signal, while an obvious induced CD signal centered at 307 nm appears upon binding to stDNA (Fig. 2). CD spectra clearly show that the chirality can transfer from stDNA to copper(II) center. As positive induced signals in CD spectroscopy are generally obtained for compounds that bind in the DNA minor groove, we propose that the binding mode between Cu-**L4** and stDNA is minor groove binding.[17] Based on the results of UV–vis spectra and CD spectra, a possible catalytic model is proposed in Scheme 1.

3. Conclusions

Enantioselective Michael reactions of malononitrile and cyanoacetates to α,β-unsaturated 2-acylimidazoles have been achieved in water using DNA-based catalysts. Quantitative conversions for a wide scope of substrates and good enantioselectivities up to 84% ee can be obtained. Based on the spectroscopic studies, a minor groove binding mode is proposed. This work presents another example for the double-stranded DNA-based asymmetric catalysis and might provide an opportunity to reveal catalytic functions of DNA.

4. Experimental section

4.1. Materials and methods

Salmon testes DNA (stDNA) and calf thymus DNA (ctDNA) were purchased from Sigma–Aldrich. 3-(*N*-morpholino)propanesulfonic acid (MOPS) and 2-(*N*-morpholino)ethanesulfonic acid (MES) were purchased from Sangon (Shanghai, China). 1,10-Phenanthroline (**L1**, phen), 2,2′-bipyridine (**L3**, bpy), 4,4′-dimethyl-2,2′-bipyridine (**L4**, dmbpy) were purchased from J&K (Beijing, China). 5,6-Dimethyl-1,10-phenanthroline (**L2**, 5,6-dmp) was purchased from TCI. Malononitrile (**2a**) and cyanoacetates (**2b**–**e**) were purchased from Alfa Aesar (Tianjin, China). All other chemicals and solvents were obtained from commercial sources and used as supplied without further purification. Water was distilled and deionized (specific resistance of 18.2 MΩ at 25 °C) using a Milli-Q A10 water

purification system. Copper complexes were prepared according to the procedure.[18] α,β-unsaturated 2-acylimidazoles **1a**–**f** were prepared according to the literature.[19]

Circular dichroism (CD) spectra were recorded on a dual beam DSM 1000 CD spectrophotometer (Olis, Bogart, GA) with a 10 mm quartz cell. Each measurement was recorded at room temperature (about 20 °C). The average scan for each sample was subtracted by a background CD spectrum of corresponding buffer solution. UV–vis experiments were carried out on a Shimadzu 2450 spectrophotometer (Shimadzu, Japan) equipped with a Peltier temperature control accessory. All UV–vis spectra were measured using a sealed quartz cell with a path length of 1.0 cm. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS or residual protic solvent signals as internal standard. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or unresolved, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, parts per million). High resolution mass spectra (HRMS) were obtained by the ESI ionization sources. The enantioselectivity was determined by chiral HPLC analysis using Daicel Chiralpak-AD or AD-H column with a UV-detector by using isopropanol and *n*-hexane as eluents at 25 °C.

4.2. General procedure for the conjugate addition of malononitrile or methyl cyanoacetate to 1

A DNA-based catalyst in MOPS buffer (1000 μL, 20 mM, pH 6.5) was prepared by mixing a solution of $Cu(L)(NO_3)_2$ (100 μL, 3 mM in 20 mM MOPS buffer) and stDNA solution (900 μL, 1.6 mg/mL in 20 mM MOPS buffer). After stirring for 1 h at 4 °C, α,β-unsaturated 2-acylimidazole **1** (10 μL of 0.1 M in CH_3CN) and malononitrile **2a** (6.6 mg, 0.1 mmol, 100 equiv) or methyl cyanoacetate **2b**–**e** (9.9 mg, 0.1 mmol, 100 equiv) were added consecutively. The reaction mixture was stirred for 24 h at 4 °C, and then extracted with diethyl ether (3×5 mL), dried over Na_2SO_4, and then removed the solvent under reduced pressure. After a short flash chromatography, the crude product was directly analyzed by using ^{1}H NMR and chiral HPLC.

*4.2.1. 2-(3-(1-Methyl-1H-imidazol-2-yl)-3-oxo-1-phenylpropyl)malononitrile (**3a**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.32 (m, 5H), 7.19 (s, 1H), 7.08 (s, 1H), 4.48 (d, *J*=5.1 Hz, 1H), 4.06–3.86 (m, 5H), 3.87–3.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 142.3, 136.5, 129.9, 129.3, 129.1, 128.2, 127.9, 112.0, 111.7, 41.6, 40.6, 36.2, 29.3; $[\alpha]_D^{20}$ −1.2° (*c* 0.8, $CHCl_3$, 68% ee); HRMS (ES^+) calcd for $C_{16}H_{15}ON_4$ $[M+H]^+$: 279.1246, found: 279.1241; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 21.1 (minor) and 33.6 (major) mins (68% ee).

*4.2.2. 2-(3-(1-Methyl-1H-imidazol-2-yl)-3-oxo-1-p-tolylpropyl)malononitrile (**3b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J*=7.7 Hz, 2H), 7.20 (d, *J*=7.7 Hz, 2H), 7.17 (s, 1H), 7.07 (s, 1H), 4.45 (d, *J*=5.2 Hz, 1H), 4.02–3.83 (m, 5H), 3.83–3.67 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 142.3, 139.0, 133.5, 129.9, 129.8, 128.0, 127.9, 112.1, 111.8, 41.2, 40.6, 36.2, 29.5, 21.2; HRMS (ES^+) calcd for $C_{17}H_{17}ON_4$ $[M+H]^+$: 293.1402, found: 293.1397; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 19.7 (minor) and 25.4 (major) mins (72% ee).

*4.2.3. 2-(1-(4-Methoxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malononitrile (**3c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J*=8.6 Hz, 2H), 7.16 (s, 1H), 7.06 (s, 1H), 6.91 (d, *J*=8.6 Hz, 2H), 4.43 (d, *J*=5.2 Hz, 1H), 4.02–3.83 (m, 5H), 3.80 (s, 3H), 3.78–3.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 160.1, 142.3, 129.9, 129.4, 128.4, 127.9, 114.6, 112.1, 111.8, 55.4, 41.0, 40.7, 36.2, 29.6; HRMS (ES^+) calcd for $C_{17}H_{17}O_2N_4$ $[M+H]^+$: 309.1352, found: 309.1345; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 30.7 (minor) and 37.0 (major) mins (64% ee).

*4.2.4. 2-(1-(4-Bromophenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malononitrile (**3d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 2H), 7.17 (s, 1H), 7.08 (s, 1H), 4.46 (d, *J*=4.8 Hz, 1H), 4.01–3.85 (m, 5H), 3.79–3.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 142.2, 135.4, 132.5, 130.0, 129.9, 128.1, 123.4, 111.8, 111.4, 41.2, 40.4, 36.3, 29.2; HRMS (ES^+) calcd for $C_{16}H_{14}ON_4Br$ $[M+H]^+$: 357.0351, found: 357.0345; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 24.4 (minor) and 33.2 (major) mins (57% ee).

*4.2.5. 2-(1-(2-Bromophenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malononitrile (**3e**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.0 Hz, 1H), 7.54 (d, *J*=7.8 Hz, 1H), 7.36 (*t*, *J*=7.6 Hz, 1H), 7.22 (t, *J*=7.7 Hz, 1H), 7.18 (s, 1H), 7.07 (s, 1H), 4.70–4.59 (m, 1H), 4.50 (d, *J*=5.4 Hz, 1H), 4.11 (dd, *J*=18.1, 7.6 Hz, 1H), 3.95 (s, 3H), 3.77 (dd, *J*=18.1, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 142.3, 135.7, 133.9, 130.5, 129.9, 128.6, 128.5, 127.9, 125.0, 111.8, 111.2, 39.9, 39.8, 36.2, 27.8; HRMS (ES^+) calcd for $C_{16}H_{14}ON_4Br$ $[M+H]^+$: 357.0351, found: 357.0348; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 19.3 (minor) and 41.0 (major) mins (31% ee).

*4.2.6. 2-(4-(1-Methyl-1H-imidazol-2-yl)-4-oxobutan-2-yl)malononitrile (**3f**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 1H), 7.03 (s, 1H), 4.33 (d, *J*=4.3 Hz, 1H), 3.94 (s, 3H), 3.40 (dd, *J*=17.8, 4.8 Hz, 1H), 3.24 (dd, *J*=17.8, 8.0 Hz, 1H), 2.84–2.62 (m, 1H), 1.30 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.3, 142.1, 129.5, 127.9, 112.5, 111.6, 41.7, 36.3, 31.9, 28.20, 17.3; HRMS (ES^+) calcd for $C_{11}H_{13}ON_4$ $[M+H]^+$: 217.1089, found: 217.1085; ee's were determined by HPLC analysis (Daicel Chiralpak-AD-H, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ=254 nm). Retention times: 21.8 (major) and 23.0 (minor) mins (36% ee).

*4.2.7. Methyl 2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxo-3-phenylpentanoate (**4a**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.45–7.19 (m, 5H), 7.12 (s, 1H), 7.03 (s, 1H), 4.26 (d, *J*=5.7 Hz, 1H), 3.94 (s, 3H), 4.19–3.58 (m, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 189.0, 165.6, 165.6, 142.6, 142.5, 139.0, 138.2, 129.5, 129.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 115.5, 115.3, 53.5, 53.3, 44.2, 43.8, 41.7, 41.0, 40.4, 36.1, 36.1; $[\alpha]_D^{20}$ −11.6° (*c* 0.5, $CHCl_3$, 71% ee); HRMS (ES^+) calcd for $C_{17}H_{18}O_3N_3$ $[M+H]^+$: 312.1348, found: 312.1344; ee's were determined by HPLC analysis (Daicel Chiralpak-AD, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 22.6 (minor) and 25.0 (major) mins (71% ee).

*4.2.8. Methyl 2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxo-3-p-tolylpentanoate (**4b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.29–7.21 (m, 2H), 7.17–7.08 (m, 3H), 7.03 (s, 1H), 4.22 (d, *J*=5.6 Hz, 1H), 3.95 (s, 3H), 4.14–3.62 (m, 3H), 3.67 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 189.1, 165.8, 165.6, 142.6, 142.5, 137.9, 137.8, 135.9, 135.1, 129.7, 129.5, 129.4, 128.0, 127.7, 127.5, 127.4, 115.6, 115.4, 53.5, 53.4, 44.3, 44.0, 41.7, 41.0, 40.6, 40.1, 36.2, 36.2, 21.2, 21.2; HRMS (ES^+) calcd for $C_{18}H_{20}O_3N_3$ $[M+H]^+$: 326.1505, found: 326.1497; ee's were determined by HPLC analysis

(Daicel Chiralpak-OD, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ=254 nm). Retention times: 22.7 (minor) and 24.2 (major) mins (76% ee).

*4.2.9. Methyl 2-cyano-3-(4-methoxyphenyl)-5-(1-methyl-1H-imidazol-2-yl)-5-oxopentanoate (**4c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.33–7.25 (m, 2H), 7.15 (s, 1H), 7.04 (s, 1H), 6.88–6.81 (m, 2H), 4.21 (s, 1H), 3.96 (s, 3H), 4.15–3.61 (m, 3H), 3.78 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 189.2, 165.8, 165.7, 159.4, 159.3, 142.7, 142.6, 130.9, 130.2, 129.6, 129.5, 129.3, 129.0, 127.5, 127.4, 115.7, 115.5, 114.3, 114.2, 55.3, 53.5, 53.4, 44.4, 44.1, 41.9, 41.2, 40.5, 39.8, 36.2, 36.2; HRMS (ES^+) calcd for $C_{18}H_{20}O_4N_3$ $[M+H]^+$: 342.1454, found: 342.1449; ee's were determined by HPLC analysis (Daicel Chiralpak-OD, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ=254 nm). Retention times: 35.2 (minor) and 37.5 (major) mins (84% ee).

*4.2.10. Methyl 3-(4-bromophenyl)-2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxopentanoate (**4d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.44 (d, J=3.7 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.15 (s, 1H), 7.05 (s, 1H), 4.23 (s, 1H), 3.96 (s, 3H), 4.15–3.59 (m, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 188.7, 165.5, 165.4, 142.6, 142.4, 138.0, 137.2, 132.2, 132.1, 130.0, 129.7, 129.7, 129.6, 127.7, 127.6, 122.4, 122.2, 115.3, 115.1, 53.7, 53.6, 43.9, 43.6, 41.5, 40.8, 40.5, 39.9, 36.3, 36.2. HRMS (ES^+) calcd for $C_{17}H_{17}O_3N_3Br$ $[M+H]^+$: 390.0453, found: 390.0448; ee's were determined by HPLC analysis (Daicel Chiralpak-AD-H, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, λ=254 nm). Retention times: 20.1 (minor diastereomers), 23.7 (minor enantiomer, major diastereomer) and 25.9 (major enantiomer, major diastereomer) mins (67% ee, major diastereomer).

*4.2.11. Ethyl 2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxo-3-phenylpentanoate (**5**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.42–7.21 (m, 5H), 7.13 (s, 1H), 7.03 (s, 1H), 4.24 (d, J=5.8 Hz, 1H), 3.95 (s, 3H), 4.18–3.62 (m, 5H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 189.1, 165.2, 165.1, 142.7, 142.5, 139.0, 138.2, 129.6, 129.4, 128.9, 128.8, 128.3, 128.2, 128.1, 128.0, 127.5, 127.4, 115.7, 115.5, 77.5, 77.2, 76.9, 62.9, 62.75, 44.3, 43.8, 41.9, 41.2, 41.1, 40.5, 36.2, 36.1, 13.9. HRMS (ES^+) calcd for $C_{18}H_{20}O_3N_3$ $[M+H]^+$: 326.1505, found: 326.1502; ee's were determined by HPLC analysis (Daicel Chiralpak-AD-H, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 20.2 (minor enantiomer, minor diastereomer), 22.1 (major enantiomer, minor diastereomer), 26.8 (minor enantiomer, major diastereomer), and 28.8 (major enantiomer, major diastereomer) mins (64% ee, major diastereomer).

*4.2.12. Isopropyl 2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxo-3-phenylpentanoate (**6**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.37 (d, J=7.2 Hz, 2H), 7.30–7.16 (m, 3H), 7.09 (s, 1H), 7.01 (s, 1H), 4.88 (tq, J=11.8, 5.9 Hz, 1H), 4.20 (d, J=5.8 Hz, 1H), 3.91 (s, 3H), 4.13–3.57 (m, 3H), 1.15 (s, 3H), 0.99 (d, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 188.9, 164.6, 164.5, 142.6, 142.5, 138.9, 138.2, 129.5, 129.3, 128.8, 128.7, 128.3, 128.1, 128.0, 127.9, 127.5, 127.3, 115.8, 115.6, 70.9, 70.8, 44.3, 43.8, 42.0, 41.3, 41.2, 40.4, 36.1, 36.0, 21.4, 21.3; HRMS (ES^+) calcd for $C_{19}H_{22}O_3N_3$ $[M+H]^+$: 340.1661, found: 340.1656; ee's were determined by HPLC analysis (Daicel Chiralpak-AD-H, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 16.5 (minor enantiomer, minor diastereomer), 17.5 (major enantiomer, minor diastereomer), 25.7 (major enantiomer, major diastereomer), 26.7 (minor enantiomer, major diastereomer) mins (63% ee, major diastereomer).

*4.2.13. tert-Butyl 2-cyano-5-(1-methyl-1H-imidazol-2-yl)-5-oxo-3-phenylpentanoate (**7**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by): δ 7.44–7.19 (m, 5H), 7.12 (s, 1H), 7.02 (s, 1H), 4.15 (d, J=5.9 Hz, 1H), 3.94 (s, 3H), 4.12–3.58 (m, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 189.1, 164.0, 163.9, 142.7, 142.5, 139.0, 138.5, 129.5, 129.4, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.5, 127.4, 116.2, 116.0, 84.3, 84.1, 77.5, 77.2, 76.9, 45.0, 44.5, 42.3, 41.6, 41.3, 40.4, 36.2, 36.1, 27.7. HRMS (ES^+) calcd for $C_{20}H_{24}O_3N_3$ $[M+H]^+$: 354.1818, found: 354.1812; ee's were determined by HPLC analysis (Daicel Chiralpak-AD-H, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, λ=254 nm). Retention times: 13.8 (major enantiomer, minor diastereomer), 15.0 (minor enantiomer, minor diastereomer), 24.0 (major enantiomer, major diastereomer), 25.8 (minor enantiomer, major diastereomer) mins (45% ee, major diastereomer).

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Supplementary data

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