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Synthesis and application of novel imidazole and 1*H*-tetrazolic acid containing catalysts in enantioselective organocatalyzed Diels–Alder reactions

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ABSTRACT

Herein we report studies on the organocatalytic Diels–Alder reaction using a variety of catalysts capable of activating α,β-unsaturated carbonyl compounds for reactions with dienes. The structurally attractive catalysts **4** and **14** were utilized in the enantioselective organocatalytic Diels–Alder reactions. Catalyst **4** provided the products in fair yields and more importantly in good enantioselectivities of up to 83% ee. Catalyst **14** was synthesized in high yield and was assessed in the enantioselective organocatalytic Diels–Alder reaction. Catalyst **14** proved to be a highly active and selective catalyst providing the products in high yield and high enantioselectivities up to 95% ee.

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1. Introduction

The enantioselective Diels–Alder reaction has attracted much interest over the past twenty years. The asymmetric catalysis of Diels–Alder reactions mediated by chiral Lewis acids, including early transition metals, has dominated this field at the outset.[1] However, the enantioselective organocatalytic Diels–Alder reaction discovered by MacMillan has changed the way chemists think about conducting asymmetric catalysis,[2] and was one of the first studies[3] that attracted interest in the area of asymmetric organocatalysis.[4]

The concept of organocatalytic enantioselective Diels–Alder reactions[5] catalyzed by chiral-secondary-amine-containing molecules relies on the reversible covalent attachment of the catalyst to α,β-unsaturated aldehydes, leading to iminium ions. This in turn leads to LUMO-lowering activation (Fig. 1), and significantly increases the reactivity of the parent dienophile toward reaction with the diene.[6] The increased reactivity of α,β-unsaturated iminium ions in Diels–Alder reactions was first reported some thirty years ago.[7]

Important aspects of MacMillan's initial catalyst design include the control of iminium-ion geometry and enantiofacial discrimination with respect to the incoming diene.[8] MacMillans original catalyst **1**, has proven to be a highly active and selective catalyst for the enantioselective organocatalytic Diels–Alder reaction. In this case, the stereocontrolling elements include the selective formation of (*E*)-iminium isomers to avoid non-bonding interactions between the substrate olefin and geminal methyl substituents, and the benzyl group on the catalyst that effectively shields the *Re*-face of the dienophile, leaving the *Si*-face exposed (Fig. 2).[6,8]

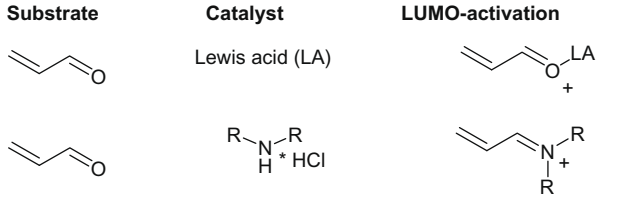

Figure 1. Comparision between Lewis acid and organocatalytic LUMO activation of α,β-unsaturated aldehydes.

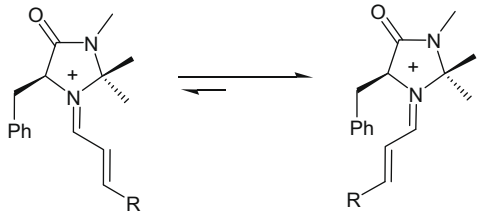

Figure 2. Catalyst (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **1**, developed by MacMillan et al. for the enantioselective Diels–Alder reaction.[2] The figure shows the preferred (*E*)-iminium ion after reaction with the α,β-unsaturated aldehyde.

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As part of our ongoing efforts to optimize organocatalysts for various enantioselective reactions,[9] we became interested in testing the catalysts available in house in the organocatalytic asymmetric Diels–Alder reaction. Herein we wish to report our findings in this area.

2. Results and discussion

During the course of our work in the area of organocatalysis we have prepared a variety of catalysts i.e. **1**–**4** (Fig. 3). Catalyst **1** represents the original MacMillan catalyst,[2] especially designed for the Diels–Alder reaction. Catalyst **2** is the tetrazolic acid analogue of L-proline, which was originally described by Ley et al., Yamamoto et al., and by us for the organocatalytic aldol reaction.[10] This catalyst has since then been widely used in the organocatalytic community for a variety of purposes.[11] Catalyst **3** is the homologated tetrazole analogue originally described by Ley et al.[12] The imidazole containing catalyst **4** was designed by us,[13] especially for the organocatalytic addition of nitro-alkanes to α,β-unsaturated aldehydes.

The potential of these catalysts to facilitate the reaction between *trans*-2-hexenal **5** and cyclopentadiene **6** to give cycloaddition products **7** was investigated (Table 1).

The results as shown in Table 1 reveal several interesting issues. As previously known, catalyst **1** developed by MacMillan provides a high reaction rate and excellent enantioselectivity. Catalyst **1** was also shown to react well in an acetonitrile/water mixture (cf. entries 1 and 2) albeit with a slightly lower conversion; this procedure greatly simplifies the work-up in preparative applications, as no hydrolysis of the dimethyl-acetal formed in MeOH solution is needed. Interestingly, catalyst **4** showed promising results, which prompted us to evaluate this catalyst further.

Catalyst **4** also worked in both MeOH and acetonitrile solutions. The TFA salt of **4** gave a slightly better conversion (approx. 5%) in MeCN, as compared to MeOH, while the HCl salt provided better conversions in MeOH. We therefore evaluated both the HCl salt and the TFA salt of catalyst **4** in the Diels–Alder reaction between cyclopentadiene and the three α,β-unsaturated aldehydes as shown in Table 2.

As can be seen in Table 2, the isolated yields obtained with catalyst **4** are fair, although apparently a lot of product was lost during the isolation (cf. Table 1, entry 16 and Table 2, entry 2). Still, the Diels–Alder adducts were obtained in fair yields and moderate-to-high enantiomeric excesses for both aliphatic and aromatic dienophiles. The diastereoselectivity, between the *exo*- and *endo*-products, was poor with this catalyst, just as observed with the MacMillan catalyst **1** for these substrates.[2a] Catalyst **4** continuously provided the *exo*-isomer in higher enantiomeric excess than the *endo*-products (Table 2, entries 1–6).

The initial investigation presented in Table 1 revealed other interesting data. It can be seen that the tetrazole containing catalyst **2** offers very high reactivity, in most cases matching the reactivity of catalyst **1**, but provides Diels–Alder adducts in low enantiomeric excesses. The low enantioselectivity of the reaction can be explained by the fact that catalyst **2** lacks the two methyl groups at the α-position with respect to the secondary amine, which are necessary for controlling the iminium-ion geometry. The selective (*E*)-iminium isomer formation plays an important role in determining the degree of enantioselective induction. We therefore reasoned out that a re-design of catalyst **2** to more closely match catalyst **1**, should lead to a novel catalyst (i.e., **14**) in which both the vital di-methyl motif and the beneficial 1*H*-tetrazole moiety are present. Catalyst **14** was synthesized from commercially available N_α-(9-fluorenylmethoxycarbonyl)-N_γ-trityl-L-asparagine according to Scheme 1.

The synthesis made use of the highly sterically demanding Trt group in order to differentiate between the two amide groups during the cyclization leading to the imidazolidinone. The synthesis started from commercially available N_α-(9-fluorenylmethoxycarbonyl)-N_γ-trityl-L-asparagine **8**, which has a Fmoc-protected amine functionality and a bulky trityl protecting group on the amide. Staring material **8** was converted to methyl amide **9** in 88% isolated yield using an analogous route to that reported by Biondi et al.[14] The Fmoc group was selectively cleaved using 20% piperidine in DMF to furnish the free amine **10** in high yield after column chromatography. The next step involved acid-catalyzed imine formation with acetone, followed by cyclization to the five-membered imidazolidinone **11** in 95% isolated yield. The trityl group of **11** seems to have an important effect on the reaction by firstly preventing cyclization to the six-membered ring through the other amide, and secondly by favoring the cyclized product **11**, presumably via a six-membered intramolecular hydrogen bond between the imidazolidinone nitrogen and the side-chain amide bond that diminishes steric interactions between the bulky Trt-group and the imidazolidinone ring. The trityl group was then cleaved off in refluxing TFA to give **12**. Dehydration, using a modified procedure including 4 Å MS in DMF and 1.5 equiv of cyanuric chloride, provided nitrile **13** in 85% isolated yield. The nitrile **13** was converted to the tetrazolic acid **14** in 71% yield (Scheme 1). The addition of HCl in methanol gave the salt of the catalyst, that is, **14a**, which was assessed in the enantioselective organocatalytic Diels–Alder reaction of various dienophiles with cyclopentadiene (Table 3).

As can be seen in Table 3, the new catalyst facilitates the enantioselective organocatalytic Diels–Alder cycloaddition reaction in a highly stereoselective manner. The Diels–Alder adducts were obtained in high yields and enantioselectivities for both aliphatic and aromatic dienophiles (Table 3, entries 1–4). This catalyst also offered an increased diastereoselectivity, as compared to catalysts **1** and **4** (Tables 1 and 2) for most substrates, with the *exo*-isomer being the major product. In contrast to catalysts **4**, the new catalyst **14** provided the *endo*-isomer in higher enantiomeric excess than the *exo*-isomer. This outcome correlates to the results reported for catalyst **1** (Table 1 and Ref. 2a), suggesting that the organizational control imposed in the transition state by the two methyl groups in the original MacMillan catalysts is effective also in the new catalyst **14**.

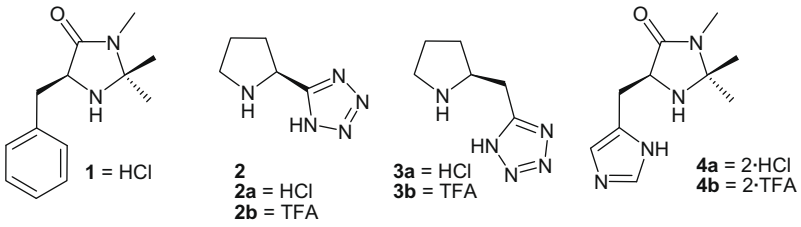
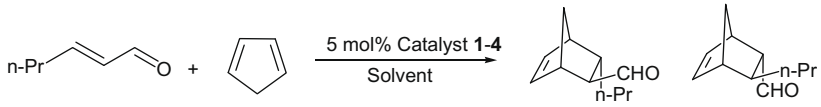


Figure 3. Molecular structures of the catalysts assessed (alphabetic characters label different salt-forms).

Table 1
Organocatalyzed [4+2] cycloaddition between *trans*-2-hexenal **5** and cyclopentadiene **6** to give cycloaddition products *exo*- and *endo*-**7** using catalysts **1**–**4** in various solvents

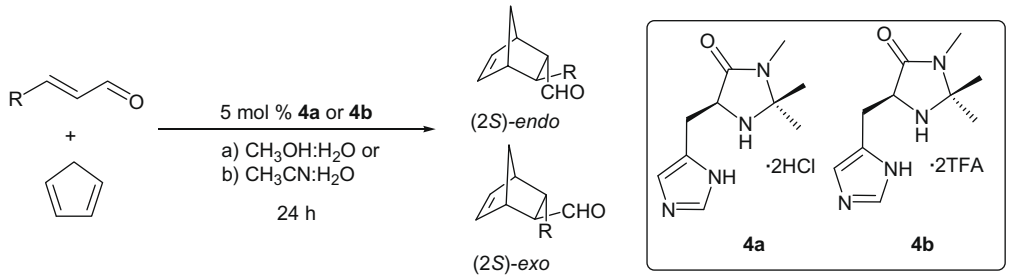


5 **6** (2*S*)-*exo*-**7** (2*S*)-*endo*-**7**

Entry	Solvent	HCl[g]	Time (h)	Catalyst	Conversion (%)	Yield[h] (%)	*exo*:*endo*[i]	ee[j] *exo*-**7** (%)	ee[j] *endo*-**7** (%)
1[a]	CH_3OH[d]	—	2	**1**	99	—	1.05:1	86	96
2[a]	CH_3CN[d]	—	2	**1**	69	—	1.1:1	79	96
3[b]	$CHCl_3$[f]	—	34	**2**	—	12	1.7:1	0	2
4[b]	DMF[f]	—	34	**2**	—	4	1.6:1	0	2
5[b]	THF[f]	—	34	**2**	—	4	1.7:1	0	5
6[a]	CH_3CN[d]	—	2	**2a**	68	—	1.9:1	36	36
7[a]	CH_3CN[d]	1	2	**2a**	65	—	1.9:1	19	10
8[b]	CH_3CN[e]	1	4	**2a**	—	59	1.7:1	19	8
9[a]	CH_3CN[d]	2	2	**2a**	98	—	1.7:1	17	10
10[a]	CH_3CN[d]	10	2	**2a**	89	—	1.7:1	9	8
11[a]	CH_3CN[d]	20	2	**2a**	99	—	3.3:1	3	4
12[a]	CH_3CN[d]	40	1	**2a**	99	—	3.6:1	3	0
13[a]	CH_3CN[d]	—	2	**2b**	94	—	1.9:1	43	41
14[c]	CH_3CN[e]	1	4	**3a**	—	42	3.6:1	3	0
15[a]	CH_3CN[d]	—	2	**3b**	54	—	1.7:1	17	9
16[a]	CH_3OH[d]	—	2	**4a**	85	—	1.2:1	56	76

[a] The reaction was performed by using *trans*-2-hexenal (0.61 mmol), cyclopentadiene (1.83 mmol) and catalyst (0.031 mmol).
[b] The reaction was performed with *trans*-2-hexenal (1.22 mmol), cyclopentadiene (3.66 mmol) and catalyst (0.061 mmol).
[c] The reaction was performed by using *trans*-2-hexenal (1.22 mmol), cyclopentadiene (2.44 mmol) and catalyst (0.061 mmol).
[d] 30.5 μL of the solution of solvent/H_2O 95/5.
[e] 61 μL of the solution of solvent/H_2O 95/5.
[f] 61 μL of the solvent without any water.
[g] Equivalents of HCl(37%) to catalyst.
[h] Isolated yield after column chromatography.
[i] The product ratios were determined by correlation of retention times in GC analysis to product mixtures obtained from the reaction with catalyst **1**.
[j] Absolute and relative configurations were determined by correlation of GC retention times. The absolute and relative configurations were initially determined by chemical correlation to known compounds.

Table 2
Organocatalyzed Diels–Alder cycloadditions between cyclopentadiene **6** and representative dienophiles utilizing catalysts **4**



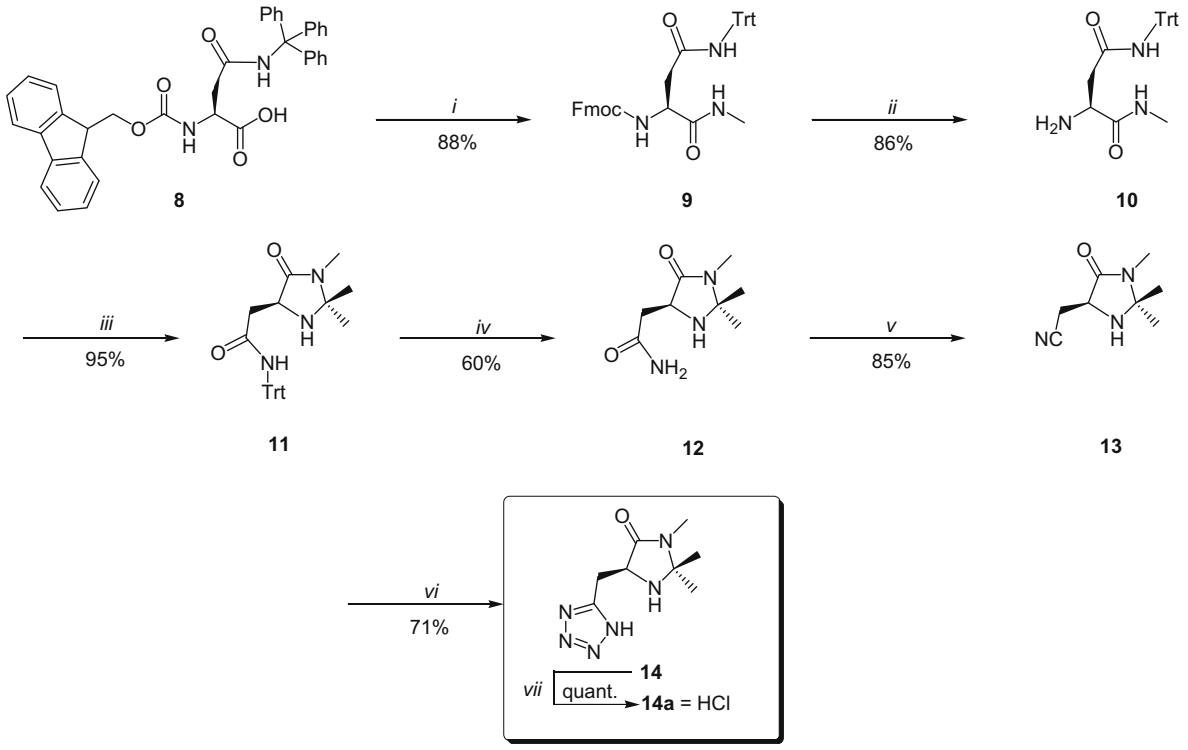
Entry[a]	R	Solvent[b]	Catalyst	Yield[c]	*exo*:*endo*[d]	*exo* ee[e] (%)	*endo* ee[e] (%)
1	Me	CH_3OH	**4a**	45	1.1:1	66 (2*S*)	57 (2*S*)
2	*n*-Pr	CH_3OH	**4a**	49	1.2:1	69 (2*S*)	58 (2*S*)
3	Ph	CH_3OH	**4a**	52	1.2:1	68 (2*S*)	60 (2*S*)
4	Me	CH_3CN	**4b**	72	1.25:1	89 (2*S*)	83 (2*S*)
5	*n*-Pr	CH_3CN	**4b**	61	1:1	72 (2*S*)	45 (2*S*)
6	Ph	CH_3CN	**4b**	75	1.1:1	84 (2*S*)	58 (2*S*)

[a] Reaction was performed at 23 °C.
[b] Each reaction was performed in 61 μL of a (95:5) MeOH/MeCN:H_2O mixture.
[c] Isolated yield after column chromatography.
[d] The product ratios were determined by correlation of GC retention times to product mixtures obtained from reaction with catalyst **1**.
[e] Absolute and relative configurations were determined by correlation of GC retention times. The absolute and relative configurations were initially determined by chemical correlation to known compounds.

3. Conclusion

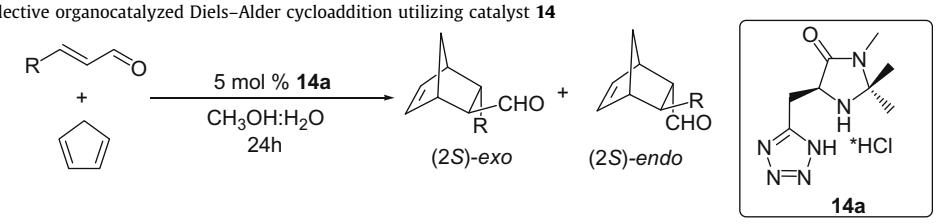
We have shown that the side-chain modification of catalyst **1** to include an imidazole function rather than a phenyl group, that is, yielding catalyst **4**, did not seriously affect the stereoselectivity of the Diels–Alder reaction. The catalyst originally designed for use in the asymmetric conjugate addition of nitroalkanes to enals can thus successfully be employed in the enantioselective organocatalytic Diels–Alder reaction as well.

In the second part of this study a highly potent and selective catalyst was developed for the enantioselective organocatalytic Diels–Alder reaction. The new catalyst possesses a functional tetrazole



Scheme 1. Reagents and conditions: (i) HOBT·H_2NMe, EDC, DMF, rt, 24 h (ii) 20% piperidine in DMF, rt (iii) acetone, *p*-TsOH, MeOH, reflux, 12 h; (iv) 100% TFA, reflux, 10 h; (v) cyanuric chloride, 4 Å MS, DMF, 100 °C, 24 h; (vi) NaN_3, NH_4Cl, DMF, 95 °C, 12 h; and (vii) 2 M HCl in MeOH, DEE, rt, 5 min.

Table 3
Results from the enantioselective organocatalyzed Diels–Alder cycloaddition utilizing catalyst **14**



Entry[a]	R	Yield[b]	*exo*:*endo*[c]	*exo* ee[d] (%)	*endo* ee[d] (%)
1	Me	86	1.3:1	90 (2*S*)	95 (2*S*)
2	*n*-Pr	83	1.5:1	85 (2*S*)	93 (2*S*)
3	*i*-Pr	92	1:1	92 (2*S*)	92 (2*S*)
4	Ph	89	1.5:1	89 (2*S*)	90 (2*S*)

[a] Reaction was performed at 23 °C.
[b] Isolated yield after column chromatography.
[c] The product ratios were determined by correlation of GC retention time to product mixtures obtained from the reaction with catalyst **1**.
[d] Absolute and relative configurations were determined by correlation of GC retention time. The absolute and relative configurations were initially determined by chemical correlation to known compounds.

motif combined with the organizational control imposed by the catalyst core. These favorable structural features should make the new catalyst **14** highly interesting for other enantioselective organocatalytic reactions.

4. Experimental

4.1. General

Chemicals and solvents were either purchased pure from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated 0.25 mm silica plates (Macherey-Nagel 60 Alugram® Sil G/UV254) were used and spots were visualized either with UV light, by heating after soaking the TLC plate in a solution consisting of 0.5% 2,4-dinitrophenylhydrazine in 2 M HCl, by a ninhydrine solution or by an ethanol solution of phosphomolybdic acid. Column chromatography was performed on silica gel (Matrex™ 60A, 37–0 μm) and preparative reversed phase chromatography was carried out using a MEGA BOND ELUT (Varian) SS-C18 Cartridge (1 g, 6 mL, 60 Å.). ^{1}H NMR 500 MHz and ^{1}H 300 MHz spectra were recorded on a Varian Unity 500 MHz and Varian Mercury plus 300 MHz spectrometer, respectively; ^{13}C NMR 75 MHz spectra were recorded on a Varian Mercury plus 300 MHz spectrometer. All spectra were acquired at ambient temperature. Chemical shifts (δ) in ppm are reported using residual chloroform, dimethylsulfoxide or methanol as an internal reference (^{1}H δ 7.26,

^{13}C δ 77.0), (^{1}H δ 2.49, ^{13}C δ 39.5) or (^{1}H δ 3.30, ^{13}C δ 49.0) and coupling constants (J) are given in hertz. Infrared spectra were recorded on a Perkin–Elmer Spectrum 100 FT/IR spectrometer. Optical rotation measurements were carried out using a Perkin–Elmer 241 spectropolarimeter. The purity of catalysts and intermediates was confirmed by means of a high pressure liquid chromatography (HPLC) system coupled to a MS detector and an evaporative light-scattering detector (ELSD); the system consisted of a Gilson 322 pump, Gilson 233 XL autosampler and a Gilson UV/VIS 152 detector, coupled in series with a Finnigan AQA mass spectrometer and an ELSD (Sedex 85 CC) from Sedere. GC–MS determination of enantiomeric excesses was done using a Varian CP-8410 auto injector and a Varian Saturn 2100T GC–MS system equipped with an Astec Chiraldex gamma-TA column (30 m * 0.25 mm), with helium gas at 10 psi as a carrier gas and electron impact ionization (EI, 70 eV). Chromatograms and retention times for all chiral products were comparable to those reported in Ref. 2a.

4.2. General procedure for catalytic asymmetric cycloaddition reactions

To a vial containing the catalyst (0.061 mmol) as a 1 M solution in CH_3OH/H_2O (95/5 v/v) or $MeCN/H_2O$ (95/5 v/v) were added the α,β-unsaturated aldehyde (1.22 mmol) and cyclopentadiene (302 μL; 3.66 mmol). After consumption of the limiting reagent, the reaction mixture was diluted with Et_2O and washed successively with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. When MeOH was used as solvent, the product was isolated as the dimethyl acetal, which was hydrolyzed by stirring the product mixture in $TFA/H_2O/CHCl_3$ (1:1:2) for 2 h at room temperature, followed by neutralization with satd aq $NaHCO_3$ and extraction with Et_2O. The resulting mixture was purified by silica gel chromatography and analyzed as described in the supporting information to Ref. 2a.

4.2.1. Synthesis of catalysts 1–4

These catalysts were prepared as described in the references provided for each catalyst in the main text above.

4.2.2. Synthesis of catalysts 14

4.2.2.1. Methyl-(2*S*)-(9*H*-fluoren-9-yl)-1-(methylamino)-1,4-dioxo-4-tritylamino-2-ylcarbamat 9. The material was prepared from commercially available N_α-(9-fluorenylmethoxycarbonyl)-N_γ-trityl-L-asparagine in analogy to a known literature procedure.[14]

4.2.2.2. Methyl-(2*S*)-2-amino-N^1-methyl-N^4-tritylsuccinamide 10. To the crystalline **9** (17.7 g; 29 mmol), obtained above, was added 100 mL of 20% piperidine in DMF. The resulting mixture was stirred at room temperature for 2 h after which the solution was concentrated under reduced pressure to give a yellow residue which was further purified by means of column chromatography (silica gel; 5% MeOH in DCM), R_f = 0.2, to give the product as a white powder (9.89 g; 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90 (s, 2H), 2.42 (d, J = 7 Hz, 2H), 2.58 (d, J = 4.6 Hz, 3H), 3.44 (t, J = 6.7 Hz, 1H), 7.17–7.21 (m, 9H), 7.24–7.30 (m, 6H), 7.82 (dd, J = 10.2, 4.6 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.5 (1C), 41.3 (1C), 52.0 (1C), 69.2 (1C), 126.3 (6C), 127.4 (6C), 128.5 (3C), 145.0 (3C), 170.1 (1C), 174.4 (1C); ESI-MS: m/z calcd for $C_{24}H_{25}N_3O_2$: 387; found 388 $[M+H]^+$, 775 $[2\,M+H]^+$; $[\alpha]_D^{23} = -1.1$ (c 1, MeOH).

4.2.2.3. (5*S*)-5-(*N*-Trimethylacetamide-5-yl)-2,2,3-trimethyl-imidazolidin-4-one 11. To a mixture of methyl-(2*S*)-2-amino-N^1-methyl-N^4-tritylsuccinamide **10** (4.48 g; 11.6 mmol) in 35 mL dry methanol were added acetone (7 mL; 5.5 g; 95 mmol) and p-TsOH (0.10 g; 0.59 mmol). The resulting mixture was stirred at reflux for 12 h after which the solution was allowed to reach room temperature. The solution was concentrated under reduced pressure to give a light yellow residue which was further purified by means of column chromatography (silica gel, 10% MeOH in DCM), R_f = 0.55, to give the product as a white powder (4.56 g; 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20 (d, J = 4.2 Hz, 6 H), 2.50 (d, J = 6.1 Hz, 2H), 2.70 (s, 3H), 3.12 (d, J = 9 Hz, 1H), 3.68 (m, 1H), 7.17–7.21 (m, 9H), 7.24–7.28 (m, 6H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.3 (1C), 25.6 (1C), 27.9 (1C), 49.5 (1C), 56.0 (1C), 70.3 (1C), 76.0 (1C), 127.3 (6C), 128.4 (6C), 129.4 (3C), 145.7 (3C), 170.5 (1C), 173.5 (1C); ESI-MS: m/z calcd for $C_{27}H_{29}N_3O_2$: 427; found 428 $[M+H]^+$, 450 $[M+Na]^+$, 775 $[2\,M+Na]^+$; $[\alpha]_D^{23} = -25.6$ (c 1, MeOH).

4.2.2.4. (5*S*)-5-(Acetamide-5-yl)-2,2,3-trimethyl-imidazolidin-4-one 12. To (5*S*)-5-(*N*-trimethylacetamide-5-yl)-2,2,3-trimethyl-imidazolidin-4-one **11** (2.25 g; 5.27 mmol) was added 40 ml TFA. The resulting yellow mixture was stirred at reflux for 10 h. The mixture was allowed to cool to room temperature after which TFA was removed under reduced pressure. The residue was further purified by means of column chromatography (silica gel, 20% MeOH in DCM), R_f = 0.23, to give the product as a colorless oil (0.56 g; 60%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20 (s, 3H), 1.26 (s, 3H), 2.15 (dd, J = 15.1, 9.0 Hz, 1H), 2.43 (dd, J = 15.1, 3.7 Hz, 1H), 2.64 (s, 3H), 3.02 (br s, 1H), 3.70 (d, J = 6.2 Hz, 1H), 6.80 (s, 1H), 7.40 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.2 (1C), 25.3 (1C), 27.9 (1C), 49.3 (1C), 55.7 (1C), 75.7 (1C), 173.0 (1C), 173.5 (1C); ESI-MS: m/z calcd for $C_8H_{15}N_3O_2$: 185; found 186 $[M+H]^+$; $[\alpha]_D^{23} = +11.6$ (c 2.85, MeOH).

4.2.2.5. (5*S*)-5-(Acetonitrile-5-yl)-2,2,3-trimethyl-imidazolidin-4-one 13. To a mixture of (5*S*)-5-(acetamide-5-yl)-2,2,3-trimethyl-imidazolidin-4-one **12** (1.5 g; 8.1 mmol) in 15 mL DMF was added approximately 2 g of 4 Å MS. The mixture was stirred for 10 min after which cyanuric chloride (2.3 g; 12.1 mmol) was added. The mixture was stirred for 1 h at room temperature after which the mixture was stirred at 100 °C for 12 h. The mixture was allowed to reach room temperature, and concentrated under reduced pressure to give a reddish oil. The crude product was purified by means of column chromatography (silica gel, 5% MeOH in DCM), R_f = 0.45, to give product as colorless oil (1.15 g; 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.67 (s, 3H), 1.73 (s, 3H), 2.86 (s, 3H), 3.11 (dd, J = 18, 5.9 Hz, 1H), 3.28 (dd, J = 18, 2.2 Hz, 1H), 4.85 (d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2 (1C), 22.5 (1C), 23.3 (1C), 24.7 (1C), 54.9 (1C), 81.5 (1C), 117.0 (1C), 164.3 (1C); ESI-MS: m/z calcd for $C_8H_{13}N_3O$: 167; found 168 $[M+H]^+$; $[\alpha]_D^{23} = +112.1$ (c 1.8, MeOH).

4.2.2.6. (5*S*)-5-((1*H*-Tetrazole-5-yl)methyl)-2,2,3-trimethyl-imidazolidin-4-one 14. To a mixture of (5*S*)-5-(acetonitrile-5-yl)-2,2,3-trimethyl-imidazolidin-4-one **13** (200 mg; 1.2 mmol) in 5 mL DMF were added sodium azide (95 mg; 1.3 mmol) and ammonium chloride (2.4 mmol; 0.13 g). The mixture was stirred at 95 °C for 10 h after which the mixture was allowed to cool down to room temperature. The solution was concentrated under reduced pressure to give a light-brown oil. Purification of this oil was performed using preparative reversed-phase chromatography on a SS-C18 cartridge (1 g, 6 mL, 60 Å) (gradient: 20–90% acetonitrile–water, with the product eluting at 80% acetonitrile), to provide after concentration a white crystalline mass. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.71 (s, 3H), 1.80 (s, 3H), 2.90 (s, 3H), 3.20 (dd, J = 16.5, 4.3 Hz, 1H), 3.40 (dd, J = 16.5, 2.4 Hz, 1H), 4.80 (d, J = 4.5 Hz, 1H), 9.20 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2 (1C), 22.5 (1C), 24.8 (1C), 33.9 (1C), 54.9 (1C), 81.5 (1C), 164.3 (1C). 177.8 (1C); ESI-MS: m/z calcd for $C_8H_{14}N_6O$: 210; found 211 $[M+H]^+$, $[\alpha]_D^{23} = -72.2$ (c 1.0, MeOH).

4.2.2.7. (5*S*)-5-((1*H*-Tetrazole-5-yl)methyl)-2,2,3-trimethyl-imidazolidin-4-one hydrochloric acid salt 14a. (5*S*)-5-((1*H*-Tetrazole-5-yl)methyl)-2,2,3-trimethyl-imidazolidin-4-one **14** (200 mg; 0.95 mmol) was converted to the corresponding hydrochloric acid salt by the addition of a solution of 2 M HCl in MeOH (1.9 mL; 3.8 mmol) followed by dry diethyl ether (10 mL). The homogeneous solution became turbid, and a precipitate formed. The heterogeneous solution was concentrated under reduced pressure to give the title compound as a white solid, which was directly dissolved in CH_3OH/H_2O (95/5 v/v) to provide the 1 M catalyst solution used in the reactions.

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