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Direct organocatalytic enantioselective α-aminomethylation of ketones

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Abstract—The scope and limitations of the direct organocatalytic asymmetric α-aminomethylation of ketones are disclosed. The proline-catalyzed classical Mannich reactions between unmodified ketones, aqueous formaldehyde and aromatic amines furnished the desired Mannich bases in high yield with up to >99% ee. Moreover, methyl alkyl ketones were regioselectively α-aminomethylated at the methylene carbon affording the corresponding Mannich products with up to >99% ee. In addition, the proline-catalyzed one-pot three-component reaction between *p*-anisidine, aqueous formaldehyde and 4,4-dimethyl-2-cycloxehen-1-one furnished the corresponding bicyclic aza-Diels–Alder adduct with >99% ee.

1. Introduction

The classical Mannich reaction,[1] in which an aminomethyl group is introduced in the α-position to a carbonyl compound, is an important transformation in organic chemistry.[2] The resulting Mannich bases are of particular interest due to their use as synthetic building blocks and precursors of pharmaceutically valuable γ-amino alcohols for different therapeutic areas.[2] However, there are only a few enantioselective α-aminomethylation reactions that have been developed and most of them are diastereoselective employing chiral auxiliaries or enantiomerically pure substrates.[3] For example, Enders and co-workers have developed excellent diastereoselective α-aminomethylation reactions.[4]

The initial stoichiometric and indirect stereoselective Mannich-type reactions utilize preformed chiral enol equivalents or imines.[5] Thus, the first successful example of catalytic asymmetric additions of preformed enolates to imines by Kobayashi and co-workers was an important advancement.[6] These results inspired the research and development of several catalytic indirect stereoselective Mannich reactions catalyzed by organometallic complexes.[7–9] Shibasaki and co-workers reported the first example of direct catalytic enantioselective Mannich-type reactions that were catalyzed by heterobimetallic complexes.[10] Recently, Shibasaki and Matsunaga,[11] and Trost and co-workers[12] developed di-nuclear zinc organometallic complexes as catalyst for the direct catalytic enantioselective Mannich-type reactions between hydroxyarylketones and preformed imines. In addition, Jørgensen and co-workers have developed elegant direct asymmetric Mannich reactions involving activated ketones as donors and chiral copper(II) bisoxazoline (BOX) complexes as catalysts.[13] The rapidly growing research in organocatalysis has also led to development of several amino acid catalyzed stereoselective reactions.[14] List reported the first one-pot three-component Mannich reaction between in situ generated imines and unmodified ketones as donors.[15] This initial report led to the development of several novel Mannich-type reactions by several groups that are catalyzed by amino acid derivatives.[16] More recently, we developed the first direct organocatalytic one-pot three-component Mannich reaction involving aldehydes as nucleophiles.[17] Moreover, Jacobsen,[18] Terada,[19] Akiyama[20] and Jørgensen[21] have reported excellent catalytic asymmetric Mannich-type reactions that are catalyzed by organocatalysts.

The first attempt to catalyze the one-pot three-component direct catalytic α-aminomethylation reaction of a ketone was reported by Shibasaki and co-workers.[10] In this reaction, the desired Mannich base was isolated in 16% yield and 64% ee. Inspired by this initial attempt and our interest in amino acid catalysis,[22] we most recently disclosed the first organocatalytic α-aminomethylation of ketones.[23] Herein, we present the scope and limitations of this one-pot three-component reaction, which also led to

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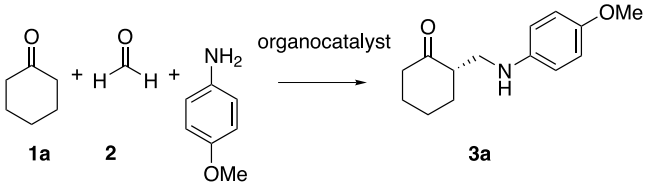
the discovery of the first one-pot three-component aza-Diels–Alder reaction.[24]

2. Results and discussion

The focus of our project was to develop a direct amino acid-catalyzed classical one-pot three-component Mannich reaction between aqueous formaldehyde, aromatic amines and ketones to furnish chiral Mannich bases in high yields and enantioselectivities. We initially investigated the proline-catalyzed reaction between cyclohexanone **1a**, aqueous formaldehyde **2** and *para*-anisidine that yields Mannich product **3a** as a model system (Eq. 1).



(1)

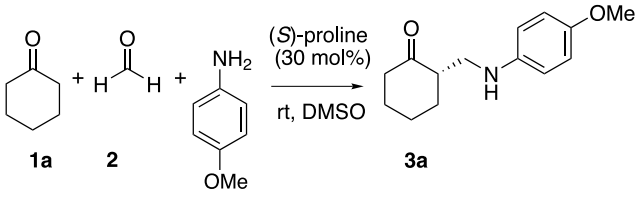
We conducted the reaction in different organic solvents and found that the highest enantioselectivity as well as efficiency was obtained in DMSO (Table 1).

In this solvent, *p*-methoxyphenyl (PMP) protected Mannich base **3a** is isolated in high yield with >99% ee. Increasing the equivalents of ketone **1a** from two to ten significantly increased the enantioselectivity as well as the rate of the reaction in DMF (Entry 5). Importantly, we found that the Mannich bases should be purified by neutral aluminium oxide column chromatography since they racemize upon silica-gel column chromatography.

In addition to proline, we also investigated other organo-catalysts ability to mediate the model reaction (Table 2).

All the investigated catalysts catalyzed the reaction and furnished the desired Mannich base **3a** in high yield. However, (*S*)-proline-catalyzed the reaction with the highest stereoselectivity under the set reaction conditions.

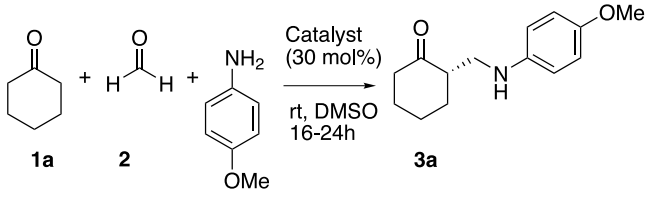
Table 1. Selected examples from the solvent screen[a]

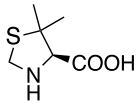
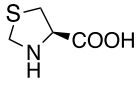
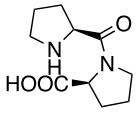
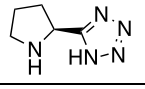


Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	DMSO	16	94	>99
3	NMP	33	87	77
4	DMF	33	80	87
5	DMF	14[d]	61[d]	98[d]
6	Acetonitrile	33	87	25

[a] Experimental conditions: a mixture of **1a** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.
[d] Ten equivalents ketone **1a** was used.

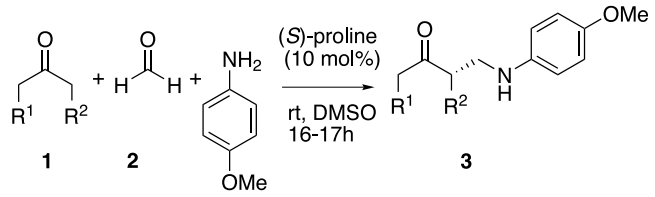
Table 2. Catalyst screened for the direct asymmetric α -hydroxymethylation of ketone **1a**[a]

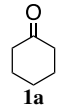
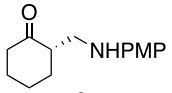
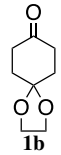
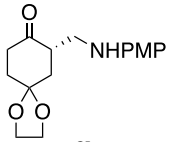
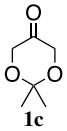
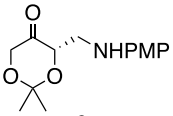
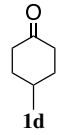
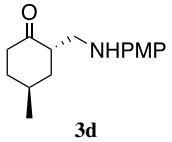
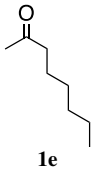
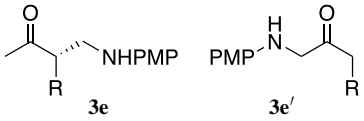
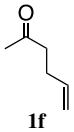
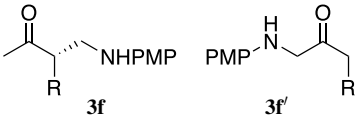
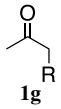
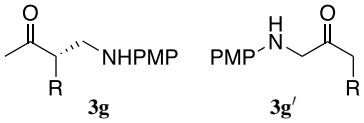
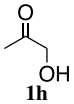
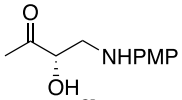


Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	(*S*)-proline	16	94	>99
3		33	71	<5
4		33	92	<5
5		33	62	<5
6		17	96	51

[a] Experimental conditions: a mixture of **1a** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and chiral organocatalyst was stirred at room temperature for 16–33 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.

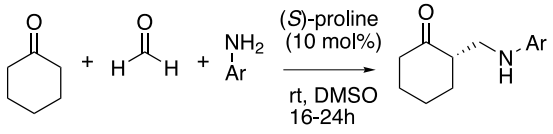
Table 3. Proline-catalyzed one-pot three-component direct α-aminomethylation fo different ketones[a]



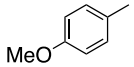
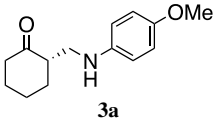
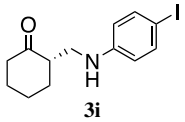
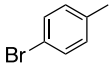
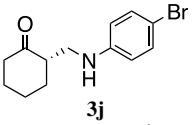
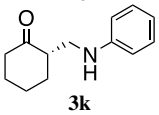
Entry	Ketone	Product	Yield (%)[b]	3/3′	ee (%) of 3[c]
1	 **1a**	 **3a**	90		>99
2	 **1b**	 **3b**	85		>99
3	 **1c**	 **3c**	84[d]		>99[d]
4	 **1d**	 **3d**	85[e]		>99[f]
5	 **1e**	 **3e** **3e′** R=*n*-pent	80	2:1	>99
6	 **1f**	 **3f** **3f′** R=$CH_2CH=CH_2$	94	4:1	84
7	 **1g**	 **3g** **3g′** R=*n*-hept	72	6:1	>99
8	 **1h**	 **3h**	60[d,g]		70[d,g]

[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16–17 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.
[d] Proline (30 mol%) was used.
[e] Trans/cis 3:1.
[f] ee of the trans-isomer.
[g] Purified by silica-gel column chromatography.

Table 4. Direct catalytic one-pot three-component α-aminomethylation reactions with different aromatic amines[a]



1a 2 3

Entry	Ar	Product	Yield (%)[b]	ee (%)[c]
1		 **3a**	90	>99
2		 **3i**	45	>99
3		 **3j**	71	>99
4		 **3k**	92	>99

[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), aniline (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16–24 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated combined yield after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.

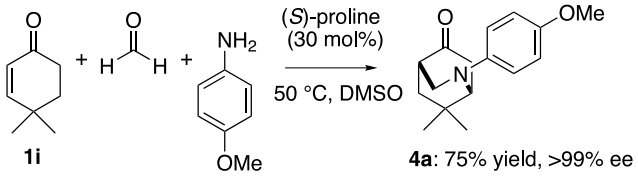
Based on these results and the practical aspects of employing proline catalysis we decided to investigate the proline-catalyzed one-pot three-component direct catalytic asymmetric Mannich reactions for a set of different aliphatic ketones (Table 3).

The reactions proceeded smoothly, and the corresponding Mannich bases **3a**–**3h** were isolated in high yield with up to >99% ee. For example, the proline-catalyzed α-aminomethylation of dihydroxyacetone phosphate mimic **1c** furnished aminosugar **3c** in 84% yield with >99% ee.[25] The reactions exhibited excellent chemoselectivity and no aldol adducts could be detected. Moreover, reactions with linear ketones were regioselective and the α-aminomethylation occurred predominantly at the methylene carbon atoms of the ketones. The amino acid-catalyzed one-pot three-component reaction was also extended to other aromatic amines than *p*-anisidine (Table 4).

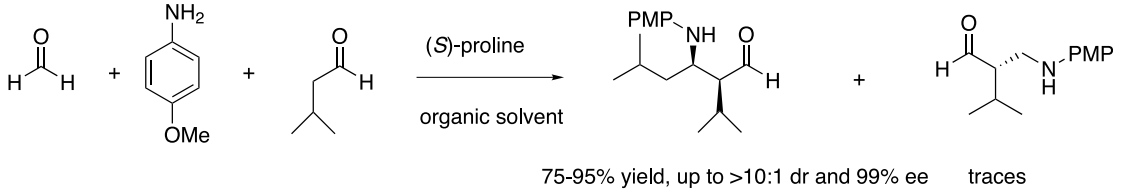
The proline-catalyzed reactions between substituted anilines, aqueous formaldehyde and cyclohexanone **1a** yielded the corresponding Mannich bases **3i**–**3k** in 45–92% yield with >99% ee, respectively. Thus, α-aminoarylated ketones can be synthesized in moderate to high yield with almost absolute stereocontrol.

We also investigated the proline-catalyzed direct asymmetric one-pot three-component α-aminomethylation of aldehydes (Scheme 1). However, under all the reaction conditions tested the self-Mannich adducts were formed with excellent stereoselectivity and only trace amounts of the desired product was detected. Thus, in this case, proline exhibited a high chemoselectivity for the formation of the self-Mannich adduct.

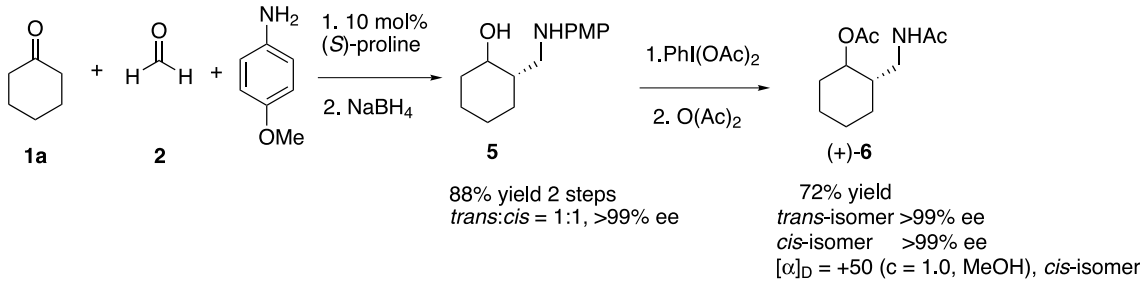
The high efficiency and stereoselectivity of the amino acid catalyzed direct catalytic asymmetric α-aminomethylation



Scheme 2. Proline-catalyzed one-pot three-component asymmetric aza-Diels–Alder reaction.



Scheme 1. Chemoselectivity in the proline-catalyzed asymmetric α-aminomethylation of aldehydes.

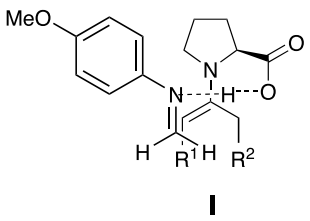


Scheme 3. Asymmetric synthesis of diacetylated *cis*-**6** and *trans*-**6**.

reactions of ketones inspired us to investigate the reactions between aqueous formaldehyde, *p*-anisidine and α,β-unsaturated cyclic ketones. The transformations constitute the first examples of direct catalytic asymmetric aza-Diels–Alder reactions.[24] For example, the proline-catalyzed aza-Diels–Alder reaction between *p*-anisidine, aqueous formaldehyde and 2-cyclohexenone **1h** furnished the aza-Diels–Alder product **4a** in 75% yield and >99% ee (Scheme 2).

The absolute configuration of the amino acid derived Mannich bases was determined by converting Mannich product **3a** into the known diacetylated amino alcohol **6** (Scheme 3). Thus, α-aminomethylated ketone **3a** was reduced with $NaBH_4$ in situ to the corresponding mono-protected amino alcohol **5**, which was isolated in 88% yield, over the two steps, with dr 1:1 (trans/cis) and >99%ee. Removal of the *p*-methoxyphenyl (PMP) group under oxidative conditions followed by acetylation afforded the *cis*- and *trans*-diacetylated amino alcohols **6** in 72% combined yield. The optical rotation of the cis-isomer and comparison with the literature revealed that the absolute configuration of the product was *cis*-(1*S*,2*S*)-**6** ($[\alpha]_d^{25}+50.2$ (*c* 1.0, MeOH), $[\alpha]_d^{25}+55.9$ (*c* 0.8, MeOH)[26]).

On the basis of the absolute configuration, we propose transition-state model **I** to account for the regio- and enantio-selectivity of the α-aminomethylation reaction of unmodified substituted ketones (Fig. 1). Hence, (*S*)-proline derivative forms an enamine with the ketone that is attacked by the imine from its *Si*-face providing (2*S*)-α-aminomethylated ketones. This is in accordance with the transition states of previously reported proline-catalyzed Mannich reactions, in which a *Si*-facial attack occurs.[15–17]



I

Figure 1. Transition state models evoked to account for the enantioselectivity of the (*S*)-proline-catalyzed reaction.

In summary, our catalytic enantioselective one-pot three-component α-aminomethylation of various ketones represents a direct approach for the construction of nearly enantiomerically pure Mannich bases in high yield. The reactions were simply performed without tedious elaboration in wet solvents and in the presence of air. In addition, other proline-derivatives including dipeptides catalyzed the reaction. The proline-catalyzed one-pot three-component α-aminomethylation of ketones opens up a new entry for the construction of pharmaceutically active Mannich bases.

3. Experimental

3.1. General

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2\cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concd H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard (δ 0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ 77.0 ppm) for ^{13}C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (λ=589 nm, 1 dm cell). High resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

3.2. Typical experimental procedure for the direct asymmetric α-aminomethylation of ketones

To a vial containing **2** (1 mmol, 36% aqueous solution), aniline (1.1 mmol) and a catalytic amount of (*S*)-proline (10 or 30 mol%) in DMSO (4 mL) was added the ketone **1** (2 mmol). After 20 h of vigorously stirring the reaction was quenched by addition of aqueous NH_4Cl and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by neutral aluminum oxide

column chromatography (EtOAc/pentane 1:10) to afford α-aminomethylated ketone **3**. The ee of the ketones was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD column, $\lambda=244$ nm, *v* 0.5 mL/min, hex/*i*-PrOH).

3.2.1. (2*S*)-(4-Methoxyphenylamino-methyl)-cyclohexanone 3a. Yellow solid (219 mg), 94% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, CH [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, CH [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, CHC=O), 3.05 (dd, $J=13.3$, 4.7 Hz, 1H, C*H*HN), 3.37 (dd, $J=13.3$, 7.8 Hz, 1H, CH*H*N), 3.74 (s, 3H, OCH_3), 6.59 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.3, 42.5, 45.6, 50.0, 56.1, 114.9, 115.2, 142.2, 152.6, 213.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 96:4, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=44.31$ min; minor isomer: $t_R=58.79$ min; $[\alpha]_D^{25}+4.6$ (*c* 2, $CHCl_3$); MALDI-TOF MS: 256.1008; $C_{14}H_{19}NO_2$ ($M+Na^+$: calcd 256.1313).

3.2.2. Compound (2*S*)-3b. 248 mg, 85% ^{1}H NMR (400 MHz, $CDCl_3$) white solid δ (ppm): 1.99 (m, 2H, CH_2 [Cy]), 2.08 (m, 2H, CH_2 [Cy]), 2.38 (m, 1H, CH [Cy]), 2.65 (m, 1H, CH [Cy]), 2.95 (m, CH, [Cy]), 3.10 (dd, $J=13.2$, 4.7 Hz, 1H, C*H*HN), 3.33 (dd, $J=13.2$, 7.3 Hz, 1H, CH*H*N), 3.73 (s, 3H, OCH_3), 4.00 (m, 4H, $2\times OCH_2$), 6.56 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 34.4, 38.4, 38.7, 44.8, 45.9, 55.7, 64.6, 107.2, 142.1, 152.2, 211.8; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=148.04$ min; minor isomer: $t_R=160.40$ min; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$).

3.2.3. Compound (2*S*)-3c. 223 mg, 84% ^{1}H NMR (400 MHz, $CDCl_3$) yellowish oil δ (ppm): 1.44 (s, 3H, Me), 1.96 (s, 3H, Me), 3.29 (m, 1H), 3.37 (m, 1H), 3.73 (s, 3H, OMe), 4.0 (d, $J=17.8$ Hz, 1H), 4.27 (d, $J=17.8$ Hz, 1H), 4.43 (m, 1H), 6.65 (d, $J=8.9$ Hz, 2H, ArH), 6.78 (d, $J=8.9$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.8, 24.2, 44.5, 55.8, 66.8, 73.4, 101.1, 115.0, 115.4, 141.7, 152.9, 208.9; (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=44.63$ min; minor isomer: $t_R=54.14$ min; $[\alpha]_D^{25}-129.3$ (*c* 2.5, $CHCl_3$).

3.2.4. Compound *trans*-(2*S*)-3d. (**3d**+**3d′**, 210.2 mg, 85%) yellow solid, major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.0 (d, $J=6.3$ Hz, 3H, $CHCH_3$), 1.29 (m, 1H, CH [Cy]), 1.71 (m, 2H, CH_2 [Cy]), 2.01 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.7 (m, 1H, CH [Cy]), 3.05 (m, H, C*H*HN), 3.35 (m, 1H, CH*H*N), 3.73 (s, 3H, OCH_3), 6.56 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.2, 31.7, 35.6, 40.2, 41.6, 45.0, 48.6, 55.7, 114.4, 114.9, 142.2, 152.1, 213.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 96:4, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=48.8$ min; minor isomer: $t_R=52.9$ min.

3.2.5. Compound 3e. Yellow oil 211 mg, 80% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.80 (m, 3H), 1.30 (m, 8H), 2.15 (s, 3H), 2.82 (m, 1H), 3.17 (dd, $J=12.8$, 4.7 Hz, 1H), 3.32 (dd, $J=12.8$, 8.6 Hz, 1H), 3.73 (s, 3H), 6.56 (d, $J=9.1$ Hz, 2H), 7.26 (d, $J=9.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.3, 42.5, 45.6, 50.0, 56.1, 114.9, 115.2, 142.2, 152.6, 213.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=25.40$ min; minor isomer: $t_R=26.98$ min; $[\alpha]_D^{25}+6.1$ (*c* 1.1, $CHCl_3$).

3.2.6. Compound 3f. Yellow oil, 219 mg, 94% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.16 (s, 3H, CH_3C=O), 2.27 (m, 1H, C*H*CH=CH_2), 2.47 (m, 1H, C*H*CH=CH_2), 3.93 (m, 1H, C*H*CH_2), 3.20 (dd, $J=12.8$, 4.8 Hz, 1H, C*H*HN), 3.35 (dd, $J=12.9$, 8.3 Hz, 1H, CH*H*N), 3.74 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2=CH), 5.75 (m, 1H, CH_2=C*H*), 6.57 (d, $J=8.9$ Hz, 2H, ArH), 6.77 (d, $J=8.9$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 30.1, 34.1, 45.8, 51.8, 56.0, 114.7, 115.2, 117.8, 135.0, 142.0, 152.7, 211.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=43.40$ min; minor isomer: $t_R=47.20$ min; $[\alpha]_D^{25}+3.6$ (*c* 2.5, $CHCl_3$).

3.2.7. Compound 3g. Yellow oil (220 mg, 72%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J=6.7$ Hz, 3H), 1.28 (m, 12H), 2.15 (s, 3H), 2.82 (m, 1H), 3.17 (dd, $J=12.8$, 4.6 Hz, 1H), 3.32 (dd, $J=12.9$, 8.6 Hz, 1H), 3.73 (s, 3H), 6.56 (d, $J=8.9$ Hz, 2H), 6.77 (d, $J=9.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 22.8, 27.5, 29.2, 29.8, 29.9, 32.0, 46.2, 52.6, 114.5, 115.1, 120.0, 142.2, 152.5, 212.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=41.50$ min; minor isomer: $t_R=43.10$ min; $[\alpha]_D^{25}+2.0$ (*c* 1.4, $CHCl_3$).

3.2.8. Compound 3h. Yellow oil (126 mg, 60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (s, 3H, CH_3), 3.76 (s, 3H, OMe), 4.56 (dd, $J=5.5$, 7.8 Hz, 1H, C*H*OH), 4.86 (d, $J=2.5$ Hz, 1H, CH_2NHAr), 5.04 (d, $J=2.5$ Hz, 1H, CH_2-NHAr), 6.60 (d, $J=9.0$ Hz, 2H), 6.85 (d, $J=9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.5, 50.6, 55.9, 83.7, 114.9, 115.8, 140.4, 153.6, 209.5; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 90:10, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=18.97$ min; minor isomer: $t_R=23.53$ min; $[\alpha]_D^{25}-9.4$ (*c* 1, $CHCl_3$).

3.2.9. Compound 3i. Yellow solid (148 mg, 45%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, C*H* [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.07 (dd, $J=13.3$, 4.5 Hz, 1H, CH_2NHAr), 3.37 (dd, $J=13.6$, 7.8 Hz, 1H, CH_2NHAr), 6.36 (d, $J=8.8$ Hz, 2H, Ar*H*), 7.39 (d, $J=8.8$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.2, 42.5, 44.0, 49.9, 115.4, 117.4, 138.0, 147.8, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=53.80$ min; minor isomer: $t_R=78.80$ min; $[\alpha]_D^{25}+2.2$ (*c* 1.1, $CHCl_3$).

3.2.10. Compound 3j. Yellow solid (200 mg, 71%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, CH [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.07 (dd, $J=13.3$, 4.5 Hz, 1H, CH_2NHAr), 3.37 (dd, $J=13.4$, 7.7 Hz, 1H, CH_2NHAr), 6.45 (d, $J=8.9$ Hz, 2H, Ar*H*), 7.21 (d, $J=8.9$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 27.9, 32.2, 42.4, 44.1,

45.0, 109.0, 114.7, 132.1, 147.3, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=45.22$ min; minor isomer: $t_R=63.04$ min; $[\alpha]_D^{25}-5.6$ (*c* 1.0, $CHCl_3$).

3.2.11. Compound 3k. Yellow solid (187 mg, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, C*H* [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.12 (dd, $J=13.5$, 4.7 Hz, 1H, CH_2NHAr), 3.44 (dd, $J=13.5$, 7.7 Hz, 1H, CH_2NHAr), 6.6 (d, $J=8.4$ Hz, 2H, Ar*H*), 6.70 (m, 1H, Ar*H*), 7.18 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.0, 27.9, 32.2, 42.4, 43.9, 49.9, 113.0, 117.4, 129.4, 148.2, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=35.86$ min; minor isomer: $t_R=30.95$ min; $[\alpha]_D^{25}+7.5$ (*c* 2.4, $CHCl_3$).

3.3. Typical experimental procedure for the direct catalytic aza-Diels–Alder reactions

To a vial containing aqueous formaldehyde (1 mmol, 36% aqueous solution), aniline (1.1 mmol) and a catalytic amount of (*S*)-proline (30 mol%) in DMSO (4 mL) was added the 4,4-dimethyl-2-cyclohexen-1-one **1h** (2 mmol). After 24–37 h of vigorously stirring at 50 °C the reaction was quenched by directly purifying the reaction mixture by silica-gel column chromatography (EtOAc/pentane-mixtures) to afford the desired aza-Diels–Alder products **4** (194.5 mg, 75%). Alternatively the reactions can also be quenched by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by neutral aluminum oxide column chromatography (EtOAc/pentane-mixtures) to furnish pure **4** as a yellow solid. The ee of the aza-Diels–alder products **4** were determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda=244$ nm, $v=0.5$ mL/min, Hex/IPA) or chiral-phase GC analyses.

3.3.1. Compound 4a. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 3H), 1.77 (d, $J=2.98$ Hz, 2H), 2.47 (dd, $J=18.7$, 3.4 Hz 1H), 2.62 (m, 1H), 2.68 (dd, $J=18.9$, 2.3 Hz 1H), 3.48 (d, $J=2.5$ Hz, 2H), 3.75 (m, 1H), 3.76 (s, 3H), 6.61 (d, $J=9.2$ Hz, 2H), 6.84 (d, $J=9.2$ Hz, 2H); ^{13}C NMR δ 28.8 (CH_3), 30.2 (CH_3), 36.1 (C), 38.9 (CH_2), 41.3 (CH), 46.0 (CH_2), 47.9 (CH_2), 56.1 (CH_3), 58.5 (CH), 112.1 (CH), 115.5 (CH_3), 141.1, 151.4, 214.0; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 1.2 mL/min, $\lambda=254$ nm): major isomer: $t_R=24.94$ min; minor isomer: $t_R=27.31$ min; $[\alpha]_D-71.8$ (*c* 1.7, $CHCl_3$); MALDI-TOF MS: 256.1689; $C_{16}H_{22}NO_2$ ($M+H^+$: calcd 261.1683). Mp 71–73 °C.

3.4. Experimental procedure for protective group removal and the preparation of *cis*-6

To the reaction mixture (Table 3, entry 1), 5 mL of MeOH was added, and then 10 equiv of $NaBH_4$ at 0 °C. After 15 min, 15 mL of brine was added, and the mixture extracted with EtOAc (2×25 mL). The organic phases were dried ($MgSO_4$), evaporated and, after purification by column chromatography, the corresponding reduced alcohols **5** (trans/cis 1:1) were obtained (82%, 193 mg). Subsequent acetylation for 2 h in CH_2Cl_2 (10 mL) using Ac_2O (10 equiv, 1 mL) and catalytic 4,4′-dimethylaminopyridine (DMAP), extraction with water, drying with $MgSO_4$ and evaporation of the organic phase, and purification by column chromatography afforded the cis-monoacetylated compound. This compound was dissolved in MeOH (2 mL) and added to and an oxidant solution of iodobenzene acetate (1.5 g, 4.5 mmol in 15 mL of MeOH) over 30 min, the reaction allowed to stir for an additional 30 min and then acidified with 1 N HCl (30 mL) and allowed to stir for 1.5 h. The reaction mixture was washed with CH_2Cl_2 (2×30 mL) and the combined organics were back extracted with 0.1 N HCl (20 mL). CH_2Cl_2 was added to the combined acidic aqueous layers with vigorous stirring to yield a biphasic system. The reaction was brought to pH ~ 10–11 with solid Na_2CO_3. After 1.5 h the two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL). The combined organics were dried with $MgSO_4$ and concentrated. The oil obtained was dissolved in CH_2Cl_2 (5 mL), and Ac_2O (1 mL) and catalytic DMAP were added. After 2 h, the reaction was extracted with water, the organic phase dried and evaporated, and then purified by column chromatography, obtaining the pure *cis*-2-aminocyclohexanol diacetylated with 40% yield (86 mg).

N,*O*-diacetylated-*cis*-(1*S*, 2*S*)-2-aminomethyl-1-cyclohexanol **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (m, 9H, 4×CH_2 and C*H*CH_2N), 1.97 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.95 (m, 1H, C*H*HNH), 3.53 (m, 1H, CH*H*NH), 4.58 (m, 1H, C*H*OOCH_3), 6.13 (br s, 1H, NH); $[\alpha]_D^{25}+50.2$ (*c* 1.0, MeOH).

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