Asymmetric Catalysis

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Direct Catalytic Enantioselective Aza-Diels–Alder Reactions**

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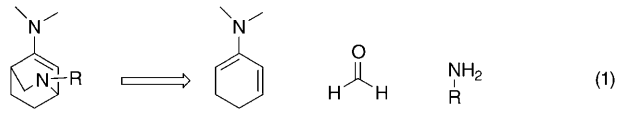
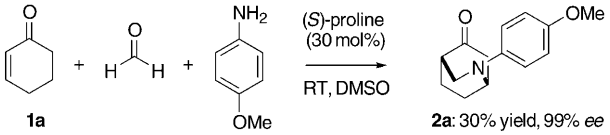
The synthesis of optically active nitrogen-containing compounds is a very important task in chemistry as they are key building blocks for the construction of valuable compounds such as amino acids, aza sugars, and alkaloids. The aza-Diels–Alder reaction is one of the most powerful C–C bond-forming reactions for the preparation of nitrogen-containing compounds such as piperidines and quinolidine derivatives,[1,2] and thus chemists have developed several diastereoselective aza-Diels–Alder reactions.[3,4] Despite the potential advantages of utilizing asymmetric catalysis, there are only a few examples of catalytic asymmetric indirect aza-Diels–Alder reactions between preformed imines and dienes or enolethers. For example, the research groups of Kobayashi and Jørgensen have successfully used chiral Lewis acid complexes as catalysts for these transformations.[5–7] However, there is to our knowledge no report of a direct catalytic enantioselective aza-Diels–Alder reaction. Organocatalysis is a rapidly growing research field and has been applied successfully to several different enantioselective reactions.[8] In particular, amino acid derivatives have been utilized as catalysts for enantioselective cycloadditions such as the Diels–Alder reaction.[9–13] This research and our interest in applying amino acids as catalysts in asymmetric synthesis[14] led to us becoming interested in whether an amino acid derivative would be able to mediate the classical aza-Diels–Alder reaction through a catalytic enamine mechanism. Retrosynthetic analyses suggested that an imine generated in situ would be able to react with a catalytically generated chiral diene and form an aza-Diels–Alder product [Eq. (1)].[15] Thus, we embarked on the quest to develop a one-pot three-component asymmetric aza-Diels–Alder reaction. Herein, we report the first direct catalytic enantioselective aza-Diels–Alder reaction that yields the corresponding products with excellent stereoselectivity.



(1)

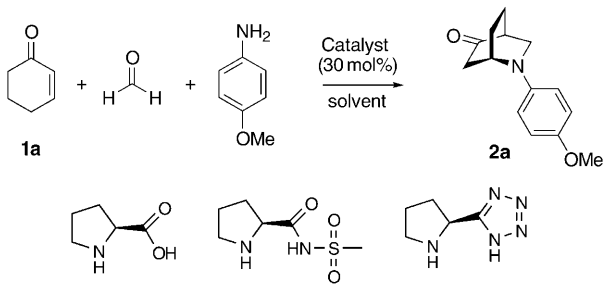
In an initial experiment, 2-cyclohexen-1-one (**1a**, 2 mmol), aqueous formaldehyde (1 mmol, 36 vol% aqueous solution), and *p*-anisidine (1.1 mmol) were mixed in the presence of a catalytic amount of (*S*)-proline (30 mol%). After vigorously stirring the mixture for 24 h, the reactions were quenched by extraction and the crude product purified by column chromatography on silica gel to furnish the desired aza-Diels–Alder product **2a** in 30% yield with excellent chemoselectivity and 99% *ee* [Eq. (2)]. Encouraged by this



(2)

experiment, we investigated different reaction conditions and the utilization of different proline derivatives as catalysts to increase the yield of the reaction (Table 1).

Table 1: Amine-catalyzed direct enantioselective aza-Diels–Alder reaction.[a]



Entry	Cat.	Solvent	*t* [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**3**	DMSO	24	RT	30	99
2	**3**	DMSO	24	50	52	99
3	**3**	DMSO	24	50	82[d]	99
4	**3**	DMSO	24	75	45	99
5	**4**	DMSO	48	RT	31	94
6	**5**	DMSO	24	RT	61	99
7	**3**	DMF	24	50	35	98
8	**3**	NMP	24	50	10	97
9	**3**	toluene	24	50	< 5	n.d.

[a] Experimental conditions: A mixture of **1a** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), aqueous formaldehyde (1 mmol), and catalyst (30 mol%) was stirred at the temperature and conditions displayed for 20–37 h. The crude product **2a** obtained after aqueous workup was purified by column chromatography. [b] Yield of the isolated pure products after column chromatography on silica gel. [c] Determined by chiral-phase HPLC analyses. [d] Yield of the corresponding alcohol (1:1 *cis*/*trans*) obtained by in situ reduction of **2a** with excess $NaBH_4$ after column chromatography on silica gel.

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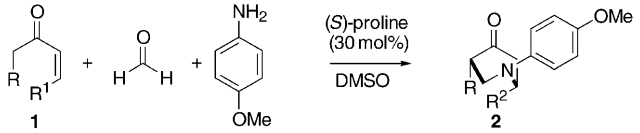
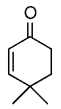
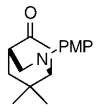
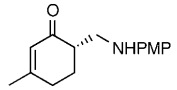
We found that the organocatalytic aza-Diels–Alder reaction was most efficient in DMSO and that the yield of **2a** could be increased from 30 to 52% by performing the reaction at 50°C without affecting the stereoselectivity of the reaction.[16] Furthermore, in situ reduction of **2a** with excess $NaBH_4$ furnished the corresponding bicyclic alcohol product in 82% yield and 99% *ee*. We also investigated the novel direct enantioselective aza-Diels–Alder reaction with amine catalysts **4** and **5**.[17,18] Both catalysts **4** and **5** were able to catalyze the direct three-component reaction with excellent regio- and enantioselectivity to furnish the corresponding aza-Diels–Alder adduct **2a** in 31 and 61% yields and 94 and 99% *ee*, respectively. Hence, of all the amino acid derivatives tested proline (**3**) and tetrazole **5** were the most efficient catalysts for the aza-Diels–Alder reaction. The amino acid derivatives also catalyzed the reaction in *N*-methylpyrrolidine (NMP) and DMF with high enantioselectivity.

We next investigated the one-pot three-component aza-Diels–Alder reaction for a set of different cyclic α,β-unsaturated ketones (Table 2). We found that α,β-unsaturated cyclohexenones and heptenones were excellent substrates for the direct catalytic enantioselective aza-Diels–Alder reactions with amino acids as the catalysts, and the corresponding bicyclic amines **2a**–**2c** protected with *p*-methoxyphenyl (PMP) groups were isolated in high yield with high *ee* values (up to >99% *ee*). For example, azabicyclooctanone **2b** was isolated in 72% yield with >99% *ee*. Thus, protected azabicycles can be assembled asymmetrically in one chemical manipulation from simple inexpensive readily available starting materials. Proline was the most efficient organic catalyst when unsaturated ketone **1c** was utilized as the donor and furnished the corresponding bicycle **2c** in high yield with 98% *ee*. Furthermore, the amino acid catalyzed aza-Diels–Alder reactions were operationally simple and performed in wet solvents. The proline-catalyzed one-pot three-component reaction with 3-substituted cyclohexanone **1d** only furnished the α,β-unsaturated Mannich adduct **2d** in 40% yield and 94% *ee* and not the aza-Diels–Alder product. The reaction with 2-cyclopentenone (**1e**) only furnished trace amounts of the desired aza-Diels–Alder adduct **2e**. Proline-catalyzed reactions between *trans*-4-phenyl-3-buten-2-one, formaldehyde, and *p*-anisidine did not provide any product under our reaction conditions. The PMP group of the aza-Diels–Alder adduct **2b** was removed with cerium ammonium nitrate (CAN) followed by treatment with $(Boc)_2O$

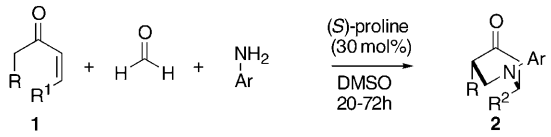
Table 2: Proline-catalyzed direct three-component enantioselective aza-Diels–Alder reaction.[a]

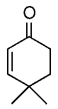
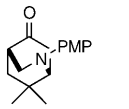
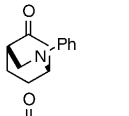
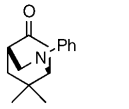
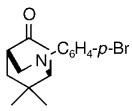
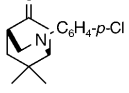


Entry	Ketone	Product		*t* [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1		**1a** 	**2a**	24	50	82[d]	99
2		**1b** 	**2b**	48	50	72	>99
3				17	RT	70	>99
4		**1c** 	**2c**	24	50	90[e]	98
5				24	RT	75	98
6				24	RT	20[f]	96[f]
7		**1d** 	**2d**	24	RT	40	94
8		**1e** 	**2e**	24	RT	10	n.d.[g]

[a] Experimental conditions: A mixture of **1** (2 mmol, 2 equiv), aniline (1.1 mmol), aqueous formaldehyde (1 mmol), and (*S*)-proline (30 mol%) was stirred at the temperature and conditions displayed for 20–72 h. The crude product **2** obtained after aqueous workup was purified by column chromatography. [b] Yield of the isolated pure products after column chromatography on silica gel. [c] Determined by chiral-phase HPLC analyses. [d] Yield of the corresponding alcohol (1:1 *cis*/*trans*) obtained by in situ reduction of **2a** with excess $NaBH_4$ after column chromatography on silica gel. [e] Combined yield of **2c** and the minor amount of the *retro*-Michael adduct, which was formed upon column chromatography. [f] Reaction performed with catalyst **5**. [g] Not determined.

Table 3: Proline-catalyzed direct three-component enantioselective aza-Diels–Alder reaction with different anilines.[a]



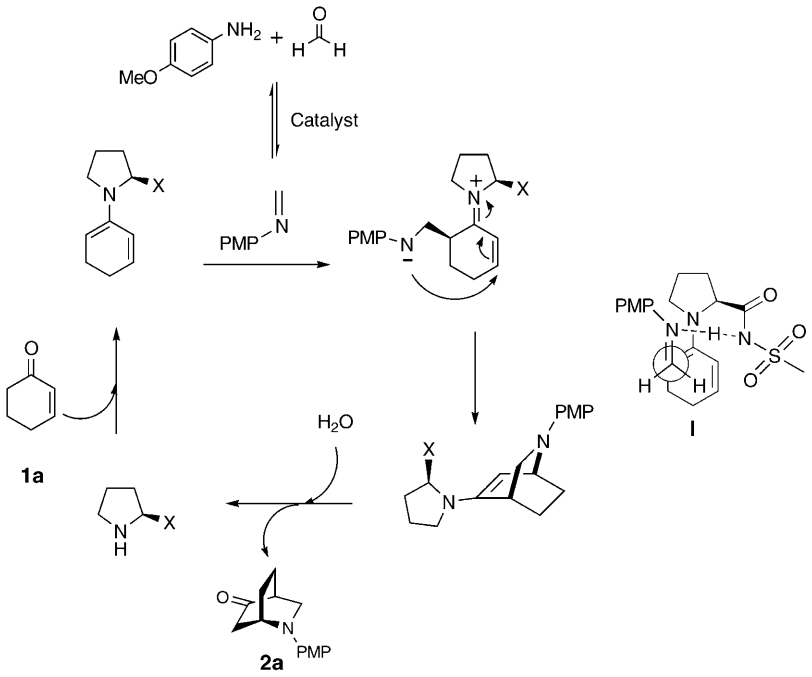
Entry	Ketone	Ar	Product		*T* [°C]	Yield [%][b]	*ee* [%][c]
1	 **1b**	PMP		**2b**	RT	70	>99
2	**1a**	Ph		**2f**	RT	54	>96
3	**1b**	Ph		**2g**	RT	69	98
4	**1b**	4-BrC_6H_4		**2h**	RT	20	>99
5	**1b**	4-ClC_6H_4		**2i**	RT	32	>99

[a] Experimental conditions: A mixture of **1** (2 mmol, 2 equiv), aniline (1.1 mmol), aqueous formaldehyde (1 mmol), and (*S*)-proline (30 mol%) was stirred at the temperature and conditions displayed for 20–72 h. The crude product **2** obtained after aqueous work-up was purified by column chromatography. [b] Yield of the isolated pure products after column chromatography on silica gel. [c] Determined by chiral-phase HPLC analyses.

(Boc = *tert*-butoxycarbonyl) to furnish the desired Boc-protected azabicycle.

We next investigated the effect of the amine component on the reaction catalyzed by an amino acid (Table 3). The reaction advanced with excellent chemo-, regio-, and stereoselectivity to yield the corresponding bicycles **2b** and **2f–2i** with up to >99% *ee*. In particular, the hetero-Diels–Alder reactions with anilines having an electron-donating substituent at the *para* position furnished the corresponding aza-Diels–Alder products with excellent stereocontrol. The yields of the products derived from the aza-Diels–Alder reactions with *p*-chloro- and *p*-bromoanilines were moderate in comparison to the reactions with aniline and *p*-anisidine.

The stereochemical outcome of the reaction was determined by X-ray structure analysis of **2b** (Figure 1), which revealed that bicycle (1*R*,4*S*)-**2b** was assembled asymmetrically when amino acid derivatives **3**, **4**, and **5** were used as catalysts.



Scheme 1. The plausible reaction pathway and transition state.

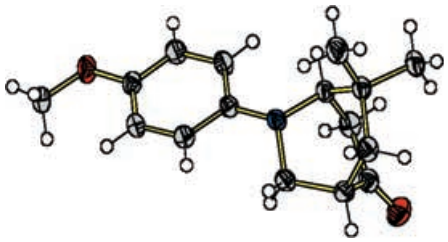
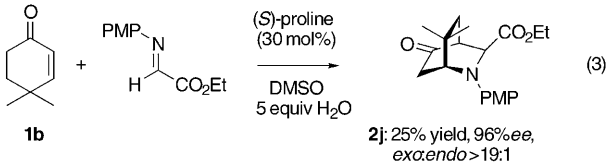


Figure 1. Structure of aza-Diels–Alder product **2b** (ORTEP picture).

On the basis of the absolute stereochemistry of the aza-Diels–Alder adducts and the isolation of Mannich adduct **2d**,[19] we propose the following reaction mechanism to account for the stereochemical outcome of the reaction (Scheme 1). The first step is that the proline-derived catalyst forms a chiral enamine with the α,β-unsaturated ketone **1**. Next, the in situ generated imine attacks the *si* face of the chiral diene via transition state **I**, and an activated iminium salt is formed. The secondary amine of the chiral iminium salt performs a subsequent selective 6-*endo-trig* cyclization to furnish the corresponding chiral azabicycle. Next, the amino acid derivative is released and the desired aza-Diels–Alder adduct **2** is obtained by hydrolysis and the catalytic cycle can be repeated. Thus, the reaction proceeds through a tandem one-pot three-component Mannich/Michael reaction pathway. The stepwise mechanism was further supported by the fact that in the aza-Diels–Alder reactions with *p*-chloroaniline and *p*-bromoaniline, minor amounts of the corresponding α,β-unsaturated Mannich bases were formed in addition to products **2h** and **2i**. This result is in accordance with the lower nucleophilicity of the secondary amine intermediate in the Michael step as compared to *p*-anisidine. Furthermore, the proline-catalyzed reaction with the substituted ketone **1d** failed to ring-close and provided the α,β-unsaturated Mannich base **2d** with excellent enantioselectivity.[16] Attempts to perform 6-*endo-trig* cyclizations of the unsaturated Mannich bases failed under our reaction conditions.

The proline derivatives also catalyzed the direct enantioselective aza-Diels–Alder reaction with preformed imines. For example, proline catalyzed the aza-Diels–Alder reaction between ketone **1b** and ethyl *N*-PMP-α-imino glyoxylate in wet DMSO, and the corresponding synthetically valuable bicyclic amino acid derivative **2j** was isolated exclusively as the *exo* adduct in moderate yield with 96% *ee* [Eq. (3)].



In summary, we have reported the first one-pot three-component direct catalytic enantioselective aza-Diels–Alder reaction. The reaction is catalyzed by proline and its derivatives with excellent chemo-, regio-, and stereoselectivity. For example, the amino acid catalyzed asymmetric aza-Diels–Alder reactions between aqueous formaldehyde, α,β-unsaturated cyclic ketones, and aromatic amines furnished the desired azabicyclic ketones with up to >99% *ee*. The reactions are operationally simple, performed in wet solvents, and environmentally friendly. Moreover, the reaction can be applied for the synthesis of protected azabicyclic amino acids with excellent *exo* and enantioselectivity. Further elaboration of this transformation and its synthetic application is ongoing.

Experimental Section

Typical experimental procedure (Table 2, entry 2): Ketone **1b** (2 mmol) was added to a vial containing aqueous formaldehyde (1 mmol, 36% aqueous solution), *p*-anisidine (1.1 mmol), and a catalytic amount of (*S*)-proline (30 mol%) in DMSO (4 mL). After vigorously stirring the mixture for 24 h at 50 °C, the reaction was quenched by purifying the reaction mixture by column chromatography on silica gel (EtOAc/pentane 1:5) to afford **2b** in 72% yield as a slightly yellow solid. The *ee* value of **2b** was >99% as determined by HPLC analysis on a chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (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), 6.61–6.63 (m, 2H), 6.84–6.86 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.8$, 30.2, 36.1, 38.9, 41.3, 46.0, 47.9, 56.1, 58.5, 112.1, 115.54, 141.1, 151.4, 214.0 ppm; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH 99:1, flow rate 1.2 mL min^{-1}, $\lambda = 254$ 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.

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[19] CCDC-265109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

