Asymmetric Catalysis

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Organocatalytic Asymmetric Inverse-Electron-Demand Aza-Diels–Alder Reaction of *N*-Sulfonyl-1-aza-1,3-butadienes and Aldehydes

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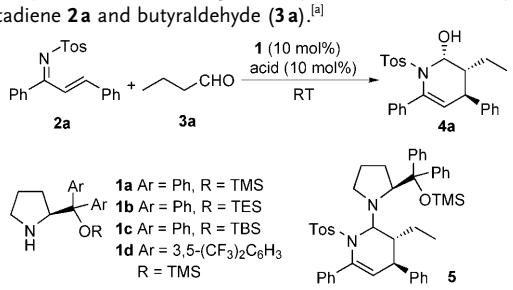
The development of efficient procedures to access optically pure piperidines has provoked continuing interest, as such compounds have been used widely in the construction of natural products and pharmaceutical compounds.[1] The stereoselective aza-Diels–Alder reaction (ADAR) is one of the most convergent strategies for the synthesis of chiral piperidine derivatives. As a complementary alterative to the well-established formal cycloaddition of dienes and imines catalyzed by metal complexes or organic molecules,[2,3] Boger and co-workers introduced inverse-electron-demand aza-Diels–Alder reactions of *N*-sulfonyl-1-aza-1,3-butadienes and electron-rich alkenes.[4] These reactions generally exhibited high regiospecificity and diastereoselectivity with the characteristics of a concerted [4+2] cycloaddition mechanism. Although the utility of these reactions has been explored fruitfully over the past two decades, quite limited progress has been made in catalytic asymmetric variants.[5] Recently, Bode and co-workers developed an asymmetric ADAR of *N*-sulfonyl α,β-unsaturated aldimines and β-activated enals with a chiral N-heterocarbene catalyst,[6] and later Carretero and co-workers reported a Lewis acid catalyzed ADAR of *N*-(heteroaryl)sulfonyl α,β-unsaturated ketimines with vinyl ethers.[7]

In 2003, Juhl and Jørgensen reported an inverse-electron-demand hetero-Diels–Alder reaction of aldehydes and β,γ-unsaturated α-ketoesters catalyzed by a chiral secondary amine.[8a] The chiral enamine generated in situ as an electron-rich alkene is crucial for the success of the reaction.[8] Encouraged by these elegant achievements, we envisaged that an unprecedented asymmetric ADAR of *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes might be developed by employing a similar strategy.

We initially investigated the reaction of the *N*-tosyl imine of chalcone, **2a**, with butyraldehyde (**3a**) in the presence of the readily available α,α-diphenylprolinol trimethylsilyl ether **1a** (10 mol%) and benzoic acid (10 mol%) in toluene.[9,10] The ADAR product **4a** was obtained in less than 10% yield at ambient temperature after 72 h (Table 1, entry 1). Subsequently, it was found that the adduct **5** was formed as a rather stable compound in the reaction.[8a] Similar phenomena were observed in THF or MeOH (Table 1, entries 2 and 3). The conversion was improved in acetonitrile: The expected hemiaminal **4a** was formed with excellent stereoselectivity and isolated as a fairly stable compound in moderate yield (Table 1, entry 4; d.r. > 99:1, 96% *ee*). Moreover, we found that the addition of water led to a dramatic acceleration of the reaction (Table 1, entry 5); better results were observed when a 10:1 mixture of CH_3CN and H_2O was used (Table 1, entry 6).[11] Apparently, water is helpful for the hydrolysis of intermediate **5** to release the catalyst **1a** and thus enable catalytic turnover. The acid additive has a great effect on the reaction; almost no reaction occurred when the stronger *p*-toluenesulfonic acid (*p*-TSA) was used in place of benzoic acid (Table 1, entry 7). The enantioselectivity could be

Table 1: Optimization of the organocatalytic ADAR of the *N*-tosyl-1-aza-1,3-butadiene **2a** and butyraldehyde (**3a**).[a]



Entry	1	Acid	Solvent	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	BzOH	toluene	< 10	n.d.[e]
2[d]	**1a**	BzOH	THF	< 10	n.d.
3[d]	**1a**	BzOH	MeOH	< 10	n.d.
4[d]	**1a**	BzOH	MeCN	66	96
5[f]	**1a**	BzOH	$MeCN/H_2O$	69	92
6	**1a**	BzOH	$MeCN/H_2O$	89	95
7	**1a**	*p*-TSA	$MeCN/H_2O$	< 10	n.d.
8	**1a**	AcOH	$MeCN/H_2O$	88	97
9[d]	**1a**	AcOH	$MeOH/H_2O$	88	95
10[d]	**1a**	AcOH	THF/H_2O	63	96
11	**1a**	AcOH	$dioxane/H_2O$	86	92
12	**1b**	AcOH	$MeCN/H_2O$	60	94
13	**1c**	AcOH	$MeCN/H_2O$	49	95
14	**1d**	AcOH	$MeCN/H_2O$	< 10	n.d.

[a] Reaction conditions (unless otherwise noted): **2a** (0.1 mmol), **3a** (0.2 mmol), **1** (0.01 mmol), acid (0.01 mmol), organic solvent/H_2O (1.1 mL, 10:1), room temperature, 24 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC on a chiral phase; d.r. > 99:1. [d] Reaction time: 72 h. [e] Not determined. [f] The reaction was carried out in CH_3CN/H_2O (5:1). Bz = benzoyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

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improved slightly by adding acetic acid (Table 1, entry 8). Inferior results were obtained with other organic solvent/H_2O mixtures (Table 1, entries 9–11). The bulkier silyl ethers **1b** and **1c** gave similar enantioselectivity but with lower catalytic activity (Table 1, entries 12 and 13); the secondary amine **1d** with strong electron-withdrawing substituents on the aryl rings failed to catalyze the model reaction (Table 1, entry 14).

Having established optimal reaction conditions, we explored the scope of this ADAR. Thus, *N*-sulfonyl-1-aza-1,3-butadienes **2** were treated with aldehydes **3** in the presence of **1a** (10 mol%) and AcOH (10 mol%) in a mixture of CH_3CN and H_2O (10:1) at room temperature. Hemiaminals **4** with excellent diastereomeric ratios (d.r. > 99:1) were isolated directly and were stable enough for analysis by various methods. For the reactions with butyraldehyde, a wide range of substituents could be present at the β position of the *N*-tosyl α,β-unsaturated ketimine **2**. A variety of aryl or heteroaryl groups at this position of the C=C bond had a limited effect on the enantioselectivity of the reaction, and excellent *ee* values were observed (Table 2, entries 1–8). Good results were also attained with an α,β-unsaturated ketimine with a β-alkyl group (Table 2, entry 9). A β-activated ketimine, with an ester substituent in the β position, exhibited higher reactivity, and excellent enantioselectivity was also observed (Table 2, entry 10).

The substituent on the C=N bond was also varied. Outstanding enantioselectivities were observed for substrates with electron-donating or electron-withdrawing aryl groups at this position (Table 2, entries 11–15). The ketimine derived from dibenzylideneacetone was a good substrate, and thus another functionality could be introduced into the product (Table 2, entry 16). However, an alkyl-substituted ketimine showed no reactivity toward butyraldehyde (Table 2, entry 17), and an α,β-unsaturated aldimine underwent decomposition (Table 2, entry 18).

Other linear aliphatic aldehydes could be applied smoothly as substrates in the ADAR reaction (Table 2, entries 19 and 20); however, the attempted reaction of branched isovaleraldehyde with 1-aza-1,3-butadiene **2a** failed, probably because of steric reasons (Table 2, entry 21). The use of aqueous acetaldehyde was also unsuccessful under the current catalytic conditions (Table 2, entry 22).[13] When this catalytic ADAR was conducted on a

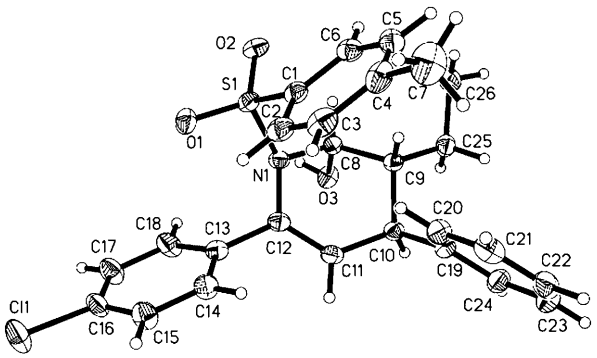
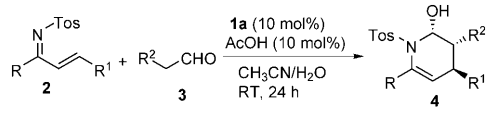


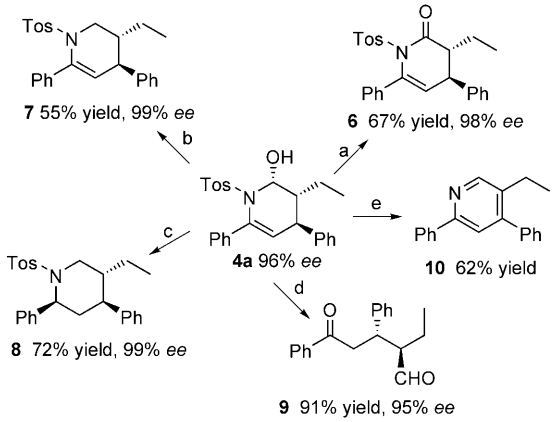
Figure 1. X-ray crystal structure of the enantiomerically pure hemiaminal **4l**.

Table 2: Asymmetric ADAR of *N*-tosyl-1-aza-1,3-butadienes **2** and aldehydes **3**.[a]



Entry	R	R^1	R^2	4	Yield[b] [%]	*ee*[c] [%]
1	Ph	Ph	Et	**4a**	88	97
2	Ph	*p*-ClC_6H_4	Et	**4b**	85	98
3	Ph	*m*-ClC_6H_4	Et	**4c**	92	99
4	Ph	*m*-$MeOC_6H_4$	Et	**4d**	81	95
5	Ph	*p*-MeC_6H_4	Et	**4e**	78	96
6[d]	Ph	1-Np	Et	**4f**	40	99
7[e]	Ph	2-furyl	Et	**4g**	83	98
8[e]	Ph	2-thienyl	Et	**4h**	87	98
9	Ph	Me	Et	**4i**	83	93
10[f]	Ph	COOEt	Et	**4j**	95	99
11	*p*-MeC_6H_4	Ph	Et	**4k**	85	99
12	*p*-ClC_6H_4	Ph	Et	**4l**	82	98[g]
13	*o*-ClC_6H_4	Ph	Et	**4m**	74	99
14	*m*-BrC_6H_4	Ph	Et	**4n**	86	99
15[e]	1-Np	Ph	Et	**4o**	83	94
16[d]	PhCH=CH	Ph	Et	**4p**	91	99
17	Me	Ph	Et	–	–	–
18	H	Ph	Et	–	–	–
19	Ph	Ph	Me	**4q**	92	98
20[d]	Ph	Ph	$BnO(CH_2)_2$	**4r**	72	99
21	Ph	Ph	*i*Pr	–	–	–
22	Ph	Ph	H	–	–	–
23[h]	Ph	Ph	Et	**4a**	82	96

[a] Reaction conditions (unless otherwise noted): **2** (0.1 mmol), **3** (0.2 mmol), **1a** (10 mol%), AcOH (10 mol%), CH_3CN/H_2O (1.1 mL, 10:1), room temperature, 24 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC on a chiral phase; d.r. > 99:1. [d] Reaction time: 72 h. [e] Reaction time: 48 h. [f] Reaction time: 12 h. [g] The absolute configuration of **4l** was determined by X-ray crystal-structure analysis (Figure 1).[12] The absolute configuration of the other products was assigned by analogy. [h] The reaction was carried out on a 1.0 mmol scale with a reaction time of 48 h. Bn = benzyl, Np = naphthyl.



Scheme 1. Synthetic transformations of the chiral hemiaminal **4a**: a) PCC, 40°C, 6 h; b) Et_3SiH, $BF_3{\cdot}Et_2O$, −78°C, 4 h; c) Et_3SiH, $BF_3{\cdot}Et_2O$, room temperature, 12 h; d) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2, 0°C, 8 h; e) MnO_2, $CHCl_3$, room temperature, 12 h. PCC = pyridinium chlorochromate.

larger scale, similar good results were observed (Table 2, entry 23).

The chiral hemiaminal **4a** could be converted smoothly into a number of valuable compounds (Scheme 1). Upon oxidation with PCC (pyridinium chlorochromate), lactam **6** was produced without any racemization. The hydroxy group of **4a** was removed chemoselectively to give tetrahydropyridine **7** by reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ at −78 °C, whereas the enamide functionality was also reduced to afford piperidine **8** with excellent diastereoselectivity when the **4a** was treated with these reagents at ambient temperature. Hemiaminal **4a** could also be hydrolyzed to the enantiomerically enriched *anti* 1,5-dicarbonyl compound **9**. Since no direct asymmetric intermolecular Michael addition of aliphatic aldehydes to chalcones has been developed,[14] this method might serve as an alternative approach to this type of chiral building block. Finally, hemiaminal **4a** was oxidized efficiently to the trisubstituted pyridine **10**.

In conclusion, we have presented a highly stereoselective inverse-electron-demand aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes that proceeds under aminocatalysis with a chiral secondary amine. Excellent enantioselectivities (up to 99% *ee*) were observed for a broad spectrum of substrates under mild conditions. Moreover, a variety of chiral piperidine derivatives and other useful compounds could be prepared readily from the hemiaminal adducts. We are currently investigating the catalytic mechanism of the reaction[14] and the development of new asymmetric reactions catalyzed by chiral amines.

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[12] CCDC 701465 (**41**) and 701466 (**6**) contain the supplemetary 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.

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[15] As suggested by Juhl and Jørgensen for a related system,[8a] the catalyst may induce the ketimine to approach the aldehyde in an *endo*-selective manner to afford the observed chiral hemiaminal **4**. However, at present a formal Michael addition followed by a ring-closure process cannot be ruled out (see reference [8c]).

