

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 alternative 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 regioselectivity 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 CH₃CN and H₂O 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 ₂ O	69	92
6	1a	BzOH	MeCN/H ₂ O	89	95
7	1a	<i>p</i> -TSA	MeCN/H ₂ O	< 10	n.d.
8	1a	AcOH	MeCN/H ₂ O	88	97
9 ^[d]	1a	AcOH	MeOH/H ₂ O	88	95
10 ^[d]	1a	AcOH	THF/H ₂ O	63	96
11	1a	AcOH	dioxane/H ₂ O	86	92
12	1b	AcOH	MeCN/H ₂ O	60	94
13	1c	AcOH	MeCN/H ₂ O	49	95
14	1d	AcOH	MeCN/H ₂ O	< 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/H₂O (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 CH₃CN/H₂O (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/H₂O 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 CH₃CN and H₂O (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

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] [%]	<i>ee</i> ^[c] [%]
1	Ph	Ph	Et	4a	88	97
2	Ph	<i>p</i> -ClC ₆ H ₄	Et	4b	85	98
3	Ph	<i>m</i> -ClC ₆ H ₄	Et	4c	92	99
4	Ph	<i>m</i> -MeOC ₆ H ₄	Et	4d	81	95
5	Ph	<i>p</i> -MeC ₆ H 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	<i>p</i> -MeC ₆ H ₄	Ph	Et	4k	85	99
12	<i>p</i> -ClC ₆ H ₄	Ph	Et	4l	82	98 ^[g]
13	<i>o</i> -ClC ₆ H ₄	Ph	Et	4m	74	99
14	<i>m</i> -BrC ₆ H 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>i</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%), CH₃CN/H₂O (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.

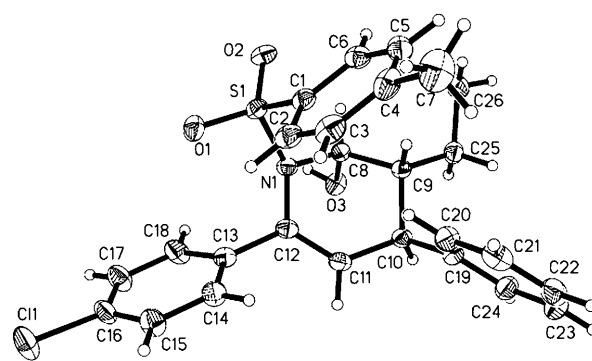
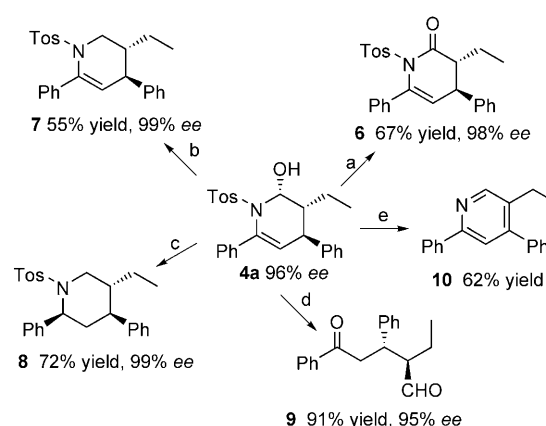


Figure 1. X-ray crystal structure of the enantiomerically pure hemiaminal **4l**.

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



Scheme 1. Synthetic transformations of the chiral hemiaminal **4a**: a) PCC, 40 °C, 6 h; b) Et₃SiH, BF₃·Et₂O, −78 °C, 4 h; c) Et₃SiH, BF₃·Et₂O, room temperature, 12 h; d) FeCl₃·6H₂O, CH₂Cl₂, 0 °C, 8 h; e) MnO₂, CHCl₃, 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 $\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{Et}_2\text{O}$ 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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