Hybrid Diamines Derived from 1,1′-Binaphthyl-2,2′-diamine and α-Amino Acids as Organocatalysts for 1,3-Dipolar Cycloaddition of Aromatic Nitrones to (*E*)-Crotonaldehyde

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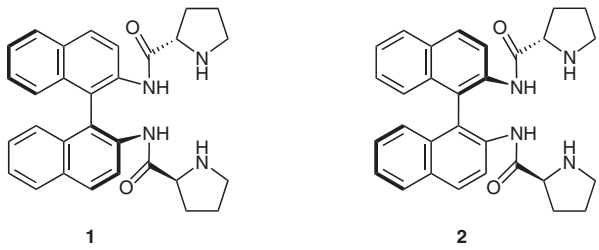
Abstract: Homochiral derivatives of 1,1′-binaphthyl-2,2′-diamine and various α-amino acids were prepared using a convenient procedure. They were tested as organocatalysts for 1,3-dipolar cycloaddition of aromatic nitrones to (*E*)-crotonaldehyde. The L-phenylalanine-based catalyst **10** afforded superior results, with good *endo* diastereoselectivity, and enantioselectivity of up to 95% ee.

Key words: α-amino acids, asymmetric organocatalysis, binaphthyl derivatives, 1,3-dipolar cycloaddition, nitrones

Recently, we reported the synthesis of novel hybrid diamines, derived from 1,1′-binaphthyl-2,2′-diamine (BINAM) and several α-amino acids.[1] These compounds combine two different stereogenic elements, namely the chiral axis of the binaphthalene system, and the stereogenic centers of the amino acid units. They can be easily synthesized in a two-step procedure from commercially available and inexpensive substrates. Originally, they were designed as chiral ligands for the transition metal catalysts to be used in asymmetric synthesis. However, the recent development of organocatalytic systems turned our attention to this new methodology.[2]

Diastereomeric hybrid proline diamides **1** and **2** (Figure 1), obtained in our laboratory,[3] were successfully applied in direct asymmetric aldol reaction. Consecutively, Nájera and co-workers started similar studies.[4]

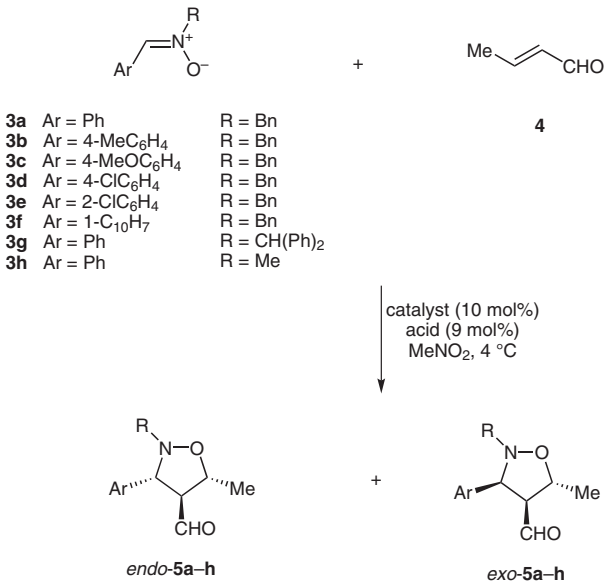
These results prompted us to study other reactions, catalyzed by the hybrid diamines. An interesting target was the 1,3-dipolar cycloaddition reaction of nitrones to α,β-unsaturated aldehydes, as recently reported by MacMillan et al.,[5] followed by others,[6] including an interesting approach by the Benaglia's group applying the solid-supported catalyst.[7] This reaction leads to isoxazolidines, five-membered heterocycles possessing up to three stereogenic centers and a labile N–O bond. Therefore, these compounds can be transformed to β-amino alcohols, synthetic intermediates in the synthesis of biologically important compounds.[8]



1 **2**

Figure 1

At the beginning of our studies, we decided to check two hybrid diamines **1** and **2** as organocatalysts in model reaction of *N*-benzylidenebenzylamine *N*-oxide (**3a**) with (*E*)-crotonaldehyde (**4**), as depicted in Scheme 1.[5,9]



Scheme 1

All reactions studied were carried out in wet nitromethane,[10] using 10 mol% of a catalyst and 9 mol% of an acid as additive. With catalysts **1** and **2**, a mixture of cycloadducts *endo*-**5a** and *exo*-**5a** was obtained in a good yield, but with low diastereoselectivity and moderate enantiomeric excess, as shown in Table 1 (entries 1 and 2).

Since the secondary amines were not very much successful as stereoselective catalysts in this case, we decided to apply the hybrid compounds **6–11** previously reported by

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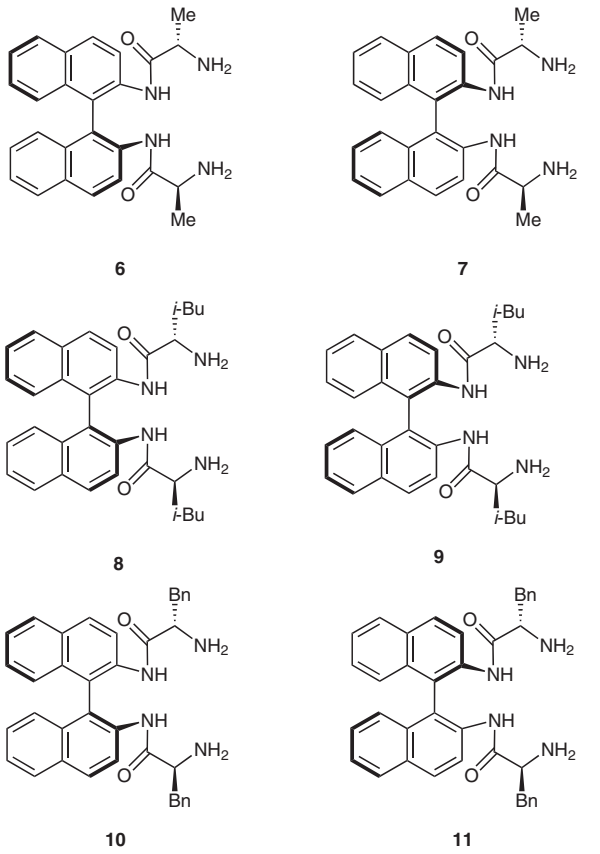

Figure 2

us,[1] that are based on α-amino acids other than proline, containing the primary amine functionality (Figure 2).

Compared to the catalysts **1** and **2**, the L-alanine derivative **6** produced the *endo* cycloadduct **5a** with 93% ee (Table 1, entry 3), but as the minor diastereomer. The L-leucine diamine **8**, tested under our conditions, produced the *endo* cycloadduct as the major diastereomer with 78% ee (entry 5). Switching to even bulkier L-phenylalanine catalyst **10** improved the enantioselectivity of the product **5a** to 92%, with much better diastereoselectivity (5.6:1 for **10** vs. 1.8:1 for **8**, entries 7 and 5, respectively).

Table 1 Results of the Model 1,3-Dipolar Cycloaddition of **3a** to **4**[a]

Entry	Catalyst	Yield[b] (%)	Ratio[c] *endo*/*exo*	Enantioselectivity[d] (%) *endo*-**5a**	*exo*-**5a**
1	**1**	90	1:2.3	(–36)	(–48)
2	**2**	80	1:1.7	(–26)	(–28)
3	**6**	80	1:2.0	93	19
4	**7**	85	1:5.0	22	38
5	**8**	94	1.8:1	78	15
6	**9**	86	1:2.5	35	25
7	**10**	94	5.6:1	92	(–2)
8	**11**	71	1.1:1	48	(–8)

[a] The reaction was carried out in the presence of various hybrid catalysts (10 mol%) and *p*-TsOH (9 mol%) for 72 h[12].
[b] Isolated yield of *endo*-**5a** + *exo*-**5a**.
[c] Determined by ^{1}H NMR of an isolated mixture.
[d] Determined by chiral HPLC. Configuration of (+)-*endo*-**5a**: 3*R*,4*S*,5*R*; configuration of (+)-*exo*-**5a**: 3*S*,4*S*,5*R*.

In all cases, only the *S* configuration of binaphthyl moiety, combined with L-amino acid, led to enhanced stereoselectivity. This supports the earlier results on aldol reaction, catalyzed by proline diamides **1** and **2**.[3]

After the best catalyst **10** had been identified, further reaction conditions were investigated. Thus we varied the quantity and type of the acid additive (Table 2). It was found that the optimal amount of an acid was 9 mol% (entries 3–5). Use of trifluoromethanesulfonic acid (entry 6) instead of *p*-TsOH led to higher diastereoselectivity, while shortening of the reaction time. Use of benzoic acid gave only traces of the product (entry 1), whereas trifluoroacetic acid produced cycloadducts in significantly lower yield (entry 2), compared to more acidic additives, as shown in Table 2. This is consistent with MacMillan's observations, that increasing pKa of the acid additive may improve catalyst activity. Moreover, these experimental

Table 2 Results of the Model 1,3-Dipolar Cycloaddition of **3a** to **4**

Entry	Acid	pK_a	Amount of acid (mol%)	Time (h)	Yield[b] (%)	Ratio[c] *endo*/*exo*	ee (%)[d] of *endo*-**5a**
1	$PhCO_2H$	4.2	9	48	trace	–	–
2	TFA	0.2	9	48	46	3.1:1	88
3	*p*-TsOH	– 2.0	5	72	85	6.1:1	76
4	*p*-TsOH	– 2.0	9	72	94	5.6:1	92
5	*p*-TsOH	– 2.0	18	72	92	5.3:1	80
6	TfOH	–14	9	40	75	7.0:1	92

[a] The reaction was catalyzed by **10** (10 mol%) in the presence of various acid additives.
[b] Isolated yield of **5a**.
[c] Determined by ^{1}H NMR of an isolated mixture.
[d] Determined by chiral HPLC; configuration of (+)-*endo*-**5a**: 3*R*,4*S*,5*R*.

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results suggest an imminium ion as a catalytic intermediate.[5]

Next, we tested the substrate generality with a range of aromatic nitrones. The results are summarized in Table **3**. The best results were obtained with *N*-benzyl nitrones, with *para* substituents on aromatic ring (entries 1–4). Other substituents were also tolerated (entries 5 and 6). Variation in the N-substituent was possible (entries 7 and 8). Among the other dipolarophiles tested, acrolein was also suitable, but the yields and diastereoselectivities were lower (with nitrone **3a**: 46% yield, 2:1 *endo*:*exo* ratio, 81% ee in favor of *endo*). Application of cinnamic aldehyde was unsuccessful. By a comparison of optical rotation values and HPLC peaks analysis, the configuration of known *endo*-isoxazolidines (entries 1–4, 7 and 8) was assigned as 4*S*.[5,11]

Table 3 Results of the 1,3-Dipolar Cycloadditions of Nitrones **3a**–**h** to **4**

Entry	Product	Yield (%)[b]	Ratio[c] *endo*/*exo*	ee (%)[d] of *endo*-**5**
1	**5a**	75	7.0:1	92
2	**5b**	95	7.4:1	88
3	**5c**	95	5.0:1	95
4	**5d**	95	6.4:1	86
5	**5e**	84	3.8:1	80[13]
6	**5f**	50	2.2:1	61[13]
7	**5g**	70	12:1	70
8	**5h**	74	5.7:1	87

[a] The reaction was catalyzed by **10** (10 mol%) in the presence of TfOH (9 mol%).
[b] Isolated yield of **5**.
[c] Determined by ^{1}H NMR of an isolated mixture.
[d] Determined by chiral HPLC; configuration of (+)-*endo*-**5**: 3*R*,4*S*,5*R*, configuration of (+)-*exo*-**5**: 3*S*,4*S*,5*R*.

In summary, we have developed a new family of catalysts for 1,3-dipolar cycloaddition of aromatic nitrones with α,β-unsaturated aldehydes.[12,13] Optimal conditions were 10 mol% of catalyst **10** with 9 mol% of trifluoromethanesulfonic acid as an additive, providing predominantly *endo* adducts with the ee values of up to 95%. According to our own experience and to the Nájera and co-workers procedure[4a,b] the catalyst may be recovered and reused. We have further proved the utility of hybrid diamines as catalysts for stereoselective transformations. We have also confirmed the earlier observations on origins of asymmetric induction generated by this class of compounds. Studies on the reaction with other class of nitrones and α,β-unsaturated aldehydes are underway.

Acknowledgment

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(12) **General Procedure for 1,3-Dipolar Cycloaddition**: A solution of the nitrone (0.25 mmol) in nitromethane (1 mL) was placed in a vial, and H_2O (3 equiv), the catalyst and the acid co-catalyst were added and the resulting mixture was cooled to 4 °C. Then the freshly distilled α,β-unsaturated

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aldehyde was added (4 equiv, followed by 3 equiv at 24 h intervals) and the mixture was left for a specific period of time. Then it was filtered through a silica gel plug with aid of CH_2Cl_2, and then concentrated. After purification by flash chromatography (hexane–EtOAc), the residual oils were reduced to the corresponding alcohols with $NaBH_4$ in MeOH. The ee values of purified alcohols were determined by chiral HPLC using CHIRALCEL OD or OD-H columns (95–98% hexane–isopropanol, flow: 1 mL/min).

(13) All new compounds obtained here had correct analytical and spectral data.

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