Primary amine-aminopyrimidinebifunctional chiral organocatalysts for the enantioselective conjugate addition of branched aldehydes to maleimides

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Abstract: Chiral primary amines **6** containing the (*R,R*)- and (*S,S*)-*trans*-cyclohexane-1,2-diamine scaffold and a 2-pyrimidinyl unit are synthesized and used as general organocatalysts for the Michael reaction of α -branched aldehydes to maleimides. The reaction takes place with 10 mol% organocatalyst loading and hexanedioic acid as co-catalyst in aqueous *N,N*-dimethylformamide at 10 °C affording the corresponding succinimides in good yields and enantioselectivities. DFT calculations support the stereochemical results for the intermolecular process and the bifunctional role played by the organocatalysts.

Key words: Asymmetric Organocatalysis / Maleimides / Succinimides / Aldehydes / Michael addition

Enamine¹ and iminium² activation mode of carbonyl compounds has promoted the development of asymmetric organocatalysis in the last 15 years. Initially chiral secondary amines have been mainly used in amino-catalysis and more recently primary amines appear in the stage based on the chemistry of type I aldolases with lysine residues.³ Chiral primary amines derived organocatalysts are crucial for enamine formation of hindered carbonyl compounds, namely α,α -disubstituted aldehydes.⁴ Several problems have to be overcome with α -branched aldehydes apart from steric hindrance,⁵ the formation of low reactive enamines,⁶ and *Z/E* mixture of diastereomeric enamines. Several enantioselective reactions have been performed such as conjugate additions, aldol and Mannich reactions, and α -heterofunctionalization of aldehydes allowing the formation of quaternary stereocenters.

Apart of amino acids derivatives, several bifunctional primary amine organocatalysts derived from chiral 1,2-diamines have been

developed. Among them, *trans*-cyclohexane-1,2-diamine, available in both enantiomeric forms, is an excellent rigid chiral scaffold to anchor a moiety able to activate the electrophile by hydrogen bonding lowering the LUMO.⁷ Since pioneers studies from Jacobsen,⁸ Schreiner,⁹ and Takemoto¹⁰ primary amines-thiourea derivatives have become the most popular organocatalysts.

^{4b,c}

Organocatalyzed conjugate addition of α,α -disubstituted aldehydes to maleimides is one of the most studied reactions using primary amine catalysts. This process allows easy access to enantiomerically substituted succinimides which are interesting core structural units in natural products and biologically active compounds such as andrimid, moiramide B and hirsutellones A-E with antibacterial activity, haterumaimides A-Q with antitumor activity, and tandospirone which is an anxiolytic and antidepressant drug.¹¹ In addition, enantioenriched succinimides can be used as chiral building blocks being easily transformed into pyrrolidines, γ -lactams, and γ -lactones.¹²

Bifunctional primary amine-derived organocatalysts from *trans*-cyclohexane-1,2-diamine (*R,R*)-**1** and its enantiomer bearing a thiourea unit **2**,¹³ **3**,¹⁴ the guanidine derivative **4**,¹⁵ the starting diamine **1**,¹⁶ and its *N*-Boc monoprotected derivative **5**¹⁷ promoted efficiently the Michael-type addition of α,α -disubstituted aldehydes to maleimides (Figure 1). Recently, we have demonstrated that the 2-aminobenzimidazole¹⁸ and 2-aminopyrimidine¹⁹ units are excellent hydrogen bond donors, the corresponding bifunctional organocatalysts **6**¹⁸ and **7**¹⁹ being used in Michael and aldol reactions, respectively (Figure 1).

Continuing on this research line and based on the experience of our group in organocatalyzed asymmetric reactions, we envisaged that a primary amine-2-aminopyrimidine organocatalyst **8** derived from *trans*-cyclohexane-1,2-diamine could be able to catalyze the conjugate addition of α,α -disubstituted aldehydes to maleimides. DFT calculations would be presented in order to clarify the role of the 2-aminopyrimidine unit as rigid guanidine-type function able to form hydrogen bonds with the carbonyl group of the maleimide acceptor.

Figure 1 *trans*-Cyclohexane-1,2-diamine derived organocatalysts

For the synthesis of the primary amine-aminopyrimidine organocatalyst **8**, *N*-Bocmonoprotected derivative *ent*-**5** was allowed to react with commercially available 2-chloropyrimidine in the presence of triethylamine under isopropanol reflux for 36 h followed by trifluoroacetic acid deprotection at room temperature in dichloromethane (Scheme

1).¹⁹ Compound **8** and its enantiomer were obtained in 71% overall yield.

Scheme 1 Synthesis of the organocatalyst (*S,S*)-**8**

As model reaction isobutyraldehyde (2 equiv) was allowed to react with *N*-phenylmaleimide (NPM) in the presence of 10 mol% of the organocatalyst **8** (Table 1). When the reaction was performed in toluene as solvent at rt for 3 d the corresponding succinimide **9a** was isolated in 78% yield as racemic compound (Table 1, entry 1). Under the same reaction conditions using THF instead of toluene the reaction failed and in dichloromethane compound **9a** was isolated in 79% yield in a modest 29% ee and with *S*-configuration (Table 1, entries 1 and 2). However, when water was used as solvent **9a** was isolated after 3 d in 74% yield and 44% ee with *R*-configuration (Table 1, entry 4). The same sense of enantiomeric bias was observed in DMF with longer reaction times (ca. 6 d), lower yield 33% in a higher 62% ee (Table 1, entry 5). Therefore, mixtures 2:1 and 4:1 of DMF and H₂O were assayed affording similar results, 70% yield and 79% ee (Table 1, entries 6 and 7). The reaction failed in the presence of bases as additives such as DABCO or imidazole (Table 1, entries 8 and 9), which were beneficial in the case of using organocatalysts **1**^[16] and **4**.^[15] On the other hand, when carboxylic acids such as trifluoroacetic, benzoic or hexanedioic (HAD) acids were used as additives the reaction was accelerated only with the two last acids (Table 1, entries 10–12). So with 10 mol% of HDA as cocatalyst product (*R*)-**9a** was obtained in 80% yield and 79% ee. Higher 20 mol% loading of catalyst and cocatalyst gave the same results (Table 1, entry 13). By using (*R,R*)-**8**, the corresponding *ent*-**9a** was obtained (Table 1, entry 14). Finally, lowering the temperature to 0 °C 2 d were necessary to the reaction completion giving the product in 83% isolated yield and in 83% ee (Table 1, entry 15). Under the last reaction conditions, this conjugate addition of isobutyraldehyde was scale up from 0.3 mmol to ca. 3.5 mmol (0.5 g of NPM) affording (*R*)-**9a** after 16 h reaction time in 99% crude yield and 85% ee. Further recrystallization from hexane-ethyl acetate gave pure succinimide in 75% yield.

Table 1 Optimization of reaction conditions^a

Entry	Solvent	Additive	T (°C)	t (h)	Yield (%) ^b	ee (%) ^c
1	PhMe	-	25	72	78	<i>rac.</i>
2	THF	-	25	96	-	-
3	CH ₂ Cl ₂	-	25	72	79	24 (<i>S</i>)
4	H ₂ O	-	25	72	74	44 (<i>R</i>)
5	DMF	-	25	140	33	62 (<i>R</i>)
6	DMF:H ₂ O (2:1)	-	25	72	70	79 (<i>R</i>)
7	DMF:H ₂ O (4:1)	-	25	72	71	79 (<i>R</i>)
8	DMF:H ₂ O (2:1)	DABCO	25	72	-	-
9	DMF:H ₂ O (2:1)	Imidazole	25	72	-	-
10	DMF:H ₂ O (2:1)	TFA	25	72	-	-
11	DMF:H ₂ O (2:1)	PhCO ₂ H	25	16	84	75 (<i>R</i>)
12	DMF:H ₂ O (2:1)	HDA ^d	25	16	80	79 (<i>R</i>)
13	DMF:H ₂ O (2:1) ^e	HDA ^e	25	15	80	79 (<i>R</i>)
14 ^f	DMF:H ₂ O (2:1)	HDA	25	18	77	79 (<i>S</i>)
15	DMF:H ₂ O (2:1)	HDA	0	48	83	86 (<i>R</i>)

^a Reaction conditions: isobutyraldehyde (0.6 mmol), NPM (0.3 mmol), catalyst **8** (10 mol%) and additive (10 mol%) in 1.0 mL of solvent.

^b Isolated yield after flash chromatography.

^c Determined by chiral HPLC.

^d Hexanedioic acid.

^e 20 mol%.

^f The reaction was carried out using *ent*-**8**.

Once the optimal reaction conditions were established, that means the use of 10 mol% of both, catalyst **8** and HAD as co-catalyst, in 2:1 DMF:H₂O solvents at 0 to 5 °C, the scope of the reaction was studied (Scheme 2). The addition of isobutyraldehyde to maleimide and *N*-alkyl maleimides such as *N*-methyl and *N*-benzyl, afforded succinimides **9b**, **c** and **d** in good yields and 78, 80 and 81% ee, respectively. In the case of the conjugate addition of isobutyraldehyde to *N*-aryl substituted maleimides the corresponding products **9e-g** were obtained in higher yields (70–92%) and ee (86–89%) (Scheme 2). In order to extend this methodology to other aldehydes cyclopentane- and cyclohexane-carbaldehyde were allowed to react with NPM. The resulting succinimides **9h** and **9i** were isolated in 84 and 89% yield and in 89 and 93% ee, respectively (Scheme 2). Low diastereoselectivity was observed in the Michael addition of α -phenylpropanal and propanal giving products **9j** and **9k** in 72 and 49% yield, respectively, and as a mixture 6/1 and 2/1 of diastereomers, respectively. The major isomers **9j** and **9k** were obtained in 81% and 72% ee, respectively.

Scheme 2 Synthesis of enantioenriched succinimides **9**

The absolute configuration was assigned according to our previous work.¹⁵ The observed enantioinduction indicates that the catalytic process should take place through a different activation mode of the 2-aminopyrimidine than the thiourea unit in Takemoto's catalyst.²⁰ Experimental work using catalyst **8** with different enantiomeric excess revealed the absence of a nonlinear effect, it means that in the rate determining step only one molecule of the catalyst is involved. From computational studies

Computational studies were carried out

As conclusion, the *trans*-cyclohexane-1,2-diamine-derived primary amine-2-aminopyrimidine organocatalysts are able to promote the conjugate addition of aldehydes to maleimides with 10 mol% loading and using hexanedioic acid as cocatalyst in good yield and up to 93% ee. The best solvent is DMF and the presence of water as cosolvent has a beneficial effect in the in good yield and up to 93% ee. reaction time and enantioselectivity. In addition, DFT calculations

All reagents were purchased from commercial sources and used without further purification. Substrates which were not commercially available were synthesized according to known literature procedures. Catalysts **8** were synthesized as previously described.^[19] Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR's were recorded on a JASCO FT-IR 4100 LE (Pike Miracle ATR) and only the structurally most relevant peaks are listed. NMR spectra were performed on a Bruker AC-300 or Bruker Avance-400 using CDCl₃ as solvent and TMS as internal standard unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and high resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model Waters ACQUITY H CLASS. Optical rotations were measured on a Jasco P-1030 Polarimeter with a 5 cm cell (c given in g/100 mL). Enantioselectivities were determined by HPLC analysis (Agilent 1100 Series HPLC) equipped with a G1315B diode array detector and a Quat Pump G1311A equipped with the corresponding Daicel chiral column and the retention time of the major enantiomer is highlighted in bold. Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed prepackaged columns (12 mm Ø × 7.5 or 15 cm) using Merck silica gel 60 (0.040–0.063 mm) and a chromatography pump Büchi Controller C-610-Module C-601. Silica gel 60 F₂₅₄ containing gypsum was employed for preparative layer chromatography.

Conjugate Addition of Aldehydes to Maleimides; General Procedure

To a solution of **8** or *ent*-**8** (0.03 mmol), the maleimide (0.3 mmol) and HDA (10% mol, 0.03 mmol) in DMF/H₂O (2/1, v/v) (0.6 mL) was added the aldehyde (0.6 mmol) and the mixture was stirred at 0 °C until completion of the reaction (TLC). Then, aqueous 2M HCl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The organic phase was washed with water (2 × 10 mL), dried (MgSO₄), filtered and evaporated (15 torr). The resulting crude was purified by flash chromatography (*n*-hexane/AcOEt) affording adducts **9**.

Supporting Information

Supporting information for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084>.

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Organocatalyzed Michael Addition