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Amine-Catalyzed Asymmetric Epoxidation of α,β-Unsaturated Aldehydes

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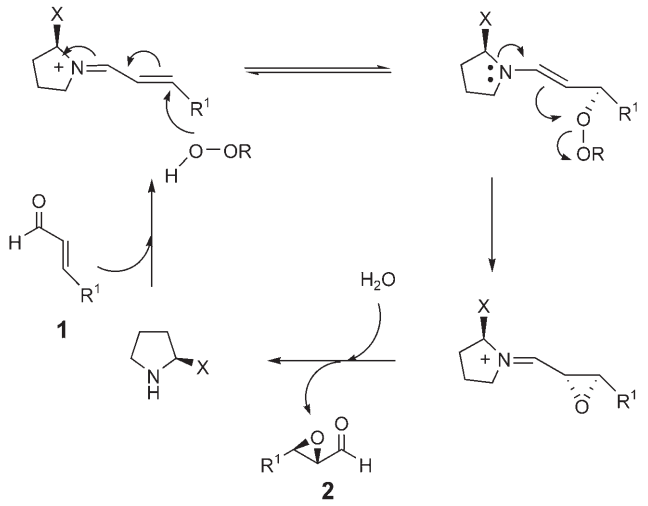
Abstract: The direct organocatalytic enantioselective epoxidation of α,β-unsaturated aldehydes with different peroxides is presented. Proline, chiral pyrrolidine derivatives, and amino acid-derived imidazolidinones catalyze the asymmetric epoxidation of α,β-unsaturated aldehydes. In particular, protected commercially available α,α-diphenyl- and α,α-di(β-naphthyl)-2-prolinols catalyze the asymmetric epoxidation reactions of α,β-unsaturated aldehydes with high diastereo- and enantioselectivities to furnish the corresponding 2-epoxy aldehydes in high yield with up to 97:3 *dr* and 98% *ee*. The use of non-toxic catalysts, water and hydrogen peroxide, urea hydroperoxide or sodium percarbonate as the oxygen sources could make this reaction environmentally benign. In addition, one-pot direct organocatalytic asymmetric tandem epoxidation-Wittig reactions are described. The reactions were highly diastereo- and enantioselective and provide a rapid access to 2,4-diepoxy aldehydes. Moreover, a highly stereoselective one-pot organocatalytic asymmetric cascade epoxidation-Mannich reaction, which proceeds *via* the combination of iminium and enamine activation, is presented. The mechanism and stereochemistry of the amino acid- and chiral pyrrolidine-catalyzed direct asymmetric epoxidation of α,β-unsaturated aldehydes are also discussed.

Keywords: asymmetric catalysis; diphenylprolinol; enantioselective epoxidation; hydrogen peroxide; one-pot reactions; unsaturated aldehydes

Introduction

The catalytic asymmetric epoxidation is one of the most important reactions in organic synthesis.[1] The seminal work of Katsuki and Sharpless resulted in the discovery of titanium-tartrate complexes as asymmetric epoxidation catalysts of allylic alcohols.[2] Jacobsen and Katsuki have independently developed chiral manganese-salen complexes that are excellent catalysts for the asymmetric epoxidation of unfunctionalized olefins.[3] In addition, Shibasaki and co-workers designed several chiral Lewis acids for the catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds.[4] Catalytic asymmetric epoxidation reactions are also catalyzed by metal-free organocatalysts.[5] For instance, asymmetric epoxidations of α,β-enones are mediated by polypeptides[6] and *Cinchona* alkaloids.[7] Moreover, Shi and Aggarwal have discovered elegant methods for the epoxidation of unfunctionalized olefins catalyzed by chiral ketones[8] and pyrrolidines,[9] respectively. Recently, Lattanzi reported that chiral diarylprolinols catalyze the direct catalytic asymmetric epoxidation of α,β-unsaturated ketones.[10] Organocatalysis has also been applied in the asymmetric α-oxidation of aldehydes and ketones with electrophilic oxidants such as nitrosobenzene,[11] iodosobenzene,[12] oxaziridines,[12] and singlet molecular oxygen.[13] More nucleophilic oxygen sources such as *tert*-butyl hydroperoxide, *m*-CPBA and hydrogen peroxide failed as oxidants for this transformation.[12] MacMillan and co-workers have demonstrated that chiral amines can catalytically activate α,β-unsaturated aldehydes and ketones towards nucleophilic attack by forming iminium ions.[14] Based on our research interest in organocatalysis[15] and the development of environmentally benign enantioselective oxidation processes,[12,13] we became intrigued in whether simple chiral amines would be able to catalyze asymmetric epoxidations of α,β-unsaturated aldehydes with nucleophilic oxidants by combination of an iminium and enamine activation mechanism (Scheme 1).

In this context, Jørgensen[16] first reported that protected α,α-bis[di(3,5-trifluoromethyl)phenyl]-2-pyrrolidinemethanol catalyzes the direct enantioselective epoxidations of α,β-unsaturated aldehydes. We[17] found that chiral amines and amino acid derivatives catalyze the direct asymmetric epoxidation of α,β-unsaturated aldehydes. We[17] and Jørgensen[16b] also



Scheme 1. Plausible amine-catalyzed epoxidation of α,β-unsaturated aldehydes by catalytic iminum and enamine activation.

found that the TMS-protected diarylprolinol-catalyzed reactions are highly enantioselective in aqueous media. Herein we describe: (i) structure/activity relationships of the chiral amine catalysts, (ii) the substrate scope of the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes, (iii) one-pot direct organocatalytic tandem asymmetric epoxidation-Wittig reaction sequences, (iv) one-pot organocatalytic asymmetric cascade epoxidation-Mannich reactions, (v) and studies concerning the reaction mechanism.

Results and Discussion

We initially investigated several simple organocatalysts (10–30 mol%) for their ability to catalyze the direct asymmetric epoxidation of cinnamic aldehyde **1a** (0.25 mmol) with hydrogen peroxide (50% wt, aqueous solution, 1.2–7 equivs.) in $CHCl_3$ (2 mL) (Table 1).

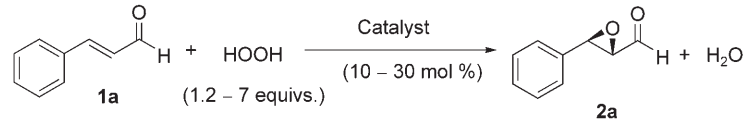
The direct asymmetric epoxidation of **1a** was mediated by several of the catalysts (**3**–**6** and **8**–**14**) tested and formed the 2-epoxy aldehyde **2a** with poor to excellent diastereo- and enantioselectivity. Notably, addition of TEA (0.8 equivs.) enabled the use of proline and tetrazole **4** as catalysts (entries 2 and 3). For instance, proline catalyzed the formation of *ent*-**2a** with 79% conversion and 36% *ee*. In addition, chiral proline-derived diamines such as **5** and **6** catalyzed the asymmetric epoxidation of **1a** with poor to good enantioselectivity. For example, catalyst **5** exhibited the highest asymmetric induction and catalyzed the enantioselective epoxidation of **1a** with good conversion (60%) to furnish **2a** in a 53:47 *dr* (*trans*/*cis*) and with 66% *ee*. We also investigated diphenyl-2-pyrrolidinemethanol (**9**, diphenylprolinol), which has been developed by Corey and co-workers,[18] as a catalyst. Diphenylprolinol **9** (30 mol%) catalyzed the stereoselective epoxidation of **1a** with excellent diastereoselectivity (5:95) and low enantioselectivity (22%). It has been shown that protection of the hydroxy group of diarylprolinols and hydroxyproline, respectively, is an excellent strategy to improve the efficiency and enantioelectivity of organocatalytic reactions catalyzed by these chiral amines.[19–21] Hence, we decided to convert the hydroxy group of the commercially available **9** to a siloxy group and synthesized the corresponding chiral pyrrolidine **10** in one-step in excellent yield. To our delight, the chiral pyrrolidine **10** (10 mol%) catalyzed the asymmetric epoxidation of **1a** within 2 h (91% conversion) and furnished epoxide **2a** in 81% yield in a 93:7 *dr* and 97% *ee*. Thus, TMS protection of the hydroxy group of **9** had a remarkable effect on the reactivity and enantioselectivity of the asymmetric epoxidation. In addition, TMS protection of diphenylprolinol **9** switched the diastereoselectivity of the reaction. Decreasing the catalyst loading of **10** to 5 mol% reduced the reaction rate (entry 15). Moreover, employment of 1 mol% of **10** only gave trace amounts of product **2a** after 24 h. We also found that TMS-protected di(β-naphthyl)prolinol **12** was an excellent catalyst. Chiral pyrrolidine **12** (10 mol%) catalyzed the asymmetric formation of **2a** in 86% conversion with 93:7 *dr* and 98% *ee*. Thus, TMS-protected diarylprolinols are excellent catalysts for the direct asymmetric epoxidation of α,β-unsaturated aldehydes. The protection of prolinol **13** with a bulky silyl group gave chiral pyrrrolidine **14** that also catalyzed the formation of **2a** with 81:8 *dr* and 68% *ee*. Moreover, we found that MacMillan's imidazolidinones such as **11** catalyzed the direct asymmetric epoxidation of α,β-unsaturated aldehydes with high diastereoselectivity and modest enantioselectivity under our reaction conditons.[22] Encouraged by our initial results, we decided to investigate the synthetic scope of the readily available, inexpensive and highly enantioselective catalyst **10**.

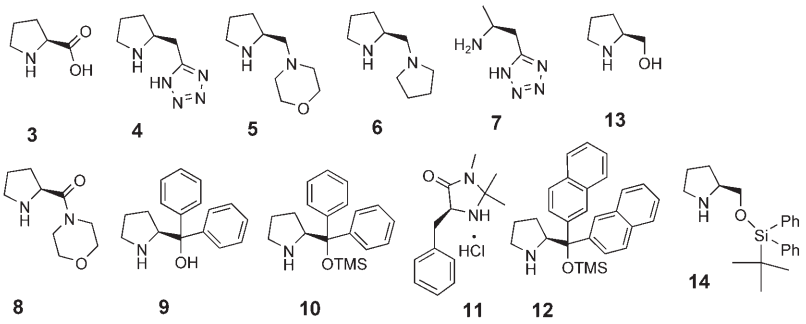
Oxidant Screen

We began to screen several different oxidants for the chiral pyrrolidine **10**-catalyzed asymmetric epoxidation of **1a** (Table 2).

The chiral amine **10** catalyzed the asymmetric epoxidation of α,β-unsaturated aldehyde **1a** with high diastereoselectivities (82:18–93:7) and excellent enantioselectivities (>95% *ee*) when hydrogen peroxide, solid SPC (sodium percarbonate), cumene hydroperoxide, urea hydrogen peroxide (UHP) and *tert*-butyl hydrogen peroxide were used as the oxidants. Thus, several environmentally benign oxidants gave excel-

Table 1. Catalyst screen for the direct catalytic asymmetric epoxidation of **1a** with hydrogen peroxide.[a]

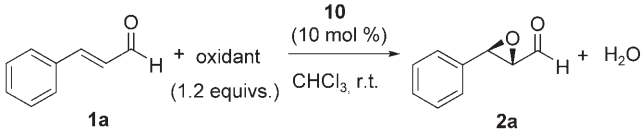




Entry	Catalyst	Time [h]	Conversion [%][b]	*dr*[c]	*ee* [%][c]
1	**3**[d]	24	<1	n.d.	n.d.
2	**3**[d,e]	16	79	60:40	–36
3	**4**[d,e]	16	82	74:26	–15
4	**5**[d]	22	60	53:47	66
5	**6**[d]	19	41	45:54	7
6	**7**[d]	24	<1	n.d.	n.d.
7	**8**[d]	14	85	79:21	24
8	**9**[d]	16	43	5:95	–22
9	**10**[f]	2	91 (81)[g]	93:7	97
10	**11**[f,h]	3	28	48:52	12
11	**11**[f,i]	18	55	96:4	12
12	**12**[f]	3	86	93:7	98
13	**13**[f]	3	6	80:20	–60
14	**14**[f]	3	40	81:8	68
15	**10**[j]	7	68	93:7	96

[a] To a stirred solution of catalyst (10-30 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3–1.75 mmol, 50% aqueous solution). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] The *dr* (*trans*/*cis*) and *ee* were determined by chiral-phase GC analyses.
[d] 30 mol% catalyst.
[e] 0.8 equivs. TEA added.
[f] 10 mol% catalyst and 1.2 equivs. H_2O_2.
[g] Isolated yield of pure **2a** after silica gel column chromatography.
[h] Reaction run in H_2O:EtOH (1:1).
[i] Reaction run in dioxane.
[j] 5 mol% catalyst and 1.2 equivs. H_2O_2.

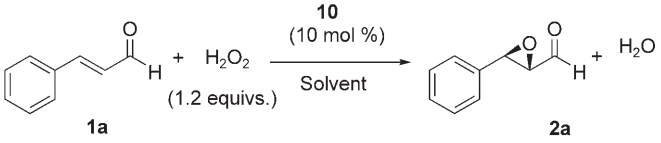
Table 2. Oxidant screen for the chiral amine **10**-catalyzed direct asymmetric epoxidation of **1a**.[a]



Entry	Oxidant	Time [h]	Conv. [%][b]	*dr*[c]	*ee* [%][c]
1	H_2O_2	2	91	93:7	97
2	SPC[d]	6	75	84:16	98
3	*t*-BuOOH	3	84	82:18	96
4	*m*-CPBA	16	<10	96:4	51
5	cumene hydroperoxide	5	63	85:15	98
6	UHP[e]	5	96	86:14	98

[a] To a stirred solution of catalyst (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1a** (0.25 mmol) and oxidant (0.3 mmol). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] The *dr* (*trans*/*cis*) and *ee* were determined by chiral-phase GC analyses.
[d] 0.38 mmol SPC + 50 μL H_2O were added.
[e] 0.6 mmol UHP + 50 μL H_2O were added.

Table 3. Solvent screen.[a]



Entry	Solvent	Temp. [°C]	Time [h]	Conv. [%][b]	*dr*[c]	*ee* [%][c]
1	$CHCl_3$	r.t.	2	91 (81)[d]	93:7	97
2	$CHCl_3$	4	7	88	95:5	98
3	CH_2Cl_2	r.t.	2	88	90:10	96
4	toluene	r.t.	2	94	91:9	97
5	THF	r.t.	2	17	95:5	90
6	EtOH	r.t.	2	94	87:13	92
7	H_2O:*t*-BuOH (1:1)	r.t.	2	84	87:13	94
8	H_2O:EtOH (1:1)	r.t.	2	67	87:13	90
9	H_2O	r.t.	5	89[e]	69:31	93

[a] To a stirred solution of catalyst (10 mol%) in solvent (2 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] The *dr* (*trans*/*cis*) and *ee* were determined by chiral-phase GC analyses.
[d] Isolated yield.
[e] 0.3 mL H_2O was used.

lent enantioselectivity. For instance, sodium percarbonate (SPC) represents one of the most powerful oxidants available.[23] It is particularly advantageous owing to its ease of handling and storage. Moreover, the asymmetric induction was slightly higher when chiral amine **10** catalyzed the asymmetric epoxidations with solid SPC or UHP as the oxygen source as compared to hydrogen peroxide. However, the reactions were slower and the order of reactivity of the oxidants was $H_2O_2 > UHP > SPC$.

The asymmetric epoxidation of aldehyde **1a** with *m*-CPBA was slow and furnished **2a** in low conversion with high diastereoselectivity (96:4 *dr*) and moderate enantioselectivity (51% *ee*).

Solvent Screen

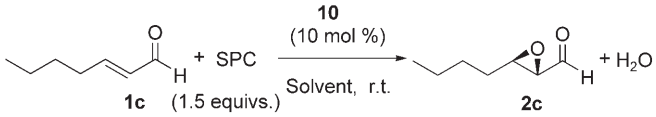
We next investigated the important aspect of performing the organocatalytic asymmetric epoxidation of **1a** in different solvents (Table 3).

The asymmetric epoxidations with hydrogen peroxide proceed smoothly in all solvents tested. The highest enantioselectivity was reached in $CHCl_3$, toluene and CH_2Cl_2. In these solvents, 2-epoxy aldehyde **2a** was formed with 96–97% *ee*. Decreasing the reaction temperature increased the diastereo- and enantioselectivity of the chiral pyrrolidine **10**-catalyzed reaction (entry 4). The organocatalyst **10**-catalyzed asymmetric epoxidation reaction with 1.2 equivalents of hydrogen peroxide exhibited a high stereoselectivity in water/alcohol solutions and EtOH. *Notably, the organocatalytic asymmetric epoxidation reaction was highly enantioselective in water.* For instance, 2-epoxy aldehyde **2a** was formed in high conversion (89%) with 93% *ee* in water (entry 9).

SPC and UHP are solids. Hence, a small amount of water was added in order to increase the rate of H_2O_2 formation and the rate of the reaction. We found that when the ratio between $CHCl_3$:H_2O was between 95:5–90:10 the highest asymmetric induction was achieved for the organocatalytic asymmetric epoxidations with SPC (Table 4).

The chiral amine **10**-catalyzed asymmetric epoxidation of aldehyde **1c** with SPC in aqueous solvent did not have a beneficial effect on the enantioselectivity of the reaction, which is in stark contrast to when hydrogen peroxide was used as the oxygen source.

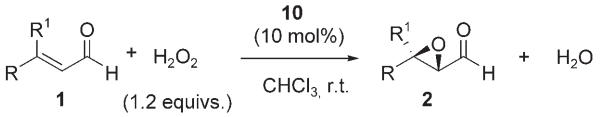
Table 4. Influence of water on the organocatalytic asymmetric epoxidations of **1c** with hydrogen peroxide.[a]



Entry	Solvent	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][c]
1	$CHCl_3$:H_2O-95:5	3	20	95:5	96
2	$CHCl_3$:H_2O-95:5	36	70	95:5	94
3	$CHCl_3$:H_2O-9:1	3	31	95:5	93
4	$CHCl_3$:H_2O-5:1	3	34	95:5	88
5	*t*-BuOH:H_2O-1:1	3	47	92:8	13

[a] To a stirred solution of catalyst (10 mol%) in $CHCl_3$ (1 mL) was added aldehyde **1c** (0.25 mmol), SPC (0.38 mmol) and H_2O. The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] The *dr* (*trans*/*cis*) and *ee* were determined by chiral-phase GC analyses.

Table 5. Organocatalytic asymmetric epoxidation of aldehydes **1** with hydrogen peroxide.[a]



Entry	R	R^1	Prod.	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	H	**2a**	2	81	93:7	97
2	*n*-propyl	H	**2b**	2	>90[e] (99)[f]	95:5 (96:4)[f]	93 (>95)[f]
3	*n*-butyl	H	**2c**	1.5	94	95:5	91
4	CO_2Et	H	**2d**	2	89	91:9	98
5	4-ClC_6H_4	H	**2e**	3	67	83:17	94[g]
6	4-BrC_6H_4	H	**2f**	3	82	87:13	95[g]
7	4-$NO_2C_6H_4$	H	**2g**	3	81	82:18	95[g]
8	3-$NO_2C_6H_4$	H	**2h**	3	86	83:17	98[g]
9	2-naphtyl	H	**2i**	3	55	85:15	96[g]
10	$BnOCH_2$	H	**2j**	3	61	87:13	91[g]
11	Me	Me	**2k**	3	69	97:3	75[g]

[a] To a stirred solution of catalyst (10 mol%) in solvent (2 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Isolated yield after silica-gel column chromatography.
[c] The *dr* (*trans*/*cis*) was determined by chiral-phase GC analyses or NMR analyses of the crude product.
[d] The *ee* was determined by chiral-phase GC or HPLC analyses.
[e] Amount of formed product as determined by chiral-phase GC analyses.
[f] Reaction performed in *t*-BuOH:H_2O, 1:1 (2 mL).
[g] The *ee* was determined on the corresponding 2-epoxy-alcohols **13** after *in situ* reduction with $NaBH_4$ by chiral-phase HPLC analyses.

Substrates

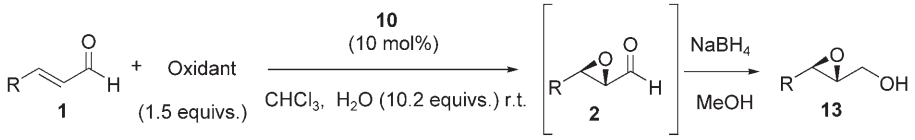
The chiral amine **10**-catalyzed asymmetric epoxidation of different α,β-unsaturated aldehydes **1** with H_2O_2 was also investigated (Table 5).

The α,β-unsaturated aldehydes **1a**–**1j** were excellent substrates for the chiral amine **10**-catalyzed stereoselective epoxidation reaction and the corresponding 2-epoxy aldehydes **2a**–**2j** were furnished in good to high yields with 91–98% *ee*. For instance, aldehyde **1h** was catalytically converted to the corresponding 2-epoxy aldeyde **2h** in 86% yield with 83:17 *dr* (*trans*:*cis*) with 98% *ee*. The 2-epoxy aldehydes **2e**–**2j** were also efficiently reduced *in situ* with excess $NaBH_4$ to the corresponding 2-epoxy alcohols **13e**–**13j**. We found that when the R group of the aldehydes **1** was aromatic a slightly higher enantiomeric excess was obtained as compared to when R was an aliphatic moiety. However, the enantioselectivity of the chiral amine **10**-catalyzed epoxidations of aliphatic α,β-unsaturated aldehydes was increased by performing the reaction in aqueous media (entry 2). In the case of 3-methyl-2-butenal **2k**, the reaction proceed with good enantioselectivity. We also investigated the direct catalytic asymmetric epoxidation of different aldehydes **1** with solid SPC or UHP (Table 6).

The organocatalytic asymmetric epoxidation reactions with SPC or UHP proceeded smoothly and the corresponding 2-epoxy aldehydes **2** or 2-epoxy alcohols **13** were isolated in high yields with high *dr* and 94–98% *ee*s. We also attempted the catalytic asymmetric epoxidation of α,β-unsaturated ketones with different oxidants and **10** or **12** as the organocatalysts. However, the TMS-protected diarylprolinols failed to furnish the desired epoxides. Instead, diarylprolinols such as **9** have been shown by Lattanzi to mediate the asymmetric epoxidation of α,β-unsaturated ketones.[10] In addition, we investigated the chiral diamines **5** and **6** for the direct catalytic asymmetric epoxidation of α,β-unsaturated aldehydes **1** (Table 7).

The diamines catalyzed the reaction with high diastereoselectivity and poor to good enantioselectivity.

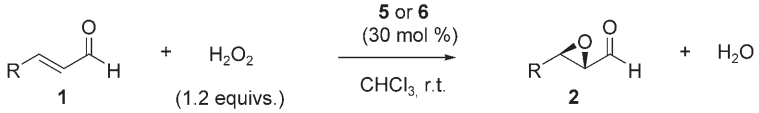
Table 6. Organocatalytic asymmetric epoxidation of aldehydes **1** with SPC and UHP.[a]



Entry	Oxidant	R	Prod.	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	SPC	Ph	**2a**	30	79	95:5	98
2	UHP[f]	Ph	**2a**	5	91	86:14	98
3	SPC	*n*-butyl	**2c**	36	70	95:5	94
4	SPC	4-ClC_6H_4	**13e**	26	73	87:13	97[e]
5	SPC	4-$NO_2C_6H_4$	**13g**	12	75	79:21	94[e]
6	UHP[f]	4-$NO_2C_6H_4$	**13g**	5	73	83:17	97[e]
7	SPC	$BnOCH_2$	**13j**	24	63	88:12	94[e]

[a] To a stirred solution of catalyst (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and oxidant (0.38 mmol + 50 μL H_2O). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The corresponding 2-epoxy alcohols, which were furnished by *in situ* reduction with $NaBH_4$, were isolated by silica-gel column chromatography.
[b] Isolated yield after silica-gel column chromatography.
[c] The *dr* (*trans*/*cis*) was determined by chiral-phase GC analyses or NMR analyses of the crude product.
[d] The *ee* was determined by chiral-phase GC or HPLC analyses.
[e] The *ee* was determined on the corresponding 2-epoxy alcohols **13** after *in situ* reduction with $NaBH_4$ by chiral-phase HPLC analyses.
[f] 0.6 mmol UHP + 50 μL H_2O were added.

Table 7. Organocatalytic asymmetric epoxidation of aldehydes **1** with catalysts **5** and **6**.



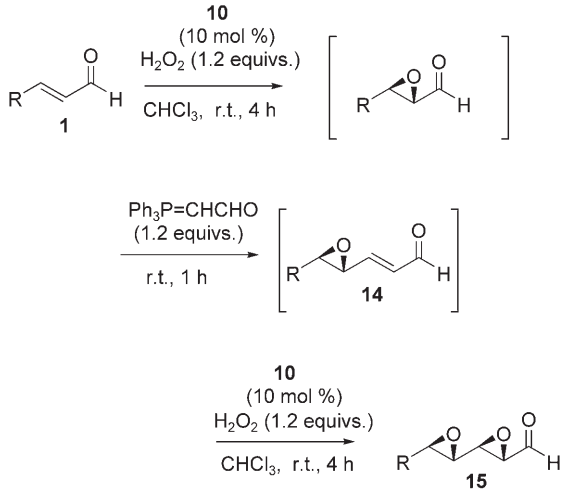
Entry	R	Cat.	Prod.	Temp. [°C]	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	**5**	**2a**	4	22	60	53:47	66
2	Ph	**5**[e]	**2a**	–20	19	94	81:19	60
2	*n*-propyl	**5**	**2b**	r.t.	20	70	81:19	14
3	*n*-propyl	**6**	**2b**	r.t.	20	81	84:16	6

[a] To a stirred solution of catalyst (30 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and oxidant (0.38 mmol + 50 μL H_2O). The reaction mixture was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The corresponding 2-epoxy aldehydes were isolated by silica-gel column chromatography.
[b] Isolated yield after silica-gel column chromatography.
[c] The *dr* (*trans*/*cis*) was determined by chiral-phase GC analyses or NMR analyses of the crude product.
[d] The *ee* was determined by chiral-phase GC analyses.
[e] 60 mol% catalyst was used.

The results show that the catalysts **5** and **6** did not have enough bulk for efficient shielding of the *Si*-face of the chiral iminium intermediate in the first Michael addition of the peroxide in the catalytic cycle (Scheme 1).

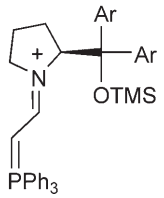
One-Pot Organocatalytic Asymmetric Tandem and Cascade Reactions

Intrigued by the biosynthesis of cells, which assemble complex molecules from simple precursors in an asymmetric fashion,[24] we decided to embark on the development of novel one-pot organocatalytic reactions based on asymmetric tandem and cascade catalysis with hydrogen peroxides and α,β-unsaturated aldehydes as the substrates.[25,26] Based on our previous investigations of one-pot asymmetric assembly of aminosugar derivatives,[27] we envisioned that one-pot direct asymmetric tandem epoxidation-Wittig reaction sequences would be excellent catalytic routes for the synthesis of α,β-unsaturated 4-epoxides **14** or 2,4-diepoxides **15** that are valuable chiral synthons (Scheme 2).



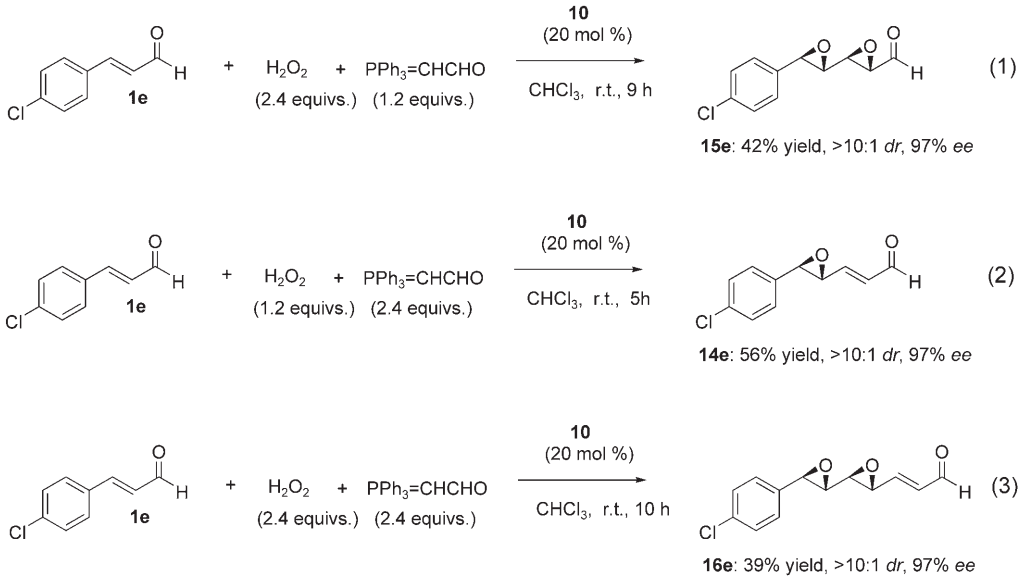
Scheme 2. The one-pot direct organocatalytic asymmetric tandem asymmetric synthesis of 2,4-diepoxy aldehydes.

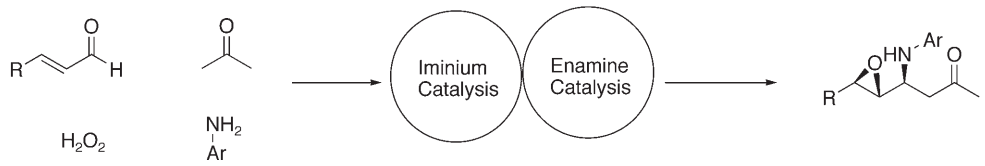
Thus, we reacted aldehyde **1e** with H_2O_2 (1.2 equivs.) in the presence of a catalytic amount of catalyst **10** (10 mol%). After 4 h the (formylmethylene)-triphenylphosphorane was added and the reaction was stirred for 1 h. Next, an additional amount of catalyst **10** (10 mol%) and H_2O_2 (1.2 equivs.) were added. More catalyst was added, since the initial catalyst may also be inhibited by forming a competing iminium intermediate with the (formylmethylene)triphenylphosphorane.



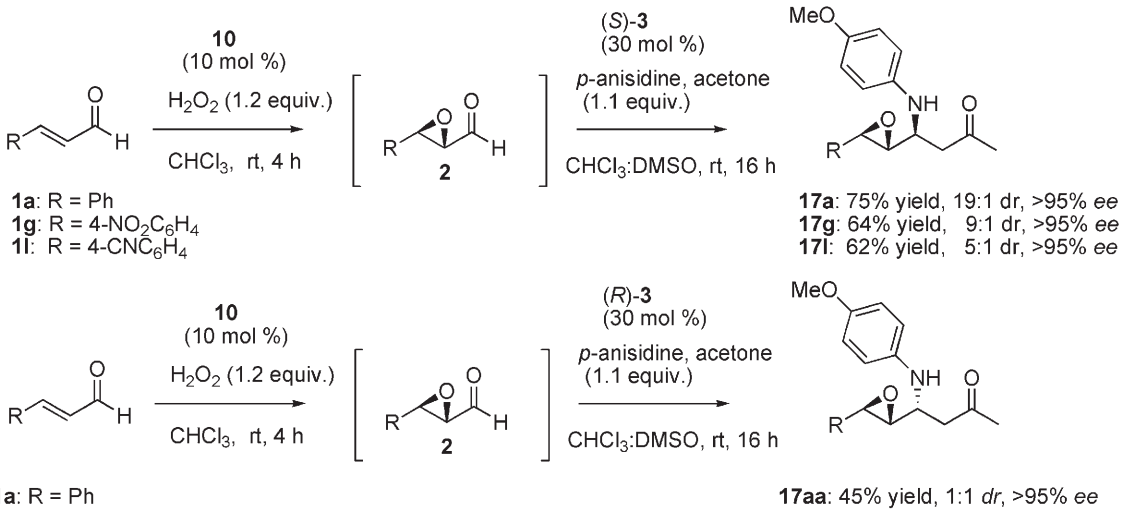
After 4 h of vigorously stirring, the reaction was quenched and the corresponding 2,4-diepoxy aldehyde **15e** was isolated in 42% yield with >10:1 *dr* and 97% *ee* [Eq. (1)].

The one-pot chiral amine **10**-catalyzed asymmetric tandem epoxidation-Wittig reaction allowed for the synthesis of α,β-unsaturated 4-epoxide **14e**, which was isolated in 56% yield with >10:1 *dr* and 97% *ee* [Eq. (2)]. Notably, a one-pot double organocatalytic asym-





Scheme 3. The one-pot direct organocatalytic asymmetric cascade epoxidation-Mannich reaction that is centered on iminium and enamine catalysis.



Scheme 4. One-pot direct organocatalytic asymmetric cascade epoxidation-Mannich reactions.

metric tandem epoxidation-Wittig reaction allowed for the synthesis of 4,6-diepoxy-α,β-unsaturated aldehyde **16e** with high stereoselectivity [Eq. (3)]. Thus, the one-pot organocatalytic asymmetric epoxidation-Wittig reaction sequences represents a simple and highly useful route for the synthesis of functional α,β-unsaturated 4-epoxides and 2,4-diepoxides. We also decided to investigate whether the concepts of iminium and enamine catalysis could be combined in a novel one-pot direct organocatalytic cascade asymmetric epoxidation-Mannich reaction (Scheme 3).[26]

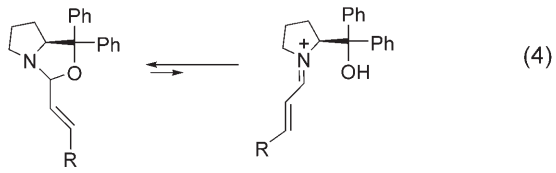
Hence, aldehydes **1** (0.25 mmol) were reacted with hydrogen peroxide (1.2 equivs.) in the presence of a catalytic amount of catalyst **10** (10 mol%) in $CHCl_3$ (1 mL) (Scheme 4 top). After 4 h of vigorous stirring DMSO (1 mL), acetone (0.5 mL), *p*-anisidine (1.1 equivs.), and a catalytic amount of (*S*)-proline **3** (30 mol%) were added to the reaction mixture. Proline was utilized as an additional organocatalyst, since catalyst **10** was a poor catalyst for the one-pot three-component Mannich reactions with ketones as donors.[28] The reactions were quenched after 16 h and the corresponding PMP (*p*-methoxyphenyl) protected 2-keto-4-amino-5-epoxides **17** were isolated in high yields and enantiomeric excesses together with a small amount of the aldol product from the reaction between acetone and 2-epoxy aldehyde **2**. Thus, the reactions proceed with high chemo- and enantioselectivity.

For instance, PMP-protected 4-amino-5-epoxy ketone **17a** was synthesized in one-step in 75% yield with 19:1 *dr* and >95% *ee*. The use of (*R*)-proline enabled the formation of the other diasterisomer **17aa** but low diastereoselectivity (Scheme 4 bottom). The novel one-pot organocatalytic asymmetric cascade reaction represents a simple way of getting access to valuable chiral synthons with high stereocontrol. Moreover, the results demonstrated that the employment of two different organocatalysts with orthogonal chemoselectivity can be a very powerful synthetic strategy.

Mechanism

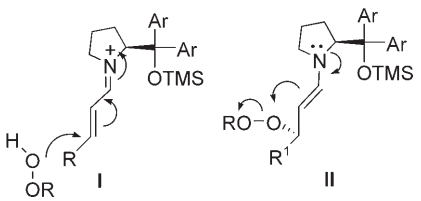
The stereochemistry of the chiral amine-catalyzed asymmetric epoxidation reactions was established by comparison of the optical rotation of aldehyde **2a** with the literature {$[\alpha]_D^{25}$: −30.1 (*c* 1.6, $CHCl_3$); Lit. *ent*-**2a** $[\alpha]_D^{23}$: +14.3 (*c* 0.48, $CHCl_3$)[4]} which revealed that the stereochemistry of the 2-epoxy aldehyde **2a** derived by chiral pyrrolidine derivative **5**, **6**, **10** and **12** catalysis was (2*S*,3*R*). The opposite enantiomer *ent*-**2a** was furnished by (*S*)-proline, (*S*)-prolinol and proline-

tetrazole **4** catalysis. The plausible mechanism of the amine-catalyzed asymmetric epoxidation reactions is depicted in Scheme 1. Accordingly, the reaction starts with iminium activation of the α,β-unsaturated aldehydes by the chiral pyrrolidine or proline followed by stereoselective nucleophilic conjugate attack on the β-carbon resulting in an enamine derivative. Next, the chiral enamine performs a nucleophilic attack on the peroxygen, followed by hydrolysis of the resulting iminium intermediate. The reverse mechanism has been observed in chiral pyrrolidine-catalyzed tandem α-aminoxylation-Michael reactions[11j,k,l] and aza-Diels–Alder[15a] reactions with α,β-unsaturated ketones, which further supports the proposed reaction mechanism. We also most recently found that catalysts **10** and **12** catalyze the enantioselective α-oxidation of aldehydes with $^1O_2$ *via* a catalytic enamine mechanism.[21] The remarkable change of reactivity by TMS protection of the diarylprolinols such as **9** was explained by prevention of aminal formation with the substrate [Eq. (4)] or product and increased hydrophobicity of the corresponding diarylprolinols **10** and **12**, which improves the rate of iminium formation with aldehydes **1**. This is in accordance with other protected diarylprolinol-catalyzed asymmetric transformations.[19,20] Moreover, the same effects are due to the rate acceleration when comparing protected prolinol **14** with prolinol **13**. The beneficial hydrophobic effect[29] also explains the rate acceleration and increased enantioselectivity of the **10**-catalyzed asymmetric epoxidation of α,β-unsaturated aliphatic aldehydes with hydrogen peroxide in aqueous media.

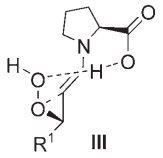


(4)

The high enantioselectivity observed for the asymmetric epoxidation reactions with catalysts **10** and **12** is plausibly due to stabilization of the configuration of the iminium ion intermediate as well as efficient shielding of the *Si*-face of the chiral iminium and enamine intermediates by the bulky aryl groups via the plausible intermediates **I** and **II**, respectively. The stabilization of the enamine intermediate **II** is supported by the high *trans*-selectivity of the asymmetric epoxidation reactions with **10** and **12**.



The stereochemistry of the chiral diamine **5**- and **6**-catalyzed asymmetric epoxidation was explained by a combination of shielding of the *Si*-face of the chiral iminium and enamine intermediates. In the case of (*S*)-proline, opposite facial attack occurs on the peroxygen by the plausible transition state **III** that results in formation of *ent*-**2**.



Investigation of the enantiomeric excess of 2-epoxyaldehyde **2a** as a function of the optical purity of the catalyst **10** revealed a slightly positive effect (Figure 1). We also found that the reaction is possibly first order with respect to the catalyst (Figure 2). In addition, the rate and consequently the conversion of the reaction decreased at lower optical purity of the catalyst (Figure 3). Thus, the barely noticeable positive non-linear effect in Figure 1 may be due to an *in situ* kinetic resolution of catalyst **10** by the chiral 2-epoxy aldehyde **2a**.[30]

Conclusions

In summary, we have shown that several simple chiral pyrrolidine derivatives and amino acid-derived imidazolidinones catalyze the direct asymmetric epoxidation of α,β-unsaturated aldehydes with peroxides. In particular, TMS-protected diarylprolinols such as **10** and **12** were excellent catalysts and furnished the corresponding 2-epoxy aldehydes in high yields, diastereo- and enantioselectivities (91–98% *ee*). Notably, the diarylprolinol **10**-catalyzed asymmetric epoxidation reaction with hydrogen peroxide was efficient and highly enantioselective in water or water alcohol solutions. In addition, highly stereoselective one-pot organocatalytic asymmetric tandem epoxidation-Wittig reaction sequences were developed. The one-pot catalytic asymmetric tandem epoxidation-Wittig reactions were done in an iterative fashion and gave 2,4-diepoxy aldehydes or α,β-unsaturated 4-epoxy aldehydes in good yield and enantiomeric excess. Moreover, a novel organocatalytic asymmetric cascade epoxidation-Mannich reaction was developed. The catalytic enantioselective cascade reaction assembled 2-keto-4-amino-5-epoxides in an asymmetric fashion with high diastereo- and enantioselectivities. The organocatalytic epoxidation reactions proceed via a plausible combined iminium and enamine mechanism. Furthermore, the high enantioselectivity observed for the asymmetric epoxidation reactions with catalysts **10**

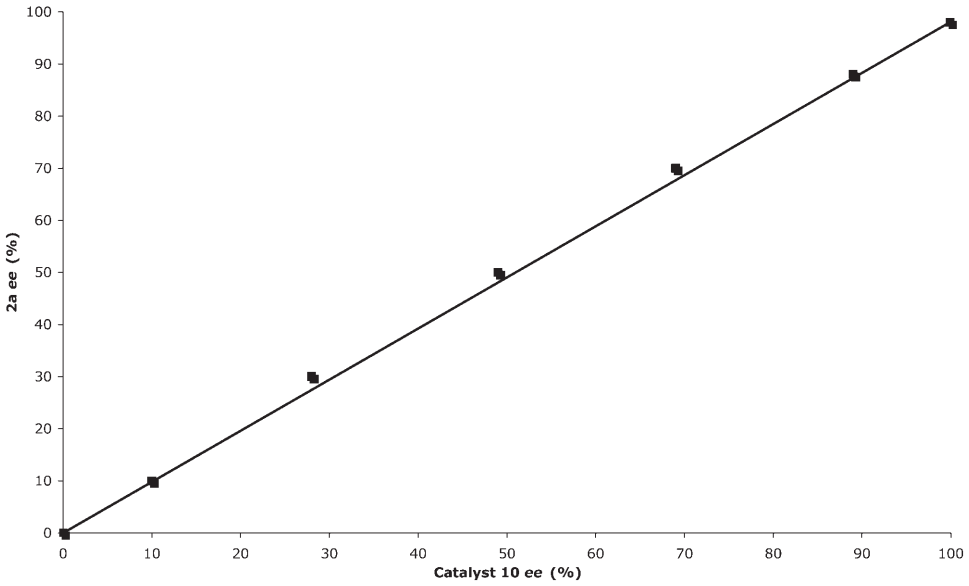


Figure 1. The enantiomeric excess of 2-epoxy aldehyde **2a** as a function of the enantiomeric excess of the (*S*)-**10** (■)-catalyzed direct asymmetric epoxidation of **1a**.

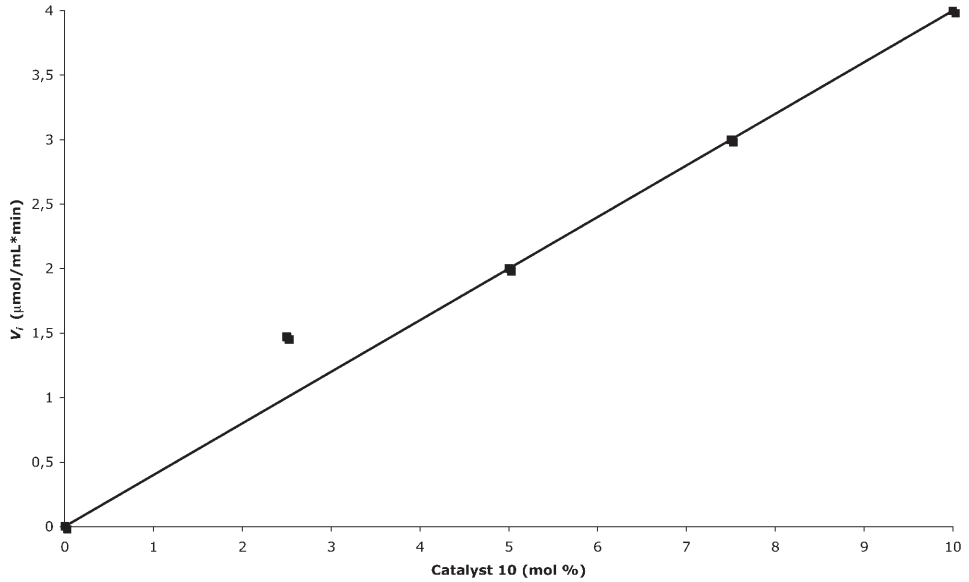


Figure 2. The initial rate V_i [µmol/(mL min)] of the asymmetric epoxidation of **1a** as a function of the amount of (*S*)-**10** (■) (mol%, 10 mol% = 25 µmol/mL). The initial rates have at least been collected 3 times and averaged.

and **12** is possibly due to efficient stabilization of the configuration of the iminium ion intermediate as well as efficient shielding of the *Si*-face of the chiral iminium and enamine intermediates by the bulky aryl groups. The ability of natural amino acids to catalyze the reaction suggest that the amine-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes might be present in Nature.[31]

Experimental Section

General Methods

Chemicals and solvents were either purchased *puriss p. A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), Ce-

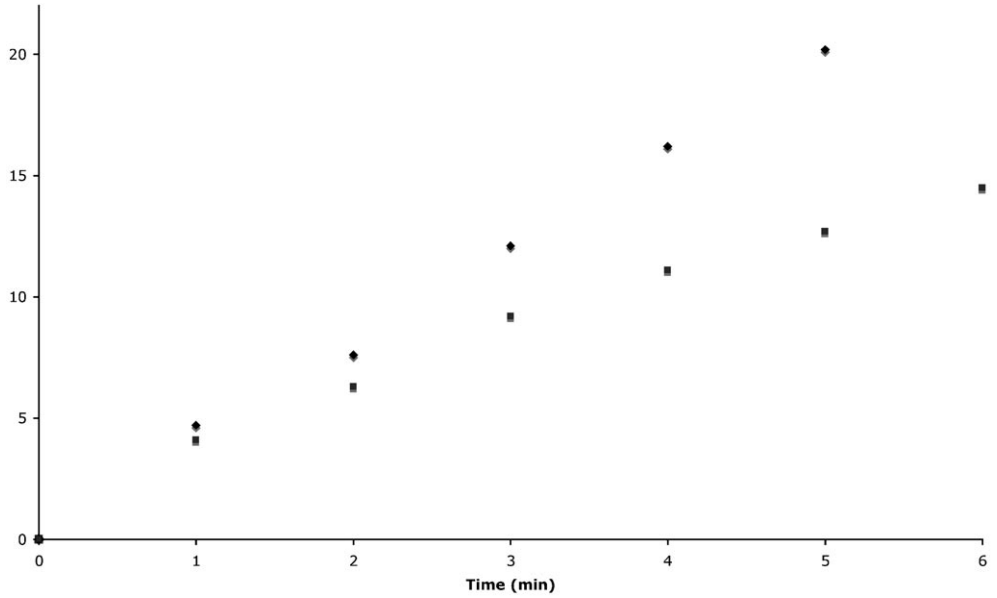


Figure 3. The amount of 2-epoxy aldehyde **2a** formed (%) when enantiopure catalyst (*S*)-**10** (◆) and (*S*)-**10** with 10% *ee* (■), respectively, were used as the catalysts for the organocatalytic asymmetric epoxidation of **1a**.

$(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400. Chemical shifts are given in d relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. GC was carried out using a Varian 3800 GC Instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 polarimeter ($\lambda = 589$ nm, 1 dm cell). High-resolution mass spectra (ESI) were obtained with a Bruker MicrOTOF spectrometer. The spectral data of chiral products **2a** are known.[4]

Preparation of Catalyst 10

The commercially available catalyst **9** (1 g, 3.95 mmol) was readily protected with TMSOTf (1.1 g, 5.1 mmol) in the presence of TEA (0.51 g, 5.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 17 h and quenched with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were stirred with $NaHCO_3$ for 15 min, dried over anhydrous Na_2SO_4 and concentrated under vacuum after filtration. Purification with silica gel column chromatography (EtOAc:pentane, 1:7→1:3) furnished **10** as a thick oil; yield: 1.3 g (99%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = -0.03$ (s, 9H), 1.53–1.71 (m, 4H), 2.81–2,93 (m, 2H), 4.09 (t, $J = 7.0$ Hz, 1H), 7.22–7.53 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 2.4$, 25.1, 28.0, 47.3, 65.5, 83.3, 126.8, 127.0, 128.0, 129.0, 146.0, 147.0.

Catalysts **12** and **14** were prepared by the same procedure.

General Procedure for the Organocatalytic Asymmetric Epoxidation of α,β-Unsaturated Aldehydes with H_2O_2 Catalyzed by 10 and 12

To a stirred solution of **10** or **12** (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). The reaction was vigorously stirred at room temperature for the times shown in the Tables. The crude reaction mixture was passed through a silica gel column (pentane/EtOAc or toluene/EtOAc mixtures) to give oxirane-2-carbaldehydes **2** or the temperature of the reaction mixture was decreased to 0 °C and MeOH (1 mL) and excess $NaBH_4$ was added. The reaction was quenched by addition of EtOAc and aqueous solution of NH_4Cl. The organic layer was dried, concentrated and the crude product purified by silica-gel column chromatography (toluene/EtOAc mixtures) to give the corresponding 2-epoxy alcohols **13**.

General Procedure for the Chiral amine 10-Catalyzed Asymmetric Epoxidation of α,β-Unsaturated Aldehydes with SPC or UHP

To a stirred solution of **10** (10 mol%) in solvent (2 mL) was added aldehyde **1** (0.25 mmol) and SPC or UHP (0.38 mmol + 50 μL H_2O). The reaction mixture was vigorously stirred at room temperature for the time shown in the Tables and monitored by chiral-phase GC analyses or NMR analysis. The crude reaction mixture was passed through a silica gel column (pentane/EtOAc or toluene/EtOAc mixtures) to give oxirane-2-carbaldehydes **2** or the temperature of the reaction mixture was decreased to 0 °C

and MeOH (1 mL) and excess $NaBH_4$ was added. The reaction was quenched by addition of EtOAc and aqueous solution of NH_4Cl. The organic layer was dried, concentrated and the crude product purified by silica-gel column chromatography (toluene/EtOAc mixtures) to give the corresponding 2-epoxy-alcohols **13**.

(2*S*,3*R*)-3-Phenyloxirane-2-carbaldehyde (2a): ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.20$ (d, $J = 6.1$ Hz, 1H), 7.39–7.29 (m, 5H), 4.17 (d, $J = 1.8$ Hz, 1H), 3.46 (dd, $J = 1.8$, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 196.7$, 134.2, 129.2, 128.8 (2C), 125.7 (2C), 62.9, 56.6; The formation and enantiomeric excess of **2a** was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature program: 70 °C to 160 °C, rate; 10 °C min^{-1}, hold 1 min, 160 °C to 200 °C, rate; 80 °C min^{-1}, hold 5 min. R_t (min) = major enantiomer 8.04 min, minor enantiomer 8.12 min; $[\alpha]_D^{25}$: −30.1 (*c* 1.6, $CHCl_3$) {Lit. *ent*-**2a**, $[\alpha]_D^{23}$: +14.3 (*c* 0.48, $CHCl_3$, 94% *ee*)[9]}; MALDI-TOF-MS: *m/z* = 171.0423; $C_9H_8NO_2$ ($M+Na^+$: calcd.: 171.0422); IR (film): $\nu = 3038$, 2823, 1732 cm^{-1}

(2*S*,3*R*)-3-Propyloxirane-2-carbaldehyde (2b):[32a,b] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.97$ (t, $J = 7.2$ Hz, 3H), 1.46–4.54 (m, 2H), 1.60–1.68 (m, 2H), 3.12 (dd, $J = 6.3$, 1.8 Hz, 1H), 3.22 (dt, $J = 5.4$, 1.8 Hz, 1H), 9.00 (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$, 19.3, 33.3, 56.7, 59.2, 198.6; The enantiomeric excess was determined on a Chromasil CP-Chirasil-DexCB column, temperature program: 70–130 °C, rate: 7 °C min^{-1}, hold 1 min, 130–200 °C, rate: 80 °C min^{-1}, hold 7 min. Major isomer: t_R = 4.799 min; minor isomer: t_R = 4.906 min; $[\alpha]_D^{25}$: −41.3 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-3-Butyloxirane-2-carbaldehyde (2c):[32c] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$–0.94 (m, 3H), 1.35–1.46 (m, 4H), 1.63–1.68 (m, 2H), 3.13 (dd, $J = 2.0$, 6.0 Hz, 1H), 3.21–3.24 (m, 1H), 9.01 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $<\iota\tau>\delta<\iota\tau> = 13.84$, 22.31, 27.84, 30.88, 56.77, 59.15, 198.49; The *ee* was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature program: 70 °C to 130 °C, rate; 7 °C min^{-1}, hold 1 min, 130 °C to 200 °C, rate; 80 °C min^{-1}, hold 7 min. R_t (min) = 5.32 (major enatiomer); 5.43(minor enationer); $[\alpha]_D^{25}$: −26.5 (*c* 0.56, $CHCl_3$).

(2*S*,3*S*)-Ethyl 3-formyloxirane-2-carboxylate (2d):[33] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (t, $J = 7.3$ Hz, 3H), 3.76 (dd, $J = 1.8$, 6.8 Hz, 1H), 3.77 (d, $J = 1.8$ Hz, 1H), 4.23 (m, 2H), 9.05 (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 50.8, 57.5, 62.6, 166.1, 195.0; The *ee* was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature program: 70 °C to 85 °C, rate; 5 °C min^{-1}, hold 20 min, R_t (min) = 17.6 (major enatiomer); 18.9 (minor enationer); $[\alpha]_D^{25}$: −33.7 (*c* 0.61, $CHCl_3$).

(2*S*,3*R*)-3-(4-Chlorophenyl)-oxirane-2-carbaldehyde (2e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.40$ (dd, $J = 1.8$, 6.0 Hz, 1H), 4.15 (d, $J = 1.8$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 9.17 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.4$, 63.1, 127.3 (2C), 129.3 (2C), 133.0, 135.3, 196.8; The *ee* was determined after $NaBH_4$ reduction to the alcohol **13e**. $[\alpha]_D^{25}$: −38.0 (*c* 1.7, $CHCl_3$). IR (film): $\nu = 3437$, 2827, 1728 cm^{-1}.

[(2*R*,3*R*)-3-(4-Chlorophenyl)oxiran-2-yl]methanol (13e):[34] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.33$ (br s, 1H), 3.15–3.18 (m, 1H), 3.78 (dd, $J = 3.9$, 12.9 Hz, 1H), 3.90 (d, $J = 1.8$ Hz, 1H), 4.03 (dd, $J = 2.1$, 12.9 Hz, 1H), 7.18–7.20 (m, 2H), 7.30–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 54.9$, 61.0, 62.5, 127.0, 128.7, 134.1, 135.2; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (92:8) as the eluent: R_t (min) = 25.283 (major enantiomer); 28.964 (minor enantiomer). $[\alpha]_D^{25}$: +32.3 (*c* 1.0, $CHCl_3$).

[(2*R*,3*R*)-3-(4-bromophenyl)oxiran-2-yl]methanol (13f):[35] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$ (br s, 1H), 3.16–3.18 (m, 1H), 3.79 (dd, $J = 3.6$, 12.8 Hz, 1H), 3.89 (d, $J = 2.0$ Hz, 1H), 4.03 (dd, $J = 2.4$, 12.8 Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 53.9$, 61.0, 62.5, 122.2, 127.3, 131.6, 135.8; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (92:8) as the eluent: R_t (min) = 28.07 (major enantiomer); 32.89 (minor enantiomer); $[\alpha]_D^{25}$: +23.1 (*c* 1.0, $CHCl_3$).

[(2*R*,3*R*)-3-(4-Nitrophenyl)oxiran-2-yl]methanol (13g):[36] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$ (br s, 1H), 3.18–3.20 (m, 1H), 3.85 (d, $J = 12.8$ Hz, 1H), 4.04–4.08 (m, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 8.18 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 54.3$, 60.7, 63.0, 123.7, 126.4, 144.4, 147.8; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (92:8) as the eluent: R_t (min) = 80.50 (major enantiomer); 91.98 (minor enantiomer); $[\alpha]_D^{25}$: +25.0 (*c* 1.0, $CHCl_3$).

[(2*R*,3*R*)-3-(3-Nitrophenyl)oxiran-2-yl]methanol (13h): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (br s, 1H), 3.20–3.22 (m, 1H), 3.85 (dd, $J = 3.6$, 12.9 Hz, 1H), 4.04–4.09 (m, 2H), 7.46–7.56 (m, 1H), 7.60–7.68 (m, 1H), 8.07–8.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 54.3$, 60.7, 62.8, 120.6, 123.1, 129.5, 131.7, 139.2, 148.4; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (92:8) as the eluent: R_t (min) = 69.60 (major enantiomer); 72.45 (minor enantiomer). $[\alpha]_D^{25}$: + 40.2 (*c* 1.0, $CHCl_3$). HR-MS(ESI): *m/z* = 196.0605, calcd. for $[M+H]^+$ ($C_9H_{10}NO_4$): 196.0604; IR (film): $\nu = 3265$, 2922, 1520 cm^{-1}.

[(2*R*,3*R*)-3-(naphthalen-1-yl)oxiran-2-yl]methanol (13i):[37] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.96$ (br s, 1H), 3.32–3.33 (m, 1H), 3.86 (dd, $J = 6.6$, 12.9 Hz, 1H), 4.07–4.12 (m, 2H), 7.32–7.50 (m, 3H), 7.80–7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.8$, 61.2, 62.5, 122.9, 123.9, 125.2, 125.4, 126.2, 126.4, 126.5, 127.8, 128.1, 128.4; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (92:8) as the eluent: R_t (min) = 93.11 (minor enantiomer); 101.29 (major enantiomer). $[\alpha]_D^{25}$: +20.8 (*c* 1.0, $CHCl_3$).

[(2*R*,3*R*)-3-(Benzyloxymethyl)oxiran-2-yl]methanol (13j):[38] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.02$ (br s, 1H), 3.09–3.10 (m, 1H), 3.22–3.24 (m, 1H), 3.53 (dd, $J = 5.6$, 12.0 Hz, 1H), 3.63 (dd, $J = 4.0$, 12.0 Hz, 1H), 3.77 (dd, $J = 2.8$, 8.4 Hz, 1H), 3.92 (dd, $J = 3.2$, 12.8 Hz, 1H), 4.52–4.61 (m, 2H), 7.27–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 54.2$, 55.7, 61.1, 69.6, 73.3, 127.7, 127.8, 128.4, 137.7; The *ee* was determined by HPLC on Daicel Chiralpak OJ column, with isohexane/*i*-PrOH (95:5) as the eluent: R_t (min) = 142.79 (major enantiomer); 160.97 (minor enantiomer). $[\alpha]_D^{25}$: +10.5 (*c* 1.0, $CHCl_3$).

(*R*)-(3,3-Dimethyloxiran-2-yl)methanol (13k):[39] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (s, 3H), 1.33 (s, 3H), 2.19 (br s, 1H), 2.95–2.99 (m, 1H), 3.66 (dd, $J = 6.8$, 12.0 Hz, 1H), 3.82 (dd, $J = 4.0$, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.8$, 24.7, 58.9, 61.4, 63.8; The *ee* was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature pro-

gram: 60 °C to 100 °C, rate: 2 °C min^{-1}, hold 1 min, 100 °C to 200 °C, rate; 100 °C min^{-1}, hold 3 min. R_t (min) = 14.839 (minor enatiomer); 15.421 (major enationer); $[\alpha]_D^{25}$: +10.2 (*c* 1.0, $CHCl_3$).

Typical Procedure for the One-Pot Organocatalytic Tandem Asymmetric Epoxidation-Wittig Reaction

To a stirred solution of **10** (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). After 4 h (formylmethylene)triphenylphosphorane (0.3 mmol) was added and the reaction mixture was stirred for 1 h. Next, the crude reaction mixture was directly loaded onto a silica gel column and chromatography with pentane/EtOAc (10/1) gave (*E*)-3-[(2*R*,3*R*)-3-(4-chlorophenyl)oxiran-2-yl]acrylaldehyde (**14e**) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53–3.55 (m, 1H), 3.87 (d, *J* = 1.6 Hz, 1H), 6.43 (ddd, *J* = 16.0, 8.0, 0.8 Hz, 1H), 6.66 (dd, *J* = 16.0, 6.8 Hz, 1H), 7.22–7.27 (m, 2H), 7.33–7.35 (m, 2H), 9.61 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.8, 61.1, 127.4, 129.3, 134.3, 134.5, 135.1, 151.2, 192.6; $[\alpha]_D^{25}$: +228.9 (*c* 1.0, $CHCl_3$). HR-MS (ESI): *m/z* = 209.0360, calcd. for $[M+H]^+$ ($C_{11}H_{10}ClO_2$): 209.0364. IR (film): ν = 3646, 3418, 1645 cm^{-1}.

Typical Procedure for the One-Pot Organocatalytic Asymmetric Tandem Epoxidation-Wittig Reaction

To a stirred solution of **10** (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). After 4 h (formylmethylene)triphenylphosphorane (0.3 mmol) was added and the reaction mixture was stirred for 1 h. Next, an additional amount of catalyst **10** (10 mol%) and H_2O_2 (1.2 equivs.) were added. After 4 h of vigorously stirring, the crude reaction mixture was directly loaded onto a silica gel column and chromatography with pentane/EtOAc (10/1) gave (2*R*,3*S*,2′*S*,3′*R*)-3′-(4-chlorophenyl)-[2,2′]bioxiranyl-3-carbaldehyde (**15e**) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (dd, *J* = 1.6 Hz, 2.0 Hz, 1H), 3.45–3.48 (m, 2H), 3.88 (d, *J* = 1.6 Hz, 1H), 7.18–7.20 (m, 2H), 7.30–7.34 (m, 2H), 9.10 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0, 55.6, 56.3, 58.6, 127.0, 128.9, 134.0, 134.6, 196.6; $[\alpha]_D^{25}$: +75.1 (*c* 1.0, $CHCl_3$); MALDI-TOF-MS: *m/z* = 247.0139; calcd. for $C_{11}H_9ClO_3$ ($M+Na^+$): 247.0138. IR (film): ν = 3508, 3019, 1732 cm^{-1}.

Typical Procedure for the One-Pot Organocatalytic Asymmetric Tandem Double Epoxidation-Wittig Reaction

To a stirred solution of **10** (10 mol%) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). After 4 h the (formylmethylene)triphenylphosphorane (0.3 mmol) was added and the reaction mixture was stirred for 1 h. Next, an additional amount of catalyst **10** (10 mol%) and H_2O_2 (1.2 equivs.) were added. After 4 h of vigorously stirring, the (formylmethylene)triphenylphosphorane (0.3 mmol) was again added and the reaction mixture stirred for 1 h. Next, the crude reaction mixture was directly loaded onto a silica gel column and chromatography with pentane/EtOAc (6/1) gave the α,β-unsaturated-4,6-diepoxy aldehyde **16e** as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (dd, *J* = 3.2, 2.0 Hz, 1H), 3.23 (dd, *J* = 3.2, 2.0 Hz, 1H), 3.68 (dd, *J* = 6.8, 2.0 Hz, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 6.44 (dd, *J* = 16.0, 7.6 Hz, 1H), 6.57 (dd, *J* = 16.0, 6.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 9.59 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9, 55.8, 58.5, 59.2, 127.1, 129.1, 134.5, 134.6, 142.7, 150.7, 192.3. $[\alpha]_D^{25}$: +56.7 (*c* 0.6, $CHCl_3$). HR-MS (ESI): *m/z* = 251.0458, calc. for $[M+H]^+$ ($C_{13}H_{12}ClO_3$): 251.0469. IR (film): ν = 3479, 2925, 1694 cm^{-1}.

Typical Procedure for the One-Pot Organocatalytic Asymmetric Cascade Epoxidation-Mannich Reaction

To a stirred solution of **10** (10 mol%) in $CHCl_3$ (1 mL) was added aldehyde **1** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). After 4 h of vigorous stirring DMSO (1 mL), acetone (0.5 mL), *p*-anisidine (0.28 mmol), and a catalytic amount of (*S*)-proline **3** or *ent*-**3** (30 mol%) were added to the reaction mixture. The one-pot reaction mixture was stirred for 16 h and quenched by extraction with brine and EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, concentrated and purified by silica-gel column chromatography (toluene/EtOAc) to give the corresponding PMP protected amino epoxides **17** as yellow oils.

17a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.84 (d, *J* = 6.5 Hz, 2H), 3.23 (t, *J* = 4.7 Hz, 1H), 3.76 (s, 3H), 3.89 (d, *J* = 2.1 Hz, 1H), 4.21 (m, 1H), 6.63 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.17–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 46.1, 49.2, 55.9, 56.7, 64.2, 115.1, 115.3, 125.8, 128.4, 129.0, 137.0, 140.8, 152.8, 207.1; $[\alpha]_D^{25}$: +21.9 (*c* 1.0, $CHCl_3$); MALDI-TOF-MS: *m/z* = 334.1420, calcd. for $C_{19}H_{21}NO_3$ ($M+Na^+$): 334.1419. IR (film): ν = 3434, 1645 cm^{-1}.

17g: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.87 (m, 2H), 3.21 (t, *J* = 2.2 Hz, 1H), 3.76 (s, 3H), 3.99 (d, *J* = 2.0 Hz, 1H), 4.23 (m, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 46.1, 48.9, 55.9, 56.0, 64.8, 115.2, 115.4, 124.0, 126.6, 140.5, 144.7, 148.1, 153.1, 206.9; $[\alpha]_D^{25}$: +26.8 (*c* 1.0, $CHCl_3$). HR-MS (ESI): *m/z* = 357.1445, calcd for $[M+H]^+$ $C_{19}H_{22}N_2O_5$: 357.1445. IR (film): ν = 3401, 1642 cm^{-1}.

17l: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.85 (m, 2H), 3.17 (t, *J* = 2.2 Hz, 1H), 3.75 (s, 3H), 3.92 (d, *J* = 2.1 Hz, 1H), 4.20 (m, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $<\iota\tau>\delta</\iota\tau>$ = 30.8, 46.1, 48.9, 55.9, 56.0, 64.6, 115.1, 115.3, 126.4, 132.51, 140.5, 141.2, 142.7, 153.0, 206.9; $[\alpha]_D^{25}$: +41.2 (*c* 1.0, $CHCl_3$). HR-MS (ESI): *m/z* = 337.1544, calcd. for $[M+H]^+$ $C_{20}H_{21}N_2O_3$: 337.1547. IR (film): ν = 3391, 1660 cm^{-1}.

17aa: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 2.84 (d, *J* = 6.0 Hz, 2H), 3.22 (t, *J* = 2.4 Hz, 1H), 3.73 (s, 3H), 3.89 (d, *J* = 2.0 Hz, 1H), 4.40 (m, 1H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.19–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 46.1, 49.3, 56.0, 56.8, 64.2, 115.2, 116.2, 126.6, 128.7, 130.5, 136.8, 140.8, 153.1, 207.1; MALDI-TOF-MS: *m/z* = 334.1419, calcd. for $C_{19}H_{21}NO_3$ ($M+Na^+$): 334.1419. IR (film): ν = 3434, 1645 cm^{-1}.

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