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Chiral pyrrolidinium salts as organocatalysts in the stereoselective 1,4-conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde

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Abstract—A variety of enantiopure proline derived pyrrolidinium $(HX)_n$ salts have been found to catalyse the 1,4-conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde with, in some cases, high diastereo- and enantioselectivity. Parameters such as water activity, choice of acidic cocatalyst $(HX)_n$ and also the amount of cocatalyst used turned out to be crucial for the diastereo- and enantioselectivity of the reaction.

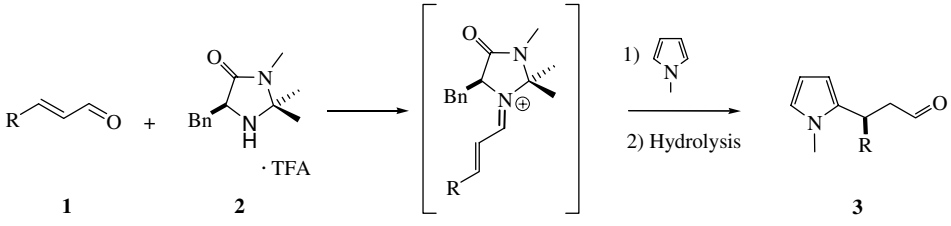
1. Introduction

The use of organocatalysts in asymmetric synthesis is rapidly increasing. One reason is that they are often easy to use (i.e., can be operated under aerobic conditions) and are environmentally friendly (i.e., less hazardous than many heavy metals used in metal catalysis).[1] The scope of organocatalytic reactions has been expanded considerably upon in the recent years and accordingly the design of novel catalysts has grown rapidly.[1–3] Organocatalysts used today, most commonly consist of a Brönsted acid and a Lewis base centre.[1,2]

The 1,4-conjugate addition has been an important reaction in organic synthesis for many years and recently Paras and MacMillan[4] increased the usefulness of this reaction when they used the chiral catalyst **2** (see Scheme 1).

This reaction is the first known enantioselective organocatalysed Fridel–Crafts alkylation. Aldehyde **1** reacts with *N*-methylpyrrole to yield the chiral aldehyde **3** via the formation of an iminum species incorporating organocatalyst **2** (see Scheme 1). The product obtained, **3**, serves as a valuable synthon for the construction of biomedical agents.[4]

To increase the scope of this organocatalysed reaction further, our interest turned to the use of a 2,2-disubstituted α,β-unsaturated aldehyde **5** (see Scheme 2). Thus, the 1,4-conjugate addition of *N*-methylpyrrole would then give a more complex adduct, which consists of



Scheme 1. Organocatalysed Friedel–Crafts alkylation via an iminium species.

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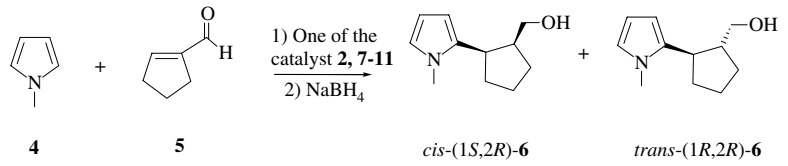
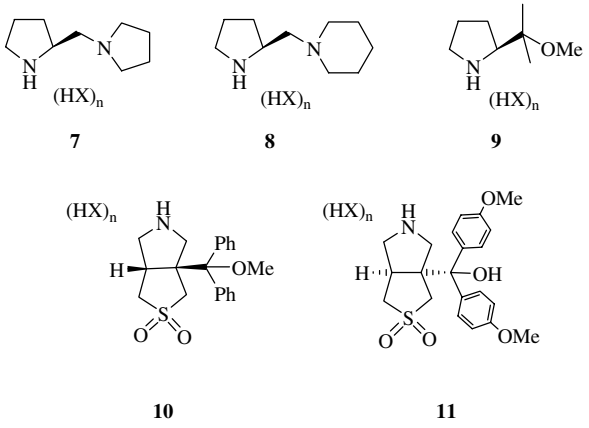


4 5 *cis*-(1*S*,2*R*)-**6** *trans*-(1*R*,2*R*)-**6**

Scheme 2. Conjugate addition of *N*-methylpyrrole **4** to the 2,2-disubstituted α,β-unsaturated aldehyde **5** catalysed by various organocatalysts.

two new stereogenic centres and these new adducts might be of synthetic interest as chiral ligands. We also investigated the catalytic performance of some other organic catalysts that have not been used in this type of reaction before (Fig. 1).



7 **8** **9** **10** **11**

Figure 1. Various organocatalysts used in the conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde.

2. Results and discussion

Catalysts **7** and **8** were prepared from L-proline following the protocol of a published four-step synthesis.[5] We obtained **7** and **8** enantiomerically pure and in a total yield of 19% and 22%, respectively. Catalyst **2** was also obtained enantiomerically pure and in a total yield of 70%, following a published procedure.[6] Catalysts **9**,[7] **10**[8] and **11**[8] were used from the same batches as the published ones.

The reaction of *N*-methylpyrrole **4** with cyclopent-1-ene carbaldehyde **5** was carried out under aerobic conditions by mixing **4**, **5** and 10 mol % of the catalyst in DMF (containing a small amount of added water). The reaction was normally complete within 72 h as judged by GC analysis. Mixtures with different ratios of the four stereoisomers of 2-(1-methyl-1*H*-pyrrol-2-yl)cyclopentane carbaldehyde were obtained.

We first investigated catalyst **2** previously used by Paras and MacMillian[4] in a similar reaction. This gave a moderate *cis*-**6**/*trans*-**6** ratio (Table 1, entry 1) and low enantioselectivity. We then tested the proline derived organocatalysts **7**, **8** and **9**. Catalyst **7** (entry 2) showed promising enantioselectivity but the *cis*-**6**/*trans*-**6** ratio was close to 1. In an attempt to improve the selectivity, we performed the reaction at lower temperatures (5 °C entry 3 and −25 °C entry 4). A slight improvement of the ratio for the *trans*-**6** enantiomers [*trans*-(1*R*,2*R*)-**6**:*trans*-(1*S*,2*S*)-**6**, 84:16] was noticed at the lower temperature (entry 4).

Adding 2 equiv of the acidic cocatalyst to the free base of the two catalysts **7** and **8** improved the ratio of the *cis*-**6** enantiomer pair [*cis*-(1*R*,2*S*)-**6**/*cis*-(1*S*,2*R*)-**6**] to 88:12 for both catalysts (entries 6 and 7), moreover this also influenced the *cis*-**6**/*trans*-**6** ratio. Catalyst **9** (entry 8) gave a very poor *cis*-**6** to *trans*-**6** ratio (51:49). Catalysts **10** (entry 9) and **11** (entry 10) gave the highest diastereoselectivity of the tested catalysts. Unfortunately, the enantiomeric ratios of *trans*-**6** and *cis*-**6** enantiomer

Table 1. The conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde catalysed by various organocatalysts[a]

Entry[a]	Catalyst	Cocatalyst $(HX)_n$	Temperature (°C)	*cis*-**6**/*trans*-**6**[b]	*cis*-(1*R*,2*S*)-**6**/*cis*-(1*S*,2*R*)-**6**[c]	*trans*-(1*R*,2*R*)-**6**/*trans*-(1*S*,2*S*)-**6**[c]
1	**2**	HCl	25	27:73	44:56	55:45
2	**7**	HCl	25	44:56	68:32	72:28
3	**7**	HCl	5	50:50	71:29	74:26
4	**7**	HCl	−25	50:50	70:30	84:16
5	**8**	HCl	25	30:70	69:31	72:28
6	**7**	2 HCl	25	35:65	88:12	83:17
7	**8**	2 HCl	25	44:56	88:12	79:21
8[d]	**9**	HCl	25	51:49	37:63	54:46
9[e]	**10**	HCl	25	9:91	54:46	74:26
10[e]	**11**	HCl	25	16:84	65:35	48:52

[a] All experiments were carried out at the specified temperature in 2 ml of DMF (with 40 μl of water added), using 84 mg (0.88 mmol) of aldehyde **5**, 10 mol % of the catalyst and 390 μl (4.4 mmol) of *N*-methylpyrrole **4**. A diastereomeric mixture of *cis*- and *trans*-**6** was obtained after reduction ($NaBH_4$) in a typical yield of 55%.

[b] The *cis*-**6**/*trans*-**6** ratio was determined using a GC EC-1 column.

[c] Enantiomeric ratio was measured on the corresponding aldehyde, using a chiral GC β-dex 325 column.

[d] The reaction was carried out with 80 μl of water added.

[e] The reaction was carried out with 20 μl of water added.

pairs remained low except for the moderate *trans*-**6** enantiomer pair ratio obtained with catalyst **10** (74:26). The amount of acidic cocatalyst used seems to influence the outcome of the reaction when using the two proline derived catalysts **7** and **8**. Thus, the influence of the $(HX)_n$ cocatalyst on stereoselectivity was investigated further by preparing a variety of different pyrrolidinium salts of **8** (Table 2).

It is obvious from entries 13 and 14 (HI) and 15 and 16 (TFA) that the dipyrrolidinium salts tested gave higher *trans*-**6** selectivity compared to the mono salts. The best *trans*-**6** selectivity (*cis*-**6**/*trans*-**6** ratio of 3:97, entry 14) was obtained with 2 equiv of HI. This entry also showed among the best ratios between the enantiomer pairs (84:16 for *cis*-**6** and 81:19 for *trans*-**6** enantiomers, respectively).

Interestingly, it is also obvious from entries 11 and 12 (HBr) and 17 and 18 (TsOH) that these dipyrrolidinium salts of acidic cocatalysts gave higher *cis*-**6** selectivity compared to the mono salts. When using the $HClO_4$ salts (entries 19 and 20), no effect was observed on the *cis*-**6**/*trans*-**6** ratio when 2 equiv were added, although both the *cis*-**6** and *trans*-**6** enantioselectivity increased as for all other entries when adding 2 equiv of acidic cocatalyst. Both enantiomers of tartaric acid were also examined as a cocatalyst, but no conversion was registered even at different water activities.

We noted in our preliminary trials that small changes in the water activity influenced the stereoselectivity of the reaction in a very interesting way. Thus, we investigated this further by using the di-iodopyrrolidinium salt from **8** in a series of experiments, where the influence of added water was studied. At low and at high water activity (Table 3 entry 22, no water added and entries 27–28, 80–200 μl water added) the *trans*-**6** selectivity was low. To obtain the *trans*-**6** enantiomers the reaction was run within an interval of 10–40 μl of added water (Table 3, entries 23–26). Thus, when 40 μl of water was added, the *cis*-**6**/*trans*-**6** ratio was as high as 3:97 (entry 26). In Table 3 we can also see that there are some useful differences in selectivity between the *cis*-**6** and the *trans*-**6** enantiomers when different amounts of water were added (see Table 3, entries 22–28).

Table 3. The conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde catalysed by **8** using 2HI as cocatalyst and with different amounts of water added[a]

Entry	Water added (μl)	*cis*-**6**/*trans*-**6**[b]	*cis*-(1*R*,2*S*)-**6**/*cis*-(1*S*,2*R*)-**6**[c]	*trans*-(1*R*,2*R*)-**6**/*trans*-(1*S*,2*S*)-**6**[c]
22	0	17:83	74:26	82:18
23	10	9:91	66:34	82:18
24	20	5:95	63:37	83:17
25	30	7:93	87:13	78:22
26	40	3:97	84:16	81:19
27	80	25:75	78:22	74:26
28	200	28:72	68:32	65:35

[a] All experiments were carried out at 25 °C in 2 ml of DMF (with different amounts of water added), using 84 mg (0.88 mmol) of aldehyde **5**, 10 mol % of catalyst **8** (2HI as cocatalyst) and 390 μl (4.4 mmol) of *N*-methylpyrrole **4**. A diastereomeric mixture *cis*- and *trans*-**6** was obtained after reduction ($NaBH_4$) in a typical yield of 55%.

[b] The *cis*-**6**/*trans*-**6** ratio was determined using a GC EC-1 column.

[c] Enantiomeric ratio was measured on the corresponding aldehyde, using a chiral GC β-dex 325 column.

MacMillan et al. noticed that the presence of water increased the enantioselectivity in their early work with organocatalysed Diels–Alder reaction between cyclopentadiene and some dienophiles.[6] They proposed that the added water facilitated the iminium ion hydrolysis step in the catalytic cycle. Recently, Peelen et al. observed that when butyraldehyde and methyl vinyl ketone reacted using a imidazolidinone catalyst, together with cocatalysts, the enantioselectivity increased when 20 mol % of water was added to the reaction.[9] Probably in our case, both the amount of water added and the acidity of the cocatalysts used influence the hydrolysis and at the end, the stereochemical outcome of the reaction.

Table 2. Various acidic cocatalysts were used together with **8** in the conjugate addition of *N*-methylpyrrole to cyclopent-1-ene carbaldehyde[a]

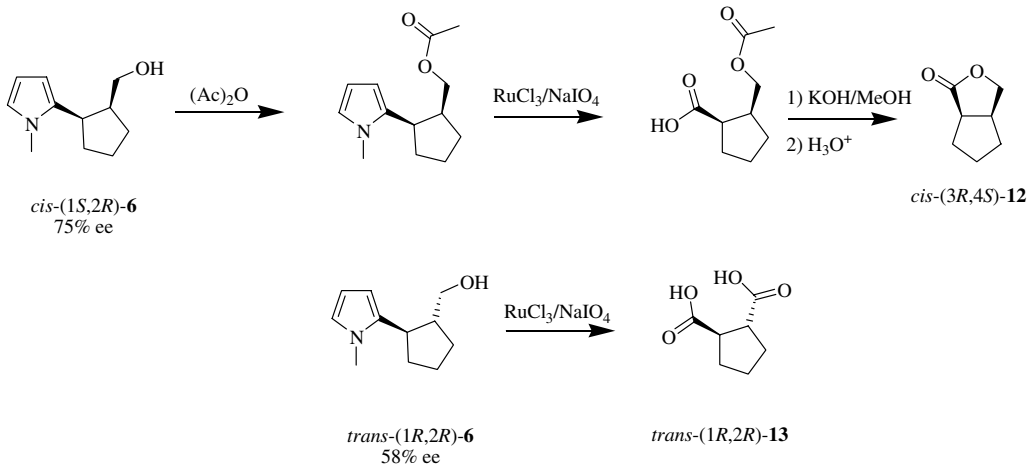
Entry	Cocatalyst $(HX)_n$	*cis*-**6**/*trans*-**6**[b]	*cis*-(1*R*,2*S*)-**6**/*cis*-(1*S*,2*R*)-**6**[c]	*trans*-(1*R*,2*R*)-**6**/*trans*-(1*S*,2*S*)-**6**[c]
11	HBr	7:93	54:46	61:39
12	2HBr	48:52	79:21	82:18
13	HI	9:91	48:52	51:49
14	2HI	3:97	84:16	81:19
15	TFA	23:77	60:40	63:37
16	2TFA	8:92	79:21	75:25
17	TsOH	24:76	51:49	56:44
18	2TsOH	37:63	73:27	74:26
19	$HClO_4$	25:75	51:49	55:45
20	$2HClO_4$	26:74	67:33	70:30
21[d]	$2HClO_4$	66:34	56:44	60:40

[a] All experiments were carried out at 25 °C in 2 ml of DMF (with 40 μl of water added), using 84 mg (0.88 mmol) of aldehyde **5**, 10 mol % of catalyst **8** and 390 μl (4.4 mmol) of *N*-methylpyrrole **4**. A diastereomeric mixture of *cis*- and *trans*-**6** was obtained after reduction ($NaBH_4$) in a typical yield of 55%.

[b] The *cis*-**6**/*trans*-**6** ratio was determined using a GC EC-1 column.

[c] Enantiomeric ratio was measured on the corresponding aldehyde, using a chiral GC β-dex 325 column.

[d] The reaction was carried out at 0 °C.



Scheme 3. Derivatisation of *cis*-(1*S*,2*R*)- and *trans*-(1*R*,2*R*)-**6** to lactone *cis*-(3*R*,4*S*)-**12** and dicarboxylic acid *trans*-(1*R*,2*R*)-**13**, respectively.

To determine the absolute configuration of the enantiomeric enriched compounds, *cis*-**6** (75% ee) and *trans*-**6** (58% ee) (both obtained using the same conditions as in entry 7 but starting from 1 g of **5**) were derived into the substances (3*R*,4*S*)-**12** $\{[\alpha]_D^{20} = -93$ (*c* 0.60, $CHCl_3$), lit.[10] $[\alpha]_D^{25} = -91.5$ (*c* 0.94, $CHCl_3$)$\}$ and (1*R*,2*S*)-**13** $\{[\alpha]_D^{20} = -46$ (*c* 0.85, MeOH), lit.[11] $[\alpha]_D^{25} = -55.25$ (*c* 0.80, MeOH)$\}$, respectively, with known configurations at the stereogenic centres (see Scheme 3). The diastereomerically pure alcohol *trans*-**6** was oxidised into the dicarboxylic acid *trans*-(1*R*,2*R*)-**13**. The enantiomeric enriched alcohol *cis*-**6** was oxidised in the same way, after protection of the hydroxyl group as acetate, and then converted into *cis*-(3*R*,4*S*)-lactone **12** via hydrolysis and ring closure under acidic conditions.

3. Experimental

Unless otherwise stated, commercially available chemicals were used as received. THF, EtOH and pyridine were distilled prior to use. Compound **9** was from the same batch as published in the literature.[7] Compounds **10** and **11** were from the same batches as published in the literature.[8] Mass spectra analyses were carried out on a Saturn 2000 MS instrument coupled to a Varian 3800 GC instrument. NMR spectra were recorded in $CDCl_3$ with TMS as internal standard using a Bruker Avance 500 or a Bruker DMX 250 instrument. For monitoring the progress of the reactions analyses were performed on a EC-1 (30 m × 0.25 mm × 0.25 mm) GC capillary column.

3.1. (*S*)-2-(Pyrrolidinomethyl) pyrrolidine 7

The title compound was prepared from L-proline over four steps in a total yield of 19%, according to the literature procedures.[5] The analytical data were similar to the data presented in the literature.[5]

3.2. (*S*)-2-(Piperidinomethyl) pyrrolidine 8

The title compound was prepared from L-proline over four steps in a total yield of 22%, according to the literature procedures.[5] The analytical data were similar to the data presented in the literature.[5]

3.3. (*S*)-5-Benzyl-2,2,3-trimethylimidazolin-4-one 2

The title compound was prepared from L-phenylalanine methyl ester hydrochloride in a total yield of 70%, according to the literature procedures.[6] The analytical data were similar to data presented in the literature.[6]

3.4. General method for the 1,4-conjugate addition exemplified by a gramme scale synthesis of *cis*-(1*S*,2*R*)- and *trans*-(1*R*,2*R*)-2-(1-methyl-1*H*-pyrrol-2-yl)cyclopentanecarbanol

Catalyst salt **8** (5 mol %, 200 mg) with 2 equiv of HCl as cocatalyst (the pyrrolidinium salt was prepared by adding the desired equivalent of the acidic cocatalyst to a solution of the used amine in methanol and then evaporation to dryness) were added to a solution of *N*-methylpyrrole (6.9 ml, 77.8 mmol), cyclopent-1-ene carbaldehyde **5** (1.5 g, 15.7 mmol) in DMF (25 ml with 360 μl water added). The reaction was monitored by GC and reached full conversion after 72 h. The reaction was quenched with brine (40 ml) and diluted with EtOAc (40 ml). The water phase was extracted with EtOAc (2 × 40 ml), the pooled organic phase dried over $MgSO_4$, concentrated and purified by flash chromatography. The identity of the product was confirmed by GC–MS and NMR and used in the next step without further purification. The diastereomeric ratio was measured on the aldehyde mixture using a EC-1 (30 m × 0.25 mm × 0.25 mm) GC capillary column isotherm at 100 °C t_r(*trans*) = 9.3 min, t_r(*cis*) = 10.2 min. The enantiomeric ratio was measured on the aldehyde mixture using a β-dex 325 (30 m × 0.25 mm × 0.25 mm) capillary GC column temperature programmed from 100 °C (1 min) to 150 °C at 1.0 °C/min, t_r(*trans*-1*R*,2*R*) = 42.3 min, t_r(*trans*-1*S*,2*S*) = 42.93 min, t_r(*cis*-1*S*,2*R*) = 44.8 min and t_r(*cis*-1*R*,2*S*) = 45.4 min.

The 2-(1-methyl-1*H*-pyrrol-2-yl)-cyclopentane carbaldehyde obtained was dissolved in EtOAc (40 ml) and MeOH (40 ml) and $NaBH_4$ (66 mg, 17.6 mmol) added.

The reaction was then stirred at room temperature until no aldehyde was seen by TLC. The reaction was quenched with brine (40 ml) and diluted with EtOAc (40 ml). The water phase was extracted with EtOAc (2×40 ml), the pooled organic phase dried over $MgSO_4$ and concentrated (yield 54% from **5**). The two diastereomers were separated by repeated flash chromatography using an increasing gradient of distilled ethyl acetate (0–60%) in distilled cyclohexane as eluent. Each diastereomer was obtained pure after bulb to bulb distillation at 135 °C/2.1 mbar. The enantiomeric ratio was measured using a β-dex 120 ($30\ m \times 0.25\ mm \times 0.25\ mm$) capillary GC column temperature programmed from 100 °C (1 min) to 160 °C at 1.0 °C/min, t_r(*trans*-1*S*,2*S*) = 95.1 min, t_r(*trans*-1*R*,2*R*) = 96.7 min, t_r(*cis*-1*S*,2*R*) = 105.9 min and t_r(*cis*-1*R*,2*S*) = 107.2 min.

cis-(1*S*,2*R*)-**6**: >99.8% de and 66% ee; $[\alpha]_D^{20} = -81$ (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.45–1.90 (m, 5H), 2.01 (m, 1H), 2.12 (m, 1H), 2.33 (m, 1H), 2.84 (dd, 1H, $J = 8.4$, 16.7 Hz), 3.60 (s, 3H), 3.62 (dd, 1H, $J = 6.3$, 10.5 Hz), 3.69 (dd, 1H, $J = 5.8$, 10.6 Hz); ^{13}C NMR ($CDCl_3$): δ 24.0, 28.7, 33.8, 34.4, 39.5, 48.2, 66.0, 103.8, 106.6, 121.4, 136,8. MS (EI): *m*/*z* (%) 179 M^+ (100), 148 (54), 120 (63), 108 (63), 94 (100), 81 (21).

trans-(1*R*,2*R*)-**6**: >99.8% de and 53% ee; $[\alpha]_D^{20} = +77$ (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.31 (s, 1H), 1.43 (m, 1H), 1.58 (m, 1H), 1.75–2.0 (m, 4H), 2.36 (m, 1H), 3.11 (m, 1H), 3.15 (dd, 1H $J = 5.3$, 11.4 Hz), 3.30 (dd, 1H, $J = 8.2$, 11.4 Hz), 3.57 (s, 3H), 5.95 (s, 1H), 6.05 (s, 1H), 6.55 (s, 1H); ^{13}C NMR ($CDCl_3$): 23.8, 28.6, 30.5, 33.8, 39.1, 43.5, 64.6, 105.2, 106.9, 121.8, 133.7 MS (EI): *m*/*z* (%) 179 M^+ (96), 148 (46), 120 (56), 108 (74), 107 (26), 94 (100), 81 (45).

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