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Full Paper

Investigation of *cis*- and *trans*-4-Fluoroprolines as Enantioselective Catalysts in a Variety of Organic Transformations

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Stereoselective fluorination is known to rigidify the ring structure of L-proline, as a result of a combination of electrostatic and hyperconjugative effects associated with the C–F bond. This is a potential strategy for enhancing the enantioselectivity of proline-catalysed reactions. In this study, *cis*- and *trans*-4-fluoroprolines were investigated as catalysts in five different organic transformations, including examples of both enamine and iminium ion catalysis. Some significant differences in enantioselectivity were observed between the *cis*- and *trans*-isomers of the fluorinated catalysts, confirming that the ring pucker is important. However, no substantial improvements were observed relative to the parent catalyst, L-proline.

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Introduction

In this 21st century, it has become imperative for synthetic chemists to develop processes that minimise harm to the environment, either by controlling hydrocarbon consumption or minimising overall waste. One way to approach this goal is by developing more efficient catalysts. Within this context, much attention has been directed towards organocatalysis, i.e. the acceleration of reactions by small molecules that are comprised exclusively of non-metal elements.[1] A particular focus has been on chiral secondary amines: such molecules are versatile entities because they can readily be converted into chiral nucleophiles (enamines)[2] or chiral electrophiles (iminium ions)[3] that can participate in a variety of enantioselective processes.[1]

The archetypal organocatalyst is L-proline (**1**, Fig. 1), which has the advantages of being cheap and readily available in optically pure form. In a celebrated example of enamine catalysis, Hajos and Parrish[4] reported in 1974 an intramolecular aldol reaction in which the product was delivered in an impressive 97 : 3 enantiomeric ratio (*er*), catalysed by just 3 mol-% of L-proline (**1**). In the intervening years, many other

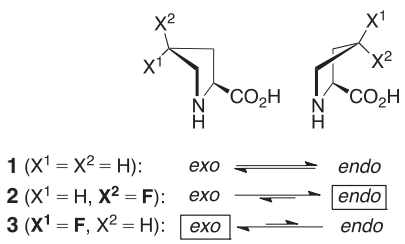


Fig. 1. The flexible ring structure of L-proline (**1**) can be rigidified by stereoselective fluorination (**2**, **3**).

enantioselective processes catalysed by L-proline have also been developed.[1] However, the results are not always so impressive: there are multiple reports of proline-catalysed reactions that proceed with only moderate enantioselectivity.[2,5–8] A possible reason for the imperfect selectivity observed in some cases is the flexibility of proline's five-membered ring (Fig. 1). Different puckers of the proline ring would lead to different possible transition state geometries, which may erode the stereoselectivity of organocatalytic reactions.

Thus, a potential strategy to enhance the enantioselectivity of proline-catalysed reactions is to rigidify the five-membered ring system. One way to achieve this is to exploit stereoselective fluorination.[9,10] Fluorine preferentially aligns *gauche* to vicinal electronegative[11] or positively-charged[12] substituents, because of a combination of hyperconjugative and electrostatic interactions. This phenomenon has been observed in both *cis*-4-fluoroproline and *trans*-4-fluoroproline (**2** and **3**, Fig. 1),[13] as well as in their enamine and iminium derivatives.[14–16] This leads to different preferred ring puckers for the *cis*- and *trans*-isomers (Fig. 1), potentially offering a strategy for improving the enantioselectivity of proline-catalysed reactions.

The concept of using fluorine to improve an organocatalyst's enantioselectivity has received considerable attention in recent years.[17] Fig. 2 illustrates some examples of secondary amine and *N*-heterocyclic carbene organocatalysts that owe their enantioselectivity to conformational pre-organisation by fluorine.[18–22] Surprisingly however, the literature on catalysis using 4-fluoroprolines **2** and **3** is very scarce. In 2008, while developing a total synthesis of the natural product hirsutene, List and co-workers[23] investigated a series of L-proline derivatives as catalysts in an enantioselective transannular aldol reaction. They found that *trans*-4-fluoroproline (**3**) was the optimal catalyst, delivering the desired aldol product in higher optical

purity ($er > 99:1$) than was obtained with either *cis*-4-fluoroproline (**2**) or L-proline (**1**) itself. A subsequent theoretical study by Díaz and Goodman[14] confirmed that the Cγ-*exo* transition state was favoured, and this contributed to the high enantioselectivity. Surprisingly, this work remains the only reported example of a reaction catalysed by 4-fluoroprolines.

Accordingly, the aim of this study is to investigate *cis*- and *trans*-4-fluoroprolines (**2** and **3**, Fig. 1) as catalysts in a variety of organic transformations, to determine whether rigidifying the proline ring structure can be a general strategy for enhancing enantioselectivity. This study will focus on examples from the literature in which L-proline (**1**) has previously been utilised successfully but with only moderate enantioselectivity: an intermolecular aldol reaction,[2] a Robinson annulation,[5] a Mannich reaction,[6] a Michael addition reaction,[7] and a multicomponent synthesis of a pyran.[8]

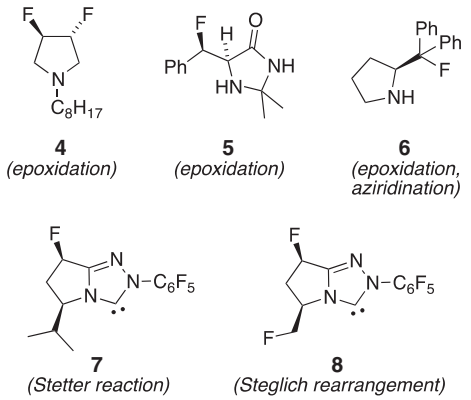
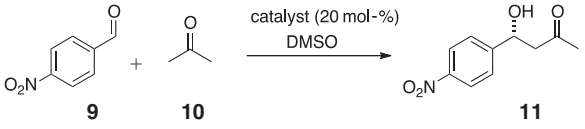


Fig. 2. Examples of fluorinated organocatalysts.[18–22]

Table 1. Organocatalysed aldol reaction



Entry	Catalyst	Isolated yield of **11**	Optical purity of **11**
1	**1**	38 %	*er* 77 : 23
2	**2**	56 %	*er* 73 : 27
3	**3**	47 %	*er* 79 : 21

Results

Synthesis of 4-Fluoroproline Catalysts

The first task was to procure the requisite catalysts, 4-fluoroprolines **2** and **3**. Both of these compounds were synthesised from *trans*-4-hydroxyproline according to the methods of Chorghade and co-workers[24] with slight modifications.[25] With the catalysts **1**–**3** in hand, attention was next turned towards their application in several enantioselective reactions.

Aldol Reaction

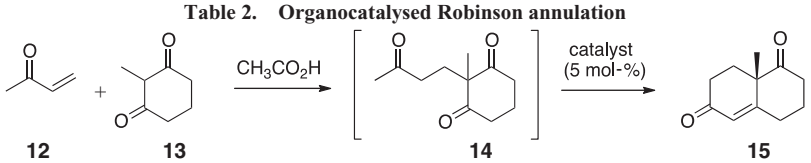
The first organocatalytic process to be investigated was an intermolecular aldol reaction between **9** and **10** (Table 1, entry 1). This reaction, which is an example of enamine catalysis, was previously reported by List and co-workers to deliver the product **11** in *er* 88 : 12.[2] In our hands, the product **11** was found to be very susceptible to dehydration, so the reaction was closely monitored by TLC and worked up immediately upon completion. In this manner, the purified aldol product **11** was obtained in 38 % yield, which was somewhat lower than List's reported[2] yield of 68 %. The reaction was then repeated using *cis*-4-fluoroproline (**2**) and *trans*-4-fluoroproline (**3**) as the catalysts (Table 1, entries 2 and 3), with the only difference in each case being the addition of one equivalent of triethylamine to neutralise the hydrochloride salts of **2** and **3**. The latter reactions resulted in yields of 56 and 47 %, respectively.

High-performance liquid chromatography (HPLC) with a chiral stationary phase was employed to determine the optical purity of the aldol product **11**. After extensive method development a partial separation of the enantiomers of **11** was able to be achieved:[25] this revealed that the catalyst L-proline (**1**) had delivered the aldol product in *er* 77 : 23 (cf. the literature result[2] of *er* 88 : 12). HPLC analysis of the aldol products **11** obtained with *cis*-4-fluoroproline (**2**) and *trans*-4-fluoroproline (**3**) revealed optical purities of *er* 73 : 27 and *ee* 79 : 21, respectively (Table 1, entries 2 and 3). Thus, a slight improvement in enantioselectivity was observed with *trans*-4-fluoroproline (**3**), while a decrease in enantioselectivity was observed with the catalyst *cis*-4-fluoroproline (**2**).

Robinson Annulation

The second organocatalytic reaction to be investigated was a variant of the Robinson annulation (Table 2). This reaction, which is an example of enamine catalysis, was previously shown by Bui and co-workers to give the product **15** in *er* 85 : 15.[5]

Table 2. Organocatalysed Robinson annulation



Entry	Catalyst	Conversion of **14** → **15**	Isolated yield of **15**	Optical purity of **15**
1	**1**	41 %	5 %	*er* 85 : 15
2	**2**	25 %	1 %	*er* 79 : 21
3	**3**	8 %	1 %	*er* 86 : 14
4	**1**[A]	nd	26 %	*er* 85 : 15
5	**3**[A]	nd	9 %	*er* 86 : 14

[A]Reaction performed with purified **14** and 20 mol-% of catalyst.

Initial experiments in our hands revealed that the purity of the precursor **12** was critical, and this reagent was therefore distilled immediately before use. Even so, the reaction remained very low-yielding in our hands, with the product **15** obtained in only 5, 1, and 1 % yield in the reactions catalysed by L-proline (**1**), *cis*-4-fluoroproline (**2**), and *trans*-4-fluoroproline (**3**), respectively (cf. the literature yield[5] of 57 %, catalysed by **1**). The extremely low yields of **15** were partly because of the need for multiple rounds of column chromatography, since the triketone **14** and product **15** eluted very close to one another. However the extents of conversion, which were estimated by ^{1}H NMR spectroscopy, were also low: 41, 25, and 8 % for the reactions catalysed by **1**–**3**, respectively. This suggests that the fluorinated catalysts exhibit decreased reactivity (see below). In an attempt to improve the yields of **15**, the organocatalytic reactions were repeated with purified triketone **14** and with a higher catalyst loading (Table 2, entries 4 and 5). The isolated yields of **15** were somewhat improved under these conditions, although still lower than the literature figure.[5]

The optical purity of the Robinson products **15** were determined using HPLC with a chiral stationary phase. The result of *er* 85 : 15 obtained with L-proline (**1**) agrees with the literature report[5] (Table 2). For the fluorinated catalysts, *cis*-4-fluoroproline (**2**) decreased the optical purity quite significantly to *er* 79 : 21, while *trans*-4-fluoroproline (**3**) delivered the product with a similar or very slightly higher level of enantioselectivity (*er* 86 : 14) than the parent catalyst **1**. This result seems to mirror the observations from the previous organocatalytic reaction (Table 1), where catalyst **2** exhibited lower enantioselectivity while catalyst **3** led to a possible marginal improvement. The reaction with a higher loading of catalyst **3** (Table 2, entry 5) did not give any further improvement.

Mannich Reaction

The next organocatalytic reaction to be investigated was a variant of the Mannich reaction (Table 3). This reaction, which is an example of iminium ion catalysis, was previously developed by List and co-workers and delivered the Mannich product **18** in *er* 87 : 13.[6] In our hands, the yield of the product **18** obtained in the reaction catalysed by L-proline (**1**) was 28 %, significantly lower than the literature yield[6] of 74 %. When substituted with the fluorinated catalysts, *cis*-4-fluoroproline (**2**) yielded a slight decrease to 23 % while *trans*-4-fluoroproline (**3**) yielded a dramatic decrease to 6 % (Table 3).

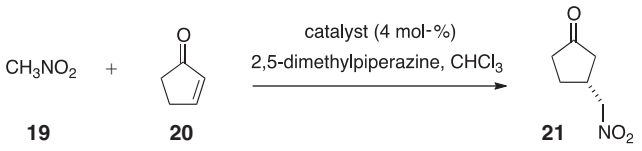
The enantiomers of **18** were readily separated by HPLC with a chiral stationary phase, and this enabled the optical purity of the products to be measured at *er* 86 : 14, 65 : 35, and 70 : 30 for the reactions catalysed by **1**–**3** respectively. The literature[6] optical purity of **18**, obtained using L-proline (**1**), was *er* 87 : 13. This is almost identical to the result obtained under the same conditions in this project, but it is obvious that the fluorinated catalysts (**2** and **3**) resulted in considerably lower optical purity.

Michael Addition

The next organocatalytic reaction to be investigated in this project was a variant of the Michael addition (Table 4). This reaction, which is an example of iminium ion catalysis, was previously developed by Hanessian and co-workers and gave the product **21** in *er* 81 : 19.[7] When this reaction was repeated in our laboratory the Michael product **21** was generated in 25 % yield, which was similar to the literature yield[7] of 30 %. The yields produced by the fluorinated catalysts (**2** and **3**) were somewhat lower, with a decrease to 13 % in the reaction catalysed by *cis*-4-fluoroproline (**2**) and 14 % in the reaction catalysed by *trans*-4-fluoroproline (**3**).

HPLC with a chiral stationary phase was found to be unsuitable for determining the optical purity of the Michael product **21**, since the enantiomers could not be resolved. Therefore, an alternative method was investigated in which ketone **21** was converted into a pair of diastereoisomeric acetals through reaction with a chiral diol (see *Experimental* section). The relative amounts of the diastereoisomeric acetals were quantified by ^{13}C NMR spectroscopy, and this revealed that the Michael product **21** was obtained in *er* 82 : 18 using L-proline (**1**) as the catalyst (Table 4, entry 1). This is very similar to the value of *er* 81 : 19 reported in the literature.[7] The reaction catalysed by *cis*-4-fluoroproline (**2**) delivered the Michael product **21** in a decreased optical purity of *er* 79 : 21, while the reaction catalysed by *trans*-4-fluoroproline (**3**) delivered the Michael product **21** in an almost identical optical purity of *er* 81 : 19. In an effort to further investigate whether catalyst **3** could represent any improvement over catalyst **1** in the Michael addition, the reaction

Table 4. Organocatalysed Michael addition

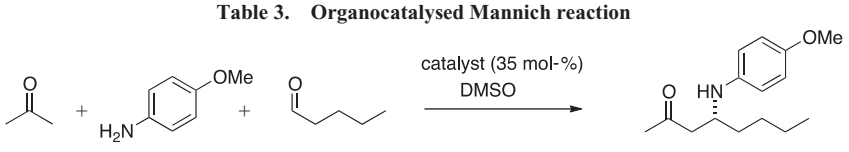


19 20 21

Entry	Catalyst	Isolated yield of **21**	Optical purity of **21**
1	**1**	25 %	*er* 82 : 18
2	**2**	13 %	*er* 79 : 21
3	**3**	14 %	*er* 81 : 19
4	**3**[A]	29 %	*er* 77 : 23

[A]Reaction performed with 20 mol-% of catalyst **3**.

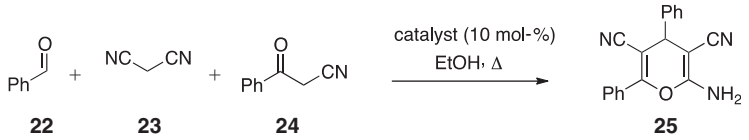
Table 3. Organocatalysed Mannich reaction



10 16 17 18

Entry	Catalyst	Isolated yield of **18**	Optical purity of **18**
1	**1**	28 %	*er* 86 : 14
2	**2**	23 %	*er* 65 : 35
3	**3**	6 %	*er* 70 : 30

Table 5. Multicomponent synthesis of a pyran



22 **23** **24** **25**

Entry	Catalyst	Isolated yield of **25**	Optical purity of **25**
1	**1**	98 %	*er* 51 : 49
2	**2**	85 %	*er* 50 : 50
3	**3**	97 %	*er* 51 : 49

was repeated with 20 mol-% of catalyst **3** (Table 4, entry 4). However this did not improve the enantioselectivity.

Multicomponent Synthesis of a Pyran

The final organocatalytic reaction examined in this work was the multicomponent synthesis of a chiral pyran (Table 5). This reaction, which is an example of enamine catalysis, was previously developed by Elnagdi and co-workers and reportedly gave pyran **25** in *er* 85 : 15.[8] In our hands, this process delivered the pyran **25** in 98, 85, and 97 % yields for the reactions catalysed by **1**–**3**, respectively (Table 5). These yields were slightly higher than the literature report[8] obtained with catalyst **1** (83 %).

Although the obtained yields of pyran **25** were gratifying (Table 5), the determination of their optical purity was otherwise. In the literature report,[8] pyran **25** was obtained in *er* 85 : 15 using L-proline (**1**) as the catalyst, but in this work under identical conditions pyran **25** was obtained in only *er* 51 : 49 as determined by HPLC with a chiral stationary phase. To rule out the possibility of any inaccuracy associated with our HPLC method, we also employed the literature method[8] for determining the optical purity of **25**. Thus, the ^{1}H NMR spectrum of **25** was recorded in the presence of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. Under these conditions, the pyran ring hydrogen of **25** (4.7 ppm) resolved into two components, integration of which confirmed that pyran **25** was essentially a racemate. The batches of **25** obtained with *cis*-4-fluoroproline (**2**) and *trans*-4-fluoroproline (**3**) were also found to be racemates (Table 5, entries 2 and 3). One possible explanation is that epimerisation occurred during these reactions, but we were not able to conclusively determine whether this was the case.

Discussion

The hypothesis tested in this study was that rigidifying the five-membered ring structure of L-proline (**1**) could be a general strategy for achieving higher enantioselectivity in organocatalytic reactions. Five different organic transformations were investigated: an aldol reaction,[2] a Robinson annulation,[5] a Mannich reaction,[6] a Michael addition reaction,[7] and a multicomponent synthesis of a pyran.[8] These reactions included examples of both enamine and iminium catalysis, and they were chosen for investigation because they have previously been reported to be catalysed by L-proline (**1**) but with only moderate enantioselectivity. The strategy employed here for rigidifying the ring structure of L-proline was to incorporate a fluorine atom stereospecifically at the 4-position, since this has previously been shown to enforce either a Cγ-*exo* or a Cγ-*endo* ring pucker depending on the fluorine stereochemistry (Fig. 1).[13–16]

The first noteworthy outcome of this study is that some significant differences in *er* were observed between *cis*- and *trans*-4-fluoroprolines (catalysts **2** and **3**), particularly in the aldol reaction (Table 1) and the Robinson annulation (Table 2). These results mirror List's previous observation[23] that *trans*-4-fluoroproline (**3**) gave substantially higher enantioselectivity in an intramolecular aldol reaction than *cis*-4-fluoroproline (**2**). Together, these findings confirm that the proline ring shape is an important determinant of selectivity.

However, no substantial improvements over the parent catalyst, L-proline (**1**), were observed in any of the reactions investigated in this study. *Cis*-4-fluoroproline (**2**) tended to decrease the enantioselectivity relative to L-proline (**1**) in all cases. The results with *trans*-4-fluoroproline (**3**) were more variable; in some cases the enantioselectivity was reduced relative to the parent catalyst **1** (e.g. Table 3), while in other cases the enantioselectivity was approximately equal to, or slightly higher than, that of **1** (e.g. Tables 1, 2 and 4). This suggests that rigidifying the proline ring structure can be beneficial in some cases, but that rigidity is not the only factor that is important for enantioselectivity.

In addition, it became clear during this study that fluorination seemed to reduce the catalysts' reactivity in most cases (e.g. Tables 2, 3 and 4). This is possibly attributable to the electron-withdrawing nature of the fluorine substituent, which presumably lowers the nucleophilicity of the amino group of the catalyst.[16] Unfortunately, the design of this study did not allow us to disentangle the different effects of fluorination (i.e. rigidification and electron-withdrawing nature).

Finally, difficulties were encountered in the multicomponent synthesis of pyran **25** (Table 5). Mechanistically, this process is more complex than the other reactions investigated in this work; our inability to reproduce the literature enantioselectivity of this process highlights that subtle variations in experimental conditions may dramatically affect reaction outcomes in certain circumstances, adding an additional challenge to the study of organocatalysis.

Conclusion

Cis-4-fluoroproline (**2**) and *trans*-4-fluoroproline (**3**) have been investigated as enantioselective organocatalysts in a variety of organic transformations, and their performance has been compared with L-proline (**1**). Significant differences in enantioselectivity are observed in some cases between **2** and **3**, confirming that the ring pucker can be an important determinant of selectivity. However, in general the fluorinated catalysts **2** and **3** did not exhibit any substantial improvements relative to the parent catalyst, **1**. It was also observed that fluorination tended to reduce the catalysts' reactivity, presumably because of the fluorine's electron-withdrawing nature. These results suggest that future applications of 4-fluoroprolines in organocatalysis may continue to be limited to specific, isolated examples.[23]

Experimental

General

All reactions were performed in oven-dried glassware under a nitrogen atmosphere with magnetic stirring unless otherwise stated. Anhydrous solvents were freshly prepared as follows: solvents were dried over activated finely ground 4 Å molecular sieves for 1 h and then filtered. All other reagents were purchased in the highest available quality and used as supplied. 'Concentration under vacuum' refers to the removal of volatile solvents under reduced pressure by means of a rotary evaporator and water bath (40°C, unless otherwise stated) and subsequent drying under high vacuum (~0.1 mmHg) at room temperature. Solution phase reactions were monitored by TLC using Merck aluminium-backed silica gel 60 F_{254} (0.2 mm) TLC plates. TLC spots were visualised under short-wave UV light (254 nm) and stained with Goofy's stain, ninhydrin, or potassium permanganate dips. Flash column chromatography was performed using Davisil 40–63 mesh silica gel. The eluent is stated as volume-to-volume ratios. Melting points were determined using a Mel-Temp. II device. Optical rotations were measured using a Perkin Elmer model 341 polarimeter ($\lambda = 589$ nm; $l = 1$ dm, and c expressed in grams per 100 mL). NMR spectra were obtained at 298 K using a Bruker Avance III 300, 400, 500, or 600 MHz instrument. High resolution mass spectra were recorded at the Bioanalytical Mass Spectrometry Facility (UNSW) using an Orbitrap LTQ XL ion trap MS in positive ion mode using an electrospray ionisation (ESI) source. HPLC was performed using a Daicel Chiralcel OD-H analytical column (250 mm × 4.6 mm ID). HPLC samples were run at isocratic elution, and retention times were confirmed by comparison with racemic samples.

(R)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (**11**)

Acetone (1.0 mL, 14 mmol) was added to a solution of catalyst (20 mol-%) and *p*-nitrobenzaldehyde (73.0 mg, 0.483 mmol) in DMSO (4.0 mL). The mixture was stirred at room temperature overnight. Saturated NH_4Cl (10 mL) was then added, and the mixture was extracted with ethyl acetate (3 × 15 mL). After washing with water (5 × 10 mL) and brine (10 mL), the organic solution was dried ($MgSO_4$) and concentrated under vacuum without heating. Purification by flash chromatography (3 : 1 *n*-hexane/ethyl acetate) provided the title compound.

Data for ketone **11**, obtained using catalyst **1**: Yellow solid (38.4 mg, 38 %); mp 55–58°C (lit.[26] 57–60°C); $[\alpha]_D$ +28.6 (*c* 0.35, $CHCl_3$), *er* 77 : 23 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 95 : 5, flow rate 1.0 mL min^{-1}, λ 280 nm, t_R(major) 37.4 min, t_R(minor) 39.4 min) (lit.[27] $[\alpha]_D$ +46.2 (*c* 1.0, $CHCl_3$), *er* 88 : 12). δ_H (400 MHz, $CDCl_3$) 8.16 (d, *J* 8.6, 2H, *p*-nitrophenyl), 7.52 (d, *J* 8.6, 2H, *p*-nitrophenyl), 5.24 (m, 1H, C*H*OH), 3.71 (br s, 1H, OH), 2.85–2.83 (m, 2H, CHCH_2), 2.20 (s, 3H, CH_3). ^{1}H NMR data in accordance with literature values.[27]

Data for ketone **11**, obtained using catalyst **2**: Yellow solid (58.5 mg, 56 %); mp 56–59°C; $[\alpha]_D$ +37.1 (*c* 0.35, $CHCl_3$), *er* 73 : 27 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 95 : 5, flow rate 1.0 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

Data for ketone **11**, obtained using catalyst **3**: Yellow solid (48.0 mg, 47 %); mp 58–60°C; $[\alpha]_D$ +45.7 (*c* 0.35, $CHCl_3$), *er* 79 : 21 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

(S)-8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione (**15**)

Catalyst (5 mol-%) was added to a solution of ketone **14** (0.950 g, 4.84 mmol) in anhydrous DMSO (5.0 mL) and stirred for 120 h. The mixture was then dissolved in ethyl acetate (200 mL), washed with water (10 × 40 mL), dried ($MgSO_4$) and concentrated under vacuum at 65°C. Purification by flash chromatography (3 : 2 *n*-hexane/ethyl acetate followed by 5 : 1 *n*-hexane/ethyl acetate) provided ketone **15**.

Data for ketone **15**, obtained using catalyst **1**: Yellow oil (76.9 mg, 5 %); $[\alpha]_D$ +68.0 (*c* 0.25, toluene), *er* 85 : 15 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH 96 : 4, flow rate 0.8 mL min^{-1}, λ 280 nm, t_R(major) 31.2 min, t_R(minor) 34.2 min) (lit.[28] $[\alpha]_D$ +68 (*c* 1.5, toluene), *er* 85 : 15). δ_H (400 MHz, $CDCl_3$) 5.79 (d, *J* 1.5, 1H, CH), 2.72–2.63 (m, 2H, CH_2), 2.47–2.37 (m, 4H, 2 × CH_2), 2.12–2.05 (m, 3H, CH_2), 1.71–1.59 (m, 1H, CH_2), 1.40 (s, 3H, CH_3). ^{1}H NMR data in accordance with literature values.[29]

Data for ketone **15**, obtained using catalyst **2**: Yellow oil (1.8 mg, 1 %); $[\alpha]_D$ +40.0 (*c* 0.25, toluene), *er* 79 : 21 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 96 : 4, flow rate 0.8 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

Data for ketone **15**, obtained using catalyst **3**: Yellow oil (4.0 mg, 1 %); $[\alpha]_D$ +4.0 (*c* 0.25, toluene), *er* 86 : 14 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 96 : 4, flow rate 0.8 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

(R)-4-((4-Methoxyphenyl)amino)octan-2-one (**18**)

A suspension of catalyst (35 mol-%), *p*-anisidine (135 mg, 1.10 mmol), freshly distilled valeraldehyde (0.11 mL, 1.0 mmol), and acetone (10 mL) was stirred at room temperature for 48 h. The reaction was filtered and concentrated under vacuum without heating. Purification by flash chromatography (5 : 1 *n*-hexane/ethyl acetate) provided ketone **18**.

Data for ketone **18**, obtained using catalyst **1**: Yellow oil (71.5 mg, 28 %); $[\alpha]_D$ +4.8 (*c* 3.2, $CHCl_3$), *er* 86 : 14 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 95 : 5, flow rate 1.0 mL min^{-1}, λ 315 nm, t_R(major) 16.4 min, t_R(minor) 10.0 min). δ_H (400 MHz, $CDCl_3$) 6.76 (m, 2H, *p*-methoxyphenyl), 6.57 (m, 2H, *p*-methoxyphenyl), 3.75–3.69 (m, 4H, OCH_3 and NCH), 3.28 (br s, 1H, NH), 2.65 (dd, *J* 5.5, 16.3, 1H, C(O)C*H*H), 2.56 (dd, *J* 6.4, 16.3, 1H, C(O)CH*H*), 2.12 (s, 3H, CH_3CO), 1.56–1.51 (m, 2H, C(N)CH_2CH_2), 1.44–1.26 (m, 4H, CH_2–CH_2–CH_3), 0.88 (t, *J* 6.9, 3H, CH_2CH_3). ^{1}H NMR data in accordance with literature values.[6]

Data for ketone **18**, obtained using catalyst **2**: Yellow oil (58.6 mg, 23 %); $[\alpha]_D$ +1.3 (*c* 2.4, $CHCl_3$), *er* 65 : 35 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 95 : 5, flow rate 1.0 mL min^{-1}, λ 315 nm). ^{1}H NMR spectrum identical to that described above.

Data for ketone **18**, obtained using catalyst **3**: Yellow oil (15.8 mg, 6 %); $[\alpha]_D$ +1.9 (*c* 0.52, $CHCl_3$), *er* 70 : 30 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 95 : 5, flow rate 1.0 mL min^{-1}, λ 315 nm). ^{1}H NMR spectrum identical to that described above.

(R)-3-(Nitromethyl)cyclopentanone (**21**)

A mixture of 2-cyclopenten-1-one (44 µl, 0.53 mmol), nitromethane (60 µl, 1.1 mmol), 2,5-dimethylpiperazine (60 mg, 0.53 mmol), and catalyst (4 mol-%) was stirred in chloroform previously passed through a bed of basic alumina (4.0 mL) for 62 h

at room temperature. The mixture was then diluted with dichloromethane (16 mL) and washed with 3 % aqueous HCl (10 mL). The organic extract was dried ($MgSO_4$) and concentrated under vacuum without heating. Purification by flash chromatography (1 : 1 *n*-hexane/ethyl acetate) provided ketone **21**.

Data for ketone **21**, obtained using catalyst **1**: Yellow oil (12.4 mg, 17 %); $[\alpha]_D$ +56.4 (*c* 0.39, $CHCl_3$), *er* 82 : 18 by chiral derivatisation with (7*R*)-2,3-dimethyl-7-(nitromethyl)-1,4-dioxaspiro[4.4]nonane (lit.[7] $[\alpha]_D$ +66.9 (*c* 0.60, $CHCl_3$), *er* 81 : 19). δ_H (400 MHz, $CDCl_3$) 4.51–4.43 (m, 2H, CH_2NO_2), 3.00 (m, 1H, C*H*–CH_2), 2.53 (dd, *J* 7.7, 18.3, 1H, CH_2), 2.40 (m, 1H, CH_2), 2.33–2.22 (m, 2H, CH_2), 2.01 (dd, *J* 10.4, 18.4, 1H, CH_2), 1.70 (m, 1H, CH_2). ^{1}H NMR data in accordance with literature values.[30]

Data for ketone **21**, obtained using catalyst **2**: Yellow oil (9.4 mg, 13 %); $[\alpha]_D$ +55.0 (*c* 0.40, $CHCl_3$), *er* 79 : 21 by chiral derivatisation with (7*R*)-2,3-dimethyl-7-(nitromethyl)-1,4-dioxaspiro[4.4]nonane. ^{1}H NMR spectrum identical to that described above.

Data for ketone **21**, obtained using catalyst **3**: Yellow oil (10.4 mg, 14 %); $[\alpha]_D$ +52.3 (*c* 0.44, $CHCl_3$), *er* 81 : 19 by chiral derivatisation with (7*R*)-2,3-dimethyl-7-(nitromethyl)-1,4-dioxaspiro[4.4]nonane. ^{1}H NMR spectrum identical to that described above.

*2-Amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile (**25**)*

A mixture of benzaldehyde (70 μL, 0.69 mmol), malononitrile (45.5 mg, 0.689 mmol), and catalyst (10 mol-%) was stirred at room temperature for 2 min. Nitrile **24** (100 mg, 0.689 mmol) was then added and the mixture was refluxed in ethanol (2.0 mL) for 6 h. After concentrating under vacuum, purification by flash chromatography (2 : 1 *n*-hexane/ethyl acetate) provided pyran **25**.

Data for pyran **25**, obtained using catalyst **1**: Yellow solid (0.202 g, 98 %); mp 159–162°C (lit.[8] 162–163°C); $[\alpha]_D$ −4.0 (*c* 0.25, $CHCl_3$), *er* 51 : 49 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 90 : 10, flow rate 1.0 mL min^{-1}, λ 280 nm, t_R(major) 33.5 min, t_R(minor) 23.3 min). δ_H (400 MHz, DMSO) 7.81–7.79 (m, 2H, ArH), 7.62–7.53 (m, 3H, ArH), 7.46–7.42 (m, 2H, ArH), 7.37–7.35 (m, 3H, ArH), 7.31 (s, 2H, NH_2), 4.84 (s, 1H, CH). ^{1}H NMR data in accordance with literature values.[8]

Data for pyran **25**, obtained using catalyst **2**: Yellow solid (0.175 g, 85 %); mp 160–162°C; $[\alpha]_D$ +4.0 (*c* 0.25, $CHCl_3$), *er* 50 : 50 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 90 : 10, flow rate 1.0 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

Data for pyran **25**, obtained using catalyst **3**: Yellow solid (0.200 g, 97 %); mp 157–159°C; $[\alpha]_D$ +8.0 (*c* 0.25, $CHCl_3$), *er* 51 : 49 by HPLC with a chiral stationary phase (*n*-hexane/*i*-PrOH, 90 : 10, flow rate 1.0 mL min^{-1}, λ 280 nm). ^{1}H NMR identical to that described above.

Supplementary Material

Synthetic procedures, NMR spectra, and HPLC traces are available on the Journal's website.

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