The Use of *N*-Alkyl-2,2′-bipyrrolidine Derivatives as Organocatalysts for the Asymmetric Michael Addition of Ketones and Aldehydes to Nitroolefins

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Abstract: The direct Michael addition of aldehydes and ketones to nitroolefins, catalyzed by *N*-*i*-Pr-2,2′-bipyrrolidine, is described. The desired 1,4-adducts are obtained in excellent yields with enantioselectivities up to 95% ee and dr up to 95:5 of the *syn* aldehyde addition product. An unexpected inversion of diastereoselectivity was observed for the addition of α-hydroxy ketones to β-arylnitroolefins with enantioselectivities up to 98% ee. The formation of an internal hydrogen bond between the OH group of the α-hydroxy ketone and the tertiary nitrogen of the catalyst leads to the formation of a rigid *cis* enamine intermediate that accounts for the inversion of the expected diastereoselectivity and the very high ees.

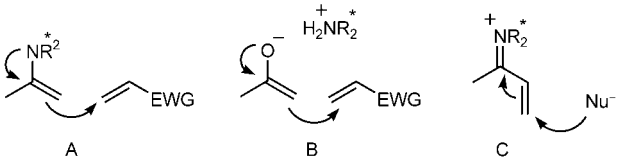
Keywords: amines; asymmetric catalysis; conjugate addition; nitroolefins; organocatalysis

Introduction

The development of non-metallic asymmetric catalysis has received much attention since its rediscovery in the beginning of the 21st century.[1–7] Indeed, since the famous asymmetric annulation catalyzed by L-proline in 1970s,[8,9] reported by Hajos et al. and Wiechert et al., almost nothing new was published, except some examples of intramolecular Michael additions catalyzed by a stoichiometric amount of L-proline.[10,11] In the 1980s, Agami[12,13] postulated a mechanism involving two molecules of L-proline based on non-linear effects in the formation of the Wieland's ketone, but recent works of Houk and List[14] have contradict his results. Only recently, many examples of reactions catalyzed by L-proline were reported, such as aldol reactions,[14–34] Mannich reactions,[35–46] conjugate additions,[47–50] α-aminations,[51–54] α-aminooxylations,[55–57] α-alkylations[58] and related reactions.[59–61] At the same time new amines were developed as catalysts. They also were used in aldol reactions,[62–68] Mannich reactions,[36,69] conjugate additions,[50,70–84] Diels–Alder reactions,[85–92] α-chlorinations[93,94] and related reactions.[95–99] All these reactions are known under the neologism of *organocatalysis*.

Among all the organocatalyzed reactions, conjugate addition has received less attention than the aldol or Mannich reaction although it was one of the most important C–C bond-forming reactions in organic chemistry.[100] This is probably due to the poorer efficiency of L-proline as a catalyst for the conjugate addition. Barbas was the first to report the asymmetric Michael addition of ketones to alkylidene malonates[71] and of aldehydes to nitrostyrene[84] catalyzed by diamines containing a pyrrolidine moiety.

Three catalytic approaches can be envisaged for the organocatalyzed Michael additions (Scheme 1). Mechanism A involves the formation of an enamine with a chiral amine, generally a chiral pyrrolidine derivative. This enamine is the nucleophile which attacks the Michael acceptor.[47,48,71,77,80,84] In the second mechanism B, the amine plays the role of a chiral base which forms an ion pair between the enolate of the ketone and the chiral ammonium.[101–103] The enolate is the nucleophilic species involved in this type of reactions. Finally, approach C is based on the activation of the Michael acceptor *via* the formation of a chiral iminium ion from an unsaturated carbonyl and a chiral amine.[49,70,72,74–76,78,79,104,105] This iminium is then reactive enough to react with a weak nucleophile. The first asymmetric addition of ketones or aldehydes to nitrostyrene described in the literature involves the first mechanism with an *in situ* catalytic for-



Scheme 1.

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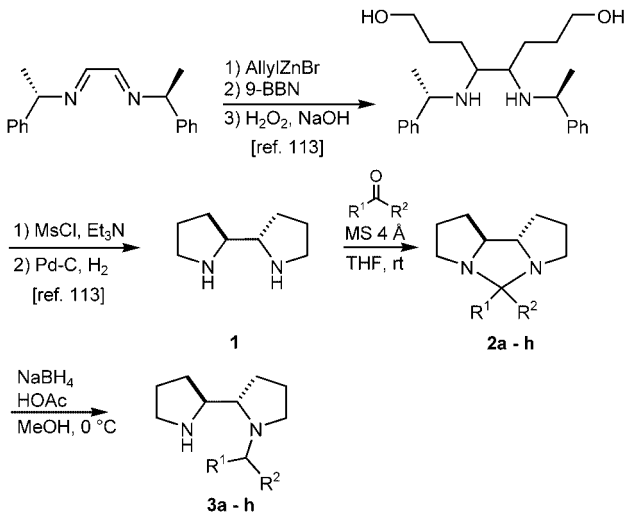
mation of a reactive enamine which reacts with the nitrostyrene as Michael acceptor.[47,48,84] We also decided to test the same approach for our study of new chiral pyrrolidine-type amines. In this full paper we describe our contribution in this field, partially reported in two communications.[77,80]

Results and Discussion

In the course of our studies on C_2 symmetrical chiral diamines[106–112] we recently reported a new asymmetric synthesis of optically pure 2,2′-bipyrrolidine[113] (Scheme 2) which can also be obtained easily by photodimerization of the pyrrolidine followed by a resolution with tartaric acid.[114] This diamine seemed to be an interesting backbone for the design of new ligands for asymmetric catalysis.[114–118] For this purpose we have synthesized many *N,N*′-dialkyl derivatives and 2,2′-bipyrrolidine itself. Among the many potential applications, we were also interested in their use as organocatalysts. We started our investigation with the study of the catalytic activity of our new diamines for the organocatalyzed Michael addition of acetone to nitrostyrene. The first attempts at conjugate addition only confirmed our doubt. Indeed, the *N,N*′-dialkylated derivatives did not catalyze the reaction at all and the 2,2′-bipyrrolidine **1** itself formed only the corresponding aminal **2g**. However, this aminal could be reduced to give the *N*-monosubstituted derivative **3g** of the 2,2′-bipyrrolidine (Scheme 2). Therefore, we were able to synthesize a variety of potential organocatalysts. By the same pathway we have prepared a wide range of aminals **2a–h** and the *N*-alkyl-2,2′-bipyrrolidines **3a–h** were obtained after reduction (Table 1).[119]

The aminals **2a–h** of aldehydes and ketones were formed easily. But, this reaction was limited by the steric hindrance of the ketones. More bulky ketones such as diisopropyl ketone, benzophenone or acetophenone did not form the corresponding aminal, even after heating. The aminal formation can be also performed in methanol starting from the tartrate salt of 2,2′-bipyrrolidine obtained after the resolution with tartaric acid.[114] The aminals were reduced without previous purification with sodium borohydride in methanol in the presence of acetic acid. The resulting mono *N*-alkylated diamines **3a–h** were purified by flash chromatography on silica gel. The yields were generally modest, around 50%, despite the cleanness of the reaction. The yields could be increase by changing the purification method. Indeed, the diamines **3c**, **3g** and **3h** were obtained in about 90% yield (Table 1, entries 3, 7 and 8) for the reduction step after purification by kugelrohr distillation instead of chromatography.



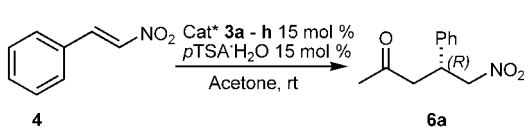
Scheme 2.

Asymmetric Addition of Ketones to Nitroolefins

Optimization of the Organocatalyst and Reaction Conditions

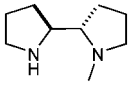
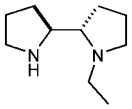
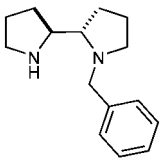
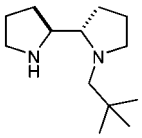
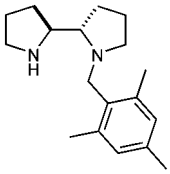
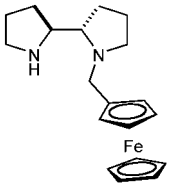
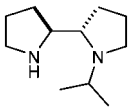
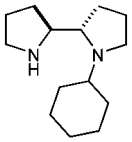
At the beginning of this work we had to elucidate the parameters that played a role in the selectivity of the asymmetric Michael addition to nitroolefins. We have started our investigation with the addition of acetone to nitrostyrene (Scheme 3), which is the simplest system. Indeed, no diastereomers were formed and acetone can be used as reactant and solvent. The first attempts revealed that the reaction catalyzed by ***i*PBP 3g** was very slow. Only 4% of adduct **6a** was formed after 15 h of reaction. The reaction rate was greatly increased when the reaction was carried out in chloroform with 20% vol of acetone. The main drawback of these new conditions was the formation of the α,α′-dialkylated acetone in about 50% yield. This product was possibly formed after an intramolecular deprotonation at the α′ position by the anion formed after the first conjugate addition. The formation of this side product was totally suppressed by the addition of pTSA · H_2O. The addition of pTSA · H_2O also enhances the reaction rate, thus the reaction was fast enough in pure acetone. We then tested diamines **3a–h** to improve the enantioselectivities of the addition (Table 2).

The influence of the substituents on the 2,2′-bipyrrolidine is not very significant. But we can say that small groups such as Me **3a** (entry 1) or Et **3b** (entry 2) are



Scheme 3.

Table 1. Formation of the aminals of 2,2′-bipyrrolidine and reduction to the corresponding *N*-monoalkylated derivatives.

Entry	R^1	R^2	Yield **2** [%][a]	Yield **3** [%][b]	Product	
1	H	H	86	44[c]		**3a**
2	H	Me	99	46		**3b**
3	H	Ph	97	90[d]		**3c**
4	H	*t*-Bu	93	64		**3d**
5	H	Mes	96	43		**3e**
6	H	$FeCp_2$	92	46		**3f**
7	Me	Me	97	88[d]		**3g**
8	$(CH_2)_5$		94	80[d]		**3h**

[a] The crude product was used for the reduction step without further purification.
[b] Yield of isolated product after column chromatography on SiO_2.
[c] $NaBH_3CN$ and TFA were used in place of $NaBH_4$ and AcOH for the reduction step.
[d] Yield after Kugelrohr distillation.

less selective than bulkier groups. When we have a primary large group on the nitrogen, the reaction rate is greatly decreased without enhancement of the enantioselectivities (entries 3–6). Finally, the most interesting results were obtained when a secondary group was used. The reaction rate remains high and the enantiomeric excesses were slightly better than for most of the other diamines. The adduct **6a** was obtained in good yield with 23% ee using **3g** (entry 7) and 30% ee with **3h** (entry 8). On further tests, it appeared that diamine **3g** gave generally the highest enantioselectivities than **3h** with other ketones or aldehydes. Thus, in this article

Table 2. Asymmetric addition of acetone to nitrostyrene catalyzed by diamines **3a–h**.

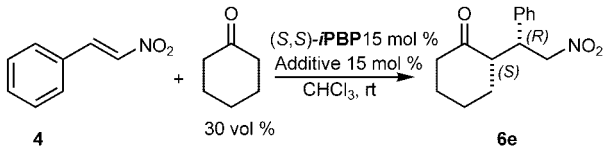
Entry	cat* **3**	Reaction time	Yield[a] [%]	ee[b] [%]
1	**3a**	15 h	88	17
2	**3b**	15 h	79	20
3	**3c**	3 d	91	17
4	**3d**	3 d	76	25
5	**3e**	7 d	25	3
6	**3f**	7 d	64	17
7	**3g**	15 h	74	23
8	**3h**	15 h	89	30

[a] Isolated yield after column chromatography.
[b] Determined by chiral GC (Lipodex E column). The absolute configuration (*R*) was determined by comparison with literature data.[47]

we have focused our attention on asymmetric reactions catalyzed with ***i*PBP 3g**.

These first results incited us to test a more crowded ketone to have a chance to obtain better enantioselectivities. Therefore, we examined the addition of cyclohexanone to nitrostyrene (Scheme 4). The racemic addition product was obtained with pyrrolidine as achiral catalyst. But, surprisingly, when we performed the asymmetric reaction with our chiral catalysts, none of them catalyzed the addition. Then, additives were tested to allow the addition reaction catalyzed by ***i*PBP 3g** to take place. Indeed, it is known that additives can have a major role in the reactivity of organocatalyzed aldol reactions,[62,64,66] Mannich reactions,[36] Diels–Alder reactions[85,86,88,89,91] or Friedel–Crafts alkylations.[72,74,75,78] Our results are summarized in Table 3.

As mentioned above ***i*PBP 3g** did not catalyze the addition of cyclohexanone to nitrostyrene. We thought that the addition of a catalytic amount of pTSA·H_2O would increase the reaction rate, as for the acetone case, by forming a mimic L-proline species with the pyrrolidine moiety and an ammonium function to replace the carboxylic group. Indeed, Enders[48] and List[47] had already reported the asymmetric addition of cyclohexanone and other ketones to nitrostyrene catalyzed by L-proline without the problem of reactivity. But the addition of pTSA·H_2O had no effect for our reaction. We then tested several additives and we found that with 15% of ammonium chloride and 1 equivalent of water the reaction does take place. We have isolated the addition product **6e** with 70% yield, 91:9 dr and 75% ee (Table 3, entry 4). The relative (*syn*) and absolute configurations of **6e**, as shown in Scheme 4, were determined by comparison with known ^{1}H NMR data and the optical rotation value.[120] We also noted that nothing happens in the presence of NH_4Cl without additional water (entry 3). That shows the crucial role of water for the protonation and hydrolysis of the intermediate species involved in the catalytic cycle. Indeed, we can consider ammonium chloride as a drying agent which traps the forming water during the catalytic cycle, thus stopping the reaction. With these new conditions we observed that the catalysts **3a** and **3h** gave lower ees and the diamine **3b** furnished almost the same ee as ***i*PBP 3g**. Moreover, the ammonium chloride can be replaced with a 1.0 molar solution of hydrochloric acid in methanol to form the hydrochloride of ***i*PBP 3g** to obtain the adduct **6e** with a slight increase of the enantioselectivity (81% ee, entry 5). Finally, a simple carboxylic acid can also be used, such as benzoic acid, to activate the reaction (entry 6).



Scheme 4.

*Asymmetric Addition of Ketones to Nitrostyrene Catalyzed by **i*PBP***

After these first encouraging results we then tested several kinds of symmetrical and non-symmetrical ketones (Scheme 5).

Table 3. Addition of cyclohexanone to nitrostyrene catalyzed by *i*PBP.

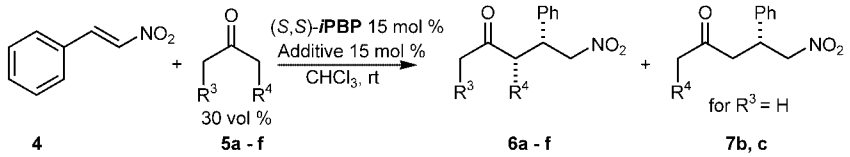
Entry	Additive	Reaction time	Yield[a] [%]	dr[b] *syn*:*anti*	ee[c] [%]
1	none	2 d	0	–	–
2	pTSA·H_2O	2 d	0	–	–
3	NH_4Cl	2 d	0	–	–
4	NH_4Cl, H_2O 1 equiv.	15 h	70	91:9	75
5	HCl[d]	15 h	74	94:6	81
6	PhCOOH	15 h	76	92:8	77

[a] Yield of isolated product after column chromatography.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by SFC employing chiral phase: Chiralpak AD.
[d] The hydrochloride of ***i*PBP 3g** was formed using a solution of 1.0 M HCl in MeOH.

Table 4. Conjugate addition of ketones **5a–f** to nitrostyrene catalyzed by ***i*PBP 3g** to afford γ-nitro ketones **6a–f** and **7b–c**.

Entry	Ketone	R^3	R^4	Additive	Conditions	Yield[a] [%]	rr[b]	dr[c] *syn*:*anti*	ee[d] (*syn*)	Product
1[e]	**5a**	H	H	None	rt, 15 h	29 (15)[g]	–	–	29	**6a**
2[e]				*p*TSA·H_2O	rt, 15 h	74 (0)[g]	–	–	23	**6a**
3[e]				HCl[f]	rt, 15 h	82 (9)[g]	–	–	25	**6a**
4	**5b**	H	Me	None	rt, 3 d	61	43:57 (70)[h]	85:15	32	**6b**+**7b**
5				*p*TSA·H_2O	rt, 4 d	99	70:30 (56)[h]	82:18	48	**6b**+**7b**
6				HCl[f]	rt, 6 d	55	74:26 (49)[h]	80:20	51	**6b**+**7b**
7	**5c**	H	Et	None	rt, 6 d	46	33:67 (53)[h]	78:22	37	**6c**+**7c**
8				*p*TSA·H_2O	rt, 6 d	trace	n.d.	n.d.	n.d.	**6c**+**7c**
9				*p*TSA·H_2O	60 °C, 7 d	81	40:60 (40)[h]	70:30	36	**6c**+**7c**
10				HCl[f]	rt, 6 d	trace	n.d.	n.d.	n.d.	**6c**+**7c**
11				HCl[f]	60 °C, 7 d	95	33:67 (38)[h]	68:32	34	**6c**+**7c**
12	**5d**	Me	Me	HCl[f]	rt, 6 d	8	–	n.d.	76	**6d**
13				HCl[f]	60 °C, 7 d	65	–	84:16	67	**6d**
14	**5e**	-$(CH_2)_3$-		HCl[f]	rt, 15 h	74	–	94:6	81	**6e**
15	**5f**	-$(CH_2)_2$-		HCl[f]	rt, 6 d	6	–	69:31	50	**6f**
16				HCl[f]	60 °C, 6 d	46	–	34:66	17	**6f**

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Regioisomeric ratio (**6b**:**7b** or **6c**:**7c**) determined by ^{1}H NMR or GC.
[c] Determined by ^{1}H NMR of crude product.
[d] Determined by GC or SFC employing chiral phases: Lipodex E, Chiralcel OB-H, Chiralpak AD. The relative and absolute configuration of **6e** were determined by comparison with literature data.[120] The stereochemistries of compounds **6a**, **6b**,**7b**, **6c**, **7c**, **6d** and **6f** have been assigned by assuming an identical reaction pathway and according to literature results.[47,48]
[e] Using only acetone as solvent.
[f] Diamine hydrochloride was formed using a solution of 1.0 M HCl in MeOH.
[g] In parenthesis is given the yield of the double addition product on acetone.
[h] Enantiomeric excess of the terminal regioisomer **7**.



Scheme 5.

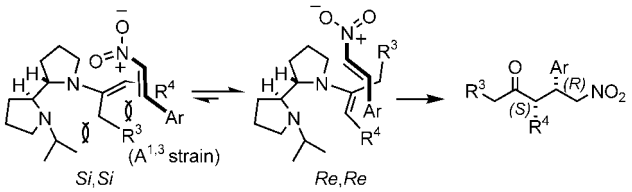
Having optimized the catalyst and the reaction conditions, we next tested the asymmetric addition of other ketones to nitrostyrene **4** using diamine ***i*PBP 3g**. Results are summarized in Table 4. As previously discussed, the reactions with acetone, catalyzed by ***i*PBP 3g**, give a non-negligible quantity of the dinitro adduct (entry 1). A catalytic amount of *p*TSA·H_2O completely eliminates the formation of this by-product and also causes an increase in the reaction rate (entry 2). Diamine ***i*PBP 3g** hydrochloride gave adduct **6a** in good yield and moderate ee (25% ee) (entry 3) but also with a small amount of by-product (9%).

The catalytic Michael addition of non-symmetrical ketones such as methyl ethyl ketone **5b** and methyl propyl ketone **5c** introduces the problem of regioselectivity. In basic conditions, the less hindered methyl group reacts preferentially, in a low regioisomer ratio (rr) for adduct **7b** (57:43) (entry 4) and modest regioisomer ratio for adduct **7c** (67:33) (entry 7). In the presence of *p*TSA·H_2O (0.15 equivs.) or the hydrochloride catalyst, the prototropy of the reactive enamine was more favourable and the equilibration between the more and the less substituted enamine could occur. That leads to the formation of the more stable substituted enamine. Thus, the regioselectivity obtained for the adduct **6b–7b** (entries 5 and 6) was inverted, indicating that the equilibrium was too slow to involve a Curtin–Hammet kinetics which had favoured the adduct **7b**. But, the equilibrium between the two enamines certainly takes partially place and does not allow us to affirm that the regiocontrol of the enamine formation is transposed to the regioisomeric ratio of adducts. Only traces of product were observed for adduct **6c** at room temperature after 7 days (entries 8 and 10), but after 7 days at 60 °C, the reaction was complete (entries 9 and 11). Nevertheless, the regioselectivity was not inverted. We assume that the enam-

ine equilibration could occur but that the substituted enamine was too hindered to react quickly. In these conditions a Curtin–Hammet kinetics was involved and the methyl adduct **7c** was obtained as the major product with a slow reaction rate. To avoid the problem of regioisomers, diethyl ketone **5d** was tested. It did not react at all, either with diamine ***i*PBP 3g** or with addition of *p*TSA·H_2O. However, the reaction catalyzed by diamine ***i*PBP 3g** hydrochloride gave adduct **6d**. At room temperature, only 8% were isolated, after 6 days, with good enantioselectivity (76% ee) (entry 12). After 7 days at 60 °C, the reaction was complete and adduct **6d** was obtained in a moderate yield (65%), good enantioselectivity (67% ee) and diastereoselectivity (84:16) (Entry 13).

Finally, the adduct **6f** was obtained in poor yield (6%) and moderate enantioselectivity (50% ee) (entry 15) after 7 days at room temperature in the presence of ***i*PBP 3g** hydrochloride. Prolonged the heating time (entry 16) gave a better yield (46%) albeit with a loss of diastereo- and enantiocontrol.

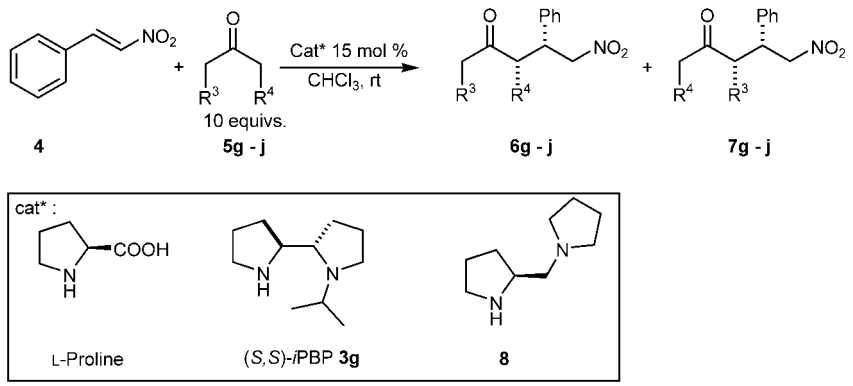
The *syn* selectivity we observe is in accordance with Seebach's model.[121–124] It is explained by an acyclic synclinal model, in which there are favourable electrostatic interactions between the nitrogen of the enamine and the nitro group in the transition state. An inverse-electron-demand hetero-Diels–Alder mechanism, concerted or not, as proposed by Jørgensen[90] for the addition of aldehydes to enones could also be postulated. But the resulting cycloadducts would be immediately hydrolyzed in the reaction mixture. Thus, we could not argue about one of these two mechanisms. A model has been proposed to explain the absolute configuration of the adducts (Scheme 6). Two factors are important for good enantioselection; firstly, one face of the enamine must be less accessible and secondly, the equilibrium between the enamine rotamers must be well shifted to one side. The isopropyl group plays these two roles, it blocks the back face against the approach of the nitroolefin and it shifts the equilibrium towards one of the two rotamers. This displacement is probably due to the bigger A value of the sp^3 carbon, compared to a sp^2 one, which interacts sterically with the isopropyl group. Moreover, the *Si*,*Si* transition state is certainly less stable on account of the allylic strain ($A^{1,3}$) present on this transition state. According to our results and to our model the *Re*,*Re* approach is favoured for ketones, but the small difference of size of the two sides of the ketones leads to modest enantioselectivities and diastereoselectivities.



Scheme 6.

The main problem with non-symmetrical ketones was the regioselectivity which was never totally controlled. This drawback was suppressed when we used α-heterosubstituted ketones such as **5g–j** (Table 5, Scheme 7). Indeed, the branched adducts **6g** and **6h** were formed exclusively when methoxyacetone **5g** or hydroxyacetone **5h** were used. This regioselectivity could be explained by the difference of the acidity of the α and α′ hydrogens of the ketones. The strongest acidity of the hydrogen next to the oxygen atom leads only to the enol-enamine species. When the oxygen atom is replaced by the nitrogen of the dimethylamino group of **5j** this behaviour is not observed. Probably the balance between acidity and steric hindrance was in favour of the terminal enamine which affords the linear addition product **7j**.

The use of α-alkoxycarbonyls has already been described in aldol reactions[15,25] and Mannich reactions,[35,37,39] catalyzed by L-proline, with very high stereo- and regioselectivities. But the result obtained for the addition of hydroxyacetone to nitrostyrene catalyzed by ***i*PBP 3g** was astonishing (Table 5, entry 2). The regioselectivity was fully controlled, as expected, but we had never obtained the *anti* adduct as major product **6h** before.

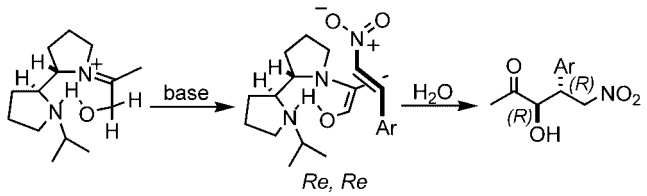


Scheme 7.

Table 5. Conjugate addition of α-heterosubstituted ketones to nitrostyrene **4**.

Entry	Ketone	Catalyst	R^3	R^4	Conditions	Yield[a] [%]	rr[b] **6**:**7**	dr[c] *syn*:*anti*	ee[d] [%]	Product[e]
1	**5g**	(*S,S*)-***i*PBP**	H	OMe	rt, 2 d	75	>99:1	83:17	69	**6g** (*S,R*)
2	**5h**	(*S,S*)-***i*PBP**	H	OH	rt, 7 d	79	>99:1	17:83	98	**6h** (*R,R*)
3		L-proline[f]	H	OH	rt, 4 d	67	>99:1	70:30	11	**6h**
4		**8**[g]	H	OH	rt, 7 d	59	>99:1	51:49	10[h]	**6h** (*R,R*)
5	**5i**	(*S,S*)-***i*PBP**	Et	OH	60 °C, 7 d	21	>99:1	8:92	98	**6i** (*R,R*)
6	**5j**	(*S,S*)-***i*PBP**	H	NMe_2	rt, 3 d	52	>1:99	–	62	**7j** (*R*)
7		L-proline[f]	H	NMe_2	rt, 3 d	24	>1:99	–	63	**7j** (*R*)
8		**8**	H	NMe_2	rt, 3 d	83	>1:99	–	75	**7j** (*R*)

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Regioisomeric ratio determined by ^1H NMR or GC.
[c] Determined by ^1H NMR of crude product.
[d] Enantiomeric excess of the major regioisomer and diastereomer determined by GC or SFC employing chiral phases: Chiralcel OJ, Chiralpak AD.
[e] Relative and absolute configurations of **6g**, **6i** and **7j** were assigned according to our transition state model (Scheme 6). Relative and absolute configurations of **6h** were attributed assuming the same reaction pathway as for **10e**.
[f] Using MeOH as solvent.
[g] (*S*)-(+)-(1-Pyrrolidinylmethyl)pyrrolidine **8**.
[h] (*anti*): 38% ee



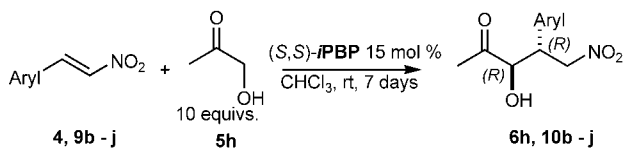
Scheme 8.

Even the *syn* adduct was obtained in the racemic version catalyzed by pyrrolidine. Furthermore, the enantioselectivity was almost total (98% ee). At this stage we had to modify our transition state model. We had assumed that the only way to explain the inversion of diastereoselectivity was the formation of the *cis* enamine. This *cis* enamine could be formed after the deprotonation of the iminium with the hydroxy group blocked at the *cis* conformation by an internal hydrogen bond (Scheme 8). This hydrogen bond remains on the enamine species and, due to the rigid conformation, the enantiomeric excesses obtained are very high. In addition, the absolute configuration of the adduct, *vide infra*, was in accordance with our model. This result was very significant, all the more so since neither L-proline (Table 5, entry 3) nor (*S*)-(+)-(1-pyrrolidinylmethyl)pyrrolidine **8** (Table 5, entry 4) gave such inversion and high enantioselectivities for this reaction. Screening of different solvents has shown that chlorinated solvents, $CHCl_3$ (78%, 98% ee) and CH_2Cl_2 (68%, 98% ee), gave higher yields and selectivities. For the aminated ketone **5j**, the best result was obtained with the less hindered diamine **8** that give the linear adduct **7j** in 83% yield and 75% ee.

*Asymmetric Addition of Hydroxyacetone to Nitroolefins Catalyzed by **iPBP***

The addition of hydroxyacetone was then extended to nitroolefins other than nitrostyrene (Scheme 9). Unfortunately, the addition of hydroxyacetone was not possible on non-aromatic nitroolefins, such as β-cyclohexylnitroethene **9l** or β-(*n*-butyl)-nitroethene **9k**. After several days some traces of the product were observed by TLC but many other products were also formed and the starting material was not totally consumed. The non-aromatic nitroolefins seem to be not reactive enough to accept hydroxyacetone and they decompose gently during the long reaction time. In a second step, the addition of hydroxyacetone to different β-arylnitroolefins **9b–j** was tested, and the results are summarized in Table 6. All reactions were carried out in chloroform with 15% catalyst and 10 equivs. of ketone for a duration of 7 days.

We have observed only little differences in enantioselectivity between the adducts **10b–j**. Generally speaking electron-withdrawing groups on the aryl moiety gave slightly higher yields and stereoselectivities. The relative configuration of the adduct **10e** was determined by X-ray diffraction of its Mosher ester **10e–mosher**[125]



Scheme 9.

Table 6. Conjugate addition of hydroxyacetone to nitroolefins catalyzed by diamine ***i*PBP**.

Entry	Substrate	Ar	Yield[a] [%]	dr[b] *anti:syn*	ee[c] [%]
1	**4**	Ph	79	83:17	97.6
2	**9b**	4-MePh	68	84:16	97.6
3	**9c**	4-MeOPh	65	81:19	97.3
4	**9d**	4-ClPh	81	87:13	97.8
5	**9e**	2-CF_3Ph	84	95:5	98.5
6	**9f**	2,6-Cl_2Ph	83	84:16	98.1
7	**9g**	3,4-Cl_2Ph	66	88:12	98.1
8	**9h**	2,4-Cl_2Ph	85	91:9	98.6
9	**9i**	1-naphthyl	68	78:22	98.3
9	**9j**	2-thienyl	66	78:22	96.3

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^{1}H NMR or SFC of the crude product.
[c] Determined by chiral SFC of the purified product.

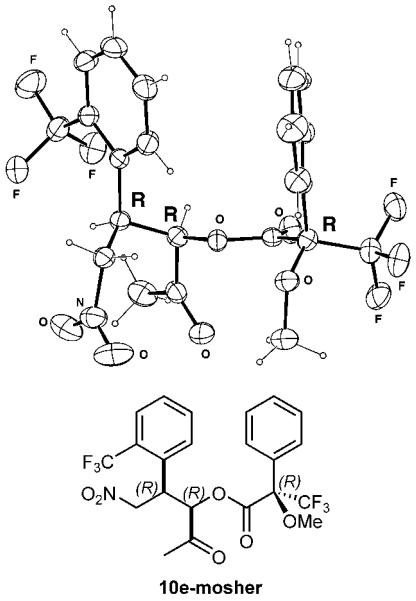


Figure 1.

(Figure 1). The absolute configuration of the centre of the starting Mosher acid being known, we deduced the absolute configuration of adduct **10e** (*R*,*R*). It may be considered that the configuration of the others adducts **10b–j** is the same.

Asymmetric Addition of Aldehydes to Nitroolefins

Barbas was the first to report the asymmetric addition of naked aldehydes to nitroolefins catalyzed by chiral diamines.[84] He has obtained good enantioselectivities, up to 78% ee, for the addition of isovaleraldehyde to **9e** but the ees decrease quickly for smaller aldehydes. We were curious to explore this chemistry with our 2,2′-bipyrrolidine derivative diamine catalysts.

Table 7. Asymmetric addition of valeraldehyde to nitrostyrene catalyzed by diamines **3a–h** in a mixture THF:DMF (3:1).

Entry	cat* **3**	Reaction time	Yield[a] [%]	dr[b] *syn/anti*	ee[c] [%]
1	**3a**	2 d	74	75:25	49
2	**3b**	2 d	77	73:27	56
3	**3c**	2 d	100[d]	76:24	53
4	**3d**	2 d	100[d]	72:28	41
5	**3e**	2 d	100[d]	76:24	51
6	**3f**	2 d	100[d]	77:23	55
7	**3g**	2 d	92	73:27	63
8	**3h**	1 d	85	77:23	60

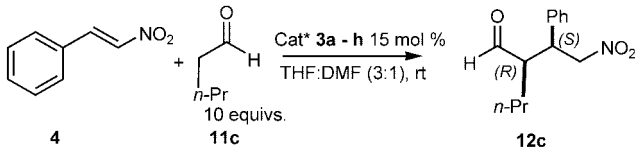
[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^{1}H NMR or SFC of the crude product.
[c] Determined by chiral SFC of the purified product.
[d] Conversion determined by GC.

Optimization of the Organocatalyst and Reaction Conditions

For the addition of ketones to nitroolefins we have shown that ***i*PBP 3g** was generally the most selective catalyst but the other ones were only slightly less efficient. This is why we decided to test again the whole range of diamines for the addition of valeraldehyde **11c** to nitrostyrene **4**. All these reaction were performed in a mixture of THF:DMF (3:1).

The results given above (Table 7) show that the nature of the catalyst does not influence much the reaction rate, in contrast to the behaviour observed with acetone. The diastereoselectivity of the adduct **12c** is also not influenced by the catalyst. However, the enantioselectivity is significantly higher for the catalysts having a secondary substituent on nitrogen. As for the ketone case, the diamine ***i*PBP 3g** (63% ee, entry 7) and **3h** (60% ee, entry 8) gave the best ees. We then focused our attention on ***i*PBP 3g** and tested other solvents in an attempt to optimize the conditions. The results are summarized in Table 8.

The conjugate addition of valeraldehyde, run in anhydrous THF, gave only 5% conversion after 2 days at room temperature (entry 2) but in wet THF the conversion was 65% after 15 hours and the enantiomeric excess



Scheme 10.

Table 8. Asymmetric addition of valeraldehyde to nitrostyrene catalyzed by diamines ***i*PBP 3g** in different solvent.

Entry	Solvent	Reaction time	Yield[a] [%]	dr[b] *syn*/*anti*	ee[c] [%]
1	THF:DMF 3:1	2 d	92	73:27	63
2	anhydrous THF	2 d	5[d]	n.d.	n.d.
3	wet THF	15 h	65[d]	78:22	70
4	THF:$CHCl_3$ 3:1	3 d	99	56:44	63
5	$CHCl_3$	15 h	99	73:27	72
6	MeOH	15 h	100[d]	72:28	59

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR or SFC of the crude product.
[c] Determined by chiral SFC of the purified product.
[d] Conversion determined by GC.

was higher (70% ee, entry 3) than for a THF:DMF mixture (entry 1). Methanol (entry 6) and THF:$CHCl_3$ mixture (entry 4) gave lower ees compared to chloroform which give the adduct in good yield (99%) and selectivity (72% ee, *syn*/*anti* 73:27). All these reactions were accompanied with the formation of a substantial amount of condensation product of the valeraldehyde which is easily removed by flash chromatography.

As we have shown previously, Barbas[84] has reported the addition of aldehydes to nitrostyrene catalyzed by (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **8** and other diamines in THF at room temperature with good enantioselectivities. We were curious to see if our new conditions would allow the catalyst **8** to be more selective than ***i*PBP 3g**. Interestingly, our conditions were not optimal at all for this diamine. The enantiomeric excesses measured remained really modest (entries 3, 5 and 8; Table 9).

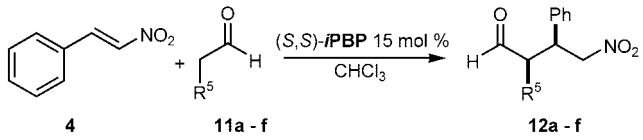
*Asymmetric Addition of Aldehydes to Nitrostyrene Catalyzed by **iPBP***

Then, with the optimal catalyst and solvent, we examined a series of aldehydes. The results are summarized in Table 9. The highest rate of reaction was observed for propionaldehyde **11a**, even at $-25\,^{\circ}C$ (entry 2), the reaction went to completion in a reasonable length of time. Decreasing the temperature had a drastic effect on the enantio- and diastereoselectivity which increased from 77% ee and 75:25 dr (entry 1) to 93% ee and 94:6 dr (entry 2) for propionaldehyde **11a**. A tangible decrease of the amount of aldehyde self-condensation was also observed with the lowering of the temperature. Butyraldehyde **11b** and valeraldehyde **11c** also reacted at $-25\,^{\circ}C$ with good enantioselectivity, 81% ee (entry 4) and 87% ee (entry 7) respectively, but the reaction took twice as long as that with propionaldehyde **11a**. Isovaleraldehyde **11d** however, reacted only at room temperature and yielded products with a modest enantiose-

Table 9. Conjugate addition of aldehydes **11a–f** to nitrostyrene **4** catalyzed by ***i*PBP 3g** to afford γ-nitro aldehydes **12a–f**.

Entry	Aldehyde	R^5	Conditions	Yield[a] [%]	dr[b] *syn*:*anti*	ee[c] (*syn*) [%]	Product
1	**11a**	Me	rt, 1h30	99	75:25	77	**12a**
2			$-25\,^{\circ}C$, 2d	71	94:6	93	**12a**
3			$-25\,^{\circ}C$, 15 h	86	94:6	60[d]	**12a**
4	**11b**	Et	$-25\,^{\circ}C$, 4 d	70	90:10	81	**12b**
5			$-25\,^{\circ}C$, 15 h	93	94:6	53[d]	**12b**
6	**11c**	Pr	rt, 15 h	99	73:27	72	**12c**
7			$-25\,^{\circ}C$, 4 d	98	96:4	87	**12c**
8			$-25\,^{\circ}C$, 15 h	83	94:6	56[d]	**12c**
9	**11d**	*i*-Pr	rt, 2 d	99	87:13	73	**12d**
10	**11e**	Ph	rt, 2 d	19	72:28	26	**12e**
11	**11f**	Me,Me[e]	rt, 3 d	72	–	80	**12f** (*R*)

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR or SFC of the crude product.
[c] Determined by chiral SFC of the purified product. Relative (*syn*) and absolute configurations of aldehydes **12a**, **12b** and **12d** were determined by comparison with known literature data.[84] The stereochemistries of aldehydes **12c**, **12e** and **12f** have been tentatively assigned by comparison to analogous compounds.
[d] Reaction catalyzed by (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **8**.
[e] Isobutyraldehyde.

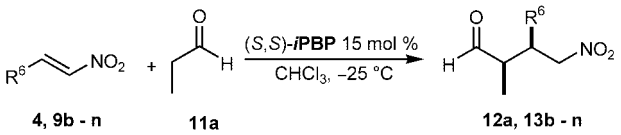


Scheme 11.

lectivity (73% ee) (entry 9). Isobutyraldehyde **11f** afford after three days at room temperature a product containing a quaternary centre, **12f**, with 80% ee (entry 11). Finally, phenylacetaldehyde **11e** gave the addition product **12e** in poor (19%) yield and enantioselectivity (26%, entry 10). This result shows the limitation of the method. In fact, when we have a too acidic hydrogen in the α position to the carbonyl, the reaction takes a new pathway. The mechanism involving a deprotonation by the amine to give an enolate (see Scheme 1, mechanism type B) could be postulated instead of the mechanism involving an enamine. This new pathway is, in our case, less selective in terms of enantio- and diastereoselectivity.

*Asymmetric Addition of Propionaldehydes to Nitroolefins Catalyzed by **iPBP***

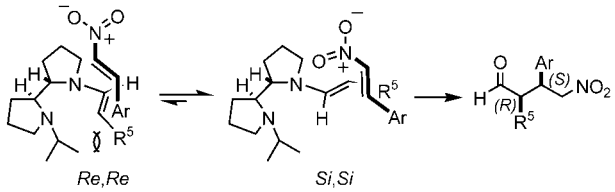
The high velocity and selectivity observed for the addition reaction of propionaldehyde to nitrostyrene led us to experiment with other nitroolefins. The results are summarized in Table 10.



Scheme 12.

We were delighted to see that the addition occurred both to the aromatic and to the non-aromatic nitroolefins, whereas this was not the case for hydroxyacetone. Interestingly, the nature of the nitroolefins has no influence on the enantioselectivity which is around 93% ee in all cases, whatever the nitroolefin, having aromatic (entries 1–5) or non-aromatic groups (entries 6–8). We just observed a decrease of the diastereoselectivity (*syn*/*anti* 73:27) with the adduct **13m** (entry 8) and a loss of reactivity with the nitroolefin **9n**.[126] Indeed, a strong withdrawing group CF_3 does not allow the reaction to take place at −25 °C (entry 9). But, the adduct **13n** was isolated after one day at room temperature in 42% yield, 91% ee and a ratio *syn*/*anti* of 77:23 (entry 10). However, a prolonged reaction time (3 days) does not increase the yield and an epimerization to the *anti* adduct occurs.

The transition state model proposed in Scheme 13 can explain the absolute configuration. There is no fundamental difference between the transition state for ketones (Scheme 6) and for aldehydes (Scheme 13) except the inversion of the relative size of the two sides of the carbonyl group or enamine. For the case of ketones, the smallest side is the one with the double bond of the enamine while the hydrogen was the smallest group for aldehydes. Hence, the *Si*,*Si* transition state is well favoured compared to the *Re*,*Re* and the enantioselectivities are high.

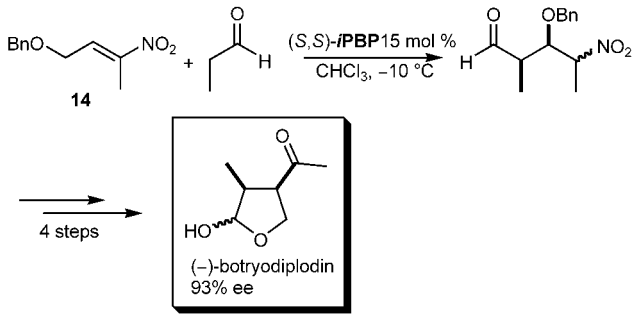


Scheme 13.

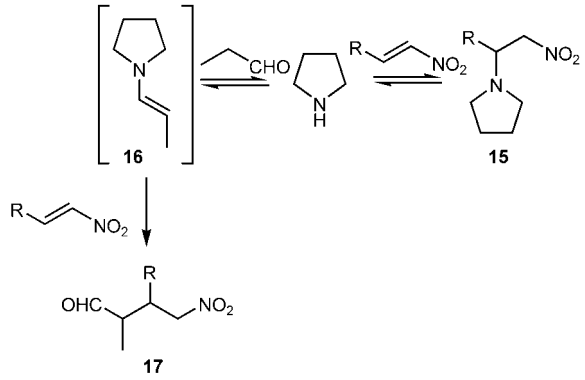
Table 10. Conjugate addition of propionaldehyde **11a** to nitroolefins catalyzed by ***i*PBP 3g** to afford γ-nitro aldehydes **12a** and **13b–n**.

Entry	Substrate	R^6	Reaction time	Yield[a] [%]	dr[b] *syn*:*anti*	ee[c] (*syn*) [%]	Product
1	**4**	Ph	2 d	71	94:6	93	**12a**
2	**9b**	4-MePh	3 d	88	95:5	94	**13b**
3	**9c**	4-MeOPh	3 d	64	94:6	93	**13c**
4	**9e**	2-CF_3Ph	3 d	74	92:8	95	**13e**
5	**9j**	2-Thienyl	2 d	66	94:6	93	**13j**
6	**9k**	Butyl	15 h	70	90:10	93	**13k**
7	**9l**	*c*-Hexyl	3 d	76	85:15	96	**13l**
8	**9m**	$CH(OMe)_2$	3 d	73	73:27	90	**13m**
9	**9n**	CF_3	3 d	traces	n.d.	n.d.	**13n**
10	**9n**	CF_3	1 d, rt	42	77:23	91	**13n**

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^{1}H NMR or SFC of the crude product.
[c] Determined by chiral SFC of the purified product. The stereochemistries of aldehydes **13b –m** have been tentatively assigned by comparison to **12a**.



Scheme 14.



Scheme 15.

From a synthetic point of view, the possibility to add propionaldehyde with high enantioselectivity on any kind of nitroolefins is very interesting. We have demonstrated this potential with the first asymmetric synthesis of (−)-botryodiplodin[127] (Scheme 14). In few steps, starting from an asymmetric addition of propionaldehyde to the nitroolefin **14** catalyzed by (*S*,*S*)-***i*PBP 3g**, we were able to isolate the natural product with 93% ee.

NMR Investigation

During our study on the asymmetric addition of propionaldehyde to the whole range of nitroolefins we have noticed significant differences of behaviour between these Michael acceptors. A better understanding of the reactivity of the nitroolefins was achieved after we had run several racemic test reactions in NMR tubes (Scheme 15).

The first things we have observed were that pyrrolidine quickly adds to most of the nitroolefins to give the adduct **15** clearly identified by ^{1}H NMR. But this 1,4 addition was not observed on the α,β-dialkylnitroethylenes, indicating their poor Michael acceptor character. The reversibility of the addition was proved with the fast isomerization of *cis*-nitrostyrene to *trans*-nitrostyrene with a catalytic amount of pyrrolidine. After having formed the pyrrolidine adduct **15** we have added propionaldehyde. This experiment has revealed two groups of nitroolefins, the first one (**4**, **9k** and **9l**) showed a partial disappearance of the pyrrolidine adduct **15** and a fast formation of propionaldehyde adduct **17** without the clear identification of the enamine **16**. The second group (**9m**, **9n** and **14**) revealed no disappearance of the pyrrolidine adduct **15** and a slower formation of the propionaldehyde adduct. By adding pyrrolidine in default to several mixtures of two nitroolefins we were able to classify them in terms of Michael acceptor character. The following sequence was obtained according to adduct **15** formed predominantly: **9l** < **4** < **9k** < **14** ≪ **9m** ≪ **9n**. When propionaldehyde was added to these mixtures we observed the normal reactivity, that means that the more of an acceptor the substrate is, the fastest the reaction takes place. Note that we have observed almost the reverse reaction rate when we performed these reactions with a unique nitroolefin.

Thus, we can say that not only the Michael acceptor character has an influence on the reaction rate but also the availability of the catalyst which is trapped by the substrate in some cases. Finally, the fastest reactions are observed with moderate Michael acceptors such as **4** or **9k**.

Conclusion

In conclusion, we have confirmed that asymmetric organocatalysis is a powerful tool for organic synthesis. Indeed, we were able to obtain the conjugate addition of aldehydes and ketones to nitroolefins without any previous protection, or particular precautions, with high yields and selectivities. Furthermore, the temperature range, −25 °C to room temperature, used for these reactions could be very interesting from an industrial point of view. The main drawbacks of organocatalysis remain its low reaction rate and high catalyst loading which must be absolutely improved in the future. Some original works using ionic liquid[46,128,129] or high pressure[28,43] have already been published; we can also imagine that microwave or sonication would increase the reaction rate. We have also shown that L-proline is not a universal organocatalyst. Generally speaking, we can say that L-proline is a catalyst for the 1,2 additions of enamine, namely aldol reaction, Mannich reaction, additions to nitroso or diaza compounds. And chiral pyrrolidines without a proton donating group, such as carboxylic or hydroxy group, are catalysts for conjugate additions to nitroolefins,[47,48,77,80,84] vinyl ketones[81] or alkylidenemalonates.[71] New catalysts and new substrates are now in development in our laboratories in accordance with this final conclusion.

Experimental Section

General Remarks

All reactions were run under an atmosphere of N_2. Tetrahydrofuran, Et_2O and CH_2Cl_2 were distilled from Na/benzophenone or CaH_2, $CHCl_3$ was stabilized with 1% of ethanol and used without previous distillation. ^1H NMR and ^{13}C NMR were measured on a Bruker 500 FT NMR or 400 FT NMR. Chemical shift are reported as δ values in ppm. Coupling constants are reported in Hz. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), dd (doublet of doublet), bs (broad singlet). IR were recorded on Perkin-Elmer 1600, $[\alpha]_D^{20}$ were recorded on a Perkin-Elmer 241 polarimeter and GC/MS on an HP6890 with EI (70 eV) as source; *m/z* (%).Gas chromatography program is given in a shortened form: 100 °C-2-10-170 indicates 100 °C as starting temperature then 2 minutes at 100 °C then an rate of 10 °C/minutes up to 170 °C. The same symbolism was used for supercritical fluid chromatography (SFC) where °C is replaced with % of methanol.

Aminal Formation Starting from 2,2′-Bipyrolidine

General Procedure 1: To a solution of 2,2′-bipyrrolidine[113] **1** or 2,2′-bipyrrolidinium tartrate salt[114] (3.57 mmol) in THF or diethyl ether (15 mL) for 2,2′-bipyrrolidine or MeOH (15 mL) for 2,2′-bipyrrolidinium tartrate salt was added molecular sieves 4 Å (~0.5 g) and ketone or aldehyde (3.57 mmol). The mixture was stirred overnight, then K_2CO_3 was added and the mixture was stirred for 1 hour and then filtered. Solvent was removed to give the crude aminal **2a–h** which was used without purification for the next step.

***(S,S)-2,2′-Bipyrrolidine formaldehyde aminal* (2a):** Product was formed according to General Procedure 1 using diethyl ether as solvent and aqueous formaldehyde 40% as aldehyde (0.27 g, 3.57 mmol). Removal of the solvent gave a pale yellow oil; yield: 467 mg (86%); ^1H NMR (400 MHz, C_6D_6): δ = 3.65 (s, 2H), 2.94–2.89 (m, 2H), 2.84 (dt, 2H, *J* = 10.1, 6.5 Hz), 2.51 (dt, 2H, *J* = 10.1, 6.8 Hz), 1.69–1.44 (m, 6H), 1.31–1.24 (m, 2H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 77.89 (t), 70.07 (2C, d), 52.82 (2C, t), 29.84 (2C, t), 25.08 (2C, t).

***(S,S)-2,2′-Bipyrrolidine acetaldehyde aminal* (2b):** Product was formed according to General Procedure 1 using THF as solvent and acetaldehyde (0.16 g, 0.2 mL, 3.57 mmol). Removal of the solvent gave a pale yellow oil; yield: 593 mg (quantitative); ^1H NMR (400 MHz, C_6D_6): δ = 3.59 (q, 1H, *J* = 6.1 Hz), 3.07–3.02 (m, 1H), 2.98 (dt, 1H, *J* = 2.6, 7.2 Hz), 2.83–2.68 (m, 3H), 2.31–2.25 (m, 1H), 1.92–1.84 (m, 1H), 1.72–1.35 (m, 6H), 1.28 (d, 3H, *J* = 6.0 Hz), 1.18–1.12 (m, 1H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 80.03 (d), 70.88 (d), 70.40 (d), 50.83 (t), 45.88 (t), 30.38 (t), 28.85 (t), 25.38 (t), 25.08 (t), 17.87 (t).

***(S,S)-2,2′-Bipyrrolidine benzaldehyde aminal* (2c):** Product was formed according to General Procedure 1 using diethyl ether as solvent and benzaldehyde (0.38 g, 0.36 mL, 3.57 mmol). Removal of the solvent gave a pale yellow oil; yield: 791 mg (97%); ^1H NMR (400 MHz, C_6D_6): δ = 7.92 (d, 2H, *J* = 7.1 Hz), 7.38 (t, 2H, *J* = 7.6 Hz), 7.28–7.23 (m, 1H), 4.96 (s, 1H), 3.36–3.27 (m, 2H), 2.95 (dt, 1H, *J* = 11.1, 6.6 Hz), 2.76 (q, 1H, *J* = 8.7 Hz), 2.50–2.46 (m, 2H), 2.08–2.00 (m, 1H), 1.77–1.55 (m, 6H), 1.43–1.32 (m, 1H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 141.07 (s), 128.42 (2C, d), 128.14 (2C, d), 127.44 (d), 87.36 (d), 71.06 (d), 70.91 (d), 51.77 (t), 47.75 (t), 30.82 (t), 29.23 (t), 26.00 (t), 24.98 (t).

***(S,S)-2,2′-Bipyrrolidine pivaldehyde aminal* (2d):** Product was formed according to General Procedure 1 using diethyl ether as solvent and pivaldehyde (0.31 g, 0.39 mL, 3.57 mmol). Removal of the solvent gave a yellow oil; yield: 690 mg (93%); ^1H NMR (400 MHz, C_6D_6): δ = 3.21–3.16 (m, 1H), 2.97 (s, 1H), 2.90 (dt, 1H, *J* = 9.8, 5.8 Hz), 2.82 (q, 1H, *J* = 7.7 Hz), 2.51 (dt, 1H, *J* = 9.1, 6.3 Hz), 2.41–2.40 (m, 2H), 1.90–1.67 (m, 2H), 1.65–1.46 (m, 4H), 1.26–1.14 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 93.31 (d), 73.00 (d), 67.66 (d), 55.38 (t), 47.65 (t), 35.12 (s), 27.66 (t), 27.52 (t), 27.28 (3C, q), 26.97 (t), 24.39 (t).

***(S,S)-2,2′-Bipyrrolidine mesitylaldehyde aminal* (2e):** Product was formed according to General Procedure 1 using diethyl ether as solvent and mesitylaldehyde (0.53 g, 0.52 mL, 3.57 mmol). Removal of the solvent gave a yellow oil; yield: 923 mg (96%); ^1H NMR (400 MHz, C_6D_6): δ = 6.82 (s, 1H), 6.79 (s, 1H), 4.98 (s, 1H), 3.08–3.06 (m, 2H), 2.82 (s, 3H), 2.74–2.67 (m, 2H), 2.55 (s, 3H), 2.42–2.33 (m, 2H), 2.13 (s, 3H), 1.90–1.82 (m, 1H), 1.65–1.38 (m, 6H), 1.30–1.22 (m, 1H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 138.05 (s), 137.76 (s), 135.80 (s), 132.85 (s), 131.26 (d), 129.13 (d), 86.23 (d), 69.71 (d), 69.61 (d), 51.95 (t), 47.44 (t), 30.22 (t), 29.40 (t), 25.89 (t), 25.60 (t), 21.88 (q), 20.44 (q), 20.37 (q).

***(S,S)-2,2′-Bipyrrolidine ferrocene carboxaldehyde aminal* (2f):** Product was formed according to General Procedure 1 using diethyl ether as solvent and ferrocenecarboxyaldehyde (764 mg, 3.57 mmol). Removal of the solvent gave a dark brown oil; yield: 1.11 g (92%); ^1H NMR (400 MHz, C_6D_6): δ = 4.76 (s, 1H), 4.58–4.57 (m, 1H), 4.33–4.32 (m, 1H), 4.02 (s, 5H), 3.99–3.95 (m, 2H), 3.13 (q, 1H, *J* = 6.7 Hz), 3.07–3.01 (m, 2H), 2.84 (dt, 1H, *J* = 10.3, 6.3 Hz), 2.57 (q, 1H, *J* = 8.8 Hz), 2.52–2.47 (m, 1H), 1.90–1.82 (m, 1H), 1.73–1.49 (m, 5H), 1.43–1.36 (m, 1H), 1.26–1.18 (m, 1H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 89.32 (s), 84.35 (d), 70.75 (d), 70.36 (d), 68.60 (5C, d), 68.13 (d), 67.62 (d), 67.14 (d), 66.31 (d, 53.12 (t), 47.39 (t), 30.18 (t), 28.60 (t), 26.86 (t), 24.57 (t).

***(S,S)-2,2′-Bipyrrolidine acetone aminal* (2g):** Product was formed according to General Procedure 1 using diethyl ether as solvent and acetone (5 mL). Removal of the solvent gave a pale yellow oil; yield: 623 mg (97%). The product was also obtained starting from bipyrrolidinium tartrate salt dissolved in methanol and acetone. ^1H NMR (400 MHz, C_6D_6): δ = 3.22–3.16 (m, 2H), 2.81–2.71 (m, 4H), 1.73–1.62 (m, 6H), 1.30–1.22 (m, 2H), 1.21 (s, 6H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 79.86 (s), 70.05 (2C, d), 46.97 (2C, t), 29.82 (2C, t), 27.10 (2C, t), 25.99 (2C, t).

***(S,S)-2,2′-Bipyrrolidine cyclohexanone aminal* (2h):** Product was formed according to General Procedure 1 using THF as solvent and cyclohexanone (0.35 g, 0.37 mL, 3.57 mmol). Removal of the solvent gave a pale yellow oil; yield: 800 mg (87%); ^1H NMR (400 MHz, C_6D_6): δ = 3.33–3.27 (m, 2H), 2.96 (dt, 2H, *J* = 9.8, 7.3 Hz), 2.90–2.84 (m, 2H), 1.95–1.67 (m, 11H), 1.48–1.36 (m, 7H); ^{13}C NMR (100.6 MHz, C_6D_6): δ = 82.26 (s), 70.01 (2C, d), 45.84 (2C, t), 34.82 (2C, t), 29.95 (2C, t), 27.14 (2C, t), 26.01 (t), 24.55 (2C, t).

Reduction of 2,2′-Bipyrrolidine Aminal to *N*-Alkyl-2,2′-bipyrrolidine

***(S,S)*-N-*Methyl-2,2′-bipyrrolidine* (3a):** To a solution of aminal **2a** (404 mg, 2.65 mmol) in MeOH (15 mL) was added in portions at 0 °C $NaBH_3CN$ (1.5 equivs., 3.98 mmol, 250 mg) then trifluoroacetic acid (4 equivs., 10.6 mmol, 1.21 g, 0.81 mL). The solution was stirred for 1.5 h at 0 °C and then diluted with ether (20 mL) and hydrolyzed with aqueous NaOH (5 mL) and water (10 mL). The solution was decanted; the aqueous phase was extracted four times with ether. The combined organic phases were washed with brine, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give a yellow oil (yield: 343 mg, 84%) which was purified by flash chromatography on silica gel (*c*-hexane/EtOAc, 7:3 + 5% MeOH +10% Et_3N) to give a pale yellow oil; yield: 178 mg (44%); $[\alpha]_D^{20}$: −22.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.03–2.93 (m, 3H), 2.81–2.75 (m, 1H), 2.42 (s, 3H), 2.27–2.17 (m, 2H), 1.95 (bs, 1H, NH), 1.88–1.79 (m, 1H), 1.77–1.62 (m, 5H), 1.55–1.45 (m, 1H), 1.39–1.29 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 69.53 (d), 63.60 (d), 58.21 (t), 46.87 (t), 42.83 (q), 28.31 (t), 28.07 (t), 24.94 (t), 23.35 (t); IR ($CHCl_3$): ν = 3148 m, 2969 s, 2875 s, 2789 m, 1672 w, 1457 m, 1270 w, 1212 m, 1144 w, 1094 w, 1047 w, 907 m cm^{-1}; MS (EI): *m/z* = 120 (4), 105 (8), 86 (7), 85 (10), 84 (100), 83 (9), 82 (9), 70 (14), 69 (4), 68 (4), 55 (5), 47 (5); HRMS: calcd. for $C_9H_{18}N_2$: 154.1461; found: 154.1470.

General Procedure 2: To a solution of aminal **2b–h** (2.5 mmol) in MeOH (10 mL) was added in portions at 0 °C $NaBH_4$ (1.5 equivs., 3.75 mmol, 142 mg) then acetic acid (4 equivs., 10.0 mmol, 0.60 g, 0.57 mL). The solution was stirred 3 hours at 0 °C and then diluted with diethyl ether (20 ml) and hydrolyzed with 30% aqueous NaOH (5 mL) and water (10 mL). The solution was decanted; the aqueous phase was extracted two times with EtOAc. The combined organic phases were washed with brine, dried over K_2CO_3, filtered, concentrated under reduced pressure and purified by flash chromatography on silica gel using (*c*-hexane/EtOAc 8:2 + 10% Et_3N) as eluent.

***(S,S)*-N-*Ethyl-2,2′-bipyrrolidine* (3b):** The aminal **2b** (300 mg, 1.80 mmol) was reduced according to General Procedure 2 to give a yellow oil; yield: 135 mg (46%); $[\alpha]_D^{20}$: −39.2 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13–3.08 (m, 1H), 3.04–2.96 (m, 2H), 2.94–2.88 (m, 1H), 2.81–2.75 (m, 1H), 2.44 (ddd, 1H, *J* = 5.7, 7.2, 8.5 Hz), 2.34–2.25 (m, 3H), 1.61 (m, 6H), 1.54–1.46 (m, 1H), 1.36–1.27 (m, 1H), 1.07 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 68.18 (d), 64.16 (d), 54.20 (t), 50.58 (t), 46.52 (t), 28.30 (t), 28.22 (t), 24.67 (t), 23.61 (t), 14.00 (q); IR ($CHCl_3$): ν = 3163 m, 2969 s, 2875 s, 2803 m, 1457 m, 1381 m, 1281 m, 1094 m, 1051 m cm^{-1}; MS (EI): *m/z* = 105 (3), 99 (17), 98 (100), 97 (5), 84 (8), 82 (3), 70 (21), 69 (3), 68 (4), 56 (3), 55 (3); HRMS: calcd. for $C_{10}H_{20}N_2$: 168.1624; found: 168.1627.

***(S,S)*-N-*Benzyl-2,2′-bipyrrolidine* (3c):** The aminal **2c** (696 mg, 3.05 mmol) was reduced according to General Procedure 2 to give after bulb-to-bulb distillation (175 °C/0.4 mbar) a colourless oil; yield: 632 mg (90%); $[\alpha]_D^{20}$: −50.7 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5H), 4.21 (d, 1H, *J* = 13.4 Hz), 3.40 (d, 1H, *J* = 13.1 Hz), 3.06 (q, 1H, *J* = 7.3 Hz), 2.98 (dt, 1H, *J* = 9.8, 6.2 Hz), 2.92 (dt, 1H, *J* = 9.8, 4.8 Hz), 2.81 (dt, 1H, *J* = 10.1, 7.6 Hz), 2.69 (ddd, 1H, *J* = 9.8, 6.8, 5.6 Hz), 2.25 (dt, 1H, *J* = 9.1, 8.3 Hz), 1.98 (bs, 1H, NH), 1.95–1.86 (m, 1H), 1.84–1.67 (m, 5H), 1.61–1.54 (m, 1H), 1.47–1.38 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.44 (s), 128.52 (2C, d), 128.13 (2C, d), 126.61 (d), 67.61 (d), 63.69 (d), 60.77 (t), 54.84 (t), 46.61 (t), 28.13 (t), 27.99 (t), 25.00 (t), 23.72 (t); IR ($CHCl_3$): ν = 3126 m, 2964 s, 2874 s, 2793 m, 2360 w, 1491 w, 1454 m, 1373 w, 1279 w, 1112 w, 1093 w, 1076 w, 905 m cm^{-1}; MS (EI): *m/z* = 162 (1), 161 (17), 160 (100), 159 (2), 108 (2), 92 (4), 91 (54), 70 (7), 65 (1), 52 (2); HRMS: calcd. for $C_{15}H_{22}N_2$: 230.1783; found: 230.1740.

***(S,S)*-N-*(2,2-Dimethylpropyl)-2,2′-bipyrrolidine* (3d):** The aminal **2d** (531 mg, 2.55 mmol) was reduced according to General Procedure 2 to give a colourless oil; yield: 344 mg (64%); $[\alpha]_D^{20}$: −49.8 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (ddd, 1H, *J* = 10.1, 6.6, 4.8 Hz), 3.03–2.97 (m, 1H), 2.94 (q, 1H, *J* = 6.9 Hz), 2.82–2.75 (m, 1H), 2.61 (q, 1H, *J* = 6.5 Hz), 2.52 (d, 1H, *J* = 13.1 Hz), 2.31 (dt, 1H, *J* = 9.8, 7.5 Hz), 2.19 (d, 1H, *J* = 13.1 Hz), 2.07 (bs, 1H, NH), 1.79–1.63 (m, 6H), 1.47–1.35 (m, 2H), 0.89 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 70.71 (t), 70.62 (d), 63.02 (d), 57.73 (t), 46.51 (t), 32.91 (s), 28.69 (3C, q), 27.34 (t), 26.98 (t), 25.09 (t), 24.57 (t); IR ($CHCl_3$): ν = 3180 m, 2946 s, 2874 m, 2342 w, 1477 w, 1459 w, 1396 w, 1360 w, 1103 w, 909 w cm^{-1}; MS (EI): 195 (2), 153 (3), 141 (11), 140 (100), 126 (2), 124 (2), 96 (2), 84 (13), 83 (4), 82 (3), 71 (6), 70 (62), 68 (2), 56 (1), 55 (5); HRMS: calcd. for $C_{13}H_{26}N_2$: 210.2096; found: 210.2100.

***(S,S)*-N-*(2,4,6-Trimethylphenyl)methyl-2,2′-bipyrrolidine* (3e):** The aminal **2e** (923 mg, 3.41 mmol) was reduced according to General Procedure 2 to give a pale yellow oil; yield: 402 mg (43%); $[\alpha]_D^{20}$: −24.9 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 2H), 3.92 (d, 1H, *J* = 12.1 Hz), 3.49 (d, 1H, *J* = 12.4 Hz), 3.14 (q, 1H, *J* = 6.9 Hz), 2.86 (ddd, 1H, *J* = 10.1, 7.3, 5.2 Hz), 2.79–2.62 (m, 3H), 2.39 (s, 6H), 2.32 (dt, 1H, *J* = 6.6, 9.1 Hz), 2.26 (s, 3H), 1.92–1.87 (m, 1H), 1.90 (bs, 1H, NH), 1.79–1.50 (m, 6H), 1.47–1.40 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.48 (2C, s), 135.95 (s), 133.31 (s), 128.89 (2C, d), 67.97 (d), 61.77 (d), 53.50 (t), 53.23 (t), 46.65 (t), 27.55 (t), 27.19 (t), 25.59 (t), 23.59 (t), 20.81 (q), 20.39 (2C, q); IR ($CHCl_3$): ν = 3009 b, 2964 s, 2918 s, 2865 m, 1743 m, 1612 w, 1459 m, 1378 m, 1116 w, 909 m, 850 m cm^{-1}; MS (EI): *m/z* = 203 (11), 202 (55), 134 (15), 133 (100), 132 (6), 131 (1), 119 (2), 118 (3), 117 (4), 116 (1), 115 (2), 105 (4), 91 (4), 88 (3), 79 (1), 77 (1), 71 (1), 70 (20), 68 (2), 55 (1); HRMS: calcd. for $C_{18}H_{28}N_2$: 272.2252; found: 272.2200.

***(S,S)*-N-*(Ferrocenyl)methyl-2,2′-bipyrrolidine* (3f):** The aminal **2f** (1.11 g, 3.30 mmol) was reduced according to General Procedure 2 to give a brown oil; yield: 513 mg (46%); $[\alpha]_D^{20}$: −35.9 (*c* 0.125, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19–4.15 (m, 2H), 4.11–4.08 (m, 7H), 3.85 (d, 1H, *J* = 12.9 Hz), 3.37 (d, 1H, *J* = 12.9 Hz), 3.03–2.89 (m, 3H), 2.80 (dt, 1H, *J* = 9.9, 7.8 Hz), 2.59 (ddd, 1H, *J* = 8.3, 7.6, 5.1 Hz), 2.32 (q, 1H, *J* = 8.5 Hz), 2.00 (bs, 1H, NH); 1.84–1.60 (m, 6H), 1.52–1.44 (m, 1H), 1.39–1.31 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 84.82 (s), 69.87 (d), 69.75 (d), 68.38 (5C, d), 67.93 (d), 67.74 (d), 66.97 (d), 63.95 (d), 55.57 (t), 54.58 (t), 46.49 (t), 28.26 (t), 27.95 (t), 24.75 (t), 23.69 (t); IR ($CHCl_3$): ν = 3009 m, 2964 s, 2865 m, 2493 w, 1743 m, 1464 w, 1373 m, 1279 w, 1098 m, 1053 w, 1026 w, 999 w, 909 s cm^{-1}; MS (EI): *m/z* = 338 (M^+, 3), 269 (4), 268 (10), 201 (2), 200 (17), 199 (100), 198 (1), 197 (7), 134 (1), 122 (2), 121 (23), 119 (1), 70 (12), 56 (3); HRMS: calcd. for $C_{19}H_{26}FeN_2$: 338.1445; found: 338.1440.

***(S,S)-N-Isopropyl-2,2′-bipyrrolidine* (3g):** The aminal **2g** (480 mg, 2.66 mmol) was reduced according to General Procedure 2 to give after bulb-to-bulb distillation (70 °C/0.2 mbar) a colourless oil; yield:427 mg (88%); $[\alpha]_D^{20}$: −29.6 (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (hept, 1H, *J* = 6.6 Hz), 3.02–2.96 (m, 1H), 2.86–2.71 (m, 4H), 2.63–2.57 (m, 1H), 2.04 (bs, 1H, NH), 1.78–1.59 (m, 6H), 1.53–1.47 (m, 1H), 1.34–1.26 (m, 1H), 1.09 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 64.67 (d), 64.37 (d), 51.09 (d), 46.22 (t), 46.09 (t), 29.07 (t), 28.10 (t), 24.55 (2C, t), 22.61 (q), 14.92 (q); IR ($CHCl_3$): ν = 3163 m, 2959 s, 2875 s, 2495 w, 1458 w, 1384 w, 1263 w, 1165 w, 1096 w, 1059 w cm^{-1}; MS (EI): *m/z* = 113 (13), 112 (100), 111 (1), 98 (4), 97 (1), 96 (2), 71 (2), 70 (38), 69 (1), 68 (2); HRMS: calcd. for $C_{11}H_{22}N_2$: 182.1783; found: 182.1780.

***(S,S)-N-Cyclohexyl-2,2′-bipyrrolidine* (3h):** The aminal **2h** (400 mg, 1.82 mmol) was reduced according to General Procedure 2 to give after bulb-to-bulb distillation (120 °C/2 mbar) a colourless oil; yield: 324 mg (80%); $[\alpha]_D^{20}$: −35.9 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01–2.97 (m, 1H), 2.85–2.54 (m, 6H), 1.93 (bs, 1H, NH), 1.80–1.56 (m, 11H), 1.56–1.45 (m, 1H), 1.30–1.15 (m, 5H), 1.09–1.01 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 64.62 (d), 64.01 (d), 60.69 (d), 47.51 (t), 46.09 (t), 33.36 (t), 28.97 (t), 27.89 (t), 26.43 (t), 26.30 (t), 26.15 (t), 25.74 (t), 24.98 (t), 24.47 (t); IR ($CHCl_3$): ν = 3148 m, 2933 s, 2845 s, 1446 m, 1374 w, 1263 m, 1090 m, 1051 w, 907 m, 889 m cm^{-1}; MS (EI): *m/z* = 153 (14), 152 (92), 105 (4), 96 (4), 83 (4), 71 (6), 70 (100), 69 (3), 55 (10); HRMS: calcd. for $C_{14}H_{26}N_2$: 222.2113; found: 222.2096.

Addition of Unmodified Aldehydes or Ketones to Nitroolefins Catalyzed by Amines

General Procedure 3: To a solution of pyrrolidine or chiral diamine (0.05 mmol, 15 mol %) in solvent (3 mL) was added at the appropriate temperature the aldehyde (10 equivs., 3.35 mmol) or the ketone (10 equivs. 3.35 mmol or 20–30 vol %) and the nitroolefin (0.335 mmol). The evolution of the reaction was controlled by TLC until the conversion was complete. The solution was then hydrolyzed with 1 N HCl (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate as eluent.

***(4R)-4-Phenyl-5-nitropentan-2-one* (6a):** From nitrostyrene and acetone according to General Procedure 3 to obtain a white solid. The enantiomeric excess was determined by GC [Lipodex E, 120 °C-0-2-170, R_t: 17.3 min (4*R*) and 17.8 min (4*S*)]; $[\alpha]_D^{20}$: −2.2 [*c* 0.67, ee = 17% (4*R*), $CHCl_3$]. Spectroscopic data are in agreement with published data.[130]

***(3S,4R)-3-Methyl-5-nitro-4-phenylpentan-2-one* (6b):** From butan-2-one **5b** and nitrostyrene according to General Procedure 3 to obtain a mixture of 2 regioisomers, **6b** and **7b**, as a colourless oil. The enantiomeric excess was determined by SFC [Chiralcel OB-H, 2 mL/min, 200 bar, 1% MeOH, 30 °C, R_t: 7.1 min (3*R*,4*S*) and 9.4 min (3*S*,4*R*)]. Spectroscopic data are in agreement with published data.[131]

***(5S)-5-Phenyl-6-nitrohexan-3-one* (7b):** The enantiomeric excess was determined by SFC [Chiralcel OB-H, 2 mL/min, 200 bar, 1% MeOH, 30 °C, R_t: 10.1 min (5*S*) and 11.8 min (5*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5H), 4.72 (dd, 1H, *J* = 6.8, 12.4 Hz), 4.63 (dd, 1H, *J* = 7.8, 12.4 Hz), 4.05 (quint, 1H, *J* = 7.2 Hz), 2.90 (d, 2H, *J* = 7.1 Hz), 2.43 (dq, 1H, *J* = 17.7, 7.3 Hz), 2.36 (dq, 1H, *J* = 17.7, 7.3 Hz), 1.02 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.22 (s), 138.93 (s), 129.05 (2C, d), 127.87 (d), 127.37 (2C d), 79.51 (t), 44.92 (t), 39.13 (d), 36.49 (t), 26.91 (t), 7.54 (q).

***1-Nitro-2-phenylheptan-4-one* (7c):** From propan-2-one **5c** and nitrostyrene according to General Procedure 3 to obtain a mixture of 2 regioisomers: *3-(2-nitro-1-phenylethyl)pentan-2-one* **6c** and **7c** as a colourless oil. The compound **6c** was not isolated for analysis. The enantiomeric excess of **7c** was determined by SFC [Chiralpak AD, 2 mL/min, 200 bar, MeOH 2%-4-2-15, 30 °C, R_t: 6.6 min (5*R*) and 7.8 min (5*S*)]; mp 32–34 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 5H), 4.72 (dd, 1H, *J* = 6.8, 12.4 Hz), 4.62 (dd, 1H, *J* = 7.8, 12.4 Hz), 4.04 (quint, 1H, *J* = 7.2 Hz), 2.91 (dd, 1H, *J* = 6.8, 17.7 Hz), 2.87 (dd, 1H, *J* = 7.1, 17.7 Hz), 2.38 (dt, 1H, *J* = 16.9, 7.3 Hz), 2.32 (dt, 1H, *J* = 16.9, 7.1 Hz), 1.56 (hex, 2H, *J* = 7.4 Hz), 0.86 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.75 (s), 138.89 (s), 128.97 (2C, d), 127.79 (d), 127.33 (2C, d), 79.45 (t), 45.22 (t), 45.12 (t), 39.02 (d), 16.96 (t), 13.51 (q); IR ($CHCl_3$): ν = 3033 w, 2973 m, 2876 w, 1713 s, 1555 s, 1495 w, 1455 w, 1428 w, 1378 m cm^{-1}; MS (EI): *m/z* = 188 (9), 145 (18), 117 (12), 105 (18), 104 (23), 91 (12), 86 (41), 84 (63), 71 (100), 49 (12), 47 (5).

***(4S,5R)-4-Methyl-6-nitro-5-phenylhexan-3-one* (6d):** From pentan-3-one **5d** and nitrostyrene according to General Procedure 3 to obtain two diastereoisomers, *syn*-**6d** (major) and *anti*-**6d** (minor) as a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OB-H, 2 mL/min, 200 bar, MeOH 2%-2-1-15, 30 °C, R_t: 4.4 min (4*R*,5*S*) and 5.7 min (4*S*,5*R*)]. *Syn* isomer **6d**: $[\alpha]_D^{20}$: +3.4 [*c* 0.83, ee = 67% (4*S*,5*R*), $CHCl_3$]. Spectroscopic data are in agreement with published data.[48]

***2-(S)-(2-Nitro-1-(R)-phenyl)-cyclohexanone* (6e):** From cyclohexanone **5e** and nitrostyrene according to General Procedure 3. The enantiomeric excess was determined by SFC [Chiralpak AD, 2 mL/min, 200 bar, 10% MeOH, 30 °C, R_t: 4.9 min (2*R*,1′*S*) and 5.7 min (2*S*,1′*R*)); $[\alpha]_D^{20}$: −17.9 [*c* 0.87, ee = 67% (2*S*,1′*R*), $CHCl_3$]. Spectroscopic data are in agreement with published data.[120]

***2-(S)-(2-Nitro-1-(R)-phenyl)-cyclopentanone* (6f):** From cyclopentanone **5f** and nitrostyrene according to General Procedure 3. The enantiomeric excess was determined by SFC [Chiralpak AD, 2 mL/min, 200 bar, 10% MeOH, 30 °C, R_t: 5.0 min (2*R*,1′*S*) and 5.9 min (2*S*,1′*R*)]. Spectroscopic data are in agreement with published data.[132]

***(3S,4R)-3-Methoxy-5-nitro-4-phenylpentan-2-one* (6g):** From methoxyacetone **5g** and nitrostyrene according to General Procedure 3 to obtain two inseparable diastereoisomers, (*syn*, major) **6g** and (*anti*, minor) **6g′** as a pale yellow oil. The enantiomeric excess was determined by GC [Hydrodex B-3P, 150 °C isotherm, R_t: 28.7 min (3*R*,4*S*) and 29.3 min (3*S*,4*R*)]. *Syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5H), 4.93 (dd, 1H, *J* = 8.4, 12.9 Hz), 4.66 (dd, 1H, *J* = 6.8, 12.9 Hz), 3.93–3.80 (m, 2H), 3.45 (s, 3H), 1.77 (s, 3H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.91 (s), 134.45 (s), 128.98 (2C, d), 128.84 (2C, d), 128.38 (d), 86.77 (d), 76.53 (t), 59.80 (q), 46.34 (d), 26.61 (q). *Anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5H), 4.86 (dd, 1H, *J* = 5.6, 13.4 Hz), 4.72 (dd, 1H, *J* = 8.6, 13.2 Hz), 3.93–3.80 (m,

2H), 3.67 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.12 (s), 135.35 (s), 129.13 (2C, d), 128.49 (d), 128.11 (2C, d), 88.16 (d), 76.73 (t), 58.82 (q), 45.90 (d), 26.23 (q). Isomer mixture: IR ($CHCl_3$): ν = 3029 m, 3011 w, 2937 w, 2834 w, 1713 s, 1556 s, 1495 w, 1456 w, 1427 w, 1378 s, 1357 m, 1120 s, 1054 w, 909 m cm^{-1}; MS (EI): *m/z* = 194 (11), 148 (12), 147 (100), 117 (29), 115 (10), 104 (14), 91 (18), 77 (10).

***(3R*,4S*)-3-Hydroxy-5-nitro-4-phenylpentan-2-one* (*syn*-6h):** From hydroxyacetone **5h** and nitrostyrene according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 75:25), *syn*-**6h** and *anti*-**6h** as a pale yellow oil. The enantiomers were separated by SFC (Chiralcel OJ, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.1 min and 3.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 5H), 5.03 (dd, 1H, *J* = 7.8, 13.4 Hz), 4.74 (dd, 1H, *J* = 7.1, 13.4 Hz), 4.54–4.52 (m, 1H), 4.03 (dt, 1H, 3.0, 7.6 Hz), 3.75 (d, 1H, *J* = 4.8 Hz), 2.17 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.30 (s), 133.81 (s), 128.99 (2C, d), 128.69 (d), 128.53 (2C, d), 77.00 (d, t), 45.72 (d), 25.52 (q).

(3R,4R)-3-Hydroxy-5-nitro-4-phenylpentan-2-one* (*anti*-6 h):** From hydroxyacetone **5h** and nitrostyrene according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 17:83), *syn*-**6h** and *anti*-**6h** as a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OJ, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.3 min (3*S*,4*S*) and 5.1 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 5H), 4.82 (dd, 1H, *J* = 76.3, 13.6 Hz), 4.66 (dd, 1H, *J* = 8.3, 13.6 Hz), 4.42–4.38 (m, 1H), 3.83 (dt, 1H, *J* = 7.6, 5.9 Hz), 3.76–3.74 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.99 (s), 137.15 (s), 129.36 (2C, d), 128.45 (d), 128.03 (2C, d), 78.70 (d), 76.06 (t), 46.90 (d), 26.51 (q). Isomer mixture: MS (EI): *m/z* = 180 (8), 134 (11), 133 (100), 105 (97), 104 (96), 103 (30), 91 (39), 79 (24), 78 (23), 77 (38), 74 (10), 55 (11), 51 (18).

***(2S*,3R*)-3-Hydroxy-1-nitro-2-phenyl-heptan-4-one* (*syn*-6i):** From 1-hydroxypentan-2-one **5i** and nitrostyrene according to General Procedure 3 using pyrrolidine as achiral catalyst in *i*-PrOH to obtain two inseparable diastereoisomers (*syn*/*anti* 69:31), *syn*-**6i** and *anti*-**6i** as a colourless oil. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 3% MeOH, 30 °C, R_t: 3.2 min and 3.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 5H), 5.04 (dd, 1H, *J* = 8.1, 13.4 Hz), 4.73 (dd, 1H, *J* = 6.9, 13.4 Hz), 4.51 (d, 1H, *J* = 2.5 Hz), 4.03 (dt, 1H, *J* = 3.2. 7.5 Hz), 3.77 (bs, 1H), 2.53–2.38 (m, 2H), 1.72–1.45 (m, 2H), 0.84 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.64 (s), 133.89 (s), 128.97 (2C, d), 128.66 (d), 128.47 (2C, d), 77.06 (t), 76.39 (d), 45.99 (d), 40.15 (t), 16.82 (t), 13.60 (q).

(2R,3R)-3-Hydroxy-1-nitro-2-phenylheptan-4-one* (*anti*-6i):** From 1-hydroxypentan-2-one **5i** and nitrostyrene according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** to obtain two inseparable diastereoisomers, *syn*-**6i** and *anti*-**6i** as a colourless oil. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 3% MeOH, 30 °C, R_t: 3.8 min (2*S*,3*S*) and 4.2 min (2*R*,3*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 5H), 4.80 (dd, 1H, *J* = 6.1, 13.4 Hz), 4.67 (dd, 1H, *J* = 8.6, 13.6 Hz), 4.38 (t, 1H, *J* = 4.8 HZ), 3.83 (dt, 1H, *J* = 8.3, 5.7 Hz), 3.68 (d, 1H, *J* = 5.3 Hz), 2.28 (t, 2H, *J* = 7.3 Hz), 1.63–1.54 (m, 2H), 0.85 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 210.42 (s), 137.18 (s), 129.37 (2C, d), 128.55 (d), 128.05 (2C, d), 78.21 (d), 76.17 (t), 47.19 (d), 41.28 (t), 16.97 (t), 13.60 (q).

***(4R)-1-Dimethylamino-5-nitro-4-phenylpentan-2-one* (7j):** From *N*,*N*-dimethylaminoacetone **5j** and nitrostyrene according to General Procedure 3 to obtain a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralpak AD, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 6.7 min (4*S*) and 7.3 min (4*R*)]; $[\alpha]_D^{20}$: −4.6 [*c* 3.20, $CHCl_3$, 75% ee (4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5H), 4.71 (dd, 1H, *J* = 7.0, 12.3 Hz), 4.63 (dd, 1H, *J* = 7.7, 12.4 Hz), 4.05 (quint., 1H, *J* = 7.2 Hz), 3.03 (dd, 1H, *J* = 7.1, 17.3 Hz), 3.02 (s, 2H), 2.90 (dd, 1H, *J* = 7.2, 17.5 Hz), 2.20 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.35 (s), 138.78 (s), 129.06 (2C, d), 127.93 (d), 127.49 (2C, d), 79.53 (t), 69.46 (t), 45.79 (2C, q), 42.78 (t), 39.13 (d); IR ($CHCl_3$): ν = 3031 w, 2950 w, 2830 w, 2783 w, 1725 m, 1556 s, 1496 w, 1456 w, 1378 m, 1217 w, 1042 w, 909 w cm^{-1}; MS (EI): *m/z* = 104 (4), 59 (9), 58 (100), 57 (4).

***(3R*,4S*)-3-Hydroxy-5-nitro-4-(4-methylphenyl)pentan-2-one* (*syn*-10b):** From hydroxyacetone **5h** and nitroolefin **9b** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 77:23), *syn*-**10b** and *anti*-**10b** as a pale yellow solid. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 2.7 min and 2.9 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, 2H, *J* = 8.1 Hz), 7.09 (d, 2H, *J* = 8.1 Hz), 5.01 (dd, 1H, *J* = 8.1, 13.4 Hz), 4.71 (dd, 1H, *J* = 7.1, 13.4 Hz), 4.52–4.51 (m, 1H), 4.00 (dt, 1H, *J* = 3.0, 7.6 Hz), 3.75–3.68 (m, 1H), 2.29 (s, 3H), 2.18 (s,3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.36 (s), 138.49 (s), 130.66 (s), 129.68 (2C, d), 128.27 (2C, d), 77.09 (t), 77.04 (d), 45.41 (d), 25.52 (q), 21.07 (q).

(3R,4R)-3-Hydroxy-5-nitro-4-(4-methylphenyl)pentan-2-one* (*anti*-10b):** From hydroxyacetone **5h** and nitroolefin **9b** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 16:84), *syn*-**10b** and *anti*-**10b** as a pale yellow solid. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.1 min (3*S*,4*S*) and 3.4 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, 2H, *J* = 8.1 Hz), 7.19 (d, 2H, *J* = 8.1 Hz), 4.81 (dd, 1H, *J* = 6.2, 13.4 Hz), 4.64 (dd, 1H, *J* = 8.5, 13.4 Hz), 4.37 (d, 1H, *J* = 5.6 Hz), 3.78 (dt, 1H, *J* = 8.6, 5.8 Hz), 3.75–3.68 (m, 1H), 2.35 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.13 (s), 138.37 (s), 133.94 (s), 130.02 (2C, d), 127.88 (2C, d), 78.76 (t), 76.31 (d), 46.72 (d), 26.65 (q), 21.11 (q); MS (EI): *m/z* = 237 (1), 190 (8), 164 (52), 148 (14), 147 (100), 119 (35), 118 (90), 117 (30), 115 (13), 105 (26), 99 (12), 97 (64), 91 (29), 87 (12), 86 (60), 85 (17), 84 (91), 77 (13), 74 (16), 71 (12), 57 (23), 47 (17); HRMS: calcd. for $C_{12}H_{15}NO_4$: 237.1001; found: 237.1008.

***(3R*,4S*)-3-Hydroxy-5-nitro-4-(4-methoxyphenyl)pentan-2-one* (*syn*-10c):** From hydroxyacetone **5h** and nitroolefin **9c** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 80:20), *syn*-**10c** and *anti*-**10c** as a pale yellow solid. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.2 min and 3.5 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, 2H, *J* = 8.6 Hz), 6.79 (d, 2H, *J* = 8.6 Hz), 4.97 (dd, 1H, *J* = 7.7, 13.4 Hz), 4.69 (dd, 1H, *J* = 7.5, 13.4 Hz), 4.50–4.48 (m, 1H), 3.97 (dt, 1H, J = 3.0, 7.6 Hz), 3.78–3.73 (m, 1H$_{syn}$ + 2H$_{anti}$), 3.74 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ =

206.55 (s), 159.63 (s), 129.57 (2C, d), 125.65 (s), 114.29 (2C, d), 77.26 (t), 77.08 (d), 55.16 (q), 45.01 (d), 25.48 (q).

***(3R,4R)-3-Hydroxy-5-nitro-4-(4-methoxyphenyl)pentan-2-one* (*anti*-10c):** From hydroxyacetone **5h** and nitroolefin **10c** according to General Procedure 3 using diamine (*S*,*S*)-*i*PBP at room temperature to obtain two diastereoisomers inseparable by column chromatography (*syn*/*anti* 19:81), *syn*-**10c** and *anti*-**10c** as a pale yellow solid. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.1 min (3*S*,4*S*) and 4.7 min (3*R*,4*R*)]. A sample was recrystallized from diethyl ether to give the isomer *anti*-**10c** optically pure for analysis; mp 109–112 °C (ether); $[\alpha]_D^{20}$: −47.3 (*c* 8.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, 2H, *J* = 8.6 Hz), 6.91 (d, 2H, *J* = 8.6 Hz), 4.80 (dd, 1H, *J* = 6.0, 13.4 Hz), 4.63 (dd, 1H, *J* = 8.6, 13.4 Hz), 4.38–4.36 (m, 1H), 3.81 (s, 3H), 3.76 (dt, 1H, *J* = 8.6, 5.9 Hz), 3.68–3.67 (m, 1H), 2.01 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.06 (s), 159.63 (s), 129.13 (2C, d), 128.80 (s), 114.71 (2C, d), 78.81 (t), 76.48 (d), 55.31 (q), 46.42 (d), 26.68 (q); MS (EI): *m/z* = 253 (3), 180 (18), 135 (16), 134 (100), 121 (8), 91 (7), 77 (5); HRMS: calcd. for $C_{12}H_{15}NO_5$: 253.0950; found: 253.0953.

***(3R*,4S*)-4-(4-Chlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*syn*-10d):** From hydroxyacetone **5h** and nitroolefin **9d** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 75:25), *syn*-**10d** and *anti*-**10d** as a colourless oil. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 55 °C, R_t: 3.5 min and 3.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 2H), 7.26–7.22 (m, 2H), 5.02 (dd, 1H, *J* = 7.6, 13.6 Hz), 4.75 (dd, 1H, *J* = 7.5, 13.6 Hz), 4.54 (dd, 1H, *J* = 3.0, 4.6 Hz), 4.05 (dt, 1H, *J* = 2.8, 7.6 Hz), 3.78 (d, 1H, *J* = 4.5 Hz), 2.21 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 205.93 (s), 134.79 (s), 132.28 (s), 129.83 (2C, d), 129.26 (2C, d), 76.97 (t), 76.89 (d), 45.12 (d), 25.48 (q).

***(3R,4R)-4-(4-Chlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*anti*-10d):** From hydroxyacetone **5h** and nitroolefin **9d** according to General Procedure 3 using diamine (*S*,*S*)-*i*PBP at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 13:87), *syn*-**10d** and *anti*-**10d** as a colourless oil. The enantiomers were separated by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 55 °C, R_t: 4.4 min (3*S*,4*S*) and 4.7 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 4H), 4.77 (dd, 1H, *J* = 6.0, 13.6 Hz), 4.64 (dd, 1H, *J* = 8.6, 13.6 Hz), 4.39 (t, 1H, *J* = 4.8 Hz), 3.89 (ddd, 1H, *J* = 4.6, 6.0, 8.3 Hz), 3.79 (d, 1H, *J* = 4.8 Hz), 2.19 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.48 (s), 135.82 (s), 134.52 (s), 129.53 (2C, d), 129.47 (2C, d), 78.60 (d), 75.66 (t), 45.99 (d), 26.32 (q); MS (EI): *m/z* = 260 (< 1), 259 (< 1), 258 (< 1), 257 (< 1), 169 (18), 165 (55), 141 (15), 140 (37), 139 (40), 138 (100), 132 (13), 125 (23), 103 (58), 102 (11), 77 (28), 75 (10), 74 (19), 51 (11).

***(3R*,4S*)-3-Hydroxy-5-nitro-4-[2-(trifluoromethyl)phenyl]pentan-2-one* (*syn*-10e):** From hydroxyacetone **5h** and nitroolefin **9e** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 74:26), *syn*-**10e** and *anti*-**10e** as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 1H, *J* = 7.8 Hz), 7.71 (d, 1H, *J* = 7.3 Hz), 7.53–7.42 (m, $2H_{syn} + 1H_{anti}$), 5.09–5.03 (m, 1H), 4.71–4.67 (m, 1H), 4.58–4.50 (m, $2H_{syn} + 2H_{anti}$), 4.02–3.96 (m, 1H), 2.07 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.85 (C=O), 133.43 (C_{quat}), 132.70 (CH), 129.80 (CH), 128.64 (CH), 128.29 (q, C_{quat}, $J_{C\text{-}F}$ = 29.6 Hz), 126.77 (q, CH, $J_{C\text{-}F}$ = 5.8 Hz), 124.13 (q, CF_3, $J_{C\text{-}F}$ = 273.7 Hz), 76.22 (CH), 75.58 (CH_2), 39.39 (CH), 25.25 (CH_3).

***(3R,4R)-3-Hydroxy-5-nitro-4-[2-(trifluoromethyl)phenyl]pentan-2-one* (*anti*-10e):** From hydroxyacetone **5h** and nitroolefin **9e** according to General Procedure 3 using diamine (*S*,*S*)-*i*PBP at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 5:95), *syn*-**10e** and *anti*-**10e** as a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OD-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.1 min (3*S*,4*S*) and 3.6 min (3*R*,4*R*)]; $[\alpha]_D^{20}$: −32.0 [*c* 3.32, $CHCl_3$, dr 95:5, 99% ee (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 8.1 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.53–7.42 (m, $1H_{anti} + 2H_{syn}$), 4.77 (dd, 1H, *J* = 7.3, 13.9 Hz), 4.61 (dd, 1H, *J* = 6.3, 13.7 Hz), 4.58–4.50 (m, $2H_{anti} + 2H_{syn}$), 4.37 (bs, 1H), 2.37 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.96 (C=O), 136.60 (C_{quat}), 132.77 (CH), 129.52 (CH), 128.01 (q, C_{quat}, $J_{C\text{-}F}$ = 29.9), 128.27 (CH), 126.47 (q, CH, $J_{C\text{-}F}$ = 5.8), 124.34 (q, CF_3, $J_{C\text{-}F}$ = 273.7), 78.31 (CH), 73.72 (CH_2), 40.10 (CH), 25.24 (CH_3); IR ($CHCl_3$): ν = 3459 w, 3029 w, 2979 w, 2928 w, 2874 w, 1717 s, 1608 w, 1559 s, 1456 w, 1380 m, 1363 m, 1314 s, 1167 s, 1118 s, 1038 m, 968 w, 909 w cm^{-1}; MS (EI): *m/z* = 201 (68), 182 (10), 181 (77), 173 (31), 172 (100), 171 (27), 169 (11), 159 (19), 153 (83), 151 (37), 140 (11), 133 (62), 127 (12), 103 (11), 97 (21), 77 (10), 75 (10), 73 (12), 61 (10), 57 (17), 55 (12).

***(2R,1′R,2′R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid 1-acetyl-3-nitro-2-(2-trifluoromethylphenyl)-propyl ester* (10e–mosher):** To a solution of alcohol (*anti*-**10e**) (33 mg, 0.113 mmol) in dry CH_2Cl_2 (0.8 mL) was added (*R*)-Mosher's acid (0.170 mmol, 40 mg) then a solution of DCC (0.198 mmol, 41 mg) and DMAP (0.028 mmol, 3.5 mg) in dry CH_2Cl_2 (1.0 mL). The white mixture was stirred overnight at room temperature then directly purified by flash chromatography on silica gel (*c*-hexane/EtOAc, 9:1) to give a colourless solid; yield: 55 mg (96%); mp 129–132 °C (ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.51–7.37 (m, 4H), 7.37 (t, 1H, *J* = 7.8 Hz), 7.10 (t, 1H, *J* = 7.7 Hz), 6.99 (d, 1H, *J* = 7.8 Hz), 5.27 (d, 1H, *J* = 1.8 Hz), 4.82–4.73 (m, 2H), 4.64 (dt, 1H, *J* = 1.8, 6.9 Hz), 3.77 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 200.82 (s), 165.74 (s), 134–120 (15C), 80.29 (d), 73.27 (t), 56.13 (q), 37.37 (d), 26.90 (q).

***(3R*,4S*)-4-(2,6-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*syn*-10f):** From hydroxyacetone **5h** and nitroolefin **9f** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 54:46), *syn*-**10f** and *anti*-**10f**, as a colourless oil. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 5.8 min and 6.4 min); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 1H), 7.34–7.32 (m, 1H), 7.21 (t, 1H, *J* = 8.0 Hz), 5.19–5.13 (m, 1H), 5.02–4.98 (m, 2H), 4.74–4.68 (m, 1H), 2.91 (d, 1H, *J* = 5.3 Hz), 2.32 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 208.67 (s), 137.80 (s), 134.87 (s), 131.74 (s), 130.30 (d), 130.00 (d), 129.19 (d), 75.96 (d), 74.44 (t), 42.42 (d), 26.32 (q).

(3R,4R)-4-(2,6-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*anti*-10f):** From hydroxyacetone **5h** and nitroolefin **9f** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** to obtain two inseparable diastereoisomers (*syn*/*anti* 16:84),

syn-**10f** and *anti*-**10f** as a colourless oil. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.3 min (3*R*,4*R*) and 5.1 min (3*S*,4*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2H), 7.25 (t, 1H, *J* = 8.0 Hz), 5.27 (dd, 1H, *J* = 6.1, 14.1 Hz), 5.04 (dd, 1H, *J* = 7.2, 14.1 Hz), 4.86 (dd, 1H, *J* = 6.6, 9.6 Hz), 4.69 (ddd, 1H, *J* = 6.3, 7.1, 9.6 Hz), 3.71 (d, 1H, *J* = 6.8 Hz), 1.85 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.69 (s), 137.19 (s), 134.84 (s), 132.09 (s), 130.53 (d), 130.40 (d), 129.50 (d), 75.04 (d), 74.88 (t), 43.81 (d), 26.73 (q); MS (EI): *m/z* = 203 (55), 201 (84), 177 (12), 176 (10), 175 (66), 174 (33), 173 (100), 172 (37), 161 (11), 159 (17), 139 (26), 138 (17), 137 (70), 136 (10), 125 (10), 103 (15), 102 (46), 101 (52), 99 (11), 77 (14), 75 (27), 74 (15), 73 (14), 63 (10), 51 (18).

***(3R*,4S*)-4-(3,4-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*syn*-10g):** From hydroxyacetone **5h** and nitroolefin **9g** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 74 26), *syn*-**10g** and *anti*-**10g**, as a colourless oil. The enantiomers were separated by SFC (Chiralcel OJ, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 6.0 min and 6.7 min); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, 1H, *J* = 2.2 Hz), 7.38 (d, 1H, *J* = 8.2 Hz), 7.13 (dd, 1H, *J* = 2.2, 8.2 Hz), 4.98 (dd, 1H, *J* = 7.5, 13.7 Hz), 4.72 (dd, 1H, *J* = 7.6, 13.7 Hz), 4.51 (t, 1H, *J* = 3.2 Hz), 4.00 (dt, 1H, *J* = 2.9, 7.6 Hz), 3.78 (d, 1H, *J* = 4.2 Hz), 2.21 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 205.56 (s), 137.67 (s), 133.93 (s), 133.19 (s), 130.95 (d), 130.37 (d), 127.83 (d), 76.74 (t), 76.73 (d), 44.80 (d), 25.44 (q).

(3R,4R)-4-(3,4-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*anti*-10 g):** From hydroxyacetone **5h** and nitroolefin **9g** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 12:88), *syn*-**10g** and *anti*-**10g** as a colourless oil. The enantiomeric excess was determined by SFC [Chiralcel OJ, 2 mL/min, 200 bar, MeOH 5%-6-2-20, 30 °C, R_t: 7.7 min (3*S*,4*S*) and 9.1 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, 1H, *J* = 2.3 Hz), 7.47 (d, 1H, *J* = 8.4 Hz), 7.27 (dd, 1H, *J* = 2.3, 8.4 Hz), 4.67 (dd, 1H, *J* = 6.2, 13.9 Hz), 4.59 (dd, 1H, *J* = 8.3, 13.9 Hz), 4.38–4.34 (m, 1H), 3.89 (ddd, 1H, *J* = 3.6, 6.3, 8.1 Hz), 3.80–3.75 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.06 (s), 136.69 (s), 133.40 (s), 132.85 (s), 131.23 (d), 130.16 (d), 127.47 (d), 78.42 (d), 75.06 (t), 45.34 (d), 26.06 (q); MS (EI): *m/z* = 292 (1), 203 (41), 202 (11), 201 (63), 188 (13), 176 (13), 175 (32), 174 (69), 172 (100), 168 (12), 16 (35), 161 (14), 159 (21), 139 (17), 138 (17), 137 (48), 125 (12), 111 (11), 103 (15), 102 (43), 101 (32), 99 (10), 77 (10), 75 (24), 74 (26), 73 (21), 55 (10), 51 (15); HRMS: calcd. for $C_{11}H_{11}{}^{35}Cl_2NO_4$: 291.00651; found: 291.00864.

***(3R*,4S*)-4-(2,4-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*syn*-10 h):** From hydroxyacetone **5h** and nitroolefin **9e** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 80:20), *syn*-**10h** and *anti*-**10h**, as a colourless oil. The enantiomers were separated by SFC (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.2 min and 3.4 min); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, 1H, *J* = 8.5 Hz), 7.41 (d, 1H, *J* = 2.2 Hz), 7.21 (dd, 1H, *J* = 2.2, 8.5 Hz), 4.98 (dd, 1H, *J* = 8.5, 13.7 Hz), 4.75 (ddd, 1H, *J* = 3.2, 6.5, 8.4 Hz), 4.61 (dd, 1H, *J* = 6.5, 13.6 Hz), 4.58 (t, 1H, *J* = 3.8 Hz), 3.79 (d, 1H, *J* = 4.1 Hz), 2.23 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 206.27 (s), 135.15 (s), 134.36 (s), 130.46 (d), 129.94 (d), 127.91 (d), 76.17 (d), 75.98 (t), 39.79 (d), 25.48 (q).

(3R,4R)-4-(3,4-Dichlorophenyl)-3-hydroxy-5-nitropentan-2-one* (*anti*-10h):** From hydroxyacetone **5h** and nitroolefin **9h** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 9:91), *syn*-**10h** and *anti*-**10h**, as a colourless oil. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.0 min (3*S*,4*S*) and 4.3 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 1H, *J* = 2.3 Hz), 7.45 (d, 1H, *J* = 8.6 Hz), 7.31 (dd, 1H, *J* = 2.2, 8.5 Hz), 4.70–4.58 (m, 3H), 4.37–4.33 (m, 1H), 3.82 (d, 1H, *J* = 4.0 Hz), 2.36 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.03 (s), 134.81 (s), 134.25 (s), 133.78 (s), 129.98 (d), 129.75 (d), 128.10 (d), 77.55 (d), 73.16 (t), 41.04 (d), 25.45 (q); MS (EI): *m/z* = 292 (1), 203 (49), 202 (10), 201 (75), 188 (12), 176 (14), 175 (50), 174 (70), 173 (77), 172 (100), 166 (15), 161 (18), 159 (28), 139 (20), 138 (16), 137 (57), 136 (12), 125 (11), 111 (10), 103 (14), 102 (44), 101 (38), 99 (12), 77 (10), 75 (26), 74 (24), 73 (19), 51 (17); HRMS: calcd. for $C_{11}H_{11}{}^{35}Cl_2NO_4$: 291.00651; found: 291.00262.

***(3R*,4S*)-4-(1-Naphthyl)-3-hydroxy-5-nitropentan-2-one* (*syn*-10i):** From hydroxyacetone **5h** and nitroolefin **9i** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 76:24), *syn*-**10i** and *anti*-**10i**, as a colourless oil. The enantiomers were separated by (Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.5 min and 5.1 min); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, 1H, *J* = 8.5 Hz), 7.88 (d, 1H, *J* = 8.5 Hz), 7.80 (d, 1H, *J* = 8.2 Hz), 7.71 (d, 1H, *J* = 7.0 Hz), 7.62 (t, 1H, *J* = 7.4 Hz), 7.53 (t, 1H, *J* = 7.7 Hz), 7.39 (t, 1H, *J* = 7.7 Hz), 5.19–5.00 (m, 2H), 4.77–4.72 (m, 2H), 3.98 (bs, 1H), 1.96 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 206.75 (s), 134.08 (s), 130.97 (s), 130.20 (s), 129.56 (d), 129.17 (d), 127.21 (d), 126.14 (d), 126.03 (d), 125.45 (d), 121.71 (d), 76.77 (d), 76.57 (t), 38.51 (d), 25.52 (q).

(3R,4R)-4-(1-Naphthyl)-3-hydroxy-5-nitropentan-2-one* (*anti*-10i):** From hydroxyacetone **5h** and nitroolefin **9i** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 22:78), *syn*-**10i** and *anti*-**10i**, as a colourless oil. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 5.8 min (3*S*,4*S*) and 7.1 min (3*R*,4*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, 1H, *J* = 8.6 Hz), 7.93–7.91 (m, 1H), 7.86 (d, 1H, *J* = 8.4 Hz), 7.66–7.49 (m, 4H), 5.19–4.83 (m, 2H), 4.77–4.69 (m, 1H), 4.55–4.49 (m, 1H), 3.85 (d, 1H, *J* = 4.8), 2.12 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.99 (s), 134.19 (s), 133.22 (s), 130.90 (s), 129.57 (d), 129.05 (d), 127.34 (d), 126.27 (d), 125.62 (d), 125.27 (d), 121.89 (d), 78.51 (d), 75.11 (t), 40 (broad signal, d), 26.22 (q); EI (MS): *m/z* = 274 (2), 273 (10), 200 (8), 183 (8), 155 (23), 154 (100), 153 (30), 152 (13), 141 (9); HRMS: calcd. for $C_{15}H_{15}NO_4$: 273.10011; found: 273.10020.

***(3R*,4S*)-3-Hydroxy-5-nitro-4-(thien-2-ylphenyl)pentan-2-one* (*syn*-10j):** From hydroxyacetone **5h** and nitroolefin **9j** according to General Procedure 3 using pyrrolidine as achiral catalyst at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 68:32), *syn*-**10j** and *anti*-**10j**, as a brown oil. The enantiomers were separated by SFC (Chiralcel OJ, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 3.5 min and 3.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, 1H, *J* = 0.8, 5.0 Hz), 6.95 (dd, 1H, *J* = 1.3, 3.5 Hz), 6.92 (dd, 1H, *J* =

3.5, 5.0 Hz), 4.96 (dd, 1H, $J=7.7$, 13.5 Hz), 4.67 (dd, 1H, $J=7.0$, 13.5 Hz), 4.48–4.42 (m, $2H_{syn}+1H_{anti}$), 3.93–3.92 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=205.67$ (s), 134.22 (s), 127.37 (d), 126.80 (d), 126.47 (d), 77.57 (t), 76.34 (d), 41.88 (d), 25.24 (q).

(3R,4R)-3-Hydroxy-5-nitro-4-(thien-2-ylphenyl)pentan-2-one* (*anti*-10j):** From hydroxyacetone **5h** and nitroolefin **9j** according to General Procedure 3 using diamine (*S*,*S*)-i*PBP** at room temperature to obtain two inseparable diastereoisomers (*syn*/*anti* 22:78), *syn*-**10j** and *anti*-**10j**, as a brown oil. The enantiomeric excess was determined by SFC [Chiralcel OJ, 2 mL/min, 200 bar, 5% MeOH, 30 °C, R_t: 4.6 min (3*S*,4*S*) and 5.0 min (3*R*,4*R*)]; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.29$ (dd, 1H, $J=1.0$, 5.1 Hz), 7.05 (dd, 1H, $J=0.8$, 3.6 Hz), 6.99 (dd, 1H, $J=3.6$, 5.1 Hz), 4.75 (dd, 1H, $J=6.0$, 13.5 Hz), 4.62 (dd, 1H, $J=8.1$, 13.5 Hz), 4.48–4.42 (m, $1H_{anti}+2H_{syn}$), 4.21 (dt, 1H, $J=8.1$, 5.4 Hz), 3.76–3.74 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=205.67$ (s), 134.22 (s), 127.37 (d), 126.80 (d), 126.47 (d), 77.57 (t), 76.34 (d), 41.88 (d), 25.24 (q); MS (EI): $m/z=211$ (1), 182 (7), 156 (20), 139 (11), 112 (7), 111 (24), 110 (100), 109 (9), 97 (17).

***(2R,3S)-2-Methyl-4-nitro-3-phenylbutyraldehyde* (12a):** From propionaldehyde and nitrostyrene according to the General Procedure 3 to give a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OD-H, 2 mL/min, 200 bar, MeOH 2% -2-1-15, 30 °C, R_t: 6.13 min (2*S*,3*R*) and 6.76 min (2*R*,3*S*)] or by GC (Hydrodex-B-3P, 135 °C isotherm, $R_t=$ 56.4 min (2*R*,3*S*) and 57.6 min (2*S*, 3*R*)); $[\alpha]_D^{20}$: +28.2 [*c* 2.69, ee = 78% (2*R*,3*S*), $CHCl_3$]. Spectroscopic data are in agreement with published data.[84]

***(2R,3S)-2-Ethyl-4-nitro-3-phenylbutyraldehyde* (12b):** From butyraldehyde and nitrostyrene according to the General Procedure 3 to give a pale yellow oil. The enantiomeric excess was determined by GC [Hydrodex-B-3P, 145 °C isotherm, R_t: 43.0 min (2*R*,3*S*) and 43.9 min (2*S*,3*R*)]. Spectroscopic data are in agreement with published data.[84]

***2-(R)-(2-Nitro-1-(S)-phenylethyl)-pentanal* (12c):** From valeraldehyde and nitrostyrene according to the General Procedure 3 to give a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OD-H, 2 mL/min, 200 bar, 2% MeOH, 10 °C, R_t: 5.6 min (1′*R*,2*S*) and 6.2 min (1′*S*, 2*R*)]; $[\alpha]_D^{20}$: +24.0 [*c* 0.89, ee = 72% (1′*S*,2*R*), $CHCl_3$]; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.74$ (d, 1H, $J=2.2$ Hz), 7.41–7.32 (m, 3H), 7.24–7.22 (m, 2H), 4.75 (dd, 1H, $J=4.4$, 10.2 Hz), 4.69 (dd, 1H, $J=4.7$, 10.2 Hz), 3.83 (dt, 1H, $J=4.3$, 7.8 Hz), 2.75 (tt, 1H, $J=2.6$, 7.6 Hz), 1.56–1.47 (m, 1H), 1.44–1.32 (m, 2H), 1.25–1.17 (m, 1H), 0.84 (t, 3H, $J=5.7$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=203.33$ (s), 136.80 (s), 129.11 (2C, d), 128.15 (d), 128.01 (2C, d), 78.44 (t), 53.78 (d), 43.13 (d), 29.44 (t), 19.75 (t), 13.94 (q).

***(2R,3S)-2-(Methylethyl)-4-nitro-3-phenylbutyraldehyde* (12d):** From isovaleraldehyde and nitrostyrene according to the General Procedure 3 to give a pale yellow oil. The enantiomeric excess was determined by SFC [Chiralcel OD-H, 2 mL/min, 200 bar, 1% MeOH, 5 °C, R_t: 7.00 min (2*S*,3*R*) and 7.53 min (2*R*, 3*S*)] or by GC (Hydrodex-B-3P, 150 °C isotherm, R_t: 38.4 min (2*R*,3*S*) and 39.8 min (2*S*,3*R*)); $[\alpha]_D^{20}$: +48.5 [*c* 0.93, ee = 68% (2*R*,3*S*), $CHCl_3$]. Spectroscopic data are in agreement with published data.[84]

***(2S,3S)-4-Nitro-2,3-diphenylbutyraldehyde* (12e):** From phenylacetaldehyde and nitrostyrene according to the General Procedure 3 to give after separation of diastereomers by chromatography a white solid. The enantiomeric excess was determined by SFC [Chiralpak AS-H, 2 mL/min, 200 bar, 2% MeOH, 30 °C, R_t: 5.6 min (2*S*,3*S*) and 7.9 min (2*R*,3*R*)]. The product was recrystallized from diethyl ether for analysis; mp 168–171 °C (racemate, ether); ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.57$ (d, 1H, $J=2.0$ Hz), 7.48–7.27 (m, 10H), 4.50 (dd, 1H, $J=10.4$, 12.6 Hz), 4.41 (dd, 1H, $J=4.3$, 12.6 Hz), 4.32 (dt, 1H, $J=4.3$, 10.4 Hz), 4.09 (dd, 1H, J = 2.0, 10.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=196.86$ (s), 137.08 (s), 132.41 (s), 129.81 (2C, d), 129.43 (2C, d), 129.12 (2C, d), 128.95 (d), 128.28 (d), 128.17 (2C, d), 78.45 (t), 61.70 (d), 44.39 (d); IR ($CHCl_3$): $\nu=3066$ w, 3033 w, 2924 w, 2828 w, 2725 w, 1728 s, 1557 s, 1495 w, 1455 w, 1431 w, 1379 m, 1077 w, 1031 w cm^{-1}; MS (EI): $m/z=269$ (5), 193 (14), 177 (10), 120 (100), 115 (21), 105 (17), 104 (91), 102 (15), 90 (71), 77 (13), 65 (12); HRMS: calcd. for $C_{16}H_{15}NO_3$: 269.1052; found: 269.1064.

***(3R)-2-Dimethyl-4-nitro-3-phenylbutyraldehyde* (12f):** From isobutyraldehyde and nitrostyrene according to the General Procedure 3 to give a white solid. The enantiomeric excess was determined by chiral GC [Hydrodex-B-3P, 140 °C isotherm, R_t: 46.8 min (3*R*) and 47.6 min (3*S*)]; mp (racemate) 74–76 °C; $[\alpha]_D^{20}$: +6.5 [*c* 0.91, ee = 80% (3*R*), $CHCl_3$]; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.55$ (s, 1H), 7.38–7.30 (m, 3H), 7.24–7.22 (m, 2H), 4.89 (dd, 1H, $J=11.2$, 13.1 Hz), 4.72 (dd, 1H, $J=4.3$, 13.1 Hz), 3.82 (dd, 1H, $J=4.1$, 11.3 Hz), 1.15 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=$ 204.36 (s), 135.44 (s), 129.13 (2C, d), 128.74 (d), 128.17 (2C, d), 76.35 (t), 48.44 (d), 48.27 (s), 21.66 (q), 18.85 (q); IR ($CHCl_3$): $\nu=3031$ w, 2969 w, 2933 w, 2816 w, 2778 w, 1727 m, 1559 s, 1496 w, 1467 w, 1455 w, 1436 w, 1378 m, 1221 s, 1217 s, 1213 s, 1210 s, 881 w cm^{-1}; MS (EI): $m/z=221(<1)$, 150 (7), 145 (14), 105 (19), 104 (100), 103 (10), 91 (48), 77 (10), 72 (29).

(2R,3S)-2-Methyl-4-nitro-3-(4-methylphenyl)butyraldehyde* (13b):** From propionaldehyde and nitroolefin **9b** according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at −25 °C for 3 days to give a pale yellow oil (yield: 88%, 94% ee). The enantiomeric excess was determined by GC [Chiraldex B-TA, 145 °C isotherm, R_t: 22.2 min (2*S*,3*R*) and 22.8 min (2*R*,3*S*)]; $[\alpha]_D^{20}$: +36.7 [*c* 0.13, ee = 94% (2*R*,3*S*), $CHCl_3$]; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.71$ (d, 1H, $J=1.8$ Hz), 7.15 (d, 2H, $J=7.8$ Hz), 7.05 (d, 2H, $J=8.1$ Hz), 4.78 (dd, 1H, $J=$ 5.6, 12.6 Hz), 4.66 (dd, 1H, $J=9.3$, 12.6 Hz), 3.78 (dt, 1H, $J=$ 5.6, 9.1 Hz), 2.79–2.71 (m, 1H), 2.33 (s, 3H), 1.00 (d, 3H, $J=$ 7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=202.45$ (s), 137.90 (s), 133.42 (s), 129.78 (2C, d), 127.95 (2C, d), 78.26 (t), 48.52 (d), 43.75 (d), 21.07 (q), 12.55 (q); MS (EI): $m/z=221$ (2), 174 (23), 146 (16), 145 (16), 131 (18), 118 (73), 117 (25), 105 (45), 99 (30), 91 (20), 71 (16), 70 (82), 59 (57), 58 (100), 57 (53), 55 (67); HRMS: calcd. for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1044.

(2R,3S)-2-Methyl-4-nitro-3-(4-methoxyphenyl)butyraldehyde* (13c):** From propionaldehyde and nitroolefin **9c** according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at −25 °C for 3 days (yield: 64%, 93% ee) to give a pale yellow oil. The enantiomeric excess was determined by GC [Chiraldex B-TA, 155 °C isotherm, R_t: 30.7 min (2*S*,3*R*) and 31.5 min (2*R*, 3*S*)]; $[\alpha]_D^{20}$: +28.1 [*c* 0.23, ee = 93% (2*R*,3*S*), $CHCl_3$]; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.73$ (d, 1H, $J=1.9$ Hz), 7.11 (d, 2H, $J=8.9$ Hz), 6.89 (d, 2H, $J=$ 8.7 Hz), 4.80 (dd, 1H, $J=5.6$, 12.6 Hz), 4.66 (dd, 1H, $J=9.3$, 12.6 Hz), 3.81 (s, 3H), 3.80 (dt, 1H, $J=5.6$, 9.2 Hz), 2.81–2.71 (m, 1H), 1.03 (d, 3H, $J=7.2$ Hz); ^{13}C NMR (100.6 MHz,

$CDCl_3$): δ = 202.49 (s), 159.30 (s), 129.15 (2C, d), 128.36 (s), 114.47 (2C, d), 78.37 (t), 55.27 (q), 48.61 (d), 43.38 (d), 12.07 (q). MS (EI) : 237 (9), 190 (11), 162 (11), 135 (11), 134 (100), 121 (24), 91 (13), 55 (11); HRMS: calcd. for $C_{12}H_{15}NO_4$: 237.1001; found: 237.0980.

(2R,3S)-2-Methyl-4-nitro-3-(2-trifluoromethylphenyl)-butyraldehyde* (13e):** From propionaldehyde and nitroolefin **9e** according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at −25 °C for 3 days to give a pale yellow oil (yield: 74%, 95% ee). The enantiomeric excess was determined by GC [Hydrodex-B-6-TBDM, 100 °C-0-2-170, R_t: 26.6 min (2*S*,3*R*) and 26.9 min (2*R*,3*S*)]; $[\alpha]_D^{20}$: +48.8 [*c* 1.02, ee = 95% (2*R*,3*S*), $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (d, 1H, *J* = 1.8 Hz), 7.73 (d, 1H, *J* = 8.1 Hz), 7.59 (t, 1H, *J* = 7.7 Hz), 7.44 (t, 1H, *J* = 7.7 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 4.86 (dd, 1H, *J* = 7.3, 12.4 Hz), 4.71 (dd, 1H, *J* = 4.8, 12.4 Hz), 4.13 (ddd, 1H, *J* = 4.8, 7.3, 9.8 Hz), 3.08 (quint, 1H, *J* = 7.8 Hz), 1.00 (d, 3H, *J* = 7.6 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 201.70 (C=O), 136.29 ($C_{quat.}$), 132.61 (CH), 129.44 (q, $J_{C\text{-}F}$ = 29.6 Hz, $C_{quat.}$), 128.15 (CH), 128.05 (CH), 126.83 (q, $J_{C\text{-}F}$ = 5.9 Hz, CH), 126.28 (q, $J_{C\text{-}F}$ = 276 Hz, CF_3), 77.92 (CH_2), 48.52 (CH), 39.24 (CH), 12.78 (CH_3); MS (EI): *m/z* = 186 (27), 177 (28), 172 (38), 159 (100), 151 (18), 133 (13), 117 (16), 58 (14), 57 (15), 55 (28).

(2R,3S)-2-Methyl-4-nitro-3-(thien-2-yl)butyraldehyde* (13j):** From propionaldehyde and nitroolefin **9j** according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at −25 °C for 2 days to give a brown oil (yield: 66%, 93% ee, not very pure). The enantiomeric excess was determined by GC [Hydrodex-B-6-TBDM, 145 °C isotherm, R_t: 22.4 min (2*R*,3*S*) and 22.9 min (2*S*,3*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, 1H, *J* = 1.2 Hz), 7.27–7.24 (m, 1H), 6.98–6.90 (m, 2H), 4.79 (dd, 1H, *J* = 5.8, 12.9 Hz), 4.69 (dd, 1H, *J* = 8.8, 12.9 Hz), 4.25 (dt, 1H, *J* = 6.1, 8.2 Hz), 2.79 (dquint, 1H, *J* = 1.2, 6.1 Hz), 1.14 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.71 (s), 138.85 (s), 127.13 (d), 126.76 (d), 125.34 (d), 78.41 (t), 48.85 (d), 39.45 (d), 11.53 (q).

***(2R,3R)-2-Methyl-3-nitromethylheptanal* (13k):** From propionaldehyde and nitroolefin **9k** according to the General Procedure 3 to give a mixture of two inseparable diastereomers as a pale yellow oil. The enantiomers were separated by chiral GC [Lipodex E, 110 °C isotherm, R_t: 25.8 min (2*S*,3*S*) and 27.0 min (2*R*,3*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 4.49 (dd, 1H, *J* = 6.0, 12.4 Hz), 4.40 (dd, 1H, *J* = 7.8, 12.4 Hz), 2.80–2.76 (m, 1H), 2.54 (dq, 1H, *J* = 4.3, 7.1 Hz), 1.39–1.23 (m, 6H), 1.14 (d, 3H, *J* = 7.1 Hz), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 202.79 (s), 77.08 (t), 47.03 (d), 37.28 (d), 29.10 (t), 28.06 (t), 22.62 (t), 13.83 (q), 8.92 (q); IR ($CHCl_3$): ν = 3029 w, 2962 m, 2933 m, 2864 w, 1727 m, 1553 s, 1466 w, 1382 m, 1108 w cm^{-1}; MS (EI): *m/z* = 83 (22), 82 (14), 81 (12), 71 (10), 70 (14), 69 (79), 67 (11), 59 (17), 58 (35), 57 (33), 56 (15), 55 (100).

***(2R,3R)-3-Cyclohexyl-2-methyl-4-nitrobutyraldehyde* (13l):** From propionaldehyde and nitroolefin **9l** according to the General Procedure 3 to give a mixture of two inseparable diastereomers as a pale yellow oil. The enantiomers were separated by chiral GC [Chirasil-dex-CB, 90 °C-0-1-170, R_t: 56.3 min (2*R*,3*R*) and 57.3 min (2*S*,3*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 4.59 (dd, 1H, *J* = 5.3, 13.4 Hz), 4.38 (dd, 1H, *J* = 6.8, 13.4 Hz), 2.61–2.54 (m, 2H), 1.81–1.56 (m, 5H), 1.50–1.41 (m, 1H), 1.27–0.90 (m, 5H), 1.20 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 203.20 (s), 75.83 (t), 46.64 (d), 43.56 (d), 38.00 (d), 31.64 (t), 30.00 (t), 26.39 (t), 26.26 (t), 26.08 (t), 10.77 (q); IR ($CHCl_3$): ν = 3028 w, 2932 s, 2856 m, 1725 m, 1554 s, 1518 w, 1450 m, 1381 w, 1333 w, 1223 w, 1157 w, 991 w cm^{-1}; MS (EI): *m/z* = 113 (10), 109 (100), 108 (15), 99 (18), 95 (28), 85 (13), 83 (94), 82 (11), 81 (55), 79 (10), 75 (99), 73 (49), 71 (13), 70 (14), 69 (20), 68 (18), 67 (53), 58 (35), 55 (100).

(2R,3R)-3-(Dimethoxymethyl)-2-methyl-4-nitrobutyraldehyde* (13m):** From propionaldehyde and nitroolefin **9m** according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at −25 °C for 3 days to give a mixture of inseparable diastereoisomer (*syn*/*anti* 75/25) as a colourless oil (yield: 73%, 90% ee). The enantiomeric excess was determined by GC [Hydrodex-B-6-TBDM, 120 °C isotherm, R_t: 20.1 min (2*S*,3*S*) and 20.8 min (2*R*,3*R*)]; *syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H), 4.61 (dd, 1H, *J* = 6.3, 13.4 Hz), 4.38 (dd, 1H, *J* = 7.1, 13.4 Hz), 4.33 (d, 1H, *J* = 6.6 Hz), 3.36 (s, 3H), 3.35 (s, 3H), 3.13 (dq, 1H, *J* = 3.6, 6.6 Hz), 2.58 (dq, 1H, *J* = 3.5, 7.2 Hz), 1.16 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.78 (s), 103.80 (d), 73.75 (t), 55.86 (q), 54.60 (q), 44.64 (d), 41.46 (d), 9.79 (q); *anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, 1H, *J* = 1.5 Hz), 4.56 (dd, 1H, *J* = 6.3, 13.7 Hz), 4.39 (dd, 1H, *J* = 6.0, 13.9 Hz), 4.37 (d, 1H, *J* = 4.9 Hz), 3.38 (s, 3H), 3.36 (s, 3H), 2.71–2.63 (m, 1H), 3.04 (quint, 1H, *J* = 5.8 Hz), 1.15 (d, 3H, *J* = 7.3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.74 (s), 104.69 (d), 73.18 (t), 55.80 (q), 55.69 (q), 44.42 (d), 41.24 (d), 11.02 (q); isomer mixture: MS (EI): *m/z* = 205(< 1), 127 (7), 101 (9), 99 (13), 83 (6), 75 (100), 71 (14), 69 (13), 67 (16), 55 (14), 47 (17).

(2R,3R)-4,4,4-Trifluoro-2-methyl-3-(nitromethyl)butyraldehyde* (13n):** From propionaldehyde and nitroolefin **9n**[126] according to the General Procedure 3 using the diamine (*S*,*S*)-i*PBP** at room temperature for 1 day to give a mixture of inseparable diastereoisomer (*syn*/*anti* 77/23) as a yellow oil (yield: 42%, 91% ee). The enantiomeric excess of *syn*-**13n** was determined by GC [Hydrodex-B-3P, 90 °C-0-1, R_t: 10.3 min (2*S*,3*S*) and 10.9 min (2*R*,3*R*)]; *syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 4.77 (dd, 1H, *J* = 6.3, 14.6 Hz), 4.56 (dd, 1H, *J* = 5.7, 14.6 Hz), 3.74–3.63 (m ,1H), 2.85 (dq, 1H, *J* = 3.3, 7.6 Hz), 1.35 (dq, 3H, *J* = 7.6, 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.38 ($C_{quat.}$), 125.63 (q, $J_{C\text{-}F}$ = 281 Hz, $C_{quat.}$), 71.17 (CH_2), 43.49 (CH), 42.15 (q, $J_{C\text{-}F}$ = 28 Hz, CH), 10.60 (CH_3); *anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 4.61 (dd, 1H, *J* = 7.6, 14.4 Hz), 4.42 (dd, 1H, *J* = 5.0, 14.4 Hz), 3.95–3.85 (m, 1H), 2.98 (dq, 1H, *J* = 3.3, 7.6 Hz), 1.31 (dq, 1H, *J* = 7.6, 0.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.36 ($C_{quat.}$), 126.07 (q, $J_{C\text{-}F}$ = 281 Hz, $C_{quat.}$), 70.27 (CH_2), 43.18 (CH), 40.27 (q, $J_{C\text{-}F}$ = 28 Hz, CH), 9.44 (CH_3); isomer mixture: IR ($CHCl_3$): ν = 3030 w, 2933 w, 1735 m, 1566 s, 1465 w, 1435 w, 1380 m, 1263 w, 1176 m, 1139 s, 984 w cm^{-1}; MS (EI): *m/z* = 153 (12), 133 (10), 123 (21), 105 (37), 104 (15), 103 (75), 101 (23), 91 (47), 85 (18), 83 (25), 77 (100), 73 (20), 69 (15), 65 (29), 62 (37), 61 (68), 59 (69), 57 (19), 56 (18), 55 (83), 53 (21), 51 (25), 47 (31), 45 (38).

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