The Scope of the Direct Proline-Catalyzed Asymmetric Addition of Ketones to Imines

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Abstract: A full account of catalytic direct asymmetric Mannich-type reactions is presented describing the scope of amino acid-catalyzed additions of unmodified ketones to a large variety of imines. These reactions are performed under very mild, operationally simple, and environmentally friendly and benign conditions employing a one-pot, three-component protocol as well as preformed imines. Typically, products were obtained with high regio- and diastereoselectivities and excellent enantioselectivities. The methodology developed was applied as a powerful approach toward the synthesis of enantiomerically pure functionalized α-amino acids, γ-lactones, oxime-functionalized amino acids as well as pharmacologically important targets such as (*R*)-cyclohexylglycine.

Keywords: asymmetric catalysis; C–C bond formation; imines; ionic liquids; Mannich-type reactions; organic catalysis; γ-oxo-α-amino acids

Introduction

Over the past few years, we and others have developed direct organocatalytic asymmetric versions of several important carbon-carbon bond-forming reactions.[1,2] Mechanistically, these reactions are based as the catalytic activation of one reaction partner to an enamine or iminium intermediate; the intermediate subsequently reacts in a highly stereospecific manner to form a new carbon-carbon bond and one or more stereocenters. Herein, we disclose our findings on the catalytic asymmetric Mannich-type reaction using ketones as donors that reveal some interesting aspects distinctly different from those of the parent aldol reaction.

Results and Discussion

In order to define the scope of the catalytic asymmetric Mannich reaction with ketone donors, we used the previously established one-pot, three-component protocol reacting acetone, an aldehyde, and *p*-anisidine in the presence of L-proline as catalyst (Table 1, entries 1–6).[1g] Thus, a number of unsymmetrical ketones, which could give rise to the formation of regioisomers as well as diastereoisomers, were evaluated as donors. For example, when 2-butanone was reacted under our standard conditions with *p*-anisidine and *p*-nitrobenzaldehyde (Table 1, entry 7), the two regioisomers **7a** and **7b** could be isolated as an inseparable ~5:2-mixture in favor of the *syn*-diastereomer. Both regioisomers were obtained with very high enantioselectivities (ees) and, in the case of **7a**, with excellent diastereoselectivity. In the parent aldol reaction, however, product formation involving the methylene moiety of the ketone donor was not observed. Interestingly, the reaction using 1-naphthaldehyde as acceptor gave **8** in 73% yield and 96% ee as the exclusive product (Table 1, entry 8), and the same regioselectivity was observed with 5-hexen-2-one as donor (Table 1, entries 11–16). The reactions with benzaldehyde, 1-naphthaldehyde, and *p*-nitrobenzaldehyde provided Mannich products **13**–**15** in good yields and in a completely regioselective manner. Likewise, *p*-nitrobenzaldehyde and 1-naphthaldehyde afforded products **14** and **15**, respectively, with high enantioselectivities (Table 1, entries 14 and 15). Both branched and linear aliphatic aldehydes were effective acceptors as shown for isovaleraldehyde and hexanal, which yielded 82% **11** and 71% **12** with 76% ee and 48% ee, respectively (Table 1, entries 11 and 12).[3] In the case of the more reactive benzyloxyacetaldehyde, however, the two regioisomers (**16a** and **16b**) were formed in nearly equal amounts; **16b** was formed as the only detectable diastereomer with 90% ee. 3-Pentanone was also successfully used as a donor, and with isovaleraldehyde and benzaldehyde as aldehyde acceptor components, led to products **9** and **10** in excellent diastereoselectivities with 73% and 62% ee, respectively (Table 1, entries 9 and 10).[4]

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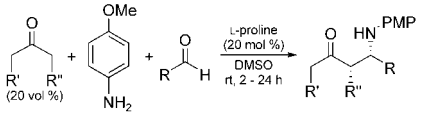
Table 1. One-pot, three-component Mannich-type reactions between various ketone donors and aldehyde acceptors and *p*-anisidine.



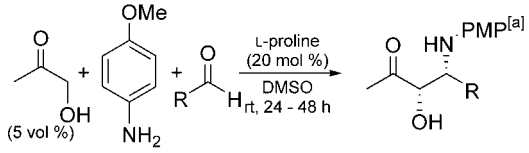
Entry	Product[a]	Entry	Product[a]	Entry	Product[a]
(1)	**1** 45%[b] (86% ee)	(7)	**7a** 66% dr >19:1 (98% ee)	(12)	**12** 71% (48% ee)
(2)	**2** 58%[b] (51% ee)	(7)	**7b** 27% (95% ee)	(13)	**13** 79% (62% ee)
(3)	**3** 52%[b] (86% ee)	(8)	**8** 73% (96% ee)	(14)	**14** 59% (86% ee)
(4)	**4** 46%[b] (69% ee)	(9)	**9** 44% dr >19:1 (73% ee)[c]	(15)	**15** 88% (95% ee)
(5)	**5** 38%[b] (62% ee)	(10)	**10** 32% dr >19:1 (62% ee)[c]	(16)	**16a** 37% (40% ee)
(6)	**6** 58% (69% ee)	(11)	**11** 82% (76% ee)	(16)	**16b** 30% dr >19:1 (90% ee)

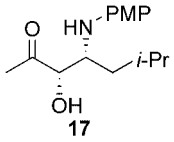
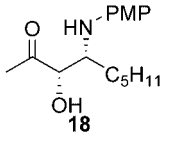
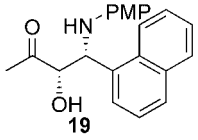
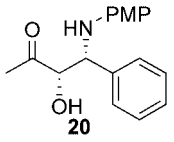
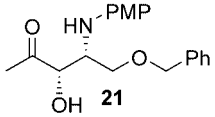
[a] PMP = *p*-methoxyphenyl.
[b] Yields of isolated pure products after column chromatography; the ee values were determined by chiral-phase HPLC analysis; dr = *syn/anti* as determined by NMR.
[c] 5,5-Dimethyl thiazolidinium-4-carboxylate was used as catalyst.

Next, we studied hydroxyacetone as donor in the one-pot, three-component Mannich-type reaction. This donor afforded *anti*-diols with excellent regio-, diastereo-, and enantioselectivities in aldol reactions.[1a, c] When this donor was reacted with *p*-anisidine and isovaleraldehyde, the corresponding Mannich product **17** was formed as a single regioisomer in 74% yield, with excellent diastereoselectivity, and with an ee of 93% (Table 2, entry 1). Hexanal, 1-naphthaldehyde, benzaldehyde, and benzyloxyacetaldehyde provided Mannich products **18** – **21** (Table 2, entries 2–5) in clean reactions with very high enantioselectivities (ee = 86–94%) and, with the exception of 1-naphthaldehyde adduct **19** (Table 2, entry 3), with excellent *syn*-diastereoselectivity.[5] In all of the cases studied, the formation of only a single regioisomeric product was observed. It is noteworthy that both isovaleraldehyde and hexanal gave products with excellent stereoselectivities with DMSO as solvent, whereas the use of chloroform provided products with lower yields and very poor diastereo- and enantioselectivities.[3] Furthermore, products **17**, **18**, and **21** represent the first examples of Mannich reactions that involved linear and α-unbranched aliphatic aldehydes as acceptor components in reactions with hydroxyacetone as donor.

Further insight into which regioisomer of the assumed enamine intermediate was involved in the addition step came from the reactions of *N*-PMP-protected α-imino ethyl glyoxylate as acceptor in these Mannich-type reactions (Table 3). In all cases studied, the Mannich products were obtained as a single enantiomer in a smooth and clean reaction. For example, the reaction with 2-butanone afforded Mannich product **23** (Table 3, entry 2) in 72% yield with an ee > 99%. In contrast to the reaction of this donor with *p*-nitrobenzaldehyde and 1-naphthaldehyde (Table 1, entries 7 and 8), exclusive regioisomer formation occurred due to the regioselective attack of the more substituted α-carbon atom of the ketone and reaction afforded predominantly the *syn*-diastereomer. Very similar results were obtained from the

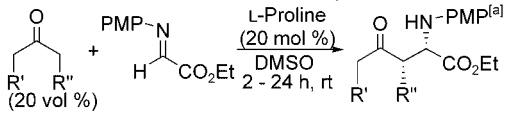
Table 2. Formation of vicinal *syn*-amino alcohols *via* catalytic Mannich reactions of hydroxyacetone.

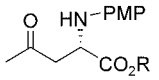
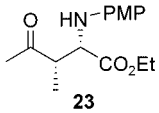
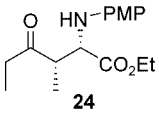
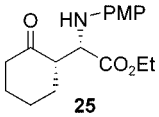
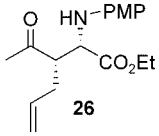
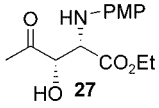
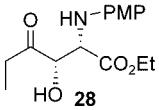
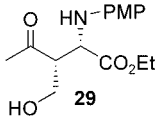


Entry	Product	Yield[b]	dr[c]	ee[d]
(1)	 **17**	74%	>20:1	93%
(2)	 **18**	46%	>20:1	94%
(3)	 **19**	83%	2.6:1	90% 76%[e]
(4)	 **20**	91%	18:1	86%
(5)	 **21**	70%	>20:1	91%

[a] PMP = *p*-methoxyphenyl.
[b] Yields of isolated pure products after column chromatography.
[c] dr = *syn/anti* as determined by NMR.
[d] The ee values were determined by chiral-phase HPLC analysis.
[e] ee of *anti*-isomer.

Table 3. Formation of functionalized γ-oxo-α-amino acids.



Entry	Product	Yield[b]	dr[c]	ee[d]
(1)	 **22a** (R = Et) **22b** (R = *i*-Pr)	**22a**: 82% 86%[e] **22b**: 85%	- - -	95% 99% 97%
(2)	 **23**	72%	>19:1	>99%
(3)	 **24**	47%	>19:1	>99%
(4)	 **25**	81%	>19:1	>99%
(5)	 **26**	79%	>19:1	>99%
(6)	 **27**	62%	>19:1	99%
(7)	 **28**	68%	~4:1	98% 85%[f]
(8)	 **29**	59%	>19:1	>99%

[a] PMP = *p*-methoxyphenyl.
[b] Yields of isolated pure product after column chromatography.
[c] dr = *syn/anti* as determined by NMR.
[d] The ee values of products were determined by chiral-phase HPLC analysis.
[e] Acetone was used as solvent.
[f] ee of *anti*-isomer.

reactions employing 3-pentanone, cyclohexanone, 5-hexen-2-one, hydroxyacetone, and two structurally interesting donors, 1-hydroxy-2-butanone and 4-hydroxy-2-butanone. The corresponding Mannich products **24**–**29** were obtained with excellent enantioselectivities (ee > 99%). In the case of unsymmetrical donors, only one regioisomer was formed, which, with the exception of Mannich product **28**, exhibited very high diastereoselectivity (dr > 19:1). On the other hand, acetophenone, 3-methyl-2-butanone, and cyclopentanone[6] did not furnish detectable amounts of the corresponding Mannich products under these conditions. Amino acids **26** and **29** (Table 3, entries 5 and 8) can also be considered products from the stereoselective allylation and hydroxymethylation, respectively, of the corresponding linear γ-keto amino acid scaffold. To the best of our knowledge, such allylated or hydroxymethylated β-amino ketone subunits have not been reported until now.[7] We confirmed the anticipated (*S*)-stereochemistry of the newly formed α-stereocenter by synthesis of known isopropyl ester **22b** (Table 3, entry 1) and by comparison to data reported earlier.[8]

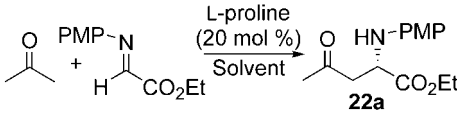
From these results, it is evident that *N*-PMP-protected α-imino ethyl glyoxylate was always attacked by the

most substituted enamine intermediate regardless of the donor. Additionally, α-substitution of the ketone donor with electron-donating heteroatoms appeared to dictate the regioselectivity of the enamine formation regardless of the acceptor component (Table 2; Table 3, entries 6 and 7). In both cases, the *syn*-diastereomers were predominant.[9] Furthermore, the results of the reaction of unsymmetrical ketone donors (e.g., 2-butanone or 5-hexen-2-one) indicated that very reactive, electron-deficient acceptor imines (e.g., glyoxylates, Table 3) were preferentially attacked by the more substituted enamine intermediate in the carbon-carbon bond-forming step leading to the corresponding *syn*-diastereomer. On the other hand, imines derived from aliphatic and aromatic aldehydes were typically attacked by the less substituted enamine intermediate with the methyl group of the ketone donors as nucleophilic center (Table 1). Benzyloxyacetaldehyde and *p*-nitrobenzaldehyde are more reactive than unsubstituted aromatic and linear aliphatic aldehydes, but less reactive than glyoxylates; the formation of a mixture of regioisomers (Table 1, entries 7 and 16) is in accord with this trend.

The Mannich reactions of ketones with *N*-PMP-protected α-imino ethyl glyoxylate were well behaved in a wide variety of organic solvents in addition to DMSO (Table 4). We were pleased to find that in the reaction using acetone as donor, **22a** was obtained in comparable yields and enantioselectivities in all the solvents studied. In the cases of dioxane and THF as solvents, the amounts of proline or ketone donor can be reduced to 5 mol % and 2 equivalents, respectively, furnishing **22a** in essentially the same yield. Reduction of catalyst loading and the amount of ketone donor led to a significantly reduced reaction rate, which required inconveniently long reaction times (>72 h) to achieve similar yields. These prolonged reaction times, however, did not affect the excellent stereoselectivities observed.[10]

A significant improvement in this reaction came with the introduction of ionic liquids as solvents. The Mannich reaction of *N*-PMP protected α-imino ethyl glyoxylate with cyclohexanone using a catalytic amount of L-proline (5 mol %) in [bmim]BF_4 at room temperature (Table 5) was studied.[11] The reaction was complete within 30 min and provided the Mannich product **25** in quantitative yield with excellent ee ($>99\%$) and diastereoselectivity ($>19:1$). In order to study catalyst and solvent recycling, the product was extracted with ether. The recovered ionic liquid containing L-proline was then used for another reaction. Again, the Mannich product was obtained with excellent yield and ees. After four consecutive reaction cycles (Table 5) there was no diminution in ee and only a slight decrease in yield when the 30 min reaction time was strictly maintained. The use of another ionic liquid, [bmim]PF_6, as reaction solvent also afforded the Mannich products with identical yields and ees. In further studies, we found that our Mannich-type reactions were generally accelerated from 4- to 50-fold using ionic liquids as solvents and the products were obtained in high yield with excellent enantioselectivity with catalyst loadings as low as 1%.

Table 4. Synthesis of functionalized γ-oxo-α-amino acids in various solvents.[a, b]



22a

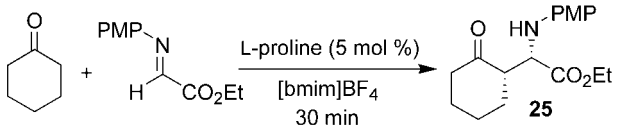
Solvent	Yield	ee
DMSO	82%	95%
Acetone	86%	99%
Toluene	81%	83%
$CHCl_3$	84%	98%
EtOAc	65%	98%
THF	79%	97%
Dioxane	79%	97%
[bmim]BF_4	80%	97%

[a] Reaction as per Table 3.
[b] dr $>19:1$ for all solvents.

We did note, however, a significant limitation in the use of ionic liquid solvents in Mannich reactions involving hydroxyacetone as a nucleophile in reactions. While the desired amino alcohol product was obtained with excellent yield, the diastereo- and enantioselectivity of the reaction was severely compromised as compared to the same reaction in organic solvents. For example, the reaction of hydroxyacetone with *N*-PMP-protected α-imino ethyl glyoxylate as an acceptor provided **27** in 97% yield albeit with a dr of 68:32 and ee of 3/24% (*syn/anti*). Other acceptor imines, however, remain to be studied. To determine if the poor performance of hydroxyacetone in ionic liquids was a general phenomenon, we studied the aldol reaction under similar conditions. Contrary to the results we obtained in the Mannich reaction, the aldol reaction using hydroxyacetone afforded the desired product with excellent diastereo- and enantioselectivity.[11]

The Mannich products described herein are versatile building blocks for a large variety of valuable synthons, and the functionalities present offer attractive sites for further modifications. For example, it has been shown that the products from the reaction of hydroxyacetone with imines (Table 2) can be readily converted into 1,2-amino alcohols by application of a four-step oxidation/reduction protocol; the conversion was accompanied by the loss of one of the newly generated stereogenic centers.[2n] We were particularly interested in exploiting the inherent access to functionalized non-proteinogenic α-amino acids. We devised a scheme for synthesis of *N*-Boc-cyclohexylglycine **34** (Scheme 1), which had been posted on "www.innocentive.com" as an interesting and exemplary target. Cyclohexylglycine itself is a constituent of effective inhibitors of the blood coagula-

Table 5. Catalyst and ionic liquid solvent recycling.

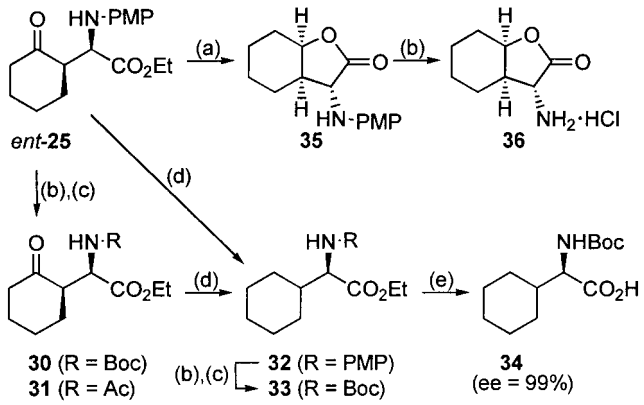


# of runs	Yield	dr	ee
1	99%	>19:1	>99%
2	92%	>19:1	>99%
3	87%	>19:1	>99%
4	83%	>19:1	>99%

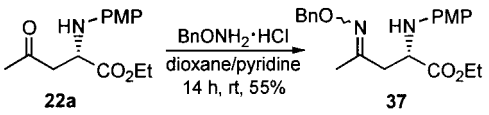
tion factor Xa and of a doxorubicin conjugate with an oligopeptide of a prostate-specific antigen.[12] Finally, cyclohexylglycine has served as a building blocks for serine protease inhibitors used as anti-inflammatory agents and as inhibitors of hepatitis C virus.[13] The starting material, *ent*-**25**, was readily available in gram quantities from the D-proline-catalyzed Mannich reaction of *N*-PMP protected α-imino ethyl glyoxylate with cyclohexanone. *N*-Boc-cyclohexylglycine **34** was synthesized in three straightforward steps. First, the *N*-PMP group of *ent*-**25** was removed oxidatively by using $PhI(OAc)_2$ and the resulting amine was protected *in situ* with Boc_2O and Ac_2O in the presence of aqueous Na_2CO_3 affording **30** and **31** in 68% and 64% yield, respectively.[14] Second, removal of the keto functionality present in **30** was accomplished by its treatment with tosylhydrazine in refluxing methanol and subsequent reduction of the intermediate hydrazone with $NaBH_4$ provided *N*-Boc-protected ethyl cyclohexylglycinate **33** in 50% overall yield. Alternatively, the keto group could be removed prior to the oxidative cleavage of the *p*-methoxyphenyl group affording **33** *via* *N*-PMP-protected cyclohexylglycine **32**. Finally, saponification of the ethyl ester moiety of **33** by means of LiOH in aqueous dioxane afforded *N*-Boc-protected (*R*)-cyclohexylglycine **34** with 99% ee.

The keto functionality in *ent*-**25** can be reduced to the secondary alcohol in a completely diastereoselective manner by treatment with L-Selectride at very low temperatures with concomitant *in situ* lactonization. Subsequent oxidative removal of the *N*-PMP group in **35** yielded α-amino γ-lactone hydrochloride **36** in 76% yield without any detectable epimerization. NMR studies (NOE experiments, *J* values) of both **35** and **36** confirmed the anticipated *syn*-stereochemistry.[1i,15]

Unnatural amino acids that contain carbonyl groups have been shown to be useful as reactive handles that provide for the facile modification of proteins and peptides,[16] and the ketone moiety provides for facile diversification. For example, the carbonyl group of these ketone donor derived amino acids was readily converted to the corresponding oxime as shown for **37** (Scheme 2).



Scheme 1. Synthesis of *N*-Boc-cyclohexylglycine **34** and α-amino-δ-lactone **36**. Reagents and conditions: (a) L-Selectride, THF, −78 °C, 89%; (b) $PhI(OAc)_2$, MeOH, 0 °C, 30 min; 1 N HCl, 0 °C, 30 min; (c) aqueous Na_2CO_3, Ac_2O (64%) or Boc_2O (68%); (d) $TsNHNH_2$, MeOH, Δ; then $NaBH_4$, 0 °C → Δ, 50% overall; (e) LiOH, dioxane/H_2O, r.t., 14 h, 78%.



Scheme 2. Synthesis of oxime-functionalized amino acids.

Oximes of this type were recently integrated into glycopeptide analogues containing unnatural sugar-peptide linkages.[17] Acetone was used as donor and solvent, the mixture was concentrated after complete consumption of the imino glyoxylate, the residue dissolved in dioxane/pyridine (10:1), and stirred together with *O*-benzylhydroxylamine hydrochloride for 14 h at room temperature. This afforded a ~2:1 mixture of oximes **37** in favor of the (*E*)-isomer.[18,19] Thus, reaction of these ketone-containing amino acids with a variety of hydroxylamines can provide for the synthesis of a diverse family of D- or L-amino acids with oxime-containing side chains which can now be considered as building blocks in combinatorial syntheses.

Conclusion

In conclusion, we have successfully further extended our concept of proline-catalysis involving enamine intermediates to the direct asymmetric Mannich-type reaction.[20] We have defined and broadened the scope of the transformation by showing that a wide variety of structurally different ketones were effective donors in a catalytic Mannich-type reaction, which could be ac-

complished in a highly chemoselective, one-pot, three-component protocol or by using preformed imines.

The Mannich products were typically formed in a highly chemo-, regio-, diastereo-, and enantioselective manner, and in many cases the Mannich products could be obtained as single stereoisomers with *syn*/*anti* ratio of $>19:1$ and ees $>95\%$. In the cases where the formation of both diastereomers occurred, two adjacent stereocenters were created with complete stereocontrol upon carbon-carbon bond formation, affording the *syn*-diastereomer with high preference. Furthermore, we were able to identify factors that control the regiochemistry of the enamine key intermediate involved in the carbon-carbon bond forming event. The use of an α-imino glyoxylate as acceptor in the reaction with ketones as donors provided a facile and stereoselective entry to functionalized amino acids, which were readily converted into α-amino-γ-lactones and oximes.

Experimental Section

Typical Three-Component, One-Pot Procedure for the Catalytic Asymmetric Mannich-Type Reaction of Ketones, Aldehydes and *p*-Anisidine

To a mixture of anhydrous DMSO (4 mL) and acetone (1 mL) was added *p*-anisidine (0.5 mmol) and the corresponding aldehyde (0.5 mmol) followed by proline (20 mol %) and the resulting homogeneous reaction mixture was stirred at room temperature for 4–48 h. Then, half saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino ketones. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases.

***(1S)-1-(4-Methoxyphenylamino)-1-phenylbutan-3-one* (1):** ^{1}H NMR: $\delta=2.06$ (s, 3H, COMe), 2.86 (m, 2H), 3.65 (s, 3H, OMe), 4.12 (bs, 1H, NH), 4.75 (m, 1H), 6.49 (d, 2H, $J=9.1$ Hz), 6.67 (d, 2H, $J=9.1$ Hz), 7.20–7.36 (m, 5H); ^{13}C NMR: $\delta=30.5$, 51.2, 55.1, 55.5, 114.6, 115.1, 126.2, 127.1, 128.6, 140.8, 142.6, 152.1, 207.2; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 97:3, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=27.06$ min; minor isomer: $t_R=21.46$ min; HRMS (MALDI-FTMS): calcd. for $C_{17}H_{19}NNaO_2$ (MNa^+): 292.1313; found: 292.1319.

***(1S)-1-(4-Acetamidophenyl)-1-(4-methoxyphenylamino)-butan-3-one* (2):** ^{1}H NMR: $\delta=2.10$ (s, 3H, COMe), 2.13 (s, 3H, COMe), 2.90 (d, 1H, $J=3.7$ Hz), 2.95 (d, 1H, $J=3.7$ Hz), 3.65 (s, 3H, OMe), 4.24 (m, 1H), 4.87 (m, 1H), 4.95 (bs, 1H), 6.56 (d, 2H, $J=8.8$ Hz), 6.75 (d, 2H, $J=8.8$ Hz), 7.21 (bs, 1H), 7.30 (d, 2H, $J=8.4$ Hz), 7.43 (d, 2H, $J=8.4$ Hz); ^{13}C NMR: $\delta=24.7$, 30.5, 51.3, 55.6, 55.6, 114.6, 120.2, 126.9, 136.4, 136.9, 138.3. 146.9, 168.2, 207.2; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 80:20, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=23.54$ min; minor isomer: $t_R=27.66$ min; HRMS (MALDI-FTMS): calcd. for $C_{19}H_{22}N_2O_3$ (MNa^+): 349.1523; found: 349.1516.

***(4S)-4-(4-Methoxyphenylamino)-4-(1-naphthyl)-butan-2-one* (4):** ^{1}H NMR: $\delta=2.13$ (s, 3H, COMe), 2.91 (dd, 1H, $J=8.3$ Hz, $J=16.3$ Hz), 3.06 (dd, 1H, $J=4.0$ Hz, $J=16.3$ Hz), 3.64 (s, 3H, OMe), 4.27 (bs, 1H, NH), 5.58 (dd, 1H, $J=8.3$ Hz, $J=4.0$ Hz), 6.44–6.48 (m, 2H), 6.62–6.65 (m, 2H), 7.37 (m, 1H), 7.51–7.60 (m, 3H), 7.74 (m, 1H), 7.90 (m, 1H), 8.15 (m,1H), ^{13}C NMR: $\delta=30.6$, 50.2, 50.9, 55.6, 122.1, 123.2, 125.5, 125.7, 126.4, 127.8, 129.3, 130.4, 134.1, 137.3, 140.8, 152.1, 207.3; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=14.94$ min; minor isomer: $t_R=19.59$ min; $[\alpha]_D$: +111.7 (*c* 1, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{21}H_{21}NO_2$ (M^+): 319.1572; found: 319.1581

***(4S)-4-Cyclohexyl-(4-methoxyphenylamino)-4-butan-2-one* (5):** ^{1}H NMR: $\delta=0.96-1.25$ (m, 5H), 1.45–1.87 (m, 6H), 2.13 (s, 3H, COMe), 2.58 (m, 2H), 3.62 (m, 1H), 3.74 (s, 3H, OMe), 6.56 (d, 2H, $J=8.8$ Hz), 6.75 (d, 2H, $J=8.8$ Hz); ^{13}C NMR: $\delta=26.3$, 26.4, 29.3, 29.5, 30.6, 41.7, 45.5, 55.7, 114.7, 114.9, 141.7, 151.9, 208.6; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=8.23$ min; minor isomer: $t_R=14.88$ min; $[\alpha]_D$: +3.1 (*c* 1, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{17}H_{26}NO_2$ (MH^+): 276.1964; found 276.1970.

***(4S)-4-(4-Methoxyphenylamino)-5-methylhexan-2-one* (6):** ^{1}H NMR: $\delta=0.89$ (d, 3H, $J=7.0$ Hz), 0.96 (d, 3H, $J=7.0$ Hz), 1.91 (m, 1H), 2.14 (s, 3H, COMe), 2.55 (m, 2H), 3.64 (m, 1H), 3.73 (s, 3H, OMe), 6.57 (d, 2H, $J=9.2$ Hz). 6.75 (d, 2H, $J=9.2$ Hz); ^{13}C NMR: $\delta=18.4$, 18.8, 30.6, 31.3, 45.2, 55.7, 56.2, 115.0, 141.6, 152.1, 208.4; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 97:3, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=15.35$ min; minor isomer: $t_R=11.90$ min; $[\alpha]_D$: +1.5 (*c* 1, $CHCl_3$); ESI-MS: calcd. for $C_{14}H_{22}NO_2$ (MH^+): 236.16; found: 236.

***(1S)-1-(4-Methoxyphenylamino)-1-(1-naphthyl)-pentan-3-one* (8):** ^{1}H NMR: $\delta=8.14$ (1H, d, $J=8.4$), 7.88 (1H, dd, $J=8.4$, 1.2 Hz), 7.71 (1H, d, $J=8.1$ Hz), 7.52 (3H, m), 7.35 (1H, t, $J=7.5$ Hz), 6.61 (2H, d, $J=9.3$ Hz), 6.44 (2H, d, $J=9.3$ Hz), 5.56 (1H, m), 3.63 (3H, s), 3.02 (1H, dd, $J=15.9$, 3.9 Hz), 2.89 (1H, dd, $J=15.9$, 8.4 Hz), 2.36 (2H, m), 0.98 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$): $\delta=209.8$, 151.9, 140.8, 137.3, 133.9, 130.3, 129.1, 127.7, 126.3, 125.6, 125.4, 123.1, 122.0, 114.8, 114.5, 55.6, 51.1, 48.9, 36.8, 7.5; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 93:7, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=10.52$ min; minor isomer: $t_R=14.07$ min; HRMS (MALDI-FTMS): calcd. for $C_{22}H_{23}NO_2$ (MNa^+): 356.1626; found: 356.1625.

***(4S,5S)-5-(4-Methoxyphenylamino)-4,7-dimethyloctan-3-one* (9):** ^{1}H NMR: $\delta=6.74$ (2H, d, *J* 9.3 Hz), 6.53 (2H, d, $J=9.3$ Hz), 3.72 (3H, s), 3.61 (1H, m), 2.77 (1H, m), 2.43 (2H, qd, $J=7.5$, 2.4 Hz), 1.73 (1H, m), 1.31 (2H, m), 1.12 (3H, d, $J=6.9$ Hz), 0.98 (3H, t, $J=6.9$ Hz), 0.92 (3H, d, $J=6.6$ Hz), 0.86 (3H, d, $J=6.6$ Hz); ^{13}C NMR: $\delta=214.0$, 151.7, 141.9, 114.9, 114.1, 55.8, 54.6, 49.6, 42.4, 35.6, 25.1, 23.4, 22.1, 12.7, 7.7. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=4.59$ min; minor isomer: $t_R=5.25$ min; $[\alpha]_D$: +14.9 (*c* 1.5, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{17}H_{27}NO_2$ (MNa^+): 300.1934; found: 300.1934.

***(1S,2S)-1-(4-Methoxyphenylamino)-2-methyl-1-phenylpentan-3-one* (10):** ^{1}H NMR: $\delta=7.27$ (5H, m), 6.64 (2H, d, $J=$

9.0 Hz), 6.43 (2H, d, $J=9.0$ Hz), 4.57 (1H, d, $J=5.7$ Hz), 3.66 (3H, s), 2.97 (1H, m), 2.34 (2H, t, $J=7.5$ Hz), 1.10 (3H, d, $J=7.2$ Hz), 0.93 (3H, t, $J=7.2$); ^{13}C NMR: $\delta=213.2$, 152.0, 141.3, 141.1, 128.4, 127.1, 126.8, 114.8, 114.6, 60.0, 55.7, 52.3, 35.6, 11.6, 7.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=7.69$ min; minor isomer: $t_R=6.72$ min; $[\alpha]_D$: +35.9 (*c* 0.7, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{19}H_{23}NO_2$ (MH^+): 298.1801; found: 298.1798.

***(3S)-3-(4-Methoxyphenylamino)-2-methylnon-8-en-5-one* (11):** ^{1}H NMR: $\delta=6.74$ (2H, d, $J=9.0$ Hz), 6.55 (2H, d, $J=9.0$ Hz), 5.75 (1H, ddt, $J=17.1$, 10.2, 6.6 Hz), 4.98 (1H, dm, $J=17.1$ HZ), 4.94 (1H, dm, $J=10.2$ Hz), 3.79 (1H, m), 3.72 (1H, s), 2.64 (1H, dd, $J=16.2$, 5.1 Hz), 2.51 (1H, dd, $J=16.2$, 6.3 Hz), 2.46 (2H, t, $J=7.2$ Hz), 2.28 (2H, q-like), 1.74 (1H, m), 1.45 (1H, m), 1.31 (1H, m), 0.92 (3H, d, $J=6.6$ Hz), 0.90 (3H, d, $J=6.3$ Hz); ^{13}C NMR: $\delta=209.4$, 152.0, 141.2, 136.9, 115.2, 115.0, 113.9, 55.8, 49.2, 47.4, 44.9, 42.9, 27.6, 25.1, 23.1, 22.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=6.26$ min; minor isomer: $t_R=6.99$ min; $[\alpha]_D$: +14.2 (*c* 2.4, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{18}H_{27}NO_2$ (MNa^+): 312.1934; found: 312.1931.

***(6S)-6-(4-Methoxyphenylamino)-dodec-11-en-8-one* (12):** ^{1}H NMR: $\delta=6.74$ (2H, d, $J=8.7$ Hz), 6.55 (2H, d, $J=8.7$ Hz), 5.75 (1H, ddt, $J=16.5$, 10.8, 6.6 Hz), 4.98 (1H, dm, $J=16.5$ Hz), 4.94 (1H, dm, $J=10.8$ Hz), 3.74 (1H, m), 3.73 (1H, s), 2.64 (1H, dd, $J=16.2$, 5.1 Hz), 2.53 (1H, dd, $J=16.2$, 6.3 Hz), 2.48 (2H, t, $J=7.2$ Hz), 2.28 (2H, q-like), 1.50 (2H, m), 1.28 (6H, m), 0.87 (3H, t, $J=6.9$ Hz); ^{13}C NMR: $\delta=209.4$, 152.1, 141.2, 136.9, 115.2, 114.9, 114.0, 55.8, 51.2, 47.2, 42.8, 35.3, 31.8, 27.6, 26.0, 22.7, 14.2; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 95:5, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=5.13$ min; minor isomer: $t_R=8.60$ min; $[\alpha]_D$: +12.1 (*c* 1, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{19}H_{29}NO_2$ (MNa^+): 326.2096; found: 326.2083.

***(1S)-1-(4-Methoxyphenylamino)-1-phenylhept-6-en-3-one* (13):** ^{1}H NMR: $\delta=7.30$ (5H, m), 6.66 (2H, d, $J=8.7$ Hz), 6.48 (2H, d, $J=8.7$ Hz), 5.69 (1H, ddt, $J=17.1$, 10.5, 6.6 Hz), 4.95 (1H, dm, $J=17.1$ Hz), 4.91 (1H, dm, $J=10.5$ Hz), 4.75 (1H, t, $J=6.3$ Hz), 3.66 (3H, s), 2.86 (2H, m), 2.41 (2H, tm, $J=6.9$ Hz), 2.24 (2H, m); ^{13}C NMR: $\delta=208.3$, 152.2, 142.6, 140.8, 136.6, 128.6, 127.1, 126.2, 115.22, 115.18, 114.6, 55.6, 55.4, 50.5, 42.6, 27.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=14.68$ min; minor isomer: $t_R=12.31$ min; $[\alpha]_D$: +5.8 (*c* 4, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{20}H_{23}NO_2$ (M^+): 309.1729; found: 309.1732.

***(1S)-1-(4-Methoxyphenylamino)-1-(4-nitrophenyl)-hept-6-en-3-one* (14):** ^{1}H NMR: $\delta=8.14$ (2H, d, $J=9.0$ Hz), 7.52 (2H, d, $J=9.0$ Hz), 6.67 (2H, d, $J=9.0$ Hz), 6.44 (2H, d, $J=9.0$ Hz), 5.72 (1H, m), 4.96 (2H, m), 4.85 (1H, t, $J=6.3$ Hz), 4.27 (1H, s, br), 3.68 (3H, s), 2.92 (2H, m), 2.47 (2H, m), 2.27 (2H, m); ^{13}C NMR: $\delta=207.3$, 152.6, 150.6, 147.0, 140.0, 136.3, 127.3, 123.9, 115.5, 115.3, 114.7, 55.6, 54.8, 49.9, 42.6, 27.5; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 86:14, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=30.70$ min; minor isomer: $t_R=23.66$ min; HRMS (MALDI-FTMS): calcd. for $C_{20}H_{22}N_2O_4$ (M^+): 354.1580; found: 354.1565.

***(1S)-1-(4-Methoxyphenylamino)-1-naphthylhept-6-en-3-one* (15):** ^{1}H NMR: $\delta=8.13$ (1H, d, $J=8.4$ Hz), 7.87 (1H, dd, $J=8.3$, 1.2 Hz), 7.71 (1H, d, $J=8.1$ Hz), 7.51 (3H, m), 7.35 (1H, t, $J=8.1$ Hz), 6.61 (2H, d, $J=9.0$ Hz), 6.44 (2H, d, $J=9.0$ Hz), 5.70 (1H, m), 5.57 (1H, dd, $J=8.3$, 4.1), 4.95 (1H, m), 4.91 (1H, m), 3.62 (3H, s), 3.02 (1H, dd, $J=16.1$, 3.9 Hz), 2.90 (1H, dd, $J=16.1$, 8.4 Hz), 2.44 (2H, t, $J=7.2$ Hz), 2.26 (2H, m); ^{13}C NMR: $\delta=208.4$, 152.1, 140.7, 137.4, 136.6, 134.0, 130.3, 129.2, 127.7, 126.3, 125.6, 125.5, 123.2, 122.0, 115.3, 114.9, 114.6, 55.7, 51.2, 49.4, 42.7, 27.5; HPLC (Daicel Chiralpak AS, hexanes/*i*-PrOH = 94:6, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=7.64$ min; minor isomer: $t_R=9.56$ min; $[\alpha]_D$: +117 (*c* 2, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{24}H_{25}NO_2$ (M^+): 359.1885; found: 359.1870.

***(2S)-1-Benzyloxy-2-(4-methoxyphenylamino)-oct-7-en-4-one* (16a):** ^{1}H NMR: $\delta=7.29$ (5H, m), 6.74 (2H, d, $J=9.3$ Hz), 6.57 (2H, d, $J=9.3$ Hz), 5.74 (1H, ddt, $J=17.1$, 10.2, 6.6 Hz), 4.98 (1H, dm, $J=17.1$ Hz), 4.93 (1H, dm, $J=10.2$ Hz), 4.47 (2H, m), 3.95 (1H, m), 3.72 (3H, s), 3.55 (2H, m), 2.71 (2H,m), 2.47 (2H, tm, $J=7.2$ Hz), 2.26 (2H, q-like); ^{13}C NMR: $\delta=209.2$, 152.4, 140.6, 137.9, 136.9, 128.2, 127.8, 127.6, 115.5, 115.1, 114.8, 73.3, 71.0, 55.7, 50.7, 43.9, 42.7, 27.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=14.00$ min; minor isomer: $t_R=11.67$ min; $[\alpha]_D$: −4.9 (*c* 1.5, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{22}H_{27}NO_3$ (MNa^+): 376.1883; found: 376.1887.

***(2S,3S)-3-Acetyl-1-benzyloxy-2-(4-methoxyphenylamino)-hex-5-ene* (16b):** ^{1}H NMR: $\delta=7.30$ (5H, m), 6.74 (2H, d, $J=8.7$ Hz), 6.56 (2H, d, $J=8.7$ Hz), 5.73 (1H, m), 5.03 (2H, m), 4.42 (2H, s), 3.73 (1H, m), 3.72 (3H, s), 3.51 (1H, dd, $J=9.6$, 4.2 Hz), 3.44 (1H, dd, $J=9.6$, 3.3 Hz), 3.00 (1H, td, $J=8.6$, 4.8 Hz), 2.45 (2H, m), 2.11 (3H, s); ^{13}C NMR: $\delta=211.0$, 152.3, 141.1, 137.7, 135.4, 128.3, 128.2, 127.7, 117.0, 115.2, 114.9, 73.4, 69.6, 55.8, 55.7, 53.8, 33.7, 31.9; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 92:8, flow rate 1.0 mL/min, $\lambda=254$ nm): major isomer: $t_R=8.28$ min; minor isomer: $t_R=9.63$ min; $[\alpha]_D$: −31.5 (*c* 1.3, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{22}H_{27}NO_3$ (MNa^+): 376.1883; found: 376.1881.

***(3S,4R)-3-Hydroxy-4-(4-methoxyphenylamino)-6-methylheptan-2-one* (17):** ^{1}H NMR: $\delta=0.95$ (d, $J=6.5$ Hz, 3H), 1.01 (d, $J=6.6$ Hz, 3H), 1.49 (m, 1H), 1.58 (m, 1H), 1.78 (m, 1H), 2.20 (s, 3H), 3.41 (bs, 1H), 3.74 (s, 3H), 3.81 (m, 1H), 3.88 (m, 1H), 4.26 (m, 1H), 6.55 (d, $J=8.8$ Hz, 2H), 6.75 (d, $J=8.8$ Hz, 2H); ^{13}C NMR: $\delta=22.1$, 23.2, 24.9, 25.0, 40.2, 53.8, 55.7, 77.7, 114.9, 115.2, 140.7, 152.4, 208.6; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 94:6, flow rate 1.00 mL/min, $\lambda=254$ nm): t_R (major) = 8.30 min; t_R (minor) = 27.46 min; HRMS (MALDI-FTMS): calcd. for $C_{15}H_{23}NO_3$ (MNa^+): 288.1570; found: 288.1559.

***(3S,4R)-3-Hydroxy-4-(4-methoxyphenylamino)-nonan-2-one* (18):** ^{1}H NMR: $\delta=0.89$ (m, 3H), 1.27–1.35 (m, 4H), 1.38–1.48 (m, 2H), 1.61–1.71 (m, 2H), 3.45 (bs, 1H), 3.74 (s, 3H), 3.76 (m, 1H), 3.83 (bs, 1H), 4.28 (m, 1H), 6.54 (d, $J=8.8$ Hz, 2H), 6.75 (d, $J=8.8$ Hz, 2H); ^{13}C NMR: $\delta=14.0$, 22.6, 24.9, 26.3, 31.3, 31.7, 55.7, 56.0, 77.6, 114.9, 115.2, 140.8, 152.4, 208.6; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 92:8, flow rate 1.00 mL/min, $\lambda=254$ nm): t_R (major) = 6.85 min; t_R (minor) = 8.10 min; HRMS (MALDI-FTMS): calcd. for $C_{16}H_{25}NO_3$ (MNa^+): 302.1727; found: 302.1737.

***(1R,2S)-2-Hydroxy-1-(4-methoxyphenylamino)-1-naphthylbutan-3-one* (19):** Major diastereomer: ^{1}H NMR: $\delta=2.46$ (s, 3H), 3.62 (d, $J=3.0$ Hz, 1H), 3.64 (s, 3H), 4.52 (bs, 1H), 4.56 (m, 1H), 5.76 (bs, 1H), 6.45 (d, $J=8.8$ Hz, 2H), 6.62 (d,

$J=8.8$ Hz, 2H), 7.41 (t, $J=7.9$ Hz, 1H), 7.46 (d, $J=7.0$ Hz, 1H), 7.55 (t, $J=7.9$ Hz, 1H), 7.64 (t, $J=7.9$ Hz, 1H), 7.78 (d, $J=8.3$ Hz, 1H), 7.94 (d, $J=8.3$ Hz, 1H), 8.18 (d, $J=8.3$ Hz, 1H); ^{13}C NMR: $\delta=14.1$, 25.5, 54.6, 55.6, 60.4, 79.0, 114.8, 114.9, 121.2, 124.7, 125.5, 125.6, 126.5, 128.2, 129.7, 130.7, 133.4, 134.1, 139.8, 152.3, 207.5. Minor diastereomer: ^{1}H NMR: $\delta=$ 2.35 (s, 3H), 3.67 (s, 3H), 3.78 (m, 1H), 4.29 (bs, 1H), 4.89 (m, 1H), 5.56 (d, $J=3.9$ Hz, 1H), 6.54 (d, $J=8.8$ Hz, 2H), 6.67 (d, $J=8.8$ Hz, 2H), 7.39–7.66 (m, 4H), 7.81 (d, $J=8.3$ Hz,1H), 7.92 (d, $J=8.3$ Hz, 1H), 8.25 (d, $J=8.3$ Hz, 1H); ^{13}C NMR: 14.2, 28.2, 55.6, 57.4, 60.4, 78.4, 114.7, 114.8, 115.2, 115.6, 122.3, 125.0, 125.5, 125.8, 126.6, 126.7, 128.7, 129.4, 130.9, 133.0, 134.1, 140.6, 152.7, 209.1; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 92:8, flow rate 1.00 mL/min, $\lambda=$ 254 nm): major diastereomer: t_R (major) = 28.58 min; t_R (minor) = 15.90 min; minor diastereomer: t_R (major) = 41.47 min; t_R (minor) = 22.35 min; HRMS (MALDI-FTMS): calcd. for $C_{21}H_{21}NO_3$ (MNa^+): 358.1419; found: 358.1416.

***(1R,2S)-2-Hydroxy-1-(4-methoxyphenylamino)-1-phenylbutan-3-one* (20):** ^{1}H NMR: $\delta=2.24$ (s, 3H), 3.62 (s, 3H), 3.84 (m, 1H), 4.33 (m, 1H), 4.40 (bs, 1H), 4.85 (m, 1H), 6.46 (d, $J=8.8$ Hz, 2H), 6.64 (d, $J=8.8$ Hz, 2H), 7.17–7.33 (m, 5H); ^{13}C NMR: $\delta=25.1$, 55.4, 58.9, 80.6, 114.6, 115.0, 126.9, 127.4, 128.4, 139.2, 140.0, 152.1, 207.5; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 92:8, flow rate 1.00 mL/min, $\lambda=$ 254 nm): t_R (major) = 23.98 min; t_R (minor) = 16.96 min; $[\alpha]_D$: +50.2 (*c* 0.6, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for $C_{17}H_{19}NO_3$ (MNa^+): 308.1257; found: 308.1269.

***(2R,3S)-1-Benzyloxy-3-hydroxy-1-(4-methoxyphenylamino)-pentan-4-one* (21):** ^{1}H NMR: $\delta=2.19$ (s, 3H), 3.60 (dd, $J=8.34$, 9.2 Hz, 1H), 3.68 (dd, $J=4.0$, 9.2 Hz, 1H), 3.73 (s, 3H), 3.86 (m, 1H), 3.98 (m, 1H), 4.50–4.56 (m, 3H), 6.56 (d, $J=$ 8.8 Hz, 2H), 6.75 (d, $J=8.8$ Hz, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR: $\delta=25.4$, 53.4, 55.4, 55.7, 68.4, 73.6, 76.1, 115.0, 127.8, 127.9, 128.5, 137.8, 140.1, 152.6, 208.9; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 92:8, flow rate 1.00 mL/min, $\lambda=254$ nm): t_R (major) = 16.67 min; t_R (minor) = 15.42 min; HRMS (MALDI-FTMS): calcd. for $C_{19}H_{23}NO_4$ (MNa^+): 352.1525; found: 352.1527.

General Procedure for the Catalytic Asymmetric Reaction between *N*-PMP-Protected α-Imino Ethyl Glyoxylate and Ketone Donors

In a typical experiment, N-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous DMSO (4 mL), the corresponding ketone donor (1 mL) was added followed by L-proline (20 mol %) and the mixture was stirred for 2–24 h at room temperature. Following aqueous work-up with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate mixtures) to afford the corresponding Mannich addition product.

***Ethyl (2S,3S)-3-hydroxy-2-(p-methoxyphenylamino)-4-oxohexanoate* (28):** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.12$ (t, 3H, J = 7.4 Hz), 1.24 (t, 3H, $J=7.4$ Hz), 2.61 (q, 2H, $J=$ 7.3 Hz), 3.73 (s, 3H, OMe), 3.92 (d, 1H, $J=3.7$ Hz), 4.08 (m, 1H), 4.23 (m, 2H), 4.45 (m, 1H), 4.63 (m, 1H), 6.60 (d, 2H, $J=8.8$ Hz), 6.76 (d, 2H, $J=8.8$ Hz); ^{13}C NMR: $\delta=7.4$, 14.1, 30.7, 55.6, 59.5, 61.8, 76.9, 114.8, 115.9, 140.2, 153.4, 170.9, 208.9; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 89:11, flow rate 1.00 mL/min, $\lambda=254$ nm): *syn*-isomer: t_R (major) = 9.06 min; t_R (minor) = 15.54 min; *anti*-isomer: t_R (major) = 12.30 min; t_R (minor) = 18.46 min; $[\alpha]_D$: +23.6 (*c* 0.4, $CHCl_3$); HRMS (MALDI-FTMS): calcd. for; $C_{15}H_{21}NO_5$ (MNa^+): 318.1312; found: 318.1319.

***Ethyl (2S,3R)-3-hydroxymethyl-2-(p-methoxyphenylamino)-4-oxo-pentanoate* (29):** ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=$ 1.22 (t, 3H, $J=7.0$ Hz), 2.39 (s, 3H), 3.09 (bs, 1H), 3.15 (m, 1H), 3.74 (s, 3H, OMe), 3.94 (dd, 1H, $J=4.4$, 11.8 Hz), 4.07 (dd, 1H, $J=5.3$, 11.8 Hz), 4.17 (q, 2H, $J=7.0$ Hz), 4.29 (bs, 1H), 4.50 (d, 1H, $J=6.1$ Hz), 6.68 (d, 2H, $J=8.8$ Hz), 6.77 (d, 2H, $J=8.8$ Hz); ^{13}C NMR: $\delta=14.0$, 29.2, 55.6, 56.0, 58.4, 60.9, 61.6, 114.8, 116.1, 140.4, 153.3, 172.7, 208.1; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 98:2, flow rate 1.00 mL/min, $\lambda=254$ nm): t_R (major) = 24.86 min; t_R (minor) = 22.49 min; HRMS (MALDI-FTMS): calcd. for $C_{15}H_{21}NO_5$ (MNa^+): 318.1312; found: 318.1309.

***Ethyl (R)-N-(p-methoxyphenyl)-cyclohexylglycinate* (32):** To a solution of *ent*-**25** (500 mg, 1.637 mmol) in MeOH (32 mL, 0.05M) was added tosylhydrazine (427 mg, 1.4 equivs.), and the mixture was heated to reflux for 2 h. After cooling to 0 °C, $NaBH_4$ (620 mg) was added in small portions over 45 min. After stirring for 30 min at 0 °C, the mixture was heated to reflux for 2 h. Then brine was added and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate = 3:1) to afford **32**; yield: 241 mg (50%); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=1.11-1.32$ (m, 8H), 1.65–1.89 (m, 6H), 3.73 (s, 3H), 3.75 (d, 1H, $J=7.5$ Hz), 3.86 (bs, 1H), 4.15 (m, 2H), 6.60 (d, 2H, $J=8.7$ Hz), 6.75 (d, 2H, $J=8.7$ Hz); ^{13}C NMR: 14.3, 26.0. 26.1, 26.2, 29.5, 30.0, 41.6, 56.0, 61.0, 63.6, 115.1, 115.4, 141.9, 152.9, 174.3; $[\alpha]_D$: +42.3 (*c* 0.7, CH_2Cl_2); HRMS (MALDI-FTMS): calcd. for $C_{17}H_{25}NO_3$ (MNa^+) 314.1727; found: 314.1724.

***Ethyl (R)-N-(tert-butoxycarbonyl)-cyclohexylglycinate* (33):** A solution of **32** (500 mg, 1.717 mmol) in MeOH (2 mL) was added *via* syringe over 30 min to a solution of iodobenzene diacetate (2.2 g, 6.7 mmol, 4 equivs.) in MeOH (20 mL). Following exactly the protocol described by Hoveyda and Snapper,[14] using $(Boc)_2O$ (1.9 g, 8.8 mmol) instead of acetic anhydride, afforded **33** after column chromatography (hexanes/ethyl acetate, 4:1); yield: 330 mg (67%) ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=1.04-1.30$ (m, 9H), 1.44 (s, 9H), 1.56–1.77 (m, 5H), 4.16–4.22 (m, 3H), 5.01 (m, 1H); ^{13}C NMR: $\delta=14.2$, 26.0, 28.1, 28.3, 29.4, 41.1, 58.3, 61.0, 79.6, 155.6, 172.4; $[\alpha]_D$: −13.5 (*c* 2, CH_2Cl_2); HRMS (MALDI-FTMS): calcd. for $C_{15}H_{27}NO_4$ (MNa^+): 308.1832; found: 308.1836.

***(R)-N-(tert-Butoxycarbonyl)-cyclohexylglycine* (34):** To a solution of **33** (200 mg, 0.7 mmol) in dioxane/water (10 mL, 1:1) was added LiOH (250 mg) and the mixture was stirred at room temperature for 14 h. Then, the mixture was acidified with 1 N HCl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate = 1:5) afforded known *N*-Boc-protected cyclohexylglycine **34**; yield: 141 mg (78%).

***Ethyl (E)-(2S)-4-benzyloxyimino-2-(p-methoxyphenylamino)-pentanoate* (37):** *N*-PMP-Protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous acetone (5 mL) and L-proline (20 mol %) was added. After stirring

overnight at room temperature, the acetone was evaporated and anhydrous dioxane (5 mL), *O*-benzylhydroxylamine hydrochloride (0.7 mmol) and pyridine (0.5 mL) were added to the residue. After stirring for 14 h at room temperature, the mixture was filtered through Celite, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate = 3/1) to afford oxime **37**; yield: 102 mg (55%); ^{1}H NMR (400 MHz): δ = 1.17 (t, 3H, OCHC*H*$_3$), 1.88 (s, 3H), 2.64 (d, 2H), 3.69 (s, 3H, OC*H*$_3$), 3.99 (bs, 1H, ArN*H*CH), 4.07 (q, 2H, OC*H*$_2$CH$_3$), 5.07 (s, 2H, PhC*H*$_2$), 6.45 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.72 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.25–7.40 (m, 6H, Ar*H* and *H*C=N); ^{13}C NMR (125 MHz): δ = 173.0, 154.0, 152.6, 140.5, 138.2, 128.2, 127.8, 127.5, 115.1, 114.6, 75.3, 60.9, 55.4, 55.2, 38.4, 14.6, 14.0; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm); t_R (major) = 26.30 min; t_R (minor) = 33.10 min; HRMS (MALDI-FTMS): calcd. for $C_{21}H_{26}N_2O_4$ (MNa^+): 393.1785; found: 393.1792.

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[3] Chloroform, which was reported to be a more effective solvent than DMSO for the Mannich-type reaction between acetone, *p*-anisidine, and both linear and α-unbranched aliphatic aldehydes (see Ref.[2q]) did not afford any products in these studies.

[4] Products **9** and **10** were formed in a clean reaction but at a slower rate as opposed to the other donors studied. 3-Pentanone was recently reported not to react under these conditions. See Ref.[2q]

[5] Similar *syn*-selectivities in Mannich-type reactions and alkylations of imines have been reported earlier; see: a) R. Hirabayashi, C. Ogawa, M. Sugiura, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 9493–9499; b) Y. Yamamoto, T. Komatsu, K. Maruyama, *J. Org. Chem.* **1985**, *50*, 3115–3121; c) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; both the absolute and relative stereochemistry of these Mannich-products has been established earlier, See Refs.[2n, q]

[6] As monitored by TLC, the reaction of these donors gave rise to a mixture of multiple products presumably due to self-aldolization or polymerization. This could not be

avoided by reducing the donor amount to 2 equivalents, by switching to different solvents, by decreasing the reaction temperature, nor by reducing the catalyst loading to as low as 2%.

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[18] See: R. J. Mears, H. E. Sailes, J. P. Watts, A. Whiting, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3250–3263.

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