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The Brønsted Acid Catalyzed, Enantioselective Vinylogous Mannich Reaction

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Abstract: The first catalytic, enantioselective vinylogous Mannich reaction of acyclic silyl dienolates is reported. A second-generation 2,2′-dihydroxy-1,1′-binaphthyl (BINOL)-based phosphoric acid has been developed and further optimized as an enantioselective organocatalyst. Upon protonation of the imines, chiral contact ion pairs are generated in situ and attacked highly diastereoselectively by the nucleophile. γ-Substituted silyl dienolates that lead to more highly substituted Mannich products with a second stereogenic center in good diastereoselectivity have been employed in these reactions. The reaction path has been elucidated with NMR spectroscopy and mass spectrometry, which suggest that the protic reaction medium found to be optimal in these reactions serves to trap the cationic silicon species as silanol. A crystal structure of a phosphoric acid bound imine was obtained that provides insight into the binding mode and a rationale for the stereochemical course of the reaction.

Keywords: BINOL · enantioselectivity · organocatalysis · Mannich reaction · phosphoric acids

Introduction

The asymmetric Mannich reaction is a fundamental C–C bond-forming process in organic chemistry; it furnishes valuable β-amino carbonyl systems.[1] The extension of the enolate component into a dienolate offers the opportunity for a vinylogous Mannich reaction that generates a new C–C bond from the γ site within the dienolate component and leads to δ-amino α,β-unsaturated carbonyl compounds. This divergent regioselectivity is typically governed by the magnitude of the atomic orbital coefficients in the HOMO of the dienolate. Whereas in lithium dienolates the size of this coefficient is larger at the α position, thereby leading to α-substituted products preferentially, silicon dienolates have a different electronic distribution and a larger coefficient at the γ site, thus giving rise to γ-substituted products in acid-catalyzed Mukaiyama-type reactions predominantly.[2]

The highly functionalized vinylogous Mannich products are valuable synthetic intermediates in organic synthesis and have been frequently employed in natural product synthesis in particular.[3] Despite the documented synthetic potential, only very few catalytic, enantioselective processes had been developed prior to our studies; these were limited to very special substrate patterns. The first protocol was devised by Martin et al. who employed a Ti–BINOL (BINOL = 2,2′-dihydroxy-1,1′-binaphthyl) catalyst for the reaction of silyloxy furans with imines and obtained amino-substituted γ-butenolides with good diastereoselectivity and up to 54% *ee*.[4] Subsequently, Hoveyda and Snapper and co-workers developed a chiral silver catalyst with a dipeptide-based P,N ligand for exactly the same reaction, thus giving rise to excellent diastereo- and enantioselectivities of up to 98% *ee*.[5] Recently, Akiyama et al. documented a phosphoric acid catalyzed vinylogous Mannich reaction of silyloxy furans and imines that furnished the products with typically good diastereocontrol and good to excellent enantiocontrol.[6] Shibasaki et al. reported a direct vinylogous Mannich reaction for the asymmetric synthesis of γ-butenolides by using a chiral lanthanum–pybox (pybox = pyridine bisoxazoline) complex.[7] A second substrate class that was employed with great success in direct asymmetric vinylogous Mannich reactions is 1,1-dicyanoalkenes, which were reacted with activat-

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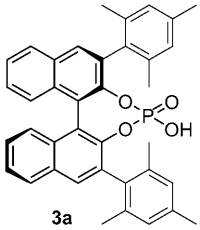
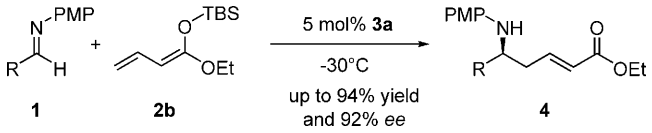
ed imines catalyzed by a chiral thiourea Brønsted acid catalyst that contained a basic amine moiety.[8] The products were obtained with complete regio- as well as excellent diastereo- and enantioselectivities. The same substrates were later shown by Jørgensen et al. to also react under chiral phase-transfer conditions with imines to yield products with up to 95% *ee*.[9]



In 2008, we reported the first catalytic, enantioselective, vinylogous Mannich reaction of an acyclic silyl dienolate **2b** with imines **1** that was catalyzed by the chiral Brønsted acid **3a**.[10a] A BINOL-based phosphoric acid of the same type that Akiyama and Terada[11,12] had introduced into the field of asymmetric organocatalysis independently was employed under carefully optimized reaction conditions and delivered vinylogous Mannich products **4** in good yields, complete γ-regioselectivity, and *ee* values of up to 92% (Scheme 1).



Scheme 1. Brønsted acid catalyzed vinylogous Mannich reaction of acyclic silyl dienolate **2b** (*E*/*Z* 1:2.5).[10a]

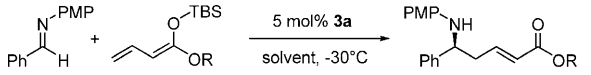
Later we could extend this process successfully to reactions of amide-based silyl dienolates.[10b] Subsequently, Carretero and co-workers successfully developed a chiral copper catalyst that could be applied both to silyloxy furans as well as acyclic silyl dienolates as nucleophiles in vinylogous Mannich reactions.[13]

We have now further optimized this process with respect to catalyst structure and scope. In particular, we have developed a superior second-generation Brønsted acid catalyst that typically furnishes vinylogous Mannich products with above 90% *ee* for most substrates investigated and with >95% *ee* in select cases. Additionally, we have also found γ-substituted silyl dienolates to be suitable substrates for this process, thus giving rise to products with two new chiral centers in good diastereo- and enantiocontrol. Also, NMR spectroscopic as well as mass spectrometric investigations were performed to elucidate the reaction mechanism and in particular the mode of regeneration of the chiral catalyst. Finally, we have obtained structural information on the imine-bound catalyst that allows for a transition-state proposal of this reaction.

Results and Discussion

Initial studies: We first focused on the identification of the most suitable alkoxy group within the silyl dienolate that gave rise to the best enantioselectivity. Thus, we performed reactions of **1a** and various silyl dienolates **2** with **3a** as catalyst under otherwise identical reaction conditions (Table 1).

Table 1. Optimization of the vinylogous Mannich reaction with different alkoxy dienolates.[a]



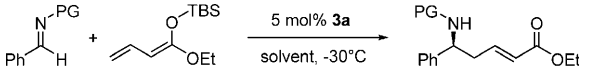
Entry	R	2	4	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	Me	**2a**	**4a**	8	73	83
2	Et	**2b**	**4b**	8	88	88
3	*n*Pr	**2c**	**4c**	8	87	78
4	*n*Bu	**2d**	**4d**	8	85	67
5	*i*Pr	**2e**	**4e**	24	86	43
6	*t*Bu	**2f**	**4f**	48	64	22

[a] Reaction conditions: **1a** (1 equiv), **2** (3 equiv), **3a** (5 mol%), −30°C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv); TBS = *tert*-butyldimethysilyl, PMP = *p*-methoxyphenyl. [b] Conversion >99% (HPLC). [c] Isolated yield. [d] Determined through HPLC on chiral stationary phases.

It turned out that small alkoxy groups in silyl dienolate **2** gave higher enantioselectivities than larger alkoxy groups. The highest selectivity of 88% *ee* was obtained with the ethoxy group (Table 1, entry 2), whereas a *tert*-butyl ester derived silyl dienolate furnished the vinylogous Mannich product with only 22% *ee* (entry 6).

Secondly, we varied the *N*-aryl group that had been shown to be the most suitable N-substituent for this reaction. Generally, we found *para*-substituted aryl groups such as the PMP group to give rise to the best selectivities (Table 2). In contrast, *ortho*-substituted aryl groups such as the *ortho*-hydroxyphenyl group that Akiyama et al. had preferentially employed in their studies furnished a racemic product under our reaction conditions.

Table 2. Optimization of the vinylogous Mannich reaction with different imine protecting groups (PGs).[a]

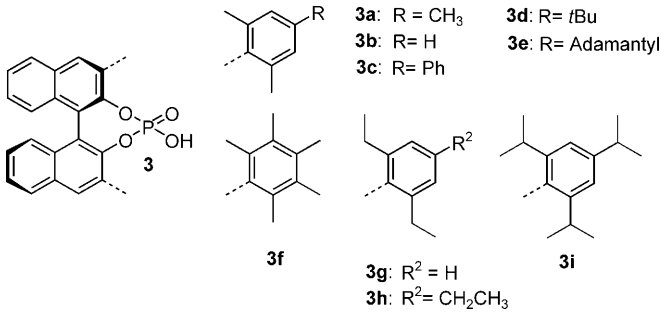


Entry	PG	4	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	*p*-Ph-O-Me	**4b**	8	88	88
2	*p*-Ph-O-Et	**4g**	6	92	88
3	*p*-Ph-O-Bn	**4h**	48	86	86
4	*p*-Me-Ph	**4i**	17	91	88
5	Ph	**4j**	12	83	89
6	*o*-HO-Ph	**4k**	1	81	0
7	*o*-MeO-Ph[e]	**4l**	36	20[e]	32

[a] Reaction conditions: **1** (1 equiv), **2b** (*E*/*Z* = 1:2.5, 3 equiv), **3a** (5 mol%), −30°C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv). [b] Conversion >99% (HPLC). [c] Isolated yield. [d] Determined through HPLC on chiral stationary phases. [e] 20% conversion.

Optimization of the process: In previous studies we had identified the 3,3′-bismesityl-substituted BINOL-phosphoric acid **3a** as the optimal Brønsted acid for the vinylogous Mannich reaction in a solvent system containing equal amounts of *t*BuOH, 2-methyl-2-butanol, and THF with 1 equiv of water.[10a] The products were obtained in good yields and a maximum of 92% *ee*. Some products, however, were formed with significantly lower enantioselectivities; these were synthetically not useful. In an attempt to further increase the enantioselectivity of the reaction and possibly develop a chiral Brønsted acid catalyst for a broader substrate range, we investigated some more BINOL-based phosphoric acids with different 3,3′-substituents. In particular, we systematically varied the size of the *ortho* and *para* substituents within the 3,3′-aryl groups, as these positions had been found earlier to be of prime importance for the enantioselectivity of the reaction.[10a]

Thus, a broad range of different phosphoric acids **3** (Scheme 2) that met these criteria were synthesized following established procedures and tested in the vinylogous

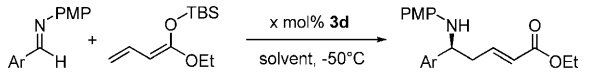


Scheme 2. Phosphoric acids **3a–i** investigated in the vinylogous Mannich reaction.

Mannich reaction of silyl dienolate **2b** ($E/Z = 1{:}2.5$)[14] and imine **1b** using our previously optimized reaction conditions (Table 3). Catalyst **3b** lacking only the *para*-methyl group within the 3,3′-aryl groups still gave 88% *ee* in excellent yield (Table 3, entry 2). Replacing this *para*-methyl group with a phenyl group did not have a strong effect on the enantioselectivity of the reaction (entry 3). However, placing a *t*Bu group instead of a methyl group in the *para* position significantly increased the selectivity to 96% *ee* while maintaining a high yield of product **5a** (entry 4). A further increase of the steric size at this position did not correspond to a higher selectivity, as exemplified by the adamantyl-substituted catalyst **3e** (entry 5). Interestingly, the pentamethyl-substituted catalyst **3f** furnished the product in excellent yield and with almost the same selectivity as catalyst **3d** (entry 6).

With respect to the effect of the steric size of the *ortho* substituents within the 3,3′-aryl groups, we had earlier discovered that any catalyst lacking *ortho* substituents gave very low selectivity.[10a] Increasing the size of the *ortho* substituent from methyl to ethyl and keeping the *para* position

Table 3. Optimization of the vinylogous Mannich reaction with phosphoric acids **3**.[a]



1b **2b** **5a** Ar=*p*-Et-Ph

Entry	Catalyst **3**	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	**3a**	2.0	92	92
2	**3b**	3.0	91	88
3	**3c**	1.5	90	91
4	**3d**	3.0	88	96 (98)[e]
5	**3e**	5.0	88	93
6	**3f**	1.0	96	95 (96)[e]
7	**3g**	2.0	91	93
8	**3h**	1.0	92	96 (97)[e]
9	**3i**	22	63	88

[a] Reaction conditions: **1b** (1 equiv), **2b** ($E/Z = 1{:}2.5$, 3 equiv), **3** (5 mol%), −30°C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv). [b] Conversion >99% (HPLC). [c] Isolated yield. [d] Determined through HPLC on chiral stationary phases. [e] Enantioselectivity at −50°C.

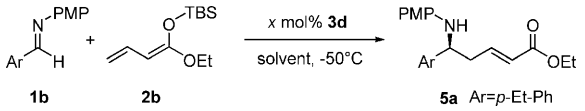
unsubstituted furnished a highly selective catalyst **3g**, which gave rise to the product in 93% *ee* (Table 3, entry 7). More importantly, catalyst **3h** with a 2,4,6-triethyl substitution pattern within the 3,3′-aryl groups furnished the vinylogous Mannich product **5a** in excellent yield and 96% *ee* in a very short reaction time (entry 8). Finally, use of the TRIP catalyst **3i** developed by List and co-workers,[15] which was a highly promising catalyst candidate for our reaction, too, gave rise to the product in moderate yield and 88% *ee* (entry 9).

With the three Brønsted acid catalysts **3d**, **3f**, and **3h** in hand, which were identified as the most enantioselective ones, we briefly attempted to further optimize the selectivity of the reaction by lowering the reaction temperature. Indeed, the enantioselectivity of the reaction could be slightly improved by running the reaction at −50°C, which proved to be the lowest temperature at which the reaction mixture was still liquid and could be stirred. All three catalysts now exhibited synthetically very useful levels of selectivity of 97–98% *ee*. Considering the exceptional *ee* and the ease of preparation, we selected catalyst **3d** as our standard Brønsted acid catalyst to study the vinylogous Mannich reaction further.

To further reduce the catalyst loading, we performed experiments with 1–5 mol% of catalyst in a model reaction of **1b** with **2b** under otherwise identical reaction conditions. As can be seen from Table 4, even with only 2 mol% of phosphoric acid **3d** vinylogous Mannich product **5a** was obtained in 90% yield and 97% *ee* after 48 h at −50°C (Table 4, entry 4). In some cases, precipitation of the imine and/or the iminium salt occurred at this low temperature, thereby resulting in quite long reaction times. Eventually, we settled on a catalyst loading of 3 mol% in an attempt to reduce the reaction time to an acceptable level and could still isolate product **5a** in 93% and 97% *ee* (entry 3).

As previously discovered, the reaction could be performed in a three-component fashion, thereby obviating the

Table 4. Optimization of catalyst loading.[a]



1b 2b 5a Ar=*p*-Et-Ph

Entry	Catalyst loading [mol%]	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	5	14	95	98
2	4	16	93	97
3	3	24	93	97
4	2	48	90	97
5	1	288	90	97

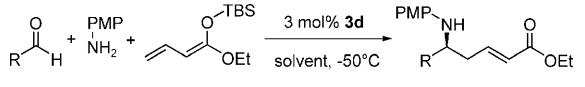
[a] Reaction conditions: **1** (1 equiv), **2b** (*E*/*Z* = 1:2.5, 3 equiv), **3d** (5 mol%), −50 °C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv). [b] Conversion > 99% (HPLC). [c] Isolated yield. [d] Determined through HPLC on chiral stationary phases.

need to synthesize the imine in a separate reaction. The water formed in this condensation reaction did not harm the reactions, as water was actually shown to accelerate the turnover of the reaction (vide infra). Thus, all vinylogous Mannich reactions reported herein were performed starting from the respective aldehydes, *para*-anisidine, and silyl dienolate **2a** (*E*/*Z* = 1:2.5, 2 equiv) in a solvent mixture of equal amounts of *t*BuOH, 2-methyl-2-butanol, and THF containing 1 equiv of water at −50 °C. By using these carefully optimized reaction conditions, we set out to investigate the substrate scope of the vinylogous Mannich reaction (Table 5).

Our previously established conditions had furnished products typically with 80% *ee* or slightly above and resulted in 90–92% *ee* only for select cases.[10a] Also, some heteroaromatic and aliphatic aldimines gave rise to only about 70% *ee*. With the new conditions, enantioselectivities increased substantially and approached or even exceeded 90% *ee* for most substrates.

Thus, the best selectivities were obtained for benzaldehydes and *para*-substituted benzaldehydes with well above 90% *ee* (Table 5, entries 1–4). Yields and reaction times varied depending on the reactivity and solubility of the in situ formed imines. Use of *meta*- and *ortho*-substituted benzaldehydes furnished Mannich products in excellent yields and *ee* values in the high eighties or even 90% (entries 5–10). Heteroaromatic aldimines were also good substrates for this process; they furnished Mannich products with up to 92% *ee* (entries 11–14). Interestingly, in some cases, enantioselectivities increased dramatically compared with reactions catalyzed with phosphoric acid **3a**. Thus, 2-furyl aldehyde now gave rise to 89% *ee*, whereas with **3a** the selectivity was just 74% *ee* (entry 12). Also, the 2-thiophene-substituted vinylogous Mannich product **5m** was now obtained with 90% *ee* (entry 14). Aliphatic α-branched aldehydes could also be employed as reaction partners in a three-component reaction and delivered Mannich products **5n–p** in good yields and 80–87% *ee*, again typically exceeding the selectivities obtained with catalyst **3a** (entries 15–17). Aliphatic unbranched aldehydes, however, gave rise to vinylogous Mannich products with only moderate selectivities (e.g., entry 18).

Table 5. Scope of the three-component vinylogous Mannich reaction.[a]

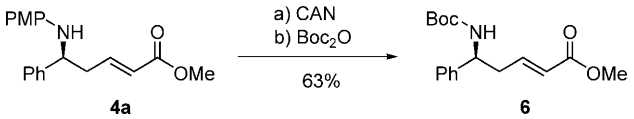


2b 4/5

Entry	R	Product	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	Ph	**4b**	18	97	95
2	*p*-Et-Ph	**5a**	12	93	97
3	*p*-MeO-Ph	**5b**	144	40	93
4	*p*-F-Ph	**5c**	48	97	90
5	*m*-Me-Ph	**5d**	48	95	88
6	*m*-Cl-Ph	**5e**	6.5	97	90
7	*o*-Me-Ph	**5f**	21	97	90
8	*o*-Br-Ph	**5g**	6	97	85
9	*o*-NO_2-Ph	**5h**	48	96	87
10	2-naphthyl	**5i**	144	88	90
11	3-furyl	**5j**	96	90	92
12	2-furyl	**5k**	14	97	89
13	3-thiophenyl	**5l**	72	95	84
14	2-thiophenyl	**5m**	144	81	90
15	*t*Bu	**5n**	72	91	82
16	*i*Pr	**5o**	48	91	80
17	cyclohexyl	**5p**	72	89	87
18	*n*-heptyl	**5q**	72	88	70

[a] Reaction conditions: aldehyde (1.1 equiv), *p*-anisidine (1.0 equiv), **2b** (*E*/*Z* = 1:2.5, 2 equiv), **3d** (3 mol%), −50 °C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv). [b] Conversion > 99% (HPLC). [c] Isolated yield. [d] Determined through HPLC on chiral stationary phases.

The absolute configuration of the vinylogous Mannich products was established explicitly for **4a** (83% *ee*) through cleavage of the PMP group with subsequent *tert*-butoxycarbonyl (Boc) protection, which delivered the known ester **6** and was applied to all other products in analogy (Scheme 3; $[\alpha]_D^{20} = -23.0$ ($c = 0.4$) for the *S* enantiomer; refs. [16]: $[\alpha]_D^{20} = +27.4$ ($c = 0.4$) for the *R* enantiomer).[17]

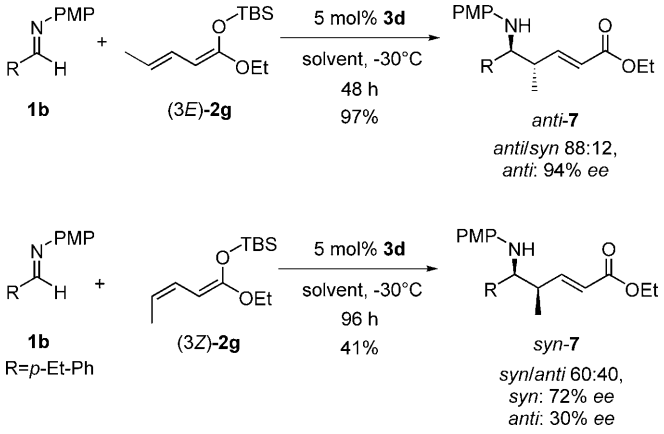


4a 6

Scheme 3. Determination of absolute configuration.

γ-Substituted dienolates: After the successful optimization of the process, we investigated the use of γ-substituted silyl dienolates (*E*)-**2g** and (*Z*)-**2g**, respectively, as nucleophiles in the reaction (Scheme 4). Here an additional stereochemical aspect had to be taken into account: the existence of four double-bond stereoisomers of the substrate. Whereas we had previously observed that the geometry of the double bond directly attached to the acetal moiety had no effect on the stereochemical outcome of the reaction (vide infra), it was of interest to us to study the influence of the geometry of the attached propenyl group.

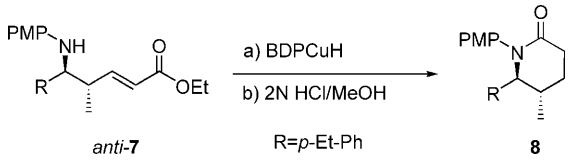
Accordingly, we submitted the stereoisomeric silyl dienolates (3*E*)-**2g** and (3*Z*)-**2g** separately to our model reaction with catalyst **3d** (5 mol%). As can be seen from Scheme 4, the 3*E*-configured silyl dienolate **2g** delivered vinylogous



Scheme 4. Vinylogous Mannich reaction of substituted acyclic silyl dienolates (3*E*)-**2g** and (3*Z*)-**2g**.

Mannich product *anti*-**7** in 97% yield and with excellent enantioselectivity of 94% *ee* and good diastereoselectivity of 88:12. On the other hand, 3*Z*-configured silyl dienolate **2g** did not give rise to a high-yielding reaction, even after prolonged reaction time, and furnished Mannich product *syn*-**7** in only very moderate yield and low enantio- and diastereoselectivity.[18]

Determination of the relative configuration of *anti*-**7** was accomplished through Stryker reduction and cyclization under acidic conditions to afford lactam **8**, the configuration of which was unambiguously proven by *J* coupling constants and NOESY measurements (Scheme 5).

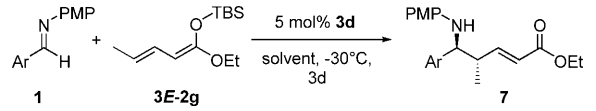


Scheme 5. Determination of the relative configuration of Mannich product *anti*-**7**.

Subsequently, we submitted a range of different aromatic imines to the phosphoric acid (**3d**)-catalyzed vinylogous Mannich reaction with silyl dienolate (3*E*)-**2g** and obtained δ-amino esters *anti*-**7a**–**j** in moderate to good yields, good diastereoselectivities, as well as typically excellent enantioselectivities above 90% *ee* (Table 6). We note that both aromatic as well as heteroaromatic aldimines proved to be good substrates for this reaction.

Mechanistic investigations: In previous studies, we had found a solvent system containing equal amounts of *t*BuOH, 2-methyl-2-butanol, and THF with 1 equiv of water to be optimal for the Mukaiyama-type vinylogous Mannich reaction of silyl dienolates.[10a] In particular, the alcohol components were shown to be important for the rate of the reaction with the small water content further accelerating the reaction. 2-Methyl-2-butanol was used as additional solvent to keep the mixture liquid at the lowest possible reaction temperature. On the other hand, THF had a beneficial effect on the selectivity of the reaction.

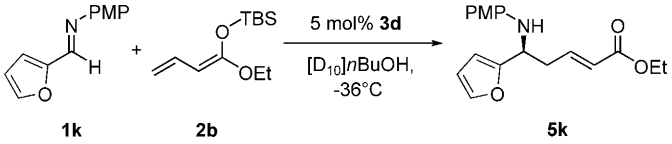
Table 6. Scope of the two-component vinylogous Mannich reaction.[a]



Entry	R	Product **7**	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Ph	**7b**	75	94:6	96
2	*p*-Et-Ph	**7a**	97[e]	88:12	94
3	*p*-Cl-Ph	**7c**	35	88:12	92
4	*m*-Me-Ph	**7d**	77	91:9	97
5	*m*-Cl-Ph	**7e**	43	94:6	93
6	*o*-Me-Ph	**7f**	44	88:12	90
7	*o*-I-Ph	**7g**	82	91:9	92
8	3-pyridyl	**7h**	96	90:10	93
9	3-furyl	**7i**	65	74:26	91
10	2-furyl	**7j**	83	88:12	93

[a] Reaction conditions: **1** (1 equiv), (3*E*)-**2g** (1*E*/1*Z* = 1:1.5, 3 equiv), **3d** (5 mol%), −30 °C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), H_2O (1.0 equiv). [b] Isolated yield. [c] Determined through HPLC and ^{1}H NMR spectroscopy. [d] Determined through HPLC on chiral stationary phases. [e] Reaction complete after 2 d.

To further elucidate the reaction pathway and in particular propose a model for the catalytic turnover, we followed the reaction of imine **1k** with silyl dienolate **2b** in [D_{10}]*n*BuOH online by ^{1}H NMR spectroscopy (Scheme 6,



Scheme 6. Online NMR spectroscopic investigation with imine **1k**.

Figures 1 and 2). Over the course of the reaction, the amount of imine and nucleophile decreased as the signals of product **5k** and *tert*-butyldimethysilyl (TBS)−OH/TBS−OD and TBS−O[D_{10}]*n*Bu gradually increased. The formation of TBS−OH was presumably caused by adventitious water present in the reaction mixture. In our standard reaction mixture containing 1 equiv of water, TBS−OH was formed exclusively as byproduct of the reaction, as was identified by NMR spectroscopy and comparison with a reference sample. This observation is consistent with the assumption that the cationic silicon species generated upon nucleophilic addition to the imine is trapped immediately by the solvent mixture as TBS−OH. In addition, this implies that the phosphate anion is readily protonated by the protic medium to regenerate the active catalyst, which was additionally proved by ESIMS (vide infra).

Another important conclusion that was drawn from the online NMR spectroscopy experiment is related to the *E*/*Z* ratio of silyl dienolate **2b**, which we have always employed

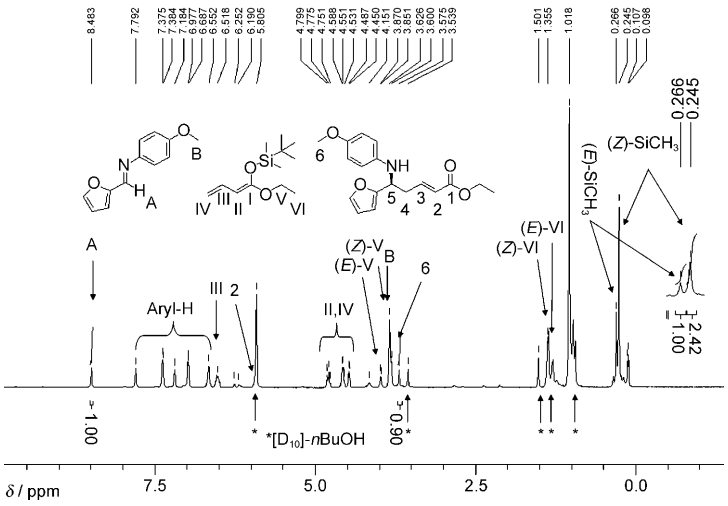


Figure 1. Online NMR spectrum (600 MHz, $[D_{10}]n$BuOH) after 10 min at −36 °C (23 % conversion).

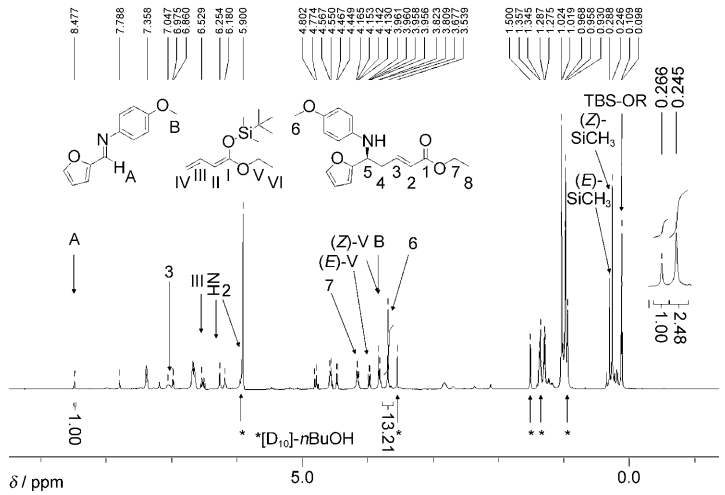
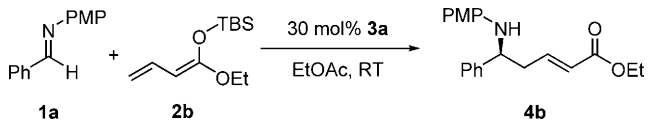


Figure 2. Online NMR spectrum (600 MHz, $[D_{10}]n$BuOH) after 80 min at −36 °C (80 % conversion).

as a 1:2.5 (*E*/*Z*) mixture. Over the course of the entire reaction, this ratio remained virtually constant, thereby suggesting that both isomers either reacted with very similar rates and selectivities or isomerized readily under the reaction conditions.

To further substantiate this mechanistic proposal and possibly detect reaction intermediates we decided to follow the reaction by ESI mass spectrometry (Scheme 7). Because the reaction was too rapid under the established conditions at room temperature to follow by ESIMS, we employed an aprotic solvent such as ethyl acetate for the ESIMS experiments in an attempt to slow down the reaction and detect relevant reaction intermediates.[19,20]



1a 2b 4b

Scheme 7. Model reaction for ESIMS/MS.

A prominent complex with *m*/*z* 1024.5 was detected in ethyl acetate; this represented the contact ion pair **10** (Figure 3). In addition, the protodesilylated counterion pair with *m*/*z* 910.4 was also observed.

To further identify the observed peaks, ESIMS/MS experiments were conducted (Figure 4). In the ion trap, the complex *m*/*z* 1024.5 fragmented predominantly into the TBS-protected catalyst (*m*/*z* 669) and vinylogous Mannich product **4b** (*m*/*z* 326). The assignment of the detected species was further supported through high-resolution masses (Table 7).

On the basis of the accumulated NMR spectroscopic and MS data, we propose that complex *m*/*z* 1024.5 is formed as the initial reaction product by nucleophilic addition of silyl

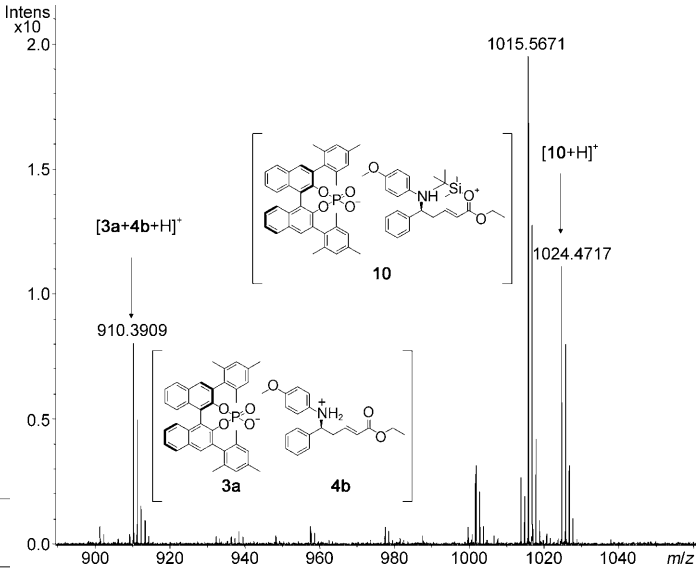


Figure 3. Part of the ESIMS spectrum of the reaction represented in Scheme 6 after 2 h at RT.

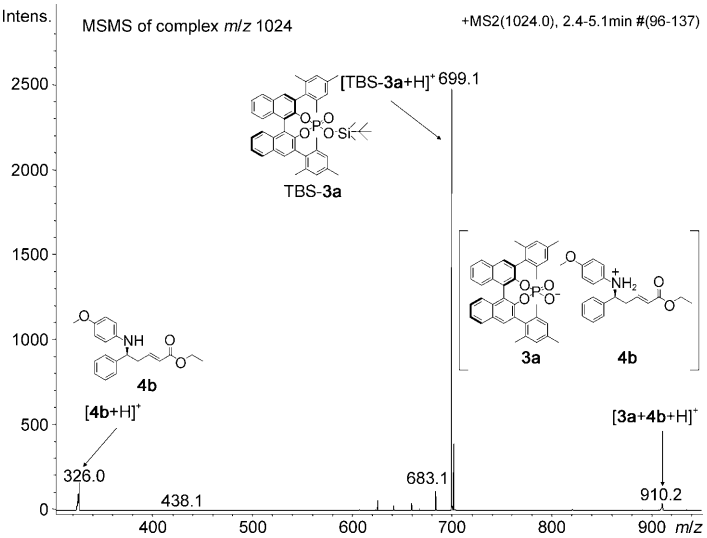
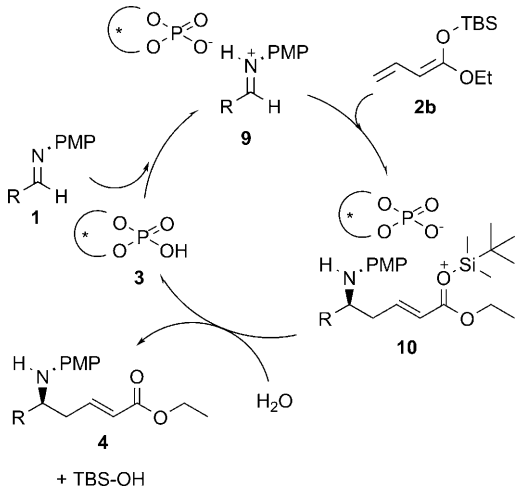


Figure 4. ESIMS/MS spectrum of complex *m*/*z* 1024.5.

Table 7. High-resolution mass data of detected species.

Species[a]	Mass (calcd)	Mass (found)	Formula	Error [ppm]
[**4b**+H]$^+$	326.17507	326.17518	$C_{20}H_{24}NO_3$	0.3
[TBS-**3a**+H]$^+$	699.30540	699.30690	$C_{44}H_{47}O_4PSi$	2.0
[**10**+H]$^+$	1024.47319	1024.47144	$C_{64}H_{71}NO_7PSi$	1.7
[**3a**+2**4b**+H]$^+$	1235.57291	1235.57001	$C_{78}H_{80}N_2O_{10}P$	2.0

dienolate **2b** to imine **1a**. This counterion pair **10** is subsequently hydrolyzed into vinylogous Mannich product **4b** and TBS–OH with concomitant regeneration of Brønsted acid catalyst **3a** (Scheme 8). We cannot rule out, however,



Scheme 8. Proposed catalytic cycle.

that the silylated Brønsted acid catalyst TBS-**3a** is formed first from counterion pair **10**, as detected in the ESIMS/MS experiment, which is subsequently hydrolyzed to generate phosphoric acid **3a** and TBS–OH. In the aqueous reaction medium, the lifetime of TBS-**3a** should, however, be very short, if it exists at all.[21]

Crystal structure of an imine-bound phosphoric acid: To shed some light on the way the chiral Brønsted acid binds to the imine and possibly on the origin of asymmetric induction, we attempted a cocrystallization of phosphoric acid **3d** and benzaldimine **1a**. Single crystals suitable for X-ray diffraction analysis were eventually obtained by slow evaporation of a solution of both components in $CHCl_3$. The iminium phosphate crystallized as a dimer in a "crown ether" arrangement in which the space group symmetry C_2 is generated by a twofold rotation axis. For the sake of clarity, Figure 5 only shows the monomer of this iminium phosphate. As there is no significant difference in the bond lengths between P1–O3 (1.476(3) Å) and P1–O4 (1.464(4) Å), we conclude that the hydrogen atom is most likely localized on the N2 atom. Thus, the adduct can be formulated as a close-contact ion pair of the composition $[C_{44}H_{45}PO_4]^-[C_{14}H_{13}NO]^+$. Moreover, the iminium ion is

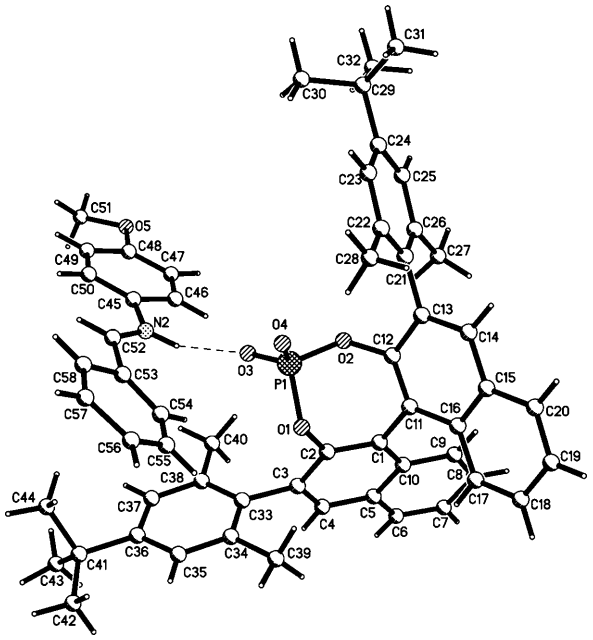


Figure 5. Crystal structure of the imine (**1a**)–phosphoric acid (**3d**) adduct. Both selected bond lengths P1–O1 and P1–O2 are 1.613(3) Å. Hence, these bonds can be considered to be P–O single bonds. Bond lengths between P1–O3 and P1–O4 are 1.476(3) and 1.464(4) Å, respectively.

fixed by a strong N–H···O bond (N2–H 0.87 Å, N2–O3 2.653(6) Å, N2-H2-O3 160.2°).

Figure 5 suggests that the right upper *Re* face of the iminium ion is effectively shielded by the 3-aryl group at C13 (X-ray numbering). Hence the nucleophilic attack of silyl dienolate **2b** is directed to the opposite *Si* face, which is consistent with the predominant formation of the *S* enantiomer **4a** as discussed above. It also nicely supports the important role that the *para-t*Bu group within the 3-aryl group acts in blocking the upper side even more efficiently and making Brønsted acid **3d** the more enantioselective catalyst.

Conclusion

We have established the first catalytic, enantioselective, vinylogous Mannich reaction of acyclic silyl dienolates to furnish valuable δ-amino α,β-unsaturated esters **4** in excellent yields and regioselectivity as well as typically good to very good enantioselectivity of up to 97% *ee*. A second-generation chiral Brønsted acid catalyst **3d** was developed that increased the previously obtained enantioselectivities substantially. The γ-substituted silyl dienolate (3*E*)-**2g** furnished vinylogous Mannich products with two new stereogenic centers that were established with good diastereo- and high enantioselectivity. Mechanistic investigations including NMR spectroscopy and mass spectrometry led to the conclusion that the protic reaction medium, which has been found optimal for the reaction, serves to trap the cationic silicon species as silanol and to regenerate the chiral Brønst-

ed acid catalyst through protonation. A crystal structure of the imine-bound chiral catalyst was obtained, which revealed that one of the 3-aryl groups within the Brønsted acid catalyst shields the *Re* face of the imine, thereby directing the incoming nucleophile to the opposite side.

Experimental Section

General: All vinylogous Mannich reactions were performed in flame-dried glassware under an air atmosphere. Preparation of catalysts and nucleophiles was performed in flame-dried glassware under an atmosphere of dry nitrogen or argon. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (CaH_2), tetrahydrofuran ($LiAlH_4$, triphenylmethane), diethyl ether (Na, benzophenone), toluene (Na, benzophenone), *N*,*N*-dimethylformamide (Acros ACS grade), acetonitrile (Acros ACS grade), and chloroform (Acros ACS grade). Diethyl ether, petroleum ether, and ethyl acetate for chromatography were of technical grade and distilled from KOH or $CaCl_2$. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel SIL G/UV254 plates (Machery, Nagel & Co.) or HPLC; spots were visualized by treatment with a solution of vanillin (0.5 g), concentrated acetic acid (10 mL), and concentrated H_2SO_4 (5 mL) in methanol (90 mL) or molybdophosphoric acid (5 g) in ethanol (250 mL). Flash column chromatography was performed by using Merck silica gel 60 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded using VARIAN Gemini 200 (200 MHz) and VARIAN Gemini 300 (300 MHz) spectrometers, or a Bruker Avance DRX 400 (400 MHz) spectrometer in $CDCl_3$ at 25 °C with TMS as internal standard. Online NMR spectroscopic investigations were recorded using a Bruker DRX-600 (600 MHz). IR spectra were obtained using a FTIR spectrometer (Genesis ATI, Mattson/Unicam). UV spectra were obtained using a Beckmann DU-650 spectrometer. Melting points are uncorrected. Optical rotations were measured using a Polarotronic polarometer (Schmidt & Haensch). HPLC analyses were performed using a JASCO MD-2010 plus instrument with a chiral stationary phase column (Chiralcel OD, ODH, OJ, ADH purchased from Daicel Co., Ltd.). Mass spectra were measured at 70 eV (EI) using a Finnigan MAT 95A spectrometer. High-resolution mass spectra (HRMS; ESI/Na^+) were measured using a Bruker Daltonics APEX II FT-ICR spectrometer. ESIMS/MS were measured using a Bruker Daltonics Esquire 3000+. The nucleophiles **2** were prepared according to the literature.[14,18,22]

General procedure for three-component vinylogous Mannich reaction (Table 5): In an oven-dried 10 mL flask, a solution of *p*-anisidine (0.40 mmol, 1.00 equiv) and chiral phosphoric acid **3d** (8.0 mg, 0.012 mmol, 0.03 equiv) in a freshly prepared solvent mixture (THF, *t*BuOH, 2-Me-2-BuOH 1:1:1 and 1.0 equiv H_2O; 2.50 mL) was stirred for 1 min at RT, after which the respective aldehyde (0.44 mmol, 1.10 equiv) was added and the mixture was cooled to −50 °C. Subsequently dienolate **2b** (185 mg, 0.80 mmol, 2.00 equiv, *E*/*Z* 1:2.5) was added in one portion. The resulting mixture was stirred rapidly for the indicated times, whereupon the solvent was removed in vacuo. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:5) to afford the vinylogous Mannich products. In all cases, the data are given for the 2*E*,5*S* isomer (except for **5q**: 2*E*,5*R*).

Compound 4b: 18 h; yield 97 %; 95 % *ee*; R_f = 0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$ = +30.7 (*c* = 2.0 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.10 (m, 5H; ArH), 6.90 (dt, *J* = 15.5, 7.5 Hz, 1H; 3-CH), 6.68 (m, 2H; ArH), 6.46 (m, 2H; ArH), 5.91 (dt, *J* = 15.5, 0.5 Hz, 1H; 2-CH), 4.42 (dd, *J* = 7.5, 6.0 Hz, 1H; N-CH), 4.18 (q, *J* = 7.0 Hz, 2H; O-CH_2), 3.69 (s, 3H; O-CH_3), 2.70 (m, 2H; CH_2), 1.28 ppm (t, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 152.4, 144.3, 142.8, 140.9, 128.9, 127.5, 126.4, 124.3, 114.8, 114.7, 60.52, 57.87, 55.82, 41.42, 14.36 ppm; IR (film): $\tilde{\nu}$ = 3389, 3060, 3027, 2981, 2933, 2832, 1713, 1653, 1618, 1511, 1452, 1384, 1237, 1160, 1095, 1038, 982, 820, 756, 702 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 245 (4.343), 308 nm (3.868); MS (ESI): *m*/*z* (%): 348 (40) $[M+Na]^+$, 651 (10) $[2M+H]^+$, 673 (100) $[2M+Na]^+$; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ = 250 nm; 76.19 (5*R*), 81.14 min (5*S*); elemental analysis calcd (%) for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found: C 73.64, H 7.05, N 4.29.

Compound 5a: 12 h; yield 93 %; 97 % *ee*; R_f = 0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$ = +7.7 (*c* = 0.7 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 2H; ArH), 7.17 (m, 2H; ArH), 6.94 (dt, *J* = 15.5, 7.5 Hz, 1H; 3-CH), 6.71 (m, 2H; ArH), 6.49 (m, 2H; ArH), 5.94 (dt, *J* = 15.5, 1.5 Hz, 1H; 2-CH), 4.43 (dd, *J* = 7.0, 6.0 Hz, 1H; N-CH), 4.19 (q, *J* = 7.0 Hz, 2H; O-CH_2), 3.84 (s, 1H; NH), 3.70 (s, 3H; O-CH_3), 2.72–2.60 (m, 4H; CH_2, $ArCH_2$), 1.30 (t, *J* = 7.0 Hz, 3H; CH_3), 1.24 ppm (t, *J* = 7.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 152.1, 145.0, 143.3, 141.2, 140.1, 128.3, 126.3, 124.1, 114.8, 114.8, 60.43, 57.58, 55.85, 41.37, 28.52, 15.52, 14.32 ppm; IR (film): $\tilde{\nu}$ = 3391, 2963, 2932, 2831, 2066, 1905, 1715, 1694, 1618, 1512, 1441, 1367, 1311, 1238, 1179, 1160, 1114, 1095, 1039, 981, 819, 759, 713, 550, 520 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 244 (4.297), 311 nm (3.722); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064; found: 354.2063; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 80:20, flow 1.0 mL min^{-1}): λ = 250 nm; 11.12 (5*R*), 13.90 min (5*S*).

Compound 5b: 144 h; yield 40 %; 93 % *ee*; R_f = 0.15 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$ = +15.6 (*c* = 0.9 in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (m, 2H; ArH), 7.54 (m, 2H; ArH), 6.87 (dt, *J* = 15.5, 7.5, 0.5 Hz, 1H; 3-CH), 6.68 (m, 2H; ArH), 6.47 (m, 2H; ArH), 5.90 (dt, *J* = 15.5, 0.5 Hz, 1H; 2-CH), 4.38 (t, *J* = 7.0 Hz, 1H; 5-CH), 4.18 (q, *J* = 7.0 Hz, 2H; O-CH_2), 3.79 (s, 3H; O-CH_3), 3.69 (s, 3H; O-CH_3), 2.70 (m, 2H; CH_2), 1.28 ppm (t, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 158.5, 151.9, 144.4, 140.6, 134.4, 127.0, 123.8, 114.6, 114.4, 113.8, 60.03, 56.88, 55.38, 54.91, 40.98, 14.36 ppm; IR (film): $\tilde{\nu}$ = 3401, 2994, 2933, 2833, 1717, 1654, 1611, 1511, 1463, 1441, 1368, 1302, 1245, 1178, 1110, 1095, 1039, 983, 819, 787, 761, 548 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 247 (4.439), 309 nm (3.888); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1856; found: 356.1857; enantiomeric assay: Chiralcel OD, isocratic (hexane/2-propanol 90:10, flow 0.5 mL min^{-1}): λ = 250 nm; 27.17 (5*R*), 30.10 min (5*S*).

Compound 5c: 48 h; yield 97 %; 90 % *ee*; R_f = 0.25 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$ = +39.6 (*c* = 2.1 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 2H; ArH), 7.04–6.98 (m, 2H; ArH), 6.87 (dt, *J* = 15.5, 7.5 Hz, 1H; 3-CH), 6.68 (m, 2H; ArH), 6.44 (m, 2H; ArH), 5.90 (dt, *J* = 15.5, 1.5 Hz, 1H; 2-CH), 4.41 (t, *J* = 7.0 Hz, 1H; N-CH), 4.18 (q, *J* = 7.0 Hz, 2H; O-CH_2), 3.69 (s, 3H; O-CH_3), 2.65 (m, 2H; CH_2), 1.28 ppm (t, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 162.0 (*J*(C,F) = 245.0 Hz), 152.6, 144.2, 140.8, 138.1 (d, *J*(C,F) = 3.0 Hz), 128.0 (d, *J*(C,F) = 8.0 Hz), 124.7, 115.7 (*J*(C,F) = 21.5 Hz), 115.3, 114.8, 60.58, 57.45, 55.79, 41.31, 14.35 ppm; IR (film): $\tilde{\nu}$ = 3389, 3060, 3027, 2981, 2933, 2832, 1713, 1653, 1618, 1511, 1452, 1384, 1237, 1160, 1095, 1038, 982, 820, 756, 702 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 243 (4.115), 309 nm (3.217); MS (ESI): *m*/*z* (%): 124 (100), 344 (80) $[M+H]^+$; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ = 250 nm; 42.46 (5*R*), 44.88 min (5*S*); elemental analysis calcd (%) for $C_{20}H_{22}FNO_3$: C 69.95, H 6.46, N 4.08; found: C 69.82, H 6.45, N 4.12.

Compound 5d: 48 h; yield 95 %; 88 % *ee*; R_f = 0.25 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$ = +27.6 (*c* = 1.3 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.14 (m, 3H; ArH), 7.06 (d, *J* = 7.0 Hz, 1H; ArH), 6.93 (dt, *J* = 15.5, 7.5 Hz, 1H; 3-CH), 6.70 (m, 2H; ArH), 6.48 (m, 2H; ArH), 5.93 (d, *J* = 15.5 Hz, 1H; 2-CH), 4.40 (dd, *J* = 7.0, 6.0 Hz, 1H; N-CH), 4.19 (q, *J* = 7.0 Hz, 2H; O-CH_2), 3.80 (s, 1H; NH), 3.68 (s, 3H; O-CH_3), 2.73 (ddd, *J* = 14.5, 7.5, 6.0 Hz, 1H; CHH), 2.73 (ddd, *J* = 14.5, 7.5, 7.0 Hz, 1H; CHH), 2.34 (s, 3H; $ArCH_3$), 1.27 ppm (t, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 152.2, 144.9, 142.9, 141.2, 138.4, 128.7, 128.2, 127.0, 124.1, 123.4, 114.9, 114.8, 60.47, 57.83, 55.79, 41.40, 21.65, 14.35 ppm; IR (film): $\tilde{\nu}$ = 3391, 2982, 2932, 2831, 1715, 1653, 1607, 1590, 1513, 1463, 1442, 1367, 1242, 1178, 1119, 1095, 1039, 981, 819, 788, 769, 704, 521, 446 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) = 244 (4.132), 310 nm (3.631); MS (ESI): *m*/*z* (%): 340 (35) $[M+H]^+$, 362 (100) $[M+Na]^+$; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 90:10, flow 0.5 mL min^{-1}): λ = 250 nm; 34.32 (5*R*), 36.84 min

(5*S*); elemental analysis calcd (%) for $C_{21}H_{25}NO_3$: C 74.31, H 7.42, N 4.13; found: C 74.12, H 7.29, N 4.20.

Compound 5e: 6.5 h; yield 97%; 90% *ee*; R_f=0.35 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+24.8 (c=1.9 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (s, 1H; ArH), 7.24–7.21 (m, 3H; ArH), 6.87 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.69 (m, 2H; ArH), 6.45 (m, 2H; ArH), 5.91 (d, J=15.5 Hz, 1H; 2-CH), 4.39 (dd, J=7.5, 5.5 Hz, 1H; N-CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 3.70 (s, 3H; O-CH_3), 2.68 (m, 2H; CH_2), 1.28 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 152.6, 145.3, 144.0, 140.6, 134.8, 130.2, 127.7, 126.6, 124.6, 124.6, 115.0, 114.9, 60.62, 57.51, 55.82, 41.32, 14.36 ppm; IR (film): $\tilde{\nu}$=3389, 2982, 2934, 2832, 1712, 1654, 1619, 1511, 1464, 1368, 1312, 1239, 1191, 1094, 1076, 981, 878, 819, 787, 760, 697, 402 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=243 (4.027), 308 nm (3.556); HRMS (ESI): m/z: calcd for $C_{40}H_{44}Cl_2N_2O_6Na$ $[2M+Na]^+$: 741.2470; found: 741.2470; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 90:10, flow 1.0 mL min^{-1}): λ=250 nm; 23.81 (5*R*), 26.66 min (5*S*).

Compound 5f: 21 h; yield 97%; 90% *ee*; R_f=0.30 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+42.4 (c=1.6 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.36 (m, 1H; ArH), 7.20–7.12 (m, 3H; ArH), 6.95 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.68 (m, 2H; ArH), 6.40 (m, 2H; ArH), 5.93 (d, J=15.5 Hz, 1H; 2-CH), 4.62 (dd, J=9.0, 5.0 Hz, 1H; N-CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 3.68 (s, 3H; O-CH_3), 2.62 (m, 2H; 4-CH_2), 2.43 (s, 3H; ArCH_3), 1.27 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 152.2, 145.0, 141.2, 140.6, 134.8, 127.2, 126.8, 125.3, 124.3, 114.9, 114.6, 60.55, 55.83, 53.94, 39.75, 19.25, 14.28 ppm; IR (film): $\tilde{\nu}$=3393, 2928, 2854, 2832, 1712, 1651, 1620, 1512, 1462, 1384, 1368, 1237, 1162, 1111, 1092, 1040, 981, 819, 782, 756, 727, 627, 552, 482 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.060), 309 nm (3.541); MS (14 eV, EI): m/z (%): 226 (100), 340 (80) $[M]^+$; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 90:10, flow 1.0 mL min^{-1}): λ=250 nm; 14.76 (5*R*), 19.84 min (5*S*); elemental analysis calcd (%) for $C_{21}H_{25}NO_3$: C 74.31, H 7.42, N 4.13; found: C 74.45, H 7.52, N 4.15.

Compound 5g: 6 h; yield 97%; 85% *ee*; R_f=0.25 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+179.8 (c=2.2 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.56 (dd, J=7.5, 1.5 Hz, 1H; ArH); 7.40 (dd, J=7.5, 1.5 Hz, 1H; ArH); 7.24 (td, J=7.5, 1.5 Hz, 1H; ArH), 7.11 (td, J=7.5, 1.5 Hz, 1H; ArH), 6.98 (ddd, J=15.5, 7.5, 6.5 Hz, 1H; CH), 6.68 (m, 2H; ArH), 6.38 (m, 2H; ArH), 5.91 (d, J=15.5 Hz, 1H; CH), 4.83 (dd, J=8.5, 4.0 Hz, 1H; N-CH), 4.19 (q, J=7.0 Hz, 2H; O-CH_2), 3.90 (s, 1H; NH), 3.68 (s, 3H; O-CH_3), 2.79 (dddd, J=15.0, 6.5, 4.0, 1.5 Hz, 1H; CHH), 2.50 (dddd, J=15.0, 8.5, 7.5, 1.0 Hz, 1H; CHH), 1.28 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 152.4, 144.8, 140.6, 132.8, 130.0, 128.6, 127.5, 124.5, 123.1, 114.9, 114.7, 60.57, 56.58, 55.58, 39.37, 14.37 ppm; IR (film): $\tilde{\nu}$=3389, 2982, 2934, 2832, 1712, 1654, 1619, 1511, 1464, 1368, 1312, 1239, 1191, 1094, 1076, 981, 878, 819, 787, 760, 697, 402 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=243 (4.367), 309 nm (3.540); MS (ESI): m/z (%): 404/406 (100) $[M+H]^+$, 426/428 (20) $[M+Na]^+$; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 80:20, flow 0.5 mL min^{-1}): λ=250 nm; 13.70 min (5*R*), 15.67 min (5*S*); elemental analysis calcd (%) for $C_{20}H_{22}BrNO_3$: C 59.42, H 5.48, N 3.46; found: C 59.46, H 5.76, N 3.56.

Compound 5h: 48 h; yield 96%; 87% *ee*; R_f=0.20 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+166.7 (c=1.3 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95 (dd, J=8.0, 1.0 Hz, 1H; ArH), 7.69 (dd, J=8.0, 1.0 Hz, 1H; ArH), 7.55 (ddd, J=8.0, 7.0, 1.0 Hz, 1H; ArH), 7.40 (ddd, J=8.0, 7.0, 1.0 Hz, 1H; ArH), 6.95 (ddd, J=15.5, 8.0, 7.0 Hz, 1H; 3-CH), 6.65 (m, 2H; ArH), 6.37 (m, 2H; ArH), 5.96 (dt, J=15.5, 1.5 Hz, 1H; 2-CH), 5.14 (dd, J=8.5, 4.5 Hz, 1H; N-CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 3.92 (s, 1H; NH), 3.68 (s, 3H; O-CH_3), 2.88 (m, 1H; CHH), 2.58 (dddd, J=15.0, 8.5, 8.0, 1.0 Hz, 1H; CHH), 1.29 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.0, 152.7, 149.1, 143.8, 140.1, 138.6, 133.8, 128.4, 125.2, 124.9, 124.6, 114.9, 114.7, 60.64, 55.79, 53.29, 40.31, 14.37 ppm; IR (film): $\tilde{\nu}$=3390, 2983, 2934, 2833, 1711, 1655, 1619, 1511, 1463, 1441, 1351, 1239, 1161, 1095, 1039, 982, 820, 760, 738, 690, 627 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=247 (4.422), 296 nm (3.967); MS (ESI): m/z (%): 371 (100) $[M+H]^+$, 393 (95) $[M+Na]^+$; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 80:20, flow 1.0 mL min^{-1}): λ=250 nm; 10.96 (5*R*), 13.49 min (5*S*); elemental analysis calcd (%) for $C_{20}H_{22}N_2O_5$: C 64.85, H 5.99, N 7.56, O 21.60; found: C 64.45, H 5.86, N 7.48, O 21.20.

Compound 5i: 144 h; yield 88%; 90% *ee*; R_f=0.25 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+14.7 (c=0.4 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.84–7.81 (m, 4H; ArH), 7.49–7.43 (m, 3H; ArH), 6.95 (dt, J=15.5, 7.0 Hz, 1H; 3-CH), 6.68 (m, 2H; ArH), 6.51 (m, 2H; ArH), 5.94 (d, J=15.5 Hz, 1H; 2-CH), 4.59 (dd, J=7.0, 5.5 Hz, 1H; N-CH), 4.17 (q, J=7.0 Hz, 2H; O-CH_2), 3.67 (s, 3H; O-CH_3), 2.77 (m, 2H; CH_2), 1.27 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 152.4, 144.6, 141.1, 140.5, 133.6, 133.0, 128.8, 128.0, 127.8, 126.3, 125.9, 125.2, 124.5, 124.4, 115.0, 114.9, 60.52, 58.09, 55.82, 41.43, 14.36 ppm; IR (film): $\tilde{\nu}$=3399, 3058, 2983, 2933, 2831, 1717, 1654, 1601, 1512, 1463, 1441, 1368, 1309, 1238, 1178, 1126, 1095, 1040, 982, 893, 857, 818, 787, 761, 624, 521, 478 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=247 (4.141), 316 nm (3.416); MS (70 eV, EI): m/z (%): 262 (100), 375 (80) $[M]^+$; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 80:20, flow 1.5 mL min^{-1}): λ=250 nm; 18.73 (5*R*), 24.99 min (5*S*); elemental analysis calcd (%) for $C_{24}H_{25}NO_3$: C 76.77, H 6.71; found: C 76.56, H 6.57.

Compound 5j: 96 h; yield 90%; 92% *ee*; R_f=0.30 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+6.6 (c=1.1 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (dd, J=1.5, 1.5 Hz, 1H; ArH), 7.28–7.23 (m, 1H; ArH), 6.84 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.68 (m, 2H; CH), 6.48 (m, 2H; ArH), 6.26 (dd, J=1.5, 0.5 Hz, 1H; ArH), 5.82 (dt, J=15.5, 1.5 Hz, 1H; 2-CH), 4.39 (t, J=6.5 Hz, 1H; N-CH), 4.10 (q, J=7.0 Hz, 2H; O-CH_2), 3.65 (s, 3H; O-CH_3), 2.62 (m, 2H; CH_2), 1.20 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 152.6, 144.5, 143.6, 140.9, 139.7, 127.2, 124.4, 115.3, 114.9, 108.9, 60.53, 55.84, 50.21, 39.13, 14.38 ppm; IR (film): $\tilde{\nu}$=3399, 2929, 2854, 2832, 1719, 1654, 1512, 1464, 1441, 1368, 1312, 1243, 1206, 1165, 1096, 1041, 984, 874, 786, 600 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.275), 289 nm (3.751); HRMS (ESI): m/z: calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543; found: 316.1545; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 62.00 (5*R*), 66.67 min (5*S*).

Compound 5k: 14 h; yield 97%; 89% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−51.0 (c=0.5 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32 (dd, J=2.0 Hz, J=1.0 Hz, 1H; ArH), 6.89 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.75 (m, 2H; ArH), 6.58 (m, 2H; ArH), 6.28 (dd, J=3.5, 2.0 Hz, 1H; ArH), 6.16 (d, J=3.5 Hz, 1H; ArH), 5.89 (dt, J=15.5, 1.5 Hz, 1H; 2-CH), 4.57 (t, J=6.5 Hz, 1H; N-CH), 4.17 (q, J=7.0 Hz, 2H; O-CH_2), 3.73 (s, 3H; O-CH_3), 2.62 (td, J=6.5, 1.5 Hz, 2H; 4-CH_2), 1.28 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 154.9, 152.9, 144.2, 141.9, 140.5, 124.4, 115.6, 114.9, 110.4, 106.8, 60.51, 55.81, 52.25, 37.48, 14.38 ppm; IR (film): $\tilde{\nu}$=3373, 2982, 2935, 2832, 1715, 1656, 1620, 1513, 1441, 1368, 1238, 1164, 1119, 1095, 1070, 1039, 982, 914, 883, 739, 598, 522; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.162), 306 nm (3.470); HRMS (ESI): m/z: calcd for $C_{36}H_{43}N_2O_8$ $[2M+H]^+$: 631.3014; found: 631.3018; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 80:20, flow 1.0 mL min^{-1}): λ=250 nm; 9.07 (5*S*), 14.81 min (5*R*).

Compound 5l: 72 h; yield 95%; 84% *ee*; R_f=0.30 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−11.7 (c=0.9 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (dd, J=5.0, 3.0 Hz, 1H; ArH), 7.17–7.12 (m, 1H; ArH), 7.03 (dd, J=5.0, 1.5 Hz, 1H; ArH), 6.90 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.72 (m, 2H; ArH), 6.52 (m, 2H; ArH), 5.90 (dt, J=15.5, 1.5 Hz, 1H; 2-CH), 4.58 (t, J=6.0 Hz, 1H; N-CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 3.72 (s, 3H; O-CH_3), 3.70 (s, 1H; NH), 2.77 (ddd, J=7.5, 6.0, 1.5 Hz, 2H; CH_2), 1.28 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.2, 152.5, 144.6, 144.3, 141.1, 126.5, 126.0, 124.3, 121.2, 115.1, 114.9, 60.50, 55.84, 53.97, 40.07, 14.36 ppm; IR (film): $\tilde{\nu}$=3384, 3102, 2981, 2933, 2831, 1814, 1713, 1652, 1618, 1510, 1441, 1367, 1237, 1177, 1117, 1094, 1036, 982, 892, 858, 820, 787, 692, 656, 521 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.384), 309 nm (3.728); HRMS (ESI): m/z: calcd for $C_{36}H_{43}N_2O_6S_2$ $[2M+H]^+$: 663.2557; found: 663.2562; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 80:20, flow 0.5 mL min^{-1}): λ=250 nm; 30.06 (5*R*), 33.63 min (5*S*).

Compound 5m: 144 h; yield 81%; 90% *ee*; R_f=0.25 (ethyl acetate/petroleum ether: 1:5); $[\alpha]_D^{22}$=+18.4 (c=1.0 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.19 (dd, J=5.0, 1.0 Hz, 1H; ArH), 6.97–6.87 (m, 3H; CH, 3-CH, ArH), 6.74 (m, 2H; ArH), 6.58 (m, 2H; ArH), 5.91 (d, J=15.5 Hz, 1H; 2-CH), 4.74 (t, J=6.5 Hz, 1H; N-CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 3.72 (s, 3H; O-CH_3), 2.81 (t, J=6.5 Hz, 2H; CH_2), 1.28 ppm (t, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 152.8, 147.8, 144.1, 140.7, 127.0, 124.6, 124.3, 124.0, 115.5, 114.9, 60.50, 55.77, 54.15, 41.09, 14.34 ppm; IR (film): $\tilde{\nu}$=3379, 3104, 3066, 3031, 2982, 2934, 2903, 2831, 1712, 1653, 1617, 1592, 1513, 1483, 1441, 1408, 1368, 1239, 1176, 1116, 1094, 1038, 980, 851, 820, 794, 757, 704, 578, 521 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.162), 306 nm (3.470); HRMS (ESI): m/z: calcd for $C_{18}H_{22}NO_3S$ $[M+H]^+$: 332.1315; found: 332.1316; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 90:10, flow 1.0 mL min^{-1}): λ=250 nm; 24.25 (5*R*), 27.20 min (5*S*).

Compound 5n: 72 h; yield 91%; 82% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+21.2 (c=0.4 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.95 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.72 (m, 2H; ArH), 6.52 (m, 2H; ArH), 5.80 (dt, J=15.5, 1.0 Hz, 1H; 2-CH), 4.12 (q, J=7.0 Hz, 2H; O-CH_2), 3.73 (s, 3H; O-CH_3), 3.19 (s, 1H; NH), 3.15 (dd, J=9.0, 4.0 Hz, 1H; N-CH), 2.58 (dddd, J=14.5, 7.5, 4.0, 1.0 Hz, 1H; CHH), 2.20 (dddd, J=14.5, 9.0, 7.5, 1.0 Hz, 1H; CHH), 1.20 (t, J=7.0 Hz, 3H; CH_3), 0.96 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.4, 151.8, 147.6, 143.3, 122.8, 115.1, 114.5, 62.91, 60.22, 55.94, 36.20, 35.20, 27.08, 14.36 ppm; IR (film): $\tilde{\nu}$=3395, 2956, 2831, 1713, 1650, 1618, 1511, 1440, 1367, 1234, 1159, 1095, 1042, 979, 817, 752, 522 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=245 (3.995), 315 nm (3.411); HRMS (ESI): m/z: calcd for $C_{18}H_{28}NO_3$ $[M+H]^+$: 306.2064; found: 306.2063; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 20.69 (5*R*), 22.41 min (5*S*).

Compound 5o: 48 h; yield 91%; 80% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+48.5 (c=0.4 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.96 (dt, J=15.5, 7.0 Hz, 1H; 3-CH), 6.75 (m, 2H; ArH), 6.52 (m, 2H; ArH), 5.84 (d, J=15.5 Hz, 1H; 2-CH), 4.17 (q, J=7.0 Hz, 2H; O-CH_2), 3.74 (s, 3H; O-CH_3), 3.28 (m, 2H; N-CH, NH), 2.44 (dddd, J=14.5, 9.0, 7.0, 1.5 Hz, 1H; CHH), 2.34 (dddd, J=14.5, 7.0, 7.0, 1.5 Hz, 1H; CHH), 1.87 (m, 1H; CH), 1.27 (t, J=7.0 Hz, 3H; CH_3), 1.27 (d, J=7.0 Hz, 3H; CH_3), 1.27 ppm (d, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 151.0, 146.2, 141.9, 123.4, 115.1, 114.8, 60.30, 58.77, 55.89, 34.16, 30.78, 18.80, 18.43, 14.34 ppm; IR (film): $\tilde{\nu}$=3391, 2958, 2831, 1714, 1651, 1619, 1512, 1441, 1386, 1235, 1177, 1095, 1041, 981, 819, 755, 712, 586, 520 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=245 (4.028), 315 nm (3.464); MS (ESI): m/z (%): 292 (50) $[M+H]^+$, 314 (100) $[M+Na]^+$; enantiomeric assay (determination after reduction with diisobutylaluminium hydride (DIBAL) to corresponding allyl alcohol): Chiralcel OD-H, isocratic (hexane/2-propanol 80:20, flow 1.0 mL min^{-1}): λ=250 nm; 6.57 (5*S*), 7.72 min (5*R*); elemental analysis calcd (%) for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81; found: C 69.96, H 8.48, N 4.81.

Compound 5p: 72 h; yield 89%; 87% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+16.5 (c=0.6 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.96 (dt, J=15.5, 7.0 Hz, 1H; 3-CH), 6.75 (m, 2H; ArH), 6.52 (m, 2H; ArH), 5.84 (dt, J=15.5, 1.5 Hz, 1H; 2-CH), 4.17 (q, J=7.0 Hz, 2H; O-CH_2), 3.74 (s, 3H; O-CH_3), 3.38 (s, 1H; NH), 3.26 (ddd, J=9.0, 5.5, 5.5 Hz, 1H; N-CH), 2.44 (dddd, J=14.5, 9.0, 7.0, 1.5 Hz, 1H; CHH), 2.34 (dddd, J=14.5, 7.0, 5.5, 1.5 Hz, 1H; CHH), 1.85–1.00 ppm (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 151.9, 146.3, 142.0, 123.5, 115.2, 114.7, 60.35, 58.32, 55.93, 41.24, 34.41, 29.56, 29.19, 26.65, 26.44, 26.41, 14.41 ppm; IR (film): $\tilde{\nu}$=3392, 2980, 2926, 2851, 1715, 1651, 1618, 1511, 1448, 1367, 1317, 1237, 1179, 1113, 1096, 1042, 978, 892, 818, 754, 520 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=246 (4.062), 313 nm (3.505); MS (ESI): m/z (%): 332 (50) $[M+H]^+$, 354 (100) $[M+Na]^+$; enantiomeric assay (determination after reduction with DIBAL to corresponding allyl alcohol): Chiralcel OD-H, isocratic (hexane/2-propanol 80:20, flow 1.0 mL min^{-1}): λ=250 nm; 6.53 (5*S*), 7.65 min (5*R*); elemental analysis calcd (%) for $C_{20}H_{29}NO_3$: C 72.47, H 8.82, N 4.23; found: C 72.37, H 8.47, N 4.23.

Compound 5q: 72 h; yield 88%; 70% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=+30.6 (c=0.4 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.97 (dt, J=15.5, 7.5 Hz, 1H; 3-CH), 6.79 (m, 2H; ArH), 6.55 (m, 2H; ArH), 5.86 (d, J=15.5 Hz, 1H; 2-CH), 4.19 (q, J=7.0 Hz, 2H; O-CH_2), 3.76 (s, 3H; O-CH_3), 3.65 (pent, J=6.5 Hz, 1H; N-CH), 3.22 (s, 1H; NH), 2.44 (m, 2H; CH_2), 1.60–1.00 (m, 15H; (CH_2)$_6$, CH_3), 0.88 ppm (t, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 152.2, 145.6, 141.5, 123.8, 115.2, 114.9, 60.41, 55.96, 53.34, 37.75, 34.75, 31.93, 29.71, 29.37, 26.22, 22.77, 14.41, 14.23 ppm; IR (film): $\tilde{\nu}$=3389, 2928, 2855, 1719, 1652, 1511, 1464, 1368, 1317, 1242, 1178, 1095, 1043, 983, 877, 819, 787, 762 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (3.989), 310 nm (3.426); MS (ESI): m/z (%): 348 (80) $[M+H]^+$, 360 (100) $[M+Na]^+$; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 98:2, flow 0.5 mL min^{-1}): λ=250 nm; 30.31 (5*R*), 32.96 min (5*S*); elemental analysis calcd (%) for $C_{21}H_{33}NO_3$: C 72.58, H 9.57, N 4.03; found: C 72.54, H 9.72, N 3.78.

General procedure for two-component vinylogous Mannich reaction (Table 6): An oven-dried, 10 mL flask containing a solution of aldimine (0.400 mmol, 1.00 equiv) and chiral phosphoric acid **3d** (13.4 mg, 0.020 mmol, 0.05 equiv) in a freshly prepared solvent mixture (THF, *t*BuOH, 2-Me-2-BuOH 1:1:1 and H_2O (1.0 equiv); 2.50 mL) was cooled to −30 °C. Subsequently dienolate (3*E*)-**2g** (290 mg, 1.20 mmol, 3.00 equiv) was added in one portion. The resulting mixture was stirred rapidly at −30 °C for 72 h after which the solvent was removed in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:10) to afford vinylogous Mannich product in the indicated yield and *ee* values. In all cases, the data is given for the 2*E*,4*S*,5*S* isomer.

Compound *anti*-7a: 48 h; yield 97%; *anti*/*syn*: 88:12, *anti*: 94% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−33.2 (c=0.7 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–7.23 (m, 2H; ArH), 7.14 (m, 2H; ArH), 6.93 (dd, J=15.5, 7.5 Hz, 1H; CH), 6.71 (m, 2H; ArH), 6.49 (m, 2H; ArH), 5.93 (dd, J=15.5, 1.5 Hz, 1H; CH), 4.19 (q, J=7.0 Hz, 2H; O-CH_2), 4.13 (d, J=7.0 Hz, 1H; N-CH), 3.82 (s, 1H; NH), 3.67 (s, 3H; O-CH_3), 2.66–2.59 (m, 3H), 1.30 (t, J=7.0 Hz, 3H; CH_3), 1.24 (t, J=7.5 Hz, 3H; CH_3), 1.04 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 152.1, 150.7, 143.3, 141.5, 139.1, 128.1, 127.3, 122.4, 114.8, 114.8, 62.95, 60.53, 55.85, 40.08, 28.59, 17.17, 15.51, 14.39 ppm; IR (film): $\tilde{\nu}$=3399, 2929, 1713, 1650, 1504, 1441, 1384, 1039, 876, 819, 767, 554 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=246 (4.220), 310 nm (3.686); HRMS (ESI): m/z: calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220; found: 368.2220; enantiomeric assay: Chiralcel OD, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 19.73 (4*S*,5*S*), 23.48 min (4*R*,5*R*).

Compound *anti*-7b: Yield 75%; *anti*/*syn*: 94:6, *anti*: 96% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−6.5 (c=1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31–7.22 (m, 5H; ArH), 6.95 (dd, J=16.0, 8.0 Hz, 1H; CH), 6.66 (m, 2H; ArH), 6.44 (m, 2H; ArH), 5.93 (dd, J=16.0, 1.5 Hz, 1H; CH), 4.18 (q, J=7.0 Hz, 2H; O-CH_2), 4.15 (d, J=7.0 Hz, 1H; N-CH), 3.67 (s, 3H; O-CH_3), 2.69 (m, 1H; CH), 1.30 (t, J=7.0 Hz, 3H; CH_3), 1.04 ppm (d, J=6.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 152.2, 150.4, 141.9, 141.4, 128.6, 127.4, 127.3, 122.5, 114.8, 114.8, 63.25, 60.58, 55.85, 44.05, 17.17, 14.38 ppm; IR (film): $\tilde{\nu}$=3401, 2980, 2933, 2832, 1715, 1650, 1513, 1453, 1384, 1280, 1180, 1040, 985, 820, 788, 762, 702 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=245 (4.229), 309 nm (3.656); HRMS (ESI): m/z: calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907; found: 340.1907; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 25.49 (4*S*,5*S*), 29.25 min (4*R*,5*R*).

Compound *anti*-7c: Yield 35%; *anti*/*syn*: 88:12, *anti*: 92% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−36.5 (c=0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30–7.25 (m, 4H; ArH), 6.89 (dd, J=16.0, 8.0 Hz, 1H; CH), 6.66 (m, 2H; ArH), 6.41 (m, 2H; ArH), 5.93 (dd, J=16.0, 1.5 Hz, 1H; CH), 4.21 (q, J=7.0 Hz, 2H; O-CH_2), 4.14 (d, J=7.0 Hz, 1H; N-CH), 3.67 (s, 3H; O-CH_3), 2.64 (m, 1H; CH), 1.30 (t, J=7.0 Hz, 3H; CH_3), 1.04 ppm (d, J=7.0 Hz, 3H; CH-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.2, 152.3, 149.7, 141.1, 139.3, 133.2, 128.9, 128.7, 122.9, 115.5, 114.8, 62.99, 60.63, 55.80, 43.68, 16.97, 14.36 ppm; IR (film): $\tilde{\nu}$=3398, 2980, 2932, 2832, 1716, 1651, 1595, 1512, 1489, 1463, 1409, 1384, 1242, 1180, 1014, 1038, 1014, 982, 819, 761, 521 cm^{-1}; UV/Vis ($CHCl_3$):

λ_{max} ($\log\varepsilon$)=244 (3.995), 310 nm (3.402); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{25}ClNO_3$ $[M+H]^+$: 374.1517; found: 374.1515; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 30.57 (4*S*,5*S*), 40.61 min (4*R*,5*R*).

Compound *anti*-7d: Yield 77%; *anti*/*syn*: 91:9, *anti*: 97% *ee*; R_f=0.50 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=-15.6$ (c=2.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24–7.04 (m, 4H; ArH), 6.99 (dd, J=16.0, 8.0 Hz, 1H; CH), 6.68 (m, 2H; ArH), 6.48 (m, 2H; ArH), 5.93 (dd, J=16.0, 1.5 Hz, 1H; CH), 4.22 (q, J=7.0 Hz, 2H; O-CH_2), 4.13 (d, J=6.5 Hz, 1H; N-CH), 3.67 (s, 3H; O-CH_3), 2.66 (m, 1H; CH), 2.34 (s, 3H; CH_3), 1.31 (t, J=7.0 Hz, 3H; CH_3), 1.04 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 152.1, 150.6, 141.8, 141.3, 137.9, 128.4, 128.3, 128.0, 124.5, 122.4, 115.9, 114.8, 66.31, 60.47, 55.75, 43.93, 21.61, 17.13, 14.33 ppm; IR (film): $\tilde{\nu}$=3399, 2931, 2831, 1713, 1650, 1606, 1512, 1442, 1384, 1242, 1180, 1094, 1037, 985, 865, 819, 788, 766, 704 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.107), 312 nm (3.552); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064; found: 354.2064; enantiomeric assay: Chiralcel OJ, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 17.93 (4*S*,5*S*), 19.81 min (4*R*,5*R*).

Compound *anti*-7e: Yield 43%; *anti*/*syn*: 94:6, *anti*: 93% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=-11.9$ (c=1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33 (m, 1H; ArH), 7.22–7.17 (m, 3H; ArH), 6.98 (dd, J=16.0, 8.0 Hz, 1H; CH), 6.67 (m, 2H; ArH), 6.41 (m, 2H; ArH), 5.93 (dd, J=16.0, 1.0 Hz, 1H; CH), 4.23 (q, J=7.0 Hz, 2H; O-CH_2), 4.11 (d, J=6.5 Hz, 1H; N-CH), 3.67 (s, 3H; O-CH_3), 2.65 (m, 1H; CH), 1.30 (t, J=7.0 Hz, 3H; CH_3), 1.07 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 152.5, 149.7, 144.4, 141.0, 134.7, 129.9, 127.8, 127.4, 125.6, 122.9, 114.9, 114.9, 62.90, 60.66, 55.85, 43.94, 17.20, 14.38 ppm; IR (film): $\tilde{\nu}$=3398, 2981, 2934, 2833, 1714, 1651, 1621, 1595, 1512, 1465, 1384, 1369, 1243, 1180, 1095, 1038, 984, 820, 787, 763, 698 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=243 (4.007), 308 nm (3.502); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{25}ClNO_3$ $[M+H]^+$: 374.1517; found: 374.1518; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 29.12 (4*S*,5*S*), 32.45 min (4*R*,5*R*).

Compound *anti*-7f: Yield 44%; *anti*/*syn*: 88:12, *anti*: 90% *ee*; R_f=0.45 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=-11.0$ (c=0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.12 (m, 4H; ArH), 6.99 (dd, J=16.0, 7.5 Hz, 1H; CH), 6.68 (m, 2H; ArH), 6.38 (m, 2H; ArH), 5.94 (dd, J=16.0, 1.0 Hz, 1H; CH), 4.47 (d, J=6.5 Hz, 1H; N-CH), 4.21 (q, J=7.0 Hz, 2H; O-CH_2), 3.79 (s, 3H; O-CH_3), 2.73 (m, 1H; CH), 2.47 (s, 3H; CH_3), 1.31 (t, J=7.0 Hz, 3H; CH_3), 1.14 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 152.1, 150.1, 141.5, 140.0, 135.2, 130.8, 127.0, 126.6, 126.3, 122.6, 114.8, 114.6, 60.48, 58.91, 55.75, 43.08, 19.62, 16.84, 14.33 ppm; IR (film): $\tilde{\nu}$=3398, 2978, 2831, 1713, 1650, 1620, 1513, 1462, 1384, 1368, 1241, 1181, 1037, 983, 867, 818, 790, 761, 730, 647, 556, 521, 462 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.072), 299 nm (3.454); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064; found: 354.2062; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 95:5, flow 0.25 mL min^{-1}): λ=250 nm; 36.42 (4*R*,5*R*), 38.87 min (4*S*,5*S*).

Compound *anti*-7g: Yield 82%; *anti*/*syn*: 91:9, *anti*: 92% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=+82.0$ (c=0.8 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.87 (d, J=8.0 Hz, 1H; ArH), 7.26–7.22 (m, 2H; ArH), 6.97–6.91 (m, 3H; ArH, CH), 6.68 (m, 2H; ArH), 6.36 (m, 2H; ArH), 5.90 (dd, J=16.0, 1.0 Hz, 1H; CH), 4.56 (d, J=6.5 Hz, 1H; N-CH), 4.21 (q, J=7.0 Hz, 2H; O-CH_2), 3.93 (d, J=6.5 Hz, NH), 3.67 (s, 3H; O-CH_3), 2.83 (m, 1H; CH), 1.31 (t, J=7.0 Hz, 3H; CH_3), 1.14 ppm (d, J=7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 152.2, 148.7, 143.2, 140.8, 139.9, 129.3, 128.7, 128.5, 123.1, 114.9, 114.8, 100.1, 65.58, 60.53, 55.75, 42.10, 16.88, 14.34 ppm; IR (film): $\tilde{\nu}$=3398, 2980, 2932, 2832, 1716, 1651, 1595, 1512, 1489, 1463, 1409, 1384, 1242, 1180, 1014, 1038, 1014, 982, 819, 761, 521 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.086), 299 nm (3.574); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{25}INO_3$ $[M+H]^+$: 466.0874; found: 466.0871; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 21.13 (4*S*,5*S*), 25.08 min (4*R*,5*R*).

Compound *anti*-7h: Yield 96%; *anti*/*syn*: 90:10, *anti*: 93% *ee*; R_f=0.20 (ethyl acetate/petroleum ether 1:2, 10% NEt_3); $[\alpha]_D^{22}=-6.0$ (c=1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.60 (d, J=2.0 Hz, 1H; ArH), 8.50 (dd, J=5.0, 2.0 Hz, 1H; ArH); 7.66 (dt, J=8.0, 2.0 Hz, 1H; ArH), 7.21 (dd, J=8.0, 5.0 Hz, 1H; ArH), 6.90 (dd, J=15.5, 8.5 Hz, 1H; CH), 6.65 (m, 2H; ArH), 6.41 (m, 2H; ArH), 5.90 (dd, J=15.5, 1.5 Hz, 1H; CH), 4.22–4.15 (m, 3H; N-CH, O-CH_2), 3.93 (s, 1H; NH), 3.64 (s, 3H; O-CH_3), 2.67 (m, 1H; CH), 1.28 (t, J=7.0 Hz, 3H; CH_3), 1.04 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.1, 152.5, 149.4, 149.1, 148.8, 140.6, 137.3, 134.6, 123.6, 123.0, 114.9, 114.8, 60.91, 60.54, 55.68, 43.66, 16.94, 14.26 ppm; IR (film): $\tilde{\nu}$=3369, 2927, 2854, 1716, 1651, 1590, 1577, 1512, 1463, 1426, 1383, 1243, 1180, 1095, 1038, 984, 787, 716 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.262), 289 nm (3.755); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1860; found: 341.1858; enantiomeric assay: Chiralcel OJ, isocratic (hexane/2-propanol 90:10, flow 1.0 mL min^{-1}): λ=250 nm; 44.42 (4*S*,5*S*), 54.11 min (4*R*,5*R*).

Compound *anti*-7i: Yield 65%; *anti*/*syn*: 74:26, *anti*: 91% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=-7.8$ (c=1.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.35 (m, 1H; ArH), 7.33–7.29 (m, 1H; ArH), 6.95 (dd, J=16.0, 7.5 Hz, 1H; CH), 6.74 (m, 2H; ArH), 6.53 (m, 2H; ArH), 6.34–6.31 (m, 1H; ArH), 5.85 (dd, J=16.0, 1.0 Hz, 1H; CH), 4.26 (d, J=6.5 Hz, 1H; N-CH), 4.23 (q, J=7.5 Hz, 2H; O-CH_2), 3.71 (s, 3H; O-CH_3), 2.71 (m, 1H; CH), 1.30 (t, J=7.5 Hz, 3H; CH_3), 1.12 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 152.5, 150.4, 143.4, 141.4, 140.4, 126.2, 122.5, 115.2, 114.9, 109.3, 60.56, 55.87, 55.54, 42.20, 16.25, 14.39 ppm; IR (film): $\tilde{\nu}$=3389, 3055, 2981, 2933, 2903, 2831, 1712, 1651, 1619, 1562, 1511, 1460, 1437, 1384, 1363, 1310, 1239, 1179, 1128, 1094, 1073, 1038, 980, 911, 755, 662 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=244 (4.362); 311 nm (3.645); HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700; found: 330.1699; enantiomeric assay: Chiralcel OD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 29.94 (4*S*,5*S*), 39.57 min (4*R*,5*R*).

Compound *anti*-7j: Yield 83%; *anti*/*syn*: 88:12, *anti*: 93% *ee*; R_f=0.40 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}=-59.7$ (c=2.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.34 (m, 1H; ArH), 6.95 (dd, J=16.0, 7.5 Hz, 1H; CH), 6.74 (m, 2H; ArH), 6.53 (m, 2H; ArH), 6.30–6.27 (m, 1H; ArH), 6.18–6.15 (m, 1H; ArH), 5.92 (dd, J=16.0, 1.0 Hz, 1H; CH), 4.34 (d, J=6.5 Hz, 1H; N-CH), 4.22 (q, J=7.5 Hz, 2H; O-CH_2), 3.71 (s, 3H; O-CH_3), 2.92 (m, 1H; CH), 1.30 (t, J=7.5 Hz, 3H; CH_3), 1.12 ppm (d, J=6.5 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 154.5, 152.6, 150.3, 141.8, 141.4, 122.5, 115.4, 114.9, 110.3, 107.7, 60.53, 57.50, 55.83, 41.33, 16.38, 14.37 ppm; IR (film): $\tilde{\nu}$=3373, 2979, 2935, 2905, 2833, 1711, 1652, 1619, 1513, 1464, 1369, 1242, 1182, 1097, 1037, 984, 923, 883, 867, 737, 599, 520 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=245 (4.180), 306 nm (3.665); HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700; found: 330.1700; enantiomeric assay: Chiralcel AD-H, isocratic (hexane/2-propanol 95:5, flow 0.5 mL min^{-1}): λ=250 nm; 24.16 (4*R*,5*R*), 25.55 min (4*S*,5*S*).

Determination of the relative configuration of 7 through conversion into (5*S*,6*S*)-8: A solution of (BDP)CuH solution (BDP=1,2-bis(diphenylphosphino)benzene; 0.60 mL, 1M in toluene, preparing following procedure)[23] was added dropwise to an oven-dried 2 mL test tube that contained a solution of (2*E*,4*S*,5*S*)-**7** (110 mg, 0.30 mmol, *anti*/*syn* 3.5:1, *anti*: 91% *ee*) and *t*BuOH (88 μL, 3 equiv) in dry, degassed toluene (1 mL) at RT. The solution was stirred for 24 h at RT and the solvent was removed in vacuo. A mixture of MeOH/HCl (2N)/THF (7 mL, 5:1:1) was added to the residue and heated to reflux for 48 h. The solution was extracted two times with ethyl acetate (10 mL) and the combined organic phases were washed with 1N HCl (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was purified by short silica gel chromatography (ethyl acetate/petroleum ether 1:5 to ethyl acetate) to afford the (5,6)-*trans*-piperidin-2-one in 57% yield (55 mg, 91% *ee*) and (5,6)-*cis*-piperidin-2-one in 11% yield (11 mg). R_f=0.15 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{22}=-117.2$ (c=0.7 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.07 (m, 4H; ArH), 6.90 (m, 2H; ArH), 6.70 (m, 2H; ArH), 4.39 (d, J=6.5 Hz, 1H; CH), 3.70 (s, 3H; O-CH_3), 2.69 (t, J=7.0 Hz, CH_2), 2.59 (t, J=7.0 Hz, 2H; Ar-CH_2), 2.13 (m, 1H; CH), 1.99 (m, 1H; CHH), 1.64 (ddt, J=14.0, 7.0, 7.0 Hz, 1H; CHH), 1.24 (t, J=

7.5 Hz, 3H; Ar-CH_2), 1.14 ppm (d, J=7.0 Hz, 3H; CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.0, 158.0, 143.5, 138.6, 135.3, 128.8, 127.9, 127.4, 114.2, 72.42, 55.37, 36.44, 30.86, 28.48, 25.76, 18.54, 15.42 ppm; IR (film): $\tilde{\nu}$=3434, 2961, 2931, 2873, 1722, 1654, 1607, 1510, 1498, 1456, 1440, 1405, 1384, 1337, 1283, 1243, 1215, 1172, 1148, 1037, 938, 827, 798, 770, 541 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=242 (3.842), 268 nm (3.490); HRMS (ESI): m/z: calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 324.1958; found: 368.1958.

Determination of the absolute configuration of vinylogous Mannich products through conversion into (1*S*,3*E*)-6: $[Ce(NO_3)_6(NH_4)_2]$ (CAN; 822 mg, 1.5 mmol, 5 equiv) in H_2O (6 mL) was added to a solution of (2*E*,5*S*)-**4a** (93 mg, 0.30 mmol, 1.0 equiv, 83% *ee*) in CH_3CN (7.5 mL) at 0°C. The solution was stirred for 4 h at 0°C. Boc_2O (785 mg, 3.6 mmol, 12 equiv) was added and the solution was stirred for another 18 h at RT. Saturated $NaHCO_3$ solution (5 mL/0.1 mmol) was added to the mixture and extracted three times with ethyl acetate (10 mL), and the combined organic phases were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to afford the title compound in 63% yield (83% *ee*). R_f=0.55 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{22}$=−23.0 (c=0.4 in CH_2Cl_2), ref. [16]: for (*R*) (>99% *ee*): $[\alpha]_D^{22}$=+27.4 (c=0.4 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.23 (m, 5H; ArH), 6.84 (dt, J=15.5, 7.0 Hz, 1H; CH), 5.86 (d, J=15.5 Hz, 1H; CH), 4.82 (m, 2H; NH, N-CH), 3.70 (s, 3H; O-CH_3), 2.69 (m, 2H; CH_2), 1.41 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 155.1, 144.4, 141.1, 128.9, 127.7, 126.4, 123.9, 79.97, 53.89, 51.64, 39.50, 28.45 ppm; IR (film): $\tilde{\nu}$=3385, 3063, 3035, 2963, 2928, 2852, 1720, 1680, 1517, 1458, 1439, 1390, 1366, 1315, 1294, 1267, 1222, 1172, 1020, 980, 758, 702, 676, 562, 524 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=238 (3.367), 241 (3.366), 295 nm (2.597); HRMS (ESI): m/z: calcd for $C_{18}H_{28}NO_3$ $[M+H]^+$: 306.2064; found: 306.2063.

Preparation of phosphoric acid 3d

4-tert-*Butyl-2,6-dimethylphenylboronic acid* (***11***): *n*BuLi (32.0 mL, 79.7 mmol, 2.5 M in hexane, 1.5 equiv) was slowly added to a cooled (−78°C), stirred solution of 5-*tert*-butyl-2-bromo-1,3-dimethylbenzene (12.8 g, 53.1 mmol, 1.0 equiv)[24] in dry THF (500 mL), and the reaction mixture was allowed to stir for 2 h at −78°C. Trimethoxyborate (18.1 mL, 159 mmol, 3.0 equiv) was added dropwise within 10 min. The reaction mixture was stirred for another 2 h at −78°C and at RT overnight. The colorless solution was treated with 1 N HCl (180 mL) and the mixture was stirred for 5 h and extracted three times with CH_2Cl_2 (200 mL). The combined organic phases were washed with 1 N HCl, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was treated with petroleum ether at −30°C to crystallize the title compound in 51% (5.61 g) yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.03 (s, 2H; ArH), 4.44 (s, 2H; $B(OH)_2$), 2.39 (s, 6H; CH_3); 1.30 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.9, 142.2, 139.6, 124.4, 34.61, 31.32, 23.41 ppm; IR (KBr): $\tilde{\nu}$=3328, 2962, 2864, 1726, 1607, 1434, 1359, 1342, 1297, 862 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=235 nm (3.352); HRMS (ESI): m/z: calcd for $C_{24}H_{37}B_2O_4$ $[2M-H]^-$: 411.2883; found: 411.2888.

3,3′-(4-tert-*Butyl-2,6-dimethylphenyl)-2,2′-dimethoxy-1,1′-binaphthyl* (***12***): An oven-dried, 250 mL flask was filled stepwise with 3,3′-bisiodo-2,2′-dimethoxy-1,1′-binaphthyl[25] (2.50 g, 4.43 mmol, 1.0 equiv), boronic acid **11** (3.65 g, 17.7 mmol, 4.0 equiv), $BaOH_2{\cdot}8H_2O$ (5.59 g, 17.7 mmol, 4.0 equiv), and $[Pd(PPh_3)_4]$ (512 mg, 0.44 mmol, 0.1 equiv) under an argon atmosphere. An argon-degassed solution of DME/H_2O (5:1, 60 mL) was added to the solids and heated to reflux for 48 h, after which 1 N HCl (100 mL) was added and extracted three times with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was purified by short silica gel chromatography (CH_2Cl_2/petroleum ether 1:6) to afford the title compound in 93% (2.64 g) yield as white foam. R_f=0.30 (CH_2Cl_2/petroleum ether 1:5); $[\alpha]_D^{22}$=+31.5 (c=0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (d, J=8.0 Hz, 2H), 7.75 (s, 2H), 7.40–7.30 (m, 6H), 6.99 (s, 4H), 3.10 (s, 6H; OCH_3), 2.24 (s, 6H; CH_3), 2.19 (s, 6H; CH_3), 1.38 ppm (s, 18H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.7, 150.2, 136.0, 136.0, 135.6, 134.6, 133.9, 130.9, 130.7, 127.9, 126.1, 125.9, 125.5, 124.7, 124.5, 124.4, 60.08, 34.49, 31.62, 21.38, 21.22 ppm; IR (KBr): $\tilde{\nu}$=3054, 2962, 2927, 2851, 1607, 1453, 1401, 1376, 1249, 1041, 749 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=232 nm (4.463); MS (ESI): m/z (%): 635 (10) $[M+H]^+$, 657 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{46}H_{50}O_2$: C 87.02, H 7.94; found: C 87.15, H 8.07.

3,3′-(4-tert-*Butyl-2,6-dimethylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl* (***13***): A precooled solution (0°C) of BBr_3 (1.5 mL, 15.8 mmol, 5.0 equiv) was added dropwise to an oven-dried, 250 mL flask containing a solution of **12** (2.05 g, 2.84 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) at 0°C under a nitrogen atmosphere. The solution was stirred for 2 h at 0°C and 48 h at RT, after which H_2O (100 mL) was added carefully at 0°C. The resulting mixture was stirred for 10 min and extracted three times with CH_2Cl_2 (100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was purified by short silica gel chromatography (CH_2Cl_2/petroleum ether 1:4) to afford the title compound in 99% (1.93 g) yield as white foam. R_f=0.40 (CH_2Cl_2/petroleum ether 1:2); $[\alpha]_D^{22}$=+26.0 (c=0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (d, J=8.0 Hz, 2H), 7.82 (s, 2H), 7.39 (ddd, J=8.0, 6.5, 1.5 Hz, 2H), 7.32 (ddd, J=8.0, 6.5, 1.5 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.21 (s, 4H), 5.01 (s, 2H; OH), 2.19 (s, 6H; CH_3), 2.11 (s, 6H; CH_3), 1.37 ppm (s, 18H; $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.0, 150.1, 136.9, 136.8, 133.6, 132.9, 130.7, 129.7, 129.5, 128.4, 126.9, 124.9, 124.8, 124.7, 123.9, 113.2, 34.57, 31.53, 21.06, 20.98 ppm; IR (KBr): $\tilde{\nu}$=3524, 3498, 3391, 3055, 2962, 2885, 1622, 1604, 1571, 1495, 1482, 1437, 1379, 1361, 1313, 1278, 1261, 1246, 1195, 1179, 1145, 1115, 1061, 1024, 992, 973, 930, 907, 868, 852, 820, 786, 749 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} ($\log\varepsilon$)=234 (4.051), 244 (4.667), 291 (3.991), 333 nm (3.956); MS (ESI): m/z (%): 605 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_{44}H_{46}O_2$: C 87.09, H 7.64; found: C 87.07, H 7.83.

Phosphoric acid (R)-***3d***: $POCl_3$ (1.37 g, 820 μL, 8.91 mmol, 3.0 equiv) was added carefully to an ice-cooled stirred solution of **13** (1.80 g, 2.97 mmol, 1.0 equiv) in dry pyridine (20 mL), and the reaction mixture was stirred for 18 h at RT. The reaction mixture was cooled to 0°C, and H_2O (2.0 mL, 0.1 mol) was added carefully and the mixture was stirred for another 24 h at RT. The mixture was treated with 1 N HCl (20 mL) and the mixture was stirred for 5 h and extracted two times with Et_2O (50 mL). The combined organic phases were washed five times with 1 N HCl (25 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to afford the title compound in 91% (1.89 g) yield as gray powder. R_f=0.05 (CH_2Cl_2); $[\alpha]_D^{22}$=−87.7 (c=1.0 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.92 (s, 1H; POOH), 7.91 (d, J=8.0 Hz, 2H), 7.80 (s, 2H), 7.50 (dd, J=8.0, 7.5 Hz, 2H), 7.38–7.32 (m, 4H), 6.96 (s, 4H), 2.19 (s, 6H; CH_3), 2.03 (s, 6H; CH_3), 0.96 ppm (s, 18H; $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=150.2, 145.1 (d, J(P,C)=6.5 Hz), 136.3, 136.2, 133.2 (d, J(P,C)=3.5 Hz), 132.9, 132.1, 132.0, 131.8, 128.3, 127.3, 126.4, 125.8, 124.9, 124.0, 122.4 (d, J(P,C)=3.0 Hz), 34.08, 31.11, 21.50, 21.04 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ=7.18 ppm; IR (KBr): $\tilde{\nu}$=3433, 3062, 2962, 2865, 1608, 1574, 1497, 1407, 1377, 1377, 1264, 1243, 1190, 1022, 969, 906, 864, 749 cm^{-1}; UV/Vis (CH_3CN): λ_{max} ($\log\varepsilon$)=222 (4.998), 294 (4.667), 291 (4.003), 333 nm (4.079); HRMS (ESI): m/z: calcd for $C_{44}H_{44}O_4P$ $[M-H]^-$: 667.2983; found: 667.2974.

X-ray crystallography: Obtained data were collected using a STOE IPDS1 diffractometer ($Mo_{K\alpha}$ radiation). The program SIR2004[26] was used for solving the structure and SHELX-97[27] for the refinement. Crystal data for the adduct $[C_{44}H_{45}PO_4]^-[C_{14}H_{13}NO]^+{\cdot}CHCl_3$: monoclinic; C_2 (no. 5); a=22.287(2), b=15.9325(9), c=16.336(1) Å; β=92.19(1)°; V=5796.6(7) Å^3; Z=4; T=213 K; μ=0.231 mm^{-1}; ρ_{calcd}=1.145 g cm^{-3}; $2\theta_{max}$=50.0°; 16532 reflections measured; 8763 unique (R_{int}=0.0355); R_1=0.0538 (4836 reflections with ($I>2\sigma(I)$)); wR_2=0.1410 (all data); absolute structure parameter 0.00(9); GOF=0.796; 622 parameters and 8 constraints. CCDC-744893 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] Reviews: a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; b) S. E. Denmark, O. J.-C. Nicaise, *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 923; c) M. Arend, *Angew. Chem.* **1999**, *111*, 3047; *Angew. Chem. Int. Ed.* **1999**, *38*, 2873; d) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; e) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; f) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797.

[2] a) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience, New York, **1996**; b) S. E. Denmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.

[3] Reviews: a) S. F. Martin, *Acc. Chem. Res.* **2002**, *35*, 895; b) S. K. Bur, S. F. Martin, *Tetrahedron* **2001**, *57*, 3221.

[4] S. F. Martin, O. D. Lopez, *Tetrahedron Lett.* **1999**, *40*, 8949.

[5] a) E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2006**, *118*, 7388; *Angew. Chem. Int. Ed.* **2006**, *45*, 7230; b) H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961; for an extension of this methodology to the reaction with ketimines, see: c) L. C. Wieland, E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 570; for a similar catalyst system with a different chiral ligand, see: d) Z.-L. Yuan, J.-J. Jiang, M. Shi, *Tetrahedron* **2009**, *65*, 6001.

[6] T. Akiyama, Y. Honma, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2008**, *350*, 399.

[7] A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319.

[8] T.-Y. Liu, H.-L. Cui, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878.

[9] B. Niess, K. A. Jørgensen, *Chem. Commun.* **2007**, 1620.

[10] a) M. Sickert, C. Schneider, *Angew. Chem.* **2008**, *120*, 3687; *Angew. Chem. Int. Ed.* **2008**, *47*, 3631; b) D. S. Giera, M. Sickert, C. Schneider, *Org. Lett.* **2008**, *10*, 4259.

[11] Excellent reviews: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 and references cited therein; b) M. Terada, *Chem. Commun.* **2008**, 4097 and references cited therein.

[12] For select applications of BINOL-based phosphoric acids in enantioselective imine addition reactions, see: reduction of imines or nitrogen heterocycles with Hantzsch esters: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; f) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830; g) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562; aza Diels–Alder reactions with imines: h) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; i) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; Friedel–Crafts reactions: j) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804; k) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292; l) G. B. Rowland, E. B. Rowland, Y. Liang, J. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609; Mannich reactions: m) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; n) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756; o) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; p) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360; for select further applications, see: q) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; r) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; s) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802; t) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086; u) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; v) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 15786; w) M. Rueping, A. P. Antonchick, K. Grenader, E. Sugiono, *Angew. Chem.* **2009**, *121*, 925; *Angew. Chem. Int. Ed.* **2009**, *48*, 908; x) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2009**, *121*, 2591; *Angew. Chem. Int. Ed.* **2009**, *48*, 2553; y) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598; z) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *Angew. Chem.* **2009**, *121*, 6845; *Angew. Chem. Int. Ed.* **2009**, *48*, 6717; aa) J. Jiang, J. Qing, L.-Z. Gong, *Chem. Eur. J.* **2009**, *15*, 7031.

[13] A. S. Gonzalez, R. G. Arrayas, M. R. Rivero, J. C. Carretero, *Org. Lett.* **2008**, *10*, 4355.

[14] S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800.

[15] G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31 and references cited therein.

[16] A. Satake, I. Shimizu, A. Yamamoto, *Synlett* **1995**, *1*, 64.

[17] The vinylogous Mannich reaction with silyloxy furans developed by Akiyama et al. gave rise to the opposite absolute configuration in the Mannich products when 2-hydroxyaniline-based imines were employed (ref. [6]). The authors proposed a nine-membered chelate in the transition state of the reaction.

[18] A similar and significant effect of the influence of double-bond geometry of a silyl dienolate was observed by Kalesse et al. in B-$(C_6F_5)_3$-activated vinylogous aldol reactions to afford excellent diastereoselectivities with a 3*Z*-configured dienolate and only moderate diastereoselectivities with a 3*E*-configured dienolate. See: J. Hassfeld, M. Christmann, M. Kalesse, *Org. Lett.* **2001**, *3*, 3561.

[19] In ethyl acetate, Et_2O, and THF, the reaction proceeded to 40% conversion after 24 h at RT and to 56% conversion after 48 h at RT. ESIMS/MS samples were collected after 2, 24, and 48 h to identify complex *m*/*z* 1024. After 6 d, the reaction was complete.

[20] For the characterization of key intermediates in organocatalyic reactions by ESIMS, see also: W. Schrader, P. P. Handayani, J. Zhou, B. List, *Angew. Chem.* **2009**, *121*, 1491; *Angew. Chem. Int. Ed.* **2009**, *48*, 1463; for a review, see: L. S. Santos, *Eur. J. Org. Chem.* **2008**, 235.

[21] A similar counterion pair to **10** containing the negatively charged chiral phosphate and positively charged silylated Mannich product was postulated and calculated in a Brønsted acid catalyzed Mannich reaction: M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756.

[22] TMS-protected dienolates: B. Bazán-Tejeda, G. Bluet, G. Broustal, J.-M. Campagne, *Chem. Eur. J.* **2006**, *12*, 8358.

[23] B. A. Baker, Ž. V. Bošković, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 289.

[24] J. E. Field, T. J. Hill, D. Venkataraman, *J. Org. Chem.* **2003**, *68*, 6071.

[25] T. Akiyama, PCT Int. Appl. WO200409675, **2004**.

[26] M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, SIR2004, package for solving crystal structures by Direct and Patterson Methods, Istituto di Cristallografia, CNR and Dipartimento di Scienze della Terra, Università di Perugia (Italy); http://www.ic.cnr.it/sir2004.

[27] G. M. Sheldrick, SHELX-97, University of Göttingen, Göttingen (Germany), **1996**; "A short history of SHELX": G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112–122.

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