JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Promotion of a Ti-Mediated Mannich Reaction by a Proton Source

John Limanto,* Naoki Yoshikawa, Robert A. Reamer, Lushi Tan, Andrew Brunskill, and Mikhail Reibarkh

Department of Process Chemistry, Merck Research Laboratories Merck & Company, Inc., Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: Low temperature NMR studies revealed that a diastereoselective Mannich reaction between a phenyl oxazolidone-derived titanium enolate and an aromatic aldimine was found to occur only after introduction of a proton source. While various protic additives could be used to promote the transformation, the best results were obtained using AcOH to afford the corresponding Mannich products in high diastereoselectivities and yields.

β-Amino acids are ubiquitous in nature[1] and they have become increasingly important building blocks for new drug development and peptide modifications.[2] While there are many asymmetric approaches to this class of compounds,[3] one of the more common methods involves a Mannich-type reaction.[4] Among these transformations, reactions between chiral titanium (Ti) enolates and aldimines/ketimines have been widely investigated and most of these studies involved strongly activated imines (or iminium ions) as the electrophiles.[5]

The use of less activated aromatic aldimines in diastereoselective Mannich reactions in conjunction with chiral oxazolidone-derived Ti-enolates was initially reported by the Schering-Plough group[6] and subsequently investigated by others.[7] The original authors noted that unless the reactions were quenched at low temperatures, yield variability was often observed, presumably due to the reversibility of the transformation.[6e]

In support of a drug development program, we began evaluating a similar transformation, where we were interested in accessing β-amino acid derivative **3a** as a useful synthetic intermediate. Our initial experiment showed that treatment of aldimine **1** with *in situ* generated Ti-enolate[8] of phenyl oxazolidone **2**[9] (**2-enol-Ti**) at −40 °C in CH_2Cl_2, followed by quenching the reaction with aqueous HCl at −20 °C afforded the desired Mannich adducts, with concomitant removal of the TMS group, in a 5:1 anti/syn diastereoselectivity[10] and a 52% combined yield (Scheme 1). Initial attempts to optimize the reaction did indeed afford variable chemical yields and poor reproducibility, even when the reaction was quenched at low temperatures (<−20 °C).

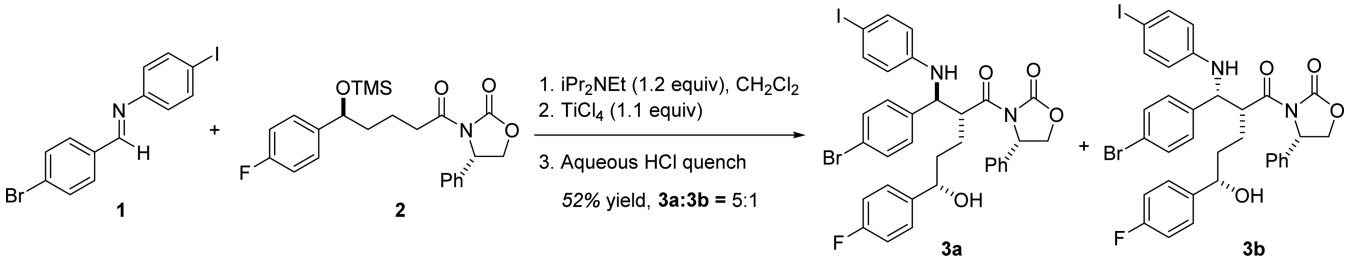
In order to better understand these findings, we decided to monitor the transformation more carefully by using low temperature NMR spectroscopy, for which the data are presented in Figure 1. As a reference, the spectrum of isolated *anti*-Mannich product **3a**[11] is shown at the top of the figure (**1D**). The spectrum at the bottom (**1A**) represents a mixture of aldimine **1** (1.2 equiv) and phenyl-oxazolidone **2** (1 equiv) in CD_2Cl_2, kept between −30 and −40 °C. Addition of $TiCl_4$ (1.1 equiv) to this mixture produced a new species, presumably a complex between **2** and $TiCl_4$,[12] as evident by the splitting of the CH_2 protons α to the carbonyl group into two separate peaks (**1B**). Subsequent exposure to Hunig's base (1.2 equiv) generated the corresponding Ti-enolate species (**2-enol-Ti**), having a distinct sp^2C-H enolate peak with a chemical shift of 3.8 ppm (**1C**).[12] To our surprise, due to the absence of the product's signature peaks around δ 6.3 ppm, ***no** Mannich product(s) appeared to form*, even after warming up the NMR sample to 25 °C.[13]

We initially thought that the lack of reactivity might have been due to the low solubility of aldimine **1** and apparent heterogeneity of the reaction mixture at low temperature. To eliminate this possibility, we repeated the NMR experiment using a more soluble aldimine **4**, and the results are presented in Figure 2. Similarly, no desired Mannich reaction was observed between **2-enol-Ti** and aldimine **4** as illustrated in the NMR spectrum **2A** (vs product spectrum in **2D**). Furthermore, the transformation did not appear to be promoted by the presence of excess $TiCl_4$. However, upon addition of 1 mol equiv of AcOH at −40 °C, the corresponding Mannich product **5a** started to form, as evidenced by appearance of product signature peaks around δ 6.2 ppm (**2B**). Treatment with another equivalent of AcOH drove the reaction further (**2C**) with concomitant formation of starting oxazolidone **2**, presumably via quenching of the Ti-enolate species.[14] To the best of our knowledge, this is the first reported observation where a protic additive such as acetic acid is actually required to

Received: October 23, 2015
Published: December 10, 2015

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728

Scheme 1. Initial Result on Ti-Mediated Mannich Reaction



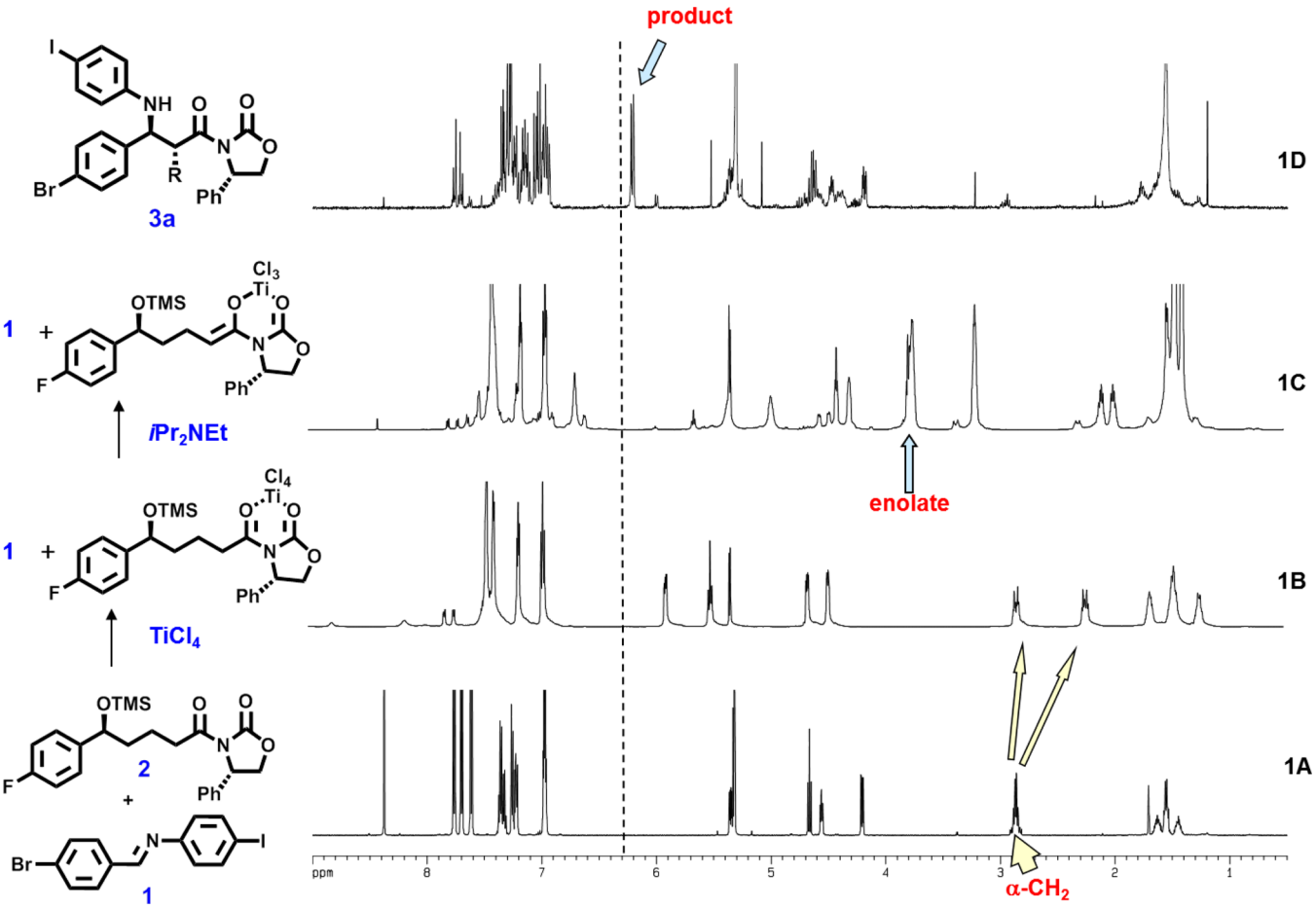


Figure 1. Low temperature NMR studies of imine **1** and Ti-enolate of **2**. The NMR studies were conducted in CD_2Cl_2 at an initial temperature of −40 °C under an inert atmosphere and further monitored at rt. **1A**: ^{1}H NMR of a mixture of iodo-bromophenyl aldimine **1** and oxazolidone **2**. **1B**: ^{1}H NMR of the mixture after charging $TiCl_4$. **1C**: ^{1}H NMR of the mixture after charging Hunig's base at −40 °C and allowed to warm up to rt. **1D**: ^{1}H NMR of authentic *anti*-Mannich product **3a**.

promote a Mannich reaction between a Ti-derived enolate and an aromatic aldimine.

Regeneration of starting oxazolidone **2** during addition of an acid promoter suggests that, depending on the proton source and how it is introduced, protonation of the **2-enol-Ti** intermediate could compete favorably with the Mannich reaction, resulting in overall lower conversions. Supporting this hypothesis, we found that fast addition of AcOH (i.e., over 5−10 min) led to incomplete conversions (70−80%) with respect to oxazolidone **2** as the limiting reagent, whereas higher conversions (>90%) were obtained over 1−2 h of addition rate. In attempts to further optimize the desired transformation, a variety of proton sources were also evaluated and the results are tabulated in Table 1. In all experiments, Ti-enolate formation was performed in the presence of aldimine at −40 °C in CH_2Cl_2 prior to exposure to the proton source, slowly added over 2 h as a solution in CH_2Cl_2. The mixture was subsequently treated with 1 N HCl to effect removal of the TMS protecting group. Entries 1−3 showed that simple alcohols such as ethanol or 2-propanol or more acidic alcohols, such as trifluoroethanol, afforded the Mannich products in decent *anti*/*syn* diastereoselectivities and high combined assay yields. Catechol also appeared to promote the reaction with good diastereoselectivy, albeit in lower assay yield (entry 4). The use of chiral alcohol sources, such as menthol or *R*-/*S*-BINOL,[15] did not improve the diastereoselectivities, but retained the high assay yields (entries 5−6). On the other hand, promoting the reaction with more acidic proton sources, such as PPTS or mandelic acid,

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728

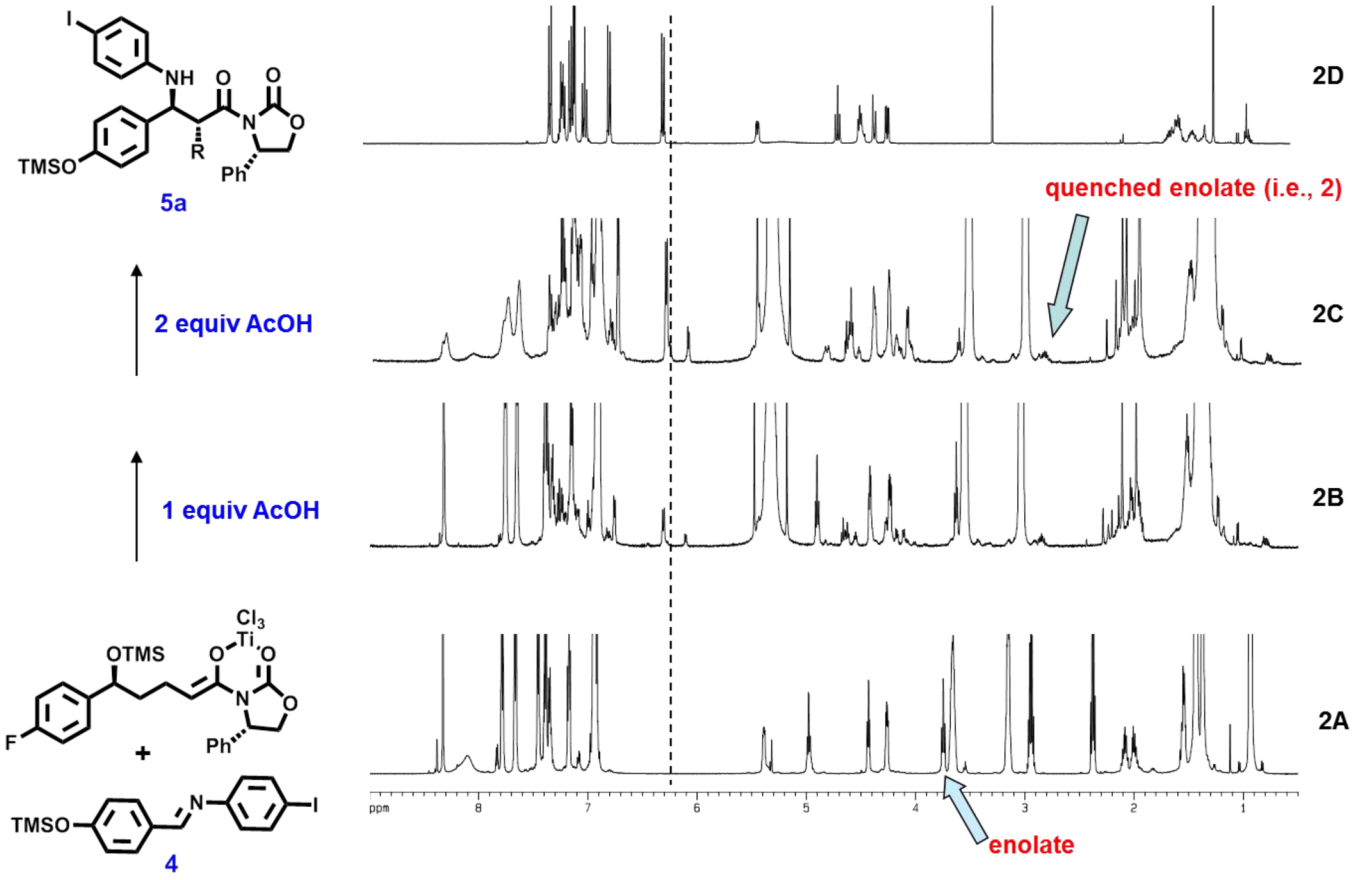


Figure 2. Low temperature NMR studies of imine **4** and Ti-enolate of **2**. The NMR studies were conducted in CD_2Cl_2 at an initial temperature of −40 °C under an inert atmosphere and further monitored at rt. **2A**: ^{1}H NMR of a mixture of aldimine **4** and **Ti-enolate** of **2**. **2B**: ^{1}H NMR of the mixture postaddition of 1 equiv of AcOH at −40 °C and aged for 1 h. **2C**: ^{1}H NMR of the mixture postaddition of 2 equiv of AcOH at −40 °C and aged for 1 h. **2D**: ^{1}H NMR of authentic *anti*-Mannich product **5a** (both TMS groups are intact).

gave similar diastereoselectivities, albeit with much lower assay yields (entries 7−8).

By looking more closely at AcOH as a promoter, a diastereoselectivity as high as 10:1 and an assay yield of 95% could actually be obtained (entry 9) upon adding the acid slowly as described above. While addition of a premade slurry of aldimine **1** and AcOH in CH_2Cl_2 at −40 °C into a preformed Ti-enolate solution of **2** in CH_2Cl_2 over 1−2 h also effected the Mannich reaction, the best conversion observed was only 80%, accompanied by a less clean reaction profile. Due to this reason and the inconvenience of maintaining the slow addition of a heterogeneous mixture of presumed protonated imine species, the best practical mode is to slowly add a solution of AcOH into a mixture of aldimine and **2**-enol-Ti in the corresponding solvent at −50 to −40 °C to effect the transformation efficiently.

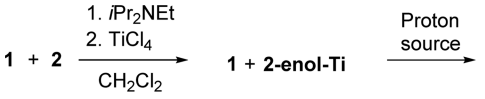
Focusing on AcOH as a reaction promoter, we next evaluated the potential impact of amines and solvents on reaction yields and diastereoselectivities. It was found early on that the formation of Ti-enolate **2-enol-Ti** could be generated more efficiently in CH_2Cl_2 than in any other solvents listed in Table 2. Hence, for the remainder of the study, the enolate formation was always carried out in CH_2Cl_2 and a cosolvent was introduced to the reaction mixture after enolization was complete, prior to exposure to AcOH. Common solvents, such as toluene, DME, or NMP, afforded lower diastereoselectivities and assay yields (entries 2−4) relative to THF or no cosolvent (entry 1). The use of EtOAc slightly improved the diastereoselectivity, while maintaining a high assay yield (entry 5). Other tertiary alkyl amines, such as nBu$_3$N, Cy$_2$NMe, and TMEDA, afforded the Mannich products with comparable diastereoselectivities (entries 6−8). It is interesting to note that the use of (−)-sparteine appeared to deteriorate the selectivity, but retained the good yield (entry 9). Upon scaling-up the conditions in entry 5, diastereomerically pure *anti*-Mannich product **3a** could be isolated in 86% yield after crystallization of the crude product from a mixture of the CH_2Cl_2/MTBE/heptane system.

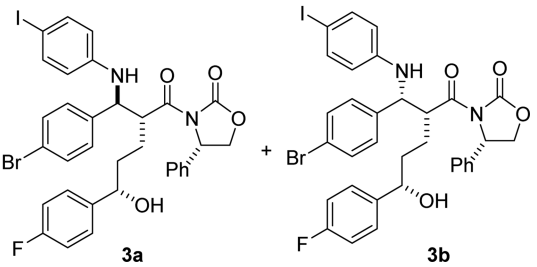
The preference for the *anti*- and facial selectivity could be rationalized by a six-member ring chelated transition state **TS1** or **TS2** (Figure 3),[6e] involving a (*Z*)-Ti-enolate[16] and the thermodynamically more stable (*E*)-imine.[17] This proposal, however, does not take into consideration the essential role of a proton source as the reaction promoter, as discovered through our experimental findings. In this regards, an alternative transition state **TS3** is proposed to be in effect, where the hydroxyl group of the proton source (ROH) coordinates to the Ti-center, thereby providing an acidic proton for imine activation.[18]

In summary, we have found that an *in situ* generated Ti-enolate of oxazolidone such as **2-enol-Ti** *only reacts* with unactivated aldimines such as **1** *in the presence of a proton source*. To the best of our knowledge, this is the first report of this observation. Specifically, addition of AcOH over 2−3 h to a mixture of **2-enol-Ti** and **1** in a 1:1 mixture of CH_2Cl_2/EtOAc at −50 to −40 °C triggered the Mannich reaction to afford the

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728

Table 1. Proton Sources Screen for Mannich Reaction[a]





entry	proton source[b]	d.r.[c]	assay yield[d]
1	EtOH	6:1	93%
2	2-propanol	5:1	99%
3	CF_3CH_2OH	5:1	99%
4	Catechol	10:1	75%
5	Menthol	6:1	88%
6	(*R*)- or (*S*)-BINOL	5:1	95%
7	PPTS	7:1	34%
8	Mandelic acid[e]	8:1	75%
9	**AcOH**[f]	**10:1**	**95%**

[a]Reaction conditions: [Oxazolidone **2**] = 0.45 M in CH_2Cl_2, Aldimine **1** (1.2 equiv), $TiCl_4$ (1.1 equiv), iPr_2NEt (1.2 equiv), aged for 1h at −40 °C for enolate formation. [b]Added at −40 °C over 2 h in CH_2Cl_2 followed by 1 N HCl to affect TMS removal. [c]Measured by HPLC or ^{1}HNMR analysis of crude reaction mixture. [d]Combined assay yields, calculated by HPLC method against a product standard. [e]Added as a solution in anhydrous THF. [f]Added as a solution in anhydrous THF or CH_2Cl_2 over 2−3 h between −50 and −40 °C.

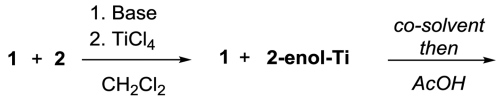
corresponding *β*-amino products in a 12:1 *anti*/*syn* diastereoselectivity and in 95% assay yield. The *anti* diastereomer was selectively crystallized (after *in situ* TMS group removal) to give pure product **3a** in 86% isolated yield. Under these reaction conditions, the competing protonation was kept to a minimum, while maintaining high conversions and reaction yields.

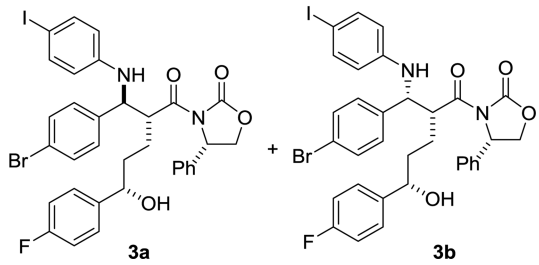
EXPERIMENTAL SECTION

General Methods. All reactions were conducted under an inert (N_2) atmosphere. Commercial reagents and commercial HPLC and anhydrous solvents were used without further purification. Concentration *in vacuo* refers to removal of the solvent using a rotary evaporator at reduced pressure (10−20 Torr). Reaction mixtures and Mannich products were analyzed using reversed phase high performance liquid chromatography (RP-HPLC) with MeCN and 0.1%v H_3PO_4/H_2O as the mobile phase. The ^{1}H NMR experiments were conducted on either a 500 or 600 MHz instrument, and ^{1}H and ^{13}C NMR spectra were all measured on a 500 MHz instrument. The high resolution mass spectroscopy (HRMS) spectra were obtained using a UPLC H-class system with QTOF and an electrospray ionization (ESI) ion source. The melting point data were measured by a differential scanning calorimetry (DSC) instrument. The concentration for specific optical rotations was reported in grams/100 mL of solvent.

Low Temperature NMR Experiments (Figures 1−2). The samples for NMR experiments were prepared in small 10 mL vials according to the general Mannich procedure described below. For example, a mixture of OTMS-oxazolidone (400 mg scale) and imine **1** or **4** in either CD_2Cl_2 (4 mL, KF < 100 ppm, for imine **1**) or extra dry CH_2Cl_2 (4 mL, KF < 20 ppm, for imine **4**) was treated with neat $TiCl_4$ followed by Hunig's base at −40 °C. After aging for 1 h, an aliquot of sample (0.5−0.6 mL) was then transferred into a precooled NMR tube

Table 2. Amine and Cosolvent Effect on Mannich Reaction[a]





entry	amine	cosolvents[b]	d.r.[c]	assay yield[d]
1	**iPr_2NEt**	**THF or none**	**10:1**	**95%**
2	iPr_2NEt	$PhCH_3$	9:1	88%
3	iPr_2NEt	DME	6:1	90%
4	iPr_2NEt	NMP	3:1	83%
5	**iPr_2NEt**	**EtOAc**	**12:1**	**95%**
6	nBu_3N	THF	9:1	95%
7	Cy_2NMe	THF	8:1	95%
8	TMEDA	THF	8:1	83%
9	(−)-sparteine	THF	5:1	93%

[a]Reaction conditions: [Oxazolidone **2**] = 0.45 M in CH_2Cl_2, Aldimine **1** (1.2 equiv), $TiCl_4$ (1.1 equiv), Amine (1.2 equiv), aged for 1 h between −40 °C for enolate formation. AcOH was added over 2−3 h between −50 and −40 °C, followed by 1 N HCl to affect TMS group removal. [b]Added after enolate formation at 50% of total volume. [c]Measured by HPLC. [d]Calculated by HPLC method against a product standard.

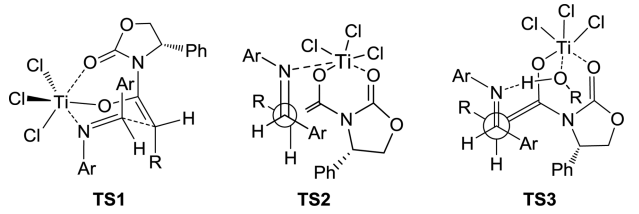


Figure 3. Possible transition states.

(−40 °C), via a thin cannula, under air-free conditions. The ^{1}H NMR spectra were then taken using a 500 MHz instrument, where the probe was precooled to −40 °C and then warmed up gradually to rt, at which point no desired Mannich product was observed (Figure 1). For the experiment involving imine **4** (Figure 2), neat AcOH was incrementally added (2 × 1 equiv wrt remaining Ti-enolate) to the mixture of Ti-enolate of **2** and imine **4** (freshly prepared and aged for 1 h at −40 °C) and an aliquot was sampled after 1 h of aging using the same technique described above. Formation of the desired Mannich product was observed after an initial equivalent charge of AcOH and continued to form after an additional charge and aging for another hour.

(*E*)-1-(4-Bromophenyl)-*N*-(4-iodophenyl)methanimine (1). To a solution of *p*-bromobenzaldehyde (10 g, 54 mmol, 1 equiv) in dry MeOH (120 mL) was added *p*-iodoaniline (12.1 g, 54 mmol, 1 equiv) portionwise as a solid. Within a few minutes, precipitation was obtained and the mixture was aged at rt overnight. The slurry was filtered, washed with cold MeOH (50 mL), and dried *in vacuo*. The desired aldimine was obtained in 96% isolated yield (20 g) and used as is in the next step. **Mp** 172 °C. **^{1}H NMR** ($CDCl_3$, 500 MHz) *δ* 8.37 (s, 1H), 7.76 (dm, *J* = 8.4 Hz), 7.71 (dm, *J* = 8.7 Hz), 7.62 (dm, *J* = 8.4 Hz), 6.97 (dm, *J* = 8.7 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 159.3,

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728

151.3, 138.3, 134.8, 132.1, 130.2, 126.2, 122.9, 90.7. **HRMS** (ESI) *m/z*: calcd for $C_{13}H_9BrIN$ + H $[M + H]^+$: 385.9041, found 385.9040.

(*S*)-3-((*S*)-5-(4-Fluorophenyl)-5-((trimethylsilyl)oxy)-pentanoyl)-4-phenyloxazolidin-2-one (2). To a solution of (*S*)-3-((*S*)-5-(4-fluorophenyl)-5-hydroxypentanoyl)-4-phenyloxazolidin-2-one[9] (31.2 g, 36.5 mmol, 1 equiv) in a 1:3 mixture of toluene/MTBE (130 mL) at −10 °C was added neat TMSCl (5.13 mL, 40.1 mmol, 1.1 equiv), followed by dropwise addition of Et_3N (5.59 mL, 40.1 mmol, 1.1 equiv). The resulting thick slurry was allowed to warm up to 20 °C overnight and then filtered. The wet cake was washed with dry MTBE (50 mL), and the resulting solution was concentrated to give the product as a pale yellow oil (15 g, 95% yield), which was used as-is in the next step. If desired, the product can be precipitated by trituration from cold hexanes at 5 °C overnight. Upon filtration and drying under N_2, the product was isolated as a white solid. **Mp** 43 °C. α_D^{25} +55 (*c* 1.14, $CDCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.42−7.33 (m, 3H), 7.32−7.28 (m, 2H), 7.27−7.22 (m, 2H), 6.99 (mt, 2H, *J* = 8.7 Hz), 5.42 (dd, 1H, *J* = 8.7, 3.7 Hz), 4.69 (app t, 1H, *J* = 8.7 Hz), 4.62 (dd, 1H, *J* = 7.2, 4.7 Hz), 4.28 (dd, 1H, *J* = 8.7, 3.7 Hz), 2.96 (t, 2H, *J* = 7.1 Hz), 1.79−1.53 (m, 4H), 0.02 (s, 9H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 172.7, 162.1 (d, *J* = 245.2 Hz), 153.9, 141.1 (d, *J* = 3.1 Hz), 139.4, 129.4, 128.9, 127.5 (d, *J* = 8.0 Hz), 126.1, 115.1 (d, *J* = 21.1 Hz), 74.2, 70.1, 57.8, 40.0, 35.4, 20.6, 0.3. **^{19}F NMR** ($CDCl_3$, 470 MHz) δ −116.1. **HRMS** (ESI) *m/z*: calcd for $C_{23}H_{28}FNO_4Si$ + H $[M + H]^+$: 430.1850; $C_{20}H_{19}FNO_3^+$ [M-OTMS]: 340.1343; found 340.1346 [M-OTMS].

(*S*)-3-((2*R*,5*S*)-2-((*S*)-(4-Bromophenyl)((4-iodophenyl)amino)-methyl)-5-(4-fluorophenyl)-5-hydroxypentanoyl)-4-phenyl-oxazolidin-2-one (3a). General procedure for Mannich reaction. A mixture of OTMS-oxazolidone **2** (2g, 4.65 mmol, 1 equiv) and I−Br−Imine **1** (2.15g, 5.58 mmol, 1.2 equiv) in dry CH_2Cl_2 (20 mL) was cooled to −40 °C and then treated with neat $TiCl_4$ (0.56 mL, 5.12 mol, 1.1 equiv), followed by Hünig's base (0.97 mL, 5.58 mmol, 1.2 equiv), to affect Ti-enolate formation (**2-enol-Ti**). The resulting solution was aged at −40 °C for 1 h and then diluted with dry EtOAc (10 mL). The resulting mixture was then treated with a solution of AcOH (391 mg, 6.51 mmol, 1.4 equiv) in CH_2Cl_2 (16 mL) over 2−3 h, while maintaining the temperature between −50 and −40 °C. At the end of the addition, the reaction mixture was diluted with EtOAc (20 mL), treated with 1 N aqueous HCl (10 mL), while allowing the temperature to warm to rt and aging until complete TMS removal was observed. The organic layer was separated and washed successively with H_2O (10 mL), 10 wt % aqueous K_2CO_3 (10 mL), and brine (20 mL). Assaying the organic layer revealed a 95% combined assay yield of Mannich products in 12:1 *anti*/*syn* diastereoselectivity, or an 88% assay yield of the desired *anti* diastereomer. Upon crystallization from CH_2Cl_2/MTBE/Heptane (1:4:5), the desired product **3a** was isolated as a single diastereomer in 86% yield (3.2 g, 93.4 wt %) as an MTBE-containing crystalline solid. **Mp** 120 °C (desolvation) and 178 °C (post recrystallization from the melt). α_D^{25} −52.6 (*c* 1.05, $CDCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.35−7.28 (m, 4H), 7.28−7.22 (m, 3H), 7.17 (mt, 2H, *J* = 7.8 Hz), 7.06−7.01 (m, 4H), 6.96 (dm, 2H, *J* = 7.5 Hz), 6.23 (dm, 2H, *J* = 9.8 Hz), 5.39 (dd, 1H, *J* = 8.4, 3.2 Hz), 5.32 (br s, 1H), 4.66 (t, 1H, *J* = 8.8 Hz), 4.64−4.56 (m, 2H), 4.43 (br s, 1H), 4.20 (dd, 1H, *J* = 8.8, 3.2 Hz), 2.00−1.55 (m, 5H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.9, 162.5 (d, *J* = 245.9 Hz), 154.3, 146.1, 140 (d, *J* = 3.4 Hz), 139.4, 138.3, 137.9, 132.1, 129.3, 128.7, 127.7 (d, *J* = 8.0 Hz), 125.5, 121.6, 116.0, 115.6 (d, *J* = 21.5 Hz), 73.5, 70.2, 59.3, 58.1, 47.5, 36.3, 27.0. **^{19}F NMR** ($CDCl_3$, 470 MHz) δ −114.6. **HRMS** (ESI) *m/z*: calcd for $C_{33}H_{29}BrFIN_2O_4$ + H $[M + H]^+$:743.0418, found 743.0415.

(*S*)-3-((2*R*,5*S*)-5-(4-Fluorophenyl)-2-((*S*)-((4-iodophenyl)-amino)(4-((trimethylsilyl)oxy)phenyl)methyl)-5-((trimethyl-silyl)oxy)pentanoyl)-4-phenyloxazolidin-2-one (5a). Same procedure as above. The imine **4** was obtained by reacting *p*-hydroxy benzaldehyde (15 g, 123 mmol, 1 equiv) and *p*-iodoaniline (27 g, 123 mmol, 1 equiv) in MeOH to afford the desired product in 91% yield (36 g). To a slurry of the imine (1.6 g, 4.97 mmol, 1.2 equiv) in dry CH_2Cl_2 (10 mL) was added neat TMSCl (0.7 mL, 5.47 mmol, 1.3 equiv) followed by Hunig's base (0.9 mL, 5.18 mmol, 1.25 equiv) at −10 °C and aged for 1 h. In a separate flask, a solution of OTMS-oxazolidone **2** (2 g, 4.14 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was treated with $TiCl_4$ (0.5 mL, 4.5 mmol, 1.1 equiv) followed by Hunig's base (0.9 mL, 5.18 mmol, 1.25 equiv) at −40 °C. The resulting mixture was aged at this temperature for 1 h and then treated with the solution of TMS-protected imine. A solution of AcOH (0.47 mL, 8.28 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was then added over 2 h at −40 °C, and the mixture was diluted with EtOAc, allowed to warm up to 0 °C, and treated with 2 N H_2SO_4 to effect TMS removal and extraction of titanium species into the aqueous layer. The organic layer was then separated and washed accordingly. Because isolation of the free alcohol Mannich product was not as efficient as in compound **3a**, the crude product was resilylated using BSA (2.1 g, 10.35 mmol, 2.5 equiv) in refluxing CH_2Cl_2 (25 mL) for 3 h to afford bis-TMS *anti*-Mannich product **5a**, which was isolated by crystallization from MTBE/hexane as a white solid (2.5 g, 73% yield). **Mp** 180 °C. α_D^{25} −75.9 (*c* 1.10, $CDCl_3$). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.31 (dm, 2H, *J* = 8.8 Hz), 7.22−7.16 (m, 3H), 7.11 (dm, 2H, *J* = 8.6 Hz), 7.10−7.06 (m, 4H), 6.98 (tm, 2H, *J* = 8.8 Hz), 6.76 (dm, 2H, *J* = 8.4 Hz), 6.27 (dm, 2H, *J* = 8.8 Hz), 5.40 (dd, 2H, *J* = 8.2, 2.5 Hz), 5.13 (d, 1H, *J* = 10.0 Hz), 4.66 (t, 1H, *J* = 8.7 Hz), 4.50−4.40 (m, 2H), 4.37−4.30 (m, 1H), 4.20 (dd, 1H, *J* = 8.8, 3.2 Hz), 1.68−1.28 (m, 5H), 0.28 (s, 9H), −0.06 (s, 9H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.3, 162.1 (d, *J* = 244.6 Hz), 154.9, 154.6, 146.4, 140.9 (d, *J* = 3.1 Hz), 138.4, 137.8, 133.3, 128.5, 128.2, 127.5 (d, *J* = 8.0 Hz), 125.4, 120.3, 116.4, 115.2 (d, *J* = 21.4 Hz), 74.2, 70.2, 60.9, 58.4, 48.6, 38,4, 27.6, 0.5, 0.1. **^{19}F NMR** ($CDCl_3$, 470 MHz) δ −115.7. **HRMS** (ESI) *m/z*: calcd for $C_{39}H_{46}FIN_2O_5Si_2$ + H $[M + H]^+$: 825.2052, found 825.2068.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02452.

NMR spectra and single crystal structure of Mannich product **3a** and **5a** (PDF)
Crystallographic data for **5a** (CIF)
Crystallographic data for **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: john_limanto@merck.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Feng Xu, Jeongchul Kim, Paul Devine, Tim Wright, Dave Tschaen, and Jerry Murry for useful scientific discussions. We also thank Alfred Lee for collecting the DSC information, Dr. Richard Staples from Crystallographic Resources, Inc. for crystallographic support, and Rebecca Arvery for measuring specific optical rotations.

■ REFERENCES

(1) Spiteller, P.; Von Nussbaum, F. *β*-Amino Acids in Natural Products. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: New York, 2005; pp 19−91.

(2) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. −I. *Curr. Med. Chem.* **2002**, *9*, 811.

(3) See for examples: (a) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. *Synthesis* **2009**, *2009*, 1. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, *2000*, 1.

(4) For recent reviews of enantioselective Mannich reactions, see: (a) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728

(5) See for examples: (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (b) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S. *Org. Lett.* **1999**, *1*, 107. (c) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731. (d) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. (e) Abrahams, I.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1994**, *50*, 12755.

(6) (a) Thiruvengadam, T. K.; Fu, X.; Tann, C.-H.; McAllister, T. L.; Chiu, J. S.; Colon, C. U.S. Patent 6,207,822 B1, 2001. (b) Thiruvengadam, T. K.; Tann, C.-H.; McAllister, T. L. U.S. Patent 5,561,227, 1996. (c) Thiruvengadam, T. K.; Tann, C.-H.; Lee, J.; McAllister, T.; Sudhakar, A. U.S. Patent 5,306,817, 1994. (d) Chen, L.-y.; Zaks, A.; Chackalamannil, S.; Dugar, S. *J. Org. Chem.* **1996**, *61*, 8341. (e) Thiruvengadam, T. K.; Sudhakar, A. R.; Wu, G. Practical Enantio- and Diastereoselective Processes for Azetidones. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999; pp 221−242.

(7) See for examples: (a) Zhu, L.; Lu, C.; Chen, Z.; Yang, G.; Li, Y.; Nie, J. *Tetrahedron: Asymmetry* **2015**, *26*, 6. (b) Ferstl, E. M.; Venkatesan, H.; Ambhaikar, N. B.; Snyder, J. P.; Liotta, D. C. *Synthesis* **2002**, *2002*, 2075. (c) Pinheiro, S.; Greco, S. J.; Veiga, L. S.; de Farias, F. M. C.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1157. For a review on Gilman−Speeter type reactions, see: (d) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447.

(8) For standard Ti-enolate generation conditions, see: (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. For examples of Aldol reactions involving chiral Ti-enolates, see: (b) Crimmins, M. T.; She, J. *Synlett* **2004**, *8*, 1371. (c) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (e) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301.

(9) See ref 6. Also, see: (a) Chen, X.; Liu, Z.-Q.; Huang, J.-F.; Lin, C.-P.; Zheng, Y.-G. *Chem. Commun.* **2015**, *51*, 12328. (b) Bertrand, B.; Durassier, S.; Frein, S.; Burgos, A. *Tetrahedron Lett.* **2007**, *48*, 2123.

(10) The *anti*-Mannich product being the major diastereomer was consistent with the previous finding reported by the Schering-Plough team (see ref 6) and is supported by the proposed transition state complex shown in Figure 3.

(11) In addition to confirmation from the previous report by the Schering-Plough team, the absolute and relative stereochemistry configuration of the desired *anti*-Mannich product are confirmed by single crystal structure analysis (see Supporting Information)

(12) The proposed six-member ring chelated complex between the two carbonyl groups and $TiCl_4$, as well as the corresponding six-member ring chelated Ti-enolate species, have been widely accepted based on the significant body of work in this area (see ref 8), for examples. Furthermore, the presence of such chelated species appears to be supported by expected *downfield* shifts of relevant carbon signals observed in our ^{13}C NMR experiments (see Supporting Information).

(13) Lack of reactivity was also observed using $Ti(O\text{-}iPr)Cl_3$ in lieu of $TiCl_4$.

(14) Subsequent experiments showed that prolonged aging of the quenched reaction mixture with AcOH at rt resulted in no increase in the quantity of oxazolidone **2**, suggesting irreversibility of the transformation and that the amount of **2** observed during the quench was due to competing protonation of the enolate.

(15) For examples on chiral protic acid-promoted reactions, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

(16) For Ti-enolate-mediated Aldol reactions, see (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (b) Ha, D.-c.; Hart, D. J.; Yang, T.-k. *J. Am. Chem. Soc.* **1984**, *106*, 4819.

(17) Yeh, H. J. C.; Ziffer, H.; Jerina, D. M.; Boyd, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 2741. ^1H NMR of imine **2** in $CDCl_3$ showed only one single isomer.

(18) For a similar proposed transition state in the proline-catalyzed Mannich reaction, see: Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.

DOI: 10.1021/acs.joc.5b02452
J. Org. Chem. 2016, 81, 723−728