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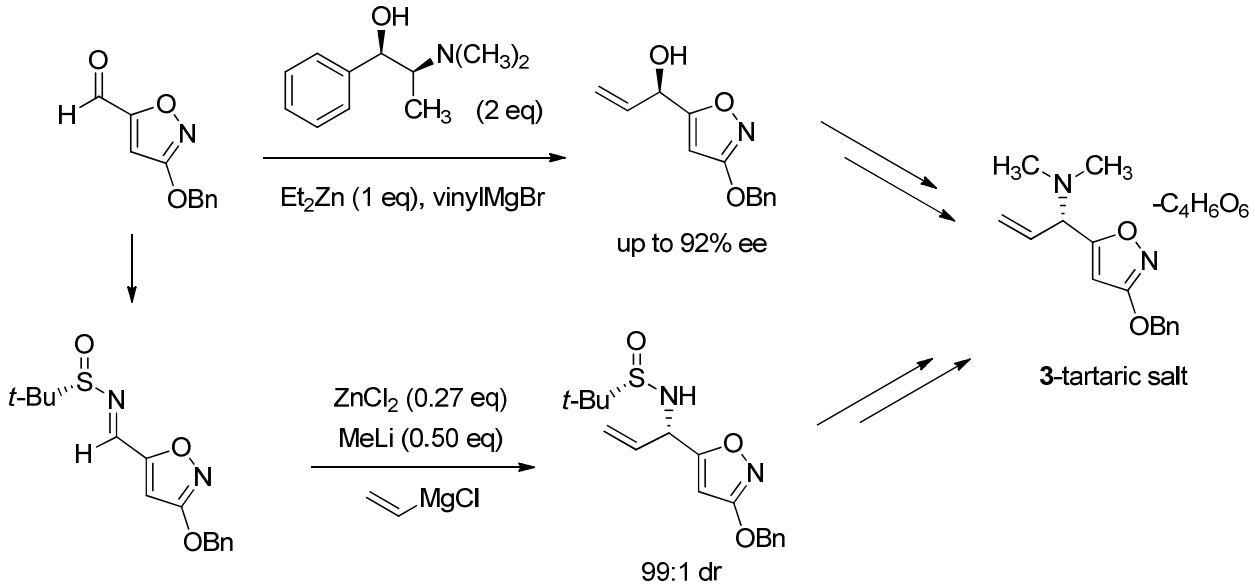


ABSTRACT

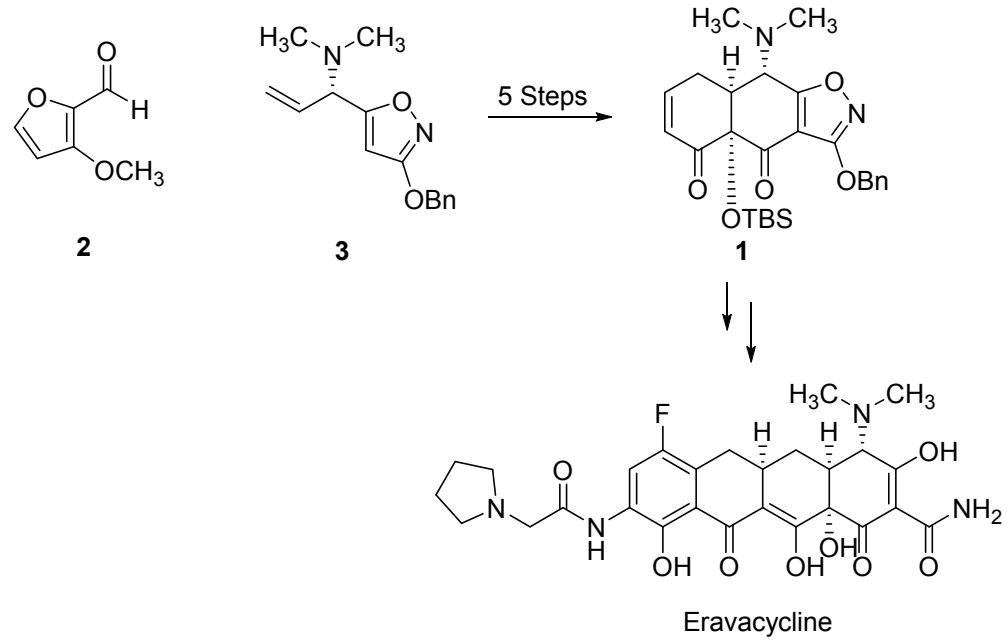
A robust, cost effective and high yielding manufacturing process for enantiomerically enriched (*S*)-allylic amine **3**, a key intermediate for fully synthetic tetracyclines have been developed. Two novel and scalable asymmetric vinylations resulting in high to excellent stereoselectivity have been developed for the key step. The final product is purified by an efficient crystallization of a L-tartaric salt. The process described has been used to manufacture ~350 kg of the tartaric salt of **3** with 99.0% ee in 8 steps (35% overall yield) from cheap and readily available dimethyl maleate.

Key Words: allylic amine, eravacycline, tetracycline, asymmetric vinylation, isoxazole, sulfonamide

Introduction

As part of our ongoing program to develop an efficient manufacturing approach to enone **1**, a key intermediate in the manufacture of fully synthetic tetracyclines, including our lead candidate eravacycline,[1] we have devoted significant efforts to develop manufacturing routes to intermediates **2** and **3**. These two key intermediates are used as building blocks for the convergent synthesis of enone **1** (Figure 1).[2] Here we present process research and development of intermediate **3**.

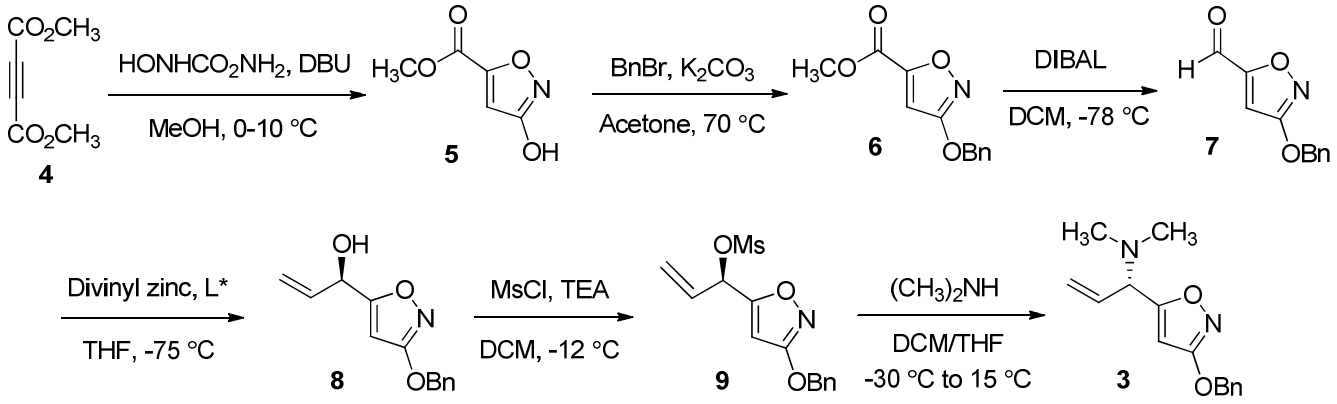
Figure 1 Manufacture of eravacycline from 2 and 3



The original Myers-Brubaker route towards **3** was initially developed into a fit for purpose process to provide material for the initial supply of enone **1** (shown in Scheme 1).[2d] The cost of the starting material, acetylene dicarboxylic acid methyl ester (**4**), was high (>$1000/kg) and the

yield of the isoxazole forming step to provide **5** was modest (~50%) on laboratory scale when attempted at Tetraphase. The second step, benzylation of the hydroxyl group of intermediate **5**,[3] gave the desired benzyl ether **6** but was contaminated with varying amounts of the regioisomeric *N*-Bn-isoxazole (10-20%, vide infra) that could only be removed by chromatography. The reduction of the ester **6** to the aldehyde **7** performed well on small scale, but increasing the scale led to the formation of over-reduced material (the corresponding alcohol) as well as substantial amounts of unconsumed **6**, necessitating chromatographic purification to isolate **7**. The reported asymmetric addition of vinylzinc to the aldehyde within **7** provided **8** with ~90% yield and 92% ee, but manufacturing **8** on a significant scale was complicated by the large amounts of solids formed during the preparation of divinyl zinc. The filtration to remove the formed solids was extremely slow, and if the reaction was done in the presence of these solids, essentially racemic alcohol **8** was obtained. The mesylation of the alcohol **8** and subsequent substitution of the allylic mesylate **9** with dimethylamine to provide **3** produced a mixture of regioisomeric substitution products as well as another significant side product (vide infra).

Scheme 1 Initially reported route to the isoxazole 3

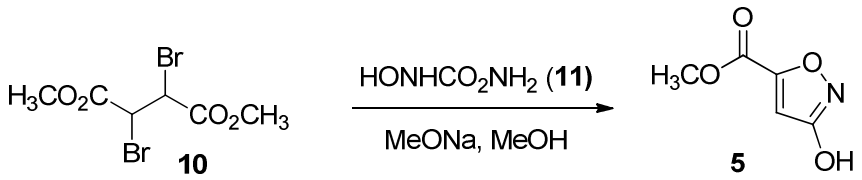


Results and Discussion

Formation of isoxazole 5

A literature search revealed a reported preparation of the hydroxyl isoxazole **5** from dimethyl 2,3-dibromosuccinate (**10,** see Scheme 2) using hydroxyurea (**11**) as the hydroxylamine source promoted by sodium methoxide.[4] We were intrigued by this report as we imagined that **10** would be easily manufactured by bromination of dimethyl maleate or dimethyl fumarate.

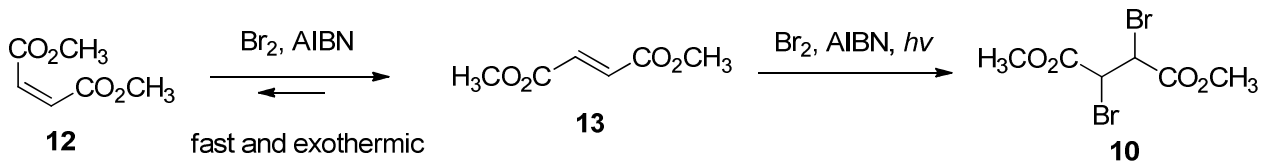
Scheme 2 Preparation of 5 from dimethyl dibromo succinate (10)



Experimentation revealed that **10** could be simply prepared by refluxing a solution of dimethyl maleate (**12,** see Scheme 3, chosen due to its cost relative to dimethyl fumarate) in dichloromethane (DCM) with molecular bromine (1.1-1.3 equiv.) over 2-3 days. In the laboratory, the reaction times could be shortened to as little as 24 h by the inclusion of azo-bis(isobutyronitrile) (AIBN). Further investigations led to the discovery that the bromination proceeded smoothly in the presence of a small amount of water and was significantly accelerated under light radiation from a regular incandescent light bulb. Using a combination of AIBN, water and light, this reaction is normally completed in 7 h in a plant setting. We observed a significant exotherm at the beginning of the reaction as the addition of bromine commenced. Analysis of the reaction mixture by HPLC and ^{1}H-NMR after a small amount of bromine was added indicated a nearly complete isomerization of **12** into dimethyl fumarate (**13**), and we attributed the observed

exotherm to this phenomenon (Scheme 3).[5] After the consumption of both **12** and **13** by HPLC, excess bromine was carefully quenched by the addition of aqueous solutions of inorganic reducing reagents, typically sodium thiosulfate, sodium sulfite or sodium bisulfite. During laboratory runs, the dibromide **10** was typically isolated in quantitative yield as a solid comprised of two diastereomers. During one of manufacturing campaigns, a significant amount of **13**(~20%) was observed after the quench. Investigation showed that if solutions of **10** are left in prolonged contact with concentrated solutions of these inorganic reducing reagents at room temperature (~20 °C), the reduction of significant amounts of **10** to produce **13** readily occurs over the course of a few hours. The debromination of *vicinal*-dibromide to the corresponding (*E*)-alkenes has been well documented.[6] The rate of this reverse reaction was dependent on both the concentration of the reducing reagent in the aqueous layer as well as the temperature during the quench and phase cut. Experimentation revealed sodium bisulfite to be the mildest of the reagents screened, and that if a dilute solution (5 wt%) was used at colder temperatures (0-5 °C) **10** was stable for several hours. Typically, the plant yields were 90-92% after isolation of the product by precipitation with heptane. Since **10** is a skin irritant, a solvent switch from DCM to methanol was performed after work up and **10** was directly used in the next step without isolation during manufacturing.

Scheme 3 Bromination of dimethyl maleate (12)

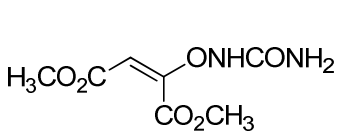


We next investigated the conversion of **10** to isoxazole **5**, which has been reported in the presence of hydroxyurea and sodium methoxide at ambient temperatures using methanol as a solvent.[4] In our development work, the best results were obtained by the addition of sodium methoxide in methanol (4 equiv.) to a suspension of **10** (1 equiv.) and hydroxyurea (**11**, 1.05 equiv.) in methanol while keeping the temperature below 5 °C. Sodium methoxide could also be replaced by potassium *t*-butoxide. Isoxazole **5** was rapidly formed along with a significant side-product (~25%) whose structure is tentatively assigned as that of **14** based on LC/MS and NMR (Figure 2). This side-product is consumed upon warming the reaction to 20-30 °C. However, yield assays for **5** before and after warming were similar, suggesting that **14** is not a productive intermediate. This was further confirmed by following the area % integration of the product and side product by HPLC against an internal standard of chlorobenzene as the reaction was warmed from 0 °C to room temperature. Results demonstrated a slow disappearance of the side product while the concentration of **5** remained constant throughout the process. Significant effort was devoted to lower the initial ratio of the side-product **14**. However, the formation of **14** proved to be surprisingly resilient in a wide range of reaction conditions but fortunately compound **14** decomposes when the reaction mixture is warmed up and ends up being purged during the precipitation of product **5** from the aqueous solution (see discussion below).

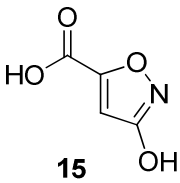
The isoxazole **5** is quite stable in the basic methanolic solutions as long as moisture is excluded. Direct aqueous acidic quench of the reaction mixture led to varying amounts of hydrolysis of the methyl ester within **5** to give the carboxylic acid **15** (Figure 2) even if the quench is performed rapidly. On the other hand, addition of the reaction mixture containing **5** to an aqueous acidic solution led to a smooth quench without the formation of **15**. On laboratory scales, after quench and removal of some inorganics by filtration, the methanol was distilled and

5 could be isolated by extraction from the resulting aqueous mixture using MTBE or 2-methyltetrahydrofuran (MeTHF), the latter performing more efficiently due to better solubility. On larger scales, two observations were made. At very low pH (<2) a substantial amount of **15** was formed even after just a few hours at distillation temperature (30-40 °C). A pH range of 3-4 provided some additional stability. And at an even higher pH (6-7) the process appeared to be quite robust during the long distillation times required to remove the methanol in the plant. Another observation was that **5** precipitated from acidic aqueous solutions once the methanol had been removed by distillation. The product obtained from this precipitation was >95% pure and it could be recovered directly in good yield (~70%). For manufacturing, the reaction mixture is quenched into a mixture of aqueous HCl/H_3PO_4 targeting a final pH of 3 to 6. The pH of the mixture is adjusted to 6-7 and the methanol is distilled to give an aqueous solution of **5**. The hydroxyl proton within **5** is acidic enough to form a salt at this pH range. Re-acidification of this mixture results in precipitation of **5** which can be collected by filtration.

Figure 2 Side products formed *en route* to 5.



14

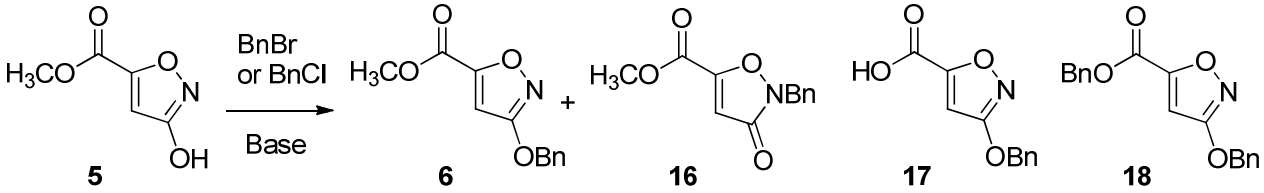


15

Benzylation of 5

The regioselective (O vs. N, 91:9 ratio) benzylation of the hydroxyl group of **5** using benzyl bromide in acetone has been described,[3] and was successful in our hands at small scale. However, modest scale up of the heterogeneous reaction conditions provided the undesired *N*-Bn derivative **16** in 5- 20% yield depending on the scale (Scheme 4).

Scheme 4 Benzylation of 5



This benzylation was examined in several solvents (i.e., THF, acetone, toluene, DMF or NMP), with bases such as K_2CO_3, Na_2CO_3, DBU, or DIPEA and at temperature ranging from room temperature up to 60 °C. The best results were achieved by adding benzyl bromide (1.1-1.2 equiv.) slowly (3-4 h) into a mixture of **5** and K_2CO_3 (2 equiv.) in **5** volumes of NMP at 60 °C. These reaction conditions resulted in acceptable yields of the desired product with ~2% of **16** present. Recrystallization and re-slurry experiments were performed in an attempt to remove **16**, but proved unsuccessful due to the high solubility of **6** in most organic solvents and led to significant losses of product to the mother liquor. Recrystallization with aqueous systems was sometimes successful, but oiling out of **6** was often a problem. Finally it was found that a filtration of the toluene extract through a small pad of silica gel could remove the more polar **16** as well as other baseline impurities. The final solution of the product in toluene could then be telescoped directly into the subsequent reduction step. This procedure was used for initial manufacturing campaigns with reasonable success with varying amounts of the side products **17** and **18** observed. The formation of **17** is also exacerbated during the work up if non-acidic aqueous mixtures are added directly to the reaction mixture, particularly if done slowly. The carboxylic acid **17** is easily removed into basic aqueous washes and any **18** formed is recovered with **6**.

After the initial campaigns, we re-visited using DBU as base. When DBU was used in conjunction with benzyl bromide, only 4-5% of **16** was observed, however DBU was rapidly converted to a quaternary salt with benzyl bromide leading to unproductive consumption of both reagents. The use of benzyl chloride led to a significantly cleaner reaction with nearly undetectable amounts of **16** and with the quaternization reaction being much slower. The reaction could be completed using an acceptable excess of both DBU and BnCl. Additionally, as long as the moisture levels are low at the start of the reaction (KF<0.1%), very little **17** and **18** are observed. For current manufacturing campaigns the solid **5** is dissolved in NMP (4 volumes). DBU (~1.25 equiv.) and BnCl (~1.28 equiv.) are charged and the resulting mixture is stirred for 24 h at 5-10 °C. When the reaction is complete, the mixture is added to aqueous HCl and toluene to mitigate the formation of **17**. The toluene solution obtained can be used directly in the next step.

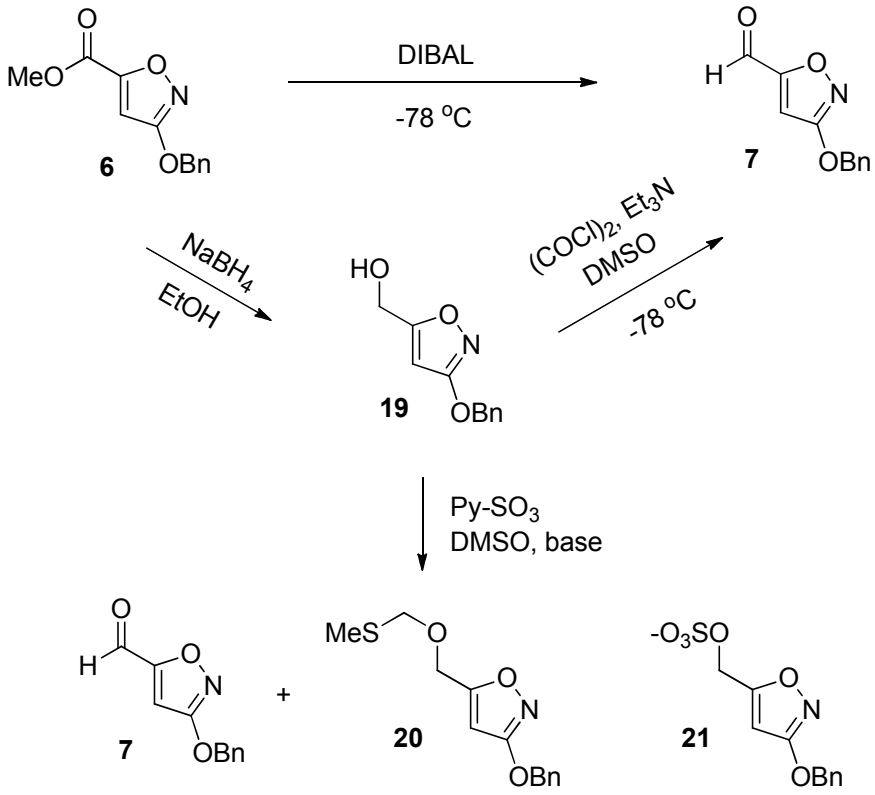
Preparation of the aldehyde 7 from 6

As described previously, ester **6** can be reduced to aldehyde **7** using DIBAL.[3] However, the product was frequently contaminated with unacceptable amount of alcohol **19** necessitating a chromatographic purification. Since the downstream products resulting from the processing of **19** were difficult to remove, our focus shifted to a two-step reduction oxidation sequence that uses the alcohol **19** as an intermediate in the preparation of **7** from **6** (Scheme 5).

The reduction of **6** to produce **19** generated excellent yields using $NaBH_4$ in ethanol. Additionally, the alcohol **19** was a solid that could be recrystallized to high purity. The oxidation of **19** to produce **7** proved more complex than initially anticipated. We initially used a DMSO-SO_3*pyridine based system which we had successfully used in another program. This reagent generated good yield of the desired aldehyde in reactions up to 50 g scale, but in larger reactions

the conversion was not complete and the reaction stalled at 50-70% product. Addition of more reagents did not result in complete conversion; instead an increase in impurities was observed, the two most problematic being tentatively assigned as the methyl thio-methyl ether **20** and the sulfate ester **21.** These two impurities were formed in 3-10% and up to 25%, respectively. Despite efforts to optimize this reaction by changing solvents, amount of reagents, addition times and addition order we were not successful in developing a robust oxidation with this reagent. Additionally, we screened a number of oxidation conditions including activated MnO_2, several conditions using TEMPO and various Swern-like conditions. The TEMPO-based conditions invariably led to substantial over oxidation of **19** to the carboxylic acid **17**. The best results were achieved using the cryogenic Swern condition. This system was selected for further development. The reaction proceeded by adding a solution of **19** to the reagent obtained from DMSO (2 equiv) and oxalyl chloride (1.3 equiv) at -70 to -60 °C for 1 h. Triethylamine (3 equiv.) was added and the mixture was warmed up slowly to produce, after workup, **7** in 91% yield in a manufacturing campaign. Critical to obtaining a good yield of **7** was the hold time at colder temperature after addition of triethylamine as the consumption of **19** took approximately 1 h at -70 to -60 °C. If the reaction was allowed to warm up too soon, the yield was significantly reduced due to the formation of deleterious side products. This two-step reduction-oxidation sequence was used to produce sufficient **7** to support both discovery and early development.

Scheme 5 Preparation of 7 by a two-step sequence from 6 or direct reduction of 6



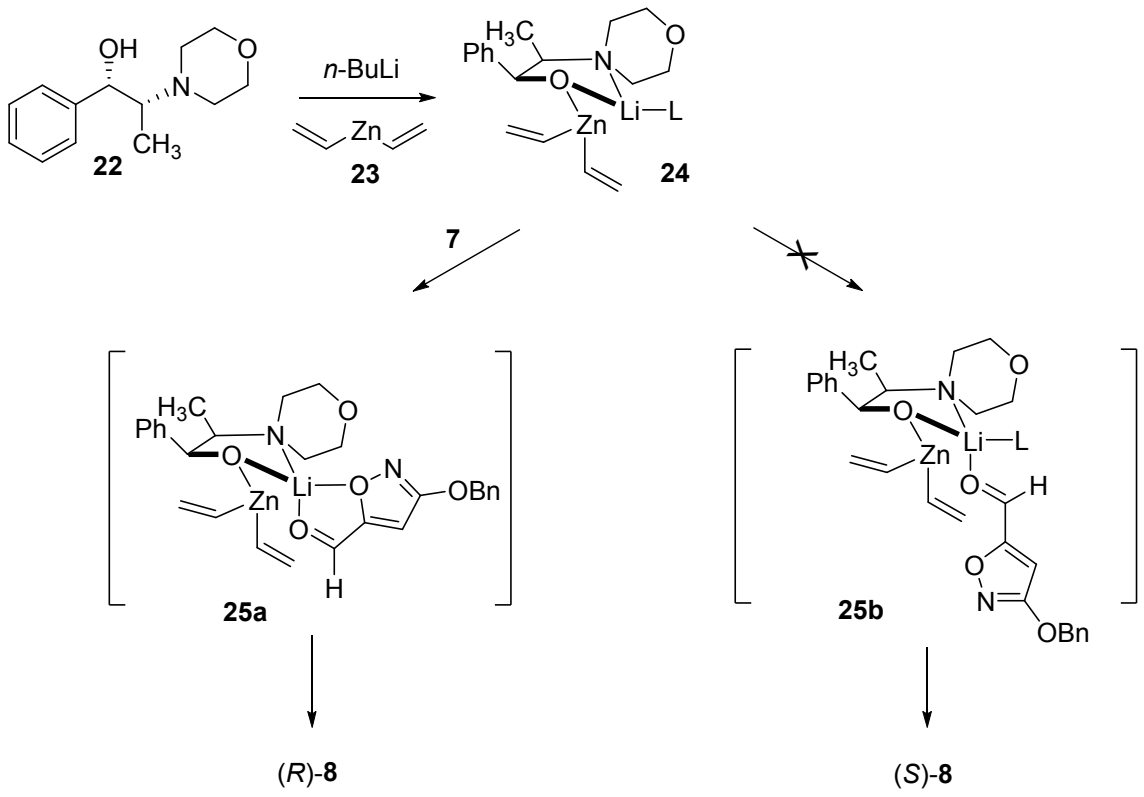
We were disappointed that the cryogenic condition could not be avoided in the two-step approach and reexamined the direct DIBAL reduction of **6** to **7.** Further investigations revealed the key factors necessary for a successful scale up in the manufacturing facility. We used toluene as solvent to allow for telescoping of the material from the previous step. On larger scales the starting material in the reaction mixture precipitated when cooling to <-70 °C and we believed this precipitation was responsible for the formation of significant amounts of alcohol **19** as well as the incomplete consumption of **6**. We found that inclusion of DCM increased the solubility of **6** under the reaction condition and thereby avoiding the precipitation. After the reduction is complete, methanol is slowly added while maintaining the internal temperature below -70 °C to quench the remaining reagent. The low temperature is critical to avoid reduction of **7** during the

quench. To date, yields in the manufacturing facility have been consistently high (89-99%) with >92% HPLC purity.

Enantioselective vinyl addition to 7

A chiral vinyl addition to aldehyde **7** has been developed by Myers and Brubaker (Scheme 6) using the putative stoichiometric complex **24** derived from the norephedrine derivative **22**. The stereochemical model **25a** was proposed to explain the sense of induction observed.[2d]

Scheme 6 Myers-Brubaker vinyl addition to 7



The use of divinylzinc (**23**) as reported provided **8** in high yield and ee in our laboratory. Divinylzinc was prepared by the addition of vinylmagnesium bromide to a solution of $ZnCl_2$ in

diethyl ether. After addition of 1,4-dioxane, a large amount of magnesium halide salts formed and was removed by a slow and impractical filtration. Attempt to use **23** without filtration resulted in the formation of essentially racemic **8.** Use of ZnI_2 or $ZnBr_2$ as the zinc source while omitting the filtration resulted in improved, but still unacceptable, ee of **8** (60% ee and 66% ee respectively). From earlier experiments where $ZnCl_2$ was used to produce the divinyl zinc it was clear that removing inorganic salts was necessary to obtain **8** with acceptable optical purity. We hypothesized that the excess magnesium salts generated interfered with a highly organized transition state for asymmetric induction and this prompted us to think about ways to generate an organized complex absent of excessive amounts of Lewis acidic salts. We thought this could be achieved by incorporating all the Lewis acid salts in the system into the transition complex. We investigated the use of alkyl zinc reagents both as a base to deprotonate amino alcohol ligands as well as a zinc source that could participate in an organized complex[7] to deliver a vinyl group to **7** in a highly enantioselective manner. After initial screen, a study was performed using the combination of different alkyl zinc reagents, vinyl magnesium bromide and amino alcohol **26,** which can be easily prepared from ephedrine, shown to be a privileged additive for this substrate (Scheme 7).

The reaction of a dialkylzinc (1 equiv.) with **26** (2 equiv.) followed by the addition of vinylmagnesium bromide (2 equiv.) provided a complex that reacted with **7** (1 equiv.) at ~ -78 °C to provide **8** with acceptable ee. In this procedure the magnesium atom is part of the transition complex and filtration is avoided. As can be seen from Table 1 below the reaction is relatively insensitive to the solvent used (Entries 1-6). However, the use of only 1 equiv. of vinylmagnesium bromide led to loss of selectivity (Entry 7).

Scheme 7 New enantioselective vinylation of 8

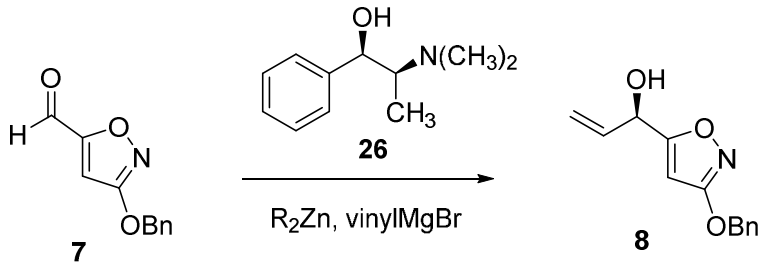


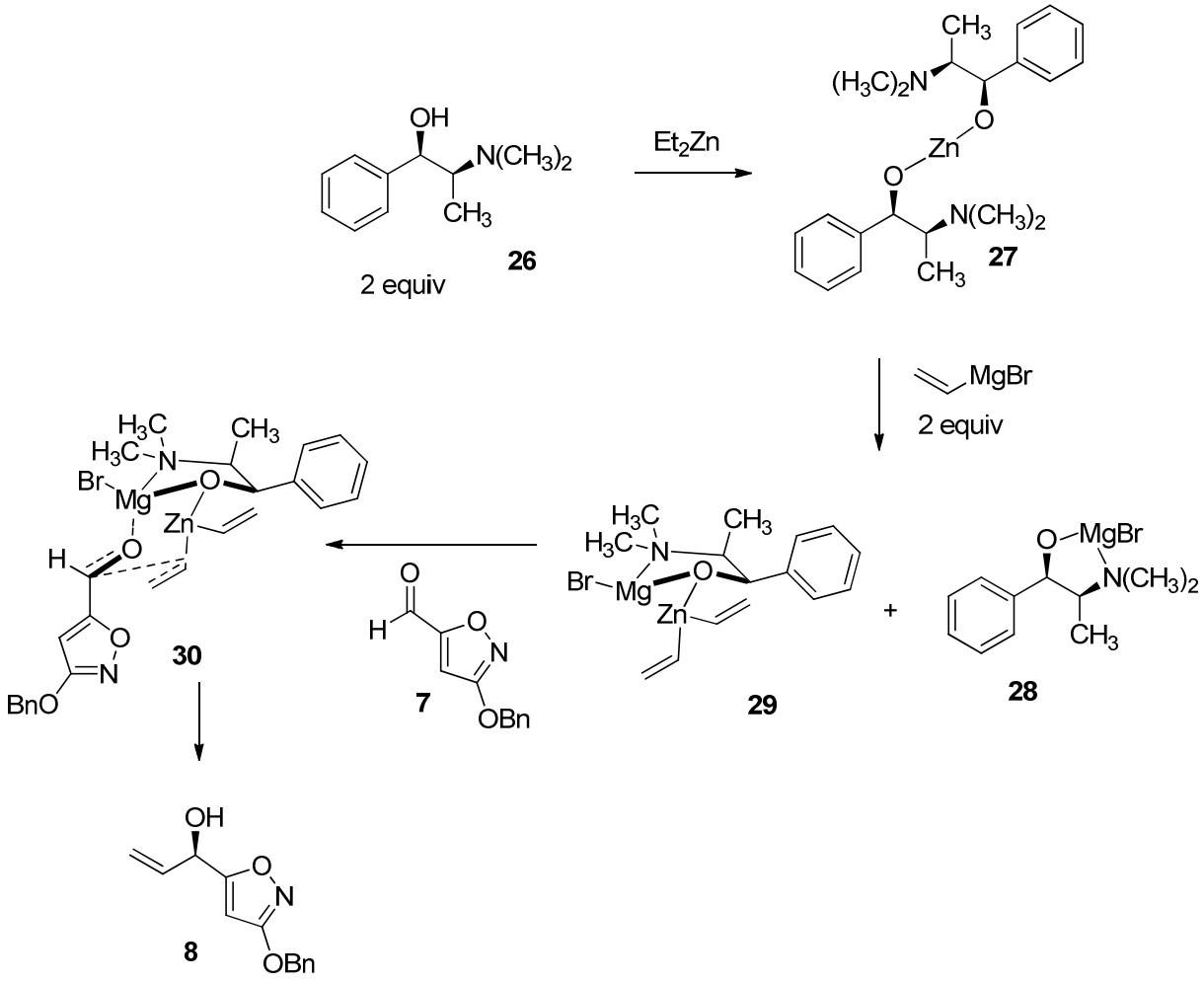
Table 1 Optimization of second generation vinylation of 7

Entry	Alkyl zinc (1eq.)	vinylMgBr (eq.)	Solvent	Temperature (°C)	ee (%)
1	Et_2Zn	2	Toluene	-78	76
2	Et_2Zn	2	THF	-78	84
3	Me_2Zn	2	Toluene	-78	77
4	Me_2Zn	2	MTBE	-78	73
5	Me_2Zn	2	Diethyl ether	-78	80
6	Me_2Zn	2	1,4-dioxane	-78	81
7	Et_2Zn	1	THF	-75	-2

Our mechanistic hypothesis is shown in Scheme 8. The diethylzinc reacts with **26** to provide the Zn (II) alkoxide **27**. Addition of vinylmagnesium bromide (2 equiv.) to this complex would formally lead to **28** (2 equiv.) and divinylzinc (1 equiv.). Complexation of divinylzinc with **28** analogous to **24** shown above produces **29**. Reaction of **7** with **29** followed by delivery of the vinyl group as shown in **30**, where the aldehyde oxygen is chelated with magnesium atom and the vinyl group is transferred via a six-membered transition state to exert the aldehyde *re*-face

selectivity. This could be an extension of the Oppolzer system where the lithium atom is replaced by magnesium.[8]

Scheme 8 Mechanistic hypothesis for second generation vinylation



On multiple occasions, the use of diethylzinc led to the appearance of a by-product derived from the addition of ethyl group to the aldehyde within **7**. We attributed this side reaction to the incomplete reaction of diethyl zinc with **26**. The most reproducible results were obtained when **26** and diethylzinc were heated at 60 °C for several hours to complete the consumption of

diethylzinc, followed by cooling and the addition of vinylmagnesium bromide (2 equiv.). A solution of **7** was added to the resulting reagent at -78 °C to reproducibly provide **8** in good yields (~90%) and ee (89% to 92%) for up to 0.5 kg scale of intermediate **7**. After work up, dimethyl ephedrine **26** can be easily recovered by acid/base extraction and re-used. This process was transferred to a manufacturing facility where 60 kg of the desired alcohol was produced using a 1500 L reactor in multiple batches with an average ee of 86.4% and 88% yield. We discovered that the formation of **27,** which required high temperature, and vinylation of **7,** which required cryogenic conditions, must be conducted in one reactor to avoid loss of selectivity. Switching flasks/reactors after the formation of **27** resulted in lower ee both at lab scale and in a manufacturing facility. Because the cryogenic condition requires a different heat transfer media from heating in a manufacturing facility setting, a significant amount of engineering planning is necessary to convert the reactor for heating into a cryogenic vessel in a short timeframe. This prompted us to develop an alternative vinylation approach (vide infra).

Conversion of 8 to 3

The mesylation of **8** proceeded quickly and cleanly, but the following displacement led to loss of yield mainly due to two major impurities, tentatively assigned as vinylmesylate **31** and linear amine **32** (Scheme 9). To minimize the two impurities, the displacement should initiate at low temperature (-20 to -15 °C) followed by a gradual warm up to 0 °C to drive the reaction to completion. We initially screened different leaving groups (i.e., tosyl, 4- and 2-nitrophenylsulfonyl and trifluoro methylsufonyl) in an attempt to suppress these impurities but we concluded that mesylate was optimal. We investigated several sources of dimethylamine along with various solvents (Table 2). In all cases, the mesylate was formed at -20 °C, dimethylamine was added at the same temperature and then warmed up to 0 °C and quenched.

For all conditions the amount of linear amine **32** was approximately 5%. DCM was the best solvent and that dimethyl amine in EtOH gave the least amount of vinylmesylate **31** (Table 2).

Scheme 9 Mesylation and dimethylamine displacement

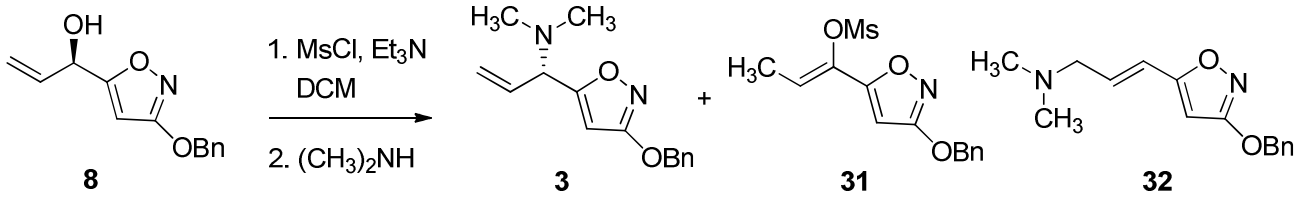


Table 2 Optimization of mesylation-substitution to form 3

Entry	Solvent	Amine solution (6eq)	**31**:**3**
1	DCM (10v)	THF	6.7:1
2	DCM (10v)	EtOH	8.3:1
3	Toluene (5v)	EtOH	3.6:1
4	Toluene (10v)	EtOH	4.3:1
5	2-MeTHF (10v)	EtOH	1.7:1
6	MTBE (10)	EtOH	3.8:1
7	EOAc (10v)	EtOH	2.6:1
9	DCM (20v)	EtOH	12.5:1
10	DCM (10v)	aqueous	6.7:1
12*	THF (10v)	aqueous	

* In this reaction, most of the starting material **8** was recovered.

Salt formation of allylic amine

The allylic amine, which is an oil, is first purified by an acid/base extraction. It could be further purified by column chromatography but we wanted to investigate a salt formation for the purpose of purity upgrade as well as an upgrade of chiral purity in addition to a preference for crystalline solid during large scale manufacture, storage and shipping. A screen using 12 different chiral acids (i.e., L-(-)-10-camphorsulfaonic acid, (+)-10-camphorsulfaonic acid, di-*p*-toluoyl-D-tartaric acid, L-(+)-tartaric acid, D-tartaric acid, D-(-)-mandelic acid, L-(+)-mandelic acid, N-acetyl-L-leucine, D-(-)-quinic acid, L-pyroglutanic acid, L-(-)-malic acid and D-(+)-malic acid) was initiated using 7 different solvents for each one (i.e., toluene, ethyl acetate, MTBE, IPA, acetone, water and acetonitrile). From the screen we found that amine **3** formed crystalline salts with di-*p*-toluoyl-D-tartaric acid (DTTA), L-(+)-tartaric acid and D-tartaric acid with good recovery. While D-tartaric acid did not improve the ee, DTTA improved the ee by 4% only in acetonitrile, and L-tartaric acid improved the ee by approximately 5% in all solvents except in toluene since L-tartaric acid did not dissolve in toluene. NMR revealed that the ratio of amine and DTTA in the salt was always 1:1, regardless if 1 equiv. or 0.5 equiv. of acid was added.

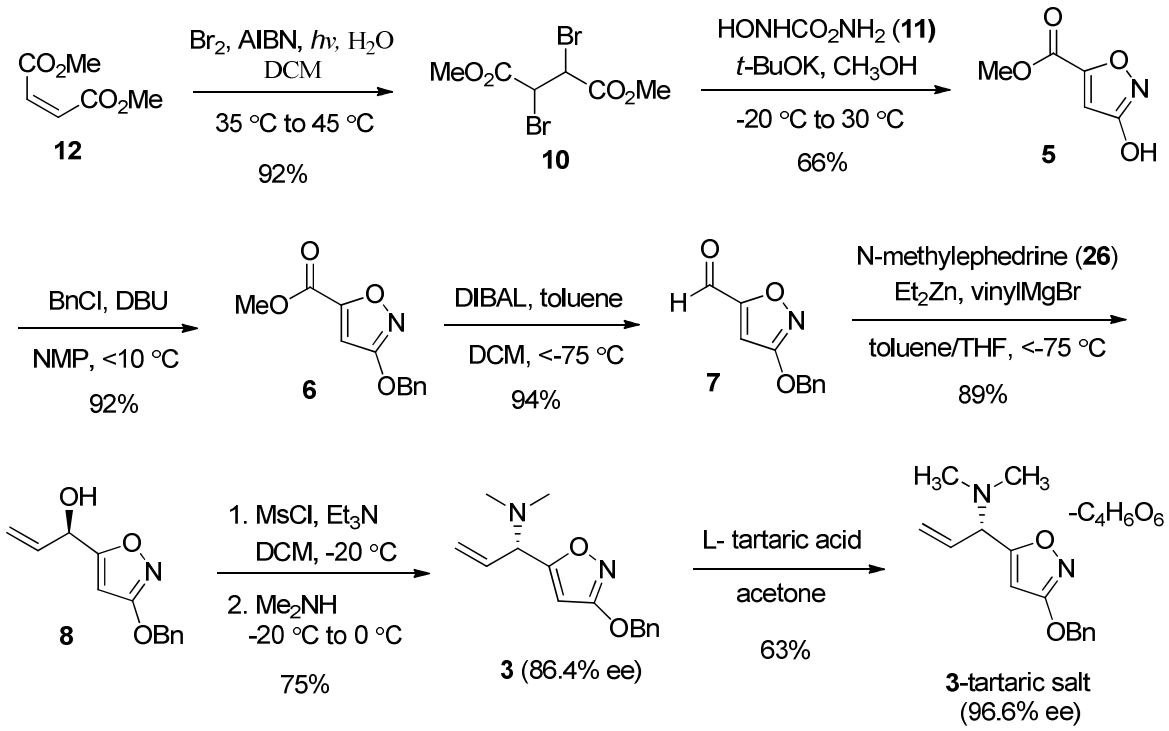
Larger scale (2 g) experiments were carried out to compare these two acids and a variety of solvent system (Table 3) with allylic amine **3** having an ee of 89%. Best results were achieved with L-(+)-tartaric acid using acetone/toluene as solvents, which was selected for further scale-up and manufacturing. The ratio of acetone and anti-solvent toluene can be adjusted depending on the ee of the crude product and the target ee of the final product.

Table 3 Further optimization of salt formation of 3

Entry	Acid	Solvent	Yield	ee of **3** in the Salt	ee of **3** in the Mother Liquor
1	L-(+)-Tartaric acid	Acetone 10 mL Toluene 10 mL	93%	95.2%	14.2%
2	L-(+)-Tartaric acid	IPA 10 mL Toluene 28 mL	81%	98.0%	44.2%
3	L-(+)-Tartaric acid	ACN 10 mL Toluene 12 mL	93%	90.3%	35.0%
4	Di-*p*-toluoyl-D-tartaric acid	ACN 10 mL Water 15 mL	78%	93.6%	81.8%

After this development, an in-house manufacturing campaign was successfully performed to evaluate robustness at scale. The procedure was then transferred to a manufacturing facility that produced approximately 48 kg of the tartaric acid salt. The results for this first generation manufacturing of **3** are summarized in Scheme 10.[9]

Scheme 10 First generation route to 3 from dimethyl maleate 12

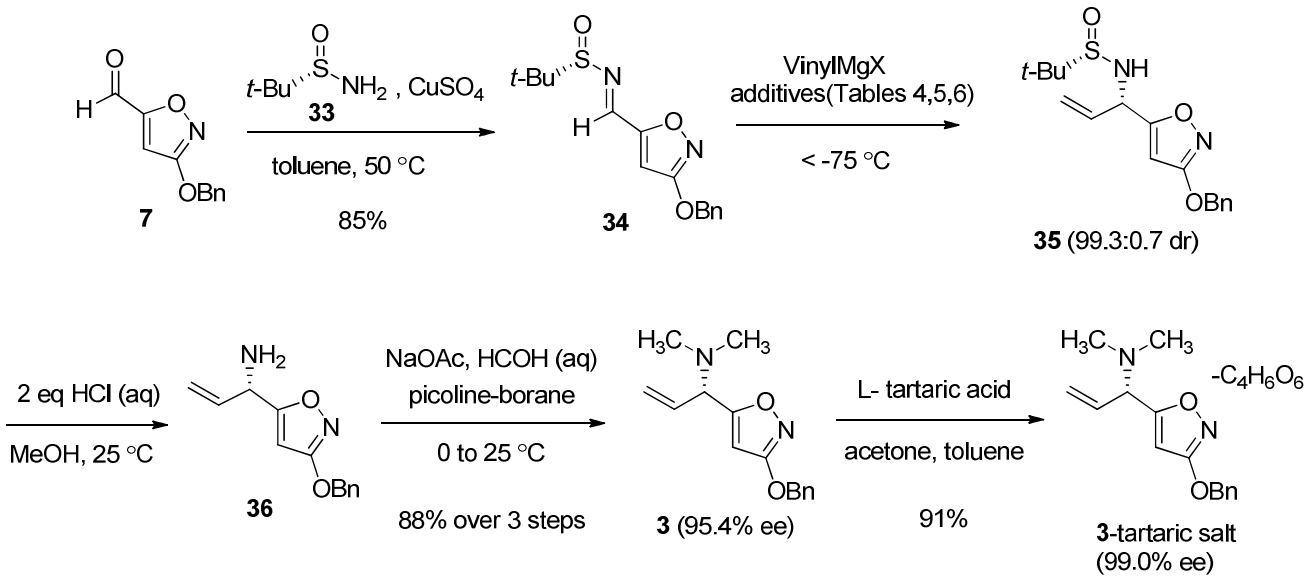


Second Generation route to 3

Despite the process described above was successfully scaled up, we were not satisfied with the complicated operations of the vinyl addition and the modest yield of the dimethylamine displacement. With an adequate route to aldehyde **7** in hand, we explored the possibility of a chiral sulfinamide auxiliary[10]- based approach (Scheme 11). Initial screen of both (*R*)- and (*S*)-2-methylpropylsulfinamide (**33**) revealed that (*S*)-**33** led to desired chirality. Condensation of **7** with (*S*)-**33** in toluene in the presence of copper (II) sulfate at 40 °C proceeded smoothly to produce the imine **34**. The copper sulfate was removed first by filtration then by extraction using aqueous citric acid. The toluene was switched to 2-propanol and **34** was then crystallized by the addition of water. In the laboratory, yields of the condensation/crystallization sequence to produce **34** were as high as 95%, but in the manufacturing facility yield dropped slightly to a still

satisfactory ~85% likely due to some oiling of the material. Improvements for this isolation are ongoing.

Scheme 11 Second generation route to 3 from 7[11]



With the imine **34** in hand we extensively investigated the use of the commercially available vinylmagnesium bromide and vinylmagnesium chloride for the nucleophilic addition of a vinyl group to the imine **34** to provide the amine **35**. Our results are summarized in Table 4.

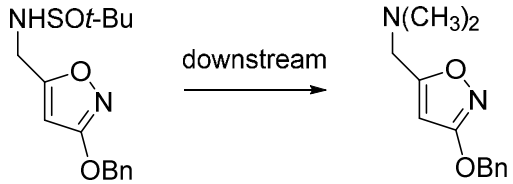
Table 4 Initial Screening of the vinylation of 34

Entry	Nucleophile (2eq)	Solvent (10V)	Temp (°C)	Additive	dr of **35** (^{1}H-NMR)
1	VinylMgCl (1.6 M) in THF	DCM	-78	-	5.4:1
2	VinylMgBr (1.0 M) in THF	DCM	-78	-	9.6:1
3	VinylMgBr (1.0 M) in THF	Toluene	-78	-	2.8:1
4	VinylMgBr (1.0 M) in THF	THF	-78	-	4.7:1

5	VinylMgCl (1.6 M) In THF	THF	-78		2:1
6	VinylMgBr (1.0 M) in THF	CPME	-78	-	3.1:1
7	VinylMgBr (1.0 M) in THF	DCM	-78	TMEDA	1:2.6
8	VinylMgBr (1.0 M) in THF	DCM	-78	$AlMe_3$	15.5:1
9	VinylMgBr (1.0 M) in THF	Toluene	-78	$AlMe_3$	6.5:1
10	VinylMgBr in DCM	Toluene	-78	$AlMe_3$	14.7:1

Although only relatively modest diastereoselectivity was achieved by the use of the commercially available vinylmagnesium halides (Table 4, entries 1 to 6), we did use the best conditions (Table 4, entry 2) successfully for a manufacturing campaign. Subsequent deprotection and reductive amination provided crude **3** (vide infra). Our optimal conditions for the tartaric acid salt formation of **3** produced a 63% yield with 94.2% ee. Attempts to obtain the tartaric salt of **3** in higher yield invariably led to a lower than acceptable ee. After the first manufacturing, further screens found that addition of $AlMe_3$ (3 equiv.) could improve the diastereoselectivity (Table 4, entries 8 to 10).

Scheme 12 Reduction product of 34 and resultant downstream product



37 **38**

Improving the diasteroselectivity of the vinyl addition was clearly critical to improving the overall yield and the use of vinylmagnesium chloride was preferable due to the lower cost of this

reagent and its stability. The use of older bottles vinylmagnesium bromide (3-6 months old) often led to the formation of the reduction product **37**, which in turns led to the formation of a downstream impurity **38** that was difficult to remove (Scheme 12). To date only traces of **37** have been formed using vinylmagnesium chloride (VMC), even when older lots (>6 months old) have been used. The use of VMC THF solution (1.5 equiv.) in conjunction with additives in different solvents was explored (Table 5).

Table 5 Additive screening in vinylation of 34

Entry	Solvent	Temp (°C)	Additive (equiv.)	dr of **35** (^{1}H-NMR)	SM **34**	**37**
1	DCM	-48	$ZnCl_2$ (1.1)		> 90%	
2	THF	-78	$AlMe_3$ in toluene (1.7)	2:1	1.2 %	trace
3	DCM	-78	Dimethylzinc (1.7)	10:1	nd	trace
4	THF	-78	Dimethylzinc (1.7)	9:1	nd	nd
5	THF	-78	Diethylzinc (1.7)	6.5:1	10%	40%
6	DCM	-78	$MgBr_2$ etherate (1.1)	4:1	1.4%	nd
7	DCM	-78	$Ti(OEt)_4$ (1.1)	5:1	64%	nd
8	THF	0	$ZnCl_2$ (1.1)	4:1	> 50%	nd

nd: not detected

Encouraged by the promising dr obtained in entries 3 and 4, we studied literature reports using mixed zincate ligands between vinylmagnesium halides and dimethyl zinc to affect nucleophilic transfer with high diastereoselectivites.[12] In addition to the pyrophoric nature of dimethylzinc, the use of this reagent on scale in stoichiometric amounts was considered cost-prohibitive. On the other hand, methyllithium (MeLi) and $ZnCl_2$ are relatively inexpensive, and we speculated that dimethylzinc could be generated *in situ* by mixing these reagents in a 2:1 stoichiometry. When a solution of $ZnCl_2$ (1.5 equiv.) in diethylether or 2-Me-THF was mixed with MeLi in diethoxymethane (3 equiv.) and VMC (1.5 equiv.) followed by the addition of a solution of **34** (1

equiv.) in THF at -78 °C, we were pleased to observe that **35** was formed in > 99% dr with 10% residual **34** remaining (Table 6, entry 1).

Table 6 Optimization of Zinc catalyst used in the vinylation of 34

Entry	$ZnCl_2$ equiv.	MeLi equiv.	Vinyl MgCl equiv.	LiCl equiv.	**37** (%)	dr of **35** (^{1}H-NMR)	**34** (%)
1	1.5 in ether	3	1.5	0	0.3	99.6:0.4	10
2	1.5 in ether	3	1.7 + 0.25	0	0.2	99.4:0.6	nd
3	1.5 in ether	2.25	2.25	0	0.64	97.9:2.1	36
4	0.5 in ether	1	1.5	0	0.2	99.3:0.7	nd
5	0.1 in ether	0.2	1.5	2.25	nd[b]	97.3:2.7	15.3
6	0	0	1.5	2.2	1.23	75:25	nd
7	0.275 in MeTHF	0	2	0	nd	90:10	nd
8	0.275 (solid)	0	2	3	nd	90:10	nd
9[a]	0.275 in MeTHF	0.5	1.5	0	nd	99.8:0.2	nd
10	0.275 in MeTHF	0.5	1.5	0	nd	99.0:1.0	nd

[a] The solvent THF used in this reaction was intentionally spiked with 250 ppm water and 250 ppm BHT

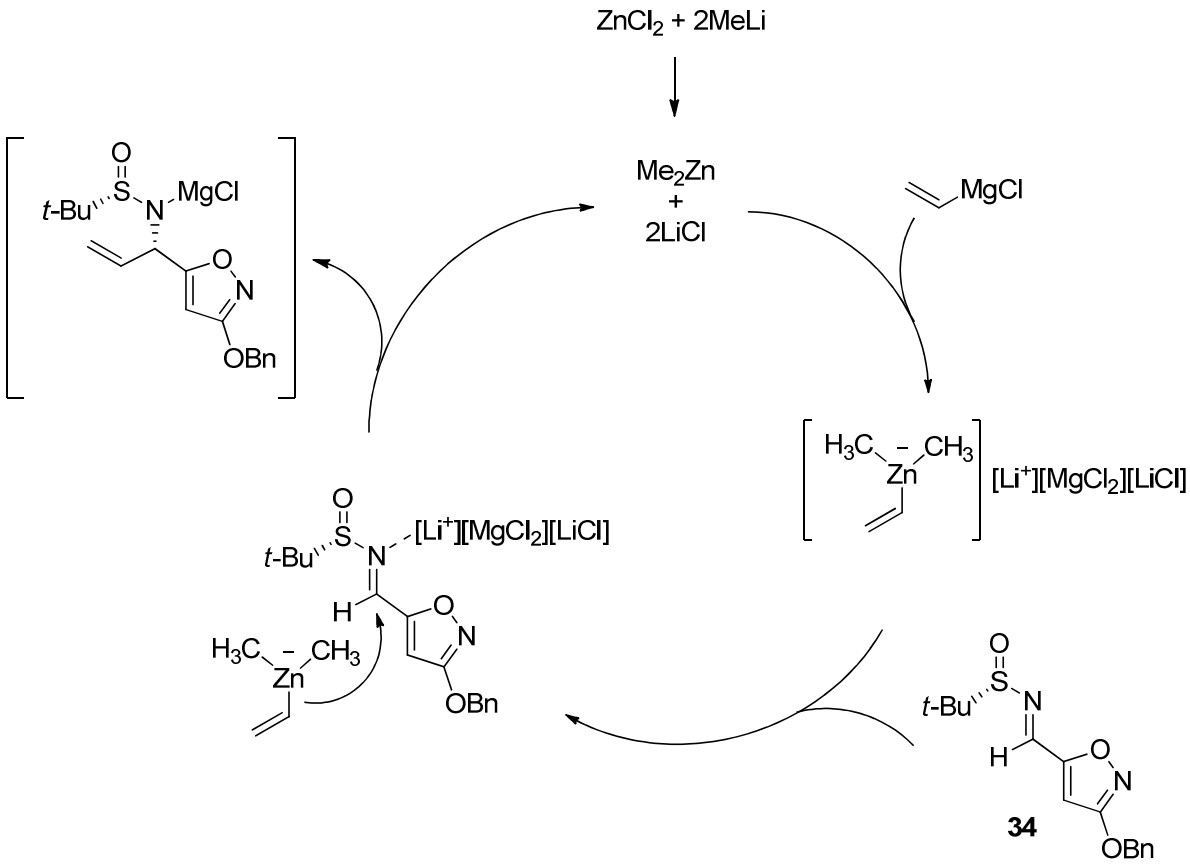
[b] nd: not determined or not detected

The use of additional VMC to drive the reaction to completion did not lead to a significant loss of dr (Entry 2). Lowering the ratio of MeLi to $ZnCl_2$ did however lead to a slight drop in dr (Entry 3). We also observed that when maintaining a 2:1 MeLi/$ZnCl_2$ ratio, the amount of $ZnCl_2$ used could be lowered to 25-50 mol% (Entries 4 and 9) without loss of dr. When only 10 mol % $ZnCl_2$ was used, it did lead to some dr erosion (Entry 5). Several other conditions were also

examined as control experiments. Omission of MeLi and $ZnCl_2$, with the inclusion of LiCl provided a modest 3:1 dr (Entry 6). Omission of MeLi and LiCl provided a 9:1 dr (entry 7). And finally the omission of MeLi with the inclusion of LiCl also provided a 9:1 dr (entry 8). Previous experiment (Table 5, entry 4) showed that dimethylzinc alone provided 9:1 dr. We concluded that the methyl ligands on Zn as well as the presence of LiCl, both formed *in situ*, are critical for achieving the highest diastereomeric ratios observed. These results are in accordance with the observations of Hatano et al[13] that the presence of LiCl is critical for the turnover of zinc in the dialkylzinc catalyzed addition of organomagnesiums to carbonyl systems. A possible catalytic cycle is depicted in Figure 3. The vinyl group is delivered *via* an *in situ* generated zincate which is more reactive towards the imine compared to the vinyl magnesium chloride. In addition, the imine is also activated by the lithium/magnesium complexation. Therefore, under the more sensitive environment, the stereochemical effect from the chiral auxiliary group is amplified leading to better stereoselectivity. Finally, the steric hindrance of the triorganozincate relative to vinylmagnesium may contribute to the enhancement as well. It is worth noting that no significant difference in diastereoselectivity was observed when the additional sequence was changed (i.e., **34** was added to a mixture of MeLi, $ZnCl_2$ and VMC *vs*. VMC was added to a mixture of MeLi, $ZnCl_2$ and **34**). A significant advantage with this is that if the reaction is not complete more VMC can be added. The highly diasteroselective vinylation of the imine **34** has been implemented in a manufacturing setting with a high degree of success (typically 99:1 dr). To the best of our knowledge, this is the first observation where the stereoselectivitiy of a vinylation is significantly improved by dimethyl zinc and LiCl, particularly when only catalytic amounts are required. In addition, compared to other alkyl zinc, the use of dimethyl zinc avoids the risk of addition of the alkyl group to the imine (e.g., the addition of ethyl group to **7**, vide

supra). And the *in situ* formation of dimethyl zinc and LiCl from $ZnCl_2$ and MeLi provides a safe and cost- effective approach for scale up.

Figure 3 Proposed catalytic cycle



Cleavage of the chiral auxiliary within 35 and reductive methylation to 3

The *t*-butylsulfinyl group of **35** was smoothly cleaved to the primary amine **36** under a variety of conditions. Our initial conditions used HCl/THF, where the primary amine was isolated as the free base after extractive workup. The use of Eschweiler–Clarke conditions (HCO_2H, H_2CO, 65 °C) provided only modest yields. Initially, the use of sodium triacetoxyborohydride (STAB) was explored, but in our hands was generally not efficient, needing ~5 equiv. of reducing reagent to provide an acceptable conversion of **36** into **3**. Additionally, on larger laboratory scales, thick

emulsions were observed during aqueous workups. We were intrigued by the use of other boron based reducing reagents for this transformation and examined the pyridine-borane family as these have recently gained attention as useful reagents for reductive aminations, particularly in polar protic solvents including water and methanol.[14] Attempted reductive aminations with pyridine-borane produced **3** but also generated significant amounts of unidentified further reduced products by LC/MS. The use of the commercially available 2-methyl-5-ethyl-pyridine-borane complex provided an excellent chemical transformation, but unfortunately the removal of the 2-methyl-5-ethylpyridine by-product proved to be problematic in downstream operations. The use of 2-picoline-borane as a hydride source provided the same selective and high-yield reaction as 2-methyl-5-ethylpyridine, with the added advantage that the by-product (2-picoline) was easily removed by azeotropic distillation with toluene after workup to provide a solution of crude **3** for the salt-forming step. Further optimization led to a streamlined process where the two steps (cleavage of the chiral auxiliary of **35** and reductive methylation of **36**) were executed in one pot using methanol as solvent to produce **3** without any significant side-products. Best results were achieved when the pH of the reaction mixture is adjusted using NaOAc before the addition of picoline-borane. With this optimized procedure, 80-90% yield from **34** and ~99% ee were achieved including tartaric salt formation. We have observed a 2% to 3% drop of the ee from **35** to crude **3** irrespective of the scale. Stress studies were performed to ensure this slight loss of chiral purity would not be exacerbated with longer reaction time at larger scale.[15]

Conclusion: We have developed a robust and stereoselective process for the manufacture of **3** starting from readily available dimethyl maleate with an overall yield of up to 45%. This approach was demonstrated in our kilo laboratory and in a manufacturing facility making ~ 450 kg of tartaric salt (see experimental section). Two scalable stereoselective vinylation methods

have been developed for the key step. One used a highly efficient one-pot asymmetric vinylation of aldehyde **7** with an ephedrine based ligand together with diethyl zinc and vinyl Grignard to form an allylic alcohol with high ee. The other consist a vinyl addition to (*S*)-*t*-butylsulfinyl imine catalyzed by *in situ* formed dimethyl zinc and lithium chloride with excellent diastereoselectivity. The final product chiral and chemical purity are improved by recrystallization of its L-tartaric acid salt.

Experimental Section:

Preparation of dibromo-succinate 10: To a solution of dimethyl maleate (205 kg, 1.42 kmol, 1 equiv.), DCM (1087 kg) and AIBN (1.15 kg, 9.41 mol, 0.007 equiv.) in a 2000 L reactor was charged bromine (~4.1 kg, 25.7 mol, 0.02 equiv.) in one portion and the resultant mixture was reacted at 35~40 °C for 1 h. IPC (^{1}H-NMR) deemed that all dimethyl maleate was converted into dimethyl fumarate. To the reaction mixture water (12.3 kg) was added in one portion. Bromine (246 kg, 1.54 kmol, 1.08 equiv.) was added over 5h maintaining the internal temperature at 35 to 40 °C. After addition, the reaction mixture was stirred at 35-45 °C for 7 h with light radiation (Type: Ocean's King Lighting, JW7101/LT) until the reaction was complete. The mixture was cooled to 0 ºC and aqueous sodium thiosulfate (5%, 430 kg) was added at such a rate that the internal temperature was maintained below 5 ºC. After layer separation, the organic layer was washed with aqueous sodium thiosulfate (5%, 430 kg) followed by brine (26%, 410 kg). The solvent (DCM) was distilled off and the residual DCM was removed to ≤1.0% by azeotropic distillation with methanol to give a solution of **10** in MeOH (1512 kg with an assay of 26.3% corresponding to 397.7 kg of **10** and 91.9% yield) with water content of 0.035% by KF. The ^{1}H-NMR spectral data were consistent with those reported.[16]

Preparation of isoxazole 5: To a 5000 L reactor was charged the methanol solution of **10** (1512 kg, 26.3 % assay, 397.7 kg of **10**, 1.31 kmol, 1 equiv.) and N-hydroxyurea (103.4 kg, 1.36 kmol, 1.04 equiv.). The resultant heterogeneous mixture was cooled to -20 ºC. A solution of *t*-BuOK solution in methanol (2400 kg, 25w/w%, 5.35 kmol, 4.08 equiv.) was charged over 5 h maintaining temperature at -15±5 ºC. After the addition was completed, the mixture was stirred for 2 h at -15±5 ºC and then warmed to 20-30 ºC. The reaction was deemed complete by HPLC after stirring for 10 h at 20-30 ºC. The reaction mixture was transferred into another reactor containing a pre-cooled solution of conc. HCl (181.7 kg), phosphoric acid (78.3 kg) and water (954 kg) over a period of 4 h maintaining temperature below 5 ºC. After quench, the pH was approximately 6. The solids were filtered off and the resulting filtrate was concentrated under reduced pressure maintaining the internal temperature at 20-25 ºC until no obvious distillate was observed. The pH of the solution (~6) was adjusted to 2 with conc. HCl (22.6 kg). After pH adjustment, the product precipitated and was collected by filtration. The wet product was dried under vacuum at 60 ºC for 26 h to give 124.2 kg of **5** (66.3% yield) as a yellow solid. Water content by KF: 0.1%; Assay: 97.6%; HPLC Purity: 100%. The ^{1}H-NMR spectral data were consistent with those reported.[4]

Preparation of 6: To a 3000 L reactor was charged NMP (452 kg) and **5** (114.5 kg, assay 97.6%, 781 mol, 1 equiv.). After the reaction mixture was cooled to below -5 $^{\circ}$C, DBU (152.3 kg, 1.0 kmol, 1.28 equiv) was charged slowly followed by benzyl chloride (126.0 kg, 1.0 kmol, 1.26 equiv.) maintaining the internal temperature below 0 ºC. After charging the reaction mixture was warmed to 5-10 ºC and was stirred for 24 h at which point the reaction was deemed

complete by HPLC. Toluene (652 kg) was added and the mixture was cooled to 0±5 °C. Aqueous HCl (0.5N, 1097 kg) was added to the mixture maintaining temperature at 0±5 °C. The phases were split and the aqueous layer was extracted with toluene (520 kg). The combined organics were filtered through a pad of silica gel (30 kg) and the pad was washed with 60 kg of toluene. The combined filtrate and washing were then washed sequentially with brine (11%, 1200 kg), aqueous sodium bicarbonate (5%, 1076 kg) and brine (26%, 1082 kg). The organics were dried over Na_2SO_4 (65.3 kg) to give, after filtration, 1400 kg toluene solution of **6** with an assay of 11.97% corresponding to 167.6 kg of **6** and 91.7% yield. HPLC purity: 98.4%. The ^{1}H-NMR spectral data were consistent with those reported.[3]

Preparation of 7: The toluene solution of **6** (1400 kg, 11.97% assay, 719 mol, 1 equiv.) was charged into a 5000 L cryogenic-reactor followed by 580 kg of toluene and 640 kg of dichloromethane. The mixture was cooled to -85 °C. DIBAL (toluene solution, 410 kg, 25wt%, 721 mol, 1.0 equiv.) was charged slowly over a period of 9 h maintaining the internal temperature below -80 °C. After the reaction was deemed complete by HPLC, 127 kg of anhydrous methanol was slowly added maintaining temperature below -78 °C. The mixture was then allowed to warm to -40 to -30 °C and was transferred into another reactor containing an aqueous HCl (4N, 2368 kg). After stirring at 20-25 °C for 30 min the two layers were separated. The aqueous layer was extracted with 1024 kg of MTBE. The combined organics were washed with water (1536 kg) and brine (25%, 2049 kg × 2), and dried over Na_2SO_4 (127 kg). After filtration, the filtrate was concentrated to give 874 kg solution of **7** with an assay of 15.64% corresponding to 136.7 kg of **7** and 93.6% yield. HPLC purity: 95.6%. The ^{1}H-NMR spectral data were consistent with that reported.[3]

Preparation of 8: Toluene was degassed with nitrogen for 4 h and then added to a 1500 L reactor. Dimethyl ephedrine **26** (46.7 kg, 260 mol, 2.6 equiv.) was charged to the reactor through a solid addition funnel. The solution was then degassed with nitrogen for 6 h. Diethyl zinc solution in toluene (30wt%, 54 kg, 130 mol, 1.3 equiv.) was charged maintaining temperature at 10-20 °C. The mixture was heated to 60-65 °C and stirred at this temperature for 2 h. The mixture was then cooled to 0-5 °C, and at this temperature a solution of vinyl magnesium bromide in THF (151.4 kg, 20.4 wt%, 240 mol, 2.3 equiv.) was charged. The mixture was warmed to 20-25 °C and stirred at this temperature for 2 h before being cooled to -85 to -80 °C. A solution of **7** in toluene (99.5 kg solution, containing 20.5 kg of **7**, 100 mol, 1 equiv.), which was pre-degassed with nitrogen for 3 h, was added to the reaction mixture slowly maintaining temperature at -85 to -80 °C. After addition the mixture was stirred for another hour and then warmed to -55 °C followed by stirring at -55 to -50 °C for 0.5 h to drive the reaction to completion. Aqueous citric acid (20%, 332 kg) was added to quench the reaction. The mixture was warmed up to room temperature and filtered. The two layers were separated.[17] The aqueous layer was extracted with toluene. The combined organics were washed with brine (25%, 148 kg) and concentrated to give a thick brown solution (28.4 kg, 73.2 wt%, 20.8 kg corrected, 89.1% yield). HPLC purity: 90.2%. The ^{1}H-NMR spectral data were consistent with those reported.[2d]

The chiral purity was not measured at this step. The material was combined with other similar batches and converted to **3**.

Preparation of 3 from 8: A solution of **8** in DCM (60.6 kg containing 40.3 kg **8**, 174.2 mol, 1.0 equiv.) and 803 kg of DCM were charged into a 1500 L reactor followed by trimethylamine

(22.9 kg, 226.3 mol, 1.3 equiv.). The reaction mixture was cooled to -25 to -20 °C, and at this temperature mesyl chloride (22.9 kg, 199.8 mol, 1.15 equiv.) was charged at a rate of 6.0 kg per hour. After charging, the reaction mixture was stirred for another 0.5 h and the reaction was deemed complete by HPLC. Maintaining at -25 to -20 °C, dimethylamine in ethanol solution (106.7 kg, 44.1 wt%, 1044 mol, 6.0 equiv.) was added into the reaction mixture. After addition, the mixture was warmed up to -17 to -13 °C and was stirred at this temperature for 2 h. The mixture was then gradually warmed up to 0 °C and stirred at 0 °C for 1 h. After the reaction was deemed complete by HPLC, water (403 kg) was added to the reaction mixture maintaining temperature at < 10 °C. The mixture was warmed up to 20-30 °C and the layers were separated. The organic phase was distilled until no obvious distillate was observed. To the residue was added 245 kg of MTBE. The MTBE solution was extracted with 1.0 N HCl twice (236 kg and 131 kg). The combined aqueous layers were washed with MTBE (98 kg) and then cooled to 0-5 °C. After charging MTBE (245 kg), 6 N NaOH (87 kg) was added at < 13 °C to adjust the pH to 13-14. The two layers were separated and the aqueous layer was extracted with MTBE (122 kg). The combined organics were washed with saturated brine (209 kg) and concentrated at 40-45 °C until no distillate was observed to give a thick brown oil (37.8 kg, 89.0 wt%, 33.6 kg corrected, 74.7% yield). HPLC purity: 91.8%; ee by chiral HPLC: 86.4%. The ^{1}H-NMR spectral data were consistent with those reported.[2d]

Preparation of 34: A solution of **7** in toluene (1412 kg solution,[18] containing 261 kg of **7**, 1.28 kmol, 1 equiv.) was charged into a 3000 L reactor followed by (*S*)-*tert*-butyl sulfinylamine (170 kg, 1.40 kmol, 1.09 equiv.) and anhydrous $CuSO_4$ (117.5 kg, 736 mol, 0.57 equiv.). The mixture was heated to 50±2 °C and stirred at this temperature for 16 h. After the reaction was deemed

complete by HPLC the mixture was filtered. The filtrate was washed with 0.5M citric acid (1120 kg) and brine (16.7%, 1178 kg x 3). The organics were concentrated under vacuum at 50-60 °C. The residual toluene was removed by azetropic distillation with IPA. To the residual IPA solution, additional IPA (820 kg) was added and the mixture was heated to 45±5 °C. Water (697 kg) was added at 45±5 °C over a period of 5 h. After water addition, seeding using **34** (0.3 kg) was performed and after stirring for 30 min, new crystal solids formed. Additional water (350 kg) was added over 5 h at 45±5 °C. After addition the mixture was cooled to 0±3 °C at a rate of 10 °C/h and stirred at this temperature for 5 h. The solids were filtered off and the wet cake was dried under vacuum at 40-45 °C for 90 h to give 333.8 kg **34** as a pale yellow solid (84.8% yield). Residual IPA: 0.04%; Water content by KF: 0.05%; HPLC purity: 97.2%; Chiral HPLC: 99.5% to 0.5%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.46-7.33 (m, 5 H), 6.44 (s, 1 H), 5.31 (s, 2 H), 1.25 (s, 9 H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 171.56, 165.13, 149.25, 135.22, 128.59, 128.28, 126.22, 99.10, 72.04, 58.73, 22.55; MS (ESI) *m/z* 307.2 (calcd for M+H: 307.1).

Preparation of 35: To a 5000 L cryogenic reactor was charged 1702 kg of anhydrous THF followed by $ZnCl_2$ (40.6 kg, 298 mol, 0.27 equiv.) under nitrogen. After stirring for 30 min the mixture was cooled to -80 °C. MeLi (3.0 M in diethoxymethane, 183.6 kg, 550 mol, 0.50 equiv.) was charged into the mixture at -85±5 °C followed by vinylmagnesium chloride in THF (1.6M, 1001 kg, 1.64 kmol, 1.50 equiv.). Imine **34** (333.8 kg, 1.09 kmol, 1 equiv.) in 872 kg of THF was added to the reaction mixture at 85±5 °C over a period of 9 h. The reaction mixture was stirred for another 1 h and then transferred to another reactor containing 4000 kg of aqueous NH_4Cl (16.6 wt%) solution maintaining the temperature at -5 to 5 °C. After layer separation, the aqueous layer was extracted with MTBE (1230 kg). The combined organics were washed with

aqueous NH_4Cl (16.6wt%, 2000 kg) and brine (2000 kg x 2), and then evaporated under reduced pressure at 45-55 °C until no obvious distillate was observed. The residue was dissolved in 2162 kg of MeOH and the methanol solution of **35** was directly used in the next step. HPLC purity: 94.5%, dr selectivity: 99.3:0.7. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.29 (m, 5 H), 5.97-5.87 (m, 2 H), 5.46-5.35 (m, 2 H), 5.23 (s, 2 H), 5.01 (t, *J* = 2.4 Hz, 1 H), 3.69 (d, *J* = 4.3 Hz, 1 H), 1.22 (s, 9 H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 171.70, 171.43, 135.56, 133.72, 128.52, 128.43, 128.15, 119.87, 94.05, 71.54, 56.22, 54.87, 22.46 ; MS (ESI) *m/z* 335.2 (calcd for M+H: 335.1).

Preparation of compound 3: To the solution of **35** in MeOH from the previous step (1.09 kmol, 1 equiv.) was charged conc. HCl (211 kg) and the mixture was stirred at 22-28 ºC for 3 h. HPLC deemed that the *t*-butylsulfinyl group of **35** was completely removed. The mixture was cooled to 0-5 ºC and sodium acetate (270 kg, 3.29 kmol, 3.0 eq) was added followed by formaldehyde (37wt% in water, 850 kg, 10.47 kmol, 9.62 equiv.). 2-Picoline-borane complex (233 kg, 2.18 kmol, 2.0 eq) was dissolved in THF (727 kg) and the solution was added to the reaction mixture maintaining the internal temperature below 10ºC. After addition the mixture was stirred for 30 min and then warmed to 22-28 ºC and stirred at this temperature for 16 h. After the reaction was deemed complete by HPLC solvents were removed by distillation under reduced pressure until no obvious distillate was observed. Water (1981 kg) and conc. HCl (553 kg) were added to adjust the pH to ~ 1 and the mixture was extracted with MTBE (1636 kg). The pH of the aqueous layer was adjusted to 8.5-8.8 using aqueous NaOH solution (40wt%, 737 kg). The mixture was extracted with toluene (1650 kg x 2). The combined toluene extracts were washed with water (720 kg) and then distilled under reduced pressure at 55 °C to remove residual 2-picoline. The residue was dissolved in 480 kg of acetone to give a solution of **3** (777.4 kg,

31.93% assay corresponding to 248.2 kg of **3**, 88.3% yield from **34**). HPLC purity: 96.0 %; ee by chiral HPLC: 95.4%. The ^{1}H-NMR spectral data were consistent with those reported.[2d]

Preparation of 3 tartaric salt: The acetone solution containing 247 kg (0.96 kmol, 1 equiv.) of **3** was charged into a 5000 L reactor followed by another 508 kg of acetone and L-tartaric acid (158 kg, 1.05 kmol, 1.1 equiv.). The mixture was heated to 55-56 ºC and stirred at this temperature for 2 h. The mixture was cooled to 43-45 ºC in 1 h. Seeds (0.24 kg) were charged and the mixture was stirred at 43-45 ºC for 4 h, during which time crystals formed. Additional toluene (1432 kg) was added over a period of 5 h at 43-45 ºC. After stirring for additional 2 h at 43-45 ºC, the reaction mixture was gradually cooled to 33-35 ºC and stirred at this temperature for 16 h. The reaction mixture was then cooled to 10-20 ºC and stirred at this temperature for 4 h. The product was filtered and the cake was washed with toluene (232 kg). The wet cake was dried under vacuum at 45 ºC for 26 h to give 372.9 kg product (assay 95%, 354.3 kg corrected, 90.7% yield). HPLC purity: 98.3%; ee by chiral HPLC: 99.0%; Elemental analysis: C 55.39%, H 5.90%, N 6.67%, calculated C 55.88%, H 5.92%, N 6.86%; KF: 0.09%; ROI: 0.07%.

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Compound **3** has been manufactured at Asymchem in Tianjin, China and ChemPartner in Shanghai, China.

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[9] (a) The first 4 steps to **7** represent the current manufacturing process detailed in the experimental section. The last 3 steps used **7** manufactured from an earlier campaign with a non-optimal process. (b) In order to purge impurities (e.g., **32**), the last step crystallization of **3**-tartaric salt used acetone as the sole solvent. The purity of crude **3** (91.8%) was upgraded to 97.5%. This was not typical as it gave low yield. It was not further optimized as the 2nd generation route was already under development.

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[17] The N-methyl ephedrine **26** was in the aqueous layer and was recovered by an acid/base extraction.

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