1
Efavirenz®, a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), and a Previous Structurally Related Development Candidate

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There are a few key enzymes for the proliferation of human immunodeficiency virus (HIV). Reverse transcriptase is one of them since HIV is a member of the DNA viruses. Efavirenz® (**1**) is an orally active non-nucleoside reverse transcriptase inhibitor (NNRTI) and was discovered at Merck Research Laboratories [1] for treatment of HIV infections. Efavirenz® was originally licensed to DuPont Merck Pharmaceuticals which was later acquired by Bristol-Myers Squibb.[1)] The typical adult dose is 600 mg once a day and **1** is one of three key ingredients of the once-a-day oral HIV drug, Atripla® (Figure 1.1).

Efavirenz® (**1**) is the second NNRTI development candidate at Merck. Prior to the development of **1**, we worked on the preparation of the first NNRTI development candidate **2** [2]. During synthetic studies on **2**, we discovered and optimized an unprecedented asymmetric addition of an acetylide to a carbon–nitrogen double bond. The novel asymmetric addition method for the preparation of **2** also provided the foundation for the process development of Efavirenz®. Therefore, in this chapter we will first discuss chemistries for the preparation of **2** in two parts; process development of large scale synthesis of **2** and new chemistries. Then, we will move into process development and its chemistries on Efavirenz®.

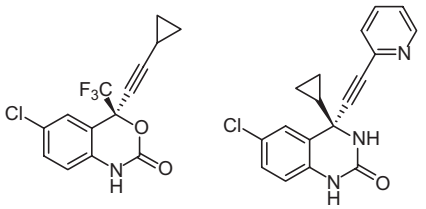

Figure 1.1 NNRTI candidates.

1) Currently, Bristol-Myers Squibb is marketing Efavirenz® under their brand name of Sustiva® and Merck under the brand name of Stocrin®.

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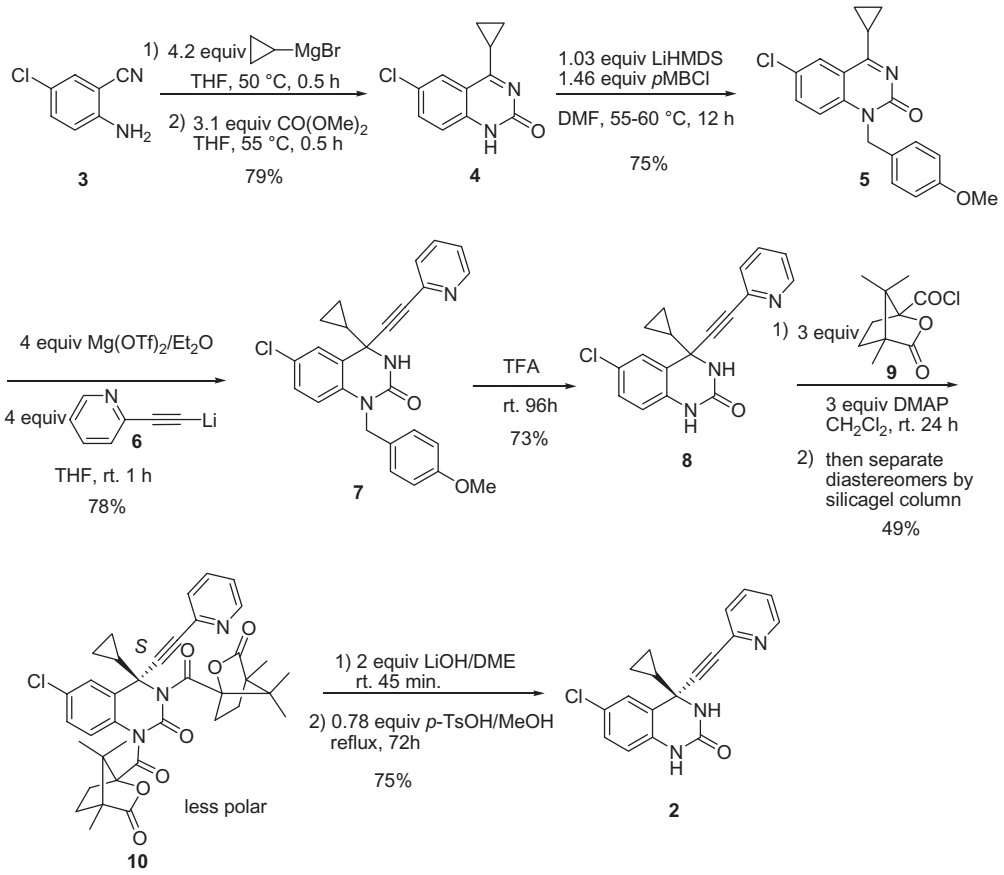
1.1
First Drug Candidate 2

1.1.1
Project Development

1.1.1.1 Medicinal Route

The first NNTRI drug candidate **2** was selected for development in 1992. Compound **2** exhibits very potent antivirus activity of IC_{50} = 12 nM (inhibition HIV-1 RT using rC-dG template/primer). The Medicinal Chemistry original preparation route is depicted in Scheme 1.1 [2].

Medicinal chemists at Merck prepared **2** in eight linear steps with an overall yield of 12%. Their starting material, 4-chloro-3-cyanoanline (**3**), was reacted with



Scheme 1.1 Medicinal original route.

4.2 equiv of cyclopropyl Grignard without protection of the aniline. The resulting imidate was trapped *in situ* with dimethoxycarbonate in THF at 55–60 °C to provide quinazolin-2(1*H*)-one **4** in 79% yield. The free nitrogen of **4** was protected with a *p*-methoxybenzyl (*p*MB) group in 75% yield by treatment with $LiN(TMS)_2$ and *p*MB chloride in DMF at 55–60 °C for 12 h. 1,2-Addition to the carbon-nitrogen double bond in **5** required 4 equiv of lithium 2-pyridylacetylide (**6**) in the presence of 4 equiv of $Mg(OTf)_2$. A racemic mixture of adduct **7** was obtained in 78% yield. TFA treatment of **7** provided the target molecule **8** as a racemic mixture in 73% isolated yield. Reaction of **8** with 3 equiv of camphanyl chloride **9** and DMAP provided a diastereomeric mixture of bis-camphanyl imidate **10** and its diastereomer, which was separated by silica gel column chromatography. The less polar isomer **10** had the desired stereochemistry and afforded **2** after solvolysis. The absolute stereochemistry of **2** was determined as *S* from the single crystal X-ray structure of the enatiomer of **10** (the more polar isomer).

1.1.1.1.1 Problems of the Original Route

Several limitations of the original method were identified at the beginning of the project as follows;

1) When we started this project, the starting material **3** was not commercially available on a large scale (currently, large amounts of **3** are available for around $1000 per kg).
2) A large excess of cyclopropyl Grignard was required.
3) Chiral separation of the racemic product required silica gel separation of bis-camphanyl derivatives.
4) Furthermore, camphanyl chloride is quite expensive ($113.5 per 5 g from Aldrich) and resolving a racemic mixture at the final step of the preparation is not an efficient method for large scale synthesis.

1.1.1.2 Process Development

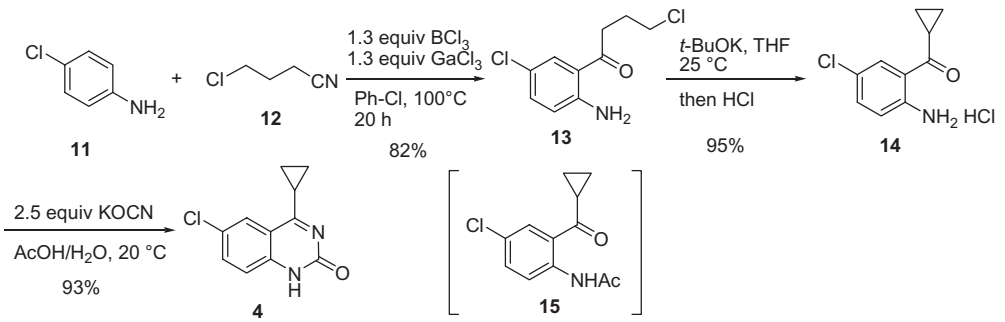
Even though there are a few drawbacks, as mentioned above, we felt that the Medicinal Chemistry route was straightforward and we should be able to use the original synthetic scheme for a first delivery with modifications as follows;

1) Our starting material had to be changed due to the limited availability of **3**. Our new starting material was readily available and was converted to **4**, where our new route intercepted the original synthetic Scheme 1.1.
2) Protection of the nitrogen in **4** faced the classical *N*- versus *O*-alkylation selectivity issue, which was solved by selection of the solvent system. The original protecting group, *p*MB, was replaced with 9-anthrylmethyl (ANM), which provided the best enantioselectivity with the newly discovered asymmetric addition to the ketimine.
3) Asymmetric acetylene addition should be pursued to avoid the tedious final enantiomer separation by silica gel column after derivatization with an excess of expensive camphanyl chloride.

4) The final deprotection step must be modified to accommodate the new protective group (ANM) and an isolation method for a suitable crystalline form of **2** had to be developed.

1.1.1.2.1 Selection of the Starting Material

The starting material for the Medicinal route, 4-chloro-2-cyanoaniline (**3**), was difficult to obtain on a large scale. We decided to use affordable and readily available 4-chloroaniline (**11**), as our starting material [3] and we envisioned introduction of a ketone function by using *ortho*-directed Friedel–Craft acylation of a free aniline, which was reported by Sugasawa *et al*, in 1978 [4], as shown in Scheme 1.2. After optimization of the Sugasawa reaction based on the elucidated reaction mechanism as described later, the desired *ortho*-acylated aniline **13** was isolated in 82% yield from 4-chlorobutyronitrile (**12**) with 2 equiv of **11**, 1.3 equiv of BCl_3 and 1.3 equiv of $GaCl_3$ at 100 °C for 20 h. The resulting chloro-ketone **13** was cyclized to the corresponding cyclopropyl ketone **14** in 95% yield by treatment with KO*t*-Bu. Reaction with **14** and 2.5 equiv of potassium cyanate in aqueous acetic acid nicely intercepted the same intermediate **4** in the original route, in 93% yield. It was important to use the corresponding HCl salt of **14**, instead of a free base, as the starting material, as shown in Scheme 1.2. When the free aniline was used for the cyclization reaction, ~10% of *N*-acetyl impurity **15** was generated under the same conditions.

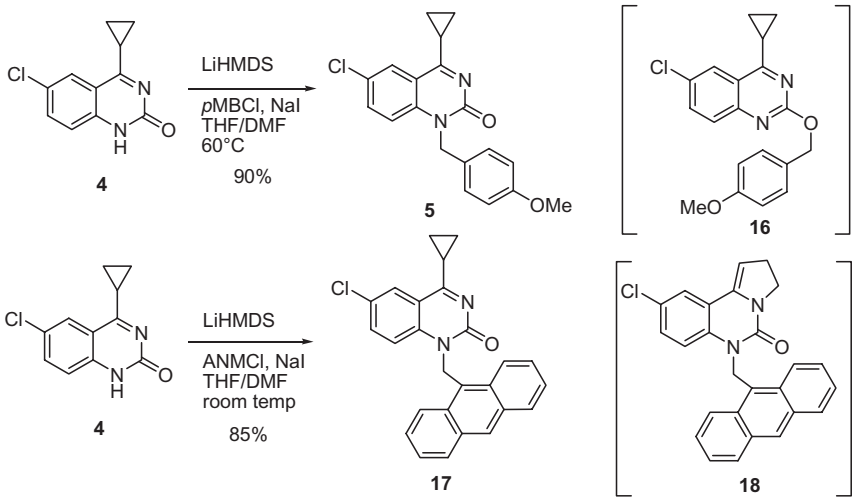


Scheme 1.2 Selection of starting material.

1.1.1.2.2 Protection of Nitrogen in 4

At the beginning of the project, we had studied the introduction of the *p*MB group to **4** as a nitrogen protecting group, as used in the Medicinal Chemistry route. There was a classical regioselectivity problem, *O*- versus *N*-alkylation. Under the Medicinal Chemistry conditions, the desired *N*-alkylated product **5** was mainly formed, but around 10–12% of the corresponding *O*-alkylated product **16** was also

generated in DMF. The desired **5** was isolated in only 75% yield after triturating the crude product mixture with diethyl ether. Theoretically, *N*-alkylation is favored over *O*- when nonpolar solvents are used. The reaction in THF (instead of DMF) was extremely slow but formation of *O*-alkyl **16** was suppressed to about 2%, as expected. Ultimately, it was found that reaction in THF with 8 to 10 vol% DMF proceeded at a similar rate to straight DMF and the formation of **16** was suppressed to about 3%. A methanol swish of the crude product mixture was highly efficient, obtaining **5** with a high purity in an excellent yield. The isolated yield of **5** was increased from 75% to 90% by a combination of these modifications (Scheme 1.3).

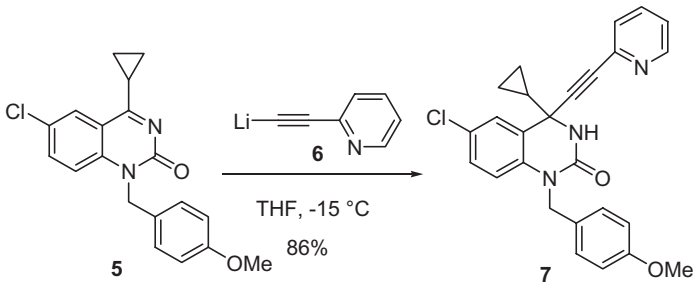


Scheme 1.3 Protection of nitrogen.

Later, we discovered that the nitrogen protecting group of **4** had a strong influence on the enantioselectivity of the newly discovered asymmetric addition of acetylides to the ketimines. After screening potential protective groups, the 9-anthranylmethyl (ANM) group was selected as the most suitable protective group and provided the best ee, as high as 97%, in the next asymmetric addition step. The reaction conditions for protection with the ANM group were modified slightly from those with *p*MB. The reaction temperature was lowered from 60 °C to room temperature to avoid generation of impurities. The desired ANM derivative **17** was obtained in 85% yield as a crystalline compound after swishing the crude product sequentially with chlorobutane and methanol. It was noted that compound **17** was not thermodynamically stable and rearranged into a by-product **18** upon heating in toluene.

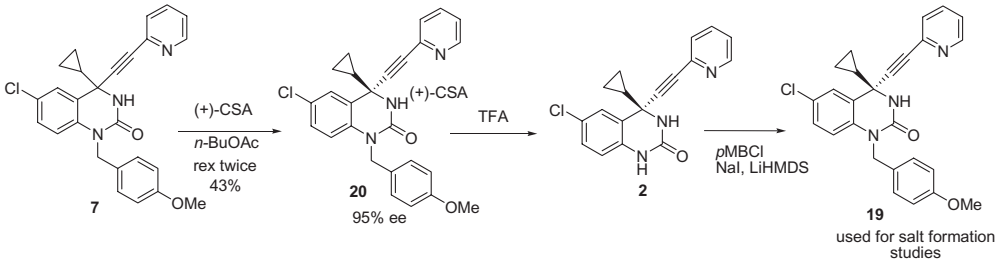
1.1.1.2.3 Addition of Acetylene and Early Development of Final Product Isolation

Acetylide addition in the racemic version Originally, 4 equiv of lithium 2-pyridylacetylide (**6**) in THF/hexane was added to a mixture of **5** and 4 equiv of $Mg(OTf)_2$ in Et_2O at room temperature. Precoordination with $Mg(OTf)_2$ and **5** was reported to be essential to prevent reduction of the carbon–nitrogen double bond in **5** [2]. However, it turned out that precoordination was unnecessary for this reaction, as shown in Scheme 1.4, and racemic adduct **7** was obtained in 86% yield by treatment with 1.3 equiv of **6** at −15 °C in THF without $Mg(OTf)_2$.



Scheme 1.4 Racemic addition of acetylene.

Classical chiral resolution with camphorsulfonic acid, followed by removal of *p*MB It is always a good idea to have some back-up synthetic scheme which is workable, especially with tight project timelines, if at all possible. Of course, asymmetric addition of acetylide is the ideal solution for the project, but at the beginning of the project we investigated a "quick fix", classical chiral resolution [5] (Scheme 1.5).



Scheme 1.5 Acetylene addition, chiral resolution with (+)-CSA.

Our approach for chiral resolution is quite systematic. Instead of randomly screening different chiral acids with racemic **7**, optically pure *N*-*p*MB **19** was prepared from **2**, provided to us from Medicinal Chemistry. With **19**, several salts with both enantiomers of chiral acids were prepared for evaluation of their crystallinity and solubility in various solvent systems. This is a more systematic way to discover an efficient classical resolution. First, a (+)-camphorsulfonic acid salt of **19** crystallized from EtOAc. One month later, a diastereomeric (-)-camphorsulfonic acid salt of **19** also crystallized. After several investigations on the two diastereomeric crystalline salts, it was determined that racemic **7** could be resolved nicely with (+)-camphorsulfonic acid from *n*-BuOAc *kinetically*. In practice, by heating racemic **7** with 1.3 equiv (+)-camphorsulfonic acid in *n*-BuOAc under reflux for 30 min then slowly cooling to room temperature, a crude diastereomeric mixture of the salt (59% ee) was obtained as a first crop. The first crop was recrystallized from *n*-BuOAc providing 95% ee salt **20** in 43% isolated yield. (The optical purity was further improved to ~100% ee by additional recrystallization from *n*-BuOAc and the overall crystallization yield was 41%). This chiral resolution method was more efficient and economical than the original bis-camphanyl amide method.

Deprotection of the *p*MB group from **20** proceeded smoothly in TFA to provide the drug candidate **2**. The isolation conditions of a suitable crystal form of **2** for development were optimized later since we had to change the protective group of the nitrogen of **4** for the subsequent asymmetric addition reaction.

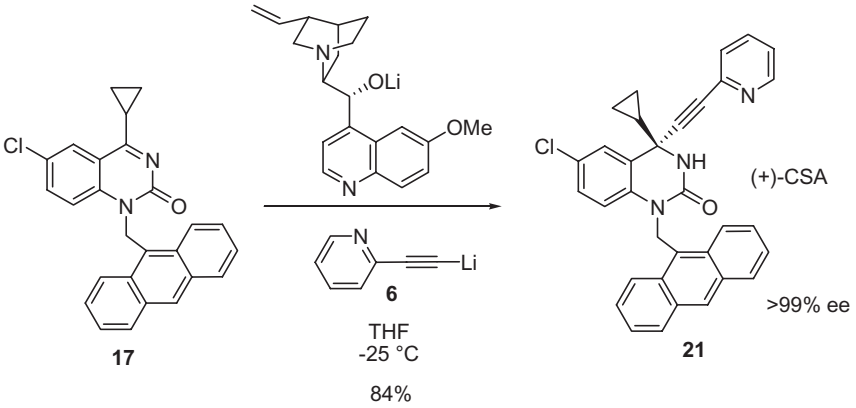
Asymmetric addition of 2-pyridylacetylide to ketimines 5 and 17 Even though the chiral resolution was much more efficient than the chromatographic method, we felt this resolution method was still not efficient enough for larger scale preparation of **2**. However, this resolution method provided us some assurance for investigation of the unprecedented asymmetric addition of the acetylide, since upgrades of ee of adduct **7**, even low ee, had been achieved upon recrystallization with (+)-camphorsulfonic acid.

There are many reports on the asymmetric addition of nucleophiles to carbon–nitrogen double bonds [6]. However, the majority of these reports are based on substrate control and rely on chiral auxiliaries in imines. Moreover, almost all of these reports are just for aldo-imine cases [7].

Regarding the reagent control asymmetric addition to imines, there were three reports with aldo-imines. Based on our best knowledge, no asymmetric addition to ketimine was reported prior to our work (*vide infra*).

Taking Tomioka's pioneering work [8] as a precedent, we have screened β-amino alcohols as chiral modifiers [9] in the nucleophilic addition of lithium 2-pyridinylacetylide **6** to the *p*MB protected ketimine **5**. We were pleased to discover that when **5** was treated with a mixture prepared from 1.07 equiv each of quinine and 2-ethynylpyridine by addition of 2.13 equiv of *n*-BuLi in THF at −40 to −20 °C, the desired adduct **19** was obtained in 84% yield with maximum 64% ee. Soon after, we found selection of the nitrogen protective group had great influence on the outcome of the asymmetric addition and the ANM (9-anthranylmethyl)

derivative **17** gave us the best result (97% ee in high yield). On a large scale, 2.63 mol of **17** was reacted with 1.4 equiv of 2-ethynylpyridine, 1.5 equiv of quinine, and 2.98 equiv of *n*-BuLi in THF at −25 °C for 14 h. The assay yield of the organic layer, after aqueous quench, was 87% with >97% ee. The product **21** was isolated as a (+)-camphorsulfonate salt in 84% yield with >99%ee (HPLC area% at 220 nm was 99 A%), as shown in Scheme 1.6 [10].

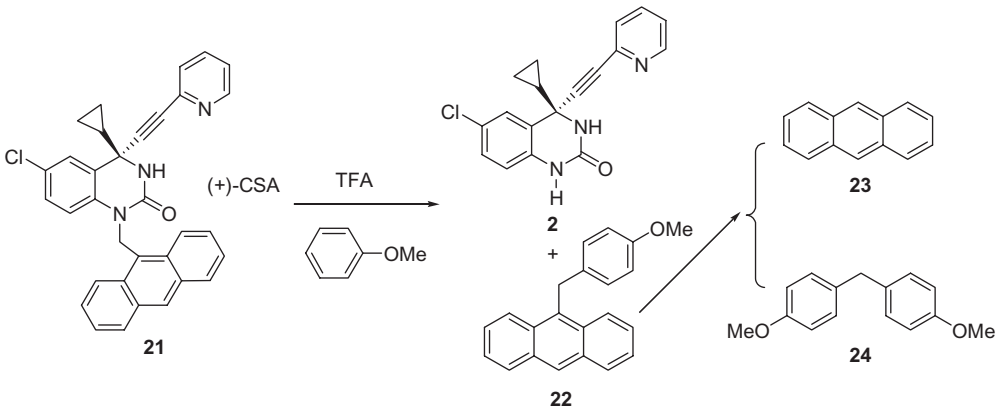


Scheme 1.6 Asymmetric addition of 2-pyridinylacetylide.

1.1.1.2.4 **Deprotection and Isolation of the Drug Candidate 2**

The ANM group in **21** could be removed under conditions similar to those for the removal of the *p*MB group, and the reaction was faster than that of *p*MB, since anthranylmethyl cation is more stable than *p*MB cation. However, the anthranylmethyl cation also reacted with the product **2** under the reaction conditions. Therefore, we had to add cation-trap reagents, such as anisole or thioanisole, to the reaction mixture. Both reagents were equally effective but anisole was selected due to easier handling and benign smell. The reaction proceeded smoothly with (+)-camphorsulfonate salt **21** in 1 volume of anisole and 1.5 volume of TFA at room temperature overnight and the assay yield of **2** was almost quantitative. However, the work-up was a little more complicated than we anticipated. It was found that the anthranylmethyl cation was successfully trapped with anisole to form a major by-product **22**. Moreover, a portion of compound **22** further reacted with anisole under the reaction conditions, to generate anthracene (**23**) and bis-anisyl-methane (**24**), as depicted in Scheme 1.7. Direct crystallization of **2** from the crude mixture failed because **2** tends to cocrystallize with **23**.

The work-up process was optimized for large scale preparation. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, which was washed with aqueous NaOH (adjusted to pH 8.5). The solvent of organic



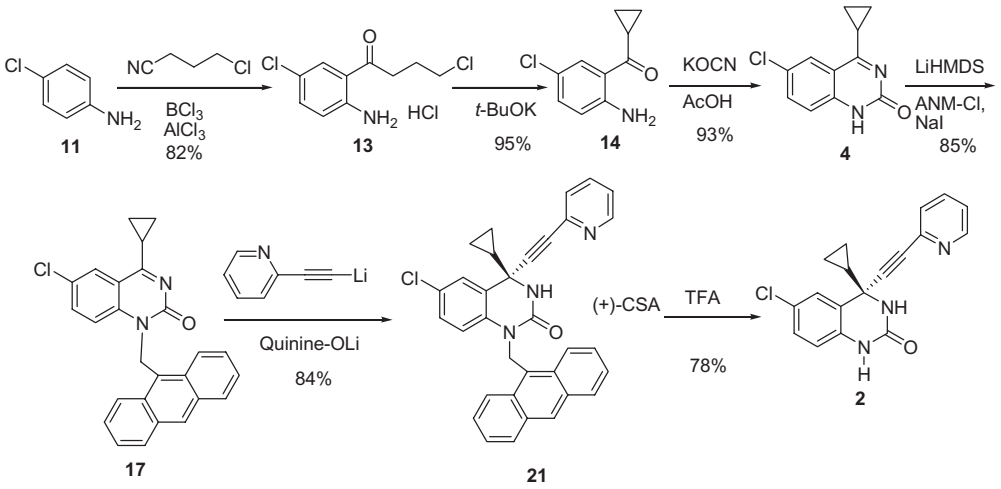
Scheme 1.7 Deprotection of ANM group from **21**.

extract was switched from EtOAc to MeOH. The residual water amount in the MeOH solution was adjusted to 2% by addition of water. The major impurity **22** was precipitated out from the solution and was removed by filtration. Anthracene (**23**) was removed by passing though SP206 (polystyrene resin; 30 volumes based on assay yield of **2**) with elution of 98% MeOH/H_2O (anthracene remained on the resin). The rich cut (typically 1.5 bed volumes) was concentrated and the solvent was switched to EtOAc. Compound **2** was crystallized as a EtOAc solvate, with ~13% loss to the mother liquor. Isolation of EtOAc solvate was performed to ensure removal of trace amounts of anisole from the product. EtOAc was removed by co-distillation of water from a suspension of EtOAc solvate of **2** in water and compound **2** was isolated as its monohydrate in 99.9 A% with 100% ee and overall isolated yield was 78%. It is noted that the X-ray diffraction pattern of EtOAc solvate and monohydrate are almost identical. Thus, EtOAc and water would share the same position in its crystal lattice. Isolation as EtOAc solvate might be eliminated with further development and the isolated yield is expected to be improved, if **2** were selected for late stage development.

1.1.1.2.5 **Overall Preparation Scheme**

Thus, our developed process route is depicted in Scheme 1.8 and process improvements are summarized as follows:

1) Development of drug candidate **2** was supported by providing sufficient amounts of the bulk in a short period of time.
2) Target compound **2** was prepared in six chemical steps in 41% overall yield.
3) Our starting material was changed from non-commercially available 2-cyano-4-chloroaniline (**3**) to readily available 4-chloroaniline (**11**).



Scheme 1.8 Developed process for preparation of **2**.

4) The Sugasawa reaction (*ortho*-acylation of aniline) was optimized for this route using a combination of $BCl_3/GaCl_3$.
5) Installation of an *N*-protecting group was optimized to suppress formation of *O*-benzylation.
6) A classical chiral resolution method was established, prior to investigation of the asymmetric addition of lithium acetylide to the ketimine **5**.
7) The novel asymmetric nucleophilic substitution to the ketimine was discovered and optimized for this preparation.
8) The ANM group was selected as the nitrogen protecting group for the novel asymmetric nucleophilic substitution providing the optimum enantioselectivity.
9) The deprotection process was optimized and unexpectedly generated anthracene was removed by resin treatment.

1.1.2 Chemistry Development

The large scale preparation of the drug candidate **2** was accomplished via the Sugasawa reaction (an *ortho*-selective Friedel–Craft acylation on anilines) and the asymmetric addition to ketimines. *Understanding the reaction mechanism and reaction parameters is the only way to gain confidence that the reactions will perform as required upon scale up*. Below we discuss both subjects in detail.

1.1.2.1 Sugasawa Reaction

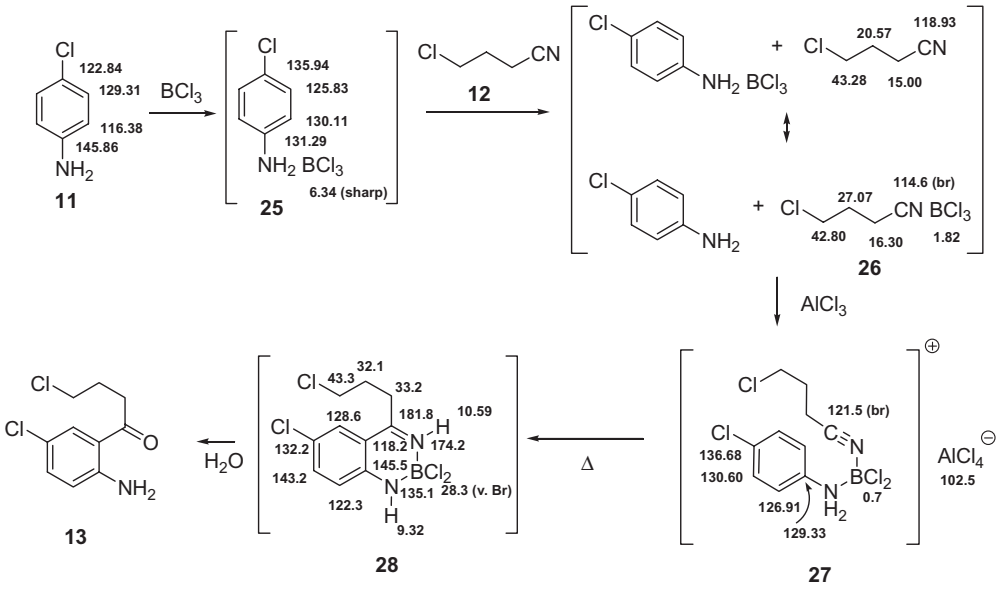
The first time we encountered the Sugasawa reaction was in the early 1990s, when we worked on anti-MRSA carbapenem projects. We were very interested in this

unique reaction and started to investigate it in detail. Generally speaking, Friedel–Craft reaction on anilines is very difficult even though anilines are electron-rich aromatic rings. The reaction requires Lewis acids to activate electrophiles. However, Lewis acids are more prone to coordinate aniline nitrogen instead of electrophiles, and, as a result, the Lewis acid coordinated anilines become electron-deficient aromatic rings and shut down the desired reaction [11]. Thus, to progress the Friedel–Craft reaction with anilines, the nitrogen atom in anilines has to be protected. For example, Kobayashi, *et al.*, reported *para*-selective Friedel–Craft acylation with acetanilide in the presence of a catalytic amount of $Ga(OTf)_3$ [12].

In 1978, Sugasawa *et al.*, at Shionogi Pharmaceutical Co. reported *ortho*-selective Friedel–Craft acylation with free anilines with nitrile derivatives [4]. Sugasawa reported that the reaction requires two different Lewis acids (BCl_3 and $AlCl_3$) and does not proceed when *N,N*-dialkyl anilines are used. He proposed that boron bridging between nitriles and anilines led to exclusive *ortho*-acylation but a conclusive mechanism was not elucidated. The report did not offer any reason why two different Lewis acids were required and why the reaction did not progress with *N,N*-dialkyl anilines. Therefore, we initiated mechanistic studies.

1.1.2.1.1 NMR Studies on the Mechanism of the Sugasawa Reaction

Elucidation of the reaction mechanism of the Sugasawa reaction was initiated under the initiative of Dr. Alan Douglas who was the head of our NMR group [13]. The results are summarized in Scheme 1.9.



Scheme 1.9 NMR studies on the Sugasawa reaction.

By addition of BCl_3 to aniline **11** in an NMR tube, formation of a boron complex **25** was confirmed by high-field shifts of the α- and γ-carbons of the anilines and low-field shifts of the β- and δ-carbons in ^{13}C NMR, as indicated in Scheme 1.9. When nitrile **12** was added to the mixture, an equilibrium mixture of **25** and the boron complex **26** of the nitrile was observed. The structure of **26** was also confirmed by the similar ^{13}C NMR chemical shift changes. Next, $AlCl_3$ was added to this mixture. The most striking observation was the formation of the sharp NMR signal of Al. The NMR signal of Al atom is typically broad due to the tendency to form dimeric (or polymeric) complexes. The observed sharp signal indicated that the environment around the Al atom should be highly symmetrical, and the ^{27}Al chemical shift (102.5 ppm) was identical to that reported for $AlCl_4^-$. These data indicated that the Al atom existed as aluminum tetrachloride anion. Based on ^{13}C NMR and ^{11}B NMR, a structure of a so-called "supercomplex" **27** was elucidated. In **27**, both the aniline nitrogen and the nitrile nitrogen were simultaneously coordinated to the boron, which lost one of three chlorine atoms to $AlCl_3$. No cyclization of **27** was observed when the reaction mixture was kept at room temperature. Upon heating **27**, a new six-membered complex **28** was identified by ^{13}C NMR and ^{11}B NMR. ^{15}N NMR (Figure 1.2) of the six-membered complex **28** confirmed there were two protons (9.32 and 10.59 ppm), clearly coordinated to two distinct nitrogen atoms (two doublets; 135 and 174 ppm) in **28** and provided additional support for elucidation of **28**. ^{15}N NMR of the crude reaction mixture was very clean showing only **28** and the protonated aniline **11** (a quartet; ~50 ppm). Solvolysis of **28** should lead to the desired *ortho*-acylated aniline **13**, and the six-

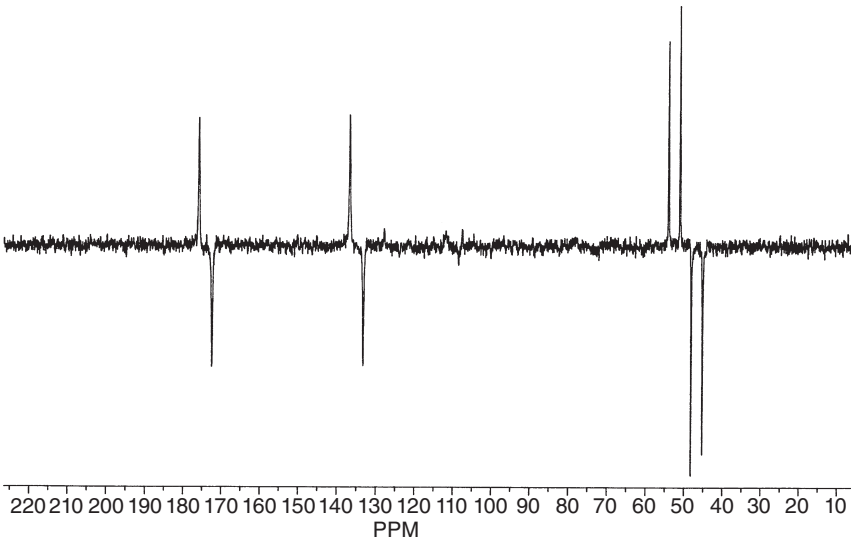


Figure 1.2 ^{15}N NMR (INEPT) of intermediate **28**. The quartet signal around 51 ppm is protonated 4-chloroaniline.

membered complex formation is the origin of the observed *ortho*-selectivity of the Sugasawa reaction.

However, is supercomplex 27 the true intermediate? As previously mentioned, Sugasawa reported that reaction did not proceed with *N,N*-dialkyl anilines. Do *N,N*-dialkylanilines form a similar supercomplex? We examined the following three anilines, $ArNH_2$, ArNHMe, and $ArNMe_2$, as shown in Figure 1.3. Under Sugasawa conditions at room temperature, formation of the corresponding supercomplex, respectively (**29**, **30**, and **31**) was confirmed, based on their NMR analyses (Complex **29** and **31** were derived from toluidine and complex **30** comes from aniline).

Upon heating and subsequent solvolysis, supercomplexes **29** and **30** provided the desired *ortho*-acylated anilines (**32** and **33**) in high yields. On the other hand, supercomplex **31** from *N,N*-dimethyl *p*-toluidine did not cyclize upon heating and only starting material was recovered, as Sugasawa reported. The failure elucidated that the supercomplex was not the true intermediate, at least in the case of *N,N*-dialkyl anilines. Since the structures of the supercomplex **27** and the six-membered complex **28** share common structural features, the true intermediate should also have a similar framework. The electron density of the aniline ring in the supercomplex should be very low since the aniline moiety is a part of an electron deficient cationic species. So, it would be reasonable to expect that electrophilic acylation on such an electron-poor ring would be prohibited. A proton should be eliminated from the supercomplex to form the true intermediate **34**, which is a neutral compound, prior to acylation to form the 6-membered complex, as shown in Scheme 1.10. Since there is no removable proton available in the supercomplex from *N,N*-dialkyl aniline such as **31**, the Sugasawa reaction could not proceed from *N,N*-dialkyl cases, as reported.

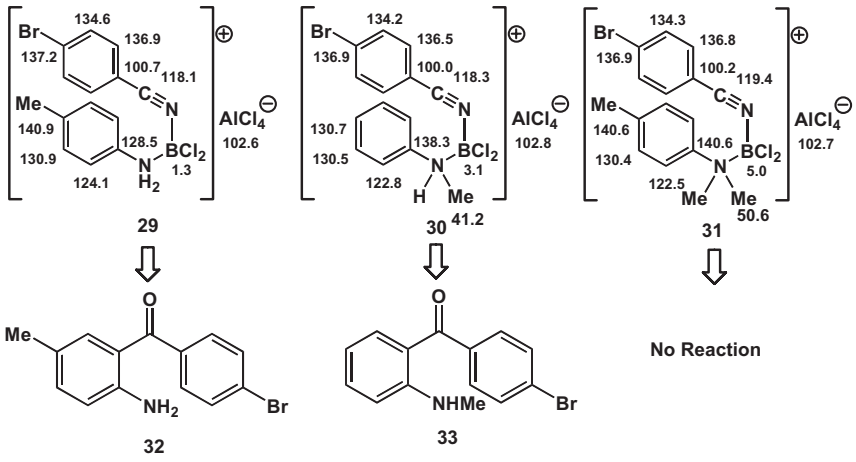
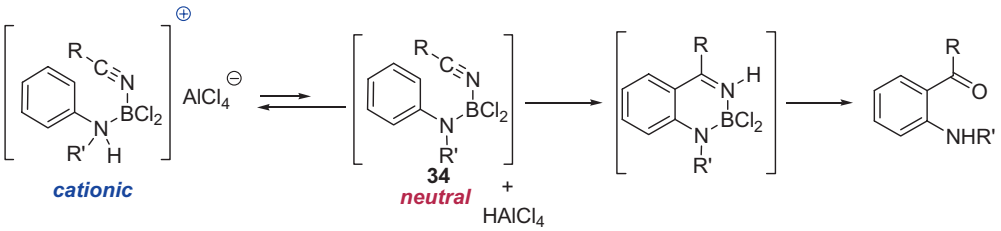


Figure 1.3 Structure of the "supercomplex" from NH_2, NHMe, and NMe_2 anilines.



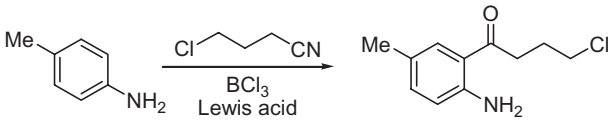
Scheme 1.10 What is the true intermediate?

1.1.2.1.2 Further Optimization of the Sugasawa Reaction Based on the Reaction Mechanism

Based on the elucidated mechanism, the role of an auxiliary Lewis acid has become clearer. The auxiliary Lewis acid bonds strongly with one chlorine of BCl_3. As a result, the boron can coordinate both nitrogen atoms in aniline and nitrile to form the supercomplex. The most chlorophilic Lewis acid is reported as gallium [14]. In fact, various Lewis acids were tested as an auxiliary, and formation of a supercomplex was confirmed in every case. Among them, $GaCl_3$ provided the best result, as shown in Table 1.1. Sugasawa reaction with $GaCl_3$ proceeded under milder conditions than with $AlCl_3$. When cyclopropyl nitrile was used, the product was isolated in 74% yield together with a cyclopropyl ring-opening product (~4%) with $GaCl_3$ as an auxiliary Lewis acid. However, the same reaction with $AlCl_3$ provided only 30–40% desired product, together with 15–20% ring-opening product. $GaCl_3$ appeared to be more effective, especially for electron deficient anilines. It is also noticed that BCl_3 is essential for this reaction and no reaction was found with an $AlCl_3$ and $GaCl_3$ combination. This is quite interesting since B, Al, Ga, Tl are in Group 13 in the Periodic Table.

This reaction generates 1 mole of $HAlCl_4$, which protonates anilines. Since protonated anilines could not coordinate with BCl_3, the reaction shuts down.

Table 1.1 Other auxiliary Lewis acids for the Sugasawa reaction.



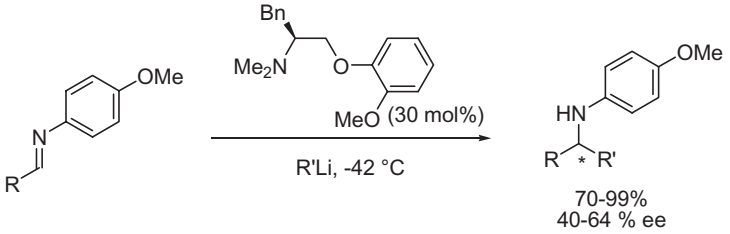
Lewis acid	$GaCl_3$	$InCl_3$	$AlCl_3$	$FeCl_3$	$SbCl_5$	AgOTf
Conditions	c, 26 h, 80 °C	c, 4 h, 132 °C	c, 4 h, 132 °C	t, 17 h, 96 °C	t, 5 h, 78 °C	c, 7 h, 100 °C
Yield (%)	72	63	45	44	26	24

c = chlorobenzene; t = toluene.

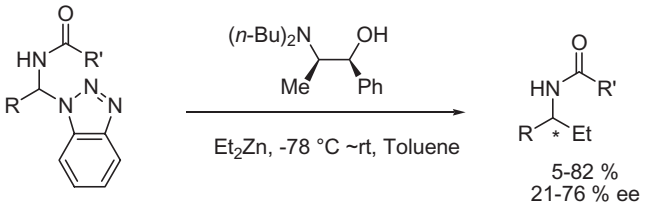
Therefore, addition of bases was studied. Gallium metal[2)] and amine bases were screened. However, the use of 2 equiv of aniline provided the best result.

1.1.2.2 Asymmetric Addition of 2-Pyridinylacetylene Anion to Ketimine 5 and 17

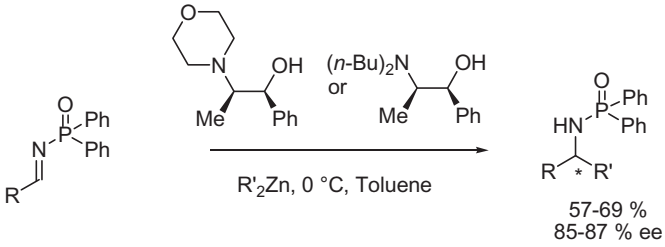
Asymmetric addition to ketimine in a reagent controlled manner has seldom been reported, even by 2008. When we investigated the potential for this asymmetric addition around 1992, there were no known examples. In 1990, Tomioka *et al.*, reported the first asymmetric addition of alkyl lithium to *N*-*p*-methoxyphenyl aldoimines in the presence of a chiral β-amino ether with 40–64% ee [8] (Scheme 1.11). In 1992, Katritzky reported the asymmetric addition of Et_2Zn to *in situ* prepared *N*-acyl imine in the presence of a chiral β-amino alcohol with 21–70% ee [15] (Scheme 1.12). In the same year, Soai *et al.*, reported the asymmetric addition of dialkylzinc to diphenylphosphinoyl imines in the presence of chiral β-amino alcohols with 85–87% ee [16] (Scheme 1.13). These three reports were, to the best of



Scheme 1.11 Tomioka's report in 1990.



Scheme 1.12 Katritzky's report in 1992.



Scheme 1.13 Soai's report in 1992.

2) It was reported that Ga metal reacts with HCl to generate $GaCl_3$ and 1.5 equiv of H_2.

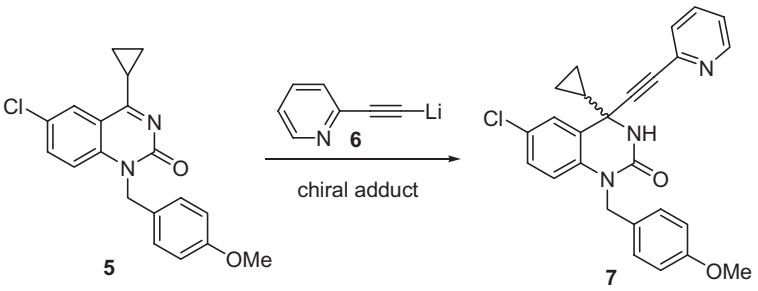
our knowledge, the only examples when we started our investigation on our ketimine **5**.

Based on these reports, we started investigation of the asymmetric addition of acetylide to *p*MB protected **5**, mainly in the presence of chiral β-amino alcohols. Many types of chiral amines were also screened (e.g., diamines, diethers), and it was soon found that addition of β-amino alkoxides effectively induced enantioselectivity on the addition. Since the best result was obtained with a stoichiometric amount of chiral amino alcohols, we focused our screen on readily available chiral β-amino alcohols and the results are summarized in Table 1.2.

While ephedrine derivatives showed some selectivity, the most promising results were obtained with cinchona alkaloids. Lithium alkoxides and lithium acetylides (*n*-BuLi or LiHMDS used to deprotonate both the acetylene and the alcohol) gave better results than the corresponding sodium or magnesium salts. Higher enantioselectivity was obtained in THF (homogeneous) than in toluene or diethyl ether (heterogeneous).

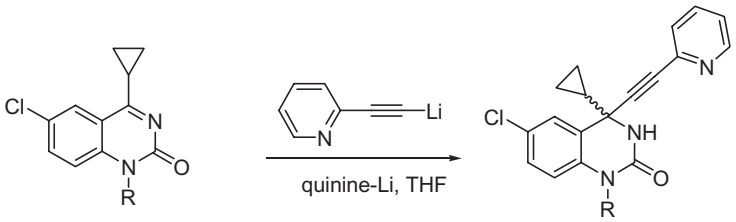
Both quinine and dihydroquinine favored the required (*S*)-enantiomer. A small ee difference of the product might be due to inconsistent purity of the naturally obtained cinchona alkaloids. It was noted that quinidine (the pseudo-enantiomer of quinine) gave the (*R*)-enantiomer with a similar 55% ee. Since quinine was

Table 1.2 Asymmetric addition of 2-pyridiylacetylide to *p*MB protected ketimine 5.



β-Amino alcohol	ee %	Configuration
(1*R*,2*S*)-Ephedrine	1	*S*
(1*R*,2*S*)-*N*-Methylephedrine	10	*R*
(*S*)-1-Methylpyrrolidine-2-methanol	0	
(*S*)-α,α-Diphenylpyrrolidine-2-methanol	0	
Quinine	59	*S*
Dihydroquinine	64	*S*
Cinchonidine	26	*S*
Quinidine	55	*R*
Dihydroquinidine	39	*R*
9-Epiquinine	28	*S*

Table 1.3 Optimization on protective group of ketimine.



R	ee (%)
4-Methoxybenzyl (*p*MB)	64
Benzyl	56
4-Chlorobenzyl	37
Methyl	70
2,4,6-Trimethylbenzyl (TMB)	74
2,6-Dichlorobenzyl	80
9-Anthrylmethyl (ANM)	97

readily available and more affordable than dihydroquinine, we decided to optimize this asymmetric addition with quinine.

The effect of the protective group at the nitrogen was studied and the results are summarized in Table 1.3. Reaction conditions were optimized for each individual substrate.

There was a substantial electronic influence with electron-withdrawing substituents decreasing enantioselectivity. Interestingly, steric bulkiness at this remote part of the molecule was found to be highly effective for asymmetric induction. The bulky ANM group provided 97% ee with a high isolated yield.

Furthermore, it was important to note that this reaction system was very dynamic. There was a large temperature effect on ee and optimum temperature was dependent on the protective groups, as depicted in Figure 1.4. The best yields with *N*-ANM, *N*-trimethylbenzyl (TMB), and *N*-*p*MB were obtained at −25, −20, and −30 °C, respectively. Either higher or lower temperatures resulted in poor enantioselectivity. These phenomena might be a hint, suggesting that thermodynamic change of the anion species' aggregation stage played a key role in enantioselectivity. This was eventually confirmed during process development of Efavirenz®.

The scope and limitations were briefly studied. Unfortunately the scope of the reaction was rather narrow, as shown in Table 1.4. The limit of generality may originate from differences in aggregation of each individual lithium acetylide. For instance, changing 2-pyridyl to 3-pyridyl, the ee dropped to 36%. Furthermore, changing to 4-pyridyl, the ee further decreased to 13%. Fortunately, asymmetric addition of a TMS protected acetylide provided the desired adduct in 82% ee. Since

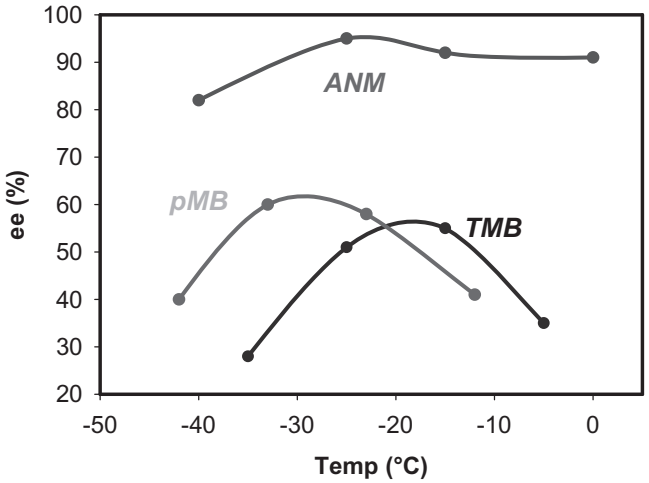
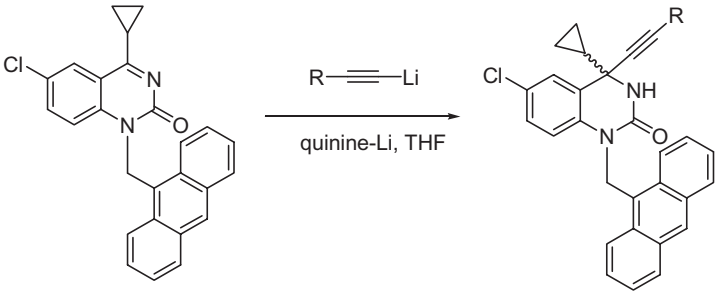


Figure 1.4 Temperature effect on asymmetric addition.

Table 1.4 Scope of acetylide.



R	Temperature (°C)	ee %
2-Pyridyl	–25	94
2-Pyridyl	–15	92
3-Pyridyl	–25	22
3-Pyridyl	–15	36
4-Pyridyl	–25	6
4-Pyridyl	–15	13
4-MeO-Ph-	–25	86
Ph-	–15	65
4-Cl-Ph-	–15	58
Bu-	–25	77
TMS-	–25	82

the Sonogashira reaction allows any substitution on acetylene, this method became a general method, even though it required additional reaction steps.

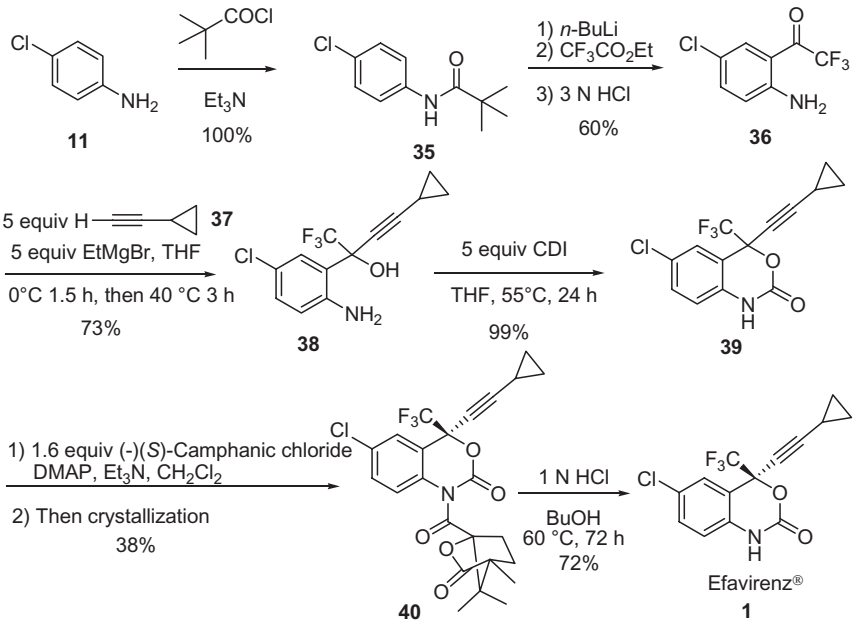
Thus, we discovered the first asymmetric nucleophilic addition of acetylides to ketimines. The reaction mechanism was unfortunately not clear during this study but we felt that aggregation of lithium species might play an important role.

1.2 Efavirenz®

1.2.1 Project Development

1.2.1.1 Medicinal Route

Efavirenz® (**1**) was chosen over compound **2** as a developmental candidate in 1993 based on its better antivirus activities, especially against resistant strains [1, 17]. Efavirenz® is the first HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) which was approved by the FDA on September 21, 1998. The original Medicinal Chemistry method to prepare Efavirenz® is depicted in Scheme 1.14.



Scheme 1.14 Original Medicinal Chemistry route for Efavirenz® (**1**).

Efavirenz® (**1**) was prepared from 4-chloroaniline (**11**) rather straightforwardly in seven chemical steps in an overall yield of 12%. *Ortho*-Trifluoroacetylation of

aniline **11** was carried out via a traditional three-step method yielding trifluorobenzophenone **36** [18] in 60% overall yield. First, the aniline nitrogen was protected as a pivalate **35** in quantitative yield. The dianion of **35**, generated by addition of *n*-BuLi, was reacted with ethyl trifluoroacetate to provide an *ortho*-acylated intermediate. Subsequent acidic solvolysis of the pivalate group gave the desired ketone **36**.

Addition of an acetylide to ketone **36** was sluggish and required 5 equiv of magnesium acetylide, even at 40 °C. This sluggishness may be due to reduction of electrophilicity of the carbonyl group by deprotonation of free aniline **36**. Nevertheless, the desired racemic *tert*-alcohol **38** was isolated in 73% yield by direct crystallization. When we started this project, cyclopropylacetylene (**37**) was rather limited in supply, and expensive. Therefore, the requirement of large excess amounts of **37** was one of the biggest issues in this project. After intensive research and efforts in the chemical industry, acetylene **37** is now one of the most affordable acetylenes due to its large demand for Efavirenz® production [19]. Racemic cyclic carbamate **39** was isolated in 99% yield after reacting alcohol **38** with carbonyldiimidazole (CDI). Racemic **39** was reacted with 1.6 equiv of (-)(*S*)-camphanyl chloride in the presence of triethylamine and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). The desired diastereomer **40** was isolated by simple crystallization in 38% yield. The undesired diastereomer is an oily compound and readily rejected into the mother liquor. Acidic solvolysis of **40** provided Efavirenz® in 72% yield as a crystalline compound.

1.2.1.1.1 Problems of the Original Route

The original Medicinal Chemistry route was straightforward but, from a process chemistry point of view [20], several problems were identified at the beginning of the project and some of them were quite similar to those for the previous development candidate:

1) A large excess of cyclopropylacetylene (**37**) was required. The compound was expensive and its supply was limited.
2) The target compound was obtained as a racemic mixture. Enantiomeric pure Efavirenz® had to be isolated via a classical chiral resolution of a diastereomixture of (-) camphanate imide.
3) (–)(*S*)-Camphanyl chloride is expensive and limited in supply. And the diastereomeric imide formation required 1.6 equiv of the reagent.

1.2.1.2 Process Development

All three previously mentioned issues associated with the Medicinal Chemistry route were rooted in cyclopropylacetylide (**37**) addition to the ketone **36**. Other steps in the Medicinal route are suitable for large scale preparation. Thus, our effort for this process development focused on asymmetric addition to ketone **36** with close to 1 equiv of **37** [21].

Naturally, we thought our novel asymmetric acetylide addition on ketenimine **5** (Scheme 1.6) could also be applicable in the preparation of Efavirenz®. The structure of **36** in Scheme 1.14 is somewhat misleading. We should expect that one of

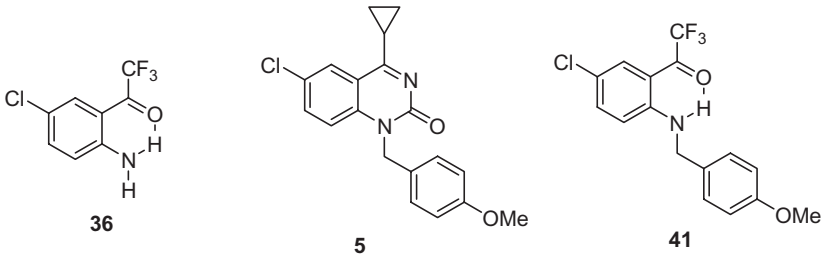


Figure 1.5 Structure resemblance between ketone aniline **36** and ketimine **5**.

the aniline hydrogens of **36** would hydrogen bond strongly to the ketone carbonyl, as shown in Figure 1.5. Therefore, ketone and aniline should consist of a six membered ring and the trifluoromethyl group should be located outside the ring. The other hydrogen in **36** should be protected to avoid deactivation of the ketone toward nucleophilic attack through *N*-anion formation. Once protected as a mono-*N*-*p*MB **41**, the special environment around the ketone of **41** would be quite similar to that of ketimine **5**. Thus, asymmetric addition of a lithium acetylide to **41**, mediated by the lithium alkoxide of cinchona alkaloids, should proceed similarly to the reaction with **5**. This working assumption was our starting point.

In the first half of this section for Efavirenz®, we will discuss the process development of the first and the current manufacturing route by going through each topic shown in the following list.

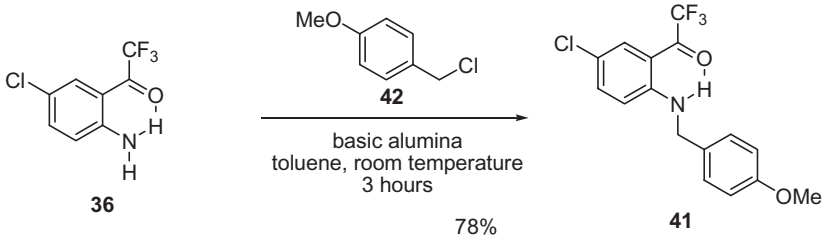
1) Selective mono-*N*-protection of **36**.
2) The first generation of asymmetric addition of lithium-cyclopropylacetylide to **41**.
   - Introduction
   - Preparation of the chiral modifier
   - Preparation of cyclopropylacetylene
   - Asymmetric addition of acetylide to the ketone
3) Preparation and isolation of Efavirenz® (first manufacturing route).
4) The second generation of asymmetric addition of zinc-cyclopropylacetylide to *N*-*p*MB ketone **41** (part of the current manufacturing route).

In the second half of this section, we will discuss the *mechanistic understanding of this chiral addition with lithium acetylide*, the cornerstone of the first manufacturing process. Based on the mechanism of asymmetric lithium acetylide addition, we will turn our attention toward *the novel highly efficient zincate chemistry*. This is an excellent example in which mechanistic studies paid off handsomely.

1.2.1.2.1 Preparation of Mono *N*-*p*-Methoxybenzyl Ketone 41

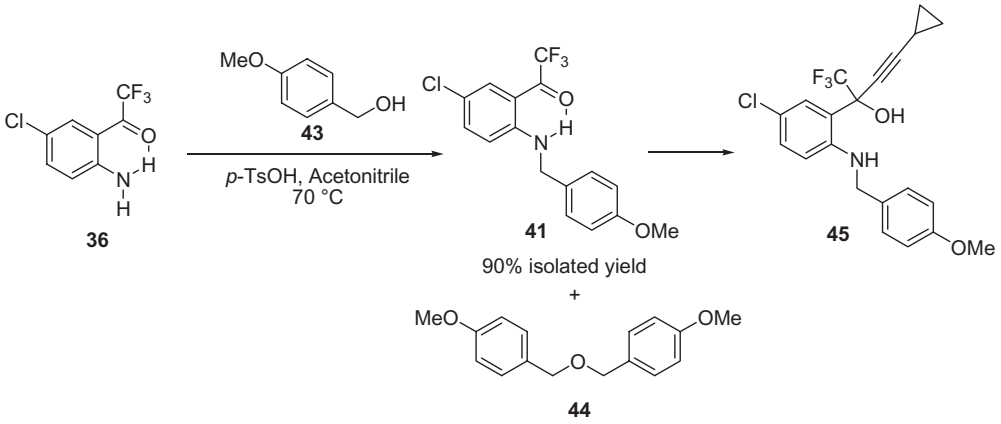
Initially, preparation of **41** was not an easy task and it very unexpectedly seems to be more difficult than the following key asymmetric acetylide addition. *N*-Mono alkylation of **36** with *p*MBCl **42** under various standard reaction conditions did not proceed as expected. It was found that the desired **41** was formed when **36** and chloride **42** were co-spotted on the TLC. So we turned our attention to reaction of

36 and **42** under acidic conditions. The reaction proceeded in the presence of silica gel, molecular sieves, or basic alumina in toluene, and among these, basic alumina worked the best. To the suspension of **36** and basic alumina in toluene was added chloride **42** and the reaction was complete in 3 h at room temperature with an assay yield of 85%. After filtering the alumina, the desired product **41** was isolated in 78% yield as a crystalline compound (Scheme 1.15).



Scheme 1.15 Installation of *p*MB on **36**.

However, *p*MBCl **42** has a thermal stability issue and is expensive (Aldrich price: 25 g for $69.90; the largest bottle). On the other hand, *p*MBOH **43** is stable and economically viable (Aldrich price; 500 g for $84.90; the largest bottle). It was found that mono-*N*-alkylation of **36** proceeded well by slow addition (over 3 h) of **43** to a solution of **36** in acetonitrile in the presence of a catalytic amount of acid (*p*-TsOH) at 70 °C, as shown in Scheme 1.16. Slow addition of alcohol **43** minimized the self-condensation of **43** to form symmetrical ether **44**, which was an equally effective alkylating agent. The product **41** was then directly crystallized from the reaction mixture by addition of water and was isolated in 90% yield and in >99% purity. A toluene solution of **41** can be used for the next reaction without isolation but the yield and optical purity of the asymmetric addition product were more robust if isolated **41** was used. In general, the more complex the reaction, the purer the starting materials the better.

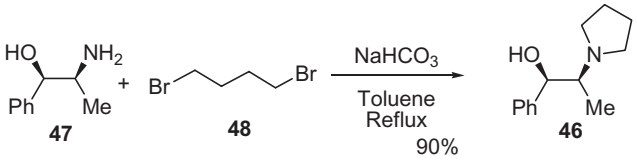


Scheme 1.16 Alternative installation of *p*MB on **36**, followed by acetylide addition.

1.2.1.2.2 The First Generation of Asymmetric Addition of Lithium Cyclopropylacetylide to the Ketone 41

Introduction Since we had already developed the novel asymmetric addition of lithium acetylide to ketimine **5**, we did not spend any time on investigating any chiral resolution methods for Efavirenz®. Our previous method was applied to **41**. In the presence of the lithium alkoxide of cinchona alkaloids, the reaction proceeded to afford the desired alcohol **45**, as expected, but the enantiomeric excess of **45** was only in the range 50–60%. After screening various readily accessible chiral amino alcohols, it was found that a derivative of ephedrine, (1*R*,2*S*) 1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**46**), provided the best enantiomeric excess of **45** (as high as 98%) with an excellent yield (*vide infra*). Prior to the development of asymmetric addition in detail, we had to prepare two additional reagents, the chiral modifier **46** and cyclopropylacetylene (**37**).

Preparation of the chiral modifier – (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidiny)propan-1-ol (46) Our best chiral modifier **46** has been utilized in many asymmetric transformations by Mukaiyama [22] and Soai [23], and recently by Bolm [24]. The ligand **46** was prepared by heating norephedrine (**47**) with 1,4-dibromobutane (**48**) in the presence of K_2CO_3 in either EtOH or acetonitrile. The isolated yield by distillation was reported as only 33% [25]. It was found that $NaHCO_3$ was a better choice for the base, as shown in Scheme 1.17. A suspension of **47**, 1.1 equiv of **48**, and 2 equiv of $NaHCO_3$ in toluene was heated under reflux for 18–22 h. The solid was removed by simple filtration. The toluene solution could be used directly for the asymmetric addition reaction after washing with water and azeotropic drying. Free base can be isolated as a crystalline solid by switching the solvent to heptane at <0 °C. More conveniently, its HCl salt could be isolated by the addition of HCl in isopropyl alcohol in 90% yield [21, 26]. The HCl salt can be converted to the free base by neutralization.

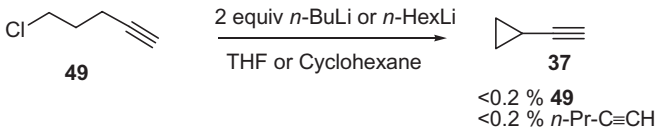


Scheme 1.17 Preparation of the chiral modifier **46**.

Preparation of cyclopropylacetylene (37) Cyclopropylacetylene (**37**) was a known compound and its synthetic method from vinylcyclopropane via dibromination had been reported [27] when we started our investigation. Large scale preparation of **37** was not an easy task. Actually, many chemists in our department worked on establishing the process for such a simple compound as **37** at the peak of the project.

Since the final product is a pharmaceutical, high purity of the product is definitely required. Furthermore, the amount of any impurities in the final product has to be rigorously regulated under ICH guidelines. Rejection of impurities related to cyclopropylacetylene (**37**) was difficult throughout this whole process [28]. Thus, not only the isolated yield but the impurity profile of **37** was critical.

The well documented synthetic method for **37** is chlorination of cyclopropylmethylketone followed by base treatment [29]. However, this method did not provide a suitable impurity profile. The most convenient and suitable method we found was the one-step synthesis from 5-chloro-1-pentyne (**49**) by addition of 2 equiv of base, as shown in Scheme 1.18 [21, 30]. Two major impurities, starting material **49** and reduced pentyne, had to be controlled below 0.2% each in the final bulk of **37**, to ensure the final purity of Efavirenz®. Acetylene **37** was isolated by distillation after standard work-up procedure.



Scheme 1.18 Preparation of cyclopropylacetylene **37**.

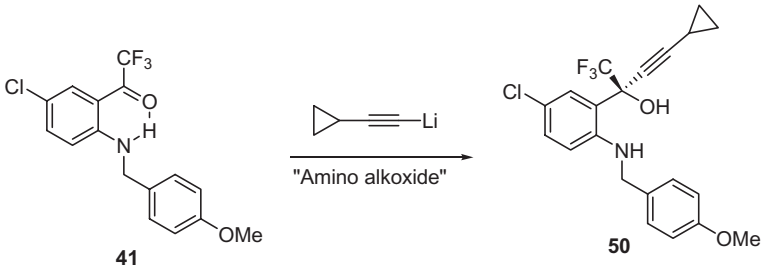
Scientists at DuPont Merck Pharmaceuticals [31] had also developed a new process to prepare **37**, based on a modification of the Corey–Fuchs method, from cyclopropylaldehyde, prepared by thermal rearrangement of butadiene monoxide.

Asymmetric addition of acetylide to the ketone Having the two key reagents in hand, we optimized the asymmetric addition reaction on ketone **41**. First, chiral modifiers were screened from among readily accessible β-amino alcohols and the results are summarized in Table 1.5.

Among them, (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**46**) was selected as a chiral modifier for further optimization. It is interesting to point out that *N*-methyl ephedrine was not a suitable chiral modifier for ketimine **5** (only 10% ee as shown in Table 1.2), but in the case of ketone **41**, *N*-methyl ephedrine provided a respectable 53% ee, as shown in Table 1.5.

During optimization, a few important factors for this reaction were identified. First, 2 equiv of lithium acetylide and 2 equiv of the chiral modifier **46** were required for better chemical yield and high enantiomeric excess. Secondly, warming the mixture of lithium acetylide and chiral modifier to at least 0 °C prior to addition of ketone **41** is the key to ensuring consistently high selectivity and high yield. By doing so, the enantiomeric excess was improved from 82% to 96–98%. Thirdly, the reaction temperature had little effect, as summarized in Table 1.6, as long as the mixture of lithium acetylide and **46** was warmed prior to addition of ketone **41**.

Table 1.5 Amino alcohol-mediated addition to ketone **41**.



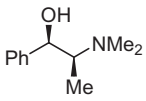
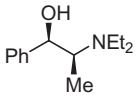
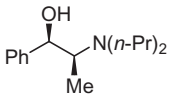
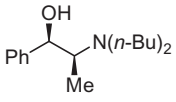
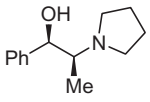
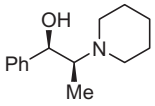
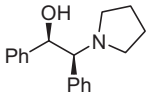
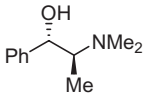
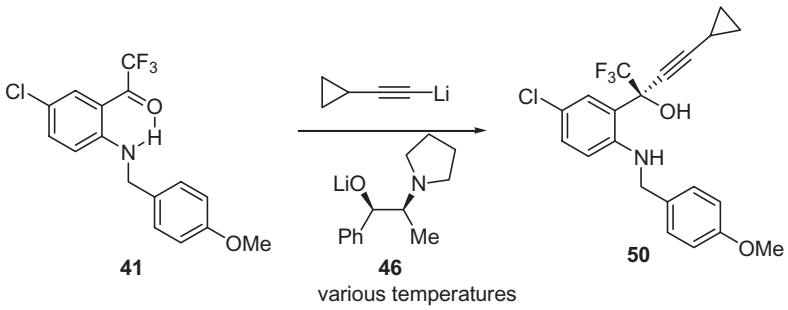
Amino alcohol	Structure	Product ee%
N-Methyl ephedrine		53
(1*R*,2*S*)-2-(*N*,*N*-Diethylamino)-1-phenylpropan-1-ol		70
(1*R*,2*S*)-(*N*,*N*-Di-*n*-propylamino)-1-phenylpropan-1-ol		59
(1*R*,2*S*)-(*N*,*N*-Di-*n*-butylamino)-1-phenylpropan-1-ol		60
(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	 **46**	82
(1*R*,2*S*)-1-Phenyl-2-(1-piperdinyl)propan-1-ol		72
(1*R*,2*S*)-2-(1-Pyrrolidinyl)-1,2-diphenylethanol		61
N-Methyl pseudoephedrine		35

Table 1.6 Temperature effect.

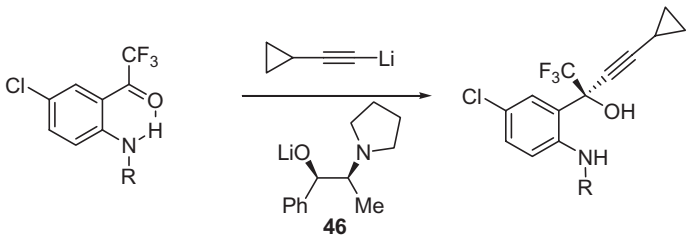


Reaction temperature (°C)	Enantiomeric excess (%)
–30	91
–40	95
–50	97–98
–60	99
–70	99

The effect of the nitrogen protective group in **37** was briefly studied and the results are summarized in Table 1.7. The *p*MB group provided a good selectivity. It is also noted that the reaction was sluggish and provided a lower enantiomeric excess (72%) if the nitrogen atom was not protected.

Experimentally, a chiral nucleophile was prepared by reaction of *n*-BuLi (or *n*-HexLi) with a mixture of chiral modifier **46** and cyclopropylacetylene **37** at –10 to

Table 1.7 Effect of the protecting group.



R =	Enantiomeric excess (%)
p-Methoxybenzyl (*p*MB)	96–98
H	72
3,4-Dimethoxybenzyl	99
Triphenylmethyl	90

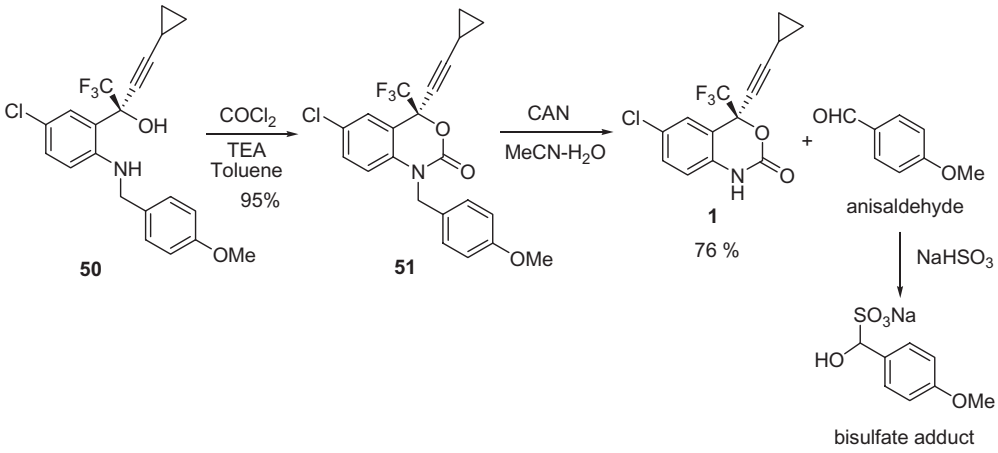
0 °C in a THF–toluene–hexane mixture. After the mixture was cooled below –50 °C, ketone **41** was added. After ~60 min, the reaction was quenched with aqueous citric acid. The organic layer was then solvent switched into toluene, and the product **50** was crystallized by the addition of heptane (91–93% isolated yield, >99.5% ee). The chiral modifier **46** is easily recycled from the aqueous layer by basification with NaOH and extraction into toluene to recover **46** (>99% purity, 98% recovery yield). The modifier has been recycled up to nine times in subsequent chiral addition reactions without any problem.

This asymmetric addition method is robust and provides the desired chiral alcohol **50** with high ee % and good overall yield and it became a cornerstone for our first manufacturing route of Efavirenz®.

1.2.1.2.3 Preparation of Efavirenz® (1)

Obviously, there are two ways to prepare Efavirenz® from the *p*MB protected chiral amino alcohol **50**; (i) creation of the benzoxazinone first then removal of the *p*MB group; or (ii) removal of the *p*MB first then formation of benzoxazinone. Preparation of the benzoxazinone was demonstrated by Medicinal Chemistry from the amino-alcohol with CDI.

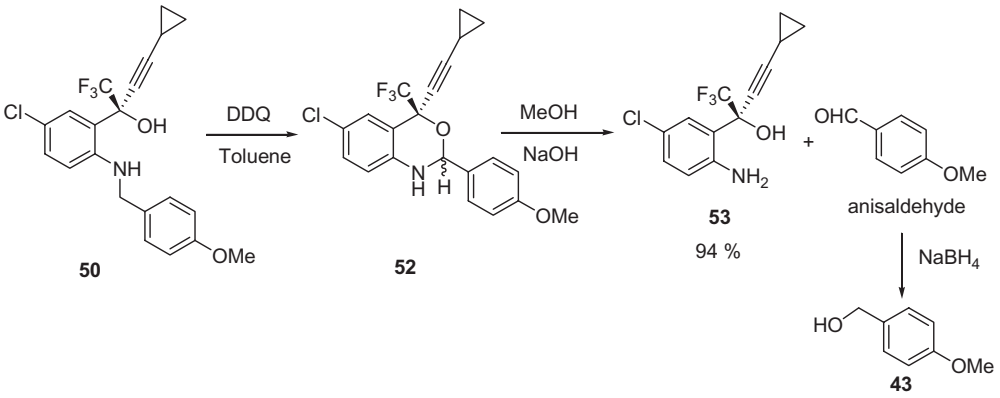
Initially, **50** was converted into the benzoxazinone **51** by reaction with phosgene in the presence of triethylamine and **51** was isolated in 95% yield upon crystallization from methanol. Deprotection of the *p*MB group from **51** was accomplished with ceric ammonium nitrate (CAN) in aqueous acetonitrile. Efavirenz® was isolated in 76% yield after crystallization from EtOAc-heptane (5 : 95), as shown in Scheme 1.19. There were two issues identified in this route. First, 1 equiv of anisaldehyde was generated in this reaction, which could not be cleanly rejected from product **1** by simple crystallization to an acceptable level under the ICH guideline. Anisaldehyde was removed from the organic extract as a bisulfite adduct by washing with aqueous $Na_2S_2O_5$ twice, prior to the crystallization of **1**. Secondly,



Scheme 1.19 Initial end game for Efavirenz®.

residual cerium salt in the water layer was difficult to recycle, thus the aqueous waste was an environmental issue which added an extra e-factor number to this process.

In order to overcome these two issues, we reversed the order of the reaction sequence, as summarized in Scheme 1.20. We took advantage of the alcohol functional group in **50**. Oxidation of *p*MB of **50** with DDQ proceeded smoothly to form cyclic aminal **52** (as a mixture of α and β = 11.5 : 1) in toluene at 0–10 °C. The resulting DDQH, which is insoluble in toluene, was filtered off, and isolated DDQH could be recycled as we demonstrated in the Proscar process (see p. 92) [32]. Thus, this process minimizes the impact to the environment from an oxidizing reagent. Cyclic aminal **52** was solvolyzed with NaOH in MeOH at 40 °C. The resulted anisaldehyde was reduced *in situ* to *p*MBOH **43** by addition of $NaBH_4$ and the desired amino alcohol **53** was isolated by direct crystallization from the reaction mixture, upon neutralization with acetic acid, in 94% yield and >99.9% ee after crystallization from toluene–heptane.

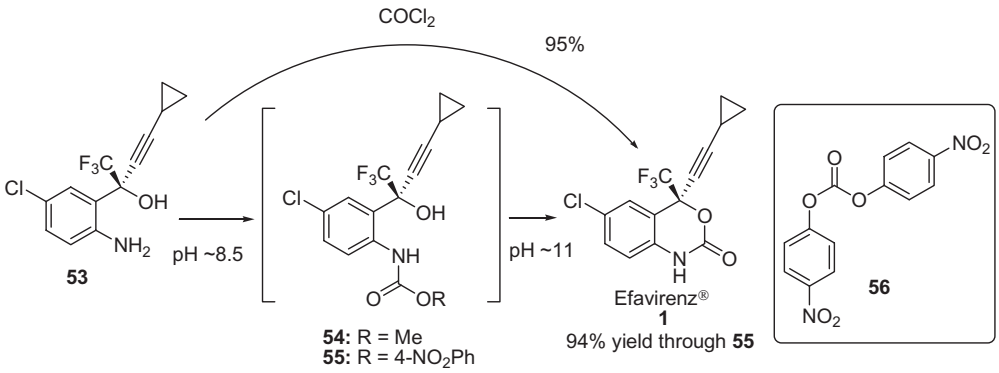


Scheme 1.20 Removal of *p*MB from **50**.

Conversion of the amino alcohol **53** to Efavirenz® (**1**) was readily accomplished by reaction with phosgene or phosgene equivalents. The most convenient and economically sound method is to react **53** with phosgene in the absence of base in THF–heptane at 0–25 °C. After aqueous work-up, Efavirenz® was crystallized from THF–heptane in excellent yield (93–95%) and purity (>99.5%, >99.5% ee).

Alternatively, two phosgene equivalents were studied, methyl chloroformate and *p*-nitrophenyl chloroformate. When methyl chloroformate was used for the end game, *N*-carbamate **54** was obtained smoothly but subsequent cyclization to benzoxazinone **1** was sluggish. Furthermore, removal of the unreacted intermediate methyl carbamate **54** from Efavirenz® was not trivial, thus we did not pursue this method. On the other hand, reaction of **53** and *p*-nitrophenyl chloroformate initially provided the corresponding *p*-nitrophenyl carbamate **55** under mild basic conditions ($KHCO_3$). Carbamate **55** was smoothly cyclized to **1** upon increasing

the pH by addition of KOH, and **1** was isolated in 94% yield. When *p*-nitrophenyl chloroformate was added to amino alcohol **53** under stronger basic conditions (pH > 11) from the beginning of the reaction, the generated *p*-nitrophenol reacted with *p*-nitrophenyl chloroformate to form symmetric carbonate **56**. Thus, stepwise pH adjustment was critical for this reaction, as summarized in Scheme 1.21.



Scheme 1.21 Optimized end game for Efavirenz®.

1.2.1.2.4 **The Second Generation Asymmetric Addition of Zinc-Cyclopropylacetylide to 36 (Part of the Current Manufacturing Route)**

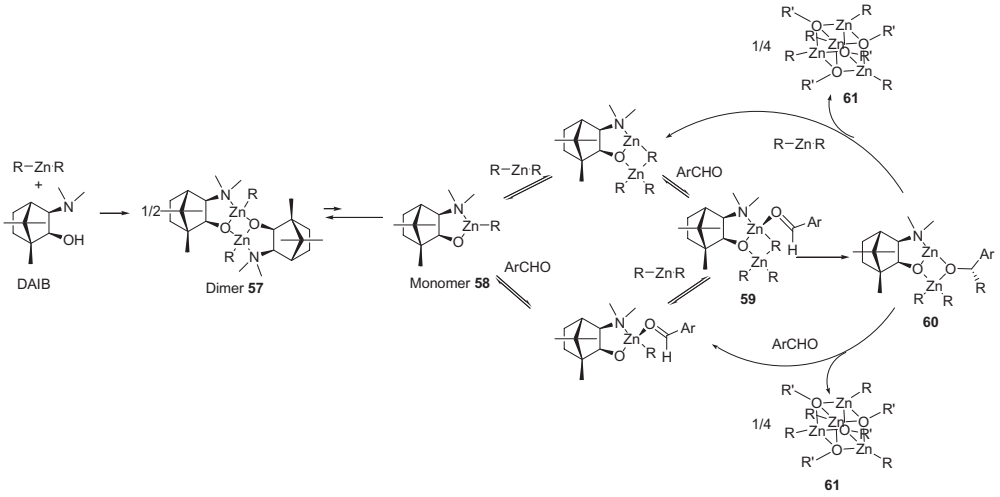
The overall process from amino ketone **36** to Efavirenz® (**1**) required four steps with an overall yield of 72% and quite high purity of the isolated **1**, as described above. This process supported initial marketing of Efavirenz® but there were a few drawbacks. The key asymmetric addition of acetylide required 2 equiv of precious cyclopropylacetylene (**37**). In addition, two steps out of the total four steps were protection with *p*MB and its deprotection.

It would be ideal if the asymmetric addition could be done without a protecting group for ketone **36** and if the required amount of acetylene **37** would be closer to 1 equiv. Lithium acetylide is too basic for using the non-protected ketone **36**, we need to reduce the nucleophile's basicity to accommodate the acidity of aniline protons in **36**. At the same time, we started to understand the mechanism of lithium acetylide addition. As we will discuss in detail later, formation of the cubic dimer of the 1 : 1 complex of lithium cyclopropylacetylide and lithium alkoxide of the chiral modifier[3)] was the reason for the high enantiomeric excess. However, due to the nature of the stable and rigid dimeric complex, 2 equiv of lithium acetylide and 2 equiv of the lithium salt of chiral modifier were required for the high enantiomeric excess. Therefore, our requirements for a suitable metal were to provide: (i) suitable nucleophilicity; (ii) weaker basicity, which would be

3) Many of the papers from Merck reported the 1 : 1 complex of lithium acetylide and lithium alkoxide of the chiral modifier as monomer and the dimer of the 1 : 1 complex as tetramer.

compatible with free aniline; and (iii) a favorable equilibrium between a monomer and a dimer to reduce the requirement of acetylene.

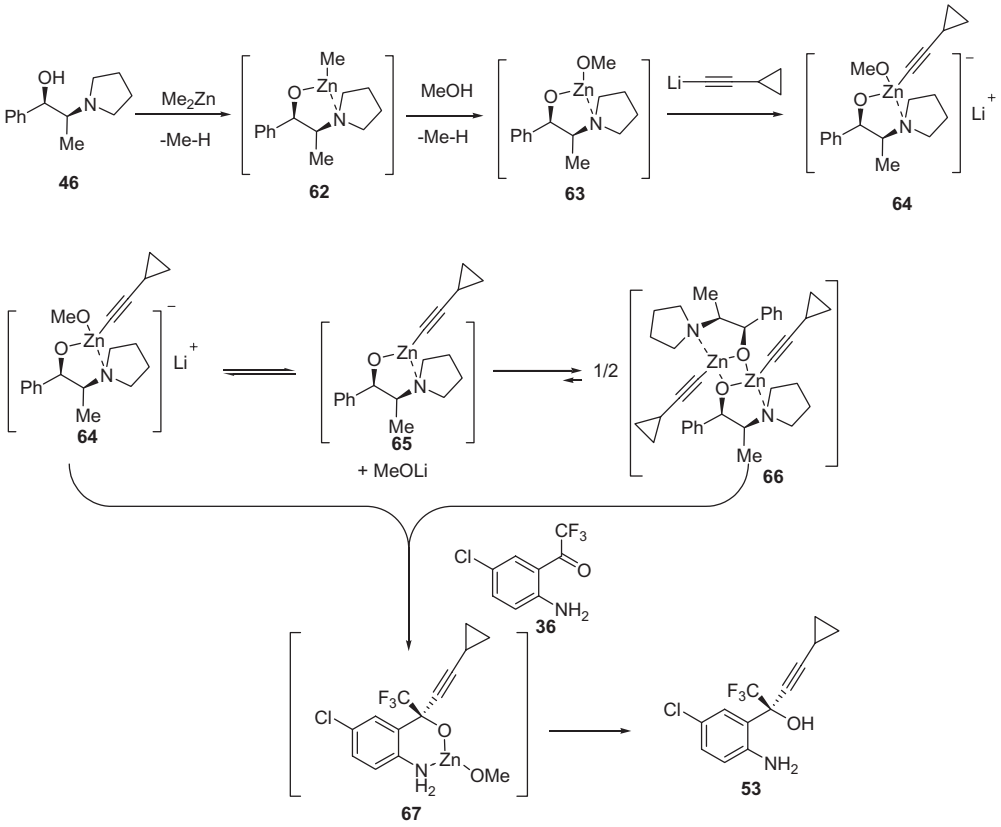
Kitamura and Noyori have reported mechanistic studies on the highly diastereomeric dialkylzinc addition to aryl aldehydes in the presence of (-)-3-*exo*-(dimethylamino)isoborneol (DAIB) [33]. They stated that DAIB (a chiral β-amino alcohol) formed a dimeric complex **57** with dialkylzinc. The dimeric complex is not reactive toward aldehydes but a monomeric complex **58**, which exists through equilibrium with the dimer **57**, reacts with aldehydes via bimetallic complex **59**. The initially formed adduct **60** is transformed into tetramer **61** by reaction with either dialkylzinc or aldehydes and regenerates active intermediates. The high enantiomeric excess is attributed to the facial selectivity achieved by clear steric differentiation of complex **59**, as shown in Scheme 1.22.



Scheme 1.22 Kitamura and Noyori's mechanism of the asymmetric addition of dialkyl zinc to aryl aldehydes.

These facts are perfectly matched with our above-mentioned desired requirements. In addition, alkyl zinc is known to be less basic and deprotonation of ketone-aniline **36** by zinc reagent is highly unlikely. However, one of the issues for this reaction was the requirement for two alkyl groups on the zinc metal since the product ends up as tetramer **61**, where the zinc atom still has one alkyl group, recalling that our cyclopropylacetylene (**37**) is not easy to obtain.

We came up with the idea of using a dummy ligand, as shown in Scheme 1.23 [34]. Reaction of dimethylzinc with our chiral modifier (amino-alcohol) **46** provided the methylzinc complex **62**, which was subsequently reacted with 1 equiv of MeOH, to form chiral zinc alkoxide **63**, generating a total of 2 moles of methane. Addition of lithium acetylide to **63** would generate an ate complex **64**. The ate complex **64** should exist in equilibrium with the monomeric zincate **65** and the dimer **66**. However, we expected that the monomer ate complex **64** and the mono-



Scheme 1.23 Our initial thoughts on the organo-zinc reaction.

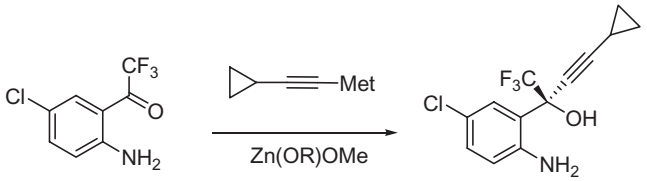
meric zincate **65** would react with the unprotected amino-ketone **36** to provide the desired non-protected amino alcohol **53**. Since the product **53** would remain as polymeric complexes of MeO–Zn–O–Product **67**, we expected only 1 equiv of cyclopropylacetylene to be needed for the completion of the reaction.

Chiral modifiers were screened in the zinc chemistry. Once again, in the case of aniline ketone **36**, chichona alkaloids, binaphthol, and tartaric acid derivatives gave very poor selectivity and ephedrine derivatives provided good selectivity. The results are summarized in Table 1.8.

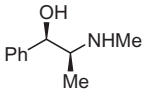
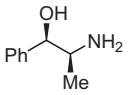
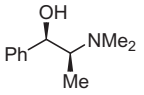
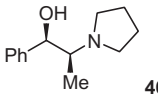
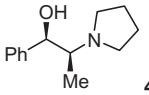
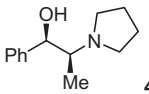
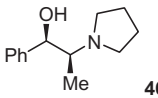
The same chiral modifier used in the previous lithium chemistry also provided the best result in this case, with as high as 83% ee. Interestingly, the countercation also had a significant effect on the enantioselectivity. For example, with the chloromagnesium acetylide, the desired adduct **53** was obtained with 87% ee but only ~50% ee was obtained with the bromo- and iodomagnesium acetylide.

Furthermore, variation of the achiral adduct for formation of alkoxy zinc such as **63** (shown in Scheme 1.23) had a profound influence on the enantioselectivity of the alkynylation reaction; the results are summarized in Table 1.9.

Table 1.8 Effect of chiral modifiers on organo-zinc chemistry.

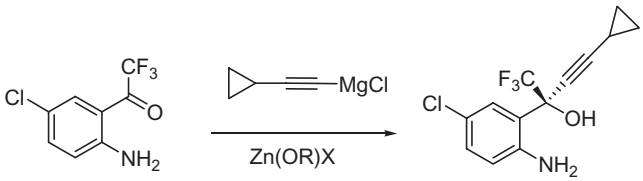


36 **53**

Met	Ephedrine derivatives		ee% of 53
Li	Ephedrine		28
Li	Norephedrine		42
Li	*N*-Methyl ephedrine		81
Li	(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	 **46**	83
MgCl	(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	 **46**	87
MgBr	(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	 **46**	54
MgI	(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	 **46**	51

The use of ethanol as an achiral auxiliary gave the adduct **53** with 55% ee, while neopentyl alcohol and methanol gave 96 and 87% ee, respectively. These results suggested that the achiral alcohol might exert a steric effect on the stereoselectivity. However, the increase in enantioselectivity from 55% to about 96% when 2,2,2-trifluoroethanol (TFE) was used instead of ethanol indicates a possible significant inductive effect also. Good enantioselectivities were also obtained with carboxylic acids and phenols.

Table 1.9 Effect of achiral alcohol on organo-zinc chemistry.



36 **53**

All reactions were carried out at 25 °C in THF/toluene with 1 equiv each of chiral modifier, achiral alcohol, dimethylzinc, and cyclopropylacetylide, and 0.83 equiv of **36**

Alcohol adduct	ee % of 53
MeOH	87
EtOH	55
$(CH_3)_3CCH_2OH$	96
CH_2=$CHCH_2OH$	90
$PhCH_2OH$	89
CF_3CH_2OH (TFE)	96
CF_3CO_2H	89
$(CH_3)_3CCO_2H$	72
4-NO_2-PhOH	89

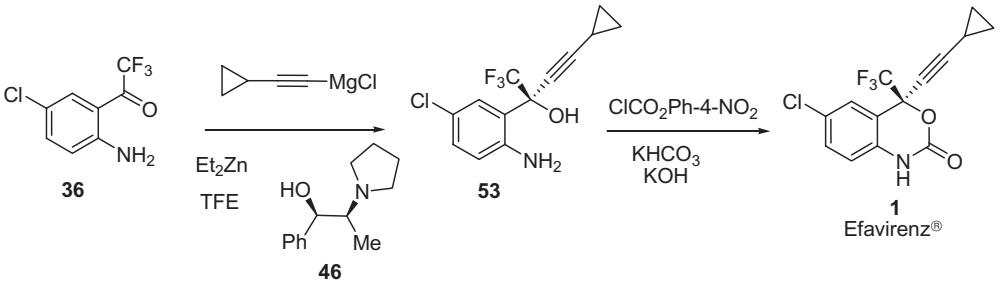
Further optimization of this reaction was carried out with TFE as an achiral adduct, since reaction with TFE is much faster than that with neopentyl alcohol. We found that dimethyl- and diethylzinc were equally effective, and the chiral zinc reagent could be prepared by mixing the chiral modifier, the achiral alcohol and dialkylzinc reagent in any order without affecting the conversion and selectivity of the reaction. However, the ratio of chiral to achiral modifier does affect the efficiency of the reaction. Less than 1 equiv of the chiral modifier lowered the ee %. For example with 0.8 equiv of **46** the enantiomeric excess of **53** was only 58.8% but with 1 equiv of **46** it was increased to 95.6%. Reaction temperature has a little effect on the enantiomeric excess. Reactions with zinc alkoxide derived for **46** and TFE gave **53** with 99.2% ee at 0 °C and 94.0% ee at 40 °C.

Reaction procedure After optimization, the reaction was run as follows: diethylzinc (1.2 equiv in toluene) was slowly added to a solution of TFE (0.9 equiv) and **46** (1.5 equiv) in THF below 30 °C. To the solution was added a solution of chloromagnesium cyclopropylacetylide (1.2 equiv), prepared from cyclopropylacetylene and *n*-butylmagnesium chloride in THF. To the mixture was added a solution of **36** (1 equiv) in THF at 0 °C and then the mixture was aged for 15 h at room temperature. The solution was quenched by addition of aqueous K_2CO_3. The resulting inorganic salts were removed by filtration. The filtrate and washings were

combined and washed with citric acid. The aqueous layer was kept for the recovery of **46**. The pH of the aqueous solution was adjusted to pH 11; toluene extraction and solvent switch to heptane afforded a solution which crystallized at low temperature to recover **46** in 95% yield. The organic layer was washed with water and solvent-switched to heptane and **53** was isolated by crystallization from heptane at 0 °C in 95.3% isolated yield with 99.2% ee.

With this novel zinc chemistry, the protection and deprotection sequence were eliminated, the requirement of expensive cyclopropylacetylene was reduced from 2.2 to 1.2 equiv and the previously required cryogenic temperature was eliminated. Finally, the overall yield was improved to 87% (in two steps) from 72% (in four steps).

The overall process for Efavirenz® is summarized in Scheme 1.24.



Scheme 1.24 Overall Efavirenz® synthesis.

1.2.2
Chemistry Development

When we worked on asymmetric addition to the ketimine **5**, we could not figure out the mechanism of this asymmetric addition. One of the authors still remembers his supevisor, Dr. Ed Grabowski, coming to his office just a few weeks before the final step of the large scale preparation of **2** and he did not ask about the preparation schedule but asked about the mechanism, especially the kinetics. Unfortunately, kinetic studies of the asymmetric addition to ketimine **5** were not fruitful, partially because the reaction was not totally homogeneous at low temperature. The only thing we were clear about was that the aggregation status of some lithium species would be important for this excellent enantiomeric excess based on the very unique temperature effect (Figure 1.4).

On the other hand, asymmetric addition of lithium acetylide in the presence of the ephedrine derivative **46** is a homogeneous reaction and reveals great detail about the reaction mechanism.

Here, we will discuss the reaction mechanism of the asymmetric lithium acetylide addition to *p*MB protected amino ketone **41**. Then we will discuss some speculation about the asymmetric addition via the novel zinc acetylide addition.

1.2.2.1 Reaction Mechanism for the Lithium Acetylide Addition to *p*MB Protected Amino Ketone 41

1.2.2.1.1 Circumstantial Evidence for the Reaction Mechanism

Before starting to describe detailed studies on the mechanism, we would like to summarize what we know about the reaction so far:

1) Two equiv of cyclopropylacetylene and two equiv of norephedrine derivative **46** are required to obtain good conversion and high enantiomeric excess.
2) Aging a mixture of lithium acetylide and the lithium alkoxide of **46** at higher temperature (–10 to 0 °C) prior to addition of ketone **41** is needed to obtain constantly high enantiomeric excess.

For the ketimine **5** case, the enantiomeric excess of adduct was dependent on the reaction temperature (there was an optimum temperature, lower or higher than that temperature gave lower enantiomeric excess). Thus, we assume the aggregation of the lithium complex with 2-ethynylpyridine and quinine dynamically changes with temperature. However, in this amino ketone **41** case, the suitable aggregate consisting of **46** and cyclopropylacetylene (**37**) seems to be stable once it is formed at higher temperature. Thus, lower temperature gave better enantiomeric excess with the pre-formed aggregate.

A few questions come to mind. What is the structure of the aggregate and why are 2 equiv of each reagent essential? Is it due to the acidic proton (N–H) in **41**? Before going into the detail of the mechanism, let us assemble more circumstantial evidence on this reaction.

First, we found a strong nonlinear effect on the adduct's enantiomeric excess, as indicated in Figure 1.6. The nonlinear effect strongly suggested there would be

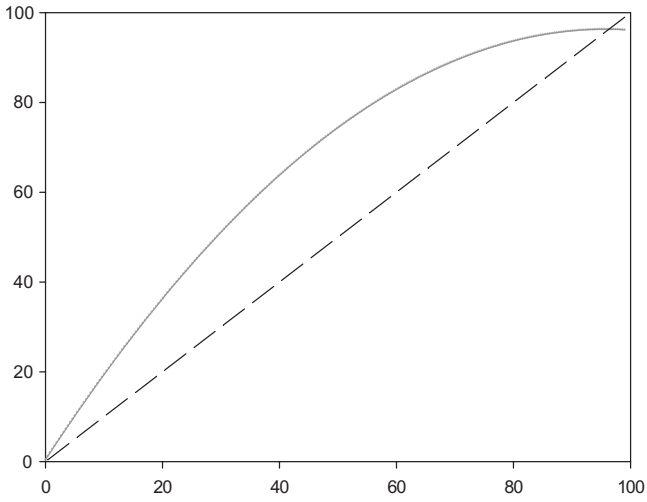


Figure 1.6 Nonlinearity of asymmetric acetylide addition.

polymeric species (including dimer), which participated in the rate-determining step.

When 1.2 equiv and 1.5 equiv of both lithium acetylide and chiral modifier **46** were used, the adduct **50** was obtained with high ee but the isolated yield was 59%. If deprotonation of the N–H of **41** by lithium acetylide is facile, 1.2 equiv and 1.5 equiv of reagents should afford a yield of 20%. However just 0.5 equiv of reagents gave adduct **50**. This experiment indicated that deprotonation of the N–H of **41** might not happen and only half of the reagent could be reacted with aminoketone **41**. Substituting deuterium in **41** (N–D) had no effect on the course of the reaction. Initial NMR and ReactIR studies eventually confirmed that no proton was abstracted from **41** under the reaction conditions (*vide infra*).

Thus, three additional pieces of circumstantial evidence are added to the list.

1) A strong nonlinearity relationship was observed between ee % of chiral modifier **46** and the adduct **50**.
2) Only half of the molar equivalents of the reagents are utilized.
3) No deprotonation of N–H in **41** was observed.

1.2.2.1.2 Structure Elucidation for Reaction Intermediates and Product by NMR Studies

In collaboration with Professor Collum and coworkers, ^{6}Li NMR (including ^{13}C-labeled acetylene **37** and ^{15}N-labeled chiral modifier **46** experiments) and Li aggregation studies were implemented to assist in the understanding of some of the factors responsible for the stereoselective nature of this chemistry [35].

All labeled compounds including *n*-Bu^{6}Li (from ^{6}Li ingot) were prepared by us. When *n*-Bu^{6}Li was added to a solution of cyclopropylacetylene (**37**) and chiral modifier **46** (1 : 1 ratio) in THF–pentane, the ^{6}Li NMR at –125 °C (**A**) is shown in Figure 1.7. A few sets of aggregates could be identified. (See Ref [35a] for full assignment).

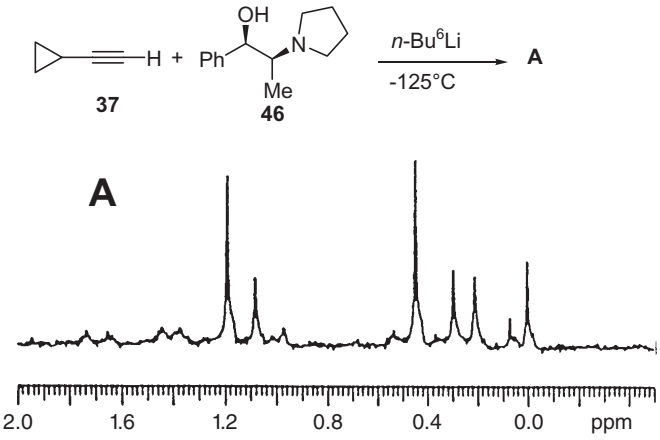


Figure 1.7 ^{6}Li NMR of initial aggregate at –125 °C.

The solution was warmed to 0 °C then cooled to –125 °C (**B**), the ^{6}Li NMR is much simpler than the original spectrum **A**, as shown in Figure 1.8. There are two equal intensity sets of lithium species (major and minor). This mixture is stable at various temperatures once formed. Generation of the stable set of aggregates provides a good correlation with our experimental data (the need to warm the lithium complex prior to addition to ensure high ee). The minor species was later assigned as a cubic aggregate from **37** and **46** (1 : 3).

The structure of the major aggregate was identified by labeling studies. Since the major set has two equal intensity ^{6}Li signals, these signals could be assigned as a 1 : 1 complex **68** of lithium acetylide and lithium alkoxide or a dimer (such as **69**) of the 1 : 1 complex **68** shown in Figure 1.9. Both structures have two different Li species. In order to discriminate between **68** and **69**, a terminal acetylene carbon of **37** was labeled with ^{13}C. In the case of **68**, both lithium signals will be a doublet

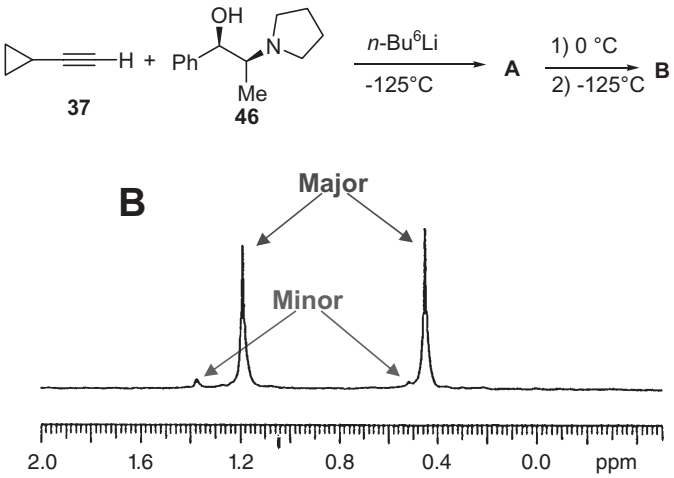


Figure 1.8 ^{6}Li NMR of Li aggregate after aging at higher temperature.

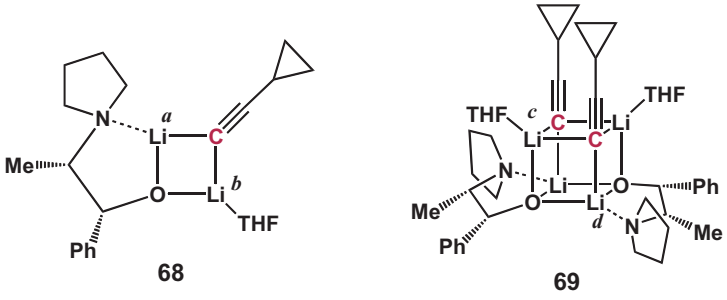


Figure 1.9 Proposed structures of a 1 : 1 complex and a 2 : 2 complex.

because both Li-***a*** and Li-***b*** coordinate to one ^{13}C atom. On the other hand, **69** will show one set of doublets due to Li-***d*** (coordinates with only one ^{13}C) and one set of triplets since Li-***c*** coordinates two ^{13}C.

^{6}Li NMR data from ^{13}C labeled cyclopropylacetylene (**37**) are shown in Figure 1.10. This spectrum is the definitive evidence that the aggregate is not **68**, as also proven by our experimental results such as nonlinearity of ee. Based on the coupling, the triplet signal at 1.2 ppm is assigned to Li-***c***, and the doublet signal at 0.42 ppm is assigned to Li-***d***.

Of course, there are two possible dimeric structures of the 1 : 1 complex **68**, as shown in Figure 1.11, namely **69** and **70**. Both dimers of **68** should behave in similar fashion in ^{6}Li NMR to the previous experiment. To differentiate those two structures, the nitrogen atom in the chiral modifier **46** was labeled with ^{15}N. Li-***d*** (~0.42 ppm) would be a doublet if the intermediate is **69**. However, Li-***c*** (~1.2 ppm) would be a doublet if it is **70**.

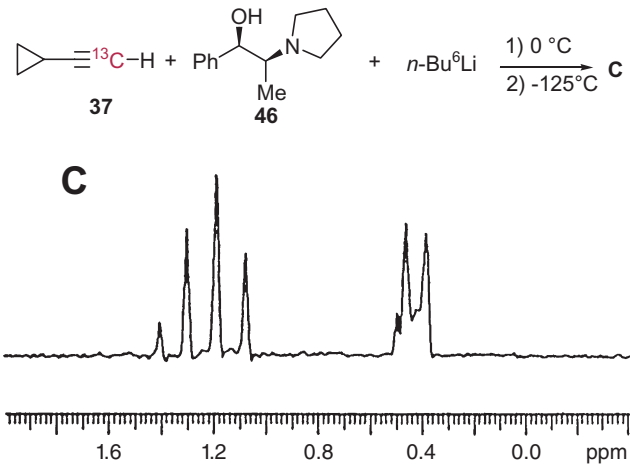


Figure 1.10 ^{6}Li NMR for ^{13}C-labeled aggregate.

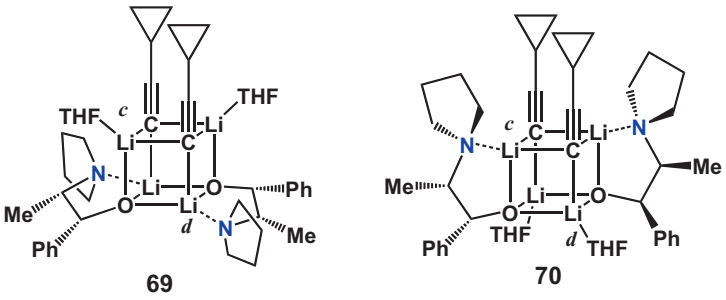


Figure 1.11 Two potential dimeric lithium aggregates of the 1 : 1 complex **68**.

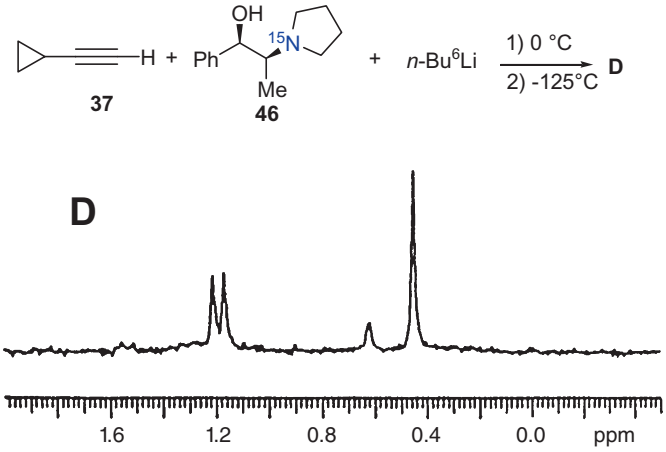


Figure 1.12 ^{6}Li NMR of ^{15}N-labeled aggregate.

The ^{6}Li NMR with ^{15}N labeled **46** is shown in Figure 1.12. Therefore, the aggregate **70** is the true intermediate for this asymmetric addition.

Next, we investigated the structure of the product by NMR, as shown in Figure 1.13 (0.5 equiv of **41** was added to **70**). The asymmetric addition to the dimer **70** proceeded almost instantaneously at –90 °C. Generation of cyclopropylacetylene was not observed by NMR. Following React-IR at the reaction temperature, no-C=O absorbance of **41** at 1660 cm^{-1} is observed until 0.5 equiv of the amino-ketone **41** was added to **70**. Absorbance of **41** was observed after more than 0.5 equiv of **41** was added. This is also consistent with our conclusion that no deprotonation of **41** occurs during the reaction.

When Li-NMR was measured with ^{13}C labeled cyclopropylacetylide (0.5 equiv of Li-acetylide), there was a major set of four singlets with equal intensity (Li-***a***, ***b***, ***c***, ***d***, assignments are depicted in Figure 1.14) as shown in Figure 1.13a under ^{13}C-decoupling conditions. When Li-NMR of the same sample was taken under ^{13}C-coupling conditions (Figure 1.13b), one of the singlets remained as a singlet but the other three singlets became doublets. Therefore, one of the Li atoms (***d***) in the product does not connect to ^{13}C and the other three Li atoms (***a***, ***b***, ***c***) connect to one of the ^{13}C. This is consistent with the proposed cubic aggregate **71**, assembled from two molecules of alkoxide of **46**, one molecule of cyclopropyl acetylide, and one molecule of product, as shown in Figure 1.14.

The aggregate **71** is not reactive toward amino-ketone **41** at low temperature, where the reaction runs typically. The loss of the reactivity of **71** may be attributed to the reduced Lewis acidity of lithium atoms.

These stereochemistry outcomes would be easily predicted based on the assumption that the carbonyl oxygen is coordinated to the lithium atom such as ***d*** in **70**. The larger aryl function will locate in the less sterically hindered side (left-hand side in **70**), providing the desired stereoselectivity. Semiempirical (MENO) computational methods were applied and the results supported our conclusion.

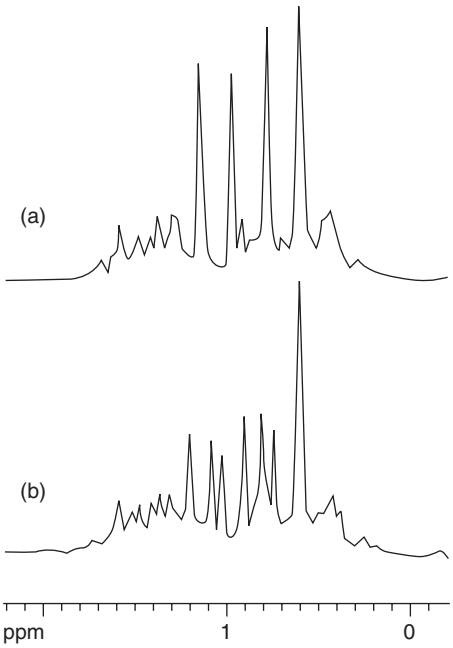
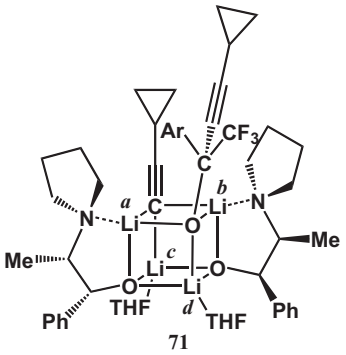


Figure 1.13 ^{6}Li NMRs of the product with ^{13}C-labeled acetylide (0.5 equiv of **41**). (a) ^{13}C-deoupled, (b) ^{13}C-coupled.



71

Figure 1.14 Proposed structure of the product.

1.2.2.2 **Reaction Mechanism for the Zinc Acetylide Addition to Amino Ketone 36**

Nonlinearity was also found for this asymmetric organozinc addition, for example, using 50% ee of chiral modifier **46** resulted in 80% ee of adduct **53**. The enantioselectivity is also dependent on the reaction concentration; >98% ee was obtained at 0.1–0.5 M but only 74% ee at 0.005 M. Kitamura and Noyori's work strongly suggested that heterodimer **72** might be more thermally stable than the homodimer

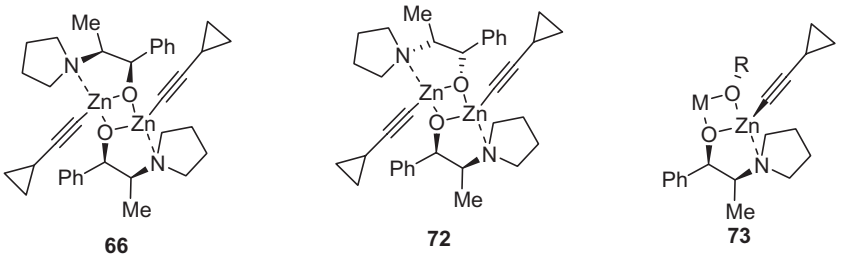


Figure 1.15 Other organo-zinc species.

66, thus asymmetric amplification of the reaction was observed. However, the thermodynamical equilibrium itself cannot explain a few things: (i) the effect of the counter cation of acetylide; (ii) the role of achiral alcohol; (iii) the effect of reaction concentration on the enantiomeric excess? Unfortunately, investigation of the zinc addition reaction with NMR and IR was so complex that these issues could not be resolved. However, intermediate **64** (Scheme 1.23) might exist as a mixed bimetallic species like **73**, which would be similar to the reactive intermediate **59** in Kitamura and Noyori's paper. The structure of **73** might offer some answers to these questions, but the structure of the key intermediate is still unknown (Figure 1.15).

1.3 Conclusion

A highly efficient manufacturing method for a non-nucleoside reverse transcriptase inhibitor, Efavirenz®, was devised and implemented. The final manufacturing method was crafted based on our chemistry knowledge accumulated from a previous drug candidate (first asymmetric acetylide addition to the ketimine), and a clear understanding of the asymmetric addition of lithium acetylide to the ketone for Efavirenz®, through many collaborations not only within our department but also with academic colleagues. It is also important to note that such accumulation of chemistry knowledge is not only applicable in this project but should be applicable to other projects. A good example is the Sugasawa reaction, which was first studied in carbapenem projects, and was then successfully applied in other projects including the first non-nucleoside reverse transcriptase inhibitor.

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