Introduction to Process Chemistry

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1. Introduction

The mission of Process Chemistry in the Pharmaceutical industry is constituted from two aspects. The first one is to support drug development. This aspect requires the timely supply of drug candidates in large quantities from Process Chemistry. As the environment in Pharmaceutical industry has become more competitive, the fastest supply of drug candidates can be one of the key factors for success. The second one is development of a manufacturing process which should be robust, economically sound, and environmentally friendly. To accomplish both goals, Process chemists should be the front runner in the synthetic organic chemistry field. Today, I would like to discuss two topics as showcases.

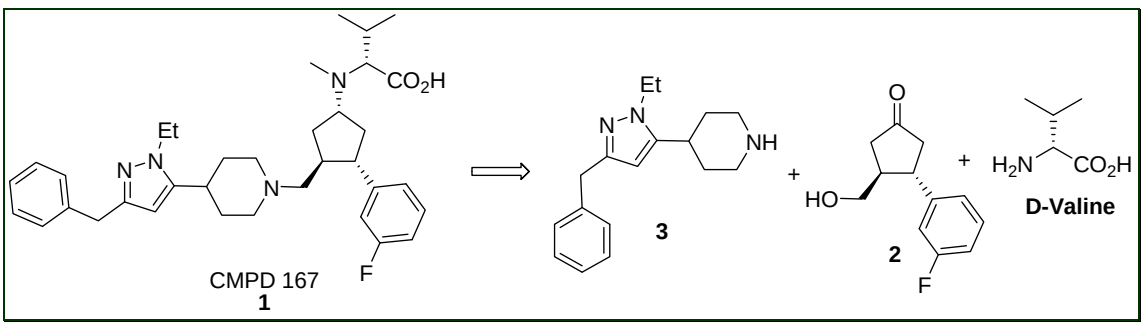
2. CCR5 Antagonist

CCR5 Antagonist drug candidate **1** was discovered at Merck Research Labs in Rahway for treatment of HIV infectious diseases. Currently, **1** has been licensed out royalty free to the International Partnership for Microbicides, which receives funding from many governments.

a) Preparation of candidate **1**

Compound **1** was prepared from three key components, namely cyclopentanone moiety **2**, pyrazole moiety **3** and commercially available D-Valine, by Merck medicinal chemists as shown in Scheme 1.

Scheme 1 Three components coupling strategy for **1** by Medicinal chemists

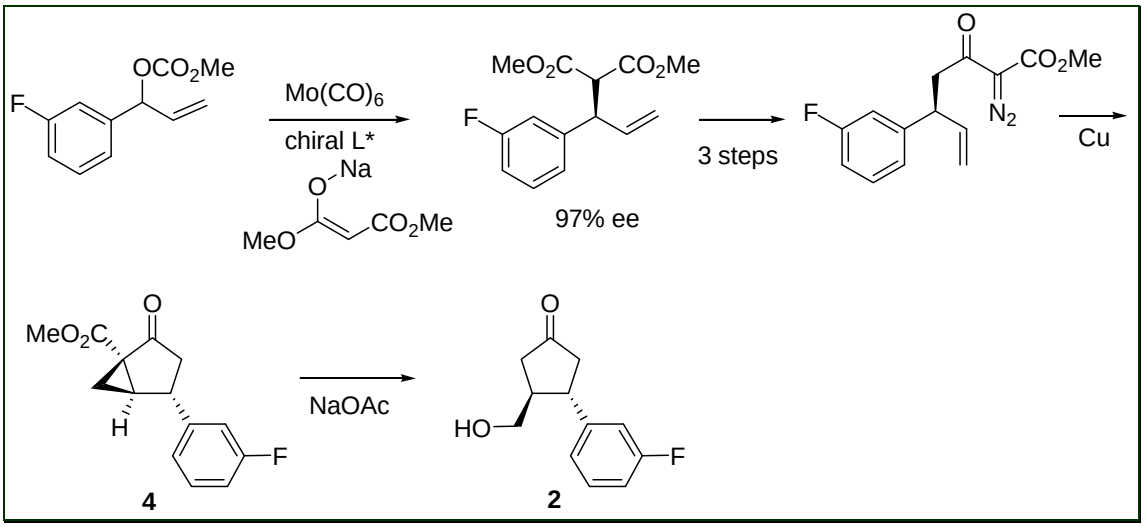


Pyrazole moiety **3** was easily prepared. Thus, our focus was the preparation of cyclopentanone moiety **2**. The medicinal chemistry route was not applicable to large

scale. Thus, we decided to totally change the route for the preparation of **2**.

We envisioned that Trost's asymmetric nucleophilic addition to π-ally Mo complex was a good choice to introduce the chirality on the cyclopentanone ring system. We expected the desired cyclopentanone **2** could be constructed via ring opening of bicyclo[3.1.0]hexane **4** as shown in Scheme 2.

Scheme 2 Process route for compound **2**

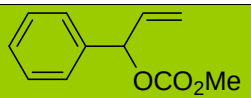
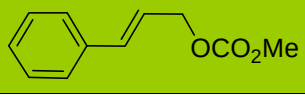


For the key π-ally Mo chemistry, we modified the Trost reaction conditions which allowed us to use commercially available and inexpensive $Mo(CO)_6$ instead of more sophisticated Mo pre-catalysts. In addition, we refined the preparation of the chiral ligand which was suitable for kg scale. With these optimizations, we were able to provide drug candidate **1** in short notice to support its development.

b) π-Ally Mo complex chemistry

During this preparative work, we were more interested in the mechanism of the Mo chemistry. Without knowing the mechanism, it was difficult to optimize the conditions and we were not comfortable running these reactions on large scale. We noticed that there was a little difference in the outcome when the π-Ally Mo complex was independently applied to the branched carbonate or the linear carbonate as shown in Table 1.

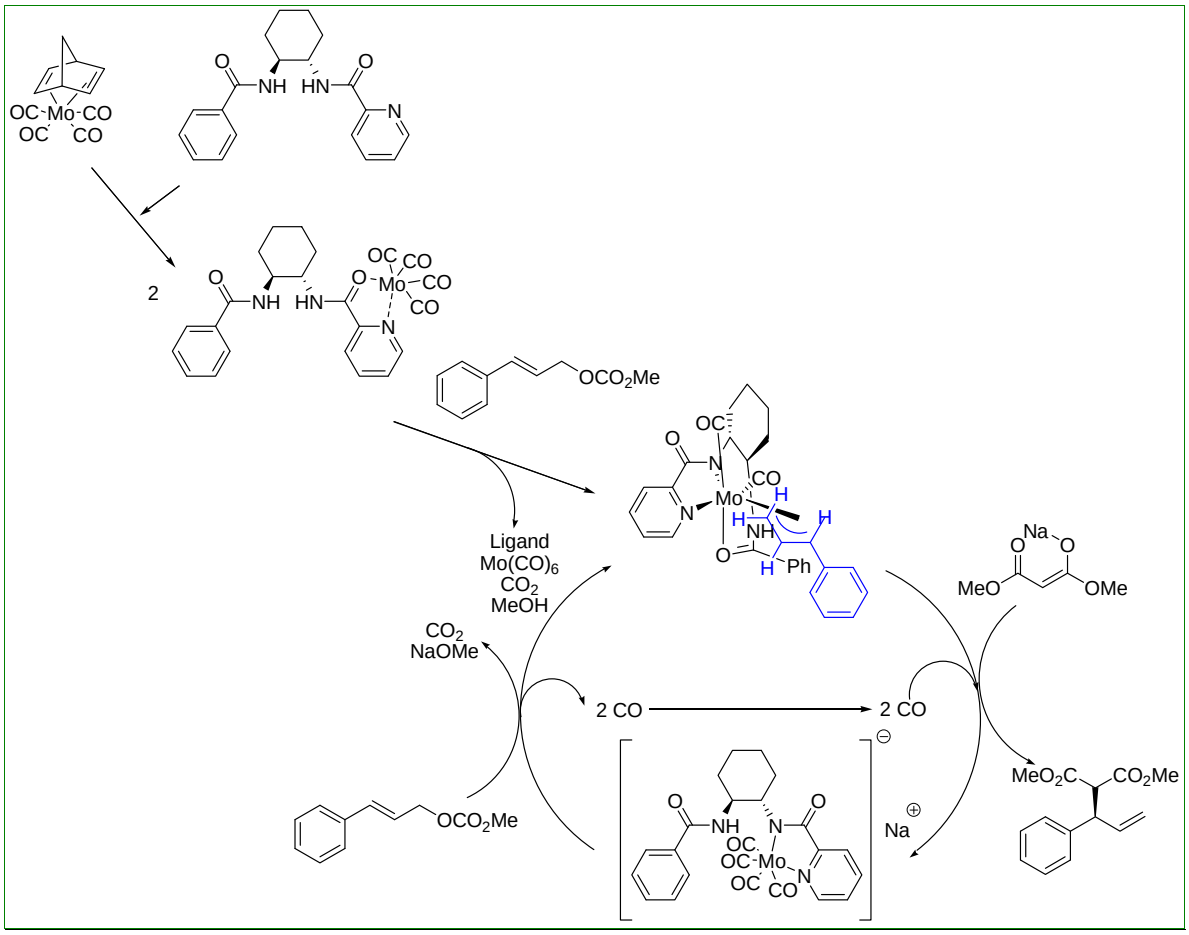
Table 1 $Mo(CO)_6$ method for other substrates

Entry	Structure	ee %	Branched/Linear	Isolated Yield (%)
1		96	93 : 7	76
2		99	95 : 5	80

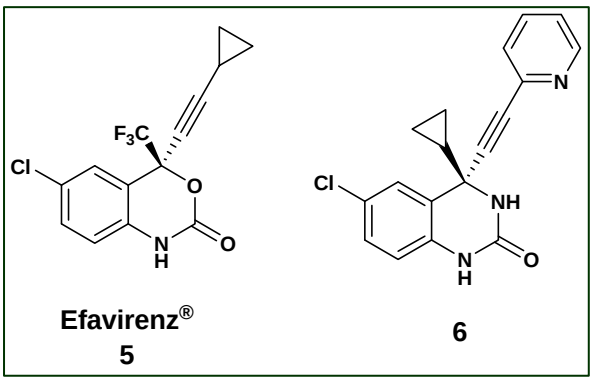
A similar phenomenon was also reported in the original Trost paper. This fact indicated

this reaction was a little bit off from Curtain-Hammett. This was the beginning of our investigation of Mo Chemistry. We found that this reaction proceeded with highly effective kinetic resolution. Eventually, we elucidated the reaction mechanism as shown in Scheme 3.

Scheme 3. Reaction mechanism for Trost π-allyl Mo chemistry



3. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

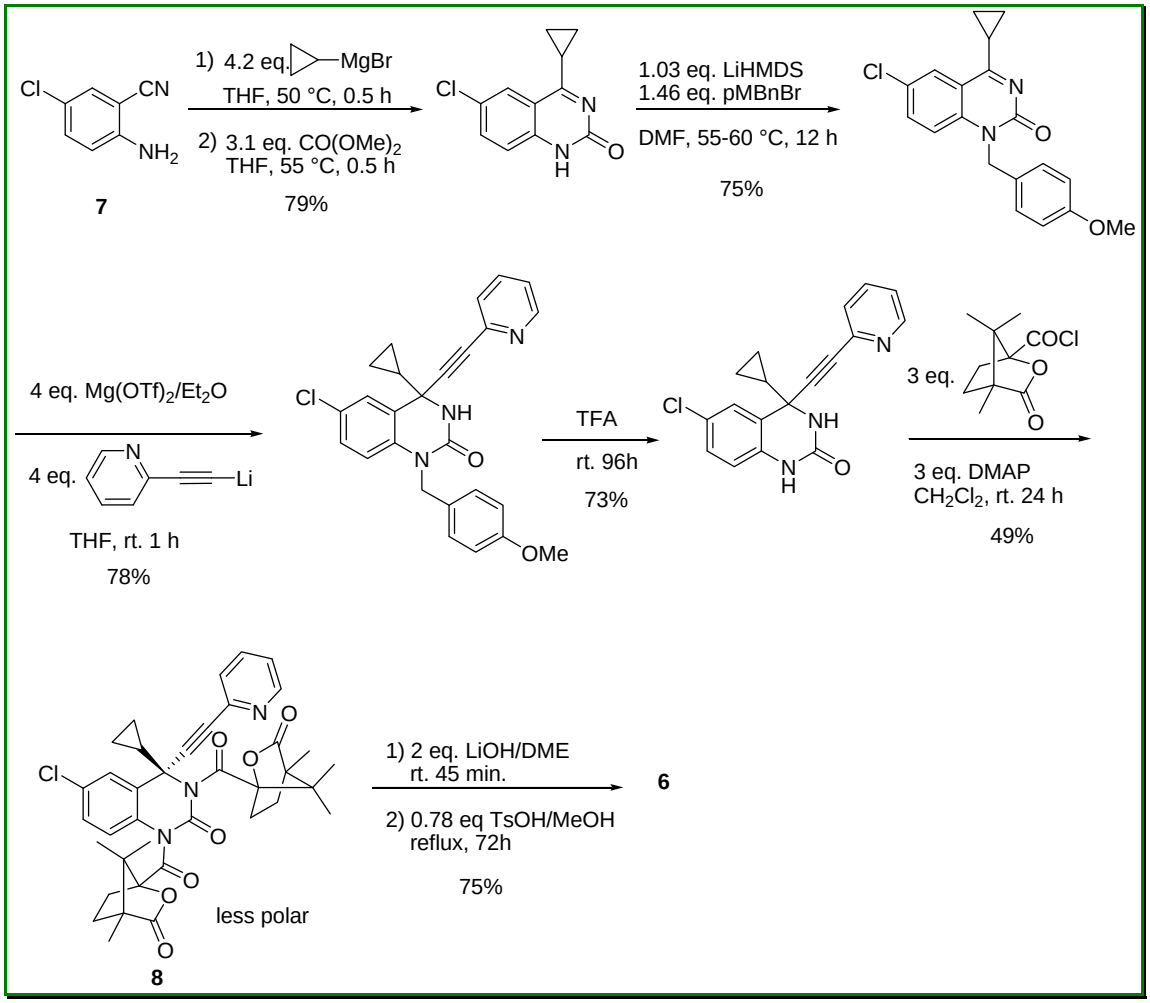


Efavirenz **5** is an orally active non-nucleoside reverse transcriptase inhibitor (NNRTI), discovered in Merck Research Labs in West Point, and is now commercially available for the treatment of HIV infection from Bristle-Mayer-Squibb. Compound **6** was the first development candidate for a NNRTI.

a) Preparation of **6**

The original medicinal chemistry method is summarized in Scheme 4. The starting material **7** was not available in large scale and chiral resolution by silica gel column chromatography separation of expensive bis-camphanyl derivative **8** was tedious and not very effective.

Scheme 4. The original Medicinal method for **6**

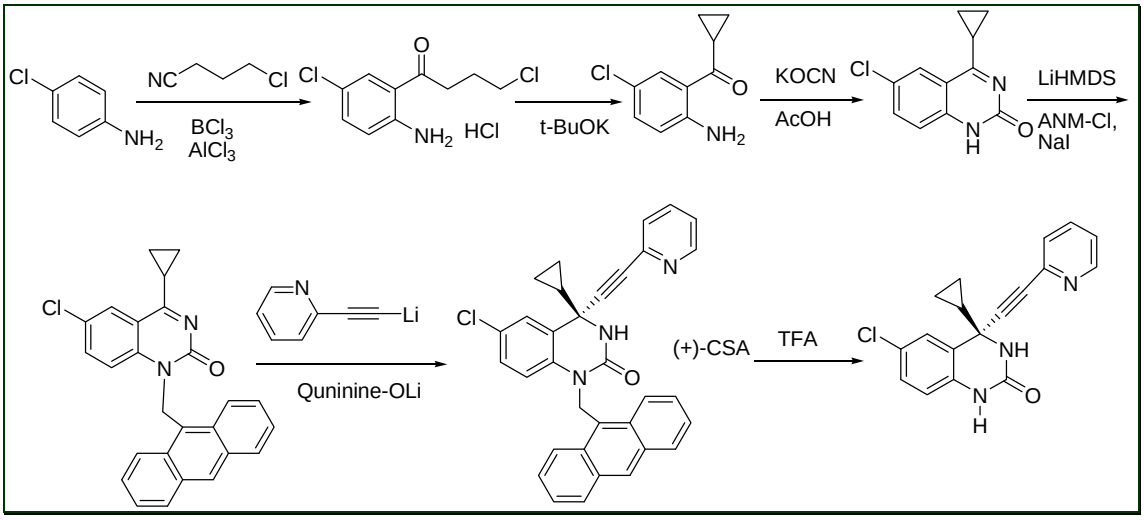


In order to overcome these difficulties, we envisioned installation of the ketone functionality at the α-position of aniline via a Sugasawa reaction and to add acetylene moiety to the properly protected ketimine asymmetrically, even though there was no literature precedent, as shown in Scheme 5.

The Sugasawa reaction worked as expected to provide the key ketone in good yield. Based on Tomioka's pioneering work on aldoimines, we screened various commercially available chiral β-aminoalcohols as chiral modifiers. We discovered the desired adduct was obtained in 84 % isolated yield with >99% ee in the presence of quinine-OLi. We observed some very interesting temperature effects on ee%. We presumed this effect

would be due to the change of state of aggregation of the lithium intermediate. By removing the 9-anthranylmethyl group under acidic conditions, our target **6** was isolated in very high yield. Thus, we supported this project in a very timely fashion.

Scheme 5. Our optimized method for **6**

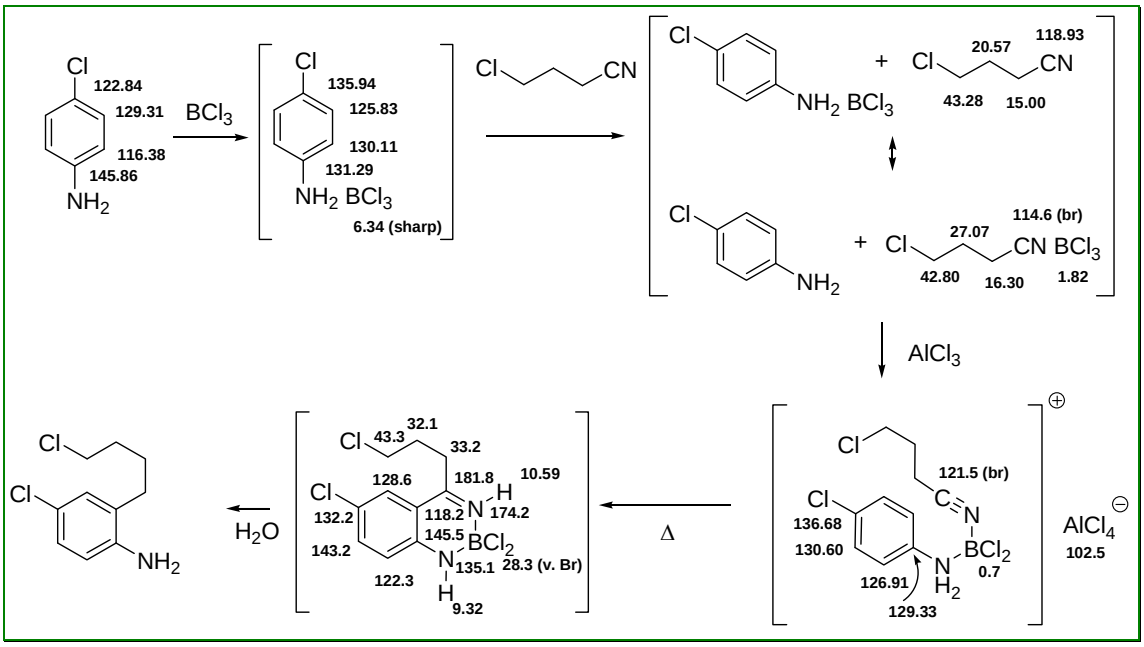


b) Sugasawa Reaction

We have successfully used the Sugasawa reaction in a few projects for ortho selective acylation of anilines. The reaction was quite unique and required two Lewis acids. The reaction mechanism was not clearly understood. Therefore, we investigated its mechanism mainly by NMR studies.

The mechanism was elucidated as shown in Scheme 6.

Scheme 6. Reaction mechanism of Sugasawa Reaction



4. Conclusion

We, as process chemists, have to contribute not only for supporting facilitated drug development but also for advancing organic chemistry. Accomplishment of these two goals hand-in-hand would be an ideal outcome for any process chemistry group.