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## Development of A Concise Synthesis of (–)-Oseltamivir (Tamiflu®)

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### Abstract

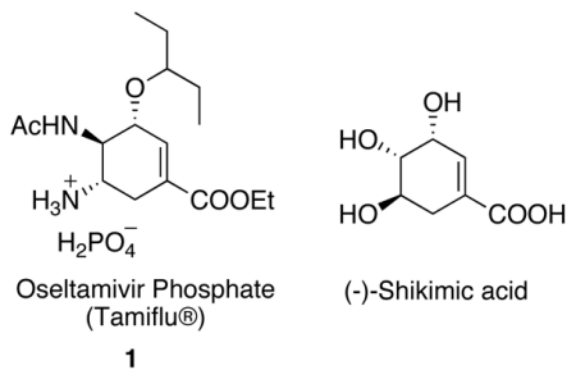
We report a full account of our work towards the development of an eight-step synthesis of anti-influenza drug (–)-oseltamivir (Tamiflu®) from commercially available starting material. The final synthetic route proceeds with an overall yield of 30 %. Key transformations include a novel palladium-catalyzed asymmetric allylic alkylation reaction (Pd-AAA) as well as a rhodium-catalyzed chemo-, regio-, and stereoselective aziridination reaction.

### Keywords

Tamiflu; palladium catalysis; deracemization; rhodium catalysis; aziridination

### Introduction

Tamiflu® (oseltamivir phosphate, **1**), developed by Gilead Sciences, is an orally active neuraminidase inhibitor, which had been widely used for the treatment of H5N1 influenza as well as a recent outbreak of H1N1 flu.<sup>1</sup> In order to be effective in treating infected patients, tamiflu must be administered to influenza patients no later than 36–48 h after the manifestation of the symptoms. With a daily dose of 150 mg per patient, sufficient stockpiles of tamiflu are necessary in times of a flu pandemic, as it is both a therapy and a preventive agent.



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Such high public demands raise the challenge of providing large quantities of tamiflu to meet the worldwide need.<sup>2</sup> Currently, tamiflu is marketed by Roche and is prepared *via* a semisynthetic approach starting from (–)-shikimic acid, which is still a limited resource given the massive demand.<sup>3</sup> Therefore, the development of alternative synthetic approaches that start from simple materials has drawn extensive attention from the chemical community.<sup>4</sup> Our group, among many others, have contributed to the development of alternative chemical synthetic routes and completed an eight-step azide-free synthesis of (–)-oseltamivir in 2008, which represents the shortest synthesis to date.<sup>4i</sup> This article elaborates in detail our development of the aforementioned synthetic route.

## Results and Discussion

### 1. Retrosynthetic Analysis

In our first-generation retrosynthetic analysis, the alkyl chain of (–)-oseltamivir **2** would be installed by etherification of the allylic alcohol **3**, which could come from isomerization of epoxide **4**. The epoxide would in turn result from an allyl amine **5**. To install the second amino group, aziridination was proposed starting from alkene intermediate **7**. Finally, a novel Pd-AAA reaction is envisioned, where a nitrogen-centered nucleophile is to be used to directly open racemic *cis*-lactone **8** and to set the requisite stereochemistry for the entire synthesis. (Scheme 1)

### 2. Pd-AAA Opening of Lactone

Commercially available lactone **8** was chosen as the starting material because of its six-membered carbon backbone, the *cis*-disubstituted stereochemistry, and its potential to undergo a deracemization.<sup>5</sup> Scheme 2 illustrates how a Pd-AAA deracemization process differs from the normal nucleophilic opening of lactone **8**: Instead of a normal nucleophilic attack at the carbonyl carbon C4 to generate ring-opened product **9**, a Pd-AAA process results in nucleophilic attack at the ether carbon C1, generating an alternative ring-opened product **10**, forming a new bond on the six-membered ring.

When a chiral ligand is used, this Pd-AAA opening of lactone process also generates enantiomeric excess. Thus, lactone **8** is not only opened by the incoming nucleophile, but also deracemized. The deracemization mechanism is shown in Scheme 3. A chiral palladium complex reacts with a racemic mixture of **8** to form a *pseudo-meso*  $\pi$ -allyl intermediate with the attached carboxylate as a leaving group. Chiral ligand biased nucleophilic attack yields an enantiomerically enriched product **10**.

Our group had demonstrated that stabilized carbon-nucleophiles such as nitromethane and malonate can deracemize the lactone with high enantioselectivity (Table 1, entry 1 and 2).<sup>6,7</sup> Using similar strategies, several stabilized nitrogen nucleophiles that were successfully used in previous Pd-AAA reactions were examined to deracemize lactone **8** and install the first amino group at C1. Literature known compound HN(Boc)<sub>2</sub><sup>8,9</sup> was examined as the initial nucleophile. Using standard Pd-AAA conditions, no reaction was observed (Table 1, entry 3). We hypothesized that the HN(Boc)<sub>2</sub> was not sufficiently nucleophilic, therefore, a variety of bases (Table 1, entry 4, 5 and 6) were tested, however, still no reaction was observed. Then more reactive Pd-source, [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, was examined, both with and without base, showing no improved reactivities (Table 1, entry 7 and 8). HN(Cbz)<sub>2</sub> has also shown promising results in related Pd-AAA reactions.<sup>10,11</sup> However, as shown in Table 1, no reaction was observed in the Pd-AAA opening lactone reaction at various temperatures (Table 1, entry 9 10, and 11). Another known Pd-AAA nucleophile, NaN(CHO)<sub>2</sub><sup>12</sup>, also failed to proceed with or without phase-transfer reagent THAB (Table 1, entry 12 and 13). Phthalimide, either in salt form<sup>13</sup> or neutral form<sup>14</sup>, has shown to function as good

nucleophiles in AAA reactions. First, sodium phthalimide was tested but showed zero reactivity in Pd-AAA reaction with **8**. Considering the charge repulsion between the negatively-charged carboxylate leaving group and the incoming sodium phthalimide may have prevented the addition (Table 1, entry 14),<sup>15</sup> neutral phthalimide was tested as the nucleophile with base as an additive to increase the nucleophilicity. However, no reaction occurred with either buffered system (CsOAc/HOAc) or with the addition of excess base (Table 1, entry 15 and 16).

As nitrogen-centered nucleophiles were not effective for the desired Pd-AAA reaction for lactone **8**, a subsequent strategy involving ring-opening of the lactone prior to the Pd-AAA was envisioned. Lactone **8** was transformed in two steps into the ring-opened **15**. Interestingly, in contrast to the reactions with lactone **8**, the Pd-AAA reaction with **15** proceeded excellently with phthalimide as the nucleophile in the presence of Cs<sub>2</sub>CO<sub>3</sub>, affording **13** in high yield and enantiomeric excess (Scheme 4).

A rationale for the different reactivities between **8** and **15** is provided in Scheme 4. Upon oxidative insertion of the Pd(0) catalyst into substrate **15**, an intermediate involving a *pseudo-meso* Pd(II)  $\pi$ -allyl complex bearing an attached carboxylate ester is formed (**16**). The chiral ligand biases the nucleophilic attack by the deprotonated phthalimide and leads to enantiomerically enriched **13**. However, when using lactone **8** as the substrate, it generates an intermediate **12** with an attached carboxylate anion. Presumably, the approach of an anionic phthalimide towards the Pd  $\pi$ -allyl complex is disfavored by repulsion between the negative charges on the nitrogen atom and the carboxylate group. In addition, it is also possible that the intramolecular reaction with the carboxylate is favored over the intermolecular reaction with the phthalimide, therefore the reverse reaction of **12** back to **8** is faster than the formation of **13**. We hypothesized that, to overcome the repulsion and the intramolecular trapping of **12**, the carboxylate anion of **12** must be trapped prior to the attack of the phthalimide without diminishing the nucleophilicity of the phthalimide.

Based upon the above analysis, we proposed using a trimethylsilyl (TMS) group, whose oxophilicity would result in a selective trapping of the carboxylate oxygen over the nitrogen (Scheme 5). Considering the simple addition of external silylating reagent did not facilitate the reaction (Table 1, entry 6), we considered bringing in the TMS group attached to the nitrogen nucleophile, wherein silyl transfer should capture the carboxylate and simultaneously reveal the imide nucleophile (**17**). Therefore, we chose commercially available TMS-phthalimide. Utilizing another advantage of the TMS group, that is, its susceptibility to acid hydrolysis, esterification could be carried out in the same pot, forming the carboxylic ethyl ester.

To our delight and in stark contrast to phthalimide itself, with [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> and ligand (*R,R*)-**11** as the catalyst, and TMS-phthalimide as the nucleophile, the racemic lactone **8** was opened and desymmetrized, and the resulted TMS-carboxylate was *in situ* converted to the ethyl ester affording the desired compound **13**. The initial conditions afforded **13** in 24% yield and 96% ee (Scheme 6). This approach installed both the amino group and the ester functionality in one step and established the desired stereochemistry for the entire synthesis. (*R,R*) Ligand was randomly chosen at this point and was later confirmed to lead to the desired absolute stereochemistry.

Further optimization of this reaction is shown in Table 2. Our goal was to improve the yield without using large excess of reagents. Therefore, higher reaction concentration, temperature, and various esterification conditions were examined (Table 2, entry 1–3). The enantioselectivity was optimal at 0.2 M. Unfortunately, the yield was still unacceptable. TMS-phthalimide was stored and handled in the glove box. Despite this precaution and the

use of rigorous drying techniques, the TMS-phthalimide was found to undergo competitive hydrolysis to the unreactive phthalimide during the AAA reaction. This undesired side reaction explained the low conversion. To rectify this observation, we first decided to add 1 equiv external silylating reagent BSA to maintain the effective concentration of TMS-phthalimide in the reaction. Satisfyingly, such method led to full conversion in the Pd-AAA step, however, the following esterification became problematic with BSA present (Table 2, entry 4). Finally, we decided to use excess amount of TMS-phthalimide. As little as 1.5 equiv of the nucleophile was sufficient enough to lead to full conversion to **13** with an isolated yield of 80% (Table 5, entry 5 and 6). The yield improved further when scaled up (Table 5, entry 7).

In summary, the first amino group was successfully installed *via* a novel Pd-AAA deracemizing lactone reaction with a unique *N*-centered nucleophile in high yield and ee, and in the same pot the desired ethyl ester was formed. This reaction set up the absolute stereochemistry for the entire synthesis.

### 3. Installation of the Second Amino Group

With **13** in hand, we turned to install the second amino group onto the ring. Before following our synthetic plan of utilizing aziridination reaction to form aziridine **6**, we made an attempt of accessing allylic amine **5** directly from **13**. Initially, ene reaction was examined. It is known that an ene type reaction between an alkene and a nitroso compound affords an allylic amine.<sup>16</sup> It is proposed that the reaction occurs via a six-membered transition state (Scheme 7). Nitroso compound **17** is highly reactive and thus cannot be isolated. Therefore, it is generated *in situ* and subsequently trapped by the olefin species via an ene reaction.<sup>17</sup> However, under literature conditions the ene reaction with **13** failed to proceed, even when heated to 80 °C (Scheme 7). Starting material **13** was recovered in both cases. We hypothesized that the alkene of **13** is not electron-rich enough to react with **17**.

Alternatively, the second amino group could be installed *via* a reaction between olefin **13** and a highly reactive AcNH<sup>+</sup> equivalent.<sup>18</sup> A straightforward way to generate AcNH<sup>+</sup> equivalence is reacting *N*-haloacetamide such as **19** with a silver salt, such as AgBF<sub>4</sub>. A non-nucleophilic base, 2,6-di-*tert*-butylpyridine, was added to deprotonate the allylic proton of intermediate **21** thus leading to the formation of allylic amine **20**. Unfortunately, although the AgBr precipitation was observed under the reaction conditions, none of the desired amination product was detected (Scheme 8).

Acknowledging the challenge of installing the second amino group on an electron deficient double bond *via* ene or acyl cation strategy, we decided to investigate aziridination reactions as originally planned, as they are more developed amination reactions for electron deficient double bonds.<sup>19</sup> Gratifyingly, under standard aziridination conditions, the desired aziridine **22** was formed in 69–74% yield as a single diastereoisomer (Scheme 9). One major drawback of the reaction was the requirement of large excesses of PhI=NTs and high catalyst loading. Previously, our group had reported that Cu(IPr)Cl is an effective aziridination catalyst.<sup>20</sup> However, in this case, it led to no reaction for substrate **13**.

In summary, the second amine was installed *via* a copper-catalyzed diastereoselective aziridination in good yield. The next step in the total synthesis of oseltamivir was regioselective ring opening of the aziridine **22**.

### 4. Further Conversions

In order to obtain the desired allylic amine **23** from aziridine **22**, an elimination reaction was proposed (Table 3). In the literature, allyl amines can be accessed from aziridines utilizing either R<sub>2</sub>NLi or RLi to promote the desired eliminative rearrangement.<sup>21,22</sup> However, in our

case, it would lead to the undesired regioisomer due to chelating effects of such bases. Nonetheless, when we did perform the reaction with LDA, it simply led to decomposition even at  $-78\text{ }^{\circ}\text{C}$  (Table 3, entry 1). Additionally, nucleophilic bases would attack the ester functionality, which should also be avoided. Therefore, our initial studies focused on non-nucleophilic, non-coordinating bases and E2 type elimination conditions to promote the formation of **23**. When 1 equiv of potassium *tert*-butoxide (KO*t*Bu) was used, no desired product was observed (Table 3, entry 2). Adding excess amount of potassium *tert*-butoxide resulted in messy results, where attack of the ester group by the base was observed (Table 3, entry 3). Superbase LIDAKOR<sup>21,23</sup> was used with the intention to minimize the nucleophilic attack at the ester. However, either no reaction was observed in hexanes or decomposition occurred in THF (Table 3, entry 4 and 5). Changing to organic base DBU gave no reaction (Table 3, entry 6). Next, instead of only using base to promote the elimination, Lewis acid–non-nucleophilic base combinations were used to generate a “push-pull” effect. However, still no reaction was observed (Table 3, entry 7 and 8). In order to force the reaction under the “push-pull” conditions to occur, chlorobenzene was used as the solvent in order to increase the substrate solubility as well as the reaction temperature (Table 3, entry 9). Oxophilic lanthanide holmium triflate (Ho(OTf)<sub>3</sub>) was examined as a Lewis acid to activate the sulfonyl group on the aziridine. However, no reaction occurred even at  $100\text{ }^{\circ}\text{C}$ . As lanthanides did not assist the aziridine opening, main group Lewis acids were studied. Gratifyingly, Al(OTf)<sub>3</sub> gave nearly quantitative yield of aziridine opening product **24**, which could potentially lead to allylic amine **23** via a dehydration reaction (Table 3, entry 10). Delightfully, by switching to less Lewis acidic indium triflate, at an elevated temperature, elimination product **23** was observed for the first time, although irreproducible, in 23% yield (Table 3, entry 11). The desired product **23** coeluted with another product, which is believed to be **25**. In addition to **23** and **25**, the reaction also afforded 30% yield of **24**. We hypothesized that water was acting as the nucleophile for the opening of aziridine **22** to form **24**, in which case, addition of molecular sieves might prevent this undesired reaction. However, when 3 Å MS was added, no reaction was observed after 24 h (Table 3, entry 12).

Taking the good result from Table 3, entry 10, we tried to convert **24** into **23** (Scheme 10). Various one-step dehydration conditions were investigated, however, no desired product was observed. Therefore, a step-wise procedure was pursued. Interestingly, after transforming **24** to its corresponding triflate, DBU induced elimination afforded aziridine **22** instead of the desired allylic amine **23**, presumably due to adjacent group participation.

At the same time we were studying the one-step E2 rearrangement, we also started investigating a two-step sequence to access **23** as a backup plan (Scheme 11). Because of the observed adjacent group participation indicated in Scheme 10, we proposed to open the aziridine utilizing a nucleophile that would not participate in the intramolecular S<sub>N</sub>2 reactions. Therefore, PhSe<sup>−</sup> was chosen to generate intermediate **26**, followed by oxidative thermal elimination to afford the allylic amine **23**. One major challenge of this strategy was the regioselectivity of the aziridine-opening step. Electronically, the equatorial attack to afford desired product **26** is favored (Scheme 11, path **a**; similar result has been observed in Table 3, entry 10). However, stereoelectronically, the axial attack of the selenide to afford the undesired regioisomer **27** is favored (Scheme 11, path **b**), leading to allylic amine **28**. A mixture of regioisomers may also be generated due to the competition between the two pathways (as already shown in Table 3, entry 11). With this in mind, we started to look into the reactivity and the selectivity of the aziridine opening reaction.

As shown in Scheme 12, the aziridine opening reaction was carried out in ethanol, however, only 10% conversion was observed; this was presumably due to the low solubility of **22** in ethanol. The conversion increased to 62% when THF was added as a co-solvent to dissolve

the starting material. When TFA was added to activate the Ts-aziridine, full conversion was achieved with a 90% isolated yield for the opening of aziridine. Unfortunately, the subsequent elimination did not occur under the standard oxidative conditions. Later it was discovered, the reaction yielded **27** rather than the desired **26**, which explained the difficulty of elimination due to lack of aligned proton. This intriguing result indicates that the axial attack (Scheme 11, path **b**) predominates under those reaction conditions, suggesting that the torsional strain in the transition state is dictating the regioselectivity when a nucleophile is used, leading to the formation of undesired **27** (Scheme 11 and 12).

## 5. Revised Synthetic Plan

In observation of the difficulties in the direct E2 type elimination from **22**, we decided to revise our synthetic plan. As shown in Table 3, Al(OTf)<sub>3</sub> and In(OTf)<sub>3</sub> assisted the ring-opening of aziridine **22** with small nucleophiles such as water to afford the desired regioisomer **24**. We decided to take advantage of this result. With a careful choice of the nucleophile employed to open **22** and a slight alteration of our synthetic plan, the target molecule **2** may be accessed with equal efficiency as the first generation synthetic plan. As shown in Scheme 13, oxidative opening of aziridine **22** with DMSO may be followed by further oxidation to the enone **30**. Subsequent selective reduction would afford allylic alcohol **31**. Finally, an etherification reaction would complete the synthesis of oseltamivir.

Oxidative opening of aziridine **22** was examined and the results are summarized in Table 4. At 80 °C with In(OTf)<sub>3</sub> and DMSO, no reaction occurred (Table 4, entry 1). Increasing the reaction temperature to 200 °C and applying a microwave reactor resulted in aromatization of the starting material (Table 4, entry 2). Further screening showed that at 120 °C the desired ketone **29** could be obtained in moderate yields together with a significant amount of alcohol **24** (Table 4, entry 3). Water was considered to be the source of the formation of **24**. Therefore, several methods were applied in order to minimize water's presence in the reaction. Utilization of ultra dry In(OTf)<sub>3</sub> as well as freshly distilled DMSO led to no improvement in the yield of **29** (Table 4, entry 4). Addition of desiccant Na<sub>2</sub>SO<sub>4</sub> into the reaction increased the yield of **29** to 58% (Table 4, entry 5). Finally, while keeping the catalyst concentration unchanged, increasing the substrate concentration, and therefore lowering the water concentration in the reaction resulted in 54% yield of **29** (Table 4, entry 6).

Having ketone **29** in hand, enone **30** was successfully formed by IBX oxidation (Scheme 14).<sup>24</sup> Fortunately, by doubling the equivalence of IBX, alcohol **24** could be directly oxidized to enone **30**, albeit in a modest yield.

Since the ring opening of aziridine **22** and subsequent oxidation both took place in DMSO, we investigated a one-pot procedure for the two steps (Scheme 15). By adding all reagents at once, enone **30** was formed in a modest 30% yield and was accompanied by 49% yield of the unoxidized alcohol **24**. When IBX was added after the opening of aziridine but still in the same pot, the yield of **30** can be improved to 52%.

Moving forward in the synthesis, enone **30** was reduced to allylic alcohol **31** as a single stereoisomer in 76% yield (Scheme 16). The relative stereochemistry was determined by comparison of the NMR spectra with the other isomer **35** obtained later in the synthesis.

Further transformation of **31** to **2** showed interesting results (Scheme 17): The planned mesylation of the allylic alcohol **31** in order to install the alkyl chain *via* an S<sub>N</sub>2 displacement led to the formation of aziridine **34** rather than the mesylate, despite the *cis*-configuration of the sulfonamide and hydroxy groups.

At this point, we decided to take advantage of the formation of **34** and install the 3-pentoxy side chain *via* a Lewis acid catalyzed opening of vinyl aziridine reaction with 3-pentanol as the nucleophile. Such method should lead to **2** in the same number of steps as the planned mesylation-displacement protocol. Encouragingly, in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , reaction between **34** and 3-pentanol gave a 26% yield of the desired product **32**, along with a substantial amount of hydrated product **35** (Scheme 18). Attempted reductive etherification of **35** to form **32** gave only 9% yield.<sup>25</sup>

In addition to the low yield in the alkylation step, later it was found the removal of the tosyl group on **32** was rather difficult. Both direct deprotection of tosyl<sup>26</sup> and the acylation<sup>27</sup> of tosylamine to facilitate the tosyl removal failed. In addition to the deprotection problem, this synthetic route suffered several low yielding steps after the Pd-AAA step (Scheme 19). Therefore, we decided to investigate an alternative synthetic plan to address these problems.

## 6. Final Synthetic Plan

As shown in Scheme 19, from the aziridine **22** to the vinyl aziridine **34**, many oxidation stage changes were made only to install one double bond as a net result. It was against our initial goal of developing an efficient synthesis. Therefore, a major revision of the previous synthetic route is needed to access the vinyl aziridine **34** from the amino ester intermediate **13** more efficiently.

To avoid the multiple oxidation stage changes involved in installing the C-C double bond in **34**, we proposed to first take advantage of the existing double bond in **13** to introduce a second double bond in conjugation (**38**), and then install the aziridine by a selective aziridination reaction. In the mean time, we sought alternative protecting groups, in the hope of improving the yields of the aziridination and opening of the aziridine, as well as easy deprotection. Accordingly, a final revision of our synthetic plan is shown in Scheme 20.

First, we attempted to oxidatively form **38** directly from **13**. Similar strategy to form  $\alpha,\beta$ -unsaturated system from carbonyl compound has been reported for ketones and was also demonstrated in our synthetic study in Scheme 14.<sup>24</sup> However, under similar or more rigorous conditions, the formation of **38** was not observed (Scheme 21).

Hence, a stepwise strategy was undertaken. Starting with **22**,  $\alpha$ -selenation followed by oxidative thermal elimination should afford diene **38**. However, the  $\alpha$ -selenation only afforded about 10% NMR yield of **37** (Scheme 22).

Alternatively, a highly reactive sulfenylating reagent phenyl benzenethiosulfonate ( $\text{PhSSO}_2\text{Ph}$ ) discovered by our group has been successfully utilized in  $\alpha$ -sulfenylation of ketones and esters.<sup>28</sup> Compared with  $\text{PhSeCl}$ , the reactions with it are cleaner, less odoriferous and much less toxic. In this case, it led to satisfying sulfenylation of **13** (Scheme 23).  $\text{KHMDS}$  was found to be the optimal base after careful screening. Sulfenylation of **13** with  $\text{PhSSO}_2\text{Ph}$  and  $\text{KHMDS}$  yielded an approximately 1:1 diastereomeric mixture of  $\beta$ -ketosulfide **39** in 94% yield (Scheme 23). The sulfide was oxidized to the sulfoxide and a subsequent thermal elimination occurred upon refluxing in toluene. The elimination afforded diene **38**<sup>29</sup> and **40** in 5.8:1 ratio. Lower temperature gave higher ratio of **38** with a lower conversion. Further investigation revealed that one diastereomer of **39** spontaneously eliminated after oxidation to give a 11:1 regioselectivity favoring **38** (Scheme 24). Unfortunately, the other diastereomer of **39**, upon oxidation, was stable up to room temperature. When heated to 60 °C, a 2.7:1 ratio of **38** : **40** was obtained. After optimization, DBU was found effective in increasing the regioselectivity in the elimination step (Scheme 25). After chromatography, **38** and **40** was obtained as a 10:1 regioisomeric mixture in 85% yield (Scheme 25). This mixture was carried on to the next step.

With diene **38** in hand, we would like to install the second amino group via a selective aziridination reaction. Considering the difficulty of removing the tosyl group in the previous synthetic route, this time we wanted to carefully choose a protecting group on the nitrogen.

Ideally, we wanted to bring in the acyl-protected amine directly as it is present in the final product. But considering the difficulties of performing a metal catalyzed aziridination of acyl nitrene, a 1,6-conjugate addition-elimination process was proposed instead to install an acyl aziridine on the double bond distal to the ester.<sup>30,31</sup> Unfortunately, utilizing *O*-acetyl acetamide as nucleophile, and copper thiophenecarboxylate (CuTC) as the catalyst, no reaction occurred with reaction temperatures up to 40 °C (Scheme 26).

In order to develop conditions for the conjugate addition, a model compound **42** was studied under a variety of Lewis Acid catalyzed 1,4-conjugate addition reaction conditions (Table 5, entry 1). No reaction was observed under all conditions. Since Lewis acidic conjugate addition didn't work, we turned our attention to basic conditions. Commonly used conjugate addition reagents lithium anion and cuprates gave no reaction with **42** (Table 5, entry 2 and 3). Using strongly basic sodium hydride along with with heating still led to no reaction (Table 5, entry 4). Lastly, suspecting the  $\alpha$ -protons of the acyl group may be deprotonated under basic conditions, we changed the acyl amine to a Boc protected amine, and switched the acetate leaving group to a more active phosphate leaving group. However, such changes did not give improved results (Table 5, entry 5).

Delightfully, diphenylsulfilimine, a good nucleophile for 1,4-conjugate addition,<sup>32</sup> reacted with model compound **42** via 1,6-conjugate addition to yield the desired aziridine product **43** as a single regioisomer (Scheme 27). Unfortunately, the same conditions on real system **38** led to exclusive addition to the carbonyl group of the phthalimide functionality.

Considering the difficulties in conjugate 1,6-addition, a selective aziridination was proposed using copper as catalyst.<sup>33</sup> First, we tried to find a good protecting group on the aziridine. 4-Nitrobenzenesulfonyl group is known for its ease of removal. However, it led to decomposition in the aziridination step. A more stabilized, yet relatively easy-to-remove protecting group, benzenesulfonyl group, was then quickly examined. Unfortunately, standard benzenesulfonyl group removal condition led to decomposition. Therefore, finding a sulfonyl group which deprotected under mild conditions was necessary for the synthesis. 2-(Trimethylsilyl)ethanesulfonyl (SES) group was known for its ease of removal by fluoride sources and thus was chosen to be the protecting group on the aziridine. A variety of conditions and catalysts were examined for the aziridination of **38** with SESNH<sub>2</sub> (Table 6).

An unexpected difficulty arose in the regio- and stereoselective aziridination of **38**. Extensive conditions were screened; selected examples are shown in Table 6. Copper catalysts, which were commonly used in aziridination reactions, showed virtually no selectivity between the  $\alpha,\beta$ - and the  $\gamma,\delta$ -double bonds of **38** and formed an inseparable mixture of **44** and **45**. This lack of selectivity was seen throughout extensive screening of ligands (Selected results: Table 6, entry 1 and 2). Additionally, changing copper for larger metals such as Ag or Au, resulted in low reactivity though excellent regioselectivity of the desired  $\gamma,\delta$ -aziridine **44** was obtained (Selected results: Table 6, entry 3 and 4).<sup>34</sup> Guthikonda and Du Bois reported a rhodium-catalyzed intermolecular aziridination reaction, highlighting *in situ* generation of a nitrene species. In these reactions the olefin is the limiting reagent.<sup>35</sup> Screening of Rh-catalysts revealed Du Bois's C-H insertion catalyst, Rh<sub>2</sub>(esp)<sub>2</sub> (bis[rhodium( $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)]),<sup>36</sup> gave higher conversions than Rh<sub>2</sub>(O<sub>2</sub>CPh<sub>3</sub>)<sub>4</sub>, Rh<sub>2</sub>(O<sub>2</sub>CMe<sub>3</sub>)<sub>4</sub> or Rh<sub>2</sub>(CF<sub>3</sub>CONH)<sub>4</sub> (Table 6, entry 5–8). The catalyst loading could be lowered to 2 mol% without decay in yield (Table 6, entry 9). Moreover, changing the oxidant from PhI(OAc)<sub>2</sub> to PhI(O<sub>2</sub>CMe<sub>3</sub>)<sub>2</sub> afforded even better



conversion to **44** (Table 11, entry 10).<sup>37</sup> The environmentally benign solvent isopropyl acetate could be used, replacing chlorobenzene, and leading to similar yield and selectivity, however, with a slightly inconvenient workup. Most satisfyingly,  $\gamma,\delta$ -aziridine **44** was observed as the exclusive product in all Rh-catalyzed cases. Finally, in chlorobenzene, using  $\text{Ph}(\text{O}_2\text{CCMe}_3)_2$  and  $\text{SESNH}_2$ , 2 mol%  $\text{Rh}_2(\text{esp})_2$ , and MgO as the base and desiccant, an 86% isolated yield of a single isomer **44** was obtained from the diene mixture **38** (Scheme 28). Replacing chlorobenzene with isopropyl acetate gave the same result (entry 11).

With **44** in hand, similar opening of aziridine as shown in Scheme 18 was performed with good regio- and diastereoselectivity (Table 7). Similar to tosyl aziridine, the alcohol **47** was a major byproduct in this ring-opening reaction (Table 7, entry 1). At lower temperatures, **46** was formed more slowly than **47**, resulting in less **46** formation (Table 7, entry 2). Running the reaction at higher temperature accelerated the formation of **46** relative to **47** (Table 7, entry 3). Weaker Lewis acids, such as  $\text{In}(\text{OTf})_3$  or  $\text{Cu}(\text{OTf})_2$  also slowed down the formation of **46**, and thus increased the yield of the undesired **47** (Table 7, entry 4 and 5). Entry 1–5 in Table 6 were performed when **44** still contained **45** as an impurity and yields were calculated based on the assay of **44**. Later, with pure **44** in hand, a third product with an unconfirmed structure **48** was isolated (Table 7, entry 6–12). Therefore **46**, **47** and **48** nicely account for all the mass balance of this reaction. Lowering the substrate concentration in order to increase the concentration of the nucleophile 3-pentanol did not improve the yield (Table 7, entry 6 and 7). Adding molecular sieves to minimize water's presence also did not reduce the formation of **47** (Table 7, entry 8). Preformation of the 3-pentyl borate and subjection of it to the reaction conditions led to no conversion (Table 7, entry 9). However, thoroughly drying **44** slightly improved the yield of **46** (Table 7, entry 10). Adding 1 equiv *N,O*-bis[trimethylsilyl]acetamide (BSA) to chemically remove any residual or newly generated water afforded a lower yield of **46** (Table 7, entry 11). Eventually, after premixing BSA with dry **44** followed by full removal of all volatiles, the aziridine-opening gave a 65% isolated yield of **46** (Table 7, entry 12).

As the formation of **47** could not be avoided, conditions to convert **47** to **46** were studied. Unfortunately, various attempts to directly convert **47** to **46** failed. However, under Mitsunobu conditions, we were able to convert compound **47** back to **44** which would allow the recycling of **44** (Scheme 29).

The next step in the synthesis of **2** was to deprotect the SES group. However, direct removal of the SES group was unsuccessful under a variety of literature conditions. Therefore, we decided to acylate the SES-amino group prior to the deprotection. Optimization of the acylation step is summarized in Table 8. Under standard acylation conditions, no reaction occurred at room temperature even with large excesses of reagents (Table 8, entry 1 and 2). At elevated temperature as high as 120 °C with acetic anhydride as solvent, conversion was observed (Table 8, entry 3). Addition of pyridine improved the yield from to 64% after 3 hrs and 74% after overnight heating (Table 8, entry 4 and 5). Eventually, a microwave reactor was used and 84% yield was obtained at 150 °C after 1 hr (Table 8, entry 6).

The optimized acylation conditions and the final steps in the synthesis are summarized in Scheme 30. After acylation, the SES group was easily removed by TBAF. Finally, removal of the phthaloyl with hydrazine finished the synthesis of **2**.

## Conclusion

In summary, we have accomplished an azide-free eight-step synthesis of (–)-oseltamivir from commercially available materials with 30% overall yield. Key transformations involve a novel Pd-catalyzed AAA deracemization of a lactone with a nitrogen nucleophile and an

unprecedented Rh-catalyzed chemo-, regio- and stereoselective direct aziridination reaction on an electron deficient conjugated diene system. The final synthetic route for (-)-oseltamivir is shown in Scheme 31.<sup>4i</sup>

## Experimental Section

Selected experimental procedures for the two key steps, Pd-AAA deracemization of lactone and Rh-catalyzed selective aziridination, are shown below. Full experimental details for all new compounds and (-)-oseltamivir are given in the Supporting Information.

### Pd-AAA of deracemization Lactone **8**: (1*S*,5*S*)-ethyl 5-(1,3-dioxoisindolin-2-yl)cyclohex-3-enecarboxylate (**13**)

All glassware was flame-dried under high vacuum. All chemicals were flushed with N<sub>2</sub> by evacuating under high-vacuum then refilling with N<sub>2</sub> for 5 cycles prior to the reaction. THF was degassed using a freeze-thaw technique under N<sub>2</sub> for 5 cycles. Lactone **8** was redistilled before use and TMS-phthalimide was stored and weighed in a glove box. To a 100 ml pear shaped flask was loaded [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (183 mg, 0.50 mmol), (*R,R*)-**11** (1.04 g, 1.50 mmol) and a stir bar. Degassed dry THF (70 ml) was injected into the flask and the mixture was stirred for 20 min at 40 °C to give a yellow solution. At 40 °C under N<sub>2</sub>, lactone **5** (2.48 g, 20 mmol) in 5 ml THF was cannulated into the solution. THF (2 × 5 ml) was used to rinse the flask containing **8** and was also cannulated into the yellow solution. After 5 min, TMS-phthalimide (6.58 g, 30 mmol) in 15 ml THF was cannulated into the yellow solution under N<sub>2</sub>. The reaction was then stirred at 40 °C under N<sub>2</sub> for 8 h at which time the TLC showed the disappearance of **8**. THF was removed *in vacuo*. To the residue was added TsOH•H<sub>2</sub>O (380 mg, 2.0 mmol) and 67 ml absolute ethanol. The mixture was heated at reflux for 10 h monitored by TLC. Ethanol was removed *in vacuo*, and the resulting solid mixture was mixed evenly with 33 g silica gel by dissolving in DCM and concentrating *in vacuo*. The silica gel containing crude product was loaded on top of a silica gel column. Eluting with 15:1 petroleum ether : ethyl acetate yielded 5.0 g **13** as a white solid. *R<sub>f</sub>* = 0.76 (1:1 petroleum ether : ethyl acetate). HPLC OD 220 nm 90:10 heptane : 2-propanol 0.8 ml/min, *t*<sub>major</sub> = 11.44 min, *t*<sub>minor</sub> = 15.54 min. [ $\alpha$ ]<sub>D</sub> = -93.8 ° (CHCl<sub>3</sub>, *c* = 1.05) mp 108–112 °C. IR (neat): 3033, 2984, 1770, 1731, 1702, 1613, 1464, 1387, 1179, 1105 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.75 (dd, 5.59, 3.07, 2H), 7.65 (dd, 5.4, 3.1, 2H), 5.85 (m, 1H), 5.52 (d, 10.2, 1H), 4.92 (m, 1H), 4.07 (q, 7.0, 2H), 2.72 (m, 1H), 2.34 (m, 2H), 2.27 (q, 12.4, 1H), 2.13 (m, 1H), 1.18 (t, 7.6, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  174.05, 167.8, 133.9, 131.9, 127.9, 126.6, 123.1, 60.5, 47.3, 39.4, 29.0, 27.0, 14.1. Anal. Calc'd for C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>: C, 68.21; H, 5.72. Found: C, 67.88; H, 6.00. HRMS Calc'd for C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>(M<sup>+</sup>): 299.1158. Found: 299.1171.

### Rh-catalyzed selective aziridination: (1*S*,5*S*,6*R*)-ethyl 5-(1,3-dioxoisindolin-2-yl)-7-(2-(trimethylsilyl)ethylsulfonyl)-7-aza-bicyclo[4.1.0]hept-2-ene-3-carboxylate (**44**)

All glassware was flamed dried under high vacuum. MgO was activated by flame-dry under high vacuum before use. Chlorobenzene was distilled over P<sub>2</sub>O<sub>5</sub> and stored under inert atmosphere over 4 Å MS beads. Under a positive pressure of N<sub>2</sub>, to SESNH<sub>2</sub> in 1 ml C<sub>6</sub>H<sub>5</sub>Cl was added sequentially mixture **38** (149 mg, 0.5 mmol), MgO (46 mg, 1.15 mmol), Rh<sub>2</sub>(esp)<sub>2</sub> (7.6 mg, 0.01 mmol). The reaction was cooled to 0 °C. PhI(OPiv)<sub>2</sub> (264 mg, 0.65 mmol) was added in one portion. The reaction was slowly warmed to rt and stirred for 4 hrs till the disappearance of **38** by TLC. The MgO was filtered and washed thoroughly with DCM. The combined filtrate was concentrated *in vacuo* with gentle heating and loaded to a silica gel column. Eluting with 10:1 petroleum ether : ethyl acetate yielded 206 mg **44** as a white foam. *R<sub>f</sub>* = 0.50 (2.5:1 petroleum ether : ethyl acetate). MP = 55–58 °C. IR (film): 2955, 1775, 1715, 1468, 1388, 1327, 1263, 1144, 1109, 1005 cm<sup>-1</sup>. [ $\alpha$ ]<sub>D</sub> = +42.1 ° (CHCl<sub>3</sub>,

c = 1.08).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.75(dd, 5.4, 3.1, 2H), 7.67(dd, 5.5, 3.1, 2H), 7.15(dd, 4.5, 2.4, 1H), 4.90(ddd, 7.6, 3.5, 2.2, 1H), 4.14-4.07(m, 2H), 3.47(dd, 6.6, 4.5, 1H), 3.40(dt, 6.6, 1.7, 1H), 3.06-3.02(m, 2H), 2.78(dd 17.9, 3.3, 1H), 2.53(ddd, 17.7, 7.6, 2.6, 1H), 1.20(t, 7.1, 3H), 1.04-1.00(m, 2H), 0.005(s, 9H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  167.5, 165.4, 134.3, 132.4, 131.4, 130.9, 123.3, 61.0, 49.2, 42.9, 40.3, 36.5, 26.1, 14.1, 9.5, -2.1. HRMS Calc'd for  $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_6\text{SSi}$  ( $\text{M}^+ + \text{H}$ ): 477.1516 Found: 477.1494.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

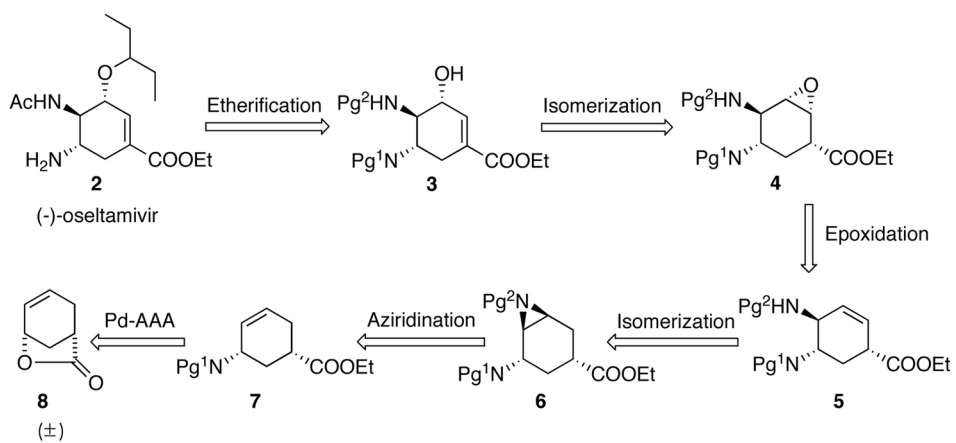
We thank the National Institutes of Health (GM 033049) and the National Science Foundation for their generous support of our programs. T.Z. thanks Novartis and Roche for graduate fellowships. Mass spectra were provided, in part, by the Mass Spectrometry Regional Center of the University of California, San Francisco. Palladium salts were generously supplied by Johnson-Matthey. We thank Gilead Sciences for a reference sample of Tamiflu.

## References

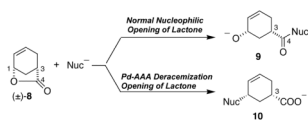
1. For information on H5N1 avian flu and H5N1 virus, visit: <http://www.nature.com/avianflu/index.html>. For information on H1N1 flu and H1N1 virus, visit: <http://www.cdc.gov/h1n1flu/>
2. For reviews on Tamiflu synthesis, see: a) Farina V, Brown JD. *Angew Chem Int Ed.* 2006; 45:2. b) Shibasaki M, Kanai M. *Eur J Org Chem.* 2008; 11:1839. (c) Magano J. *Chem Rev.* 2009; 109:4398. [PubMed: 19537777]
3. Contributions from Gilead Sciences: a) Kim CU, Lew W, Williams MA, Liu H, Zhang L, Swaminathan S, Bischofberger N, Chen MS, Mendel DB, Tai CY, Laver G, Stevens RC. *J Am Chem Soc.* 1997; 119:681. [PubMed: 16526129] b) Rohloff JC, Kent KM, Postich MJ, Becker MW, Chapman HH, Kelly DE, Lew W, Louie MS, McGee LR, Prisbe EJ, Schultze LM, Yu RH, Zhang L. *J Org Chem.* 1998; 63:4545. c) Bischofberger NW, Kim CU, Lew W, Liu H, Williams MA, US Patent 5763483, 1998. Extensive studies at Roche: d) Abrecht S, Harrington P, Iding H, Karpf M, Trussardi R, Wirz B, Zutter U. *Chimia.* 2004; 58:621. e) Karpf M, Trussardi R. *Angew Chem Int Ed.* 2009; 48:5760.
4. a) Yeung YY, Hong S, Corey EJ. *J Am Chem Soc.* 2006; 128:6310. [PubMed: 16683783] b) Fukuta Y, Mita T, Fukuda N, Kanai M, Shibasaki M. *J Am Chem Soc.* 2006; 128:6312. [PubMed: 16683784] c) Cong X, Yao ZJ. *J Org Chem.* 2006; 71:5365. [PubMed: 16808528] d) Mita T, Fukuda N, Roca FX, Kanai M, Shibasaki M. *Org Lett.* 2007; 9:259. [PubMed: 17217279] e) Yamatsugu K, Kamijo S, Suto Y, Kanai M, Shibasaki M. *Tetrahedron Lett.* 2007; 48:1403. f) Bromfield KM, Graden H, Hagberg DP, Olsson T, Kann N. *Chem Commun.* 2007; 3183. g) Satoh N, Akiba T, Yokoshima S, Fukuyama T. *Angew Chem.* 2007; 119:5836. *Angew Chem Int Ed.* 2007; 46:5734. *Angew Chem Int Ed.* 2007; 46:5734. h) Shie JJ, Fang JM, Wang SY, Tsai KC, Cheng YSE, Yang AS, Hsiao SC, Su CY, Wong CH. *J Am Chem Soc.* 2007; 129:11892. [PubMed: 17850083] i) Trost BM, Zhang T. *Angew Chem Int Ed.* 2008; 47:3759. j) Ishikawa H, Suzuki T, Hayashi Y. *Angew Chem Int Ed.* 2009; 48:1304. k) Mandai T, Oshitari T. *Synlett.* 2009:787. l) Nie LD, Shi XX. *Tetrahedron: Asymmetry.* 2009; 20:124. m) Matveenko M, Willis AC, Banwell MG. *Tetrahedron Lett.* 2008; 49:7018. n) Yamatsugu K, Yin L, Kamijo S, Kimura Y, Kanai M, Shibasaki M. *Angew Chem Int Ed.* 2009; 48:1070. o) Satoh N, Akiba T, Yokoshima S, Fukuyama T. *Tetrahedron.* 2009; 65:3239. p) Sullivan B, Carrera I, Drouin M, Hudlicky T. *Angew Chem Int Ed.* 2009; 48:4229. q) Yamatsugu K, Kanai M, Shibasaki M. *Tetrahedron.* 2009; 65:6017. r) Sun H, Lin YJ, Wu YL, Wu Y. *Synlett.* 2009:2473. s) Osato H, Jones IL, Chen A, Chai CLL. *Org Lett.* 2010; 12:60. [PubMed: 19938847] t) Ma J, Zhao Y, Ng S, Zhang J, Zeng J, Than A, Chen P, Liu XW. *Chem Eur J.* 2010; 16:4533. u) Kamimura A, Nakano T. *J Org Chem.* 2010; 75:3133. [PubMed: 20364872] v) Zhu S, Yu S, Wang Y, Ma D. *Angew Chem Int Ed.* 2010; 49:4656.
5. The lactone can also be synthesized in two steps: Barlett PA, McQuaid LA. *J Am Chem Soc.* 1984; 106:7854.

6. Trost BM, Surivet J-P. *Angew Chem Int Ed.* 2000; 39:3122.
7. Trost BM, Bunt RC. *J Am Chem Soc.* 1996; 118:235.
8. Grehn L, Ragnarsson U. *Synthesis.* 1987:275.
9. Pd-catalyzed AAA with HN(Boc)<sub>2</sub>: Evans DA, Campos KR, Tedrow JS, Michael FE, Gagne MR. *J Am Chem Soc.* 2000; 122:7905.
10. Pd-catalyzed stereospecific allylic alkylation with HN(Cbz)<sub>2</sub>: FairhurstRATaylorRJWO Patent20080065632008
11. Pd-catalyzed AAA with HN(Cbz)<sub>2</sub>: Fandrick, DR. PhD thesis. Stanford University; 2006.
12. Pd-catalyzed AAA with NaN(CHO)<sub>2</sub>: Zhang R, Yu L, Xu L, Wang Z, Ding K. *Tetrahedron Lett.* 2001; 42:7659.
13. Pd-catalyzed AAA with sodium phthalimide: Trost BM, Radinov R. *J Am Chem Soc.* 1997; 119:5962.
14. Pd-catalyzed AAA with phthalimide: a) Trost BM, Bunt RC. *J Am Chem Soc.* 1994; 116:4089. b) Trost BM, Bunt RC, Lemoine RC, Calkins TL. *J Am Chem Soc.* 2000; 122:5968. c) Trost BM, Krueger AC, Bunt RC, Zambrano J. *J Am Chem Soc.* 1996; 118:6520. d) Trost BM, Jiang C, Hammer K. *Synthesis.* 2005:3335. e) Trost BM, Horne DB, Woltering MJ. *Angew Chem, Int Ed.* 2003; 42:5987. f) Trost BM, Horne DB, Woltering MJ. *Chem-Eur J.* 2006; 12:6607. g) Trost BM, Aponick A. *J Am Chem Soc.* 2006; 128:3931. [PubMed: 16551099] h) Trost BM, Aponick A, Stanzl BN. *Chem-Eur J.* 2007; 13:9547. i) Trost BM, O'Boyle BM. *Org Lett.* 2008; 10:1369. [PubMed: 18318539]
15. Bunt, RC. PhD thesis. Stanford University; 1996.
16. Adam W, Bottke N, Krebs O, Sahoo-Moller CR. *Eur J Org Chem.* 1999:1963.
17. Keck GE, Webb RR, Yates JB. *Tetrahedron.* 1981; 37:4007.
18. a) Lessard J, Mondon M, Touchard D. *Can J Chem.* 1981; 59:431. b) Lessard J, Tuaille J. *J Org Chem.* 1982; 47:5013. c) Koser GF, Kokil PB, Shah M. *Tetrahedron Lett.* 1987; 28:5431. d) Glover SA, Goosen A, McClelland CW, Schoonraad JL. *Tetrahedron.* 1987; 43:2577. e) Glover SA, Rowbottom CA, Scott AP. *Tetrahedron.* 1990; 46:7247.
19. For aziridination reactions, see a recent review and references therein: Watson IDG, Yu L, Yudin AK. *Acc Chem Res.* 2006; 39:194. [PubMed: 16548508]
20. Trost BM, Dong G. *J Am Chem Soc.* 2006; 128:6054. [PubMed: 16669672]
21. Mordini A, Russo F, Valacchi M, Zani L, Degl'Innocenti A, Reginato G. *Tetrahedron.* 2002; 58:7153.
22. O'Brien P, Rosser CM, Caine D. *Tetrahedron.* 2003; 59:9779.
23. Mordini A, Sbaragli L, Valacchi M, Russo F, Reginato G. *Chem Commun.* 2002:778.
24. Nicolaou KC, Montagnon T, Baran PS, Zhong YL. *J Am Chem Soc.* 2002; 124:2245. [PubMed: 11878978]
25. a) Kato, J-i; Iwasawa, N.; Mukaiyama, T. *Chem Lett.* 1985:743. b) Hatakeyama S, Mori H, Kitano K, Yamada H, Nishizawa M. *Tetrahedron Lett.* 1994; 35:4367. c) Lee SH, Park YJ, Yoon CM. *Tetrahedron Lett.* 1999; 40:6049. d) Iwanami K, Seo H, Tobita Y, Oriyama T. *Synthesis.* 2005:183. e) Iwanami K, Yano K, Oriyama T. *Chem Lett.* 2007; 36:38.
26. Hill DC, Flugge LA, Petillo PA. *J Org Chem.* 1997; 62:4864.
27. Kumar V, Ramesh NG. *Chem Commun.* 2006:4952.
28. Trost BM, Massiot GS. *J Am Chem Soc.* 1977; 99:4405.
29. A similar diene intermediate bearing an NH-Boc group rather than an N-phthaloyl group was reported in Corey's synthesis ( Yeung YY, Hong S, Corey EJ. *J Am Chem Soc.* 2006; 128:6310. [PubMed: 16683783] ). In their approach, the synthesis of the diene required 8 steps, whereas in our approach, compound **38** took only 3 steps. From the conjugate diene, they applied a two-step haloamination-S<sub>N</sub>2 displacement sequence to form the desired aziridine while we developed a direct aziridination process.
30. Examples for 1,4-conjugate addition to form aziridines: a) Fioravanti S, Colantoni D, Pellacani L, Tardella PA. *J Org Chem.* 2005; 70:3296. [PubMed: 15822999] b) Colantoni D, Fioravanti S, Pellacani L, Tardella PA. *Org Lett.* 2004; 6:197. [PubMed: 14723527] c) Fioravanti S, Morreale A, Pellacani L, Tardella PA. *Synlett.* 2004; 6:1083. d) Vyas R, Gao GY, Harden JD, Zhang XP.

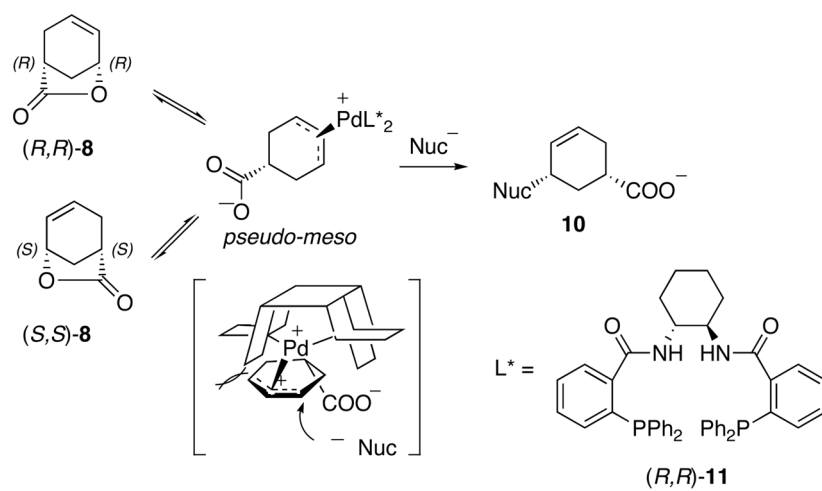
- Org Lett. 2004; 6:1907. [PubMed: 15176780] e) Fioravanti S, Morreale A, Pellacani L, Tardella PA. Eur J Org Chem. 2003;4549. f) Jain SL, Sain B. Tetrahedron Lett. 2003; 44:575. g) Gasperi T, Loreto MA, Tardella PA, Gambacorta A. Tetrahedron Lett. 2002; 43:3017. h) Aires-de-Sousa J, Prabhakar S, Lobo AM, Rosa AM, Gomes MJS, Corvo MC, Williams DJ, White AJP. 2001; 12:3349. i) Fioravanti S, Morreale A, Pellacani L, Tardella PA. J Org Chem. 2002; 67:4972. [PubMed: 12098316] j) Ishikawa T, Kudoh T, Yoshida J, Yasuhara A, Manabe S, Saito S. Org Lett. 2002; 4:1907. [PubMed: 12027644]
31. Example of 1,6-addition onto diene esters: Bernardi L, Lopez-Cantarero J, Niess B, Jorgensen KA. J Am Chem Soc. 2007; 129:5772. [PubMed: 17411052]
32. a) Schirmeister T. Leibigs Ann. 1997:1895. b) Clark DA, De Riccardis F, Nicolaou KC. Tetrahedron. 1994; 50:11391.
33. For a recent review on metal-catalyzed aziridination reactions, see: Halfen JA. Current Organic Chemistry. 2005; 9:657.
34. For a recent report on Ag catalyzed aziridination reactions, see: a) Cui Y, He C. J Am Chem Soc. 2003; 125:16202. [PubMed: 14692757] For a recent report on Au catalyzed aziridination reactions, see: b) Li Z, Ding X, He C. J Org Chem. 2006; 71:5876. [PubMed: 16872166]
35. a) Guthikonda K, Du Bois J. J Am Chem Soc. 2002; 124:13672. [PubMed: 12431086] b) Guthikonda K, Wehn PM, Caliendo BJ, Du Bois J. Tetrahedron. 2006; 62:11331.
36. a) Espino CG, Fiori KW, Kim M, Du Bois J. J Am Chem Soc. 2004; 126:15378–15379. [PubMed: 15563154] b) Fiori KW, Du Bois J. J Am Chem Soc. 2007; 129:562–568. [PubMed: 17227019]
37. a) Chan J, Baucom KD, Murry JA. J Am Chem Soc. 2007; 129:14106. [PubMed: 17967011] b) Zalatan DN, Du Bois J. J Am Chem Soc. 2009; 131:7558. [PubMed: 19441831]



**Scheme 1.**  
Retrosynthetic analysis. Pg = protecting group.

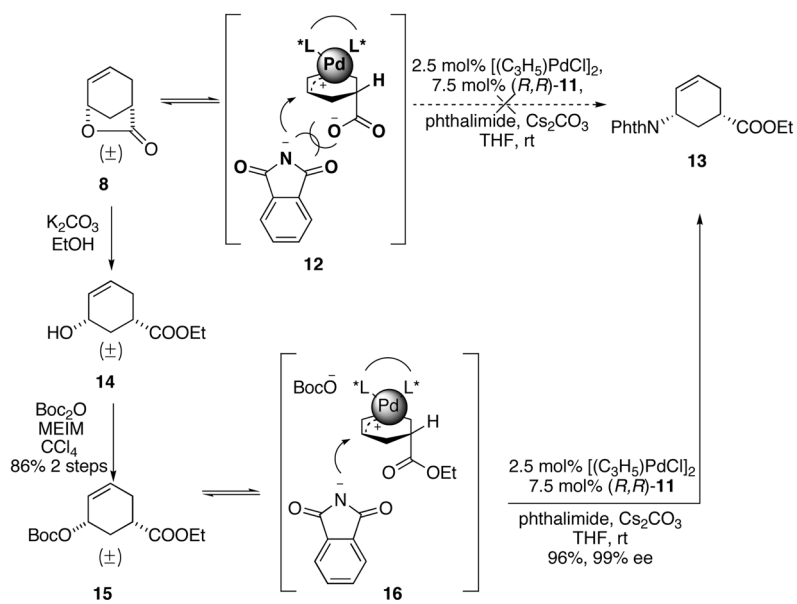
**Scheme 2.**

Different product outcome between normal nucleophilic opening of lactone and Pd-AAA deracemizing lactone.

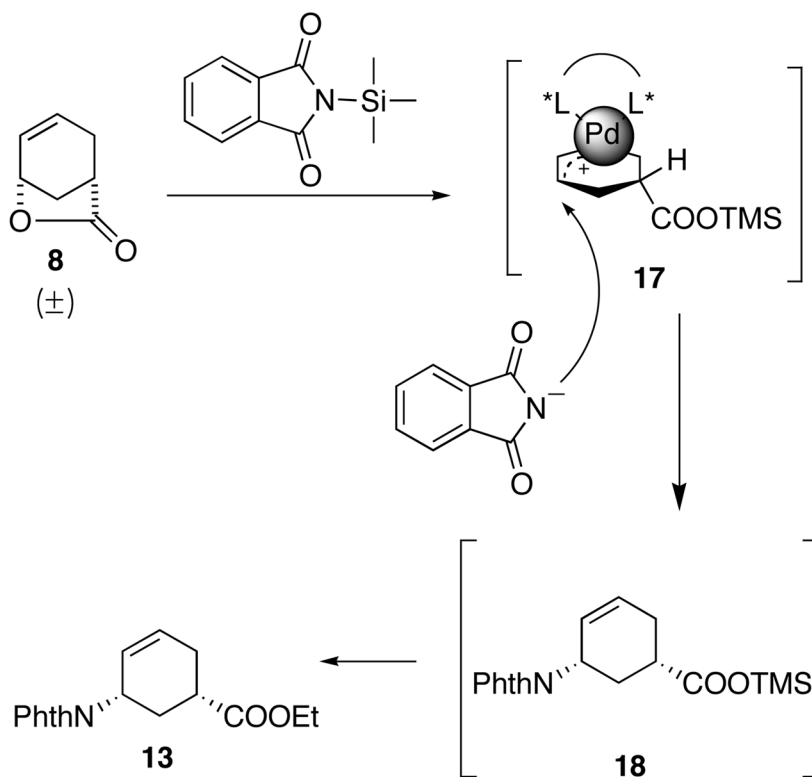


**Scheme 3.**  
Mechanism of Pd-AAA deracemizing lactone.

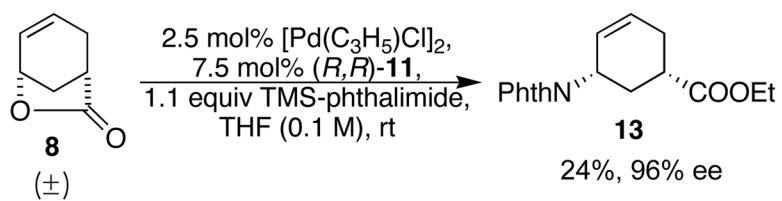




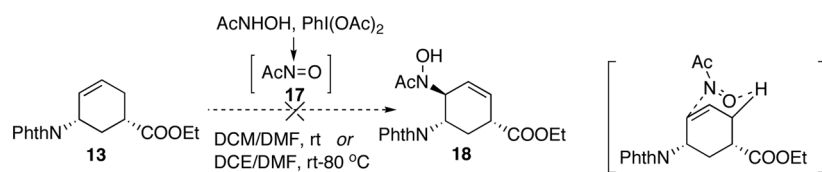
**Scheme 4.**  
Pd-AAA with phthalimide.



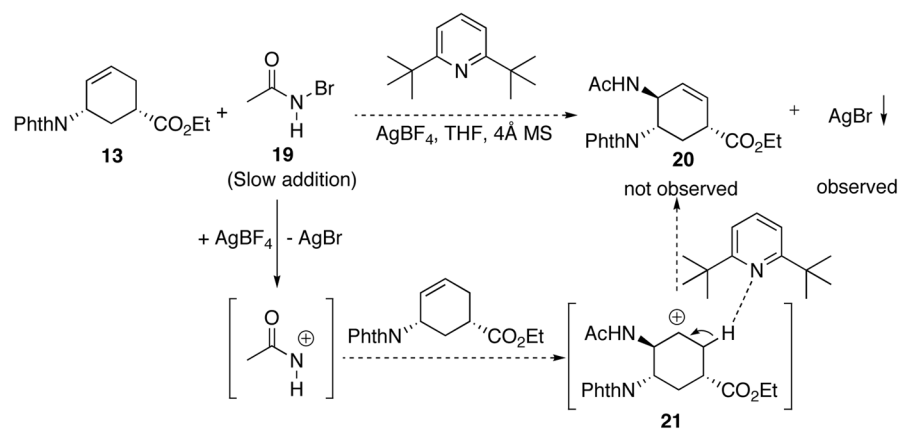
**Scheme 5.**  
Opening of lactone with TMS-phthalimide.



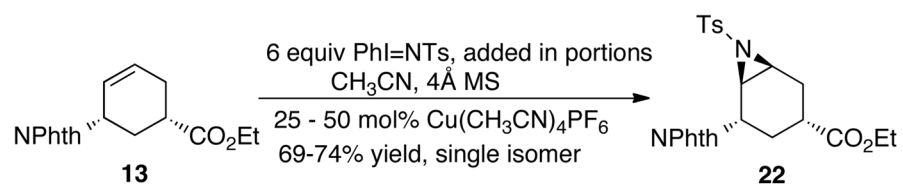
**Scheme 6.**  
Initial results of the opening of lactone with TMS-phthalimide.



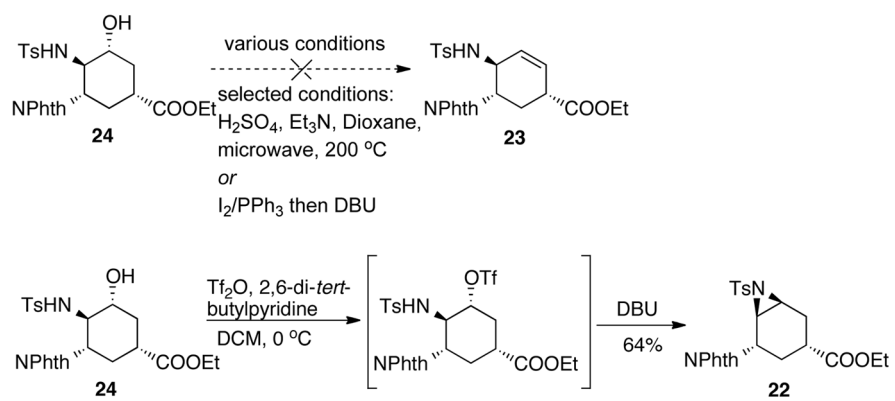
**Scheme 7.**  
Attempted second amination via ene reaction.



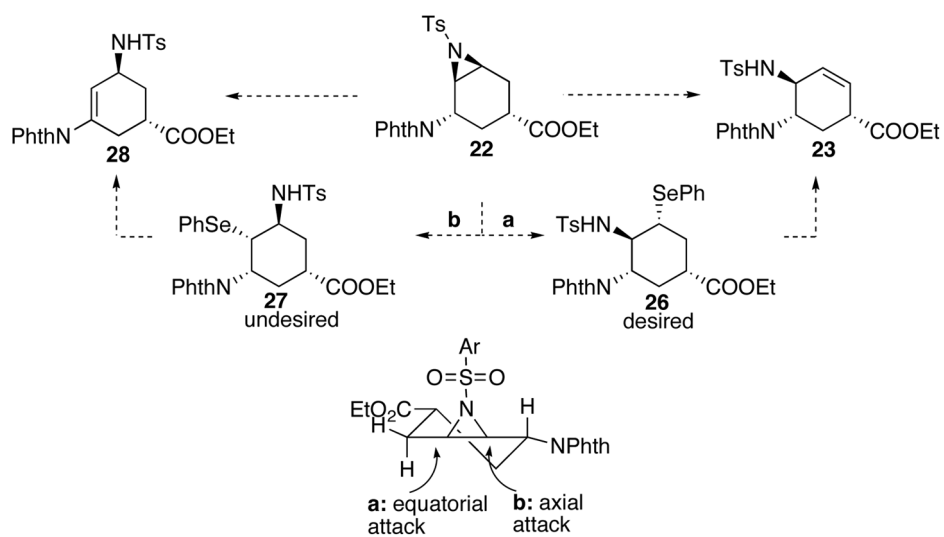
**Scheme 8.**  
Attempted amination with acyl cation equivalent.



**Scheme 9.**  
Copper-catalyzed aziridination.

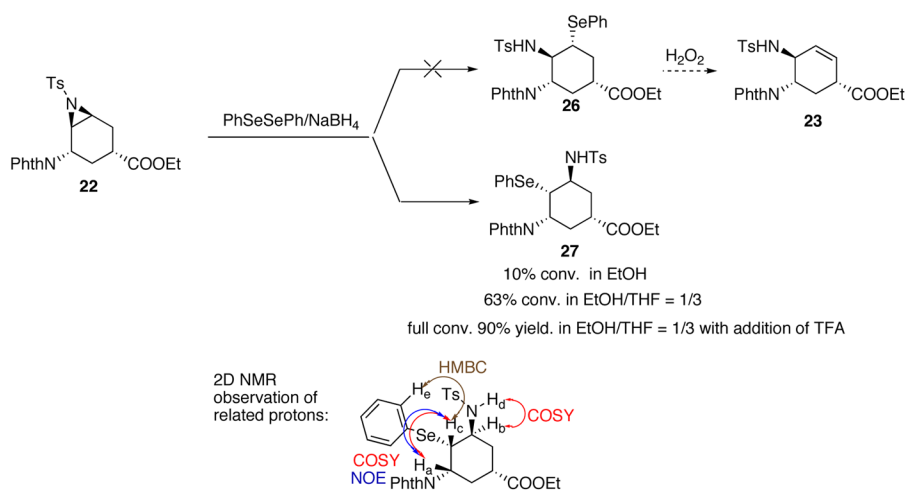


**Scheme 10.**  
Attempted dehydration of alcohol **24**.

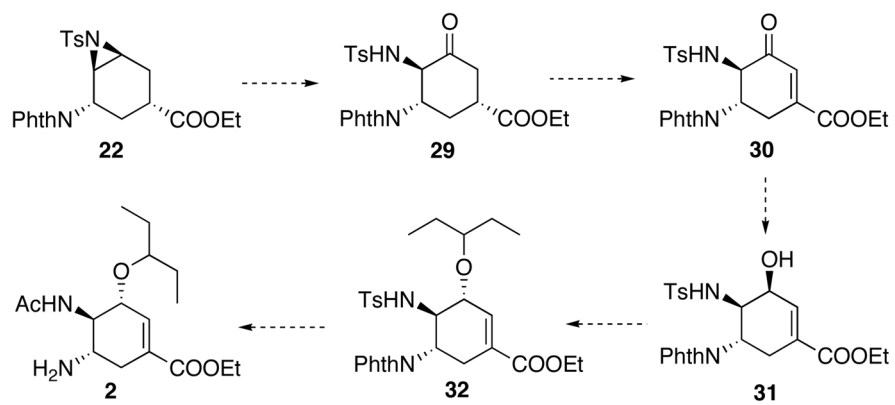


**Scheme 11.**  
Planned two-step sequence to form allylic amine **23**.

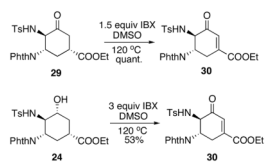




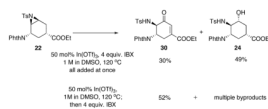
**Scheme 12.**  
Opening of aziridine **22** with selenide.



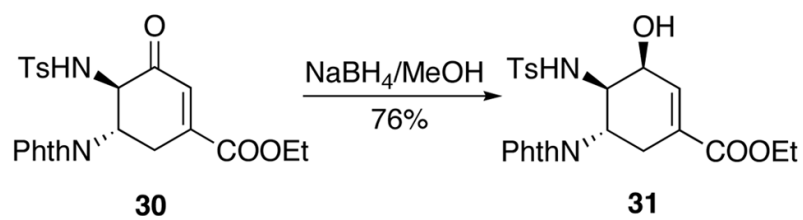
**Scheme 13.**  
Revised Synthetic Plan.



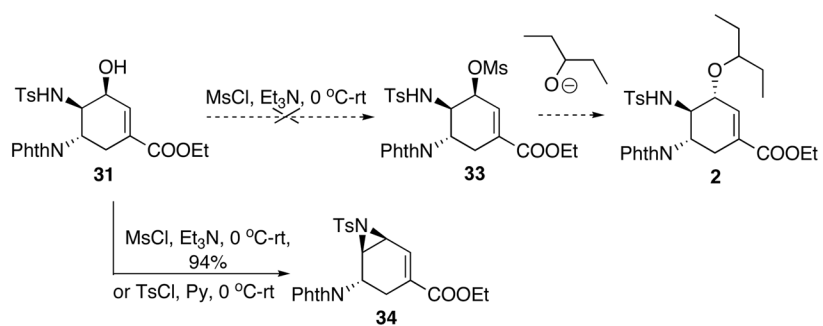
**Scheme 14.**  
Further oxidation to enone.



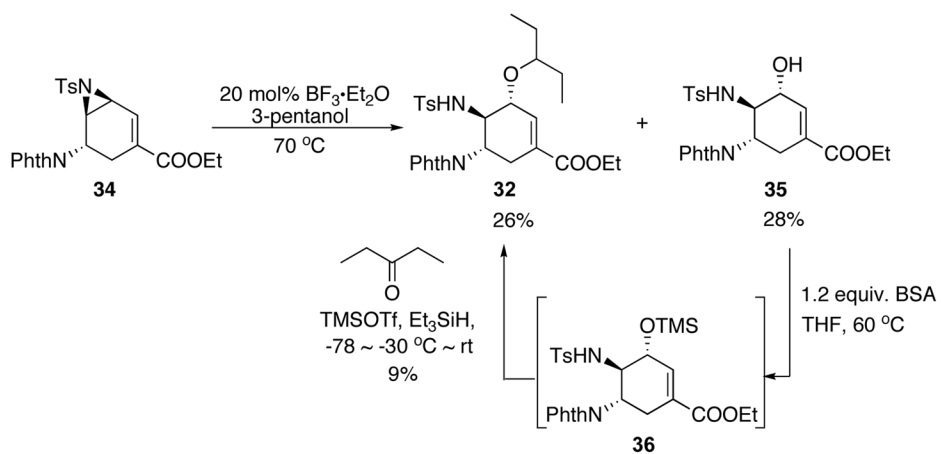
**Scheme 15.**  
One-step procedure for transforming aziridine to enone.



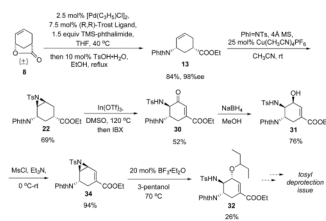
**Scheme 16.**  
Reduction of enone **30** to allylic alcohol **31**.



**Scheme 17.**  
Attempted installation of alkyl fragment.

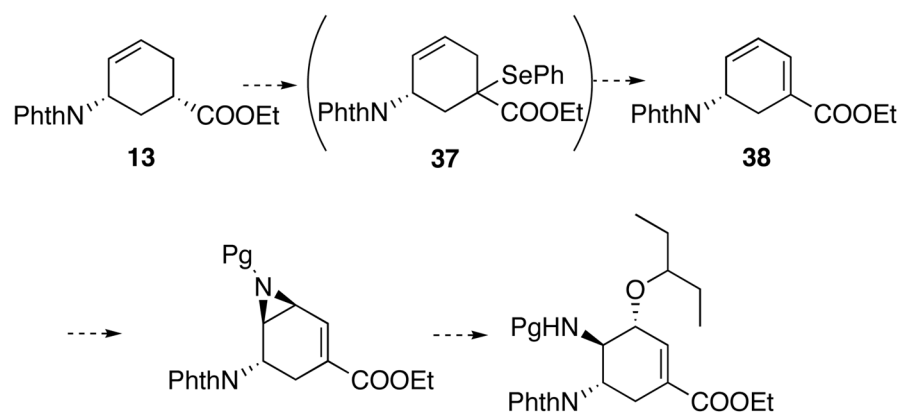


**Scheme 18.**  
Opening of vinyl aziridine with 3-pentanol.

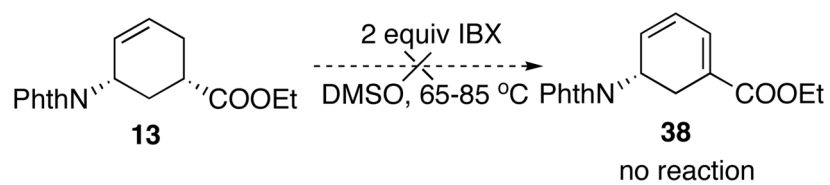


**Scheme 19.**  
Overview of the early synthetic route.

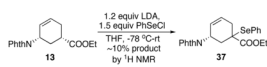




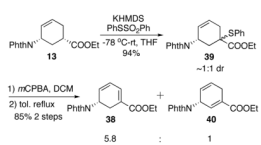
**Scheme 20.**  
Final synthetic plan. Pg = protecting group.



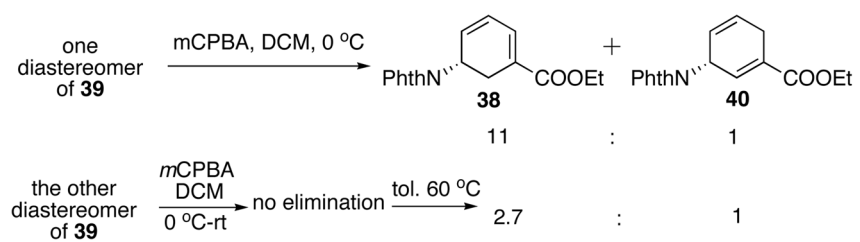
**Scheme 21.**  
Attempted oxidative installation of conjugation.



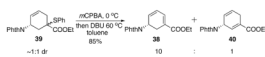
**Scheme 22.**  
 $\alpha$ -Selenation.



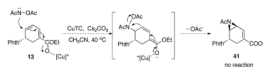
**Scheme 23.**  
Sulfonylation-elimination.

**Scheme 24.**

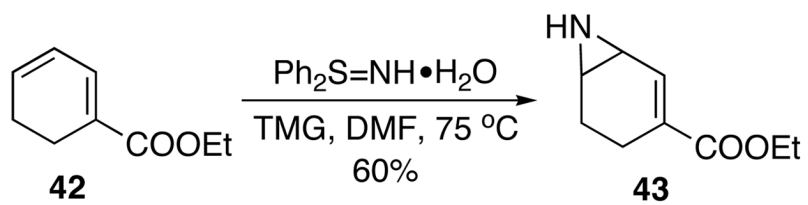
Difference in elimination of the two  $\alpha$ -thioester isomers.



**Scheme 25.**  
Optimized elimination conditions.

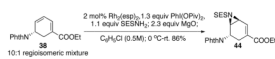


**Scheme 26.**  
Planned 1,6-conjugate addition.

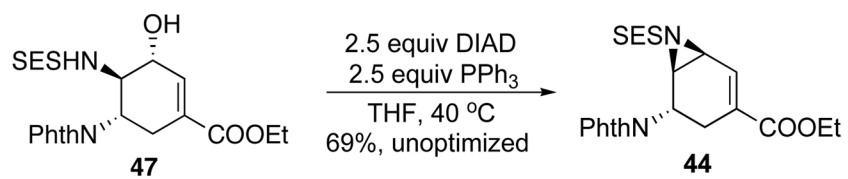
**Scheme 27.**

1,6-Conjugate addition on model compound. TMG = 1,1,3,3-tetramethylguanidine

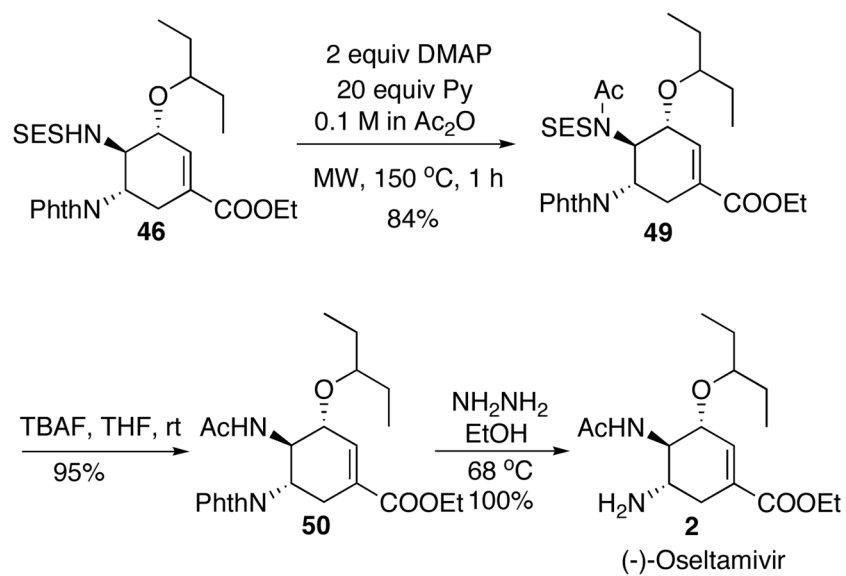




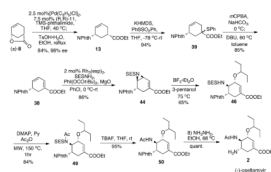
**Scheme 28.**  
Optimized aziridination condition.



**Scheme 29.**  
Attempted alkylation of allylic alcohol **47**.



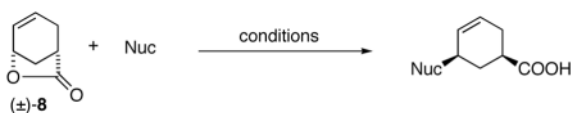
**Scheme 30.**  
Completion of the synthesis.



**Scheme 31.**  
Final synthetic scheme.

Table 1

Opening of lactone with imide nucleophiles.

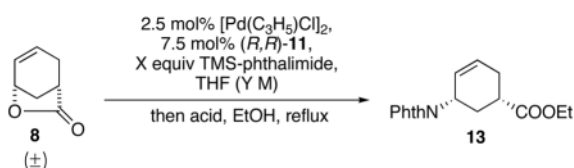


Entry	Nuc	Conditions	Results <sup>[a]</sup>
1	CH <sub>3</sub> NO <sub>2</sub> <sup>[6]</sup>	2 mol% Pd <sub>2</sub> (dba) <sub>3</sub> •CHCl <sub>3</sub> , 6 mol% (S,S)- <b>11</b> , (C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> NCl, BSA, DCM, rt	74% yield, 99%ee
2	malonate <sup>[7]</sup>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , 1 equiv NaH, DCM, 1eq THAB <sup>[b]</sup> , rt	57%, 85%ee
3	HN(Boc) <sub>2</sub> <sup>[8,9]</sup>	2.5 mol% Pd <sub>2</sub> (dba) <sub>3</sub> •CHCl <sub>3</sub> , 7.5 mol% (S,S)- <b>11</b> , DCM, rt-40 °C	NR
4	HN(Boc) <sub>2</sub>	2.5 mol% Pd <sub>2</sub> (dba) <sub>3</sub> •CHCl <sub>3</sub> , 7.5 mol% (S,S)- <b>11</b> , 1.1 equiv Cs <sub>2</sub> CO <sub>3</sub> , DCM, rt-40 °C	NR
5	HN(Boc) <sub>2</sub>	2.5 mol% Pd <sub>2</sub> (dba) <sub>3</sub> •CHCl <sub>3</sub> , 7.5 mol% (S,S)- <b>11</b> , 1 equiv NaH, DCM, rt-40 °C	NR
6	HN(Boc) <sub>2</sub>	2.5 mol% Pd <sub>2</sub> (dba) <sub>3</sub> •CHCl <sub>3</sub> , 7.5 mol% (S,S)- <b>11</b> , 1 equiv BSA, DCM, rt-40 °C	NR
7	HN(Boc) <sub>2</sub>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , 1.1 equiv Cs <sub>2</sub> CO <sub>3</sub> , DCM, rt-40 °C	NR
8	HN(Boc) <sub>2</sub>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , DCM, rt-40 °C	NR
9	HN(Cbz) <sub>2</sub> <sup>[10,11]</sup>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , 1.1eq Cs <sub>2</sub> CO <sub>3</sub> , DCM, rt-40°C	NR
10	HN(Cbz) <sub>2</sub>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , DCM, rt-40°C	NR
11	HN(Cbz) <sub>2</sub>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , 1.2equiv Cs <sub>2</sub> CO <sub>3</sub> , THF, 50°C	NR
12	NaN(CHO) <sub>2</sub> <sup>[12]</sup>	2 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 6 mol% (S,S)- <b>11</b> , CH <sub>3</sub> CN, rt-50 °C	NR
13	NaN(CHO) <sub>2</sub>	2 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 6 mol% (S,S)- <b>11</b> , CH <sub>3</sub> CN, 1equiv THAB <sup>[b]</sup> , rt-60 °C	NR
14	NaPhth <sup>[13][c]</sup>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , THAB, THF, rt	NR
15	HPhth <sup>[14]</sup>	2.5 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 7.5 mol% (S,S)- <b>11</b> , 20 mol% CsOAc, 10 mol% THF, rt-60 °C	NR
16	HPhth	2 mol% [Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> , 6 mol% (S,S)- <b>11</b> , 3 eq Cs <sub>2</sub> CO <sub>3</sub> , THF, 50 °C	NR

<sup>[a]</sup>NR = no reaction.<sup>[b]</sup>THAB = tetrahexylammonium bromide.<sup>[c]</sup>NaPhth = sodium phthalimide.

**Table 2**

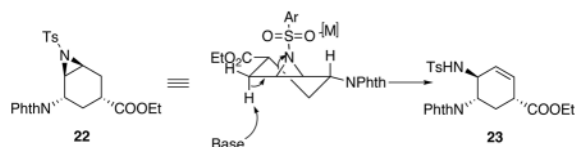
Optimization of opening of lactone with TMS-phthalimide.



Entry	X	Y	Acid	Results
1	1.1	0.1	conc. $\text{H}_2\text{SO}_4$ , rt	24%, 96% ee
2	1	0.2	conc $\text{H}_2\text{SO}_4$ , 40 °C	32%, 97% ee
3	1	0.3	10 mol% $\text{TsOH}\cdot\text{H}_2\text{O}$ , 40 °C	47%, 94% ee
4	1	0.2	1 equiv BSA, 10 mol% $\text{TsOH}\cdot\text{H}_2\text{O}$ , 40 °C	Full conv. in Pd-AAA; low conv. in hydrolysis step
5	2	0.2	10 mol% $\text{TsOH}\cdot\text{H}_2\text{O}$ , 40 °C	80%, 97% ee (0.3 mmol)
6	1.5	0.2	10 mol% $\text{TsOH}\cdot\text{H}_2\text{O}$ , 40 °C	80%, 98% ee (3 mmol)
7	1.5	0.2	10 mol% $\text{TsOH}\cdot\text{H}_2\text{O}$ , 40 °C	84%, 98% ee (20 mmol)

Table 3

Attempted elimination conditions.



Entry	Conditions	Notes
1	2 equiv. LDA, THF, $-78\text{ }^{\circ}\text{C}$	Decomposition to baseline by TLC
2	1 equiv. KO $t$ Bu, THF, $0\text{--}40\text{ }^{\circ}\text{C}$	No desired product
3	5 equiv. KO $t$ Bu, THF, rt	Messy, $t\text{-BuO}^-$ attacked ester
4	1 eq LIDAKOR <sup>[a]</sup> , hexanes, $0\text{ }^{\circ}\text{C}$ –rt	NR (substrate not dissolving)
5	1 eq LIDAKOR, THF, $-78\text{ }^{\circ}\text{C}$	Decomposition to baseline by TLC
6	1.5 eq DBU, toluene, reflux	NR
7	50 mol% In(OTf) <sub>3</sub> , 2,6-di- <i>tert</i> -butylpyridine, THF, $50\text{ }^{\circ}\text{C}$	NR
8	20 mol% In(OTf) <sub>3</sub> , proton-sponge, THF, reflux	No desired reaction. In(OTf) <sub>3</sub> reacted with proton-sponge to form insoluble solids in the reaction.
9	Ho(OTf) <sub>3</sub> , 2,6-di- <i>tert</i> -butylpyridine, chlorobenzene, $100\text{ }^{\circ}\text{C}$	NR, recovered starting material
10	Al(OTf) <sub>3</sub> , 2,6-di- <i>tert</i> -butylpyridine, DCM, $0\text{ }^{\circ}\text{C}$ –rt	100% NMR yield <sup>[c]</sup> of
		 24
11	In(OTf) <sub>3</sub> , 2,6-di- <i>tert</i> -butylpyridine, chlorobenzene, $100\text{ }^{\circ}\text{C}$	NMR yields: 23% 23, 30% 24,
		 25 30%
12	In(OTf) <sub>3</sub> , 2,6-di- <i>tert</i> -butylpyridine, chlorobenzene, 3Å MS, $100\text{ }^{\circ}\text{C}$	NR, recovered starting material

<sup>[a]</sup>LIDAKOR=LDA + *t*BuOK.

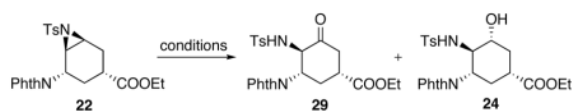
[b] NR = no reaction

[c] NMR yields were determined by using 1,3,5-trimethoxybenzene as an internal standard.



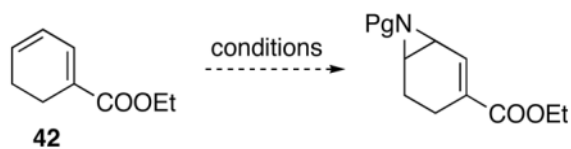
Table 4

Oxidative opening of aziridine.



Entry	Conditions	Results
1	50 mol% In(OTf) <sub>3</sub> , 0.1 M DMSO, 80 °C	No reaction
2	50 mol% In(OTf) <sub>3</sub> , 0.1 M DMSO, MW, 200 °C, 30 min	aromatization
3	50 mol% In(OTf) <sub>3</sub> (wet), 0.1 M DMSO, 120 °C	46% <b>29</b> , 50% <b>24</b>
4	50 mol% In(OTf) <sub>3</sub> (dry), 0.1 M DMSO (distilled), 120 °C	43% <b>29</b> , 42% <b>24</b>
5	50 mol% In(OTf) <sub>3</sub> (dry), 0.1 M DMSO, 1 equiv Na <sub>2</sub> SO <sub>4</sub> , 120 °C	58% <b>29</b> , 34% <b>24</b>
6	5 mol% In(OTf) <sub>3</sub> (dry), 1M in DMSO, 120 °C	54% <b>29</b> , 22% <b>24</b>

Table 5

Attempted 1,6-conjugate addition on model compound.<sup>[a]</sup>

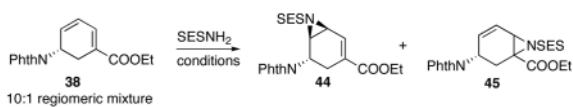
Entry	Conditions	Results
1	AcNHOAc, Cs <sub>2</sub> CO <sub>3</sub> , LA <sup>[b]</sup> , CH <sub>3</sub> CN, rt-80 °C	NR <sup>[c]</sup>
2	<i>n</i> BuLi, AcNHOAc, THF, -40 °C-rt,	NR
3	(AcNOAc) <sub>2</sub> CuLi-LiCN, THF, -78-0 °C	NR
4	AcNHOAc, NaH, DMF, rt-90 °C	NR
5	BocNHOP(O)(OEt) <sub>2</sub> , NaH, DMF, rt -70 °C	NR

<sup>[a]</sup>Pg = protecting group.

<sup>[b]</sup>LA = Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>, Sc(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, In(OTf)<sub>3</sub>, or Cu(OTf)<sub>3</sub>.

<sup>[c]</sup>NR = no reaction.

Table 6

Selected conditions for the aziridination of diene **38**.

Entry	Catalyst	Conditions	Result <sup>[b]</sup>
1	10 mol% Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	PhI=O; 3 Å MS; CH <sub>3</sub> CN; rt	84%; <b>44</b> : <b>45</b> = 1.7 : 1
2	10 mol% Cu(IPr)Cl <sup>[c]</sup> + AgBF <sub>4</sub>	PhI=O; 3 Å MS; CH <sub>3</sub> CN; 0 °C	(80%); <b>44</b> : <b>45</b> = 1.6 : 1
3	10 mol% Ag <sub>2</sub> (tBu <sub>3</sub> Py) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> <sup>[d]</sup>	PhI=O; 3 Å MS; CH <sub>3</sub> CN; 0 °C-rt	(< 48%); <sup>[e]</sup> <b>44</b> only
4	10 mol% Au(tBu <sub>3</sub> Py)OTf <sup>[d]</sup>	PhI(OAc) <sub>2</sub> ; 4 Å MS; CH <sub>3</sub> CN; 80-50 °C	(< 53%); <sup>[e]</sup> <b>44</b> only
5	2 mol% Rh <sub>2</sub> (CF <sub>3</sub> CONH) <sub>4</sub>	PhI(OAc) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	(18%); <b>44</b> only
6	5 mol% Rh <sub>2</sub> (OCOCPh <sub>3</sub> ) <sub>4</sub>	PhI(OAc) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	(35%); <b>44</b> only
7	5 mol% Rh <sub>2</sub> (OCOCMe <sub>3</sub> ) <sub>4</sub>	PhI(OAc) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	(56%); <b>44</b> only
8	5 mol% Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OAc) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	(71%); <b>44</b> only
9	2 mol% Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OAc) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	(72%); <b>44</b> only
10	2 mol% Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub> ; MgO; C <sub>6</sub> H <sub>5</sub> Cl; 0 °C-rt	86% (91%); <b>44</b> only
11	2 mol% Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub> ; MgO; isopropyl acetate; 0 °C-rt	(91%); <sup>[f]</sup> <b>44</b> only

<sup>[a]</sup>The stereochemistry of **45** is undetermined. Compound **44** and **45** are inseparable on column.

<sup>[b]</sup>Yields in parentheses were determined by <sup>1</sup>H NMR with 1,3,5-trimethoxybenzene as an internal standard.

<sup>[c]</sup>IPr = 1,3-bis(2,6-di-*i*-propylphenyl)imidazol-2-ylidene.

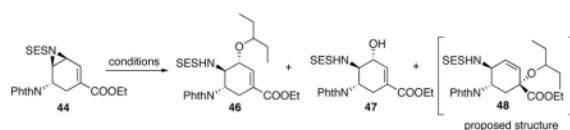
<sup>[d]</sup>tBu<sub>3</sub>Py = 4,4',4''-tri-*tert*-butyl-2,2';6',2''-terpyridine.

<sup>[e]</sup>Conversion was accompanied by decomposition, resulting in irreproducible results.

<sup>[f]</sup>Dry isopropyl acetate (IPAC), a non-halogenated solvent, gave the same result as dry chlorobenzene.

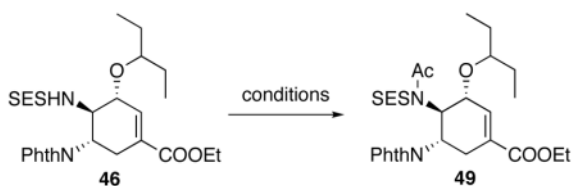
Table 7

Opening of vinyl aziridine.



Entry	Conditions	Yields
1	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, rt	31% <b>46</b> , 54% <b>47</b>
2	1.2 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, $-20^\circ\text{C}$	20% <b>46</b> , 41% <b>47</b>
3	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	60% <b>46</b> , 22% <b>47</b>
4	1.5 equiv $\text{In}(\text{OTf})_3$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	17% <b>46</b> , 71% <b>47</b>
5	10 mol% $\text{Cu}(\text{OTf})_2$ , 0.1 M in 3-pentanol, 0-rt- $100^\circ\text{C}$	87% <b>47</b>
6	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	54% <b>46</b> , 36% <b>47</b> , 12% <b>48</b>
7	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.05 M in 3-pentanol, $70^\circ\text{C}$	54% <b>46</b> , 34% <b>47</b> , 12% <b>48</b>
8	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.05 M in 3-pentanol, $3\text{\AA}$ MS, $70^\circ\text{C}$	50% <b>46</b> , 34% <b>47</b> , 16% <b>48</b>
9	1.5 equiv $\text{B}(\text{OCHEt}_2)_3$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	No reaction
10	Azeotropically dried with toluene, then 1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	60% <b>46</b> , 26% <b>47</b> , 13% <b>48</b>
11	1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 1 equiv BSA in rxn, 0.15 M in 3-pentanol, rt	25% <b>46</b> , 57% <b>47</b> , 7% <b>48</b> , 11% starting material
12	Pre-mixed with BSA, volatile fully removed; then 1.5 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , 0.15 M in 3-pentanol, $75^\circ\text{C}$	65% <b>46</b> , 20% <b>47</b> , 15% <b>48</b>

Table 8

Acylation of **46**.

Entry	Conditions	results
1	10 equiv. AcCl, 10 equiv. DMAP, DMF, rt	sm <sup>[a]</sup> + elimination
2	10 equiv Ac <sub>2</sub> O, 10 equiv DMAP, Py, rt	sm
3	3 equiv. DMAP, 0.1 M in Ac <sub>2</sub> O, 120 °C, 4 hr	54% product+sm
4	1 equiv. DMAP, 10 equiv. Py, 0.1 M in Ac <sub>2</sub> O, 120 °C, 3 h	64% product + 36% sm
5	1 equiv. DMAP, 10 equiv. Py, 0.1 M in Ac <sub>2</sub> O, 120 °C, overnight	74% product
6	2 equiv. DMAP, 20 equiv. Py, 0.1 M in Ac <sub>2</sub> O, MW 150 °C, 1 h	84% product

<sup>[a]</sup> sm = starting material.