# アルキニルアジリジンの 1,5 - 水素移動反応を鍵とする

# 置換ピリジン及びピペリジンの選択的合成

2016

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本文中，以下の用語及び反応剤は下記のように略記した.

| | |
|---|---|
| Ac | acetyl |
| Ar | aryl |
| ATR | attenuated total reflectance |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bt | benzotriazole |
| Bu | butyl |
| ca. | circa (= about) |
| cat. | catalytic amount |
| CSA | 10-camphorsulfonic acid |
| Cy | cyclohexyl |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dba | dibenzylideneacetone |
| DDQ | 2,3-dichloro-5,6-dicyano-p-benzoquinone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DMAP | *N*,*N*-dimethyl-4-aminopyridine |
| DMF | *N*, *N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| EDCl | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| eq | equivalent |
| ESI | electrospray |
| Et | ethyl |
| HRMS | high-resolution mass spectrum |
| IR | Infrared |
| *J* | coupling constant |
| LDA | lithium diisopropylamide |
| m | multiplet |
| Me | methyl |

| | |
|---|---|
| MHz | megaherz |
| mp | melting point |
| MS | mass spectrometry |
| m/z | mass to charge ratio |
| NMP | 1-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| NOESY | NOE correlation spectroscopy |
| Nos | 4-nitrobenzenesulfonyl |
| Nu | nucleophile |
| oct | octet |
| Ph | phenyl |
| ppm | parts per million |
| Pr | propyl |
| quant | quantitative yield |
| quint | quintet |
| rt | room temperature |
| sept | septet |
| sext | sextet |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | p-toluenesulfonyl |

# 総論

医薬品の合成研究はアスピリンの合成を皮切りに飛躍的な発展を遂げた．今日では抗がん剤であるエリブリン **S-1** をはじめとした巨大分子の医薬品製造にも成功しており [1] (Figure S-1)，どのように複雑な化合物であっても医薬品開発が可能と思われるほど，創薬における合成研究は成熟しつつある．この発展を支えたのは天然物の存在と合成技術の進歩である．古くは優れた薬理作用を有する天然物が研究対象とされ，研究者たちはその合成法を精査することで医薬品の開発を成し遂げた．特に多様な生理活性をもつ含窒素複素環化合物は良い標的となり，骨格構築や誘導体化の手法が挙って開発された．今や含窒素複素環は低分子医薬品の代表的な骨格であり，現代の医療に大きく貢献している．

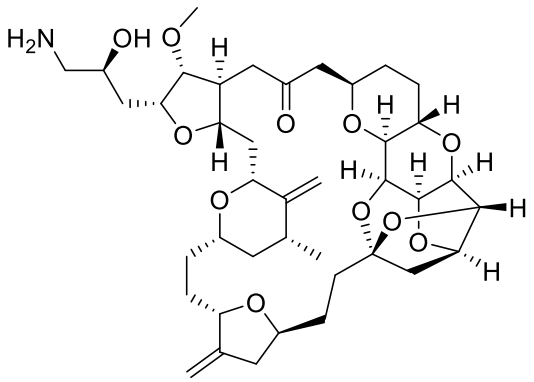
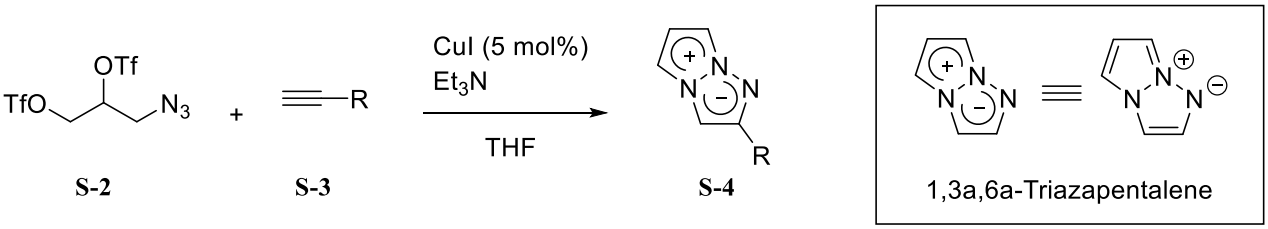



**Figure S-1**

また含窒素複素環化合物は有機機能材料としても優れた一面をもち，医薬分野だけでなく化学分野においても幅広く研究開発がなされてきた．例えば，現在普及している有機 EL では電子の輸送や発光のために π 電子共役型の含窒素環化合物が採用されており，効率的な発光システムを実現している [2].

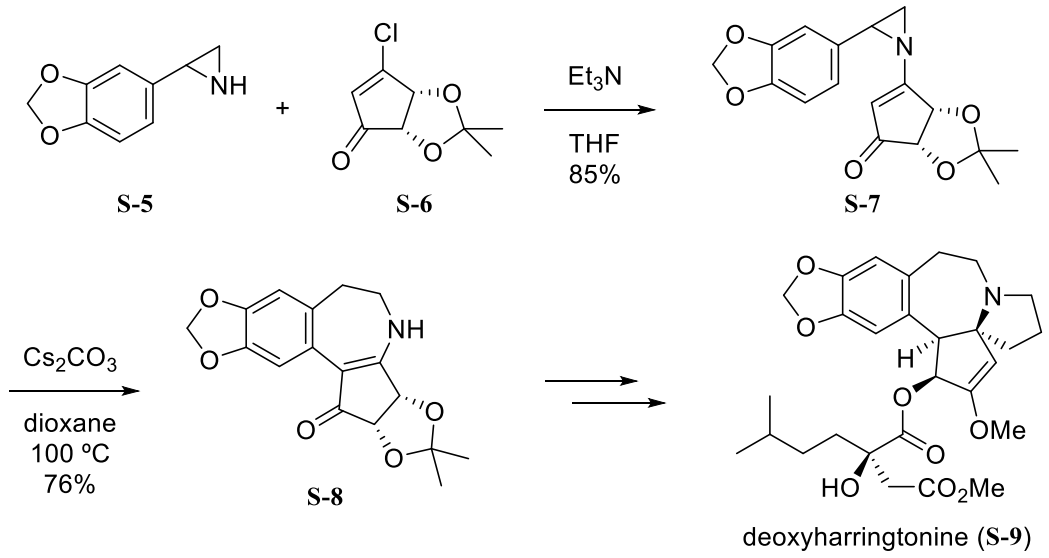
更に最近の研究では難波らが 1,3a,6a-トリアザペンタレン **S-4** の合成法を確立し，その性質を明らかにすることで世界最少となる蛍光発色団の開発に成功している [3] (Scheme S-1). 本化合物はアジド **S-2** とアルキン **S-3** のクリック反応による一段階合成が可能であり，導

入する置換基によって蛍光波長の調整ができる．そのため画期的な波長調節型蛍光分子として様々な研究に応用されている．




**Scheme S-1**

このように含窒素複素環化合物は有用性の高さから盛んに研究がなされており，その骨格構築法に限ってみても驚くほど多くの手法が開発されていることが分かる．中でも窒素原子を含む三員環化合物であるアジリジンを利用した骨格構築法は，効率的かつ多様性に富んでおり注目を集めている [4,5].

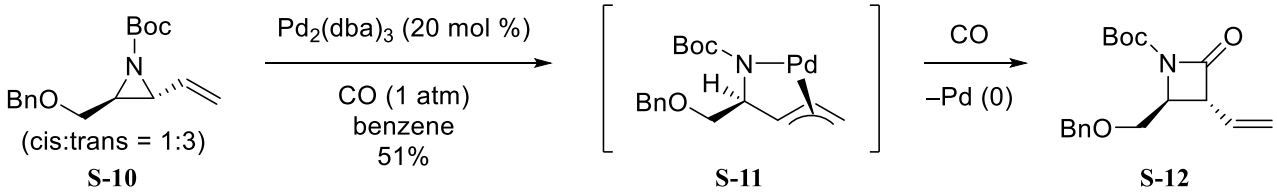



**Scheme S-2**

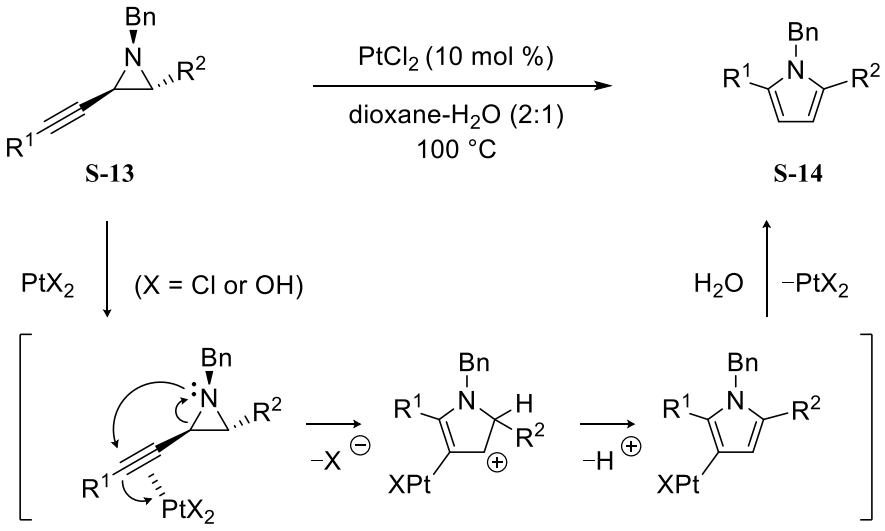
この一例として Gin らの deoxyharringtonine (**S-9**)の全合成研究が挙げられる [6] (Scheme S-2). Gin らはアジリジン環の特性を活かすことで含窒素七員環化合物の効率的合成を達成

した．即ち基質 **S-5** 及び **S-6** を縮合し *N*–アルケニルアリールアジリジン **S-7** とした後，$Cs_2CO_3$ 存在下反応溶液を加熱することで骨格転位を進行させ，ジヒドロアゼピン **S-8** を合成した．その後，種々の変換により deoxyharringtonine (**S-9**)の全合成を成し遂げている．

また大船らはアルケニルアジリジンを利用した β–ラクタムの合成法を開発している [7] (Scheme S-3)．基質 **S-10** に対してパラジウム触媒を作用させることでπ–アリルパラジウム中間体 **S-11** を生成し，その後の一酸化炭素挿入及びパラジウムの還元的脱離により β–ラクタム **S-12** を立体選択的に合成した．




**Scheme S-3**



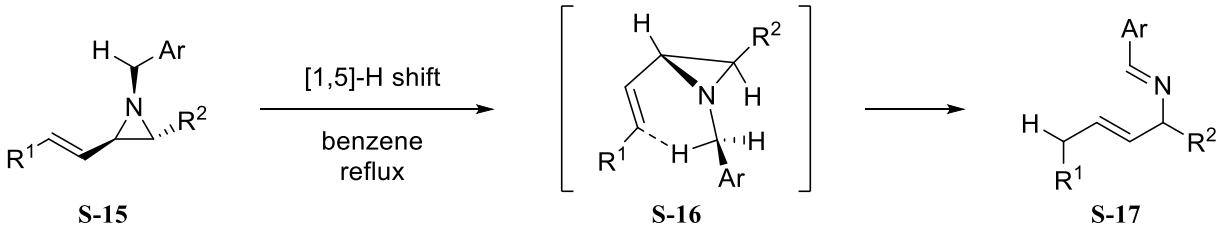

**Scheme S-4**

更に吉田らは白金触媒を用いたアルキニルアジリジンの環化異性化反応による置換ピロール合成法の開発に成功している [8] (Scheme S-4)．本反応ではアルキニルアジリジン **S-13**

に対して触媒量の塩化白金を作用させることで，アジリジン環の開環 - 環化が進行し一挙に置換ピロール **S-14** を合成することができる．

以上の 3 例は分子内にアルケニル基もしくはアルキニル基を導入したアジリジンを反応基質に用いることで効率的な環構築を達成している．アジリジン環は歪みエネルギーが大きく，開環が容易に進行することが知られているが [9]，上例のように不飽和結合を介した開環を進行させることで，多様な含窒素複素環化合物の合成に利用することができる．今回著者はこの特異な反応性に注目し，アルキニルアジリジンの新規変換法を開発，応用することで含窒素複素環化合物の効率的合成を試みた．

新規合成法の開発を行うにあたり，著者はアルケニルアジリジンの 1,5−水素移動反応に着目した．*N*−アリールメチルビニルアジリジン **S-15** は加熱還流により 1,5−水素移動が進行し，遷移状態 **S-16** を経てアリルイミン **S-17** へと定量的に変換されることが報告されている [10] (Scheme S-5).

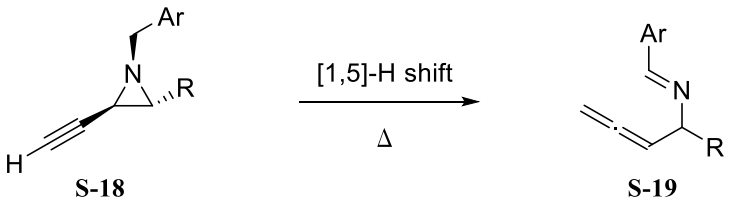



**S-15** **S-16** **S-17**

**Scheme S-5**

著者は本反応の応用としてビニル基をアルキニル基に変換した基質 **S-18** に対し 1,5−水素移動を進行させると，アレニルイミン **S-19** が得られると予想した(Scheme S-6)．またこのとき生じる **S-19** は分子内に反応性の高いイミン及びアレン部位を有することから, **S-19** を合成素子として活用することで多種の含窒素複素環化合物を合成できると考え，本研究に着手した．

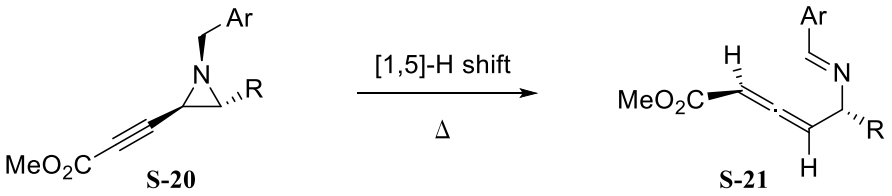
検討の結果，基質 **S-18** を加熱しながら撹拌することで予期した 1,5-水素移動反応が進行し，アレニルイミン **S-19** を定量的に得ることに成功した．詳細については第一章第一節で述べる．




**S-18** **S-19**

**Scheme S-6**

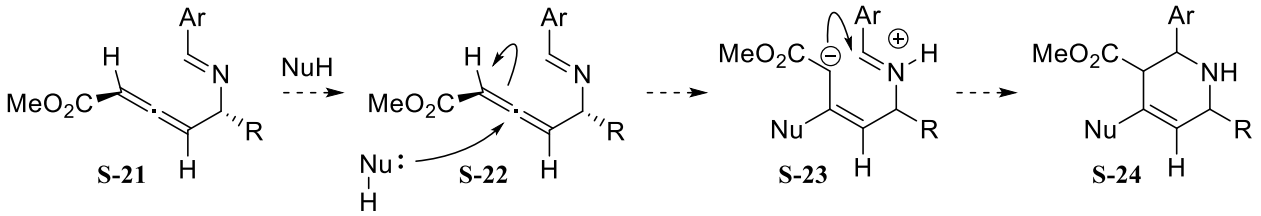
次にアルキニルアジリジン **S-18** のアルキン末端にメチルエステルを導入した基質 **S-20** に対して 1,5−水素移動反応の検討を行った(Scheme S-7). **S-20** を加熱条件下撹拌したところ, 良好に反応が進行しアレニルイミン**S-21**が立体選択的かつ定量的に生成することを見出した [11]. 詳細については第一章第二節で述べる.




**S-20** **S-21**

**Scheme S-7**

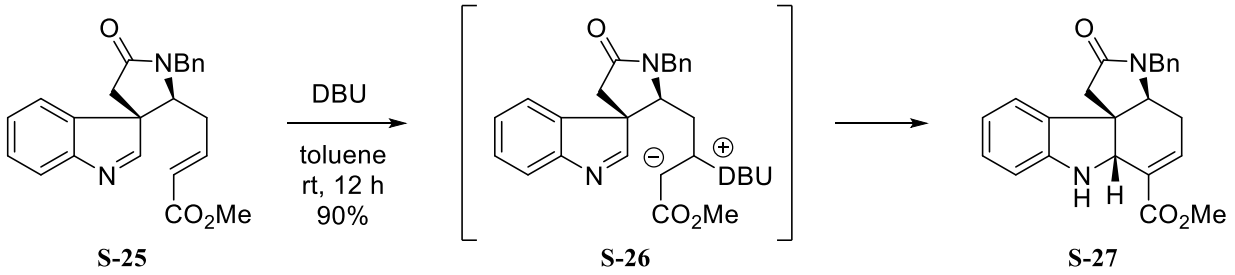
アレニルイミン**S-21**は電子吸引基であるエステルの効果によりアレン中心炭素の求電子性が高まっているため，求核剤を作用させることで付加−環化反応が進行し **(S-22**, **S-23)**, 環化体 **S-24** が得られると推測される [12] (Scheme S-8). そこで次に **S-21** を合成素子とした含窒素複素環化合物の新規合成法の開発に取り組んだ.




**S-21** **S-22** **S-23** **S-24**

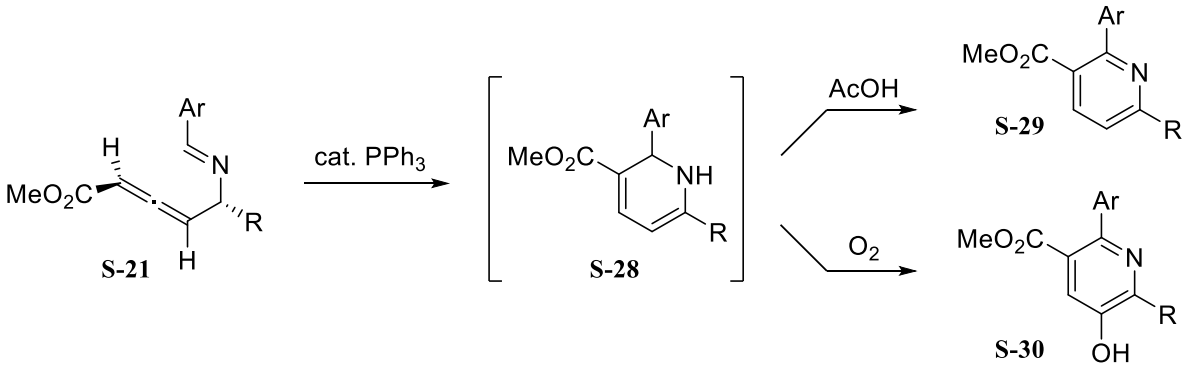
**Scheme S-8**

Scheme S-9 に示すように分子内にイミン及び不飽和エステル部位をもつ基質 **S-25** に対して DBU を作用させると分子内アザベイリスヒルマン反応が進行し，DBU 付加体 **S-26** の生成を経て環化体 **S-27** が得られることが知られている [13]．1,5-水素移動により合成したアレニルイミン **S-21** にも **S-25** と類似の構造が含まれることから，**S-21** に対して分子内アザベイリスヒルマン型の反応が進行するか検討を行うこととした．



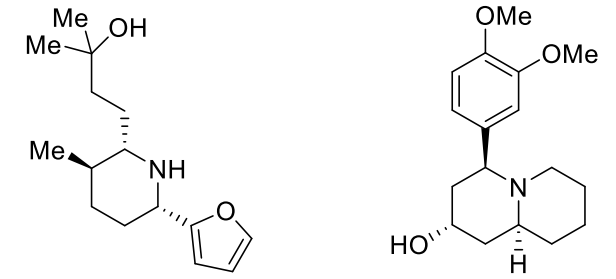

**Scheme S-9**

検討の結果，アレニルイミン **S-21** に触媒量の $PPh_3$ を作用させることで良好に環化が進行し，ジヒドロピリジン **S-28** が生成することを見出した．またこのとき生じる **S-28** は酸化条件下，容易にピリジンへと変換されることが分かった．更に酸化の際，条件を変えることで三置換ピリジン **S-29** または四置換ピリジン **S-30** の選択的合成が可能であることを明らかにした [11](Scheme S-10)．本反応の詳細については第二章で述べる．




**Scheme S-10**

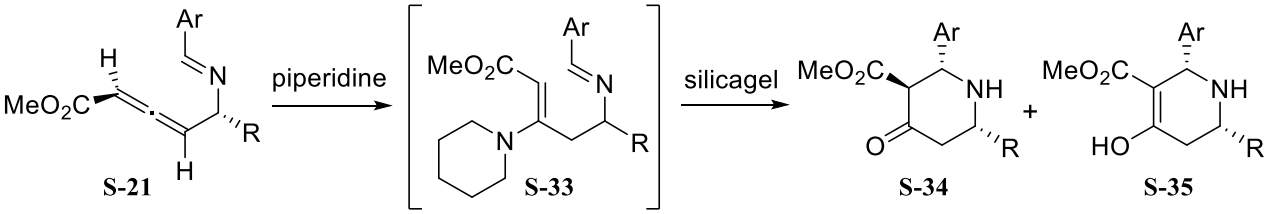
次にアレニルイミン **S-21** に対して求核剤を作用させることで，ピペリジン環の構築を試みた．ピペリジン環は(–)-nupharamine (**S-31**)や(–)-lasubine II (**S-32**)をはじめとする生理活性天然物に多数みられる構造であり [14] (Figure S-2)，立体選択的なピペリジン環構築法の開発は有機合成上重要である [15].




(–)-nupharamine (**S-31**)　　(–)-lasubine II (**S-32**)

**Figure S-2**

種々検討の結果，基質 **S-21** に対しピペリジンを作用させた後，酸性シリカゲルで処理したところ，ピペリジン付加体 **S-33** の生成を経る分子内環化が進行し，置換ピペリジン **S-34** 及び **S-35** が立体選択的に生成することを見出した(Scheme S-11)．本反応の詳細は第三章で述べる．




**S-21**　　**S-33**　　**S-34**　　**S-35**

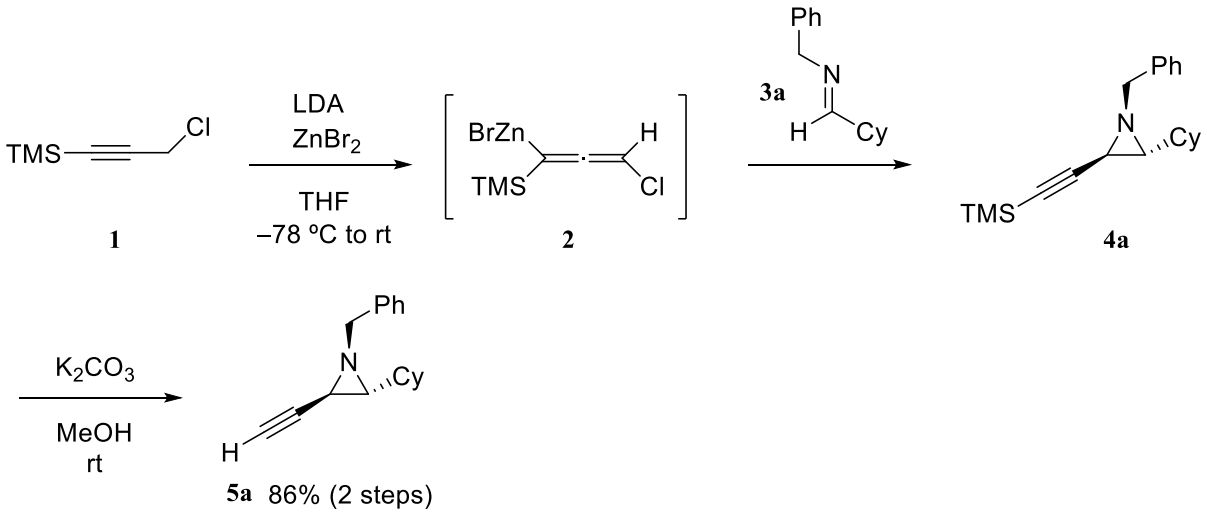
**Scheme S-11**

# 第一章　アルキニルアジリジンの 1,5−水素移動反応の開発

## 第一節　アレニルイミンの合成

アジリジン環は歪みエネルギーが大きいことから，開環を伴う多様な変換反応が開発されている [9]．そのため近年では含窒素複素環構築の強力なツールとして研究者たちの注目を集め，精力的な研究が行われている [4-8]．総論で述べたように著者はアルキニルアジリジンの新たな変換法として 1,5−水素移動反応を考案し，本反応から得られるアレニルイミンを用いた含窒素複素環化合物の効率的合成法の開発を目指した．

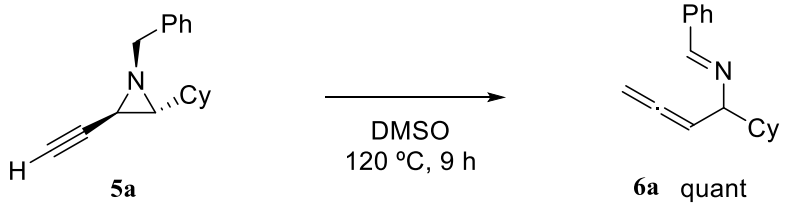
まず 1,5−水素移動反応の基質となる *N*−ベンジルアルキニルアジリジン **5a** を既知の合成法 [16]に従い合成した(Scheme 1)．即ち塩化プロパルギル **1** に臭化亜鉛及び LDA を作用させアレニル亜鉛 **2** とした後，イミン **3a** を反応させることでアルキニルアジリジン **4a** を立体選択的に得た．その後 TMS 基を脱保護することで **5a** を合成した．




**Scheme 1**

合成した基質を用いて 1,5−水素移動反応の検討を行った(Scheme 2)．その結果，*N*−ベンジルアルキニルアジリジン **5a** を DMSO 溶媒中 120 ºC に加熱し 9 時間撹拌することで，アレニルイミン **6a** が定量的に生成することを見出した. 本反応は精製操作を必要としない簡便な変換法であり，反応後に溶媒を留去するだけで目的のアレニルイミンを単一化合物と

して得ることができる.

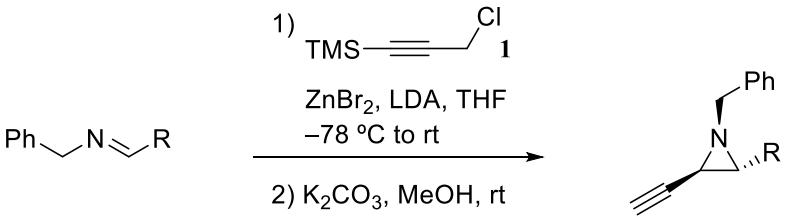



**5a** **6a** quant

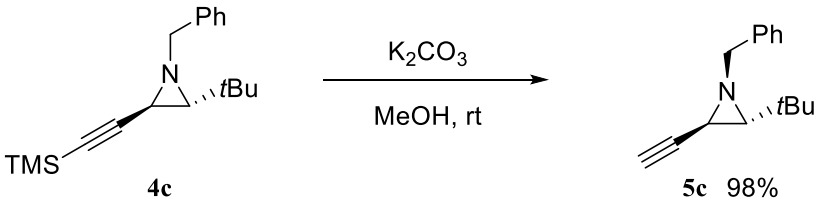
**Scheme 2**

次に本反応の一般性を確認すべく，様々な基質を用いて 1,5-水素移動反応を行うこととした．尚，反応基質 **5b-5m** は以下のように合成した(Scheme 3)．即ち塩化プロパルギル **1** に臭化亜鉛及び LDA を作用させた後，イソプロピル基，ブチル基，フェネチル基，ベンジルオキシプロピル基のようなアルキル基をもつイミン **3b**, **3d-3f** を加えアジリジン環を構築し，その後 TMS 基を脱離させることでアルキニルアジリジン **5b**, **5d-5f** を合成した．また文献既知である *tert*−ブチル基をもつアルキニルアジリジン **4c** に対し TMS 基の除去を行うことで基質 **5c** を得た．更に *N* - TMS 置換イミン **7** を用いたアジリジン環の構築及び TMS 基の脱離によりアルキニルアジリジン **8** を合成した．合成した **8** に対し，ベンゼン環の 2 位に臭素をもつ臭化ベンジル **9g** または 4 位に臭素，塩素，フッ素，メトキシ基をもつ臭化ベンジル **9h-9k** を作用させることで，アジリジン環窒素原子上に置換基が導入されたアルキニルアジリジン **5g-5k** を合成した．同様に **8** に対してナフチル基やチエニル基を有する臭化物 **9l**, **9m** を反応させることで **5l**, **5m** を得た.

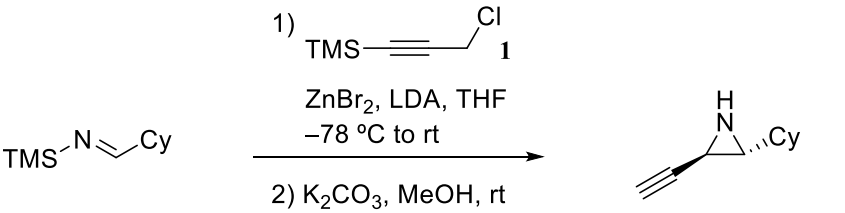
以上のように合成した種々のアルキニルアジリジンに対して 1,5−水素移動反応を試みた．まずアジリジン環上のアルキル側鎖を変えた基質 **5b-5f** を用いて検討を行ったところ(Table 1)，イソプロピル基，*tert*−ブチル基，ブチル基をもつ基質 **5b-5d** では，DMSO 溶媒中 120 ºC の条件下円滑に反応が進行し，相当するアレニルイミン **6b-6d** が定量的に得られた．またフェネチル基やベンジルオキシプロピル基を導入した基質 **5e**, **5f** においても良好に反応が進行し，対応するアレニルイミン **6e**, **6f** を定量的に与えた.



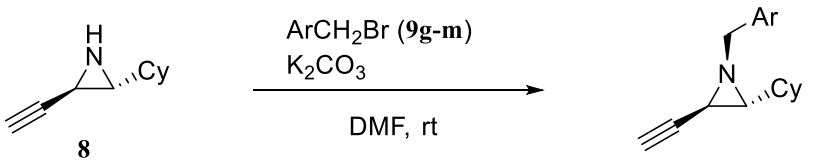

| | | | |
|---|---|---|---|
| **3b** | : R = *i*Pr | **5b** : R = *i*Pr | 79% (2 steps) |
| **3d** | : R = *n*Bu | **5d** : R = *n*Bu | 67% (2 steps) |
| **3e** | : R = -$(CH)_2$Ph | **5e** : R = -$(CH)_2$Ph | 66% (2 steps) |
| **3f** | : R = -$(CH_2)_3$OBn | **5f** : R = -$(CH_2)_3$OBn | 72% (2 steps) |




**4c** **5c** 98%




**7** **8** 65% (2 steps)

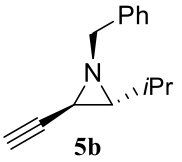
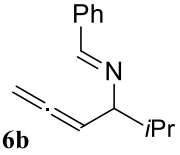
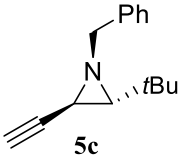
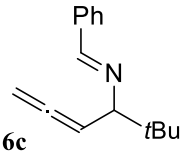
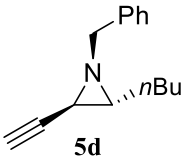
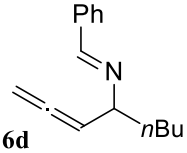
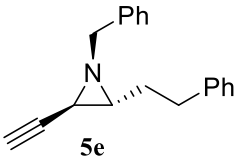
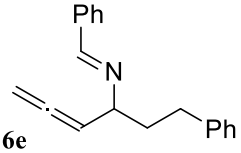
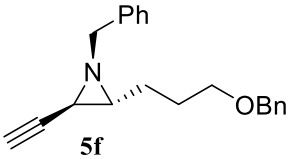
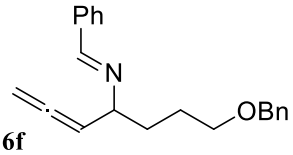



**8**

| | | | | |
|---|---|---|---|---|
| **9g** | : Ar = 2-$BrC_6H_4$ | **5g** | : Ar = 2-$BrC_6H_4$ | 77% |
| **9h** | : Ar = 4-$BrC_6H_4$ | **5h** | : Ar = 4-$BrC_6H_4$ | 78% |
| **9i** | : Ar = 4-$ClC_6H_4$ | **5i** | : Ar = 4-$ClC_6H_4$ | 80% |
| **9j** | : Ar = 4-$FC_6H_4$ | **5j** | : Ar = 4-$FC_6H_4$ | 80% |
| **9k** | : Ar = 4-$MeOC_6H_4$ | **5k** | : Ar = 4-$MeOC_6H_4$ | 70% |
| **9l** | : Ar = 2-naphthyl | **5l** | : Ar = 2-naphthyl | 81% |
| **9m** | : Ar = 2-thienyl | **5m** | : Ar = 2-thienyl | 63% |

**Scheme 3**

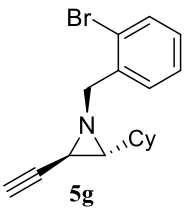
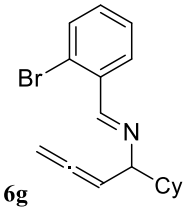
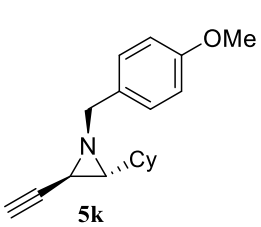
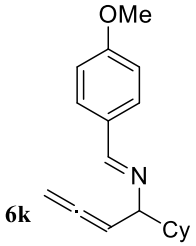
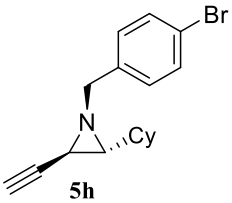
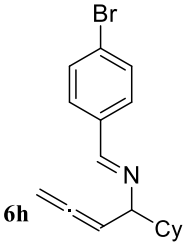
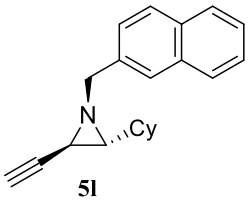
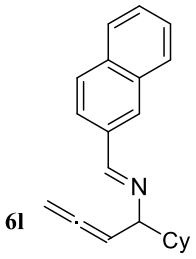
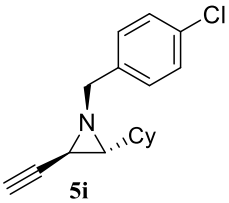
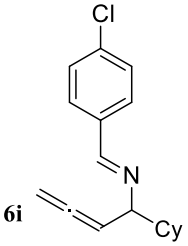
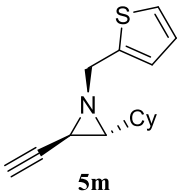
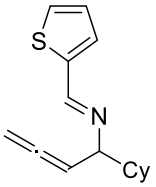
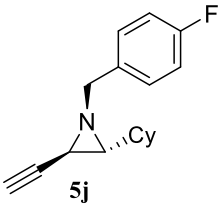
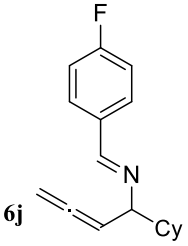
**Table 1. [1,5]-Hydrogen Shift of *N*-Benzyl-2-Alkynylaziridines**[a]

| substrate | product | yield |
|---|---|---|
|  **5b** |  **6b** | quant |
|  **5c** |  **6c** | quant |
|  **5d** |  **6d** | quant |
|  **5e** |  **6e** | quant |
|  **5f** |  **6f** | quant |

[a]All the reactions were carried out in DMSO at 120 ºC for 7-9 h.

続いて窒素上のアリールメチル基を変換した基質 **5g-5m** を用いて検討を行った(Table 2). ベンゼン環の 2 位に臭素を導入した基質 **5g** または 4 位に臭素，塩素，フッ素，メトキシ基を導入した基質 **5h-5k** に対して反応を試みたところ，いずれも反応が進行し相当するアレニルイミン **6g-6k** を定量的に与えた．またナフチル基やチエニル基をもつ基質 **5l**, **5m** においても同様に反応し，対応するアレニルイミン **6l**, **6m** が定量的に生成した．

**Table 2. [1,5]-Hydrogen Shift of *N*-Aryl Mehtyl-2-Alkynylaziridines**[a]

| substrate | product | yield | substrate | product | yield |
|---|---|---|---|---|---|
|  **5g** |  **6g** | quant |  **5k** |  **6k** | quant |
|  **5h** |  **6h** | quant |  **5l** |  **6l** | quant |
|  **5i** |  **6i** | quant |  **5m** |  **6m** | quant |
|  **5j** |  **6j** | quant | | | |

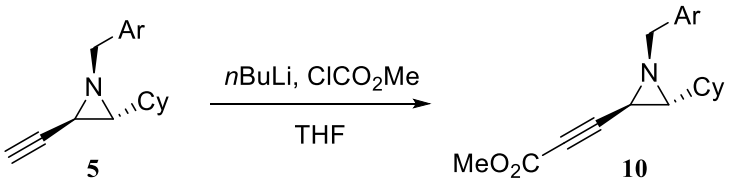
[a]All the reactions were carried out in DMSO at 120 ºC for 5-8 h.

以上のようにアルキニルアジリジンの 1,5−水素移動反応の開発に成功し，アレニルイミンの効率的合成法を確立した.

## 第二節　エステルを導入したアレニルイミンの立体選択的合成 [11)]

前節にて著者は *N*-アリールメチルアルキニルアジリジンを用いた，1,5-水素移動反応によるアレニルイミンの効率的合成を達成した．アレニルイミンは分子内に反応性の高いイミン及びアレン部位をもつため有用な合成素子となり得るが，総論で述べたようにアレン部位に電子吸引基であるエステルを導入することで，より反応性の高い合成素子となることが推測される [12)]．またアルキン末端に置換基を導入することで生じる立体化学にも興味を抱き，エステルを有するアルキニルアジリジンに対する 1,5-水素移動反応の研究開発に着手した.

エステルを導入した反応基質 **10a-10m** はアルキニルアジリジン **5a-5m** に対してブチルリチウムを加えた後，クロロギ酸メチルを作用させることで合成した(Scheme 4).

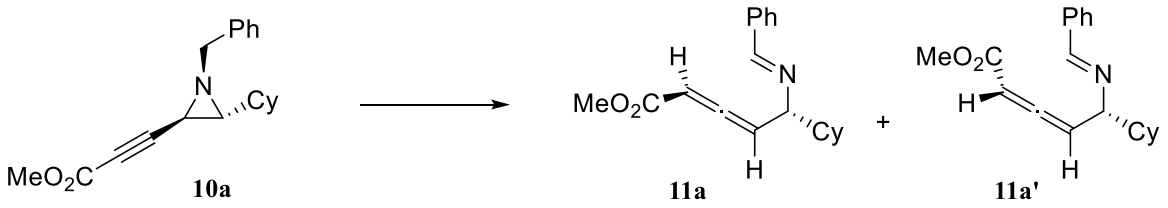



| | | | |
|---|---|---|---|
| **5a** | : R = Cy | **10a** | : R = Cy　50% |
| **5b** | : R = *i*Pr | **10b** | : R = *i*Pr　59% |
| **5c** | : R = *t*Bu | **10c** | : R = *t*Bu　70% |
| **5d** | : R = *n*Bu | **10d** | : R = *n*Bu　42% |
| **5e** | : R = -$(CH)_2$Ph | **10e** | : R = -$(CH)_2$Ph　42% |
| **5f** | : R = -$(CH_2)_3$OBn | **10f** | : R = -$(CH_2)_3$OBn　41% |
| **5g** | : Ar = 2-$BrC_6H_4$ | **10g** | : Ar = 2-$BrC_6H_4$　50% |
| **5h** | : Ar = 4-$BrC_6H_4$ | **10h** | : Ar = 4-$BrC_6H_4$　45% |
| **5i** | : Ar = 4-$ClC_6H_4$ | **10i** | : Ar = 4-$ClC_6H_4$　66% |
| **5j** | : Ar = 4-$FC_6H_4$ | **10j** | : Ar = 4-$FC_6H_4$　64% |
| **5k** | : Ar = 4-$MeOC_6H_4$ | **10k** | : Ar = 4-$MeOC_6H_4$　31% |
| **5l** | : Ar = 2-naphthyl | **10l** | : Ar = 2-naphthyl　63% |
| **5m** | : Ar = 2-thienyl | **10m** | : Ar = 2-thienyl　36% |

**Scheme 4**

はじめに基質 **10a** を用いて 1,5-水素移動反応を試みた. **10a** を DMSO 溶媒中 100 ºC に加熱し 3.5 時間撹拌したところ，アレニルイミンが定量的に得られたものの，2 つのジアステ

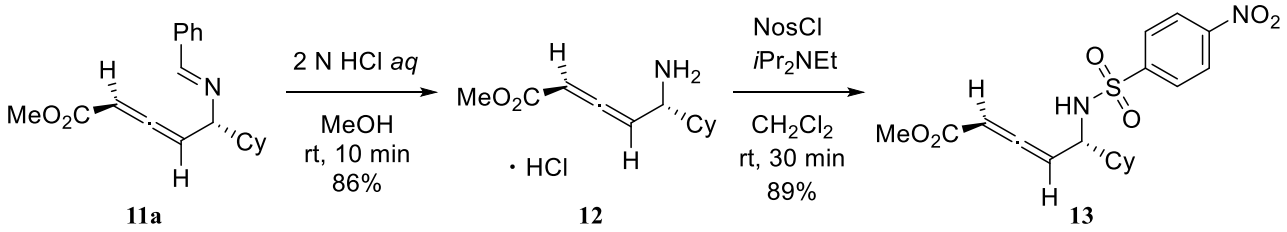
レオマー**11a** 及び **11a'**が生じていることが明らかとなった．そこで溶媒の検討を行った結果，トルエン溶媒中 100 ºC にて 9 時間撹拌することで，アレニルイミン **11a** を単一のジアステレオマーとして得ることに成功した(Scheme 5).



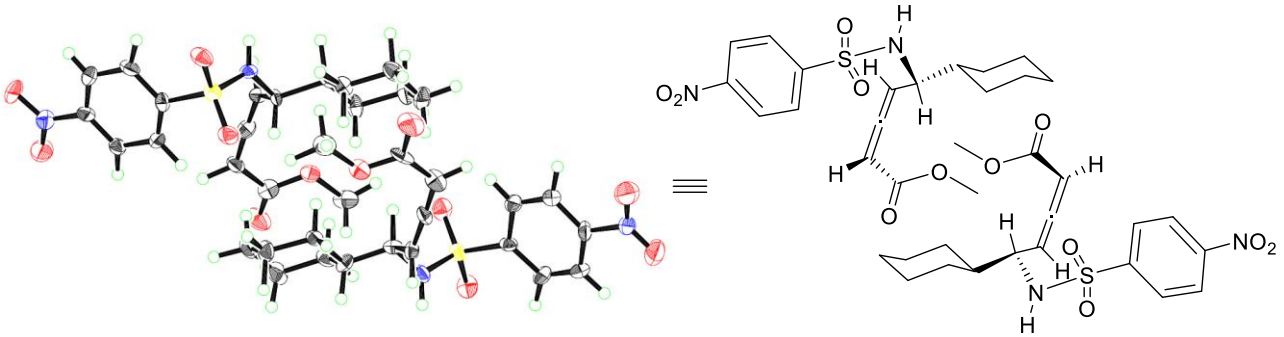

| conditions | yield | product |
|---|---|---|
| DMSO, 100 ºC, 3.5 h | quant | diastereomixture of **11a and 11a'** |
| toluene, 100 ºC, 9 h | quant | **11a** only |

**Scheme 5**

尚，アレニルイミン **11a** の立体化学は X 線結晶構造解析及び NOE 測定の結果から明らかにした．即ち **11a** に対して塩酸を作用させアレニルアミン塩酸塩 **12** とした後に，ノシル基を導入し化合物 **13** を合成した(Scheme 6)．得られた **13** に対して X 線結晶構造解析を行うことで図に示す立体化学をもつことを明確にした(Figure 1)．またアレニルイミン **11a** のイミン部の幾何異性については，NOE 測定を行うことでトランス配置であることを決定している(Figure 2).

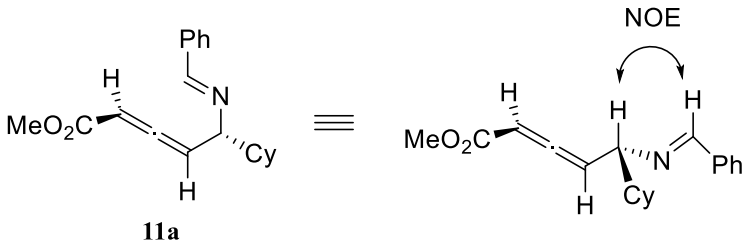



**Scheme 6**



X-ray crystal structure of **13** (dimer) **13** (dimer)

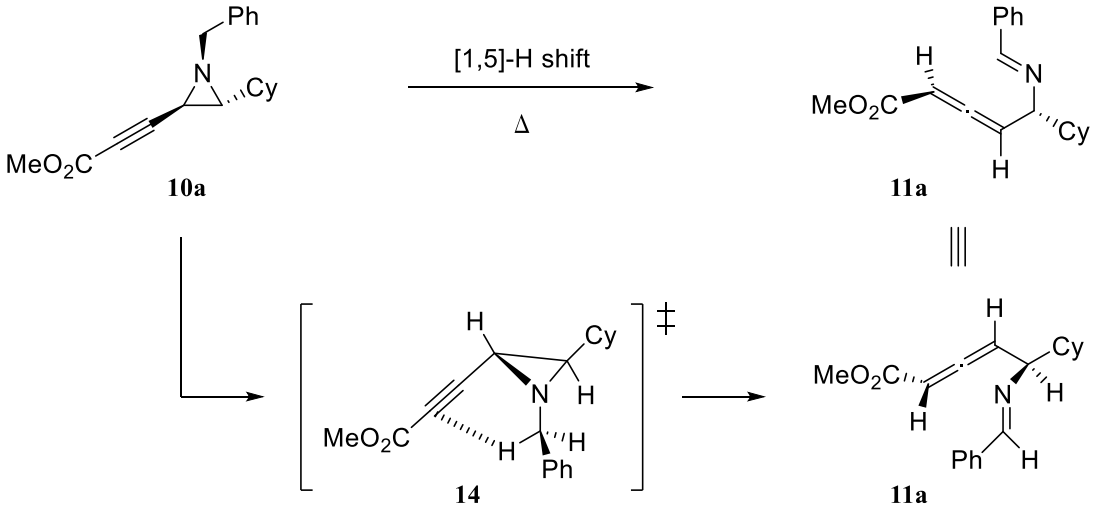
**Figure 1**



**11a**

**Figure 2**

本反応では高い立体選択性が発現しているが，この理由として 1,5−水素移動の際，基質 **10a** が遷移状態 **14** を経てアレニルイミン **11a** へと変換されることが考えられる(Scheme 7)

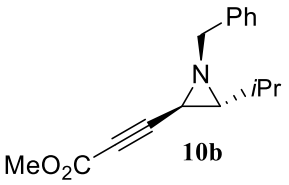
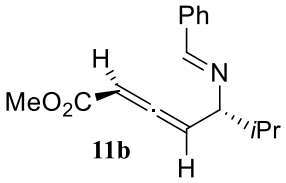
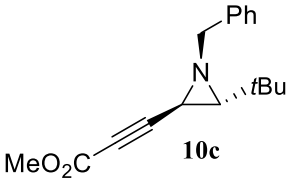
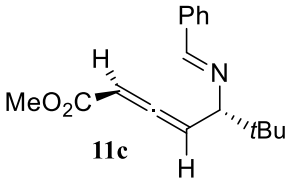
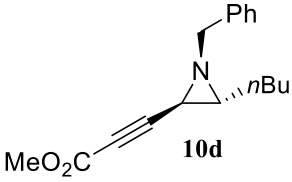
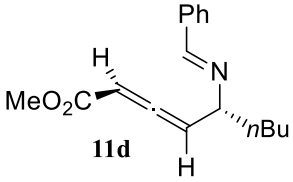
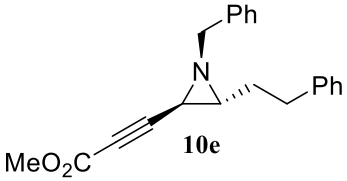
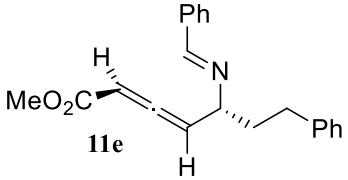
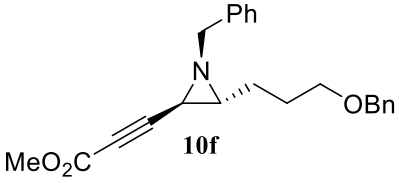
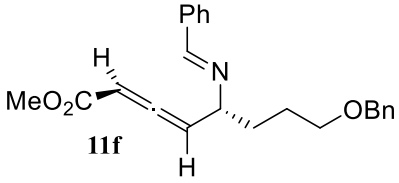


**10a** **11a** **14** **11a**

**Scheme 7**

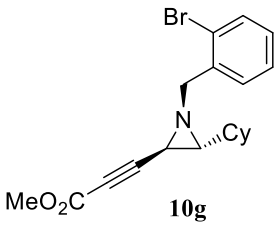
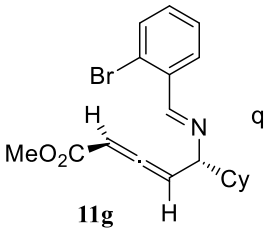
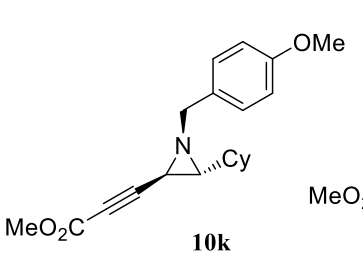
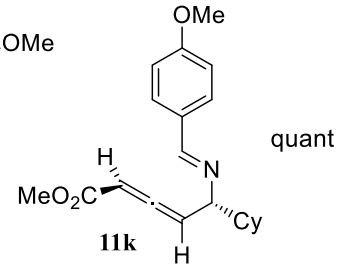
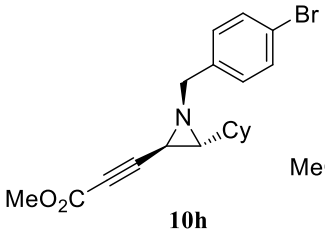
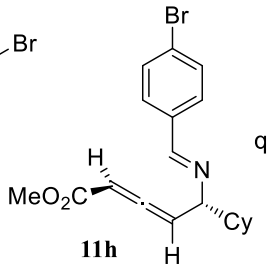
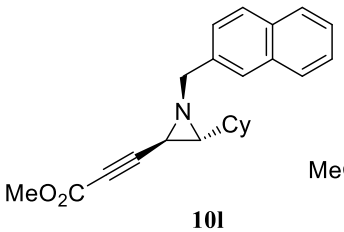
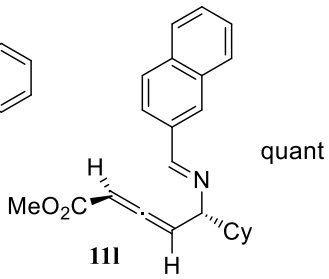
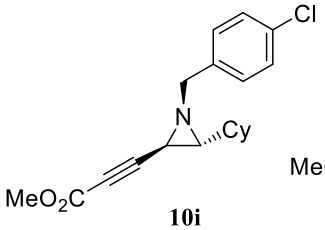
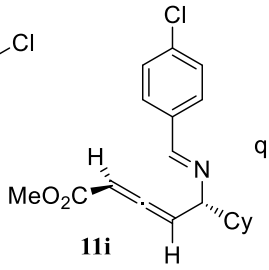
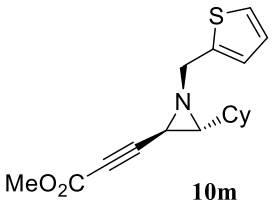
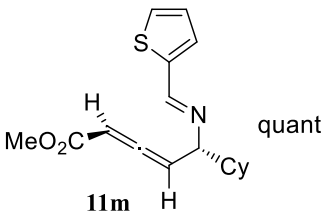
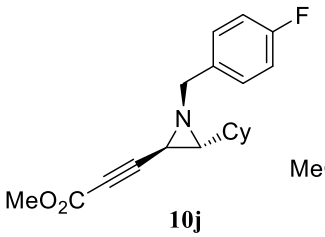
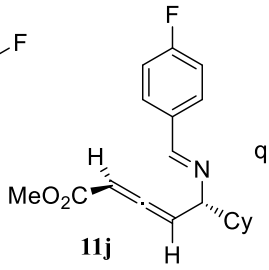
次に本反応の一般性を明らかにするため，様々な基質を適用することとした．アジリジン環上に種々のアルキル側鎖を導入した基質 **10b-10f** を反応させたところ，いずれの基質においても反応が進行し相当するアレニルイミン **11b-11f** が定量的に生成することを見出した(Table 3).

**Table 3. [1,5]-Hydrogen Shift of *N*-Benzyl 3-Aziridinylpropiolate Esters**[a]

| substrate | product | yield |
|---|---|---|
|  **10b** |  **11b** | quant |
|  **10c** |  **11c** | quant |
|  **10d** |  **11d** | quant |
|  **10e** |  **11e** | quant |
|  **10f** |  **11f** | quant |

[a]All the reactions were carried out in toluene at 100 ºC for 9-10 h.

**Table 4. [1,5]-Hydrogen Shift of *N*-Aryl mehtyl 3-Aziridinylpropiolate Esters**[a]

| substrate | product | yield | substrate | product | yield |
|---|---|---|---|---|---|
|  **10g** |  **11g** | quant |  **10k** |  **11k** | quant |
|  **10h** |  **11h** | quant |  **10l** |  **11l** | quant |
|  **10i** |  **11i** | quant |  **10m** |  **11m** | quant |
|  **10j** |  **11j** | quant | | | |

[a]All the reactions were carried out in toluene at 100 ºC for 9-21 h.

続いてアジリジン環窒素原子上のアリールメチル基を変換した基質 **10g-10m** を用いて検討を行った．その結果，いずれの基質においても反応は良好に進行し，相当するアレニルイミン **11g-11m** を定量的に与えることが分かった(Table 4)．以上の結果から，アルキン末端にエステルを導入したアルキニルアジリジンにおいても，1,5−水素移動反応は高い一般

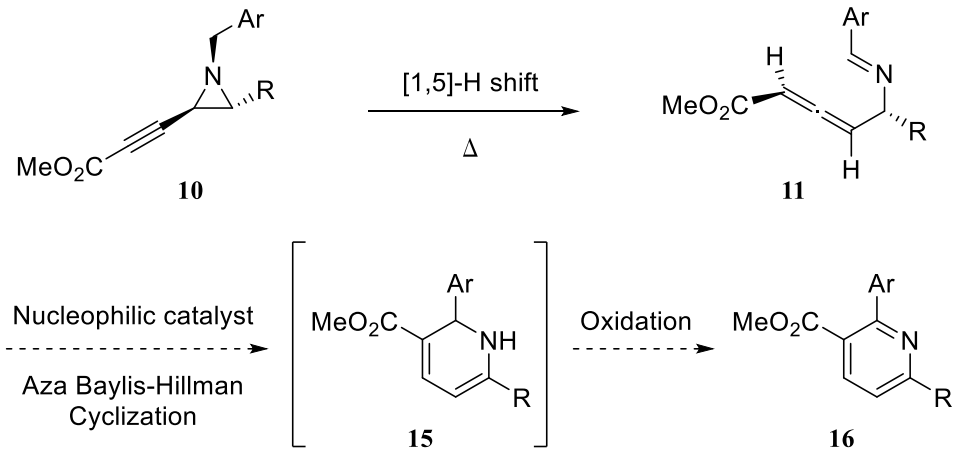
性を示すことが明らかとなった.

以上のように著者はアルキニルアジリジンの 1,5-水素移動反応を開発し，アレニルイミンの効率的合成法を確立した．またアルキン末端にエステルを導入した基質に対して 1,5-水素移動反応を行うと，立体選択的かつ定量的に反応が進行することを見出した.

# 第二章　アルキニルアジリジンの 1,5−水素移動反応を鍵とする多置換ピリジンの効率的合成法の開発 [11)]

置換ピリジンは古くから化学的研究が行われてきた化合物群であり，医薬品や農薬，機能性分子など幅広い分野での応用がなされている [14, 17)]．ピリジン環の構築法開発の歴史も古く，hantzsch のピリジン合成をはじめとする種々のピリジン環構築法が現在に至るまで多数報告されている [18)]．しかしながら置換ピリジンの合成法の多くは、導入する置換基の制御が困難であること，多段階の反応を要し効率性に欠けること等の問題点が残されており，より効率的な合成法の開発が今なお望まれている。

著者は開発したアルキニルアジリジンの 1,5−水素移動反応を応用することで，効率的な多置換ピリジンの合成を試みることとした. 即ち *N*−アリールメチルアルキニルアジリジン **10** から合成したアレニルイミン **11** に対し，求核触媒を用いたアザベイリスヒルマン型の環化反応を進行させることでジヒドロピリジン **15** へと変換した後，得られた **15** を酸化することで置換ピリジン **16** の合成を目指した(Scheme 8).

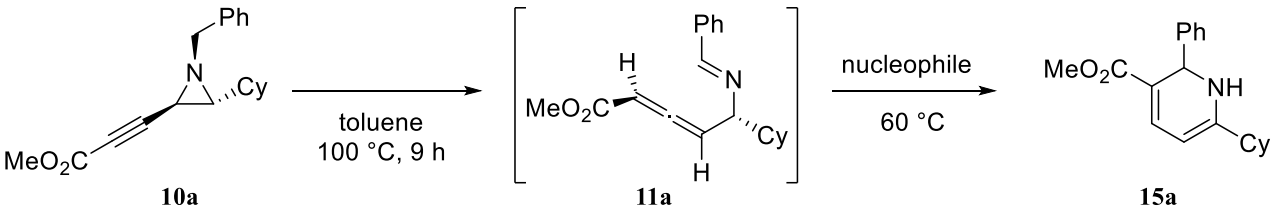



**Scheme 8**

はじめにアレニルイミンに対するアザベイリスヒルマン型環化反応の検討を行った (Table 5). アルキニルアジリジン **10a** から合成したアレニルイミン **11a** に対し求核剤として

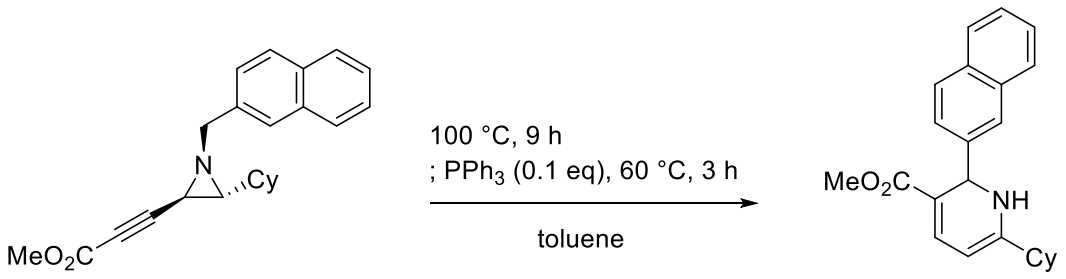
2 当量の DBU を作用させたところ，基質が分解することがわかった(entry 1)．また求核剤として DABCO や DMAP を用いても同様に基質の分解が確認され(entry 2,3)，$PBu_3$ を作用させると複雑な混合物が生じるのみであった(entry 4)．しかしながら $PPh_3$[19]を反応させたとき環化反応が良好に進行し，ジヒドロピリジン **15a** がほぼ定量的に生成することを見出した(entry 5)．さらに $PPh_3$ を 10 mol% まで減じることに成功し，効率的な **15a** の合成を達成した(entry 6)．尚，ジヒドロピリジン **15a** は不安定であったため単離はできなかったが，検討の結果，ベンゼン環をナフチル基で置き換えた基質 **10l** より，同条件で導いたジヒドロピリジン **15l** において，化合物の単離に成功している(Scheme 9)．

**Table 5. Intramolecular Cyclization with Various Nucleophiles**




**10a** **11a** **15a**

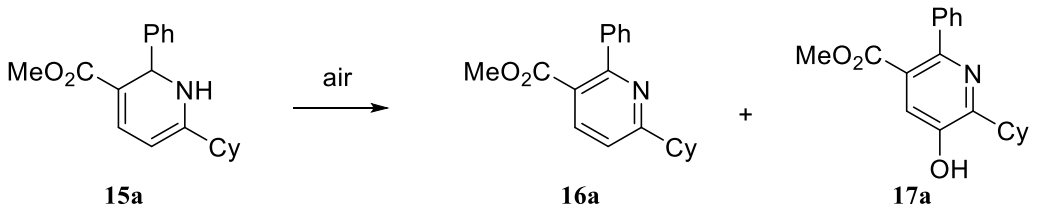
| entry | nucleophile | time (h) | result |
|---|---|---|---|
| 1 | DBU (2.0 eq) | 1 | decomp. |
| 2 | DABCO (2.0 eq) | 24 | decomp. |
| 3 | DMAP (2.0 eq) | 1 | decomp. |
| 4 | $PBu_3$ (2.0 eq) | 0.5 | complex mixture |
| 5 | $PPh_3$ (2.0 eq) | 1 | 99% NMR yield |
| 6 | $PPh_3$ (0.1 eq) | 3 | 99% NMR yield |




**10l** **15l** 75% yield

**Scheme 9**

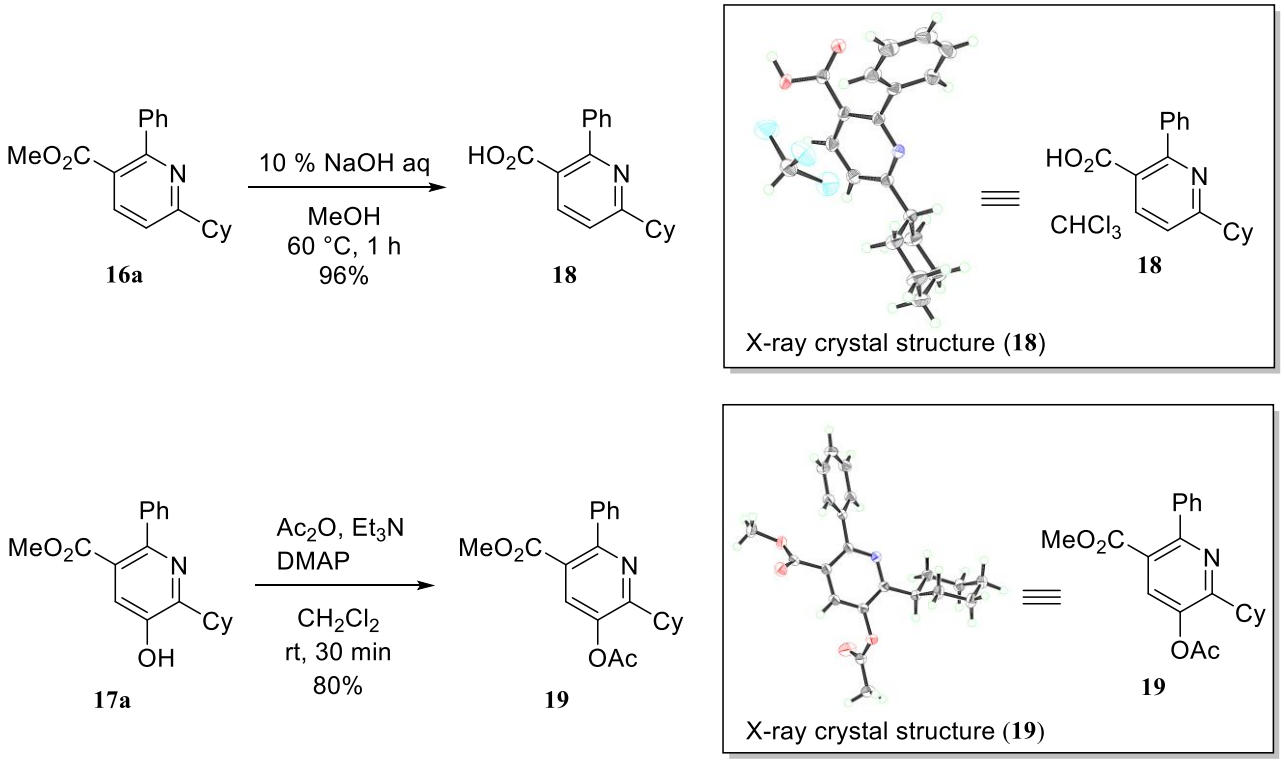
また生成したジヒドロピリジン **15a** は空気に不安定であることが分かり，空気中で徐々に酸化され 2 種の置換ピリジン **16a** 及び **17a** に変換されることが明らかとなった(Scheme 10).




**15a** **16a** **17a**

**Scheme 10**

置換ピリジンの構造は各々誘導体へと変換後，X 線結晶構造解析により決定した．即ち三置換ピリジン **16a** に関してはエステルの加水分解を行いカルボン酸 **18** とした後，X 線結晶構造解析によりその構造を決定した．四置換ピリジン **17a** に関してはアセチル化体 **19** を合成し，その X 線結晶構造解析から構造を導いた(Scheme 11).

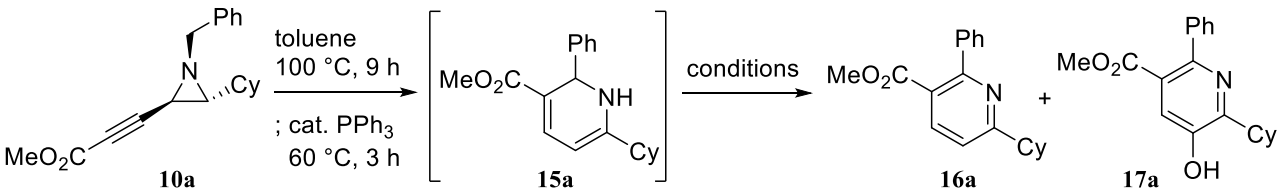



**Scheme 11**

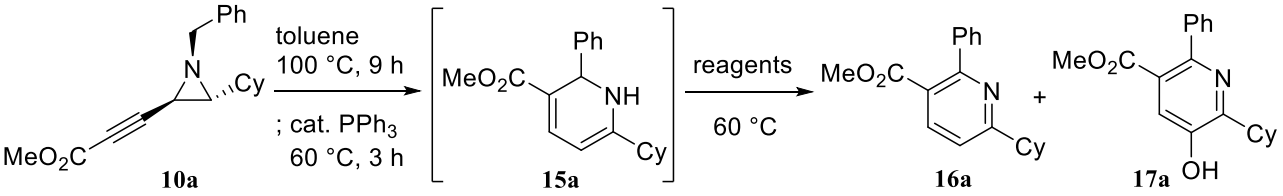
以上のようにジヒドロピリジンは空気中で酸化され三置換ピリジン及び四置換ピリジンに変換されることが分かった．そのため次に酸化条件を変えることで各々を選択的に合成できないか検討を行った(Table 6). アルキニルアジリジン **10a** から合成したジヒドロピリジン **15a** に対して酸化剤である DDQ を作用させたところ，三置換ピリジン **16a** が 69%の収率で選択的に得られた(entry 1)．更なる検討の結果，ジヒドロピリジン **15a** に酸を作用させると三置換ピリジン **16a** が優先的に生じることを見出した．即ち **15a** に対し 60 ºC で CSA または安息香酸を添加するとそれぞれ 37%, 53%の収率で **16a** が得られた(entry 2, 3)．また酢酸を作用させたとき収率及び選択性が向上し 71%の収率で **16a** が生成することを明らかにした(entry 4). 更に酢酸の量を検討したところ, 1.5 当量用いたとき収率の向上がみられ，三置換ピリジン **16a** を 77%の収率で得ることに成功した(entry 5)．酢酸の量を 1.0 当量にすると収率及び選択性が低下することが分かった(entry 6)．次にジヒドロピリジン **15a** を 1 気圧の酸素雰囲気下にて反応させたところ，四置換ピリジン **17a** が 51%の収率で優先的に生じることが分かった(entry7). 更に反応温度を 0 ºC にしたとき選択性が向上し四置換ピリジン **17a** が 80%の収率で生成することを見出した(entry 8)．本検討結果から，三置換ピリジン合成における最適条件を 60 ºC で 1.5 当量の酢酸を作用させる entry 5 とし，四置換ピリジン合成における最適条件を 0 ºC で 1 気圧の酸素を作用させる entry 8 とした．

また本反応に関して更なる検討を行ったところ，酢酸の添加の有無のみで選択性を制御できることが明らかとなった．以下の実験はジヒドロピリジン **15a** の酸化を，酢酸存在下または非存在下で試みたものであるが，選択性が逆転していることが分かる (Scheme 12). 即ち **10a** より合成したジヒドロピリジン **15a** に対して 1 気圧の酸素雰囲気下，酢酸を用いることなく反応を行うと四置換ピリジン **17a** が 51%の収率で優先的に得られるのに対し，酢酸存在下では三置換ピリジン **16a** が 67%の収率で選択的に生成した．

**Table 6. Selective Synthesis of Substituted Pyridines**




| entry | conditions | | time | yield of **16a** (%) | yield of **17a** (%) |
|---|---|---|---|---|---|
| | reagent | temp. | | | |
| 1 | DDQ (1.2 eq) | rt | 20 min | 69 | - |
| 2 | CSA (2.0 eq) | 60 °C | 3 h | 37 | < 15 |
| 3 | $PhCO_2H$ (2.0 eq) | 60 °C | 21 h | 53 | 14 |
| 4 | AcOH (2.0 eq) | 60 °C | 6 h | 71 | trace |
| 5 | AcOH (1.5 eq) | 60 °C | 10 h | 77 | trace |
| 6 | AcOH (1.0 eq) | 60 °C | 18 h | 50 | 34 |
| 7 | $O_2$ (1 atm) | 60 °C | 2 h | 18 | 51 |
| 8 | $O_2$ (1 atm) | 0 °C | 4 h | 8 | 80 |

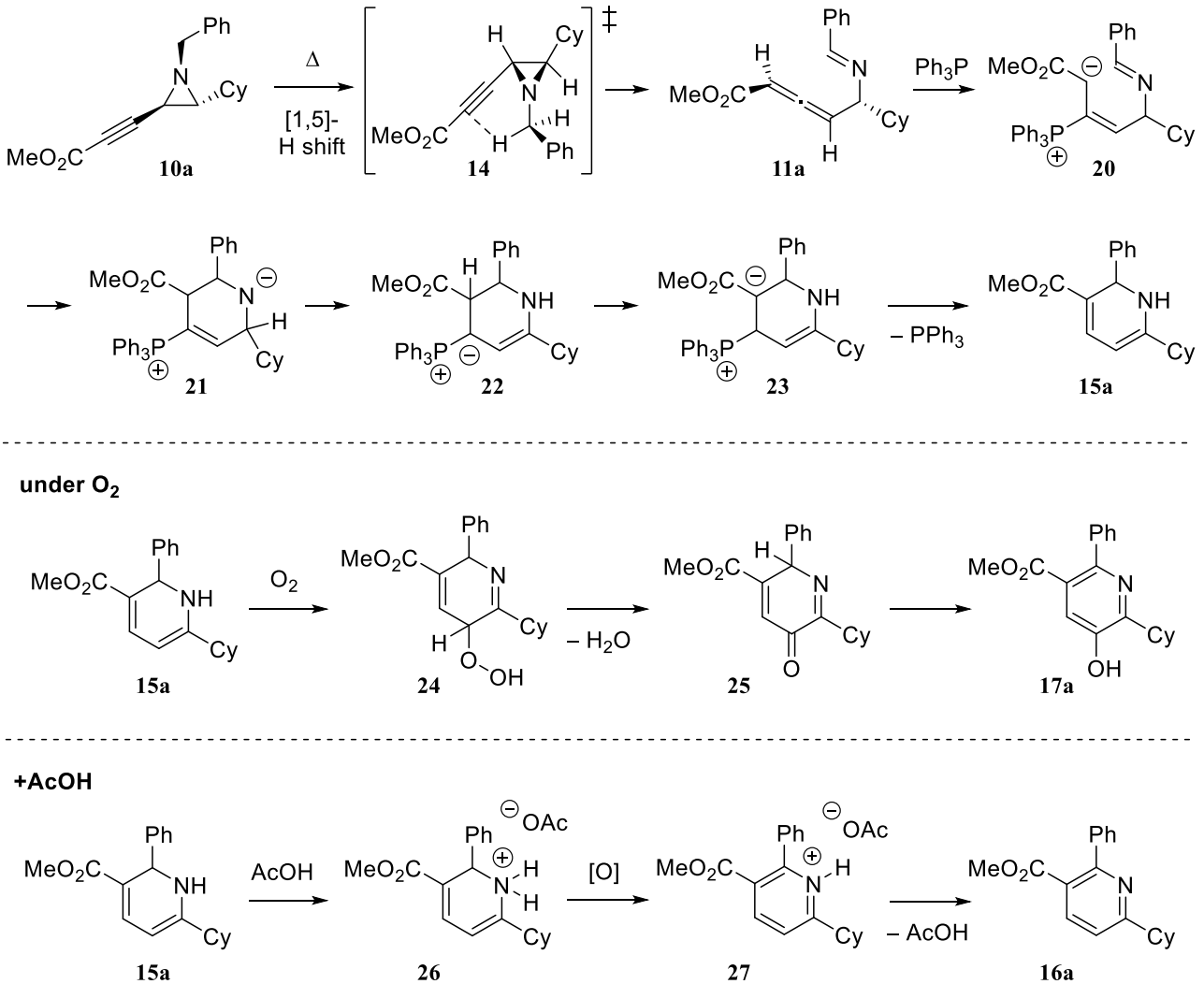



| reagents | time | **16a** | **17a** |
|---|---|---|---|
| $O_2$ (1 atm) | 2 h | 18% yield | 51% yield |
| $O_2$ (1 atm), AcOH (5.0) | 20 min | 67% yield | 7% yield |

**Scheme 12**

これまでに得られた実験データを基に予想される反応機構を以下に示す(Scheme 13). まず *N*–ベンジルアルキニルアジリジン **10a** を加熱すると, 1,5–水素移動が遷移状態 **14** を経て進行することで立体選択的にアレニルイミン **11a** が生じる. 続いて **11a** に対し $PPh_3$ を作用させると, 分子内アザベイリスヒルマン型の付加ー環化反応が進行し中間体 **21** となった後, 窒素上の負電荷が図の水素原子を引き抜き異性化することでリンイリド **22** が生成する. そ

して **22** の負電荷がエステル付け根の水素原子を攻撃し中間体 **23** となった後，$PPh_3$ が脱離することでジヒドロピリジン **15a** が得られると考えられる．**15a** の生成後，四置換ピリジン合成の場合は **15a** に対し酸素を作用させることで付加反応が進行し過酸化物 **24** が生成する [20]．その後水が脱離しケトン **25** となった後，芳香環化することで四置換ピリジン **17a** が生じると予想される．また三置換ピリジン合成の場合，酢酸を作用させることで **15a** がプロトン化し中間体 **26** となり，この状態のまま系中に微量含まれる酸素によって酸化されることで，三置換ピリジン **16a** が得られると推定される．

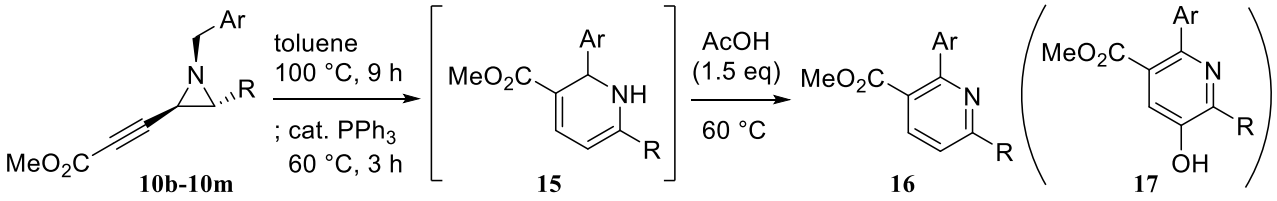



**Scheme 13**

次に本反応の一般性を明らかにするために，様々な置換アルキニルアジリジン **10b-10m** に対し本反応の適用を試みた．まず三置換ピリジン合成における基質一般性を検討した(Table 7). 三置換ピリジンが選択的に生成する最適条件下(Table 6, entry 5)にて基質検討を行った結果，イソプロピル基，*tert*−ブチル基，ブチル基をもつアルキニルアジリジン **10b-10d** を用いたとき，相当する三置換ピリジン **16b-16d** をいずれも優先的に得ることに成功した．またフェネチル基やベンジルオキシプロピル基を導入した基質 **10e**，**10f** においても良好に反応が進行し，対応する三置換ピリジン **16e**, **16f** が選択的に得られた．更にベンゼン環の 2 位に臭素を導入した基質 **10g** または 4 位に臭素，塩素，フッ素，メトキシ基を導入した基質 **10h-10k** に対して反応を試みたところ，いずれも相当する三置換ピリジン **16g-16k** を優先的に与えた. またナフチル基やチエニル基をもつ基質 **10l**, **10m** においても同様に反応し，対応する三置換ピリジン **16l**, **16m** が選択的に生成した．尚，基質 **10d**, **10e**, **10f**, **10l** において，酢酸添加時の反応温度を 100ºC に上げることで選択性の改善がみられ，収率良く相当する三置換ピリジン **16d**, **16e**, **16f**, **16l** を合成することに成功している．

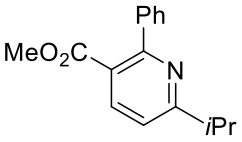
続いて四置換ピリジン合成における基質一般性を検討した(Table 8). 四置換ピリジンが選択的に生成する最適条件下(Table 6, entry 8)にて基質検討を行った結果，基質 **10b-10m** のいずれを用いた場合でも反応が円滑に進行し，望む四置換ピリジン **17b-17m** が選択的に生成することを見出した．

**Table 7. Synthesis of Various Trisubstituted Pyridines**

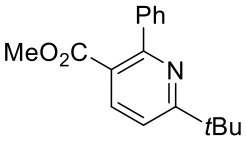



**10b-10m** **15** **16** **17**

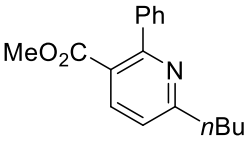
---



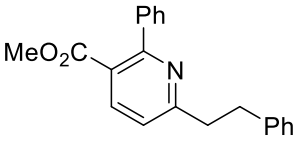

**16b** 79% (**17b** 17%)



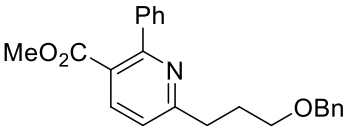

**16c** 75% (**17c** 13%)



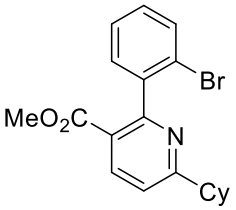

**16d** 55% (**17d** 25%)
**16d** 66% (**17d** 8%)[a]



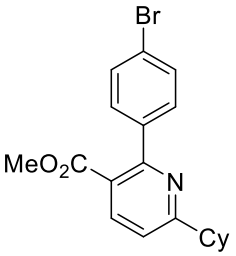

**16e** 53% (**17e** 31%)
**16e** 73% (**17e** 6%)[a]



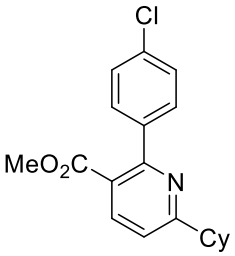

**16f** 60% (**17f** 13%)
**16f** 65% (**17f** 7%)[a]



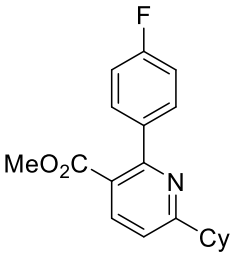

**16g** 72% (**17g** 8%)



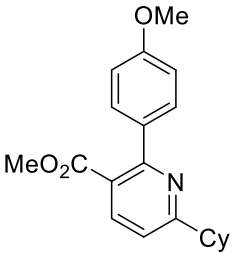

**16h** 85% (**17h** 2%)



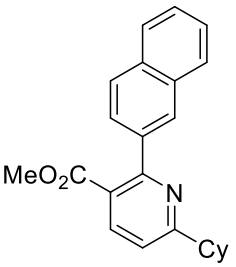

**16i** 71% (**17i** 10%)



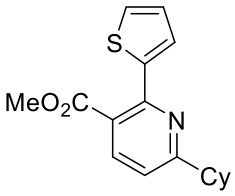

**16j** 74% (**17j** 8%)




**16k** 67% (**17k** 13%)



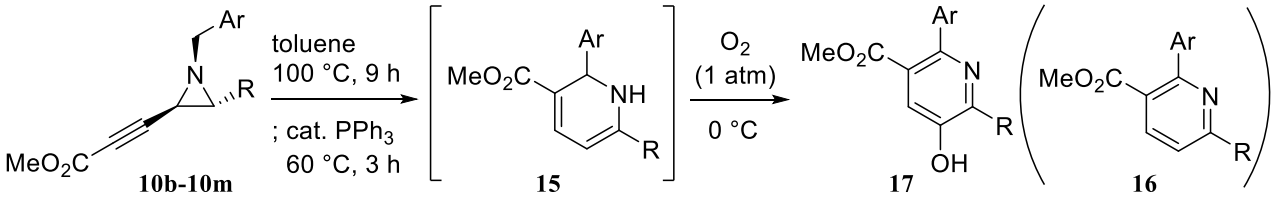

**16l** 45% (**17l** 38%)
**16l** 68% (**17l** 6%)[a]

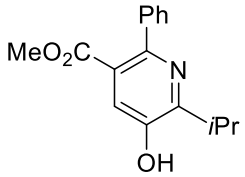



**16m** 60% (**17m** trace)

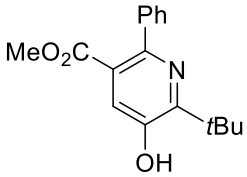
[a] AcOH was added at 100 ºC.

**Table 8. Synthesis of Various Tetrasubstituted Pyridines**

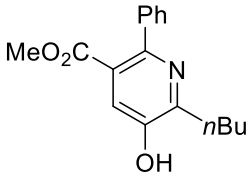


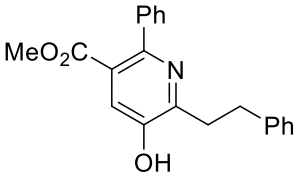

**17b** 81% (**16b** 4%)



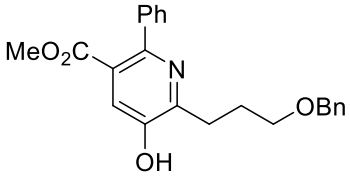

**17c** 67% (**16c** 13%)



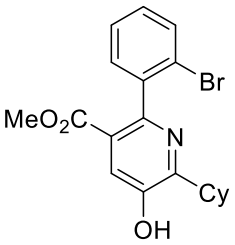

**17d** 70% (**16d** 3%)



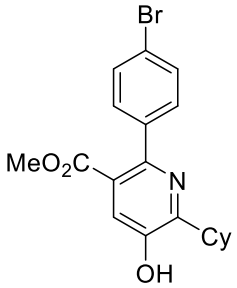

**17e** 75% (**16e** 4%)



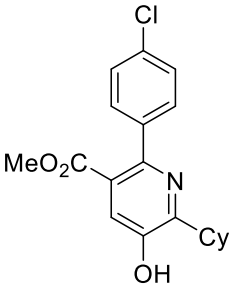

**17f** 69% (**16f** 5%)



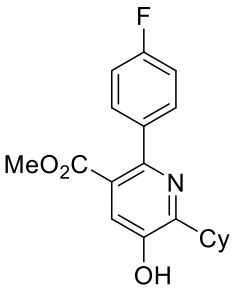

**17g** 58% (**16g** 8%)



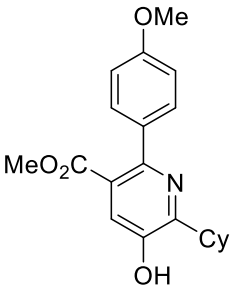

**17h** 78% (**16h** 6%)



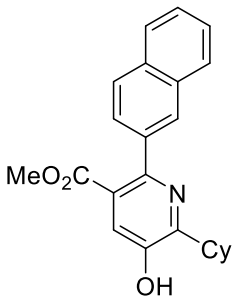

**17i** 72% (**16i** 5%)



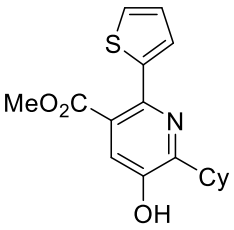

**17j** 72% (**16j** 5%)




**17k** 64% (**16k** 3%)

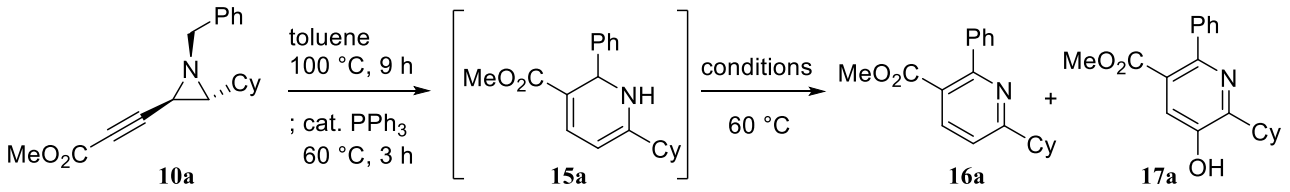



**17l** 83% (**16l** 7%)




**17m** 63% (**16m** 4%)

次に本反応をよりクリーンな反応とするため，酸素の代わりに空気を用いた酸化反応の検討を行った(Scheme 14)．アルキニルアジリジン **10a** より合成したジヒドロピリジン **15a** を空気中，60ºC に加熱し撹拌したところ，四置換ピリジン **17a** が 62%の収率で選択的に得られた．また同条件にて酢酸を加え反応を行ったところ，選択性が逆転し三置換ピリジン **16a** が 57%の収率で得られることが明らかとなった．以上の結果から，本反応では酸化に空気を用いても良好な選択性が発現することを見出した．




| conditions | 16a | 17a |
|---|---|---|
| open air | 7% yield | 62% yield |
| open air, AcOH (5.0) | 57% yield | 20% yield |

**Scheme 14**

また本反応の有用性を示すために，合成した多置換ピリジンを用いてナイアシン誘導体の合成を試みることとした. ナイアシンはニコチン酸及びニコチン酸アミドの総称であり，エネルギー代謝における酸化還元酵素の補酵素として重要な役割を担っている [21] (Figure 3). 三置換ピリジン **16a** に対して加水分解を試みたところ，効率的にニコチン酸誘導体 **18** を得ることに成功した(Scheme 15). また合成した誘導体 **18** に対する塩化アンモニウム及び Hünig's 塩基を用いた縮合反応により，ニコチンアミド誘導体 **28** の合成を達成した. 四置換ピリジン **17a** に対しても同様の条件に付すことで相当するニコチン酸誘導体 **29** 及びニコチンアミド誘導体 **30** の合成に成功した.

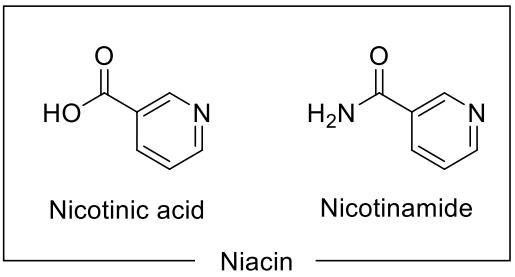
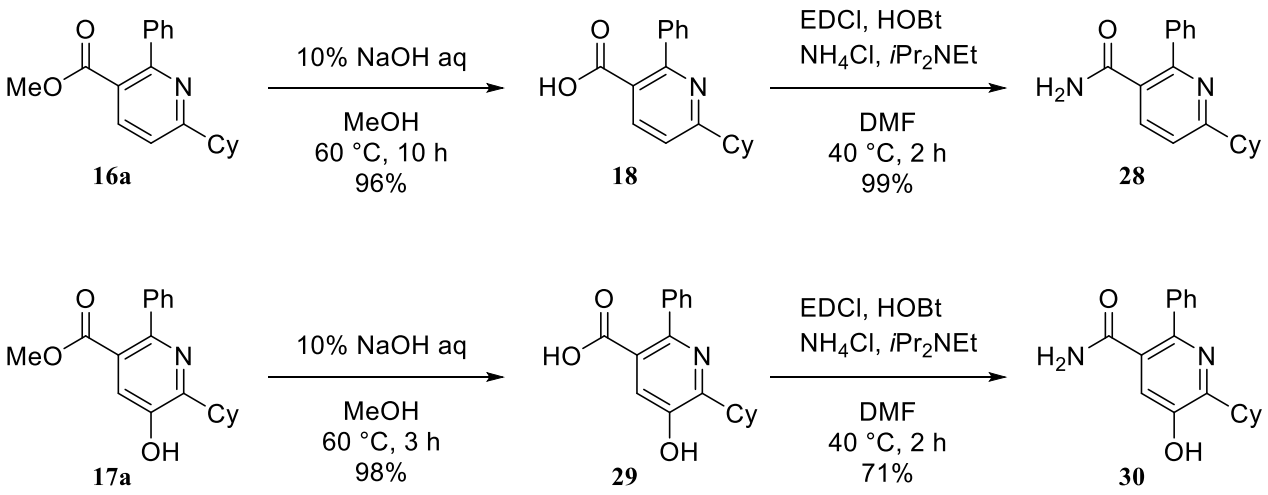



**Figure 3**

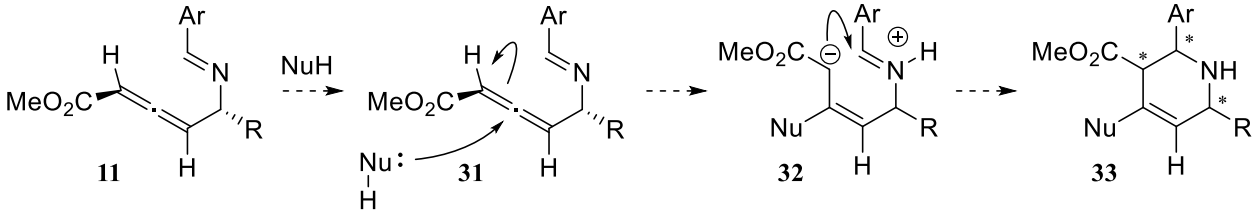



**Scheme 15**

以上のように著者は，アルキニルアジリジンの 1,5-水素移動反応を鍵とする多置換ピリジンの効率的合成法の開発を達成した．本手法はアルキニルアジリジンからワンポットで多置換ピリジンを合成する効率的変換法であり，酸化条件を変えることで三置換ピリジンまたは四置換ピリジンを各々選択的に合成することが可能である．

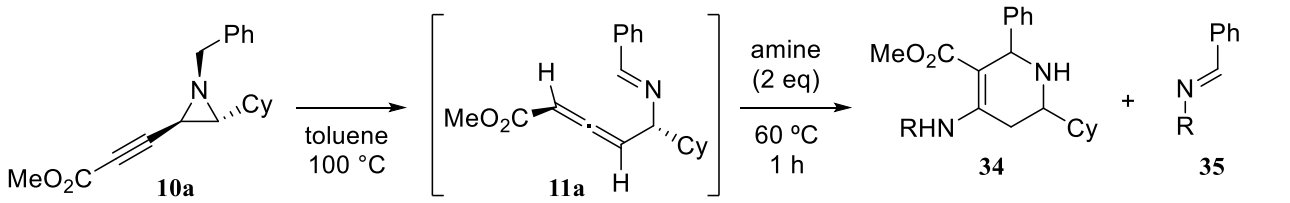
# 第三章　アルキニルアジリジンの 1,5−水素移動反応を鍵とする置換ピペリジンの効率的合成法の開発

ピペリジン環は多くの生理活性天然物に含まれる重要な骨格であるため[14]，有機合成において効率的な置換ピペリジン合成法の開発が望まれている[15]．著者は開発したアルキニルアジリジンの 1,5−水素移動反応で得られるアレニルイミン **11** に対して求核剤を作用させることで，アレン部位への求核剤の付加(**31**, **32**)，続く分子内環化が進行し，置換ピペリジン **33** が生成すると考えた(Scheme 16)．また本反応によって得られる置換ピペリジンは 3つの不斉中心を有することから，本反応における立体選択性にも興味を抱き置換ピペリジンの効率的合成法の研究開発に着手した．




**Scheme 16**

まず求核剤として 1 級アミンを選択し置換ピペリジンの合成を試みた(Scheme 17)．*N*−アリールメチルアルキニルアジリジン **10a** を加熱しアレニルイミン **11a** とした後にベンジルアミンを作用させたところ，予期した環化反応が進行し環化体 **34a** が 45%の収率で得られた．しかしながら同時に副生成物 **35a** が生じていることが分かった．**35a** はベンジルアミンが **11a** のイミン部位に攻撃することで生成したものと考えられる．また求核剤としてプロピルアミンを用いた場合も，環化体 **34b** の生成と共に副生成物 **35b** が生じる結果となった．そこで副反応を抑えるために求核剤として 2 級アミンを用いることとした．

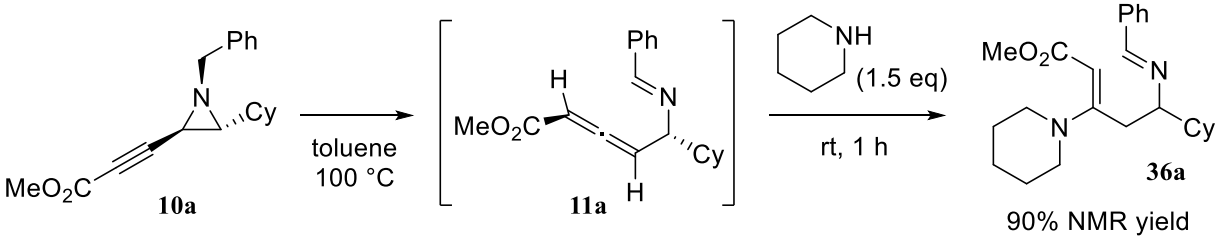



**34a** : R = Bn　　**35a** : R = Bn
**34b** : R = Pr　　**35b** : R = Pr

| amine | yield of **34** | yield of **35** |
|---|---|---|
| $BnNH_2$ | 45% (**34a**) | ca. 30% (**35a**) |
| $PrNH_2$ | 51% (**34b**) | ca. 15% (**35b**) |

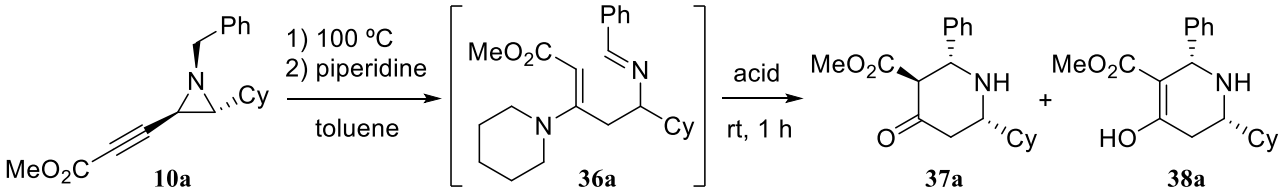
**Scheme 17**

アルキニルアジリジン **10a** より合成したアレニルイミン **11a** に対して 2 級アミンであるピペリジンを作用させたところ，アレニルエステルへの共役付加は進行したが環化は起きず，ピペリジン付加体 **36a** が生じることが分かった(Scheme 18)．望む環化体は得られなかったものの効率よく付加体を合成できたため，本付加体から環化体への変換を試みた(Table 9)．検討の結果，ピペリジン付加体 **36a** に対して酢酸を作用させると，環化及びピペリジンの脱離が進行し 80%の NMR 収率で環化体 **37a**，**38a** を立体選択的に得ることに成功した．このとき得られた環化体はわずかながら異性化しており，ケトン体 **37a** とエノール体 **38a** の比率は 12:1 であった．また酸として TsOH を用いた場合にも同等の収率で環化体 **37a** 及び **38a** が得られ，**37a** と **38a** の比率は 10:1 となった．更なる検討の結果，酸性シリカゲル(Silica gel 60 [Kanto, spherical 40-100 μm])を添加した際最も良好に反応が進行し，NMR 収率 85%で環化体 **37a** 及び **38a** を得ることに成功した. このとき **37a** と **38a** の比率は 15:1 であった．尚，合成した置換ピペリジンの立体化学はケトン体 **37a** の NOESY 測定の結果から決定している(Figure 4).




**Scheme 18**

**Table 9. Intramolecular Cyclization with Various Acids**




| acid | yield (NMR yield) | **37a**:**38a** |
|---|---|---|
| AcOH (1.5 eq) | 80% | 12:1 |
| TsOH (1.5 eq) | 80% | 10:1 |
| silica gel[a] (2.0 w/w) | 85% | 15:1 |

[a] Silica gel 60 [Kanto, spherical 40-100 μm] was used.

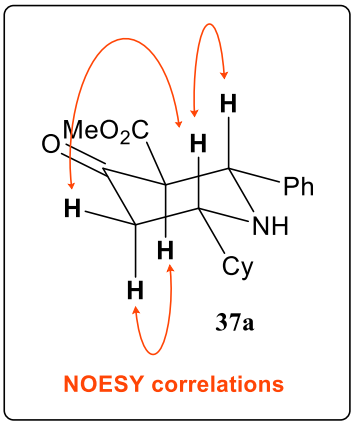
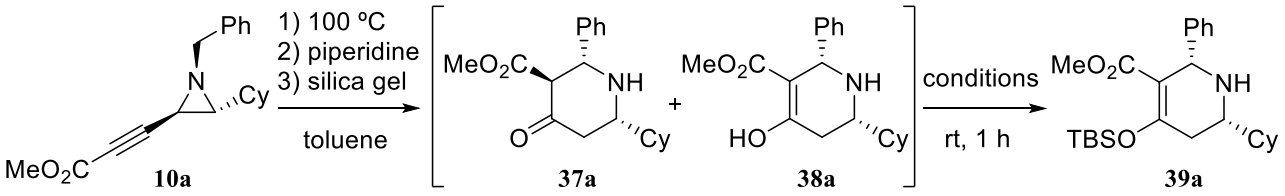



**Figure 4**

続いて合成した環化体 **37a**, **38a** のカラム精製を試みたが，精製後に収量の低下が確認された．そのため本反応の正確な収率と化合物データを得る目的で，シリルエノールエーテルへの変換を行うこととした(Scheme 19)．アルキニルアジリジン **10a** より合成した環化体 **37a**, **38a** に対して TBSCl 及びイミダゾールを用いてシリル化を試みたところ，複雑な混合物となり目的の化合物を得ることはできなかった．そのためより反応性の高い硝酸銀を用いる条件[22]に付したところ，望むシリルエノールエーテル **39a** を 4 工程収率 48%で得ることに成功した．

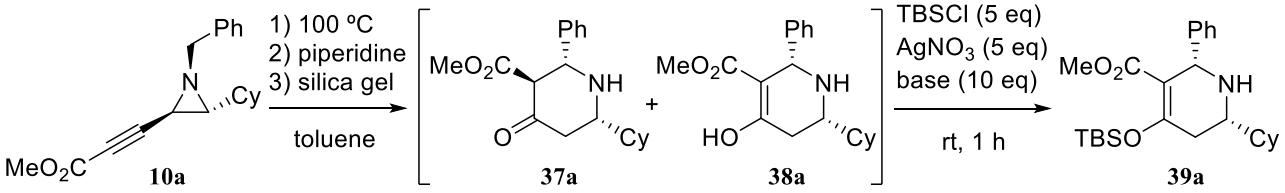



| conditions | result |
|---|---|
| TBSCl, imidazole, DMF | multi products |
| TBSCl, $AgNO_3$, pyridine, DMF | 48% yield (4 steps) |

**Scheme 19**

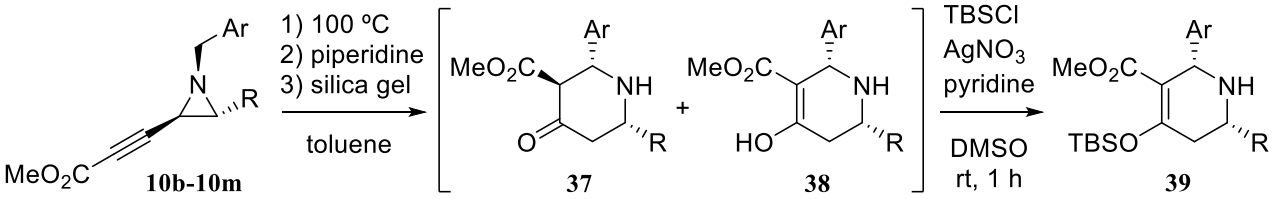
次に収率の向上を目指し更なる検討を行った(Table 10). 溶媒を変更し反応を行った結果, THF 溶媒中で反応を行うと収率の低下がみられたが，NMP または DMSO を用いると収率が向上し，それぞれ 59%, 64%の収率でシリルエノールエーテル **39a** を得ることに成功した (entry 1-3). また塩基を pyridine から $Et_3N$, DABCO, 2,6-lutidine に変更するといずれも収率が大幅に低下することが分かった(entry 4-6). 以上の結果から溶媒として DMSO，塩基として pyridine を用いる entry 3 を最適条件とした.

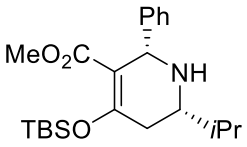
**Table 10. Reaction Optimization for the Synthesis of Silyl Enol Ether**



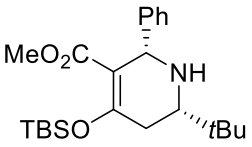

| entry | solvent | base | yield (4 steps) |
|---|---|---|---|
| 1 | THF | pyridine | 15% |
| 2 | NMP | pyridine | 59% |
| 3 | DMSO | pyridine | 64% |
| 4 | DMSO | $Et_3N$ | 5% |
| 5 | DMSO | DABCO | trace |
| 6 | DMSO | 2,6-lutidine | <10% |

**Table 11. Synthesis of Various Silyl Enol Ethers**

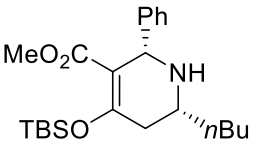


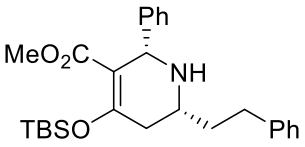

**39b** 75%



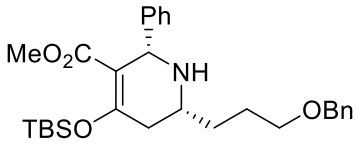

**39c** 67%



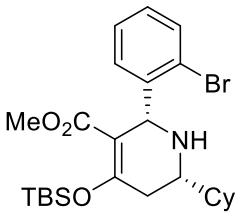

**39d** 66%



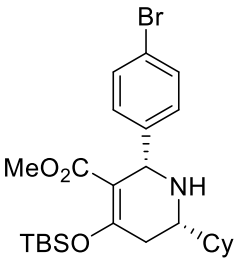

**39e** 49%



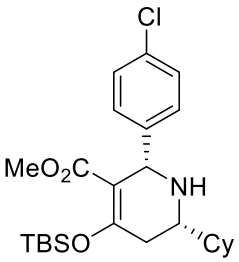

**39f** 41%



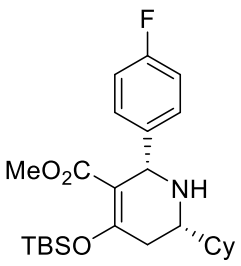

**39g** 55%



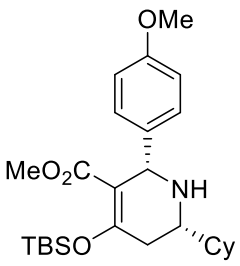

**39h** 76%



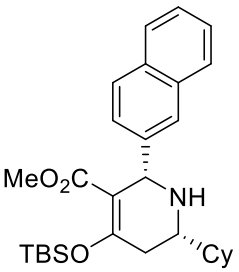

**39i** 68%



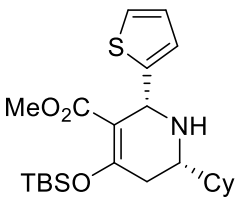

**39j** 67%




**39k** 52%




**39l** 61%




**39m** 42%

続いて本反応の一般性を明らかにすべく，様々なアルキニルアジリジン **10b-10m** を用いて置換ピペリジンの合成を試みた(Table 11)．プロピル基，*tert*-ブチル基，ブチル基をもつアルキニルアジリジン **10b-10d** を基質として本反応を行ったところ，相当するシリルエノールエーテル **39b-39d** がいずれも良好な収率で得られた．またフェネチル基やベンジルオキシプロピル基を導入した基質 **10e**, **10f** を用いると，収率の低下がみられたものの中程度の収率で **39e**, **39f** を得ることに成功した．更にベンゼン環の 4 位にハロゲンを導入した基

質 **10h-10j** またはナフチル基もつ基質 **10l** に対して反応を試みたところ, 対応するシリルエノールエーテル **39h-39j**, **39l** が収率よく生成した. ベンゼン環の 2 位に臭素を導入した基質 **10g**，4 位にメトキシ基を導入した基質 **10k**，またはチエニル基もつ基質 **10m** では中程度の収率で **39g**, **39k**, **39m** を得ることができた.

以上のように著者は，アレニルイミンに対するピペリジンの求核付加－環化反応による置換ピペリジンの立体選択的合成法を開発した．本反応ではアルキニルアジリジンからワンポットで置換ピペリジンを合成することが可能である.

# 結論

著者はアルキニルアジリジンの特異な反応性に着目し，新規変換法として 1,5 - 水素移動反応を考案した．また 1,5 - 水素移動反応により得られるアレニルイミンは優れた合成素子になり得ると考え，含窒素複素環化合物の合成への応用を検討することとした．

まず $N$ - アリールメチルアルキニルアジリジンを加熱条件下撹拌すると，1,5 - 水素移動反応が進行し定量的にアレニルイミンが生成することを見出した．更にアルキン末端にエステルを導入した基質に対しても良好に反応が進行し，定量的かつ立体選択的にアレニルイミンを得ることに成功した．本反応は精製の必要がなく，反応後溶媒を留去するだけでアレニルイミンを単一化合物として得ることができる効率的な合成法である．

次にアレニルイミンを用いた置換ピリジンの合成を試みた．その結果，アレニルイミンに対し $PPh_3$ を作用させることでアザベイリスヒルマン型の環化が進行し，ジヒドロピリジンが効率的に生成することを見出した．更にジヒドロピリジンに対し条件を変えて酸化することで，三置換ピリジンまたは四置換ピリジンを各々選択的かつ高収率で得ることに成功した．本反応はアルキニルアジリジンから反応条件の選択により，2 種の置換ピリジンを各々選択的かつワンポットで合成できる効率的変換法である．

続いてアレニルイミンを用いた置換ピペリジンの合成を試みた．その結果，アレニルイミンに対しピペリジン及びシリカゲルを作用させることで分子内環化が進行し，立体選択的に置換ピペリジンが生成することを見出した．本反応はアルキニルアジリジンからワンポットで置換ピペリジンを合成することができる．

以上のように著者はアルキニルアジリジンの 1,5 - 水素移動反応を開発し，本反応を応用することで置換ピリジン及び置換ピペリジンの効率的合成法の開発に成功した．

# 謝辞

本研究に際して終始御懇篤なる御指導ならびに御鞭撻を賜りました徳島文理大学薬学部薬学科教授　吉田昌裕先生，徳島大学ヘルスバイオサイエンス研究部教授　難波康祐先生に謹んで感謝いたします．更に本研究を行うにあたり，御指導、御協力頂きました徳島大学ヘルスバイオサイエンス研究部特任教授 宍戸宏造先生, 徳島文理大学薬学部薬学科講師 松本健司先生, 徳島大学ヘルスバイオサイエンス研究部助教 中山淳先生に篤く御礼申し上げます．また日々研究室でサポートしてくださった徳島文理大学薬学部薬化学研究室及び徳島大学薬学部付属医薬創製教育研究センター有機合成薬学分野の諸氏に心から感謝致します．加えて質量分析等の御協力を頂きました徳島文理大学薬学部薬学科助教　岡本育子先生，徳島大学中央機器室 北池秀次技官に御礼申し上げます．　最後にこれまで様々な面で支援してくれた家族に心から感謝致します．

# Experimental Section

**General.** All reactions for the preparation of substrates were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocol. Imines **3a**[23], **3b**[23], **3c**[23], **3d**[24], **3e**[25], **3f**[26], **7**[27], ethynylaziridine **4c**[16] and arylbromide **9m**[28] were prepared according to the procedures described in the literature. Column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 63-210 μm), and flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40-50 μm) using the indicated solvent. IR spectra were recorded on JASCO FT/IR-4200 and FT/IR-410 spectrometer. NMR spectra were recorded JEOL JNM-AL400 (400 MHz) and VARIAN VNMRS-500 (500 MHz), spectrometer with tetramethyl silane or chloroform as an internal standard. Mass spectra were obtained on JEOL JMS-SX102A and JEOL AX-500 spectrometer and Waters MICRO MASS LCT-premier spectrometers. Optical rotations were determined on JASCO P-1010-GT. All melting points were measured with Yanaco MP-500D and BUCHI 535 melting point apparatuses.

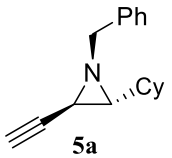
# Experiments in Chapter I-1

**Synthesis of *N*-arylmethyl ethynylaziridines 5. (Scheme 1 and Scheme 3)**

**General procedure for the synthesis of *N*-arylmethyl ethynylaziridines 5a, 5b and 5d-5f.**

**Synthesis of 5a. (Scheme 1)**

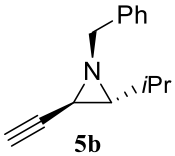
(3-Chloroprop-1-ynyl)trimethylsilane **1** (3.10 g, 21.1 mmol) was added at −78 °C to a solution of $ZnBr_2$ (7.92 g, 35.2 mmol) in THF (57 mL). To the mixture was added a freshly prepared solution of lithium diisopropylamide (0.81 M in THF, 43.5 mL, 35.2 mmol) at the same temperature. After stirring was continued for 30 min, imine **3a** (3.54 g, 17.6 mmol) in THF (6 mL) was added to reaction solution at the same temperature. The mixture was allowed to warm slowly to room temperature, and further stirring was continued for 30 min at the same temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$, and then the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure to give 2-[(trimethylsilyl)ethynyl]aziridine as a crude. To a stirred solution of this crude in MeOH (88 mL) was added $K_2CO_3$ (4.86 g, 35.2 mmol) at room temperature, and stirring was continued for 30 min at the same temperature. The reaction mixture was diluted with water and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (97:3 v/v) as eluent to give *N*-arylmethyl ethynylaziridine **5a** (3.61 g, 2 steps 86%) as a colorless oil.




**5a**

**1-Benzyl-2-cyclohexyl-3-ethynylaziridine (5a)**

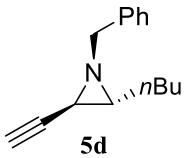
Yield 86% (2 steps); colorless oil; IR (KBr) 3297, 2925, 2851, 1496, 1450, 1355, 1024, 734, 697 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.78–1.01 (2H, m), 1.01–1.22 (4H, m), 1.50–1.65 (4H, m), 1.65–1.75 (2H, m), 2.22 (1H, d, *J* = 2.0 Hz), 2.42 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.48 (1H, d, *J* = 13.2 Hz), 3.90 (1H, d, *J* = 13.2 Hz), 7.21–7.29 (1H, m), 7.33 (2H, t, *J* = 7.2 Hz), 7.38 (2H, d, *J* = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.6 ($CH_2$), 25.8 ($CH_2$), 26.3 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.7 (CH), 40.8 (CH), 53.4 (CH), 58.7 ($CH_2$), 71.6 (CH), 80.7 (Cq), 127.0 (CH), 128.3 (CH), 128.7 (CH), 139.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NNa$ $[M+Na]^+$ 262.1572, found 262.1573.




**5b**

**1-Benzyl-2-ethynyl-3-isopropylaziridine (5b)**

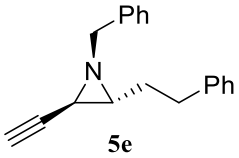
Yield 79% (2 steps); colorless oil; IR (KBr) 3297, 3030, 2959, 1496, 1454, 1356, 1281, 1026, 734, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 1.25 (1H, septd, *J* = 6.8 and 8.0 Hz), 1.54 (1H, dd, *J* = 3.2 and 8.0 Hz), 2.23 (1H, d, *J* = 2.0 Hz), 2.41 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.49 (1H, d, *J* = 13.2 Hz), 3.92 (1H, d, *J* = 13.2 Hz), 7.21–7.30 (1H, m), 7.33 (2H, t, *J* = 7.2 Hz), 7.39 (2H, d, *J* = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 19.2 ($CH_3$), 19.8 ($CH_3$), 30.9 (CH), 31.4 (CH), 54.6 (CH), 58.6 ($CH_2$), 71.6 (CH), 80.6 (Cq), 127.0 (CH), 128.2 (CH), 128.7 (CH), 139.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNa$ $[M+Na]^+$ 222.1259, found 222.1261.




**5d**

**1-Benzyl-2-butyl-3-ethynylaziridine (5d)**

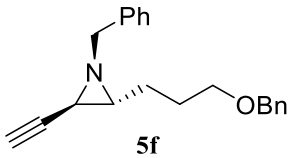
Yield 67% (2 steps); colorless oil; IR (KBr) 3300, 3030, 2957, 2930, 2858, 1496, 1454, 1356, 1248, 1028, 732, 697 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 6.8 Hz), 1.22–1.31 (4H, m), 1.31–1.50 (2H, m), 1.74 (1H, dt, *J* = 3.2 and 6.4 Hz), 2.23 (1H, d, *J* = 1.6 Hz), 2.37 (1H, dd, *J* = 1.6 and 3.2 Hz), 3.55 (1H, d, *J* = 13.2 Hz), 3.91 (1H, d, *J* = 13.2 Hz), 7.22–7.29 (1H, m), 7.33 (2H, t, *J* = 7.2 Hz), 7.39 (2H, d, *J* = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 13.9 ($CH_3$), 22.2 ($CH_2$), 29.0 ($CH_2$), 31.7 (CH), 32.2 ($CH_2$), 48.2 (CH), 58.3 ($CH_2$), 71.8 (CH), 80.4 (Cq), 126.9 (CH), 128.3 (CH), 128.4 (CH), 139.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNa$ $[M+Na]^+$ 236.1415, found 236.1412.




**5e**

**1-Benzyl-2-ethynyl-3-phenethylaziridine (5e)**

Yield 66% (2 steps); colorless oil; IR (KBr) 3290, 3028, 2921, 2853, 2116, 1604, 1496, 1454, 1357, 1244, 1075, 1029, 732 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.61–1.71 (1H, m), 1.75–1.86 (2H, m), 2.24 (1H, d, *J* = 2.0 Hz), 2.38 (1H, dd, *J* = 2.0 and 3.2 Hz), 2.51–2.67 (2H, m), 3.52 (1H, d, *J* = 13.6 Hz), 3.90 (1H, d, *J* = 13.6 Hz), 7.07–7.12 (2H, m), 7.15–7.21 (1H, m), 7.24–7.30 (3H, m), 7.32–7.37 (2H, m), 7.37–7.42 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 31.7 (CH), 33.1 ($CH_2$), 34.3 ($CH_2$), 47.4 (CH), 58.1 ($CH_2$), 72.0 (CH), 80.2 (Cq), 125.8 (CH), 127.0 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 139.1 (Cq), 141.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NNa$ $[M+Na]^+$ 284.1415, found 284.1416.

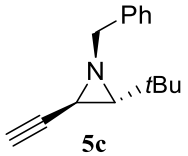



**5f**

**1-Benzyl-2-[3-(benzyloxy)propyl]-3-ethynylaziridine (5f)**

Yield 72% (2 steps); colorless oil; IR (KBr) 3289, 3030, 2933, 2855, 1604, 1496, 1454, 1359, 1102, 1028, 733, 697 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.36–1.48 (1H, m), 1.55–1.64 (3H, m), 1.73–1.80 (1H, m), 2.23 (1H, d, *J* = 2.0 Hz), 2.38 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.36–3.45 (2H, m), 3.53 (1H, d, *J* = 13.6 Hz), 3.90 (1H, d, *J* = 13.6 Hz), 4.45 (2H, s), 7.23–7.40 (10H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 27.0 ($CH_2$), 29.2 ($CH_2$), 31.7 (CH), 47.7 (CH), 58.2 ($CH_2$), 69.5 ($CH_2$), 71.9 (CH), 72.7 ($CH_2$), 80.2 (Cq), 127.0 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 138.4 (Cq), 139.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NONa$ $[M+Na]^+$ 328.1677, found 328.1677.

**Procedure for the synthesis of *N*-arylmethyl ethynylaziridines 5c. (Scheme 3)**



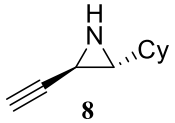

**5c**

**1-Benzyl-2-tert-butyl-3-ethynylaziridine (5c)**

To a stirred solution of 2-[(trimethylsilyl)ethynyl]aziridine **4c** (441 mg, 1.54 mmol) in MeOH (7.7 mL) was added $K_2CO_3$ (427 mg, 3.09 mmol) at room temperature, and stirring was continued for 30 min at the same temperature. The reaction mixture was diluted with water and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (97:3 v/v) as eluent to give *N*-arylmethyl ethynylaziridine **5a** (323 mg, 98%) as a colorless oil; IR (KBr) 3299, 3031, 2956, 1496, 1455, 1411, 1362, 1227, 1025, 845, 734, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.76 (9H, s), 1.59 (1H, d, *J* = 3.2 Hz), 2.19 (1H, d, *J* = 2.0 Hz), 2.47

(1H, dd, *J* = 2.0 and 3.2 Hz), 3.47 (1H, d, *J* = 13.2 Hz), 3.95 (1H, d, *J* = 13.2 Hz), 7.24–7.28 (1H, m), 7.32 (2H, t, *J* = 7.2 Hz), 7.40 (2H, d, *J* = 7.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.5 ($CH_3$), 28.1 (CH), 30.5 (Cq), 57.5 (CH), 58.8 ($CH_2$), 71.3 (CH), 80.9 (Cq), 127.0 (CH), 128.2 (CH), 128.8 (CH), 139.5 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N$ $[M+H]^+$ 214.1596, found 214.1599.

**Procedure for the synthesis of ethynylaziridines 8. (Scheme 3)**




**8**

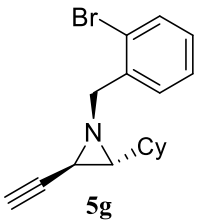
**2-Cyclohexyl-3-ethynylaziridine (8)**

(3-Chloroprop-1-ynyl)trimethylsilane **1** (1.80 g, 12.3 mmol) was added at −78 °C to a solution of $ZnBr_2$ (4.61 g, 20.5 mmol) in THF (35 mL). To the mixture was added a freshly prepared solution of lithium diisopropylamide (0.99 M in THF, 20.8 mL, 20.5 mmol) at the same temperature. After stirring was continued for 30 min, imine **7** (1.88 g, 10.2 mmol) in THF (6 mL) was added to reaction solution at the same temperature. The mixture was allowed to warm slowly to room temperature, and further stirring was continued for 30 min at the same temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$, and then the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. This crude product was distilled under reduced pressure to give ethynylaziridine **8** (992 mg, 2 steps 65%); colorless oil; bp 55.0 °C/0.2 mmHg; IR (KBr) 3305, 2925, 2851, 1449, 1195, 921, 846, 798, 651 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.55 (1H, brs), 0.81–0.92 (1H, m), 1.04–1.29 (5H, m), 1.61–1.69 (1H, m), 1.69–1.80 (3H, m), 1.80–1.89 (1H, m), 2.01–2.16 (3H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 23.0 (CH), 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 30.1 ($CH_2$), 30.4 ($CH_2$), 41.3 (CH), 45.0 (CH), 67.6 (CH), 84.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{10}H_{15}NNa$ $[M+Na]^+$ 172.1102, found 172.1107.

**General procedure for the synthesis of *N*-arylmethyl ethynylaziridines 5g-5m.**

**Synthesis of 5g. (Scheme 3)**

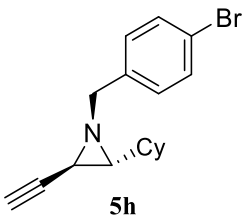
To a stirred solution of ethynylaziridine **8** (169 mg, 1.13 mmol) in DMF (1.1 mL) was added $K_2CO_3$ (312 mg, 2.26 mmol) and arylmethyl bromide **9g** (339 mg, 1.36 mmol) at room temperature, and stirring was continued for 2 h at the same temperature. The reaction mixture was diluted with water and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (97:3 v/v) as eluent to give *N*-arylmethyl ethynylaziridine **5g** (277 mg, 77%) as colorless plates.




**5g**

**1-(2-Bromobenzyl)-2-cyclohexyl-3-ethynylaziridine (5g)**

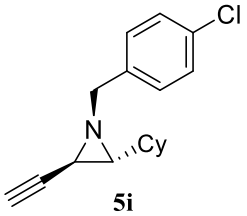
Yield 77%; colorless plates; mp 66.2–67.4 °C (recrystallized from EtOAc/hexane); IR (KBr) 3190, 2925, 2841, 1569, 1439, 1267, 1236, 1119, 1023, 824, 798, 745 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.92–1.24 (6H, m), 1.58–1.76 (6H, m), 2.18 (1H, d, *J* = 2.0 Hz), 2.47 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.82 (2H, s), 7.13 (1H, dt, *J* = 1.2 and 8.0 Hz), 7.31 (1H, dt, *J* = 1.2 and 8.0 Hz), 7.54 (1H, dd, *J* = 1.2 and 8.0 Hz), 7.60 (1H, dd, *J* = 1.2 and 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.7 ($CH_2$), 25.8 ($CH_2$), 26.3 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.7 (CH), 40.8 (CH), 53.3 (CH), 57.8 ($CH_2$), 71.7 (CH), 80.3 (Cq), 123.6 (Cq), 127.3 (CH), 128.3 (CH), 130.2 (CH), 132.4 (CH), 138.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BrNNa$ $[M+Na]^+$ 340.0677, found 340.0674.




**5h**

**1-(4-Bromobenzyl)-2-cyclohexyl-3-ethynylaziridine (5h)**

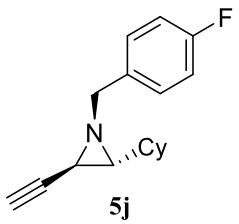
Yield 78%; colorless oil; IR (KBr) 3170, 2926, 2850, 1487, 1449, 1239, 1067, 1011, 857, 821, 782 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.82–1.00 (2H, m), 1.00–1.23 (4H, m), 1.52–1.66 (4H, m), 1.66–1.76 (2H, m), 2.21 (1H, d, *J* = 2.0 Hz), 2.41 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.47 (1H, d, *J* = 13.2 Hz), 3.81 (1H, d, *J* = 13.2 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.6 ($CH_2$), 25.7 ($CH_2$), 26.2 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.6 (CH), 40.7 (CH), 53.4 (CH), 58.0 ($CH_2$), 71.8 (CH), 80.4 (Cq), 120.9 (Cq), 130.3 (CH), 131.3 (CH), 138.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BrNNa$ $[M+Na]^+$ 340.0677, found 340.0675.




**5i**

**1-(4-Chlorobenzyl)-2-cyclohexyl-3-ethynylaziridine (5i)**

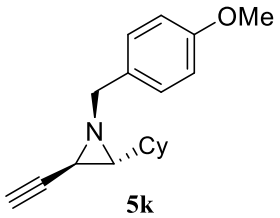
Yield 80%; colorless oil; IR (KBr) 3300, 3182, 2925, 2850, 1491, 1448, 1238, 1091, 1015, 856, 808 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.82–0.98 (2H, m), 0.98–1.22 (4H, m), 1.52–1.66 (4H, m), 1.66–1.74 (2H, m), 2.21 (1H, d, *J* = 2.0 Hz), 2.41 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.48 (1H, d, *J* = 13.2 Hz), 3.83 (1H, d, *J* = 13.2 Hz), 7.28–7.34 (4H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.6 ($CH_2$), 25.7 ($CH_2$), 26.2 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.6 (CH), 40.7 (CH), 53.4 (CH), 58.0 ($CH_2$), 71.7 (CH), 80.4 (Cq), 128.4 (CH), 130.0 (CH), 132.7 (Cq), 137.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}ClNNa$ $[M+Na]^+$ 296.1182, found 296.1181.




**5j**

**2-Cyclohexyl-3-ethynyl-1-(4-fluorobenzyl)aziridine (5j)**

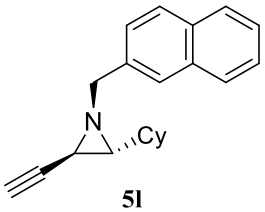
Yield 80%; colorless oil; IR (KBr) 3177, 2928, 2851, 1601, 1510, 1450, 1339, 1220, 1119, 1025, 862, 822, 791, 725 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.79–0.97 (2H, m), 0.97–1.23 (4H, m), 1.49–1.66 (4H, m), 1.66–1.74 (2H, m), 2.23 (1H, d, *J* = 2.0 Hz), 2.40 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.46 (1H, d, *J* = 13.2 Hz), 3.85 (1H, d, *J* = 13.2 Hz), 7.02 (2H, t, *J* = 8.4 Hz), 7.33–7.36 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.7 ($CH_2$), 26.2 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.7 (CH), 40.8 (CH), 53.3 (CH), 57.9 ($CH_2$), 71.7 (CH), 80.5 (Cq), 115.1 (CH, d, *J* = 20.6 Hz), 130.2 (CH, d, *J* = 8.3 Hz), 135.0 (Cq, d, *J* = 3.3 Hz), 162.0 (Cq, d, *J* = 234.7 Hz); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}FNNa$ $[M+Na]^+$ 280.1479, found 280.1479.




**5k**

**2-Cyclohexyl-3-ethynyl-1-(4-methoxybenzyl)aziridine (5k)**

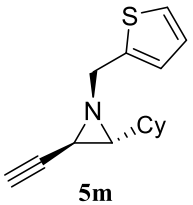
Yield 70%; colorless oil; IR (KBr) 3274, 2925, 2850, 1614, 1514, 1449, 1245, 1178, 1038, 820, 759 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.77–0.96 (2H, m), 0.96–1.23 (4H, m), 1.48–1.64 (4H, m), 1.64–1.74 (2H, m), 2.22 (1H, d, *J* = 2.0 Hz), 2.39 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.40 (1H, d, *J* = 13.2 Hz), 3.81 (3H, s), 3.84 (1H, d, *J* = 13.2 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 7.30 (2H, d, *J* = 8.8 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.6 ($CH_2$), 25.7 ($CH_2$), 26.2 ($CH_2$), 29.9 ($CH_2$), 30.5 ($CH_2$), 30.7 (CH), 40.8 (CH), 53.3 (CH), 55.2 ($CH_3$), 58.1 ($CH_2$), 71.6 (CH), 80.8 (Cq), 113.7 (CH), 129.9 (CH), 131.4 (Cq), 158.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NONa$ $[M+Na]^+$ 292.1677, found 292.1678.




**5l**

**2-Cyclohexyl-3-ethynyl-1-(naphthalen-2-ylmethyl)aziridine (5l)**

Yield 81%; colorless needles; mp 61.8–63.8 °C (recrystallized from EtOAc/hexane); IR (KBr) 3293, 2924, 2850, 1508, 1448, 1268, 1124, 856, 815, 746, 610 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.80–1.01 (2H, m), 1.01–1.22 (4H, m), 1.50–1.61 (3H, m), 1.63 (1H, dd, *J* = 3.2 and 7.6 Hz), 1.65–1.75 (2H, m), 2.23 (1H, d, *J* = 2.0 Hz), 2.47 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.66 (1H, d, *J* = 13.2 Hz), 4.05 (1H, d, *J* = 13.2 Hz), 7.42–7.50 (2H, m), 7.53 (1H, d, *J* = 9.2 Hz), 7.79–7.87 (4H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 ($CH_2$), 30.4 ($CH_2$), 30.6 (CH), 40.7 (CH), 53.4 (CH), 58.8 ($CH_2$), 71.7 (CH), 80.6 (Cq), 125.4 (CH), 125.7 (CH), 127.0 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 132.6 (Cq), 133.4 (Cq), 136.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NNa$ $[M+Na]^+$ 312.1728, found 312.1729.




**5m**

**2-Cyclohexyl-3-ethynyl-1-(thiophen-2-ylmethyl)aziridine (5m)**

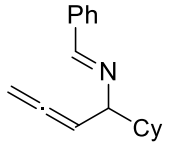
Yield 63%; colorless oil; IR (KBr) 3296, 2924, 2850, 1448, 1331, 1267, 1236, 1021, 852, 697 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.82–1.25 (6H, m), 1.52–1.66 (4H, m), 1.66–1.75 (2H, m), 2.23 (1H, d, *J* = 2.0 Hz), 2.42 (1H, dd, *J* = 2.0 and 3.2 Hz), 3.69 (1H, d, *J* = 13.2 Hz), 4.04 (1H, d, *J* = 13.2 Hz), 6.94–6.99 (2H, m), 7.23 (1H, dd, *J* = 1.2 and 4.8 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.6 ($CH_2$), 25.7 ($CH_2$), 26.2 ($CH_2$), 29.8 ($CH_2$), 30.4 ($CH_2$), 30.7 (CH), 40.6 (CH), 53.2 ($CH_2$), 53.6 (CH), 71.8 (CH), 80.3 (Cq), 124.7 (CH), 125.6 (CH), 126.5 (CH), 141.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NS$ $[M+H]^+$ 246.1316, found 246.1316.

**Conversion of 5 to allenylimines 6. (Scheme 2, Table 1 and Table 2)**

**General procedure for the synthesis of allenylimines 6a-m.**

**Synthesis of 6a. (Scheme 2)**

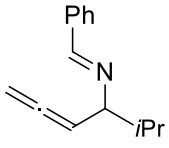
To a stirred solution of 3-aziridinylpropiolate ester **5a** (59.8 mg, 0.25 mmol) in DMSO (1.3 mL) was heated at 120 °C, and stirring was continued for 7 h at the same temperature. The reaction mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure to give allenylimine **6a** (59.8 mg, quant) as a pale yellow oil.




**6a**

**(*E*)-*N*-(1-Cyclohexylbuta-2,3-dien-1-yl)-1-phenylmethanimine (6a)**

Quantitative yield; pale yellow oil; IR (KBr) 2924, 2851, 1955, 1644, 1580, 1449, 1309, 1026, 842, 755, 693 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.87–1.07 (2H, m), 1.08–1.34 (3H, m), 1.59–1.80 (5H, m), 1.84–1.94 (1H, m), 3.53 (1H, t, *J* = 7.6 Hz), 4.73 (2H, d, *J* = 6.4 Hz), 5.34 (1H, dt, *J* = 6.4 and 7.6 Hz), 7.37–7.43 (3H, m), 7.71–7.77 (2H, m), 8.24 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.8 ($CH_2$), 43.2 (CH), 75.4 ($CH_2$), 76.2 (CH), 92.1 (CH), 128.2 (CH), 128.4 (CH), 130.5 (CH), 136.3 (Cq), 160.1 (CH), 208.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NNa$ $[M+Na]^+$ 262.1572, found 262.1577.

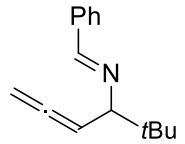



**6b**

**(*E*)-*N*-(2-Methylhexa-4,5-dien-3-yl)-1-phenylmethanimine (6b)**

Quantitative yield; pale yellow oil; IR (KBr) 2957, 2870, 1956, 1644, 1580, 1451, 1384, 1311, 1218, 1170, 1036, 843, 754, 693 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d,

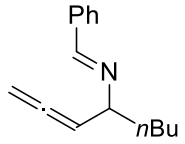
*J* = 6.8 Hz), 1.97 (1H, sextd, *J* = 6.8 and 7.6 Hz), 3.52 (1H, t, *J* = 7.6 Hz), 4.74 (2H, d, *J* = 6.4 Hz), 5.34 (1H, dt, *J* = 6.4 and 7.6 Hz), 7.38–7.45 (3H, m), 7.72–7.79 (2H, m), 8.27 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 19.2 ($CH_3$), 19.3 ($CH_3$), 33.9 (CH), 75.4 ($CH_2$), 76.8 (CH), 92.0 (CH), 128.2 (CH), 128.5 (CH), 130.5 (CH), 136.3 (Cq), 160.1 (CH), 208.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNa$ $[M+Na]^+$ 222.1259, found 222.1264.




**6c**

**(*E*)-*N*-(2,2-Dimethylhexa-4,5-dien-3-yl)-1-phenylmethanimine (6c)**

Quantitative yield; pale yellow oil; IR (KBr) 2953, 2867, 1955, 1645, 1451, 1362, 1054, 843, 752, 692 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, d, *J* = 6.8 Hz), 3.47 (1H, d, *J* = 8.4 Hz), 4.71 (2H, d, *J* = 6.4 Hz), 5.37 (1H, dt, *J* = 6.4 and 8.4 Hz), 7.38–7.43 (3H, m), 7.73–7.79 (2H, m), 8.26 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.6 ($CH_3$), 35.5 (Cq), 74.9 ($CH_2$), 80.0 (CH), 90.5 (CH), 128.2 (CH), 128.5 (CH), 130.4 (CH), 136.5 (Cq), 160.0 (CH), 208.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNa$ $[M+Na]^+$ 236.1415, found 236.1414.

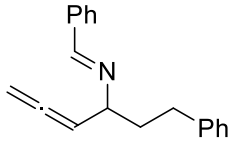



**6d**

**(*E*)-*N*-(Octa-1,2-dien-4-yl)-1-phenylmethanimine (6d)**

Quantitative yield; pale yellow oil; IR (KBr) 2957, 2931, 2858, 1956, 1643, 1580, 1451, 1379, 845, 755, 693 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz), 1.22–1.40 (4H, m), 1.74 (2H, q, *J* = 7.2 Hz), 3.82 (1H, dd, *J* = 7.2 and 7.6 Hz), 4.78 (2H, d, *J* = 7.6 Hz), 5.31 (1H, q, *J* = 7.6 Hz), 7.38–7.45 (3H, m), 7.73–7.78 (2H, m), 8.29 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 22.5 ($CH_2$), 28.5 ($CH_2$), 36.2 ($CH_2$), 70.1 (CH), 76.1 ($CH_2$), 93.6 (CH), 128.2 (CH), 128.5 (CH), 130.6 (CH),

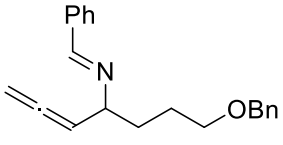
136.2 (Cq), 160.1 (CH), 208.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNa$ $[M+Na]^+$ 236.1415, found 236.1411.




**6e**

**(*E*)-1-Phenyl-*N*-(1-phenylhexa-4,5-dien-3-yl)methanimine (6e)**

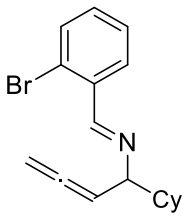
Quantitative yield; pale yellow oil; IR (ATR) 3026, 2920, 2854, 1955, 1642, 1496, 1451, 1309, 1041, 909, 846, 752, 693 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.04–2.14 (2H, m), 2.59–2.75 (2H, m), 3.84–3.90 (1H, m), 4.80 (2H, dd, *J* = 2.0 and 6.5 Hz), 5.33 (1H, q, *J* = 6.5 Hz), 7.15–7.21 (3H, m), 7.25–7.30 (2H, m), 7.48–7.56 (3H, m), 7.74–7.80 (2H, m), 8.28 (1H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 32.5 ($CH_2$), 37.8 ($CH_2$), 69.0 (CH), 76.4 ($CH_2$), 93.3 (CH), 125.7 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 130.7 (CH), 136.1 (Cq), 141.8 (Cq), 160.8 (CH), 208.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N$ $[M+H]^+$ 262.1596, found 262.1595.




**6f**

**(*E*)-*N*-[7-(Benzyloxy)hepta-1,2-dien-4-yl]-1-phenylmethanimine (6f)**

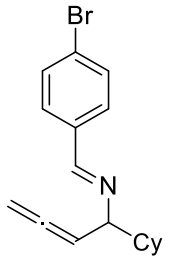
Quantitative yield; pale yellow oil; IR (ATR) 2927, 2853, 1955, 1640, 1452, 1361, 1098, 847, 734, 693 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.62–1.70 (2H, m), 1.76–1.90 (2H, m), 3.50 (1H, t, *J* = 7.0 Hz), 3.81–3.88 (1H, m), 4.49 (2H, s), 4.74–4.81 (2H, m), 5.31 (1H, q, *J* = 7.0 Hz), 7.24–7.38 (5H, m), 7.38–7.44 (3H, m), 7.71–7.76 (2H, m), 8.23 (1H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 26.6 ($CH_2$), 33.0 ($CH_2$), 69.8 ($CH_2$), 70.1 (CH), 72.9 ($CH_2$), 76.3 ($CH_2$), 93.4 (CH), 127.5 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 130.6 (CH), 136.1 (Cq), 138.5 (Cq), 160.5 (CH), 207.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1858, found 306.1855.




**6g**

**(*E*)-1-(2-Bromophenyl)-*N*-(1-cyclohexylbuta-2,3-dien-1-yl)methanimine (6g)**

Quantitative yield; pale yellow oil; IR (ATR) 2924, 2850, 1956, 1632, 1448, 1268, 1022, 908, 843, 753, 732 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.91–1.07 (2H, m), 1.10–1.33 (3H, m), 1.61–1.81 (5H, m), 1.86–1.94 (1H, m), 3.61 (1H, t, *J* = 7.0 Hz), 4.76 (2H, d, *J* = 7.0 Hz), 5.33 (1H, q, *J* = 7.0 Hz), 7.25 (H, dt, *J* = 2.0 and 7.5 Hz), 7.33 (1H, t, *J* = 7.5 Hz), 7.56 (1H, d, *J* = 7.5 Hz), 8.02 (H, dt, *J* = 2.0 and 7.5 Hz), 8.58 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.8 ($CH_2$), 43.3 (CH), 75.5 ($CH_2$), 76.1 (CH), 91.9 (CH), 124.9 (Cq), 129.6 (CH), 131.7 (CH), 135.2 (Cq), 158.8 (CH), 208.4 (Cq); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.8 ($CH_2$), 43.1 (CH), 75.6 ($CH_2$), 76.0 (CH), 91.9 (CH), 124.9 (Cq), 127.5 (CH), 129.0 (CH), 131.6 (CH), 132.9 (CH), 134.7 (Cq), 159.3 (CH), 208.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NBr$ $[M+H]^+$ 318.0857, found 318.0852.

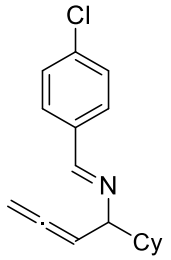



**6h**

**(*E*)-1-(4-Bromophenyl)-*N*-(1-cyclohexylbuta-2,3-dien-1-yl)methanimine (6h)**

Quantitative yield; pale yellow amorphous; IR (KBr) 2922, 2850, 1953, 1639, 1588, 1567, 1486, 1376, 1068, 1010, 847, 822 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.80–1.05 (2H, m), 1.05–1.35 (3H, m), 1.57–1.80 (5H, m), 1.84–1.95 (1H, m), 3.52 (1H, t, *J* = 7.6 Hz), 4.73 (2H, d, *J* = 6.4 Hz), 5.32 (1H, dt, *J* = 6.4 and 7.6 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.62 (2H, d, *J* = 8.4 Hz), 8.18 (1H, s); $^{13}$C-NMR (100

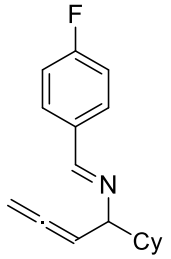
MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.8 ($CH_2$), 43.3 (CH), 75.5 ($CH_2$), 76.1 (CH), 91.9 (CH), 124.9 (Cq), 129.6 (CH), 131.7 (CH), 135.2 (Cq), 158.8 (CH), 208.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BrNNa$ $[M+Na]^+$ 340.0677, found 340.0680.




**6i**

**(*E*)-1-(4-Chlorophenyl)-*N*-(1-cyclohexylbuta-2,3-dien-1-yl)methanimine (6i)**

Quantitative yield; pale yellow oil; IR (ATR) 2923, 2850, 1956, 1641, 1595, 1490, 1449, 1087, 1013, 822, 756, 733 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.87–1.04 (2H, m), 1.08–1.32 (3H, m), 1.59–1.80 (5H, m), 1.85–1.92 (1H, m), 3.52 (1H, t, *J* = 8.0 Hz), 4.74 (2H, d, *J* = 6.5 Hz), 5.32 (1H, dt, *J* = 6.5 and 8.0 Hz), 7.37 (2H, d, *J* = 6.5 Hz), 7.68 (2H, d, *J* = 6.5 Hz), 8.20 (1H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.8 ($CH_2$), 43.2 (CH), 75.5 ($CH_2$), 76.2 (CH), 91.9 (CH), 128.8 (CH), 129.4 (CH), 134.7 (Cq), 136.4 (Cq), 158.8 (CH), 208.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NCl$ $[M+H]^+$ 274.1363, found 274.1363.

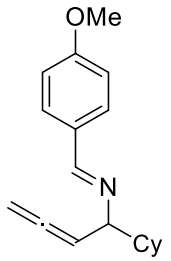



**6j**

**(*E*)-*N*-(1-Cyclohexylbuta-2,3-dien-1-yl)-1-(4-fluorophenyl)methanimine (6j)**

Quantitative yield; pale yellow oil; IR (ATR) 2923, 2850, 1956, 1642, 1602, 1508, 1449, 1228, 1151, 1014, 833, 733 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.87–1.04 (2H, m), 1.08–1.33 (3H, m), 1.58–1.80

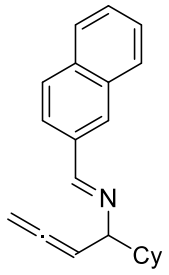
(5H, m), 1.85–1.93 (1H, m), 3.51 (1H, t, *J* = 8.0 Hz), 4.73 (2H, d, *J* = 6.5 Hz), 5.32 (1H, dt, *J* = 6.5 and 8.0 Hz), 7.06–7.11 (2H, m), 7.72–7.77 (2H, m), 8.20 (1H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 43.2 (CH), 75.5 ($CH_2$), 76.2 (CH), 92.0 (CH), 115.6 (CH, d, *J* = 21.8 Hz), 130.1 (CH, d, *J* = 8.5 Hz), 132.5 (Cq, d, *J* = 2.8 Hz), 158.6 (CH), 164.2 (Cq, d, *J* = 249.5 Hz), 208.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NF$ $[M+H]^+$ 258.1658, found 258.1657.




**6k**

**(*E*)-*N*-(1-Cyclohexylbuta-2,3-dien-1-yl)-1-(4-methoxyphenyl)methanimine (6k)**

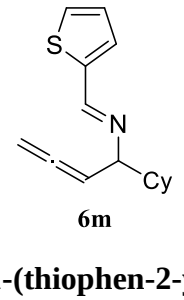
Quantitative yield; pale yellow amorphous; IR (KBr) 2919, 2840, 1955, 1641, 1607, 1577, 1513, 1449, 1299, 1256, 1164, 1026, 831 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.81–1.06 (2H, m), 1.07–1.33 (3H, m), 1.57–1.79 (5H, m), 1.85–1.94 (1H, m), 3.48 (1H, t, *J* = 7.6 Hz), 3.84 (3H, s), 4.72 (2H, d, *J* = 6.4 Hz), 5.33 (1H, dt, *J* = 6.4 and 7.6 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 7.69 (2H, d, *J* = 8.4 Hz), 8.17 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.9 ($CH_2$), 29.9 ($CH_2$), 43.3 (CH), 55.3 ($CH_3$), 75.3 ($CH_2$), 76.2 (CH), 92.3 (CH), 113.9 (CH), 129.3 (Cq), 129.8 (CH), 159.4 (CH), 161.5 (Cq), 208.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO$ $[M+H]^+$ 270.1858, found 270.1858.




**6l**

**(*E*)-*N*-(1-Cyclohexylbuta-2,3-dien-1-yl)-1-(naphthalen-2-yl)methanimine (6l)**

Quantitative yield; pale yellow amorphous; IR (KBr) 2925, 2851, 1961, 1720, 1637, 1438, 1216, 1161, 1033, 860, 822, 747 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.91–1.09 (2H, m), 1.09–1.35 (3H, m), 1.62–1.81 (5H, m), 1.88–1.97 (1H, m), 3.59 (1H, t, *J* = 7.6 Hz), 4.75 (2H, d, *J* = 6.4 Hz), 5.38 (1H, dt, *J* = 6.4 and 7.6 Hz), 7.47–7.54 (3H, m), 7.82–7.91 (3H, m), 8.01 (1H, d, *J* = 8.8 Hz), 8.05 (1H, s), 8.40 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.4 ($CH_2$), 26.6 ($CH_2$), 26.9 ($CH_2$), 30.2 ($CH_2$), 30.3 ($CH_2$), 43.6 (CH), 75.8 ($CH_2$), 76.7 (CH), 92.5 (CH), 124.5 (CH), 126.7 (CH), 127.3 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 130.1 (CH), 133.4 (Cq), 134.3 (Cq), 135.0 (Cq), 160.5 (CH), 208.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NNa$ $[M+Na]^+$ 312.1728, found 312.1728.




**6m**

**(*E*)-*N*-(1-Cyclohexylbuta-2,3-dien-1-yl)-1-(thiophen-2-yl)methanimine (6m)**

Quantitative yield; pale yellow oil; IR (KBr) 2925, 2851, 1955, 1631, 1541, 1448, 1385, 1216, 843, 709 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.84–1.04 (2H, m), 1.06–1.33 (3H, m), 1.58–1.80 (5H, m), 1.83–1.92 (1H, m), 3.48 (1H, t, *J* = 7.6 Hz), 4.73 (2H, d, *J* = 6.4 Hz), 5.31 (1H, dt, *J* = 6.4 and 7.6 Hz), 7.06 (1H, dd, *J* = 3.6 and 5.2 Hz), 7.30 (1H, d, *J* = 3.6 Hz), 7.39 (1H, d, *J* = 5.2 Hz), 8.33 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 43.1 (CH), 75.4 ($CH_2$), 76.0 (CH), 92.0 (CH), 127.3 (CH), 128.7 (CH), 130.3 (CH), 142.6 (Cq), 153.2 (CH), 208.4

(Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NS$ $[M+H]^+$ 246.1316, found 246.1313.

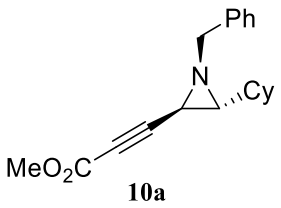
# Experiments in Chapter I-2

**Synthesis of 3-aziridinylpropiolate esters 10. (Scheme 7)**

**General procedure for the synthesis of 3-aziridinylpropiolate esters 10a, 10b and 10d-10f.**

**Synthesis of 10a.**

To a stirred solution of *N*-arylmethyl ethynylaziridine **5a** (500 mg, 2.09 mmol) in THF (10 mL) was added *n*BuLi (2.6 M in hexane, 0.96 mL, 2.51 mmol) at −78 °C. After stirring was continued for 30 min at same temperature, methyl chloro carbonate (0.24 mL, 3.12 mmol) was added to reaction solution, and the reaction mixture was allowed to warm slowly to room temperature. After further stirring was continued for 30 min at the same temperature, the reaction mixture was diluted with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (98:2 v/v) as eluent to give 3-aziridinylpropiolate ester **10a** (310 mg, 50%) as a colorless oil.

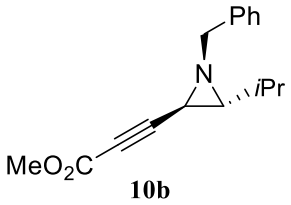



**10a**

**Methyl 3-(1-benzyl-3-cyclohexylaziridin-2-yl)propiolate (10a)**

Yield 50%; colorless oil; IR (KBr) 2927, 2851, 2225, 1714, 1496, 1435, 1260, 1119, 1066, 829, 735, 698 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.81–0.92 (1H, m), 0.92–1.07 (2H, m), 1.07–1.20 (3H, m), 1.49–1.73 (5H, m), 1.74 (1H, dd, *J* = 3.2 and 7.2 Hz), 2.48 (1H, d, *J* = 3.2 Hz), 3.49 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.90 (1H, d, *J* = 13.2 Hz), 7.25–7.30 (1H, m), 7.33 (2H, t, *J* = 7.6 Hz), 7.37 (2H, d, *J* = 7.6 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 (CH), 29.9 ($CH_2$), 30.4 ($CH_2$), 40.8 (CH), 52.7 ($CH_3$), 54.6 (CH), 59.3 ($CH_2$), 75.4 (Cq), 86.1 (Cq), 127.3 (CH), 128.3

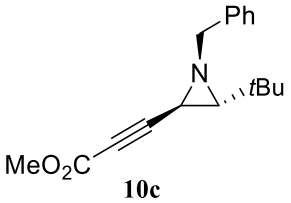
(CH), 128.8 (CH), 138.4 (Cq), 153.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1804.




**10b**

**Methyl 3-(1-benzyl-3-isopropylaziridin-2-yl)propiolate (10b)**

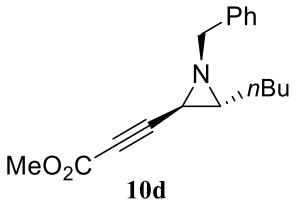
Yield 59%; colorless oil; IR (KBr) 3294, 2959, 2225, 1714, 1496, 1435, 1266, 1119, 1065, 829, 735, 698 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 1.30 (1H, septd, *J* = 6.8 and 8.0 Hz), 1.72 (1H, dd, *J* = 3.2 and 8.0 Hz), 2.48 (1H, d, *J* = 3.2 Hz), 3.50 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.92 (1H, d, *J* = 13.2 Hz), 7.24–7.29 (1H, m), 7.34 (2H, t, *J* = 7.6 Hz), 7.39 (2H, d, *J* = 7.6 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 19.1 ($CH_3$), 19.8 ($CH_3$), 30.0 (CH), 31.4 (CH), 52.6 ($CH_3$), 55.9 (CH), 59.2 ($CH_2$), 75.4 (Cq), 86.0 (Cq), 127.3 (CH), 128.3 (CH), 128.8 (CH), 138.5 (Cq), 153.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1494, found 258.1494.




**10c**

**Methyl 3-(1-benzyl-3-*tert*-butylaziridin-2-yl)propiolate (10c)**

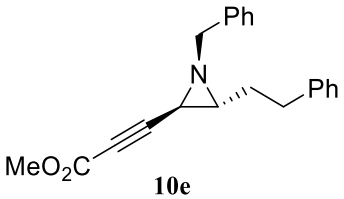
Yield 70%; colorless oil; IR (KBr) 2955, 2227, 1716, 1435, 1363, 1267, 1125, 1088, 736, 698 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.79 (9H, s), 1.76 (1H, d, *J* = 3.2 Hz), 2.54 (1H, d, *J* = 3.2 Hz), 3.49 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.95 (1H, d, *J* = 13.2 Hz), 7.24–7.29 (1H, m), 7.33 (2H, t, *J* = 7.6 Hz), 7.39 (2H, d, *J* = 7.6 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.4 ($CH_3$), 27.4 (CH), 30.8 (Cq), 52.6 ($CH_3$), 58.8 (CH), 59.3 ($CH_2$), 75.2 (Cq), 86.5 (Cq), 127.2 (CH), 128.2 (CH), 128.8 (CH), 138.7 (Cq), 153.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2Na$ $[M+Na]^+$ 294.1470, found 294.1470.




**10d**

**Methyl 3-(1-benzyl-3-butylaziridin-2-yl)propiolate (10d)**

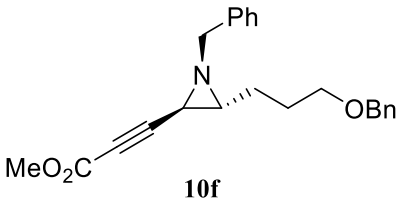
Yield 42%; colorless oil; IR (KBr) 2956, 2931, 2858, 2227, 1715, 1496, 1455, 1435, 1267, 1113, 1061, 734, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.38 (3H, t, *J* = 8.0 Hz), 1.20–1.31 (4H, m), 1.37–1.50 (2H, m), 1.92 (1H, dt, *J* = 3.2 and 8.0 Hz), 2.44 (1H, d, *J* = 3.2 Hz), 3.57 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.90 (1H, d, *J* = 13.2 Hz), 7.25–7.30 (1H, m), 7.33 (2H, t, *J* = 7.6 Hz), 7.39 (2H, d, *J* = 7.6 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 13.8 ($CH_3$), 22.2 ($CH_2$), 28.9 ($CH_2$), 30.9 (CH), 32.2 ($CH_2$), 49.5 (CH), 52.6 ($CH_3$), 58.9 ($CH_2$), 75.5 (Cq), 85.8 (Cq), 127.2 (CH), 128.3 (CH), 128.5 (CH), 138.5 (Cq), 153.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2Na$ $[M+Na]^+$ 294.1470, found 294.1471.




**10e**

**Methyl 3-(1-benzyl-3-phenethylaziridin-2-yl)propiolate (10e)**

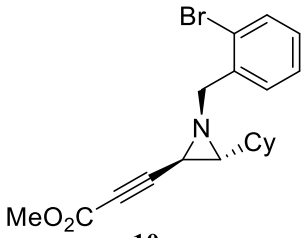
Yield 42%; colorless oil; IR (KBr) 3028, 2951, 2853, 2227, 1715, 1496, 1454, 1435, 1268, 1120, 748, 699 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.69 (1H, qd, *J* = 7.2 and 13.2 Hz), 1.83 (1H, qd, *J* = 7.2 and 13.2 Hz), 1.90–1.96 (1H, m), 2.44 (1H, d, *J* = 2.8 Hz), 2.51–2.68 (2H, m), 3.53 (1H, d, *J* = 13.6 Hz), 3.79 (3H, s), 3.89 (1H, d, *J* = 13.6 Hz), 7.05–7.10 (2H, m), 7.15–7.21 (1H, m), 7.23–7.31 (3H, m), 7.32–7.41 (4H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 30.9 (CH), 33.0 ($CH_2$), 34.2 ($CH_2$), 48.7 (CH), 52.7 ($CH_3$), 58.7 ($CH_2$), 75.6 (Cq), 85.5 (Cq), 126.0 (CH), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 138.4 (Cq), 140.9 (Cq), 153.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO_2Na$ $[M+Na]^+$ 342.1470, found 342.1470.




**10f**

**Methyl 3-{1-benzyl-3-[3-(benzyloxy)propyl]aziridin-2-yl}propiolate (10f)**

Yield 41%; colorless oil; IR (KBr) 3030, 2951, 2855, 2227, 1715, 1496, 1455, 1435, 1360, 1267, 1103, 735, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.40–1.52 (1H, m), 1.54–1.68 (3H, m), 1.91–1.98 (1H, m), 2.45 (1H, d, *J* = 2.8 Hz), 3.36–3.42 (2H, m), 3.55 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.89 (1H, d, *J* = 13.2 Hz), 4.42 (1H, d, *J* = 12.0 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 7.25–7.39 (10H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.9 ($CH_2$), 29.3 ($CH_2$), 30.9 (CH), 49.1 (CH), 52.6 ($CH_3$), 58.8 ($CH_2$), 69.3 ($CH_2$), 72.8 ($CH_2$), 75.5 (Cq), 85.6 (Cq), 127.2 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 138.4 (Cq), 138.4 (Cq), 153.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_3Na$ $[M+Na]^+$ 386.1732, found 386.1734.

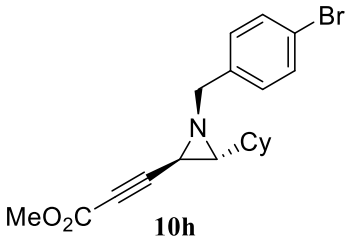



**10g**

**Methyl 3-[1-(2-bromobenzyl)-3-cyclohexylaziridin-2-yl]propiolate (10g)**

Yield 50%; colorless oil; IR (KBr) 2925, 2851, 2226, 1716, 1436, 1349, 1261, 1117, 1067, 1027, 748 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.88–1.08 (3H, m), 1.08–1.22 (3H, m), 1.55–1.76 (5H, m), 1.84–1.89 (1H, m), 2.54 (1H, d, *J* = 3.2 Hz), 3.77 (3H, s), 3.78 (1H, d, *J* = 13.2 Hz), 3.88 (1H, d, *J* = 13.2 Hz), 7.14 (1H, dt, *J* = 1.2 and 8.4 Hz), 7.31 (1H, dt, *J* = 1.2 and 8.4 Hz), 7.53 (1H, dd, *J* = 1.2 and 8.4 Hz), 7.56 (1H, dd, *J* = 1.2 and 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.7 ($CH_2$), 29.9 (CH), 30.4 ($CH_2$), 40.7 (CH), 52.6 ($CH_3$), 54.4 (CH), 58.3 ($CH_2$), 75.4 (Cq), 85.8 (Cq), 123.8 (Cq), 127.4 (CH), 128.6 (CH), 130.3 (CH), 132.6 (CH), 138.1 (Cq), 153.6 (Cq);

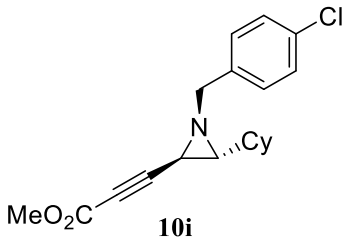
HRMS (ESI) *m/z* calcd for $C_{19}H_{22}BrNO_2Na$ $[M+Na]^+$ 398.0732, found 398.0734.




**10h**

**Methyl 3-[1-(4-bromobenzyl)-3-cyclohexylaziridin-2-yl]propiolate (10h)**

Yield 45%; colorless needles; mp 53.2–54.2 °C (recrystallized from EtOAc/hexane); IR (KBr) 2919, 2849, 2227, 1712, 1489, 1432, 1261, 1230, 1069, 867, 807, 749 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.82–1.08 (3H, m), 1.06–1.23 (3H, m), 1.55–1.77 (6H, m), 2.47 (1H, d, *J* = 3.2 Hz), 3.49 (1H, d, *J* = 13.2 Hz), 3.78 (3H, s), 3.80 (1H, d, *J* = 13.2 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.7 (CH), 29.7 ($CH_2$), 30.4 ($CH_2$), 40.6 (CH), 52.6 ($CH_3$), 54.6 (CH), 58.5 ($CH_2$), 75.4 (Cq), 85.8 (Cq), 121.1 (Cq), 130.3 (CH), 131.4 (CH), 137.5 (Cq), 153.5 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{23}BrNO_2$ $[M+H]^+$ 376.0912, found 376.0907.

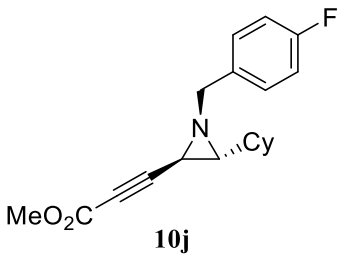



**10i**

**Methyl 3-[1-(4-chlorobenzyl)-3-cyclohexylaziridin-2-yl]propiolate (10i)**

Yield 66%; colorless oil; IR (KBr) 2925, 2851, 2226, 1715, 1492, 1435, 1348, 1261, 1120, 1067, 1015, 865, 808, 748 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.81–1.07 (3H, m), 1.07–1.22 (3H, m), 1.48–1.77 (6H, m), 2.47 (1H, d, *J* = 3.2 Hz), 3.50 (1H, d, *J* = 13.2 Hz), 3.78 (3H, s), 3.83 (1H, d, *J* = 13.2 Hz), 7.31 (4H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 (CH), 29.8

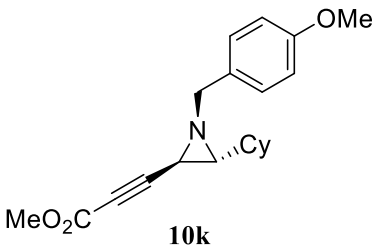
($CH_2$), 30.5 ($CH_2$), 40.7 (CH), 52.7 ($CH_3$), 54.7 (CH), 58.5 ($CH_2$), 75.4 (Cq), 85.8 (Cq), 128.5 (CH), 130.0 (CH), 133.0 (Cq), 137.0 (Cq), 153.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}ClNO_2Na$ $[M+Na]^+$ 354.1237, found 354.1237.




**10j**

**Methyl 3-[3-cyclohexyl-1-(4-fluorobenzyl)aziridin-2-yl]propiolate (10j)**

Yield 64%; colorless oil; IR (KBr) 2926, 2852, 2226, 1716, 1604, 1510, 1436, 1261, 1224, 1156, 1120, 1067, 835, 749 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.79–1.07 (3H, m), 1.07–1.23 (3H, m), 1.46–1.54 (1H, m), 1.56–1.74 (5H, m), 2.48 (1H, d, *J* = 2.8 Hz), 3.48 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.84 (1H, d, *J* = 13.2 Hz), 7.02 (2H, t, *J* = 8.4 Hz), 7.34 (2H, dd, *J* = 5.6 and 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 ($CH_2$), 29.9 (CH), 30.4 ($CH_2$), 40.7 (CH), 52.7 ($CH_3$), 54.6 (CH), 58.5 ($CH_2$), 75.4 (Cq), 85.9 (Cq), 115.2 (CH, d, *J* = 21.5 Hz), 130.3 (CH, d, *J* = 8.3 Hz), 134.2 (Cq, d, *J* = 3.3 Hz), 153.6 (Cq), 162.1 (Cq, d, *J* = 243.7 Hz); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}FNO_2Na$ $[M+Na]^+$ 338.1532, found 338.1532.

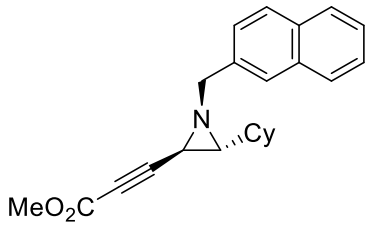



**10k**

**Methyl 3-[3-cyclohexyl-1-(4-methoxybenzyl)aziridin-2-yl]propiolate (10k)**

Yield 31%; colorless needles; mp 42.9–44.1 °C (recrystallized from EtOAc/hexane); IR (KBr) 2926, 2851, 2224, 1715, 1613, 1514, 1435, 1259, 1120, 1037, 749 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ

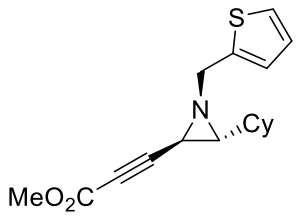
0.78–1.07 (3H, m), 1.07–1.20 (3H, m), 1.47–1.72 (5H, m), 1.72 (1H, dd, *J* = 3.2 and 7.2 Hz), 2.46 (1H, d, *J* = 3.2 Hz), 3.42 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 3.81 (3H, s), 3.84 (1H, d, *J* = 13.2 Hz), 6.87 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 (CH), 29.8 ($CH_2$), 30.4 ($CH_2$), 40.8 (CH), 52.6 ($CH_3$), 54.6 (CH), 55.2 ($CH_3$), 58.7 ($CH_2$), 75.4 (Cq), 86.2 (Cq), 113.7 (CH), 130.0 (CH), 130.6 (Cq), 153.7 (Cq), 158.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NO_3Na$ $[M+Na]^+$ 350.1732, found 350.1737.




**10l**

**Methyl 3-[3-cyclohexyl-1-(naphthalen-2-ylmethyl)aziridin-2-yl]propiolate (10l)**

Yield 63%; colorless plates; mp 92.2–94.6 °C (recrystallized from EtOAc/hexane); IR (KBr) 2926, 2847, 2224, 1703, 1432, 1277, 1121, 857, 822, 749 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.79–0.94 (1H, m), 0.94–1.20 (5H, m), 1.50–1.63 (3H, m), 1.63–1.73 (2H, m), 1.81 (1H, dd, *J* = 3.2 and 7.2 Hz), 2.53 (1H, d, *J* = 3.2 Hz), 3.69 (1H, d, *J* = 13.2 Hz), 3.79 (3H, s), 4.04 (1H, d, *J* = 13.2 Hz), 7.42–7.50 (2H, m), 7.53 (1H, d, *J* = 8.4 Hz) 7.80–7.85 (4H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.8 (CH), 29.8 ($CH_2$), 30.4 ($CH_2$), 40.7 (CH), 52.6 ($CH_3$), 54.7 (CH), 59.4 ($CH_2$), 75.4 (Cq), 86.1 (Cq), 125.6 (CH), 125.9 (CH), 127.0 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 132.8 (Cq), 133.4 (Cq), 136.0 (Cq), 153.6 (Cq) ; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_2Na$ $[M+Na]^+$ 370.1783, found 370.1783.




**10m**

**Methyl 3-[3-cyclohexyl-1-(thiophen-2-ylmethyl)aziridin-2-yl]propiolate (10m)**

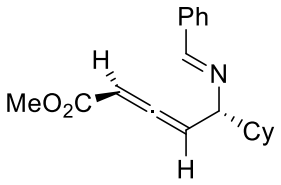
Yield 36%; colorless oil; IR (KBr) 2925, 2851, 2226, 1714, 1435, 1260, 1119, 749, 700 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.86–1.08 (3H, m), 1.08–1.20 (3H, m), 1.56–1.73 (5H, m), 1.74 (1H, dd, *J* = 3.2 and 7.2 Hz), 2.50 (1H, d, *J* = 3.2 Hz), 3.72 (1H, d, *J* = 13.6 Hz), 3.79 (3H, s), 4.06 (1H, d, *J* = 13.6 Hz), 6.95–7.01 (2H, m), 7.25 (1H, dd, *J* = 1.2 and 4.8 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.5 ($CH_2$), 25.6 ($CH_2$), 26.1 ($CH_2$), 29.7 (CH), 29.8 ($CH_2$), 30.3 ($CH_2$), 40.6 (CH), 52.7 ($CH_3$), 53.7 ($CH_2$), 54.8 (CH), 75.5 (Cq), 85.7 (Cq), 125.1 (CH), 126.0 (CH), 126.6 (CH), 141.0 (Cq), 153.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2SNa$ $[M+Na]^+$ 326.1191, found 326.1188.

**Conversion of 10 to allenylimines 11. (Scheme 4, Table 3 and Table 4)**

**General procedure for the synthesis of allenylimines 11a-m.**

**Synthesis of 11a. (Scheme 4)**

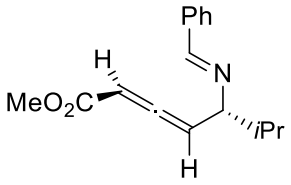
To a stirred solution of 3-aziridinylpropiolate ester **10a** (66.1 mg, 0.22 mmol) in toluene (2.2 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure to give allenylimine **11a** (66.1 mg, quant) as a pale yellow oil.




**11a**

**Methyl 5-(benzylideneamino)-5-cyclohexylpenta-2,3-dienoate (11a)**

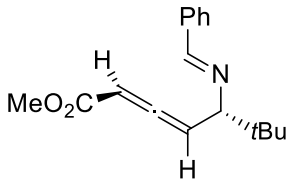
Quantitative yield; pale yellow oil; IR (KBr) 2925, 2851, 1962, 1722, 1643, 1449, 1259, 1161, 756, 694 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.93–1.13 (2H, m), 1.13–1.36 (3H, m), 1.60–1.84 (5H, m), 1.96–2.07 (1H, m), 3.67 (1H, t, *J* = 8.0 Hz), 3.73 (3H, s), 5.64 (1H, d, *J* = 6.0 Hz), 5.84 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.39–7.45 (3H, m), 7.71–7.78 (2H, m), 8.25 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 43.4 (CH), 51.9 ($CH_3$), 75.3 (CH), 88.5 (CH), 97.2 (CH), 128.3 (CH), 128.6 (CH), 130.8 (CH), 136.0 (Cq), 161.1 (CH), 166.4 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1807.




**11b**

**Methyl 5-(benzylideneamino)-6-methylhepta-2,3-dienoate (11b)**

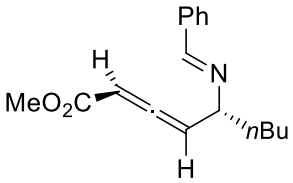
Quantitative yield; pale yellow oil; IR (KBr) 2957, 1962, 1723, 1644, 1599, 1436, 1387, 1259, 1162, 756, 695 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 2.02 (1H, septd, *J* = 6.8 and 7.6 Hz), 3.67 (1H, dd, *J* = 7.6 and 8.0 Hz), 3.73 (3H, s), 5.65 (1H, d, *J* = 6.0 Hz), 5.83 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.39–7.44 (3H, m), 7.72–7.78 (2H, m), 8.27 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 19.0 ($CH_3$), 19.2 ($CH_3$), 34.2 (CH), 51.9 ($CH_3$), 75.9 (CH), 88.5 (CH), 97.1 (CH), 128.3 (CH), 128.6 (CH), 130.8 (CH), 136.1 (Cq), 161.1 (CH), 166.3 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1494, found 258.1489.




**11c**

**Methyl 5-(benzylideneamino)-6,6-dimethylhepta-2,3-dienoate (11c)**

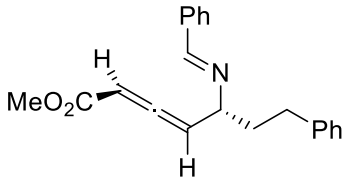
Quantitative yield; pale yellow amorphous; IR (KBr) 2953, 2868, 1961, 1722, 1644, 1438, 1261, 1161, 1029, 809, 753, 693 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 3.60 (1H, d, *J* = 8.4 Hz), 3.72 (3H, s), 5.63 (1H, d, *J* = 6.0 Hz), 5.86 (1H, dd, *J* = 6.0 and 8.4 Hz), 7.39–7.44 (3H, m), 7.73–7.78 (2H, m), 8.26 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.6 ($CH_3$), 25.6 (Cq), 51.9 ($CH_3$), 79.2 (CH), 88.2 (CH), 95.8 (CH), 128.3 (CH), 128.6 (CH), 130.7 (CH), 136.2 (Cq), 161.1 (CH), 166.4 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2Na$ $[M+Na]^+$ 294.1470, found 294.1469.




**11d**

**Methyl 5-(benzylideneamino)nona-2,3-dienoate (11d)**

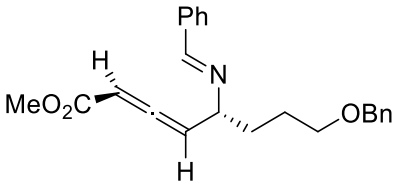
Quantitative yield; pale yellow oil; IR (KBr) 2954, 2859, 1962, 1721, 1642, 1579, 1438, 1378, 1261, 1162, 1027, 872, 805, 757, 694 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 6.8 Hz), 1.30–1.40 (4H, m), 1.79 (2H, dt, *J* = 7.2 and 8.0 Hz), 3.73 (3H, s), 3.98 (1H, q, *J* = 7.2 Hz), 5.67 (1H, d, *J* = 6.0 Hz), 5.82 (1H, dd, *J* = 6.0 and 7.2 Hz), 7.39–7.44 (3H, m), 7.71–7.78 (2H, m), 8.31 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 22.4 ($CH_2$), 28.3 ($CH_2$), 36.6 ($CH_2$), 52.0 ($CH_3$), 69.2 (CH), 89.0 (CH), 98.5 (CH), 128.3 (CH), 128.6 (CH), 130.8 (CH), 136.0 (Cq), 161.0 (CH), 166.2 (Cq), 211.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2Na$ $[M+Na]^+$ 294.1470, found 294.1472.




**11e**

**Methyl 5-(benzylideneamino)-7-phenylhepta-2,3-dienoate (11e)**

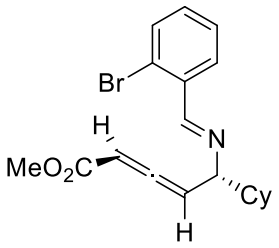
Quantitative yield; pale yellow oil; IR (KBr) 3027, 2949, 2854, 1961, 1719, 1641, 1496, 1437, 1262, 1163, 1029, 755, 696 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 2.13 (2H, q, *J* = 7.6 Hz), 2.73 (2H, t, *J* = 7.6 Hz), 3.74 (3H, s), 4.03 (1H, q, *J* = 7.6 Hz), 5.70 (1H, d, *J* = 6.0 Hz), 5.84 (1H, dd, *J* = 6.0 and 7.6 Hz), 7.15–7.22 (3H, m), 7.25–7.31 (2H, m), 7.38–7.46 (3H, m), 7.72–7.78 (2H, m), 8.29 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 32.2 ($CH_2$), 38.2 ($CH_2$), 52.0 ($CH_3$), 68.2 (CH), 89.2 (CH), 98.3 (CH), 125.9 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 131.0 (CH), 135.9 (Cq), 141.5 (Cq), 161.6 (CH), 166.1 (Cq), 211.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO_2Na$ $[M+Na]^+$ 342.1470, found 342.1469.




**11f**

**Methyl 5-(benzylideneamino)-8-(benzyloxy)octa-2,3-dienoate (11f)**

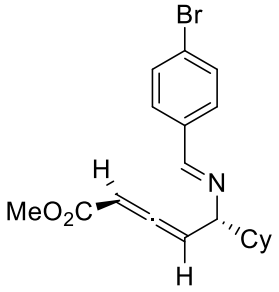
Quantitative yield; pale yellow oil; IR (KBr) 2949, 2855, 1962, 1720, 1641, 1452, 1261, 1163, 1101, 1027, 738, 695 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.61–1.76 (2H, m), 1.84–1.94 (2H, m), 3.51 (2H, t, *J* = 6.4 Hz), 3.72 (3H, s), 4.00 (1H, q, *J* = 7.6 Hz), 4.45 (2H, s), 5.68 (1H, d, *J* = 6.0 Hz), 5.82 (1H, dd, *J* = 6.0 and 7.6 Hz), 7.22–7.37 (5H, m), 7.37–7.46 (3H, m), 7.69–7.75 (2H, m), 8.29 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.4 ($CH_2$), 33.5 ($CH_2$), 52.0 ($CH_3$), 68.9 (CH), 69.9 ($CH_2$), 72.9 ($CH_2$), 89.1 (CH), 98.4 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 128.3 (CH), 128.6 (CH), 130.9 (CH), 135.9 (Cq), 138.5 (Cq), 161.4 (CH), 166.2 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_3Na$ $[M+Na]^+$ 386.1732, found 386.1733.




**11g**

**Methyl 5-(2-bromobenzylideneamino)-5-cyclohexylpenta-2,3-dienoate (11g)**

Quantitative yield; pale yellow oil; IR (KBr) 2925, 2851, 1963, 1721, 1634, 1437, 1259, 1161, 1024, 757 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.95–1.13 (2H, m), 1.13–1.36 (3H, m), 1.62–1.84 (5H, m), 1.96–2.05 (1H, m), 3.73 (3H, s), 3.76 (1H, t, *J* = 8.0 Hz), 5.67 (1H, d, *J* = 6.0 Hz), 5.84 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.26 (1H, dt, *J* = 1.2 and 8.0 Hz), 7.34 (1H, dt, *J* = 1.2 and 8.0 Hz), 7.56 (1H, dd, *J* = 1.2 and 8.0 Hz), 8.00 (1H, dd, *J* = 1.2 and 8.0 Hz), 8.59 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.9 ($CH_2$), 26.1 ($CH_2$), 26.3 ($CH_2$), 29.5 ($CH_2$), 29.7 ($CH_2$), 43.2 (CH), 51.9 ($CH_3$), 75.0 (CH), 88.6 (CH), 97.0 (CH), 124.9 (Cq), 127.5 (CH), 128.9 (CH), 131.8 (CH), 132.9 (CH), 134.4 (Cq), 160.1 (CH), 166.2 (Cq), 211.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}BrNO_2Na$ $[M+Na]^+$ 398.0732, found 398.0731.

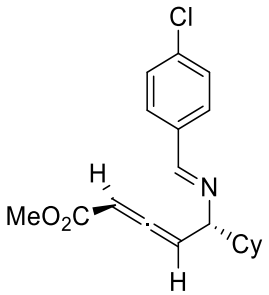



**11h**

**Methyl 5-(4-bromobenzylideneamino)-5-cyclohexylpenta-2,3-dienoate (11h)**

Quantitative yield; pale yellow amorphous; IR (KBr) 2925, 2851, 1962, 1720, 1643, 1589, 1486, 1437, 1259, 1161, 1068, 1011, 821 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.93–1.12 (2H, m), 1.12–1.35 (3H, m), 1.62–1.84 (5H, m), 1.94–2.05 (1H, m), 3.67 (1H, t, *J* = 8.0 Hz), 3.72 (3H, s), 5.64 (1H, d, *J* = 6.0

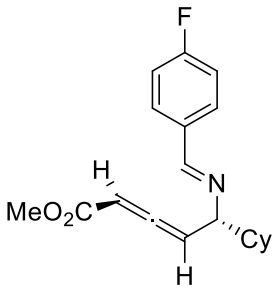
Hz), 5.81 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 7.61 (2H, d, *J* = 8.4 Hz), 8.19 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.4 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 43.3 (CH), 51.9 ($CH_3$), 75.1 (CH), 88.6 (CH), 97.1 (CH), 125.2 (Cq), 129.7 (CH), 131.8 (CH), 134.9 (Cq), 159.8 (CH), 166.3 (Cq), 211.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}BrNO_2Na$ $[M+Na]^+$ 398.0732, found 398.0735.




**11i**

**Methyl 5-(4-chlorobenzylideneamino)-5-cyclohexylpenta-2,3-dienoate (11i)**

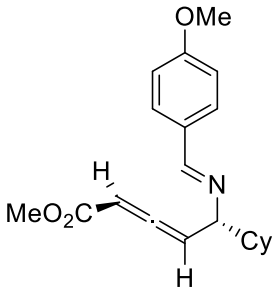
Quantitative yield; pale yellow oil; IR (KBr) 2926, 2851, 1962, 1720, 1643, 1595, 1490, 1437, 1259, 1161, 1088, 1014, 826 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.91–1.11 (2H, m), 1.11–1.36 (3H, m), 1.63–1.83 (5H, m), 1.95–2.04 (1H, m), 3.67 (1H, t, *J* = 8.0 Hz), 3.72 (3H, s), 5.64 (1H, d, *J* = 6.0 Hz), 5.82 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.67 (2H, d, *J* = 8.4 Hz), 8.20 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 43.3 (CH), 51.9 ($CH_3$), 75.1 (CH), 88.5 (CH), 97.1 (CH), 128.8 (CH), 129.4 (CH), 134.4 (Cq), 136.7 (Cq), 159.7 (CH), 166.3 (Cq), 211.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}ClNO_2Na$ $[M+Na]^+$ 354.1237, found 354.1237.




**11j**

**Methyl 5-cyclohexyl-5-(4-fluorobenzylideneamino)penta-2,3-dienoate (11j)**

Quantitative yield; pale yellow oil; IR (KBr) 2925, 2852, 1962, 1719, 1643, 1602, 1508, 1438, 1260, 1229, 1162, 1036, 868, 837, 809 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.92–1.11 (2H, m), 1.11–1.35 (3H, m), 1.63–1.83 (5H, m), 1.96–2.04 (1H, m), 3.66 (1H, t, *J* = 8.0 Hz), 3.72 (3H, s), 5.64 (1H, d, *J* = 6.0 Hz), 5.82 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.06–7.13 (2H, m), 7.71–7.76 (2H, m), 8.20 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 43.3 (CH), 51.9 ($CH_3$), 75.1 (CH), 88.5 (CH), 97.2 (CH), 115.5 (CH, d, *J* = 21.5 Hz), 130.2 (CH, d, *J* = 8.3 Hz), 132.3 (Cq, d, *J* = 2.5 Hz), 159.6 (CH), 164.4 (Cq, d, *J* = 249.4 Hz), 166.3 (Cq), 211.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}FNO_2Na$ $[M+Na]^+$ 338.1532, found 338.1532.

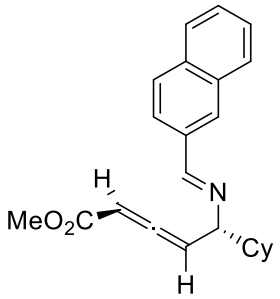



**11k**

**Methyl 5-cyclohexyl-5-(4-methoxybenzylideneamino)penta-2,3-dienoate (11k)**

Quantitative yield; pale yellow amorphous; IR (KBr) 2926, 2851, 1961, 1721, 1644, 1605, 1512, 1448, 1253, 1163, 1032, 833, 757 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.92–1.10 (2H, m), 1.10–1.35 (3H, m), 1.62–1.83 (5H, m), 1.96–2.06 (1H, m), 3.63 (1H, t, *J* = 8.0 Hz), 3.72 (3H, s), 3.84 (3H, s), 5.63 (1H, d, *J* = 6.0 Hz), 5.82 (1H, dd, *J* = 6.0 and 8.0 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 7.68 (2H, d, *J* = 8.4

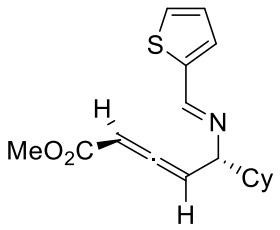
Hz), 8.17 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 43.4 (CH), 51.9 ($CH_3$), 55.3 ($CH_3$), 75.2 (CH), 88.3 (CH), 97.4 (CH), 114.0 (CH), 129.0 (Cq), 129.9 (CH), 160.4 (CH), 161.8 (Cq), 166.4 (Cq), 211.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NO_3Na$ $[M+Na]^+$ 350.1732, found 350.1732.




**11l**

**Methyl 5-cyclohexyl-5-(naphthalen-2-ylmethyleneamino)penta-2,3-dienoate (11l)**

Quantitative yield; pale yellow amorphous; IR (KBr) 2925, 2851, 1961, 1720, 1637, 1438, 1261, 1161, 1033, 860, 822, 747 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.95–1.14 (2H, m), 1.14–1.37 (3H, m), 1.63–1.85 (5H, m), 2.00–2.08 (1H, m), 3.68–3.76 (1H, m), 3.73 (3H, s), 5.66 (1H, d, *J* = 6.0 Hz), 5.88 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.49–7.56 (2H, m), 7.81–8.01 (3H, m), 7.99 (1H, d, *J* = 8.4 Hz), 8.05 (1H, s), 8.40 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 43.4 (CH), 51.9 ($CH_3$), 75.4 (CH), 88.5 (CH), 97.3 (CH), 124.0 (CH), 126.5 (CH), 127.2 (CH), 127.9 (CH), 128.4 (CH), 128.6 (CH), 130.1 (CH), 133.1 (Cq), 133.7 (Cq), 134.8 (Cq), 161.2 (CH), 166.4 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_2Na$ $[M+Na]^+$ 370.1783, found 370.1784.



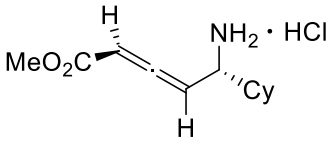
**11m**

**Methyl 5-cyclohexyl-5-(thiophen-2-ylmethyleneamino)penta-2,3-dienoate (11m)**

Quantitative yield; pale yellow oil; IR (KBr) 2925, 2851, 1961, 1720, 1631, 1435, 1259, 1162, 1043, 809, 712 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.86–1.09 (2H, m), 1.09–1.35 (3H, m), 1.61–1.83 (5H, m), 1.94–2.03 (1H, m), 3.62 (1H, t, *J* = 8.0 Hz), 3.73 (3H, s), 5.64 (1H, d, *J* = 6.0 Hz), 5.81 (1H, dd, *J* = 6.0 and 8.0 Hz), 7.07 (1H, dd, *J* = 3.6 and 5.2 Hz), 7.31 (1H, d, *J* = 3.6 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 8.33 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 29.7 ($CH_2$), 29.9 ($CH_2$), 43.3 (CH), 51.9 ($CH_3$), 75.1 (CH), 88.4 (CH), 97.1 (CH), 127.4 (CH), 129.1 (CH), 130.7 (CH), 142.2 (Cq), 154.2 (CH), 166.4 (Cq), 211.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2SNa$ $[M+Na]^+$ 326.1191, found 326.1189.

**Conversion of 11a to 4-nitrobenzenesulfonamide 13. (Scheme 5)**

**Procedure for the synthesis of amine hydrochloride 12.**



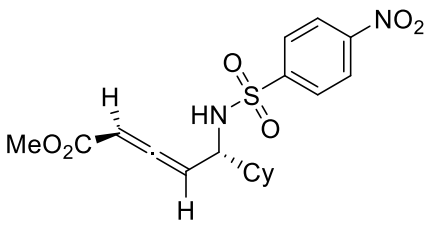
**12**

**Methyl 5-amino-5-cyclohexylpenta-2,3-dienoate hydrochloride (12)**

To a stirred solution of allenylimine **11a** (66.1 mg, 0.22 mmol) in MeOH (5.0 mL) was added 2 N HCl (1.0 mL) at room temperature, and stirring was continued for 10 min at the same temperature. The reaction mixture was washed with AcOEt and concentrated to give amine hydrochloride **12** (47.2 mg, 86%) as a colorless powder; mp 146.2–147.9 °C; IR (KBr) 2925, 2844, 1970, 1720, 1612, 1489, 1438,

1305, 1198, 1166, 908, 810 $cm^{-1}$; $^1$H-NMR (400 MHz, $CD_3OD$) δ 1.04–1.41 (5H, m), 1.66–1.92 (6H, m), 1.61–1.83 (5H, m), 1.94–2.03 (1H, m), 3.70 (1H, dt, *J* = 1.2 and 8.0 Hz), 3.74 (3H, s), 5.85 (1H, dd, *J* = 6.4 and 8.0 Hz), 5.95 (1H, dd, *J* = 1.2 and 6.4 Hz); $^{13}$C-NMR (100 MHz, $CD_3OD$) δ 26.7 ($CH_2$), 26.8 ($CH_2$), 27.0 ($CH_2$), 29.0 ($CH_2$), 30.0 ($CH_2$), 42.1 (CH), 52.8 ($CH_3$), 56.2 (CH), 91.4 (CH), 93.1 (CH), 166.8 (Cq), 213.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}NO_2$ $[M+H]^+$ 210.1494, found 210.1493.

**Procedure for the synthesis of 4-nitrobenzenesulfonamide 13.**




**13**

**Methyl 5-cyclohexyl-5-(4-nitrophenylsulfonamido)penta-2,3-dienoate (13)**

To a stirred solution of amine hydrochloride **12** (23.0 mg, 93.6 μmol) in $CH_2Cl_2$ (0.5 mL) was added NosCl (22.8 mg, 103 μmol) and *i*$Pr_2$NEt (41 μL, 234 μmol) at 0 °C, and stirring was continued for 30 min at room temperature. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (80:20 v/v) as eluent to give 4-nitrobenzenesulfonamide **13** (32.8 mg, 89%) as a colorless plates; mp 145.0–146.2 °C (recrystallized from EtOAc/hexane); IR (KBr) 3290, 2925, 2857, 1965, 1709, 1537, 1438, 1348, 1270, 1166, 1028, 855, 737, 698 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 0.91–1.29 (5H, m), 1.48–1.58 (1H, m), 1.58–1.81 (5H, m), 3.69 (3H, s), 3.84–3.91 (1H, m), 4.86 (1H, d, *J* = 8.4 Hz), 5.43 (1H, t, *J* = 6.4 Hz), 5.58 (1H, dd, *J* = 2.0 and 6.4 Hz), 8.04 (2H, d, *J* = 8.4 Hz), 8.35 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.7 ($CH_2$), 25.7 ($CH_2$), 26.0 ($CH_2$), 28.6 ($CH_2$), 28.8 ($CH_2$), 43.0 (CH), 52.2 ($CH_3$), 57.5 (CH), 90.3 (CH), 95.6 (CH), 124.3 (CH), 128.4

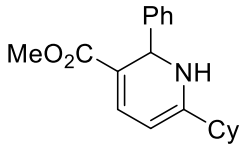
(CH), 146.6 (Cq), 150.0 (Cq), 165.3 (Cq), 211.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_2O_6SNa$ $[M+Na]^+$ 417.1096, found 417.1097.

**X-Ray crystallographic analysis of compound 13.** A colorless chunk crystal having approximate dimensions of 0.60 x 0.20 x 0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 6878 observed reflections ($I > 0.00\sigma(I)$) and 531 variable parameters, and converged (largest parameter shift was 4.66 times its esd) with unweighted and weighted agreement factors of $R = 0.039$ and $R_W = 0.077$. Crystal data for **13**: $C_{18}H_{22}N_2O_6S$, M = 394.44, monoclinic, space group P1 (#1), a = 8.8726(5) Å, b = 10.4814(6) Å, c = 11.8995(7) Å, $\alpha = 71.434(2)^\circ$, $\beta = 69.467(2)^\circ$, $\gamma = 70.435(2)^\circ$, V = 950.83(9) $Å^3$, Z = 2, $D_c = 1.378$ g/$cm^3$, F(000) = 416.00, $\mu$(MoKα) = 2.07 $cm^{-1}$.

# Experiments in Chapter II

**Synthesis of dihydropyridines 15. (Table 5 and Scheme 9)**

**Procedure for the synthesis of dihydropyridine 15a. (Table 5, entry 6)**

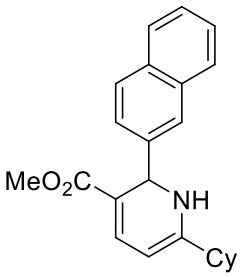



**15a**

**Methyl 6-cyclohexyl-2-phenyl-1,2-dihydropyridine-3-carboxylate (15a)**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (29.7 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (2.6 mg, 9.91 μmol) was successively added to reaction solution. After further stirring was continued for 3 h at 60 °C, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to give 1,2-dehydropyridine **15a** as a crude. The NMR yield was determined as 99% from $^1$H-NMR spectrum by the addition of pyrazine (8.0 mg, 0.10 mmol) as an internal standard. $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.08–1.32 (5H, m), 1.64–1.72 (1H, m), 1.72–1.86 (4H, m), 1.90–2.01 (1H, m), 3.65 (3H, s), 4.67 (1H, brs), 4.75 (1H, dd, *J* = 2.0 and 6.8 Hz), 5.60 (1H, d, *J* = 3.2 Hz), 7.20–7.36 (5.5H, m, **15a**+$PPh_3$), 7.40–7.45 (2H, m), 8.60 (4.05H, s, pyrazine).

**Procedure for the synthesis of dihydropyridine 15l. (Sceme 9)**




**15l**

**Methyl 6-cyclohexyl-2-(naphthalen-2-yl)-1,2-dihydropyridine-3-carboxylate (15l)**

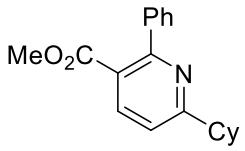
To a stirred solution of 3-aziridinylpropiolate ester **10l** (34.7 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (2.6 mg, 9.91 μmol) was successively added to reaction solution. After further stirring was continued for 3 h at 60 °C, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was washed with hexane to give 1,2-dehydropyridine **15l** (26.0 mg, 75%) as a yellow powder; IR (KBr) 3346, 2928, 2852, 1669, 1556, 1474, 1434, 1294, 1228, 1096, 907, 856, 734 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.08–1.32 (5H, m), 1.62–1.71 (1H, m), 1.71–1.86 (4H, m), 1.90–2.02 (1H, m), 3.64 (3H, s), 4.75 (1H, brs), 4.79 (1H, d, *J* = 6.4 Hz), 5.76 (1H, d, *J* = 3.2 Hz), 7.31 (1H, d, *J* = 6.4 Hz), 7.39–7.47 (2H, m), 7.65 (1H, d, *J* = 8.4 Hz), 7.74–7.82 (4H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.9 ($CH_2$), 26.1 ($CH_2$), 26.2 ($CH_2$), 31.4 ($CH_2$), 31.4 ($CH_2$), 43.3 (CH), 51.0 ($CH_3$), 54.9 (CH), 90.5 (CH), 109.8 (Cq), 124.4 (CH), 125.0 (CH), 125.7 (CH), 125.9 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 133.1 (Cq), 133.3 (Cq), 136.7 (CH), 142.3 (Cq), 157.3 (Cq), 167.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{26}NO_2$ $[M+H]^+$ 348.1964, found 348.1967.

**Synthesis of trisubstituted pyridines 16. (Table 6 and Table 7)**

**General procedure for the one-pot synthesis of trisubstituted pyridines 16a-m.**

**Synthesis of 16a. (Table 6, entry 5)**

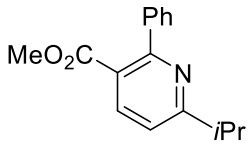
To a stirred solution of 3-aziridinylpropiolate ester **10a** (40.5 mg, 0.14 mmol) in toluene (1.4 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (3.6 mg, 13.6 μmol) was successively added to reaction solution. After further stirring was continued for 3 h at 60 °C, the mixture was added AcOH (11.7 μL, 0.20 mmol) at the same temperature. Stirring was continued for 10 h at the same temperature, and the solvent was evaporated under the reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (95:5 v/v) as eluent to give trisubstituted pyridine **16a** (30.9 mg, 77%) as a colorless oil.




**16a**

**Methyl 6-cyclohexyl-2-phenylnicotinate (16a)**

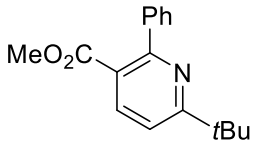
Yield 77%; colorless oil; IR (KBr) 2926, 2852, 1723, 1587, 1430, 1395, 1289, 1137, 1102, 1051, 769, 699 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.29 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.42 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.55 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.71–1.81 (1H, m), 1.81–1.92 (2H, m), 1.97–2.06 (2H, m), 2.82 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.67 (3H, s), 7.18 (1H, d, *J* = 8.0 Hz), 7.37–7.46 (3H, m), 7.52–7.58 (2H, m), 8.02 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.7 ($CH_2$), 46.6 (CH), 52.1 ($CH_3$), 118.5 (CH), 124.1 (Cq), 128.0 (CH), 128.4 (CH), 128.7 (CH), 138.2 (CH), 140.6 (Cq), 158.1 (Cq), 168.8 (Cq), 168.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO_2Na$ $[M+Na]^+$ 318.1470, found 318.1469.




**16b**

**Methyl 6-isopropyl-2-phenylnicotinate (16b)**

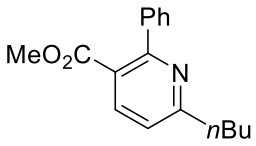
Yield 77%; colorless oil; IR (KBr) 2964, 2871, 1732, 1588, 1430, 1394, 1288, 1140, 1051, 844, 810, 769, 700 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.34 (6H, d, *J* = 6.8 Hz), 3.17 (1H, sept, *J* = 6.8 Hz), 3.67 (3H, s), 7.20 (1H, d, *J* = 8.0 Hz), 7.38–7.45 (3H, m), 7.53–7.59 (2H, m), 8.02 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 22.3 ($CH_3$), 36.5 (CH), 52.1 ($CH_3$), 118.2 (CH), 124.2 (Cq), 128.0 (CH), 128.4 (CH), 128.7 (CH), 138.3 (CH), 140.5 (Cq), 158.0 (Cq), 168.9 (Cq), 169.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_2Na$ $[M+Na]^+$ 278.1157, found 278.1160.




**16c**

**Methyl 6-+-butyl-2-phenylnicotinate (16c)**

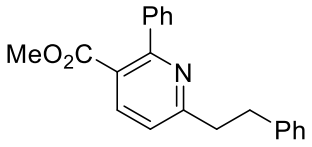
Yield 75%; colorless plates; mp 94.7–96.4 °C (recrystallized from EtOAc/hexane); IR (KBr) 2955, 2867, 1724, 1588, 1430, 1382, 1282, 1149, 1050, 770, 700 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s), 3.69 (3H, s), 7.34 (1H, d, *J* = 8.0 Hz), 7.38–7.46 (3H, m), 7.56–7.63 (2H, m), 8.00 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 30.0 ($CH_2$), 37.9 (CH), 52.1 ($CH_3$), 116.7 (CH), 123.7 (Cq), 127.9 (CH), 128.5 (CH), 128.9 (CH), 138.1 (CH), 140.5 (Cq), 157.0 (Cq), 169.2 (Cq), 171.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2Na$ $[M+Na]^+$ 292.1313, found 292.1315.




**16d**

**Methyl 6-butyl-2-phenylnicotinate (16d)**

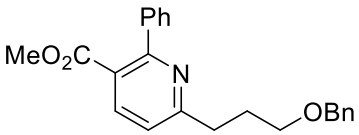
Yield 66%; colorless oil; IR (KBr) 2954, 2860, 1723, 1589, 1460, 1431, 1392, 1290, 1209, 1135, 1115, 1051, 768, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 6.8 Hz), 1.41 (2H, qt, *J* = 6.8 and 7.6 Hz), 1.74 (2H, tt, *J* = 7.6 and 8.0 Hz), 2.89 (2H, t, *J* = 8.0 Hz), 3.67 (3H, s), 7.18 (1H, d, *J* = 8.0 Hz), 7.38–7.45 (3H, m), 7.50–7.54 (2H, m), 8.20 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 13.9 ($CH_3$), 22.5 ($CH_2$), 31.7 ($CH_2$), 38.2 ($CH_2$), 52.1 ($CH_3$), 120.5 (CH), 124.1 (Cq), 128.1 (CH), 128.4 (CH), 128.6 (CH), 138.2 (CH), 140.5 (Cq), 158.5 (Cq), 165.0 (Cq), 168.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2Na$ $[M+Na]^+$ 292.1313, found 292.1312.




**16e**

**Methyl 6-phenethyl-2-phenylnicotinate (16e)**

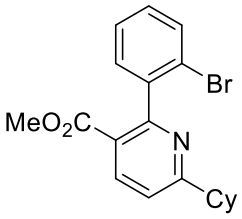
Yield 73%; colorless oil; IR (KBr) 3027, 2950, 2857, 1717, 1588, 1496, 1430, 1392, 1291, 1207, 1135, 1104, 1052, 808, 769 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 3.12 (2H, dt, *J* = 2.8 and 8.4 Hz), 3.21 (2H, dt, *J* = 2.8 and 8.4 Hz), 3.68 (3H, s), 7.10 (1H, d, *J* = 8.0 Hz), 7.17–7.22 (3H, m), 7.26–7.30 (2H, m), 7.39–7.47 (3H, m), 7.52–7.56 (2H, m), 8.00 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 35.4 ($CH_2$), 40.0 ($CH_2$), 52.1 ($CH_3$), 120.8 (CH), 124.3 (Cq), 126.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 138.2 (CH), 140.3 (Cq), 141.2 (Cq), 158.6 (Cq), 163.6 (Cq), 168.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{19}NO_2Na$ $[M+Na]^+$ 340.1313, found 340.1313.




**16f**

**Methyl 6-[3-(benzyloxy)propyl]-2-phenylnicotinate (16f)**

Yield 65%; colorless oil; IR (KBr) 3030, 2949, 2856, 1717, 1588, 1559, 1456, 1431, 1393, 1290, 1207, 1108, 739, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 2.12 (2H, tt, *J* = 6.4 and 7.6 Hz), 2.99 (2H, t, *J* = 7.6 Hz), 3.55 (2H, t, *J* = 6.4 Hz), 3.68 (3H, s), 4.51 (2H, s), 7.17 (1H, d, *J* = 8.0 Hz), 7.26–7.35 (5H, m), 7.38–7.45 (3H, m), 7.50–7.55 (2H, m), 8.00 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 29.3 ($CH_2$), 35.0 ($CH_2$), 52.1 ($CH_3$), 69.5 ($CH_2$), 72.9 ($CH_2$), 120.7 (CH), 124.2 (Cq), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 138.2 (CH), 138.5 (Cq), 140.4 (Cq), 158.5 (Cq), 164.1 (Cq), 168.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_3Na$ $[M+Na]^+$ 384.1576, found 384.1578.

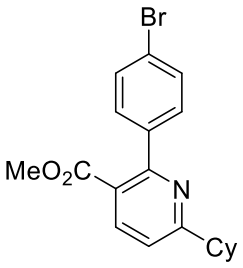



**16g**

**Methyl 2-(2-bromophenyl)-6-cyclohexylnicotinate (16g)**

Yield 72%; colorless oil; IR (KBr) 2926, 2852, 1733, 1584, 1432, 1394, 1276, 1202, 1142, 1065, 1025, 807, 759 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.27 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.41 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.52 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.71–1.79 (1H, m), 1.81–1.90 (2H, m), 1.98–2.06 (2H, m), 2.84 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.68 (3H, s), 7.22–7.29 (2H, m), 7.33–7.42 (2H, m), 7.61 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.9 ($CH_2$), 26.3 ($CH_2$), 32.7 ($CH_2$), 46.6 (CH), 52.2 ($CH_3$), 119.3 (CH), 122.2 (Cq), 123.8 (Cq), 127.2 (CH), 129.3 (CH), 130.1 (CH), 132.2 (CH), 138.6 (CH), 142.2 (Cq), 158.5 (Cq), 166.4 (Cq), 169.6 (Cq); HRMS (ESI) *m/z* calcd

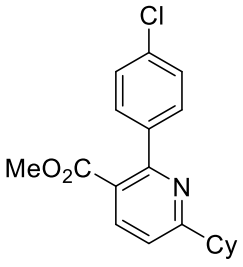
for $C_{19}H_{20}BrNO_2Na$ $[M+Na]^+$ 396.0575, found 396.0575.




**16h**

**Methyl 2-(4-bromophenyl)-6-cyclohexylnicotinate (16h)**

Yield 85%; colorless needles; mp 84.9–86.8 °C (recrystallized from EtOAc/hexane); IR (KBr) 2933, 2855, 1716, 1583, 1434, 1400, 1291, 1128, 1068, 1011, 838, 799, 735 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.28 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.42 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.49–1.62 (2H, m), 1.72–1.80 (1H, m), 1.82–1.91 (2H, m), 1.94–2.04 (2H, m), 2.80 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.71 (3H, s), 7.19 (1H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 8.04 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.6 ($CH_2$), 46.6 (CH), 52.2 ($CH_3$), 119.0 (CH), 122.9 (Cq), 123.9 (Cq), 130.4 (CH), 131.2 (CH), 138.5 (CH), 139.5 (Cq), 157.1 (Cq), 168.4 (Cq), 169.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}BrNO_2Na$ $[M+Na]^+$ 396.0575, found 396.0578.

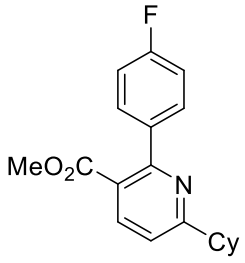



**16i**

**Methyl 2-(4-chlorophenyl)-6-cyclohexylnicotinate (16i)**

Yield 71%; colorless needles; mp 84.1–85.6 °C (recrystallized from EtOAc/hexane); IR (KBr) 2934, 2856, 1716, 1584, 1434, 1402, 1289, 1129, 1089, 1014, 839, 799, 741 $cm^{-1}$; $^1$H-NMR (400 MHz,

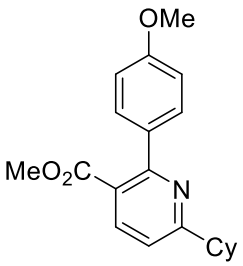
$CDCl_3$) δ 1.28 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.42 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.54 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.72–1.80 (1H, m), 1.82–1.91 (2H, m), 1.95–2.03 (2H, m), 2.81 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.71 (3H, s), 7.19 (1H, d, *J* = 8.0 Hz), 7.39 (2H, d, *J* = 8.4 Hz), 7.49 (2H, d, *J* = 8.4 Hz), 8.04 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.6 ($CH_2$), 46.6 (CH), 52.2 ($CH_3$), 118.9 (CH), 123.9 (Cq), 128.2 (CH), 130.1 (CH), 134.6 (Cq), 138.5 (CH), 139.0 (Cq), 157.0 (Cq), 168.4 (Cq), 169.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}ClNO_2Na$ $[M+Na]^+$ 352.1080, found 352.1079.




**16j**

**Methyl 6-cyclohexyl-2-(4-fluorophenyl)nicotinate (16j)**

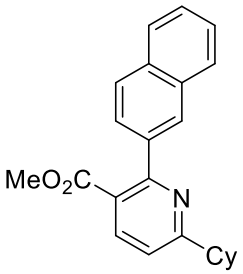
Yield 74%; colorless oil; IR (KBr) 2927, 2852, 1732, 1581, 1510, 1455, 1288, 1137, 1101, 1049, 844, 800 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.28 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.42 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.54 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.72–1.80 (1H, m), 1.82–1.90 (2H, m), 1.96–2.04 (2H, m), 2.81 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.70 (3H, s), 7.11 (2H, t, *J* = 8.4 Hz), 7.18 (1H, d, *J* = 8.0 Hz), 7.53 (2H, dd, *J* = 5.6 and 8.4 Hz), 8.03 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.7 ($CH_2$), 46.6 (CH), 52.2 ($CH_3$), 115.0 (CH, d, *J* = 21.4 Hz), 118.7 (CH), 123.9 (Cq), 130.6 (CH, d, *J* = 8.3 Hz), 136.6 (Cq, d, *J* = 2.5 Hz), 138.5 (CH), 157.1 (Cq), 163.1 (Cq, d, *J* = 246.2 Hz), 168.6 (Cq), 168.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}FNO_2Na$ $[M+Na]^+$ 336.1376, found 336.1375.




**16k**

**Methyl 6-cyclohexyl-2-(4-methoxyphenyl)nicotinate (16k)**

Yield 67%; colorless needles; mp 90.0–91.2 °C (recrystallized from EtOAc/hexane); IR (KBr) 2931, 2851, 1714, 1585, 1514, 1435, 1390, 1297, 1249, 1173, 1139, 1028, 843, 798 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.28 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.41 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.55 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.71–1.81 (1H, m), 1.81–1.90 (2H, m), 1.98–2.04 (2H, m), 2.80 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.71 (3H, s), 3.85 (3H, s), 6.95 (2H, d, *J* = 8.4 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.98 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.7 ($CH_2$), 46.6 (CH), 52.1 ($CH_3$), 55.3 ($CH_3$), 113.6 (CH), 118.1 (CH), 123.8 (Cq), 130.1 (CH), 133.0 (Cq), 138.2 (CH), 157.5 (Cq), 160.1 (Cq), 168.6 (Cq), 169.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_3Na$ $[M+Na]^+$ 348.1576, found 348.1575.

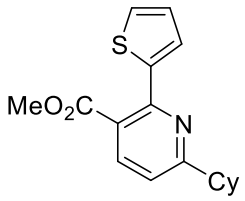



**16l**

**Methyl 6-cyclohexyl-2-(naphthalen-2-yl)nicotinate (16l)**

Yield 68%; colorless needles; mp 67.4–68.7 °C (recrystallized from EtOAc/hexane); IR (KBr) 2926, 2852, 1731, 1583, 1431, 1397, 1288, 1136, 1096, 1056, 902, 822, 800, 745 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.30 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.43 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.58 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.72–1.81 (1H, m), 1.83–1.92 (2H, m), 1.99–2.07 (2H, m), 2.86 (1H, tt, *J* = 3.6 and 11.6

Hz), 3.64 (3H, s), 7.22 (1H, d, *J* = 8.0 Hz), 7.47–7.53 (2H, m), 7.65 (1H, dd, *J* = 1.2 and 8.0 Hz), 7.83–7.93 (3H, m), 8.04–8.08 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.7 ($CH_2$), 46.7 (CH), 52.2 ($CH_3$), 118.6 (CH), 124.4 (Cq), 126.1 (CH), 126.3 (CH), 126.6 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 133.2 (CH), 133.3 (Cq), 138.0 (Cq), 138.4 (CH), 158.0 (Cq), 168.9 (Cq), 168.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_2Na$ $[M+Na]^+$ 368.1626, found 368.1629.




**16m**

**Methyl 6-cyclohexyl-2-(thiophen-2-yl)nicotinate (16m)**

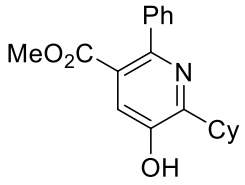
Yield 60%; colorless oil; IR (KBr) 2926, 2852, 1731, 1583, 1434, 1388, 1285, 1137, 1097, 990, 821, 795, 706 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.29 (1H, tq, *J* = 3.2 and 12.4 Hz), 1.42 (2H, tq, *J* = 3.2 and 12.4 Hz), 1.56 (2H, dq, *J* = 3.2 and 12.4 Hz), 1.72–1.80 (1H, m), 1.82–1.91 (2H, m), 1.94–2.02 (2H, m), 2.76 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.86 (3H, s), 7.06 (1H, t, *J* = 4.8 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 7.37 (1H, d, *J* = 4.8 Hz), 7.41 (1H, d, *J* = 4.8 Hz), 7.84 (1H, d, *J* = 8.0 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.4 ($CH_2$), 32.5 ($CH_2$), 46.2 (CH), 52.4 ($CH_3$), 118.5 (CH), 122.8 (Cq), 127.3 (CH), 127.5 (CH), 128.2 (CH), 137.8 (CH), 143.6 (Cq), 149.8 (Cq), 168.3 (Cq), 169.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2SNa$ $[M+Na]^+$ 324.1034, found 324.1038.

**Synthesis of tetrasubstituted pyridines 17. (Table 6, Table 8)**

**General procedure for the one-pot synthesis of tetrasubstituted pyridines 17a-m.**

**Synthesis of 17a. (Table 6, entry 8)**

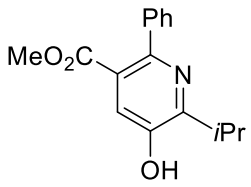
To a stirred solution of 3-aziridinylpropiolate ester **10a** (40.5 mg, 0.14 mmol) in toluene (1.4 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (3.6 mg, 13.6 μmol) was successively added to reaction solution. After further stirring was continued for 3 h at 60 °C, the reaction mixture was cooled to 0 °C, and stirring was continued for 10 h under $O_2$ (1 atm) at the same temperature. The solvent was evaporated under the reduced pressure, and the residue was chromatographed on silica gel with hexane-AcOEt (80:20 v/v) as eluent to give tetrasubstituted pyridine **17a** (33.8 mg, 80%) as a colorless solid.




**17a**

**Methyl 6-cyclohexyl-5-hydroxy-2-phenylnicotinate (17a)**

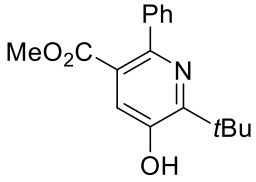
Yield 80%; colorless needles; mp 126.0–127.1 °C (recrystallized from EtOAc/hexane); IR (KBr) 3399, 2928, 2847, 1739, 1688, 1589, 1436, 1232, 1098, 894, 754, 702 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.50 (3H, m), 1.69–1.81 (3H, m), 1.82–1.90 (4H, m), 3.05 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.67 (3H, s), 5.36 (1H, brs), 7.33–7.43 (3H, m), 7.45 (1H, s), 7.50–7.55 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.7 ($CH_2$), 40.0 (CH), 52.3 ($CH_3$), 123.3 (CH), 124.0 (Cq), 127.9 (CH), 127.9 (CH), 128.7 (CH), 140.2 (Cq), 147.8 (Cq), 150.1 (Cq), 156.4 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO_3Na$ $[M+Na]^+$ 334.1419, found 334.1424.




**17b**

**Methyl 5-hydroxy-6-isopropyl-2-phenylnicotinate (17b)**

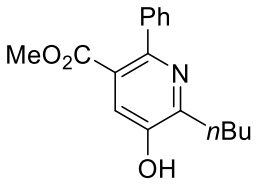
Yield 81%; colorless plates; mp 152.2–153.9 °C (recrystallized from EtOAc/hexane); IR (KBr) 2952, 2874, 2612, 1726, 1584, 1439, 1335, 1249, 1226, 1174, 1099, 1059, 900, 806, 780, 696 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, d, *J* = 6.8 Hz), 3.43 (1H, sept, *J* = 6.8 Hz), 3.67 (3H, s), 5.86 (1H, brs), 7.32–7.42 (3H, m), 7.44 (1H, s), 7.50–7.55 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 20.6 ($CH_3$), 30.1 (CH), 52.3 ($CH_3$), 123.4 (CH), 124.2 (Cq), 127.8 (CH), 127.9 (CH), 128.7 (CH), 140.1 (Cq), 148.0 (Cq), 150.0 (Cq), 157.3 (Cq), 169.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_3Na$ $[M+Na]^+$ 294.1106, found 294.1103.




**17c**

**Methyl 6-*tert*-butyl-5-hydroxy-2-phenylnicotinate (17c)**

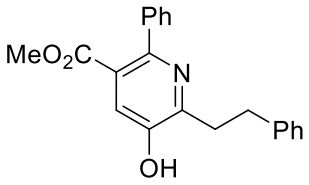
Yield 67%; colorless plates; mp 188.4–190.2 °C (recrystallized from EtOAc/hexane); IR (KBr) 3439, 3383, 2963, 2868, 1693, 1594, 1442, 1403, 1322, 1268, 1196, 1032, 900, 799, 706 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 3.69 (3H, s), 5.84 (1H, brs), 7.33–7.43 (3H, m), 7.46 (1H, s), 7.54–7.59 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 28.3 ($CH_3$), 38.1 (Cq), 52.3 ($CH_3$), 124.3 (Cq), 124.6 (CH), 127.9 (CH), 128.0 (CH), 128.8 (CH), 140.1 (Cq), 148.8 (Cq), 148.8 (Cq), 157.7 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$ 308.1263, found 308.1264.




**17d**

**Methyl 6-butyl-5-hydroxy-2-phenylnicotinate (17d)**

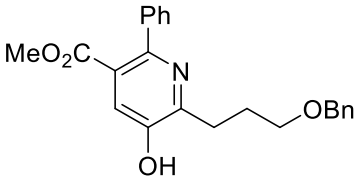
Yield 70%; colorless needles; mp 116.2–117.4 °C (recrystallized from EtOAc/hexane); IR (KBr) 2932, 2861, 2603, 1733, 1583, 1444, 1222, 1162, 1109, 1079, 1032, 797, 702 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 1.43 (2H, sext, *J* = 7.6 Hz), 1.75 (2H, tt, *J* = 7.6 and 8.0 Hz), 2.90 (2H, t, *J* = 8.0 Hz), 3.66 (3H, s), 5.29 (1H, brs), 7.33–7.42 (3H, m), 7.45 (1H, s), 7.45–7.50 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 13.9 ($CH_3$), 22.8 ($CH_2$), 30.5 ($CH_2$), 32.1 ($CH_2$), 52.2 ($CH_3$), 123.4 (CH), 124.6 (Cq), 127.9 (CH), 128.0 (CH), 128.6 (CH), 139.8 (Cq), 149.2 (Cq), 150.1 (Cq), 153.7 (Cq), 168.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$ 308.1263, found 308.1260.




**17e**

**Methyl 5-hydroxy-6-phenethyl-2-phenylnicotinate (17e)**

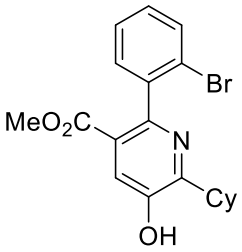
Yield 75%; colorless plates; mp 128.2–129.7 °C (recrystallized from EtOAc/hexane); IR (KBr) 3026, 2945, 2868, 2629, 1733, 1585, 1413, 1321, 1224, 1172, 1105, 1033, 751, 699 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 3.06 (2H, dt, *J* = 2.8 and 8.4 Hz), 3.22 (2H, dt, *J* = 2.8 and 8.4 Hz), 3.64 (3H, s), 6.85 (1H, brs), 7.16–7.27 (5H, m), 7.27–7.38 (4H, m), 7.41–7.46 (2H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 34.3 ($CH_2$), 34.3 ($CH_2$), 52.2 ($CH_3$), 123.7 (CH), 124.9 (Cq), 126.0 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 139.6 (Cq), 141.6 (Cq), 149.3 (Cq), 150.1 (Cq), 152.3 (Cq), 168.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{19}NO_3Na$ $[M+Na]^+$ 356.1263, found 356.1261.




**17f**

**Methyl 6-[3-(benzyloxy)propyl]-5-hydroxy-2-phenylnicotinate (17f)**

Yield 69%; colorless oil; IR (KBr) 3031, 2949, 2859, 1716, 1588, 1436, 1409, 1225, 1108, 1032, 905, 739, 698 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 2.09 (2H, tt, *J* = 6.4 and 7.6 Hz), 3.05 (2H, t, *J* = 7.6 Hz), 3.54 (1H, t, *J* = 6.4 Hz), 3.67 (3H, s), 4.61 (2H, s), 7.32–7.42 (8H, m), 7.44–7.49 (2H, m), 7.56 (1H, s), 7.76 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 27.9 ($CH_2$), 28.6 ($CH_2$), 52.2 ($CH_3$), 68.4 ($CH_2$), 73.1 ($CH_2$), 124.8 (CH), 125.6 (Cq), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 137.0 (Cq), 140.1 (Cq), 150.0 (Cq), 150.4 (Cq), 151.1 (Cq), 168.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_4Na$ $[M+Na]^+$ 400.1525, found 400.1524.

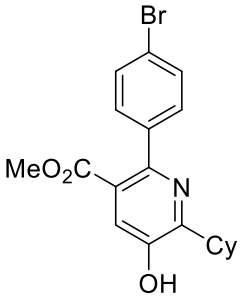



**17g**

**Methyl 2-(2-bromophenyl)-6-cyclohexyl-5-hydroxynicotinate (17g)**

Yield 58%; colorless needles; mp 147.1–148.3 °C (recrystallized from EtOAc/hexane); IR (KBr) 2931, 2901, 2846, 1736, 1577, 1431, 1408, 1224, 1149, 1106, 1054, 1005, 803, 753 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.21–1.48 (3H, m), 1.65–1.79 (3H, m), 1.80–1.89 (4H, m), 3.07 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.66 (3H, s), 5.56 (1H, brs), 7.18–7.25 (1H, m), 7.32–7.39 (2H, m), 7.58 (1H, d, *J* = 8.4 Hz), 7.66 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25.9 ($CH_2$), 26.5 ($CH_2$), 30.7 ($CH_2$), 40.3 (CH), 52.3 ($CH_3$), 122.9 (Cq), 123.5 (CH), 124.2 (Cq), 127.0 (CH), 129.0 (CH), 130.7 (CH), 132.1 (CH), 141.9 (Cq), 148.4 (Cq), 150.3 (Cq), 157.1 (Cq), 167.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}BrNO_3Na$

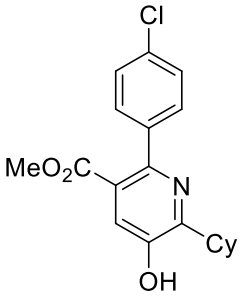
$[M+Na]^+$ 412.0524, found 412.0524.




**17h**

**Methyl 2-(4-bromophenyl)-6-cyclohexyl-5-hydroxynicotinate (17h)**

Yield 78%; colorless needles; mp 188.1–189.0 °C (recrystallized from EtOAc/hexane); IR (KBr) 2930, 2852, 1715, 1594, 1437, 1414, 1244, 1108, 1016, 794 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.49 (3H, m), 1.63–1.79 (3H, m), 1.80–1.91 (4H, m), 3.05 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.70 (3H, s), 5.55 (1H, brs), 7.39 (2H, d, *J* = 8.4 Hz), 7.46 (1H, s), 7.52 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.8 ($CH_2$), 40.0 (CH), 52.4 ($CH_3$), 122.4 (Cq), 123.5 (CH), 123.8 (Cq), 130.5 (CH), 131.0 (CH), 139.2 (Cq), 147.9 (Cq), 149.2 (Cq), 156.6 (Cq), 168.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}BrNO_3Na$ $[M+Na]^+$ 412.0524, found 412.0520.

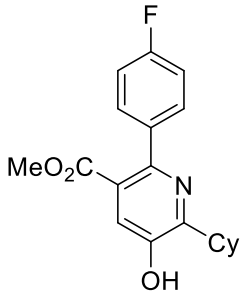



**17i**

**Methyl 2-(4-chlorophenyl)-6-cyclohexyl-5-hydroxynicotinate (17i)**

Yield 72%; colorless plates; mp 178.8–180.0 °C (recrystallized from EtOAc/hexane); IR (KBr) 2932, 2854, 1716, 1590, 1438, 1415, 1319, 1245, 1156, 1110, 1019, 843, 795, 746 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.48 (3H, m), 1.65–1.79 (3H, m), 1.80–1.90 (4H, m), 3.04 (1H, tt, *J* = 3.6 and 11.6

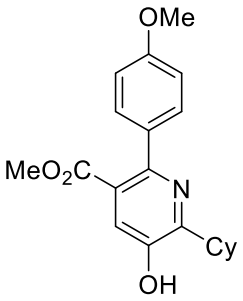
Hz), 3.70 (3H, s), 5.40 (1H, brs), 7.36 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 7.47 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.8 ($CH_2$), 40.0 (CH), 52.4 ($CH_3$), 123.5 (CH), 123.8 (Cq), 128.1 (CH), 130.1 (CH), 134.1 (Cq), 138.7 (Cq), 148.0 (Cq), 149.1 (Cq), 156.7 (Cq), 168.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}ClNO_3Na$ $[M+Na]^+$ 368.1029, found 368.1029.




**17j**

**Methyl 6-cyclohexyl-2-(4-fluorophenyl)-5-hydroxynicotinate (17j)**

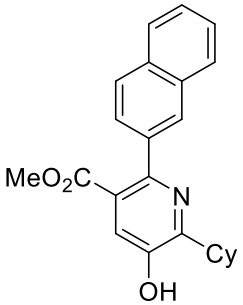
Yield 72%; colorless plates; mp 161.9–163.3 °C (recrystallized from EtOAc/hexane); IR (KBr) 3420, 2930, 2844, 1685, 1600, 1513, 1441, 1415, 1267, 1218, 1157, 1009, 844, 796 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.20–1.48 (3H, m), 1.65–1.79 (3H, m), 1.80–1.89 (4H, m), 3.07 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.69 (3H, s), 6.18 (1H, brs), 7.06 (2H, t, *J* = 8.4 Hz), 7.44 (1H, s), 7.48 (2H, dd, *J* = 5.6 and 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.8 ($CH_2$), 40.0 (CH), 52.4 ($CH_3$), 114.8 (CH, d, *J* = 21.5 Hz), 123.5 (CH), 123.8 (Cq), 130.5 (CH, d, *J* = 7.8 Hz), 136.3 (Cq, d, *J* = 3.4 Hz), 147.8 (Cq), 149.3 (Cq), 156.5 (Cq), 162.8 (Cq, d, *J* = 245.7 Hz), 169.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}FNO_3Na$ $[M+Na]^+$ 352.1325, found 352.1322.




**17k**

**Methyl 6-cyclohexyl-5-hydroxy-2-(4-methoxyphenyl)nicotinate (17k)**

Yield 64%; colorless needles; mp 174.2–174.6 °C (recrystallized from EtOAc/hexane); IR (KBr) 3245, 2923, 2845, 1690, 1592, 1517, 1418, 1252, 1175, 1113, 1036, 832 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.48 (3H, m), 1.69–1.81 (3H, m), 1.81–1.90 (4H, m), 3.03 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.71 (3H, s), 3.84 (3H, s), 5.28 (1H, brs), 6.93 (2H, d, *J* = 8.4 Hz), 7.41 (1H, s), 7.48 (2H, d, *J* = 8.4 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.8 ($CH_2$), 40.0 (CH), 52.3 ($CH_3$), 55.3 ($CH_3$), 113.4 (CH), 123.4 (CH), 123.6 (Cq), 130.0 (CH), 132.8 (Cq), 147.3 (Cq), 149.8 (Cq), 156.1 (Cq), 159.6 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_4Na$ $[M+Na]^+$ 364.1525, found 364.1524.

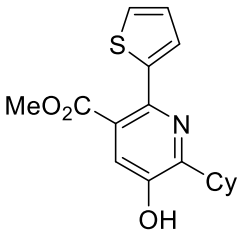



**17l**

**Methyl 6-cyclohexyl-5-hydroxy-2-(naphthalen-2-yl)nicotinate (17l)**

Yield 83%; colorless needles; mp 183.7–185.4 °C (recrystallized from EtOAc/hexane); IR (KBr) 3248, 2928, 2847, 1693, 1586, 1432, 1406, 1268, 1242, 1101, 743 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.50 (3H, m), 1.70–1.84 (3H, m), 1.84–1.92 (4H, m), 3.07 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.64 (3H, s), 5.43 (1H, brs), 7.46–7.52 (3H, m), 7.65 (1H, d, *J* = 8.4 Hz), 7.83–7.92 (3H, m), 8.00 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.5 ($CH_2$), 30.7 ($CH_2$), 40.1 (CH), 52.4 ($CH_3$), 123.4

(CH), 124.2 (Cq), 126.0 (CH), 126.1 (CH), 126.9 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 133.0 (Cq), 133.2 (Cq), 137.7 (Cq), 147.9 (Cq), 149.9 (Cq), 156.6 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_3Na$ $[M+Na]^+$ 384.1576, found 384.1573.



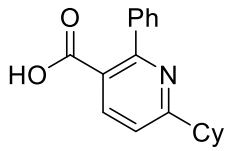

**17m**

**Methyl 6-cyclohexyl-5-hydroxy-2-(thiophen-2-yl)nicotinate (17m)**

Yield 63%; colorless plates; mp 124.1–125.1 °C (recrystallized from EtOAc/hexane); IR (KBr) 3231, 2925, 28550, 1684, 1585, 1442, 1403, 1285, 1077, 884, 849, 777, 711 $cm^{-1}$;

δ 1.26–1.48 (3H, m), 1.66–1.79 (3H, m), 1.82–1.92 (4H, m), 2.99 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.85 (3H, s), 5.17 (1H, brs), 7.03 (1H, dd, *J* = 3.6 and 5.2 Hz), 7.26 (1H, d, *J* = 3.6 Hz), 7.30 (1H, s), 7.35 (1H, d, *J* = 5.2 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.5 ($CH_2$), 30.9 ($CH_2$), 39.7 (CH), 52.6 ($CH_3$), 123.0 (CH), 123.0 (Cq), 126.1 (CH), 127.2 (CH), 127.3 (CH), 142.6 (Cq), 143.6 (Cq), 147.3 (Cq), 155.8 (Cq), 168.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3SNa$ $[M+Na]^+$ 340.0983, found 340.0984.

**Procedure for the synthesis of nicotinic acid 18. (Scheme 11)**




**18**

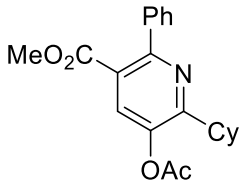
**6-Cyclohexyl-2-phenylnicotinic acid (18)**

To a stirred solution of trisubstituted pyridine **16a** (49.2 mg, 0.17 mmol) in MeOH (1.0 mL) was added 10% aqueous NaOH (0.4 mL) at room temperature, and stirring was continued for 12 h at 60 °C. The reaction mixture was diluted with $Et_2O$ and extracted with 10% aqueous NaOH. The combined aqueous layers were added 2 N HCl and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure to give nicotinic acid **18** (45.2 mg, 96%) as a colorless plates; mp 185.1–186.9 °C (recrystallized from $CHCl_3$); IR (KBr) 3442, 2927, 2851, 1709, 1588, 1401, 1286, 1150, 1108, 811, 765, 697 $cm^{-1}$; $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 1.25 (1H, tq, *J* = 3.2 and 12.8 Hz), 1.38 (2H, tq, *J* = 3.2 and 12.8 Hz), 1.54 (2H, tq, *J* = 3.2 and 12.0 Hz), 1.66–1.75 (1H, m), 1.76–1.85 (2H, m), 1.85–1.94 (2H, m), 2.75 (1H, tt, *J* = 3.2 and 12.0 Hz), 7.31 (1H, d, *J* = 8.0 Hz), 7.38–7.46 (3H, m), 7.52–7.58 (2H, m), 7.99 (1H, d, *J* = 8.0 Hz), 13.05 (1H, brs); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 25.5 ($CH_2$), 25.9 ($CH_2$), 32.1 ($CH_2$), 45.5 (CH), 119.1 (CH), 125.6 (Cq), 127.8 (CH), 128.3 (CH), 128.6 (CH), 137.9 (CH), 140.1 (Cq), 156.2 (Cq), 167.1 (Cq), 169.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1313, found 304.1310.

**X-Ray crystallographic analysis of compound 18 chloroform complex.** A colorless chunk crystal having approximate dimensions of 0.50 x 0.40 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares

refinement on F was based on 4431 observed reflections ($I > 0.00\sigma(I)$) and 246 variable parameters, and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R = 0.042 and $R_W$ = 0.067. Crystal data for **18** chloroform complex: $C_{19}H_{20}NO_2Cl_3$, M = 400.73, monoclinic, space group P21/n (#14), a = 10.3825(5) Å, b = 17.2549(9) Å, c = 11.1134(7) Å, β = 102.249(2)°, V = 1945.6(2) Å$^3$, Z = 4, $D_c$ = 1.368 g/cm$^3$, F(000) = 832.00, μ(MoKα) = 4.82 cm$^{-1}$.

**Procedure for the synthesis of pyridinylacetate 19. (Scheme 11)**




**19**

**Methyl 5-acetoxy-6-cyclohexyl-2-phenylnicotinate (19)**

To a stirred solution of tetrasubstituted pyridine **17a** (16.5 mg, 53.0 μmol) in $CH_2Cl_2$ (265 μL) was added $Et_3N$ (22.1 μL, 159 μmol), $Ac_2O$ (7.5 μL, 79.5 μmol) and DMAP (0.6 mg, 5.3 μmol) at room temperature, and stirring was continued for 30 min at the same temperature. The reaction mixture was diluted with $H_2O$ and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue upon work up was chromatographed on silica gel with hexane-AcOEt (90:10 v/v) as eluent to give acetate **19** (15.0 mg, 80%) as a colorless plates; mp 98.4–100.2 °C (recrystallized from $CHCl_3$); IR (KBr) 2936, 2854, 1756, 1712, 1596, 1429, 1398, 1307, 1257, 1200, 1148, 1114, 799, 749, 695 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.22–1.44 (3H, m), 1.77–1.90 (7H, m), 2.39 (3H, s), 2.85 (1H, tt, *J* = 3.6 and 11.6 Hz), 3.69 (3H, s), 7.38–7.46 (3H, m), 7.52–7.59 (2H, m), 7.77 (1H, s); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 20.9 ($CH_3$), 25.9 ($CH_2$), 26.4 ($CH_2$), 31.2 ($CH_2$), 40.4 (CH), 52.2 ($CH_3$), 124.4 (Cq), 127.9 (CH), 128.5 (CH), 128.9 (CH), 131.6 (CH), 139.9 (Cq), 142.6 (Cq), 155.6 (Cq), 160.4 (Cq), 167.6

(Cq), 169.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ 376.1525, found 376.1526.

**X-Ray crystallographic analysis of compound 19.** A colorless block crystal having approximate dimensions of 0.60 x 0.40 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 4182 observed reflections ($I > 0.00\sigma(I)$) and 258 variable parameters, and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of $R = 0.039$ and $R_W = 0.073$. Crystal data for **19**: $C_{21}H_{23}NO_4$, M = 353.42, triclinic, space group P-1 (#2), a = 5.9884(3) Å, b = 9.7086(7) Å, c = 16.597(1) Å, α = 80.492(2)°, β = 77.830(2)°, γ = 81.850(2)°, V = 924.5(1) Å$^3$, Z = 2, $D_c$ = 1.269 g/cm$^3$, F(000) = 376.00, μ(MoKα) = 0.88 cm$^{-1}$.

**Synthesis of substituted pyridines using air as an oxidant. (Scheme 14)**

**Synthesis of 16a.**

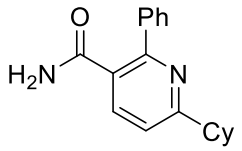
To a stirred solution of 3-aziridinylpropiolate ester **10a** (29.7 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (2.6 mg, 9.91 μmol) was successively added to reaction solution. After stirring was continued for 3 h at 60 °C, the reaction mixture was cooled to 0 °C, and then AcOH (28.6 μL, 0.50 mmol) was added at the same temperature. Further stirring was continued for 4 h under air atmosphere at the same temperature, and the solvent was evaporated under the reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (95:5 v/v) as eluent to give trisubstituted pyridine **16a** (16.9 mg, 57%) as a colorless oil.

**Synthesis of 17a.**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (30.2 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PPh_3$ (2.7 mg, 10.3 μmol) was successively added to reaction solution. After stirring was continued for 3 h at 60 °C, the reaction mixture was cooled to 0 °C, and further stirring was continued for 9 h under air atmosphere at the same temperature. The solvent was evaporated under the reduced pressure, and the residue was chromatographed on silica gel with hexane-AcOEt (80:20 v/v) as eluent to give tetrasubstituted pyridine **17a** (19.6 mg, 62%) as a colorless solid.

**Synthesis of niacin derivatives 28-30. (Scheme 15)**

**Procedure for the synthesis of nicotinamide 28.**



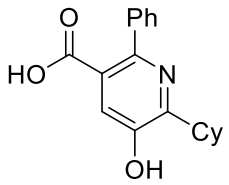

**28**

**6-Cyclohexyl-2-phenylnicotinamide (28)**

To a stirred solution of nicotinic acid **18** (20.0 mg, 71.0 μmol) in DMF (0.7 mL) was added $NH_4Cl$ (5.7 mg, 0.11 mmol), EDCl (21.8 mg, 0.11 mmol), HOBt (16.3 mg, 0.12 mmol) and DIPEA (54.8 μl, 0.32 mmol) at 0 °C, and stirring was continued for 2 h at 40 °C. The reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure to give nicotinamide **28** (19.8 mg, 99%) as colorless needles; mp 198.2–200.2 °C (recrystallized from EtOAc/hexane); IR (KBr) 3377, 3177, 2917, 2851, 1649, 1589, 1575, 1555, 1462, 1385, 768, 697 $cm^{-1}$; $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 1.18–1.31 (1H, m), 1.32–1.45 (2H, m), 1.49–1.62 (2H, m), 1.67–1.75 (1H, m), 1.76–1.85 (2H, m), 1.85–1.94 (2H, m), 2.74 (1H, tt, *J* = 3.2 and 12.0 Hz), 7.27

(1H, d, *J* = 8.0 Hz), 7.37–7.46 (4H, m), 7.66–7.72 (2H, m), 7.73 (1H, d, *J* = 8.0 Hz), 7.82 (1H, brs) ; $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 25.6 ($CH_2$), 25.9 ($CH_2$), 32.2 ($CH_2$), 45.5 (CH), 118.8 (CH), 127.8 (CH), 128.2 (CH), 128.6 (CH), 130.2 (Cq), 136.4 (CH), 139.8 (Cq), 153.8 (Cq), 165.6 (Cq), 170.5 (Cq); HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O$ $[M]^+$ 280.1576, found 280.1576.

**Procedure for the synthesis of nicotinic acid 29.**

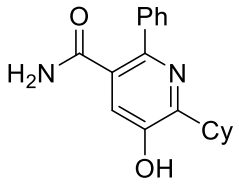



**29**

**6-Cyclohexyl-5-hydroxy-2-phenylnicotinic acid (29)**

To a stirred solution of tetrasubstituted pyridine **17a** (30.2 mg, 97.0 μmol) in MeOH (0.6 mL) was added 10% aqueous NaOH (0.25 mL) at room temperature, and stirring was continued for 3 h at 60 °C. The reaction mixture was diluted with $Et_2O$ and extracted with 10% aqueous NaOH. The combined aqueous layers were added 2 N HCl and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure to give nicotinic acid **29** (30.0 mg, 99%) as colorless needles; mp 167.8–169.6 °C (recrystallized from EtOAc/hexane); IR (KBr) 3060, 2929, 2855, 1699, 1558, 1447, 1415, 1321, 1240, 762, 698 $cm^{-1}$; $^1$H-NMR (400 MHz, $CD_3OD$) δ 1.24–1.38 (1H, m), 1.38–1.51 (2H, m), 1.68–1.89 (7H, m), 3.17 (1H, tt, *J* = 3.6 and 11.6 Hz), 7.31–7.39 (3H, m), 7.44 (1H, s), 7.49–7.54 (2H, m); $^{13}$C-NMR (100 MHz, $CD_3OD$) δ 27.2 ($CH_2$), 27.7 ($CH_2$), 31.8 ($CH_2$), 41.0 (CH), 123.9 (CH), 127.3 (Cq), 128.7 (CH), 128.9 (CH), 130.0 (CH), 141.5 (Cq), 149.6 (Cq), 150.6 (Cq), 157.0 (Cq), 171.6 (Cq); HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ 320.1263, found 320.1259.

**Procedure for the synthesis of nicotinamide 30.**



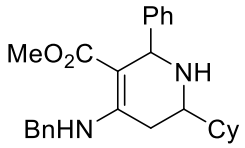

**30**

**6-Cyclohexyl-5-hydroxy-2-phenylnicotinamide (30)**

To a stirred solution of nicotinic acid **29** (23.1 mg, 77.9 μmol) in DMF (0.8 mL) was added $NH_4Cl$ (6.3 mg, 0.12 mmol), EDCl (23.9 mg, 0.12 mmol), HOBt (17.9 mg, 0.13 mmol) and DIPEA (60.0 μl, 0.35 mmol) at 0 °C, and stirring was continued for 2 h at 40 °C. The reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (60:40 v/v) as eluent to give nicotinamide **30** (16.4 mg, 71%) as colorless needles; mp 217.8–219.5 °C (recrystallized from EtOAc/hexane); IR (KBr) 3323, 3177, 2928, 2853, 1620, 1590, 1445, 1313, 1227, 1205, 1177, 754, 701 $cm^{-1}$; $^1$H-NMR (400 MHz, $CD_3OD$) δ 1.24–1.38 (1H, m), 1.38–1.51 (2H, m), 1.66–1.90 (7H, m), 3.16 (1H, tt, *J* = 3.6 and 11.6 Hz), 4.58 (1H, brs), 7.19 (1H, s), 7.31–7.41 (3H, m), 7.62–7.68 (2H, m) ; $^{13}$C-NMR (100 MHz, $CD_3OD$) δ 27.3 ($CH_2$), 27.8 ($CH_2$), 32.0 ($CH_2$), 40.9 (CH), 122.2 (CH), 128.9 (CH), 129.0 (CH), 129.9 (CH), 130.6 (Cq), 141.1 (Cq), 147.2 (Cq), 150.5 (Cq), 156.5 (Cq), 174.6 (Cq); HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_2Na$ $[M+Na]^+$ 319.1422, found 319.1419.

# Experiments in Chapter III

**Synthesis of piperidine 34a. (Scheme 17)**

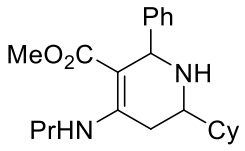



**34a**

**Methyl 4-(benzylamino)-6-cyclohexyl-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (34a)**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (30.0 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $BnNH_2$ (22.0 μL, 0.20 mmol) was successively added to this reaction mixture. After further stirring was continued for 30 min at 60 °C, the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (90:10 v/v) as eluent to give piperidine **34a** (18.2 mg, 45%) as colorless oil; IR (ATR) 2923, 2850, 1651, 1596, 1450, 1226, 1073, 908, 772, 731, 698 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.90–1.47 (6H, m), 1.59–1.85 (5H, m), 2.12 (1H, dd, *J* = 11.0 and 16.0 Hz), 2.48 (1H, dd, *J* = 2.5 and 16.0 Hz), 2.56 (1H, ddd, *J* = 2.5, 6.0 and 11.0 Hz), 3.30 (3H, s), 4.47 (2H, d, *J* = 6.0 Hz), 4.76 (1H, s), 7.15–7.19 (1H, m), 7.22–7.39 (9H, m), 9.25 (1H, t, *J* = 6.0 Hz); HRMS (ESI) *m/z* calcd for $C_{26}H_{33}N_2O_2$ $[M+H]^+$ 405.2542, found 405.2539.

**Synthesis of piperidine 34b. (Scheme 17)**

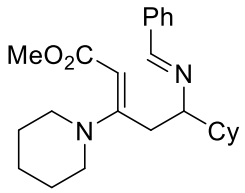



**34b**

**Methyl 6-cyclohexyl-2-phenyl-4-(propylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (34b)**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (30.0 mg, 0.10 mmol) in toluene (1.0 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then $PrNH_2$ (16.6 μL, 0.20 mmol) was successively added to this reaction mixture. After further stirring was continued for 30 min at 60 °C, the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (90:10 v/v) as eluent to give piperidine **34b** (18.5 mg, 51%) as colorless oil; IR (ATR) 2923, 2851, 1705, 1650, 1596, 1450, 1230, 1061, 762, 699 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.91–1.40 (6H, m), 1.02 (3H, t, *J* = 7.5 Hz),1.46–1.89 (7H, m), 2.13 (1H, dd, *J* = 11.0 and 16.5 Hz), 2.48 (1H, dd, *J* = 2.5 and 16.5 Hz), 2.59 (1H, ddd, *J* = 2.5, 6.5 and 11.0 Hz), 3.13–3.29 (2H, m), 3.28 (3H, s), 4.74 (1H, s), 7.13–7.19 (1H, m), 7.21–7.40 (9H, m), 8.88 (1H, brs); HRMS (ESI) *m/z* calcd for $C_{22}H_{33}N_2O_2$ $[M+H]^+$ 357.2542, found 357.2542.

**Synthesis of piperidine adduct 36a. (Scheme 18)**




**36a**

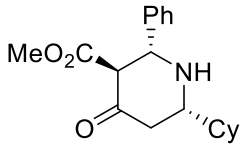
**Methyl 5-{[(*E*)-benzylidene]amino}-5-cyclohexyl-3-(piperidin-1-yl)pent-2-enoate (36a)**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (20.0 mg, 67.3 μmol) in toluene (0.7 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then piperidine (10.0 μL, 0.10 mmol) was successively added to this reaction mixture. After further stirring was continued for 1 h at room temperature, the solvent was evaporated under reduced pressure to give piperidine adduct **36a** as a crude. The NMR yield was determined as 90% from $^{1}$H-NMR spectrum by the addition of pyrazine (5.4 mg, 67.3 μmol) as an internal standard; IR (ATR) 2924, 2850, 1686, 1642, 1560, 1448, 1342, 1217, 1147, 1022, 948, 908, 731, 696 cm$^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 1.02–1.91 (19H, m), 3.10–3.31 (5H, m), 3.62 (3H, s), 4.66 (1H, s), 7.34–7.46 (3H, m), 7.65–7.71 (2H, m), 8.01 (1H, s); HRMS (ESI) *m/z* calcd for $C_{24}H_{35}N_2O_2$ $[M+H]^+$ 383.2699, found 383.2697.

**Synthesis of piperidine 37a and 38b. (Table 9)**

To a stirred solution of 3-aziridinylpropiolate ester **10a** (40.0 mg, 0.13 mmol) in toluene (1.3 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then piperidine (19.9 μL, 0.20 mmol) was successively added to this reaction mixture. After further stirring was continued for 1 h at room temperature, the mixture was added silica gel 60 [spherical 40-100 μm] (80.0 mg). Stirring was continued for 1 h at the same temperature, the mixture was added a drop of water. After reaction mixture was filtrated, the

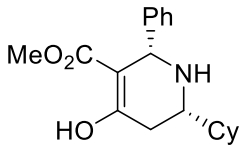
solvent was evaporated under reduced pressure to give **37a** + **38a** as a crude. The NMR yield was determined as 85% from $^{1}$H-NMR spectrum by the addition of pyrazine (10.8 mg, 0.13 mmol) as an internal standard.




**37a**

**Methyl-6-cyclohexyl-4-oxo-2-phenylpiperidine-3-carboxylate (37a)**

colorless needles; mp 98.0–99.5 °C (recrystallized from EtOAc/hexane); IR (ATR) 2926, 2850, 1729, 1700, 1431, 1354, 1252, 1130, 1002, 801, 752, 697 cm$^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.96–1.36 (5H, m), 1.36–1.47 (1H, m), 1.62–1.88 (5H, m), 2.32 (1H, dd, *J* = 12.0 and 13.6 Hz), 2.55 (1H, dd, *J* = 3.2 and 13.6 Hz), 2.88 (1H, ddd, *J* = 3.2, 5.6 and 12.0 Hz), 3.56 (1H, d, *J* = 7.2 Hz), 3.56 (3H, s), 4.23 (1H, d, *J* = 7.2 Hz), 7.25–7.36 (3H, m), 7.41–7.45 (2H, m) ; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 26.1 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.1 ($CH_2$), 43.0 (CH), 45.1 ($CH_2$), 51.8 ($CH_3$), 61.3 (CH), 63.3 (CH), 65.3 (CH), 127.4 (CH), 128.3 (CH), 128.7 (CH), 140.7 (Cq), 168.5 (Cq), 204.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found 316.1908.




**38a**

**Methyl 6-cyclohexyl-4-hydroxy-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (38a)**

IR (ATR) 2923, 2851, 1654, 1620, 1442, 1359, 1274, 1218, 1064, 843, 729 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.69–0.79 (1H, m), 0.85–0.95 (1H, m), 0.98–1.33 (4H, m), 1.53–1.82 (5H, m), 2.22 (1H, dd, *J* = 10.5 and 18.5 Hz), 2.30 (1H, dd, *J* = 5.0 and 18.5 Hz), 2.50 (1H, ddd, *J* = 5.0, 5.5 and 10.5 Hz),

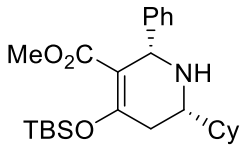
3.59 (3H, s), 4.94 (1H, d, *J* = 7.2 Hz), 7.22–7.28 (3H, m), 7.29–7.34 (2H, m), 12.39 (1H, brs); HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found 316.1912.

**Synthesis of silyl enol ethers 39. (Table 10, Table 11)**

**General procedure for the synthesis of silyl enol ethers 39a-m.**

**Synthesis of 39a. (Table 10, entry 3)**

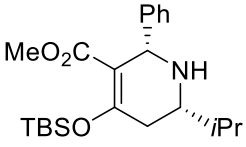
To a stirred solution of 3-aziridinylpropiolate ester **10a** (19.7 mg, 66.2 μmol) in toluene (0.66 mL) was heated at 100 °C, and stirring was continued for 9 h at the same temperature. The reaction mixture was then cooled to room temperature, and then piperidine (9.8 μL, 99.2 μmol) was successively added to this reaction mixture. After further stirring was continued for 1 h at room temperature, the mixture was added silica gel 60 [spherical 40-100 μm] (39.4 mg). Stirring was continued for 1 h at the same temperature, the mixture was added a drop of water. After reaction mixture was filtrated, the solvent was evaporated under reduced pressure to give **37a** + **38a** as colorless oil. To a stirred solution of **37a** + **38a** in DMSO (0.22 mL) was added pyridine (53.5 μL, 0.66 mmol), $AgNO_3$ (56.3 mg, 0.33 mmol) and TBSCl (49.9 mg, 0.33 mmol) at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with AcOEt, filtrated and extracted with AcOEt. The combined organic layers were washed with saturated brine, dried over $MgSO_4$, and then the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (95:5 v/v) as eluent to give silyl enol ethers **39a** (18.1 mg, 64%) as colorless oil.




**39a**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39a)**

Yield 64% (2 steps); colorless oil; IR (ATR) 2918, 2850, 1699, 1614, 1451, 1349, 1246, 1207, 1163, 1056, 932, 913, 838, 789, 762, 703 $cm^{-1}$; $^{1}$H-NMR (400 MHz, $CDCl_3$) δ 0.23 (3H, s), 0.25 (3H, s), 0.90–1.03 (1H, m), 0.97 (9H, s), 1.08–1.36 (5H, m), 1.60–1.78 (4H, m), 1.78–1.85 (1H, m), 2.12–2.18 (2H, m), 2.61–2.70 (1H, m), 3.38 (3H, s), 4.79 (1H, dd, *J* = 2.8 and 3.6 Hz), 7.17–7.32 (5H, m); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.3 (Cq), 25.8 ($CH_3$), 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 28.6 ($CH_2$), 29.7 ($CH_2$), 36.2 ($CH_2$), 42.3 (CH), 50.5 ($CH_3$), 58.1 (CH), 60.7 (CH), 113.4 (Cq), 127.2 (CH), 127.8 (CH), 128.3 (CH), 143.9 (Cq), 157.0 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{25}H_{40}NO_3Si$ $[M+H]^+$ 430.2777, found 430.2781.

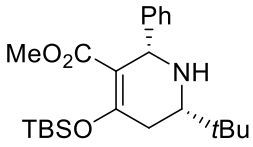



**39b**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-isopropyl-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39b)**

Yield 75% (2 steps); colorless oil; IR (ATR) 2953, 2858, 1720, 1640, 1434, 1362, 1250, 1204, 1064, 932, 836, 780, 731, 699 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.25 (3H, s), 0.92 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.97 (9H, s), 1.64 (1H, oct, *J* = 7.0 Hz), 2.12–2.17 (2H, m), 2.64 (1H, td, *J* = 7.0 and 8.0 Hz), 3.39 (3H, s), 4.81 (1H, t, *J* = 3.0 Hz), 7.21 (1H, tt, *J* = 1.5 and 7.0 Hz), 7.25–7.33 (4H, m) ; $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.8 ($CH_3$), 18.2 (CH), 18.3 (Cq), 19.2 (CH), 25.7 ($CH_3$), 32.4 ($CH_2$), 35.9 (CH), 50.5 ($CH_3$), 58.9 (CH), 60.7 (CH), 113.4 (Cq), 127.2

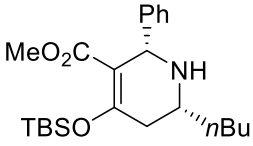
(CH), 127.8 (CH), 128.3 (CH), 143.8 (Cq), 156.9 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{22}H_{36}NO_3Si$ $[M+H]^+$ 390.2464, found 390.2466.




**39c**

**Methyl-6-(*tert*-butyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39c)**

Yield 67% (2 steps); colorless oil; IR (ATR) 2952, 2858, 1723, 1643, 1434, 1363, 1251, 1203, 1060, 930, 838, 780, 699 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.25 (3H, s), 0.91 (9H, s), 0.96 (9H, s), 2.10 (1H, td, *J* = 3.0 and 16.5 Hz), 2.19 (1H, ddd, *J* = 3.0, 10.5 and 16.5 Hz), 2.59 (1H, dd, *J* = 3.0 and 10.5 Hz), 2.96 (3H, s), 4.78 (1H, t, *J* = 3.0 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 7.27 (2H, t, *J* = 7.5 Hz), 7.31 (2H, d, *J* = 7.5 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), 18.3 (Cq), 25.8 ($CH_3$), 26.1 ($CH_3$), 32.9 ($CH_2$), 33.8 (Cq), 50.5 ($CH_3$), 60.9 (CH), 62.0 (CH), 113.6 (Cq), 127.1 (CH), 127.9 (CH), 128.2 (CH), 144.0 (Cq), 157.2 (Cq), 167.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{38}NO_3Si$ $[M+H]^+$ 404.2621, found 404.2615.

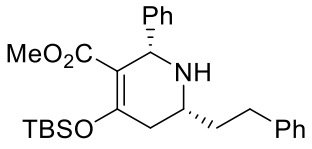



**39d**

**Methyl-6-butyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39d)**

Yield 66% (2 steps); colorless oil; IR (ATR) 2927, 2857, 1722, 1640, 1434, 1362, 1250, 1203, 1045, 932, 838, 778, 699 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.23 (3H, s), 0.25 (3H, s), 0.89 (3H, t, *J* = 7.0 Hz), 0.97 (9H, s), 1.23–1.54 (6H, m), 2.10 (1H, ddd, *J* = 3.5, 10.0 and 17.0 Hz), 2.17 (1H, ddd, *J* =

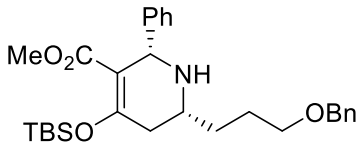
2.5, 4.0 and 17.0 Hz), 2.85–2.92 (1H, m), 3.38 (3H, s), 4.83 (1H, dd, *J* = 2.5 and 3.5 Hz), 7.21 (1H, tt, *J* = 1.5 and 7.0 Hz), 7.24–7.32 (4H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 14.0 ($CH_3$), 18.3 (Cq), 22.7 ($CH_2$), 25.7 ($CH_3$), 27.9 ($CH_2$), 35.9 ($CH_2$), 39.0 ($CH_2$), 50.6 ($CH_3$), 53.3 (CH), 60.6 (CH), 113.3 (Cq), 127.2 (CH), 127.7 (CH), 128.4 (CH), 143.7 (Cq), 156.8 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{38}NO_3Si$ $[M+H]^+$ 404.2621, found 404.2620.




**39e**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenethyl-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39e)**

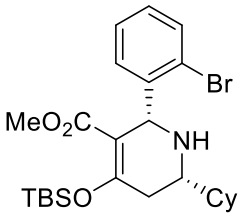
Yield 49% (2 steps); colorless plates; mp 104.7–106.8 °C (recrystallized from EtOAc/hexane); IR (ATR) 2926, 2853, 1701, 1618, 1450, 1242, 1206, 932, 910, 837, 788, 698 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.21 (3H, s), 0.24 (3H, s), 0.96 (9H, s), 1.71–1.84 (2H, m), 2.13 (1H, ddd, *J* = 3.0, 9.5 and 17.0 Hz), 2.18 (1H, ddd, *J* = 2.0, 4.5 and 17.0 Hz), 2.64–2.76 (2H, m), 2.88–2.94 (1H, m), 3.38 (3H, s), 4.81 (1H, dd, *J* = 2.0 and 3.0 Hz), 7.16–7.24 (4H, m), 7.24–7.32 (6H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 32.1 ($CH_2$), 37.6 ($CH_2$), 39.0 ($CH_2$), 50.6 ($CH_3$), 52.7 (CH), 60.5 (CH), 113.3 (Cq), 125.9 (CH), 127.3 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 141.5 (Cq), 143.6 (Cq), 156.5 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{27}H_{38}NO_3Si$ $[M+H]^+$ 452.2621, found 452.2612.




**39f**

**Methyl-6-[3-(benzyloxy)propyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39f)**

Yield 41% (2 steps); colorless oil; IR (ATR) 2928, 2856, 1720, 1638, 1434, 1361, 1250, 1203, 1100, 932, 838, 781, 734, 697 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.25 (3H, s), 0.96 (9H, s), 1.50–1.56 (2H, m), 1.64–1.73 (2H, m), 2.11 (1H, ddd, *J* = 3.0, 10.0 and 17.0 Hz), 2.18 (1H, ddd, *J* = 2.0, 4.5 and 17.0 Hz), 2.88–2.95 (1H, m), 3.38 (3H, s), 3.44–3.50 (2H, m), 4.48 (2H, s), 4.82 (1H, dd, *J* = 2.0 and 3.0 Hz), 7.18–7.24 (1H, m), 7.24–7.38 (9H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.8 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 26.1 ($CH_2$), 32.9 ($CH_2$), 38.9 ($CH_2$), 50.6 ($CH_3$), 53.1 (CH), 60.5 (CH), 70.1 ($CH_2$), 73.0 ($CH_2$), 113.3 (Cq), 127.2 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 128.4 (CH), 138.3 (Cq), 143.6 (Cq), 156.6 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{29}H_{42}NO_4Si$ $[M+H]^+$ 496.2883, found 496.2878.

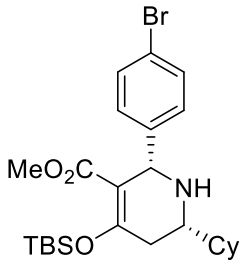



**39g**

**Methyl-2-(2-bromophenyl)-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39g)**

Yield 55% (2 steps); colorless amorphous; IR (ATR) 2926, 2854, 1724, 1634, 1435, 1362, 1250, 1204, 1056, 934, 837, 781, 752 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.24 (3H, s), 0.27 (3H, s), 0.94–1.05 (1H, m), 0.98 (9H, s), 1.10–1.35 (5H, m), 1.55–1.78 (4H, m), 1.82–1.89 (1H, m), 2.14–2.23 (2H, m),

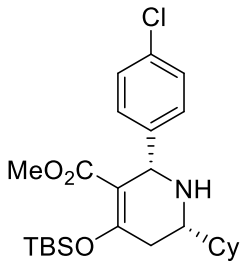
2.66 (1H, dt, *J* = 6.0 and 7.0 Hz), 3.41 (3H, s), 5.28 (1H, s), 7.05 (1H, t, *J* = 7.0 Hz), 7.19–7.28 (2H, m), 7.50 (1H, d, *J* = 7.5 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.7 ($CH_3$), –3.6 ($CH_3$), 18.4 (Cq), 25.8 ($CH_3$), 25.9 ($CH_2$), 26.0 ($CH_2$), 26.3 ($CH_2$), 28.7 ($CH_2$), 29.5 ($CH_2$), 35.6 ($CH_2$), 42.0 (CH), 50.7 ($CH_3$), 58.3 (CH), 69.2 (CH), 111.9 (Cq), 124.0 (Cq), 127.9 (CH), 128.6 (CH), 132.8 (CH), 142.9 (Cq), 158.8 (Cq), 166.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{25}H_{39}NO_3SiBr$ $[M+H]^+$ 508.1883, found 508.1875.




**39h**

**Methyl-2-(4-bromophenyl)-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39h)**

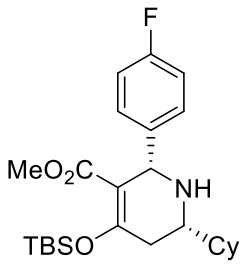
Yield 76% (2 steps); colorless amorphous; IR (ATR) 2926, 2854, 1723, 1635, 1434, 1362, 1250, 1204, 1055, 1011, 933, 838, 780 $cm^{-1}$;$^1$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.24 (3H, s), 0.91–1.04 (1H, m), 0.97 (9H, s), 1.08–1.35 (5H, m), 1.61–1.78 (4H, m), 1.78–1.84 (1H, m), 2.10–2.20 (2H, m), 2.61–2.67 (1H, m), 3.42 (3H, s), 4.76 (1H, dd, *J* = 2.0 and 3.0 Hz), 7.18 (2H, dd, *J* = 2.0 and 8.0 Hz), 7.39 (1H, dd, *J* = 2.0 and 8.0 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 26.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.6 ($CH_2$), 36.3 ($CH_2$), 42.3 (CH), 50.7 ($CH_3$), 58.0 (CH), 60.0 (CH), 112.8 (Cq), 120.9 (Cq), 129.6 (CH), 131.4 (CH), 143.1 (Cq), 157.7 (Cq), 166.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{25}H_{39}NO_3SiBr$ $[M+H]^+$ 508.1883, found 508.1874.




**39i**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(4-chlorophenyl)-6-cyclohexyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39i)**

Yield 68% (2 steps); colorless oil; IR (ATR) 2926, 2854, 1724, 1635, 1435, 1363, 1250, 1204, 1087, 1055, 1015, 926, 838, 781 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.24 (3H, s), 0.90–1.04 (1H, m), 0.97 (9H, s), 1.09–1.36 (5H, m), 1.62–1.78 (4H, m), 1.78–1.84 (1H, m), 2.10–2.20 (2H, m), 2.62–2.67 (1H, m), 3.42 (3H, s), 4.77 (1H, t, *J* = 2.5 Hz), 7.22–7.25 (4H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 26.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.6 ($CH_2$), 36.2 ($CH_2$), 42.2 (CH), 50.6 ($CH_3$), 58.0 (CH), 60.0 (CH), 112.8 (Cq), 128.4 (CH), 129.2 (CH), 132.8 (Cq), 142.5 (Cq), 157.6 (Cq), 166.7 (Cq); HRMS (ESI) *m/z* calcd for $C_{25}H_{39}NO_3SiCl$ $[M+H]^+$ 464.2388, found 464.2380.

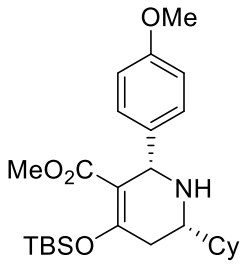



**39j**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-2-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (39j)**

Yield 67% (2 steps); colorless oil; IR (ATR) 2926, 2854, 1724, 1640, 1508, 1435, 1363, 1250, 1205, 1055, 938, 836, 780 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.24 (3H, s), 0.90–1.05 (1H, m), 0.97 (9H, s), 1.08–1.36 (5H, m), 1.63–1.78 (4H, m), 1.78–1.85 (1H, m), 2.10–2.20 (2H, m),

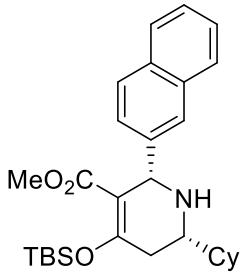
2.62–2.68 (1H, m), 3.41 (3H, s), 4.78 (1H, t, *J* = 2.5 Hz), 6.92–6.98 (2H, m) , 7.24–7.30 (2H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 26.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.6 ($CH_2$), 36.2 ($CH_2$), 42.3 (CH), 50.6 ($CH_3$), 58.0 (CH), 59.9 (CH), 113.2 (Cq), 115.1 (CH, d, *J* = 21.8 Hz), 129.4 (CH, d, *J* = 8.5 Hz), 139.7 (Cq, d, *J* = 2.9 Hz), 157.2 (Cq), 161.9 (Cq, d, *J* = 243.8 Hz), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{25}H_{39}NO_3FSi$ $[M+H]^+$ 448.2683, found 448.2679.




**39k**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-2-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (39k)**

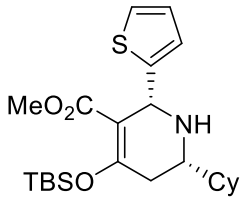
Yield 52% (2 steps); colorless oil; IR (ATR) 2926, 2854, 1722, 1611, 1511, 1435, 1362, 1246, 1203, 1038, 936, 833, 780 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s), 0.24 (3H, s), 0.91–1.05 (1H, m), 0.96 (9H, s), 1.08–1.36 (5H, m), 1.62–1.78 (4H, m), 1.78–1.86 (1H, m), 2.09–2.19 (2H, m), 2.62–2.67 (1H, m), 3.41 (3H, s), 3.77 (3H, s), 4.75 (1H, t, *J* = 2.5 Hz), 6.80 (2H, d, *J* = 2.5 Hz), 7.22 (2H, d, *J* = 2.5 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.3 (Cq), 25.8 ($CH_3$), 26.1 ($CH_2$), 26.2 ($CH_2$), 26.5 ($CH_2$), 28.6 ($CH_2$), 29.7 ($CH_2$), 36.1 ($CH_2$), 42.3 (CH), 50.6 ($CH_3$), 55.2 ($CH_3$), 58.1 (CH), 60.0 (CH), 113.7 (CH), 113.7 (Cq), 128.8 (CH), 136.0 (Cq), 156.5 (Cq), 158.6 (Cq), 167.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{26}H_{42}NO_4Si$ $[M+H]^+$ 460.2883, found 460.2885.




**39l**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-2-(naphthalen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (39l)**

Yield 61% (2 steps); colorless plates; mp 68.8–69.9 °C (recrystallized from EtOAc/hexane); IR (ATR) 2926, 2854, 1710, 1638, 1431, 1347, 1249, 1213, 1098, 1049, 964, 831, 790, 741 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.26 (3H, s), 0.28 (3H, s), 0.90–1.08 (1H, m), 0.99 (9H, s), 1.08–1.39 (5H, m), 1.61–1.79 (4H, m), 1.79–1.87 (1H, m), 2.16–2.29 (2H, m), 2.69–2.76 (1H, m), 3.35 (3H, s), 4.97 (1H, s), 7.40–7.47 (3H, m) , 7.74–7.81 (4H, m); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.7 ($CH_3$), 18.4 (Cq), 25.8 ($CH_3$), 26.0 ($CH_2$), 26.1 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.6 ($CH_2$), 36.3 ($CH_2$), 42.3 (CH), 50.6 ($CH_3$), 58.1 (CH), 60.7 (CH), 113.3 (Cq), 125.5 (CH), 125.7 (CH), 126.1 (CH), 126.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 132.9 (Cq), 133.4 (Cq), 141.4 (Cq), 157.3 (Cq), 166.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{29}H_{42}NO_3Si$ $[M+H]^+$ 480.2934, found 480.2932.




**39m**

**Methyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-cyclohexyl-2-(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (39m)**

Yield 42% (2 steps); colorless oil; IR (ATR) 2926, 2853, 1723, 1636, 1435, 1362, 1251, 1204, 1054, 935, 835, 782, 695 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.21 (3H, s), 0.24 (3H, s), 0.89 (3H, t, *J* = 7.0 Hz), 0.92–1.05 (1H, m), 0.96 (9H, s), 1.08–1.38 (5H, m), 1.63–1.78 (4H, m), 1.81–1.88 (1H, m),

2.08–2.19 (2H, m), 2.61–2.67 (1H, m), 3.50 (3H, s), 5.17 (1H, dd, *J* = 2.0 and 3.0 Hz), 6.88 (1H, dd, *J* = 3.5 and 5.0 Hz), 6.97 (1H, dd, *J* = 0.5 and 3.5 Hz), 7.14 (1H, dd, *J* = 0.5 and 5.0 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ –3.8 ($CH_3$), –3.8 ($CH_3$), 18.3 (Cq), 25.7 ($CH_3$), 26.1 ($CH_2$), 26.2 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_2$), 29.6 ($CH_2$), 36.1 ($CH_2$), 42.2 (CH), 50.8 ($CH_3$), 55.4 (CH), 57.9 (CH), 113.6 (Cq), 124.1 (CH), 124.7 (CH), 126.2 (CH), 148.1 (Cq), 156.9 (Cq), 166.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{23}H_{38}NO_3SiS$ $[M+H]^+$ 436.2342, found 436.2346.

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