The thesis entitled "**DEVELOPMENT OF ENYNE-ASSISTED ANNULATIONS TOWARDS THE SYNTHESIS OF PYRIDINES, PYRROLES AND MYRMICARIN**" has been divided into three chapters.

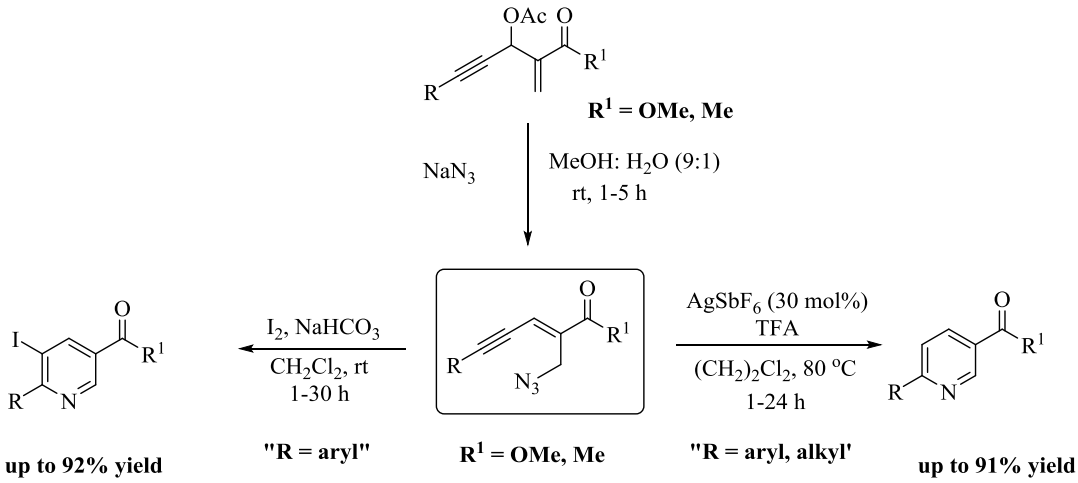
CHAPTER-I: Synthesis of Substituted Pyridines *via aza*-Annulation of Enynyl Azides

Introduction:

Pyridine is a nitrogen containing heterocyclic organic compound with the chemical formula C_5H_5N. It is widely distributed in natural products, bioactive molecules, functional materials, and pharmaceuticals. In the literature, both intermolecular and intramolecular approaches towards the synthesis of pyridines have been reported. In this chapter, we have described a novel intramolecular *aza*-annulation of enynyl azides which can be readily prepared from Morita-Baylis-Hillman acetates of acetylenic aldehyde to access substituted pyridines.

Methodology:

We envisioned that an intermolecular allylic substitution of MBH-acetate of acetylenic aldehyde with sodium azide followed by Ag-catalyzed *aza*-annulation of (*E*)-2-en-4-ynyl azide and iodine-mediated electrophilic cyclization of enynyl azide would be a convenient process for the synthesis of substituted pyridines and iodopyridines (**scheme 1.1**).

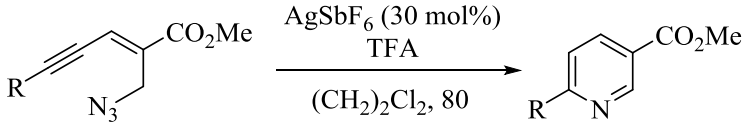


Scheme 1.1: *aza*-Annulation of enynyl azides derived from MBH-acetate of acetylenic aldehydes.

Results and discussion:

To check the hypothesis for the proposed *aza*-annulation of enynyl azide **1**, derived from MBH-acetate (Prepared from the reaction of 3-phenylpropiolaldehyde with methyl acrylate) was employed as a model substrate. Initially, the *aza*-annulation of **1** was tested in the presence of $AgSbF_6$ and TFA in DCE. To our delight, the reaction proceeded smoothly to completion providing 6-phenyl nicotinate **2** in 82% yield. Encouraged by this result, the scope of the reaction was then explored using variety of enynyl azides, and the results are summarized in **Table 1.1**.

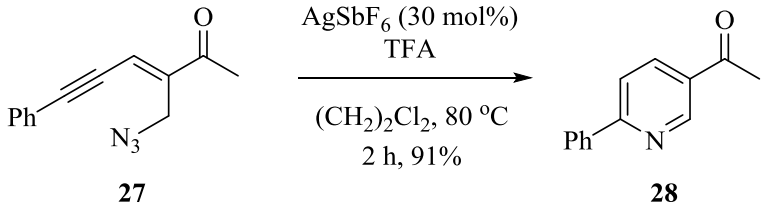
Table 1.1: Ag-Catalyzed *aza*-Annulation of (*E*)-2-en-4-ynyl azides



Entry	Enynyl azide	Time (h)	Pyridine	Yield (%)
1	R = Ph, **1**	10	R = Ph, **2**	82
2	R = 1-Napthyl, **3**	22	R = 1-Napthyl, **4**	81
3	R = 2-Thiophenyl, **5**	8	R = 2-Thiophenyl, **6**	78
4	R = 4-Me-C_6H_4, **7**	12	R = 4-Me-C_6H_4, **8**	81
5	R = 4-MeO-C_6H_4, **9**	12	R = 4-MeO-C_6H_4, **10**	86
6	R = 4-Cl-C_6H_4, **11**	14	R = 4-Cl-C_6H_4, **12**	84
7	R = 4-CN-C_6H_4, **13**	12	R = 4-CN-C_6H_4, **14**	81
8	R = 4-NO_2-C_6H_4, **15**	12	R = 4-NO_2-C_6H_4, **16**	86
9	R = 3-CF_3-C_6H_4, **17**	14	R = 3-CF_3-C_6H_4, **18**	84
10	R = 4-$COCH_3$-C_6H_4, **19**	18	R = 4-$COCH_3$-C_6H_4, **20**	88
11	R = 3-*NBoc*-Indole, **21**	18	R = 3-*NH*-Indole, **22**	88
12	R = *n*C_3H_7, **23**	20	R = *n*C_3H_7, **24**	84
13	R = *n*C_6H_{13}, **25**	26	R = *n*C_6H_{13}, **26**	86

Reaction conditions: Enynyl azides (0.20 mmol), $AgSbF_6$ (30 mol%), TFA (0.4 mmol), $(CH_2)_2Cl_2$,80°C

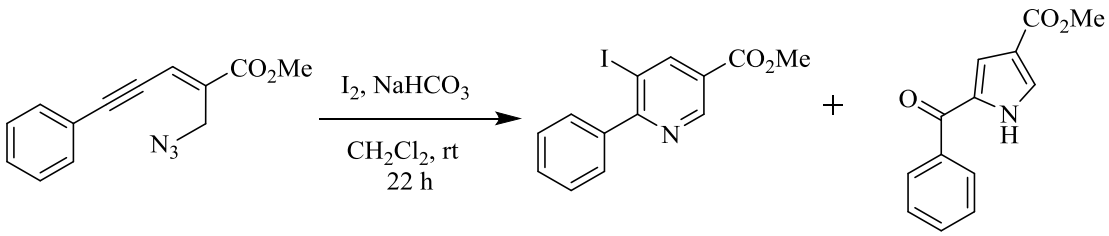
Interestingly, the annulation reaction of enynyl azide **27** containing keto functionality also proceeded well to furnish the 3-acetyl pyridine **28** under the Ag-catalyzed reaction (**scheme 1.2**).



27 **28**

Scheme 1.2

Next, the intramolecular *aza*-annulation was investigated under iodine-mediated electrophilic reaction conditions to obtain 5-iodo-3,6-disubstituted pyridine. To test the feasibility of the annulation, enynyl azide **1** was employed as a model substrate and treated with I_2/$NaHCO_3$ in CH_2Cl_2 at room temperature to provide the desired 5-iodo pyridine derivative **29** as the major product (60%) along with the 5-*exo*-*dig*-cyclized product, 2-benzoylpyrrole-4-carboxylate, **30** as minor product (21%, **Scheme 1.3**).

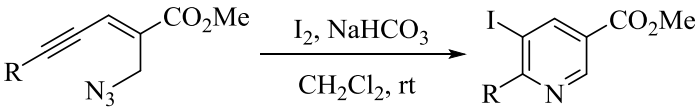


1 **29** (60%) **30** (21%)

Scheme 1.3

Gratifyingly, enynyl azide having 1-Naphthyl, electron-donating and heteroaromatic groups gave iodo-pyridine exclusively. These results are summarized in **Table 1.2**.

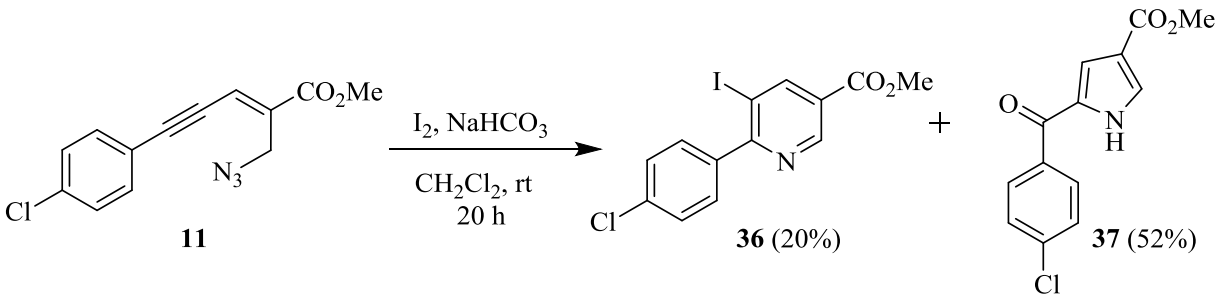
Table 1.2: I_2-Mediated *aza*-Annulation of (*E*)-2-en-4-ynyl azides



Entry	Enynyl azide	Time (h)	Iodo-Pyridine	Yield (%)
1	R = 1-Napthyl, **3**	23	R = 1-Napthyl, **31**	89
2	R = 2-Thiophenyl, **5**	20	R = 2-Thiophenyl, **32**	90
3	R = 4-Me-C_6H_4, **7**	16	R = 4-Me-C_6H_4, **33**	72
4	R = 4-MeO-C_6H_4, **9**	12	R = 4-MeO-C_6H_4, **34**	92
5	R = 3-*NBoc*-Indole, **21**	20	R = 3-*NBoc*-Indole, **35**	90

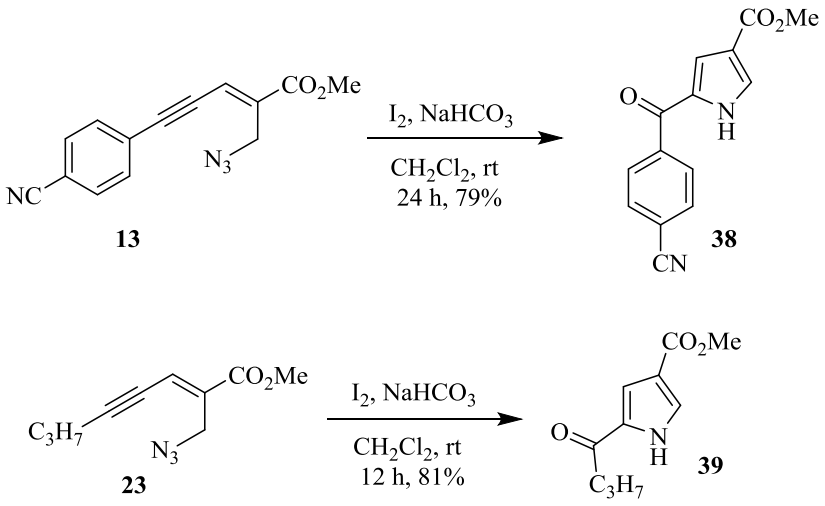
Reaction conditions: Enynyl azides (0.20 mmol), $NaHCO_3$ (0.20 mmol), I_2 (1.00 mmol), CH_2Cl_2, rt.

However, the enynyl azide **11** having 4-Chloro phenyl group on the alkyne functionality gave mixture of iodo-pyridine **36** as minor (20%) and benzoyl-pyrrole **37** as major product (52%, **scheme 1.4**).



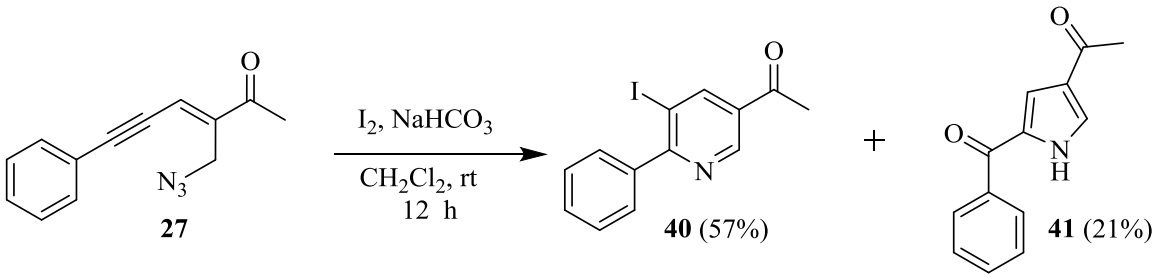
Scheme 1.4

Noteworthy to mention, enynyl azides having 4-*CN*-Ph **13** and *n*-propyl **23** groups underwent 5-*exo*-*dig* cyclization to furnish exclusively acyl pyrrole **38** and **39** respectively, in good yield (**scheme 1.5)**.



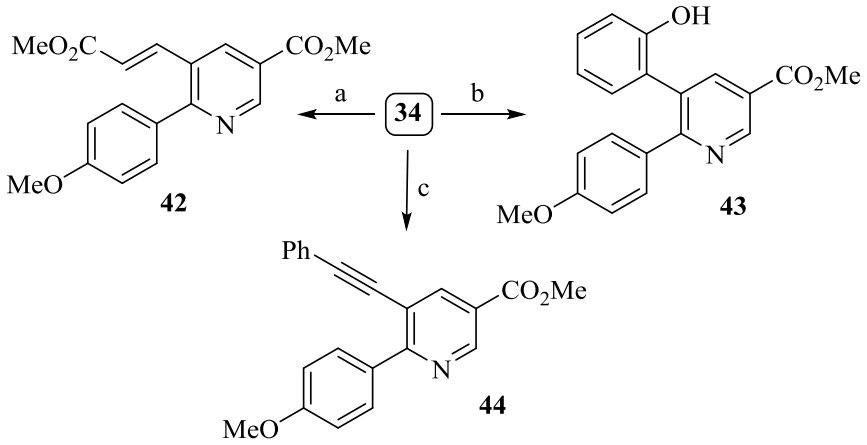
Scheme 1.5

Additionally, we extended the scope of enynyl azide derived from MBH acetate having activated alkene such as methyl vinyl ketone **27** also participated well in intramolecular *aza*-annulation (**Scheme 1.6**).



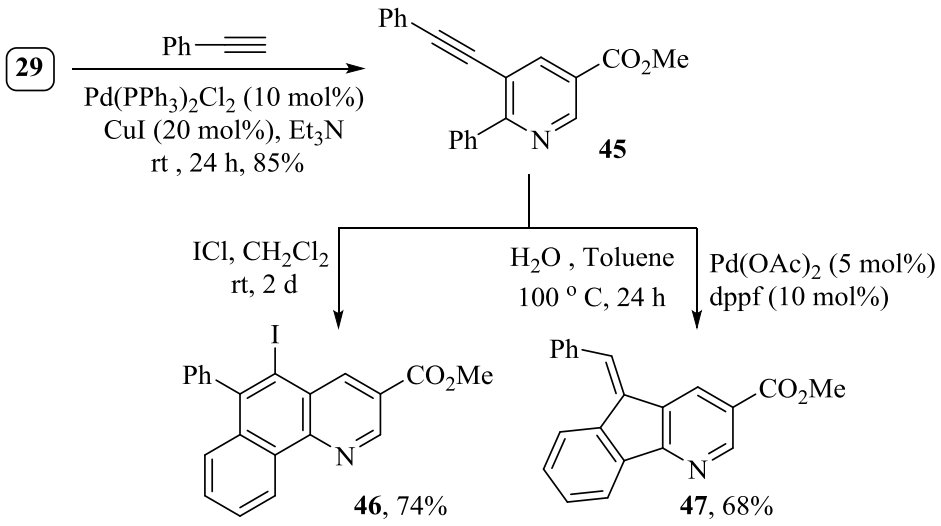
Scheme 1.6

After the successful synthesis of iodo-pyridines from various enynyl azides, we next focused our attention to find the potential application of this method in organic synthesis, because the obtained pyridine has iodo group at C-5 position which acts as a handy synthon to perform various Pd-coupling reactions to access highly functionalized derivatives. Indeed, this assumption was proved for further exploration using **34** as substrate (**scheme 1.7**).



Scheme 1.7 (a) Methyl acrylate, $Pd(OAc)_2$ (10 mol%), Bu_4NBr, $NaHCO_3$, DMF, 80 ^oC, 2 h 86%; (b) (2-Hydroxyphenyl)boronic acid, $Pd(PPh_3)_4$ (10 mol%), K_3PO_4, DMF, 80 ^oC, 6 h; (c) Phenylacetylene, $Pd(PPh_3)Cl_2$ (10 mol %), CuI (20 mol%), Et_3N, rt, 24 h, 93%.

In addition, 6-aryl-5-iodopyridine-3-carboxylate **29** provided an interesting route for the generation of novel pyridine-fused scaffolds (**scheme 1.8**). Thus, 6-phenyl-5-iodopyridine-3-carboxylate **29** was subjected to Sonogashira coupling with phenylacetylene to obtain the corresponding 5-alkynylpyridine **45** which further underwent ICl-promoted 6-*endo-dig* cyclization to produce 5-iodo-6-phenylbenzo[h]quinoline **46**. Alternatively, Pd-catalyzed 5-*exo-dig*-cyclization of **45** allowed the synthesis of 4-azafluorene **47** in 68% yield.



Scheme 1.8: Synthesis of fused-pyridine derivatives from **29**

Conclusion:

Novel and efficient methods have been established for the synthesis of substituted pyridines *via* the *aza*-annulation of (*E*)-2-en-4-yn-1-azides. Ag-catalyzed cyclization was found to be regioselective to provide pyridine-carboxylates. Whereas, in the case of I_2-promoted annulation, a substituent controlled reactivity switch was observed to give either iodopyridine or acyl-pyrrole. Further elaboration of the products to fully substituted pyridines was also described.

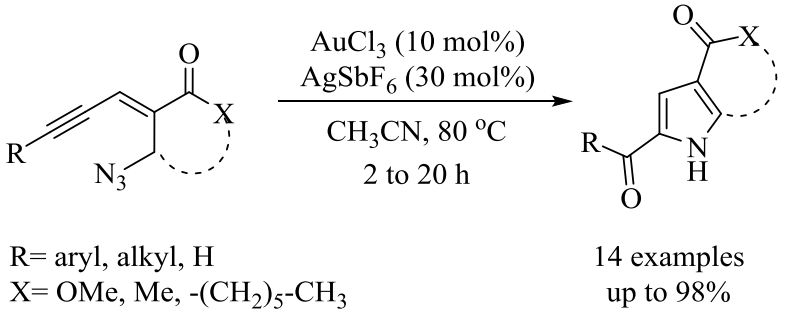
CHAPTER-II: Synthesis of Substituted Acyl Pyrroles from Enynyl Azides

Introduction:

Pyrrole is an important structural motif, frequently found in natural products and synthetic molecules with diverse pharmacological properties. Precisely, pyrrole containing a C-2 carbonyl (keto or formyl) group is of great synthetic significance due to their presence as a prevalent structure in several natural products with potential biological activities. In this chapter, we report a new route for the synthesis of 2-ketopyrroles through an oxidative intramolecular *aza*-annulation of enynyl azides under Au/Ag-mediated reaction condition.

Methodology:

In the previous chapter, we described the *aza*-annulation reaction of enynyl azides for the synthesis of substituted pyridines and the formation of ketopyrrole was observed in few cases depending on the electronic nature of the substituent under I_2-mediated condition. This result prompted us to explore the possibility to find the suitable condition for the synthesis of 2-ketopyrrole as the exclusive product from enynyl azide irrespective of the substitution on the aryl ring tethered to an alkyne.



R= aryl, alkyl, H
X= OMe, Me, -$(CH_2)_5$-CH_3

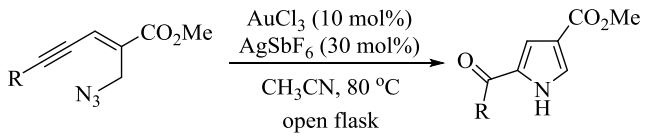
14 examples
up to 98%

Scheme 2.1: Oxidative *aza*-annulation of enynyl azides

Results and discussion:

We envisioned that, the enynyl azide obtained from MBH-acetate would undergo *aza*-annulation to give the acyl pyrrole under the suitable reaction condition. For testing this hypothesis, the *(E)*-2-(azidomethyl)-5-phenylpent-2-en-4-ynoate **1** was chosen as model substrate. From the optimization studies, we were pleased to found that the desired acyl pyrrole **2**, was accomplished in 82% yield using 10 mol% of $AuCl_3$/ 30 mol% of $AgSbF_6$ in acetonitrile at 80 ^oC. Under the optimized reaction conditions, the scope of the *aza*-annulation was explored with various enynyl azides and the results are summarized in **Table 2.1**.

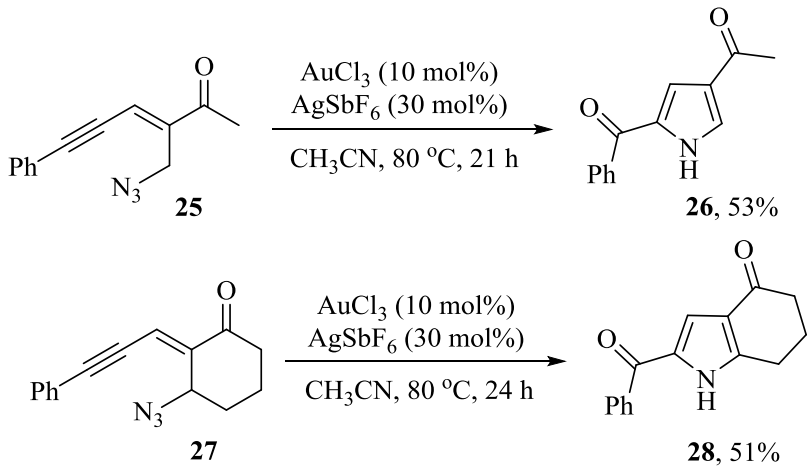
Table 2.1: Substrate Scope for *aza*-Annulation of Enynyl Azides.



Entry	Enynyl azide	Time (h)	Acyl Pyrrole	Yield (%)
1	R = Ph, **1**	7	R = Ph, **2**	82
2	R = 1-Napthyl, **3**	23	R = 1-Napthyl, **4**	89
3	R = 2-Thiophenyl, **5**	20	R = 2-Thiophenyl, **6**	83
4	R = 4-Me-C_6H_4, **7**	20	R = 4-Me-C_6H_4, **8**	79
5	R = 4-MeO-C_6H_4, **9**	7	R = 4-MeO-C_6H_4, **10**	86
6	R = 4-Cl-C_6H_4, **11**	23	R = 4-Cl-C_6H_4, **12**	78
7	R = 4-CN-C_6H_4, **13**	20	R = 4-CN-C_6H_4, **14**	85
8	R = 4-NO_2-C_6H_4, **15**	20	R = 4-NO_2-C_6H_4, **16**	84
9	R = 3-CF_3-C_6H_4, **17**	7	R = 3-CF_3-C_6H_4, **18**	81
10	R = 4-$COCH_3$-C_6H_4, **19**	7	R = 4-$COCH_3$-C_6H_4, **20**	86
11	R = *n*C_6H_{13}, **21**	7	R = *n*C_6H_{13}, **22**	64
12	R = *2-I*-C_6H_4, **23**	7	R = *2-I*-C_6H_4, **24**	98

Reaction conditions: Enynyl azides (1.0 mmol), $AuCl_3$ (10 mol%), $AgSbF_6$ (30 mol%), CH_3CN, 80 ^oC, Open Flask.

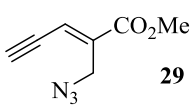
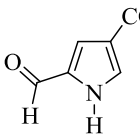
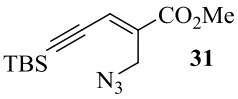
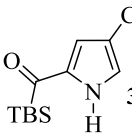
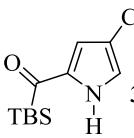
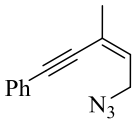
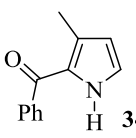
Additionally, the scope of enynyl azides was extended to MBH-acetates derived from different activated alkenes such as methyl vinyl ketone or cyclohexenone. Gratifyingly, the annulation reaction of substrates **25** and **27** worked well to furnish the pyrrole **26** and **28** (**scheme 2.2**).



Scheme 2.2

Further, the reactivity of enynyl azide **29** having the terminal alkyne was verified to get 2-formylpyrrole **30**. But disappointingly, decomposition of the starting material was observed. However, the reaction of **29** under $I_2/NaHCO_3$ in CH_2Cl_2 2-formylpyrrole **30** was obtained in 45% yield. Further, enynyl azide **31** bearing a TBS group on the alkyne was also tested under both the reaction conditions and found that 2-silylketopyrrole **32** was obtained in 34% and 48% yield, respectively. Interestingly, that the enynyl azide **33**, prepared from a non-MBH-product, was also successful in providing the corresponding 2-ketopyrrole **34** under Au/Ag- catalysis and however no reaction observed in $I_2/NaHCO_3$ condition (**Table 2.2**).

Table 2.2: Oxidative *aza*-Annulations of Enynyl Azides

Entry	Enynyl azide	$AuCl_3/AgSbF_6$ CH_3CN, 80 °C (a)	$I_2/NaHCO_3$ CH_2Cl_2, rt (b)
1	 **29**	Starting Material Decomposition	 **30**, 2 h, 45%
2	 **31**	 **32,** 20 h, 34%	 **32**, 20 h, 48%
3	 **33**	 **34**, 20 h, 38%	No Reaction

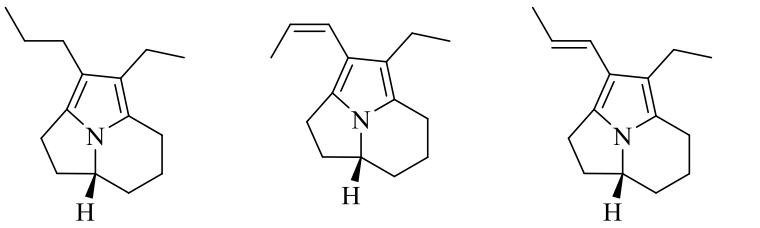
Conclusion

In summary, we have demonstrated a facile and direct oxidative *aza*-annulation approach to access structurally diversified 2-keto/formylpyrrole derivatives. The method uses commercially available catalysts ($AuCl_3$ and $AgSbF_6$) and delivers the product through a cascade C−N and C−O bond formation reactions of enynyl azides.

CHAPTER-III: Enyne-assisted approach towards the synthesis of Myrmicarins

Introduction:

The Myrmicarins are a family of structurally fascinating alkaloids isolated from the poison gland secretion of the African ant species *Myrmicaria opaciventris.* In 1996, Schroder and coworkers first isolated 1.4 mg of Myrmicarin 217 and 3.8 mg of a 2:1 mixture of Myrmicarins 215A and 215B from 40 dissected poison gland secretion of *Myrmicaria* ants, a genus of Myrmicinae (*M. striata, M. eumenoides, and M. opaciventris*) and named Myrmicarin. Myrmicarin 217 (**1**), 215A (**2**) and 215B (**3**) were identified as the first examples of naturally occurring pyrrolo[2,1,5-*cd*]indolizines as shown in **Figure: 3.1**.

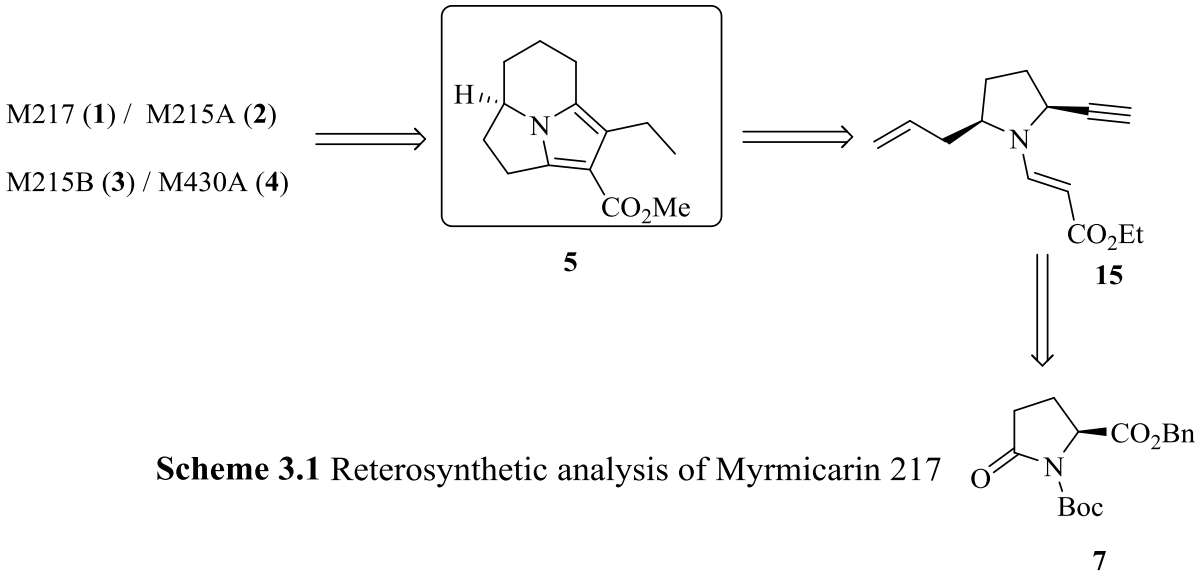


Myrmicarin 217 (**1**) Myrmicarin 215A (**2**) Myrmicarin215B (**3**)

Figure: 3.1

Methodology (Retrosynthetic analysis):

Enyne-assisted annulation based linear route is envisaged for the synthesis of target molecule (**1**-**4**), which could be accessed from intermediate **5** by the conversion of ester to the required carbon chain (**scheme 3.1**). The tricyclic core of Myrmicarin **5** could be made from **15** by *aza*-Clasien rearrangement of Enyne **15**, which in turn was planned from **7** *via* enamine formation.

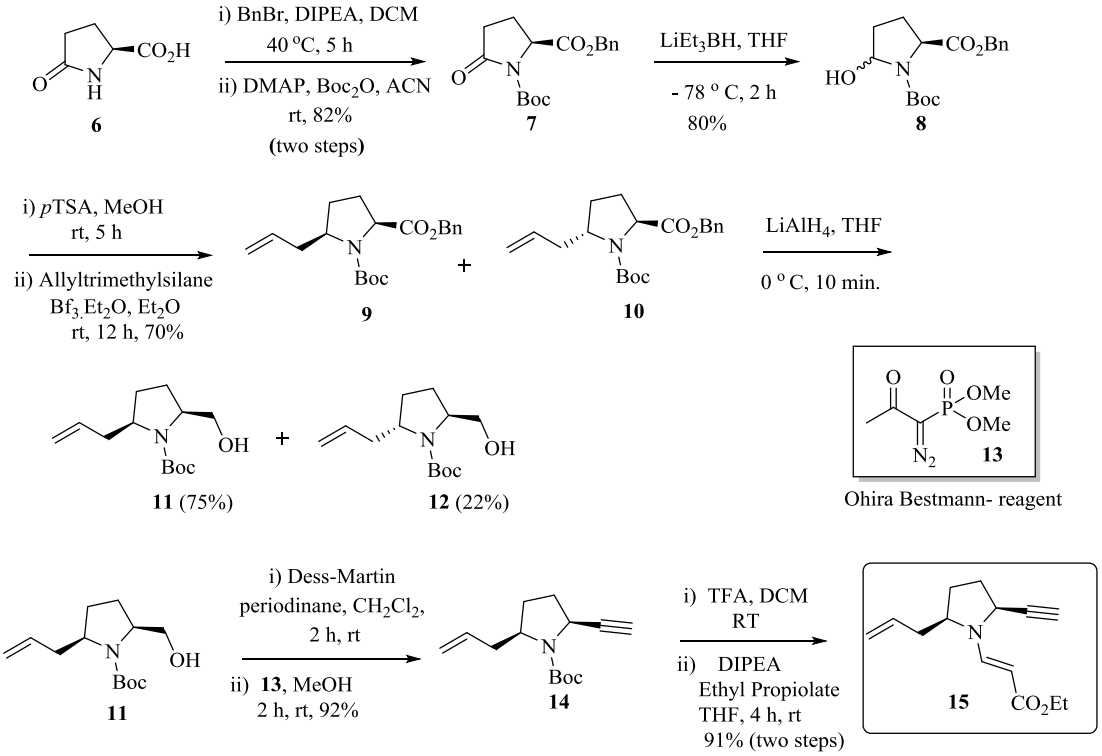


Scheme 3.1 Reterosynthetic analysis of Myrmicarin 217

Results and Discussion:

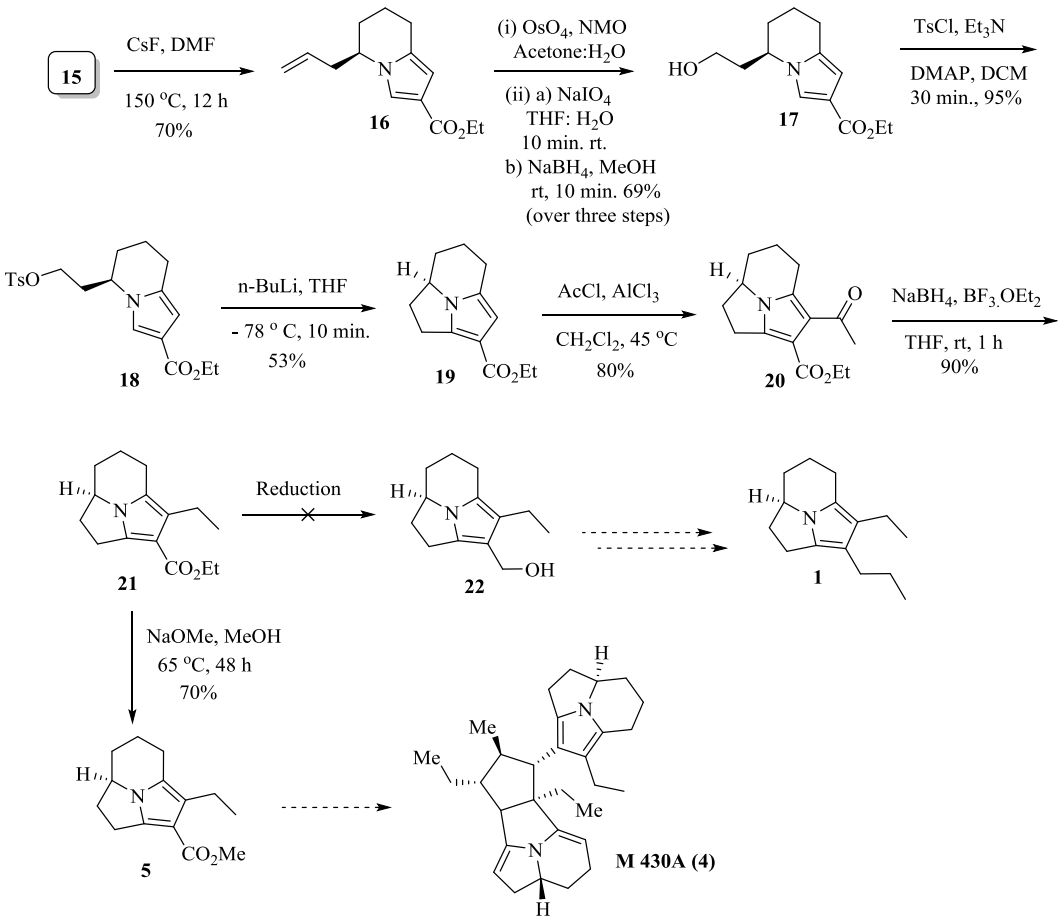
The synthesis began from commercially available starting material *L*-Pyroglutamic acid **6** which was first subjected to benzyl protection by the treatment with benzyl bromide in DCM followed by Boc protection to afford Boc protected benzyl ester **7** in two steps (**scheme 3.2**). Ester **7** was treated with lithium triethylborohydride in THF to selectively reduce the cyclic amide to hemiaminal **8**. The resulting hemiaminal **8** underwent etherification with *p*TSA/ methanol and subsequent treatment with $BF_3.Et_2O$/allyl trimethylsilane to afford the inseparable diastereomeric mixture **9** and **10**. The mixture was reduced to a separable diastereomeric mixture of *cis:trans* (**11 : 12**) in (8:2) ratio by $LiAlH_4$ in THF. The spectroscopic data of **11** was in full agreement with reported data in literature. The specific rotation observed for **11** {$[\alpha]_D^{20}$ = +6.3 (*c* = 0.3, CH_2Cl_2); comparable with the reported value $[\alpha]_D^{20}$ = +10.3 (*c* = 0.3, CH_2Cl_2)} and the specific rotation of *trans* alcohol **12** {$[\alpha]_D^{20}$ = -44.88 (*c* = 0.3, CH_2Cl_2); was observed **scheme 3.2**.

The major isomer **11** was carried forward to get the desired Myrmicarin skeleton. Hence, alcohol **11** subjected to oxidation with Dess-Martin Periodinane in DCM to give aldehyde, which was treated with Ohira-Bestmann reagent **13** in the presence of K_2CO_3, MeOH to afford the alkyne **14**. Deprotection of Boc group in **14** using TFA followed by treatment with ethyl propiolate and DIPEA in THF provided the enamine **15**.



Scheme 3.2

Enamine **15** was converted to tetrahydroindolizine **16** by the treatment of CsF in DMF *via aza*-Claisen rearrangement. Tetrahydroindolizine **16** was subjected to dihydroxylation in presence of OsO_4 and NMO followed by oxidative cleavage with $NaIO_4$ to furnish unstable aldehyde, which immediately reduced to alcohol **17** upon treatment with $NaBH_4$ in MeOH (69% over three steps). The alcohol **17** was converted to tosylate **18** using TsCl and Et_3N in DCM. Compound **18** underwent base-mediated intramolecular cyclization to accomplish tricyclic core moiety **19**. Friedel-Crafts acylation was carried out on substrate **19** to introduce an acetyl group at C-4 of the pyrrole ring, using acetyl chloride and $AlCl_3$ in DCM to provide **20**. The reduction of keto carbonyl in compound **20** was successfully achieved in presence of $NaBH_4/BF_3.OEt_2$ in THF to install ethyl substituent at C-4 position of pyrrole. Next, we tried to reduce ester carbonyl of **21**, subsequent oxidation followed by Wittig reaction and hydrogenation to build *n*-propyl functionality on C-3 position. However, the reduction of ester group was unsuccessful under various conditions.



(**Scheme 3.3**)

Therefore, the ethyl ester of **21** was subjected to transesterification to get methyl ester **5** (a known intermediate) using freshly prepared methanolic solution of NaOMe.

Conclusion:

In conclusion, a novel enantioselective approach has been described towards the synthesis of Myrmicarin alkaloids synthesis. Enyne-assisted annulation strategy for pyrrole-piperidine ring system *via aza*-Claisen rearrangement. Tricyclic core of Myrmicarin alkaloids was prepared in 18-steps.