Development of a Parallel Strategy for the Synthesis of a Library of 2-(3-Formyl-5-arylfuran-2-yl)ethylcarbamates from Dihydropyridinones

By

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Chairperson

Committee members

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An Na Kim, M.S.

The University of Kansas, 2008

2,3-Dihydropyridin-4(1*H*)-ones were utilized as scaffolds for the syntheses of libraries of 5-arylethynyl-2,3-dihydropyridin-4(1*H*)-ones and 2-(3-formyl-5-arylfuran-2-yl)ethylcarbamates. 2,3-Dihydropyridin-4(1*H*)-ones were prepared from piperidones, ynones, and pyridones and used for the synthesis of a library of 5-arylethynyl-2,3-dihydropyridin-4(1*H*)-ones employing a Sonogashira coupling reaction. Further reaction of these compounds using an Au(III)-catalyzed cyclization method yielded formylfurans.

N-Boc and N-benzyl protected 2,3-dihydropyridin-4(1*H*)-ones were prepared for the Sonogashira coupling reaction. N-Boc-protected 5-iodo-2,3-dihydropyridin-4(1*H*)-ones provided *tert*-butyl 5-arylethynyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylates in moderate to excellent yields while the N-Bn-protected enaminones provided very low yields of 5-arylethynyl-1-benzyl-2,3-dihydropyridin-4(1*H*)-ones.

Furan formation was achieved by Au(III)-catalyzed and Cu-mediated cyclizations. *tert*-Butyl 1-(3-formyl-5-phenylfuran-2-yl)propan-2-ylcarbamates were

obtained during the Sonogashira coupling reactions catalyzed by Cu(I), while *tert*-Butyl 1-(3-formyl-5-phenylfuran-2-yl)-3-phenylpropan-2-ylcarbamates were formed by the Au(III)-catalyzed cyclization. Some of the furans were obtained by both methods. Only in the case of *tert*-butyl 4-methoxy-2-*p*-tolyl-6,7-dihydrofuro[3,2-*c*]pyridine-5(4*H*)-carboxylate was the –OMe group retained under Au(III)-catalyzed cyclization conditions, which involved methanol as a nucleophile. In all other cases, N-Boc 3-formyl furans were formed. A library of 16 compounds of functionalized furans possessing the N-Boc adehyde functionality was constructed in moderate to excellent yields.

Acknowledgements

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Table of Contents

List of Compounds

Chapter 1. Introduction

1.1 Background of Enaminone Chemistry

Enaminones, indicating any compound with the conjugated system N–C= C–C=O shown in **Figure 1**, have been known for many years.[1, 2]

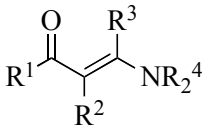
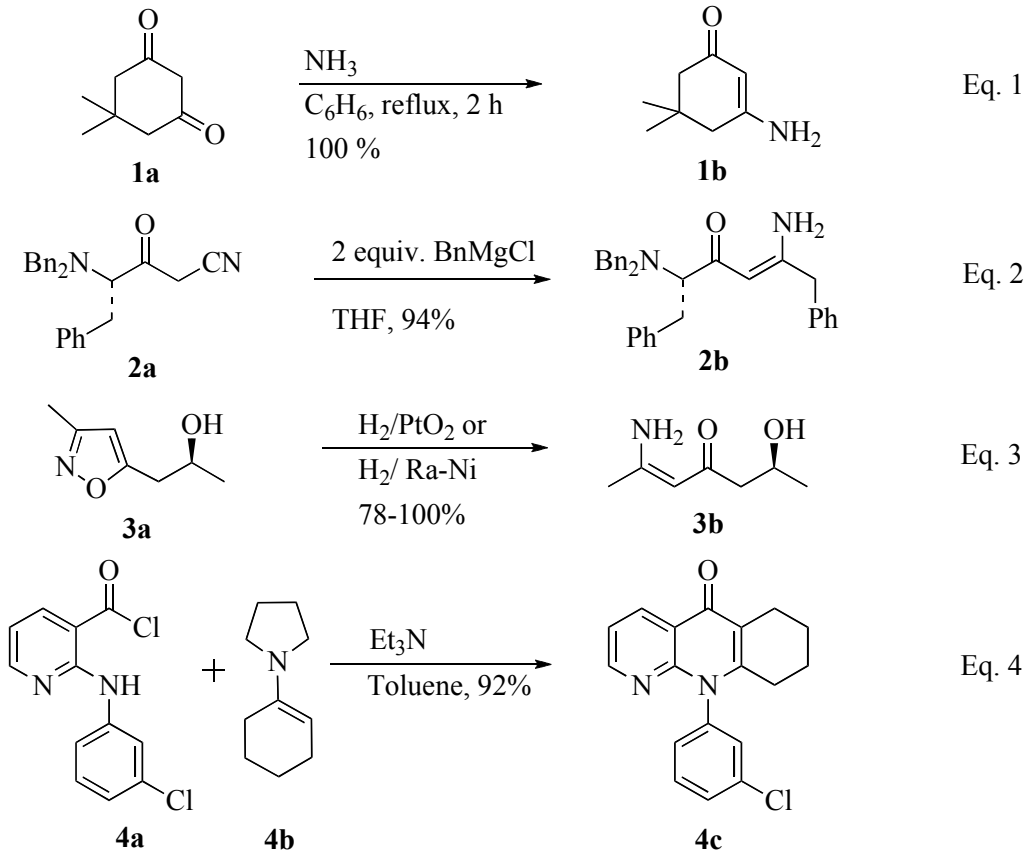


Figure 1. A symbolized structure of enaminones.

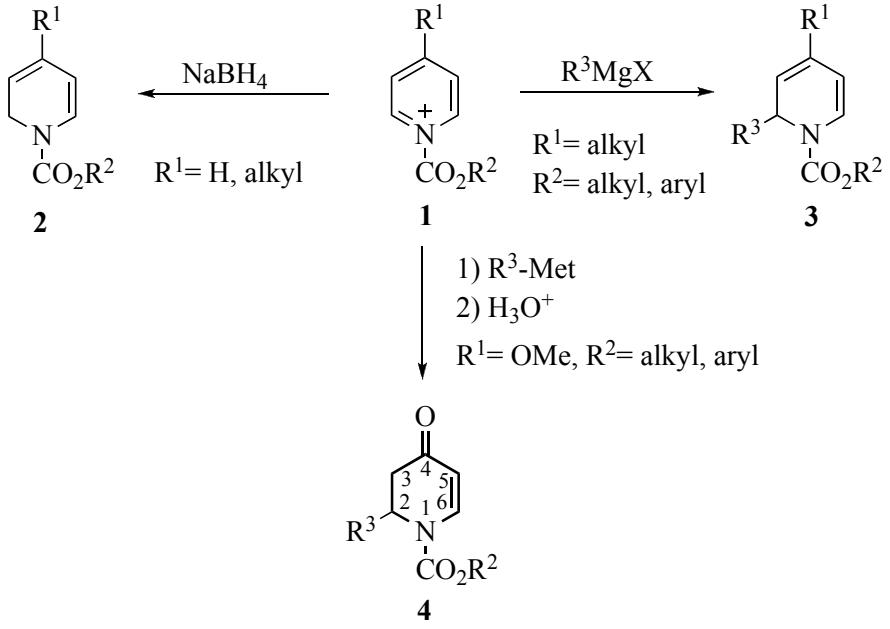
There are various synthetic methods of enaminone formation such as addition reactions, cleavage of heterocycles, acylations of enamines and so on.[2] Eq.1 (**Scheme 1**) is shown an example of enaminone formation by a condensation reaction. Dimedone **1a** reacts with ammonia under refluxing condition to provide enaminone **1b**. Eq.2 of **Scheme 1** is an example of an addition reaction. Benzylmagnesium chloride was added to nitrile **2a** to form enaminone **2b** in a very good yield.[3] The reduction of isoxazole derivatives has also been studied toward enaminone formation, shown in Eq. 3 (**Scheme 1**). A classical reduction method is applied in Eq. 3 to cleave the isoxazole ring of **3a** using hydrogen with PtO_2 or Raney Ni to give 78 and 100% yield of enaminone **3b**, respectively.[4, 5] Eq. 4 (**Scheme 1**) shows an example of acylation of an enamine.[6] Acid chloride **4a** reacts with enamine **4b** in the presence of Et_3N to give tricyclic pyridone **4c** in 92% yield. Furthermore, there are many examples of enaminone formations reported using condensation reactions.[1, 7, 8]



Scheme 1. Enaminone formations from various reactions; Eq.1[8]: condensation reaction, Eq.2[3]: addition reaction, Eq. 3[4, 5] cleavage of heterocycles, and Eq. 4[6]: acylation of enamines.

In 1972, Foowler[9] published a useful method for enaminone formation by the reduction of pyridines with sodium borohydride in the presence of alkyl chloroformate resulting in 2-unsubstitued 1-(alkoxycarbonyl)-1,2-dihydropyridines **2** via 1-acylpyridinium salt **1** (**Scheme 2**). These heterocyclic compounds are particularly useful for the syntheses of various alkaloids and novel ring systems. Applications of these heterocycles for the Diels-Alder and other reactions have been investigated by several research groups.[10-13]

In 1970, prior to Foowler's report, Fraenkel and co-workers reported that 4-picoline reacted with Grignard reagents in the presence of ethyl chloroformate to give



Scheme 2. Cyclic enaminone formation.

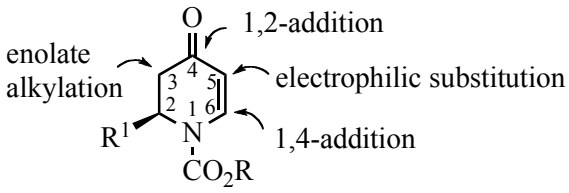
2-substituted 1-(ethoxycarbonyl)-1,2-dihydropyridines **3**.[14] These substituted 1,2-dihydropyridines **3** and 2,3-dihydro-4-pyridones **4** were prepared by the addition of nucleophiles to 1-acylpyridinium salts **1** and were utilized as building blocks for the syntheses of natural products. The C2 substitutents of **3** and **4** are in a pseudoaxial orientation due to A(1,3) strain,[15] providing a conformational restriction in the molecules. This effect results in high facial selectivity in the Diels-Alder reaction of **3**.[16, 17] Similarly, the reaction with molecule **4** shows stereoselectivity as a result of conformational preference of **4** for 1,2- and 1,4- additions[18-20] to the enone moiety, C3 alkylation,[21-23] Luche reduction of the C4 carbonyl,[18-20, 24] and intramolecular radical cyclization.[25] Furthermore, Comins and his co-workers have studied extensively the

addition of Grignard reagents to 1-acylpyridinium salts and developed the syntheses and synthetic applications of heterocycles **3** and **4** since 1982.[26] Since the piperidine moiety are found in many natural products, Comins and co-workers utilized **3** and **4** as synthetic intermediates for the preparation of various natural products, such as piperidine, indolizidine, quinolizidine, and *cis*-/*trans*-decahydroquinoline alkaloids.[27, 28]

1.2 Current Study

Syntheses of natural products are challenging subjects to organic and medicinal chemists. Although many natural products are biologically active, their isolated yields from natural resources are often too low for extensive studies of their properties. Many natural products, however, have common moieties such as pyrroles, indolizidines, quinolizidines, perhydroindoles, and piperidine.[27, 29] The development of new synthetic methodology of these heterocycles will provide better access to these structures to medicinal chemists. As mentioned earlier, since the piperidine moiety is quite common in many natural products, especially in alkaloids, the preparation of these alkaloids through cyclic enaminone intermediates is well known in the literature.[27, 29-33]

Cyclic enaminones provide the scaffolds for annulations toward systems such as pyrroles, indolizidines, quinolizidines, and perhydroindoles.[2, 27, 29, 34] **Figure 2** shows



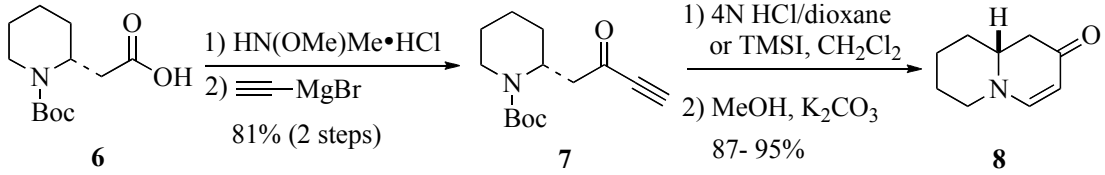
5

Figure 2. Synthetic utilities of *N*-acyldihydropyridones **5**.[35]

the synthetic utility of cyclic enaminones. Cyclic enaminone, 2,3-dihydropyridin-4-one, has a simple "enone" structure acting as a Michael acceptor in conjugate additions.[34] Substituents at C4[36] and C6[19, 20, 24] can be installed via 1,2 additions and 1,4-conjugate additions, respectively.[35]

For example, 1,2-addition at C4 was achieved by using a cerium-mediated addition of an alkyllithium to **5** to afford allylic tertiary alcohols.[36] Enolate alkylation at C3[22, 37] was carried out in the presence of LiHMDS/MeI to afford *trans*-2,3-dialkyl-2,3-dihydropyridin-4-one in 87% yield.[21] Electrophilic substitution at C5 was also reported by Comins and co-workers.[35] They preformed the iodination at C5 of **5** in the presence of NIS and a catalytic amount of [hydroxy(tosyloxy)-iodo]benzene(HTIB) followed by a palladium-catalyzed cross-coupling reaction to give 5-iodo-2,3-dihydropyridin-4-one in high yield.

Recently, our group started investigating the cyclic enaminone formation through amino-ynone intermediates (**Scheme 3**).[38] The formation of enaminone **8** was initiated from N-Boc-homopipecolic acid, followed by Weinreb amide formation and the addition of ethynylmagnesium bromide to provide ynone **7**. Subsequent amine deprotection and cyclization furnished **8** in excellent yield.



Scheme 3. Enaminone formation from *β*–amino acid.

1.3 The Purpose of the Research

Highly substituted furans are molecular fragments present in many biologically active natural products, as shown in **Figure 3**.[39, 40] In 2004, Larock and co-workers

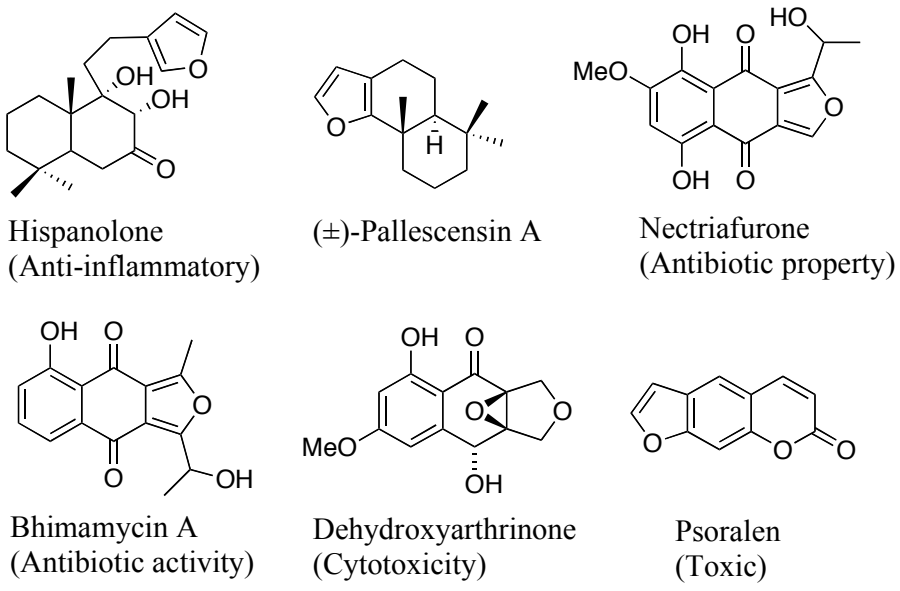
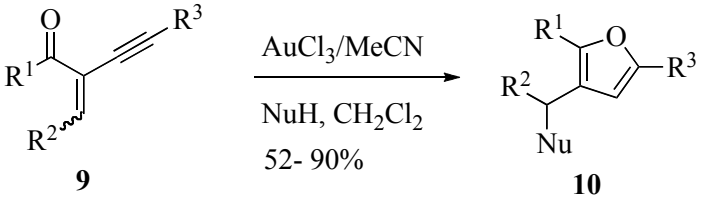


Figure 3. Furan containing natural products.

published an efficient method to synthesize highly functionalized furans from 2-(1-alkynyl)-2-alken-1-ones (**Scheme 4**) using Au(III) as a catalyst.[41] They installed the alkynyl group on the C2 position in the cyclohexenone system via a Sonogarshira coupling reaction, and then the β–ynone **9** reacted with the $AuCl_3$ catalyst in the

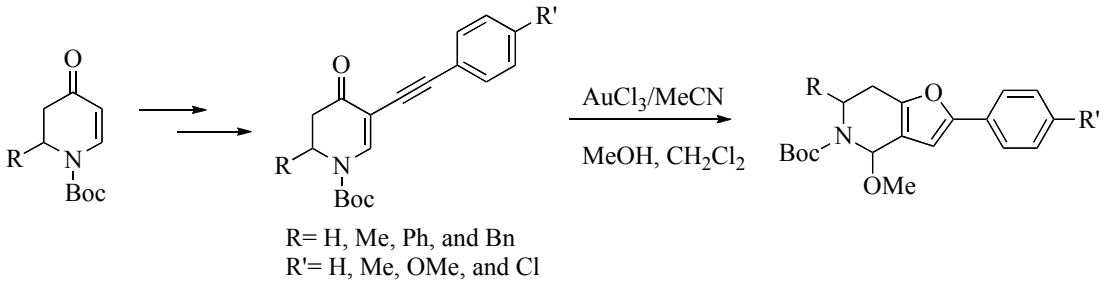
presence of nucleophiles to afford highly functionalized furans **10**. Larock's



9 **10**

Scheme 4. The Au(III)-catalyzed cyclization toward functionalized furans.[41]

methodology inspired us to explore the utility of enaminones toward furans synthesis as shown in **Scheme 5**. The furan moiety is very attractive in drug discovery since many natural products that contain the furan moiety are biologically active.[42]



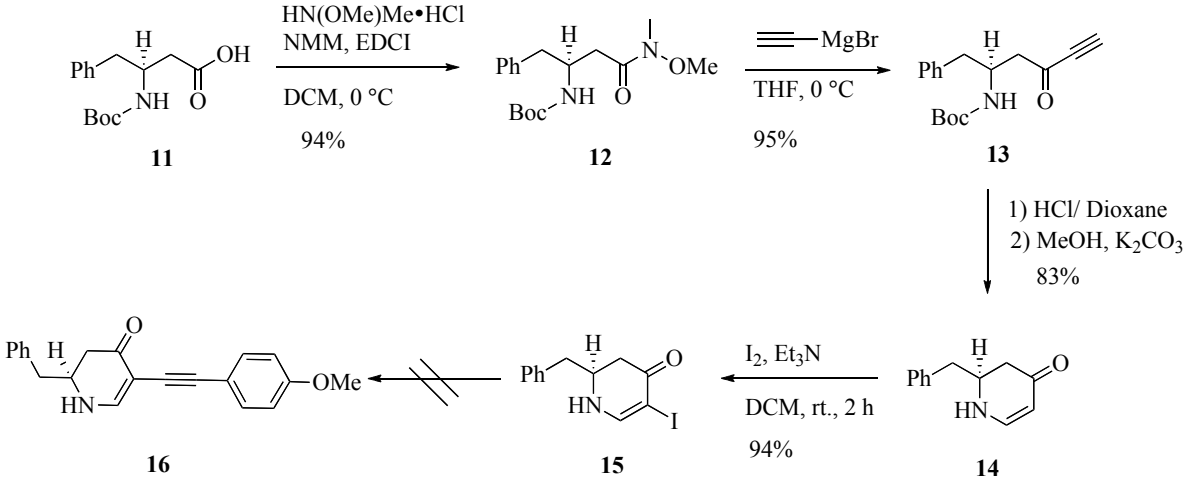
Scheme 5. The utilization of enaminones toward the synthesis of furans using $AuCl_3$ as a catalyst.

We hypothesized that arylalkynyl groups can be installed at C5 of our enaminone systems by a Sonogashira coupling reaction and that the products can be converted to functionalized furans in the presence of an Au(III) catalyst. Ultimately, this strategy can be extended to construct libraries of alkynyl-enaminones as well as functionalized furans in a combinatorial parallel synthesis fashion.

Chapter 2. Chemistry and Results

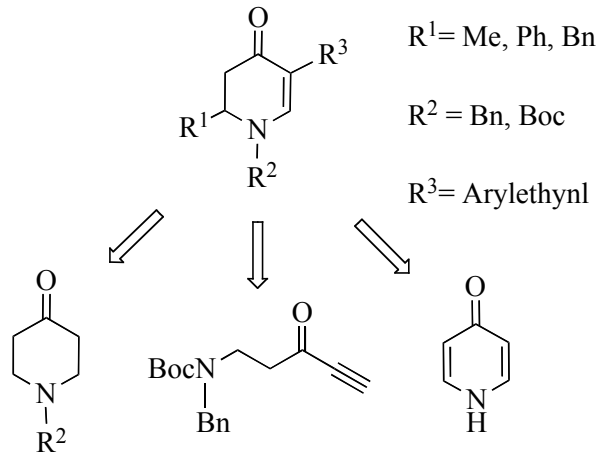
2.1 The Syntheses of 2-Alkyl-5-iodo-2,3-dihydropyridin-4-ones

Scheme 6 shows the initial attempt to prepare a key intermediate towards the synthesis of 2-ethynyl-2,3-dihydropyridin-4-one. We attempted to generate the desired 2-benzyl-2,3-dihydropyridin-4-one (**14**)[38] and then performed α–halogenation at C5 of **14**. Amide **12** was generated by reacting HN(OMe)Me with EDCI and commercially available N-*Boc* protected homo-phenylalanine (**11**). Ynone **13** was prepared by adding ethynyl magnesium bromide to **12**. After Boc deprotection 2-benzyl-2,3-dihydropyridin-4-one (**14**) was obtained. Compound **14** was halogenated at C5 with I_2 and Et_3N at room temperature to afford 2-benzyl-5-iodo-2,3-dihydropyridin-4(1*H*)-one (**15**) in 94% yield.



Scheme 6. The synthesis of (*S*)-2-benzyl-5-iodo-2,3-dihydropyridin-4(1*H*)-one (**15**) from *(S)*-N-Boc-β-phenylalanine (**11**).

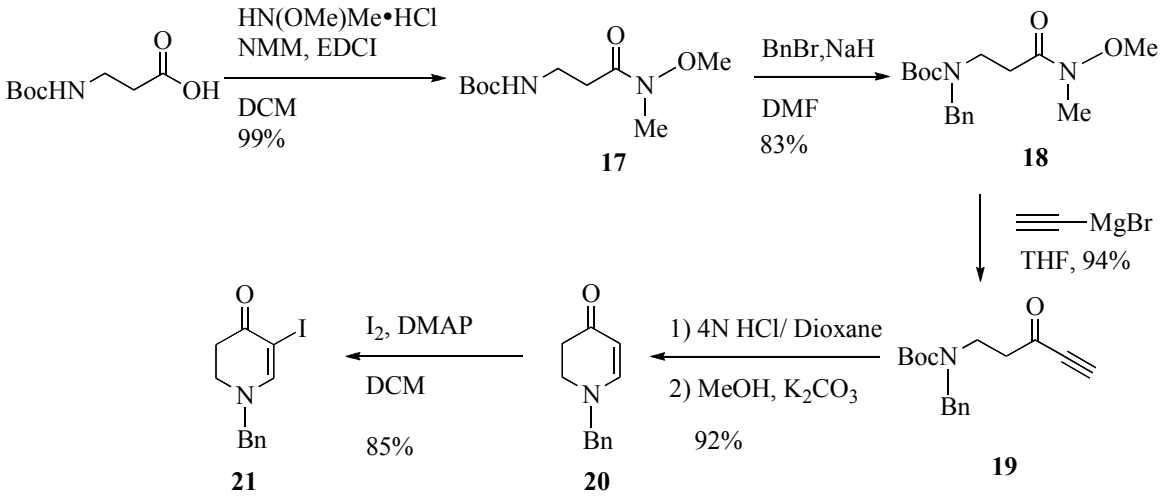
However, the installation of an aryl-ethynyl group at C5 of enaminone **15** using the Sonogashira reaction was not successful. Presumably the free nitrogen was a poison to the Pd (II) catalyst and C5 was not electrophilic enough toward Pd (0). We, therefore, synthesized additional enaminones (**Scheme 7**) to further examine this reaction. As shown in **Scheme 7**, enaminones can be prepared from three different starting materials, such as piperidones, ynones, and pyridone. Starting with piperidones or pyridone shortened our synthetic procedures toward the preparation of enaminones. Enaminone analogues can be obtained in one step synthetic procedures by oxidation of piperidones or conjugate additon to pyridones. N-Bn-protected enaminones can be synthesized from *β*–amino acid via an amino-ynone intermediate.



Scheme 7. Retro-synthetic routes for enaminone formations.

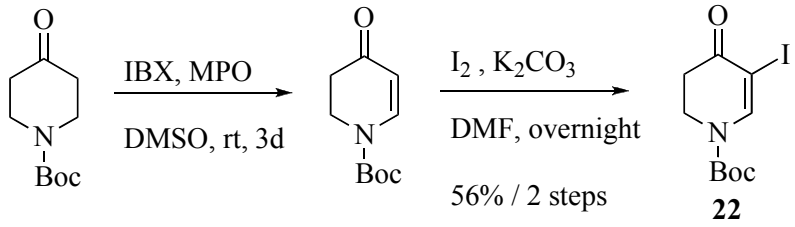
We prepared two different intermediates, the N-Bn-protected iodoenaminone **21** (**Scheme 8**) and N-Boc-protected iodoenaminone **22** (**Scheme 9**), for the coupling reaction. As shown in the **Scheme 8**, N-Boc-β-alanine was reacted with HN(OMe)Me

and EDCI to provide amide **17**. Subsequently Bn-protection of the amine was



Scheme 8. The preparation of N-Bn-5-iodo-2,3-dihydropyridin-4-one from N-Boc-Alanine.

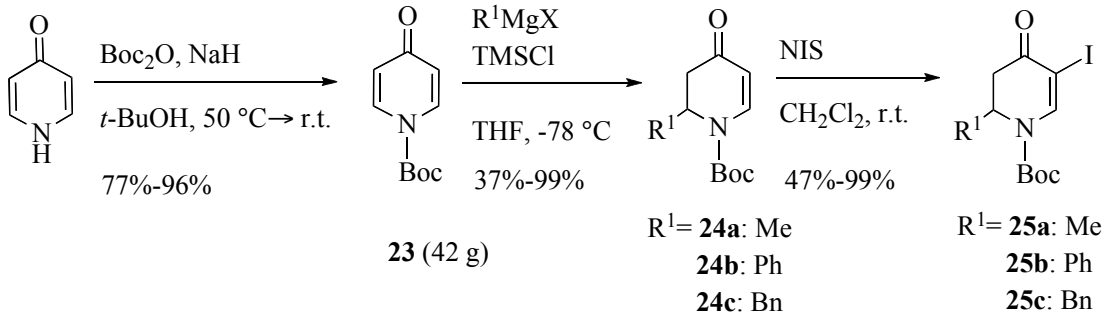
performed to afford amide **18** and ynone **19** was prepared by the addition of ethynylmagnesium bromide. After amine deprotection and cyclization, ynone **19** was converted to cyclic enaminone **20**. Enaminone **21** was prepared by iodination of enaminone **20**. The synthesis of N-Boc-protected enaminone, however, was carried



Scheme 9. The synthesis of N-Boc-5-iodo-enaminone from N-Boc-piperidone.

out by oxidation of N-Boc-piperidone (**Scheme 9**). As shown in **Scheme 9**, we started from commercially available N-Boc-protected piperidone. The piperidone was treated

with freshly prepared IBX with 4-methoxypyridine-*N*-oxide (MPO) in DMSO at room temperature to afford the desired enaminone.[43, 44] Iodination of the enaminone provided us with a good yield of intermediate **22**.



Scheme 10. The synthesis of N-Boc-5-iodo-enaminone from pyridone.

Additionally, N-Boc-protected iodo-enaminones **25** were prepared from pyridone. Commercially available pyridone was treated with Boc-anhydride and NaH in *t*-BuOH at 50 °C to give N-Boc-pyridone **23** in moderate to excellent yields.[45] Pyridone **23** was used to obtain three different enaminone scaffolds **24** upon reactions with three different Grignard reagents in the presence of TMSCl in THF at -78 °C. Then, iodo-enaminones **25a-25c** were prepared using NIS in DCM for the library of 2-alkyl-5-arylethynyl-2,3-dihydropyridin-4-ones (**Scheme 10**).[46]

2.2 The Syntheses of 5-Arylethynyl-2,3-dihydropyridin-4-ones

From the initial failure of the aryl-ethynyl-enaminone synthesis, it was suspected that the cause of failure in the Sonogashira reaction might be the poor electrophilicity at C5 and the free nitrogen. To investigate these hypotheses, we prepared two different precursors for the coupling reaction, N-Bn-enaminone **21** and N-Boc-enaminone **22**.

In order to install the aryl-ethynyl moiety at C5, we tried not only the Sonogashira reaction[41] but also other coupling reactions, such as Suzuki,[47] Negishi,[48] Castro-Stephens,[49] and Suzuki-Miyaura coupling reactions (**Scheme 11**).[50] Preliminary studies had been carried out on enaminone **15** for the Sonogashira reaction, using a series of bases at various reaction temperatures before we carried out the coupling

Table 1. Initial results of cross-coupling reaction with iodoenaminone **15**

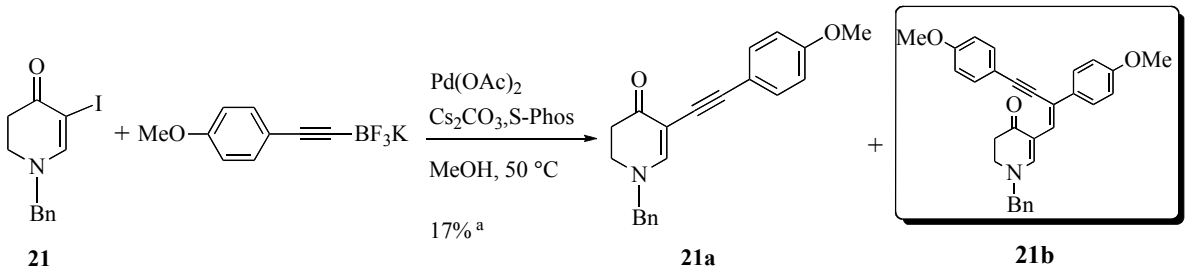
Base	Solvent	Temp.(°C)	Time (h)	Product
[a]DIPA	THF	0→ r.t.	24	Dehalogenated **14**
[a]Et_3N	DMF	r.t.	24	Dehalogenated **14**
[a]Et_3N	DMF	45	24	a dimer of **14**
[b]K_2CO_3	DMF	110	27	Decomposition of **15**

a: Sonogashira coupling reaction ($Pd(PPh_3)_4$, CuI, and 4-methoxy-1-ethynyl benzene were used additionally.)
b: Castro-Stephens coupling reaction (CuI and PPh_3 were used additionally.)

reaction of enaminone **21** and **22**. **Table 1** is shown the initial results of cross-coupling reaction with iodoenaminone **15**. DIPA in THF (0 °C to room temperature overnight) and Et_3N in DMF at room temperature provided the dehalogenated enaminone **14**. Reaction at 45 °C for 24 h produced the dimer of **14**. The Catro-Stephens coupling reaction[49] was also carried out at 110 °C in DMF for 27 h and decompositon of enaminone **15** was observed. In additon, Suzuki coupling reaction[47] of enaminone **15** with a different coupling partner, 4-methoxy-phenyl boronic acid, provided the same dehalogenated enaminone **14** and unreacted starting material. The free nitrogen and the poor elecrophilicity of **15** were problematic for the coupling

reaction. Therefore, iodoenaminones **21** and **22** were expected to perform better in the coupling reaction.

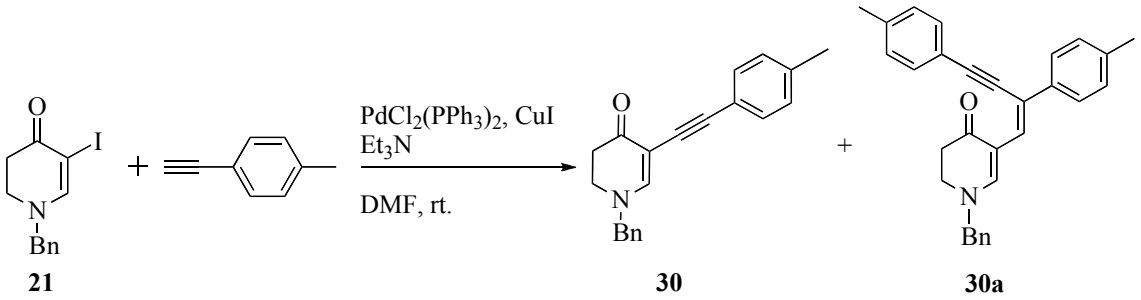
A Negishi coupling reaction[48] was the first attempt of a coupling reaction with enaminone **21** but only dehalogenated enaminone **20** and starting material **21** were observed. From the results of the Negishi coupling reaction, it appeared that the cause of failure in the coupling reaction was due to the poor eletrophilicity of enaminone **21**. We, therefore, performed a Suzuki-Miyaura coupling reaction of enaminone **21** (**Scheme 11**). Only trace amounts of our desired product **21a** were observed. Also the double addition product **21b** and dehalogenated enaminone **20** were obtained. We found a very weak signal of **21a** by mass spectroscopy while the ^{1}H NMR showed **21b** as the major product.



Scheme 11. Suzuki-Miyaura coupling reaction with N-Bn-iodo-enaminone.[50]a: The yield is a mixture of **21a** and **21b**.

From the Suzuki-Miyaura coupling reaction, we observed the production of the major by-product **21b,** as shown in **Scheme 11.** Arylenynes, such as **21b**, have been observed by Pal and co-workers during their studies of the palladium-catalyzed reaction of 3-iodothioflavone with a terminal alkyne.[51] It is known that Cu(I) acts as a co-catalyst in Sonogashira reactions to activate terminal alkynes to form a Cu-

acetylide. The Cu-acetylide undergoes transmetallation with the arylpalladium halide to generate the alkynylpalladium and subsequent reductive elimination gives the final product.[51, 52] Therefore, Pal and co-workers carried out the Sonogashira coupling



Scheme 12. Sonogashira coupling reaction with N-Bn-iodo-enaminone **21**.[51]

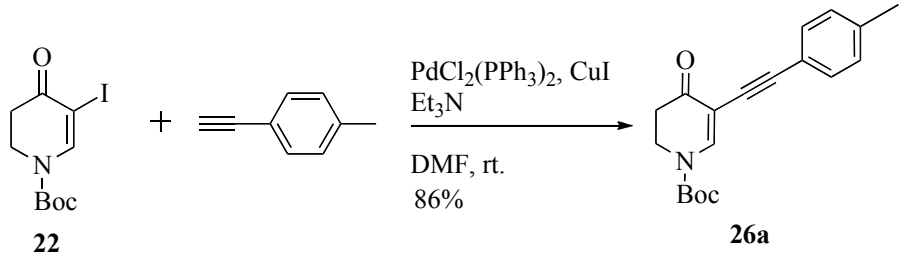
Table 2. Optimization of Sonogashira reaction with iodo-enaminone **21**.

Conc.	Pd	Cu	Cu/Pd	Time	Temp	Yield		
(M)	(eq)	(eq)	ratio	h	°C	**30**	**30a**	**21**
0.01	0.04	0.05	1.25	20	rt	>6%	23%	<7%
0.01	0.04	0.4	10	96	rt	10%	0%	50%
0.1	**0.05**	**0.25**	**5**	**3**	**rt**	**50%**	**11%**	**0%**
a, 0.1	0.05	0.5	10	19	rt	18%	trace	trace
b, 0.1	0.05	0.5	10	21	rt	11%	trace	trace
0.1	0.05	0.5	10	48	0->rt	Lost	trace	0%
0.1	0.1	0.5	5	21	0->rt	18%	5%	0%
0.1	0.1	1	10	18	0->rt	trace	trace	0%
0.1	0.1	1	10	10	0	>16%	trace	0%

a: $Pd(PPh_3)_4$ was used instead of $PdCl_2(PPh_3)_2$,b: 4 eqiv. of (*S*)-prolinol was used instead of Et_3N.[53]

reaction under Cu-free conditions and observed an increased yield in the desired product. Additionally, they performed the reaction using lesser amounts of alkynes

and found that the generation of the double addition product was not dependent on the quantity of alkynes used but possibly was due to the use of Cu as a co-catalyst. These observations were consistent with our findings from the experiments of the Suzuki-Miyaura coupling reaction as well as the Songashira reaction with iodo-enaminone **21**. We did not observe the bis-addition by-product, seen in the Suzuki-Miyaura coupling reaction, as shown in **Scheme 11**. The same reaction conditions were applied to N-Bn-5-iodo-dihydropyridin- 4-one (**21**). We subsequently optimized the reaction conditions, as shown in **Scheme 12** and **Table 2**. We carried out a series of Sonogashira coupling reactions with various amounts of CuI, as shown in **Table 2.** In **Table 2**, the yield of our desired product **30** increased while the amount of **30a** decreased as the ratio of Cu to Pd increased. The results indicated that the Cu catalyst played a critical role in suppressing the formation of **30a**, although the precise role of the Cu catalyst is unknown. We, however, did not observe the bis-addition by-product formation in the Sonogashira reaction of N-Boc-protected enaminones **25a**-**25c**, while N-Bn-protected enaminone **21** was converted to **30** and **31a** in very low yield. Therefore, the amount of CuI we used was a key element to control for the Sonogashira reaction of enaminone **21** in order to prevent forming **30a**.

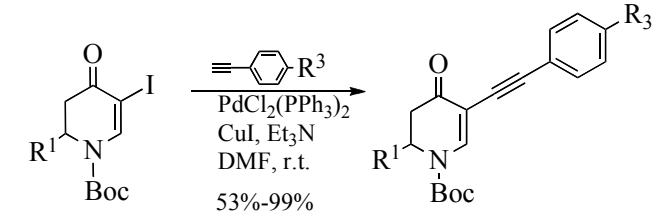


22 **26a**

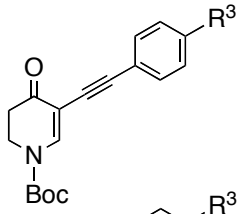
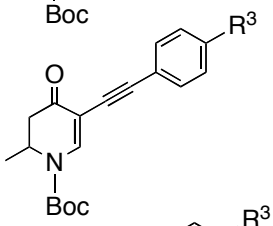
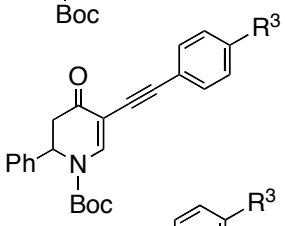
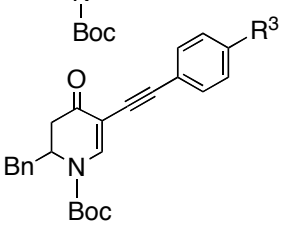
Scheme 13. Sonogashira coupling reaction with N-Boc-iodo-enaminone.[51]

N-Boc-2,3-dihydropyridin-4-one (**22**) transformed smoothly to the coupled product **26a** in 86%, as shown in **Scheme 13**.[51] Since the Sonogashira coupling

Table 3. The syntheses of 2-arylethynyl-enaminone by Sonogashira reaction.



R^1= H, Me, Ph, Bn R^3 = H, Me, OMe, Cl

Product	R^3	Yield(%)
	**26**: H	trace[a]
	26a: Me	86
	26b: OMe	64
	26c: Cl	trace[a]
	**27**: H	60[b]
	27a: Me	53
	27b: OMe	70
	27c: Cl	64
	**28**: H	86
	28a: Me	98
	28b: OMe	86
	28c: Cl	86
	**29**: H	92
	29a: Me	98
	29b: OMe	94
	29c: Cl	93

a:Compound **26** and **26c** were observed (^{1}H NMR spectra) but the functionalized furans **31a** and **31d** were isolated.

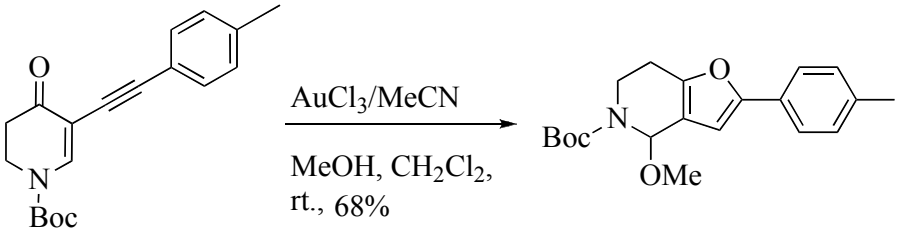
b: The yield is based on ^{1}H NMR (2:1 ratio of compound **27** to furan **32a**).

reaction was successful in the case of N-Boc-5-iodo-2,3-dihydropyridin-4-one (**22**), we decided to build a library of 2-alkyl-5-arylethynyl-2,3-dihydropyridin-4-ones. **Table 3** shows the library of 14 compounds prepared by the Sonogashira coupling reaction in moderate to excellent yield. The optimized conditions, as shown in **Table 2**, were successfully applied to enaminones **25b** and **25c**. These enaminones were converted to compounds **28**-**29c** in 86-98% yield, while enaminone **22** and **25a** provided 5-arylethynyl-2,3-dihydropyridin-4-one as well as the corresponding functionalized furans, depending on the alkynyl and enaminone substrates.

Therefore, enaminone scaffold **24** provided excellent opportunities for the synthesis of a library of 2-alkyl-5-arylethynyl-2,3-dihydropyridin-4-one with various reactivities among enaminones **21**, **22**, and **25a-25c** in the Sonogashira reaction.

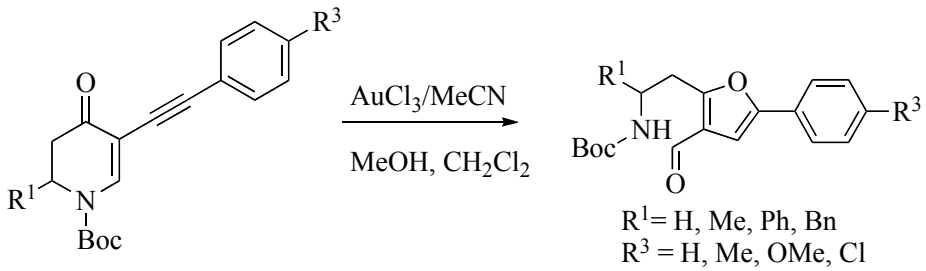
2.3 The Syntheses of Functionalized Furans

In 2004, Larock and co-workers published the Au(III)-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones to generate highly substituted furans.[41] This methodology was successfully applied to the enaminone system **26a**. The synthesis of



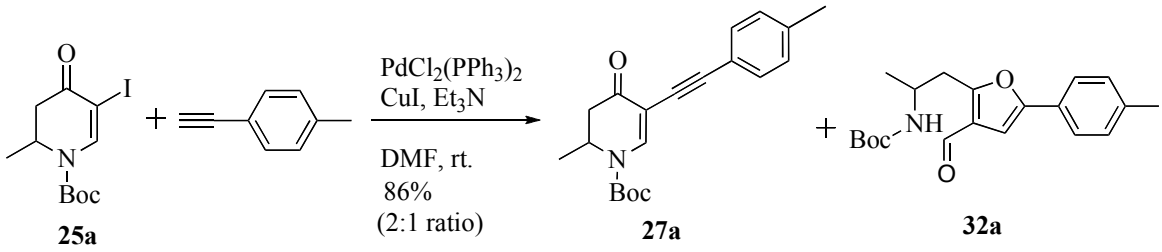
26a **31**

Scheme 14. The synthesis of tetrahydrofuropyridines by $AuCl_3$-catalyzed cyclization.



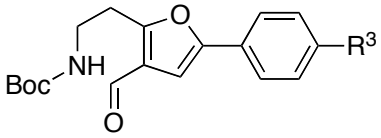
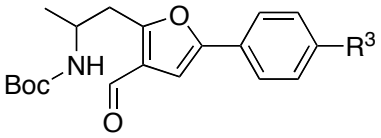
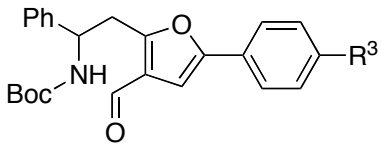
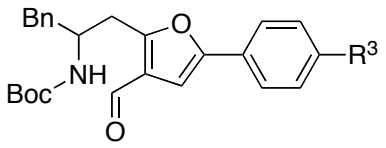
Scheme 15. Au(III)-catalyzed cyclization of ynones and demethylation of functionalized furans.

functionalized furans was established using Au(III)-catalyzed cyclization, as shown in **Scheme 14** and **Table 4**. However, an unexpected result was found during the cyclization using the Au catalyst. The cyclization, as shown in **Scheme 14**, was the only case in which the -OMe group at C4 was retained. With precursors **26b-29c** (**Scheme 15** and **Table 4**) the corresponding aldehyde analogues were obtained. Additionally, we observed formyl furans as by-products of the Sonogashira coupling reactions of enaminone **22** and **25a**, as shown in **Scheme 16**. Compounds **26** and **26c** were converted to furans directly during the coupling reaction.



Scheme 16. Furan formation during the Sonogashira coupling reaction.

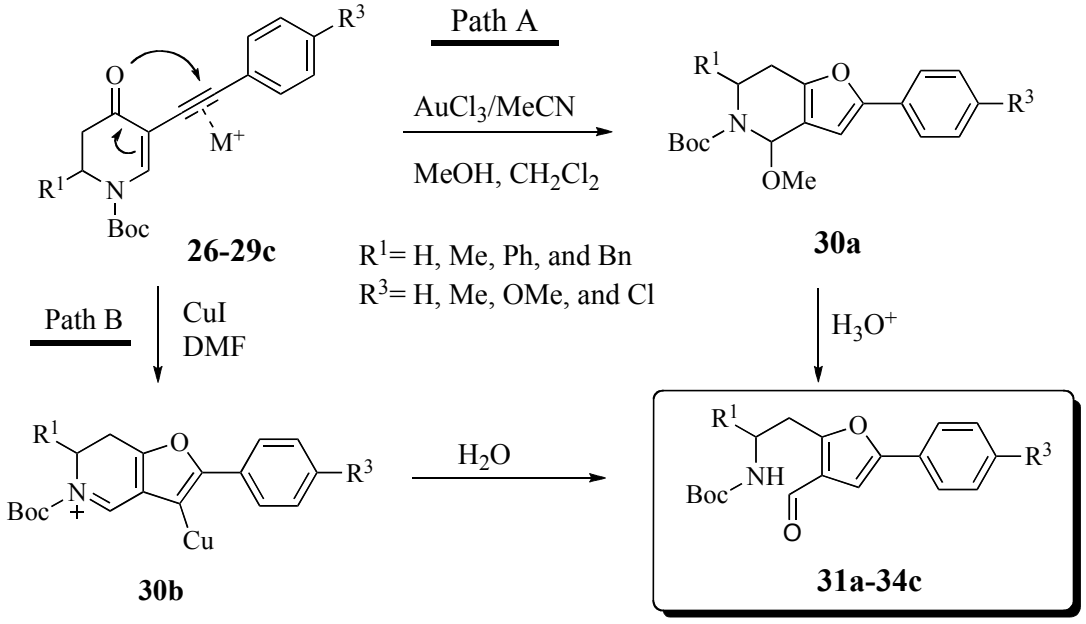
Table 4. Au(III)-catalyzed cyclization of ynones and formyl functionalized furans.

Product	R^3	Method	Yield (%)
	**31a**: H	**B**	67
	31b: Me	**A**	trace
	31c: OMe	**B**	60
	31d: Cl	**B**	57
	**32** : H	**B**	15[a]
	32a: Me	**B**	74
	32b: OMe	**B**	70
	32c: Cl	**B**	40
	**33** : H	**A** (**B**)	23 (38)[a]
	33a: Me	**A**	48
	33b: OMe	**A**	77
	33c: Cl	**A**	36
	**34** : H	**A** (**B**)	63 (89)
	34a: Me	**A**	71
	34b: OMe	**A**	77
	34c: Cl	**A**	43

Method **A** : Au(III)-catalyzed cyclization, Method **B** : Cu(I)-catalyzed cyclization
a : based on ^{1}H NMR

Schemes 15 and **16** show the methods for furan synthesis using Au(III) and Cu(I). Both schemes are showing that aldehydes were formed, instead of the methoxy derivatives. Initially, it was believed that Au(III) might be involved in the elimination of the methoxy group. Because the reaction took more than 2 h go to completion, we explored a shorter reaction time (less than 1 h). Even the reduced reaction time provided the 3-formyl furan. Additionally, when furan **31** was treated with the Au(III) catalyst in MeCN, conversion to the 3-formyl furan took place. **Scheme 17** shows the proposed pathways for the cleavage of the bicyclic intermediate **30a** to provide furans

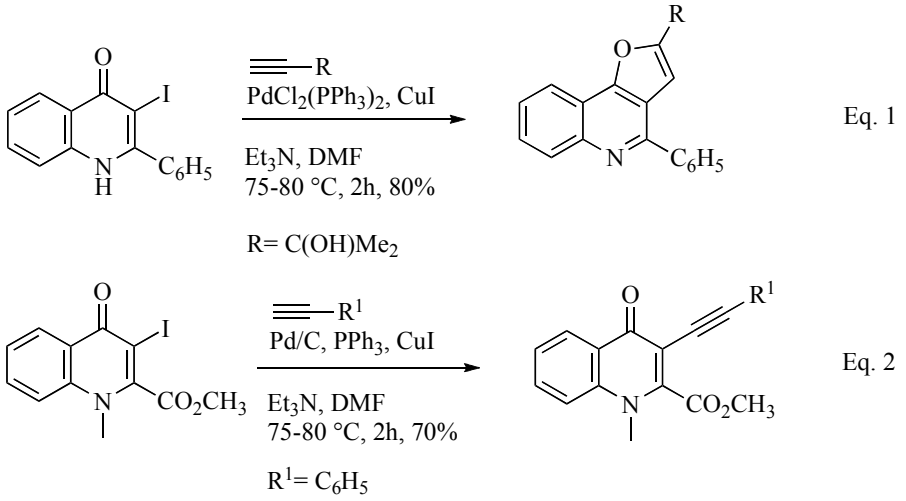
31a-34c. We believe that the Au(III)-catalyzed cyclization provides bicyclic intermediate **30**, which is hydrolyzed under acidic conditions to form an aldehyde (Path A, **Scheme 17**). We observed aldehyde formation on a TLC plate, indicating that the bicyclic system was very sensitive to acid. ^{1}H and ^{13}C NMR data showed signals at 9.5 ppm and 185 ppm, respectively, verifying aldehyde formation. Alternatively, furan formation could occur without nucleophiles such as methanol,



Scheme 17. Proposed pathways of 3-formyl furan formation.

since we observed an unexpected furan formation during our studies on the Sonogashira coupling reaction. Furans could be generated by an intramolecular pathway, whereby the lone-pair electrons of N in the enaminone moiety could be involved in furan formation (Path B, **Scheme 17**). Adventitious water could also play a role in these reactions.

In 2006, Pal and co-workers published the results of Sonogashira coupling reactions as a continuation of their research on 2-substituted 3-iodo-1*H*-quinolin-4-one to synthesize furoquinolines as shown in **Scheme 18**.[54] They observed furan formation as well as coupling products during the Sonogashira reaction. They claimed that the N-H of the quinolone ring was responsible for the cyclization after the coupling step (Eq.1) because they only isolated the coupling product when methyl 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylates with terminal alkynes were treated under the Sonogashira reaction conditions (Eq. 2). They did not observe the formation of furoquinoline.



Scheme 18. Furan formation during the Sonogashira coupling reaction.[54]

In 2005, furan formation by Cu-mediated cyclization was reported by Yamamoto and co-workers.[55] In their study, Cu-mediated cyclization of 2-(1-alkynyl)-2-alken-1-ones occurred in the presence of alcohols with a catalytic amount of Cu salt in DMF at 80 °C. We used 10 % Cu(I) in DMF at room temperature, in order to suppress the formation of undesired double addition products. Consequently,

some of our enaminone substrates underwent Cu-mediated cyclization while others did not. N-Boc-iodo enaminone **25a**, for instance, was converted to two major products after Sonogashira coupling reactions (**Scheme 16** and **Table 4**), in 2:1 ratio of **27a** to **32a** based on ^{1}H NMR.

Therefore, the formations of highly substituted furan analogues were achieved by two methods. Au(III)-catalyzed cyclization and Cu(I)-mediated cyclization[55] during the Sonogashira reaction, both effected furan formation. Moreover, a library of 16 compounds of functionalized furans was constructed via Sonogashira reaction and Au(III)-catalyzed cyclization in moderate to excellent yield (**Table 4**). Finally, construction of the library of functionalized furans from an enaminone scaffold demonstrated useful opportunities for the synthesis of diversity libraries.

2.4 Conclusion

There are many biologically active compounds containing a furan moiety as a structural unit. We hypothesized that highly substituted furans can be synthesized using Au(III)-catalyzed cyclization on enaminone derivatives functionalized with an arylalkynyl group at C5. A library of functionalized furans was constructed in moderate to excellent yields.

Enaminones were prepared through three different routes with various starting materials, such as β-amino acids, piperidones, and pyridone. Using N-Boc-protected pyridone provided excellent opportunities for the syntheses of various enaminones toward molecular library construction. Palladium-catalyzed Sonogashira coupling

reactions of enaminones were successfully carried out under mild conditions. We also observed furan formation during the coupling reaction of substrates **22** and **25a**.

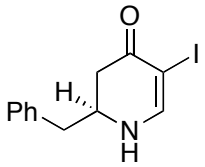
Highly substituted furans were prepared by Au(III) and Cu(I)-catalyzed cyclization. Further investigations should be carried out to evaluate the role of nucleophiles for the Au(III)-catalyzed cyclization as well as the elimination process during the cyclization reaction. It is necessary to investigate the furan formation by Cu(I)-mediated cyclization in future studies. Finally, the molecular library of functionalized furans can be utilized for the syntheses of sub-libraries in future studies.

Experimental Section

General Method

All starting materials and reagents are commercially available unless otherwise specified. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DRX400 MHz (400 and 100 MHz, respectively), or DRX 500 MHz (500 and 125.5 MHz, respectively). All NMR samples were dissolved in $CDCl_3$ and the spectra were recorded in parts per million (ppm). All abbreviations are as following: s, singlet; d, doublet; t, triplet; br s, broad singlet; m, multiplet; dd, a set of doublet. High-resolution mass spectra (HRMS) were provided by the Bruker BioTOF II mass spectrometer with electrospray ionization (ESI) method.

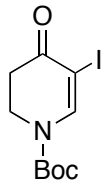
(*S*)-2-Benzyl-5-iodo-2,3-dihydropyridin-4(1*H*)-one (15).



(*S*)-2-Benzyl-2,3-dihydropyridin-4(1*H*)-one (**14**) (14.0 mg, 0.075 mmol) was dissolved in dry CH_2Cl_2 (3 mL) under N_2 at room temperature. Then the solution of I_2 (29.0 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added and subsequently Et_3N (1.0 μL, 0.08 mmol) was added. The resulting mixture was stirred for 30 min. The solution was diluted with CH_2Cl_2. The solvent was removed under reduced pressure. The

crude mixture was purified by silica gel column chromatography (5% Methanol in CH_2Cl_2) to afford 22 mg (94%) of the product as a yellow powder. mp 124-126 °C; R_f 0.71 (5% Methanol in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (d, J = 6.6 Hz, 1H), 7.3-7.1 (m, 5H), 5.1 (br s, 1H), 3.9 (m, 1H), 2.9-2.8 (dd, J = 5.1, 13.7 Hz, 1H), 2.8-2.7 (m, 2H), 2.6-2.5 (dd, J = 3.7, 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7, 156.3, 135.4, 128.6, 128.1, 126.3, 97.5, 54.6, 41.3, 40.1; HRMS (TOF MS ESI) *m/z* calcd for $C_{12}H_{12}INO$ $[M+H]^+$ 314.0042; found 314.0024.

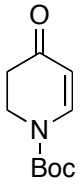
tert-Butyl 5-Iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (22).



A mixture (96.8 mg) of *tert*-butyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate and 1-Boc-4-piperidone (56:44 ratio, based on ^{1}H NMR) was dissolved in dry CH_2Cl_2 (17 mL) under N_2 at room temperature. Then the solution of I_2 (141 mg, 0.561 mmol) in CH_2Cl_2 (11 mL) was added dropwise. Immediately, *N,N*-4-dimethylaminopyridine (128.6 mg, 1.020 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2. Saturated NH_4Cl was added at 0 °C. Then, the organic layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 5 EtOAc/ hexanes) to afford 57 mg (53%) of the product as a

white solid. mp 106-108 °C; R_f 0.46 (1:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (br s, 1H), 4.0 (t, J = 7.2, 7.5 Hz 2H), 2.9 (t, J = 7.4, 7.3 Hz, 2H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 149.1, 148.5, 83.4, 74.0, 41.4, 33.5, 27.1; HRMS (TOF MS ESI) *m/z* calcd for $C_{10}H_{15}INO_3$ $[M+H]^+$ 324.0096; found 324.0078.

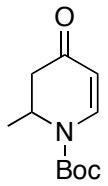
***tert*-Butyl 4-Oxo-3,4-dihydropyridine-1(2H)-carboxylate (24).**



IBX (28.07g, 100.2 mmol) and 4-methoxypyridine-N-oxide (MPO) (12.59 g, 100.2 mmol) were added and dissolved in DMSO (129.0 mL) under Argon gas at room temperature and then stirred for 30 min. Then 1-Boc-4-piperidone (15.4 g, 77.1 mmol) was added and CH_2Cl_2 (64.0 mL) was added. The resulting mixture stirred for 3 days. Reaction mixture was diluted with 5% $NaHCO_3$ and the organic layer was extracted with ethyl ether. Combined organic layers were filtered through a pad of celite and washed with saturated $NaHCO_3$, H_2O and brine. Then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The ^{1}H NMR of the crude mixture (12.74 g) was shown 53% of desired product and 47 % of starting materials. R_f 0.52 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): 7.8 (br s, 1H), 5.3 (d, J = 8.2 Hz, 1H), 3.9 (t, J = 7.3, 2H), 2.5 (t, J = 7.3, Hz, 2H), 1.5 (s, 9H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ193.6, 151.3, 144.0, 111.9, 83.5, 41.9, 35.7, 28.1; HRMS (TOF MS ESI) *m/z* calcd for $C_{10}H_{15}INO_3$ $[M+H]^+$ 324.0096; found 324.0078.

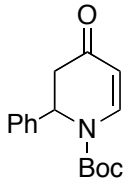
***tert*-Butyl 2-Methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (24a).**



tert-Butyl 4-oxopyridine-1(4*H*)-carboxylate (10.0 g, 51.2 mmol) was dissolved in THF (450 mL) under Ar at room temperature. TMSCl (9.50 mL, 76.8 mmol) was added and the resulting mixture was cooled to -78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then MeMgBr (3M in Et_2O, 39.3 mL, 117.8 mmol) was added slowly. The reaction mixture was stirred overnight and the reaction temperature warmed to room temperature while stirring. The reaction mixture was diluted with EtOAc then quenched with 10% HCl at 0 °C. The resulting mixture was stirred for 10 min. and then the organic layer was extracted with EtOAc. The combined organic layers were washed with Brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 1 EtOAc/ hexanes) to afford 8.55 g (79%) of the product as a yellow solid. R_f 0.62 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, J = 7.8 Hz, 1H), 5.3 (d, J = 8.2 Hz, 1H), 4.7 (t, J = 5.8 Hz, 1H), 2.9 (dd, J = 6.8, 16.4 Hz, 1H), 2.3 (t, J = 16.4 Hz, 1H), 1.6 (s, 9H), 1.3 (d, J = 6.7 Hz, 3H) ;^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 150.0, 139.9, 103.7, 81.3, 46.9, 39.9, 26.1, 14.6;

HRMS (BioTOF II ESI) *m/z* calcd for $C_{11}H_{16}INO_3$ $[M+Na]^+$ 234.1101; found 234.1110.

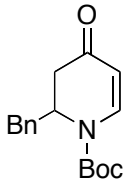
tert-Butyl 4-Oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (24b).



tert-Butyl 4-oxopyridine-1(4*H*)-carboxylate (10.0 g, 51.2 mmol) was dissolved in THF (400 mL) under Ar at room temperature. TMSCl (10.0 mL, 76.8 mmol) was added and the resulting mixture was cooled to -78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then PhMgBr (1.0 M in Et_2O, 56.1 mL, 56.3 mmol) was added slowly. The reaction mixture was stirred overnight and the reaction temperature warmed to room temperature while stirring. The reaction mixture was diluted with EtOAc then quenched with 10% HCl at 0 °C. The resulting mixture was stirred for 10 min. and then the organic layer was extracted with EtOAc. The combined organic layers were washed with Brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 7.96 g (57 %) of the product as a white solid. R_f 0.63 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, J = 8.3 Hz, 1H), 7.3-7.2 (m, 5H), 5.7 (d, J = 7.2 Hz, 1H), 5.3 (d, J = 7.7 Hz, 1H), 3.2-3.1 (dd, J = 7.7, 16.5 Hz, 1H), 2.8 (d, J = 16.5 Hz, 1H),1.4 (s, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 191.9, 151.2, 143.0, 138.8, 128.6, 127.6, 125.6, 106.8, 83.5, 55.6, 41.6, 28.0.

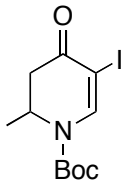
tert-Butyl 2-Benzyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (24c).



tert-Butyl 4-oxopyridine-1(4*H*)-carboxylate (5.00 g, 25.5 mmol) was dissolved in THF (250 mL) under Ar at room temperature. TMSCl (5.00 mL, 38.3 mmol) was added and the resulting mixture was cooled to -78 °C. The reaction mixture was stirred for 30 min at -78 °C, then BnMgCl (2.0 M in Et_2O, 29.3 mL, 58.7 mmol) was added slowly. The reaction mixture was stirred overnight and the reaction temperature warmed to room temperature while stirring. The reaction mixture was diluted with EtOAc then quenched with 10% HCl at 0 °C. The resulting mixture was stirred for 10 min. and then the organic layer was extracted with EtOAc. The combined organic layers were washed with Brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 5.87g (80%) of the product as a white solid. R_f 0.53 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (br s, 1H), 7.3-7.1 (m, 5H), 5.3 (br s, 1H), 4.6 (br s, 1H), 2.9 (dd, J = 6.2, 13.2 Hz, 1H), 2.7 (dd, J = 9.0, 13.2 Hz, 1H), 2.6 (dd, J = 1.8, 16.5 Hz, 1H), 2.3 (d, J = 16.5 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 151.0, 142.0, 136.8,

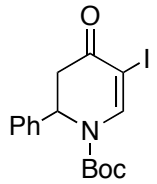
129.6, 128.7, 126.9, 106.4, 83.4, 54.3, 38.7, 36.2, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$310.1414; found 310.1403.

***tert*-Butyl 5-Iodo-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (25a).**



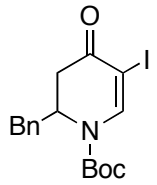
tert-Butyl 2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**24a**) (911.0 mg, 4.310 mmol) was dissolved in dry CH_2Cl_2 (70 mL) under N_2 at room temperature. Then N-iodo-succinimide (4.687 g, 20.68 mmol) was added and the resulting mixture stirred for 3 days. The solution was diluted with CH_2Cl_2. The reaction was quenched with H_2O at 0 °C. The organic layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 986 mg (68%) of the product as a yellow solid. mp 133 -134 °C; R_f 0.43 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (s, 1H), 4.7 (m, 1H), 3.0 (dd, J = 6.7, 16.3 Hz, 1H), 2.6 (dd, J = 1.6, 16.3 Hz, 1H), 1.6 (s, 9H), 1.3 (d, J= 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 149.8, 147.3, 84.2, 73.2, 49.3, 40.6, 28.0, 16.8; HRMS (BioTOF II ESI) *m/z* calcd for $C_{11}H_{16}INO_3$ $[M+Na]^+$ 360.0067; found 360.0067.

***tert*-Butyl 5-Iodo-4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (25b).**



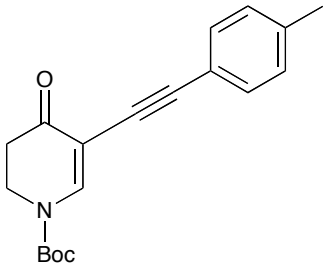
tert-Butyl 4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**24b**) (499.0 mg, 1.850 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under N_2 at room temperature. Then N-iodo-succinimide (1.02 g, 4.52) mmol was added and the resulting mixture stirred for 3 days. The solution was diluted with CH_2Cl_2. The reaction was quenched with H_2O at 0 °C. The organic layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 540 mg (73%) of the product as a yellowish powder. mp 100 -102 °C; R_f 0.42 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5 (s, 1H), 7.3-7.1 (m, 5H), 5.7 (d, J = 7.0 Hz, 1H), 3.2 (dd, J = 7.4, 16.4 Hz, 1H), 3.0 (dd, J = 1.7, 16.4 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 149.8, 147.9, 137.9, 128.6, 127.8, 125.2, 84.1, 74.2, 55.7, 40.4, 27.6; HRMS (BioTOF II ESI) *m/z* calcd for $C_{16}H_{18}INO_3$ $[M+Na]^+$ 422.0224; found 422.0233.

***tert*-Butyl 2-Benzyl-5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (25c).**



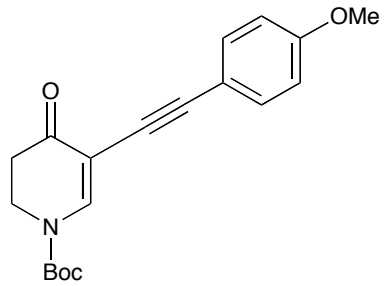
tert-Butyl 2-benzyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**24c**) (495.0 mg, 1.750 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under N_2 at room temperature. Then N-iodo-succinimide (0.956 g, 4.20 mmol) was added and the resulting mixture stirred overnight. The solution was diluted with CH_2Cl_2. The reaction was quenched with H_2O at 0 °C. The organic layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 598 mg (83%) of the product as a yellowish powder. mp 134 °C; R_f 0.47 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (br s, 1H), 7.3-7.1 (m, 5H), 4.7 (br s, 1H), 3.0 (dd, J = 6.2, 13.2 Hz, 1H), 2.8 (dd, J = 9.0, 13.2 Hz, 1H), 2.7 (dd, J = 1.8, 16.5 Hz, 1H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 149.8, 147.4, 136.2, 129.5, 128.7, 127.0, 84.3, 74.0, 54.7, 37.6, 36.4, 28.0; HRMS (BioTOF II ESI) *m/z* calcd for $C_{17}H_{20}INO_3$ $[M+Na]^+$ 436.038; found 436.0384.

***tert*-Butyl 4-Oxo-5-(4-tolylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (26a).**



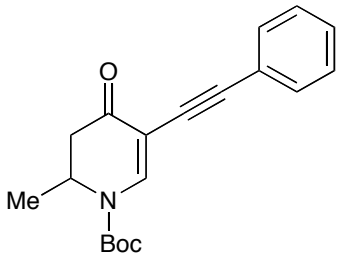
tert-Butyl 5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**22**) (72.0 mg, 0.223 mmol), $PdCl_2(PPh_3)_2$ (8.6 mg, 0.012 mmol) and CuI (21.5 mg, 0.113 mmol) were dissolved in dry DMF (2.2 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methylbenzene (5.0 μL, 0.34 mmol) was added and then, Et_3N (25.0 μL, 1.78 mmol) was added slowly. The reaction mixture was stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 5 EtOAc/ hexanes) to afford 60 mg (86%) of the product as a yellow powder. mp 140 -142 °C; R_f 0.22 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (br s, 1H), 7.4 (d, J= 8.1 Hz, 2H), 7.2 (d, J = 7.9 Hz, 2H), 4.0 (t, J = 7.4 Hz, 2H), 2.7 (t, J = 7.4 Hz, 2H), 2.4 (s, 3H), 1.6 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 150.5, 147.1, 138.2, 131.5, 128.7, 120.1, 103.3, 91.3, 84.4, 81.7, 42.3, 35.6, 28.0, 21.5.

tert-Butyl 5-((4-Methoxyphenyl)ethynyl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (26b).



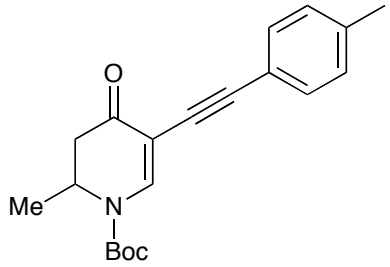
tert-Butyl 5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**22)** (99.6 mg, 0.309 mmol), $PdCl_2(PPh_3)_2$ (10.4 mg, 0.015 mmol) and CuI (28.2 mg, 0.155 mmol) were dissolved in dry DMF (3.1 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methoxybenzene (6.0 μL, 0.46 mmol) was added and then, Et_3N (34.0 μL, 2.47 mmol) was added slowly. The reaction mixture was stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 65 mg (64%) of the product as a yellow oil.; R_f 0.19 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (br s, 1H), 7.4 (d, J = 8.1 Hz, 2H), 6.7 (d, J = 7.9 Hz, 2H), 4.0 (t, J = 7.4 Hz, 2H), 3.8 (s, 3H), 2.6 (t, J = 7.4 Hz, 2H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 158.0, 145.3, 131.6, 124.0, 112.7, 112.3, 101.9, 89.5, 82.7, 79.5, 53.8, 40.7, 34.1, 26.8; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{21}NNaO_4$ $[M+Na]^+$ 350.1363; found 350.1381.

***tert*-Butyl 2-Methyl-4-oxo-5-(phenylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (27).**



tert-Butyl 5-iodo-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**25a**) (995.0 mg, 2.951 mmol), $PdCl_2(PPh_3)_2$ (136.0 mg, 0.1938 mmol) and CuI (294.0 mg, 1.544 mmol) were dissolved in dry DMF (25 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynylbenzene (50.0 μL, 4.43 mmol) was added and then Et_3N (3.30 mL, 23.8 mmol) was added slowly. The reaction mixture was stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 747 mg (92%) of the product as a yellow powder. mp 92- 93 °C; R_f 0.21 (1:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H), 7.4 -7.2 (m, 5H), 4.0 (m, 1H), 2.8 (dd, J = 6.6, 16.0 Hz, 1H), 2.3 (dd, J = 1.4, 16.3 Hz, 1H), 1.5 (s, 9H), 1.2 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 154.0, 145.2, 131.2, 128.0, 127.0, 123.3, 102.1, 91.0, 84.2, 83.8, 49.2, 41.7, 27.8, 16.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{21}NO_3$ $[M+Na]^+$ 334.1414; found 334.1423.

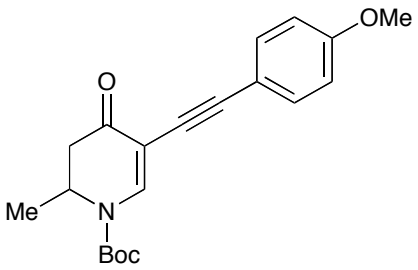
***tert*-Butyl 2-Methyl-4-oxo-5-(*p*-tolylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (27a).**



tert-Butyl 5-iodo-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**25a**) (996.0 mg, 2.951 mmol), $PdCl_2(PPh_3)_2$ (142.0 mg, 0.1938 mmol) and CuI (291.0 mg, 1.544 mmol) were dissolved in dry DMF (20 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methylbenzene (0.60 mL, 4.4 mmol) was added and then Et_3N (3.30 mL, 23.8 mmol) was added slowly. The reaction mixture was stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 489 mg (51%) of the product as a yellow powder. mp 104-106 °C; R_f 0.21 (1:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (br s, 1H), 7.3 (d, J = 8.1 Hz, 2H), 7.0 (d, J = 7.9 Hz, 2H), 4.6 (s, 1H), 2.8 (dd, J = 6.7, 16.4 Hz, 1H), 2.4 (dd, J = 1.6, 16.4 Hz, 1H), 2.3 (s, 3H), 1.5 (s, 9H), 1.2 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 150.2, 145.1, 138.1, 129.2, 123.5, 120.1, 105.7, 94.7, 84.2,

81.8, 46.0, 41.7, 28.3, 21.2, 16.6; HRMS (BioTOF II ESI) *m/z* calcd for $C_{20}H_{23}NNaO_3$ $[M+Na]^+$ 348.157; found 348.1581.

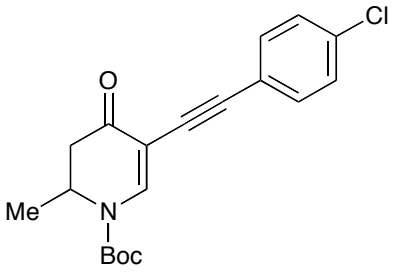
***tert*-Butyl 5-((4-Methoxyphenyl)ethynyl)-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (27b).**



tert-Butyl 5-iodo-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**25a**) (998.0 mg, 2.951 mmol), $PdCl_2(PPh_3)_2$ (145.0 mg, 0.1938 mmol) and CuI (291.0 mg, 1.544 mmol) were dissolved in dry DMF (20 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methoxybenzene (0.60 mL, 4.4 mmol) was added and then Et_3N (3.30 mL, 23.8 mmol) was added slowly. The reaction mixture was stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 516 mg (51%) of the product as a yellow powder. mp 104-106 °C; R_f 0.2 (1:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (br s, 1H), 7.4 (d, J = 9.4 Hz, 2H) 6.8 (d, J = 9.4 Hz, 2H) 4.7 (br t, J = 6.6 Hz 1H), 3.7 (s, 3H), 2.9-2.8 (dd, J = 6.7,

16.4 Hz, 1H), 2.4 (dd, J = 1.6, 16.3 Hz, 1H), 1.5 (s, 9H), 1.2 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 159.4, 150.1, 144.8, 133.0, 115.3, 113.8, 102.6, 90.9, 84.1, 81.1, 55.1, 49.3, 41.6, 28.5, 16.8; HRMS (BioTOF II ESI) *m/z* calcd for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$ 364.1519; found 364.1503.

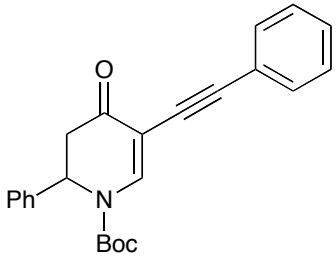
***tert*-Butyl 5-((4-Chlorophenyl)ethynyl)-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (27c).**



tert-Butyl 5-iodo-2-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**25a**) (302.0 mg, 0.8957 mmol), $PdCl_2(PPh_3)_2$ (43.0 mg, 0.0613 mmol) and CuI (88.0 mg, 0.462 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 4-chloro-1-ethynylbenzene (186.0 mg, 1.350 mmol) was added and then Et_3N (0.99 mL, 7.2 mmol) was added slowly. The reaction mixture was stirred for 3 h. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 201 mg (64%) of the product as a yellow powder. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.0 (s, 1H), 7.4 (d, J = 8.5 Hz, 2H), 7.2 (d, J = 8.5 Hz, 2H), 4.6 (m, 1H), 2.8 (dd, J = 6.7, 16.5 Hz, 1H), 2.4 (dd, J = 1.5, 16.4 Hz, 1H), 1.5 (s, 9H), 1.2 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 150.1, 145.7, 134.1, 132.8, 128.7, 121.9, 101.9, 90.1, 84.5, 83.6, 49.3, 33.8, 28.1, 14.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{20}NaClO_3$ $[M+Na]^+$ 368.1024; found 368.1011.

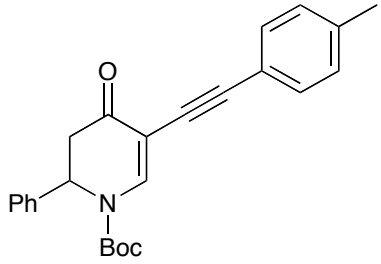
tert-Butyl 4-Oxo-2-Phenyl-5-(phenylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (28).



tert-Butyl 2-phenyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25b**) (302.0 mg, 0.7569 mmol), $PdCl_2(PPh_3)_2$ (28.0 mg, 0.0399 mmol) and CuI (72.0 mg, 0.378 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynylbenzene (12.0 μL, 1.10 mmol) was added and then Et_3N (84.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 226 mg (81%) of

the product as a yellow powder. mp 116 °C; R_f 0.37 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (s, 1H), 7.4-7.1 (m, 10H), 5.6 (d, J = 7.0 Hz, 1H), 3.1 (dd, J = 7.6,16.5 Hz, 1H), 2.8 (dd, J = 1.7, 16.5 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 150.6, 146.2, 138.3, 131.6, 129.0, 128.8, 128.2, 128.1, 125.7, 123.8, 103.4, 91.4, 84.6, 82.5, 56.0, 41.8, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{24}H_{23}NO_3$ $[M+Na]^+$ 396.157; found 396.1551.

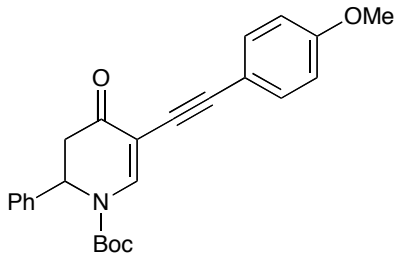
***tert*-Butyl 4-Oxo-2-phenyl-5-(*p*-tolylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (28a).**



tert-Butyl 2-phenyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25b**) (302.0 mg, 0.7565 mmol), $PdCl_2(PPh_3)_2$ (29.0 mg, 0.0413 mmol) and CuI (75.0 mg, 0.394 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methylbenzene (14.4 μL, 1.13 mmol) was added and then Et_3N (84.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude

mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 283 mg (98%) of **22a** as a yellow powder. mp 134-136 °C; R_f 0.23 (1:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (s, 1H), 7.3-7.0 (m, 9H), 5.6 (d, J = 7.0 Hz 1H), 3.1 (dd, J = 7.5, 16.5 Hz, 1H), 2.8 (dd, J = 1.5, 16.5 Hz, 1H), 2.2 (s, 3H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 150.6, 146.0, 138.3, 138.2, 131.5, 129.0, 128.8, 128.1, 125.7, 120.1, 103.6, 91.5, 84.5, 81.7, 55.9, 41.8, 27.9, 21.5; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 410.1727; found 410.1740.

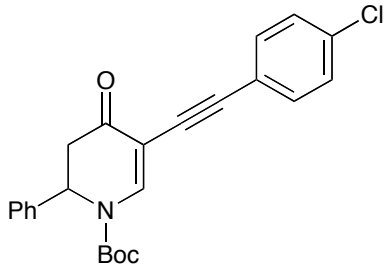
***tert*-Butyl 5-((4-Methoxyphenyl)ethynyl)-4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (28b).**



tert-Butyl 2-phenyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25b**) (308.0 mg, 0.7715 mmol), $PdCl_2(PPh_3)_2$ (28.0 mg, 0.0399 mmol) and CuI (74.0 mg, 0.389 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methoxybenzene (15.0 μL, 1.13 mmol) was added and then Et_3N (84.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc.

The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 267 mg (86%) of **22b** as a yellow powder. mp 138-140 °C; R_f 0.30 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (br s, 1H), 7.4-6.7 (m, 9H), 5.6 (d, J = 7.0 Hz, 1H), 3.1 (dd, J = 7.5, 16.4 Hz, 1H), 2.9 (d, J = 1.7 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 159.5, 150.6, 145.8, 138.2, 133.1, 128.8, 128.1, 126.2, 125.2, 114.1, 103.7, 91.3, 84.5, 80.9, 55.9, 55.2, 41.8, 27.8; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 426.1676; found 426.1667.

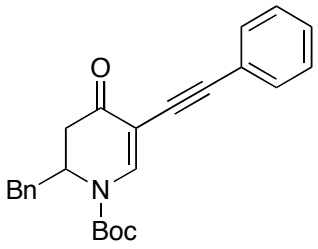
(±)*tert*-Butyl 5-((4-Chlorophenyl)ethynyl)-4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (28c).



tert-Butyl 2-phenyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25b**) (308.0 mg, 0.7715 mmol), $PdCl_2(PPh_3)_2$ (28.0 mg, 0.0399 mmol) and CuI (72.0 mg, 0.388 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-chloro-4-ethynylbenzene (160.0 mg, 1.171 mmol) was added and then Et_3N (84.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and

quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 4 EtOAc/ hexanes) to afford 269 mg (86%) of the product as a yellow powder. mp 132-134 °C; R_f 0.43 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3 (s, 1H), 7.3-7.1 (m, 9H), 5.6 (d, J = 7.1 Hz 1H), 3.1 (dd, J = 7.5, 16.5 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 150.1, 146.4, 138.1, 134.0, 132.4, 128.8, 128.3, 127.8, 125.3, 121.7, 103.1, 90.3, 84.5, 83.5, 56.7, 41.8, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{24}H_{22}ClNO_3$ $[M+Na]^+$ 430.118; found 430.1186.

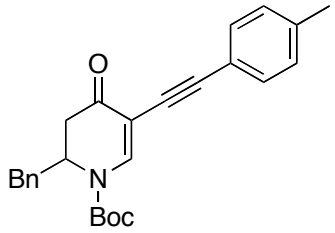
***tert*-Butyl 2-Benzyl-4-oxo-5-(phenylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (29).**



tert-Butyl 2-benzyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25c**) (305.1 mg, 0.7383 mmol), $PdCl_2(PPh_3)_2$ (28.0 mg, 0.0399 mmol) and CuI (80.0 mg, 0.420 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynylbenzene (12.0 μL, 1.10 mmol) was added and then Et_3N (81.0 μL, 5.84 mmol) was added slowly. The reaction

mixture stirred for 3 h. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 263 mg (92%) of the product as a yellowish powder. mp 140 -142 °C; R_f 0.54 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (br s, 1H), 7.4-7.0 (m, 10H), 4.6 (br s, 1H), 2.9 (dd, J = 6.3, 13.2 Hz, 1H), 2.7 (dd, J = 9.1, 13.2 Hz, 1H), 2.6 (dd, J = 6.4, 16.6 Hz, 1H), 2.4 (dd, J = 1.6, 16.6 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 150.1, 145.4, 136.4, 131.2, 129.6, 128.7, 128.2, 128.1, 127.0, 123.3, 102.6, 91.4, 84.3, 82.4, 54.7, 38.7, 36.5, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{25}NO_3$ $[M+Na]^+$ 410.1727; found 410.1737.

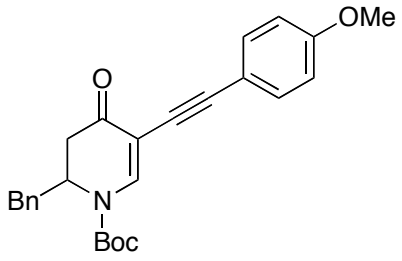
***tert*-Butyl 2-Benzyl-5-(4-toluylethynyl)-3,4-dihydropyridin-1(2*H*)-carboxylate (29a).**



tert-Butyl 2-benzyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25c**) (299.6 mg, 0.7260 mmol), $PdCl_2(PPh_3)_2$ (29.0 mg, 0.0413 mmol) and CuI (86.0 mg, 0.452 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The

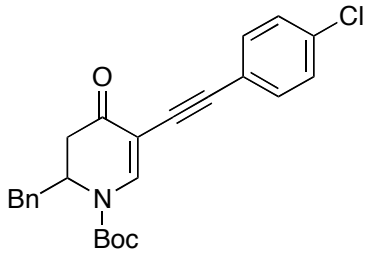
reaction mixture was stirred for 5 min and 1-ethynyl-4-methylbenzene (15.0 μL, 1.08 mmol) was added and then Et_3N (81.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred for 3 h. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 286 mg (98%) of the product as a yellowish powder. mp 152 -154 °C; R_f 0.30 (1:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (br s, 1H), 7.4-7.1 (m, 9H), 4.8 (br s, 1H), 3.0 (dd, J = 6.2, 13.2 Hz, 1H), 2.8 (dd, J = 9.3, 13.3 Hz, 1H), 2.7 (dd, J = 6.4, 16.6 Hz, 1H), 2.5 (dd, J = 1.6, 16.5 Hz, 1H), 2.4 (s, 3H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 150.3, 145.1, 138.1, 136.4, 131.5, 129.6, 128.9, 128.7, 127.0, 120.2, 103.0, 91.5, 84.2, 81.7, 54.6, 38.7, 36.5, 27.9, 21.5; HRMS (BioTOF II ESI) *m/z* calcd for $C_{26}H_{27}NO_3$ $[M+Na]^+$ 424.1883; found 424.1883.

***tert*-Butyl 2-Benzyl-5-((4-methoxyphenyl)ethynyl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (29b).**



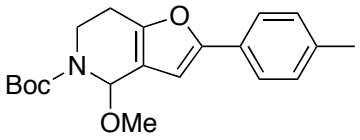
tert-Butyl 2-benzyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25c**) (295.8 mg, 0.7158 mmol), $PdCl_2(PPh_3)_2$ (29.0 mg, 0.0413 mmol) and CuI (69.0 mg, 0.362 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynyl-4-methoxybenzene (15.0 μL, 1.08 mmol) was added and then Et_3N (81.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 3 EtOAc/ hexanes) to afford 280 mg (94%) of the product as a yellow powder. mp 158 -160 °C; R_f 0.44 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (br s, 1H), 7.4-6.7 (m, 9H), 4.6 (br s, 1H), 3.7 (s, 3H), 2.9 (dd, J = 6.2, 13.1 Hz, 1H), 2.7 (dd, J = 9.2, 13.2 Hz, 1H), 2.6 (dd, J = 6.4, 16.6 Hz, 1H), 2.4 (dd, J = 1.6, 16.6 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 159.5, 150.2, 144.9, 136.4, 133.0, 129.6, 128.7, 127.0, 115.4, 113.9, 103.2, 91.3, 84.2, 81.0, 55.3, 54.7, 38.7, 36.5, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{26}H_{27}NNaO_4$ $[M+Na]^+$ 440.1832; found 440.1836.

tert-Butyl 2-Benzyl-5-((4-chlorophenyl)ethynyl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (29c).



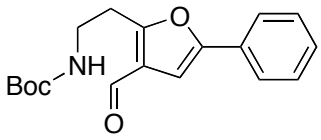
tert-Butyl 2-benzyl-5-iodo-4-oxo-3,4-dihydropyridin-1(2*H*)-carboxylate (**25c**) (315.0 mg, 0.7623 mmol), $PdCl_2(PPh_3)_2$ (29.0 mg, 0.0413 mmol) and CuI (81.0 mg, 0.425 mmol) were dissolved in dry DMF (9 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-chloro-4-ethynylbenzene (151 mg, 1.11 mmol) was added and then Et_3N (81.0 μL, 5.84 mmol) was added slowly. The reaction mixture stirred for 2 h. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 289 mg (90%) of the product as a brown powder. mp 146 -148 °C; R_f 0.60 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (br s, 1H), 7.4-7.1 (m, 9H), 4.6 (br s, 1H), 2.9 (dd, J = 6.2, 13.1 Hz, 1H), 2.7 (dd, J = 9.3, 13.1 Hz, 1H), 2.6 (dd, J = 6.0, 16.6 Hz, 1H), 2.4 (d, J = 16.6 Hz, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 150.1, 145.4, 136.3, 133.7, 132.7, 129.0, 128.7, 128.6, 127.0, 121.8, 102.5, 90.3, 84.4, 83.6, 54.7, 38.7, 36.5, 28.2; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{24}ClNNaO_3$ $[M+Na]^+$ 444.1337; found 444.1331.

***tert*-Butyl 4-Methoxy-2-*p*-tolyl-6,7-dihydrofuro[3,2-*c*]pyridine-5(4*H*)-carboxylate (31).**



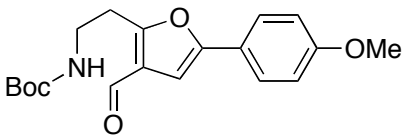
tert-Butyl 4-oxo-5-(4-tolylethynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (**26a**) (51.0 mg, 0.164 mmol) was dissolved in dry CH_2Cl_2 under N_2 at room temperature and stirred for 10 min. Then $AuCl_3$ (1.0 mL, 1.6 mM in CH_3CN) solution was added in one portion and MeOH (0.20 mL, 4.9 mmol) was added. The resulting reaction mixture was stirred for 5 h. The solvent was removed under reduced pressure. The crude mixture was purified by preparatory thin layer chromatography (1: 4 EtOAc/ hexanes) to afford 27 mg (63%) of the product as colorless oil. In addition, 12 mg of starting material was recovered. R_f = 0.76 (product **31**, 1/1 EtOAc/ Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (d, J = 7.0 Hz, 2H), 7.1 (d, J = 7.0 Hz, 2H), 6.6 (s, 1H), 3.5 (s, 3H), 2.9 (m, 2H), 2.6 (m, 2H), 2.4 (s, 3H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 154.3, 150.8, 137.1, 129.5, 128.1, 123.6, 118.9, 103.0, 81.0, 80.2, 79.5, 55.6, 36.6, 28.4, 23.6, 21.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{20}H_{27}NO_4$ $[M+H]^+$ 344.1862; found 344.1864.

***tert*-Butyl 2-(3-Formyl-5-phenylfuran-2-yl)ethylcarbamate (31a).**



tert-Butyl 5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**22**) (104.0 mg, 0.3219 mmol), $PdCl_2(PPh_3)_2$ (15.0 mg, 0.0214 mmol) and CuI (30.0 mg, 0.160 mmol) were dissolved in dry DMF (3.0 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 1-ethynylbenzene (5.0 μL, 0.48 mmol) was added and then, Et_3N (36.0 μL, 2.56 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 64 mg (67%) of the product as brown oil. R_f 0.67 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.9 (s, 1H), 7.6-7.2 (m, 5H), 6.9 (s, 1H), 4.7 (br s, 1H), 3.5 (t, J = 6.3 Hz, 2H), 3.2 (t, J = 6.3 Hz, 2H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.8, 161.9, 155.8, 154.1, 129.0, 128.7, 128.4, 124.0, 123.5, 102.5, 79.7, 39.2, 28.4, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.1363; found 338.1348.

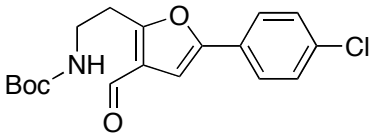
***tert*-Butyl 2-(3-Formyl-5-(4-methoxyphenyl)furan-2-yl)ethylcarbamate (31c).**



tert-Butyl 5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**22**) (98.0 mg, 0.303 mmol), $PdCl_2(PPh_3)_2$ (15.0 mg, 0.0214 mmol) and CuI (30.0 mg, 0.160 mmol) were dissolved in dry DMF (3.0 mL) under N_2 at room temperature. The reaction mixture

was stirred for 5 min and 1-ethynylbenzene (6.0 μL, 0.45 mmol) was added and then, Et_3N (33.0 μL, 2.40 mmol) was added slowly. The reaction mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 6 EtOAc/ hexanes) to afford 62 mg (60%) of the product as yellow oil. R_f 0.51 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5 (d, J = 8.5 Hz, 2H), 6.8 (d, J = 8.5 Hz, 2H) 6.7 (s, 1H), 4.7 (br s, 1H), 3.4 (t, J = 6.2 Hz, 2H), 3.1 (t, J = 6.2 Hz, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.8, 161.5, 159.7, 155.8, 154.2, 125.7, 125.1, 122.4, 114.1, 100.7, 79.7, 55.3, 39.3, 28.3, 27.6; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{23}NNaO_5$ $[M+Na]^+$ 368.1474; found 368.1468.

***tert*-Butyl 2-(5-(4-Chlorophenyl)-3-formylfuran-2-yl)ethylcarbamate (31d).**

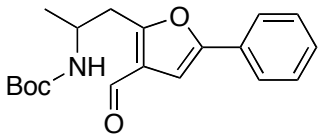


tert-Butyl 5-iodo-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**22**) (503.0 mg, 1.550 mmol), $PdCl_2(PPh_3)_2$ (58.0 mg, 0.080 mmol) and CuI (148.0 mg, 0.777 mmol) were dissolved in dry DMF (15.0 mL) under N_2 at room temperature. The reaction mixture was stirred for 5 min and 4-chloro-1-ethynylbenzene (322.0 mg, 2.358 mmol) was added and then Et_3N (1.73 μL, 12.4 mmol) was added slowly. The reaction

mixture stirred overnight. The solution was diluted with EtOAc and quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted with EtOAc. The combined organic layers were washed with water, brine and then, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude mixture was purified by CombiFlash chromatography (1: 1 EtOAc/ hexanes) to afford 292 mg (57%) of the product as a brown powder. mp 98 -100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5 (d, *J*= 8.5 Hz, 2H), 7.3 (d, *J*= 8.5 Hz, 2H), 6.8 (s, 1H), 4.7 (br s, 1H), 3.5 (t, *J* = 5.8 Hz, 2H), 3.2 (t, *J* = 6.1 Hz, 2H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 162.1, 155.8, 153.0, 134.1, 133.7, 128.9, 127.9, 125.3, 103.0, 79.8, 39.2, 29.7, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{18}H_{20}ClNNaO_4$ $[M+Na]^+$ 372.0973; found 372.0960.

Synthetic procedures of compounds **32-32c**: See the procedures of the corresponding Sonogashira coupling reactions for compounds **27-27c**.

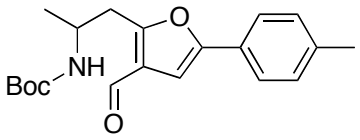
***tert*-Butyl 1-(3-Formyl-5-phenylfuran-2-yl)propan-2-ylcarbamate (32).**



15% of **32** were observed by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.6 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 7.8 Hz, 2H), 6.8 (s, 1H), 4.6 (br s, 1H), 4.5 (t, *J* = 6.4 Hz, 1H), 4.0 (m, 2H), 1.3 (s, 9H), 1.2 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 161.5, 155.0, 150.1, 141.8, 129.5, 127.5, 126.2, 124.0, 102.4, 79.4,

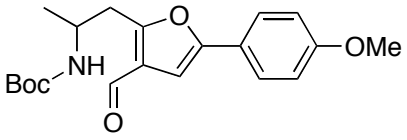
46.0, 41.8, 28.3, 16.7; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{23}NNaO_4$ $[M+Na]^+$ 352.1525; found 352.1546.

***tert*-Butyl 1-(3-Formyl-5-*p*-tolylfuran-2-yl)propan-2-ylcarbamate (32a).**



R_f 0.42 (1:3 EtOAc/hexanes); 140 mg (14 %), a yellow powder, mp 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5 (d, J = 8.2 Hz, 2H), 7.1 (d, J = 8.0 Hz, 2H), 6.8 (s, 1H), 4.5 (br s, 1H), 4.0 (br s, 1H), 3.2 (m, 2H), 2.3 (s, 3H), 1.3 (s, 9H), 1.2 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 161.1, 155.0, 154.4, 138.3, 129.5, 126.8, 126.0, 124.0, 101.7, 79.5, 46.0, 33.5, 28.3, 21.0, 19.0; HRMS (BioTOF II ESI) *m/z* calcd for $C_{20}H_{25}NNaO_4$ $[M+Na]^+$ 366.1676; found 366.1677.

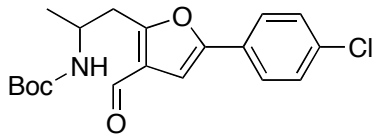
***tert*-Butyl 1-(3-Formyl-5-(4-methoxyphenyl)furan-2-yl)propan-2-ylcarbamate (32b).**



R_f 0.41 (1:6 EtOAc/hexanes); a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.9 (s, 1H), 7.6 (d, J = 9.6 Hz, 2H), 7.3 (d, J = 9.6 Hz, 2H), 6.7 (s, 1H), 4.8 (d, J = 8.0 Hz, 1H), 4.1 (br s, 1H), 3.8 (s, 3H), 3.2-3.1 (m, 2H), 1.4 (s, 9H), 1.2 (d, J = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 161.1, 155.1, 154.1, 144.8, 133.0, 126.0,

125.5, 114.2, 100.6, 79.3, 55.2, 41.7, 33.5, 28.5, 20.2; HRMS (BioTOF II ESI) *m/z* calcd for $C_{20}H_{25}NNaO_5$ $[M+Na]^+$ 382.1630; found 382.1636.

***tert*-Butyl 1-(5-(4-Chlorophenyl)-3-formylfuran-2-yl)propan-2-ylcarbamate (32c).**



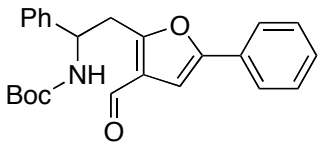
R_f 0.44 (1:3 EtOAc/hexanes), a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5 (d, J = 8.5 Hz, 2H), 7.3 (d, J = 8.5 Hz, 2H), 6.8 (s, 1H), 4.6 (t, J = 6.3 Hz, 1H), 4.5(br s, 1H), 3.1 (m, 2H), 1.5 (s, 9H), 1.2 (d, J = Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 161.8, 155.8, 153.2, 134.1, 132.9, 129.1, 128.0, 125.4, 103.0, 79.8, 46.0, 41.8, 28.1, 17.0; HRMS (BioTOF II ESI) *m/z* calcd for $C_{19}H_{22}NaClNO_4$ $[M+Na]^+$ 386.1135; found 386.1100.

General method of the Syntheses of *tert*-Butyl 2-(3-Formyl-5-arylfuran-2-yl)propan-2-ylcarbamate (33-33c).

tert-Butyl 5-arylethynyl-4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**28-28c**) (100 mg, 0.248-0.268 mmol) was dissolved in dry CH_2Cl_2 under N_2 at room temperature and stirred for 10 min. Then $AuCl_3$ (15 μL, 0.2 M in CH_3CN) solution was added in one portion and MeOH (14.9 mL, 0.368 mmol) was added. The resulting reaction mixture stirred until all starting material was consumed unless

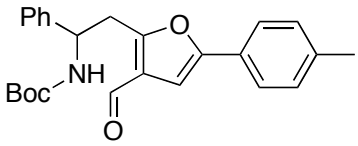
otherwise specified. The solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1: 4 EtOAc/ hexanes).

***tert*-Butyl 2-(3-Formyl-5-phenylfuran-2-yl)-1-phenylethylcarbamate (33).**



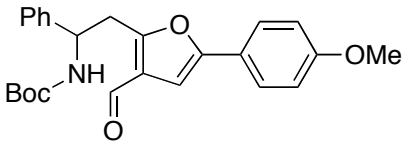
24 mg (23%), a yellow powder, mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.6 (s, 1H), 7.5-7.2 (m, 10H), 6.8 (s, 1H), 5.1 (m, 2H), 3.5 (m, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 155.0, 154.2, 132.0, 129.4, 128.8, 128.5, 128.3, 126.9, 126.1, 125.8, 124.1, 102.7, 83.7, 80.0, 54.4, 34.6, 28.3.

***tert*-Butyl 2-(3-Formyl-5-*p*-tolylfuran-2-yl)-1-phenylethylcarbamate (33a).**



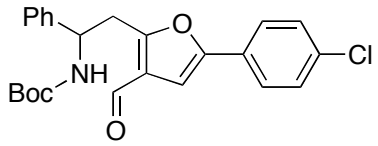
50 mg (48%), a yellow powder, mp 150 -151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.6 (s, 1H), 7.4-7.2 (m, 9H), 6.7 (s, 1H), 5.1 (br s, 2H), 3.5 (m, 2H), 2.3 (s, 3H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 159.7, 155.0, 154.4, 140.6, 138.3, 129.5, 128.8, 127.9, 126.7, 126.1, 125.8, 124.0, 101.8, 79.9, 54.4, 34.6, 28.3, 21.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{27}NNaO_4$ $[M+Na]^+$ 428.1835; found 428.1815.

***tert*-Butyl 2-(3-Formyl-5-(4-methoxyphenyl)furan-2-yl)-1-phenylethylcarbamate (33b).**



80 mg (77%, 15 mg of starting material recovered.), a yellow powder, mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.5 (s, 1H), 7.5-6.8 (m, 9H), 6.6 (s, 1H), 5.1 (br s, 2H), 3.8 (s, 3H), 3.5-3.5 (m, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 159.7, 155.0, 154.3, 128.8, 128.2, 127.9, 126.1, 125.8, 125.6, 122.4, 114.2, 114.0, 101.0, 79.9, 55.4, 54.3, 34.6, 28.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{27}NNaO_5$ $[M+Na]^+$ 444.1781; found 444.1774.

***tert*-Butyl 2-(5-(4-Chlorophenyl)-3-formylfuran-2-yl)-1-phenylethylcarbamate (33c).**

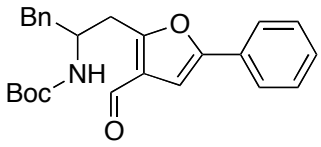


38 mg (36%), a yellow powder, mp 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.6 (s, 1H), 7.5-7.2 (m, 9H), 6.8 (s, 1H), 5.1 (br s, 2H), 3.5-3.4 (m, 2H), 1.43(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 155.0, 153.1, 134.1, 132.7, 129.0, 128.9, 128.5, 128.0, 126.2, 125.8, 125.6, 125.3, 103.1, 80.0, 54.4, 34.6, 28.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{24}H_{24}ClNNaO_4$ $[M+Na]^+$ 448.1286; found 448.1270.

General method of the Syntheses of *tert*-Butyl 1-(3-Formyl-5-arylfuran-2-yl)-3-phenylpropan-2-ylcarbamate (34-34c).

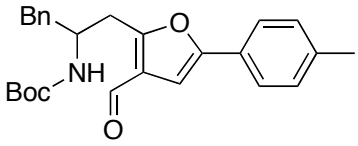
tert-Butyl 5-arylethynyl-4-oxo-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**29-29c**) (100 mg, 0.237-0.258 mmol) was dissolved in dry CH_2Cl_2 under N_2 at room temperature and stirred for 10 min. Then $AuCl_3$(12 μL, 0.2 M in CH_3CN) solution was added in one portion and MeOH (15.7 mL, 0.387 mmol) was added. The resulting reaction mixture was stirred for 1 h, or 2 h in case of **34b** and **34c**. The solvent was removed under reduced pressure. The crude mixture was purified by CombiFlash chromatography (1: 4 EtOAc/ hexanes).

***tert*-Butyl 1-(3-Formyl-5-phenylfuran-2-yl)-3-phenylpropan-2-ylcarbamate (34).**



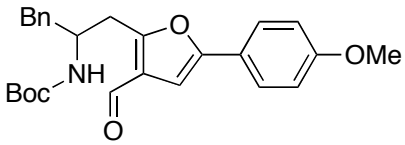
66 mg (63%), a white powder, mp 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5-7.1 (m, 10H), 6.8 (s, 1H), 4.6 (d, J = 7.9 Hz, 1H), 4.2 (d, J = 6.4 Hz, 1H), 3.2 (m, 2H), 2.8 (m, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1, 161.3, 155.1, 154.2, 137.3, 129.5, 129.3, 128.8, 128.7, 128.3, 127.3, 126.8, 124.1, 102.6, 79.7, 51.3, 40.4, 31.1, 28.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{27}NNaO_4$ $[M+Na]^+$ 428.1838; found 428.1832.

***tert*-Butyl 1-(3-Formyl-5-*p*-tolylfuran-2-yl)-3-phenylpropan-2-ylcarbamate (34a).**



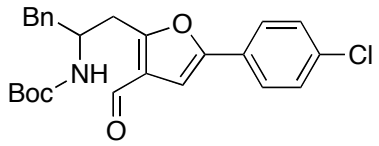
74 mg (71%), a yellow powder, mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.5-7.1 (m, 9H), 6.8 (s, 1H), 4.6 (d, J = 7.6 Hz, 1H), 4.2 (d, J = 6.5 Hz, 1H), 3.2-3.1 (m, 2H), 2.9-2.8(m, 2H), 2.3 (s, 3H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 155.0, 154.2, 132.0, 129.4, 129.1, 128.8, 128.3, 127.9, 126.9, 126.1, 125.8, 124.1, 102.7, 80.0, 57.7, 54.4, 34.6, 28.3, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{26}H_{29}NNaO_4$ $[M+Na]^+$442.1994; found 442.1989.

***tert*-Butyl 1-(3-Formyl-5-(4-methoxyphenyl)furan-2-yl)-3-phenylpropan-2-ylcarbamate (34b).**



81 mg (77%), a yellow powder, mp 155-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.7 (s, 1H), 7.5-6.8 (m, 9H), 6.7 (s, 1H), 4.6 (d, *J* = 7.8 Hz, 1H), 4.2 (m, 1H), 3.7 (s, 3H), 3.6-3.1 (m, 2H), 3.1-2.8 (m, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1,160.7, 159.7, 155.1, 154.3, 137.4, 129.3, 128.7, 126.8, 126.1, 125.6, 122.4, 114.3, 100.8, 79.7, 55.4, 51.2, 40.4, 31.0, 28.3; HRMS (BioTOF II ESI) *m/z* calcd for $C_{26}H_{29}NNaO_5$ $[M+Na]^+$458.1938; found 458.1937.

***tert*-Butyl 1-(5-(4-Chlorophenyl)-3-formylfuran-2-yl)-3-phenylpropan-2-ylcarbamate (34c).**



45 mg (43%), a white powder, mp 182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H), 7.3-7.2 (m, 9H), 6.8 (s, 1H), 4.6 (d, J = 7.9 Hz, 1H), 4.2 (m, 1H), 3.2-3.1 (m, 2H), 2.9-2.8 (m, 2H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 161.4, 155.1, 153.1, 137.2, 134.1, 129.3, 129.1, 128.7, 127.9, 126.9, 126.1, 125.3, 103.1, 79.7, 51.2, 40.5, 31.3, 27.9; HRMS (BioTOF II ESI) *m/z* calcd for $C_{25}H_{26}ClNNaO_4$ $[M+Na]^+$ 462.1448; found 462.1404.

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