SECTION-I

CHAPTER 3.

RESULTS AND DISCUSSION

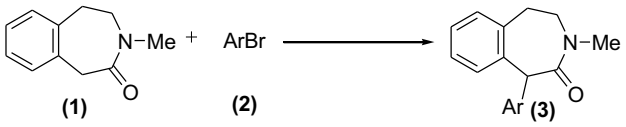
3. RESULTS AND DISCUSSION

α-Aryl cyclic amides have been synthesized by intramolecular cyclization of pre-arylated cyclic amides. Only one example of α-arylation of amide enolate could be traced in the literature. So, it was thought of using newly developed palladium chemistry for the preparation of our targeted compounds. Palladium chemistry in last few decades has emerged as a useful methodology for such chemical transformations which were considered difficult, traditionally. α-Arylation of amides is one of those transformations, which is highly valuable for the synthesis of natural products and bioactive compounds. An exhaustive literature survey revealed that not much work has been done towards this transformation. It has been shown in the literature that the palladium-catalyzed intermolecular coupling of halides and keto-enolates or ester-enolates is a useful method for synthesizing α-aryl ketones and α-aryl esters. α-Arylation of amides is comparatively less common.[30] Amides require a stronger base than the ketones and esters to generate the enolate, and the use of strong base has several significant drawbacks. For example, the need for a strong base limits the scope of coupling reactions to electron-neutral or electron-rich aryl halides, and aryl halides that lack electrophilic functionality. In addition, the strongly basic conditions lead to catalyst's decomposition, and the coupling of amides require higher loadings of palladium than the catalytic loading required for coupling of ketone or ester enolates. Further, the α-aryl amide product quenches the starting enolate, and diarylation products have been formed. Finally, the strongly basic conditions prevent asymmetric α-arylations that would form tertiary stereocenters.

To overcome these problems, reactions that occur with enolates that are less basic than alkali metal enolates of amides need to be developed. Few methods have

emphasized the use of zinc metal as milder basic functionality for α-arylation. To some extent zinc enolates have demonstrated promising results, although zinc enolates of lactams are not that common reagents because they need to be formed from the α-bromoamides[31] or by quenching of alkali metal amide enolates with zinc halides.[32] On the other hand copper (I) as a co-catalyst with palladium has been extensively used for the coupling of sp and sp^2 carbon-carbon bond formation. Considering the reports of greater functional group tolerance of the coupling of aryl and alkyl zinc reagents than the aryl and alkyl magnesium, sodium or lithium reagents, and the successful use of copper as a co-catalyst in Sonogashira coupling,[33] it was anticipated that the use of copper (I/II) as a co-catalyst with sp^3 carbon could work efficiently, offering milder reaction conditions for the α-arylation of amide enolates. The coupling of copper enolates of amides could also address the problem of functional group tolerance under a given set of reaction conditions, additionally.

At first, it was planned to exploit previously reported protocols,[34] basically developed for the α-arylation of carbonyl compounds. α-Arylation of compound (**1**) was first tried as per the previously reported process for esters. (**Scheme 15**).



Scheme 15

N-Methyl-3-benzazepin-2-one (**1**) (1.0 equiv.) was taken in THF and BuLi (1.5 equiv.) at -70^0 C was added to it followed by the addition of Pd_2dba_3 (5 mol%), xantphos, (7.5 mol%) and aryl bromide (1.5 equiv.) at RT. No arylation product was obtained. As reported for α-arylation of amides that the use of strong base may lead to the failure of reaction, it was thought of using copper (I) enolate of amides from the

displacement of alkali metal enolates and their cross-coupling with aryl halides by palladium catalysts.

To improve the process, the same reaction was repeated with the addition of Cu(I) iodide (1.1 equiv.) (Process **A**). Reaction proceeded for the first time and an arylated product was obtained but in about 25-35% yield (**Table 1 and 2**).

Table 1. Processes explored for obtaining products (**3**)

Process	Conditions	Base (equiv)	Source of energy (reaction temp.)	Reaction time
A	BuLi, Pd_2dba_3 (5 mol %), Cu_2I_2 (1.1) (L) Xantphos (7.5 mol %)	BuLi (1.5)	Mechanical stirring (RT)	24 Hrs
B	NaH, Pd_2dba_3 (5 mol %), Cu_2I_2 (1.1) (L) Xantphos (7.5 mol %)	NaH (2.5)	Conventional Heating (100 ^{0}C)	12 Hrs
C	NaH, $PdCl_2$ (5 mol %), Cu_2I_2 (1.1) (L) TPP[a] (5 mol %)	NaH (2.5)	Conventional Heating (100 ^{0}C)	12 Hrs
D	NaH, $Pd(OAc)_2$ (3 mol %), (L) TPP[a] (5 mol %), Cu_2I_2 (1.1)	NaH (2.5)	Conventional Heating (100 ^{0}C)	8 Hrs
E	-do-	-do-	Microwave, 100 W (100 ^{0}C)	10-25 Min

[a] *triphenylphosphine*

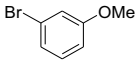
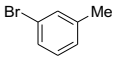
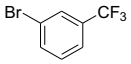
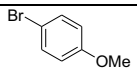
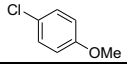
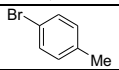
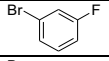
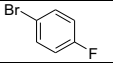
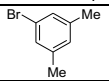
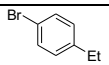
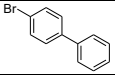
In 1979, Orito and Matsuzuki[35] studied and reported α-alkylation of *N*-methyl-3-benzazepin-2-one with the help of sodium hydride and alkyl halides. In this study NaH emerged as the most appropriate base in different solvents at different temperatures to generate the enolate ion and improve the yields. To an obvious extension of this observation to improve the α-arylation yields of products (**3**), BuLi was replaced with NaH as the base. Simultaneously, different solvents and mixture of solvents suitable for the generation of amidic enolate ion were explored. Best results were obtained with 1:5 ratio of DMF:dioxane mixture for the generation of enolate ion with NaH (2.5 equiv) as a base at 100 ^{0}C. Replacing BuLi with NaH plus Pd_2dba_3 and Xantphos in DMF:dioxane (1:5) improved the yields up to 70% for different aryl

halides (Process **B**) (**Table 2**). It is noteworthy that much better yields were obtained with the copper enolate of **1** than with its lithium or sodium enolates. Formation of the copper enolate with Cu_2I_2 is crucial, as the arylated product (**2)** was not obtained at all when the reaction was performed in presence of Cu(II) acetate in place of Cu_2I_2. Generation of carbanion also proved very critical for the reaction as the use of KTB, Cs_2CO_3 or K_2CO_3 yielded back the starting material (**1**) only, even in the presence of cuprous iodide. To examine the effect of counter ions in alkali metal bases, LiH and KH were also used apart from NaH for the generation of enolate ion. The yields of the products were reduced in case of LiH but KH was as effective as NaH or slightly better in some experiments.

The influence of palladium catalyst was also studied. As in Sonogashira reaction $PdCl_2$ is the most commonly used reagent, it was thought of using $PdCl_2$ in place of Pd_2dba_3. To further explore the reactivity of Pd catalysts $Pd(OAc)_2$ was also used. Both the catalysts were used in presence of **L** (triphenylphosphine) (5.0 mol %) in DMF:dioxane (1:5) mixture at 100 ^{0}C. Both of these catalysts improved the yields but $Pd(OAc)_2$ along with triphenylphosphine offered higher yields especially for the hindered aryl halides (**Table 2**).

To widen the scope of the developed method, other aryl halides like chloro and iodo derivatives were also used (**Table 2**). Aryl iodides yielded the best results while aryl chlorides did not offer the products at all even for the most reactive substituents (**3d & 3e**). Although aryl iodides were offering somewhat higher yields over the aryl bromides but considering the availability and the cost of aryl halides, bromo derivatives were used in rest of the study.

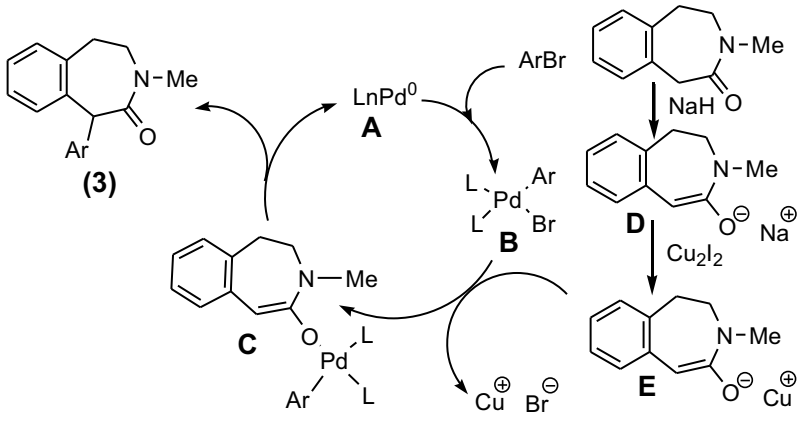
Table 2. Processes applied for obtaining the product (**3**)

Entry	ArBr	Process	Reaction time	Yield (%)
3a		A	24 Hrs	35
		B	12 Hrs	58
		C	12 Hrs	70
		D	8 Hrs	68
		E	10 min	86
3b		A	24 Hrs	31
		B	12 Hrs	65
		C	12 Hrs	82
		D	8 Hrs	80
		E	10 min	89
3c		A	24 Hrs	25
		B	12 Hrs	40
		C	12 Hrs	55
		D	8 Hrs	60
		E	20 min	72
3d		A	24 Hrs	30
		E	10 min	93
		E	25 min	0
3e		A	24 Hrs	0
		C	12 Hrs	65
		D	8 Hrs	70
		E	25 min	92
		E	20 min	93
		E	25 min	0
3f		E	25 min	86
		E	25 min	88
3g		E	15 min	93
3h		E	15 min	79
3i		E	15 min	72
3j		E	15 min	86
3k		E	10 min	93
3l		E	10 min	92
3m		E	10 min	95

Since microwave irradiation has been used for improving the yields of endothermic reactions, it was thought of inducting microwaves in this cross coupling reaction. The generation of amidic enolate of **1** with NaH in DMF:dioxane mixture (1:5), treatment of sodium enolate with cuprous iodide and transmetallation with palladium in presence of microwaves afforded the best results amongst all of the tried methods, and the yields improved up to 95% (**Table 2**); so **method E** was used as a general method for rest of the reactions. The microwave irradiation method was well tolerated by the substituents present on ArBr (**2**). The coupling of copper enolate generated by compound (**1**) occurred in high yields at 100 ^{0}C under microwave irradiation with a variety of aryl bromides, including those with electron-rich, electron-deficient and electroneutral groups. Previous studies have reported steric hindrance in ArBr as a major stumbling block in not offering the hindered products; the microwave-assisted method proved to be a big success for the sterically hindered products (**Table 2**, entry **3e, 3f, 3k**). It is noteworthy that electron-donating groups in the *ortho* and/or *para* positions increased the yields (**Table 2**, entries **3d, 3e, 3m**) and the presence of an electron-donating group in the *meta* position slightly decreased the yield (**Table 2**, entry **3a**). But presence of electron-withdrawing groups at *meta* and *para* positions always decreased the yields of the products remarkably (entries **3c, 3h, 3i**).

The α-arylation of *N*-methyl-3-benzazepin-2-one can be explained by a mechanism similar to the one proposed previously for the Sonogashira cross-coupling reaction, except that the copper acetylide is replaced by a copper (I) enolate of the amide (**Scheme 16**). The active palladium catalyst complex Pd(0)Ln (**A**) reacts with the aryl halide in an oxidative addition manner to produce a Pd(II) intermediate

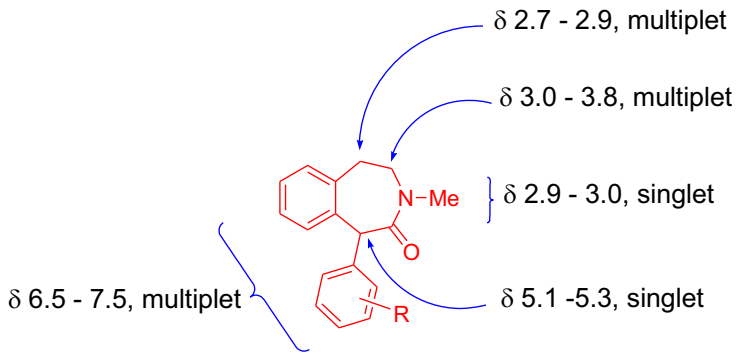
complex (**B**). In a transmetallation reaction, complex (**B**) reacts with the copper enolate of amide complex (**E**), which is produced by the quenching of the alkali metal enolate with copper(I) iodide, to give complex (**C**) expelling the copper halide. Compound (**E**) continues to react with the palladium intermediate (**B**) with elimination of the copper(I) halide. In the final step, complex (**C**) undergoes reductive elimination to produce 1-aryl-N-methyl-3-benzazepin-2-one, with the regeneration of the palladium catalyst.



Scheme 16

The above discussed process offers good to high yields of the α-arylated 3-benzazepine derivatives (**3a-3m**). As all of the synthesized compounds were unknown, they were characterized by different analytical techniques viz. IR, ^{1}H-NMR and mass spectroscopy. The protons in aromatic region appeared as multiplet in range of δ 6.5-7.5. Hydrogen at C-1 carbon showed a singlet at δ 5.1-5.3 and protons of N-methyl appeared as a singlet at δ 2.9-3.0. The two protons at C-4 split in to multiplet at δ 3.0-3.8 and the last two protons at C-5 also split in to multiplet because of the splitting of protons at C-4 position. The amide carbonyl appeared at 1650-1630 cm^{-1}

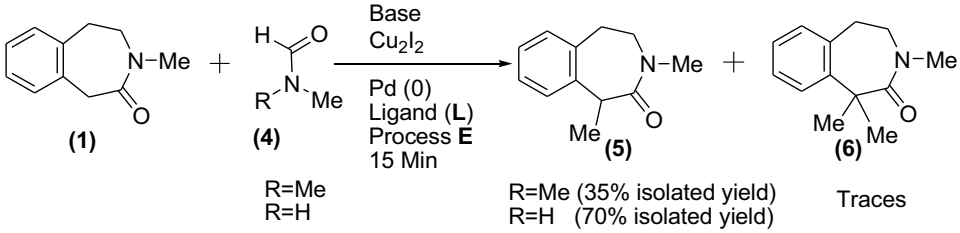
and the aromatic C-H stretching was observed at 3130-3110 cm^{-1} in the IR spectra of the final products (**3a-3m**).



^{1}H-NMR values of 3-benzazepine derivatives (3a-3m)

An interesting observation was made when the reactions were carried out using aryl bromides having electron withdrawing groups (Cl, F, CF_3) at *ortho*- position or with highly hindered 2,6-dimethylphenyl bromide. Instead of the normal products, an abnormal product in low yield was obtained all the times. The abnormal product was identified as the α-methylated benzazepinone derivative (**5**). As N,N-dimethylformamide (DMF) along with dioxane was used as an ideal solvent system for all these reactions, DMF was suspected to be acting as methyl donor in these reactions. In that eventuality an equivalent amount of N-methylformamide (NMF) should have also been formed theoretically during the course of reaction. The reaction mixture after suitable dilution with water was submitted for HPLC analysis. To our surprise in addition to NMF, formamide was also detected in the reaction mixture. Formamide, NMF and DMF were characterized by their retention times in HPLC analysis which were further confirmed by spiking the analyte samples with formamide, NMF and DMF (**Fig. 1** & **2**). Moreover, formamide was detected in a

higher concentration in the reaction mixture than expected. This indicated that probably NMF was more actively participating as methyl donor in the reaction than DMF. To further strengthen this observation a reaction of compound (**1**) was performed under exactly the same conditions as performed previously but in presence of NMF (1.5 equiv.) and additional (1.5 equiv.) quantity of NaH. The yield of the product (**5**) doubled to almost 70%. LC-MS analysis (**Fig 3**) of the reaction mixture offered another interesting result. α,α-Dimethyl derivative (**6**) was also detected in the reaction mixture although in trace amounts (**Scheme 17**).



Scheme 17

Figure1. HPLC chromatogram of reaction mixture diluted with water.

Peaks 1= formamide; 3= *N*-methylformamide; 7= *N,N*-dimethylformamide.

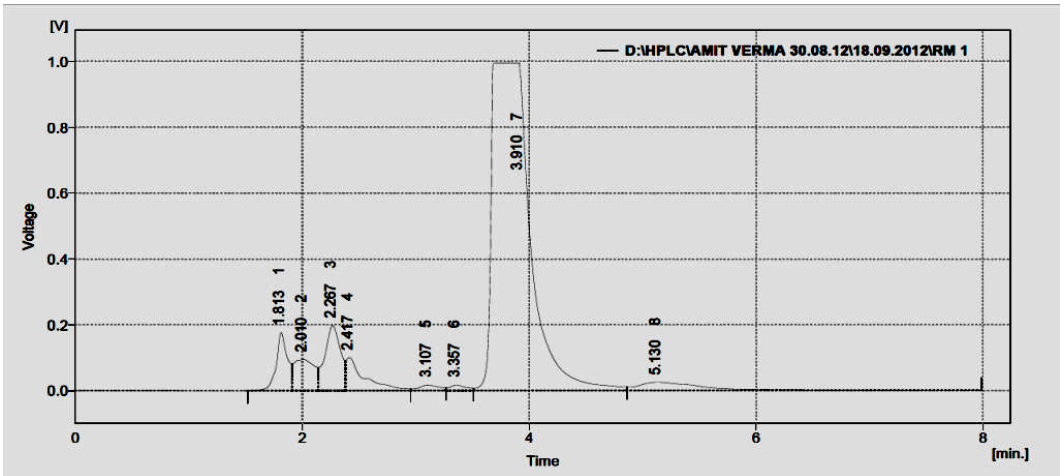
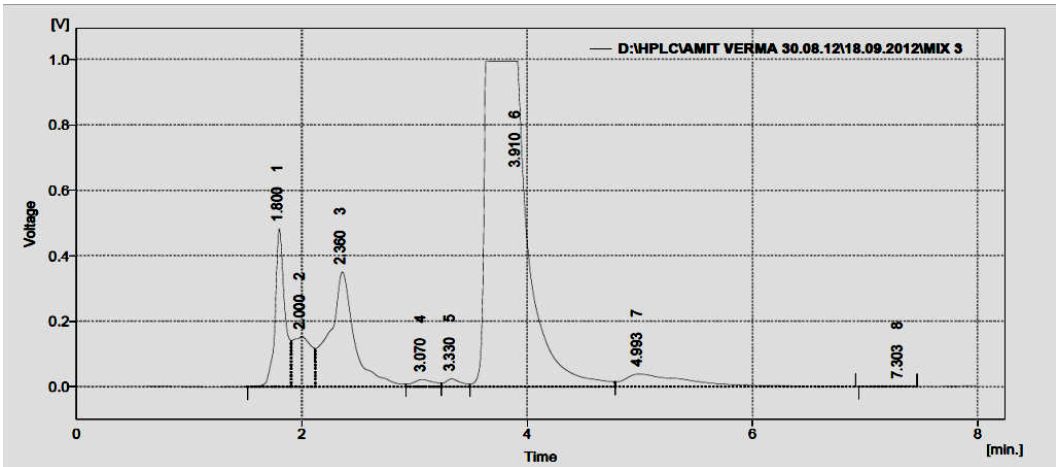


Figure 2. HPLC chromatogram of reaction mixture spiked with standard solutions of formamide (100 ppm), NMF (100 ppm) and DMF (100 ppm).

Peaks 1 = formamide; 3 = *N*-methylformamide; 6 = *N,N*-dimethylformamide.



The IR pattern for compound (**5**) was found to be similar to compounds (**3a-3m**). In NMR spectroscopy proton at C-1 position appeared at δ 4.25 with a quartet and a doublet of CH_3 protons appeared at δ 1.49. Rest of the peaks were similar to compounds (**3a-3m**).

Figure 3. LC-MS chromatogram of reaction mixture.

In given spectrum (**Fig. 3**), LCMS chromatogram of crude reaction mixture is shown. Peak results of mass scan (Peak Channel SQ1: MS Scan) shows the following peaks:

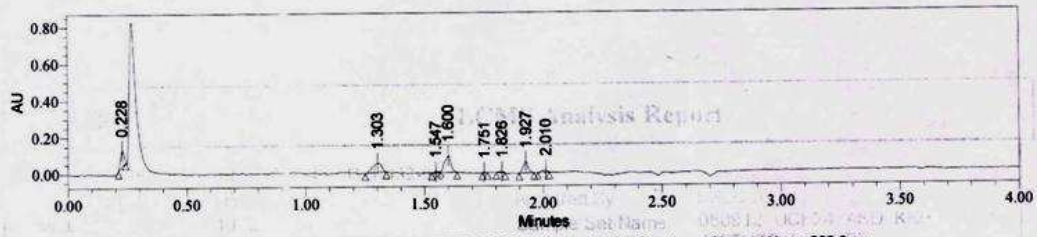
Peak no. **2** = 3-Benzazepin-2-one,

Peak no. **4** = 1-Methyl-3-benzazepin-2-one,

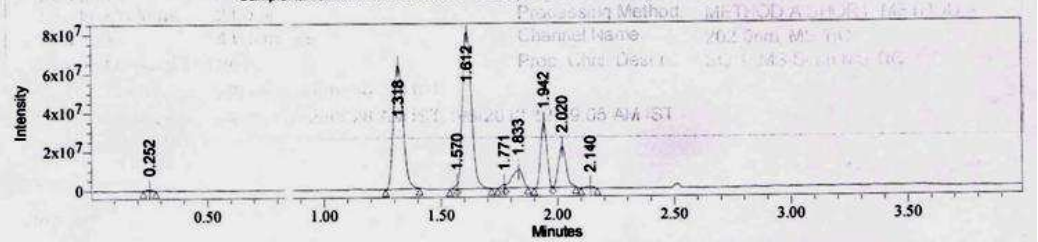
Peak no. **6** = 1,1-Dimethyl-3-benzazepin-2-one

LCMS Analysis Report

Sample Name:	MF2-O2B-843-MT-T-432-06		
Sample Type:	Unknown	Acquired By:	UPLC-03
Vial:	1:F,2	Sample Set Name:	050912_UCH24_ASD_KKP
Injection #:	1	Acq. Method Set:	METHOD A SHORT
Injection Volume:	2.00 ul	Processing Method:	METHOD A SHOR1, METHOD A
Run Time:	4.0 Minutes	Channel Name:	202.0nm, MS TIC
Project Name SEPT_2012		Proc. Chnl. Descr.:	SQ 1: MS Scan MS TIC,
Date Acquired:	9/5/2012 11:49:33 PM IST		
Date Processed:	9/6/2012 12:48:28 AM IST, 9/6/2012 12:49:05 AM IST		



SampleName: MF2-O2B-843-MT-T-432-06; Channel: PDA Spectrum; Channel Name 202.0nm



SampleName: MF2-O2B-843-MT-T-432-06; Channel: SQ 1: MS Scan; Channel Name MS TIC

Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	0.228		88361	92425	17.66	PDA Spectrum	202.0nm
2	1.303		50730	133342	25.47	PDA Spectrum	202.0nm
3	1.547		6175	9095	1.74	PDA Spectrum	202.0nm
4	1.600		91075	167789	32.05	PDA Spectrum	202.0nm
5	1.751		3466	2273	0.43	PDA Spectrum	202.0nm
6	1.826		6472	8480	1.62	PDA Spectrum	202.0nm
7	1.927		62245	88942	16.99	PDA Spectrum	202.0nm
8	2.010		13732	21152	4.04	PDA Spectrum	202.0nm

Peak Results
Channel: SQ 1: MS Scan

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	0.252	103.40	642871	1245104	0.23	SQ 1: MS Scan	MS TIC
2	1.318	176.34	63571613	183415746	33.30	SQ 1: MS Scan	MS TIC
3	1.570	230.34	2668755	1886514	0.34	SQ 1: MS Scan	MS TIC

KKP 6/9/12

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LCMS Analysis Report

Peak Results
Channel: SQ 1: MS Scan

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
4	1.612	190.39	81076600	218113662	39.60	SQ 1: MS Scan	MS TIC
5	1.771	306.49	1902927	2238156	0.41	SQ 1: MS Scan	MS TIC
6	1.833	204.39	9341013	29588387	5.37	SQ 1: MS Scan	MS TIC
7	1.942	279.44	33615548	63756701	11.58	SQ 1: MS Scan	MS TIC
8	2.020	377.59	21116476	48845078	8.87	SQ 1: MS Scan	MS TIC
9	2.140	391.64	843800	1678764	0.30	SQ 1: MS Scan	MS TIC

Match Plot

SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 103.40 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 0.252

Match Plot

SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 176.34 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 1.318

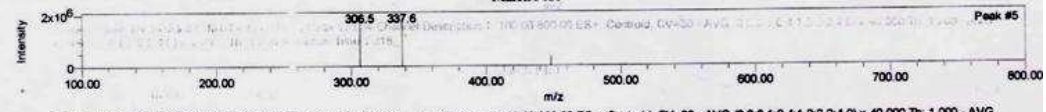
Match Plot

SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 230.34 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 1.570

Match Plot

SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 190.39 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 1.612

Match Plot



SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 306.49 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 1.771

Match Plot

SampleName: MF2-O2B-843-MT-T-432-06 Base Peak 204.39 Channel Description 1: 100.00-800.00 ES+, Centroid, CV=30 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 40.000 Th: 1.000 - AVG (0.0:0.1;0.4:1.2;2.2:4.0) x 10.000 Th: 1.000 Retention Time 1.833

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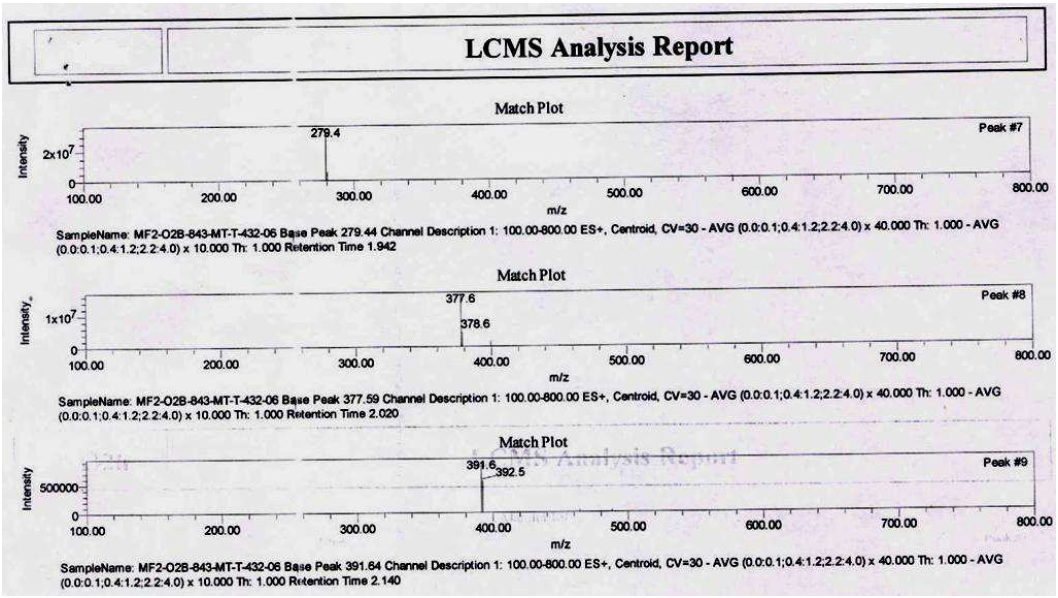
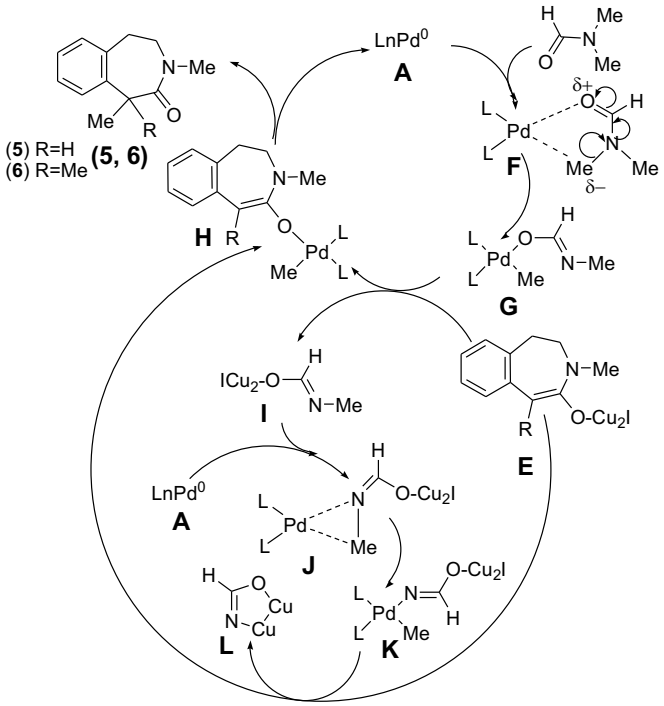


Keeping the above discussed observations in mind a plausible mechanism for α-methylation of *N*-methyl-3-benzazepin-2-one (**1**) involving DMF and/or NMF as sources of methyl group is depicted in **Scheme 18.**

In absence of a reactive aryl bromide the active palladium catalyst [Pd(0)Ln] complex (**A**) activates the otherwise unreactive DMF in an oxidative addition manner to produce a Pd-DMF complex (**F**). Transfer of π-electron density in DMF for the formation of Pd-O bond eliminates one methyl group attached to N-atom yielding an oxidative addition intermediate (**G**). In a transmetallation reaction, the complex (**G**) reacts with the copper enolate of the amide (**E**) to afford complex (**H**) expelling the copper enolate (**I**) of NMF. Quenching of the reaction mixture with water would obviously afford NMF. The complex (**H**) would offer the α-methylated product in the normal reductive elimination step. On the other hand, in the continuing catalytic process the [Pd(0)Ln] complex (**A**) can further activate the copper enolate (**I**) of NMF to form the intermediates (**J** & **K**) which on further reaction with **E** can form **H** by eliminating **L**. Formamide would be formed from the complex **L** when the reaction



Scheme 18

mixture is quenched with water. It may be noted that some α-methylated 3-benzazepin-2-one (**5**) can also enter the catalytic reaction cycle to offer the dimethylated product (**6**). This has been possible because it has been reported[14] that at elevated temperatures a tertiary carbanion can be formed by abstraction of a proton by the secondary carbanion through intermolecular reaction. In case of copper enolate of NMF (**I**), insertion between the N-Me bond by the palladium catalyst seems to be more relevant as the N-atom in NMF is well exposed unlike DMF wherein N-atom is highly hindered and unapproachable.