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Microwave assisted palladium catalyzed intermolecular α-arylation of copper-amide enolate of benzazepine

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ABSTRACT

Intermolecular α-arylation of copper enolate of 3-benzazepin-2-one with aryl halides in the presence of palladium as catalyst is reported as a general method. To the best of our knowledge this is the first Letter of the use of copper enolates of amides for C–C bond formation. The scope of the base, solvent, ligand, and catalysts used has also been investigated.

The palladium-catalyzed process has been sufficiently explored as a mild catalytic method to form the C–C bond between an aryl ring and the α-position of a carbonyl compound.[1] α-Arylation of carbonyl compounds has been considered a difficult transformation traditionally, but with palladium catalysis it is achieved with simpler and milder methods.[2] It has been shown 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.[3] The α-arylation of amide-enolate, with one exception,[4] has been limited to the cyclization for obtaining lactams or intramolecular reactions of acyclic amides.[5] Amide requires a stronger base than ketones and esters to generate the enolate, and the use of strong base has several significant drawbacks.

To overcome these problems, reactions that occur with enolates that are less basic than alkali metal enolates of amides need to be developed. A few methods have emphasized the use of zinc metal as milder basic functionality for α-arylation.[6] 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[7] or by quenching of alkali metal amide enolates with zinc halides.[8] 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. Sonogashira et al.[9] discovered and reported a process of sp–sp^2 coupling that could be performed easily at room temperature using palladium as a catalyst source, combined with co-catalytic amounts of Cu(I) in an amine. In another Letter Sulikowski and co-workers[10] have demonstrated the use of Cu(II) enolates of acetates, generated in situ from that silyl enol ethers in the presence of copper (II) fluoride for palladium catalyzed sp^3–sp^2 cross coupling to afford α-aryl ketones. Considering the Letters of greater functional group tolerance of the coupling of aryl and alkyl zinc reagents[11] than the aryl and alkyl magnesium, sodium or lithium reagents,[12] and the successful use of copper as a co-catalyst in Sonogashira coupling, we anticipated that the use of copper (I) 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.

We were interested in the in situ generation of copper (I) enolates of amides from the displacement of alkali metal enolates and their cross-coupling with aryl halides by palladium catalysts. Herein, we report the palladium catalyzed α-arylation of benzo-fused cyclic amide, 3-benzazepin-2-one with co-catalyst copper (I) iodide (Scheme 1). To the best of our knowledge this is the first Letter on the use of copper enolates of amides for α-arylation.

α-Arylation of compound (**1**) was first tried as per the previously reported process for esters.[13] *N*-Methyl-3-benzazepin-2-one (1.0 equiv) was taken in THF and BuLi (1.5 equiv) at −70 °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. To improve the process, the reaction was repeated with the addition of Cu(I) iodide (1.1 equiv) (Process

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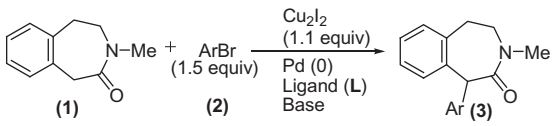


Scheme 1. α-Arylation of 3-benzazepin-2-one.

A). Reaction proceeded and an arylated product was obtained in about 25–35% yield (Tables 1 and 2).

In 1979, Orito et al.[14] 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 our products BuLi was replaced with NaH as the base. Simultaneously we worked on the use of different solvents and a mixture of solvents that were more suitable for the generation of amidic enolate ion. 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 °C. Replacing BuLi with NaH plus Pd_2dba_3 and Xantphos in DMF:dioxane (1:5) improved the yields upto 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. The 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 the 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 ion 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 the case of LiH but KH was as effective as NaH or slightly better in some experiments.

The influence of palladium catalyst was also studied. Since $PdCl_2$ is the most commonly used reagent in Sonogashira reaction, we 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 the presence of L (triphenylphosphine) (5.0 mol %) in DMF:dioxane (1:5) mixture at 100 °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 and 3e**). Although aryl iodides offer higher yields over the aryl bromides, considering the availability and the cost of aryl halides, bromo derivatives were used in rest of the study.

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 the presence of microwaves afforded the best results among all of the tried methods, and the yields improved up to 95% (Table 2); so it was used as a general method (Method E) for the 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 yield at 100 °C under microwave irradiation with a variety of aryl bromides, including those with electron-rich, electron-deficient, and electroneutral groups. Previous studies[6b] have reported steric hindrance in ArBr as a major stumbling block in not offering these hindered products; the microwave-assisted method proved to be a big success for the sterically hindered products (Table 2, entries 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 decreased the yield slightly (Table 2, entry 3a). But the 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 2). 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 after quenching of the alkali metal enolate with copper(I) iodide, to give complex **C**. 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 the 1-aryl-*N*-methyl-3-benzazepin-2-one, with the regeneration of the palladium catalyst.

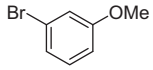
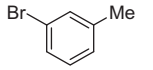
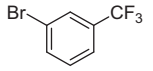
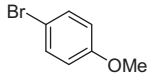
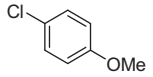
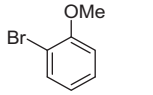
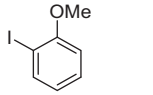
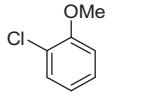
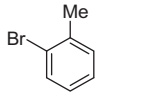
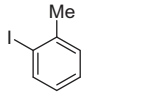
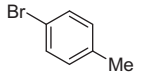
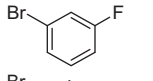
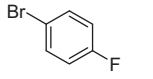
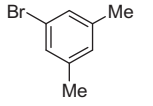
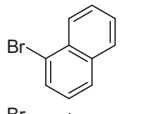
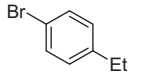
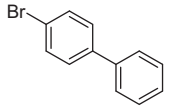
An interesting observation was made when the reactions were carried out using aryl bromides having electron withdrawing groups (Cl, F, CF_3) at *ortho*- position or with highly hindered 2,6-dimethylphenyl bromide. Instead of the normal products, an abnormal product in low yield was always obtained. The 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. If that was the case then an equivalent amount of *N*-methylformamide (NMF) should have also been formed during the 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. Moreover, formamide was existing in a greater concentration in the reaction mixture than expected. That means NMF was more actively participating as methyl donor in the reaction than DMF. To further strengthen this observation a

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

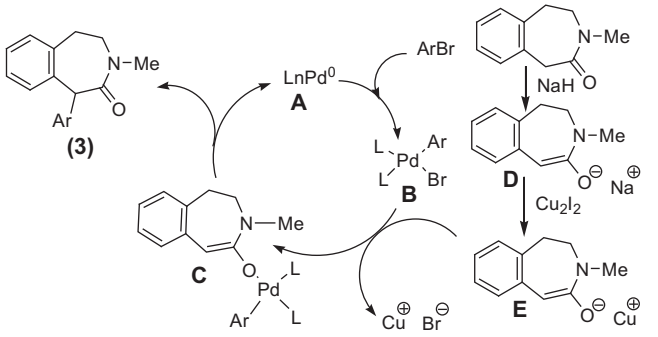
Process	Conditions	Base (equiv)	Source of energy (rean. temp.)	Rean. time
A	BuLi, Pd_2dba_3 (5 mol %), (L) Xantphos (7.5 mol %)	BuLi (1.5)	Mechanical stirring (RT)	24 h
B	NaH, Pd_2dba_3 (5 mol %), (L) Xantphos (7.5 mol %)	NaH (2.5)	Conventional heating (100 °C)	12 h
C	NaH, $PdCl_2$ (5 mol %), (L) TPP[a] (5 mol %)	NaH (2.5)	Conventional heating (100 °C)	12 h
D	NaH, $Pd(OAc)_2$ (3 mol %), (L) TPP[a] (5 mol %)	NaH (2.5)	Conventional heating (100 °C)	8 h
E	–do–	–do–	Microwave, 100 W (100 °C)	10–25 min

[a] Triphenylphosphine.

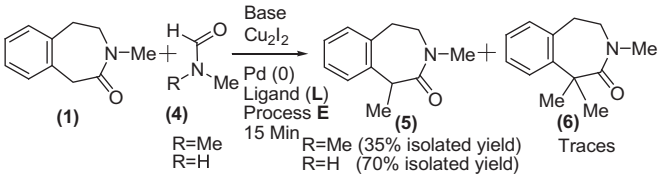
Table 2
Processes applied for obtaining the product (**3**)

Entry	ArBr	Process	Rean. time	Yield (%)
3a		**A**	24 h	35
		B	12 h	58
		C	12 h	70
		D	8 h	68
		E	10 min	86
3b		**A**	24 h	31
		B	12 h	65
		C	12 h	82
		D	8 h	80
		E	10 min	89
3c		**A**	24 h	25
		B	12 h	40
		C	12 h	55
		D	8 h	60
		E	20 min	72
3d		**A**	24 h	30
		E	10 min	93
		**E**	25	0
3e		**A**	24 h	0
		C	12 h	65
		D	8 h	70
		E	25 min	92
		**E**	20 min	93
		**E**	25	0
3f		**E**	25 min	86
		**E**	25	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

reaction of compound **1** was performed under exactly the same conditions as performed previously but in the presence of NMF (1.5 equiv) and additional (1.5 equiv) quantity of NaH. The yield



Scheme 2. α-Arylation of 3-benzazepin-2-one.



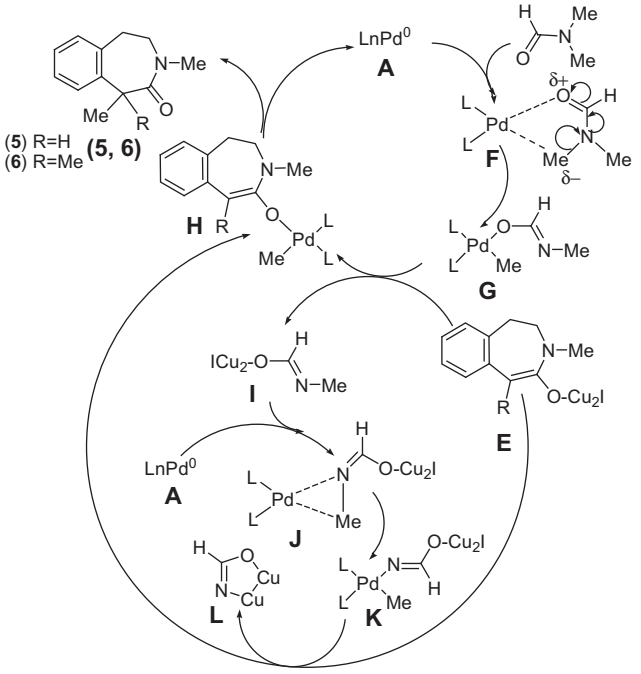
Scheme 3. Mono-/di-alkylation of (**1**).

of product **5** doubled to almost 70%. LC–MS analysis 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 3).

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 carbon sources is depicted in Scheme 4.

In the 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, complex **G** reacts with the copper enolate of amide **E** to afford complex **H** expelling the copper enolate (**I**) of NMF. Quenching of the reaction mixture with water would obviously afford NMF. 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** and **K** which on further reaction with **E** can form **H** by eliminating **L**. Formamide would be formed from complex **L** when the reaction 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 is 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 the 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.

To summarize, a rapid and high yielding convenient process for α-arylation of 3-benzazepin-2-one has been developed with introduction of Cu(I) as a co-catalyst and microwaves as energy source. The process offers good to high yields of the α-arylated products using different type of aryl bromides. The aryl bromides possessing electron withdrawing or donating groups either at *para* or *meta* positions were active enough to offer the desired products.



Scheme 4. A plausible mechanism for α-alkylation.

Electron donors at *ortho* position of the aryl bromide yielded the best results by offering highest yields of the desired products. But hindered aryl bromides or those possessing electron withdrawing groups at *ortho*- position offered abnormal α-methylated product instead of the normal desired products. A plausible mechanism for the formation of the abnormal products (monomethylated and dimethylated) has been discussed.

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Supplementary data

Supplementary data (experimental procedures and characterization data of all the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.026.

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