# AgI promoted one-pot synthesis of aminoindolizines via sequential Mannich-Grignard addition and intramolecular cyclization in water

Veeranna Guguloth[a], Ramesh Balaboina[a], Suresh Paidakula[a], Narasimha Swamy Thirukovela[b*], Ravinder Vadde[a*]

[a]Department of Chemistry, Kakatiya University, Warangal, T.S. India; Email: ravichemkuc@gmail.com

[b]Department of Chemistry, Chaitanya (Deemed to be University), Warangal, T.S. India; Email: thirukovelann@gmail.com

## Abstract:

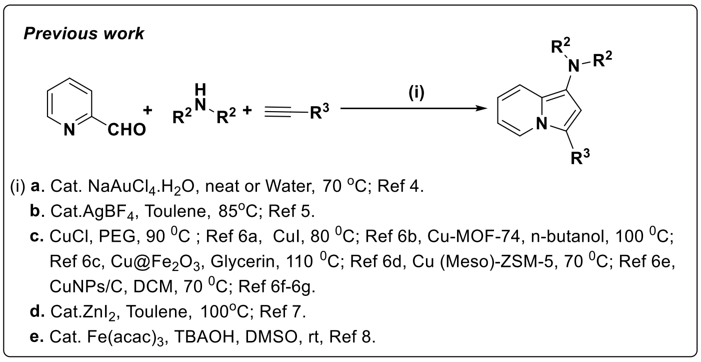
The efficient synthesis of aminoindolizines in eco-friendly water with broad substrate scope from the mild and readily available AgI catalyzed one-pot three-component reaction of pyridine-2-carboxaldehyde, secondary amines and terminal alkynes proceeds *through* the sequential Mannich-Grignard addition as well as intramolecular cyclization was reported for the first time**.**

## Introduction:

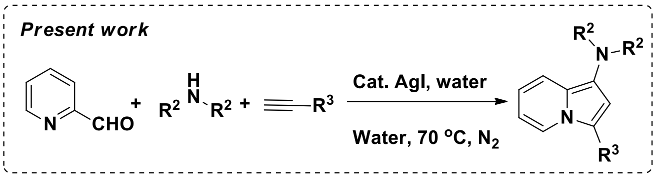
The Indolizine is a significant heterocycle, since it is an important skeleton for several biologically active compounds, few of them are naturally available [1], whereas, others are only synthetically obtainable. In addition, this nucleus was found as a potent pharmacophore which exhibit numerous pharmacological activities such as anti-leishmanial [2a], anti-convulsant [2b], anti-inflammatory [2c], anti-tubercular [2d] calcium entry blocker [2e], herbicidal [2f], anti-oxidant [2g], histamine H3 receptor antagonist [2h], anti-herpes [2i] and anti-HIV [2j] activities. It also acts as CNS depression agent [2k] and even displays active cardiovascular properties [2l]. Furthermore, indolizines have the capability to converse multi-drug resistance [2m] as well as persuade apoptosis *via* mitochondrial path over several cancer cell lines [2n].

Consequently, the great efforts were made to develop suitable and efficient protocols for the synthesis of indolizine derivatives in recent years [3]. Interestingly, in majority of the cases, transition metals promoted C–C and C–N bond formations have been well employed to afford these moieties. Remarkably, metal catalyzed three-component coupling reaction of 2-pyridinecarboxaldehyde, secondary amines and terminal alkynes have been emerged as one of the efficient protocol to synthesize these scaffolds, in terms of easy availability of starting materials, atom economy and energy consumption etc., As a result, few metal catalysts like Au [4], Ag [5], Cu [6], Zn [7] and Fe [8] were used for the above one-pot synthesis. Despite the efficiency of these catalytic systems, few limitations have been noticed such as (i) the use of expensive catalyst [4], additive [8] and organic solvents [5, 6a, c-g, & 7-8], (ii) high reaction temperature [6, 7a-d, 8] and catalyst loading [5, 6a-b, 7-8], (iii) low substrate scope and [6c and 6e] and (iv) the use of heterogeneous Cu catalysts which have special synthetic procedures [6c-g].

The application of sustainable organic synthesis, according to green chemistry principles, the reactions performing in aqueous solvent system have always been a special and motivating attention to both the scientific and industrial community [9]. Accordingly, we have developed some metal catalyzed organic transformations namely hydroformylation [10], hydrothiolation [11], cross dehydrogenative coupling [12], nitrile hydration [13] and tandem Sonogashira coupling-intramolecular cyclizations [14-15] in environmentally benign aqueous media. Due to the outstanding catalytic proficiency of silver, in the activation of alkyne functionality via its π or σ-coordination leading to achieve successive organic transformations [16] and in continuation of our group interest towards the sustainable chemical synthesis, we herein, report the readily available and mild AgI catalyzed one-pot three-component reaction of pyridine-2-carboxaldehyde, secondary amines and terminal alkynes to achieve aminoindolizines in green water medium.



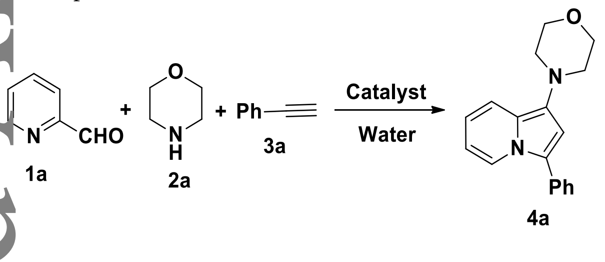
(i) **a.** Cat. $NaAuCl_4.H_2O$, neat or Water, 70 °C; Ref 4.
**b.** Cat.$AgBF_4$, Toulene, 85°C; Ref 5.
**c.** CuCl, PEG, 90 °C ; Ref 6a, CuI, 80 °C; Ref 6b, Cu-MOF-74, n-butanol, 100 °C; Ref 6c, $Cu@Fe_2O_3$, Glycerin, 110 °C; Ref 6d, Cu (Meso)-ZSM-5, 70 °C; Ref 6e, CuNPs/C, DCM, 70 °C; Ref 6f-6g.
**d.** Cat.$ZnI_2$, Toulene, 100°C; Ref 7.
**e.** Cat. $Fe(acac)_3$, TBAOH, DMSO, rt, Ref 8.



To set the appropriate catalytic conditions, initially, we have examined the one-pot three-component reaction of pyridine-2-carboxaldehyde (**1a**), morpholine (**2a**) and phenylacetylene (**3a**) at 70 °C temperature under $N_2$ condition in water using various 3 mol% metal salts. The uncatalyzed reaction was unsuccessful to give the desired product 4-(3-phenylindolizin-1-yl)morpholine (**4a)** (Table 1, entry 1). The reaction also did not take place using CuI, $Cu(OTf)_2$, CuBr, $FeCl_3$, and $ZnCl_2$ (Table 1, entries 2-6), whereas, low yields of product **4a** was obtained using CuCl, AuCl and $AuBr_3$ (Table 1, entries 7-9). In order to improve the yield of one-pot product **4a**, finally we have intended to examine the catalytic efficacy of some Ag-salts. It has been found that all the complete or partly water soluble Ag salts like $Ag_2O$, $AgNO_3$, AgOAc, $Ag_2SO_4$, AgOTf, $AgPF_6$,

$AgSbF_6$, $AgBF_4$ and AgF were provided the desired product **4a** in the range of 35-46%, along with the formation of picolinic acid with quantitative yield (Table 1, entries 10-18). In order to reduce the reduction of Ag-catalytic system by pyrdine-2-carboxaldehyde in water, we intended to use some water insoluble Ag catalytic systems. Accordingly, the water insoluble Ag-salts such as AgI, AgBr and AgCl have efficiently promoted the one-pot three-component reaction of **1a**, **2a** and **3a** to achieve the targeted **4a** in the range of 59-86% yields without the formation of picolinic acid (Table 1, entries 19-21). Particularly, the highly water insoluble AgI was found to be optimal as compared to the rest of the silver halides (Table 1, entry 21). Different catalyst concentration studies revealed that 2 mol% AgI was the optimal for the present one-pot approach (Table 1, entry 22). Reducing reaction temperature from 70 °C has also led to lessen the yield of **4a** consecutively (Table 1, entry 24). The AgI catalyzed one-pot three-component reaction of **1a**, **2a** and **3a** was also sluggish in the presence of open air (Table 1, entry 25).

**Table 1.** Optimization of reaction conditions

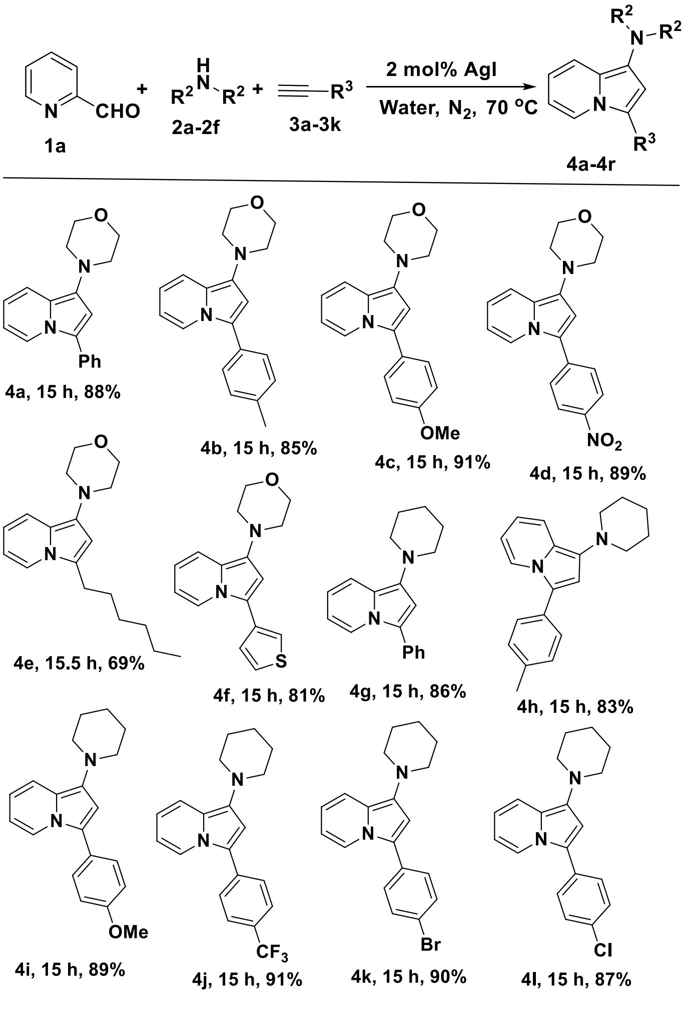


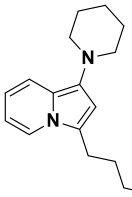
| Entry | Catalyst (mol%) | T(°C) | Time (h) | Yield **4a** (%)[b] |
|---|---|---|---|---|
| 1 | - | - | 15 | - |
| 2 | CuI (3) | 70 | 15 | - |
| 3 | $Cu(OTf)_2$ (3) | 70 | 15 | - |
| 4 | CuBr (3) | 70 | 15 | - |
| 5 | $FeCl_3$ (3)) | 70 | 15 | - |
| 6 | $ZnCl_2$3) | 70 | 15 | - |
| 7 | CuCl(3) | 70 | 15 | 17 |
| 8 | AuCl (3) | 70 | 15 | 24 |
| 9 | $AuBr_3$(3) | 70 | 15 | 29 |
| 10 | $Ag_2O$ (3) | 70 | 15 | 35 |
| 11 | $AgNO_3$ (3) | 70 | 15 | 39 |
| 12 | AgOAc (3) | 70 | 15 | 41 |
| 13 | $Ag_2SO_4$ (3) | 70 | 15 | 46 |
| 14 | AgOTf (3) | 70 | 15 | 43 |
| 15 | $AgPF_6$ (2) | 70 | 15 | 44 |
| 16 | $AgSbF_6$ (3) | 70 | 15 | 42 |
| 17 | $AgBF_4$ (3) | 70 | 15 | 43 |
| 18 | AgF (3) | 70 | 15 | 42 |
| 19 | AgCl (3) | 70 | 15 | 59 |
| 20 | AgBr (3) | 70 | 15 | 69 |
| 21 | AgI(3) | 70 | 15 | 86 |
| 22 | AgI (2) | 70 | 16 | 86 |
| 23 | AgI (1) | 70 | 19 | 53 |
| 24 | AgI (2) | 55 | 18 | 64 |
| 25 | AgI (2) | 70 | 15 | 8[c] |

[a] Pyrdine-2-carboxaldehyde **1a** (1.0 mmol), morpholine (**2a**) (1.2 mmol), phenylacetylene (**3a**) (1.2 mmol), water (2 mL) and $N_2$ atmosphere. [b] Isolated yields after column chromatography. [c] Open air atmosphere.

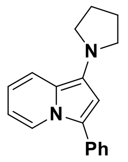
The above optimized conditions in our hand, we further expanded the present one-pot approach to various secondary amines and terminal alkynes and their results were shown in table 2. In the case of secondary amines, all the aliphatic cyclic amines and dibenzylamine were afforded the corresponding aminoindolizines in high yields(Table 2, entries 4a-4q). However, the moderate yield of corresponding aminoindolizines obtained in the case of acyclic amine (Table 2, entry 4r). In addition, phenylacetylene (Table 2, entries 4a, 4g, 4n-4o and 4r) as well as several phenylacetylenes bearing different substituents including –Me (Table 2, entries 4b and 4h), –OMe (Table 2, entries 4c and 4i), $–CF_3$ (Table 2, entry 4j), –Br (Table 2, entry 4k), –Cl (Table 2, entry 4l) and $–NO_2$ (Table 2, entry 4d) led to the respective aminoindolizines in good to excellent yields (Table 2, entries 4a-4q). On the other hand, the moderate yields of the corresponding indolizines were achieved using aliphatic alkynes (Table 2, entries 4e, 4m and 4p) may be due to the instability of the derivatives that decomposed rapidly in the course of the column chromatography. Besides, heteroaryl alkyne, 3-ethynyl thiophene was found to suitable to afford the desired aminoindolizine in good yield (Table 2, entry 4f) under the current optimization conditions devoid of any complications.

**Table 2.** Substrate scope

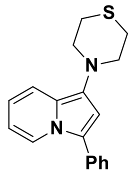




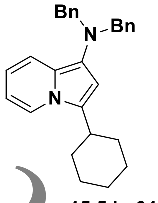
4m, 15.5 h, 72%



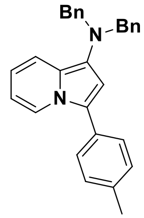
4n, 15.h, 85%



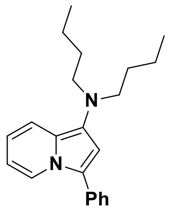
4o, 15 h, 84%



4p, 15.5 h, 64%



4q, 15 h, 84%

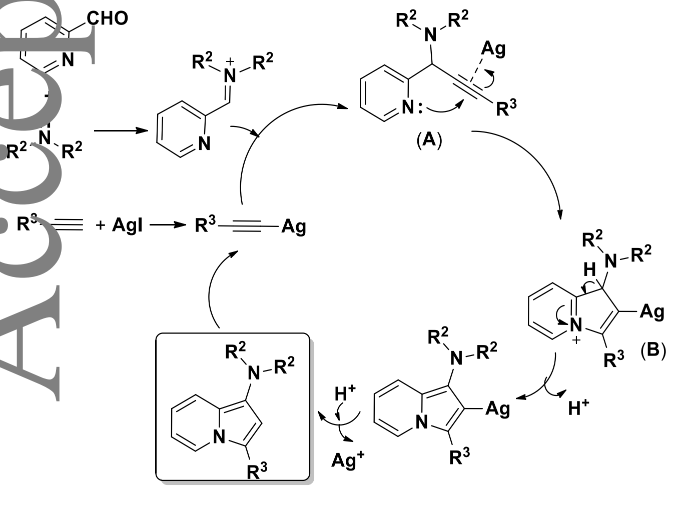


4r, 15 h, 69%

---

AgI (0.02 mmol), Pyrdine-2-carboxaldehyde **1a** (1.0 mmol), secondary amines (**2a**-**2f**) (1.2 mmol), terminal alkynes (**3a**-**3k**) (1.2 mmol), water (2 mL) and $N_2$ condition. [b]Isolated yields after coloumn chromatography.

The reaction path of Ag-promoted tandem Mannich Grignard addition and intramolecular cyclizations was well described in the literature [5, 16] Therefore, using the literature reports and from our experimental results, a plausible reaction path was proposed which is shown in scheme 1. At the outset, AgI-promoted one-pot three-component ($A^3$-type) coupling of pyridine-2-carboxaldehdye, secondary amines and terminal alkynes takes place to give the *N*-propargylamine intermediate (**A**) through the Mannich-Grignard reaction, where the electrophilicity of the alkyne functionality has been enriched as a result of the coordination of triple bond of alkyne with Ag-catalytic system. Then, the intramolecular cyclization of intermediate **A** occurs proceeds through the nucleophilic attack of lone pair of oxygen towards the activated triple bond of intermediate **A** to afford a cationic heterocyclic intermediate (**B**), in which both deprotonation and demetallation processes takes place to achieve aminoindolizines.



**Scheme 1.** A probable reaction path.

In conclusion, we have been first time applied the catalytic proficiency of mild and readily available AgI in promoting the tandem Mannich-Grignard addition and intramolecular cyclization to achieve aminoindozines with moderate to excellent yields *via* single pot in eco-friendly water. The outcomes of the present work are comparable or reasonably better as compared to prior works. Further, the efforts are under progress to enhance the substrate scope.

**Keywords:**

Aminoindolizines, One-pot three-component reaction, Mannich-Grignard addition, Intramolecular cyclization.

**Conflict of interest:**

The authors declare that they have no conflict of interest.

## Acknowledgements

The author Veeranna Guguloth thankful to UGC New Delhi, India for providing senior research fellowship.

## References:

[1] (a) S. G. Pyne, *Curr. Org. Synth.* **2005**, *2*, 39–57; (b) T.Honda, H. Namiki, H. Nagase, H. Mizutani, *Tet. Lett.* **2003**, *44*, 3035–3058; (c) L. Wei, A.Drossi, S. L. Morris-Natschke, K. F. Bastow, K. H. Lee, *In Studies in Natural Products Chemistry;Atta-ur-Rahman, Ed. Elsevier:New York*, **2008**, *34*, 3–34; (d) N. Toyooka, D. Zhou, H. Nemoto, H. M. Garraffo, T. F. Spande, W. Daly, W. John, *Beil. J. Org. Chem.* **2007**, *3*, 29; (e) S. P. Marsden, A. D. Mc Elhinney, *Beil. J. Org. Chem.* **2008**, *4,* 8; (f) F.Zumino, A. T. Kotchevar, M. Waring, M. Daoudi, N. B. Larbi, M. Mimouni, N. Sam, A. Zahidi, T. Ben-Hadda, *Molecules***,** **2002**, *7*, 628–640; (g) M. Pourashraf, P. Delair, M. O. Rasmussen, A. Greene, *E. J. Org. Chem.* **2006**, *65*, 6966–6972; (h) M. Diederich, U. Nubbemeyer, *Synthesis*, **1999**, 286–289; (i) P. Chalard, R. Remuson, Y. G.Mialhe, J. C. Gramain, I. Canet, *Tetrahedron Lett.* **1999**, *40*, 1661–1664; (j) S. H. Park, H. J. Kang, S. Ko, S. Park, S. Chang, *Tetrahedron: Asymmetry* **2001**, 12, 2621–2624; (k) M. Facompré, C. Tardy, C. Bal-Mahieu, P. Colson, C. Perez, I. Manzanares, C. Cuevas, C. Baily, *Cancer Res.* **2003**, *63*, 7392–7399; (l) M. Vanhuyse, J. Kluza, C. Tardy, G. Otero, C. Cuevas, C. Bailly, A. Lansiaux, *Cancer Lett.* **2005**, *221*,165–175.

[2] (a) L. -L. Gunderson, C. Charnock, A. H. Negussie, F. Rise, *Eur. J. Pharm. Sci.* **2007**, *30*, 26–35; (b) R. L. Krall, J. K. Penry, B. G. White, H. J. Kupferberg, E. A. Swinyard, *Epilepsia,***1978**, *19*, 409–428; (c) K. Dawood, H. Abdel-Gawad, M. Ellithey, H. A. Mohamed, B. Hegazi, *Arch. Pharm.* **2006**, *339*, 133–140;(d) L. -L. Gundersen, A. H. Negussie, F. Rise, O. B. Østby, *Arch. Pharm. Pharm. Med. Chem.* **2003,** *336*, 191–195; (e) C. Poty, V. Gibon, G. Evrard, B. Norberg, D. P. Vercauteren, J. Gubin, P. Chatelain, F. Durant, *Eur. J. Org. Chem.* **1994**, *29*, 911–923; (f) S. C. Smith, E. D. Clarke, S. M. Ridley, D. Bartlett, D. T. Greenhow, H. Glithro, A. Y. Klong, G. Mitchell, G. W. Mullier, *Pest Manag. Sci.* **2005**, *61*, 16–24; (g) O. B. Østby, B. Dalhus, L. -L. Gundersen, F. Rise, A. Bast, G. R. M. Haenen, *Eur. J. Org. Chem.* **2000**, 3763–3769; (h) W. Chai, J. G. Breitenbucher, A. Kwok, X. Li, V. Wong, T. W.Carruthers, T. W. Lovenberg, C. Mazur, S. J. Wilson, F. U. Axe, T. K. Jones, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767–1770; (i) C. Foster, M. Ritchie, D. L. Selwood, Snow W. Den, *Antivir. Chem. Chemother.* **1995**, *6*, 289–297; (J) M. Facompre, C. Tardy, C. Bal-Mahieu, P. Colson, C. Perez, I. Manzanares, C. Cuevas, C. Baily, *Cancer Res.* **2003**, *63*, 7392–7399; (k) W. B. Harrell, *J. Pharm. Sci.*

**1970**, *59*, 275–277; (l) J. Gubin, M. Descamps, P. Chatelain, D. Nisato, *Eur. Pat. Appl. EP* 235111, **1987**; (m) D. Pla, A. Marchal, C. A.Olsen, A. Francesch, C. Cuevas, F. Albericio, M. Alvarez, *J. Med. Chem.* **2006**, *49*, 3257–3268; (n) C. Ballot, J. Kluza, A. Martoriati, U. Nyman, P. Formstecher, B. Joseph, C. Bailly, P.Marchetti, *Mol. Cancer Ther.* **2009**, *8*, 3307–3317.

[3] (a) U. Bora, A. Saikia, R. C. Boruah, *Org. Lett.* **2003**, *5*, 435; (b) I. V. Seregin, A. W. Schammel, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 3433; (c) M. T. Gandas´egui, J. Alvarez-Builla, *J. Chem. Res.* **1986**, 74-75; (d) Y. Liu, Z. Song, B. Yan, *Org. Lett.* **2007**, *9*, 409; (e) D. Chernyak, S. B. Gadamsetty, V. Gevorgyan, *Org. Lett.* **2008**, *10*, 2307; (f) D. Chernyak, C. Skontos, V. Gevorgyan, *Org. Lett.* **2010**, *12*, 3242; (g) I. V. Seregin, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 12050; (h) J. Barluenga, G.Lonzi, L. Riesgo, L. A. Lopez, M. Tomas, *J. Am. Chem. Soc.* **2010**, *132*, 13200.

[4] B.Yan, L.Yuanhong, *Org. Lett.* **2007**, *9*, 4323 – 4326.

[5] B. Yaguang, J. Zeng, M. Jimei, G. Balakishan; L. Xue-Wei, *Journal of Combinatorial Chemistry*, **2010**, *12*, 696 – 699.

[6] (a) M. Sarita, N. Bikramaditya, G. Rina, *Tet. Lett.* **2012**, *53*, 5483–5487; (b) P.Changming, Z. Jianping, Z. Runsheng, *Chin. J. Chem.* **2013**, *31*, 799—804; (c) H. D. Giao, Q. L. Huy, T. N. Anh, T. L. Dung, T. S. P. Nam, *Journal of Catalysis*, **2016**, *337*, 167–176; (d) U. C. Rajesh, V. S. Pavan, S. D. Rawat, *RSC Advances*, **2016,** *6*,2935 – 2943; (e) S. Bhaskar, S. Biswarup, S. Rajendra, *RSC Advances*. **2016**, *6*,87066-87081; (f) J. A. Maria, A. Francisco, J. G. Maria, *ACS Catal.* **2015**, *5*, 3446−3456; (g) J. A. Maria, A. Francisco, Y. Miguel, *Chem. Eur. J.* **2013**, *19*, 5242 – 5245.

[7] S. Mishra, A. K. Bagdi, M. Ghosh, S. Sinha, A. Hajra, *RSC Advances*, **2014**, *4*,6672 – 6676.

[8] S. S. Patil, S. V. Patil, V. D. Bobade, *Synlett.* **2011**, *16*, 2379 – 2383.

[9] (a) C.-J. Li, T.H. Chan, *Comprehensive Organic Reactions in Aqueous Media,2nd ed., Wiley, New York,* **2007**; (b) R. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany, **2007**;(c) H. D. Velazquez, F. Verpoort, *Chem. Soc. Rev.* **2012,** *41*,7032–7060;(d) M. Lombardo, C. Trombini, *Curr. Opin. Drug Discov. Devel.* **2010**, *13*, 717–732;(e) A. A. Marianou, C. M. Michailof, A. Pineda, E. F. Iliopoulou, K. S. Triantafyllidis, A. A. Lappas, *Chem. Cat. Chem.* **2016**, *8*,1100–1110; (f) B. Cornils, W. A. Herrmann, Aqueous-Phase Organometallic Catalysis: Concepts and Applications, 2nd ed., Wiley-VCH, Weinheim, Germany, **2004.**

[10] (a) C. S. Vasam, S. Modem, S. Kankala, S. Kanne, G. Budige, R. Vadde, *Cent. Eur. J. Chem.* **2010,** *8*, 77;(b) V. Chandrasekar, M. Sarangapani, K. Shravankumar, B. Geeta, V. Ravinder, *Appl. Organometal. Chem.* **2009**, *23*,460–466.

[11] (a) S. Kankala, S. Nerella, R. Vadde, C. S. Vasam, *RSC Adv.* **2013,***3*,23582; (b) M. Sarangapani, K. Shravankumar, B. Ramesh, T. Narasimhaswamy,B.J.Sreekantha, V. Ravinder, V. Chandrasekar, *J. Eur, Org. Chem.* **2016,** *27*, 4635–4642.

[12] T. Narasimhaswamy, B. Ramesh, K. Shravankumar, V. Ravinder, V. Chandrasekar, *Tet, Lett.* **2018,** *59*, 3749-3752.

[13] T. Narasimhaswamy, B. Ramesh, V. Ravinder, V. Chandrasekar, *Tetrahedron*,**2019,***75*, 2637-2641.

[14] T. Narasimhaswamy, B. Ramesh, B. Vinayak, V. Ravinder, B. J. Sreekantha, V. Chandrasekar, *Catal. Sci. Technol***,** **2019,** *9*, 6471-6481.

[15] G. Veeranna. T. Narasimhaswamy, B. Ramesh, P. Suresh, V. Ravinder, *Tet. Lett.* **2019**, *60*, 297–299.

[16] (a) F. Guichun, X. Bi, *Chem. Soc. Rev.* **2015,** *44*, 8124.(b) V. A. Peshkov, O. P. Pereshivko, V. V. E. Erik, *Chem. Soc. Rev.* **2012**, *41*, 3790–3807. (c) Li. Ch, *Acc. Chem. Res.* **2010,** *43*, 581-590.(d) J. Zeng, Y. Bai, S. Cai, J. Ma, X.W. Liu, *Chem. Commun.* **2011**, *47*, 12855.