RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

ARTICLE

Solvent free one-pot multi-component synthesis of β-azaarene substituted ketones via Sn-catalyzed C(sp3)-H functionalization of 2-alkylazaarenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Santosh S. Chavan,[a] Mohsinkhan Y. Pathan[a] and Shafeek A. R. Mulla,[a]*

Tin-catalyzed solvent free one-pot multicomponent cascade reaction strategy for direct Michael addition/C(sp3)-H functionalization of 2-alkylazaarenes with aldhydes and ketones via aldol reaction has been developed. This is the first report and provides cost effective new access to potent biologically/medicinally important azaarene derivatives with high atom economy.

The C(sp2)-H and C(sp3)-H bond activation/ functionilization as well as C-C bond formation emerged as key strategy to construct complex structural biologically active compounds.[1] Although, direct C(sp3)-H bond activation/functionalization of 2-alkyl azaarenes using transition metal catalyst[2] have been well documented by various research groups. Nonetheless, the complement to transition metal catalyst, a Lewis acid catalyzed C(sp3)-H bond activation/functionalization of 2-alkyl azaarenes has been reported by Kanai et al as shown in previous work[3b] (Scheme 1). Even though, significant progress has been achieved for the C-H bond functionalization of 2-azzarene using Michael addition,[3] alkylation reaction,[4] aldol reaction,[5] nucleophilic addition reaction for C-C, C-N and other hetro atom bond formation,[6] however, all these strategies are limited to single step reaction as shown in previous work (Scheme 1). To our knowledge, so far kumar et al[7] has been reported multi-component protocol for the synthesis of alkyl azaarene pyridinium zwitterions via iodine mediated C-H activation of a 2-alkyl azaarene. Therefore, development of C(sp3)-H bond activation/functionalization of methyl group of azaarene using single step multi substrate protocol by implementing cascade sequential scaffold strategy is not explored so far (present work, scheme 1), which is became very interesting and an exciting research area in modern-day-organic chemistry.[8]

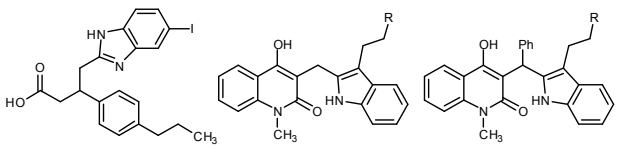
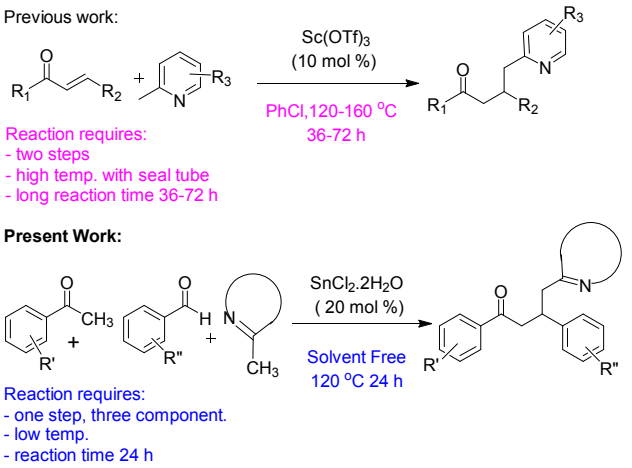


Fig. 1 Selected β-azaarenes substituted biologically active compounds.



Scheme 1 Metal-catalyzed C-H functionalization of azaarenes.

Being azaarenes derivatives are not only ubiquitous motifs in the wide range of alkaloid/natural products but also potent precursors of biological/pharmaceutical active compounds (Fig.1).[9,11c] Also 2-(azaaryl) methanes as core structural constituents of heterocyclic compound along with benziimidazole, benzooxazole, benzothiazole, pyridine, piperazine moieties have been attracted world-wide because of their huge application in therapeutic,[12] as well as pharmacophore in library design and drug discovery.[13] Hence, the development of solvent-free, more efficient, cost effective, environmentally sustainable methodologies to construct its structural units with the concept of high atom economy is a real challenge in organic synthesis. As part of our ongoing research program on development of C(sp3)-H

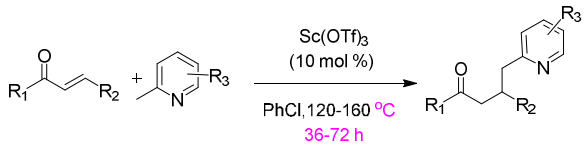
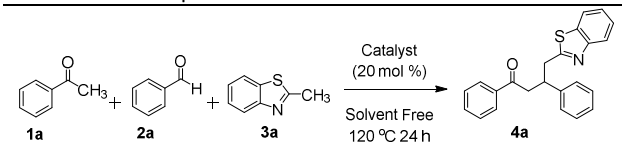
[a] Chemical Engineering and Process Development Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, Maharashtra, India. *E-mail: sa.mulla@ncl.res.in; Fax: +91 20 25902676; Tel: +91 20 25902316

† Electronic supplementary information (ESI) available: Experimental procedures, and copies of ^{1}H and ^{13}C NMR spectra of all products, See DOI: 10.1039/x0xx00000x

functionilization of 2-methyl azaarenes and (2-azaaryl)methanes[10a] and one-pot multi-component reaction (MCR) strategy[10b,c] for organic synthesis, we herein report cascade sequential scaffold strategy for an atom-economic, solvent free, and efficient synthesis of β-azaarene substituted ketones via tin catalyzed one-pot multi-component reaction (MCRs) protocol for C(sp3)-H bond activation/functionalization of 2-alkyl azaarenes, as shown in present work (Scheme 1).

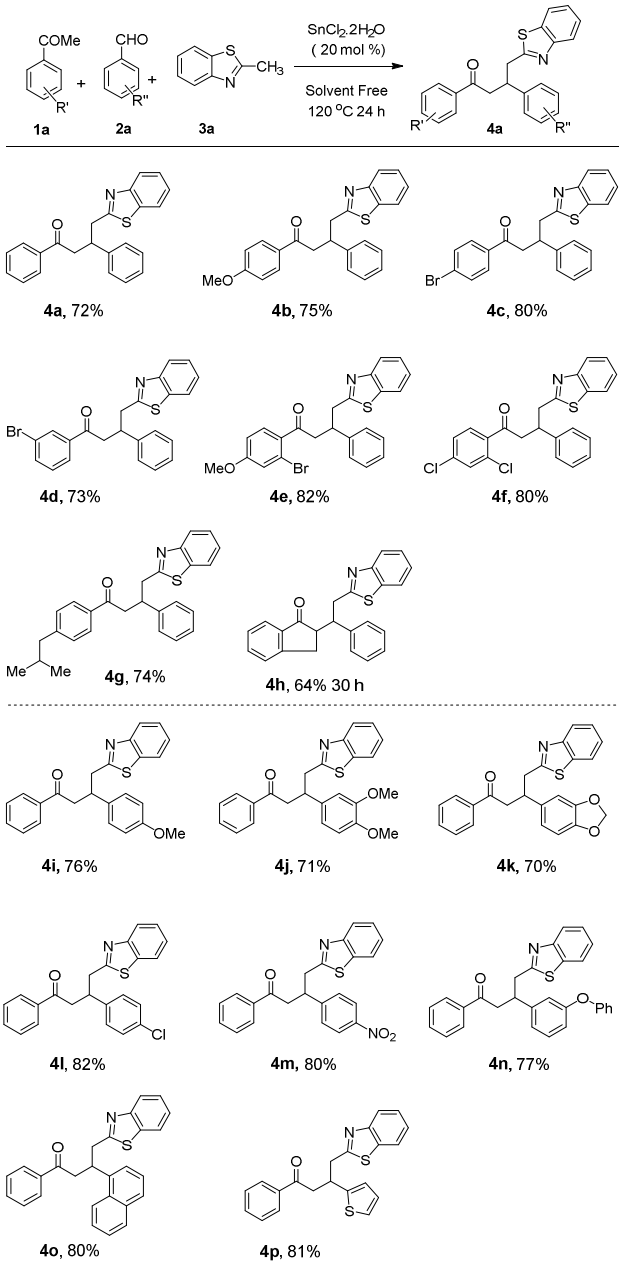
In order to test the possibility of our MCR hypothesis, acetophenone **1a**, benzaldehyde **2a** and 2-methyl benzothiazole **3a** were chosen as model substrates to optimize the reaction conditions. Initially, the screening of various Lewis acid catalysts such as $ZnCl_2$, $Cu(OAC)_2$, $FeCl_3$, $AlCl_3$, $CuCl_2$ were performed by reacting acetophenone (1 mmol) **1a**, benzaldehyde (1 mmol) **2a** and 2-methyl benzothiazole (1 mmol) in the presence and absence of 5 ml of DMF as solvent using 20 mol % catalyst at 120 °C, 24 h (Table 1). However, in the presence of DMF solvent, the formation of the desired product **4a** was not observed using $ZnCl_2$, $Cu(OAC)_2$, $FeCl_3$, $AlCl_3$, $CuCl_2$ as catalysts, whereas $InCl_3$, $SnCl_2.2H_2O$, and DTP/SiO_2 catalysts provided **4a** in 25, 38 and 16 % yields, respectively (entries 2-4). Due to highest performance of $SnCl_2.2H_2O$ catalyst compared to other catalysts in DMF, the screening of other solvents such as 1,4-dioxane, toluene, DCE, DMSO, and NMP have been also carried out, unfortunately, desired product formation was not observed. Therefore, the performance of Lewis acid catalysts were examined in the absence DMF solvent. The $Cu(OAC)_2$, $FeCl_3$, $AlCl_3$, $CuCl_2$ catalysts does not shows any sign of catalytic activity. Moreover, $SnCl_2.2H_2O$ catalyst (entry 7) exhibited excellent performance compared

Table 1 Comparison of the results between previous research work and present research work

Entry	Catalyst	Solvent	Yield (%)
Previous work			
			
1	$Sc(OTf)_3$	PhCl	60-96
Present work : Optimization of the reaction condition[a]			
			
2	$InCl_3$	DMF	25[b]
3	$SnCl_2.2H_2O$	DMF	38[b]
4[c]	DTP/SiO_2	DMF	16[b]
5	$ZnCl_2$	-	41[b]
6	$InCl_3$	-	65[b]
7	$SnCl_2.2H_2O$	-	72[b]
8[c]	DTP/SiO_2	-	40[b]

[a]Reaction conditions: 2-methyl benzothiazole (1 mmol), benzaldehyde (1 mmol), acetophenone (1 mmol), Catalyst (20 mol %), Solvent (5 mL). 90-120 °c for 24 h. [b]Isolated yield. [c]DTP/SiO_2 100 mg catalyst.

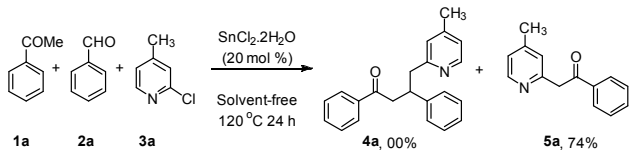
Table 2 Substrate scope of substituted acetophenone and benzaldehyde.[a,b]



[a]Reactions were conducted with 2-methyl benzothiazole (1 mmol), acetophenone (1 mmol), benzaldehyde (1 mmol), $SnCl_2.2H_2O$ (20 mol %) in Solvent free condition at 120 °C for 24 h. [b]The yields indicated are the isolated yield by column chromatography

to $ZnCl_2$, $InCl_3$, and DTP/SiO_2 catalysts (entry 4, 6, 8) under the solvent free reaction conditions. Results on the catalysts screening reveals that the $SnCl_2.2H_2O$ catalyst shows excellent performance at 120 ^oC in 24 h under solvent free reaction conditions.

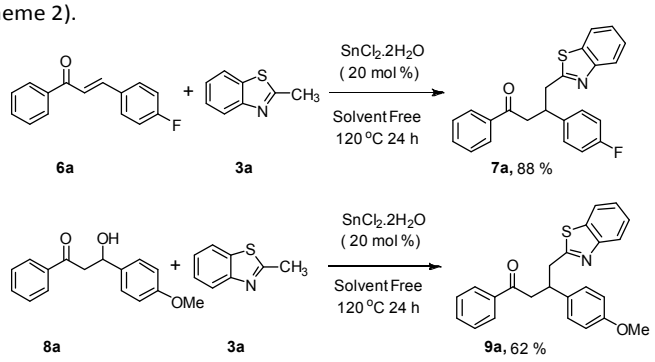
With the optimized reaction condition in hand, we then explored the substrate scope of MCR protocol for the synthesis of β-azaarene substituted ketones. To explore the substrate scope of one pot multicomponent reaction through cascade process for the synthesis of β-azaarene substituted ketones via Sn-catalyzed C(sp3)-H bond activation/functionalization of various azaarenes, initially the reactitivity of various acetophenone has been tested with benzaldehyde and 2-methylbenzothiazole, results are shown in Table 2. To our surprise, the acetophenone as well as acetophenone bearing electron-withdrawing and electron-releasing functional group at ortho, meta, para position of aryl ring are reacted smoothly with benzaldehyde and 2-methylbenzothiazole and afforded the corresponding desired product in moderate to good yield (entries **4a**-**4d**). Amazingly, the disubstituted acetophenone such as 2-bromo, 4-methoxyacetophenone, 2, 4-dichloroacetophenone, and 4-isobutyl acetophenone were also well reacted with benzaldehyde and 2-methylbenzothiazole, and delivered the desired product in good yields ranging from 82-74% (entries **4e**-**4g**). However, the results on cyclic ketone reveal that the 1-Indanone is less reactive and provided moderate yield (64%) in longer reaction time (entry **4h**). Due to encouraging results on the substituted acetophenone, the reactivity of different substituted benzaldehydes and its electronic effects were examined. The electronic rich substrate such as 4-methoxybenzaldehyde, 3, 4 dimethoxybenzaldehyde, and piperonal were well reacted with acetophenone, 2-methylbenzothiazole under optimized reaction condition and furnished the corresponding desired compounds in good yield (entries **4i-4k**). Also the electronically poor aldehydes such as 4-chlorobenzaldehyde and 4-nitrobenzaldehyde were well tolerated to optimized reaction conditions and delivered corresponding desired product (Table 1 entry **4l**, **4m**) in good yield.



Scheme 2 Sn-Catalyzed C-H functionalization of 2-chloro-4-methyl pyridine

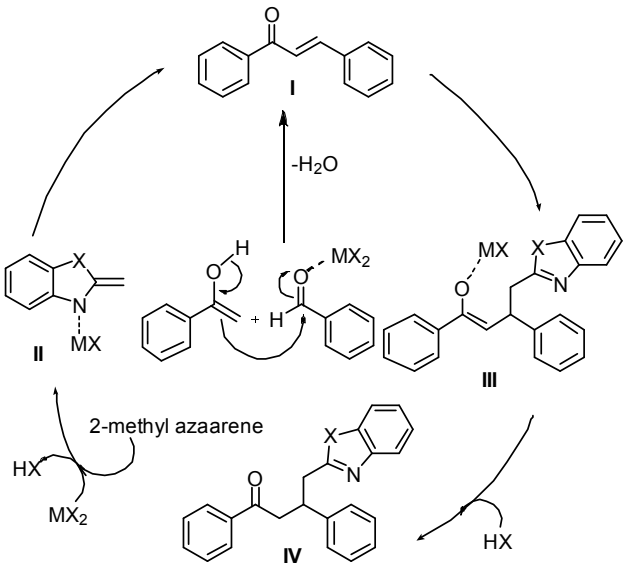
Interestingly, the 3-phenoxy benzaldehyde, neutral naphthaldehyde as well as heterocyclic 2-thiophene carboxylate were reacted smoothly with acetophenone, 2-methylbenzothiazole and furnished desired product in good (72-81%) yield (entries **4n**-4p). The results in the Table 2 reveals that electron withdrawing and electron releasing substituent on the aryl ring of acetophone as well as aldehydes plays key role and yield obtained was very much dependent on it. An ortho, para substituents on aryl rings provided higher yield compared meta substituents.

Because of excellent performance of MCR protocols using substituted acetophenones, substitiuted aldehydes and 2-methylbenzothiazole, we were keen to know the Sn-catalyzed C(sp3)-H bond activation/functionalization of 2-chloro-4-methylpyridine. Therefore acetophenone, aldehyde and 2-chloro-4-methylpyridine were reacted under optimized reaction condition, unfortunately, the reaction failed to deliver the expected compound **4a**, nonetheless we end up with unexpected α-arylated acetophenone product **5a** in 74% yield (Scheme 2).



Scheme 3 Control experiment

To gain further insight into the mechanism, various control experiments were performed (scheme 3). A result on the controlled experiments reveals that the mechanism involves via enone formation.



Scheme 4 Plausible mechanisms for the synthesis of β-azaarenes substituted ketones.

As per previous research work reported in the literature,[3b, 6a-c] and also based on the controlled experiments results a plausible reaction mechanisms scenario for one pot multi-component cascade strategies via aldol condensation, sp^3 C-H functionalization or Michael addition process is outlined in

Scheme 4. Initially, Sn-catalyzed condensation of aldehyde with ketone followed by in-situ elimination of water provides enone (**I**). Meanwhile, Sn-catalyzed in-situ generated enamine (**II**) from 2-alkylazarenes. The enone (**I**) reacted with enamine (**II**), which facilitated through C-H functionalization or Michael addition to generate the corresponding intermediate (**III**) followed by rearrangement to give the final corresponding desired product (**IV**).

Conclusions

In conclusion, we have developed Sn-catalyzed solvent free one-pot multicomponent cascade reaction strategy for direct Michael adition/ C(sp3)-H functionalization of 2-alkylazaarenes with aldhydes and ketones via aldol reaction for the synthesis of biologically relevant novel 4-(benzo(d)thiazol-2-yl)-1,3diphenylbutan-1-one and azaarenes containing other derivatives. The developed method is an efficient, mild, atom-economical and one-pot multicomponent cascade reaction via aldol condensation, C-H Functionalization or Michael additions. This strategy allows C(sp3)-H functionalization in one-pot cascade process to rationalize the complex molecule synthesis. Further applications of these newly developed methods for other substrates and the synthesis of biologically active compounds are under way in our research group.

Acknowledgements

We are grateful for the financial support from the CSIR-India (JRF and SRF fellowships to S.S.C and M.Y.P). The authors also thank Dr. V. V. Ranade, Chair of CE-PD for his encouragement and support.

Notes and references

1 For recent selected Sp2(C-H) and Sp3(C-H) Activation, see: (a) G. Rouquet, N. Chatani, *Angew. Chem., Int. Ed*. 2013, **52**, 11726; (b) X. Li, L. He, H. Chen, W. Wu, H. Jiang, *J. Org. Chem*. 2013, **78**, 3636; (c) P. B. Arockian, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* 2012, **112**, 5879; (d) J. Wencel-Delord, T. Drcge, F. Liu, F. Glorius, *Chem. Soc. Rev.* 2011, **40**, 4740; (e) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* 2012, **41**, 3651; (f) C. Tsukano, M. Okuno, Y. Takemoto, *Angew. Chem. Int. Ed.* 2012, **124**, 2817.
For C-H activation in natural product synthesis, see: (g) D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* 2012, **18**, 9452; (h) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, **51**, 8960.

2 For recent selected C-H activation on azaarenes: (a) L. Xu, Z. Shao, L. Wang, J. Xiao, *Org. Lett.* 2014, **16**, 796; (b) S. Lou, D. Xu, D. Shen, Y. Wang, Y. Liu, Z. Xu, *Chem. Commun.* 2012, **48**, 11993; (c) T. Niwa, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* 2007, **46**, 2643; (d) R. Shang, Z. Yang, Y. Wang, S. Zhang, L. Liu, *J. Am. Chem. Soc.* 2010, **132**, 14391.

3 (a) B. Qian, D. Shi, L. Yang, H. Huang, *Adv. Synth. Catal.* 2012, **354**, 2146; (b) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.* 2011, **13**, 1706.

4 (a) G. Song, Y. Su, X. Gong, K. Han, X. Li, *Org. Lett.* 2011, **13**, 1968; (b) T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* 2007, **9**, 2373; (c) P. M. Burton, J. A. Morris, *Org. Lett.* 2010, **12**, 5359.

5 (a) R. Niu, J. Xiao, T. Liang, X. Li, *Org. Lett.* 2012, **14**, 676; (b) J. J. Jin, H. Y. Niu, G. R. Qu, H. M. Guo, J. S. Fossey, *RSC Adv.,* 2012, **2**, 5968; (c) F. F. Wang, C. P. Luo, Y. Wang, G. Deng, L. Yang, *Org. Biomol. Chem*. 2012, **10**, 8605.

6 (a) Y. Yan, K. Xu, Y. Fang, Z. Wang, *J. Org. Chem.* 2011, **76**, 6849; (b) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, *Synthsis*. 2012, **44**, 2185; (c) M. Rueping, N. Tolstoluzhsky, *Org. Lett.* 2011, **13**, 1095. (d) B. S. Qian, G. J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* 2010, **132**, 3650; (e) B. Qian, P. Xie, Y. Xie, H. Huang, *Org. Lett.* 2011, **13**, 2580; (f) J. Y. Liu, H. Y. Niu, S. Wu, G. R. Qu, H. M. Guo, *Chem. Commun.,* 2012, **48**, 9723.

7 (a) A. Kumar, G. Gupta, S. Srivastava, *Org. Lett.,* 2011, **13**, 6366; (b) A. Kumar, L. P. Gupta, M. Kumar, *RSC Adv.,* 2013, **3**, 18771.

8 (a) V. Mehta, P. Garcia-Lopez, J. A.; M. F. Greaney, *Angew. Chem. Int. Ed.* 2014, **126**, 1555; (b) A. Pinto, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* 2007, **46**, 3291; (c) L. Guo, F. Zhang, W. Hu, L. Lia, Y. Jia, *Chem. Commun.* 2014, **50**, 3299; (d) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* 2010, **132**, 9585; (e) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc* 2010, **132**, 10565.

9 (a) W. Frohner, L. A. Lopez-Garcia, S. Neimanis, N. Weber, J. Navratil, F. Maurer, A. Stroba, H. Zhang, R. M. Biondi, M. Engel, *J. Med. Chem.* 2011, **54**, 6714-6723.

10 (a) S. A. R. Mulla, M. Y. Pathan, S. S. Chavan, *RSC Adv.,* 2013, **3**, 20281; (b) S. S. Chavan, M. Y. Pathan, S. H. Thorat, R. G. Gonnade, S. A. R. Mulla, *RSC Adv.,* 2015, **5**, 81103. (c) S. A. R. Mulla, T. A. Salama, M. Y. Pathan, S. M. Inamdar, S. S. Chavan, *Tetrahedron Lett.* 2013, **54**, 672.

11 (a) A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry, Elsevier, Oxford*, 2008, Vol. **7**; (b) L. C. Campeau, K. Fagnou, *Chem. Soc. Rev.* 2007, **36**, 1058; (c) J. P. Michael, *Nat. Prod. Rep*. 2005, **22**, 627; (d) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043.

12 (a) A. 0. Plunkett, *Nat. Prod. Rep.* 1992, **9**, 491; (b) I. N. Houpis, A. Molina, J. Lynch, R. A. Reamer, R. P. Volante, P. J. Reider, *J. Org. Chem.* 1993, **58**, 3176; (c) W. Frohner, L. A. Lopez-Garcia, S. Neimanis, N. Weber, J. Navratil, F. Maurer, A. Stroba, H. Zhang, R. M. Biondi, M. Engel, *J. Med. Chem.* 2011, **54**, 6714.

13 (a) D. Best, H. W. Lam, *J. Org. Chem.* 2014, **79**, 831.

Solvent free one-pot multi-component synthesis of β-azaarene substituted ketones via Sn-catalyzed C(sp^3)-H functionalization of 2-alkylazaarenes†

Shafeek A. R. Mulla,*† Santosh S. Chavan† and Mohsinkhan Y. Pathan,†

†Chemical Engineering and Process Development Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, Maharashtra, India. Tel +91-20-25902316, Fax: +91-20-25902676, E-mail: sa.mulla@ncl.res.in

Tin-catalyzed solvent free one-pot multi-component cascade reaction strategy for efficient synthesis of β-azaarene substituted ketones via Aldol-Michael addition/C(sp3)-H functionalization of 2-alkylazaarenes has been developed.