

Scheme 1 Substrate scope of C–H aryloxylation.

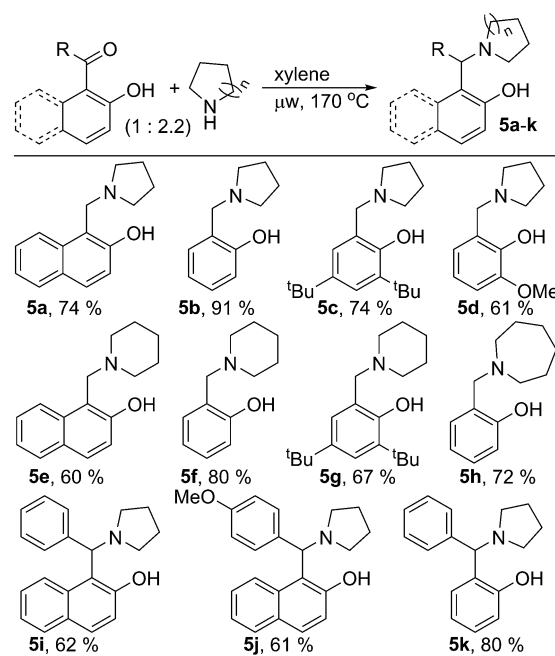
for C–H functionalization of pyrrolidine. Little less yield found for oxazine **4c** was probably due to the lower solubility of ketone **3c** in toluene. Different 2-hydroxy aryl-aldehydes and ketones were also utilized to functionalize various aliphatic secondary amines producing structurally diverse ring fused oxazines. However, ketones were found to be better substrate than the corresponding aldehydes. Ketones containing both electron donating and withdrawing groups are equally suited for the C–H functionalization of N-heterocycles. Both benzylic C–H and non-benzylic C–H containing N-heterocycles are efficiently functionalized. Substituted pyrrolidine was also functionalized efficiently. 2-Methyl pyrrolidine was reacted with aldehyde **1a** to produce oxazine **4l** with 46% yield. As usual, the reaction of 2-methyl pyrrolidine with ketone **1b** was much efficient in producing functionalized product **4m** with very good yield (82%). For both the cases, the product was isolated as the mixture of regioisomers, interestingly, with reversed selectivity.

During the optimization of reaction condition for metal and oxidant free C–H aryloxylation of saturated amines, we noticed that, for most of the cases, significant amount of N-benzylated amine was formed along with desired ring fused oxazine (ESI⁺). N-Benylation of amines is common in organic synthesis to protect the free nucleophilic amine functionality. Moreover,

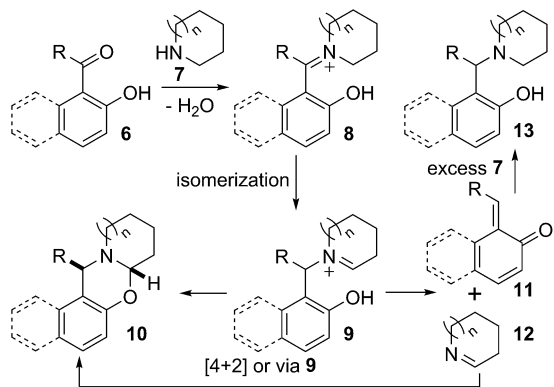
different biologically relevant natural or unnatural compounds including medicinal drugs contain arylmethylamine as main structural motif.⁸ Reductive amination of aldehyde & ketone using stoichiometric amount of metal hydride based reagent is one of the main way for N-benylation.⁹ Similar transformation without using metal hydride would be advantageous and elegant in synthetic chemistry as well as in industry. Therefore, we looked further and optimized the process of arylmethylamine formation (ESI, Table S2[†]). We observed that, the reaction could be drawn towards N-benylation by changing the relative stoichiometry of amine and carbonyl compound. 2-Hydroxy naphthaldehyde (**1a**) was reacted with two equivalent of pyrrolidine in xylene under microwave irradiation to give 2-hydroxy 1-naphthylmethyl amine **5a** as the major product (74%, Scheme 2). Similarly, various aldehydes and ketones were reacted with different cyclic saturated amine producing structurally diverse mono- or di-arylmethylamines **5b–k**. Hydroxy-phenyl based carbonyl compounds gave better results in comparison to hydroxy-naphthyl based substrates.

A mechanistic proposal for this divergent reaction is presented in Scheme 3. Carbonyl compound **6** on reaction with secondary amine **7** produced iminium ion **8**. The isomeric ion **9** could be formed from **8**.¹⁰ The iminium ion **9** could either intramolecularly cyclise to give desired oxazine **10** or undergo dissociation to give the quinone methide **11** and cyclic imine **12**. Diastereoselective intermolecular reaction occurred, probably *via* 4 + 2 cycloaddition or *via* **9**, between the quinone methide **11** and imine **12** to furnish stable oxazine **10**.^{3b,6a}

On the other hand, quinone methide **11** could react with nucleophile present in the reaction mixture.¹¹ Therefore, when the reaction was carried out in the presence of excess amine **7**, quinone methide **11** was trapped by the secondary amine providing formally reduced product **13**. However, the reduced



Scheme 2 Substrate scope of formal reductive amination.

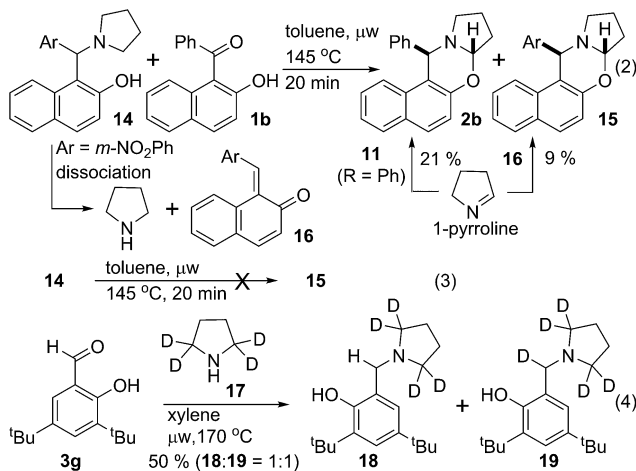


Scheme 3 Mechanistic proposal.

product can also be formed through direct reduction of iminium ion **8** or any of its mesomer by intermolecular hydride transfer from excess amine **7**.¹²

Experiments in Scheme 4 were performed to better understand the course of the reaction. Hydroxy ketone **1b** was reacted with arylmethylamine **14** in toluene at 145 °C under microwave irradiation. Two oxazines **2b** & **15** were isolated with 21% & 9% yield respectively (eqn (2)). However, no cyclized product **15** was formed from **14** under the same conditions (eqn (3)). To explain this observation, we reasoned that, **14** dissociated to pyrrolidine and quinone methide **16** under thermal condition.^{6b} Pyrrolidine then reacted with ketone **1b** to produce isomerized iminium ion similar like **9** that dissociated to quinone methide equivalent to **11** and 1-pyrroline. 1-Pyrroline then partitioned during its subsequent reaction with quinone methide **11** (R = Ph) & **16** to give corresponding oxazines **2b** & **15**. This observation supported our mechanistic proposal that the reaction or a part of it proceeded through intermolecular pathway *via* quinone methide intermediate. However, the possibility also remained for the reaction to occur through intramolecular process.

Isotope labelling experiment was performed to probe the novel *N*-benzylation reaction (eqn (4)). Deuterated pyrrolidine



Scheme 4 Experiments performed for mechanistic investigation.

17 was reacted with aldehyde **3g** under the standard reduction conditions producing a mixture of unlabelled and labelled benzyl amine **18** & **19**, respectively, with 1 : 1 ratio.¹³ Partial incorporation of the deuterium at the benzylic position accounts for the azomethine ylide intermediate for the conversion of iminium ion **8** to its isomer **9**.¹⁴ Thus the observation of ~50% deuterium incorporation eliminated the possibility of intermolecular hydride transfer process for the formation of reduced product.

Direct C–H aryloxylation of secondary aliphatic amine was achieved *via* a microwave assisted metal, oxidant and other additive free method. Structurally diverse oxazines were obtained by simply heating a mixture of suitable carbonyl compound and amine. We have also showed that the course of the reaction can be altered by changing the relative stoichiometry of carbonyl compound and amine. Upon using one fold excess amine, a formal reductive *N*-benzylation occurred producing a set of biologically relevant mono- or diarylmethylamines. Mechanistic investigation suggested that quinone methide was involved as the intermediate for the reaction.

Acknowledgements

We acknowledge the financial support from Science and Engineering Research Board (SERB), New Delhi and analytical facility from CIF, IIT Guwahati. C.K.J. is the recipient of DAE Young Scientist Research Award.

Notes and references

- For reviews see: (a) F.-X. Felpin and J. Lebreton, *Tetrahedron*, 2004, **60**, 10127; (b) A. M. Lourenco, P. Maximo, L. M. Ferreira and M. M. A. Pereira, *Studies in Natural Products Chemistry: Bioactive Natural Products (Part H)*, ed. A. Rahman, Elsevier, Amsterdam, 2002, vol. 27, p. 233; (c) J. R. Liddell, *Nat. Prod. Rep.*, 2002, **19**, 773.
- For reviews on amine functionalization see: (a) M. C. Haibach and D. Seidel, *Angew. Chem., Int. Ed.*, 2014, **53**, 5010; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) B. Peng and N. Maulide, *Chem.–Eur. J.*, 2013, **19**, 13274; (d) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (e) K. M. Jones and M. Klussmann, *Synlett*, 2012, 159; (f) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654; (g) K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069.
- (a) S. Mahato, S. Haldar and C. K. Jana, *Chem. Commun.*, 2014, **50**, 332; (b) M. L. Deb, S. S. Dey, I. Bento, M. T. Barros and C. D. Maycock, *Angew. Chem., Int. Ed.*, 2013, **52**, 9791; (c) I. D. Jurberg, B. Peng, E. Woestefeld, M. Wasserloos and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 1950; (d) Similar work is published very recently: M. T. Richers, M. Breugst, A. Y. Platonova, A. Ullrich, A. Dieckmann, K. N. Houk and D. Seidel, *J. Am. Chem. Soc.*, 2014, **136**, 6123; (e) S. Shaaban, B. Peng and N. Maulide, *Synlett*, 2013, 1722; (f) N. Cohen, J. F. Blount, R. J. Lopresti

- and D. P. Trullinger, *J. Org. Chem.*, 1979, **44**, 4005; (g) A. Modak, U. Dutta, R. Kancharla, S. Maity, M. Bhadra, S. M. Mobin and D. Maiti, *Org. Lett.*, 2014, **16**, 2602.
- 4 (a) V. Verma, K. Singh, D. Kumar, T. M. Klapötke, J. Stierstorfer, B. Narasimhan, A. K. Qazi, A. Hamid and S. Jaglan, *Eur. J. Med. Chem.*, 2012, **56**, 195; (b) B. P. Mathew, A. Kumar, S. Sharma, P. K. Shukla and M. Nath, *Eur. J. Med. Chem.*, 2010, **45**, 1502; (c) C. E. Augelli-Szafran, J. C. Jaen, D. W. Moreland, C. B. Nelson, J. R. Penvose-Yi and R. D. Schwarz, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1991.
- 5 (a) R. Csütörtöki, I. Szatmári, M. Heydenreich, A. Koch, I. Starke, F. Fülöp and E. Kleinpeter, *Tetrahedron*, 2012, **68**, 6284; (b) G. Cheng, X. Wang, D. Su, H. Liu, F. Liu and Y. Hu, *J. Org. Chem.*, 2010, **75**, 1911; (c) J. Lu, X. Xu, S. Wang, C. Wang, Y. Hu and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2900.
- 6 For selected other methods see: (a) I. Szatmári, M. Heydenreich, A. Koch, F. Fülöp and E. Kleinpeter, *Tetrahedron*, 2013, **69**, 7455; (b) I. Szatmári and F. Fülöp, *Tetrahedron Lett.*, 2011, **52**, 4440.
- 7 For related reaction and its mechanistic studies see: (a) C. Zhang, C. K. De, R. Mal and D. Seidel, *J. Am. Chem. Soc.*, 2008, **130**, 416; (b) A. Dieckmann, M. T. Richers, A. Y. Platonova, C. Zhang, D. Seidel and K. N. Houk, *J. Org. Chem.*, 2013, **78**, 4132; (c) C. L. Jarvis, M. T. Richers, M. Breugst, K. N. Houk and D. Seidel, *Org. Lett.*, 2014, **16**, 3556.
- 8 (a) F. H. Darras, B. Kling, J. Heilmann and M. Decker, *ACS Med. Chem. Lett.*, 2012, **3**, 914; (b) J. J. Li, in *Contemporary Drug Synthesis*, Wiley-Interscience, 2004, p. 221; (c) T. Onoda, H. Iinuma, Y. Sasaki, M. Hamada, K. Isshiki, H. Naganawa, T. Takeuchi, K. Tatsuta and K. Umezawa, *J. Nat. Prod.*, 1989, **52**, 1252.
- 9 For reviews on reductive amination see: (a) V. A. Tarasevich and N. G. Kozlov, *Russ. Chem. Rev.*, 1999, **68**, 55.
- 10 For related iminium ion isomerization. See: (a) X. Xiao, Y. Xie, C. Su, M. Liu and Y. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 12914.
- 11 R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367.
- 12 (a) I. Deb, D. Das and D. Seidel, *Org. Lett.*, 2011, **13**, 812; (b) H. Mao, R. Xu, J. Wan, Z. Jiang, C. Sun and Y. Pan, *Chem.–Eur. J.*, 2010, **16**, 13352.
- 13 Ratio was determined ¹H-NMR spectroscopy; see ESI.†
- 14 Deuterium labelling at benzylic position of **19** occurred probably *via* the deuteration of zwitterionic intermediate **A**.



- (a) For review on azomethine ylide see: G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (b) For selected recent report see: S. Haldar, S. Mahato and C. K. Jana, *Asian J. Org. Chem.*, 2014, **3**, 44; (c) Z.-L. He, H.-L. Teng and C.-J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 2934.