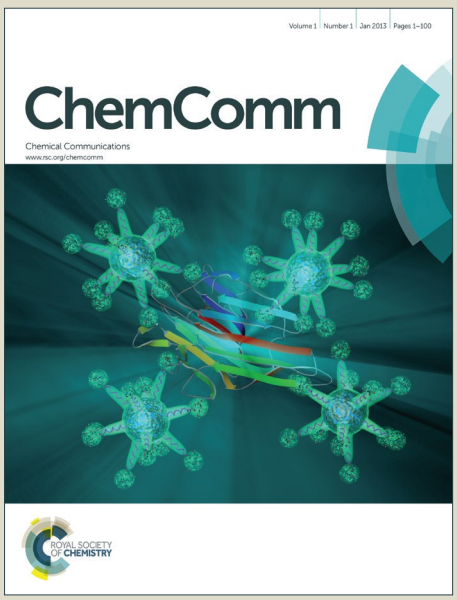
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Kumar, S. H. Thorat and S. R. Maddi, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC08081B.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

ChemComm

View Article Online
DOI: 10.1039/C6CC08081B

COMMUNICATION

Cu-Catalyzed Iminative Hydroolefination of Unactivated Alkynes En route to 4-Imino-Tetrahydropyridines and 4-Aminopyridines

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

DOI: 10.1039/x0xx00000x

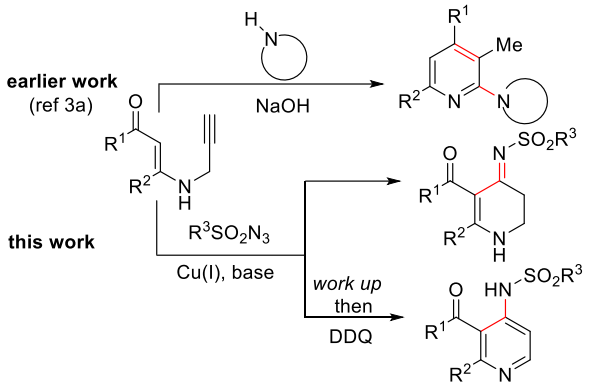
www.rsc.org/

Ravi Kumar,[a,b] Shridhar H. Thorat[c] and Maddi Sridhar Reddy*[a,b]

A general method for 4-imino tetrahydropyridine derivatives is achieved, from readily available β-enaminones and sulfonyl azides, which comprises a sequential copper catalyzed ketenimine formation and its hither to inaccessible intramolecular hydrovinylation. The products are shown as ready precursors for highly valuable 4-sulfonamidopyridine derivatives *via* DDQ mediated oxidation.

Nitrogen embedded heterocycles occupy a huge space in the realm of natural products as well as drug discovery. Particularly, six membered cycles like pyridine and its saturated (dihydro-, tetrahydro- and hexahydro-) derivatives are ubiquitous in nature and show enormous pharmaceutical properties.[1] For instance, nifedipine (antihypertensive), amlodipine (calcium ion channel blocker), clarinex (antihistamine), multiflorine (hyperglycemic), arecoline (stimulant), vulgaxanthin (antioxidant), eszopiclone (hypnotic), imatinib (kinase inhibitor), ocinaplon (an anxiolytic), nicotine (stimulant), etoricoxib (COX-2 inhibitor), rosiglitazone (antidiabetic), omeprazole (proton pump inhibitor), niacin (vitamin B_3), etc. are some of the prominent pyridine or hydropyridine containing pharmaceuticals. Consequently, organic chemists paid significant attention towards the synthesis of pyridine and its derivatives in an efficient and step economical pathways.[1-3] Alkyne based substrates were also identified as versatile precursors for the synthesis of these privileged scaffolds.[3] In this line, Cheng et al reported an elegant method for the synthesis of 2-aminopyridines from N-propargyl-β-enaminones (Scheme 1).[3a]

As part of our ongoing program of unveiling the novel reactivities of functionalized alkynes,[4] we herein report a strategy for 4-aminocounterparts of aforementioned from the same substrates *via* ketenimine formation followed by cyclization and oxidation. Prior to the oxidation, the key iminative cyclization affords highly functionalized tetrahydropyridines. Although a series of transformations from in situ formed ketenimines from acetylenes have been reported[5] since its inception in 2006 by Chang et al,[6] only a few examples in the literature revealed the use of carbon as nucleophile to attack on electrophilic central carbon of ketenimine which constitutes a C-C bond formation between rare centers, i.e. terminal carbon of acetylene and a given nucleophilic carbon.

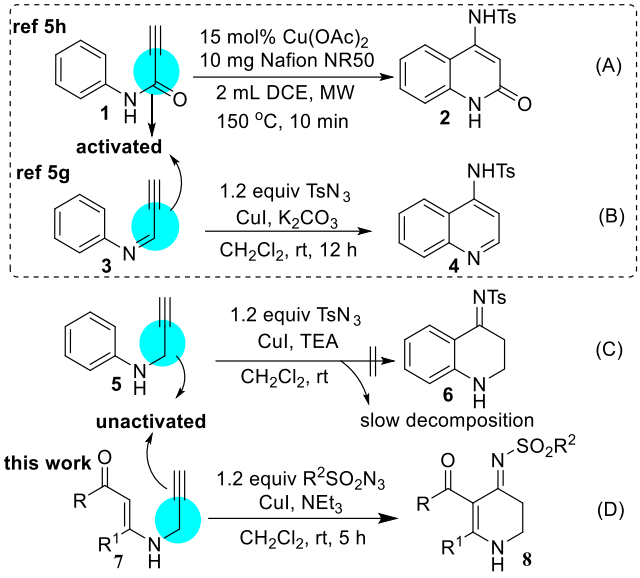


Scheme 1 Aminopyridines from propargyl enaminones

On this line, Glasnov et al and Cui et al reported an elegant cyclization of *N*-propargyl anilines (**1** to **2** and **3** to **4**)[5g-h] containing activated acetylinic group (conjugation was essential) as shown in Scheme 2 (A & B). Surprisingly, no unactivated system like **5** (a close congener of **1** & **3**) was explored, perhaps it was found to be unreactive due to weaker electrophilicity of the resultant ketenimine. Endorsing this fact, an attempt by us to convert **5** to **6** was totally failed (Scheme 2C). Infact, in any type of *N*-sulfonylketenimine chemistry from acetylenes, propargyl amines were hardly explored. Talukdar et al used *N*-propargyl 3°-amines for ketenimine formation which underwent a rare amine group migration (for amidines),[5n] where notably secondary amines were not tested again for unknown reason.

[a] *Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram extension, Sitapur Road, Lucknow 226031, India.*
[b] *Academy of Scientific and Innovative Research, New Delhi 110001, India.*
[c] *Centre for Materials Characterization, CSIR-NCL, Dr Homi Bhabha Road, Pune-411008, India.*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

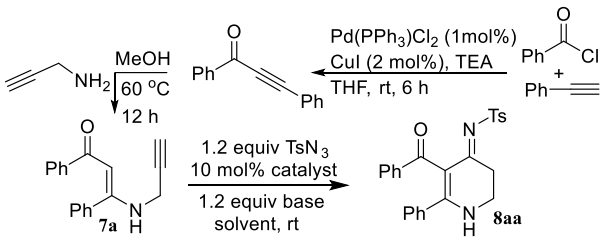


Scheme 2 Iminative cyclization of acetylenes

In light of this, our discovery of conversion of **7** to **8** has, apart from the first use of this chemistry for the synthesis of valuable tetrahydropyridines and pyridines with high new functional decoration, the following highlights: (1) an unprecedented intramolecular hydrovinylization (note: hydroarylations[5g-k] are known) of ketenimines, (2) involvement of unactivated ketenimines i.e. use of non-conjugated propargyl amines and (3) use of unprotected secondary amines.

We began our studies with the optimization of the conversion of **7a**[7] to **8aa** (Table 1). Initially, we treated **7a** with 1.2 equivalents of TsN_3 in presence of 10 mol% of CuI in MeCN

Table 1 Optimization of reaction conditions.[a]



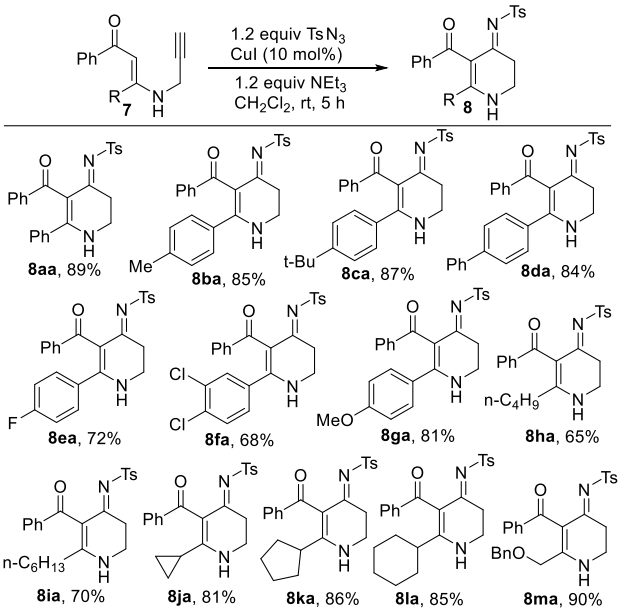
S. No.	catalyst	base	solvent	time (h)	yield[b]
1	CuI	K_2CO_3	MeCN	8	N.R.[c]
2	CuI	K_2CO_3	CH_2Cl_2	5	15
3	CuI	Cs_2CO_3	CH_2Cl_2	5	18
4	CuI	NaOH	CH_2Cl_2	5	N.R.[c]
5	CuI	K_3PO_4	CH_2Cl_2	5	trace
6	CuI	DIPEA	CH_2Cl_2	5	42
7	CuI	DABCO	CH_2Cl_2	5	67
8	CuI	2,6-lutidine	CH_2Cl_2	5	77
9	**CuI**	**TEA**	**CH_2Cl_2**	**5**	**89**
10	CuI	TEA	MeCN	5	38
11	CuI	TEA	Et_2O	5	23
12	CuI	TEA	Toluene	5	46
13	CuI	TEA	DCE	5	N.R.[c]
14	Cu(OTf)	TEA	CH_2Cl_2	5	84
15	CuBr	TEA	CH_2Cl_2	5	40
16	CuCl	TEA	CH_2Cl_2	5	52

[a]Reaction conditions: 0.5 mmol **7a**, 0.6 mmol TsN_3, 10 mol% catalyst and 0.6 mmol base in 4 mL solvent under N_2. [b]Isolated yields. [c]no reaction.

(entry 1). No reaction occurred and the starting material was recovered as such. When the solvent was switched to CH_2Cl_2, the desired product was obtained in 15% yield (entry 2). Other inorganic bases (entries 3-5) did not improve the reaction. Pleasingly, the use of organic base DIPEA led to improving the yield to 42% (entry 6). Further screening of organic bases (entries 7-9) revealed that TEA was the best choice which afforded the product in 89% yield (entry 9). The other solvents like MeCN, Et_2O, toluene and DCE were found to be inappropriate for the reaction (entries 10-13). Other copper catalysts like Cu(OTf), CuBr and CuCl were not as effective as CuI. With these observations, we decided to move on with CuI as catalyst and TEA as base in CH_2Cl_2.

With the optimized conditions in hand (Table 1, entry 9), we next investigated the scope and limitations of the Cu-catalyzed iminative ring closure of *N*-propargyl β-enaminones. The scope with respect to the substitution at β-carbon (pro C1) was initially investigated. Like **7a**, substrates bearing β-phenyl ring with pendant methyl, *t*-Bu and phenyl groups (**7b-d**) smoothly delivered the products **8ba-da** in excellent yields (84-87%). Halo groups like F and Cl were unaffected during the conversion of **7e-f** to **8ea-fa** but caused a slight erosion of yields (68-72%). Electron rich methoxy phenyl substrate **7g** smoothly afforded the desired product **8ga** in 81% yield. Next,

Table 2 Scope of enaminones.[a]

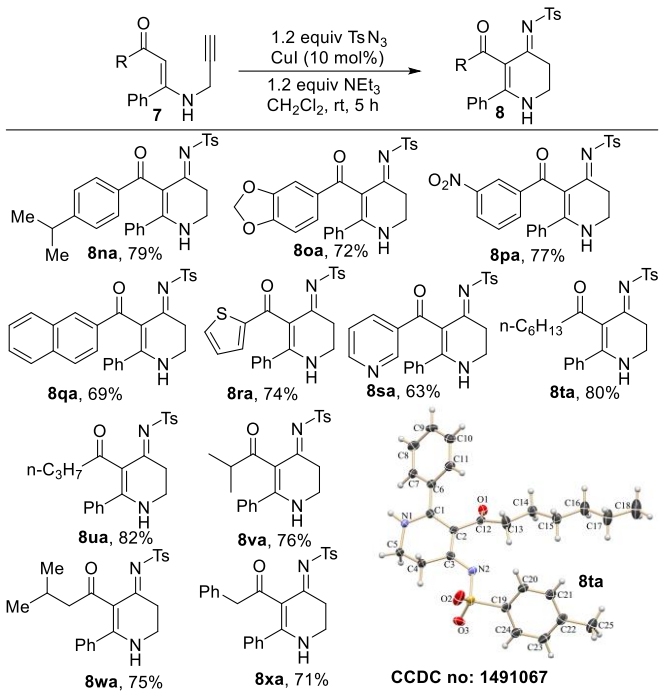


[a]Reaction conditions: 0.5 mmol of **7**, 0.6 mmol of TsN_3, 10 mol% of CuI in 4 mL CH_2Cl_2 at rt for 5 h under N_2.

β-alkyl substituted substrates were tested. Thus, 2-*n*-butyl and -*n*-hexyl adducts **8ha-ia** were successfully obtained but in somewhat lower yields (65-70%). In a little contrast, 2-cycloalkyl (cyclopropyl, cyclopentyl and cyclohexyl) adducts **8ja-la** were obtained in better yields (81-85%) compared to their non-cyclic counterparts. Finally **7m** with allylic benzoxy group was also smoothly transformed to the corresponding product **8ma** in excellent yield of 90%.

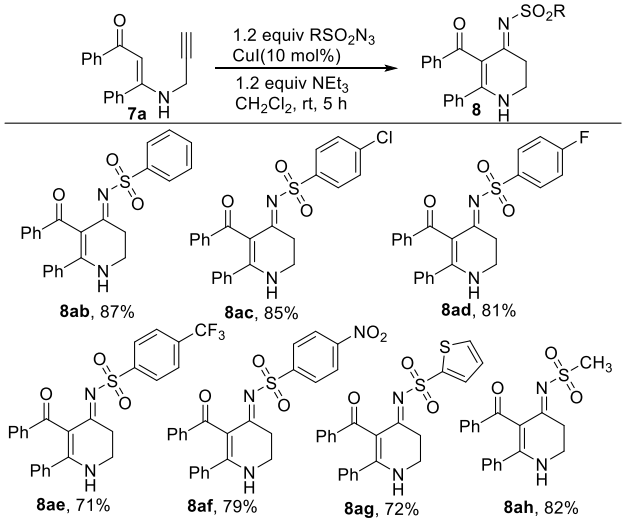
Next, the generality of the method against the variation of substitution at C1 (keto terminal) of enaminones was investigated. *p*-Isopropylphenyl substrate **7n** reacted as smoothly as **7a** to afford **8na** in 79% yield. Methylenedioxy substituted electron rich substrate **7o** and nitro bearing electron poor starting material **7p** both gave the products (**8oa-pa**) in satisfactory yields (72-77%). Similarly, naphthyl substituted adduct **8qa** was obtained in 69%. Further, heteroaryl ketones (**7r-s**) were also transformed to the corresponding products smoothly under standard conditions.

Table 3 Extended scope of enaminones.[a]



[a]Reaction conditions: 0.5 mmol of **7**, 0.6 mmol of TsN_3, 10 mol% of CuI in 4 mL CH_2Cl_2 at rt for 5 h under N_2.

Table 4 Scope of sulfonyl azides.[a]



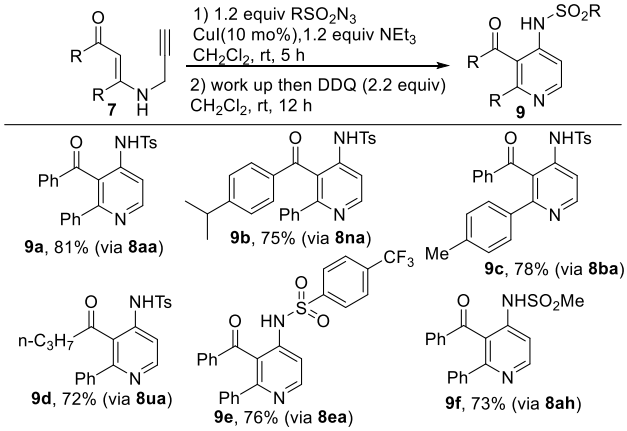
Reaction conditions: 0.5 mmol of **7a**, 0.6 mmol of RSO_2N_3, 10 mol% of CuI in 4 mL CH_2Cl_2 at rt for 5 h under N_2.

Impact of aliphatic substitution was then verified. Thus, *n*-hexyl, *n*-propyl, isopropyl and isobutyl groups on ketone terminal (**7t-w**) were undisturbed and the products (**8ta-wa**) were obtained in 75-82% yields. Benzylic enaminone **7x** was next subjected to the title cyclization to obtain the desired adduct **8xa** in 71% yield.

We next moved to verify the scope of sulfonyl azides in the reaction. Thus, various sulfonyl azides were treated with **7a** and the results are summarized in Table 4. Similar to TsN_3, benzene sulfonyl azide also reacted smoothly under the standard conditions to afford the desired product **8ab** in 87% yield. Chloro and fluoro substitution (**8ac-ad**) did not affect the yield (81-85%) whereas presence of trifluoromethyl group slightly reduced the yield to 71%. Electron poor nitrophenyl- and electron rich thiophenyl sulfonyl azides were converted to the desired adducts (**8af-ag**) without any difficulty (72-79%). Finally methylsulfonyl azide as an aliphatic variant was identified as an equally good substrate for this iminative cyclization to afford **8ah** in 82% yield.

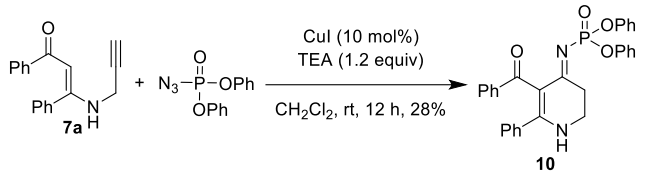
We next turned to aromatization of the above saturated adducts to privileged aminopyridine derivatives (Table 5). Treatment of the purified **8aa** with 2.2 equivalents of DDQ in CH_2Cl_2 cleanly produced the corresponding 3-acyl-4-aminopyridine derivative **9a** in 94%. To avoid a purification step, we conducted the dehydrogenation on the unpurified crude material **8aa** after the work up of the iminative cyclization step. Pleasingly, the product was obtained in 81% overall yield in 2 steps. Similarly, alkyl phenyl substituted adducts (**9b-c**) were obtained in excellent overall yields. Aminopyridine derivative with alkyl (*n*-propyl) chain on ketone terminal (**9d**) was obtained with equal ease. Similar to tosyl derivatives, trifluoromethylphenyl- (**9e**) and methyl sulfonyl amino pyridines (**9f**) were synthesized in as high as 76% overall yields.

Table 5 Aromatization of **1** to 4-aminopyridines **9**.[a]



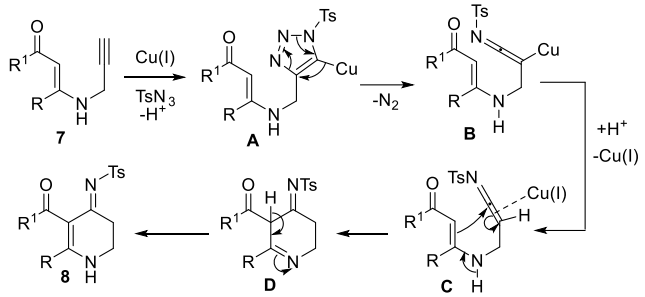
[a]Reaction conditions: 1) 0.5 mmol of **7a**, 0.6 mmol of RSO_2N_3, 10 mol% of CuI in 4 mL CH_2Cl_2 at rt under N_2. 2) 2.2 equiv. DDQ in CH_2Cl_2 at rt under air.

Subsequently, we investigated the reactivity of phosphoryl azide as amino surrogate (Scheme 3). It indeed gave the desired phosphoryl amide adduct **10** but in just 28% yield.



Scheme 3 Attempts to extrapolate the iminative cyclization

A probable mechanism for the title conversion of enaminones to tetrahydro pyridine derivatives is described in Scheme 4. The reaction of acetylene group in **7** with TsN_3 in presence of Cu(I) led to ketenimine **B** (via A) as previously demonstrated.[5] Subsequently, the nucleophilic α-C of enaminone unit attacked on electron deficient central carbon of ketenimine. Concomitant 1,3-H migration furnished the desired imino tetrahydropyridine **8**.



Scheme 4 Proposed mechanism.

In summary, we have illustrated a straightforward method for 4-imino tetrahydropyridine derivatives from readily available enaminones using sulfonylazide as amino surrogate. The reaction mainly features the first use of unactivated and unprotected propargyl amines in iminative cyclization, and a hither to untapped intramolecular hydrovinylation of intermediate ketenimine. As an application, the products are shown as ready precursors for the 4-amino pyridine derivatives. A high reaction scope with respect to both terminals of enaminone as well as sulfonylazide together with excellent product yields makes it a practical approach for the highly privileged scaffolds.

RK thanks UGC for the fellowship. We thank SAIF division CSIR-CDRI for the analytical support. We gratefully acknowledge the financial support by CSIR-THUNDER (BSC 0102). CDRI Communication No: (will be inserted if accepted)

Notes and references

1 (a) A. Ahmed, K. I. Molvia, S. Nazima, I. Baig, T. Memona and M. Rahil, *J. Chem. Pharm. Res.,* 2012, **4**, 872; (b) A. M. V. Rhee, J.-L. Jiang, N. Melman, M. E. Olah, G. L. Stiles and K. A. Jacobson, *J. Med. Chem.,* 1996, **39**, 2980; (c) S. Nara, R. Tanaka, J. Eishima, M. Hara, Y. Takahashi, S. Otaki, R. J. Foglesong, P. F. Hughes, S. Turkington and Y. Kanda, *J. Med. Chem.*, 2003, **46**, 2467; (d) K. Kaczanowska, K.-H. Wiesmeuller and P. A. Schaffner, *ACS Med. Chem. Lett.*, 2010, **1**, 530; (e) A. T. Neto, C. Q. Oliveira, V. Ilha, M. Pedroso, R. A. Burrow, I. I. Dalcol and A. F. Morel, *J. Mol. Struct.*, 2011, 1004, 174; (f) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.,* 2013, **9**, 2265. DOI: 10.1039/C6CC08081B

2 For review on synthesis of pyridine and its derivative see: (a) J. A. Bull, J. J. Mousseau, G. Pelletier and A. Charette, *Chem. Rev.*, 2012, **112**, 2642; (b) J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787; (c) B. Heller and M. Hapke, *Chem. Soc. Rev.,* 2007, **36**, 1085; (d) A. K. Chattopadhyay and S. Hanessian, *Chem. Commun.*, 2015, **51**, 16437 and references cited therein.

3 (a) G. Cheng, Y. Weng, X. Yang and X. Cui, *Org. Lett.*, 2015, **17**, 3790; (b) S. Cacchi, G. Fabrizi and E. Filisti, *Org. Lett.*, 2008, **13**, 2629; (c), C. G. Savarin, J. A. Murry and P. G. Dormer, *Org. Lett.*, 2002, **12**, 2071; (d) W. Gati, M. M. Rammah, M. B. Rammah, F. Couty and G. Evano, *J. Am. Chem. Soc.*, 2012, **134**, 9078; (e) J. Wu, W. Xu, Z.-X. Yu and J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 9489; (f) K. Tanaka, N. Suzuki and G. Nishida, *Eur. J. Org. Chem.*, 2006, 3917; (g) M. Movassaghi and M. D. Hill, *J. Am. Chem. Soc.*, 2006, **128**, 4592; (h) B. L. Gray, X. Wang, W. C. Brown, L. Kuai and S. L. Schreiber, *Org. Lett.* 2008, **13**, 2621.

4 4. (a) G. R. Kumar, Y. K. Kumar and M. S. Reddy, *Chem. Commun.*, 2016, **52**, 6589; (b) N. Thirupathi, S. Puri, T. J. Reddy, B. Sridhar and M. S. Reddy, *Adv. Synth. Catal.*, 2016, **358**, 303; (c) M. H. Babu, V. Dwivedi, R. Kant and M. S. Reddy, *Angew. Chem. Int. Ed.*, 2015, **54**, 3783; (d) Y. K. Kumar, G. R. Kumar, T. J. Reddy, B. Sridhar and M. S. Reddy, *Org Lett.*, 2015, **17**, 2226; (e) V. Dwivedi, M. H. Babu, R. Kant and M. S. Reddy, *Chem. Commun.* 2015, **51**, 14996; (f) M. Rajesh, N. Thirupathi, T. J. Reddy, S. Kanojiya and M. S. Reddy, *J. Org. Chem.*, 2015, **80**, 12311; (g) N. Thirupathi, M. H. Babu, V. Dwivedi and M. S. Reddy, *Org. Lett.,* 2014, **16**, 2908; (h) Y. K. Kumar, G. R. Kumar and M. S. Reddy, *J. Org. Chem.*, 2014, **79**, 823; (i) S. Puri, N. Thirupathi and M. S. Reddy, *Org. Lett.*, 2014, **16**, 5246; (j) M. S. Reddy, N. Thirupathi, M. H. Babu and S. Puri, *J. Org. Chem.*, 2013, **78**, 5878; (k) M. S. Reddy, Y. K. Kumar and N. Thirupathi, *Org. Lett.*, 2012, **14**, 824.

5 (a) P. Lu and Y. Wang, *Chem. Soc. Rev.*, 2012, **41**, 5687; (b) B. Yao, C. Shen, Z. Liang and Y. Zhang, *J. Org. Chem.* 2014, **79**, 936; (c) S. H. Cho and S. Chang, *Angew. Chem. Int. Ed.*, 2007, **46**, 1897; (d) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.,* 2005, **127**, 16046; (e) M. Nagaraj, M. Boominathan, D. Perumal, S. Muthusubramanian and N. Bhuvanesh, *J. Org. Chem.*, 2012, **77**, 6319; (f) W. J. Yao, L. J. Pan, Y. P. Zhang, G. Wang, X. Q. Wang and C. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 9210; (g) G. Cheng and X. Cui, *Org. Lett.* 2013, **15**, 1480; (h) B. Reichart, G. G. Cruz, K. Zangger, C. O. Kappe and T. Glasnova, *Adv. Synth. Catal.* 2016, **358**, 50; (i) Y. Li, L. Zhang, L. Zhang, Y. Wu and Y. Gong, *Org. Biomol. Chem.,* 2013, **11**, 7267; (j) J. Wang, J. Wang, Y. Zhu, P. Lu and Y. Wang, *Chem. Commun.*, 2011, **47**, 3275; (k) S. H. Cho and S. Chang, *Angew. Chem. Int. Ed.,* 2008, **47**, 2836; (l) M.-H. Shen, K. Xu, C.-H. Sun and H.-D. Xu, *Org. Lett.*, 2015, **17**, 5598; (m) H.-D. Xu, Z.-H. Jia, K. Xu, M. Han, S.-N. Jiang, J. Cao, J.-C. Wang and M.-H. Shen, *Angew. Chem. Int. Ed.*, 2014, **53**, 9284; (n) D. P. Chauhan, S. J. Varma, A. Vijeta, P. Banerjee and P. Talukdar *Chem. Commun.*, 2014, **50**, 323. (o) D. Ramanathan, K. Namitharana and K. Pitchumani, *Chem. Commun.*, 2016, **52**, 8436; (p) Y. Jiang, R. Sun, Q. Wang, X. -Y. Tang and M. Shi*, Chem. Commun.,* 2015, **51**, 16968; (q) Y. Hu, B. Zhou and C. Wang, *Org. Biomol. Chem.,* 2016, **14**, 3022.

6 (a) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.,* 2005, **127**, 2038.

7 (a) S. Cai, K. Yang and D. Z. Wang, *Org. Lett.*, 2014, **16**, 2606; (b) G.-W. Wang and C.-B. Miao, *Green Chem.*, 2006, **8**, 1080; (c) R. J. Cox, D. J. Ritson, T. A. Dane, J. Berge, J. P. H. Charmant and A. Kantacha, *Chem. Commun.,* 2005, 1037.

