RSC Advances

ROYAL SOCIETY OF CHEMISTRY

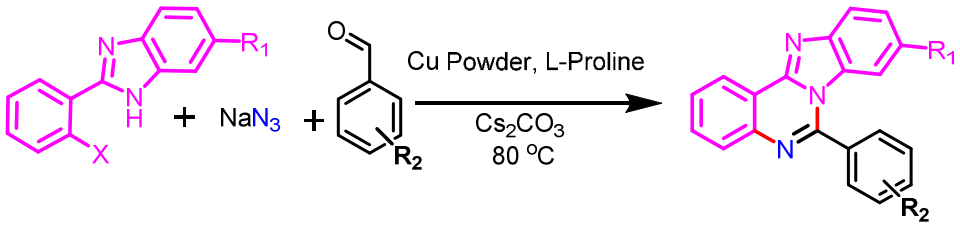
www.rsc.org/advances

Graphical abstract

Copper-mediated aerobic oxidative synthesis of Benzimidazo fused quinazolines *via* multicomponent approach

Byanju Rai, Promod Kumar and Atul Kumar

First copper mediated aerobic oxidative multi-component synthesis of benzimidazo[1,2-c]quinazolines has been developed from 2-(2-halophenyl)benzoimidazoles, aldehydes and sodium azide as nitrogen source. This protocol involves formation of three C-N bonds starting from azidation of haloaryl with sodium azide followed by *insitu* conversion of azide into arylamine, which on condensation with benzaldehyde undergoes oxidative cyclization to afford benzimidazo[1,2-c]quinazoline in good to excellent yield.



RSC *Advances*

RSCPublishing

COMMUNICATION

Copper-mediated aerobic oxidative synthesis of Benzimidazo fused quinazolines *via* multicomponent approach

Cite this: DOI: 10.1039/x0xx00000x

Byanju Rai,[a] Promod Kumar[a] and Atul Kumar*[a,b]

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

ABSTRACT: First copper mediated aerobic oxidative multi-component synthesis of benzimidazo[1,2-c]quinazolines has been developed from 2-(2-halophenyl)benzoimidazoles, aldehydes and sodium azide as nitrogen source. This protocol involves formation of three C-N bonds starting from azidation of haloaryl with sodium azide followed by *insitu* conversion of azide into arylamine, which on condensation with benzaldehyde undergoes oxidative cyclization to afford benzimidazo[1,2-c]quinazoline in good to excellent yield.

Multi-component processes have become a productive concept for the synthesis of complexes and highly diverse heterocycles in a one-pot fashion.[1] In present scenario, multicomponent reactions considered as effective chemical tool for the synthesis of polyheterocyles.[2]

Tetracyclic bridgehead nitrogen containing motif are present in many natural products,[3] and pharmaceutical agents.[4] Among them benzimidazole and quinazoline moieties are frequently encountered in several pharmaceutically active agents.[5,6] Benzimidazoles are present in Vit B-12, Pantoptazole, Omeprazole, and Albendazoleas.[7] Whereas quinazolines are part of clinically used cancer drugs such as Gefitinib, Erlotinib, Alfuzosin, Trimetrexate, and Vandetanib.[8] Inspired by the bioapplicablity of tetracyclic bridgehead nitrogen containing motifs, we were interested in development of multicompnent synthesis for benzimidazo fused quinazoline from 2-(2-halophenyl)benzoimidazoles, aldehydes and sodium azide as nitrogen source. Sodium azide is a versatile reagent and have several applications in synthesis of *N*-hetrocycles, amines, cynadies and amides (Fig 1). Here, we have first time used sodium azide for developing multicomponent synthesis of benzimidazo fused quinazoline. Mostly, benzimidazo[1,2-c]quinazoline, which exhibit wide therepeautic activities[16] were synthesied in multi step protocol starting from 2-(2-aminophenyl) benzimidazole and their precursors 2-(2-nitrophenyl)benzimidazole.[17]

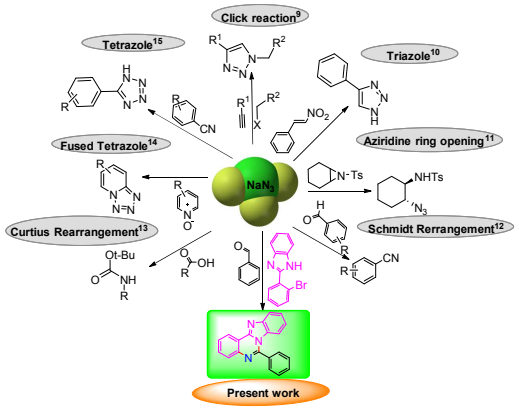
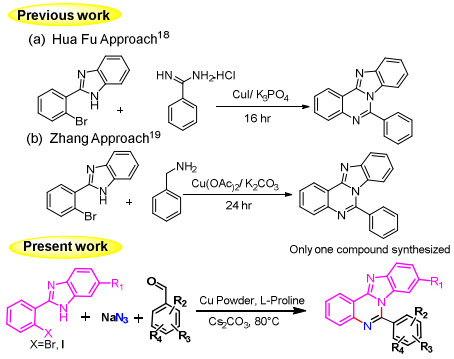


Fig. 1 Applications of sodium azide

Recently, Hua Fu *et. al.* reported the synthesis of benzimidazo[1,2-c]quinazoline via the copper catalyzed cross- coupling reaction of 2-(2-halophenyl)benzoimidazoles and amidines.[18] Zhang *et. al.* have reported synthesis of benzimidazo[1,2-c]quinazoline from 2-(2-bromophenyl benzimidazole.



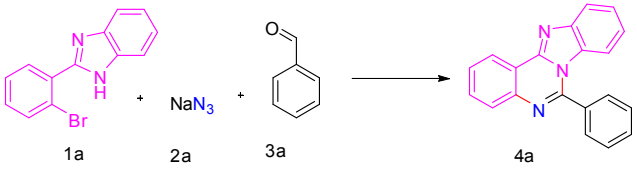
Scheme 1. Synthesis of Benzimidazo [1,2-c]quinazoline

benzoimidazole with benzyl amines(Scheme 1).[19]

In continuation of our research interest in the development of novel methodologies for the synthesis of heterocyclic compounds,[20] we wish to report here first multi-component synthesis of benzimidazo[1,2-c]quinazoline derivatives through Cu catalyzed cross-coupling reactions of 2-(2-halophenyl)benzoimidazoles with aldehydes using sodium azide as a nitrogen source. Previously, there are several protocols reported where copper catalysts have been used for oxidative C-C bond formation.[21] This multicompnent reaction involves formation of three consecutive C-N bond and as aldehyde as one of component hence it is easy to generate diversity in the molecule.

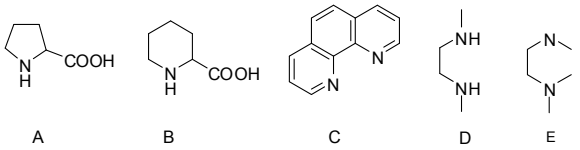
Optimization of the reaction conditions was carried out using 2-(2-bromophenyl)-1H-benzo[d]imidazole (1a), sodium azide (2a) and benzaldehyde (3a) as model substrates. Our initial attempt started by using CuI with proline and Cs_2CO_3 as a base in DMSO at 80˚C, provided desired fused heterocyclic product 4a in 70% yield (Table 1,entry 1).

Table 1. Optimization of reaction conditions for the synthesis of Benzimidazo [1,2-c]quinazoline[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield[b]
1	CuI	A	Cs_2CO_3	DMSO	70
2	CuBr	A	Cs_2CO_3	DMSO	64
3	CuCl	A	Cs_2CO_3	DMSO	60
4	$Cu(OAc)_2$	A	Cs_2CO_3	DMSO	40
5	-	A	Cs_2CO_3	DMSO	0
6	**Cu powder**	**A**	**Cs_2CO_3**	**DMSO**	**89**
7	Cu powder	B	Cs_2CO_3	DMSO	55
8	Cu powder	C	Cs_2CO_3	DMSO	50
9	Cu powder	D	Cs_2CO_3	DMSO	35
10	Cu powder	E	Cs_2CO_3	DMSO	58
11	Cu powder	A	Cs_2CO_3	DMF	76
12	Cu powder	A	K_2CO_3	DMSO	40
13	Cu powder	A	K_3PO_4	DMSO	50
14	Cu powder	A	Cs_2CO_3	CH_3CN	44
15	Cu Powder	A	Cs_2CO_3	DMSO: CH_2Cl_2 (1:3)	16
16.	Cu powder	A	Cs_2CO_3	DMSO: CH_2Cl_2 (3:1)	64

[a]Reactionconditions:2-(2-bromophenyl)-1H-benzo[d] imidazole (1.0 mmol), Benzaldehyde (1.2 mmol), Sodium azide (2.0 mmol), Cu catalyst (10 mol%), Ligand (20 mol%), and Base (1.0 mmol) in solvents (4-5 mL) , at 80 ˚C for 12hr. [b]Isolated yield.



Ligands Screened

To further optimize the reaction conditions, we screened various catalysts, bases, ligands and solvents. The copper catalysts screened are CuI, CuBr, CuCl, $Cu(Oac)_2$ and Cu powder. Out of all trials, the best result was obtained with Cu powder (Table 1, entry 6). Further optimization of solvents, bases and ligands did not provide any appreciable results (Table 1).

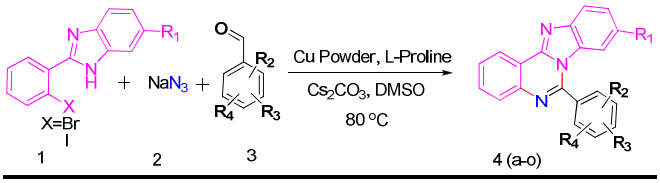
Thus, the best yield of the desired Benzimidazo[1,2-c]quinazoline was obtained by carrying out the reaction using Cu powder (10 mol%), proline (20 mol%), and Cs_2CO_3 in DMSO at 80 ˚C for 12h. (Table 1, entry 6). Recently, DMSO is considered as a recommended solvent for transformations in solvent selection guide developed by Astra Zeneca.[22]

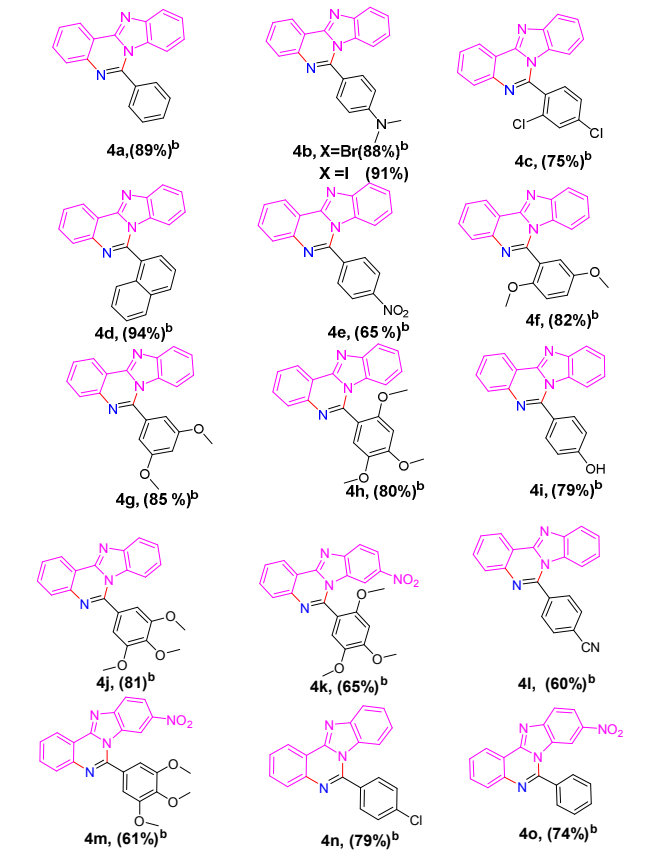
With the optimized conditions in hand, we explored the generality of this copper mediated coupling process (Scheme 2). Gratifyingly the conditions optimized for benzimidazo[1,2-c]quinazoline provided very good yields of other benzimidazo[1,2-c]quinazoline derivatives without any further optimization. The scope of different aldehydes were examined as shown in (scheme 2), we found that the reaction depends upon the substitution present on to the aldehyde ring. Electron-donating groups on phenyl ring gave better yields in comparison to electron-withdrawing groups. Aromatic aldehydes with electron withdrawing groups such as 2,4- dichloro, 4- nitro, 4-cyano and 4-chloro gave the corresponding benzimidazo[1,2-c]quinazoline in 75%, 65%, 60% and 79% yields respectively (Scheme 2, entries 4c, 4e, 4l, and 4n).

Benzaldehydes with electrondonating groups such as 4-(dimethylamino)benzaldehydes, as well as 2, 5 and 3, 5-(dimethoxy)benzaldehydes formed the desired products in good to excellent yields (Scheme 2, entries 4b, 4f, and 4g). Weak steric effects were observed for the 2, 4, 5 and 3, 4, 5-(trimethoxy) benzaldehydes (Scheme 2, entries 4h and 4j). With 1-naphthaldehyde the corresponding product was found in 94% yield (entry 4d).

2-(2-Iodophenyl) benzoimidazoles gave similar yield for benzimidazo [1,2-c]quinazoline (Scheme 2, entry 4b, X=I) but required short reaction time for the completion of reaction. These exciting preliminary result opens the door to the first multicomponent synthesis of highly diverse Benzimidazo [1,2-c]quinazolines .

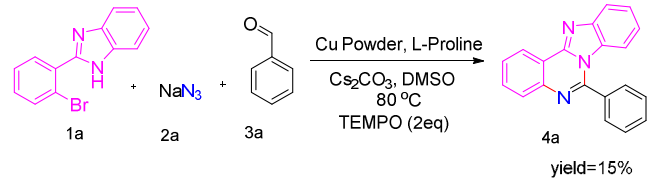
Scheme 2. Copper-Catalyzed Cascade Synthesis of Benzimidazo [1,2-c]quinazolinederivatives[a]





[a]Reaction conditions: 2-(2-bromophenyl)-1H-benzo[d]imidazole (1.0 mmol), substituted benzaldehyde (1.2 mmol), Sodium azide (2.0 mmol), Cu powder (10 mol%), L-proline (20 mol%), and Cs_2CO_3 (1.0 mmol) in DMSO (4-5 mL), at 80˚C for 12hr. [b]Isolated yield

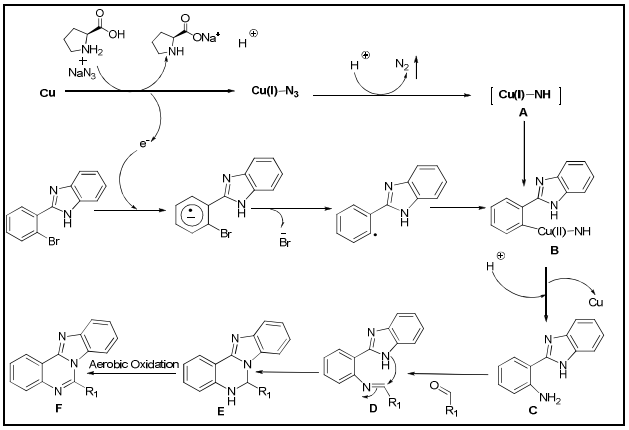
Scheme 3.Control Experiment



To better understanding of the mechanism, control experiments was carried out (Scheme 3). When 2 equiv of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction under the standard conditions, 15% of desired product (4a) was detected in the reaction mixture of eqs 1a, 2a and 3a. Which proves radical process was involved in the above reaction.

A proposed reaction mechanism is shown in Scheme 4. Initially , an aryl anion radical was generated by a single-electron transfer from Cu to an aromatic ring of the haloarene and subsequently the elimination of a bromide ion (Br−) takes place to generate the corresponding aryl radical.[23] Simultaneously, copper (I) azide would be generated together with the sodium salt of L- proline from NaN_3 and L-proline. The generation of aryl copper (II) complex (B)[24,25] takes place by the oxidative coupling of the aryl radical with the copper (I) complex (A), followed by elimination of copper species and finally, 2-(1H-benzo[d]imidazol-2-yl)aniline (C)[26] was obtained.

Scheme 4.Proposed reaction mechanisms



The condensation of 2-(1H-benzo[d]imidazol-2-yl)aniline and aldehyde afforded intermediate (D) and the intramolecular nucleophilic attack of NH in benzoimidazole group to carbon and affords the cyclized product (E) which undergo aerobic oxidation and affords targeted product benzimidazoquinazoline in good to excellent yield.

In conclusion, we have demonstrated first copper catalysed multicomponent synthesis of diverse benzimidazo[1,2-c]quinazolines in aerobic conditions from 2-(2-halophenyl) benzoimidazoles, aldehyde, and sodium azide as nitrogen source. The reaction probably proceeds through in situ conversion of azide into arylamine followed by condensation with aromatic aldehyde. We believe operational simplicity and economic of this procedure will find important applications in synthesis of nitrogen hetrocycles in the area of medicinal, and material chemistry.

ACKNOWLEDGMENT

B.R and P.K thankful to CSIR-UGC, New Delhi, India for fellow-ships. Authors also acknowledge to SAIF-CDRI for providing the spectral and analytical data. CSIR Network Project BSC0102/0108.

Notes and references

[a]*Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute (CDRI), Luck now, 226031,*
[b]*Academy of Scientific & Innovative Research (**AcSIR**) New Delhi India. E-mail:dratulsax@gmail.com;*
Fax: 91-522-26234051; Tel:91-522-2612411
†Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/b000000x/

1. (a) B. B. Toure and D. G. Hall, *Chem. Rev*., 2009, **109**, 4439–4486.(b) C. C. Razvan, E. Ruijter and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958–2975.
2. (a) Multicomponent Reactions, J. Zhu, and E. H. Bienayme, *Wiley-VCH: Weinheim, Germany*., 2005. (b) A. D€omling, W. Wang and K. Wang. *Chem. Rev*., 2012, **112**, 3083-3135. (c) D. J. Sunderhaus and E. S. Martin, *Chem.;Eur. J*., 2009, **15**, 1300-1308. (d) E. Ruijter, R. Scheffelaar and A. R. V. Orru, *Angew. Chem., Int. Ed*. 2011, **50**, 6234-6246. (e) V. Estevez, M. Villacampa and C. J. Menendez, *Chem. Soc. Rev*., 2010, **39**, 4402-4421.
3. S. T. S. Chan , P. R. Patel, T. R. Ransom , C. J. Henrich, T. C. Mc. Kee, A. K. L. Goey, K. M. Cook, W. D. Figg, J. B. McMahon, M. J. Schnermann, and K. R. Gustafson, *J. Am. Chem. Soc*., 2015, **137**, 5569–5575.
4. Tetracyclic imidazole analogs., J. P Whitten and M. Schwaebe "US 20100063046 A1.
5. (a) S. Ozden, D. Atabey and H. Goker, *Bioorg. Med. Chem*., 2005, **13**, 1587-1597; (b) H. Goker C. Kus and D. W. Boykin, *Eur. J. Med. Chem*., 2005, **40**, 1062-1069.
6. (a) W. D. Fry, J. A. Kraker, A. McMichael, A. L. Ambroso. M. J. Nelson, R. W. Leopold. W. R. Connors, Bridges, *A. J.Science*., 1994, **265**, 1093; (b) V. Colotta, D. Catarzi, F. Varano, O. Lenzi, G. Filacchioni, C. Costagli, A. Galli, C. Ghelardini, N. Galeotti, P. Gratteri, J. Sgrignani, F. Deflorian, and S. Moro, *J. Med. Chem*., 2006, **49**, 6015-6026; (c) N. Malecki, P. Carato, B. Rigo, J.-F. Goossens, R. Houssin, C. Bailly and J.-Pierre Hénichart, *Bioorg. Med. Chem*., 2004, **12**, 641-647.
7. R. S. Keri, A. Hiremathad, S. Budagumpi and B. M. Nagaraja, *Chem Biol Drug Des*., 2014.
8. P. T. Selvam and V. P. Kumar, *Research in Pharmacy*., 1(1). 2011, 1.
9. J. R. Johansson, P. Lincoln, B. Norden and N. Kann, *J. Org. Chem*. 2011, **76**, 2355–2359.
10. Xue-Jing Quan, Zhi-Hui Ren, Yao-Yu Wang, and Zheng-Hui Guan *Org. Lett.,* 2014, **16**, 5728−5731.
11. G. Sabitha, R. S. Babu, M. Rajkumar and J. S. Yadav, *Org. Lett* 2002, 4, 343–345.
12. B. V. Rokade and K. R. Prabhu, *J. Org. Chem*. 2012, **77**, 5364−5370.
13. He´le`ne Lebel and O. Leogane, *Org. Lett*., 2005, **7**, 4107–4110
14. S. Liu, D. Lentz, and C. C. Tzschucke, *J. Org. Chem*., 2014, **79**, 3249−3254.
15. D. Cantillo, B. Gutmann, and C. O. Kappe, *J. Am. Chem. Soc*., 2011, **133**, 4465–4475.
16. (a) V. L. Dalla, O. Gia, S. M. Magno, S. A Da, A. M. Marini, G. Primofiore, S. F. Da and S. Salerno, *Farmaco*., 2001, **56**, 159-167. (b) A. A. Spasov, I. N. Yozhitsa, L. I. Bugaeva and V. A. Anisimova, *Pharm. Chem. J*., 1999, **33,** 232-243. (c) B. Fernandez, J. Castellano and M. Redondo, *Eur. Pat. Appl*., 1989, **331**, 093.(d) B. A. Insuasty, H. Torres, J. Quiroga, R. Abonia, R. Rodriguez, M. Nogueras, A. Sanchez, C. Saitz, S. L. Alvarez and S. A. Zacchino, *J. Chil. Chem. Soc*., 2006, **51**, 927. (e) G. D. Galarcei, R. E. Foncea, A. M. Edwards, H. Pessoamahana, C. D. P. Mahana and R. A. Ebenspergeri, *Biol. Res*., 2008, **41**, 43-50.
17. (a) R. Rohini, K. Shanker, P. M. Reddy, Y. P. Ho and V. Ravinder, *Eur. J. Med. Chem.*, 2009, **44**, 3330–3339; (b) E. A. Lyakhova, Y. A. Gusyeva, J. V. Nekhoroshkova, L. M. Shafran and S. A. Lyakhov, *Eur. J. Med. Chem.*, 2009, **44**, 3305–3312; (c) J. A. Bleda, P. M. Fresneda, R. Orenes and P. Molina, *Eur. J. Org. Chem*., 2009, 2490–2504; (d) G. Dou, M. Wang and D. Shi, *J. Comb. Chem*., 2009, **11**, 151–154.
18. S. Xu, J. Lu and H. Fu, *Chem. Commun*., 2011,**47**, 5596-5598.
19. P. Sang, Y. Xie, J. Zou and Y. Zhang, *Org. Lett*.; 2012, **14**, 3894–3897.
20. (a) A. Kumar, V. D. Tripathi and P. Kumar, *Green Chem*., 2011, **13**, 51–54; (b) A. Kumar and S. Sharma, *Green Chem* 2011, **13**, 2017–2020; (c) A. Kumar, G. Gupta, and S. Srivastava, *Org. Lett*., 2011, **13**, 6366-6369; (d) A. Kumar, M. Kumar, S. Maurya, and R. S. Khanna, *J. Org. Chem*., 2014, **79**, 6905− 6912.
21. (a) M. B. Thathagar, J. Beckers and G. Rothenberg, *Green Chem*., 2004, 6 , 215–218.; (b) L. V. Gelderena, G. Rothenberga, V. R. Calderonea, K. Wilsonb and N. R. Shijua, *Appl. Organometal. Chem*., 2013, 27, 23–27.; (c) J. Dulle, K. Thirunavukkarasu, M. C. Mittelmeijer-Hazeleger, D. V. Andreeva, N. R Shiju and G. Rothenberg, *Green Chem*., 2013, **15**, 1238–1243.
22. D. Prat, J. Haylerb and A. Wellsc, *green chem*., 2014, **16**, 4546-4551.
23. (a) R. A. Rossi, A. B. Pierini and A. B. Penenory, *Chemical Reviews*., 2003, **103**, 71–168; (b) E. Shirakawa, Ken-ichi Itoh , T. Higashino and T. Hayashi, *J. Am. Chem. Soc*., 2010, **132**, 15537–15539; (c) E. Shirakawa,. Y. Hayashi, K. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, S. Masui, T. Hayashi, *Angew. Chem*. 2012, **124**, 11–25. *Angew. Chem. Int. Ed.* 2012, **51**, 218 –221.
24. (a) R. T. Gephart III and T. H. Warren, *Organometallics*., 2012, **31**, 7728–7752; (b) Y. M. Badiei, A. Krishnaswamy, M. M. Melzer and T. H. Warren; *J. Am. Chem. Soc*., 2006, **128** , 15056–15057; (c) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari and T. H. Warren, *Angew. Chem*., 2008, **120**, 10109 –10112, *Angew.Chem. Int. Ed.,* 2008, 47, 9961-9964; (d) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari and T. H. Warren, *Angew. Chem*., 2010, **122**, 9034–9039, *Angew. Chem. Int. Ed*., 2010, **49**, 8850-8855; (e) R. T. Gephart III, D. L. Huang, M. J. B. Aguila, G. S. A Shahu, and T. H. Warren, *Angew. Chem*., 2012, **124**, 6594 – 6598, *Angew. Chem. Int. Ed*., 2012, **51**, 6488 –6492; (f) M. J.

B. Aguila , Y. M. Badiei and T. H. Warren, *J. Am. Chem. Soc*., 2013, **135**, 9399–9406; (g) H. Han, S. B. Park, S. K. Kim and S. Chang, *J. Org. Chem*., 2008, **73**, 2862-2870.

25. Q. Meng, F. Wang, X. Qu, J. Zhou and M. Li, THEOCHEM, 2007, **815**, 111–118.
26. T. Maejima, M. Ueda, J. Nakano, Y. Sawama, Y. Monguchi and H. Sajiki, *J. Org. Chem*., 2013, **78**, 8980–8985.; (b) H. Zhao, H. Fu, and Renzhong Qiao, *J. Org. Chem*. 2010, **75**, 3311–3316.