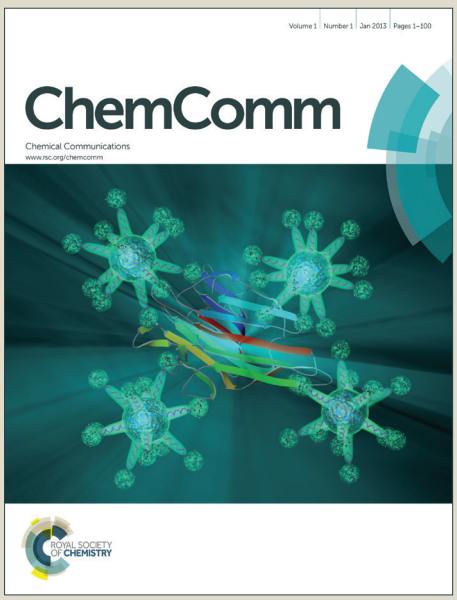
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Sulphur promoted C(sp^3)-C(sp^2) cross dehydrogenative cyclisation of acetophenone hydrazones with aldehydes: an efficient synthesis of 3, 4, 5-trisubstituted 1H-pyrazoles

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

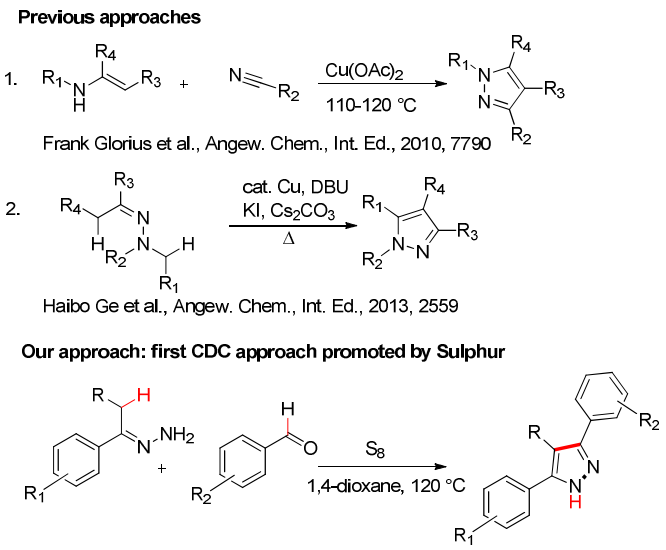
Rajeshwer Vanjari,[a] Tirumaleswararao Guntreddi,[a] Saurabh Kumar[a] and Krishna Nand Singh[a]*

A novel strategy for the cross dehydrogenative coupling (CDC) of acetophenone hydrazones and aldehydes has been developed for the synthesis of highly substituted pyrazoles. The report makes first-time use of elemental sulfur as a promoter as well as a hydrogen acceptor in effecting Csp^3-Csp^2 bond formation via C-H activation.

Pyrazoles constitute an important class of heterocyclic compounds exhibiting wide range of biological activities such as antibacterial,[1] antiobesity,[2] antitumor,[3] antileukemic,[4] anti-inflammatory,[5] and analgesic.[6] They also act as vital building blocks of many pharmaceuticals and natural products.[7] The contemporary pyrazoles syntheses involve the reaction of hydrazines with 1,3-dicarbonyl compounds/unsaturated hydrocarbons,[8,9] and 1,3-dipolar cycloaddition of diazoalkanes with alkenes or alkynes,[10] besides some other strategies.[11] Yet, novel, atom economic and environmentally benign methodologies, involving readily available starting materials, are highly desirable.

The development of advanced and ecologically benevolent means to achieve C-C and C-X bond formation is of great topical interest. In present synthetic scenario, the development of cross-coupling methods involving unactivated C–H precursors has captured a great deal of attention.[12] In this perspective, the direct catalytic coupling termed as cross-dehydrogenative coupling (CDC) from unfunctionalized C-H bonds has particularly emerged as a powerful tool for the synthesis of diverse compounds.[13] Most of the CDC reactions developed so far have been nicely applied for the formation of C–C (sp-sp, sp-sp^2 and sp^2-sp^2) bonds, but the formation of Csp^3–C bond via CDC is yet underdeveloped and more challenging.[13g] Further, most of the explored Csp^3–C bond forming reactions are limited to the coupling of C-H bonds adjacent to a heteroatom,[14] and carbonyl,[15] besides allylic, benzylic,[16] and alkane C-H bonds.[17] Also, many of the CDC reactions require transition metal catalysts and oxidants such as oxygen or peroxides as hydrogen acceptor.

The first CDC approach was reported by Miura and co-workers involving the coupling of N,N-dimethylanilines with alkynes.[14a] Li et al, and others have subsequently enriched this area by expanding the substrate scope.[14-17] An "iminium ion" intermediate is assumed to be formed via amine oxidation by a copper source in the presence of an oxidant using a single electron transfer (SET) process, which subsequently acts as an electrophile for the nucleophilic addition (intermolecular approaches). Ge et al. have successfully applied this strategy to an intramolecular CDC approach using hydrazones as potential substrates for the synthesis of pyrazoles.[18]



Scheme 1. Related reports and present strategy.

In view of the above and as a part of our interest in C-H activation,[19] and development of practical protocols,[20] we

describe herein an unprecedented intramolecular cross dehydrogenative cyclisation of acetophenone hydrazones with aldehydes for a valuable synthesis of substituted pyrazoles. The report makes first-time use of sulphur as promoter as well as hydrogen acceptor for the formation of $C(sp^3)$- $C(sp^2)$ bond via CDC approach. An illustration of the related reports and present strategy involving C-H activation is summarized in Scheme 1.

The investigation commenced with a model reaction employing acetophenone hydrazone and *p*-tolualdehyde in the presence of $Pd(OAc)_2$ as catalyst and *t*-butyl hydrogen peroxide (TBHP, 70% aq.) as oxidant in *t*-butanol at 120 °C for 24 h. In conformity with the earlier reports,[21] we envisioned the formation of product **I** via dehydrogenative coupling of imine–H and aromatic–H (Figure 1, Path A). Surprisingly but to our utmost delight, an unique formation of pyrazole **II** (74%, Path B) was exclusively observed involving intramolecular cross dehydrogenative cyclisation of Csp^3–H with imine–H under the investigated conditions.

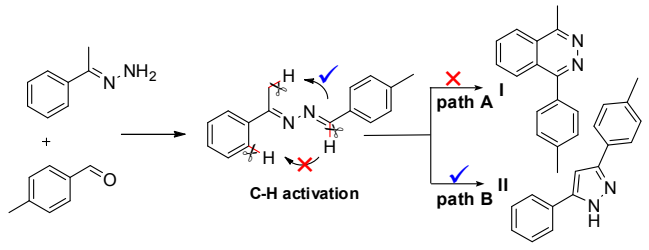
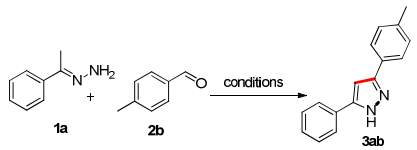


Figure 1. Selective sp^3 C–H bond cleavage.

Having observed this distinctive one pot intramolecular CDC result, the studies were directed towards the optimization of reaction conditions and the findings are presented in Table 1. To improve the reaction profile, different parameters such as catalysts, additives, oxidants and solvents were screened. Out of different catalysts tried, only $Pd(OAc)_2$ and $Cu(OAc)_2$ could perform well (entries 1 & 2). Remarkably, addition of a base like K_2CO_3 or DBU either blocked the reaction or diminished the product yield (entries 3 & 4). Replacement of TBHP by $K_2S_2O_8$ brought about a modest improvement in the yield (entry 8), but the use of solvents such as DCE, DMF and DMSO as an alternative to *t*-butanol proved completely ineffective (entries 5-7). The reaction employing $Pd(OAc)_2$ without the oxidant also proved worthless (entry 9).

A cognizance of the Willgerodt-Kindler reaction reveals the formation of "enamine" intermediate to activate elemental sulfur, which in turn stimulates the adjoining methyl group.[22] Keeping this clue in mind, the formation of enamine type intermediate in the presence of S_8 under the present investigation, was assumed to cause activation of the sp^3 C-H bond. In order to validate the idea, use was made of sulfur powder (S_8, Mol. Wt. 32) to test its efficacy as promoter as well as oxidant, and to our aspiration, a considerably enhanced yield of the product was observed (entry 10). Changing the solvent to 1,4-dioxane in the presence of S_8 without additive and oxidant resulted in further improvement of the yield (85%, entry 12), but the use of solvents such as DMF and DMSO remained ineffective (entries 14 & 15). Solvent-free conditions as well as the use of solvents such as toluene, water and chlorobenzene, also promoted the reaction to a good extent (entries16-19) under similar conditions. The use of TBHP without the catalyst or promoter (entry 11), and the addition of K_2CO_3 in the presence of S_8 (entry 13) were, however, unsuccessful.

Table 1. Optimization of reaction conditions[a]



entry	catalyst/ promoter	additive	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	-	TBHP	t-BuOH	74
2	$Cu(OAc)_2$	-	TBHP	t-BuOH	65
3	$Pd(OAc)_2$	K_2CO_3	TBHP	t-BuOH	0
4	$Pd(OAc)_2$	DBU	TBHP	t-BuOH	30
5	$Pd(OAc)_2$	-	TBHP	DCE	0
6	$Pd(OAc)_2$	-	TBHP	DMF	0
7	$Pd(OAc)_2$	-	TBHP	DMSO	0
8	$Pd(OAc)_2$	-	$K_2S_2O_8$	t-BuOH	78
9	$Pd(OAc)_2$	-	-	t-BuOH	0
10	S_8	-	-	t-BuOH	82
11	-	-	TBHP	t-BuOH	0
12	S_8	-	-	1,4-dioxane	85
13	S_8	K_2CO_3	-	1,4-dioxane	0
14	S_8	-	-	DMF	0
15	S_8	-	-	DMSO	0
16	S_8	-	-	-	65
17	S_8	-	-	toluene	59
18	S_8	-	-	water	55
19	S_8	-	-	chlorobenzene	71

[a]Reaction conditions: **1a** (0.5 mmol), **2b** (1 mmol), catalyst (10 mol%), oxidant (1 mmol), additive (1 mmol), S_8 (1 mmol), solvent (0.75 mL), 120 °C, 24 h. [b]Isolated yield.

With the optimized conditions in hand, the generality of the reaction was examined using diversely substituted acetophenone hydrazones and various aldehydes to provide the corresponding 3,4,5-trisubstituted 1H-pyrazoles in reasonably high yields. The outcome is recapitulated in Table 2. The reactions underwent smoothly with acetophenone hydrazones having different aromatic substitutions and aldehydes bearing various steric and electronic properties. Hydrazones bearing heteroaromatic and bicyclic moieties also participated well in the reaction. However, the reaction required an addition of TFA to achieve adequate conversion to the products **3as** and **3at**. The use of an aliphatic aldehyde viz. heptanal failed to give the product. The structure of a representative product **3ao** has been conclusively proved by X-ray crystal structure (Figure 2).[23]

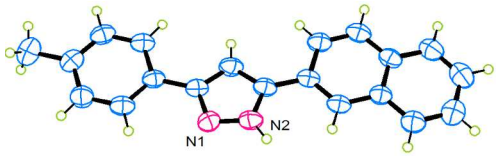
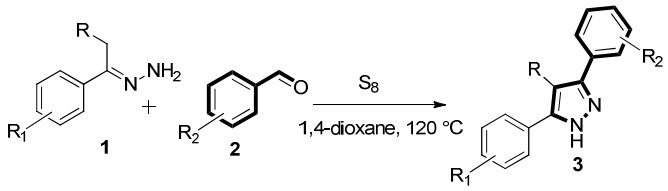
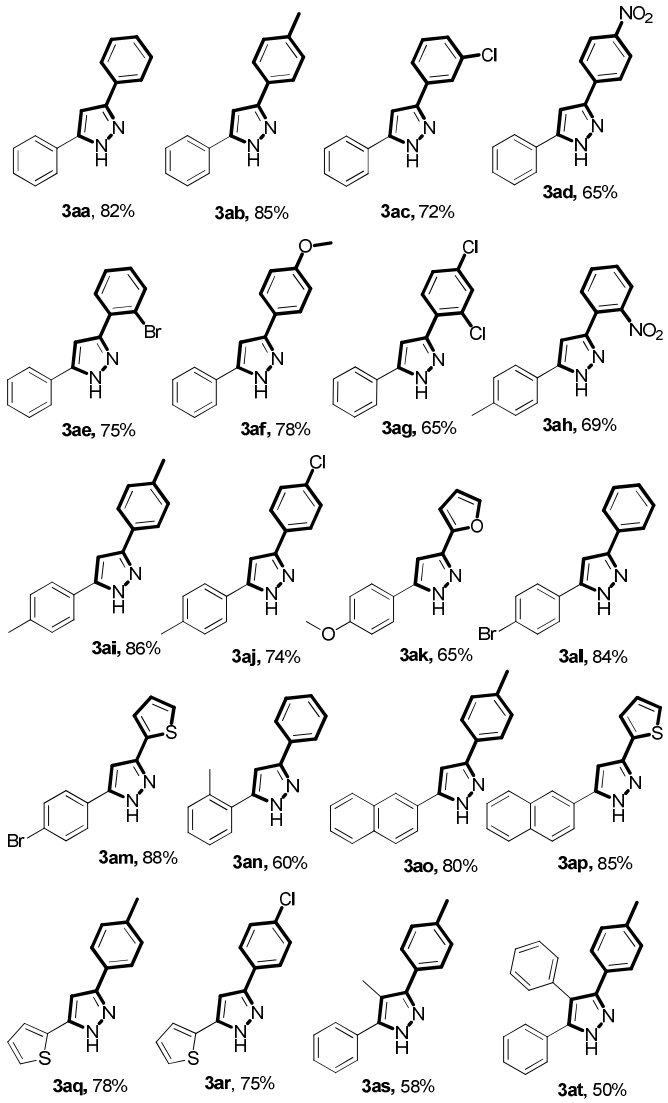


Figure 2. X-ray crystal structure of the product **3ao**.

Table 2. Reaction scope and versatility[a]





[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol, S_8 (1 mmol), 1,4-dioxane (0.75 mL), 120 °C, 24 h. Yields refer to isolated products. Addition of TFA (1.2 equiv.) was required for **3as** & **3at.**

Based on existing literature,[22] and isolation of products, a plausible mechanism is outlined in Figure 4. It is worthwhile to mention that the formation of intermediate **I** (Figure 3) was immediately observed during the reaction of acetophenone hydrazone and *p*-tolualdehyde, even at room temperature without the addition of S_8. The formation of thioamide intermediate **II** was, however, not noticed during the entire course of standard conditions, thereby discarding this path.

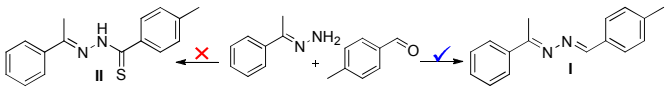


Figure 3. Mechanistic study.

The formation of an "enamine" type intermediate **Ia**, analogous to the "iminium ion" reported by Miura and Li, may therefore be postulated for the reaction. The existence of **Ia** is assumed to activate the sulfur as in the case of Willgerodt Kindler reaction to afford **Ib,** which may eventually lose H_2S and rearrange to give the product **3**. In order to explore the radical pathway, some radical trapping experiments were also conducted using BHT and TEMPO as radical scavengers, which did not inhibit the reaction, albeit the product yield was somewhat lowered.

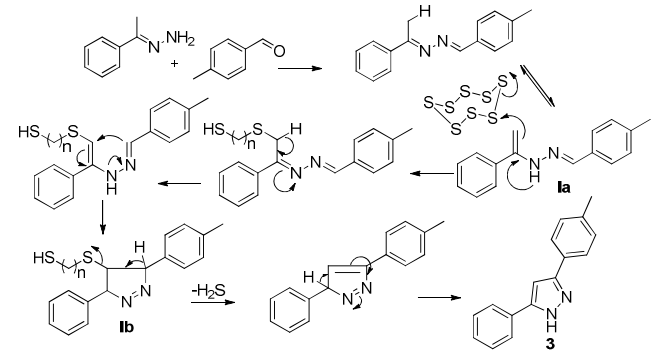


Figure 4. Proposed mechanism.

In conclusion, we have developed a novel CDC approach via sulfur promoted C-H activation for the formation of a less explored Csp^3-Csp^2 bond. The present study comprehends and demonstrates an innovative dual use of sulfur as promoter as well as oxidant in cross dehydrogenative cyclisation of acetophenone hydrazones and aldehydes.

We are thankful to the Department of Science and Technology, Government of India, New Delhi, for providing financial assistance (Grant No. SR/S1/OC-78/2012). R.V. T.G. and S.K. are thankful to the CSIR for research fellowships.

Notes and references

[a] Department of Chemistry (Centre of Advanced Study), Faculty of Science, Banaras Hindu University, Varanasi-221005, India. E-mail: knsingh@bhu.ac.in, knsinghbhu@yahoo.co.in.

† Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/c000000x/

1 (a) D. Castagnolo, F. Manetti, M. Radi, B. Bechi, M. Pagano, A. De Logu, R. Meleddu, M. Saddi and M. Botta, *Bioorg. Med. Chem.*, 2009, **17**, 5716; (b) A. Tanitame, Y. Oyamada, K. Ofuji, M. Fujimoto, N. Iwai, Y. Hiyama, K. Suzuki, H. Ito, H. Terauchi, M. Kawasaki, K. Nagai, M. Wachi and J. Yamagishi, *J. Med. Chem.*, 2004, **47**, 3693.

2 C. H. Wu, M. S. Hung, J. S. Song, T. K. Yeh, M. C. Chou, C. M. Chu, J. J. Jan, M. T. Hsieh, S. L. Tseng, C. P. Chang, W. P. Hsieh, Y. Lin, Y. N. Yeh, W. L. Chung, C. W. Kuo, C. Y. Lin, H. S. Shy, Y. S. Chao and K. S. Shia, *J. Med. Chem*., 2009, **52**, 4496.

3 D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, A. Gzella and R. Lesyk, *J. Med. Chem*., 2012, **55**, 8630.

4 P. l. G. Baraldi, P. Cozzi, C. Geroni, N. Mongelli, R. Romagnoli and G. Spalluto, *Bioorg. Med. Chem*., 1999, **7**, 251.

5 M. A. El-Sayed, N. I. Abdel-Aziz, A. M. Abdel-Aziz, A. S. El-Azab and K. E. El-Tahir, *Bioorg. Med. Chem*., 2012, **20**, 3306.

6 R. Lan, Q. Liu, P. Fan, S. Lin, S. R. Fernando, D. McCallion, R. Pertwee and A. Makriyannis, *J. Med. Chem*., 1999, **42**, 769.

7 (a) S. Fustero, M. Sa´nchez-Rosello´, P. Barrio and A. Simo´n-Fuentes, *Chem. Rev*., 2011, **111**, 6984; (b) S. Kuwata and T. Ikariya, *Chem.-Eur. J*., 2011, **17**, 3542; (c) S. N. A. Bukhari, M. Jasamai and I. Jantan, *Mini-Rev. Med. Chem*., 2012, **12**, 1394.

8 (a) Y. Schneider, J. Pre´vost, M. Gobin and C. Y. Legault, *Org. Lett*., 2014, **16**, 596; (b) S. T. Heller and S. R. Natarajan, *Org. Lett*., 2006, **8**, 2675; (c) B. S. Gerstenberger, M. R. Rauckhorst and J. T. Starr, *Org. Lett*., 2009, 11, 2097; (d) S. Peruncheralathan, T. A. Khan, H. Ila and H. Junjappa, *J. Org. Chem*., 2005, **70**, 10030; (e) G. Shan, P. Liu and Y. Rao, *Org. Lett*., 2011, **13**, 1746; (f) T. Norris, R. Colon-Cruz and D. H. B. Ripin, *Org. Biomol. Chem*., 2005, **3**, 1844.

9 (a) B. Willy and T. J. J. Muller, *Org. Lett*., 2011, **13**, 2082; (b) A. A. Dissanayake and A. L. Odom, *Chem. Commun*., 2012, **48**, 440; (c) J. D. Kirkham, S. J. Edeson, S. Stokes and J. P. A. Harrity, *Org. Lett*., 2012, **14**, 5354; (d) G. Shan,; P. Liu and Y. Rao, *Org. Lett*., 2011, **13**, 1746.

10 (a) H. Kawai, Z. Yuan, E. Tokunaga and N. Shibata, *Org. Lett*., 2012, **14**, 5330; (b) X. Deng and N. S. Mani, *Org. Lett*., 2006, **8**, 3505; (c) X. Deng and N. S. Mani, *J. Org. Chem*., 2008, **73**, 2412; (d) Y. Kong, M. Tang and Y. Wang, *Org. Lett*., 2014, **16**, 576; (e) K. Mohanan, A. R. Martin, L. Toupet, M. Smietana and J.-J. Vasseur, *Angew. Chem., Int. Ed*., 2010, 12, 49; (f) O. Jackowski, T. Lecourt and L. Micouin, *Org. Lett*., 2011, **13**, 5664; (g) X. Xu, P. Y. Zavalij, W. Hu and M. P. Doyle, *J. Org. Chem*., 2013, **78**, 1583; (h) X. Deng and N. S. Mani, *Org. Lett*., 2008, **10**, 1307.

11 (a) B. Chen, C. Zhu, Y. Tanga and S. Ma, *Chem. Commun*., 2014, **50**, 7677; (b) R. Harigae, K. Moriyama and H. Togo, *J. Org. Chem*., 2014, **79**, 2049; (c) J. Hu, S. Chen, Y. Sun, J. Yang and Y. Rao, *Org. Lett*., 2012, **14**, 5030; (d) R. Martín,; M. Rodríguez Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed*., 2006, **45**, 7079; (e) M. S. M. Ahmed, K. Kobayashi and A. Mori, Org. Lett., 2005, 7, 4487.

12 (a) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res*., 2009, **42**, 1074; (b) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev*., 2002, **102**, 1731; (c) T. W. Lyons and M. S. Sanford, *Chem. Rev*., 2010, **110**, 1147; (d) F. Zhang and D. R. Spring, *Chem. Soc. Rev*., 2014, **43**, 6906.

13 (a) C.-J. Li, *Acc. Chem. Res*., 2009, **42**, 335; (b) C. S. Yeung and V. M. Dong, *Chem. Rev*., 2011, **111**, 1215; (c) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev*., 2011, **111**, 1780; (d) B. J. Lie and Z. J. Shi, *Chem. Soc. Rev*., 2012, **41**, 5588; (e) C. J. Scheuermann, *Chem. Asian J*., 2010, **5**, 436; (f) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev*., 2011, **111**, 1293; (g) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed*., 2014, **53**, 74.

14 (a) S. Murata, K. Teramoto, M. Miura and M. Nomura, *J. Chem. Res. Synop*., 1993, 434; (b) Z. Li and C.-J. Li, *J. Am. Chem. Soc*., 2004, **126**, 11810; (c) Z. Li and C.-J. Li, *J. Am. Chem. Soc*., 2005, **127**, 6968; (d) Z. Li and C.-J. Li, *J. Am. Chem. Soc*., 2005, **127**, 3672; (e) Y. Zhang and C.-J. Li, *J. Am. Chem. Soc*., 2006, **128**, 4242.

15 (a) Z. Li, R. Yu and H. Li, *Angew. Chem., Int. Ed*., 2008, **47**, 7497; (b) Z. Meng, S. Sun, H. Yuan, H. Lou and L. Liu, *Angew. Chem., Int. Ed*., 2014, **53**, 543; (c) W.-T. Wei, R.-J. Song and J.-H. Li, *Adv. Synth. Catal*., 2014, **356**, 1703.

16 (a) S. Lin, C.-X. Song, G.-X. Cai, W.-H. Wang and Z.-J. Shi, *J. Am. Chem. Soc*., 2008, **130**, 12901; (b) G.-W. Wang, A.-X. Zhou, S.-X. Li and S.-D. Yang, *Org. Lett*., 2014, **16**, 3118; (c) P.-S. Wang, H.-C. Lin, X.-L. Zhou, L.-Z. Gong, *Org. Lett.*, 2014, **16**, 3332; (d) S. E. Ammann,; G. T. Rice and M. C. White, *J. Am. Chem. Soc*., 2014, **136**, 10834; (e) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett*., 2012, **14**, 5294; (f) D. L. Priebbenow and C. Bolm, *Org. Lett*., 2014, **16**, 1650; (g) H. Liu, G. Shi, S. Pan, Y. Jiang and Y. Zhang, *Org. Lett*., 2013, **15**, 4098; (h) Y. Cheng, W. Dong, L. Wang, K. Parthasarathy, C. Bolm, *Org. Lett*., 2014, **16**, 2000; (i) S.-L. Zhou, L.-N. Guo, S. Wang and X.-H. Duan, *Chem. Commun*., 2014, **50**, 3589.

17 (a) R. Xia, H. Y. Niu, G. R. Qu and H. M. Guo, *Org. Lett*., 2012, **14**, 5546; (b) A. P. Antonchick and L. Burgmann, *Angew. Chem., Int. Ed*., 2013, **52**, 3267; (c) Z. Li,; F. Fan, J. Yang, Z.-Q. Liu, *Org. Lett*., 2014, **16**, 3396; (d) R. Narayan and A. P. Antonchick, *Chem.-Eur. J*., 2014, **20**, 4568.

18 (a) G. Zhang, Y. Zhao and H. Ge, *Angew. Chem., Int. Ed*., 2013, **52**, 2559; (b) G.-W. Zhang, J.-M. Miao, Y. Zhao and H.-B. Ge, *Angew. Chem., Int. Ed*., 2012, **51**, 8318.

19 (a) R. Vanjari, T. Guntreddi and K. N. Singh, *Org. Lett*., 2013, **15**, 4908; (b) T. Guntreddi, R. Vanjari and K. N. Singh, *Tetrahedron,* 2014, **70**, 3887.

20 (a) T. Guntreddi, R. Vanjari and K. N. Singh, *Org. Lett*., 2014, **16**, 3624; (b) R. Vanjari, T. Guntreddi and K. N. Singh, *Green Chem*., 2014, **16**, 351; (c) N. Singh, R. Singh, D. S. Raghuvanshi and K. N. Singh, *Org. Lett*., 2013, **15**, 5874; (d) R. Singh, D. S. Raghuvanshi and K. N. Singh, *Org. Lett*., 2013, **15**, 4202; (e) D. S. Raghuvanshi, A. K. Gupta and K. N. Singh, *Org. Lett*., 2012, **14**, 4326.

21 (c) J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem., Int. Ed*., 2010, **49**, 7790; (d) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, and F. Glorius, *Angew. Chem., Int. Ed*., 2008, **47**, 7230; (e) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc*., 2012, **134**, 9098.

22 (a) J. H. Poupaert, S. Duarte, E. Colacino, P. Depreux, C. R. McCurdy, D. L. Lambert, *Phosphorus, Sulfur Silicon Relat. Elem*., 2004, **179**, 1959; (b) T. B. Nguyen, L. Ermolenko and A. Al-Mourabit *Org. Lett*., 2013, **15**, 4218.

23 Crystallographic data for compound **3ao** (CCDC 1027771) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

