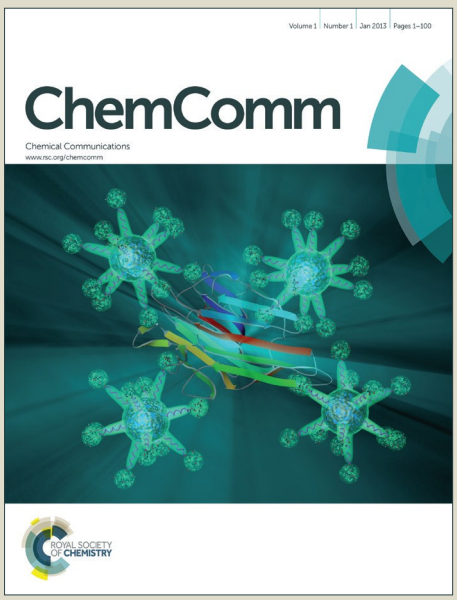
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Direct Phosphonation of Quinoxalin-2(1*H*)-ones under Transition-Metal-Free Conditions

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

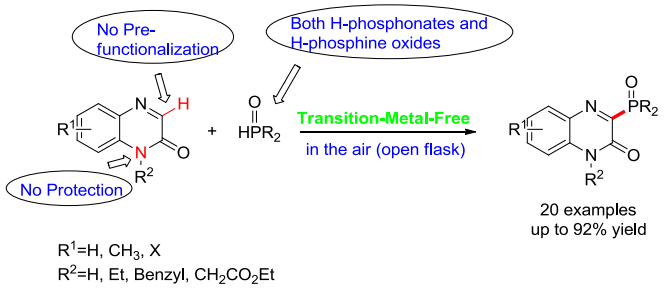
DOI: 10.1039/x0xx00000x

www.rsc.org/

Ming Gao[a], Yi Li[a], Lijuan Xie[a], Remi Chauvin[a,b,c], Xiuling Cui[a*]

A direct C-H bond phosphonation of quinoxalin-2(1*H*)-ones with H-phosphonates, H-phosphinates or H-phosphine oxides has been developed. A wide variety of heteroaryl phosphonates were obtained in up to 92% yield for 20 examples under transition-metal-free conditions. This protocol tolerates a broad scope of substrates and features practicality, high efficiency, environmental friendliness and atom economy.

Phosphorus-substituted heterocycles are found in many bioactive molecules,[1] and advanced functional materials.[2] The development of straightforward and efficient methods of C-P bond formation is the key in the construction of such heterocycles. Traditional methods for building C-P bond rely on the reaction of organometallic reagents with an electrophilic P-reagent such as $Ph_2P(O)Cl$.[3] Since the pioneering work of Hirao and co-workers on palladium-catalysed cross-coupling of aryl halides with H-phosphonates,[5] a wide variety of transition-metal-catalysed C–P bond forming reactions has been developed, in particular using palladium,[6] copper[7] or nickel.[8] In 2013, Yu *et al.* reported a pyridine-directed C-H phosphonation reaction catalysed by palladium, in which H-phosphonates were added slowly using a syringe pump to limit the excess of strongly coordinating P(III) agents (phosphite tautomers of H-phosphonates) that would hamper the C–H bond activation process at the metal center.[9] Then, the group of Murakami described a palladium-catalysed direct synthesis of phosphonate derivatives using α-hydroxyalkylphosphonates as the masked phosphonating reactants to prevent the catalyst from deactivation.[10] Very recently, Yang *et al.* had developed a Cu(I)-catalysed cross-coupling reaction for the synthesis of 3-phosphoindoles.[11] Alternatively, methods for the construction of C-P bonds through radical processes have also emerged.[12-13] Oxidants, such as manganese[12] or silver[13] salts can be here used as radical initiators. Yet, the addition of such environmentally unfriendly oxidants is detrimental for a widespread usage. Recently, we have developed a method of phosphonation of quinolone N-oxides, based on a C-H bond activation process under hazard oxidant-, additive- and metal-free conditions.[14] In continuation of our efforts, we herein disclose our recent study on direct C–H phosphonylation of quinoxalin-2(1*H*)-ones with H-phosphonates H-phosphinates or H-phosphine oxides under transition-metal-free conditions (Scheme 1). To the best of our knowledge, C–H phosphonylation of quinoxalin-2(1*H*)-ones has not been reported, in spite of the interest of the produced structural motifs in medicinal and organic chemistry.[15]

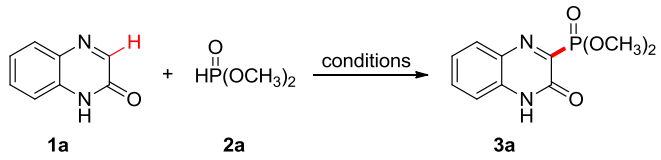


Scheme 1 Direct C–H phosphonylation under transition-metal-free conditions

Our initial study focused on the condensation of quinoxalin-2(1*H*)-one (**1a**) with dimethyl H-phosphonate (**2a**) as a model reaction for a screening of the various reaction parameters (Table 1). The phosphonated product **3a** was produced in 78% yield using 10 mol% of $Cu(OAc)_2$ as a catalyst and 3 equiv. of persulfate $Na_2S_2O_8$ as an oxidant (Table 1, entry 1). The structure of **3a** was confirmed by NMR spectroscopy and X-ray diffraction analysis of a single crystal (Figure 1). It was noticeable that 72% of **3a** could be obtained in the absence of copper, while **3a** was not observed in the absence of

Engineering Research Center of Molecular Medicine, Ministry of Education, Key Laboratory of Xiamen Marine and Gene Drugs, Institutes of Molecular Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, 361021. E-mail: cuixl@hqu.edu.cn.
[b] CNRS, LCC (Laboratoire de Chimie de Coordination), 205, route de Narbonne, BP 44099, F-31077 Toulouse Cedex 4, France.
[c] *Université de Toulouse, UPS, INPT, F-31077 Toulouse, Cedex 4, France.*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the parameters for the reaction of quinoxalin-2(1*H*)-one with dimethyl H-phosphonate[a]

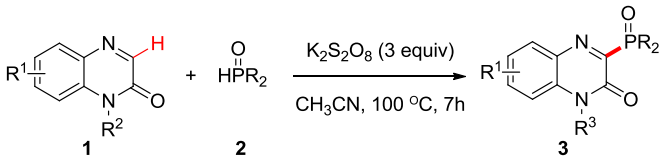


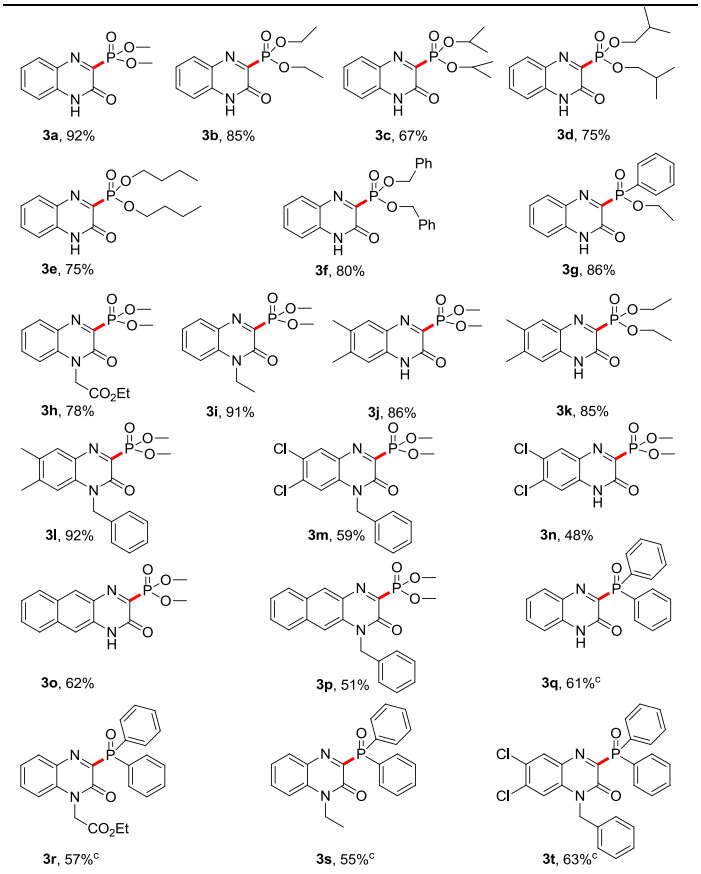
entry	oxidant	solvent	*t* (°C)	Yield[c] (%)
1[b]	$Na_2S_2O_8$	CH_3CN	100	78
2[d]	—	CH_3CN	100	trace
3	$Na_2S_2O_8$	CH_3CN	100	72
4	TBHP	CH_3CN	100	27
5	BQ	CH_3CN	100	0
6	$K_2S_2O_8$	CH_3CN	100	81
7	$PhI(OAc)_2$	CH_3CN	100	24
8	O_2	CH_3CN	100	trace
9	$K_2S_2O_8$	DMSO	100	0
10	$K_2S_2O_8$	toluene	100	40
11	$K_2S_2O_8$	DMF	100	0
12	$K_2S_2O_8$	H_2O	100	0
13	$K_2S_2O_8$	THF	100	30
14	$K_2S_2O_8$	1,4-dioxane	100	48
15	$K_2S_2O_8$	EDC	100	51
16	$K_2S_2O_8$	CH_3CN	80	74
17	$K_2S_2O_8$	CH_3CN	120	73
18[e]	$K_2S_2O_8$	CH_3CN	100	79
19[f]	$K_2S_2O_8$	CH_3CN	100	86
20[g]	**$K_2S_2O_8$**	**CH_3CN**	**100**	**92**
21[g, h]	$K_2S_2O_8$	CH_3CN	100	84
22[g, i]	$K_2S_2O_8$	CH_3CN	100	94

[a] Reaction conditions: **1a** (0.2mmol), **2a** (0.3mmol), solvent (2.0mL), oxidant (0.6mmol).[b] 10mol% $Cu(OAc)_2$ was used. [c] Isolated yields. [d] In the absence of Cu and oxidant. [e] **2a** (0.4mmol). [f] **2a** (0.5mmol). [g] **2a** (0.6mmol). [h] $K_2S_2O_8$ (0.4mmol). [i] A new tube and magnetic stirrer element were used.

$Na_2S_2O_8$, indicating that the reaction was mainly mediated by $Na_2S_2O_8$ (entries 2-3). Then, various oxidants were tested and $K_2S_2O_8$ was found to be optimal, giving the desired product in 81% yield (entries 3-8). Screening of solvents revealed that CH_3CN was the most suitable solvent (entries 5, 9-15). Polar solvents, such as DMSO, DMF and H_2O, inhibited the reaction (entries 9, 11 and 12). A temperature of 100 °C was found to be optimal (entries 6, 16 and 17). The desired product was obtained in 92% yield when the loading of **2a** was increased from 0.3 mmol to 0.6 mmol (entries 18, 19 and 20). Further study indicated that the yield of **3a** was decreased to 84% when the loading of the oxidant was 2 equiv. only (entry 21). A 94% yield could be obtained using newly purchased tube and magnetic stirrer (entry 22). Finally, the optimal reaction conditions for the direct phosphonylation of quinoxalin-2(1*H*)-ones were identified as the following ones: **1** (0.2 mmol), **2** (0.6 mmol) and $K_2S_2O_8$ (0.6 mmol) under air in CH_3CN at 100 °C for 8 hours.

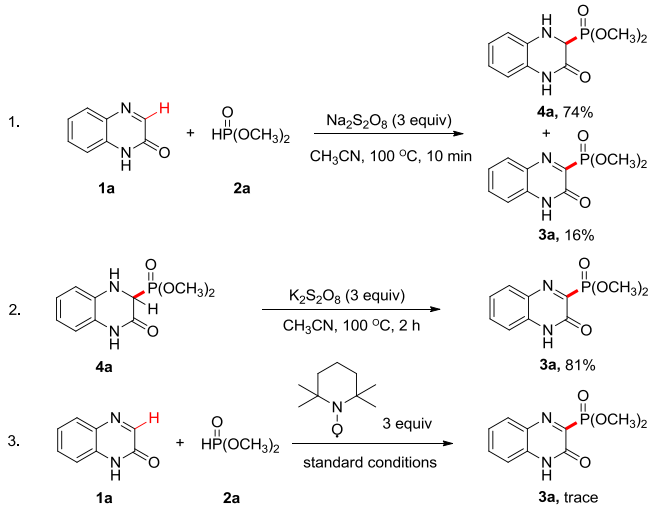
Table 2 Substrate scope for C-H phosphonation under transition-metal-free conditions.[a,b]



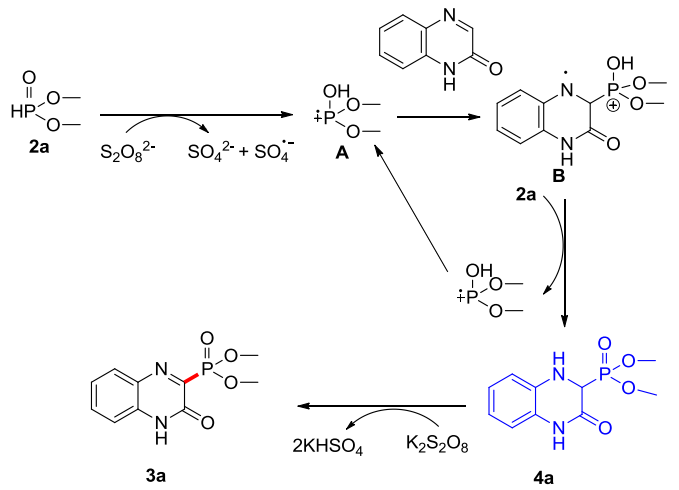


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $K_2S_2O_8$ (0.6 mmol), CH_3CN (2 mL) at 100 °C for 8h. [b]Isolated yield. [c]1.5 equiv. of H-phosphine oxide was used.

With the optimal reaction conditions in hand, the scope of the substrates was investigated (Table 2). H-phosphonates bearing various groups could thus be coupled with quinoxalin-2(1*H*)-one, affording the corresponding products **3a-3f** in fair to high yields (67%-92%). The yield decreased slightly with the steric bulk of the dialkyl H-phosphonate reactant, from 92% for **3a** to 67% for **3c**. The restored 80 % yield for **3f** might be attributed to π-π stacking pre-organization of the reactants **1** and dibenzyl H-phosphite **2f**. This hypothesis was also supported by the high yield obtained for ethyl phenylphosphinate **3g** (86 %), showing in passing a first generalization of the reaction from H-phosphonate to H-phosphinate substrates. To extend the scope of our method further, substituted quinoxalin-2(1*H*)-ones and benzo-[g]quinoxalin-2(1*H*)-one were also subjected to same coupling conditions with H-phosphonates. In general,



Scheme 2 Control experiments



Scheme 3 Proposed reaction mechanism

N-2-ethoxy-2-oxoethyl and *N*-ethyl quinoxalin-2(1*H*)-ones reacted efficiently, providing the products **3h**, **3i** in 78% and 91% yields, respectively. 6,7-Dimethyl quinoxalin-2(1*H*)-one led to the products **3j** and **3k** in 86% and 85% yields, respectively, and its *N*-benzyl derivative gave **3l** in 92% yield. The electron–withdrawing Cl substituents at the 6,7 positions were tolerated, producing the targeted products **3m** and **3n** in 59% and 48% yields, respectively. Benzo-[g]quinoxalin-2(1*H*)-one and its *N*-benzyl derivative provided the phosphonates **3o** and **3p** in 62% and 51% yields, respectively. Both of chloro and benzo-[g]quinoxalin-2(1*H*)-ones gave lower yields mainly because of low electron density on the C atom of C=N. Most remarkably, diphenylphosphine oxide (1.5 equiv) could also be used as a coupling partner of various quinoxalin-2(1*H*)-ones under the standard reaction conditions despite that the tertiary phosphine oxides **3q**-**3t** were afforded in only 55-63% yields, perhaps owing to the structural rigid and steric hindrance of diphenylphosphine oxide.

With the view of obtaining more insights into the reaction mechanism, some control experiments were carried out. Shortening the reaction time to 10 min in the presence of $Na_2S_2O_8$, 74% of the addition product **4a** was obtained along with 16% of **3a** (Scheme 2, eq 1). **4a** could then be converted into the oxidized phosphonate **3a** in 81% yield under the standard conditions (in the presence of $K_2S_2O_8$, eq 2). These results indicated that **4a** might be a key intermediate of the overall reaction. Addition of 3.0 equiv. of TEMPO to the reaction medium led to the inhibition of the oxidative phosphonation process (eq 3). This result suggested that the transformation reaction involved a radical pathway.

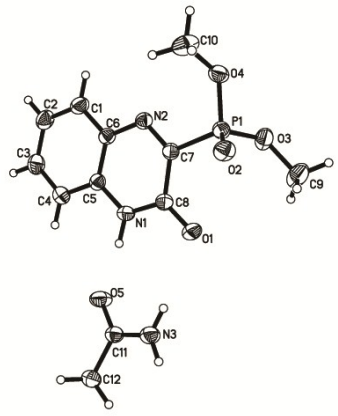


Figure 1 X-ray structure of compound **3a**.

On the basis of the experimental results and literatures,[12b, 13a, 13e, 16] a tentative mechanism was proposed (Scheme 3). First, a cationic radical **A** could be generated from dimethyl H-phosphonate upon oxidation with persulfate.[3,16a,17] Then electrophilic addition of cationic radical of **A** to the imine bond of **1a** would lead to the species **B**,[16c] which might react with dimethyl *H*-phosphonate **2a** to give intermediate **4a,** Finally, oxidative dehydrogenation of **4a** produced the C-phosphonate **3a**.

In summary, a method has been disclosed for the selective phosphonation of quinoxalin-2(1*H*)-ones with H-phosphonates, H-phosphinates or H-phosphine oxides under transition-metal-free conditions, where $K_2S_2O_8$ is the sole oxidant. This method thus exhibits excellent performance in terms of atom economy and environmental friendliness. The protocol is also compatible with a wide range of functional groups, thus providing an attractive access to C-3 phosphonated quinoxalin-2(1*H*)-ones, which are potentially useful for medicinal chemistry purposes.

Acknowledgments

This research was supported by the NSF of China (21572072), the Xiamen Southern Oceanographic Center (15PYY052SF01), Science and Technology Bureau of Xiamen City (3502Z20150054) and Huaqiao University.

Notes and references

1 (a) L. Zhou, H. Zhang, S. Tao, L. Bassit, T. Whitaker, T. R. McBrayer, M. Ehteshami, S. Amiralaei, U. Pradere, J. Hyun Cho, F. Amblard, D. Bobeck, M. Detorio, S. J. Coats, and R. F. Schinazi, *J. Med. Chem.*, 2015, **58**, 3445; (b) R. Chofor, S. Sooriyaarachchi, M. D. P. Risseeuw, T. Bergfors, J. Pouyez, C. Johny, A. Haymond, A. Everaert, C. S. Dowd, L. Maes, T. Coenye, A. Alex, R. D. Couch, T. A. Jones, J. Wouters, S. L. Mowbray, and S. V. Calenbergh, *J. Med. Chem.*, 2015, **58**, 2988; (c) M. Sawa, T. Kiyoi, K. Kurokawa, H. Kumihara, M. Yamamoto, T. Miyasaka, Y. Ito, R. Hirayama, T. Inoue, Y. Kirii, E. Nishiwaki, H. Ohmoto, Y. Maeda, E. Ishibushi, Y. Inoue, K. Yoshino and H. Kondo, *J. Med. Chem.*, 2002, **45**, 919; (d) X. Chen, D. J. Kopecky, J. Mihalic, S. Jeffries, X. Min, J. Heath, J. Deignan, S.-J. Lai, Z. Fu, C. Guimaraes, S. Shen, S. Li, S. Johnstone, S. Thibault, H. Xu, M. Cardozo, W. Shen, N. Walker, F. Kayser and Z. Wang, *J. Med. Chem.*, 2012, **55**, 3837; (e) Q. Dang, Y. Liu, D. K. Cashion, S. R. Kasibhatla, T. Jiang, F. Taplin, J. D. Jacintho, H. Li, Z. Sun, Y. Fan, J. D. Re, F. Tian, W. Li, T. Gibson, R. Lemus and P. D. Poelje, *J. Med. Chem.,* 2011, **54**, 153; (d) R. F. Roush, E. M. Nolan, F. Löhr and C. T. Walsh, *J. Am. Chem. Soc.*, 2008, **130**, 3603.

2 (a) H. Onouchi, T. Miyagawa, A. Furuko, K. Maeda and E. Yashima, *J. Am. Chem. Soc.*, 2005, **127**, 2960; (b) S. O. Jeon and J. Y. Lee, *J. Mater. Chem*., 2012, **22**, 7239; (c) T. Bock, H. Möhwald and R. Mülhaupt, *Macromol. Chem. Phys.*, 2007, **208**, 1324.

3 B. Zhang, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2014, **16**, 250.

4 (a) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (b) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (c) B. J. Stokes and T. G. Briver, *Eur. J. Org. Chem.,* 2011, **22**,4071; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147; (e) X. Zhang, K. Chen and Z.-J. Shi, *Chem Sci.* 2014, **5**, 2146.

5 (a) T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *Synthesis.,* 1981, **1**, 56.

6 (a) T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro, T. Agawa, *Bull. Chem. Soc. Jpn*., 1982, **55**, 909; (b) M. Kalek, A. Ziadi and J. Stawinski, *Org. Lett.*, 2008, **10**, 4637; (c) C. S. Demmer, K.-L. Niels. and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981; (d) S. M. Rummelt, M. Ranocchiari and J. A. van Bokhoven, *Org. Lett.*, 2012, **14**, 2188; (e) E. L. Deal, C. Petit and J.-L. Montchamp, *Org. Lett.*, 2011, **13**, 3270; (f) S. M. Rummelt, M. Ranocchiari and J. A. van Bokhoven, *Org. Lett*., 2012, **14**, 2188; (g) C. Hou, Y. Ren, R. Lang, X. Hu, C. Xia and F. Li, *Chem. Commun*., 2012, **48**, 5181; (h) X. Mi, M. Huang, J. Zhang, C. Wang and Y. Wu, *Org. Lett.*, 2013, **15**, 6266.

7 (a) D. V. Allen and D. Venkataraman, *J. Org. Chem.*, 2003, **68**, 4590; (b) Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao, Y. Zhou and L. Han, *J. Am. Chem. Soc.*, 2009, **131**, 7956; (c) R. Zhuang, J. Xu, Z. Cai, G. Tang, M. Fang and Y. Zhao, *Org. Lett*., 2011, **13**, 2110; (d) X. Li, F. Yang, Y. Wu, and Y. Wu, *Org. Lett.*, 2014, **16**, 992; (e) G. Hu, Y. Gao and Y. Zhao, *Org. Lett*., 2014, **16**, 4464;

8 (a) L. Han, C. Zhang, H. Yazawa and S. Shimada, *J. Am. Chem. Soc.,* 2004, **126**, 5080; (b) Y. Zhao, G. Wu, Y. Li, L. Gao, and F.-S.Han, *Chem. Eur. J.*, 2012, **18**, 9622; (c) H. Zhang, M. Sun, Y. N. Ma, Q. Tian and S.-D. Yang, *Org. Biomol. Chem.*, 2012, **10**, 9627; (d) C. Shen, G. Yang, and W. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 3500.

9 C. Feng, M. Ye, K. Xiao, S. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 9322.

10 C. Li, T. Yano, N. Ishida and M. Murakami, *Angew. Chem. Int. Ed.*, 2013, **52**, 9801.

11 A. Zhou, L. Mao, G. Wang and S.-D. Yang, *Chem. Commun.*, 2014, **50**, 8529.

12 (a) O. Tayama, A. Nakano, T. Iwahama, S. Sakaguchi and Y. Ishii, *J. Org. Chem.,* 2004, **69**, 5494; (b) T. Kagayama, A. Nakano, S. Sakaguchi and Y. Ishii, *Org. Lett.,* 2006, **8**, 407; (c) X.-J. Mu, J.-P. Zou, Q.-F. Qian and W. Zhang, *Org. Lett.*, 2006, **8**, 5291; (d) X.-Q. Pan, J.-P. Zou, G.-L. Zhang and W. Zhang, *Chem. Commun.*, 2010, **46**, 1721; (e) X.-Q. Pan, L. Wang, J.-P. Zou and W. Zhang, *Chem. Commun.*, 2011, **47**, 7875.

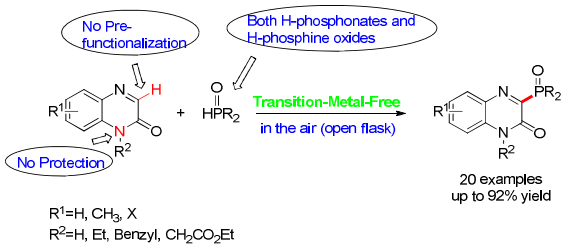
13 (a) Y.-R. Chen and W.-L. Duan, *J. Am. Chem. Soc.*, 2013, **135**, 16754; (b) Y.-M. Li, M. Sun, H.-L. Wang, Q.-P. Tian and S.-D. Yang, *Angew. Chem., Int. Ed.*, 2013, **52**, 3972; (c) L. Wang, A. Wang, Y, Xia, X. Wu, X. Liu, and Y. Liang, *Chem. Commun*., 2014, **50**, 13998; (d) C.-B. Xiang, Y.-J. Bian, X.-R. Mao and Z.-Z. Huang, *J. Org. Chem.,* 2012, **77**, 7706; (e) X. Mi, C. Wang, M. Huang, J. Zhang, Y. Wu and Y. Wu, *Org. Lett.*, 2014, **16**, 3356.

14 H. Wang, X. Cui, Y. Pei, Q. Zhang, J. Bai, D. Wei and Y. Wu, *Chem. Commun.,* 2014, **50**, 14409.

15 (a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet and P. S. Ringrose, *Nature.*, 1978, **272**, 56; (b) R. Hirschmann, A. B. Smith, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengeler and S. J. Benkovic, *Science.*, 1994, **265**, 234; (c) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193; (d) M. Rueping, Sh. Zhu and R. M. Koenigs, *Chem. Commun*., 2011, **47**, 8679.

16 (a) L. Zhu, H. Yu, Q. Guo, Q. Chen, Z. Xu and R. Wang. *Org. Lett*., 2015, **17**, 1978; (b) B. Yang, T-T. Yang, X-A. Li, J-J. Wang and S-D. Yang, *Org. Lett.*, 2013, **15**, 5024; (c) B. Zhang, C-G. Daniliuc and A. Studer, *Org. Lett.*, 2014, **16**, 250. (d) Q. Zhang, D. Wei, X. Cui, D. Zhang, H. Wang and Y. Wu, *Tetrahedron*, 2015, **71**, 6087. (e) D. P. Hari and B. König, *Org. Lett.,* **13**, 2011.

17 The radical dimer A_2, tetramethyl hypophosphate, was not detected in the medium. See: v. M. Baudler, *Z. Naturforschg*., 1953, **8b**, 326.



A direct C-H bond phosphonation of quinoxalin-2(1*H*)-ones with H-phosphonates, H-phosphinates or H-phosphine oxides has been developed.