Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Journal Name

COMMUNICATION

2-Oxo Promoted Hydrophosphonylation & Aerobic Intramolecular Nucleophilic Displacement Reaction

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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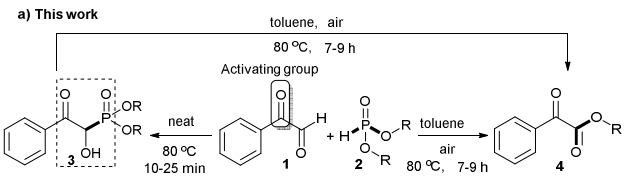
Highly efficient catalyst free methods for the synthesis of α-hydroxy-β-oxophosphonates and α-oxoesters has been described. The existence of 2-oxo group in α-oxoaldehydes is a key factor in promoting the reaction of tervalent phosphite form towards 2-oxoaldehydes in the synthesis of α-hydroxy-β-oxophosphonates. The in situ activated α-C-H atom of α-hydroxy-β-oxophosphonates sustains aerobic intramolecular nucleophilic displacement in a curious way to α-oxoester.

The most imperative feature of H-phosphonates in solution is its existence as an equilibrium mixture of i) a tetra coordinate phosphonate form and ii) a tervalent phosphite form. H-phosphonates are generally considered as week nucleophiles; that account for their low reactivity which renders their applications and needs the aid of catalyst to ensue the reaction. It is well established fact that the tautomeric equilibrium in solutions is mostly shifted towards the tetra coordinate phosphonate but it can be shifted to the phosphite (nucleophilic) form by appropriate catalysts, for example, Lewis bases and acids.[1] On the reactivity part, the distinctive reactivity of H-phosponates against C=O and C=N system has been well explored for generation of P-C bond (Pudovik,[2] Kabachnik-Fields[3] reactions). Amongst, hydrophosphonylation of carbonyl compounds is considered as a powerful and direct method for construction of α-hydroxy-β-oxophosphonates. These compounds have played a key role as a structural unit in many biologically active compounds and occupy a major position in organophosphorus chemistry.[4] Different methods reported for their synthesis include i) reduction of keto phosphonates,[5] ii) α-hydroxylation of alkyl phosphonates,[6] and iii) addition of trialkyl phosphites to aldehydes.[7] Till date, Pudovik reaction is considered to be an efficient atom economic and simple method to the synthesis of α-hydroxyphosphonates that involves nucleophilic addition of H-phosphonates to carbonyl compounds. These reactions need the aid of catalyst, including inorganic/ organic bases, acids and metal salt promoters. However, most of these reactions experience several limitations in terms of toxicity of reagents, corrosiveness due to acid or basic reagents, moisture sensitivity of the catalyst, usage of stoichiometric or even more amounts and high rates of reaction times.[2] Here in, we primarily report an efficient cayalyst free 2-oxo promoted hydrophosphonylation reaction resulting in the formation of α-hydroxy-β-oxophosphonates which is an important structural unit in bioactive natural products, viz., fosfazinomycins and Me-HPnA.[8] The versatility of these compounds has been further exploited in development of novel concept based on air oxidative intramolecular nucleophilic displacement reaction to α-oxoesters,[9] which are recognized as structural elements in many biologically active compounds[10] and are also used as synthetic tool[11] in synthesis of several heterocyclic compounds (scheme 1). This unique ability of α-hydroxy-β-oxophosphonates to generate α-oxoesters is probably due to α-C-H activation by adjacent directing groups, viz., carbonyl, hydroxy and phosphoryl group.



Scheme 1. Catalyst free hydrophosphonylation and synthesis to α- oxoesters.

In our continuing efforts with 2-oxoaldehyde, the present work began with a reaction between **1a** and **2a** in toluene at 50 °C. Surprisingly, we isolated 85 % of α-hydroxy-β-oxophosphonates **3a** in one hour without the aid of any external catalyst (entry 1, Table 1). Further screening was carried out to improve the yield of **3** (entry 2-5). Best yield of desired product **3a** was produced when we treated 1.0 mmol of phenyl glyoxal **1a** with 1.1 mmol of diethyl H-phosphonate **2a** under neat conditions (98 %, entry 5). In contrary,

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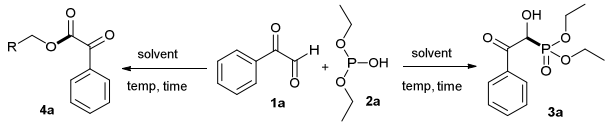
Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data for products, and NMR spectra of products. See
DOI: 10.1039/x0xx00000x

Table 1. Optimization of the reaction[a]



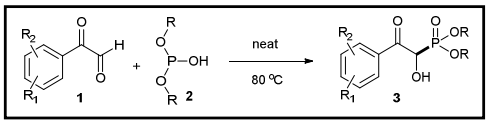
entry	additive	Temp (°C)	Time	Yields (%)[b]	
				3a	4a
1.	toluene	50	60 min	85	<5
2.	toluene	rt	60 min	<10	-
3.	toluene	80	10 min	98	-
4.	toluene	100	10 min	93	-
5.	**neat**	**80**	**10 min**	**98**	**-**
6.	toluene	80	30 min	90	8
7.	**toluene**	**80**	**7 h**	**-**	**73**
8.	toluene	100	7 h	-	65
9.	-	80	7 h	-	<10

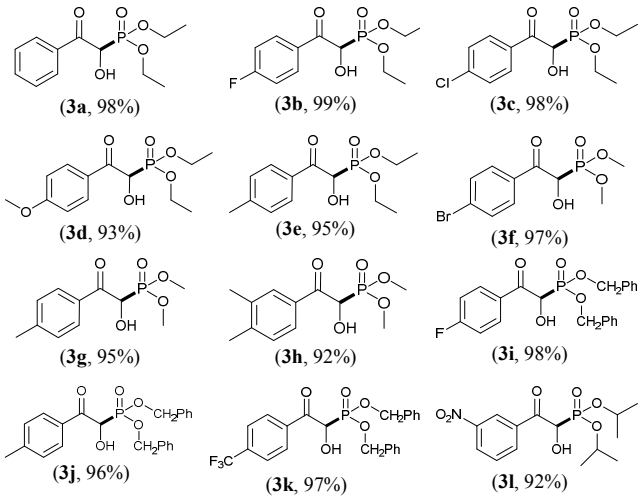
[a] Reaction condition: phenylglyoxal **1a** (0.46 mmol), diethyl phosphite **2a** (0.506 mmol), toluene (1 mL), temperature 80 °C; for synthesis of **3a**, **4a** needs 10 min and 7 h respectively. [b] Isolated yields after column chromatography.

when the same reaction was performed at 80 °C in toluene for 30 min, we isolated α-oxoester **4a** (along with **3a**) in 8 % yield (entry 6). This surprising result encouraged us, to further optimize the reaction conditions for the generation of *α*-oxoester in good yields (entry 7-9). We observed that reaction between **1a** (1.0 mmol) and **2a** (1.1 mmol) in toluene at 80 °C for 7 h furnished the unprecedented product **4a** in 73 % isolated yield (entry 7).

To establish the substrate scope of former reaction (hydrophosphonylation), several reactions were conducted between en 2-oxoaldehydes **1** and H-phosphonates **2** under the optimized condition as demonstrated in Table 2. As we observed, irrespective of the substitution, all the tested reactions were efficiently transformed to the required product **3** in 10-25 min duration (92-99 %, **3a**-**3l**).

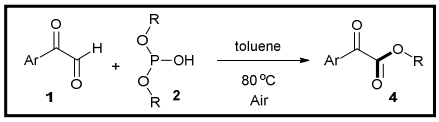
Table 2. Scope of the α-hydroxy-β-oxophosphonates synthesis[a]

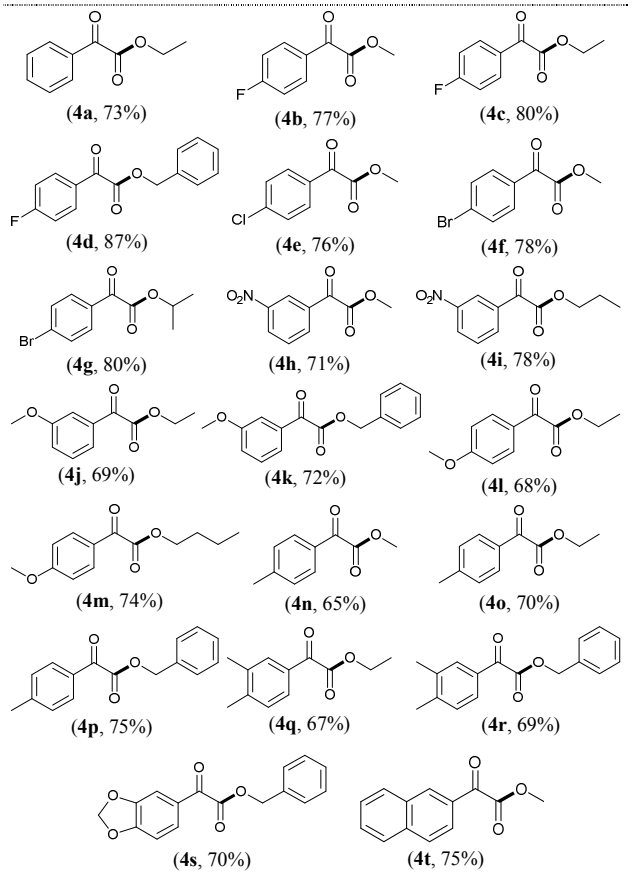




[a] Reaction condition: 2-oxoaldehyde **1** (0.46 mmol), dialkyl phosphite **2** (0.506 mmol), temperature 80 °C, reaction time 10-25 min.

Table 3. Scope the *α*-oxoester synthesis[a]



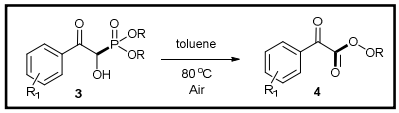


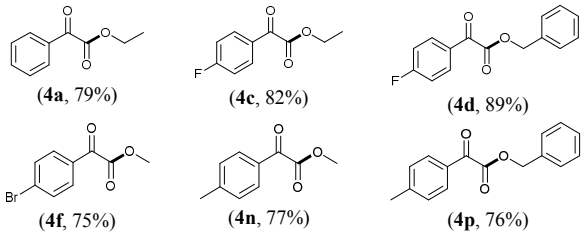
[a] Reaction condition: 2-oxoaldehyde **1** (0.46 mmol), dialkyl phosphite **2** (0.506 mmol), toluene (1 mL), temperature 80 °C, reaction time 7-9 h.

Further, several reactions were conducted to the synthesis of *α*-oxoester based on its standard reaction protocol (Table 3). It was clearly observed that electronic environment of phenyl ring in 2-oxoaldehyde had no appreciable effect on the reaction and their yields. Based on our observation, the 2-oxoaldehydes bearing electron withdrawing groups, for example, -F (**4b**, **4c**, **4d**), -Cl (**4e**), -Br (**4f**, **4g**) and -NO_2 (**4h**, **4i**) afforded a little bit higher yields than those with electron donating groups either at meta or para position, for example -OCH_3 (**4j**, **4k**, **4l**, **4m**), –CH_3 (**4n**, **4o**, **4p**) groups. The disubstituted 2-oxoaldehydes also produced comparable yields, for example, **4q**, **4r**, **4s**. In the case of naphylglyoxal, reaction was very smooth and produced desired product (**4t**) in good yield. Among different phosphite esters **2** used, benzyl phosphites comparably gave higher yields.

Looking into the unprecedented behavior of later reaction (α-oxoester generation), we initiated a test reaction where in compound **3a** [diethyl(1-hydroxy-2-oxo-2-phenylethyl)phosphonate] when heated at 80 °C in toluene generated **4a** in 80 % yield. In this direction, different reactions were conducted using our earlier generated α-hydroxy-β-oxophosphonates as starting material (Table 4). In all the reactions, we observed that the conversion of **3** to its corresponding α-oxoesters was very smooth and produced good yields. The yields of α-oxoesters from α-hydroxy-β-oxophosphonates were observed a bit higher than the direct synthesis described Table 3.

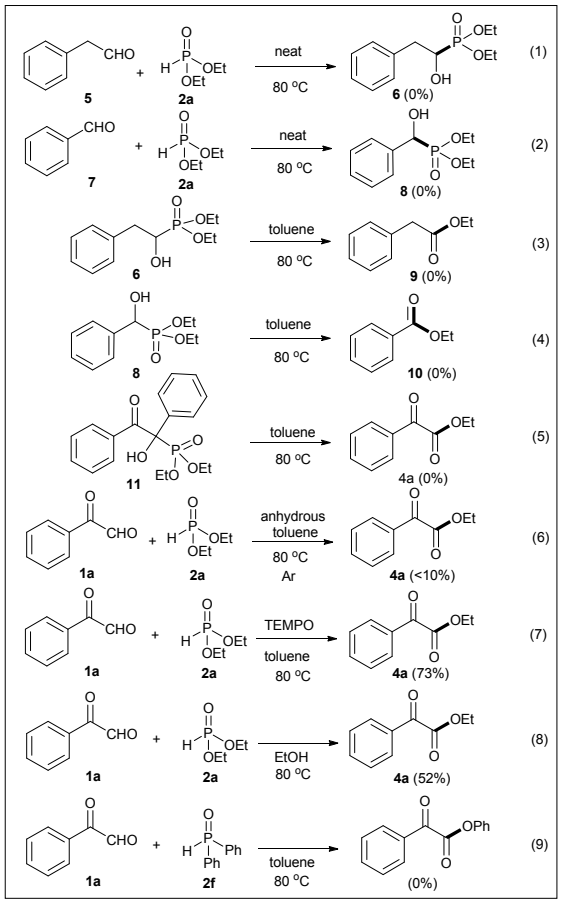
Table 4. Scope of the conversion of **3** to **4**[a]





[a] Reaction condition: α-hydroxy-β-oxophosphonates **3** (0.18 mmol) and toluene (1 mL), temperature 80 °C, reaction time 7-9 h.

To interpret the intrinsic mechanism of **3** and **4**, we performed a series of controlled reactions (Scheme 2). In the series, first two experiments (1, 2) involve reactions of 2-phenylacetaldehyde **5**/ benzaldehyde **7** with **2a** under standard conditions as mentioned in Table 2. Both the reactions failed to produce hydrophosphonylated products **6** & **8** respectively indicating the importance of 2-oxo group of 2-oxoaldehyde in promoting hydrophosphonylation reaction under catalyst free condition. In experiments (3, 4) hydrophosphonylated product **6**/or **8** (generated as per literature procedure)[12] heated at 80 °C in toluene remained stable for 24 h. These results further emphasize the role of 2-oxo group, in promoting the aerobic intramolecular nucleophilic displacement reaction/ *α*-oxoester generation. In experiment (5), no transformation of **11**[12] was observed in the synthesis of *α*-oxoester **4a** which ultimately reveal that *α*-C-H atom exhibits the central role in transformation of **3** to **4**. In one more experiment (6), a reaction was conducted at 80 °C between **1a** and **2a** in dry toluene under argon atmosphere for 24 h. We observed very low yield of **4a**, which indicates the role of air as a promoter/ oxidant. In another reaction, when performed between **1a** and **2a** in presence of TEMPO (5 mmol) under optimized conditions gave desired **4a** product in comparable yields, thereby, excluding the possibility of free radical mechanism (experiment 7). As expected in experiment 8, desired product **4a** was generated in low yields when reaction was conducted in EtOH. This clearly emphasized on role of H-bonding interactions in promoting hydrophosphonylation/ aerobic intramolecular nucleophilic displacement reaction. In addition, the failure of experiment 9, performed between diphenyl H-phosphonate **2f**, and **1a** under said conditions, undoubtedly pointed



Scheme 2. Controlled experiments

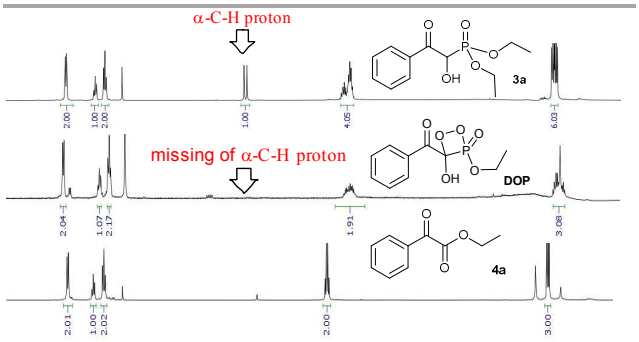
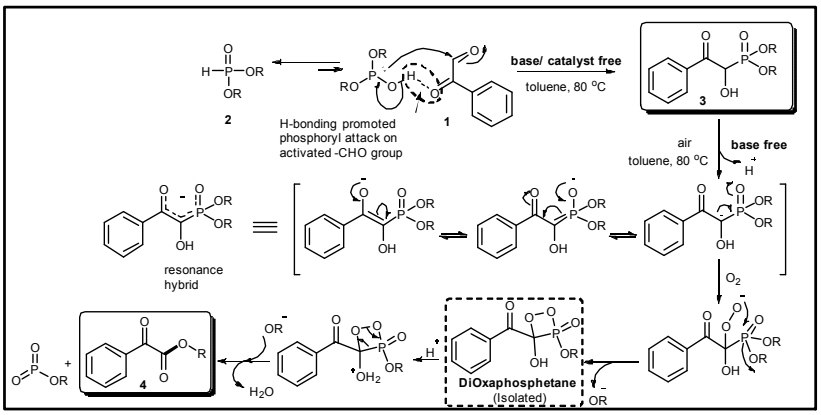


Figure 1. ^{1}H-NMR spectra of 3a, 4a along with its 1,2,3-dioxaphosphetan intermediate.

towards the low nucleophilicity and more hindrance of phenoxy group (-OPh).

In order to add further evidences to elucidate mechanism, we keenly observed the changes in reaction between **1a** and **2a** at 80 °C with time. Preliminary, we monitored the reaction using TLC (thin layer chromatography) technique. It was noticed that within 10 min, total reaction mass was converted to **3a**, which later gradually generated desired oxoester **4a** through some intermediate. Luckily, we could succeed in prediction of the unstable intermediate as dioxaphosphetane, and that intermediate was purified using preparative TLC and characterized by using ^{1}H-



Scheme 3. Plausible mechanistic scenario for synthesis of **3** and **4**.

NMR and LC-MS analysis. Based on these observations, we presume the generation of *α*-oxoester **4a** from **3a** through the dioxaphosphetane intermediate (Figure 1).

On the basis of above results, the feasible pathway for formation of **3** and **4** was presented in Scheme 3. Through the assistance of H-bonding due to 2-oxo group, the dialkyl H-phosphonate form shifts towards more nucleophilic phosphite form. The phosphite **2** later attacks 2-oxoaldehyde **1** generating desired product **3**. Compound **3** on heating in toluene loses one proton that generates a resonance stabilized carbanion. These carbanion later attacks molecular oxygen that ultimately rearranges to dioxaphosphetane intermediate and releases alkoxy nucleophile. Under *in situ* acidic environment the dioxaphosphetane undergoes nucleophilic displacement reaction to **4** through elimination of H_2O and PO_3R molecules.

Conclusions

In summary, we have developed efficient methods for the synthesis of α-hydroxy-β-oxophosphonate and α-oxoester compounds. The reaction presents simple and direct method compounds. The reaction presents simple and direct method that justifies the important role of 2-oxo group in activation/promoting the reaction through H-bonding. In view of the broad functional group tolerance, the ease of conducting such reactions, and the mild reaction conditions, we envisage this protocol will be widely tailored in synthetic chemistry. Further application towards aliphatic glyoxal is in progress and will be disclosed in due course of time.

Notes and references

1 (a) J. Stawinski and A. Kraszewski, *Acc. Chem. Res.* , 2002, **35**, 952-960; (b) A. Y. Rulev, *RSC Adv.*, 2014 **4**, 26002-26012; D. Uraguchi, T. Ito and T. Ooi, *J. Am. Chem. Soc.*, 2009, **131**, 3836-3837; (c) A. Kraszewski and J. Stawinski, *Pure Appl. Chem.*, 2007, **79**, 2217-2227.

2 (a) A. Kraszewski and J. Stawinski, *Pure Appl. Chem.*, 2007, **79**, 2217-2227; (b) J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.*, 2008 **130**, 10521-10523; (c) D. Semenzin, G. Etemad-Moghadam, D. Albouy, O. Diallo and M. Koenig, *J. Org. Chem.* , 1997, **62**, 2414-2422; (d) T. Soeta, S. M. uzaki and Y. U. ji, *Chem. Eur. J.* , 2014, **20**, 5007-5012; (e) T. P. Kee and T. D. Nixon, *Top Curr Chem*, 2003, **223**, 45-65; (f) Q. Wu, J. Zhou, Z. Yao, F. Xu and Q. Shen, *J. Org. Chem.* , 2010, **75**, 7498-7501; (g) H. R. Ramananarivo, A. Solhy, J. Sebti, A. Smahi, M. Zahouily, J. Clark and S. Sebti, *ACS Sustainable Chem. Eng.* , 2013, **1**, 403-409; (h) D. Zhao and R. Wang, *Chem. Soc. Rev.* , 2012, **41**, 2095-2108; (i) B. Liu, J.-F. Carpentier and Y. Sarazin, *Chem. Eur. J.*, 2012, **18,** 13259-13264; (j) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.* , 2008, **350**, 1195-1208.

3 (a) S. Bhagat and A. K. Chakraborti, *J. Org. Chem.*, 2007, **72**, 1263-1270; (b) G. Keglevich and E. Bálint, *Molecules* 2012, **17**, 12821-12835; (c) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani and A. Ricci, *J. Org. Chem.*, 2006, **71**, 6269-6272; (d) N. S. Zefirov and E. D. Matveeva, *Arkivoc* 2008, **(i)**, 1-17; (e) X. Zhou, D. Shang, Q. Zhang, L. Lin, X. Liu and X. Feng, *Org. Lett*., 2009, **11**, 1401-1404.

4 (a) R. U. Pokalwar, R. V. Hangarge, P. V. Maskeb and M. S. Shingare, *Arkivoc*, 2006 **(xi)** 196-204; (b) K. U. M. Rao, C. S. Sundar, S. S. Prasad, C. R. Rani and C. S. Reddy, *Bull. Korean Chem. Soc.*, 2011, **32**, 3343-3347; (c) D. V. Patel, K. Rielly-Gauvin and D. E. Ryono, *Tetrahedron Lett.* , 1990, **31**, 5587-5590; (d) N. S. Patil, G. B. Deshmukh, S. V. Patil, A. D. Bholay and N. D. Gaikwad, *Eur. J. Med. Chem.*, 2014, **83**, 490-497; (e) G. S. Reddy, C. SyamaSundar, S. S. Prasad, E. Dadapeer, C. N. Raju and C. S. Reddy, *Der Pharma Chemica*, 2012, **4**, 2208-2213; (f) K. R. M. Naidu, K. S. Kumar, P. Arulselvan, C. B. Reddy and O. Lasekan, *Arch. Pharm. Chem. Life Sci.* , 2012, **345**, 957-963.

5 O. Seven, S. Polat-Cakir, M. S. Hossain, M. Emrullahoglu and A. S. Demir, *Tetrahedron*, 2011, **67**, 3464-3469.

6 (a) L. Gu, C. Jin and H. Zhang, *New J. Chem.*, 2015, **39**, 1579-1582; (b) X. Li, C. Jin and L. Gu, *J. Org. Chem.* , 2015, **80**, 2443-2447.

7 (a) J. Guin, Q. Wang, M. v. Gemmeren and B. List, *Angew. Chem. Int. Ed.*, 2014, **53**, 1-5; (b) V. Thottempudi and K.-H. Chung, *Bull. Korean Chem. Soc.*, 2008, **29**, 1781-1783; (c) F. Jahani, B. Zamenian, S. Khaksar and M. Tajbakhsh, *Synthesis* 2010, **19**, 3315-3318.

8 (a) Z. Huang, K.-K. A. Wang, J. Lee and W. A. v. d. Donk, *Chem. Sci.*, 2015, **6**, 1282-1287; (b) J. Gao, K.-S. Ju, X. Yu, J. E. Velasquez, S. Mukherjee, Jaeheon Lee, C. Zhao, B. S. Evans, J. R. Doroghazi, W. W. Metcalf and W. A. v. d. Donk, *Angew. Chem. Int. Ed.* , 2014, **53**, 1334-1337.

9 (a) C. G. Screttas, B. R. Steele, M. Micha-Screttas and G. A. Heropoulos, *Org. Lett.*, 2012, **14**, 5680-5683; (b) C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.* , 2013, **135**, 15257-15262; (c) C. Zhang and N. Jiao, *Org. Chem. Front.*, 2014, **1**, 109-112.

10 (a) Y. Nie, R. Xiao, Y. Xu and G. T. Montelione, *Org. Biomol. Chem.*, 2011, **9** 4070-4078; (b) S. D. Burke and G. M. Sametz, *Org. Lett.*, 1999, **1**, 71-74; (c) M. F. Elsebai, S. Kehraus, U. Lindequist, F. Sasse, S. Shaaban, M. Gutschow, M. Josten, H.-G. Sahle and G. M. Konig, *Org. Biomol. Chem.*, 2011, **9**, 802-808; (d) D. J. Wardrop and W. Zhang, *Tetrahedron Lett.* , 2002, **43**, 5389-5391.

11 B. Eftekhari-Sis and M. Zirak, *Chem. Rev.* , 2015, **115**, 151-264.

12 (a) M. Drescher, Y.-F. Li and F. Hammerschmidt, *Tetrahedron* 1995, **51**, 4933-4946; (b) C. Liu, Y. Zhang, Q. Qian, D. Yuan and Y. Yao, *Org. Lett.* , 2014, **16**, 6172-6175.