ChemComm

Hypophosphite Addition to Alkenes Under Solvent-Free and Non-Acidic Aqueous Conditions

Journal:	*ChemComm*
Manuscript ID	CC-COM-12-2021-006831
Article Type:	Communication

SCHOLARONE™
Manuscripts

Please do not adjust margins

COMMUNICATION

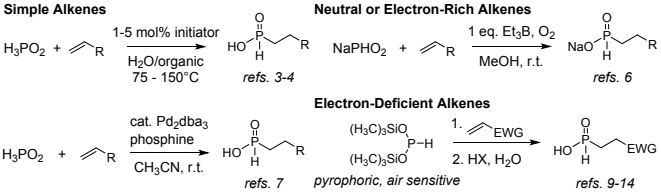
Hypophosphite Addition to Alkenes Under Solvent-Free and Non-Acidic Aqueous Conditions

Zhaorui Huang, Yuxuan Chen and Matthew W. Kanan*

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

DOI: 10.1039/x0xx00000x

Hypophosphite adds to alkenes in high yields under solvent-free conditions at elevated temperature, including α,β-unsaturated carboxylates. The reaction proceeds by a radical mediated pathway. Hypophosphite addition is also effective under non-acidic aqueous conditions employing radical initiators. These methods complement other hypophosphite addition reactions and simplify the synthesis of polyfunctional *H*-phosphinates.



Scheme 1 Current methods for adding $H_2PO_2^-$ to alkenes

The addition of hypophosphorous acid (H_3PO_2) or hypophosphite ($H_2PO_2^-$) to alkenes is an attractive strategy for P–C bond formation because it affords streamlined access to monosubstituted phosphinic acids (*H*-phosphinates), which can be elaborated to a wide range of organophosphorus compounds.[1] In addition, $H_2PO_2^-$ is made by alkaline hydrolysis of white phosphorus (P_4), thereby avoiding the need to prepare the PCl_3 reagent that is commonly employed in organophosphorus synthesis. A number of methods for adding H_3PO_2 or HPO_2^- to alkenes have been developed over the past several decades (**Scheme 1**).[2] Most methods utilize radical-mediated addition of the P–H bond to the alkene. Pioneering studies described alkene addition with H_3PO_2 using peroxide radical initiators under highly acidic conditions at elevated temperatures.[3] Subsequent developments established methods for H_3PO_2 addition at lower temperatures using AIBN as an initiator[4] or using microwave reactors without added initiators.[5] The highly acidic nature and typically forcing conditions of H_3PO_2 additions limits the functional group tolerance of these methods. The use of stoichiometric Et_3B/O_2 as an initiator enables $H_2PO_2^-$ addition at ambient temperature under neutral conditions with a substantially broader functional group tolerance.[6] Pd-catalyzed $H_2PO_2^-$ addition has also been developed as an alternative to radical-mediated processes.[7]

*Department of Chemistry, Stanford University, Stanford, California 94305, United States. * E-mail: mkanan@stanford.edu*
Electronic Supplementary Information (ESI) available: experimental methods, NMR spectra, and supplementary tables are provided. See DOI: 10.1039/x0xx00000x

The available methods for $H_3PO_2/H_2PO_2^-$ addition work well for neutral or electron-rich alkenes and a radical-mediated process is used on large scale in the synthesis of Monopril.[5, 6, 8] However, the addition of H_3PO_2 or $H_2PO_2^-$ to electron-deficient alkenes such as α,β-unsaturated carbonyl compounds is not well established. Instead, the synthesis of *H*-phosphinates from electron-deficient alkenes is commonly performed by nucleophilic addition using an excess of an activated $H_2PO_2^-$ derivative such as bis(trimethylsilyl)-phosphonite (BTSP) (**Scheme 1**).[9-14] While this method often affords high yields (with respect to alkene), BTSP is pyrophoric and its preparation requires hexamethyldisilazane. Alternatively, $H_2PO_2^-$ esters ($H_2P(O)OR$; R=alkyl) undergo nucleophilic addition to α,β-unsaturated carbonyl electrophiles in moderate to good yields,[15-18] but these reagents are difficult to handle and their preparation requires stoichiometric orthoformates or orthosilicates.[19]

Herein we describe radical-mediated addition of alkali $H_2PO_2^-$ to alkenes under either solvent-free or aqueous conditions. The methods are complementary in substrate scope and work well for a variety of α,β-unsaturated carboxylates. The results greatly simplify access to *H*-phosphinates that are currently made using BTSP methodology and provide access to some *H*-phosphinates that cannot be made by previously reported P–H addition methods.

Our studies were motivated by our recent investigations of C–H carboxylation in solvent-free alkali carboxylates at elevated temperature.[20-24] In these reactions, ordinarily non-acidic C–H bonds (pKa>35 in organic solvent) are deprotonated by

Please do not adjust margins

carbonate, yielding carbanions that react with CO_2 to form carboxylates. We originally hypothesized that addition of $H_2PO_2^-$ to α,β-unsaturated carboxylates would proceed under similar conditions by P–H deprotonation and nucleophilic attack on the alkene. While solvent-free $H_2PO_2^-$ addition proved to be effective, the substrate scope and other evidence indicated a radical rather than ionic mechanism. Subsequent investigations translated many of these reactions to aqueous variants.

Solvent-free reactions were first investigated for addition of $H_2PO_2^-$ to maleate to form 2-(oxidohydrophosphoryl)succinate (**1**). Alkali salt mixtures were prepared by treating an aqueous solution of maleic acid and H_3PO_2 with alkali carbonate (M_2CO_3) and evaporating to dryness. Reactions were performed by simply heating these salt mixtures under N_2. A variety of temperatures and reactant ratios were surveyed for salts with different alkali cations (**Table 1** and **Table S1**). Heating a mixture of cesium maleate, CsH_2PO_2, and Cs_2CO_3 in a 1:2:0.2 ratio at 190 °C for 14 h resulted in 93% yield of **1** (determined by quantitative NMR). The reaction mixture was initially a colorless, viscous liquid at 190 °C and transformed into a translucent solid over the course of the reaction. The mass balance was composed primarily of unreacted $H_2PO_2^-$ and small amounts of formate, phosphonate, succinate, and 2,2'-(oxidophosphoryl)disuccinate. Good yields were also obtained with K^+ and Na^+, although optimized performance with these cations required 210 °C and 4 equiv. of $H_2PO_2^-$. In contrast to Cs^+, the reaction mixture with K^+ ions was a translucent solid from the beginning and the Na^+ mixture was a white solid. These results suggest that $H_2PO_2^-$ addition can take place in alkali salts even without bulk melting, although these reactions may be proceeding in microscopic molten domains.

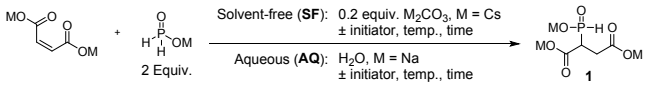
Investigation of the effects of additives revealed a substantial rate increase upon addition of nitroxyl radicals (**Table 1**, entries 4-7). At 120 °C in the absence of an additive, only 14% yield was observed after 3 h. Adding 0.05 to 1 mol% of cesium 4-carboxy-TEMPO increased the yield to 44–84% (entries 5 and 6). Control experiments using cesium piperidine-4-carboxylate demonstrated that the nitroxyl radical functionality is required for the rate enhancement. While nitroxyl radicals are often used to trap radical intermediates, they can also serve as a radical initiator by adding to alkenes.[25, 26] The rate enhancement observed upon addition of 4-carboxy-TEMPO suggests that $H_2PO_2^-$ addition in solvent-free media proceeds by a radical-mediated pathway. The product distributions observed with other substrates provided further evidence for a radical mechanism (see below).

Given the high yields under solvent-free conditions, we hypothesized that selective $H_2PO_2^-$ addition to maleate would be possible under more traditional solution-phase conditions. In the patent literature, the reaction of NaH_2PO_2 with sodium maleate in the presence of peroxide initiators was reported to form a mixture of products derived from P–H addition, alkene dimerization, and oxidation.[27] To target selective formation of **1**, we evaluated different ratios of $H_2PO_2^-$ to maleate and lower initiator loadings. Remarkably, with a 2:1 ratio of NaH_2PO_2 to sodium maleate and 1 mol% $Na_2S_2O_8$ as an initiator, **1** was produced in 94% yield after 10 min in refluxing H_2O (**Table 1**, entry 8). A yield of 95% was obtained at 80 °C after a 2 h reaction. Alternatively, nearly quantitative yield was obtained with 2 mol% sodium 4,4'-azobis(4-cyanovalerate) (NaACVA) as the initiator. Notably, high yields required using fully deprotonated substrates (NaH_2PO_2 and $Na_2CO_2CHCHCO_2$); substantial maleate decomposition was observed if even one Na^+ equivalent was substituted with H^+ (**Table S1**).

Product **1** can be isolated by using a simple methanol washing procedure to remove the remaining $H_2PO_2^-$. The minor impurities in this material are the bis addition product and sodium phosphonate. Alternatively, the protonated form of **1** was isolated with only trace phosphonosuccinic acid impurity by using ion exchange chromatography (see SI). To our knowledge, the only other reported selective synthesis of **1** entails the reaction of dimethyl fumarate with BTSP followed by hydrolysis.[12]

Solvent-free $H_2PO_2^-$ addition was readily extended to a wide variety of substrates (**Figure 1**). The highest yields were generally obtained using Cs^+ salts and four equiv. of $H_2PO_2^-$, but in many cases good yields were also seen with K^+ (**Table S2**). Minimal decomposition or oxidation of excess $H_2PO_2^-$ was observed. For acrylate and methacrylate, solvent-free reactions proceeded in good yield with high regioselectivity for C–P bond formation at the β position (products **2** and **3**). The reaction of cyclopent-1-ene-1-carboxylate yielded the β addition product (**4**) with an 1.5:1 diastereomeric ratio (dr) in favor of the thermodynamically preferred *trans* isomer when performed at 180 °C (**Table S2**). Upon heating the product mixture to 200 °C, the dr increased to 20:1 as a result of deprotonation/reprotonation of the α stereocenter. Crotonate, 3,3-dimethylacrylate, and itaconate reacted in high yields (products **5–7**) but formed three regioisomers (α, β, γ addition products) with relatively low selectivity. The additional γ regioisomer likely arises from base-catalyzed alkene isomerization prior to $H_2PO_2^-$ addition.

Table 1 $H_2PO_2^-$ Addition to Maleate Under Solvent-Free or Aqueous Conditions

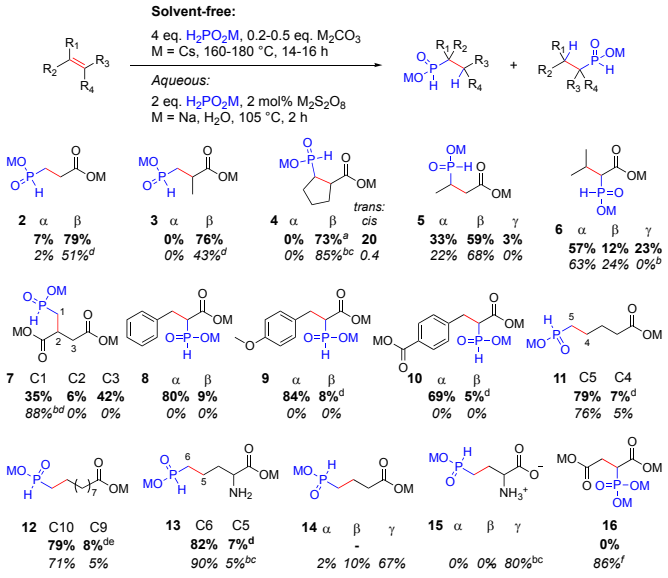


Entry	Cond.	Initiator	Initiator (mol%)	Temp. (°C)	Time (h)	Yield[a] (%)
1	**SF**	none	—	190	14	93
2[b]	**SF**	none	—	210	16	84
3[c]	**SF**	none	—	210	15	79
4	**SF**	none	—	120	3	14
5	**SF**	4-TEMPO-CO_2^-	0.05	120	3	44
6	**SF**	4-TEMPO-CO_2^-	1	120	3	84
7	**SF**	4-Piperidine-CO_2^-	0.2	120	3	13
8	**AQ**	$Na_2S_2O_8$	1	reflux	10 min	94
9	**AQ**	$Na_2S_2O_8$	1	80	2	95
10	**AQ**	NaACVA	2	reflux	2	99
11	**AQ**	none	—	reflux	2	0

[a] Yields determined by quantitative NMR. [b] M = K, 4 equiv. MH_2PO_2, 0.5 equiv. M_2CO_3. [c] M = Na, 4 equiv. MH_2PO_2, 0.5 equiv. M_2CO_3.

This journal is © The Royal Society of Chemistry 20xx

Figure 1 Substrate scope of $H_2PO_2^-$ addition



Yields determined by quantitative ^1H and ^{31}P NMR. Product drawn is the major regioisomer and corresponds to the product number. Yields of major and minor regioisomers are indicated. [a] 180 °C for 14 h followed by 200 °C for 10 h. [b] 10 mol % of $Na_2S_2O_8$, added in two portions. [c] 4 equiv. of MH_2PO_2. [d] 8 equiv. of MH_2PO_2. [e] 220 °C. [f] HPO_3M_2 was used instead of H_2PO_2M, 2 h, 50 mol% of $Na_2S_2O_8$ added over 1.5 hours.

Reactions with cinnamate and other β-aryl acrylates showed good yields with high α selectivity to form 2-(oxidohydrophosphoryl)-3-phenylpropanoate and derivatives (**8–10**). Product **8** was isolated in protonated form in 94% purity (remaining 6% is the minor β isomer) by acidification and purification using a C18 column (see SI). One previous study reported the synthesis of **8** (in protonated form) using a radical-mediated addition of BTSP to trimethylsilyl cinnamate.[12] However, the reported NMR data indicates that the compound synthesized was actually the β isomer (see Supplementary Information). To our knowledge, **8–10** have not been prepared previously. More broadly, *H*-phosphinates with carboxylic acid functionality at the α position are rare in the literature, with the exception of 2-hydroxyhydrophosphorylacetic acid and derivatives of **1**.

Unconjugated alkene carboxylates also proved to be good substrates for solvent-free reactions. Both pent-4-enoate and dec-9-enoate reacted in high yield with ~10:1 selectivity for the anti-Markovnikov product (products **11** and **12**). 2-allylglycine reacted in similarly high yield and regioselectivity (product **13**), indicating tolerance to amino functionality. However, addition to vinylacetate resulted in an identical product distribution as addition to crotonate. This result indicates that vinylacetate rapidly isomerizes to crotonate under the reaction conditions, most likely by an acid–base mechanism.

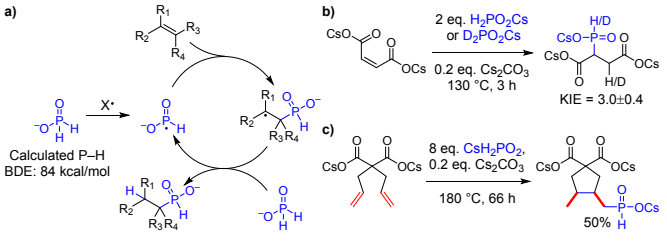
The anti-Markovnikov addition of $H_2PO_2^-$ to unconjugated alkenes strongly supports a radical-mediated mechanism for solvent-free reactions: addition of hypophosphinyl radical to an alkene generates a C-centered radical that abstracts a hydrogen atom from $H_2PO_2^-$ to propagate the radical chain (**Figure 2a**). Using the CCSD(T)//B3LYP level of theory, the calculated bond dissociation enthalpy of the P–H bond in $H_2PO_2^-$ is 84 kcal/mol (**Table S4**). An H/D KIE of 3.0±0.4 was observed for the addition of $H_2PO_2^-$ to maleate at 130 °C (**Figure 2b**). In further support of a radical mechanism, addition to 2,2-diallylmalonate yielded 50% of the cyclopentane *H*-phosphinate product (**Figure 2c**). The origin of radical initiation in the solvent-free reactions is unclear. One possibility for α,β-unsaturated carboxylates is alkene dimerization to form a diradical species.[28-30]

Having established solvent-free conditions, we assessed whether the addition reactions could be performed under aqueous conditions. The reactions were performed using $Na_2S_2O_8$ as the radical initiator, which was either added all at once or portion-wise. Optimal yields were obtained when the reactions were performed at relatively high concentrations (typically 0.3 M in alkene substrate) at 100 °C to refluxing temperature using ≥2 equiv. of NaH_2PO_2.

The aqueous conditions are compared with the solvent-free conditions in **Figure 1**. With acrylate and methacrylate, alkene polymerization tended to outcompete $H_2PO_2^-$ addition. Moderate yields of the addition products were obtained when using 8 equiv. of NaH_2PO_2. Reactions reported in the patent literature suggest that high yields for addition to acrylate could be obtained by using a slow addition protocol.[31] For crotonate and 3,3-dimethylacrylate, high yields were obtained using only 2 equiv. of NaH_2PO_2 and 2–10 mol% $Na_2S_2O_8$. The regioselectivities were comparable to the solvent-free reactions except for the absence of the γ addition product for 3,3-dimethylacrylate because the alkene is not susceptible to isomerization under aqueous conditions. The reaction of cyclopent-1-ene-1-carboxylate with 4 equiv. of NaH_2PO_2 proceeded in 85% yield of the β addition product as a 2:1 mixture of *cis*:*trans*, indicating that stereoisomerization of the addition product is not possible under the aqueous reaction conditions. For itaconate, which formed a complex mixture of products in the solvent-free reaction, the aqueous reaction with 8 equiv. of NaH_2PO_2 yielded 2-(hydroxyphosphinyl)methyl) succinate as the sole mono-addition product in 88% yield. The product was separated from excess $H_2PO_2^-$ by methanol washing (see SI).

Terminal alkene carboxylates were also good substrates using the aqueous conditions, with similar yields and selectivities as the solvent-free conditions for products **11**-**13**. In contrast to solvent-free conditions, selective addition to the

Figure 2 Solvent-free $H_2PO_2^-$ addition mechanistic studies



a) Proposed radical chain mechanism and calculated P–H BDE; X• represents a radical initiator. **b)** Kinetic isotope effect for addition of $H_2PO_2^-$ to maleate in solvent-free reaction. **c)** Addition of $H_2PO_2^-$ to 2,2-diallylmalonate.

terminal position of vinyl acetate to form 4-(oxidohydrophosphoryl)butanoate (**14**) was achieved under aqueous conditions. Addition to 2-vinylglycine resulted in 2-amino-4(oxidohydrophosphoryl)butanoate (**15**) in 80% yield with no detectable addition to the β position. Isomerization of 2-vinylglycine was avoided by using the zwitterion form. Although H_3PO_2 addition to terminal alkenes is well known, our results show that $H_2PO_2^-$ addition proceeds cleanly without highly acidic conditions or stoichiometric radical sources.

Surprisingly, aqueous reactions with cinnamate substrates failed to produce addition products in any appreciable yield. Some decomposition was observed, but the majority of the starting materials were recovered (**Table S3**). The contrast between solvent-free and aqueous conditions for cinnamate, and the absence of prior syntheses of **8–10**, suggests that solvent-free media can enable radical-mediated transformations that are very difficult to achieve in solution, complementing the unique acid–base chemistry in solvent-free media that underlies carbonate-promoted C–H carboxylation.

Finally, we assessed whether the methods described here are applicable to phosphite (HPO_3^{2-}). The addition of HPO_3^{2-} to maleate to form 2-phosphonatosuccinate (**16**) did not occur under any solvent-free conditions surveyed, but proceeded under aqueous conditions. Optimal results required 0.5 equiv. of $Na_2S_2O_8$ added over 1.5 h. While there a several methods to add dialkyl phosphite to electron-deficient alkenes,[32] to the best of our knowledge, this is the only example of addition of alkali phosphite to alkene carboxylate.

In conclusion, the addition of $H_2PO_2^-$ to alkene carboxylates using solvent-free or non-acidic aqueous conditions provides efficient access to polyfunctional *H*-phosphinates. These methods are particularly useful for addition to α,β-unsaturated carboxylates because the available alternatives require pre-activation of $H_2PO_2^-$ and super-stoichiometric toxic reagents. The non-acidic aqueous conditions are more convenient and scalable than the solvent-free conditions. For cinnamates, however, aqueous conditions failed completely whereas solvent-free reactions proceeded in good yields with the opposite regioselectivity observed for other α,β-unsaturated substrates, providing unique access to 2-(hydroxyphosphinyl)-3-aryl propanoates. All of the experimental evidence is consistent with a radical mediated mechanism under solvent-free reaction conditions. The ability to perform radical-mediated alkene addition reactions in neat alkali salts warrants a broader exploration of radical pathways in these media.

This work was supported by the Office of Naval Research (N00014-18-1-2659). We thank Jan Meisner for assistance with BDE calculations. We thank Stephen Lynch for assistance with 2D NMR experiments. Mass spectrometry data were collected at the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1. J.-L. Montchamp, *Acc. Chem. Res.*, 2013, **47**, 77-87.
2. J.-L. Montchamp, *J. Organomet. Chem.*, 2005, **690**, 2388-2406.
3. E. E. Nifant'ev, R. K. Magdeeva and N. P. Shchepet'eva, *J. Gen. Chem. USSR*, 1980, **50**, 1416.
4. D. S. Karanewsky, M. C. Badia, D. W. Cushman, J. M. DeForrest, T. Dejneka, M. J. Loots, M. G. Perri, E. W. Petrillo Jr. and J. R. Powell, *J. Med. Chem.*, 1988, **31**, 204-212.
5. P. Troupa, G. Katsiouleri and S. Vassiliou, *Synlett*, 2015, **26**, 2714-2719.
6. S. Deprèle and J.-L. Montchamp, *J. Org. Chem.*, 2001, **66**, 6745-6755.
7. S. Deprele and J.-L. Montchamp, *J. Am. Chem. Soc.*, 2002, **124**, 9386-9387.
8. N. G. Anderson, M. L. Coradetti, J. A. Cronin, M. L. Davies, M. B. Gardineer, A. S. Kotnis, D. A. Lust and V. A. Palaniswamy, *Organic Process Research & Development*, 1997, **1**, 315-319.
9. E. Andrew Boyd, M. Corless, K. James and A. C. Regan, *Tet. Lett.*, 1990, **31**, 2933-2936.
10. M. Matziari and A. Yiotakis, *Org. Lett.*, 2005, **7**, 4049-4052.
11. Y. Feng and J. K. Coward, *J. Med. Chem.*, 2006, **49**, 770-788.
12. A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Heteroat. Chem.,* 2008, **19**, 418-428.
13. J. Notni, P. Hermann, J. Havlíčková, J. Kotek, V. Kubíček, J. Plutnar, N. Loktionova, P. J. Riss, F. Rösch and I. Lukeš, *Chem. Eur. J.*, 2010, **16**, 7174-7185.
14. M. Jiajun, Y. Junxiao, H. Yawen and C. Ke, *J. Mater. Chem.*, 2012, **22**, 2007-2017.
15. L. Maier, *Helv. Chim. Acta*, 1973, **56**, 489-491.
16. S. D. Lindell and R. M. Turner, *Tet. Lett.*, 1990, **31**, 5381-5384.
17. M. Försterová, I. Svobodová, P. Lubal, P. Táborský, J. Kotek, P. Hermann and I. Lukeš, *Dalt. Trans.*, 2007, 535-549.
18. P. Řezanka, V. Kubíček, P. Hermann and I. Lukeš, *Synthesis*, 2008, **2008**, 1431-1435.
19. S. Deprèle and J.-L. Montchamp, *J. Organomet. Chem.*, 2002, **643**, 154-163.
20. A. Banerjee, G. R. Dick, T. Yoshino and M. W. Kanan, *Nature*, 2016, **531**, 215-219.
21. G. R. Dick, A. D. Frankhouser, A. Banerjee and M. W. Kanan, *Green Chem.*, 2017, **19**, 2966-2972.
22. A. Banerjee and M. W. Kanan, *ACS Cent. Sci.*, 2018, **4**, 606-613.
23. D. J. Xiao, E. D. Chant, A. D. Frankhouser, Y. Chen, A. Yau, N. M. Washton and M. W. Kanan, *Nat. Chem*, 2019.
24. A. W. Lankenau and M. W. Kanan, *Chem. Sci.,* 2020, **11**, 248-252.
25. S. Coseri and K. U. Ingold, *Org. Lett.*, 2004, **6**, 1641-1643.
26. S. Coseri, G. D. Mendenhall and K. U. Ingold, *J. Org. Chem.*, 2005, **70**, 4629-4636.
27. Gardner, R. R., Scheper, W. M., Sivik, M. R. & Arredondo, V. M. U.S. Patent No. 7,018,422, 2006.
28. V. R. P. Verneker and R. Vasanthakumari, *J. Polym. Sci. Pol. Chem.*, 1983, **21**, 1657-1664.
29. S. Srinivasan, M. W. Lee, M. C. Grady, M. Soroush and A. M. Rappe, *J. Phys.Chem. A*, 2009, **113**, 10787-10794.
30. S. Srinivasan, M. W. Lee, M. C. Grady, M. Soroush and A. M. Rappe, *J. Phys. Chem. A*, 2010, **114**, 7975-7983.
31. W. M. Huerth, W. K. Huerth and H. B. Kerpen, US Patent No. 8,097,753, 2012.
32. T.-Z. Huang, T. Chen, Y. Saga and L.-B. Han, *Tetrahedron*, 2017, **73**, 7085-7093.

This journal is © The Royal Society of Chemistry 20xx