

## EDGE ARTICLE

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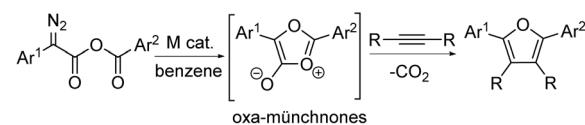
## Introduction

1,3-Dipolar cycloaddition reactions offer a powerful approach to construct five-membered ring products.<sup>1</sup> A prominent application of these systems is in the synthesis of nitrogen-containing heterocycles, such as the prototypical click reaction between substituted azides and alkynes to form triazoles.<sup>2</sup> Less nitrogen-rich heterocycles can also be assembled with other 1,3-dipoles, such as pyrroles (from *münchnones*), pyrazoles (from *sydnone*s), and related systems.<sup>3,4</sup> This breadth is driven in part by the availability of stabilized nitrogen-based 1,3-dipoles of use in cycloaddition, many of which were developed in the pioneering work of Huisgen.<sup>1</sup> In contrast, the use of oxygen-containing 1,3-dipoles to form oxygen-heterocycles, while viable, is much less prevalent. Heterocycles such as furans are important in pharmaceutically relevant structures, natural products, electronic materials, and as building blocks in organic synthesis.<sup>5–8</sup> Unfortunately, 1,3-dipoles of utility in furan synthesis are often less stable and more challenging to form in a general fashion than their nitrogen analogues. For example, oxygen variants of *münchnones* are known (Fig. 1a),<sup>9</sup> but are labile, have limited structural diversity, and importantly, are often formed from substituted diazo precursors that must themselves be synthesized. Carbonyl ylides can also allow access to partially reduced furan derivatives, but they are unstable intermediates available from synthetic diazo precursors or activated epoxide ring

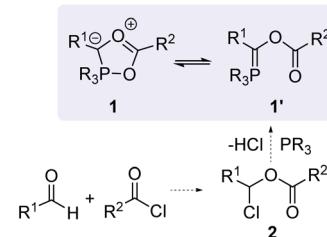
opening.<sup>10</sup> Furans are instead typically generated by more classical cyclization methods, such as the Paal–Knorr synthesis, substitutions on pre-formed furans, or more recently developed metal catalyzed cyclization or coupling reactions.<sup>11,12</sup> While all these methods are effective, they often require the initial generation of one or more substrates incorporating the correct substituents, which adds steps to the synthesis, creates waste and can limit their ease of generalization.

In considering methods to efficiently synthesize furans, we questioned if this might be enabled by forming a new 1,3-

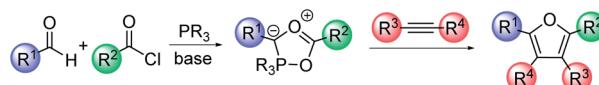
## a. 1,3-Dipolar Cycloaddition and Furan Synthesis



## b. Ester Substituted Wittig-Ylides and their Potential 1,3-Dipole Tautomer



## c. This Work: Modular Synthesis of 1,3-Dipole 1 and Furans



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Fig. 1 Cycloaddition approaches to furan derivatives and design of a new phosphorus-based 1,3-dipolar cycloaddition reagent.

dipole: the phosphorus-containing **1** (Fig. 1b). Several phosphine-mediated syntheses of furans have recently been described, including systems employing intramolecular Wittig-reactions with alkyne, acylating agent and/or aldehyde substrates, although these typically require the use of  $\alpha,\beta$ -unsaturated esters or pre-synthesized cyclization substrates.<sup>13</sup> **1** could offer a 1,3-dipolar cycloaddition route to these products with the ability to tune all four substituents and incorporate various alkyne or alkene dipolarophiles. **1** is formally a cyclized variant of a Wittig-type ylide **1'**, and while appearing complex, could be accessible by the reaction of phosphines, acid chlorides and aldehydes (*via* acyl oxonium salts **2**). We have recently reported the nitrogen version of these 1,3-dipoles prepared with imines for use in cycloaddition.<sup>14,15</sup> However, the formation of the oxygen-based dipole **1** presents several challenges. First, aldehydes are weak nucleophiles and do not readily react with acyl chlorides:<sup>16</sup> a critical first step in this transformation. Indeed, aldehydes are better known for their electrophilic reactivity and could instead undergo a direct reaction with the phosphorus reagent.<sup>17</sup> Even more intrinsic to this chemistry, the generation of this 1,3-dipole requires the unknown cyclization of **1'** to **1**, which would presumably be disfavored with the weakly chelating ester substituent. Nevertheless, previous studies have shown that the angle strain at the phosphorus center can be effective in favoring cyclization to generate a five-coordinate phosphorus,<sup>14c</sup> which led us to question if such a system might also allow the generation of this oxygen-based 1,3-dipolar cycloaddition reagent (**1**). We describe here our studies towards such a system. These studies demonstrate that the coupling of aldehydes, acylating agents and the correctly substituted phosphine can afford a multicomponent synthesis of a new class of 1,3-dipoles (Fig. 1c). Combining the formation of **1** with *in situ* 1,3-dipolar cycloaddition opens a modular synthesis of polysubstituted furans from three available reagents: aldehydes, acyl chlorides and alkynes.

## Results and discussion

Our initial studies toward this system involved the reaction of benzoyl halide, *p*-tolualdehyde, and (catechyl)PPh followed by the NEt<sup>i</sup>Pr<sub>2</sub> base. In order to test for the formation of **1a**, the electron deficient alkyne dimethylacetylenedicarboxylate (DMAD) was added in a subsequent step as a 1,3-dipolar cycloaddition substrate. Attempts at this reaction with benzoyl chloride led to no observable furan product under various conditions (*e.g.* Table 1, entry 1, see ESI Table S1† for full details). One possibility for the lack of reactivity may be slow coupling of the aldehyde with the acyl chloride, which typically requires the use of Lewis acid catalysts to activate the acyl chloride.<sup>18</sup> However, the analogous reaction with added AlCl<sub>3</sub> (entry 2) or more electrophilic benzoyl bromide or benzoyl iodide (entry 3) led to similar results, as did the generation of these acyl halides *in situ* (entries 4 and 5). It is known that aldehydes themselves can react with phosphites or phosphonites (*i.e.* the Abramov reaction),<sup>17</sup> which could also inhibit the synthetic sequence. To block this possibility, the aldehyde was first combined with an *in situ* generated benzoyl iodide,

Table 1 Development of 1,3-dipole **1** and alkyne cycloaddition<sup>a</sup>

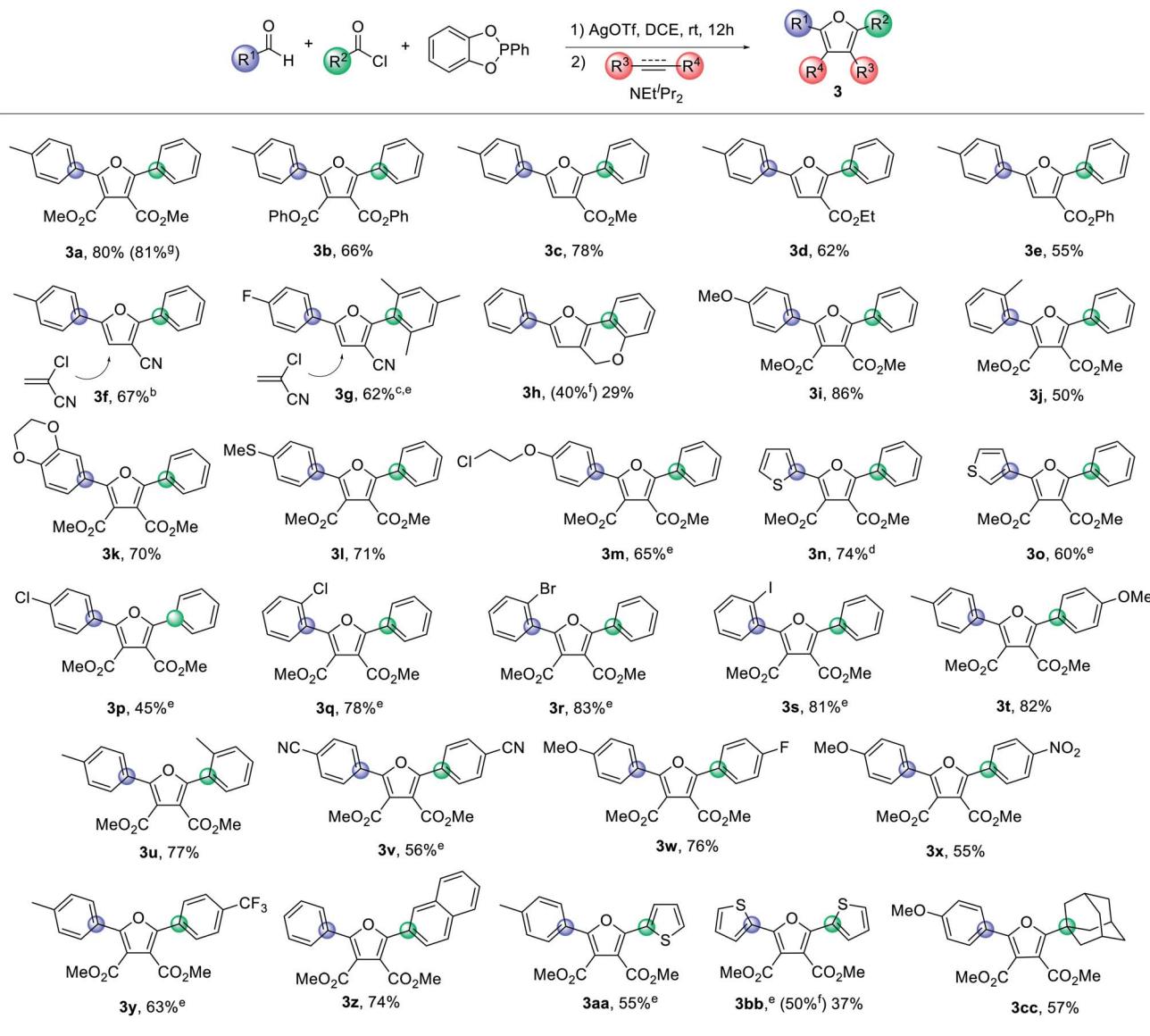
Entry	X	MX'	PR <sub>3</sub>	% <b>3a</b> <sup>c</sup>
1	Cl	—	PhP(catechyl)	—
2	Cl	AlCl <sub>3</sub>	PhP(catechyl)	—
3	Br or I	—	PhP(catechyl)	—
4	Cl	TMSBr	PhP(catechyl)	—
5	Cl	NaI	PhP(catechyl)	—
6 <sup>b</sup>	Cl	NaI	PhP(catechyl)	32
7 <sup>b</sup>	Br	—	PhP(catechyl)	45
8 <sup>b</sup>	I	—	PhP(catechyl)	70
9 <sup>d</sup>	Cl	AgOTf	PhP(catechyl)	80
10 <sup>d,e</sup>	Cl	AgOTf	PhP(catechyl)	87
11 <sup>d</sup>	Cl	AgOTf	PPh <sub>3</sub>	—
12 <sup>d</sup>	Cl	AgOTf	PCy <sub>3</sub>	—
13 <sup>d</sup>	Cl	AgOTf	P(OCH <sub>2</sub> CF <sub>3</sub> ) <sub>3</sub>	—
14 <sup>d</sup>	Cl	AgOTf	(PhO)P(catechyl)	8
15 <sup>d,e,f</sup>	Cl	AgOTf	P(OPh) <sub>3</sub>	55 (48) <sup>g</sup>

<sup>a</sup> 0.12 mmol acyl halide, 0.1 mmol aldehyde, 0.12 mmol PR<sub>3</sub>, 1 ml MeCN, and then 0.15 mmol MX' for 12 h, followed by dimethyl acetylene dicarboxylate (21 mg, 0.15 mmol) and NEt<sup>i</sup>Pr<sub>2</sub> (19 mg, 0.15 mmol) for 1 h. <sup>b</sup> Acyl halide, MX', and aldehyde in 1 ml CD<sub>3</sub>CN for 12 h, followed by the addition of PR<sub>3</sub>. <sup>c</sup> NMR yields *vs.* an internal standard. <sup>d</sup> In 1,2-dichloroethane. <sup>e</sup> 0.10 mmol AgOTf. <sup>f</sup> 2 h reaction with alkyne. <sup>g</sup> Yield after 1 h.

followed by the addition of PhP(catechyl) and then DMAD and a base. We were pleased to find that furan **3a** could now be observed in low yield (entry 6). The use of pre-formed benzoyl bromide or iodide further improves the yield of furan, with the latter now generating furan in 70% yield (entries 7 and 8).

While these results were encouraging, the stepwise addition of reagents adds a layer of complexity to the overall synthesis. In addition, the procedure was found to be sensitive to substrates and reaction times, and change in the acyl halide or aldehyde led to drastically different results. We therefore probed alternative ways to access the 1,3-dipole. One option is to generate a more potent acylating agent that might react with the aldehyde more readily than the phosphonite. After examining various conditions (see Table S1†), it was found that this can be accomplished by the simple addition of AgOTf. Thus, the one pot reaction of benzoyl chloride, aldehyde and PhP(catechyl) in the presence of AgOTf, which presumably forms an electrophilic acyl triflate intermediate,<sup>19</sup> can allow the formation of furan **3a** in high yield upon DMAD and base addition (entry 9). Performing the reaction with equimolar AgOTf, which prevents the formation of excess acyl triflate, further increases the reaction efficiency (entry 10).<sup>20</sup> As expected, the specific phosphorus reagent plays a key role in the reaction. For example, more electron rich phosphines such as PPh<sub>3</sub> or PCy<sub>3</sub> also react with aldehyde, acyl chloride and AgOTf. However, upon addition of a base and alkyne, these do not lead to cycloaddition to form furans, presumably reflecting the poor ability of these more



Table 2 Substrate diversity of tri and tetrasubstituted furan synthesis<sup>a</sup>

<sup>a</sup> 0.24 mmol of acyl chloride, 0.2 mmol of aldehyde and PhP(catechyl) (52 mg, 0.24 mmol) in 1 ml of 1,2-dichloroethane, followed by AgOTf (62 mg, 0.24 mmol) for 12 h, then alkyne (0.30 mmol) and NEt<sup>3</sup>Pr<sub>2</sub> (39 mg, 0.30 mmol), 1 h. Isolated yields. <sup>b</sup> NEt<sup>3</sup>Pr<sub>2</sub> (65 mg, 0.50 mmol) at 80°C for 12 h.

<sup>c</sup> NEt<sup>3</sup>Pr<sub>2</sub> (65 mg, 0.50 mmol), 100°C for 72 h. <sup>d</sup> Stirred for only 1 h after AgOTf addition. <sup>e</sup> Acyl chloride and AgOTf pre-mixed for 2 h before adding aldehyde and PhP(catechyl). <sup>f</sup> NMR yield vs. the internal standard of hexamethyl benzene. <sup>g</sup> Reaction on the 1.0 mmol scale.

electron rich phosphines to cyclize to a 1,3-dipolar form (entries 11 and 12). Moving to more electron poor phosphites such as P(OPh)<sub>3</sub> or P(OCH<sub>2</sub>CF<sub>3</sub>)<sub>3</sub> leads to diminished furan yields relative to PhP(catechyl) as well, arising in this case from a sluggish initial reaction of these phosphorus reagents with the aldehyde/acylating agent (entries 13 and 14), or slower subsequent cycloaddition reactivity (entry 15). Together, these results are consistent with the role of the moderate nucleophilicity of PhP(catechyl) in allowing the reaction with an *in situ* generated oxonium salt, together with that of the angle strain of the catechyl unit in favoring the formation of a five-coordinate phosphorus needed to access a 1,3-dipole (*vide infra*).<sup>21</sup>

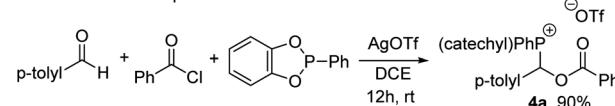
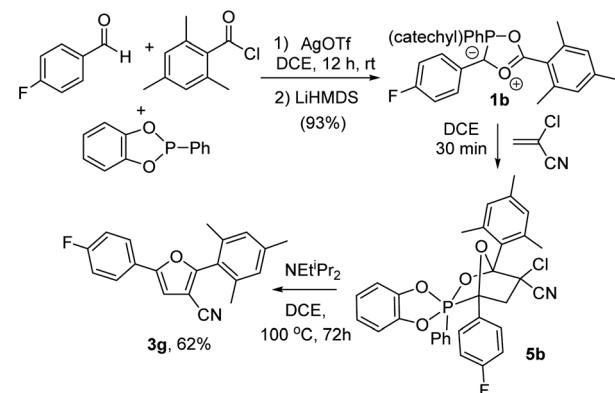
Combining these optimized conditions with the availability of acyl chlorides, aldehydes and alkynes provides a straightforward pathway to synthesize a range of furan products (Table 2). For example, various electron poor dipolarophiles can be used in cycloaddition with 1 as a method to modulate the 3,4-substituents on the furan core. Of note, unsymmetrical dipolarophiles (3c-g) lead to a single product, where the electron withdrawing unit is directed away from the former aldehyde carbon. The latter is consistent with the localization of negative charge on this carbon in the 1,3-dipole, which, together with the large PR<sub>3</sub> unit, directs cycloaddition regioselectivity.<sup>21</sup> More electron rich alkynes, such as 1-hexyne or phenyl acetylene, do



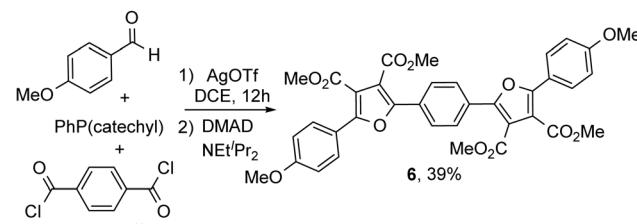
not react with **1**. However, tethering the alkyne to the aldehyde can allow this cycloaddition as well to form the polycyclic furan **3h** in moderate yield. A variety of aromatic aldehydes can be employed in the reaction, including those with either electron donating (**3i–3m**) or withdrawing groups (**3p–3s**), as well as those with meta and ortho-substitution (**3j**, **3k**, **3q–3s**). The aromatic substituents can be replaced with heteroaromatic units, such as from 3- or 2-thiophenyl aldehyde (**3n**, **3o**). The acid chloride displays similar structural flexibility in proceeding with electron donating (**3t–3u**), electron withdrawing (**3v–3y**), *ortho*- (**3u**) or even very large mesityl (**3g**) substituents, as well as with extended conjugation (**3z**). Thiophenyl acid chloride can also be employed (**3aa**), and, when used with thiophenyl aldehyde, offers access to the alternating,  $\pi$ -conjugated **3bb**. Alternatively, the use of cyano-substituted substrates generates **3v**, a precursor to derivatives of the antimicrobial furamide.<sup>22</sup> Nucleophilic heterocycles such as pyridines or pyrroles are not compatible with the electrophilic reaction conditions, nor are simple alkyl substituents on the acid chloride or aldehyde, presumably due to their  $\alpha$ -deprotonation. However, the tertiary alkyl adamantyl acid chloride (**3cc**) is a viable substrate. The reaction can also be carried out on the 1 mmol scale with similar yields (*e.g.* **3a**). Together, this offers a modular approach to access an array of substituted furans with the independent tuning of each substituent.

We next turned our attention to probing the structure of the phosphorus-based cycloaddition reagent formed in this system. Insight into the first step in the reaction can be obtained by monitoring the coupling of benzoyl chloride, *p*-tolualdehyde and PhP(catechyl) in the presence of AgOTf by  $^1\text{H}$  NMR analysis, which shows the formation of a new product (**4a**) in near quantitative yield. This compound can be precipitated from the mixture by addition of pentane, and has been characterized to be the cationic phosphonium salt shown (Fig. 2a). Of note,  $^1\text{H}$  NMR analysis shows the expected resonances for aromatic residues and the  $\alpha$ -methylene hydrogen coupled to phosphorus ( $\delta$  6.82 ppm,  $J_{\text{P}-\text{H}} = 4.5$  Hz), as well as the expected phosphorus signal in  $^{31}\text{P}$  NMR ( $\delta$  24.3 ppm).<sup>14,23</sup> The addition of the  $\text{EtN}^i\text{Pr}_2$  base at  $-35^\circ\text{C}$  to **4a** without a dipolarophile present led to the formation of a complex mixture of unidentifiable products, including PhP(catechyl)P=O, suggesting that the putative 1,3-dipole generated here is unstable. However, the stability of this intermediate can be enhanced by incorporating a sterically encumbered mesityl substituent on the acid chloride together with an electron deficient 4-fluorobenzaldehyde. The generation of this product by deprotonation with the LiHMDS base at room temperature leads to the formation of a bright red product **1b** in 93% yield (Fig. 2b). Of note, the *in situ*  $^{31}\text{P}$  NMR spectra show an upfield shift of the phosphorus in **1b** ( $\delta$  8.3 ppm) from the phosphonium salt **4b** ( $\delta$  23.5 ppm). This is consistent with the generation of a 5-coordinate phosphorus, although it is not as shielded as previously noted for a phospha-münchnone ( $\delta$  *ca.*  $-17$  ppm).<sup>14a,c</sup> In addition,  $^{13}\text{C}$  NMR data reveal that the carbonyl unit ( $\delta$  170.3 ppm) is close to the typical region for esters, although with coupling to phosphorus ( $J_{\text{C}-\text{P}} = 4.7$  Hz). Together, these data suggest that the interaction between phosphorus and the ester oxygen is weak, and does not

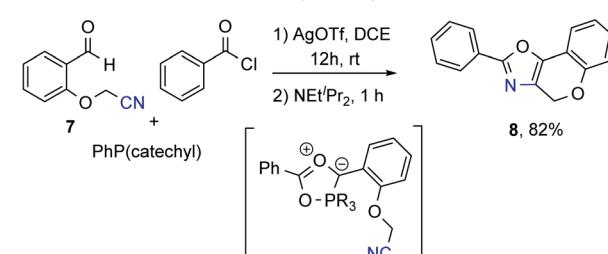
## a. Formation of Phosphonium Salt Intermediate

b. Generation and Trapping of Phosphorus 1,3-Dipole **1**Fig. 2 Characterization of the phosphorus-containing 1,3-dipole **1**.

## a. One pot synthesis of polysubstituted arene/furan oligomer



## b. Formation of fused 1,3-oxazoles by nitrile cycloaddition

Fig. 3 Synthesis of oligomeric furans and oxazoles via 1,3-dipolar cycloaddition with **1**.

significantly perturb the carbonyl unit. Nevertheless, the ability of **1b** to react as a 1,3-dipole can be seen in its reaction with 1,1-chlorocyanooethylene, which leads to the formation of what appear to be two isomeric compounds, as determined by *in situ*  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR data.<sup>24</sup> One of these can be isolated by chromatography and has been characterized as the bicyclic adduct shown in Fig. 2b. Of note,  $^{31}\text{P}$  NMR analysis of **5b** shows a signal at  $-11.3$  ppm, consistent with a five-coordinate phosphorus. The two diastereotopic methylene protons of the former alkene at  $\delta$  3.57 and 3.45 ppm are upfield from chlorocyanooethylene, as expected for cycloaddition, and show now strong coupling to phosphorus ( $J_{\text{H-P}} = 67.3$  Hz and 54.3 Hz), while  $^{13}\text{C}$  NMR analysis shows a strong upfield shift of the



former carbonyl unit to  $\delta$  109.8 ppm. NOE spectra also show the phosphorus phenyl substituent oriented near the *p*-fluorophenyl group, and away from the catechyl in the rigid bicyclic structure. All other NMR and HRMS data are consistent with the structure shown. Heating the 1,3-dipolar cycloaddition adduct **5b** in the presence of a base leads to furan in 62% overall yield, demonstrating the intermediacy of 1,3-dipole **1b**, and the cycloadduct **5b**, in furan synthesis.

Finally, the ability to generate the 1,3-dipole **1** in one pot from available reagents makes it straightforward to access new products. As an illustration, performing the reaction with available terephthaloyl chloride can allow the modular assembly of the novel oligomeric **6** in a one pot reaction incorporating an alternating and  $\pi$ -conjugated arene and furan heterocycles (Fig. 3a). Alternatively, other heterocycles can be generated by cycloaddition of new dipolarophiles. The latter can be seen with nitriles. The nitrile-tethered aldehyde **7** can be formed by O-alkylation of salicylaldehyde. The reaction of this aldehyde with benzoyl chloride and PhP(catechyl) to generate the 1,3-dipole leads to rapid cycloaddition to form the fused-ring oxazole **8** in two steps from available reagents (Fig. 3b). This represents what is to our knowledge a unique example of nitrile 1,3-dipolar cycloaddition to form oxazoles, and suggests that these 1,3-dipoles could prove to be of general utility in heterocycle formation.

## Conclusions

In conclusion, we have described a modular method to construct furans from aldehydes, acyl chlorides and alkynes. This transformation proceeds *via* the formation of a new class of 1,3-dipoles, the phosphorus-containing **1**. The latter is generated in a one pot reaction of aldehydes, acid chlorides and PhP(catechyl), and undergoes rapid and regioselective 1,3-dipolar cycloaddition with alkynes to assemble an array of substituted furans with control over each substituent. Considering the utility of 1,3-dipolar cycloaddition reactions, we anticipate that the ability to readily form these oxygen-based 1,3-dipoles should offer efficient access to a range of oxygen-containing heterocyclic products.

## Data availability

All experimental data are available in the ESI.<sup>†</sup>

## Author contribution

H.E. and C.Z. performed the research and data analysis described in the paper and conceived the ideas with B.A.A. B.A.A., H.E. and C.Z. prepared the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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