

# The Tetraethylphosphorodiamidate (OP(O)(NEt<sub>2</sub>)<sub>2</sub>) Directed Metalation Group (DMG). Directed *ortho* and Lateral Metalation and the Phospha Anionic Fries Rearrangement

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 $\bigcirc$  ur studies on the directed *ortho* metalation (DoM) reaction<sup>1</sup> have established the O-carbamate (Figure 1A)



Figure 1. Selected O-based directed metalation groups (DMGs).

as the strongest in the directed metalation group (DMG) hierarchy, <sup>1a,2,3</sup> and this class of substrates have gained considerable value in methodology and target-oriented synthesis.<sup>4</sup> Their synthetic utility is fortified by the fact that aryl *O*-carbamates undergo the anionic *ortho* Fries rearrangement (AoF) to salicylamides<sup>4b,c,k</sup> and that, after DoM chemistry, DMG conversion to the corresponding phenol derivatives may be performed via mild Schwartz reagent reduction.<sup>5</sup> The DoM strategy received considerable impetus with the development of Suzuki–Miyaura and Kumada–Corriu cross-coupling methodologies for the *O*CONR<sub>2</sub> and the *O*SO<sub>2</sub>NR<sub>2</sub> (Figure 1B) DMGs, which consolidates a proactive DoM-cross coupling nexus.<sup>6</sup> At the same time, the Ni-catalyzed hydro-

decarbamoylation of aryl O-carbamates earns this group a latent DMG status.  $^{\rm 1e}$ 

In the course of our search toward new oxygen-based DMGs,<sup>4b</sup> we noted the relevant metalation/AoF studies that had been performed by Melvin<sup>7</sup> and Cambie<sup>8</sup> on aryl phosphates [Ar-OP(O)(OEt)<sub>2</sub>] (Figure 1C), by Modro<sup>9</sup> on the phenyl OP(O)(N(Me)Ph)<sub>2</sub> system, by Dhawan and Redmore<sup>10</sup> on aryl 1,2- and 1,4-diphosphates, and by Watanabe<sup>11</sup> on the aryl phosphorodiamidate system (Figure 1D), in which the OP(O)(NMe<sub>2</sub>)<sub>2</sub> DMG was shown to also be a strong lateral metalation director. Lastly, Buono reported on the anionic phospha-Fries rearrangement of chiral phosphorodiamidates as a route to chiral phosphoric diamides,<sup>12</sup> and Knochel revisited Watanabe's DoM chemistry of the aryl OP(O)(NMe<sub>2</sub>)<sub>2</sub> system using the bimetallic base, (TMP)<sub>2</sub>Mg·LiCl.<sup>13</sup> These results speak to the current activity and the future potential of this area of anionic aromatic chemistry.

Stimulated by the above studies, we investigated the aryl tetraethylphosphorodiamidates  $(Ar-OP(O)(NEt_2)_2)$  system (Figure 1, 1-Li) as a potentially suitable P-based DMG for the development of more useful DoM, phospha AoF rearrangement, and lateral metalation reactions than heretofore established. Herein, we report the results of our work, and, in the sequel,<sup>14</sup> we describe cross coupling, remote anionic phospha-Fries rearrangement reactions of aryl  $OP(O)(NEt_2)_2$ 

Received: January 10, 2020



derivatives, and the synthesis of tricyclic oxaphosphorine oxides, of potential interest as ligands in catalytic reactions. Combined, these studies offer a contribution to the synthesis of organophosphorus compounds<sup>15</sup> and place the OP(O)-(NEt<sub>2</sub>)<sub>2</sub> group in the repertoire of *O*-based DMGs for renewed evaluation in synthetic carbanionic chemistry of aromatic molecules.

In initiating our work, the known beneficial steric effects of several CONR<sub>2</sub> DMGs<sup>16-18</sup> guided our choice of the bulkier  $OP(O)(NEt_2)_2$  DMG, which was expected to display a higher stability at metalation temperatures above -105 °C used by Watanabe on aryl  $OP(O)(NMe_2)_2^{11}$  systems. Thus, the phosphorodiamidate **1a** (Ar = C<sub>6</sub>H<sub>5</sub>, Scheme 1), readily

Scheme 1. DoM and Electrophile Quench of Aryl Tetraethylphosphorodiamidates 1a-1e



prepared by the reaction of phenol with commercially available tetraethylphosphorodiamidic chloride  $(ClPO(NEt_2)_2)^{19}$  in quantitative yield, was subjected to the standard s-BuLi/ THF/-78 °C/1 h protocol, followed by treatment with TMSCl. Gratifyingly, the 2-silylated phosphorodiamidate 4a was obtained in 84% yield without any evidence of the formation of the phospha AoF rearrangement product. Generalization of the electrophile quench reaction followed to yield derivatives 4b-4h in very good yields, with the exception of the boronic acid quench product, which was deemed to be unstable and therefore was isolated as the pinacolate 4g. Good yields of products 5a and 5b were also obtained from the ortho-metalation of o-methoxy phenyl phosphorodiamidate 1b (Ar = 2-OMe- $C_6H_4$ ), followed by TMSCl and MeI quench, respectively. To demonstrate the synthetically very useful synergism of meta-related OMe DMGs to in-between metalation,<sup>20</sup> we studied the *meta*methoxy phenyl phosphorodiamidate 1c (Ar = 3-OMe-C<sub>6</sub>H<sub>4</sub>). In this event, under these metalation conditions, followed by MeI and I<sub>2</sub> quench, compound 1c afforded exclusively 6a and **6b**, respectively, in high yields.

As expected from earlier work on naphthyl systems,<sup>21</sup> a similar outcome was observed for substrate 1d (Ar = 2-Naph) for which preferential metalation and electrophile quench occurred at the C<sub>3</sub>-position to afford compounds 7a, 7b, and 7c in good yields (see the Supporting Information). As a final example, double metalation-iodine quench of a BINOL-derived diphosphorodiamidate 1e (Ar = 1,1'-bi(2-Naph)) led to the formation of 8 albeit in low yield, together with mono-and di-iodinated products, thereby suffering in the isolation and purification procedures (see the Supporting Information).

To probe the temperature for the onset of the phospha AoF rearrangement, a solution of metalated 1a (R = H) was allowed to warm to rt and led to the formation of 2a in 95% yield (see Scheme 2). The synergistic metalation of 1c (R = 3-OMe),



Scheme 2. DoM and Phospha AoF Rearrangement of Aryl Tetraethylphosphorodiamidates 1a, 1c, 4d, and 1d

followed by phospha A*o*F rearrangement, gave 2b in very good yield. A 2-fold excess base led to a very effective phospha A*o*F on 4d (R = 2-Me), without intervention of potentially competing lateral metalation (vide infra). However, the 2- $OP(O)(NEt_2)_2$  naphthyl derivative 1d gave 3 in moderate yield (56%) with recovery of starting material (40%). Thus, the small enhancement of bulk from  $OP(O)(NEt_2)_2^{11}$  to  $OP(O)(NEt_2)_2$  tunes the stability of this DMG to approximately match that of  $OCONEt_2$  (Figure 1A), which undergoes the A*o*F rearrangement at approximately -50 °C.<sup>4c</sup>

We next explored the competitive DoM and lateral metalation capabilities of the  $OP(O)(NEt_2)_2$  DMG in the context of other previously studied DMGs. Watanabe and coworkers had shown that various substituted *ortho*-tolyl  $OP(O)(NMe_2)_2$  substrates 9 undergo highly selective lateral metalation and subsequent electrophile quench, even at -105 °C, to afford the corresponding *ortho*-alkyl substituted products 10 (E = various) in good yields (see Scheme 3).<sup>11a</sup>





Since neither the work of Watanabe<sup>11</sup> nor the work of Melvin<sup>7</sup> and Dhawan<sup>10</sup> had reported the vinylogous phospha AoF rearrangement on tetramethylphosphorodiamidate **9** (R = H), we also tested this reaction by initial deprotonation with LDA at -78 °C, followed by warming to 0 °C. The observation of an LDA-mediated cleavage to give phenol **11** in high yield predicts that the more sterically demanding tetraethylphosphorodiamidate group was required for the desired reaction to occur.

As a result, we turned our attention to the discovery of the lateral metalation reaction of compound 5b and, for comparison, that of phosphate 12 (see Scheme 4). Both



Tetraethylphosphorodiamidate 5b and Diethyl Phosphate 12



reactions are analogues of the lateral metalation-carbamoyl migration process of *o*-tolyl *O*-carbamates previously established in our laboratories.<sup>4</sup><sup>e</sup> In the event, both **12** and **5b** underwent metalation-migration but with strikingly different migratory aptitudes. Thus, *ortho*-tolyl phosphate **12** (R = OEt) underwent a 1,4- $O \rightarrow C$  phosphoryl migration smoothly to

give compound 14 in high yield, while the corresponding phosphorodiamidate **5b**, under the same conditions (*s*-BuLi/THF/-78 °C), underwent a sluggish reaction at rt and, even upon heating to 60 °C, did not give product 13. This was surprising because lateral metalation of **5b** was demonstrated by a CD<sub>3</sub>OD quench experiment at -78 °C to give **5b**' in quantitative yield with >95% deuterium incorporation. However, change of base to a mixture of LDA/TMEDA (3 equiv) at 25 °C in hexanes effected the migration reaction to give 13 in 87% yield. Parenthetically, the benzylic phosphonamide 13 and phosphonate 14 constitute potentially useful intermediates in Corey's protocol for the preparation of olefins.<sup>22</sup>

A more-complex reaction ensued for the prototype orthotolyl phosphorodiamidate 4d, which led us to perform a series of metalation-deuteration experiments on compound 4d, as a function of base concentration, time, and temperature of reaction (see Table 1). A brief reaction time (to approximate kinetic control conditions) with 1.1 equiv of s-BuLi yielded incomplete (50%) but mostly lateral metalation of 4d (15:16 = 50:3; see Table 1, entry 1), a preference also observed when the reaction proceeded extensively using a standard metalation time (15:16 = 70:23; see Table 1, entry 2). Nevertheless, while 4B undergoes phospha AoF rearrangement to 18 upon warming to rt (Table 1, entry 3), the major anion 4C, in agreement with the behavior of **5b**, as discussed earlier, escapes the similar vinylogous process and is reprotonated to 4d (Table 1, entry 3). When using 2.1 equiv of s-BuLi (Table 1, entries 4 and 5), the formation of dianion 4A may be expected but cannot be proved, because its dideuterated product resulting from CD<sub>3</sub>OD quench cannot be distinguished from a mixture of 15 and 16.<sup>23a</sup> The product 17 (Table 1, entry 4) is unlikely the result of initial anionic phospha-Fries rearrangement, followed by lateral metalation-deuteration, because the acidity of the benzylic hydrogens would be decreased by phenolate resonance. Instead, its presence supports the formation of the dianion species  $4A^{23b}$ . The absence of 4d

Table 1. DoM and Phospha-Fries Rearrangement of ortho-Tolyl Tetraethylphosphorodiamidate 4d



	Conditio	ons			Product Ratio <sup>b</sup>				
No.	s-BuLi <sup>a</sup> (equiv)	time	quench	Ε	15	16	17	18	4d
1	1.1	7 min	$CD_3OD^c$	D	50	3	-	_	47
2	1.1	1 h	$CD_3OD^c$	D	70	23	-	-	7
3	1.1	$1 h \rightarrow rt$	$NH_4Cl^d$	Н	-	-	-	20	80
4	2.1	$1 h \rightarrow rt$	$CD_3OD^d$	D	-	_	72	28	-
5	2.1	$1~h \rightarrow  rt$	$NH_4Cl^d$	Н	-	-	-	95 <sup>e</sup>	-

<sup>a</sup>s-BuLi added at -78 °C. <sup>b</sup>Ratios measured by <sup>1</sup>H NMR. <sup>c</sup>Quench at -78 °C. <sup>d</sup>Quench at rt. <sup>e</sup>75% yield of isolated product.

(Table 1, entry 5) in the product mixtures suggests that, when using 2.1 equiv of *s*-BuLi, the initial mixture of **4B** and **4C** undergoes further *ortho*-metalation to afford a mixture of monoanions and dianions **4A** and **4B**, both species undergoing phospha-AoF rearrangement as the temperature increases, forming the same product **18**.

We also addressed the important question of the DoM reactivity hierarchical positions of the powerful  $OCONEt_2$  DMG<sup>1a,4b</sup> vs  $OP(O)(NEt_2)_2$  DMG. An intermolecular competition experiment was performed by metalating an equimolar mixture of **1a** and **19** with only half the stoichiometric amount of *s*-BuLi (Scheme 5). After stirring

#### Scheme 5. Comparison of DMG Strengths: Phosphorodiamidate 1a versus O-Carbamate 19



for 1 h at -78 °C, the reaction mixture was quenched at -78 °C with excess of CD<sub>3</sub>OD, allowed to warm to 0 °C, and the products were separated and analyzed to reveal 1a' (50% yield, >95%  $d_1$ -content), 19' (38% yield, >95%  $d_1$ -content) and 6% of the AoF rearrangement product 20 (see the Supporting Information for details). With the appropriate caveat of interpretation of competition experiments,<sup>1a</sup> the outcome of this experiment implies not only that the OP(O)(NEt<sub>2</sub>)<sub>2</sub> stands in close rank to the OCONEt<sub>2</sub> group as the most powerful DMG<sup>3c</sup> but also that the former is more stable than the latter toward the AoF rearrangement reaction.<sup>24</sup>

In conclusion, the power of the  $OPO(NEt_2)_2$  DMG in DoM chemistry has been demonstrated by the development of a general and efficient synthesis of ortho-substituted aryl Ophosphorodiamidates (see Scheme 1). The choice of the  $OPO(NEt_2)_2$  over the corresponding  $OPO(NMe_2)_2$  DMG allows the use of the more practical typical DoM temperatures  $(-78 \ ^{\circ}\text{C})$  over the previously reported  $-105 \ ^{\circ}\text{C}$  conditions. In addition, the phospha-AoF rearrangement leading to orthophosphonic diamide phenol has been established (see Scheme 2). The metalation-deuteration chemistry of ortho-tolyl  $OPO(NEt_2)_2$  derivatives has been studied under a variety of conditions (Table 1) and offers methodology for the synthesis of corresponding contiguously substituted benzyl phosphonic diamides and esters (see Scheme 4). As suggested by intermolecular competition experiments, the directing power of the  $OPO(NEt_2)_2$  group is comparable to that of the OCONEt<sub>2</sub> group (see Scheme 5). The present work, combined with the accompanying study,<sup>14</sup> constitutes a contribution whose value and application to the field of synthetic aromatic organophosphorus chemistry may be anticipated.

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00094.

Full experimental details,  ${}^{1}H$  and  ${}^{13}C$  NMR spectra (PDF)

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#### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We are grateful to NSERC for support under the Discovery Grant program and to Dr. Françoise Sauriol (Department of Chemistry, Queen's University) for NMR expertise.

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(23) (a) Neither <sup>1</sup>H NMR nor MS analysis gave distinguishable peaks for integration, see SI. (b) From the product ratio 17:18 =  $\sim$  2:1, it may be deduced that under 2.0 equiv of *s*-BuLi at -78 °C  $\rightarrow$  rt conditions, substrate is converted to 4A (72%) and 4B (28%) which, since 4A requires double the amount of base, indicates consumption of 1.65 equiv of the original 2.1 equiv of *s*-BuLi.

(24) In concurrence with our results, intermolecular competition experiments at  $-105^{\circ}$ C carried out by Watanabe established that the  $OP(O)(NMe_2)_2$  is approximately three- to four-fold stronger than the OMOM,  $OCONEt_2$  and  $CONEt_2$  DMGs; see refs 13a and 13c.