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Tetraethylphosphorodiamidate-Directed Metalation Group: Directed *Ortho* and Remote Metalation, Cross Coupling, and Remote Phospha Anionic Fries Rearrangement Reactions

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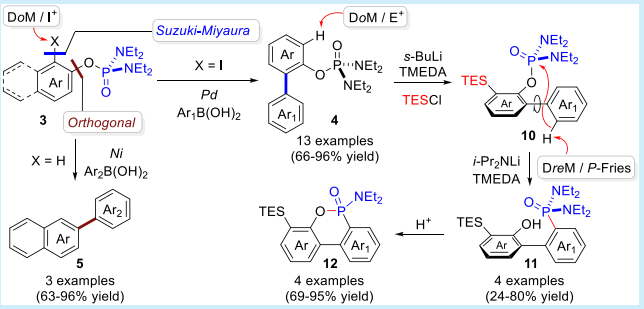
ABSTRACT: The linked directed *ortho* and remote metalation (D*o*M and D*re*M) and cross-coupling reactions of aryl phosphorodiamidates (Ar-*O*P(O)(NEt$_2$)$_2$) is reported. The *o*-iodo and *o*-boronato aryl tetraethylphosphorodiamidates **3**, prepared by D*o*M, undergo orthogonal Ni- and Pd-catalyzed Suzuki−Miyaura cross coupling to furnish biaryls **4** and **5** in good to excellent yields. Silicon group protection of biaryl **4** via D*o*M followed by previously unobserved D*re*M phospha anionic Fries rearrangement affords biaryls **11** which, under acidic conditions, furnish oxaphosphorine oxides **12**.



In our previous paper,[1] we reported on the directed *ortho* metalation (D*o*M) chemistry of the aryl *O*-tetraethylphosphorodiamidate (*O*P(O)(NEt$_2$)$_2$) directed metalation group (DMG) and delineated its scope (Figure 1, **1a**), its anionic

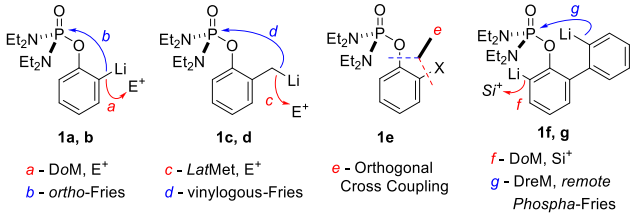


Figure 1. Directed metalation strategies for aryl *O*-tetraethylphosphorodiamidates.

ortho Fries rearrangement (A*o*F, **1b**), and its position in the *ortho*-metalation hierarchy (OCONR$_2$ ≥ *O*P(O)(NEt$_2$)$_2$).[2] Therein, we also evaluated the lateral metalation reaction of the *ortho*-tolyl *O*P(O)(NEt$_2$)$_2$ system (**1c**) and its previously unobserved vinylogous anionic Fries rearrangement (**1d**).[1]

To expand the DMG repertoire which participates in DoM−Name Reaction cross-coupling methodologies,[3,4] we now report on the Suzuki−Miyaura coupling of *o*-iodo aryl-*O*P(O)(NEt$_2$)$_2$ derivatives with aryl boronic acids(**1e**), the orthogonal cross coupling[5] of aryl tetraethylphosphorodiamidate *O*P(O)(NEt$_2$)$_2$compounds (**1e**), and the use of the thereby derived biaryl *O*P(O)(NEt$_2$)$_2$ derivatives in the DreM-induced phospha-Fries rearrangement reaction[6] (**1g**) to afford 2-hydroxy 2′-bisdiethylaminophosphinoyl biaryls (**11**) which are amenable to cyclization to the *P*-amino oxaphosphorine oxides **12** (Scheme 4). Overall, the work allows access to aryl and biaryl tetraethylphosphorodiamidate derivatives of potential value in currently active areas of synthetic chemistry and places the aryl *O*P(O)(NEt$_2$)$_2$ motif into a prominent position in synthetic phosphorus aromatic chemistry.

To initiate the study, the availability of the *o*-iodo and *o*-boronato aryl *O*-tetraethylphosphorodiamidate **3** from our sequel study[1] allowed their examination as cross coupling partners. In the event, a number of biaryls **4** were synthesized via the Suzuki−Miyaura cross-coupling reaction of *o*-iodo aryl phosphorodiamidates **3a** (X = I) with a variety of commercial aryl boronic acids, furnishing the biaryls **4a−g,j−m** in good to excellent yields (Scheme 1). For this cross coupling reaction, SPhos proved to be an exceptional, highly active ligand[7] even allowing the preparation of sterically hindered trisubstituted biaryls such as **4g** (68% yield). Since electron-deficient boronates are known to undergo cross coupling poorly,[8] the ability to invert the coupling partners to obtain high yields of products was demonstrated to provide a welcome synthetic advantage. Given the difficult isolation of **3** (X = B(OH)$_2$) as a boropinacolate, the synthesis of heterobiaryls **4h** and **4i** was accomplished in a one-pot manner. Thus, sequential metalation of **2a** (PhOP(O)(NEt$_2$)$_2$) and quench with B(OMe)$_3$ was followed by cross coupling of the crude boronic acid intermediate **3** (X = B(OH)$_2$) with 3-bromopyridine and *N*-

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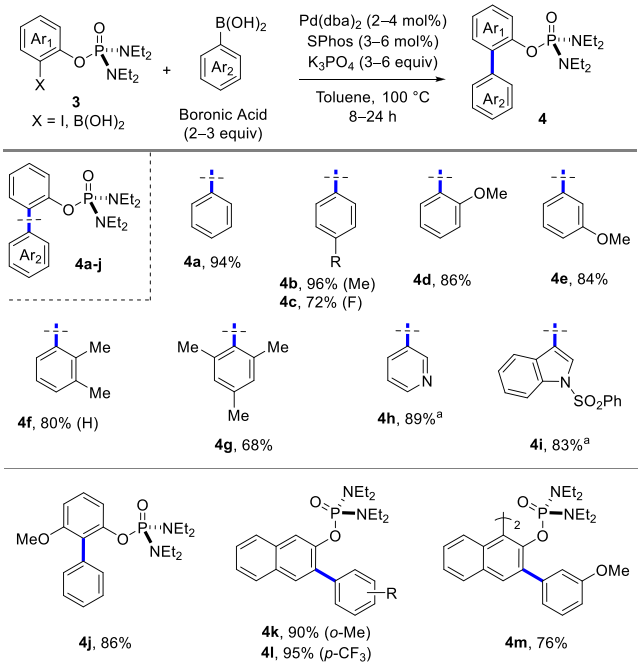
Scheme 1. Cross-Coupling Reactions of Aryl-$OP(O)(NEt_2)_2$ Derivatives with Aryl Boronic Acids



[a]Crude boronic acid (**3**, X = $B(OH)_2$) was used with heteroaryl bromide.

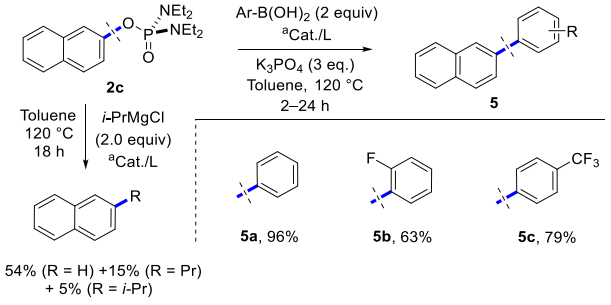
benzenesulphonyl-3-bromoindole to furnish **4h** and **4i**, respectively, in good yields over two steps. Furthermore, the 3,3′-bis-iodo BINOL derivative **3d** was found to undergo smooth cross coupling to produce the bis-arylated product **4m** in good yield. Extension to naphthalenes was successful by the synthesis of the 3-aryl naphthyl derivatives **4k** and **4l** in excellent yields.

Our previous appreciation of the synthetic possibilities unveiled by the resourceful heteroatom based *O*-carbamate,[3a] *O*-thiocarbamate,[9] *O*-sulfamate,[3c] and sulfonamide[3b] DMGs in transition-metal-catalyzed cross coupling reactions encouraged the probe of $OP(O)(NEt_2)_2$ as a cross coupling partner. We chose the naphthyl derivative **2c** for the GC/MS tracking of its reaction products and, in the absence of precedent, screened potential reaction conditions on the basis of the known coupling of the phosphonate ($OPO(OR)_2$) group[10] and our experience with Ni-catalyzed reactions.[3] After failure using these conditions and considerable screening of ligands and solvents, the conditions of Skrydstrup[11] using in situ generated PCy_3 from its fluoroborate salt, toluene as solvent, and recrystallized boronic acids afforded the biaryl products **5a–c** in good yields (Scheme 2).[12]

To extend the previous useful reductive cleavage chemistry of the $OCONEt_2$[3a] and SO_2NR_2[3b] DMGs, the 2-naphthyl $OP(O)(NEt_2)_2$ **2c** was subjected to reaction with the classical *β*-hydride donor, *i*-PrMgCl[13] under $Ni(COD)_2$-catalyzed conditions and afforded naphthalene in a promising 54% yield, together with minor amounts of 2-*n*-propyl- and 2-isopropylnaphthalenes, constituting transfer alkylation and isomerization products, respectively (Scheme 2).[14]

To determine whether biaryl $OP(O)(NEt_2)_2$ could undergo the directed remote metalation (D*re*M) like its *O*-carbamate counterpart,[3] we tested the teraryl **6a** bearing Watanabe's DMG[15] which, due to the 2,6-substitution pattern, cannot

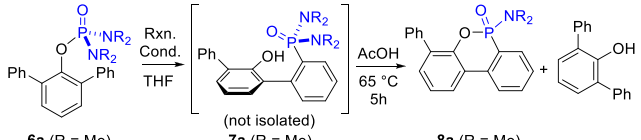
Scheme 2. Suzuki–Miyaura Cross Coupling and Reductive Cleavage of Naphthyl $OP(O)(NEt_2)_2$ Derivative



[a]Cat./L ratio: $Ni(COD)_2$ (5 mol %)/$Cy_3PH{\cdot}BF_4$ (10 mol %).

undergo the competing D*o*M reaction. The initial use of *n*-BuLi and *s*-BuLi (Table 1, entries 1 and 2) led to encouraging

Table 1. Anionic Remote Phospha-Fries Rearrangement of 2,6-Diphenylaryl Phosphorodiamidates 6a and 6b



		reaction conditions		% yield of products		
entry	substrate	base (equiv)	met. temp/time/ at rt (h)	**8a** or **8b**	**9**	**6a** or **6b**
1	**6a**	*n*-BuLi (1.4)	−78 °C/1 h/12 h	52	21	16
2	**6a**	*s*-BuLi (1.4)	−78 °C/2 h/12 h	57	16	15
3	**6a**	*t*-BuLi (1.6)	−78 °C/1 h/8 h	79		
4	**6a**	LiTMP (1.2)	−10 °C/1 h/12 h	34	37	11
5	**6b**	*t*-BuLi (1.2)	−78 °C/1 h/5 h	32		58
6	**6b**	LDA (5.0) /TMEDA (5.0)	−10 °C/0.5 h → reflux (5 h)	71		

results, affording **8a**, through cyclization of crude **7a** during acidic treatment, in addition to considerable amounts of phenol **9** resulting from dephosphorodiamidation. Upon similar treatment with the bulkier *t*-BuLi, **6a** gave product **8a** in good yield without DMG cleavage (entry 3), while the corresponding tetraethyl derivative **6b** underwent reaction sluggishly to give only 32% of cyclization product **8b** (entry 5). These results suggest that the more hindered $P(O)(NEt_2)_2$DMG has a lower migratory aptitude (entries 3 vs 5) presumably due to an incomplete lithiation by bulky *t*-BuLi and/or inappropriate Bürgi–Dunitz angle of approach[16a] of the incipient anion to the $O{-}P(O)(NEt_2)_2$ bond.[16b] The effect of dialkylamide bases was also tested; while **6a** underwent significant DMG cleavage with LiTMP (entry 4), compound **6b** gave a cleaner reaction with LDA/TMEDA and afforded oxaphosphorine oxide **8b** in 71% yield (entry 6).

With these initial results of the DreM phospha-Fries rearrangement in hand, we turned our attention to the potentially more useful substrates **10** in which A*o*F is prevented by a trialkylsilyl substituent. Based on the previous observations that the corresponding *o*-TMS *O*-carbamate derivatives tend to undergo silyl methyl deprotonation followed by A*o*F rearrangement, we chose to install an *o*-

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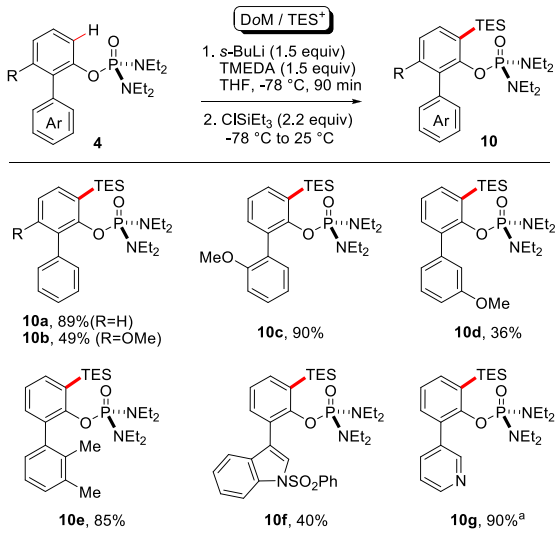
TES substitutent.[17] The TES group was also chosen based on the known ability of bulky groups to favor the equilibrium conformation of the biaryl backbone in which the $OP(O)(NEt_2)_2$ group is oriented at an optimal angle of approach toward the alternate ring, thus promoting the complex induced proximity effect (CIPE)-mediated remote metalation process.[18] Therefore, metalation-silylation of various biaryls **4a−b,d,f,i−k** using *s*-BuLi under the standard conditions was pursued and, to our delight, was successful in producing a series of 2-silylated biaryl phosphorodiamidate derivatives **10a−f** in modest to excellent yields (Scheme 3). Since C-2 and

Scheme 3. DoM-Silylation Reactions of Biaryl $OP(O)(NEt_2)_2$ Derivatives 4



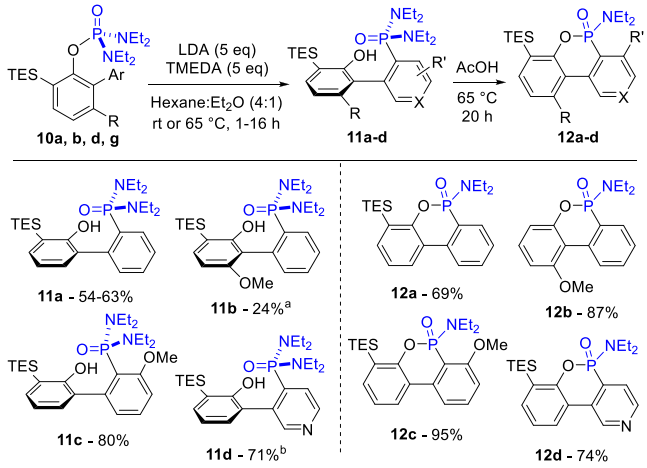
[a]2.8 equiv of LDA used.

C-4 nucleophilic addition of alkyllithium reagents to pyridine represents a well-known general process,[19] the metalation of **4i** was carried out with LDA which, following silylation, resulted in smooth formation of product **10g** in 90% yield.

With the series of biaryls **10** in hand, we were in a position to explore the DreM competence of the $OPO(NEt_2)_2$ DMG. As for the case of the lateral phospha A*o*F rearrangement,[1] DreM reactions of the phosphorodiamidate and phosphate groups have not, to the best of our knowledge, been described.[20]

After considerable experimentation (see SI), the optimized conditions of 5.0 equiv of LDA/TMEDA in a hexane−Et_2O (4:1) mixture for the D*re*M−phospha-Fries rearrangement were established on **10a** to afford product **11a** (60% average yield). These conditions were then applied to substrates **10b**, **10d**, and **10g** to furnish a series of phenolic 2′-(bis-diethylaminophosphinoyl)biaryls **11b**, **11c**, and **11d**, respectively, in good yields (Scheme 4). Optimum conditions varied as a function of the starting material. Thus, as expected on the basis of the D*o*M effect of the methoxy DMG, **11c** was obtained in very good yield (80%). On the other hand, subjecting the 2,5-disubstituted biarylphosphonic diamide **10b** to the standard conditions resulted in the formation of multiple cleavage and desilylation products. However, upon treatment with 10 equiv of LDA, **10b** afforded product **11b** in low yield (24%) together the corresponding desilylated product. In the case of aza-biaryl **10g**, a short reaction time (1 h) at rt (instead of 60 °C) was effective under the optimized conditions to

Scheme 4. DreM−Phospha-Fries Rearrangement of Biaryl $OP(O)(NEt_2)_2$ Derivatives 10



[a]Ten equiv of LDA/TMEDA used; [b]Reaction carried out at rt for 1h.

deliver product **11d** (71% yield) whose structure was established by 2D COSY NMR analysis (see the SI). Upon treatment with acetic acid, compounds **11a−d** underwent smooth cyclization to give the corresponding cyclic biaryl amino-oxaphosphorine oxides **12a−d** in good to quantitative yields. Interestingly, the TES substituent survived the reaction conditions for compounds **12a**, **12c**, and **12d**, thus offering the potential opportunity for further functionalization through *ipso*-electrophile-induced desilylation.[21]

Several of the above experiments invite comment with reference in part to the observations of Collum.[22a] The requirement for a large excess of LDA suggests that the reaction competes with the decomposition of the base. The requirement of excess TMEDA may be attributed to the decomposition of LDA/TMEDA combinations at higher temperatures in the solvent used (hexanes/Et_2O, 4:1).[22b] In accord with this fact, using the noncoordinating hexane solvent led to observed decreased reaction times and requirement for excess base. Collum has observed that additives have a minor effect on yields of product yet significantly enhance the rate of the anionic *ortho* Fries rearrangement of aryl *O*-carbamates.[22c] The observation of higher temperatures favoring the D*re*M phospha anionic Fries process may be rationalized by the increased rotational freedom at the biaryl axis to give a greater population of a planar conformer which would favor the remote metalation.

In conclusion, we have demonstrated two general cross-coupling reactions: the Pd-catalyzed coupling of *o*-iodoaryl phosphorodiamidates **3** with aryl boronic acids to afford biaryl phosphorodiamidates **4** and the Ni-catalyzed cross coupling of naphthyl phosphorodiamidates **2c** with aryl boronic acids to furnish biaryls **5**. Furthermore, we delineated a directed remote metalation (D*re*M) anionic phospha-Fries rearrangement reaction of biaryls **10** leading to the previously unknown biarylphosphonic diamides **11** which undergo cyclization under weakly acidic conditions to the biaryl amino-oxaphosphorine oxides **12**. Although harsh conditions for deprotection of the $OP(O)(NEt_2)_2$ derivatives to the corresponding phenols have been reported,[23] methanolysis to the corresponding phosphonate esters[24] and the conversion of biaryl phosphonic amides and esters to cyclic oxaphosphorine oxides in reaction with Grignard and alkyllithium reagents are

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available, thus offering pursuit of considerable synthetic chemistry in the realm of aryl organophosphorus systems,[2S] in particular, in the design and development of new ligands.[7c] As in previous work from our laboratories,[26] new directions and applications for the construction of complex aromatic and heteroaromatic frameworks, bioactive molecules, and natural products within the combined DoM-cross coupling-DreM conceptual framework may be uncovered.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01123.

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

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Dieter Enders for his immediately recognized SAMP and RAMP reagents, for caring mentorship of students, and for altruism in all forms of interaction.

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