Gold-Catalyzed Alkenylation and Arylation of Phosphorothioates

Urvashi, Sampoorna Mishra, and Nitin T. Patil*

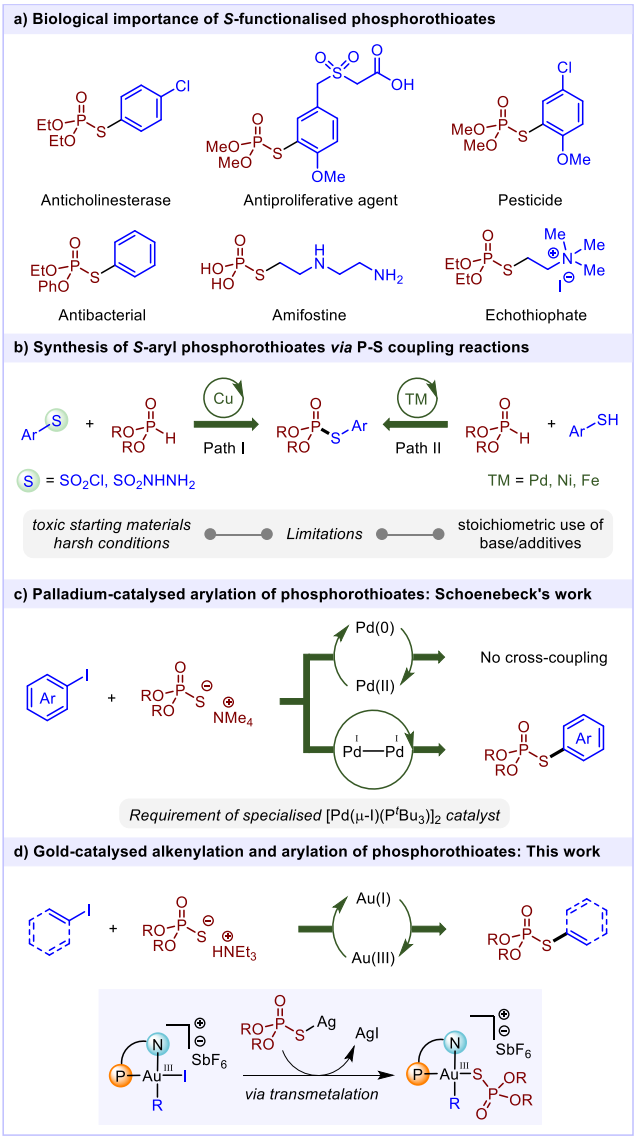
Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal - 462 066, India

ABSTRACT: Reported herein is the gold-catalyzed alkenylation and arylation of phosphorothioates using alkenyl and aryl iodides. The facile transmetalation between Ag-sulfur complex and Au(III) intermediate formed after oxidative addition is the key to the success of this transformation. This methodology operates under mild reaction conditions with catalyst loading as low as 1 mol%, thereby providing an efficient access to biologically active *S*-alkenyl and *S*-aryl phosphorothioates.

Phosphorothioates, a class of compounds with unique chemical structure, have garnered considerable attention for their remarkable biological activities and wide-ranging applications in pharmaceutical and agrochemical industries.[1] For instance, medicines like echothiophate − employed in the treatment of glaucoma,[2] and amifostine − used for cancer chemotherapy,[3] belong to the family of phosphorothioates. The role of phosphorothioates as potent synthetic intermediates further enhances their significance.[4] Especially, *S*-aryl phosphorothioates are well-known for their anticholinesterase, antiproliferative, and antibacterial properties, along with their established role as pesticides (Scheme 1a).[5] Classical methods for synthesizing phosphorothioates are centered around the P-S bond formation through the nucleophilic substitution reactions of $(RO)_2P(O)X$ or R-SX.[6] However, this approach is associated with several drawbacks *viz* the use of toxic and moisture sensitive reagents, harsh reaction conditions and low functional group tolerability. Later, a new approach which employs copper-catalysed reductive coupling of aryl sulfonyl chlorides/aryl sulfonyl hydrazides with H-phosphonates was developed (Scheme 1b, Path I).[7] Nonetheless, the requirement of toxic reagents and harsh reaction conditions such as high temperature and high catalyst loading limits the applicability of this method. Subsequently, the transition metal-catalysed cross-dehydrogenative coupling of aryl thiols with H-phosphonates has emerged as an alternative pathway for obtaining *S*-aryl phosphorothioates (Scheme 1b, Path II).[8]

One of the most appealing strategies to access *S*-functionalised phosphorothioates would be the transition metal-catalysed C(sp^2)-S cross-coupling reaction. Interestingly, while significant strides have been taken in the domain of transition metal-catalyzed C-S cross-coupling reactions,[9] the direct cross-coupling between phosphorothioate salts and organohalides has remained unexplored. In 2019, Schoenebeck and co-workers showed that the cross-coupling of phosphorothioates with aryl iodides could not be accomplished under conventional Pd(0)/Pd(II) redox catalysis. This failure can be attributed to the unfavourable ligand exchange at the Pd(II) center and high barrier for reductive elimination. Rather, the employment of dinuclear Pd(I) catalysis allowed an efficient access to *S*-aryl phosphorothioates through a distinct mechanistic paradigm (Scheme 1c).[10] Nonetheless, since the reaction demands the use of specialised dimer catalyst, there is a need for development of new transition metal-catalysed redox processes for achieving the C(sp^2)-S functionalization of phosphorothioates. Moreover, the alkenylation of phosphorothioates under transition metal catalysis has remained unprecedented, thus necessitating exploration in this direction.

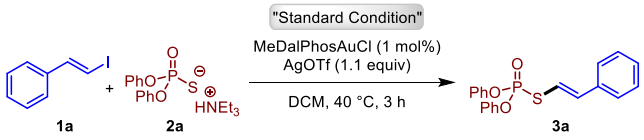
Scheme 1. Transition Metal-Catalysed Synthesis of *S*-Alkenyl/Aryl Phosphorothioates: Known and Present Work



In recent years, ligand-enabled redox gold catalysis has emerged as a promising technique to achieve various cross-coupling reactions.[11] As compared to Pd(0) compplexes, the oxidative addition of Au(I) into C(sp^2)-I bonds poses considerable challenge due to the high redox potential of the Au(I)/Au(III) couple.[12] Accordingly, the reductive elimination

step being the microscopic reverse of oxidative addition, is supposed to be facile from the Au(III) intermediate. With this background, we envisioned that the employment of Au(I)/Au(III) redox catalysis might offer a solution to the challenging reductive elimination of C(sp^2)-SPO(OR)$_2$, thereby providing a straightforward route to obtain *S*-alkenyl/aryl phosphorothioates. One of the major challenges in C-S bond formation under Au(I)/Au(III) catalysis stems from the highly thiophilic nature of gold complexes which may render the Au(I) species catalytically inactive.[13] Another potential challenge would be the transmetalation or ligand exchange processes at the Au(III) center due to the strong nature of the Au-I bond.[14] Banking on the role of silver salt as halide scavenger in ligand-enabled redox gold catalysis,[11] we hypothesized that the presence of silver salt might promote the formation of an Ag-SPO(OR)$_2$ complex (Scheme 1d). The silver complex, thus formed, could undergo transmetalation with the Au(III) intermediate which upon reductive elimination could afford the *S*-alkenyl/aryl phosphorothioates. Herein, for the first time, we report the gold-catalysed cross-coupling reactions of phosphorothioates with alkenyl iodides and aryl iodides to access *S*-alkenyl and *S*-aryl phosphorothioates.[15]

Table 1. Optimization of Reaction Conditions[a,b]

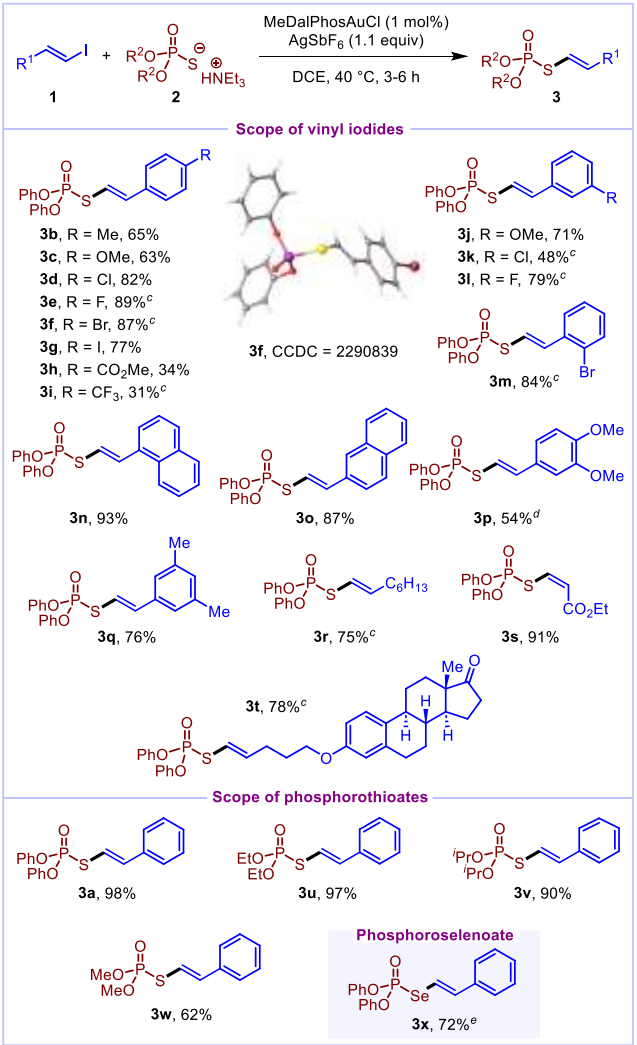


Entry	Deviation from *"Standard condition"*	Yield **3a** (%)[b]
1	none	28
2[c]	Without MeDalPhosAuCl	--
3[c]	Without AgOTf	--
4	1.1 equiv $AgBF_4$	61
5	1.1 equiv $AgSbF_6$	66
6	1.1 equiv $AgNTf_2$	<5
7	1.1 equiv AgOTs	18
8	$AgSbF_6$ and *o*-DCB	83
9	**$AgSbF_6$ and DCE**	**98**
10[c]	$AgSbF_6$ and MeOH	--
11	1 mol% MorDalPhosAuCl, $AgSbF_6$ and DCE	56

[a]Reaction conditions: 0.10 mmol **1a**, 0.10 mmol **2a**, 1 mol% MeDalPhosAuCl, 1.1 equiv AgOTf, DCM (0.1 M), 40 ºC, 3 h. [b]Isolated yields. [c]No Reaction.

We began our reaction development with the use of (2-iodovinyl)benzene **1a** (1.0 equiv) (*E*:*Z* = 97:3) and *O*,*O*-diphenyl phosphorothioate **2a** (1.0 equiv) in presence of 1 mol% MeDalPhosAuCl as catalyst along with AgOTf (1.1 equiv) as the halide scavenger in DCM at 40 °C for 3 h. Pleasingly, the desired product **3a** was obtained in 28% yield (*E*:*Z* = 97:3) (Table 1, entry 1). In an effort to enhance the yield of **3a**, we turned our attention towards the screening of silver salts. To our delight, the use of $AgBF_4$ and $AgSbF_6$ led to an increase in yield (61% and 66%, respectively) (entry 4-5); whereas, other silver salts like $AgNTf_2$ and AgOTs, bearing strongly coordinating counterion, were found to be almost ineffective for this transformation (entry 6-7). This observation suggests that silver salts with non-coordinating counterion are more efficient for this transformation. Subsequently, various solvents like *o*-DCB, DCE, MeOH, $CHCl_3$ and 1,4-dioxane were screened; amongst which, the use of DCE provided an excellent yield of 98% (entry 9).[16] Further, while screening other (P, N)-ligated gold complexes, it was found that MorDalPhosAuCl could also catalyse the reaction giving a 56% yield of the desired product (entry 11).[16]

Scheme 2. Scope of Gold-Catalyzed Alkenylation of Phosphorothioates[a,b]



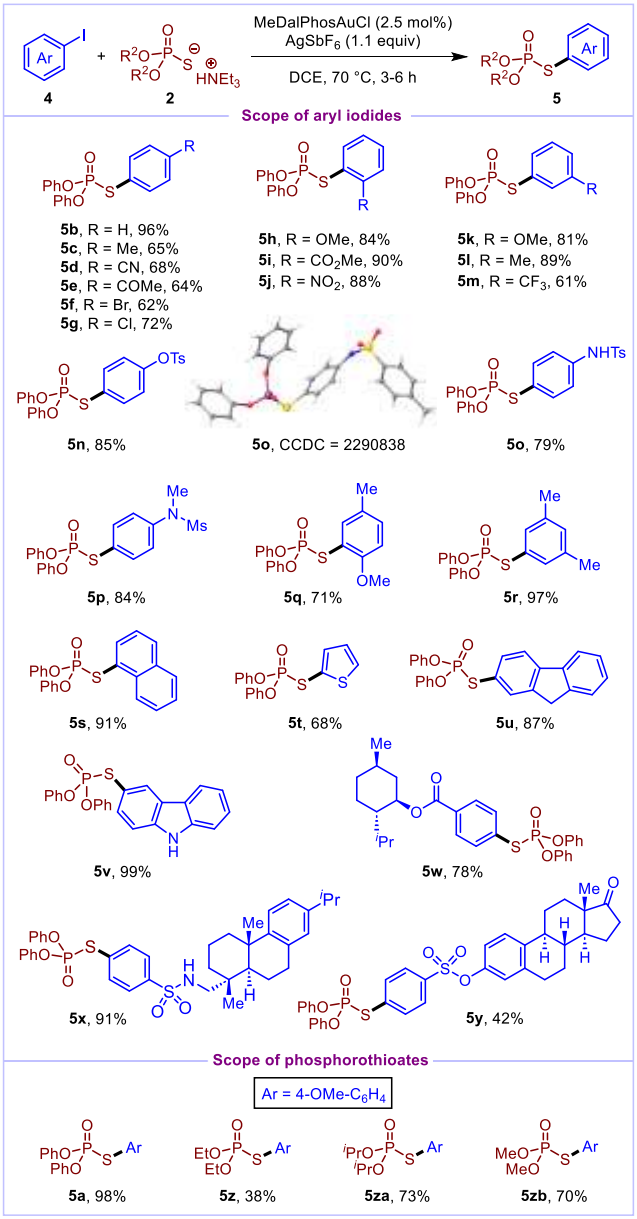
[a]Reaction conditions: 0.20 mmol **1**, 0.20 mmol **2**, 1 mol% MeDalPhosAuCl, 1.1 equiv $AgSbF_6$, DCE (0.1 M), 40 °C, 3-6 h. [b]Isolated yields. [c]Reaction was performed with 2.5 mol% MeDalPhosAuCl at 70 °C for 2 h. [d]Reaction was performed at 30 °C. [e]Reaction was performed with 10 mol% MeDalPhosAuCl at 80 °C.

With the optimized reaction conditions in hand, we turned our attention to explore the scope of alkenyl iodides **1** by treat-

ing it with *O*,*O*-diphenyl phosphorothioate **2a** (Scheme 2). To our delight, several styrenyl-based alkenyl iodides having electron-donating (-OMe, -Me) and electron-withdrawing substituents (-CO_2Me, -CF_3) at *para* position worked well in the reaction to afford the *S*-alkenyl phosphorothioates (**3b**-**3i**) in moderate to good yields (31-89%). Also, *meta* and *ortho* substituted styrenyl iodides reacted to deliver the products (**3j**-**3m**) in 48-84% yields. Notably, the styrenyl iodides bearing iodo, bromo and chloro substituents react in a chemoselective fashion to deliver the products (**3d**, **3f**, **3g**, **3k** and **3m**) in 48-87% yields. Next, naphthyl-based alkenyl iodides (**1n** and **1o**) and disubstituted styrenyl iodides **1p** and **1q** coupled efficiently to give desired products (**3n**-**3q**) in 54-93% yields. Also, octenyl-derived alkenyl iodide **1r** and ethyl-3-iodoacrylate **1s** provided the corresponding products (**3r** and **3s**) with high yields (75% and 91%, respectively). Certainly, the (*Z*)-isomer of **1s** delivers the (*Z*)-isomer of product **3s** selectively. Delightfully, estrone-derived alkenyl iodide **1t** also worked well to afford the product **3t** in 78% yield. Further, we sought to investigate the scope of phosphorothioates **2**. Both *O*,*O*-diphenyl phosphorothioate **2a** and *O*,*O*-dialkyl phosphorothioates (**2u**-**2w**) were found to react well with (2-iodovinyl)benzene **1a** to afford the desired products (**3a**, **3u**-**3w**) in moderate to excellent yields (62-98%). Remarkably, the phosphoroselenoation of alkenyl iodide **1a** could also be achieved by using phosphoroselenoate salt as the coupling partner, resulting in a 72% yield of the *S*-alkenyl phosphoroselenoate **3x**.

In order to establish the generality of this reactivity, we further envisaged the development of arylation of phosphorothioates under Au(I)/Au(III) catalysis. To validate our hypothesis, 4-iodoanisole **4a** (1 equiv), *O*,*O*-diphenyl phosphorothioate **2a** (1 equiv), MeDalPhosAuCl (5 mol%) and $AgSbF_6$ (1.1 equiv) was stirred in DCE at 70 °C for 3 h. Remarkably, the desired *S*-aryl phosphorothioate product **5a** was obtained in an excellent yield of 99%. Next, reducing the catalyst loading to 2.5 mol% did not affect the reaction outcome, resulting in a 98% yield of the product. Since no further optimization of reaction conditions was required, we sought to explore the scope of this transformation. At first, the scope of aryl iodides was investigated by utilising *O*,*O*-diphenyl phosphorothioate **2a** as the model substrate. To our delight, various aryl iodides with electron-donating (-OMe, -Me, -NHTs, -NMeMs) and electron-withdrawing (-CN, -COMe, -CO_2Me, -NO_2, -CF_3) substituents at the *ortho*/*meta*/*para* positions reacted well to deliver the *S*-aryl phosphorothioates (**5b**-**5p**) in 61-96% yields. Notably, aryl iodides bearing halo groups (-Cl, -Br) and pseudohalides (-OTs) were well-tolerated in the reaction to afford the products (**5f**, **5g** and **5n**) in 62-85% yields. Disubstituted aryl iodides (**4q** and **4r**), 1-iodonaphthalene **4s** and 9H-fluorene based aryl iodide **4u** were also well compatible (71-97%) under the optimized reaction conditions. Pleasingly, heteroaromatic scaffolds such as 2-iodothiophene and carbazole based iodoarenes also reacted well to deliver the products **5t** and **5v** in 68% and 99% yields, respectively. Complex natural products (menthol, dehydroabietylamine, and estrone) derived aryl iodides were successfully cross-coupled to deliver the corresponding products (**5w**-**5y**) in moderate to excellent yields (42−91%).

Scheme 3. Scope of Gold-Catalyzed Arylation of Phosphorothioates[a,b]

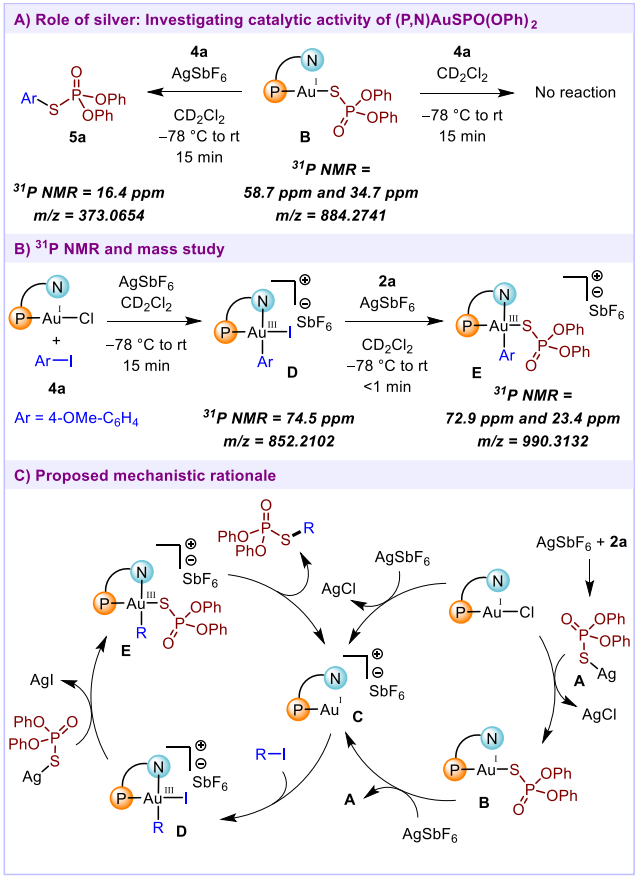


[a]Reaction conditions: 0.20 mmol **4**, 0.20 mmol **2**, 2.5 mol% MeDalPhosAuCl, 1.1 equiv $AgSbF_6$, DCE (0.1 M), 70 °C, 3-6 h. [b]Isolated yields.

Since sulfur compounds are well-known to exhibit strong coordination with gold,[13] the regeneration of active-catalyst is the key for achieving C-S cross-coupling reactivity. In order to gain insights into the reaction mechanism, some control experiments were performed. Initially, to investigate the role of silver salt, $AgSPO(OPh)_2$ complex **A** was formed by treating $AgSbF_6$ and *O*,*O*-diphenyl phosphorothioate **2a** in a 1:1 ratio.[16] The ^{31}P NMR spectra for this compound shows a single peak at 34.5 ppm. Upon addition of 1 equivalent of MeDalPhosAuCl to this mixture, the formation of $Au(I)SPO(OPh)_2$ complex **B** was observed (peaks at 58.7 ppm and 34.7 ppm),

which suggests that the $AgSPO(OPh)_2$ complex **A** is capable of undergoing ligand exchange with MeDalPhosAuCl. Next, we intended to check the catalytic activity of this $Au(I)SPO(OPh)_2$ complex **B** and when the stoichiometric reaction of 4-iodoanisole **4a** with pre-formed complex **B** was performed, no oxidative addition of Au(I) complex with the iodoarene was observed (Scheme 4A). The subsequent addition of 1 equivalent of $AgSbF_6$ led to the generation of the desired product **5a** (16.4 ppm). This indicates the role of silver in the reactivation of the complex **B** to form active cationic Au(I) species for the realization of catalytic reactivity. Further, the formation of Au(III) intermediates **D** and **E** during the reaction was confirmed by ^{31}P NMR and mass spectrometric analysis (Scheme 4B).

Scheme 4. Mechanistic Investigations and Plausible Mechanism



Based on the control experiments and ^{31}P NMR studies, the mechanistic cycle for the cross-coupling of phosphorothioates with organohalides has been proposed as shown in scheme 4C. The reaction of MeDalPhosAuCl with $AgSbF_6$ would generate the active gold catalyst **C**. Alternatively, the $Au(I)SPO(OR)_2$ complex **B** could be formed first, which acts as a catalyst resting state and in the presence of silver salt, this complex **B** would undergo a ligand exchange to generate the active cationic Au(I) complex **C**. Next, in the presence of alkenyl/aryl iodides **1**/**4**, the cationic Au(I) species **C** would undergo oxidative addition to generate the Au(III) intermediate **D** (74.5 ppm) and a subsequent transmetalation between the $AgSPO(OR)_2$ complex **A** and Au(III) intermediate **D** would lead to generation of Au(III) intermediate **E** (72.9 ppm and 23.4 ppm, doublet with J = 10 Hz). Further, a facile reductive elimination from intermediate **E** would afford the desired product **3**/**5** along with the regeneration of active catalyst.

In summary, we have developed the first alkenylation and arylation of phosphorothioates with organohalides *via* $C(sp^2)$-S cross-coupling reaction under Au(I)/Au(III) redox catalysis. This methodology offers a direct access to the biologically relevant *S*-alkenyl and *S*-aryl phosphorothioates at catalyst loading as low as 1 mol%. The mechanistic proposal demonstrates a crucial role of the in-situ formed Ag-sulfur complex, which involves in a transmetalation step essential for the successful realization of this reactivity.

ACKNOWLEDGMENT

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(15) During the final stage of preparation of this manuscript, similar work on gold-catalysed C(sp^2)-S cross-coupling appeared on ChemRxiv from Gagosz and co-workers. Muratov, K.; Zaripov, E.; Berezovski M. V.; Gagosz. F. DFT-guided Development of New Hemilabile (P^N) Ligands for Gold-(I/III) Redox Catalysis: Application to the Thiotosylation of Aryl Iodides. There are considerable differences between our work and Gagosz's work. Hence, the C(sp^2)-S cross-coupling of organohalides with phosphorothioates to achieve S-alkenylation/arylation of

phosphorothioates presented herein is complementary to the work demonstrated by Gagosz and co-workers.

(16) See supporting information for details.