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Gold-catalyzed alkenylation and arylation of phosphorothioates†

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Reported herein is the ligand-enabled gold-catalyzed alkenylation and arylation of phosphorothioates using alkenyl and aryl iodides. Mechanistic studies revealed a crucial role of the *in situ* generated Ag–sulfur complex, which undergoes a facile transmetalation with the Au(III) intermediate, thereby leading to the successful realization of the present reaction. Moreover, for the first time, the alkenylation of phosphoroselenoates under gold redox catalysis has been presented.

Phosphorothioates, a class of compounds with a unique chemical structure, have garnered considerable attention because of 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. As far as transition-metal catalysis is concerned, a new approach which employs copper-catalyzed 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-catalyzed cross-dehydrogenative coupling of aryl thiols with H-phosphonates has also been reported for obtaining *S*-aryl phosphorothioates (Scheme 1b, Path II).[8]

One of the most appealing strategies to access *S*-functionalized phosphorothioates would be transition metal-catalyzed $C(sp^2)$-S cross-coupling reactions. Interestingly, while significant strides have been made in the domain of transition metal-catalyzed C–S cross-coupling reactions,[9] the direct cross-coupling between phosphorothioate salts and organohalides has remained underexplored. 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 (Scheme 1c).[10] This failure can be attributed to the unfavourable ligand exchange at the Pd(II) center and high barrier for reductive elimination, as supported by computational studies. Rather, the employment of dinuclear Pd(I) catalysis allowed an efficient access to *S*-aryl phosphorothioates through a distinct mechanistic paradigm. Clearly, there is a need for development of a new transition metal-catalyzed redox paradigm for achieving the $C(sp^2)$-S functionalization of phosphorothioates with organohalides. Notably, there have been no prior reports on alkenylation of phosphorothioates under transition metal catalysis, emphasizing the need for further development in this field.

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) complexes, the oxidative addition of Au(I) into $C(sp^2)$–I bonds poses a 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 utilizing Au(I)/Au(III) redox catalysis could resolve the challenging reductive elimination of $C(sp^2)$-$SPO(OR)_2$, presenting a direct method for obtaining *S*-alkenyl/aryl phosphorothioates. As far as gold redox catalysis is concerned, a significant hurdle in C–S bond formation arises from the highly thiophilic nature of gold complexes, which may make the Au(I) species catalytically inactive.[13] An additional 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 salts as a halide scavenger in ligand-enabled redox gold catalysis,[11] we hypothesized that the

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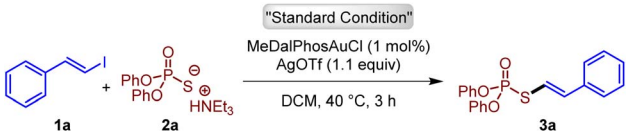
presence of silver salts might promote the formation of an Ag–$SPO(OR)_2$ complex (Scheme 1d). The resulting silver complex could undergo transmetalation with the Au(III) intermediate, subsequently triggering reductive elimination to afford *S*-alkenyl/aryl phosphorothioates. Herein, for the first time, we report the gold-catalyzed cross-coupling reactions of phosphorothioates with alkenyl iodides and aryl iodides to access *S*-alkenyl and *S*-aryl phosphorothioates.[15]

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 the presence of 1 mol% MeDalPhosAuCl as the 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); meanwhile, other silver salts like $AgNTf_2$ and AgOTs, bearing strongly coordinating counterions, were found to be almost ineffective for this transformation (entry 6–7). This observation suggests that silver salts with non-coordinating counterions are more efficient for this transformation. Subsequently, various solvents like *o*-DCB, DCE, MeOH, $CHCl_3$ and 1,4-dioxane were screened; amongst them, the use of DCE provided an excellent yield of 98% (entry 9).[16] Furthermore, 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]

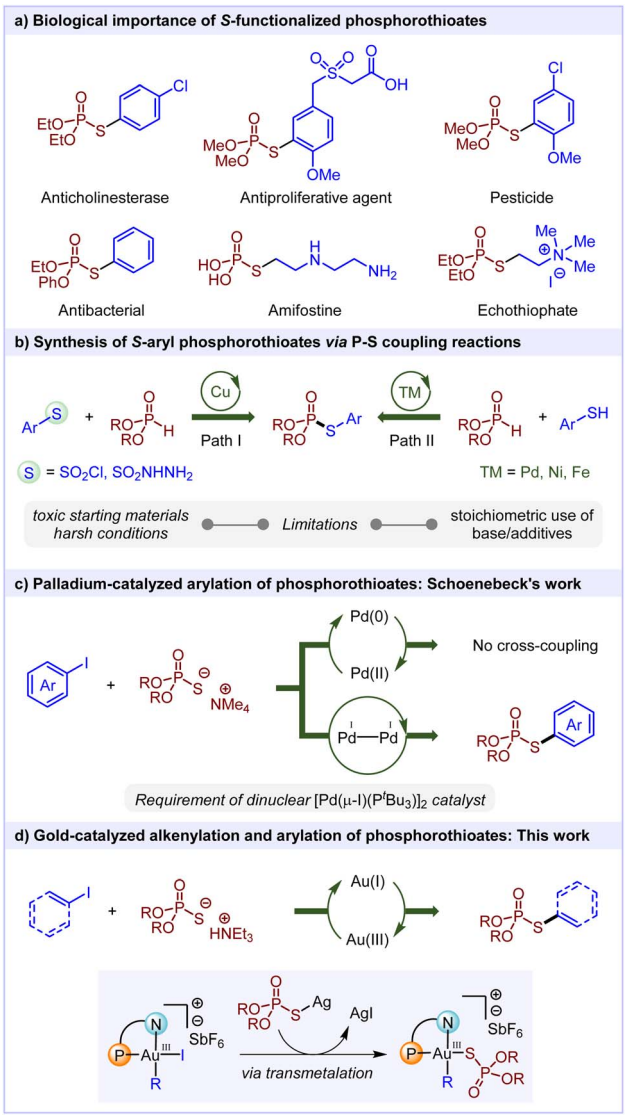
Table 1 Optimization of reaction conditions[a,b]



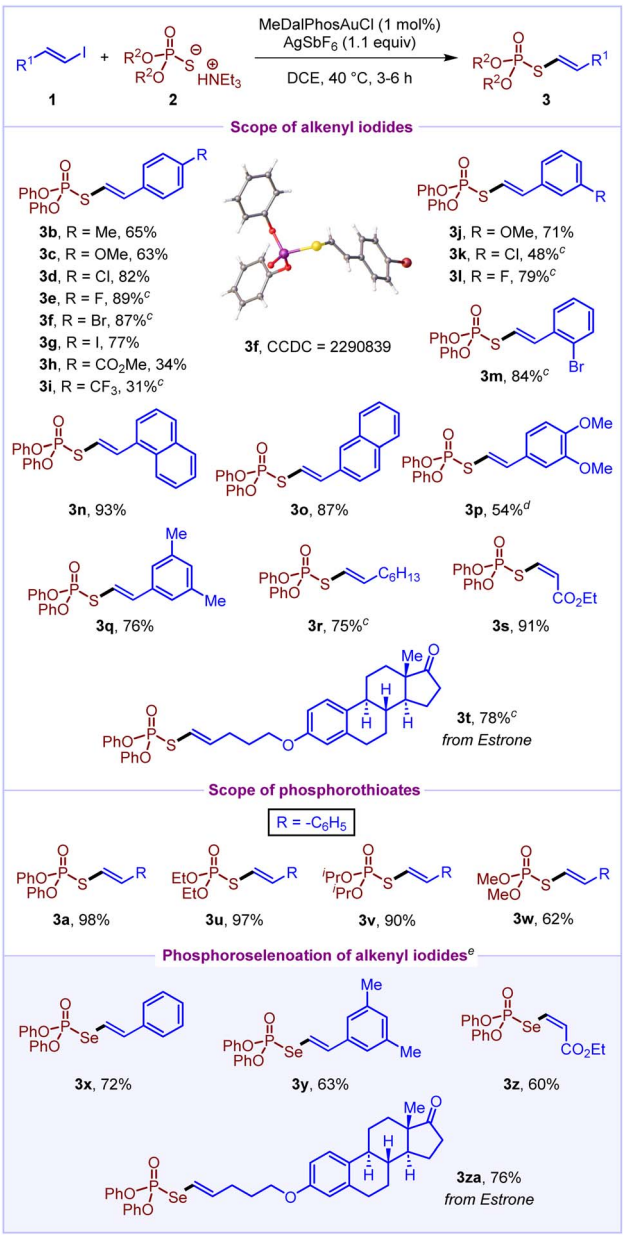
Entry	Deviation from "standard conditions"	Yield **3a**[b] (%)
1	None	28
2[c]	Without MeDalPhosAuCl	—
3[c]	Without AgOTf	—
4	1.1 equiv. $AgBF_4$	61
5	1.1 equiv. $AgSbF_6$	66
6	1.1 equiv. $AgNTf_2$	<5
7	1.1 equiv. AgOTs	18
8	$AgSbF_6$ and *o*-DCB	83
9	**$AgSbF_6$ and DCE**	**98**
10[c]	$AgSbF_6$ and MeOH	—
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 °C, and 3 h. [b] Isolated yields. [c] No reaction.

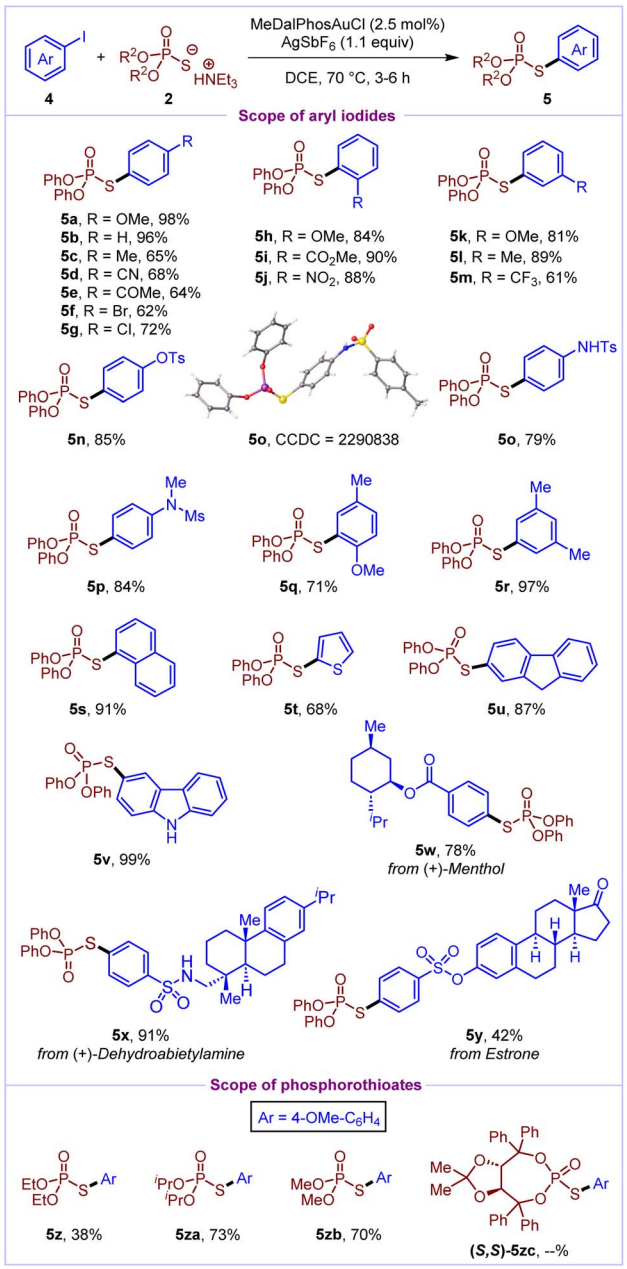
With the optimized reaction conditions in hand, we turned our attention to explore the scope of alkenyl iodides **1** by treating them with *O*,*O*-diphenyl phosphorothioate **2a** (Scheme 2). To our delight, several styrenyl-based alkenyl iodides having electron-donating (–OMe and –Me) and electron-withdrawing substituents (–CO_2Me and –CF_3) at the *para* position worked well in the reaction to afford *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. Furthermore, we sought to investigate



Scheme 1 Transition metal-catalyzed synthesis of *S*-alkenyl/aryl phosphorothioates: known and present work.



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, and 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 for 12 h.



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, and 3–6 h. [b]Isolated yields.

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%).

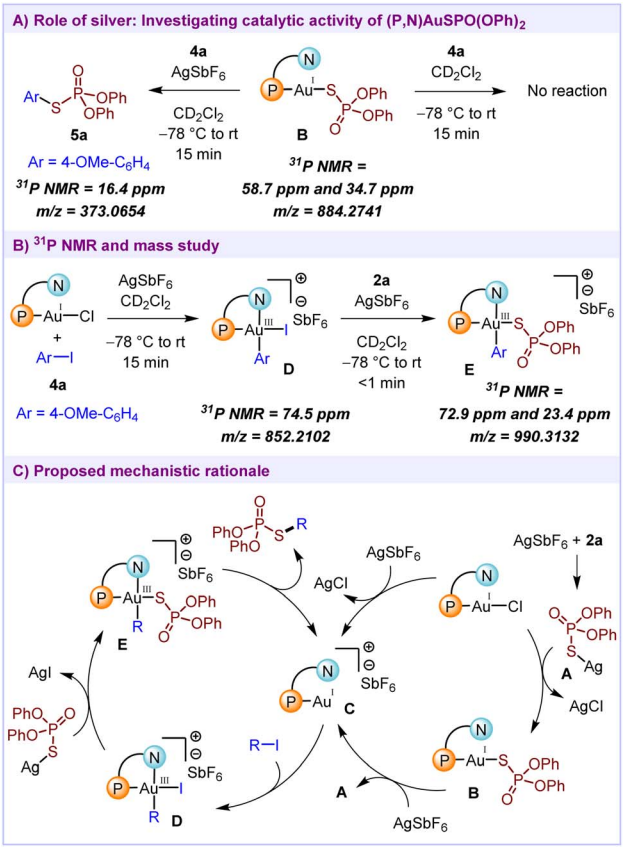
With the scope of *S*-alkenylation of phosphorothioates established, we wondered whether the reaction scope could be broadened by using phosphoroselenoates as potential coupling partners. Remarkably, the *Se*-alkenylation of phosphoroselenoates was achieved, providing an efficient access to *Se*-alkenyl phosphoroselenoates. Pleasingly, both styrenyl and alkyl derived alkenyl iodides worked well to deliver the products **3x–3za** in 60–76% yields. In addition, the reaction of alkenyl iodide **1a** with phosphoric acid was performed under the optimised reaction conditions both in the presence and absence of a base; however, it did not result in the formation of the desired C–O cross-coupling product.

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 our delight, aryl

iodides were efficiently cross-coupled with phosphorothioates to deliver the desired *S*-aryl phosphorothioates (Scheme 3). At first, the scope of aryl iodides was investigated by utilising *O*,*O*-diphenyl phosphorothioate **2a** as the model substrate. Delightfully, various aryl iodides with electron-donating (–OMe, –Me, –NHTs, and –NMeMs) and electron-withdrawing (–CN, –COMe, $–CO_2Me$, $–NO_2$, and $–CF_3$) 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 and –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 9*H*-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 product (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%). Furthermore, the scope of phosphorothioates was evaluated and it was found that *O*,*O*-dialkyl phosphorothioates react well to afford products **5z**, **5za** and **5zb** in moderate to good yields. However, axially chiral phosphorothioate **2zc** did not react to deliver the desired cross-coupled product, likely due to its incompatibility with the silver salt in the reaction mixture.

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 salts, $AgSPO(OPh)_2$ 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 show 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**. In a stoichiometric reaction of 4-iodoanisole **4a** with pre-formed complex **B**, no oxidative addition of the 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 that silver plays a role in the reactivation of the complex **B** to form active cationic Au(I) species, necessary for the realization of catalytic reactivity. Furthermore, the formation of Au(III) intermediates **D** and **E** during the reaction was confirmed by ^{31}P NMR and mass spectrometric analysis (Scheme 4B).

Based on the control experiments and ^{31}P NMR studies, the mechanistic cycle for the cross-coupling of phosphorothioates with organohalides is proposed (Scheme 4C). Initially, the reaction of MeDalPhosAuCl with $AgSbF_6$ would generate the active gold catalyst **C**. Alternatively, first $AgSPO(OPh)_2$ complex **A** could react with MeDalPhosAuCl to generate the Au(I)



Scheme 4 Mechanistic investigations and plausible mechanism.

$SPO(OPh)_2$ complex **B** which acts as a catalyst resting state. In the presence of a 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). A subsequent transmetalation between the $AgSPO(OPh)_2$ complex **A** and Au(III) intermediate **D** would lead to the 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 the active catalyst.

Conclusions

In summary, we have developed the first gold-catalyzed alkenylation and arylation of phosphorothioates with organohalides *via* a $C(sp^2)$–S cross-coupling reaction under Au(I)/Au(III) redox catalysis. This methodology offers direct access to the biologically relevant *S*-alkenyl and *S*-aryl phosphorothioates at a catalyst loading as low as 1 mol%. Moreover, the gold-catalyzed alkenylation of phosphoroselenoates has also been accomplished to afford *S*-alkenyl phosphoroselenoates. Mechanistic studies revealed a crucial role of the *in situ* generated Ag–sulfur complex, which undergoes a facile transmetalation with the Au(III) intermediate, thereby leading to the successful

realization of the desired cross-coupling reactivity. It is anticipated that harnessing the potential of this transmetalation strategy in gold catalysis could allow access to cross-coupling reactions that have remained elusive under conventional redox transition metal catalysis.

Data availability

The ESI† includes experimental procedures and characterization data supporting this article.

Author contributions

Urvashi and N. T. P. conceptualized the project. Urvashi and S. M. performed and analysed the experiments. Urvashi and N. T. P. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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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 (DOI: **https://doi.org/10.26434/chemrxiv-2023-s9w9p**). 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 the ESI† for details.