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Pd(I) dimer catalysis

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Arylation of Axially Chiral Phosphorothioate Salts via Dinuclear Pd(I) Catalysis

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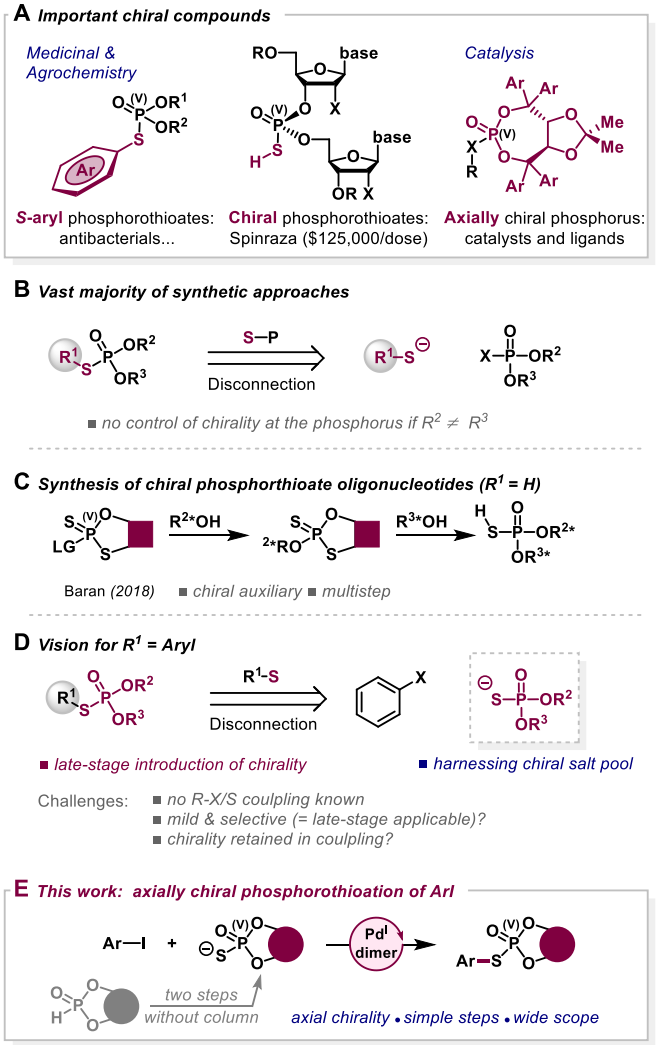
***Abstract**: S-aryl phosphorothioates are privileged motifs in pharmaceuticals, agrochemicals and catalysts; yet, the challenge of devising a straightforward synthetic route to enantioenriched S-aryl phosphorothioates has remained unsolved to date. We herein demonstrate the first direct C-SP(=O)(OR')(OR'') coupling of diverse and chiral phosphorothioate salts with aryl iodides, enabled by an air- and moisture-stable Pd(I) dimer. Our mechanistic and computational data suggest distinct dinuclear Pd(I) catalysis to be operative, which allows for operationally simple couplings with broad scope and full retention of stereochemistry.*

While phosphorothioates display privileged structure/activity features and find applications as important agrochemicals, top-selling pharmaceuticals and powerful chiral catalysts (see Scheme 1A), the control of their inherent chirality remained a daunting synthetic challenge for decades. Indeed, indirect multistep strategies *via* $P^{(III)}$ species have historically been utilized to accomplish this feat,[1] until Baran's recent announcement of accessing chiral phosphorothioate oligonucleotides *via* an indirect strategy from limonene derived $P^{(V)}$ reagents under auxiliary control (Scheme 1C).[2] On the other hand, the synthesis of chiral phosphorothioate salts has been realized through a straightforward three step sequence.[3] As such, if it were to be possible to further derivatize these salts at 'S' without compromising on their stereochemical integrity, then access to the wider phosphorothioate class of compounds would in principle be unleashed.

In this context, the synthesis of chiral *aryl phosphorothioates*, which are commonly found in drugs, pesticides and bioactive compounds,[4] would require the direct coupling of the salt with a C_{sp2} center (Scheme 1D). If realizable, this strategy would be highly powerful, as it would allow for the introduction of the phosphorothioate moiety in any desired chirality and at any stage in a synthesis. However, although thiolations of C_{sp2} sites, especially aryl halides, are well precedented and can be accomplished *via* $Pd^{(0)}$-catalyzed cross coupling reactions,[5] to date, no general, safe, robust and direct C_{sp2}-SP(=O)(OR^2)(OR^3) coupling to access aryl phosphorothioates exists.[6] Instead, the vast majority of synthetic approaches rely on a bond formation at the phosphorus center directly (*i.e.* S-P coupling, Scheme 1B),[7] which has so far not been accomplished in a stereoselective manner.

We therefore set out to develop a method to access diverse and chiral phosphorothioates in a direct coupling approach with widely available aryl halides.



Scheme 1. Motivation and synthetic strategy.

Owing to the general mildness and high functional group tolerance, which are key requirements for late-stage synthetic applications, a $Pd^{(0)}/Pd^{(II)}$ catalyzed cross-coupling approach appears ideal at first sight to accomplish this goal. However, when we subjected various $Pd^{(0)}$ catalysts to iodobenzene and $NMe_4[SP(=O)(OPh)_2]$,[8] such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/dppf, no coupling was observed (see Figure 1A). Moreover, when we subjected the phosphorothioate salt to a $Pd^{(II)}$ complex and heated the corresponding mixture, we did not observe the corresponding product **2**.[10] Our computational studies support this observation,[9] indicating that the iodide/phosphorothioate exchange at $[L_nPd^{(II)}(Ph)(I)]$,

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followed by reductive elimination of Ar-SP(=O)(OPh)$_2$ has a prohibitively high activation free energy barrier of $\Delta G^{\ddagger} \geq 30$ kcal/mol and is endergonic. For comparison, the corresponding thiolation, *i.e.* Ar-SPh reductive elimination is characterized by a ~ 10 kcal/mol lower activation free energy barrier and significantly increased driving force (see supporting information for details). As such, and in agreement with the lack of literature precedence, Pd$^{(0)}$/Pd$^{(II)}$ catalysis appears to not be an optimal strategy to accomplish C-SP(=O)(OR^2)(OR^3) coupling.

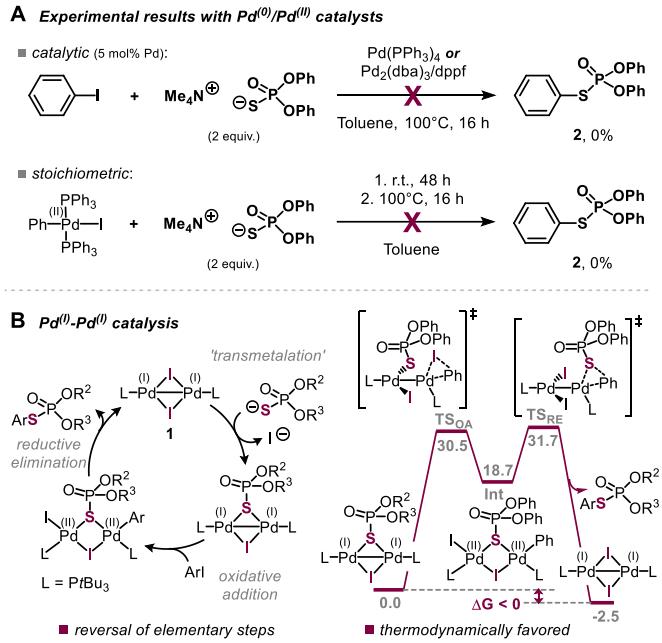


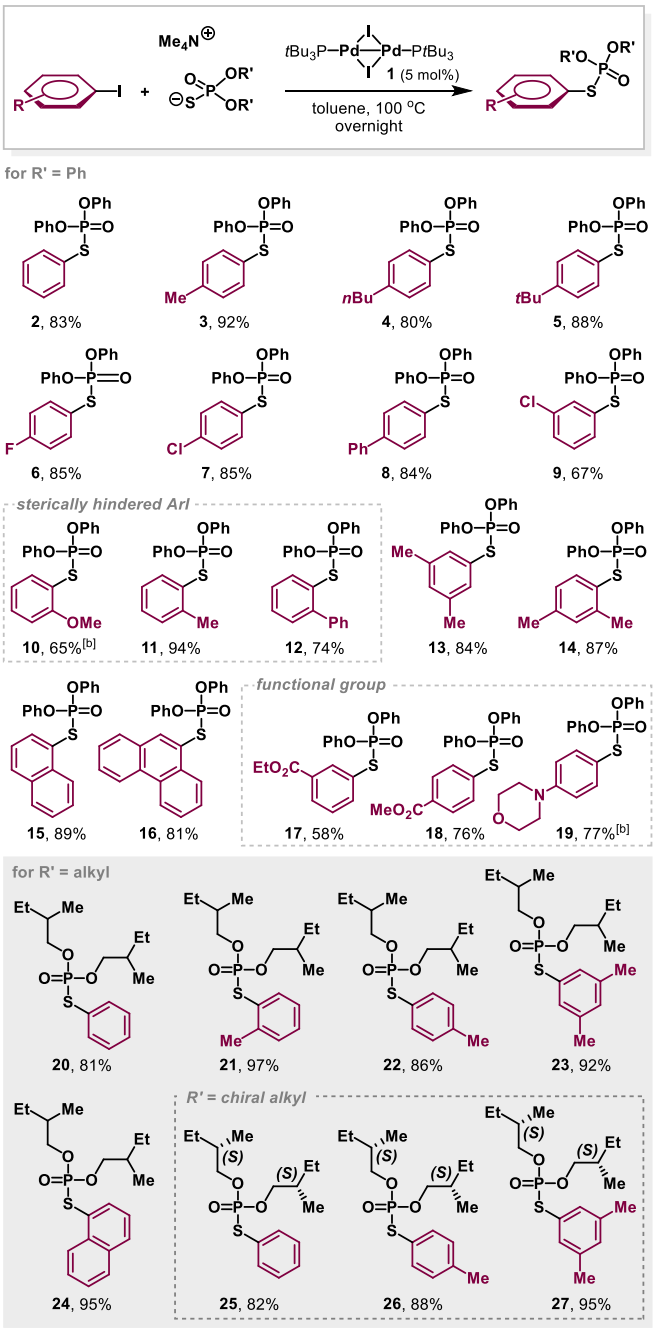
Figure 1. Free energy profile of Pd$^{(I)}$-catalyzed coupling of PhI with [SP(O)(OPh)$_2$]$^-$. Gibbs free energies (in kcal/mol) shown, calculated at the SMD (toluene) M06L/def2TZVP//B3LYP-D3/6-31G(d, p) (SDD for Pd, I) level of theory.

We previously established that dinuclear Pd$^{(I)}$ catalysis is a viable strategy to circumvent potentially poisonous Pd$^{(II)}$ intermediates as well as alter the driving force of the transformation.[11] Our extensive mechanistic studies had indicated that the dimer's bridging iodines are initially exchanged by the nucleophilic coupling partner, and the newly formed Pd$^{(I)}$ complex then reacts with the aryl halide, therefore formally reversing the sequence of elementary steps (see Figure 1B). As such, we envisioned that a dinuclear Pd$^{(I)}$ coupling protocol[11,12] might offer a solution to the phosphorothioate problem.

To assess whether Pd$^{(I)}$-dimer catalyzed phosphorothioation would be feasible, we undertook computational studies of the coupling with iodobenzene, which clearly indicated that there is a pronounced driving force to convert iodobenzene to the C-SP(=O)(OPh)$_2$ coupled product (Figure 1). The activation barrier was found to be in the range of our previous findings of dinuclear Pd$^{(I)}$ catalysis,[11,12] and as such appeared to be feasible.

A key requirement of the Pd$^{(I)}$ dimer catalysis concept is that the coupling partner will also function as a stabilizing bridging unit in the Pd$^{(I)}$ dimer. To examine this, we subjected 4 equiv. of tetramethyl ammonium phosphorothioate salt to a solution of the air-stable, iodine bridged Pd$^{(I)}$ dimer **1**. To our delight, within 2 h at room temperature we saw the appearance of a signal at 97.9 ppm upon ^{31}P-NMR spectroscopic analysis, which is very reminiscent of a functionalized Pd$^{(I)}$ dimer, suggesting that the iodine in **1** can be exchanged for a phosphorothioate.[13]

Table 1: Scope of the Pd$^{(I)}$-catalyzed phosphorothioation of aryl iodides.[a]



[a] Yields of isolated products **2**-**27** after chromatography. [b] The reaction mixture was stirred for 36 h.

We next set out to explore whether Pd$^{(I)}$ catalyzed phosphorothioation of aryl iodides is also feasible. To our delight, the desired O,O-diphenyl phosphorothioate **2**[14] was obtained in 83% yield in the presence of 5 mol% of [Pd^{I}(μ-I)(P*t*Bu$_3$)]$_2$ dimer **1** (Table 1). Encouraged by these findings, we subsequently turned to explore the wider scope of the transformation (Table 1). A series of aryl iodides bearing electron-donating or electron-withdrawing substituents (R = 4-Me, 4-*n*Bu, 4-*t*Bu, 4-F, 4-Cl and 4-Ph) reacted

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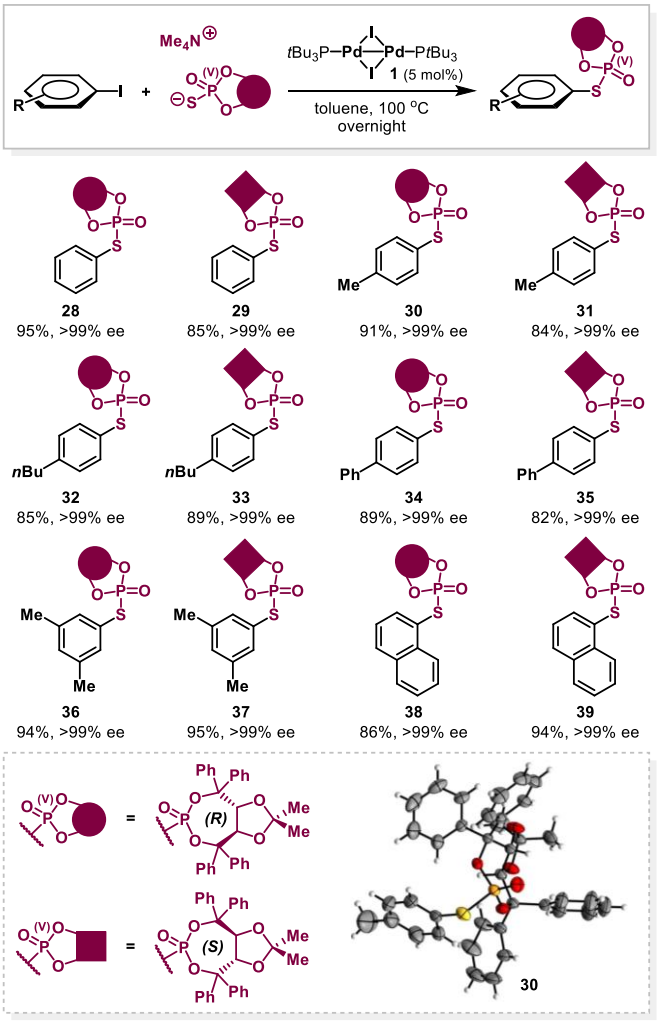
smoothly and gave the corresponding products **3**–**8** in good yields. The reactions of sterically hindered *ortho*-substituted (2-MeO, 2-Me and 2-Ph) aryl iodides also proceeded well, with slightly lower yield observed with *meta* substitution (**9**–**12**). For **10**, prolonging the reaction time increased the product yield. The reactions of disubstituted substrates were also successful without any loss of yield (**13** and **14**). This was also true for the polyaromatic iodides giving rise to products **15** and **16**. Moreover, the method tolerated a variety of functional groups, such as esters and morpholines (**17**–**19**).
The effect of O,O-dialkyl phosphorothioate salt was examined as well. Various substituted aryl iodides were readily coupled under the standard reaction conditions and the corresponding products **20**–**24** were obtained in excellent yields. Notably, the chirality in the substituents of the salt was retained (**25**–**27**).

Table 2. Applications of the coupling strategy to the efficient synthesis of axially chiral S-aryl phosphorothioates.[a]



[a] Yields of isolated products **28**-**39** after chromatography and the ee by HPLC analysis of the purified product on a chiral stationary phase.

The $P^{(V)}$-series of TADDOL derived organophosphorus compounds are usually found in various valuable chiral catalysts and ligands.[15] To further expand the synthetic utility of the present catalytic strategy, the synthesis of axially chiral S-aryl phosphorothioates was tested (Table 2). Gratifyingly, uniformly excellent enantioselectivities of up to >99% ee were obtained using C2-symmetric TADDOL-derived phosphorothioate salts with a variety of aryl iodides, resulting in the desired products **28**-**39** in very good yields. The absolute configuration of the product **30** was determined by X-ray crystallographic analysis (see Table 2), unambiguously confirming the complete retention of chirality.[16]

In conclusion, while the examined $Pd^{(0)}/Pd^{(II)}$ catalysis failed to deliver the phosphorothioation of aryl iodides as a consequence of disfavoured exchange at $Pd^{(II)}$ and a high reductive elimination barrier, the mechanistically distinct dinuclear $Pd^{(I)}$ catalysis operates with an orthogonal driving force that allows for the first catalytic S-arylation of phosphorothioate salts with aryl iodides. The method is characterized by generality, broad scope and operational simplicity, making use of an easily accessible phosphorothioate salt and an air-stable $Pd^{(I)}$ dimer. The stereochemical integrity of chiral salts was not compromised in the coupling process, allowing the efficient assembly of axially chiral S-aryl phosphorothioates. In light of the promising properties of S-aryl phosphorothioate compounds as well as the privileged $Pd^{(I)}$ catalysis reactivity, we anticipate that the presented methodology will facilitate numerous applications in the agrochemical, pharmaceutical and stereoselective synthesis arenas.

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Conflict of interest

The authors declare no conflict of interests.

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[16] CCDC 1911726 (**30**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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