Application of sSPhos as a Chiral Ligand for Palladium-Catalyzed Asymmetric Allylic Alkylation

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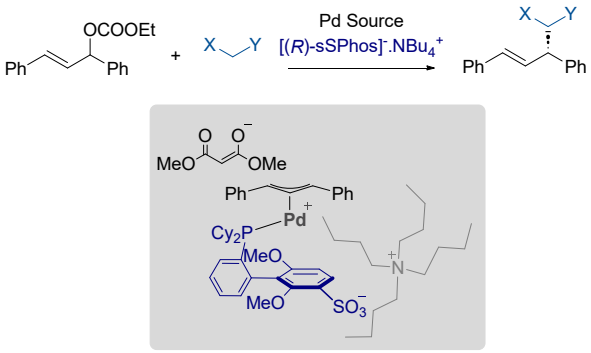
Supporting Information Placeholder



ABSTRACT: Palladium-catalyzed asymmetric allylic alkyation is a versatile method for C-C bond formation. Many established classes of chiral ligand can perform allylic alkylation reactions enantioselectively, but identification of new ligand classes remains important for future development of the field. We demonstrate that enantiopure sSPhos, a bifunctional chiral monophosphine ligand, when used as its tetrabutyl ammonium salt, is a highly effective ligand for a benchmark Pd-catalyzed allylic alkylation reaction. We explore the scope and limitations and carry out experiments to probe the origin of selectivity. In contrast with reactions previously explored using enantiopure sSPhos, it appears that steric bulk around the sulfonate group is responsible for the high enantioselectivity in this case, rather than attractive non-covalent interactions.

Within the broad field of palladium catalysis, allylic alkylation, also referred to as the Tsuji-Trost reaction, is a process which arguably offers the most versatility in terms of mechanistic possibilities and ability to combine with other reaction types. It often affords chiral products, offering numerous possibilities for asymmetric synthesis through various mechanistic manifolds.[1] A number of important classes of chiral ligand have been developed over the years, but it is important that new ligand exploration continues.[1f] Whilst the benchmark reactions may be well served, innovative new transformations based on π-allyl palladium chemistry continue to be developed, for which well-established ligand scaffolds may not suffice. We are interested in designing ligands for transition metal catalyzed reactions which harness attractive non-covalent interactions between ligand and substrate to control selectivity, a strategy that can be very powerful.[2] Ligands that incorporate non-covalent interactions into their outer coordination sphere have been applied to π-allyl palladium chemistry in the past: strategies have included the modification of established ligands with pendant functional groups,[3] the pairing of a chiral anion with a cationic palladium complex,[4] and the pairing of chiral anions with cationic ligands.[5], [6]

We have recently explored the use of the sulfonated phosphine ligand **sSPhos**, originally reported in racemic form by Anderson and Buchwald to permit water solubility,[7] as a bifunctional ligand (Figure 1A). We first used **sSPhos** in racemic form for control of site-selectivity in cross-coupling reactions (Fig. 1B, left).[8] Having developed a method to obtain sSPhos in enantiopure form via resolution using quinidine (Figure 1A, right), we subsequently used **sSPhos** in enantiopure form to control enantioselectivity in Suzuki-Miyaura cross-coupling reactions to form 2,2'-biphenols, as well as in arylative dearomatization reactions to afford a range of scaffolds (Figure 1B, center and right).[9] In all cases we believe that attractive non-covalent interactions involving the ligand sulfonate group are required for selectivity. We propose either electrostatic interactions or hydrogen bonding interactions depending on the specific reaction and conditions.[10] Our previous work with **sSPhos** has highlighted several beneficial properties: its high reactivity in many Pd-catalyzed processes by virtue of its dialkylbiaryl structure,[11] as well as its ability to engage in attractive interactions, while also being intrinsically chiral and, as we have previously demonstrated,[9a] resolvable.

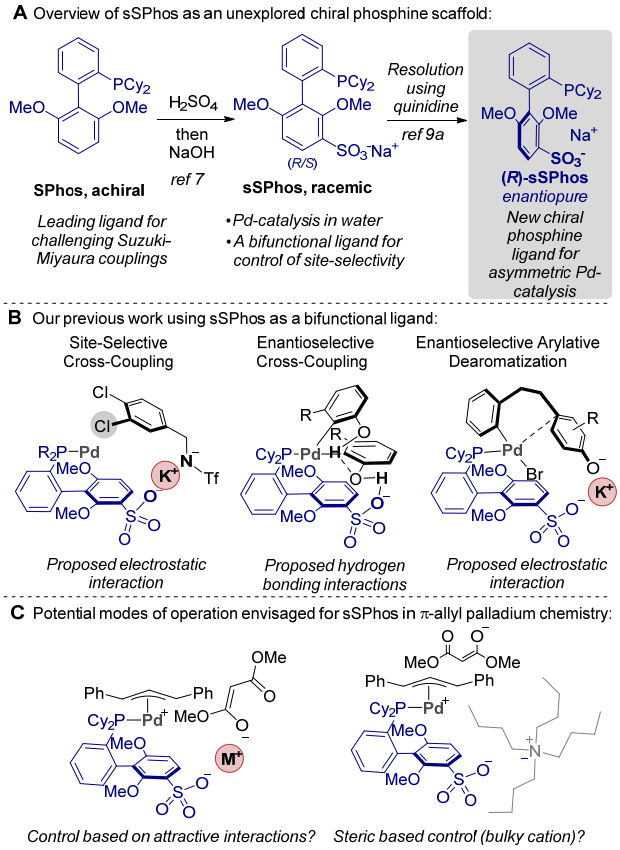
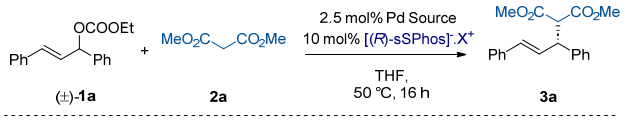


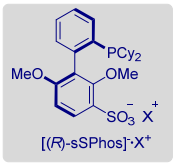
Figure 1. Use of **sSPhos** for selectivity control and potential application to π-allyl palladium chemistry

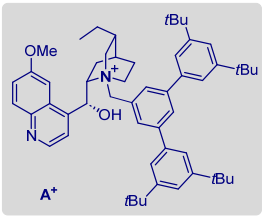
At the outset of this study, we sought to evaluate the ability of sSPhos to act as a new class of chiral phosphine ligand for asymmetric allylic alkylation. We hypothesized that this reaction type may be particularly amenable to enantioinduction using **sSPhos**, as it typically features a cationic intermediate prior to outer sphere nucleophilic attack from an anionic nucleophile. We speculated that the discrete charges on several reaction components may offer possibilities for leveraging attractive ionic interactions to enable organization at the enantiodetermining transition state. One possibility that we considered, akin to our previous work on site-selective cross-coupling,[8] was that the cation associated with an anionic nucleophile might engage in attractive electrostatic interactions with the ligand sulfonate group (Figure 1C, left). Another possibility was that steric control would predominate if the cation associated with **sSPhos** were bulky, such as tetra-*n*-butylammonium (Figure 1C, right). This steric effect on selectivity of an associated cation is one that we[12] and others[13] have previously exploited in the context of Ir-catalyzed borylation.

We commenced our study with the benchmark reaction of allylic carbonate **1a,** which reacts via a symmetrical intermediate. We opted to use an allylic carbonate electrophile, as opposed to an acetate, which would allow the reaction to proceed via a decarboxylative mechanism.[14] This would avoid the need for exogenous base, which could complicate any potential ionic interactions with the presence of additional anions and cations in the reaction mixture. With the tetra-*n*-butylammonium salt of (*R*)-**sSPhos** as the ligand, we were pleased to find that using several dimeric Pd sources, good yields and enantioselectivities could be obtained (Table 1, entries 1-3). A solvent evaluation showed a range of solvents to be compatible and we opted to continue with THF (see Supporting Information for more details). A 1 mmol scale reaction was also carried out in which high ee was retained (see Supporting Information). At this point we systematically varied the cation associated with (*R*)-**sSPhos**, moving away from Bu_4N^+. Interestingly, the three alkali metal cations evaluated, including Na^+, the default cation for **sSPhos**, all gave markedly reduced ee compared with Bu_4N^+ (entries 4-6). We then evaluated the effect of modulating the length of the alkyl chains of the tetraalkylammonium cation. Shorter alkyl chains decreased the ee significantly (methyl and ethyl, entries 7 and 8) whilst a larger one gave a similar result to Bu_4N^+, suggesting a possible size effect that may have plateaued with Bu_4N^+ (*n*-hexyl, entry 9). This apparent effect of cation size led us to consider a cation that may appear larger than an ammonium bearing linear alkyl chains. Accordingly, we paired (*R*)-**sSPhos** with a quinine-derived cation with a large quaternizing group, of the type used extensively in phase-transfer catalysis.[15] We have used these cations in recent work pairing with sulfonated ligands for Ir[16] and Rh[17] and others have used these cations to combine asymmetric phase transfer catalysis with palladium-catalyzed π-allyl chemistry.[18] Gratifyingly, this increased the ee from 84% to 90% (entry 10). We were intrigued as to whether the chirality of the cation might be contributing to this increased enantioselectivity and next probed whether there might be a matched-mismatched effect.[19] (*S*)-**sSPhos** was

Table 1: Optimization of the allylic alkylation reaction using sSPhos and allylic carbonate 1a.[a]







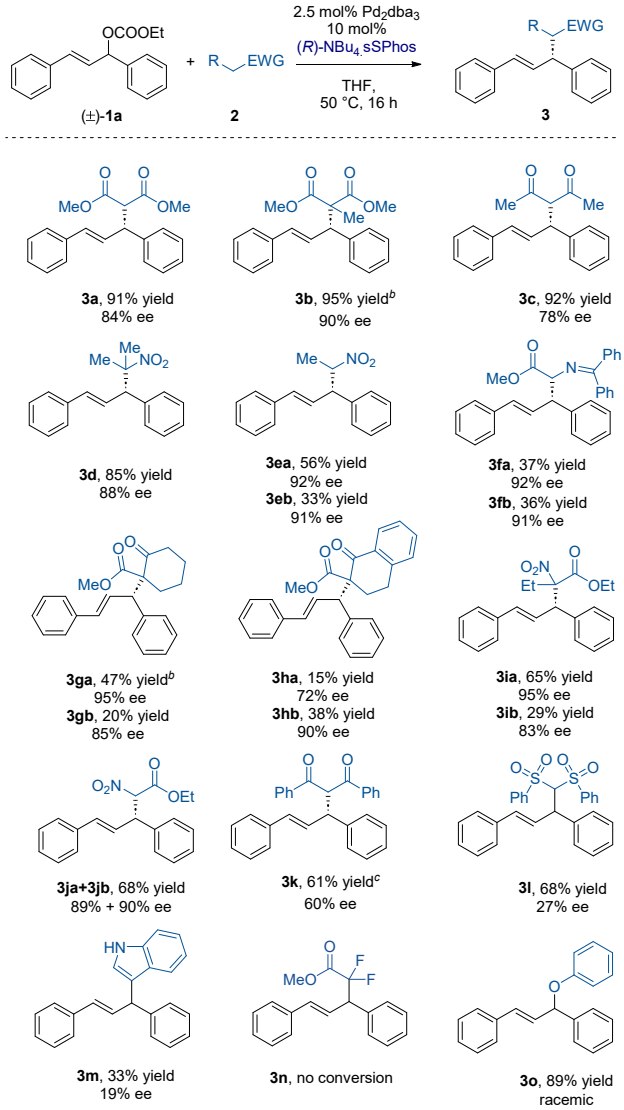
Entry	Pd Source	X^+	Yield[a] /%	Ee /%[b]
1	$[Pd(Allyl)Cl]_2$	Bu_4N^+	81	80
2	Pd_2dba_3	Bu_4N^+	90 (91)	84
3	$[Pd(Cinnamyl)Cl]_2$	Bu_4N^+	42	84
4	Pd_2dba_3	Na^+	82	44
5	Pd_2dba_3	K^+	96	32
6	Pd_2dba_3	Cs^+	79	36
7	Pd_2dba_3	NMe_4^+	66	42
8	Pd_2dba_3	NEt_4^+	72	40
9	Pd_2dba_3	$NHex_4^+$	71	82
10	Pd_2dba_3	**A**$^+$	79	90
11[b]	Pd_2dba_3	**A**$^+$	68	-90

[a]Yields determined by ^{1}H-NMR with internal standard. Value in parentheses refers to isolated yield. ee determined by SFC analysis of crude reaction mixture, except entry 2 which was isolated. [b] Using (*S*)-**sSPhos** paired with **A**$^+$.

therefore paired with the same chiral cation $\mathbf{A}^+$ and this catalyst resulted in a product ee that was -90%, exactly equal and opposite of the result using (*R*)-**sSPhos** with the same chiral cation (entry 11). These results suggests that the chirality of the cation is not contributing to the increase in enantioselectivity. We believe, therefore, that the cation effect is most likely a steric one.

We next evaluated the scope of the transformation with respect to a diverse range of acidic carbon-based nucleophiles (Scheme 1). During the optimization, only a small increase in ee was observed upon switching NBu_4^+ for chiral cation $\mathbf{A}^+$, at the expense of a great increase in complexity. We therefore decided to use (*R*)-NBu_4.**sSPhos** when evaluating the scope of the transformation, optimistic that excellent enantioselectivities might still be achievable with Bu_4N^+. We were pleased to find that the reaction was very tolerant of a broad range of variously substituted carbon nucleophiles. The absolute stereochemistry of **3a** could be readily determined by comparison with the literature

Scheme 1. Scope of the reaction.[a]



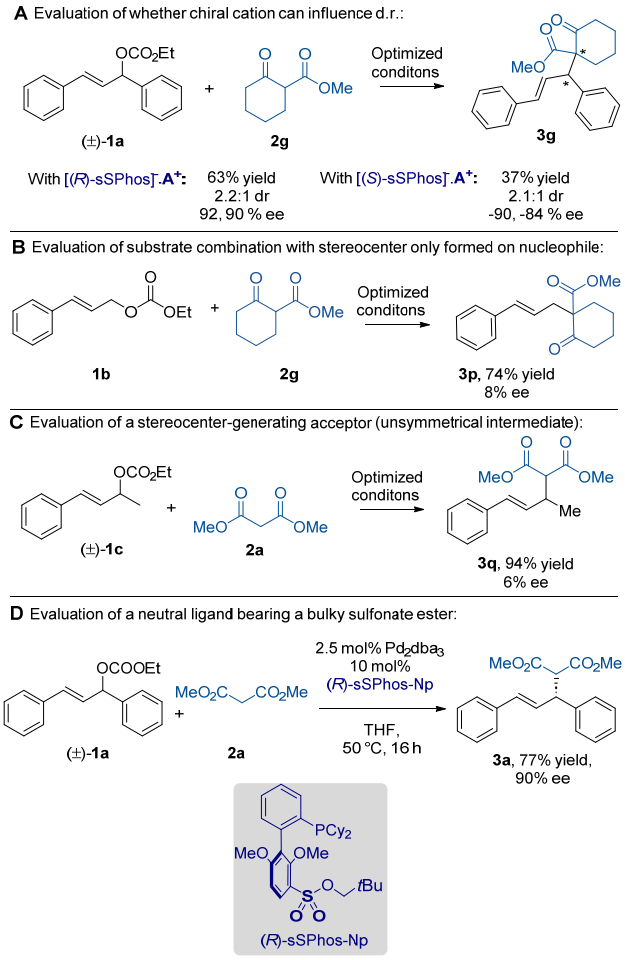
[a] Yields are isolated, ee values determined by SFC. [b]Isolated with an inseparable dibenzylideneacetone impurity. See SI for details. [c] Reaction caried out in toluene at 120 °C.

and the others are assigned by analogy (see Supporting Information for details). An alkyl group on the malonate ester gave 90% ee (**3b**). A diketone gave slightly reduced but still useful levels of selectivity (**3c**, 78% ee). Nitroalkanes worked well (**3d**, **3e**). In the case of **3e**, which affords diastereomers, no diastereocontrol was observed, but each could be isolated separately with identical ee. A glycine-derived Schiff base also worked very well (**3f**). Similarly, no diasterocontrol was observed but each diastereomer could be separately isolated in high ee. Excellent enantioselectivity outcomes were obtained for β-ketoester substrates (**3g** and **3h**), as well as β-nitroester substrates (**3i** and **3j**), emphasizing the breadth of nucleophiles with which **sSPhos** is compatible. We did identify limitations – for example, diphenylpropanedione had very low reactivity and required heating to 120 °C in toluene to obtain reasonable yield (**3k**). As expected, at this high temperature the enantioselectivity of the product was reduced. A bis-sulfone was reactive but gave poor enantioselectivity at 27% ee (**3l**), a similar outcome to that observed with indole (**3m**). A fluorinated ester gave no conversion (**3n**). We also evaluated a phenol as a heteroatom nucleophile (**3o**), for which some ee has been obtainable with other catalyst systems.[20] In our case it gave a racemate, the reason for which is presently unclear.

As the scope survey indicated, excellent ee values were often obtainable using tetra-*n*-butylammonium as the cation associated with **sSPhos**, without needing to incorporate the more complex quinine-derived chiral cation that slightly improved ee during the optimization. However, we were keen to explore whether the chiral cation might be able to influence diastereoselectivity for substrate combinations that feature a prochiral nucleophile. Cyclic β-ketoester **2g** was evaluated using chiral cation $\mathbf{A}^+$ paired with both (*R*)-**sSPhos** and (*S*)-**sSPhos**, to probe any matched/mismatched effect. However, the enantioselectivity outcomes were similar, and the bulky chiral cation did not significantly influence d.r (Scheme 2A). Based on the excellent ee values obtained with non-prochiral nucleophiles, we presumed that the poor diastereoselectivity arising with prochiral nucleophiles was a consequence of lack of catalyst control over the stereochemistry originating from the nucleophile. Support for this was provided by an experiment with allylic carbonate **1b** and prochiral β-ketoester **2g** (Scheme 2B). In this case a stereocenter is formed only on the nucleophilic component and this occurred with almost no control (8% ee). We sought to test allylic carbonate **1c**, which would give rise to a non-symmetric π-allyl intermediate and for which some ligands have shown promise in the past (Scheme 2C).[21] However, **3q** was obtained in only 6% ee. Finally, we evaluated an (*R*)-**sSPhos** derivative in which the sulfonate group is esterified as a neopentyl sulfonate ester (Scheme 2D). This would preclude it from engaging in electrostatic interactions and reduce its ability to act as a hydrogen bond acceptor, meaning that any enantioselectivity would likely arise due to repulsive steric effects at the transition state. Use of (*R*)-**sSPhos-Np** gave **3a** in a very high 90% ee, supporting our sterics-based hypothesis for control of enantioselectivity (Figure 1C, right). This stands in contrast to our previous reports of cross-coupling and arylative dearomatization, where sulfonate ester variants of (*R*)-**sSPhos** gave negligible ee, providing support in those cases for attractive non-covalent interactions.[9]

In summary, we report that enantiopure **sSPhos**, with tetra-*n*-butylammonium as the cation, is an excellent ligand in the palladium-catalyzed asymmetric allylic alkylation of bis-phenyl allylic carbonate **1a** with a variety of carbon-based

Scheme 2. Further experiments and substrate classes examined.



nucleophiles. Prochiral nucleophiles resulted in diastereomers but these could, in most cases, be independently isolated on silica. Our experiments suggest that **sSPhos** is proficient at controlling stereochemistry on the electrophilic component but not on a pro-chiral nucleophile. We had initially considered a possibility that the incoming anionic nucleophile might engage in electrostatic interactions with the cation paired with the ligand sulfonate group. However, the lack of control over forming stereocenters on the nucleophile led us to believe this is probably less likely than steric based control. The high enantioselectivity obtained with (*R*)-**sSPhos-Np** provided further support for the sterics-based model. We envisage that the competence of **sSPhos** as a chiral ligand for π-allyl palladium chemistry will prompt others to explore it when developing new reactions based on this important mechanistic pathway.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Additional optimization, full experimental details and characterization data for compounds. The Supporting Information is available free of charge on the ACS Publications website.

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