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Synthetic and Mechanistic Studies of a Versatile Heteroaryl Thioether Directing Group for Pd(II) Catalysis

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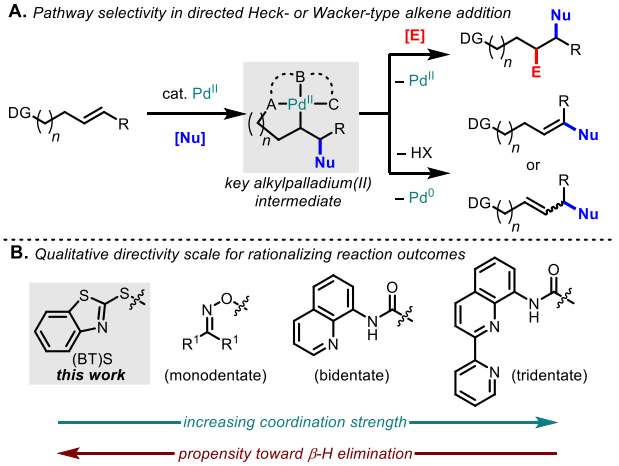
ABSTRACT: A weakly coordinating monodentate heteroaryl thioether directing group has been developed for use in Pd(II) catalysis to orchestrate key elementary steps in the catalytic cycle that require conformational flexibility in a manner that is difficult to accomplish with traditional strongly coordinating directing groups. This benzothiazole thioether, (BT)S, directing group can be used to promote oxidative Heck reactivity of internal alkenes providing a wide range of products in moderate to high yields. To demonstrate the broad applicability of this directing group, an arene C–H olefination method was also successfully developed. Reaction progress kinetic analysis provides insights into the role of the directing group in each reaction, which is supplemented with computational data for the oxidative Heck reaction. Furthermore, this (BT)S directing group can be transformed into a number of synthetically useful functional groups, including a sulfone for Julia olefination, allowing it to serve as a "masked olefin" directing group in synthetic planning. In order to demonstrate this synthetic utility, natural products (+)-salvianolic acid A and salvianolic acid F are formally synthesized using the (BT)S directed C–H olefination as the key step.

INTRODUCTION

Substrate directivity is a powerful approach for enhancing reactivity and controlling selectivity across numerous types of metal-catalyzed reactions.[1] In substrate-directed reactions, pre-association of the catalyst to one or more Lewis basic sites on the substrate promotes a desired reaction outcome by perturbing the activation barriers for possible divergent pathways along the reaction coordinate. Kinetic reactivity is typically enhanced by virtue of induced intramolecularity as well as enforced proximity between the reactive group on the substrate and a free coordination site on the metal. Regioselectivity is dictated by preferential formation of a thermodynamically and/or kinetically stabilized metallacycle over an energetically disfavored constitutional isomer. Stereoselectivity can also be controlled in key bond-making and bond-breaking steps through stereochemical information on (or in the vicinity of) the coordinating atom(s).

Strategic application of substrate directivity in palladium-catalyzed alkene functionalization is a potent platform for achieving challenging modes of bond construction.[1b] Palladium-catalyzed Wacker oxidation and Mizoroki–Heck arylation of alkenes constitute the bedrock of modern homogeneous catalysis research, with the power of these reactions stemming from their ability to forge diverse C–C and C–heteroatom bonds from simple alkene starting materials.[1d, 2] In the traditional reaction pathways, upon nucleometalation (or migratory insertion), the resulting alkylpalladium(II) intermediate undergoes facile β-H elimination to deliver the final oxidized alkene product. With substituted alkene starting materials, the regioselectivities of the initial addition step and subsequent β-H elimination step are not straightforward to control in the absence of a strong steric or electronic bias between the two alkenyl carbon atoms. Our laboratory[1e, 3] and others[1d, 4] have studied substrate-directed palladium-catalyzed alkene functionalization reactions that initiate via Wacker- or Heck-type pathways. In these systems, strongly coordinating mono-, bi-, and tri-dentate directing auxiliaries can be used

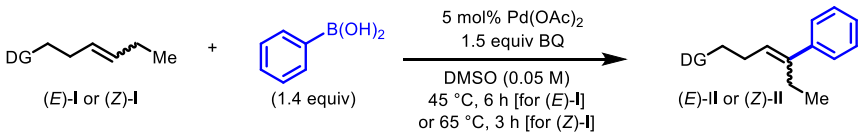


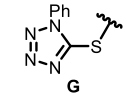
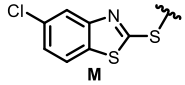
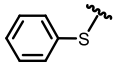
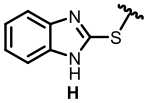
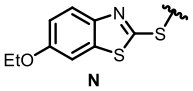
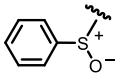
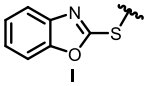
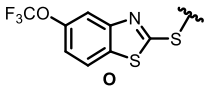
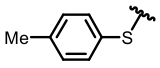
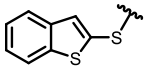
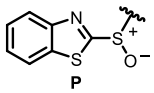
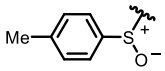
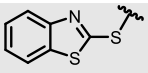
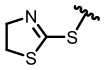
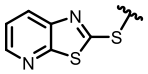
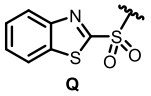
Scheme 1. Background and Synopsis

to control the regioselectivity of the alkene addition step and stabilize the resulting intermediate such that downstream elementary steps, such as protodemetalation, oxidative addition, or transmetalation, outcompete β-H elimination.

The design of new directing groups with distinct coordination properties constitutes a significant challenge and opportunity in this area of study, given the ability of the directing group to engender control of pathway selectivity during catalysis. In our past work we have used the strongly coordinating 8-aminoquinoline (AQ) and 2-pyridyl-8-aminoquinoline (PAQ) directing groups, which are efficient at suppressing β-H elimination to enable 1,2-difunctionalization and hydrofunctionalization. Based on these precedents, we hypothesized that a more weakly coordinating group may lead to a different scenario in which a β-H elimination step would now be kinetically accessible. Specifically, we sought to identify a directing group that would lie in the "goldilocks" region—

Table 1. Optimization of Directing Group for Oxidative Heck Coupling with 1,2-Dialkyl Alkenes[a]



Directing Group (DG)	Yield (II) [from (*E*)-I]	[from (*Z*)-I]	Directing Group (DG)	Yield (II) [from (*E*)-I]	[from (*Z*)-I]	Directing Group (DG)	Yield (II) [from (*E*)-I]	[from (*Z*)-I]
 A	<15%[b]	n.r.[c]	 G	45%[d]	30%[e]	 M	59%	84%
 B	n.r.[c]	n.r.[c]	 H	n.r.[c]	n.r.[c]	 N	65%	82%
 C	n.r.[c]	<15%[b]	 I	32%	23%	 O	40%	64%[f]
 D	n.r.[c]	n.r.[c]	 J	86%	80%	 P	<15%[b]	<15%[b]
 E	n.r.[c]	<15%[b]	 K (BT)S	**85%**	**91%**			
 F	<15%[b]	<15%[b]	 L	<15%[b]	25%	 Q	n.r.[c]	n.r.[c]

[a]Isolated yields except where otherwise noted. [b]Determined by ^{1}H NMR of the crude reaction using 1,3,5-trimethoxybenzene as internal standard. [c]n.r.=no reaction. [d]Inseparable from 22% of two unidentifiable isomers that contain a 1,2-disubstituted internal olefin motif. [e]Inseparable from 26% of two unidentifiable isomers that contain a 1,2-disubstituted internal olefin motif. [f]Isolated as a 7:1 mixture of isomers (*Z*:*E*).

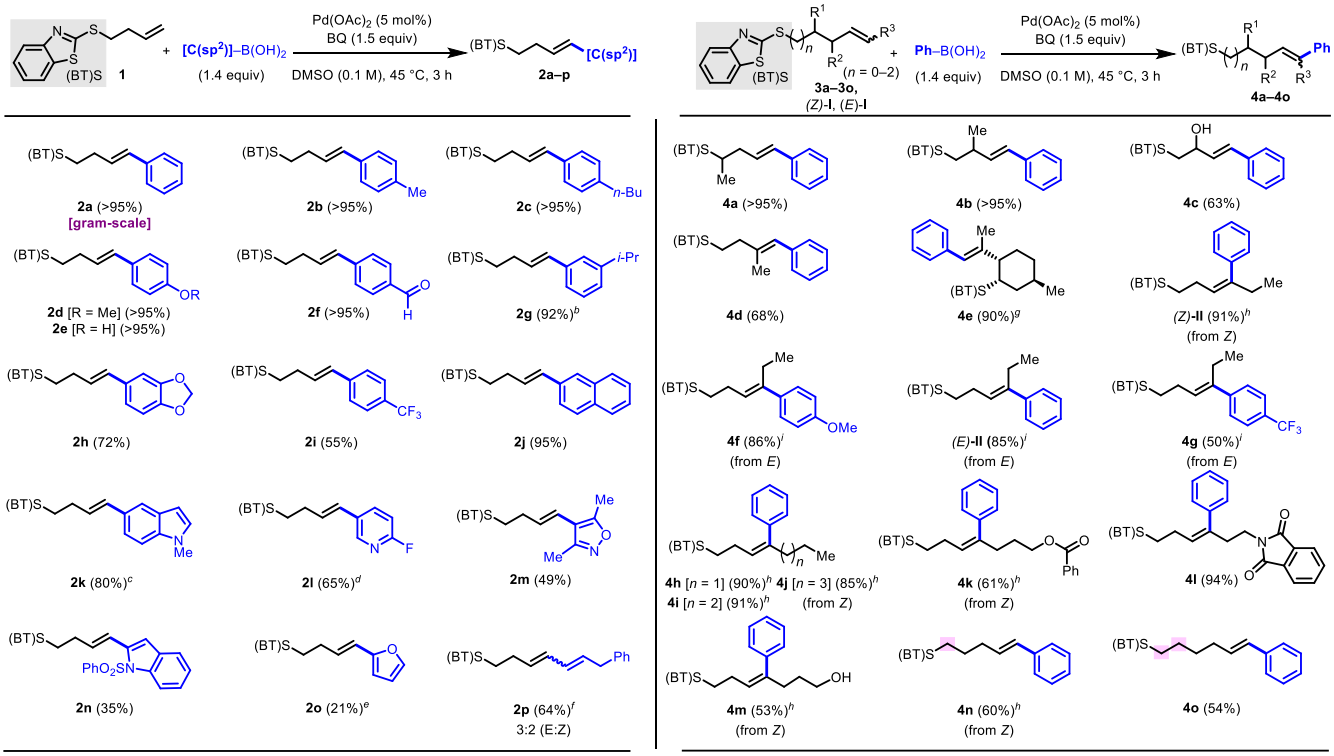
possessing sufficient coordination strength to facilitate complete selectivity in the nucleopalladation step, even with especially challenging substrates (such as 1,2-dialkyl alkenes), yet still weakly coordinating enough to allow selective β-H elimination. Such a reaction sequence would be synthetically valuable by allowing formal C(alkenyl)–H functionalization,[2d] enabling conversion of a simple alkene starting material into a regio- and stereodefined tri- or tetra-substituted alkene product (Scheme 1).

To validate this general hypothesis, we elected to focus on the palladium(II)-catalyzed oxidative Heck reaction, anticipating that newly identified directing groups would also find utility in other palladium(II)-catalyzed reactions (*vide infra*). Despite extensive efforts over the past several decades, knowledge gaps persist in Heck-type chemistry. Directed variants of the palladium(II)-catalyzed oxidative Heck reactions, for instance, are relatively rare, with White's seminal study of heteroatom-directed oxidative Heck arylation of terminal alkenes a notable exception.[5] A closely related body of literature has examined directed variants of classical-polarity palladium(0)-catalyzed Mizoroki–Heck reactions,[1d] with pioneering work here including contributions by Hallberg,[5] Carreterro,[6] Yoshida,[7] and others.[8] These studies have typically focused on heteroatom-substituted alkene substrates, including vinyl sulfides, ethers, or silanes, and in these designs, the coordinating group is built into the heteroatom linkage. For these systems, competitive binding of the phosphine ligand versus the directing group is an important consideration. Included in these studies are relatively few alkyl-substituted alkenes, with examples mostly limited to terminal allylic alcohols, amines, and their derivatives.

Across all Heck-type chemistry, internal asymmetrically substituted di- and tri-substituted alkenes remain difficult substrates. Sigman has developed elegant catalytic systems for both oxidative and non-oxidative redox relay asymmetric Heck arylation of internal alkenes.[9] In these reactions, the highly electron-deficient palladium catalyst undergoes rapid β-H elimination/reinsertion (chain-walking) to an appropriate terminating group (e.g., an alcohol). Complementing such chain-walking Heck systems with those that preserve the alkene in a precise geometric relationship to the newly installed aryl group would be desirable in situations where the alkene is required in the resulting product. In parallel to this study, Shenvi reported an intermolecular Heck coupling that can direct arylation of electronically unbiased tri- and tetra-substituted alkenes and establish quaternary carbons while migrating the olefin only one position and not into conjugation with the carboxylic acid directing group as is common in redox-relay Heck reactions.[10]

RESULTS AND DISCUSSION

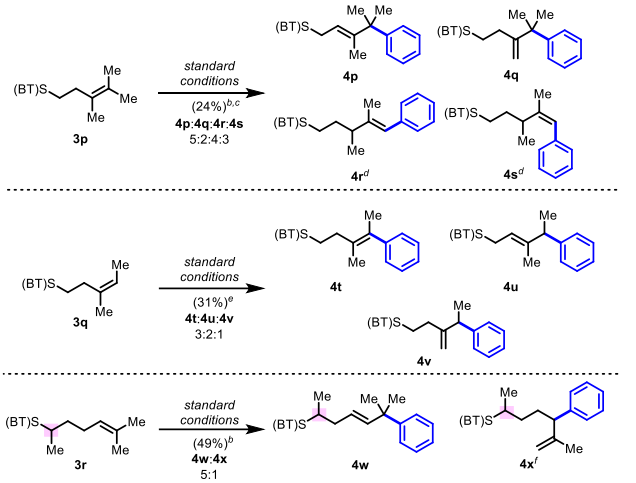
Directing Group and Reaction Optimization. The investigation commenced by testing a series of potential directing groups for their ability to promote a classically challenging oxidative Heck reaction with a 1,2-substituted alkene. We focused on thioether-based directing groups (**I**) due to on their ease of installation via nucleophilic substitution chemistry, ability to be productively removed in a variety of preparatively useful reactions (*e.g.*, Julia olefination), and established effectiveness as directing groups in palladium complex formation[11] and catalysis.[12]



Scheme 2. Scope for (BT)S-Directed Oxidative Heck Reaction[a]

[a]Isolated yields. [b]Inseparable from 8% of an unknown isomer. [c]10:1 isomeric mixture of *E* and *Z*. [d]Inseparable from 7% of an unknown isomer. [e]Isolated as a 6:1 mixture of inseparable isomers (*E*:*Z*). [f]Isolated as a 3:2 mixture; isomers separated by LC. [g]Inseparable from 10% of an unknown isomer. [h]From the *Z*-olefin; 50 mM, 65 °C. [i]From the *E*-olefin; 50 mM, 6 h.

A series of homoallylic thioether-based substrates containing internal (*E*)- or (*Z*)-alkenes were thus prepared. These substrates were subjected to Pd(II)-catalyzed oxidative Heck reaction conditions, which were optimized in parallel using a Design of Experiment workflow with automated reaction setup and sampling (see SI) (Table 1). As a control, a homoallylic alcohol substrate (**I-A**) was tested and did not deliver meaningful quantities of the desired product; similarly, simple aryl thioethers and sulfoxides (**B**–**E**) were ineffective, despite their previously established utility as directing groups in palladium(II) catalysis.[13] We then turned our attention to azaheterocyclic thioethers, reasoning that the coordination strength of sulfur would be attenuated in these cases and that such substrates offered additional opportunities for coordination of the palladium catalysts to an N(sp^2) atom during catalysis. Tetrazole directing group **G** afforded moderate yield of the desired product with both the *E*- and *Z*-alkene starting material; unfortunately, in this case the remainder of the starting material was completely converted into undesired byproducts. Based on the successful functionalization of the internal alkene with directing group **G**, we tested **F** and **H**, but found minimal to no product. Benzoxazole thioether directing group **I** provided slightly diminished yields compared to directing group **G**. However, in this case the product selectivity was improved, as we did not observe significant byproduct formation. Fortunately, we discovered that two related directing groups, **J** and **K**, the latter of which we refer to as (BT)S throughout the remainder of the manuscript, offered high reactivity and selectivity. Yields in these cases were 86% and 80% for products (*E*)-**II-J** and (*Z*)-**II-J**, and 85% and 91% for products (*Z*)-**II-K** and (*Z*)-**II-K**. Substrates with similar thiazole-type directing groups, **L–O,** with different steric and electronic properties gave lower yields of **II**. We next tested oxidized versions of (BT)S, **P** and **Q**, as controls, but minimal to no product formation was observed in these cases.



Scheme 3. Results with Tri- and Tetra-substituted Olefins[a]

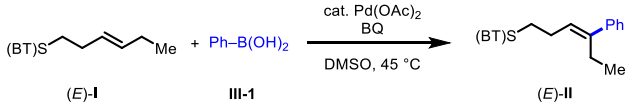
[a]Reaction conditions: alkene (0.1 mmol), phenylboronic acid (0.14 mmol), BQ (0.15 mmol), $Pd(OAc)_2$ (5 mol%), DMSO (1 mL), 45 °C, 3 h, unless otherwise noted; isolated yields. [b]Run at 65 °C and in DMSO (2 mL). [c]Isolated as a 5:2:4:3 mixture of isomers; 50 mM at 65 °C. [d]Isomers separated by HPLC. [e]Isolated as a 3:2:1 mixture of isomers; isomers separated by HPLC. [f]Observed by NMR.

Collectively, these results point to a somewhat complex relationship between structure and reactivity/selectivity, which was probed further through a detailed analysis of the possible coordination modes of **K** ((BT)S) (*vide infra*). Based on its effectiveness in this challenging oxidative Heck reaction and its potential utility in downstream chemistry (e.g., oxidation followed by modified Julia olefination), **K** ((BT)S) was selected for further investigation.

Scope of Oxidative Heck Reaction. We proceeded to investigate the substrate and coupling partner scope of this directed oxidative Heck reaction (Scheme 2). Arylboronic acids with a variety of functional groups, including electron-withdrawing and electron-donating moieties, reacted under the standard conditions to give products **2a–k** in high yields. Heteroarylboronic acids also gave the corresponding products **2l–p** in reasonable yields. Notably, (*E*)-(3-phenylprop-1-en-1-yl)boronic acid provided product in reasonable yield; however both (*E*)- and (*Z*)-isomers, **2p**, were formed in a 3:2 ratio. Two representative alkylboronic acids, methylboronic acid and neopentylboronic acid, were tested, but unfortunately these were not competent coupling partners in the reaction.

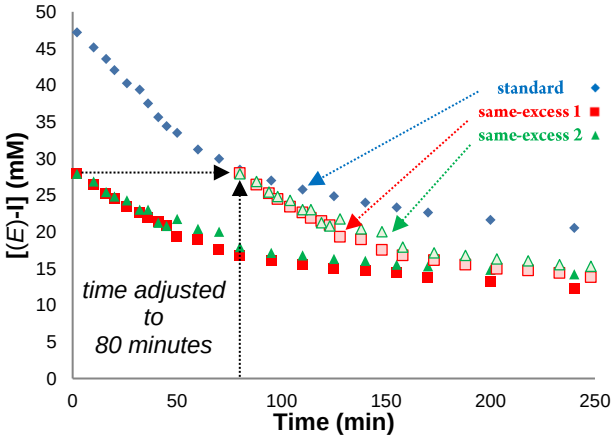
Next, we moved on to probe the alkene scope (Scheme 2). We found that alkyl branching was tolerated at both the α- and β-positions, as exemplified by products **4a** and **4b**, which were formed in nearly quantitative yields. We next tested a substrate containing an intervening alcohol, which is an established terminating group in Heck chain-walking processes. Nevertheless, in this case we observed that product **4c**, with the alcohol intact, was formed in high yield. The fact that the corresponding ketone product is not formed in this case demonstrates that the alternative *endo*-β-H elimination pathway from the putative palladacycle intermediate is disfavored. Furthermore, 1,1-disubstituted alkenes were found to be tolerated, allowing for formation of **4d** in moderately high yield and **4e**, a derivative of the natural product isopulegol, in high yield. As observed in the directing group optimization table (Table 1), both *E*- and *Z*-configured 1,2-disubstituted alkenes gave high yield of the desired products (*E*)-**II** and (*Z*)-**II**, respectively, and importantly in both cases, the products were obtained as single alkene stereoisomers. With (*E*)-**I** as a representative internal alkene, other aryl boronic acids were tested, and it was found that an electron-rich aryl group led to higher reactivity compared to an electron-poor aryl group (*vide infra*). In the case of the *p*-CF_3-substituted example, a 3:1 ratio of conjugated to non-conjugated products was obtained, suggesting that the identity of the aryl group can influence the energy barriers for competitive β-H elimination pathways following migratory insertion—at least to some extent. A series of other internal alkenes bearing different linear alkyl chains were tested (**4h–4j**) along with examples containing an additional functional group potentially capable of coordinating the catalyst or perturbing the electron properties of the alkene (**4k–4m**), and in all cases moderate to high yield of the desired, conjugated product was observed. Different tether lengths were also examined, and it was found that both γ,δ- and δ,ε-unsaturated alkenes (**4n** and **4o**) are competent in this system. No reaction was observed with the corresponding allylic substrate. Across this series of substrates, preference for aryl addition to the alkenyl carbon atom distal from the (BT)S group is consistent with the notion that the (BT)S group is coordinated during migratory insertion. Although some exceptions exist,[6b,6c,8k] directed Heck-type reactions typically favor formation of the regioisomer arising from a transition state where the migrating aryl or alkenyl group is exo-cyclic to incipient palladacycle,[1d,5–8] even with internal non-conjugated alkenes,[3h,4d,10] likely due to minimization of strain compared to the alternative possibility with the aryl group in an endo-cyclic orientation.

Tri- and tetra-substituted olefins (**3p–3r**) were also examined (Scheme 3). In these cases complex product mixtures were typically obtained, indicating that these substrate classes are generally incompatible with this method, likely due to increased steric hindrance and due to a greater number of possible side reactions.[10] With tetrasubstitued substrate **3p**, the formation of products **4r** and **4s** suggests that positional isomerization of the alkene takes place under the reaction conditions with this substrate. One interpretation of this result is that in cases where migratory insertion is sluggish due to steric hindrance, other off-cycle pathways can predominate. With substrates **3p** and **3r**, the requirement to undergo β-hydride elimination in an *endo*-fashion (towards the directing group and within the palladacycle) rather than the preferred *exo*-fashion is also likely a contributing factor to low yields.



A[a]

	[(*E*)-I]	[III-1]	[BQ]	[(*E*)-II]
standard	50 mM	70 mM	75 mM	0 mM
same-excess 1	30 mM	50 mM	55 mM	0 mM
same-excess 2	30 mM	50 mM	55 mM	20 mM



B[b]

	[(*E*)-I]	[III-1]	[BQ]	[(*E*)-II]
standard	50 mM	70 mM	75 mM	0 mM
diff.-excess (*E*)-I	30 mM	70 mM	75 mM	0 mM
diff.-excess III-1	50 mM	50 mM	75 mM	0 mM
diff.-excess BQ	50 mM	70 mM	55 mM	0 mM

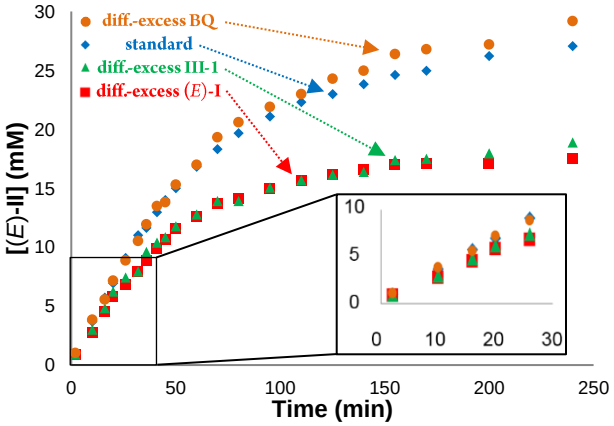
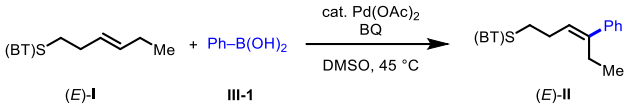


Figure 1. (A) Same-excess experiments with and without product. (B) Different-excess experiments of starting material, phenylboronic acid, and benzoquinone. [a]Due to the consumption of 1 equivalent of Benzoquinone per turnover, reactions were set up with $Pd(OAc)_2$ (2.5 mM) and with (*E*)-**I** (*variable*), **III**, BQ, and (*E*)-**II** (for same-excess 3) corresponding to the expected amounts at time = 80 min for the standard reaction in DMSO (2.0 mL), at 45 °C, and in air. [b]Reaction conditions: (*E*)-**I** (*variable*), **III** (*variable*), Benzoquinone (*variable*), $Pd(OAc)_2$ (*variable*), DMSO (2.0 mL), 45 °C, air.

With alkene **3q**, the product distribution suggests that the migratory insertion step was selective, but that subsequent β-H elimination was unselective. Of the three tri/tetrasubstitued alkenes tested, **3r** offered the highest selectivity. In this case, product **4w** containing a quaternary carbon was formed as the main product along with regioisomer **4x** in a 5:1 ratio and 49% combined yield.



	[(*E*)-**I**]	[**III-1**]	[**BQ**]	[$Pd(OAc)_2$]
10 mol%	**50 mM**	**70 mM**	**75 mM**	**5.00 mM**
7.5 mol%	50 mM	70 mM	75 mM	**3.75 mM**
5 mol%	50 mM	70 mM	75 mM	**2.50 mM**
4 mol%	50 mM	70 mM	75 mM	**2.00 mM**
3 mol%	50 mM	70 mM	75 mM	**1.50 mM**

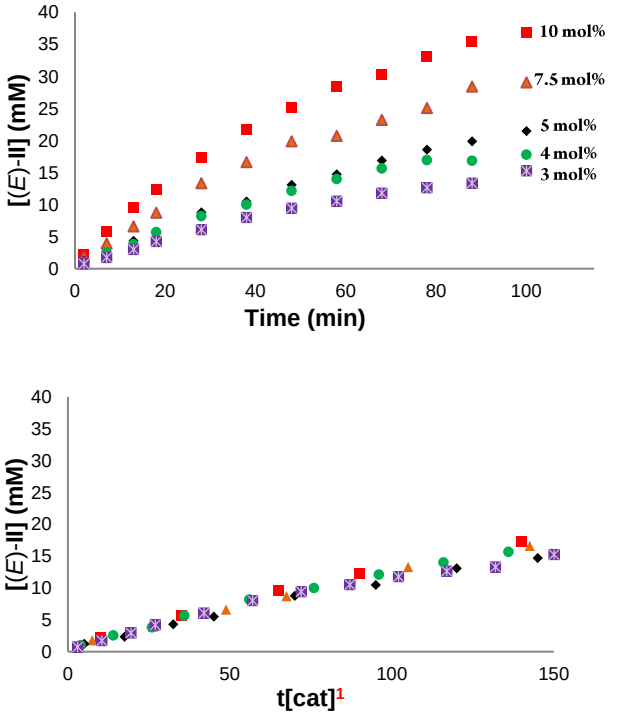


Figure 2. Reaction conditions (*E*)-**I** (50 mM), **III-1** (70 mM), Benzoquinone (75 mM), $Pd(OAc)_2$ (*variable*), DMSO (2.0 mL), 45 °C, air.

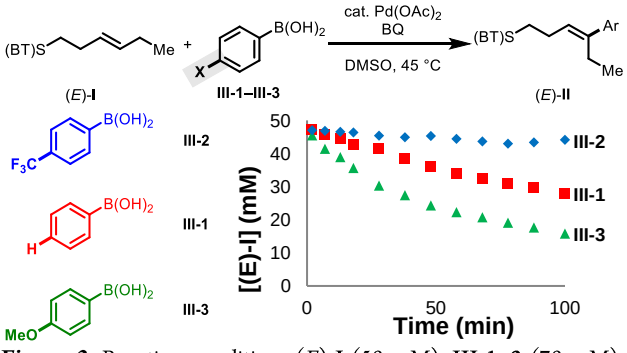
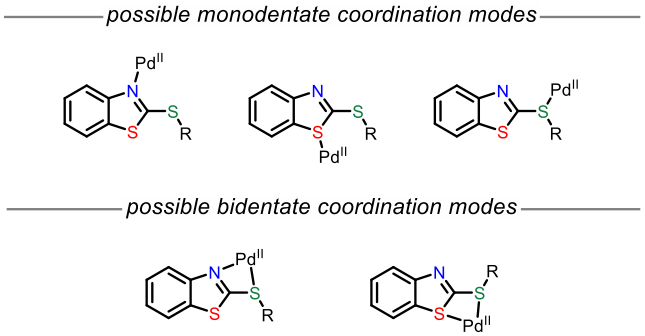
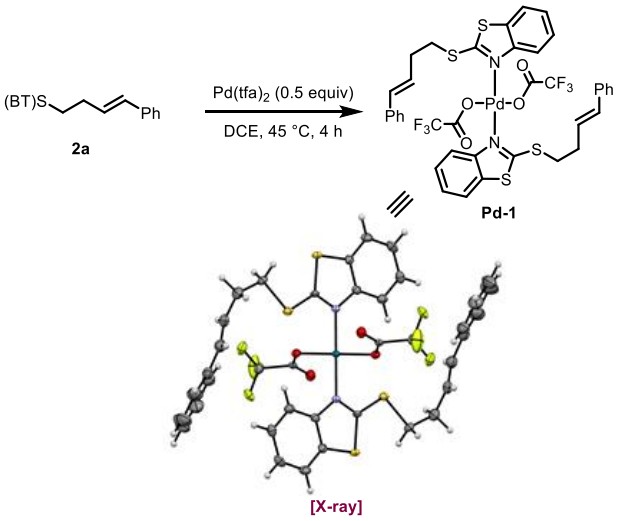


Figure 3. Reaction conditions (*E*)-**I** (50 mM), **III-1–3** (70 mM), Benzoquinone (75 mM), $Pd(OAc)_2$ (5 mol%), DMSO (2.0 mL), 45 °C, air.

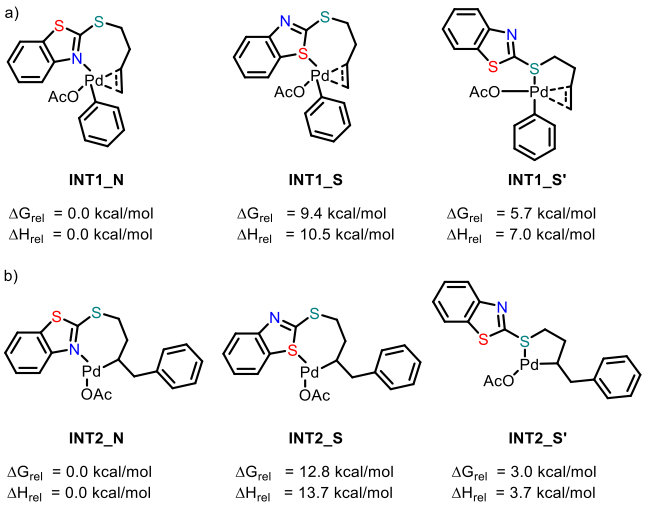
Reaction Progress Kinetic Analysis (RPKA). The high regio- and stereo selectivity of this method with diverse 1,2-disubstituted alkenes prompted us to delve into the reaction mechanism by combining reaction kinetics and computational studies. First, to elucidate the kinetic



Scheme 4. Potential Binding Modes of Pd^{II} to (BT)S Group



Scheme 5. Crystal Structure of $Pd(tfa)_2$**o2** Complex



Scheme 6. Relative energies of Possible Intermediates in the Oxidative Heck Reaction[a]

[a]Relative free energies of the intermediates of the catalytic cycle a) before and b) after migratory insertion.

features of catalytic process, we performed reaction progress kinetic analysis (RPKA)[14] using representative (*E*)- and (*Z*)-alkene substrates. Insights for both substrate types were generally mutually consistent, so the ensuing analysis focuses on the (*E*) substrate, and information regarding the (*Z*)-alkene substrate can be found in the SI. Regarding general kinetic behavior, we noted that the reaction appears to contain two regimes: one that is operative until 35–50% conversion is reached (representing approximately the first 60 min for the reaction with the (*E*)-alkene and 30 min for the reaction with the (*Z*)-alkene under standard conditions), and a second regime from that point forward where the reaction proceeds more slowly. This could arise from several different root causes, including uncharacterized catalyst deactivation processes. Though both regimes are valuable to understand, we focused our attention on this initial stage of the reaction, as it is more likely to reflect the intrinsic kinetics before other off-cycle processes predominate.

First, we performed a "same-excess" experiment, which simulates entering the catalytic cycle after multiple catalyst turnovers in order to probe for catalyst activation or deactivation pathways (Figure 1A). The time-adjusted same-excess experiment without added product was observed to proceed at a faster rate than the standard reaction, pointing to possible catalyst deactivation or product inhibition. Results were similar

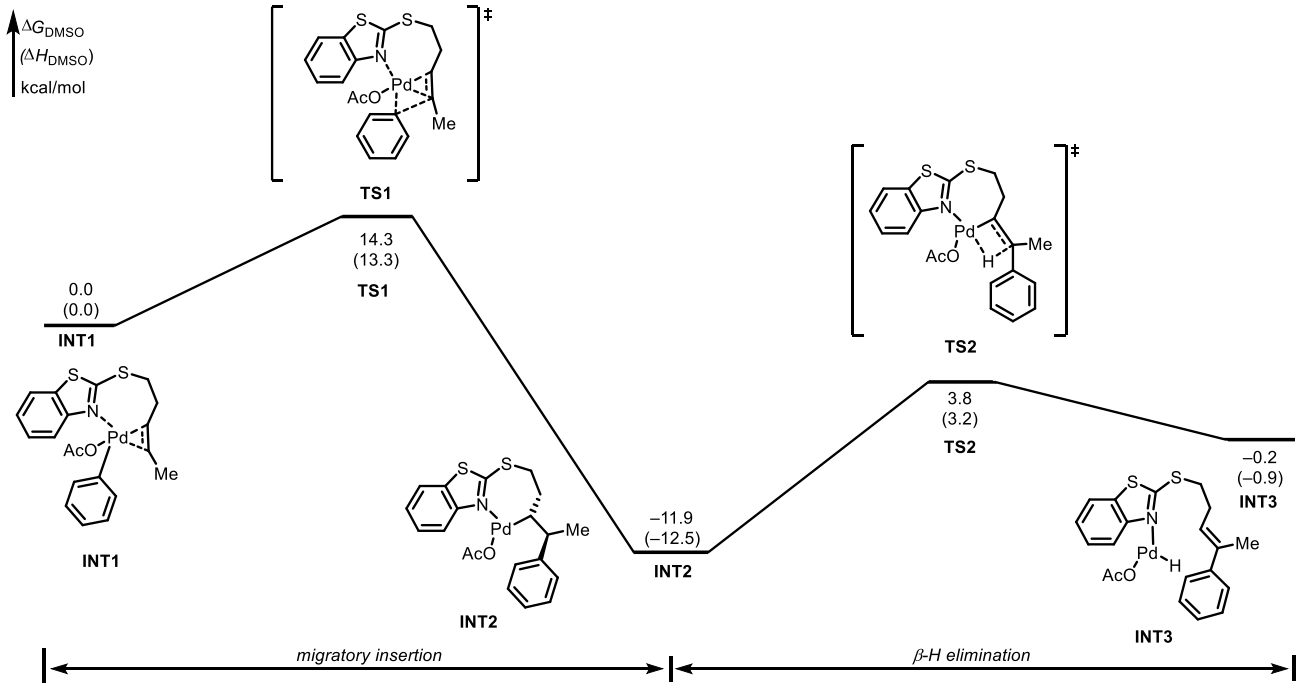


Figure 4. Computed energy profile for migratory insertion and β-hydride elimination steps.

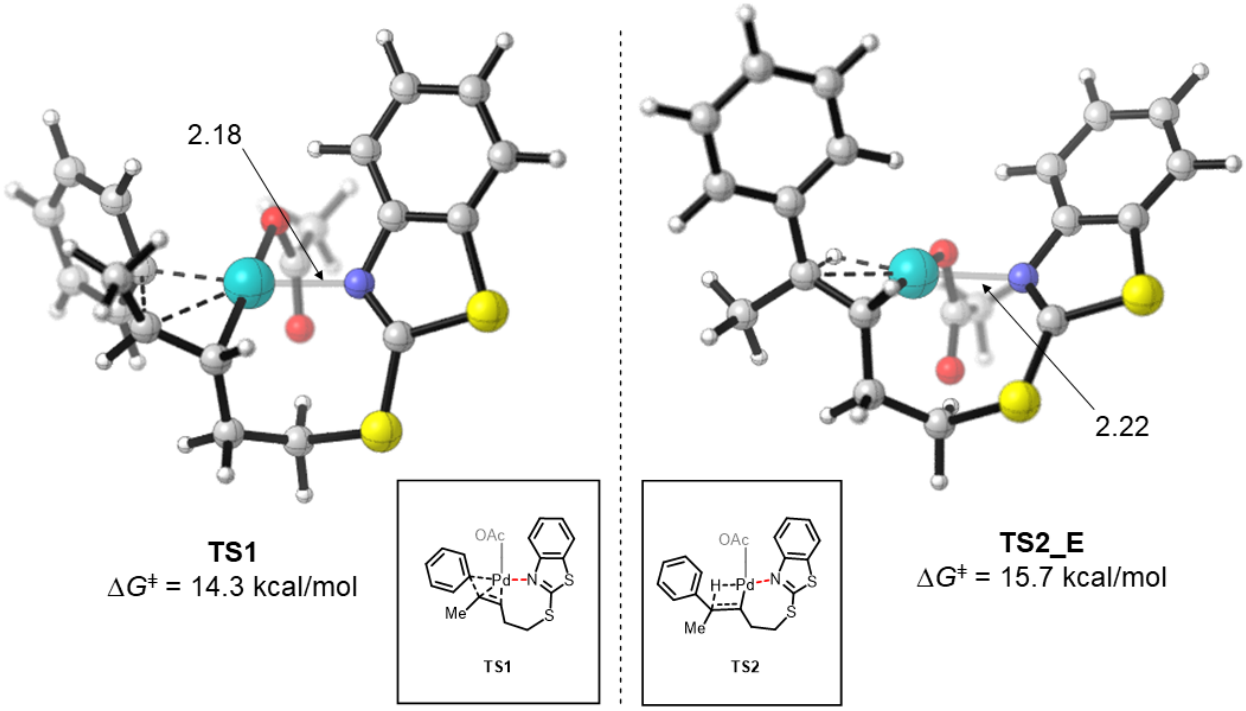


Figure 5. Computed transition states for migratory insertion (left) and β-hydride elimination (right) steps.

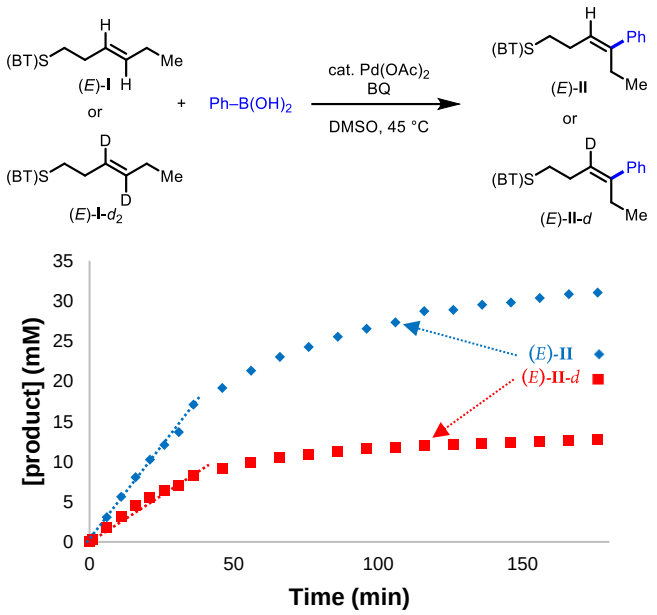
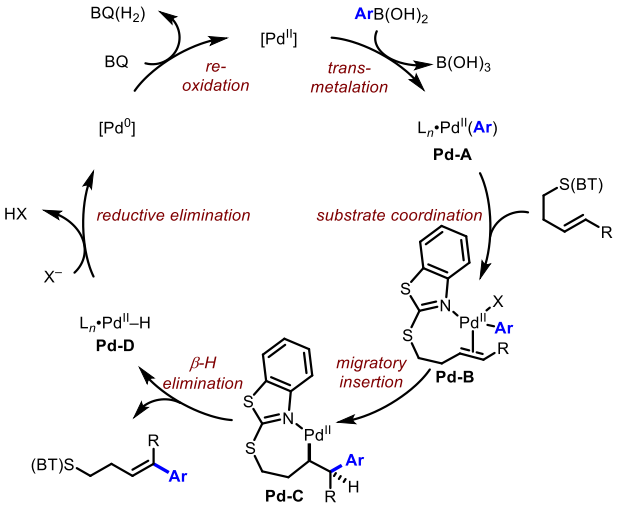


Figure 6. Deuterated starting material experiment for the directed oxidative Heck reaction. Reaction conditions (*E*)-**I** or (*E*)-**I**-d_2 (50 mM), **III-1** (70 mM), Benzoquinone (75 mM), $Pd(OAc)_2$ (5 mol%), DMSO (2.0 mL), 45 °C, air.



Scheme 7. (BT)S-directed Oxidative Heck Catalytic Cycle

with added product, suggesting that the catalyst is being deactivated through off-cycle processes. Catalyst deactivation in this reaction can take place if Pd(0) is not efficiently reoxidized, enabling precipitation of palladium black.

Next, driving forces were determined through a series of "different-excess" experiments (Figure 1B). We first varied catalyst concentration and found that the reaction rates increased at higher catalyst concentration. Visualizing the data using the Burés method (Figure 2)[15] with an x-axis that is normalized by catalyst concentration reveals that the reaction is first-order in [Pd]. We then examined the effect of changing the concentration of others reaction components, namely decreased alkene concentration [(*E*)-**I**] (different-excess [(*E*)-**I**]), decreased phenylboronic acid concentration [**III**] (different-excess [**III**]), and decreased benzoquinone concentration [BQ] (different-excess [BQ]). Overlay between the standard reaction and the different-excess BQ experiment throughout the time course is consistent with apparent zero-order kinetics in [BQ]. The different-excess (*E*)-**I** and different-excess [**III**] experiments overlay reasonably well with the standard reaction at <30% conversion (first 30 min) and then deviate as the limiting reagents are consumed. This indicates apparent zero-order kinetics in [(*E*)-**I**] and [**III**] early in the reaction. First-order kinetics in [Pd] combined with zero-order kinetics in [(*E*)-**I**], [**III**], and [BQ], rule out substrate binding, transmetalation, and reoxidation, respectively as possible turnover-limiting steps, pointing to either migratory insertion of a substrate-bound [Pd(II)–Ar] species or β-H elimination as possible turnover-limiting steps. As mentioned above, electron-rich arylboronic acids were found to be more reactive (Figure 3). To quantify this trend, we measured initial rates of the three representative arylboronic acids with *p*-CF_3, -H, and -OMe groups and found k_{rel} values of 1:3:8 across this series. This result does not necessarily allow one to disambiguate between the two mechanistic possibilities described above, as migratory insertion and β-H elimination could both potentially be facilitated by an electron-rich aryl group due to a more nucleophilic [Pd(II)–Ar] species and a more hydridic C–H bond, respectively. Since the turnover-limiting step cannot be distinguished based on the available rate dependencies, we next turned to complementary techniques to gain insight on these steps and other aspects of the catalytic cycle.

Directing Group Coordination. The results in Table 1 revealed the structural features that are required for a suitable directing group, demonstrating the importance of the embedded benzo-fused methylidene dithioacetal motif in **J** and **K**. Nevertheless, **K** ((BT)S) also posses an N(sp^2) capable of coordinating the palladium catalyst, complicating the potential coordination chemistry involved, which we sought to elucidate through crystallography and computation studies. Several different mono- and bidentate binding modes can be envisioned (Scheme 4), and to probe this, we first attempted to synthesize various palladium complexes of potential relevance to catalysis. Indeed, we were able to obtain a representative product-bound palladium species by combining **2a** and $Pd(tfa)_2$. The resulting 2:1 complex, **Pd-1**, was amenable to characterization by X-ray crystallography, and in the structure, the (BT)S directing group is coordinated in a monodentate fashion through the nitrogen atom, consistent with earlier literature precedents (Scheme 5).[16] In this case the alkene was not bound to the palladium center. The same monodentate nitrogen binding mode was also later observed with a representative starting material–palladium complex for a related C–H activation reaction (*vide infra*).

DFT Calculations. Next, we performed density functional theory (DFT) calculations to further probe key aspects of the reaction mechanism. First, the possible monodentate coordination modes were evaluated using **1** as the model substrate. Geometry optimizations were performed on the intermediates of the proposed catalytic cycle at the migratory insertion step. Three coordination modes were investigated, i.e. coordination through N (**INT1_N** and **INT2_N**), coordination through S of the heterocycle (**INT1_S, INT2_S**) and coordination through S outside the heterocycle (**INT1_S', INT2_S'**). The N-coordinated intermediates were lowest in energy, followed by the S(proximal)-coordinated intermediates (Scheme 6). The S(distal)-coordinated intermediates were highest in energy. These trends also held in the corresponding transition state energies for the migratory insertion step (see Figure S19 in the SI).

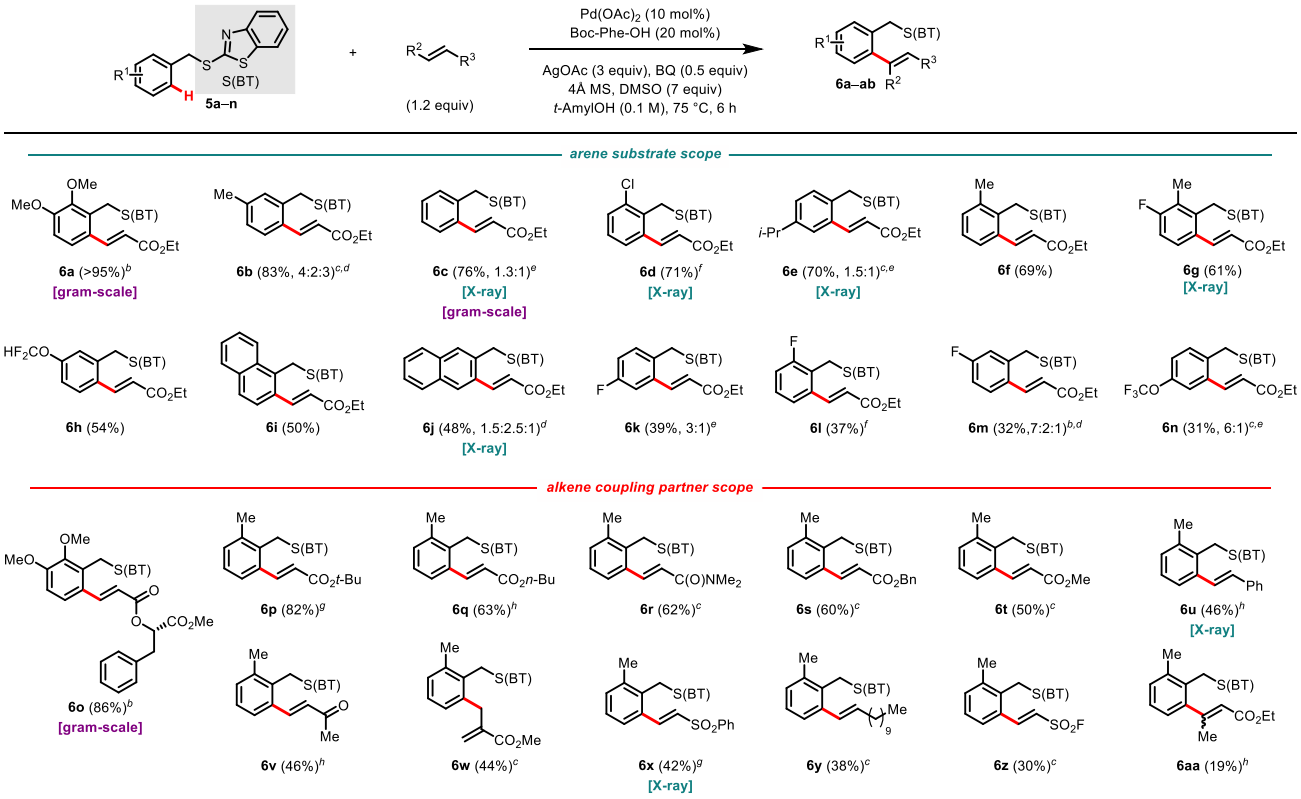
One explanation that reconciles these results with the observation that both directing groups **J** and **K** ((BT)S) are similarly effective (Table 1) is that the catalytic reaction can take place with the directing group bound either through the proximal-S atom or through the N-atom. With BT(S), the latter pathway is computationally predicted to be lower-energy, though the former is also energetically accessible. The S(proximal)-coordinated pathway is likely to be operative in cases such as **J**, where the N-atom is absent.

Probing the Turnover-Limiting Step. As experimental mechanistic investigations revealed the rate determining step to be either migratory insertion or β-hydride elimination, DFT calculations were performed to locate the transition states to determine the energetics of these two steps. A truncated (*E*) internal alkene was used as the model substrate to minimize computational time. The energy profile is shown in Figure 4. The *syn*-migratory insertion step (**TS1**) has an activation free energy barrier of 14.3 kcal/mol with respect to the π-alkene complex **INT1**. The subsequent β-hydride elimination step has a higher activation energy barrier of 15.7 kcal/mol (**TS2**) indicating that the β-hydride elimination is the turnover-limiting step. The optimized structures of **TS1** and **TS2** are shown in Figure 5. The weaker coordination of the (BT)S group is evidenced by the longer Pd···N distances of the transition states at both migratory insertion (2.18 Å) and β-hydride elimination (2.22 Å) steps. Shorter Pd···N distances have been reported for transition states with strongly coordinating directing groups such as 8-aminoquinoline and 2-pyridyl-8-aminoquinoline (2.02–2.08 Å).[3e,17] The energy profile for the migratory insertion and β-hydride elimination was also calculated for the terminal alkene, **1** (see SI; Figure S17 and S18). The calculations revealed that the formation of the *E*-isomer is kinetically favored at the rate- and stereoselectivity-determining step, β-hydride elimination, consistent with experimental selectivity (see SI).

With the computational data suggesting that β-hydride elimination is the turnover-limiting step, we next examined whether there was a kinetic isotope (KIE) in the rates between a representative substrate containing deuterated ((*E*)-**II**-d_2) and non-deuterated ((*E*)-**II**) alkenyl positions (Figure 6). By monitoring desired product formation over the initial 45 min, we indeed found a primary KIE, k_H/k_D = 2.0. Additionally, we found that with the deuterated substrate the product distribution was not as clean, potentially due to other pathways (such as β-H elimination at other positions) being kinetically competitive when the typically favored β-H is replaced with a deuterium. Overall, the experimental and computational results are consistent with β-H elimination as the turnover-limiting step.

By combining the insights gathered from both DFT calculations and the kinetics experiments, we propose the general catalytic cycle as shown in Scheme 7. For simplicity, only the N-bound intermediates are shown, although as mentioned above S(proximal)-bound intermediates are also energetically accessible and could be active participants in the catalytic cycle. The reaction begins with substrate binding and transmetallation steps (in either potential order) to give intermediate **Pd-B**. Following this, a *syn*-migratory insertion gives the palladacycle **Pd-C**. Product is then generated via β-H elimination giving the Pd-hydride species **Pd-D**, which can undergo reductive elimination and reoxidation with BQ to provide the Pd(II) species required for turnover.

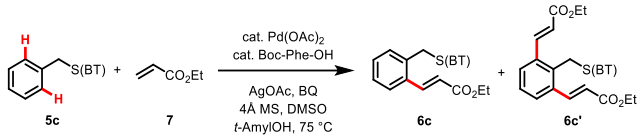
C(aryl)–H Olefination Background. Having established the efficacy of the (BT)S directing group in oxidative Heck chemistry, we were interested in exploring its utility in other palladium(II)-catalyzed reactions involving distinct elementary steps. Specifically, we were attracted to directed *ortho*-C–H olefination (Fujiwara–Moritani-type coupling)



Scheme 8. Scope for (BT)S-directed C–H Functionalization[a]

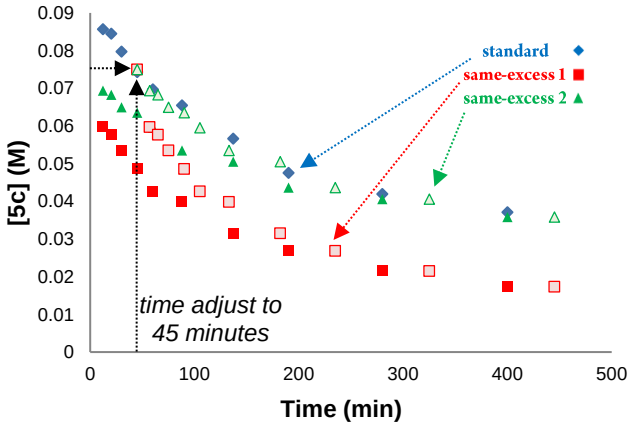
[a]Reaction conditions: **5a–aa** (0.10 mmol), Alkene (1.2 equiv), AgOAc (3 equiv) Benzoquinone (0.5 equiv), $Pd(OAc)_2$ (10 mol%), tAmylOH (1 mL), Boc-L-phenylalanine (0.2 equiv), DMSO (7 equiv), 4Å molecular sieves, 75 °C, air, 6 h. Percentages refer to isolated yields. [b]110 °C, nBu_4NPF_6 (2 equiv), 2h. [c]Alkene (2.2 equiv). [d]Ratio of mono-, mono'-, and bis-olefinated products, respectively, with the major product depicted. Mono- and mono'-olefinated products isolated as a mixture. [e]Ratio of mono- and bis-olefinated product, respectively, with the major product depicted. [f]Alkene (2.2 equiv), 24h. [g]24h. [h]Alkene (2.2 equiv), 24 h.

since the use of a versatile "masked olefin" directing group could allow rapid access to a number of conjugated natural products and materials.[18] Weakly coordinating directing groups, including those distal to the C–H bond of interest, have provided a valuable solution in many arene C–H functionalization reactions catalyzed by palladium, including amination,[19] formation of lactams,[20] construction of dihydrobenzofurans,[21] iodination,[22] and olefination.[23] We were encouraged to see that Zhang has shown the utility of using phenyl-, methyl-, and *p*-tolyl-thioethers[24] and the corresponding sulfoxides[25] for directed arene olefination, suggesting that the (BT)S directing group may provide a suitable directing group and then be able to serve as a modified Julia olefin precursor for easy transformation to the desired alkene. Furthermore, Maiti has developed an innovative sulfone directing group for *meta*-hydroxylation, which can subsequently serve as a Julia olefination precursor, and we hoped to provide a similar solution for *ortho*-C–H functionalization.[26]



A[a]

	[5c]	[7]	[6c]	[6c']
standard	0.100 M	0.200 M	0 M	0 M
same-excess 1	0.075 M	0.160 M	0 M	0 M
same-excess 2	0.075 M	0.160 M	0.020 M	0.003 M



B[b]

	[5c]	[7]	[6c]	[6c']
standard	0.100 M	0.120 M	0 M	0 M
diff.-excess 5c	0.060 M	0.120 M	0 M	0 M
diff.-excess V	0.100 M	0.200 M	0 M	0 M

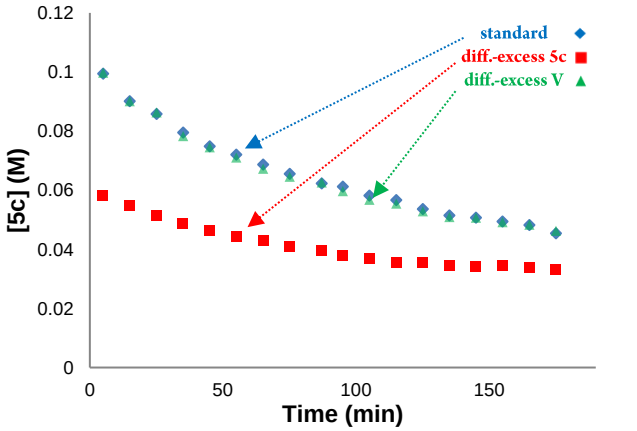
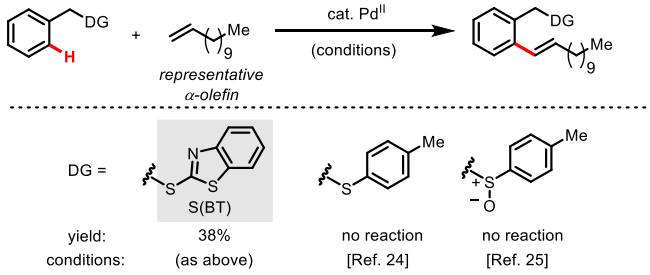


Figure 7. (A) Same-excess experiment. (B) Different-excess experiments of starting material and ethyl acrylate. [a]Due to secondary reaction of ethyl acrylate, same-excess 1 and 2 were set up with amounts of **5c**, **7**, **6c**, **6c'**, BQ (0.375 M), and AgOAc (2.250 M) to equal the amounts observed by qNMR at time = 45 min for the standard reaction (see Figure S16 in SI). [b]Reaction conditions unless otherwise stated: **5c** (*variable*), **7** (*variable*), AgOAc (3 equiv), Benzoquinone (0.5 equiv), $Pd(OAc)_2$ (10 mol%), tAmylOH (1 mL), Boc-L-phenylalanine (0.2 equiv), DMSO (7 equiv), 4Å molecular sieves, 75 °C, air.

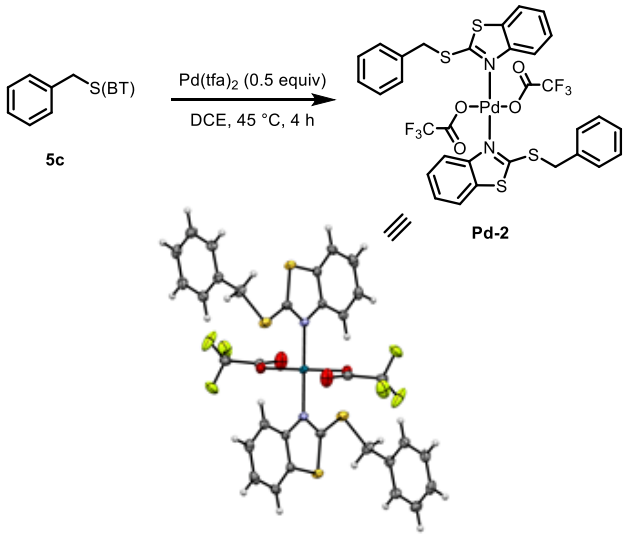
C–H Functionalization Substrate Scope. After reexamining the directing groups **A**–**H** and **K**–**Q** in Table 1 under optimized MPAA-accelerated C–H olefination reaction conditions,[27] it was clear that (BT)S again was suitable in its ability to successfully direct the desired reaction (Table S13 in supporting information).

Therefore, we next examined the scope of the (BT)S-directed C–H olefination reaction (Scheme 8). We were pleased to see that the electron-rich starting material **5a** produced a nearly quantitative yield, and electron-rich, electron-poor, and alkyl functional groups were tolerated to yield **6b**–**h** and **6k**–**n** in moderate to high yields. The (BT)S directing group can also promote *ortho*-olefination in polyaromatic ring systems, such as naphthalene producing **6i**–**j** in moderate yields. As expected, a number of acrylates can be tolerated in this reaction to give **6o**–**q** and



Scheme 9. Unactivated Alkene Reactivity[a]

[a] (BT)S directed reaction run with the following conditions: starting material (0.10 mmol), Alkene (1.2 equiv), AgOAc (3 equiv) Benzoquinone (0.5 equiv), $Pd(OAc)_2$ (10 mol%), tAmylOH (1 mL), Boc-L-phenylalanine (0.2 equiv), DMSO (7 equiv), 4Å molecular sieves, 75 °C, air, 6 h; other reactions run both under above conditions and under originally reported conditions.



Scheme 10. Crystal structureof $Pd(tfa)_2$o 5c complex

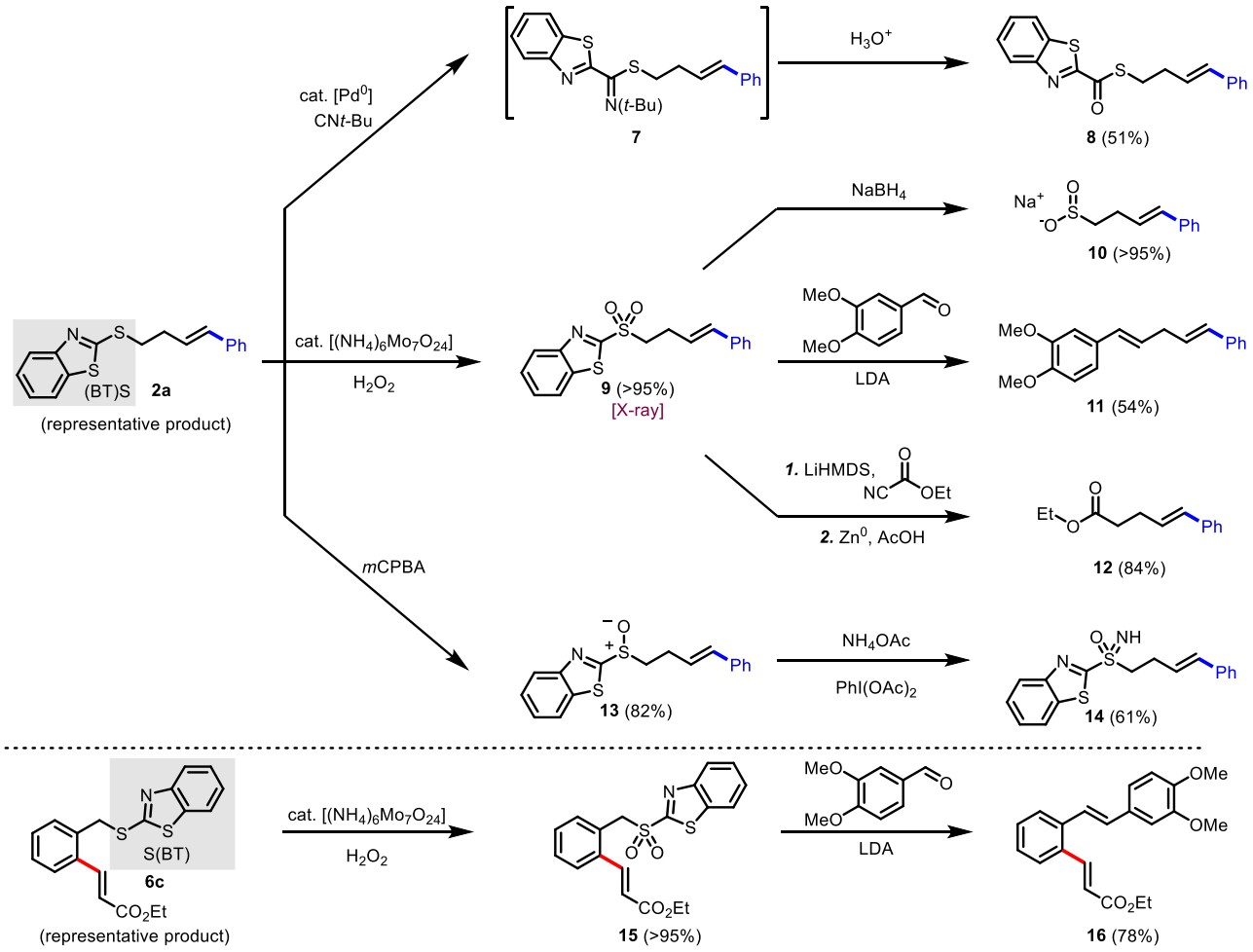
6s–t in high yields. We were excited to see that this (BT)S-directed olefination could also be expanded to other alkene classes such as acrylamide giving **6r** and styrene giving **6u**. Interestingly, methyl methacrylate gave the non-conjugated product **6w**, consistent with a mechanism in which β-H elimination proceeds *exo* to the putative metalacycle in this case. Other competent alkene coupling partners include phenyl vinyl sulfone (**6x**), dodecene (**6y**), ethenesulfonyl fluoride (**6z**)[28], and ethyl crotonate (**6aa**).

Notably, **6y** represents a somewhat unique product in directed arene olefination, as the use of non-conjugated terminal alkenes remains rare.[29] Notably, the thioether[24] and sulfoxide[25] directed reactions designed by Zhang were replicated with similar yield as previously reported for ethyl acrylate but yielded no product with dodecene showing the unique characteristics of (BT)S (Scheme 9).

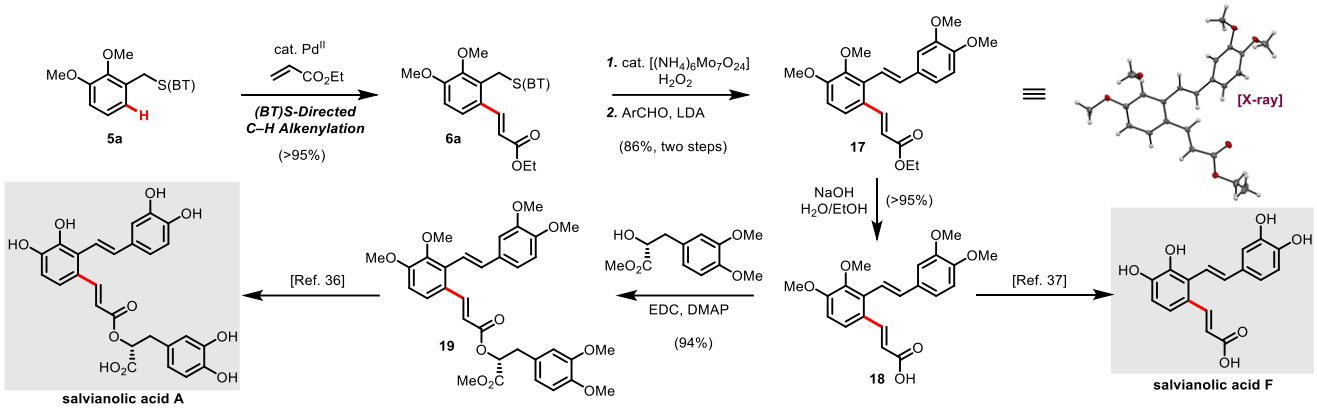
C–H Olefination RPKA. We decided to probe the catalytic cycle of this reaction in an effort to better understand the role of (BT)S in directing C–H olefination. To this end, same excess and different excess experiments were performed using the simple, unsubstituted arene **5c** as a standard substrate.

Due to unique facets of this reaction, several experimental modifications were made compared to the standard same-excess and different-excess protocols that are generally used. For both sets of data, starting material concentration, [**5c**], was plotted on the y-axis as opposed to product because both **6c** and **6c'** are formed in the reaction, with **6c** presumably being formed from which a second catalytic cycle to install an additional ethyl acrylate yields **6c'**. Moreover, the presence of a secondary reaction converting **6c** to **6c'** meant that the standard method of assuming a one-to-one coupling (and hence consumption) of starting material **5c** and coupling reagent **7** for the design of the same-excess experiment would not accurately reflect reaction conditions at 45 min. Therefore, values for **5c**, **7**, **6c**, and **6c'** as well as BQ were determined by qNMR at 45 min in the standard reaction, and those values were used when designing the same-excess experiments (see Figure S16 in the Supporting Information). The amount of AgOAc was also lowered to appropriately reflect oxidant consumption for each presumed cycle.

The same-excess data shows excellent overlay for the standard reaction and same-excess 2, which mimics the standard reaction at 45 min (Figure 7A). However, same-excess 1, which does not contain added product, shows an accelerated rate. This qualitatively implies that the decreased reaction rate is due to product inhibition rather than catalyst deactivation. This result, in combination with the result from the different-excess experiment discussed below, suggest a catalytic cycle in which palladium coordinates strongly to the products **6c** and **6c'**, and, due to this strong affinity, produces product **6c'** at a similar rate to the rate of formation of product **6c** at around 0.040M concentration of **6c**.



Scheme 11. Productive Removal and Transformation of the (BT)S Directing Group



Scheme 12. Formal Synthesis of (+)-Salvianolic acid A and Salvianolic acid F

Regarding the different excess experiments, overlay between the standard run and different-excess **V** shows a zero-order dependence in [**V**] suggesting that ethyl acrylate is not involved in the turnover-limiting step of this catalytic cycle (Figure 7B). Different-excess **5c** has a reduced rate compared to the standard reaction, showing a positive-order dependence in [**5c**]. This result is potentially consistent with either irreversible substrate binding between (BT)S and Pd or reversible substrate binding followed by turnover-limiting C–H functionalization. We favor the latter interpretation because substrate binding and dissociation is expected to be rapid. We were unable to detect the putative cyclopalladated intermediate under a variety of conditions, consistent with the notion that C–H activation may be the slow step in catalysis.

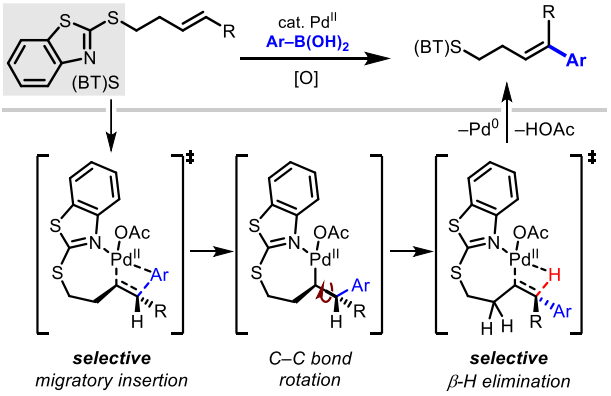
Directing Group Coordination. Similar to our mechanistic studies in the oxidative Heck reaction, we attempted to synthesize various complexes relevant to catalysis, and in this case were able to successfully isolate a starting-material-bound palladium trifluoroacetate complex **Pd-2**, which we could characterize by X-ray crystallography. As with the above crystal for the oxidative Heck reaction, the complex shows coordination of palladium through the nitrogen of the benzothiazole (Scheme 10).

Productive Removal and Transformation. Product **2a** from the oxidative Heck reaction was used as a model substrate for directing group conversion and removal (Scheme 11). Moderate yield was observed in a palladium-mediated isocyanide insertion, the product of which was isolated as **8** after acidic workup.[30] Fortunately, by treating **2a** with ammonium molybdate tetrahydrate, the sulfone product **9** could be formed in quantitative yield with no apparent oxidation of the olefin.[31] Sulfone **9** can be subsequently modified through several methods. Treatment with sodium borohydride affords a nearly quantitative yield of **10** containing the versatile sulfinic acid functional group.[32] A modified Julia olefination with vertraldehyde gave product **11** in 54% isolated yield as the (*E*)-alkene.[33] Sulfone **9** was also transformed to the carboxylic ester **12** in high yield via treatment with ethyl cyanoformate in the presence of LiHMDS and subsequent removal of the of the benzothiazole-sulfone using Zn-dust from the isolated intermediate.[34] Oxidation of **2a** with *m*CPBA also gave high yield of sulfoxide **13**. Successive treatment of **13** with ammonium acetate gave the sulfanone product **14** in 61% yield.[35] A representative C–H olefination product, **6c**, was also oxidized and subsequently transformed to the (*E*)-alkene **18** with veratraldehyde in 78% isolated yield.

Synthetic Applications. To demonstrate the utility of the (BT)S directing group in complex molecule synthesis, two natural products, salvianolic acid F and (+)-salvianolic acid A were formally synthesized using the (BT)S-directed C–H olefination reaction as the key step following a strategy inspired by the carbonyl directed synthesis by Xuan (Scheme 12).[36] Through this approach, salvianolic acid F was synthesized in 5 steps with a projected 19.2% overall yield from mercaptobenzothiazole, which represents the highest overall yield and lowest step count synthesis yet published.[37] (+)-Salvianolic acid A was also formally synthesized in 9 steps overall in 14.1% projected yield with the longest linear route being from the mercaptobenzothiazole representing 7 steps with a projected 16.6% yield. This synthesis of (+)-salvianolic acid A has a similar step-count and slightly elevated yield compared to the most recent, highest yielding synthesis yet published.[36]

CONCLUSION

In conclusion, we have demonstrated the utility of a new weakly-coordinating heteroaryl thioether directing group, (BT)S, that can facilitate catalytic transformations that require conformational flexibility for integral steps, such as β-hydride elimination (Scheme 13). This new directing group, which can be readily introduced by nucleophilic substitution of a hydroxyl or bromo functional group, serves as a versatile functional group for downstream manipulation. We probed each of the two reactions by performing RPKA and DFT, which helped to elucidate aspects of the mechanism for both catalytic cycles. We also demonstrated the utility of the (BT)S directing group by achieving high overall yields in the synthesis of two natural products.



Scheme 13. Illustration of the Selectivity of (BT)S

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Notes

The authors declare no competing financial interest.

Supporting Information

Experiment details, spectra data, copies of NMR spectra, X-ray crystallographic data, and computational details. These materials are available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

(BT)S, Benzothiazole thioether; RPKA, Reaction Progress Kinetic Analysis; BQ, benzoquinone; PTFE, Polytetrafluoroethylene; LCMS, Liquid Chromatography—Mass Spectrometry; HPLC, High Pressure Liquid Chromatography.

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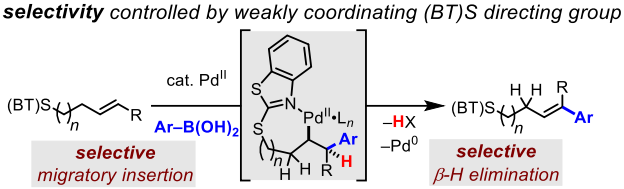
selectivity controlled by weakly coordinating (BT)S directing group
cat. Pd^II
Ar–B(OH)2
(BT)S
R
n
selective
migratory insertion
Pd^II•Ln
Ar
H
–HX
–Pd^0
H H
R
Ar
selective
β-H elimination