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Research Article

Z-Selective Dienylation Enables Stereodivergent Construction of Dienes and Unravels a Ligand-Driven Mechanistic Dichotomy

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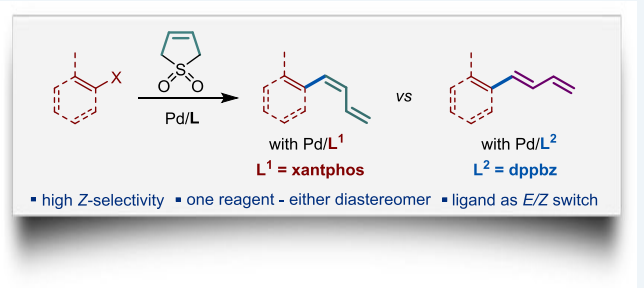
ABSTRACT: The development of stereoselective and efficient reactions for the construction of conjugated dienes and polyenes has remained at the forefront of organic chemistry, due to their key roles in medicinal chemistry, organic synthesis, and material science. The synthesis of conjugated dienes and polyenes is typically accomplished in a multistep manner by the sequential installation of individual C═C bonds because it allows for control of stereoselectivity and efficiency of formation of each double bond. A conceptually distinct dienylation approach entails a stereoselective appendage of a four-carbon unit, shortcutting diene synthesis. Dienylation with sulfolene provided a direct route to *E*-dienes, but the synthesis of substantially more challenging *Z*-dienes remained elusive. Here, we report that a highly *Z*-selective dienylation can now be achieved by a simple adjustment of a ligand, enabling stereodivergent synthesis of *E*- and *Z*-dienes from one reagent and in one step. A detailed mechanistic investigation of the *E*- and *Z*-selective dienylation provided insight into the divergent behavior of the two catalytic systems and revealed that differences in relative stabilities of catalytically active palladium phosphine complexes have a major impact on the stereochemical outcomes of the dienylation.



KEYWORDS: *conjugated dienes, cross-coupling, diastereoselectivity, palladium, phosphine*

INTRODUCTION

Conjugated unsaturated motifs are abundant among natural products and drugs.[1] They are crucial for the activity of these compounds, and the configuration of each C═C bond is important for the molecule to attain the required shape.[2] Conjugated dienes are also key synthetic precursors to a variety of functionalized intermediates because the reactive $C(sp^2)_4$ dienyl group can be transformed to a C_4 unit with up to four stereocenters and four functional groups in a stepwise fashion by a variety of cycloaddition and functionalization reactions.[3] The regio- and stereochemistry of conjugated repeating C═C units are important not only for their biological activity but also for synthetic applications, since only one diastereomer is typically required to access a specific target molecule.

To control the regio- and stereoselectivity of the dienyl group installation, a number of catalytic cross-coupling methods have been developed that install the dienyl side chain in a sequence of several steps, for example, by a sequential appendage of two C═C units (Figure 1).[4] To achieve a more convergent and efficient synthesis of conjugated dienes and polyenes, a reaction is required that enables direct installation of a C_4 unit. However, this synthetic platform remained elusive due to the lack of reactions that produce the dienyl unit in a regio- and stereoselective manner, and the lack of dienylation reagents that are stable and readily available in a variety of substitution patterns.

Existing methods, for example, Pd-catalyzed arylation reactions of conjugated dienes, produce mixtures of regio- and stereoisomers and suffer from low yields and narrow scope.[5] Although dienylboronic acids have been explored for dienylation, they are unstable and difficult to prepare.[6] Additionally, because of the stereospecificity of the cross-coupling reactions, *E*- and *Z*-C═C bonds have to be installed using independently prepared *E*- and *Z*-vinylation reagents. A conceptually distinct but hitherto unrealized approach that would obviate the necessity to synthesize separate reagents to install *E*- and *Z*-C═C bonds in a dienyl group would require the development of a stereodivergent cross-coupling with only one coupling partner. Such a stereodivergent reaction would produce either diastereomer on-demand in a highly stereoselective manner, e.g., by dialing in an appropriate ligand.

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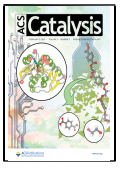

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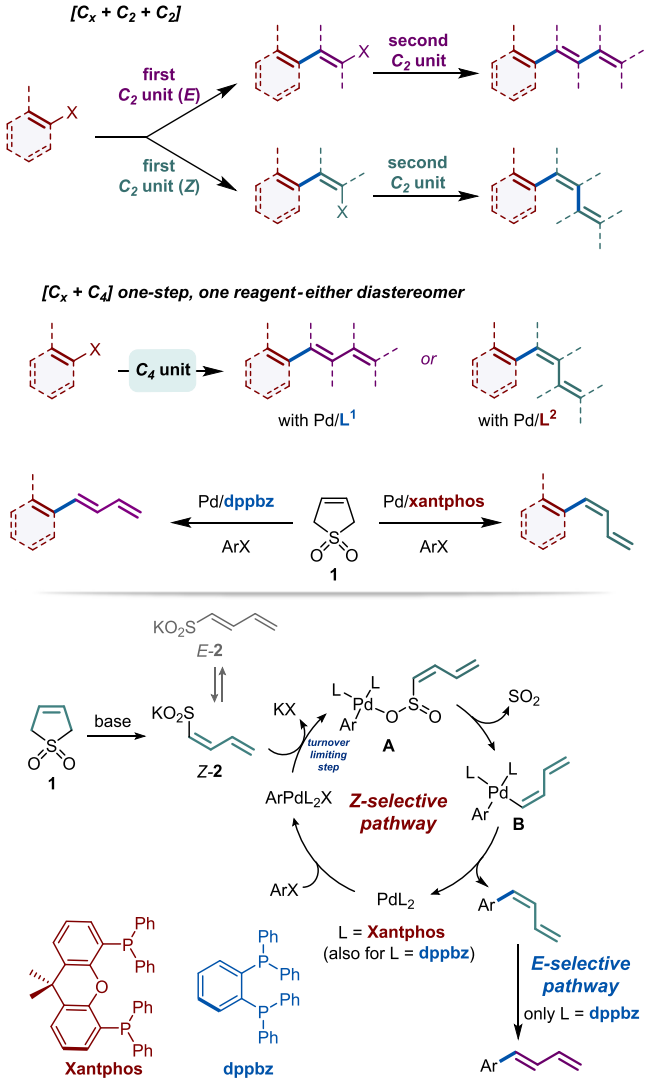


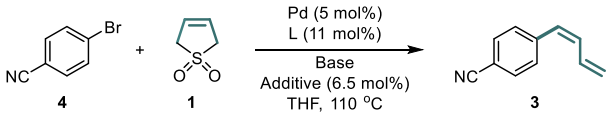
Figure 1. Stereodivergent dienylation.

We recently described the *E*-selective dienylation with bulk commodity chemical sulfolene **1** that efficiently produces *E*-dienes with high stereoselectivity, typically with >30:1 *E*/*Z* ratio.[7] We found that the use of 1,2-(diphenylphosphino)-benzene (dppbz) as a ligand was key for achieving high *E*-selectivity, although the origin of the high *E*-selectivity remained unknown. We now show that *Z*-dienes can be synthesized in a stereoselective manner by a Pd/Xantphos-catalyzed dienylation with sulfolene **1** that is stereocomplementary to the previously developed Pd/dppbz-catalyzed *E*-dienylation, thus demonstrating the feasibility of a one-step, one reagent-either diastereomer approach to conjugated dienes. We also provide a mechanistic rationale for the ligand-driven stereodisparity.

Mechanistically, the reaction is initiated by a base-induced ring-opening of sulfolene **1**, producing *Z*-dienylsulfinate *Z*-**2**.

Given the overall *E*-selectivity of the Pd/dppbz-catalyzed cross-coupling, it was initially hypothesized that the *E*-selectivity is due to *Z* → *E* isomerization of sulfinate **2**; however, it was noted that the isomerization of salt *Z*-**2** was not fast enough to account for the high *E*-selectivity of the dienylation, e.g., only 7:1 *Z*/*E* ratio was observed for sulfinate **2** after 1 h at 110 °C in tetrahydrofuran (THF).[7a] Although the dienylation reaction was highly *E*-selective, initial formation of *Z*-dienylsulfinate *Z*-**2** suggested that the dienylation could be rendered *Z*-selective, e.g., by an appropriate modification of the ligand. Successful execution of the strategy would result in a stereodivergent dienylation that could produce either diene diastereomer simply by switching the ligand. However, it would require the development of a catalytic system that could efficiently shuttle the *Z*-dienyl moiety through the catalytic cycle via sulfinate complex **A** with subsequent extrusion of sulfur dioxide en route to complex **B** and ensuing reductive elimination to the *Z*-diene product, all of the while suppressing deleterious side reactions, typically plaguing syntheses of *Z*-dienes. Conjugated *Z*-dienes are particularly challenging to synthesize, due to competing polymerization and *Z* → *E* isomerization facilitated by thermodynamic instability of *Z*-

Table 1. Reaction Conditions for the *Z*-Selective Dienylation[a]



entry	Pd/L	base	additive	*Z*/*E* ratio	yield (%)[b]
1	$Pd(OAc)_2$/dppe	$KOMe/K_2CO_3$		3:1	15[c]
2	$Pd(OAc)_2$/DPEphos	$KOMe/K_2CO_3$			<5[c]
3	$Pd(OAc)_2$/TolBINAP	$KOMe/K_2CO_3$		2:1	41[c]
4	$Pd(OAc)_2$/Xantphos	$KOMe/K_2CO_3$		10:1	42[c]
5	$Pd(OAc)_2$/Xantphos	$KOMe/K_2CO_3$		11:1	50
6	$Pd(A)_2Cl_2$/Xantphos	$KOMe/K_2CO_3$		17:1	57
7	$Pd(A)_2Cl_2$/Xantphos	$KOMe/KHCO_3$		18:1	78
8	$Pd(A)_2Cl_2$/Xantphos	KO*t*Bu/$KHCO_3$		>30:1	86
9	$Pd(A)_2Cl_2$/Xantphos	KO*t*Bu/$KHCO_3$	TEMPO	>30:1	99
10	$Pd(A)_2Cl_2$/Xantphos	KO*t*Bu/$KHCO_3$	TEMPO	>30:1	96[d]
11	$Pd(A)_2Cl_2$/Xantphos	KO*t*Bu	TEMPO	7:1	56
12	$Pd(A)_2Cl_2$/Xantphos	$KHCO_3$	TEMPO	>30:1	97[e]

[a]Reaction conditions: 4-bromobenzonitrile (**4**) (1 mmol), sulfolene 1 (2 mmol), Pd complex (5 mol %), ligand (11 mol %), base (1.6 mmol), $KHCO_3$ (2 mmol), additive (6.5 mol %), THF (9 mL), 110 °C, and 14 h. [b]Determined by ^{1}H NMR with 1,4-dimethoxybenzene as an internal standard. [c]8 mol % diphosphine. [d]The reaction was carried out in the atmosphere of air. [e]Sulfinate *Z*-**2** was used instead of sulfolene **1** and KO*t*Bu. A = MeCN.

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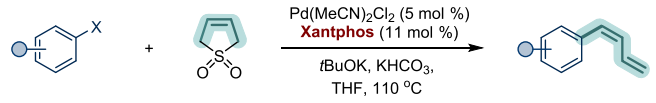
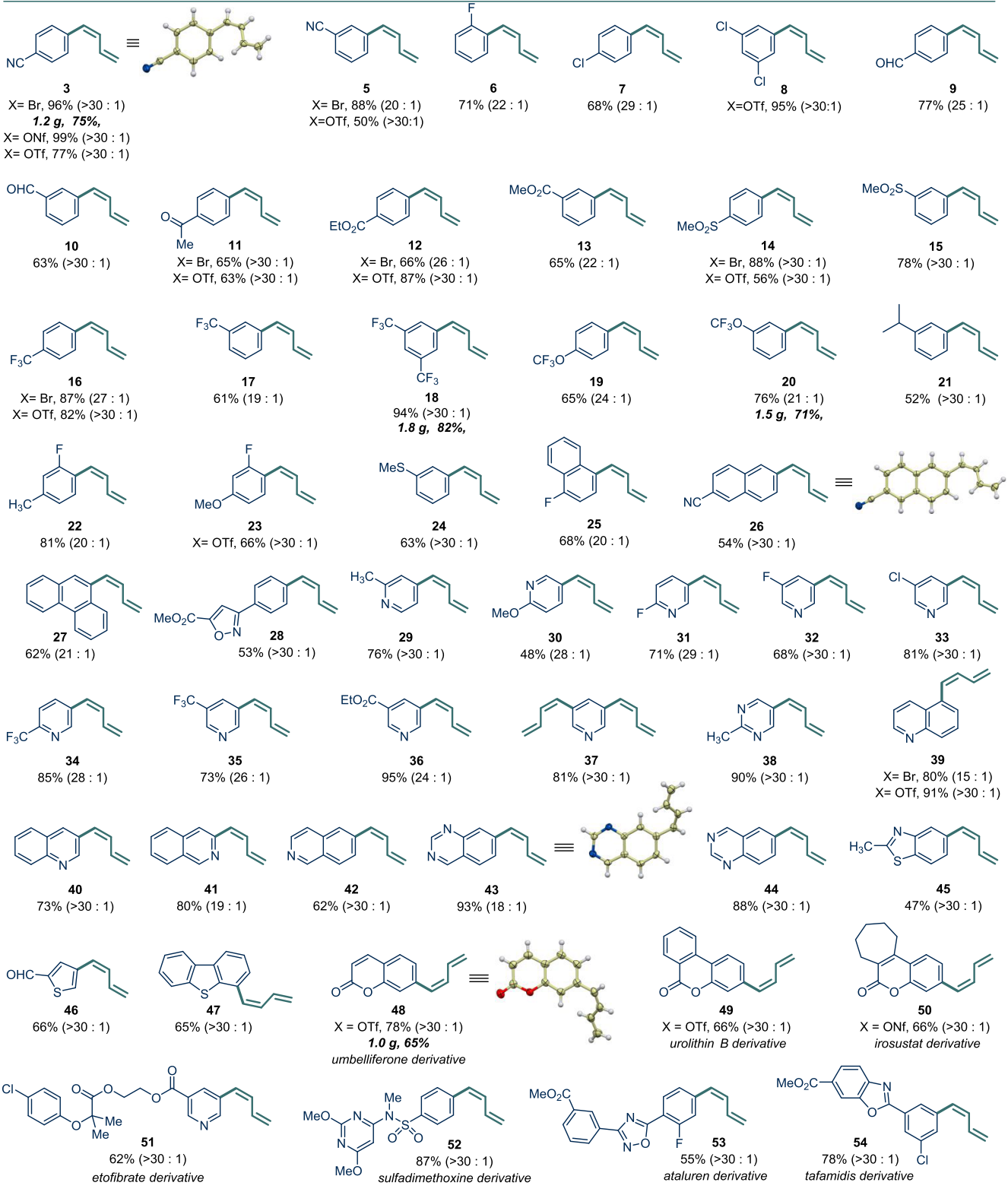
Table 2. Scope of the *Z*-Selective Dienylation[a]





[a]Reaction conditions: (hetero)aryl bromide or triflate (1 mmol), sulfolene **1** (2 mmol), $Pd(MeCN)_2Cl_2$ (5 mol %), Xantphos (11 mol %), KO*t*Bu (1.6 mmol), $KHCO_3$ (2 mmol), TEMPO (6.5 mol %), THF (9 mL), 110 °C (100 °C for sulfonate substrates), and 12−16 h.

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dienes (e.g., density-functional theory, DFT-derived ΔG = −3.9 kcal/mol for the $Z \rightarrow E$ isomerization of diene **3**, i.e., >690:1 in favor of *E*-**3** at equilibrium) and numerous kinetically accessible isomerization pathways.[8] However, even in the context of the *E*-isomer synthesis and despite the high thermodynamic driving force, most $Z \rightarrow E$ isomerizations do not produce synthetically useful *E*/*Z* ratios, due to catalyst deactivation or slow rates of isomerization.[9]

RESULTS AND DISCUSSION

We began our studies adapting the reaction conditions developed for the *E*-selective Pd/dppbz-catalyzed dienylation with potassium carbonate as sulfur dioxide-sequestering reagent and several diphosphines (8 mol %) as ligands that are capable of diverting the reaction in favor of the *Z*-isomer (entries 1−3); however, the *Z*/*E* ratio and yield remained low (Table 1). Encouraging results were obtained with Xantphos that provided promising *Z*-selectivity and yield (entry 4). Increasing the ligand loading to 11 mol % led to a moderate improvement of the *Z*-selectivity and efficiency. By contrast, a significant improvement of the *Z*-selectivity was achieved with $Pd(MeCN)_2Cl_2$, although the yield remained modest (entry 6). Switching to potassium bicarbonate brought the diene yield in the synthetically useful range, while replacement of methoxide with *tert*-butoxide drastically improved the *Z*-selectivity (entries 7 and 8). Additional experiments indicated that the formation of dienylsulfinate *Z*-**2** from sulfolene **1** with *tert*-butoxide is completed within 1 min at room temperature, while the reaction with methoxide is substantially slower, suggesting that the fast and irreversible deprotonation of sulfolene **1** with *tert*-butoxide has a beneficial effect on the *Z*-dienylation (see p. S11 in the Supporting Information, SI). Further experimentation suggested that the propensity of *Z*-dienes to undergo polymerization and other side reactions may be affecting the reaction performance. Several polymerization inhibitors were tested, with TEMPO emerging as the optimal additive, furnishing *Z*-diene **3** with high *Z*-selectivity and yield (entry 9). Of importance to further mechanistic discussion, the reaction could be carried out in the atmosphere of air without significant detriment to the selectivity and efficiency (entry 10). The omission of the bicarbonate resulted in significant erosion of the stereoselectivity, suggesting that the additive plays an important role in maintaining the stereochemical integrity of the process.[10] Additionally, consistent with the prior observations made with the Pd/dppbz-catalyzed process, no reaction was observed when butadiene was used instead of sulfolene. Finally, replacement of sulfolene **1** and KO*t*Bu with sulfinate *Z*-**2** afforded product *Z*-**3** in a comparable yield and selectivity (entry 12), supporting the conclusion that the dienylation proceeds via desulfitative coupling of *Z*-**2**. Desulfitative cross-coupling reactions of (hetero)arylsulfinates have recently attracted attention as efficient alternatives to the boronate-based Suzuki coupling.[11] However, stereoselective desulfitative cross-couplings of vinylsulfinates have remained unexplored, and the dienylation reaction sets an important precedent for the feasibility of such highly stereoselective couplings.

The scope of the *Z*-selective dienylation was explored next (Table 2, **5**−**54**). Various substitution patterns were well tolerated (**5**−**7**). Substrates bearing nitrile, halogen, aldehyde, ketone, and ester groups produced the corresponding *Z*-dienes in good yields and with high stereoselectivity (**5**−**13**). Similarly, the *Z*-dienylation can readily accommodate the medicinally relevant sulfone, trifluoromethyl, and trifluoromethoxy groups (**14**−**20**). *Z*-Dienes were also readily synthesized from substrates bearing alkyl, methoxy, and methylthio groups (**21**−**24**). The *Z*-diene moiety can also be appended to substituted naphthalenes (**25**, **26**) and to the electron-rich[9,10] C═C bond of phenanthrene (**27**). Nitrogen heterocycles are centrally important medicinal motifs; however, their installation by means of Pd-catalyzed cross-couplings may be problematic, due to catalyst inhibition.[12] Gratifyingly, the *Z*-selective dienylation performed equally well with a range of *N*-heterocyclic substrates (**28**−**45**). *Z*-Dienylated pyridines bearing methyl, methoxy, halogen, trifluoromethyl, and ester groups were synthesized with high stereoselectivity (**29**−**36**). Interestingly, two *Z*-dienyl moieties can be appended simultaneously, affording polyconjugated pyridine **37**. *Z*-Dienylpyrimidine **38** was also readily accessed. Furthermore, heterocyclic substrates of benzazine and benzazole series, including quinolines, isoquinolines, quinazolines, and benzothiazole can be converted to the corresponding products **39**−**45** bearing the *Z*-dienyl group in the proximal and distal positions. The *Z*-dienylation also proceeded efficiently with thiophene- and dibenzothiophene-derived bromides (**46**, **47**). Although aryl and heteroaryl bromides were used as the most common and synthetically useful cross-coupling precursors, the *Z*-dienylation was equally efficient and highly stereoselective with triflates and nonaflates (**3**, **5**, **8**, **11**, **12**, **14**, **16**, **23**, **39**), allowing for facile conversion of phenols to *Z*-dienes.

The reaction was further tested with several heterocyclic natural product and active pharmaceutical ingredient (API) scaffolds. The naturally occurring umbelliferone (**48**) and the skeletal muscle growth regulator urolithin B (**49**) were readily converted to the corresponding *Z*-dienes. The *Z*-diene derivative of the anticancer drug irosustat (**50**) was also prepared. The *Z*-dienyl derivatives of other API were also accessed with high stereoselectivity, including hypertriglyceridemia drug etofibrate (**51**), antibiotic sulfadimethoxine (**52**), Duchenne muscular dystrophy drug ataluren (**53**), and the polyneuropathy and cardiomyopathy drug tafamidis (**54**). Moreover, the dienylation can be carried out on a gram scale (e.g., **3**, **18**, **20**, **48**), indicating that the reaction can be useful for preparative applications. The stereochemical assignment of the *Z*-dienes was unequivocally confirmed by X-ray analysis of products **3**, **26**, **43**, and **48**.[13] In general, electron-withdrawing groups improve the stability of *Z*-diene products that are more readily isolated, due to the diminished effects of polymerization and isomerization. Similarly, vinyl-derived products proved to be prone to polymerization and could not be isolated.

Mechanistic Studies of Stereoselectivity. To show that complete stereodivergence can be achieved for the dienylation reaction by a simple switch of the phosphine ligand, the dienylation reaction was carried out with dppbz and Xantphos under otherwise identical conditions (Scheme 1A).[14]

The Pd/dppbz-catalyzed reaction produced *E*-**3** (85%, >30:1 *E*/*Z*), while the Pd/Xantphos reaction produced Z-**3** (81%, >30:1 *Z*/*E*). It is remarkable that the stereoselectivity of the dienylation can be completely inverted from >30:1 in favor of the *E*-isomer to >30:1 of the *Z*-isomer by a simple change of a phosphine ligand. The stereodivergent process has a clear synthetic advantage, as it requires only one reagent to access either diene diastereomer. More importantly, it provides a proof of principle for further development of stereodivergent dienylation reactions. In this context, elucidation of the

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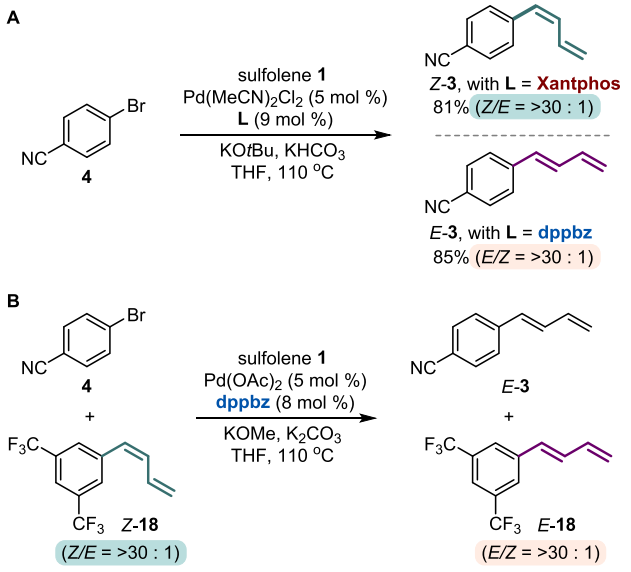
Scheme 1. Ligand-Enabled Stereodivergent Dienylation (A) and Isomerization of Diene *Z*-18 under the Conditions of the Pd/dppbz-Catalyzed Dienylation (B)



underlying causes for the drastic ligand-driven stereodivergence is key to the future successful development of other catalytic transformations based on this approach. At this juncture, we set out to investigate the kinetics of the dienylation with the two ligands. As expected, the Pd/Xantphos-catalyzed dienylation proceeded with high *Z*-selectivity that remained unchanged throughout the reaction (Figure 2A). Surprisingly, the Pd/dppbz-catalyzed dienylation exhibited an entirely different kinetic behavior (Figure 2B). The Pd/dppbz-catalyzed reaction was also *Z*-selective at low conversions, with the *Z*/*E* ratio eroding from 4.5:1 to 1:1 in the course of the first 4.5 h. Thereafter, the stereoselectivity reversed in favor of the *E*-isomer, and the *E*/*Z* ratio continued to grow gradually until the *E*/*Z* ratio exceeded 30:1 by the time the reaction was complete. Given that the switch in the stereoselectivity occurred relatively late (i.e., at ∼50% conversion), the high stereoselectivity of the Pd/dppbz process could not be explained by either *Z* → *E* isomerization of dienylsulfinate salt **2** or a faster dienylation with *E*-sulfinate *E*-**2**, as both scenarios would result in a much lower *E*-selectivity. Rather, it points to the isomerization of the less stable *Z*-diene to the *E*-product. To support this conclusion, the Pd/dppbz-catalyzed dienylation was carried out in the presence of *Z*-diene *Z*-**18**, and complete isomerization to *E*-**18** was observed (Scheme 1B). Interestingly, the lower *Z*-selectivity of the Pd/Xantphos-catalyzed dienylation under unoptimized conditions (Table 1, entry 5) was also found to be due to *Z* → *E* isomerization, albeit at a substantially slower rate than in the Pd/dppbz system.

These results suggest that Xantphos suppresses the *Z* → *E* isomerization more efficiently than dppbz. To gain insight into the mechanistic aspects of the stereodivergent dienylation, a series of kinetic experiments were carried out. The study was guided by the observation that the Pd/Xantphos-catalyzed reaction proceeds at a higher rate (Figure 2), indicating that the turnover-limiting step occurs at the transmetalation, sulfur dioxide extrusion, or reductive elimination steps. The transmetalation may be accelerated by the participation of the Xantphos oxygen atom in the displacement of bromide in ArPd(diphosphine)Br,[15] while the reductive elimination benefits from the substantially larger bite angle (111° for Xantphos, 83° for dppbz).[16]

^{31}P NMR Studies. Monitoring the reaction by ^{31}P NMR spectroscopy revealed that ArPd(Xantphos)Br was the only Pd-bound phosphine species present in the solution (Figure 3), consistent with the hypothesis that transmetalation is the turnover-limiting step in the Pd/Xantphos-catalyzed dienylation. Additionally, the absence of phosphine monoxide suggests that other reducing species, e.g., sulfinate *Z*-**2** mediate the reduction of the Pd^{II} precursor to the active Pd^{0} catalyst, reflecting the increased steric hindrance within the larger bite angle ligand.[17] In a remarkable contrast, both Pd(dppbz)$_2$ and ArPd(dppbz)Br were present in the reaction mixture in the case of the Pd/dppbz-catalyzed dienylation, with Pd(dppbz)$_2$ being the predominant species.

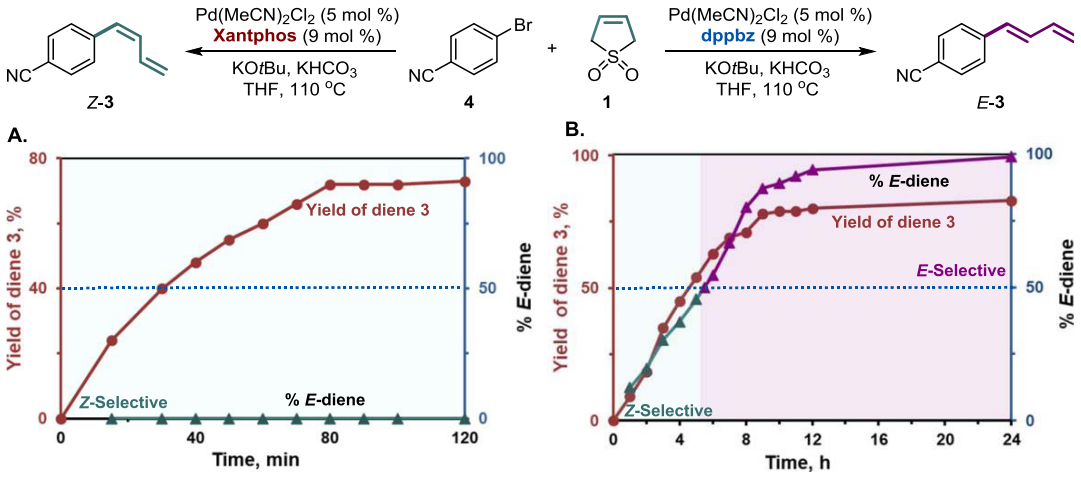


Figure 2. Time course graphs for the dienylation reaction with the diene **3** yield (●, left axis) and the percentage of the *E*-diene in the diastereomeric mixture of product **3** (▲, right axis). Green and purple parts of the *E*-diene percentage line denote *Z*- and *E*-selective periods of the reaction. The dotted bisecting line separates the top half with *E*-**3** as the major diastereomer (*E*-selective) and the bottom half with *Z*-**3** as the major diastereomer (*Z*-selective). (A) Pd/Xantphos-catalyzed dienylation is consistently *Z*-selective. (B) Pd/dppbz-catalyzed dienylation starts as a *Z*-selective process but reverses to *E*-selective and achieves high *E*-selectivity by the time of completion.

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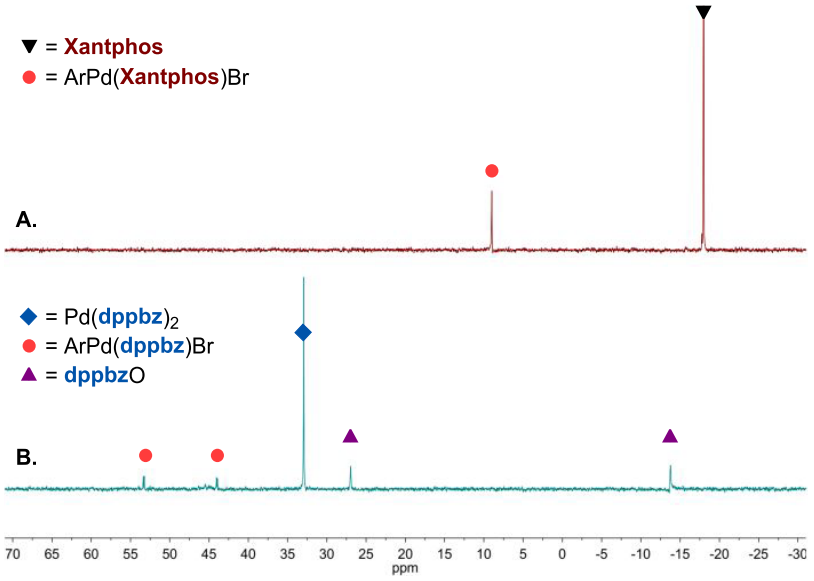

Figure 3. ^{31}P NMR study of the Pd/Xantphos- (**A**) and Pd/dppbz- (**B**) catalyzed dienylation reactions, after 1 h at 110 °C, Ar = *p*-NCC$_6$H$_4$.

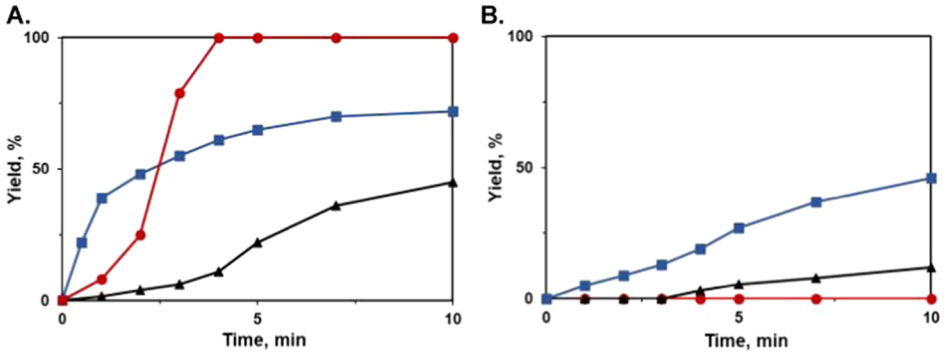

Figure 4. Kinetic study of the key steps in the Pd/Xantphos- and Pd/dppbz-catalyzed dienylation at 110 °C in THF, Ar = *p*-NCC$_6$H$_4$. Yield on the *y*-axis is for the product of each reaction as specified below. (A) Pd/Xantphos. (B) Pd/dppbz. PdL$_2$ + ArBr (2 equiv), THF, 110 °C; reaction product: ArPd(L)Br (●). ArPd(L)Br + *Z*-**2** (4 equiv) + L (1.5 equiv), THF, 110 °C; reaction product: diene **3** (▲). ArPd(L)(*Z*-**2**) + L (1.5 equiv), THF, 110 °C; and reaction product: diene **3** (■). c_{Pd} = 0.038 M. Loadings of ArBr and *Z*-**2** were one-tenth of the ones used in the dienylation reaction. Ligand was added to the reaction of ArPd(L)(*Z*-**2**) to stabilize the Pd^0 byproduct.

Kinetic Studies. To further clarify the role of individual steps, kinetic studies of the *Z*- and *E*-dienylation reactions were carried out. First order in the catalyst, aryl bromide, and sulfinate *Z*-**2** was observed for the Pd/Xantphos-catalyzed *Z*-selective reaction, consistent with the transmetalation as the turnover-limiting step.[18] To directly test this conclusion, the bromide was exchanged with the triflate to give [Pd(Xantphos)]OTf, featuring Xantphos as a tridentate P,O,P-ligand.[15] The triflate intermediate was converted to the corresponding Pd sulfinate complex ArPd(Xantphos)(Z-**2**). The rates of the oxidative addition, sulfur dioxide extrusion/reductive elimination from ArPd(Xantphos)(Z-**2**), and the reaction of ArPd(Xantphos)Br with sulfinate Z-**2** were then compared, revealing a substantially slower reaction of ArPd(Xantphos)Br with Z-**2** and supporting the conclusion that the transmetalation is the turnover-limiting step (Figure 4A). Remarkably, the Pd/dppbz system exhibited a distinctly different kinetic behavior (Figure 4B). While the reaction of ArPd(dppbz)Br with *Z*-**2** was again slower than the sulfur dioxide extrusion/reductive elimination from ArPd(dppbz)(Z-**2**), no oxidative addition was observed with Pd(dppbz)$_2$ even after prolonged heating.

The difference in the oxidation behavior of Pd(Xantphos)$_2$ and Pd(dppbz)$_2$ is remarkable and consistent with ^{31}P NMR studies that showed the presence of Pd(dppbz)$_2$ but not Pd(Xantphos)$_2$ in the reaction mixture. Notably, the reaction of ArPd(L)Br with sulfinate *Z*-**2** was slower for dppbz than for Xantphos, reflecting, as discussed above, the beneficial effects of Xantphos on the transmetalation and sulfur dioxide extrusion/reductive elimination steps. The study also allowed for direct observation of the stereoselectivity of the diene formation from ArPd(dppbz)(Z-**2**) complex. The reaction proceeded with high *Z*-selectivity (*Z*/*E* > 30:1), indicating that the Pd/dppbz-catalyzed dienylation is intrinsically highly *Z*-selective, and the *E*-selectivity is caused by the *Z* → *E* isomerization of the diene product. To further probe the distinctive roles of PdL$_2$ and ArPd(L)Br in the Pd/Xantphos and Pd/dppbz dienylation processes, the dienylation reactions were conducted with PdL$_2$ and ArPd(L)Br as catalysts (Figure 5). As expected from the spectroscopic and kinetic studies, both Pd(Xantphos)$_2$ and ArPd(Xantphos)Br were competent catalysts with regard to selectivity and efficiency. In contrast, divergent catalytic behavior was observed for Pd(dppbz)$_2$ and ArPd(dppbz)Br. While ArPd(dppbz)Br exhibited high catalytic

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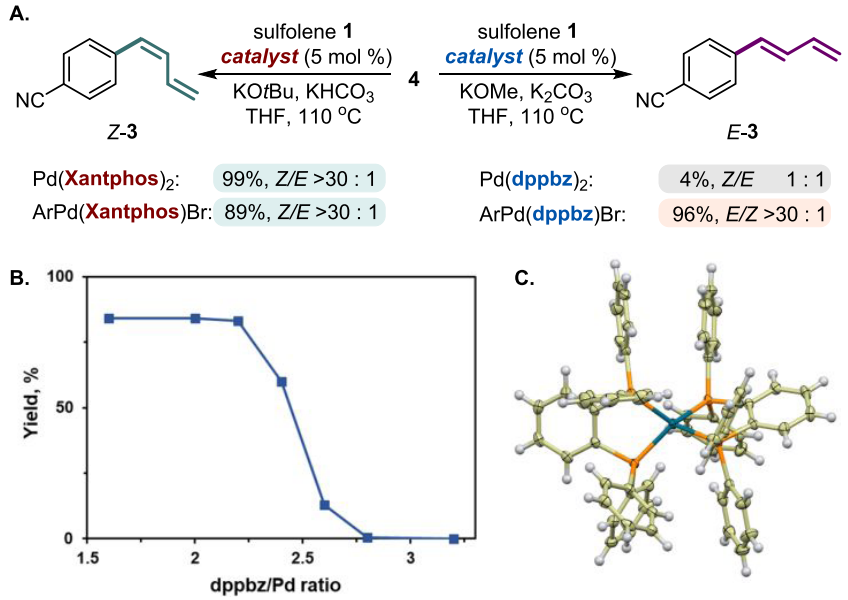

Figure 5. (A) Catalytic activity of PdL_2 and ArPd(L)Br in the dienylation reaction (Ar = *p*-NCC_6H_4). (B) Influence of the dppbz/Pd ratio on the dienylation efficiency. (C) X-ray structure of $Pd(dppbz)_2$.

activity, resulting in a highly *E*-selective dienylation, $Pd(dppbz)_2$ was essentially catalytically inactive, indicating that it is an off-cycle reservoir of Pd. Additionally, the 1:1 *E*/*Z* ratio of product **3** indicates that $Pd(dppbz)_2$ is not substantially involved in the $Z \rightarrow E$ isomerization. These results suggest that Pd(dppbz) is the actual on-cycle catalyst, which may explain the reduced dppbz loading (8 mol %) under the optimal conditions. Indeed, an increase in the dppbz loading resulted in a complete shutdown of the dienylation (Figure 5). Furthermore, no $Z \rightarrow E$ isomerization of diene **3** was observed in the presence of $Pd(dppbz)_2$ (5 mol %), at 110 °C in THF after 16 h, ruling out its involvement in the isomerization process. Taken together, the spectroscopic and kinetic studies indicate that the *E*-selective dienylation is catalyzed by Pd(dppbz) with ArPd(dppbz)Br as an on-cycle resting species. The reaction is intrinsically *Z*-selective, with the efficient $Z \rightarrow E$ isomerization effected by a side process that originates from the Pd(dppbz)/ArPd(dppbz)Br cycle, while $Pd(dppbz)_2$ is not significantly involved in the reaction.

Involvement of Heterogeneous Catalytic Channels. Although cross-coupling reactions are typically assumed to proceed by homogenous pathways via well-defined molecular catalysts, the involvement of catalytically active colloidal metal particles was shown to be central to observed net catalytic reactivities or side reactions in many metal-catalyzed processes.[19] In this context, colloidal palladium was implicated in alkene isomerizations proceeding via a reversible Pd−H addition to double C−C bonds.[9b,20] To test the involvement of a heterogenous Pd-catalyzed $Z \rightarrow E$ isomerization in the Pd/dppbz-catalyzed dienylation, hot filtration[19,21] experiments were carried out (Figure 6, see also Figures S4 and S5 in the SI), wherein the reaction was interrupted and filtered hot to remove all insoluble material including metal catalyst particulate if formed, and then allowed to continue with a fresh batch of $KHCO_3$ and *Z*-**2**. The hot filtration test can be used to distinguish heterogeneous and homogenous catalysis. For comparison, the experiment was first carried out with the Pd/Xantphos-catalyzed reaction, and no negative effects on the *Z*-selectivity were observed. In contrast, the $Z \rightarrow E$

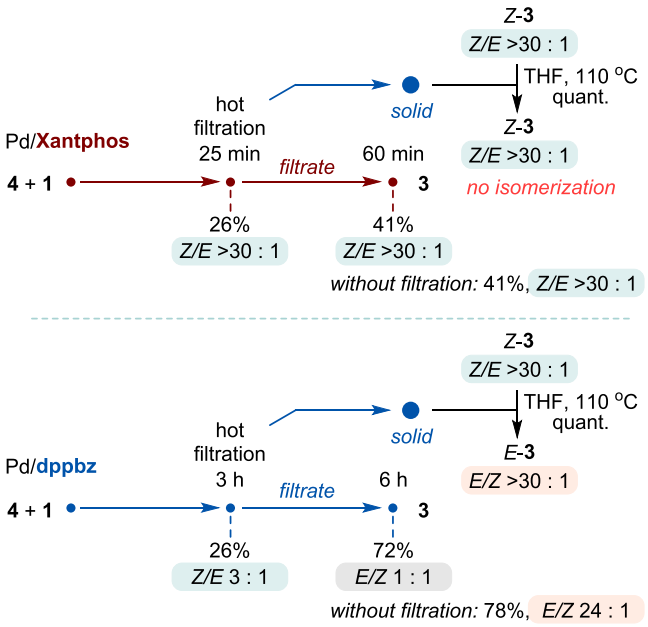

Figure 6. Hot filtration test of the Pd/Xantphos- and Pd/dppbz-catalyzed dienylation of bromide **4** to diene **3**.

isomerization was substantially slower after the hot filtration for the Pd/dppbz-catalyzed process. Importantly, and in contrast to the Pd/Xantphos system, the solid residue that was filtered from the reaction mixture efficiently catalyzed the $Z \rightarrow E$ isomerization of diene *Z*-**3**. This result supports the involvement of colloidal palladium in the $Z \rightarrow E$ isomerization as the underlying mechanism for the observed net *E*-selectivity and suggests that the catalytic colloids are formed in the early stages of the reaction.

The reversible addition of palladium hydride species that is followed by *β*-hydride elimination is a common mechanism implicated in alkene isomerizations and chain-walking processes.[20] We thus hypothesized that Pd particles implicated in the *E*-selective Pd/dppbz-catalyzed dienylation may carry

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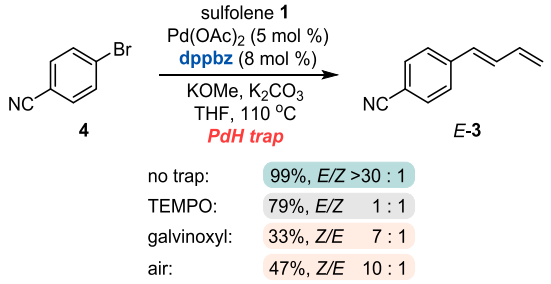
catalytically active Pd−H sites effecting the isomerization or act as catalytic reservoirs releasing and recapturing soluble Pd−H species.[19,22]

To test the involvement of the Pd−H-mediated isomerization in the Pd/dppbz-catalyzed dienylation, the reaction was carried out in the presence of palladium hydride traps (TEMPO, galvinoxyl, and air).[23] Significantly, the dienylation proceeded with substantially reduced *E*-selectivity (TEMPO) or became *Z*-selective (galvinoxyl, air), pointing to the involvement of the Pd−H-mediated pathway (Scheme 2).[24]

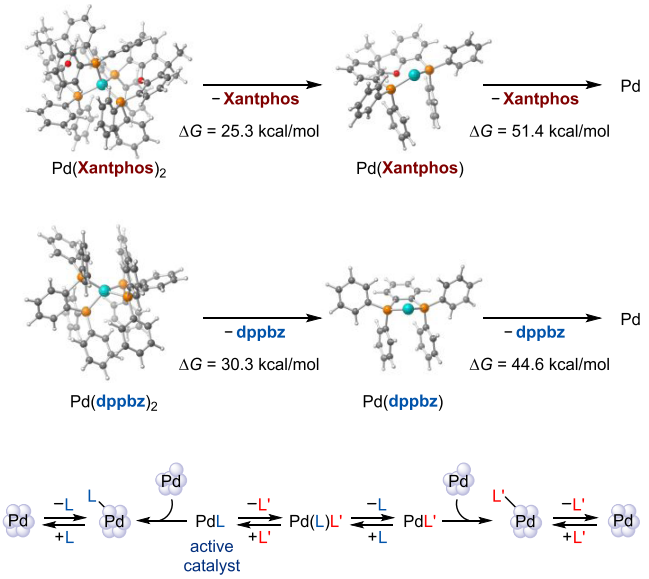
Scheme 2. Influence of Palladium Hydride Traps on the Pd/dppbz-Catalyzed Dienylation of Bromide 4 to Diene 3



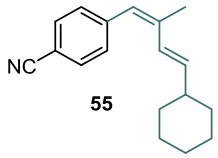
This result stands in stark contrast to the *Z*-selective Pd/Xantphos dienylation that can be performed under air without significant deterioration of the stereoselectivity and efficiency (Table 1, entry 10). Taken together, the studies indicate that the *Z* → *E* isomerization observed in the Pd/dppbz-catalyzed dienylation is effected by Pd particles that may carry catalytically active Pd−H sites or serve as reservoirs that release and recapture soluble Pd−H species. To test this mechanism, diene *Z*-**3** was subjected to palladium on charcoal that was previously shown to effect *Z* → *E* isomerization of alkenes via palladium colloids,[20a] and complete *Z* → *E* isomerization was observed. Other sources of colloidal Pd were also tested with similar results. Importantly, in all cases, the *Z* → *E* isomerization was suppressed by the palladium hydride traps.

Stability of Palladium(0)−Phosphine Complexes. The experimental evidence indicates that palladium colloids are readily formed in the Pd/dppbz system, in contrast to Pd/Xantphos, suggesting that Pd^0/dppbz complexes may be less stable and more prone to ligand dissociation that results in Pd aggregation. Indeed, the computed Gibbs free energy of dissociation for Pd(dppbz) is substantially lower than for Pd(Xantphos) in the PdL series (Scheme 3), supporting the conclusion that the dissociation is more facile in the Pd/dppbz system and may be additionally facilitated by sulfinate *Z*-**2** or the diene product acting as transient labile ligands that may promote the departure of the phosphine and the growth of Pd colloids.[19] In contrast, in the PdL_2 series, the departure of the first ligand is more thermodynamically favorable for Pd(Xantphos)$_2$. The disparity in the dissociation energies of PdL_2 and PdL highlights the more favorable profile of Xantphos, since more readily formed and more stable PdL species is beneficial for the overall reaction performance and selectivity. Substituted dienes are expected to have different reactivities toward Pd−H that may affect their stability under the Pd/dppbz conditions. Indeed, when 1*Z*-diene **55** that is formed under the Pd/dppbz conditions from the corresponding disubstituted sulfolene was subjected to palladium on charcoal, no *Z* → *E* isomerization was observed under the conditions

Scheme 3. Computed Gibbs Free Energies for the Stepwise Dissociation of Pd(Xantphos)$_2$ and Pd(dppbz)$_2$ and the Mechanism of Colloidal Pd Formation, Directly and with a Labile Transient Ligand (L = Phosphine, L′ = Diene or Sulfinate)



that led to complete isomerization of diene *Z*-**3**. Furthermore, substitution in dienylsulfinate salts and diene products can influence the reactivity, stability, size, and rates of formation of colloidal palladium (and active Pd−H species) via ligation, as shown in Scheme 3, providing additional elements of control of the stereoselectivity.



Collectively, the combined evidence from spectroscopic, kinetic, and computational studies suggest that both Pd/Xantphos and Pd/dppbz-catalyzed dienylations are intrinsically *Z*-selective (Figure 7). The *E*-selectivity of the Pd/dppbz-catalyzed reaction is explained by the efficient *Z* → *E* isomerization caused by palladium colloids that may be formed from the catalytically competent Pd(dppbz) due its lower stability, while Pd(dppbz)$_2$ does not significantly participate in the reaction because of the lower propensity to shed the first phosphine ligand. In contrast, Pd(Xantphos)$_2$ dissociates more readily, providing a pathway for efficient dienylation, while the increased stability of Pd(Xantphos) precludes the formation of Pd colloids, thus suppressing the *Z* → *E* isomerization and ensuring the high *Z*-selectivity.

CONCLUSIONS

In conclusion, we developed a Pd/Xantphos-catalyzed, highly *Z*-selective dienylation that together with the Pd/dppbz-catalyzed *E*-selective dienylation enables the synthesis of either diastereomer of conjugated dienes in one step and using the same dienylation reagent—bulk commodity chemical sulfolene **1**. We further show that the stereodivergent behavior of the Xantphos- and dppbz-based reactions is due to high *Z*-selectivity and suppression of the *Z* → *E* isomerization in the Pd/Xantphos-catalyzed reaction. In contrast, the Pd/dppbz-

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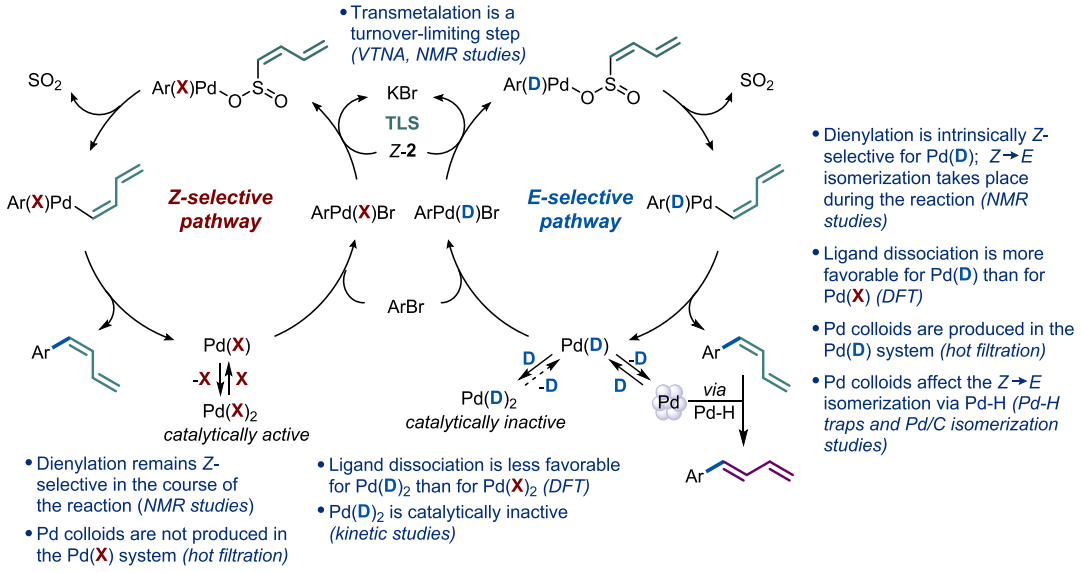

Figure 7. Summary of the mechanistic and computational studies of the Pd/Xantphos (**X**)- and Pd/dppbz (**D**)-catalyzed dienylation.

catalyzed dienylation is in fact intrinsically highly *Z*-selective but is subject to efficient $Z \rightarrow E$ isomerization that results in the overall highly *E*-selective process. The underlying cause of the disparate catalytic behavior of Pd/Xantphos and Pd/dppbz systems is the more facile first ligand dissociation for Xantphos in the PdL_2 series, and the lower stability for dppbz in the PdL series, leading to the formation of palladium colloids and the $Z \rightarrow E$ isomerization. The stereodivergent dienylation with sulfolene **1** provides a blueprint for further development of diene and polyene syntheses with other sulfolenes and electrophilic coupling partners based on the one reagent-either diastereomer concept.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05574.

Experimental, spectral, and X-ray crystallographic details for all new compounds and all reactions reported (PDF)

Crystallographic data (CIF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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