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Highly Chemo- and Regioselective Construction of Spirocarbocycles by a Pd(0)-Catalyzed Dearomatization of Phenol-Based Biaryls with 1,3-Dienes

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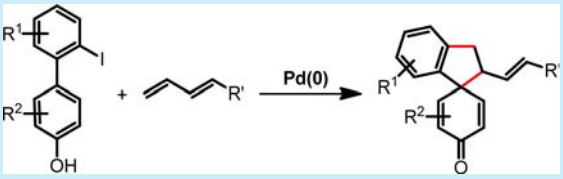
Supporting Information

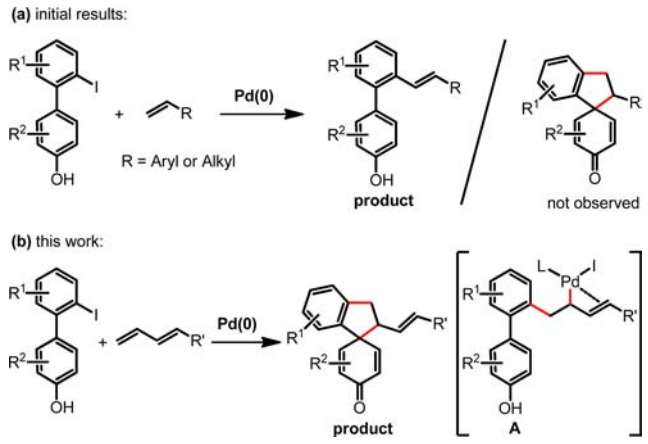
ABSTRACT: A novel Pd(0)-catalyzed intermolecular carbocyclization of phenol-derived biaryls with 1,3-dienes has been implemented through a sequence of oxidative addition to the C−I bond, regioselective olefin insertion, and allylative dearomatization. This method provides a broad range of attractive spirocyclic compounds bearing two contiguous tertiary/quaternary carbon centers in good yields with excellent chemoselectivity and regioselectivity. Moreover, preliminary results indicate that asymmetric control of this process is feasible with chiral ligands.



Phenols are a class of readily available and abundant chemical feedstock.[1] Diversified functionalization of phenolic compounds have drawn considerable attention with the emergence of a number of excellent synthetic methods,[2] which provide many efficient and convenient avenues to complex molecular frameworks. In this area, transition-metal-catalyzed dearomatization of phenols and derivatives has proven to be one of the most straightforward approaches to access the challenging but synthetically useful spirocyclohexadienones,[3] which often serve as a key structural motif in a variety of natural products and pharmaceuticals. Among them, the leading examples by Hamada,[4] You,[5] Buchwald,[6] and Feringa[7] have disclosed that several types of phenol-derived precursors were able to undergo dearomative spirocyclizations in an intramolecular manner by using transition-metal-catalyzed alkylation or arylation reactions. Soon after, we,[8] Mascareñas and Gulías,[9] Lam,[10] and You[11] independently contributed to the studies on a cooperative C−H activation/dearomatization strategy for Ru^{II}- or Rh^{III}-catalyzed [3 + 2] spiroannulations of phenol-based biaryls with internal alkynes under oxidative reaction conditions. Very recently, we have also described the successful use of a series of directly related, halogenated biaryl derivatives for the similar cyclization by using Pd(0) catalysis.[12] Nevertheless, it is important to note that the coupling partners for these dearomative [3 + 2] spiroannulations were limited to internal alkynes. From the viewpoint of synthetic and mechanistic relevance, this transformation called for exploring the performance of unsaturated partners other than alkynes.

In this context, we examined the reactivity of olefins, which are rather attractive unsaturated systems and have been scarcely studied in intermolecular dearomatization reactions,[13] for a Pd(0)-catalyzed reaction with halogenated phenol-based biaryls. At the outset, we were engrossed in evaluating the behavior of apparent terminal olefins. Disappointingly, the reaction proceeded exclusively via a facile β-hydride elimination pathway to generate a Heck adduct, but not the anticipated spirocyclic product through a dearomative [3 + 2] cyclization route under various reaction conditions (Scheme 1a). To this end, we switched to use 1,3-dienes, which possess a high potential for inhibiting the unwanted β-hydride elimination by stabilizing the palladium center through the coordination of the other C−C double bond in the intermediate **A**[14] for the envisioned transformation (Scheme 1b). Herein, we report the development of a successful example of a Pd(0)-catalyzed dearomative [3 + 2] spiroannulation process between

Scheme 1. Dearomative [3 + 2] Spiroannulation between Phenol-Derived Biaryls and Olefins



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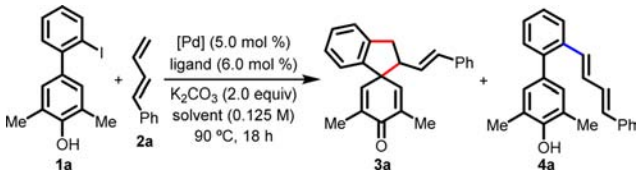
halogenated phenol biaryls and 1,3-dienes, leading to the formation of spirocyclohexadienones with two contiguous tertiary/quaternary carbon centers.

We began the study by using phenol-based biaryl **1a** and (*E*)-buta-1,3-dien-1-ylbenzene (**2a**) as the model substrates to optimize the reaction conditions. The experimental results are summarized in Table 1. Initially, with the catalytic system

Table 1. Optimization of the Reaction Conditions[a]



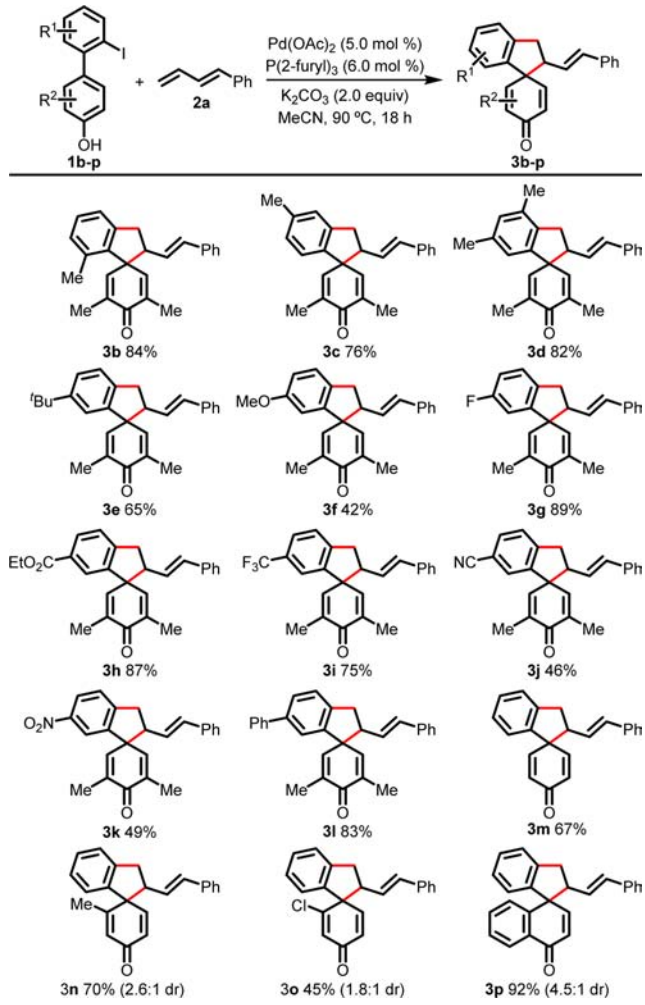
				yield[b] (%)	
entry	[Pd]	ligand	solvent	**3a**	**4a**
1	$Pd(OAc)_2$	PPh_3	toluene	0	0
2	$Pd(OAc)_2$	PPh_3	DME	0	36
3	$Pd(OAc)_2$	PPh_3	1,4-dioxane	0	61
4	$Pd(OAc)_2$	PPh_3	THF	0	49
5	$Pd(OAc)_2$	PPh_3	DMF	0	91
6	$Pd(OAc)_2$	PPh_3	MeCN	29	63
7	$Pd(OAc)_2$	PCy_3	MeCN	0	0
8	$Pd(OAc)_2$	XPhos	MeCN	36	34
9	$Pd(OAc)_2$	$P(p\text{-MeO-}C_6H_4)_3$	MeCN	17	9
10	$Pd(OAc)_2$	$P(p\text{-Cl-}C_6H_4)_3$	MeCN	0	89
11	$Pd(OAc)_2$	P(2-furyl)$_3$	MeCN	85[c]	3
12	$Pd(OAc)_2$	SIPr·HBF_4	MeCN	21	10
13	$Pd(OAc)_2$	Xantphos	MeCN	35	5
14	$Pd(OAc)_2$	dppp	MeCN	40	18
15	$Pd(OAc)_2$	dppf	MeCN	39	17
16	$Pd_2(dba)_3$	P(2-furyl)$_3$	MeCN	0	0
17	$[Pd(allyl)Cl]_2$	P(2-furyl)$_3$	MeCN	29	59
18	$PdCl_2$	P(2-furyl)$_3$	MeCN	43	12

[a]Reactions were conducted with 0.20 mmol of **1a**. [b]Determined by ^1H NMR analysis. [c]Isolated yield.

consisting of $Pd(OAc)_2$ (5.0 mol %), PPh_3 (6.0 mol %), and K_2CO_3 (2.0 equiv), a variety of solvents were briefly evaluated (entries 1−6). No reaction occurred in toluene, and other solvents such as DME, 1,4-dioxane, THF, and DMF led to the formation of undesired **4a**, while the anticipated product **3a** could be obtained in 29% yield in MeCN, albeit with low chemoselectivity. To impede the unwanted side reaction, a series of phosphine ligands and one NHC ligand were then examined (entries 7−15). Notably, P(2-furyl)$_3$ worked very well to give **3a** in high yield (85%) and excellent chemoselectivity (entry 11), whereas XPhos, $P(p\text{-MeO-}C_6H_4)_3$, SIPr·HBF_4, and bidentate phosphine ligands such as Xantphos, dppp, and dppf were found to be less effective. It is worth mentioning that PCy_3 could not promote the title transformation, and $P(p\text{-Cl-}C_6H_4)_3$ favored the formation of Heck byproduct **4a**. On the basis of these observations, it could be concluded that both steric and electronic properties of the ligand are critical for enabling the desired transformation. As a result, a relatively less bulky, electron-donating P(2-furyl)$_3$ turned out to be the optimal ligand. Moreover, we also attempted to improve the reaction performance by screening some other palladium sources, but none of them could enhance the chemoselectivity for the desired transformation (entries 16−18). Finally, it should be noted that the reaction occurred preferentially at the sterically more accessible alkene and the other one remained as the *E*-configured double bond.

With the optimized reaction conditions in hand, we first examined the substrate scope with respect to the phenolic coupling partner. As shown in Scheme 2, an important number

Scheme 2. Survey of the Scope of Phenols



of phenol-based biaryls reacted smoothly with **2a** to produce a wide spectrum of desired spirocyclic products **3b−p** in moderate to excellent yields with high chemoselectivities. Satisfactorily, various substituents on different positions of the upper phenyl ring were found to be tolerable in this process, including an electron-neutral group such as methyl (**3b−d**), electron-donating groups (EDGs) such as *tert*-butyl (**3e**) and methoxy groups (**3f**), as well as electron-withdrawing groups (EWGs) such as fluoro (**3g**), ester (**3h**), trifluoromethyl (**3i**), cyano (**3j**), nitro (**3k**), and phenyl (**3l**) groups. Remarkably, doubly *meta*-substituted substrate **1d** could undergo a synthetically more challenging cyclization with **2a** to generate a spirocyclic compound **3d** in 82% yield. Next, the phenolic ring was varied as well. Gratifyingly, the apparent phenol fragment, which is a more universal building block, was adaptable for the [3 + 2] spiroannulation process, thus providing the dearomatized **3m** in 67% yield. Moreover, unsymmetrical substrates **1n** and **1o** were compatible as well, giving a diastereomeric mixtures of **3n** and **3o**, respectively, in moderate yields (70% and 45%) but with low diastereoselectivity (2.6:1

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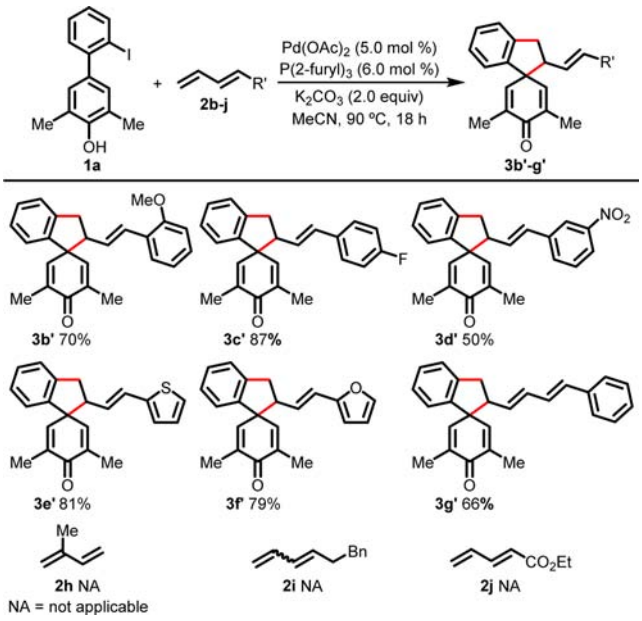
and 1.8:1 dr). The diastereomeric control of the reaction could be further enhanced by reacting an unsymmetrical naphthol substrate **1p** with **2a**, giving **3p** in 92% yield with 4.5:1 dr. Notably, the relative stereochemistry of the major diastereomer of **3p** was unambiguously revealed by X-ray studies (Supporting Information).

The scope of 1,3-dienes was then investigated (Scheme 3). Regarding the 1,3-dienes containing an aromatic substituent at

Scheme 3. Survey of the Scope of 1,3-Dienes

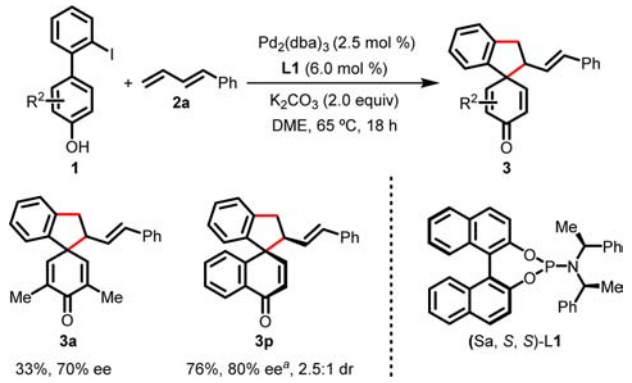


the terminal position, both EDG (methoxy) and EWGs (fluoro, nitro) were well tolerated on the aromatic ring (**3b′−d′**). The synthetic value of this method was further amplified by the successful replacement of the phenyl group with a heterocycle such as a 2-thienyl or 2-furyl group (**3e′−f′**). In all these cases, the [3 + 2] spiroannulations occurred exclusively toward the terminal olefin in a regiospecific manner, and the other possible regioisomers were not detected by ^{1}H NMR analysis. More interestingly, the reaction between **1a** and a triene substrate **2g** led to the formation of a single product **3g′** in 66% yield. In addition, it should be mentioned that the limitation of this [3 + 2] cyclization protocol became apparent when other types of 1,3-dienes **2h−j** were tested.

We next turned our attention to the development of an asymmetric version of this new reaction. Preliminary results with a commercially available chiral phosphoramidite ligand **L1**[15] demonstrated that compound **3a** could be obtained in 33% yield with a moderate but promising enantiomeric excess of 70%, and the asymmetric [3 + 2] spiroannulation of biaryl **1p** with **2a** could be realized to generate **3p** (2.5:1 dr) as a diastereomeric mixture in 76% yield, showing 80% ee for the major diastereomer with two contiguous tertiary/quaternary carbon stereocenters (Scheme 4).

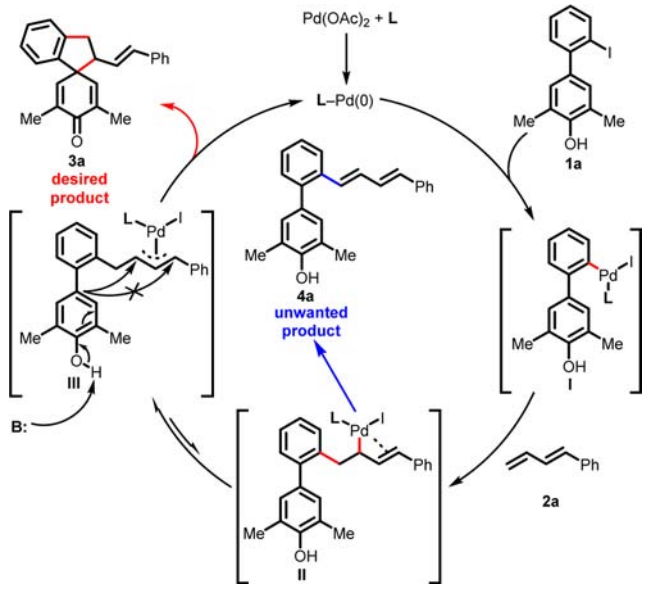
A plausible mechanism for this Pd-catalyzed dearomatization reaction, using substrates **1a** and **2a** for illustrative purposes, is depicted in Scheme 5. With in situ generated Pd(0) catalyst, **1a** undergoes oxidative addition to form Pd(II) intermediate **I**. Migratory insertion of the 1,3-diene **2a** with intermediate **I** can then occur to give an allylic Pd intermediate **II**, which will be able to undergo isomerization to form a π-allyl-Pd intermediate

Scheme 4. Preliminary Asymmetric Studies



[a]Determined by HPLC for the major diastereomer of **3p**.

Scheme 5. Proposed Mechanism



III. Consecutively, assisted by base, phenol acts as nucleophile to either attack on the π-allylpalladium carbon or attack at the metal center with C−C bond-forming reductive elimination, thus providing the desired product **3a**, meanwhile regenerating Pd(0) species to complete the catalytic cycle. It should be mentioned that the direct *syn* β-hydride elimination of intermediate **II** to generate **4a** was also observed during our optimization process. However, careful control of the reaction conditions could prevent its concomitant formation.

In summary, we have developed a novel Pd(0)-catalyzed dearomatization reaction of phenol-based biaryls with 1,3-dienes to generate a new class of spirocyclic compounds containing two contiguous tertiary/quaternary carbon centers. This reaction favors the formation of [3 + 2] cyclization products but not β-hydride elimination Heck-type byproducts and is complementary to the known method by using aryl iodides and allenyl phenols coupling partners.[13a] Moreover, the preliminary studies reveal that the asymmetric [3 + 2] spiroannulation transformation is feasible as well.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00710.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystallographic data for **3p** (CIF)

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Notes

The authors declare no competing financial interest.

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