Cyclizations

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Palladium(0)-Catalyzed Intermolecular Carbocyclization of (1,*n*)-Diynes and Bromophenols: An Efficient Route to Tricyclic Scaffolds

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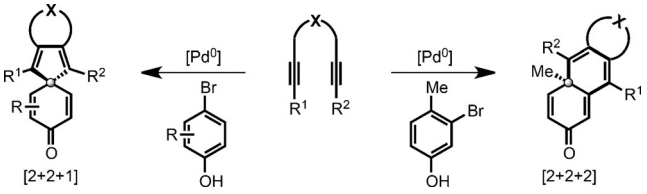
Dedicated to Professor Barry M. Trost on the occasion of his 75th birthday

Abstract: *A novel palladium(0)-catalyzed dearomative cyclization reaction of bromophenols with (1,n)-diynes has been developed for building two new types of tricyclic architectures containing a quaternary carbon center. This method employs inexpensive bromophenols, and easily accessible tethered diynes. It exhibits a broad substrate scope and tolerates various functional groups. Preliminary results with commercially available chiral ligands indicate that enantioselective variants are feasible for both cyclization processes.*

The ubiquity of various polycyclic frameworks continues to make the development of new methods for their construction an important objective in chemical synthesis. Transition-metal-catalyzed polycyclization reactions represent some of the most powerful and efficient approaches for creating highly functionalized, architecturally complex molecules from readily available precursors in a single step.[1] An illustrative example of this approach is the chemo- and regioselective cyclization of multiple unsaturated π-species with other coupling partners through a carbometallation cascade for the targeted synthesis of many synthetically valuable polycyclic compounds, which are generally not accessible through classical pericyclic reactions.[2]

Herein we disclose an unprecedented carbopalladation reaction of tethered diynes with bromophenols by a formal [2+2+1] or [2+2+2] cycloaddition route (Scheme 1), thus leading to the rapid assembly of a series of fascinating spirofused or fused tricycles, respectively, bearing a quaternary carbon center. Importantly, these unique tricyclic skeletons exist in a good number of bioactive natural products,[3] such as those shown in the Figure 1.

A characteristic feature of this current polycyclization protocol is the disruption of the aromatic π-system of phenol,



Scheme 1. Formal [2+2+1] and [2+2+2] cycloaddition routes to new tricycles.

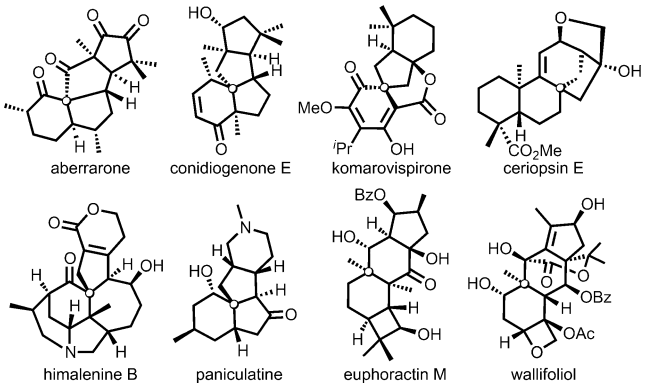


Figure 1. Examples of natural products containing these unique tricyclic cores.

thus affording a very attractive cyclohexadienone moiety. Remarkably, transition-metal-catalyzed dearomatization reactions of phenols and naphthols have served as an extraordinarily potent tool for generating some three-dimensional structures which are either difficult or impossible to form by conventional means.[4] Along with the earlier studies on the dearomatization of indoles[5] and anilines,[6] recent seminal reports by the groups of Hamada,[7] You,[8] Buchwald,[9] Feringa,[10] and Tang[11] have demonstrated that several spirocyclic and fused ring scaffolds could be obtained by transition-metal-catalyzed dearomative cyclizations of phenol-derived precursors in an intramolecular fashion by the formation of one C–C bond. Notwithstanding these excellent examples, there is a compelling need to develop more economical intermolecular cyclization processes with simpler phenol substrates which do not require costly multistep syntheses.

In this context, our groups,[12] as well as that of Mascareñas and Gulías,[13] Lam,[14] and You[15] have independently de-

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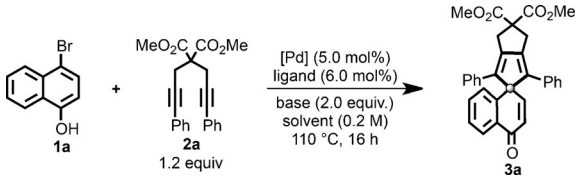
scribed the two-component intermolecular annulations between phenol-based biaryls and internal alkynes by a sequence of aryl-metal species formation, by either a C–H cleavage[12a,c,13–15] or oxidative addition to the C–Br bond,[12b,d] carbometalation of one alkyne unit, and eventually terminated by dearomatization of the phenolic ring to provide spirocycles. In 2011, Schmidt and co-workers reported an impressive example of palladium-catalyzed [2+2+1] spiroannulation of phenol diazonium salts with two equivalents of diarylalkynes by formation of three C–C bonds.[16] Soon after, we developed a similar cyclization reaction of β-naphthols with two equivalents of alkynes through consecutive carbopalladation to the C–C triple bonds under oxidative conditions.[17] These intermolecular reactions proceeded smoothly by coupling easily accessible phenol derivatives with symmetric alkynes, but a significant challenge with these processes is the ability to control the regioselective insertion of an unsymmetrical alkyne.[12–17] The lack of control is even more severe in [2+2+1] cyclizations,[16,17] generally leading to three inseparable regioisomers in a poor ratio. To address this problem, we postulated that the utilization of carbon- or heteroatom-tethered (1,*n*)-diynes, which possess an inter-intramolecular feature, to react with either phenol diazonium salts or β-naphthols would provide an effective solution by the regiospecific construction of a more interesting tricyclic framework. However, the envisioned transformations with tethered diynes did not proceed at all under the precedented reaction conditions.[16,17] Intrigued by the recent advances on palladium(0)-catalyzed domino reactions of aryl halides with (1,*n*)-diynes for generating diversified polycycles,[18] we used the most abundant, commercially available bromophenols for promoting a palladium(0)-catalyzed dearomative cyclization reaction with the tethered diynes. Our task was to find suitable reaction conditions to enable the desired $[2+2+x]$ ($x=1$ or 2) cyclization process, through the dearomatization of phenols, by preventing the unwanted [2+2+2] aromatization of two reactants[19] and the self-consumption of bromophenols either through diarylether formation[20] or dehalogenation.[16] Herein, we present our efforts on this subject.

We began the investigation by choosing the commercially available 4-bromonaphthalen-1-ol (**1a**) and simple diyne **2a** as the standard coupling partners to explore the catalytic system for the potential [2+2+1] spiroannulation (Table 1). The envisioned reaction was first realized by heating a mixture of **1a** and **2a** in THF at 110 °C in the presence of 5.0 mol % of $Pd(OAc)_2$, 6.0 mol % PPh_3, and 2.0 equivalents of K_2CO_3. The desired tricyclic product **3a** was obtained in 53 % yield (entry 1), without generating any other undesirable side products.[16,19,20] Further experimental results on the ligand screening revealed that both electron-rich monophosphine ligands (PCy_3 and XPhos) and bis(phosphine) ligands (BINAP, DPPP, and DPPF) promoted the title transformation, albeit with lower yields (entries 2–6). By using the inexpensive ligand PPh_3, several other palladium precursors were then evaluated (entries 7–9), thus showing inferior performance in comparison with that of $Pd(OAc)_2$. Next, K_3PO_4, KOAc, and Na_2CO_3 were found to be effective for the reaction (entries 10–12), whereas Cs_2CO_3 completely shut down the reaction (entry 13). Finally, a solvent screening was carried out (entries 14–18), and the reaction was dramatically improved by switching to 1,4-dioxane as the solvent, thus providing **3a** in 86 % yield upon isolation (entry 18). The optimized reaction conditions were obtained as the following: 5.0 mol % $Pd(OAc)_2$, 6.0 mol % PPh_3, and 2.0 equivalents of K_2CO_3 in 1,4-dioxane at 110 °C.

Table 1: Optimization of the reaction conditions.[a]



Entry	[Pd]	Ligand	Base	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	53
2	$Pd(OAc)_2$	PCy_3	K_2CO_3	THF	16
3	$Pd(OAc)_2$	XPhos	K_2CO_3	THF	31
4	$Pd(OAc)_2$	BINAP	K_2CO_3	THF	26
5	$Pd(OAc)_2$	DPPF	K_2CO_3	THF	32
6	$Pd(OAc)_2$	DPPP	K_2CO_3	THF	43
7	$[Pd_2(dba)_3]$	PPh_3	K_2CO_3	THF	26
8	$PdCl_2$	PPh_3	K_2CO_3	THF	38
9	$[\{Pd(allyl)Cl\}_2]$	PPh_3	K_2CO_3	THF	6
10	$Pd(OAc)_2$	PPh_3	K_3PO_4	THF	29
11	$Pd(OAc)_2$	PPh_3	KOAc	THF	36
12	$Pd(OAc)_2$	PPh_3	Na_2CO_3	THF	21
13	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	THF	< 5
14	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	< 5
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	MeCN	< 5
16	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	41
17	$Pd(OAc)_2$	PPh_3	K_2CO_3	DME	58
18	$Pd(OAc)_2$	PPh_3	K_2CO_3	1,4-dioxane	86

[a] Reactions were conducted with 0.20 mmol of **1a**. [b] Yield of isolated product. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, DME = 1,2-dimethoxyethane, DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene, DPPP = 1,2-bis(diphenylphosphi-no)ethane, THF = tetrahydrofuran, XPhos = 2-(dicyclohexylphosphino)-2′,4′,6′-tri-iso-propyl-1,1′-biphenyl.

With the optimized reaction conditions in hand, we first studied the generality of this novel transformation by reacting an important number of (1,*n*)-diynes (**2a–t**) with **1a**, and the results demonstrated that diynes could be varied on both the alkyne termini and the tether, thus affording the corresponding tricyclic compounds (**3a–t**) in good to excellent yields (71–94 %; Table 2). The terminal phenyl groups of **2a** could be replaced by heterocyclic (**2b**), alkyl (**2c–e**), and silyl (**2f–g**) groups. Moreover, the unsymmetrical diynes **2e–g**, which possess different substituents on the alkyne termini, underwent the desired [2+2+1] cyclization smoothly to form **3e–g**, thus providing the opportunity for enabling a catalytic enantioselective process. Besides a diester (**2h**), the carbon tether of the 1,6-diynes could also tolerate a dicyanide (**2i**) and diketone (**2j**). Remarkably, the reaction between **1a** and **2j** led to an unprecedented tetracyclic structure with two fused spirocycles (**3j**). Moreover, the 1,7-diyne **2k** was also tolerated, thus giving rise to **3k** in 88 % yield. Notably, nitrogen- or oxygen-tethered (1,6)-diynes (**2l–o**) were well-tolerated and provided the tricyclic compounds **3l–o**, with a heterocycle, in 81–87 % yield. Gratifyingly, the size of this

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Table 2: Scope with respect to the diynes for the [2+2+1] reaction.

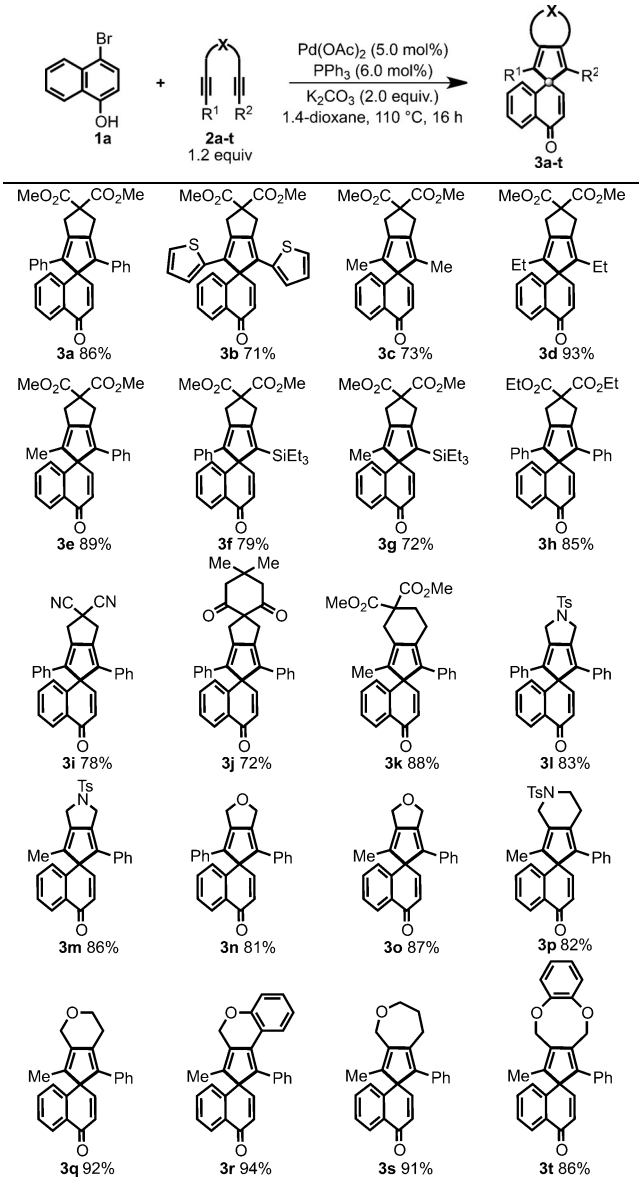
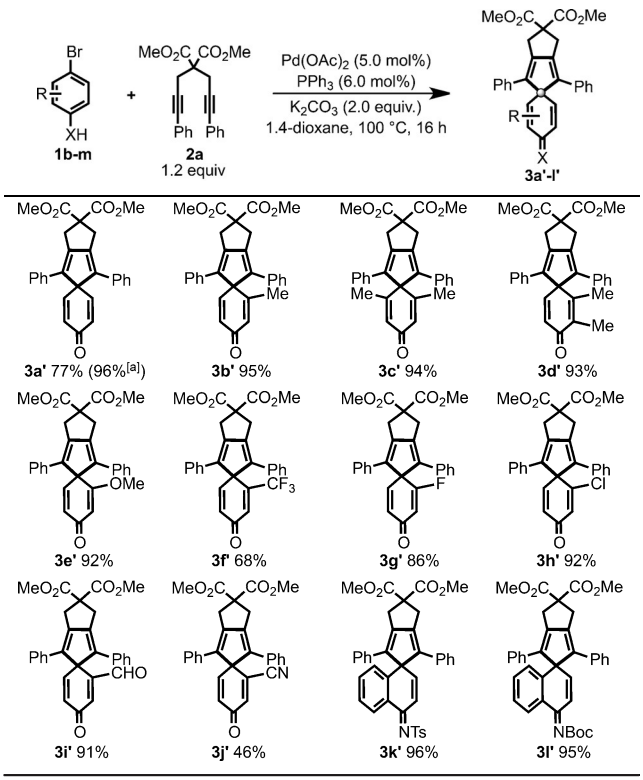


Table 3: Scope with respect to *para*-bromophenols for the [2+2+1] reaction.



[a] 4-Bromophenol was replaced with 4-iodophenol.

five-membered heterocycle could be easily increased by lengthening the tether of the diynes (**2p**–**t**). More specifically, the use of a dialkyl-diaryl mixed diyne (**2r**) led to **3r**, with a quaternary carbon center. This reaction is challenging for prior methods using two different types of individual alkynes.[16,17]

Next, we sought to investigate the scope with respect to the bromophenols for the [2+2+1] cyclization (Table 3). First, 4-bromophenol (**1b**) was tested, and the desired product **3a″** was obtained in 77% yield at 100°C. To our delight, the chemical yield of **3a′** was further increased to 96% by using 4-iodophenol (**1b′**) to replace **1b**. A series of commercially available *para*-bromophenols (**1c**–**k**) were then subjected to the same reaction conditions, and the results indicate that their corresponding reactions proceeded smoothly to provide the anticipated products **3b′**–**j′** in 46–95% yields. Satisfactorily, various substituents on the phenol ring were tolerated, including electron-neutral or electron-donating groups such as methyl (**3b′**–**d′**) and methoxy (**3e′**) groups, and electron-withdrawing groups such as trifluoromethyl (**3f′**), fluoro (**3g′**), chloro (**3h′**), formyl (**3i′**), and cyano (**3j′**) groups. In addition, it is worth mentioning that protected 4-bromonaphthalen-1-amines participated well in the dearomative process, thus leading to the formation of the imines **3k′**,**l′** in excellent yields (96% and 95%).

Furthermore, several potentially applicable *ortho*-bromophenol and *meta*-bromophenol substrates were also evaluated,[21] and the commercially avaliable 3-bromo-4-methylphenol (**4**) was found to be effective for the dearomative process following a [2+2+2] cyclization pathway under slightly modified reaction conditions.[22] By combining **4** with (1,6)-diynes,[23] the reactions gave rise to a series of fascinating polycyclic products (**5a**–**h**; Table 4). These (1,6)-diynes could be varied with phenyl, thienyl, methyl, and silyl groups on the alkyne termini. Reacting **4** with the cyclic diyne **2j** led to an attractive tetracyclic molecule (**5e**) containing both spirofused and fused ring motifs. Notably, the reaction between **4** and the unsymmetrical diyne **2e** proceeded efficiently to give **5f** as a regioisomeric mixture in 92% yield with 6:1 rr, and the major regioisomer was assigned by X-ray.[24] This observation provides evidence in support that the insertion of the methyl-substituted C–C triple bond of **2e** is more favorable than that of the phenyl-substituted alkyne during the cyclization process. Moreover, the run with the

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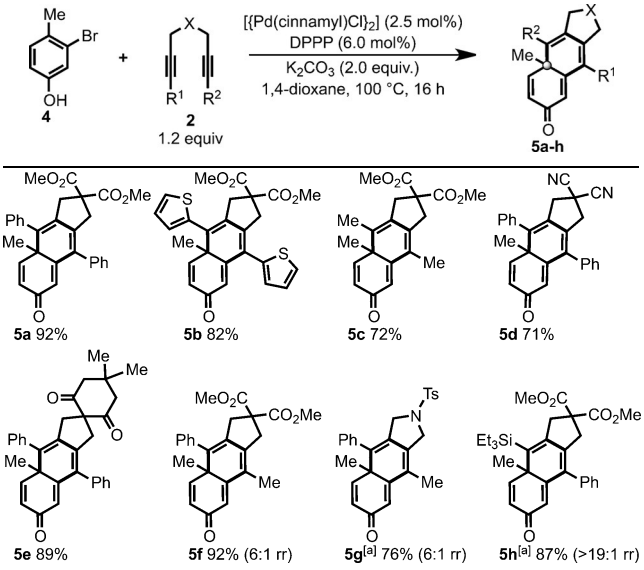
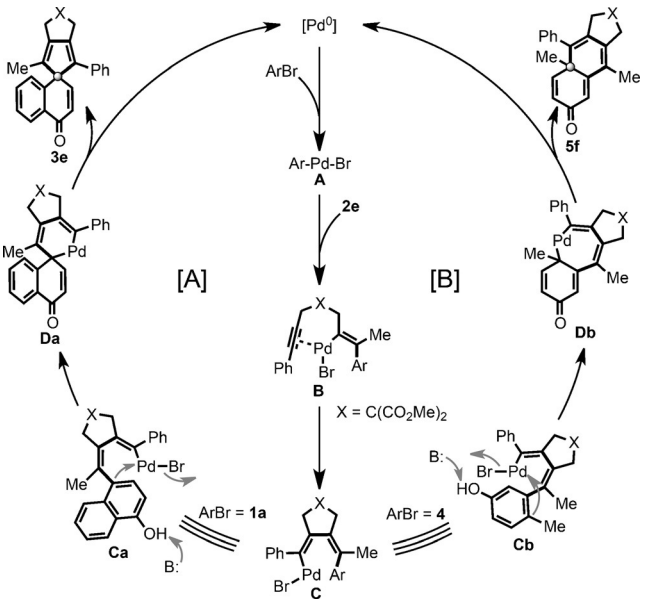
Table 4: Scope with respect to diynes for the [2+2+2] reaction.



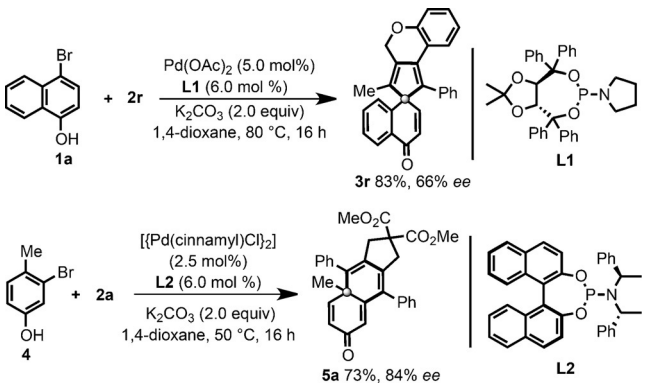
[a] DPPP was replaced with **L′**. [**L′** = *N*,*N*-bis(1-phenylethyl)dinaphtho-[2,1-*d*:1′,2′-*f*] [1,3,2]dioxaphosphepin-4-amine].



Scheme 3. Proposed mechanism.

nitrogen-bridged diyne **2m** reached the same regioselectivity as the reaction with **2e**, albeit with lower yield of **5g** (76%). Remarkably, a Ph/TES mixed diyne (**2f**) behave extremely well in the dearomative [2+2+2] cyclization process, and the anticipated product **5h** was formed as a single regioisomer in 87% yield, with the initial carbopalladation occurring on the phenyl-substituted alkyne unit. In the end, it should be noted that limitations of the reaction became apparent when replacing the methyl group of **4** with a larger alkyl or aryl group.

The asymmetric formation of quaternary stereocenters remains a formidable challenge for organic chemists.[25] With this in mind, we also investigated the development of an asymmetric version of the new cyclization reaction (Scheme 2). Preliminary attempts with some commercially available chiral phosphine ligands revealed that the TADDOL-derived **L1** enabled the formation of **3r** via a [2+2+1] spiroannulation in 83% yield with a moderate



Scheme 2. Preliminary asymmetric studies.

but promising enantiomeric excess of 66%, and the use of the Feringa ligand **L2** rendered the asymmetric synthesis of **5a**, through a [2+2+2] dearomative pathway, in 73% yield with 84% *ee* (see the Supporting Information for details).

A mechanistic pathway for the formation of **3e** and **5f** is depicted in Scheme 3. The catalytic cycle is initiated by oxidative addition of bromophenol (**1a** or **4**) to Pd^0. Subsequently, the intermediate **A** preferentially undergoes carbopalladation of the methyl substituted triple bond of diyne **2e**, and is supported by the observed regioselectivities (6:1 rr) for the generation of **5f**. Afterwards, the second alkyne unit is inserted to produce the cyclic intermediate **C**. At this point, for the reaction starting from **1a**, the dearoamtization occurs at the *ipso*-position of the substituent to generate the spirocyclic intermediate **Da**, which, after reductive elimination, leads to the formation of the tricyclic **3e** containing both the spirofused and fused rings (cycle A). For the reaction using **4** as the starting material, the fused tricyclic product **5f** is obtained by the dearomatization of phenol occurring at the *ortho*-position of methyl substituent (B cycle).

In summary, we have developed a novel and efficient palladium(0)-catalyzed dearomative cyclization of bromophenols with tethered diynes for constructing new polycyclic architectures bearing an all-carbon quaternary center. By using the *para*-bromophenols as the coupling partners for (1,*n*)-diynes ($n = 6$–9), the reaction undergoes a [2+2+1] spiroannulation, thus leading to a class of tricyclic molecules containing both spirofused and fused ring motifs. Use of a *meta*-bromophenol to react with 1,6-diynes results in a smooth transformation by a [2+2+2] route, thus providing a series of fused tricycles. Preliminary studies demonstrate that asymmetric control is feasible for both cyclizations. Remarkably, this methodology represents a rare example of transition-metal-catalyzed dearomatization reactions for building rather complex targets in an intermolecular fashion when starting from easily available substrates.

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[22] To our knowledge, there was only one example of a transition-metal-catalyzed dearomatization reaction with phenol derivatives occurring at the *ortho*-position of the tethered substituent. See Ref. [11].

[23] Attempts at the dearomative [2+2+2] cyclizations between **4** and (1,*n*)-diynes ($n=7$, 8 or 9) were failed.

[24] CCDC 1450663 (**5 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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