A 1,4-Palladium Migration/Heck Sequence with Unactivated Alkenes: Stereoselective Synthesis of Trisubstituted 1,3-Dienes

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Abstract: The palladium-catalyzed cross-coupling of *ortho*-vinyl aromatic bromides and olefins was achieved through a controllable 1,4-palladium migration/Heck cascade protocol. The reaction represents a mild, efficient and highly stereoselective method for the synthesis of trisubstituted 1,3-dienes, especially for triaryl-substituted ones.

Keywords: Palladium migration; Heck reaction; diene synthesis

Conjugated dienes are important building blocks or motifs in organic chemistry for their wide existence in natural products,^[1] numerous potential transformations to key compounds,^[2] and broad applications in material science like polybutadiene (PB).^[3] Especially, due to aggregation-induced the emission (AIE) characteristics,^[4] triphenyl-substituted 1,3-butadienes received considerable attention in the development of advanced electrochemical materials.^[5] As the geometry of the 1,3-butadienes played a critical role in their optical behaviors,^[6] a stereoselective protocol for efficient construction of this motif is very attractive and valuable.

Among diverse strategies developed to construct this structure, the cross-coupling of an alkenyl nucleophile and an alkenyl electrophile is a reliable method^[7] (Scheme 1a). However, the required prefunctionalization of the involved two coupling olefin partners often makes the target synthesis complex and challenging. In contrast, the coupling between two unactivated alkenes without the need of pre-transformations of alkenes to alkenyl nucleophiles or electrophiles has emerged as a straightfor-

ward and efficient approach to the key 1,3-diene skeleton^[8] (Scheme 1b). Usually, stoichiometric amount of oxidant is required to recycle the transition metal catalysts, limiting the substrate scope to that with relatively robust functional groups. Thus, the development of an oxidant-free protocol for cross-coupling between unactivated terminal alkenes should be important and useful.

Recently, we^[9] and others^[10] have demonstrated aryl to alkenyl 1,4-palladium migration as a powerful method for generation of stereodefined alkenyl palladium species which were applied to some stereoselective cascade

a) Cross-coupling

F



b) Oxidative cross-coupling

$$R^{3}$$
 + H R^{4} $M, [O]$ R^{3} R^{4}

c) 1,4-Pd migration/Heck sequence (this work)



Scheme 1. Transition Metal-Catalyzed Synthesis of 1,3-Dienes.



reactions with unsaturated carbony compounds,^[9c] aryl or alkenyl boronic esters,^[9a] 1,3-diene^[9b] *et al.* We wondered if an unactivated olefin was involved in a 1,4-Pd migration/Heck sequence (Scheme 1c), it would provide a new route to the challenging triaryl-substituted 1,3dienes. In addition, this oxidant-free process should also be able to provide precise stereo-control over the final product. We herein reported our research on the 1,4palladium migration/Heck cascade reaction with unactivated alkenes.

To examine the feasibility of this reaction, terminal olefin 1 a and styrene 2 a were used as model substrates, $P(2-MeO-C_6H_4)_3$ as the ligand and CsOAc as the base for initial trials (Table 1). Fortunately, medium yield of coupling product **3a** was observed but with obvious unmigrated Heck coupling product 4 (entry 1). When CsOAc was switched to CsOPiv, similar yield of 3a and better selectivity was obtained (entry 2). Then the influence of reaction temperature on this cascade process was also examined (entries 3-6). To our delight, lowering temperature to 50°C boosted the yield of 3a to 95% (entry 5). In addition, various bases were tested (entries 7-10). The unique excellent performance from the carboxylate salts indicated a concerted metalation-deprotonation (CMD) mechanism might be involved in C-H activation process.^[11] Finally, a set of monophosphate ligands were evaluated (see SI for details). Only the (2-MeO– C_6H_4)₃P gave a good yield, possibly attributing to the beneficial effect from o-MeO group as a hemiliable





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Entry	T/°C	Base	Yield of $3 a^{[b]}$	3 a:4:5 ^[b]	
1	100	CsOAc	53	86:12:2	
2	100	CsOPiv	52	91:7:2	
3	80	CsOPiv	69	92:6:2	
4	60	CsOPiv	90	94:4:2	
5	50	CsOPiv	95	94:4:2	
6	40	CsOPiv	52	94:4:2	
7	50	CsOAc	76	94:4:2	
8	50	KOPiv	90	90:8:2	
9	50	Cs_2CO_3	0	nd	
10	50	CsF	19	nd	

^[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), Pd (OAc)₂ (0.01 mmol), (2-MeO-C₆H₄)₃P (0.02 mmol), base (0.40 mmol), 1,4-dioxane (2.0 mL), Ar atmosphere, 7 h.

^[b] Determined by GC with dodecane as internal standard.

ligand.^[12] Thus, the optimal reaction condition was determined by using $Pd(OAc)_2$ (5.0 mol%) and (2-MeO-C₆H₄)₃P (10 mol%) as the catalyst, CsOPiv (2.0 equiv.) as the base in 1,4-dioxane at 50 °C.

The generality of the 1,4-migration/Heck sequence with styrene 2a was studied with a number of brominated terminal olefins 1 and the results were summarized in Table 2. The substituent effect on the brominated aryl ring was first explored. Both *para*- and *meta*-methyl-substituted arylbromide worked well with

Table 2. Scope of *Ortho*-Vinyl Aromatic Bromides for the Coupling Reactions.^[a]



^[a] Reaction conditions: 1 (0.20 mmol), 2a (0.40 mmol), Pd $(OAc)_2$ (0.01 mmol), (2-MeO-C₆H₄)₃P (0.02 mmol), CsOPiv (0.40 mmol), 1,4-dioxane (2.0 mL), Ar atmosphere, 50 °C, 7 h, unless otherwise noted.

^[b] Conducted on a 1 mmol scale at 70 °C.

^[c] Performed at 70 °C.

^[d] Performed at 90 °C.



styrene, giving the coupling product 3b and 3c in 89%and 72% yield, respectively. In contrast, the Me substituent in *ortho*-position provided no product owing to the increased steric hindrance. The presence of electron-donating group like methoxyl in *para*- (3d) or *meta*-position (3e) showed equally good reactivity. While bromide substitution can be spontaneously consumed via oxidative addition of palladium catalyst, less reactive chloride was well tolerated, providing a handle for further derivation (3f). When the reaction was conducted on 1 mmol scale, slightly elevated temperature was required for full conversion, giving a comparable yield of 85%.

The scope of substituents on the non-brominated aryl groups on the olefin **1** a was further evaluated (Table 2). Different from the influence of the methyl group on the brominated arene, the introduction of Me onto para-(3g), meta- (3h) or ortho- (3i) position of the phenyl ring afforded high yields for all cases. Both electrondonating and electron-withdrawing groups gave over 78% yields (3 j-3 m). The replacement of the phenyl ring by other groups was also tested. Naphthyl ring was well accommodated and gave an excellent yield of 99% (3n). Acceptable yields were obtained with heteroaromatic thiophene (30) or ester group (3p). Although the desired reaction still took place with alkyl substitutions, a great amount of by-products were accompanied. For example, an isolated yield of 24% was observed with isopropyl group (3q).

A set of styrenes as substrates were evaluated and the results were shown in Table 3. Similarly, the steric hindrance showed no obvious effect on the coupling: methyl group at para-, meta- or ortho- positions of the phenyl ring gave 53-94% yield of the coupling product (3r-3t). But the methyl group in *ortho*-position did suppress the reaction to some extent, due to potential steric hindrance (3t). Electron-donating group like MeO (3u) on the *para*-position of the phenyl ring worked smoothly, while the electron-withdrawing groups like CN (3v) and NO₂ (3w) gave slightly reduced yield. When phenyl group was replaced with a naphthyl (3x) or biphenyl (3y) group, excellent yields were observed for both cases. Several aliphatic alkenes were tested, but they showed lower reactivity and usually produced inseparable isomer mixture. When allyl alcohol was used, which was supposed to prevent the possible side reaction via coordination of palladium with the hydroxyl group,^[13] the desired product 3z was isolated in 50% yield.

Based on previous studies,^[9,10] a plausible reaction pathway for this cascade process was described in Scheme 2. The reaction started with the oxidative addition of palladium catalyst by arylbromide **1a** to generate Pd(II) species **A**, which may exchange its bromide with PivO⁻ anion to facilitate the following C–H activation step through CMD mechanism. Once the five-membered palladacycle **C** generated by the the C–H activation, it undergoes a formal proton transfer to render a net 1,4-palladium shift from the aryl to





^[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Pd $(OAc)_2$ (0.01 mmol), (2-MeO-C₆H₄)₃P (0.02 mmol), CsOPiv (0.40 mmol), 1,4-dioxane (2.0 mL), Ar atmosphere, 50 °C, 7 h, unless otherwise noted.

^[b] Performed at 90 °C.

^[c] Performed at 70 °C.



Scheme 2. The Plausible Reaction Pathway.

alkenyl position. The resulting vinyl palladium species **D** reacts with styrene via the classical Heck pathway to offer the product 3a and thus closes the catalytic cycle.

In summary, a stereoselective synthetic protocol of trisubstituted 1,3-dienes was established by the design of a 1,4-palladium migration/Heck cascade sequence. A wide range of trisubstituted 1,3-dienes were con-

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structed in good to excellent yields. It is noteworthy that the substrates bearing two similar aryl groups at terminal positions were able to be prepared in high stereoselectivity, which is challenging to be obtained by traditional methods.

Experimental Section

General procedure for the synthesis of 3: In a 10 mL sealed tube, a mixture of *ortho*-vinyl bromobenzene 1 (0.20 mmol, 1.0 equiv.), styrene derivative 2 (0.40 mmol, 2.0 equiv.), Pd- $(OAc)_2$ (2.2 mg, 0.010 mmol, 5.0 mol%), (2-MeO-C₆H₄)₃P (7.0 mg, 0.020 mmol, 10 mol%) and CsOPiv (94 mg, 2.0 equiv.) in 1,4-dioxane (2.0 mL) was stirred at 50 °C under argon for 7 h. After cooling to room temperature, the mixture was filtered through a celite pad and concentrated under vacuum. The residue was purified by flash chromatography (elute: hexane) to afford product **3**.

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