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Stereoselective Synthesis of Conjugated Trienes via 1,4-Palladium Migration/Heck Sequence

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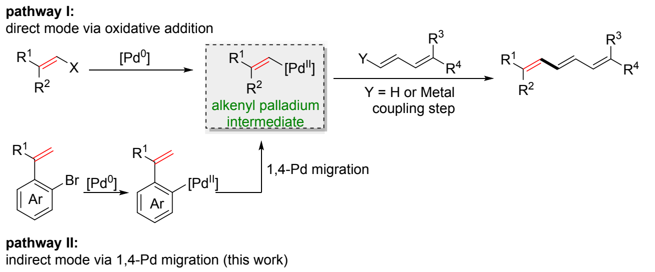
ABSTRACT: Conjugated trienes are ubiquitous structures in natural products and organic functional molecules. An efficient 1,4-palladium migration/Heck sequence was developed for the highly stereoselective synthesis of trisubstituent 1,3,5-trienes, which were found to undergo easy *E*/*Z* isomerization in the light.

Natural products containing conjugated trienic units, which are often produced as a means of chemical defense, constitute an important class of molecules and possess interesting biological activities.[1] Due to the extended *p*-electron system in trienes decrease the energy gap between the ground and excited states, they have also found applications in the optoelectronic materials.[2] As a consequence, the development of new methods for the stereocontrolled construction of this π-conjugated system has attracted considerable research interest.[3,4,5]

Although the Wittig or the Horner-Wadsworth-Emmons olefinations traditionally were used in the construction of conjugated trienes,[3] transition-metal-catalyzed reactions now have become a more popular choice, owing to a number of synthetic advantages like the easier accessibility of starting material, the better functional group tolerance of reaction conditions and the increased flexibility in stereochemical control.[4,5] Among those methods, the cross-coupling of alkenyl halides with various dienyl reagents through alkenyl palladium intermediates is particularly useful for the modular assemble of trienes in a stereocontrolled fashion (Scheme 1, pathway I).[4] However, this strategy was often hampered by the difficulties in the preparation of alkenyl halides with a specific geometry.[6] Therefore, an alternative strategy for the generation of alkenyl palladium with controlled geometry in double bond is desirable.



Scheme 1 Stereoselective Synthesis of Conjugated Trienes via Alkenyl Palladium

Palladium migration is found to bring new reactivity for the original reagents, and applied in some synthetic transformations that are inaccessible by conventional methods.[7] Recently, we[8] and others[9] have demonstrated aryl to alkenyl 1,4-palladium migration as a reliable method for the generation of stereodefined alkenyl palladium species, which was applied in some stereoselective synthesis of olefins. During our study, we found that the generated alkenyl palladium can undergo Heck reaction with active electro-withdrawing olefins.[8c] As a continuation of this work, we herein report a reaction with 1,3-dienes for the stereoselective synthesis of conjugated trienes (Scheme 1, pathway II).

We started our investigations by optimizing the coupling of terminal olefin **1a** and phenyl butadiene **2a** using $Pd(OAc)_2$ as the precatalyst and PPh_3 as the ligand (Table 1). To our delight, the desired triene **3a** was obtained in 67% yield under our initial conditions (entry 4). While electron-withdrawing $(4\text{-}CF_3Ph)_3P$ gave a decreased yield,(entry 2), electron-donating $(4\text{-}MeOPh)_3P$ showed marginal effect on the reaction yield (entry 3). However, the use of $(4\text{-}MeOPh)_3P$ as ligand boosted the formation of **3a** to 97% yield (entry 1), which may be ascribe to the beneficial effect from *o*-MeO group as a hemiliable ligand.[10] Normally, carboxylate salts played as internal bases for proton abstraction in the C-H activation via concerted metalation deprotonation (CMD) mechanism.[11] In the screening of base, all the tested carboxylate salts were competent for this transformation, and CsOPiv proved to be the best one (entry 1 *vs* entries 5 and 6).[12] The reaction also

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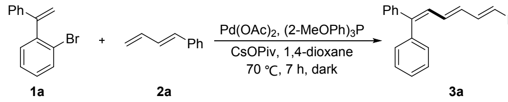
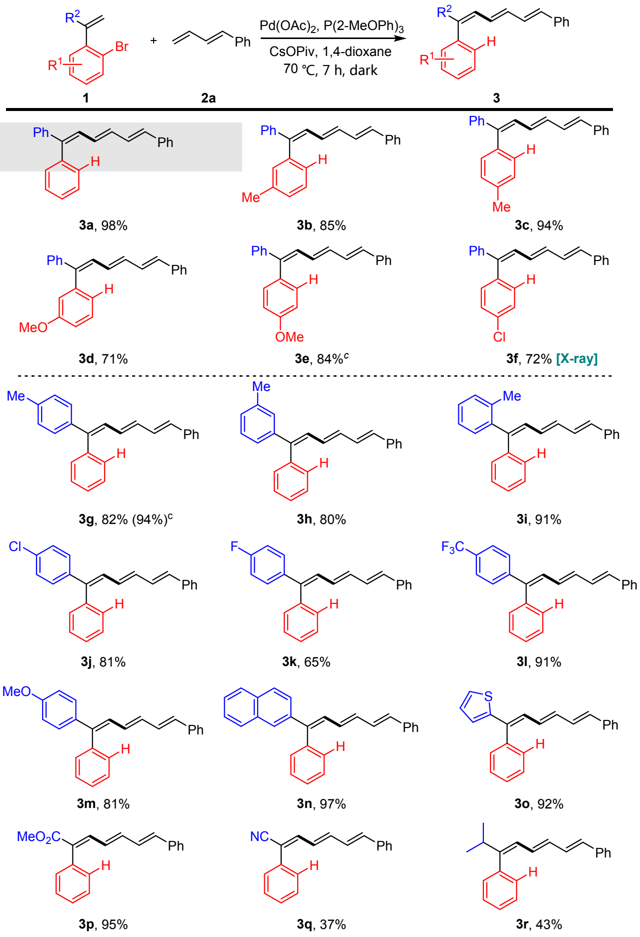
Table 1 Optimization of the Reaction Conditions[a]



entry	Deviation from standard conditions	yield(%)[b]
1	none	97
2	$(4\text{-}CF_3Ph)_3P$ instead of $(2\text{-}MeOPh)_3P$	37
3	$(4\text{-}MeOPh)_3P$ instead of $(2\text{-}MeOPh)_3P$	63
4	Ph_3P instead of $(2\text{-}MeOPh)_3P$	67
5	KOPiv instead of CsOPiv	87
6	CsOAc instead of CsOPiv	85
7	CsF instead of CsOPiv	45
8	Cs_2CO_3 instead of CsOPiv	13
9	THF instead of 1,4-dioxane	85
10	1,3-dioxolane instead of 1,4-dioxane	90
11	MeCN instead of 1,4-dioxane	86
12	DMF instead of 1,4-dioxane	67
13	DCE instead of 1,4-dioxane	42
14	DME instead of 1,4-dioxane	86

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol, 2 equiv), base (0.40 mmol, 2 equiv), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), Ligand (0.02 mmol, 10 mol %), solvent (2 mL), sealed tube, in dark, Ar atmosphere, 70 °C, 7 h. [b]Determined by GC using dodecane as an internal standard.

Table 2 Substrate Scope of Vinyl Bromides[a,b,c]



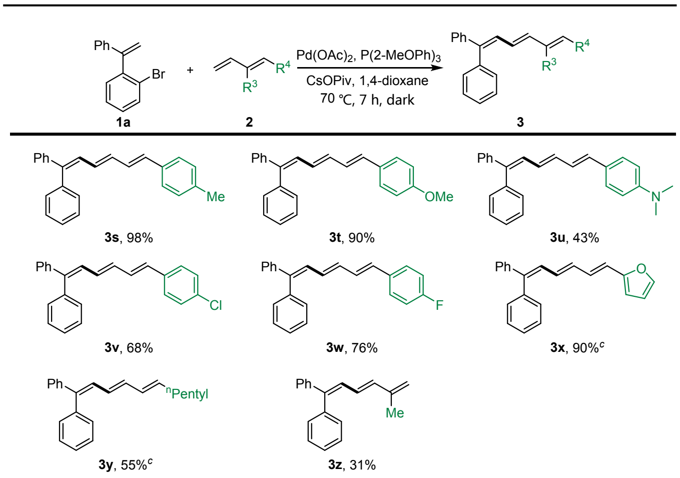
[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol, 2 equiv), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), $(2\text{-}MeOPh)_3P$ (0.02 mmol, 10 mol %), CsOPiv (0.40 mmol, 2 equiv), 1,4-dioxane (2 mL), in dark, Ar atmosphere, 70 °C, 7 h. [b]Isolated yield. [c]Performed at 90 °C. [c]With olefin **1g** (1.37g, 5 mmol) as starting material.

proceeded well in a variety of solvents, especially with ethers and MeCN (entries 9-14).

With the optimized reaction conditions in hand, the scope of the palladium-catalyzed 1,4-migration/Heck sequence for the synthesis of 1,3,5-triene was investigated (Table 2). The substituent effect on the bromide-containing phenyl ring was first examined. The methodology boded well with Me groups in both *para*- (**3b**) and *meta*-positions (**3c**) of bromide. The reaction was blocked if the Me group was switched to the *ortho*-position, which may be explained by the increased steric encumbrance. The presence of electron donating group such as MeO in both *para*- (**3d**) and *meta*-positions (**3e**) of bromide did not affect the reactivity. Chloride was tolerated in this methodology (**3f**), and the absolute configuration of the corresponding product was confirmed by X-ray diffraction.[13] Next, the phenyl group of **1a** was replaced with various groups to investigate the generality of this transformation. Introduction of Me onto the *para*- (**3g**), *meta*- (**3h**) or *ortho*- (**3i**) position of the phenyl ring afforded high yields. When electron donating group such as MeO (**3m**) was introduced to the *para* position of phenyl ring, good yield was obtained. The mild electron-withdrawing halides (F and Cl) were tolerated well in this methodology. It is interesting that the CF_3 group afforded high yield (**3l**). Replacing the phenyl ring by a naphthyl group (**3n**) is also compatible, giving a high yield of 97%. When phenyl ring was replaced by the heteroaromatic ring like thiophene, high yield was obtained (**3o**). The phenyl group also can be replaced by several nonaryclic groups (**3p-3q**), albeit with a significant amount of source material recovery for cyano (**3q**) and alkyl (**3r**) substitutions.

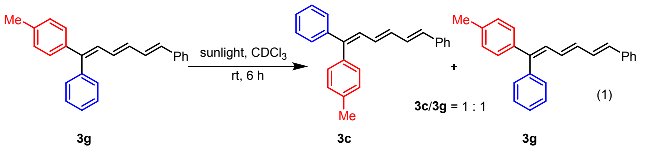
Next, the substituent effect on 1,3-dienes were examined (Table 3). At first, various 1,3-dienes with different aryl substitutions on the terminal site were tested. Electron-donating groups such as Me (**3s**) and MeO (**3t**) on the *para*-position of the phenyl ring showed a marginal effect on the reaction outcome, and excellent reaction yields were observed. The electron withdrawing group like F (**3v**) and Cl (**3w**) were tolerated but the yields decreased. Polyene molecules bearing *N,N*-dimethylaniline as donating group have been widely studied for nonlinear optical properties.[14] It is also tolerated in this methodology with medium yield (**3u**). While switching the phenyl ring to furanyl group (**3x**) gave excellent reaction yield, alky substitutions made the reaction rather sluggish and much source material was recovered (**3y and 3z**). Notably, the gram scale reaction with 5 mmol of olefin **1g** proceeded very well, affording triene **3g** in 94% yield, which is better than the small-scale trial.

Table 3 Substrate Scope of Dienes[a,b]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol, 2 equiv), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), $(2\text{-}MeOPh)_3P$ (0.02 mmol, 10 mol %), CsOPiv (0.40 mmol, 2 equiv), 1,4-dioxane (2 mL), in dark, Ar atmosphere, 70 ℃, 7 h. [b]Isolated yield. [c]Performed at 90 ℃

It is worth mentioning that the obtained trienes would undergo isomerization in the light. If a solution of **3g** in $CDCl_3$ was exposed in the light for 6 hours, the ratio of two *E/Z* isomers reached an equilibration of 1:1 (Eq 1). This phenomenon was also invested in the exposure of 20 W white LED. The charted curve of the kinetic process was roughly corresponded to the first-order reversible reaction.[15]



In summary, a stereoselective synthesis of trisubstituent 1,3,5-trienes has been realized by the 1,4-palladium migration/Heck sequence. A wide range of trisubstituted 1,3,5-trienes were produced by this transformation in medium to excellent yields. It is noteworthy that the substrates bearing two similar aryl groups at terminal positions can be obtained in high stereoselectivity, which are difficult to be prepared by traditional methods. In addition, we found that the obtained trienes can undergo easy *E/Z* isomerization in the light.

Conflicts of interest

The authors declare no competing financial interest.

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13 CCDC 2030783 (**3f**) contain 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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15 See Supplementary Information for details.

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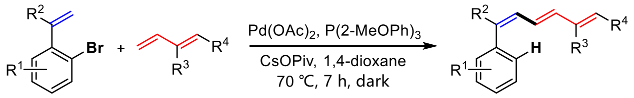
An efficient 1,4-palladium migration/Heck sequence was developed for the highly stereoselective synthesis of conjugated trienes.



- Via 1,4-palladium migration
- Geometry controllable synthesis

26 examples
up tp 98% yield