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Metal Migration

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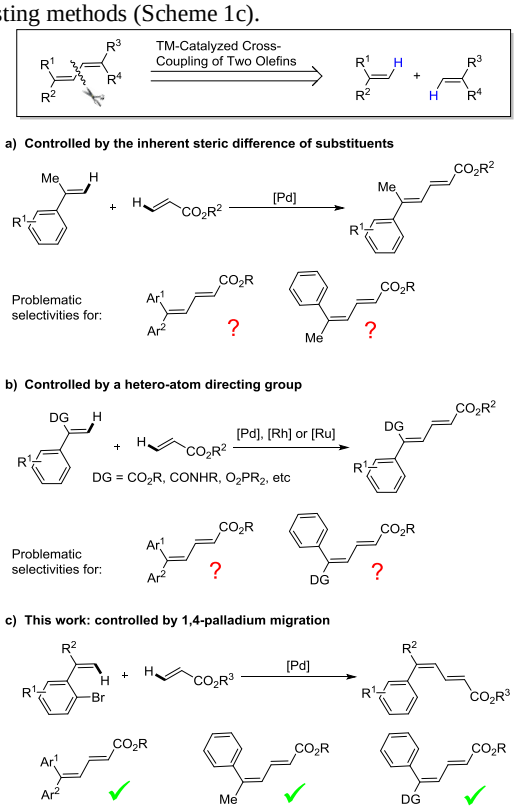
Highly Stereoselective Synthesis of 1,3-Dienes via Aryl to Vinylic 1,4-Palladium Migration/Heck Sequence**

Tian-Jiao Hu, Meng-Yao Li, Qian Zhao, Chen-Guo Feng and Guo-Qiang Lin**

1, 3-Dienes are frequently incorporated in complex natural products[1] and biologically active molecules.[2] Moreover, they are also versatile synthetic precursors for a variety of important organic transformations.[3] Consequently, numerous methods have been developed for the efficient synthesis of these useful 1,3-diene compounds.[4] Among them, the transition-metal catalyzed direct cross-coupling of two different alkenes via the activation of alkenyl C-H bond is a straightforward and atom-efficient approach, and received tremendous research interest.[5] Despite the advancements, the stereochemical control of two double bonds remains to be a challenge in this area, especially for the coupling of two terminal olefins.[6]

Currently, two strategies are often used to solve this stereoselectivity problem. The first is to mainly rely on the inherent steric properties of the reaction substrates (Scheme 1a).[7] For example, good stereoselectivity was observed for the palladium-catalyzed cross-coupling of α-methyl styrene derivatives with acrylates. Sometimes, the inherent minor difference is sufficient to offer a better stereoselectivity by applying a suitable ligand.[7e-f] However, it would become almost impossible to achieve considerable stereoselectivity when olefin substrates bear similar substituents. Another challenge in this case is to reverse the selectivity for structurally unfavored products. These problems were partially solved by introducing a directing group (Scheme 1b). Excellent stereoselectivities were obtained with various heteroatom substituents, including ester,[8] amide,[9] alcohol,[10] and phosphate[11]. Obviously, this strategy is not suitable for substrates without a heteroatom directing group. In addition, the stereoselectivity cannot be switched to the unfavored isomer due to the nature of the directing group. Therefore, new strategies to address these unsolved problems are still highly desirable.

Based on the pioneering work by Dyker,[12] Larock [13] and Miura,[14] 1, 4-migration of transition metals has become a useful synthetic tool to enable the remote functionalization of C-H bonds and bring new chemical accessibility and selectivity.[15] As one of the most studied transitional metal in this field, 1,4-palladium migration was usually applied in the intramolecular functionalization,[16] and limited success was achieved in the more elusive intermolecular process.[17] The biggest obstacle lies in controlling the extraneous functional reagents to react on the new migrated site rather than the originally generated one. Recently, we disclosed an efficient intermolecular aryl to vinylic 1, 4-palladium migration/borylation sequence for the stereospecific synthesis of tri-substituted olefins.[18] As part of our ongoing research program aimed at expanding the utility of this discovery, we became interested in developing this as a new strategy for the stereoselective synthesis of 1,3-dienes which are problematic targets according to the existing methods (Scheme 1c).



Scheme 1. Stereoselectivity control in the transition-metal catalyzed direct cross-coupling of two different olefins

Our investigation began with examination of the coupling of terminal olefin **1aa** and methyl acrylate **2a** using $Pd(OAc)_2$ as precatalyst and PPh_3 as ligand. To our delight, the direct Heck

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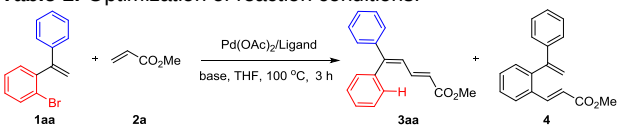
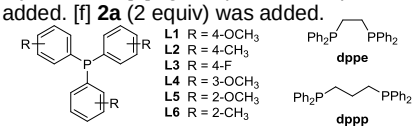
process was efficiently inhibited, and the desired diene **3aa** via the 1,4-palladium migration/Heck sequence was successfully generated in 28% yield (Table, entry 1). The low yield was attributed to several side reactions, including the dehalogenation and dimerization of **1aa**. The reaction yield could be improved by using triarylphosphine ligand bearing electron-donating MeO or Me group at the *para*-position of the phenyl ring (entries 2 and 3). A significant improvement was achieved with *ortho*-MeO substituted triarylphosphine ligand (entry 6), which may be explained by that the *o*-MeO substituents as hemilabile supporting ligands would induce the generation of active monomeric palladium intermediates.[19] Interestingly, the catalytic activity was almost completely suppressed when the *ortho*-MeO group was switched to the *ortho*-Me group, probably due to the increased steric hindrance (entry 7). Bisphosphine ligands were also effective, but failed to bring better results (entries 8 and 9). The base also played an important role for this reaction, affecting the migration efficiency, the E/Z ratio and yield of the desired product (entries 10-12). A profound increase of the direct Heck product **4** by using CsF highlighted the importance of carboxylate anion (AcO^- or $PivO^-$) for this migration sequence, most likely for the C-H activation step (entry 12).[20] Slightly increasing the amount of **2a** to 1.5 equivalents could further improve the reaction yield, but more **2a** had a deleterious effect on the catalytic activity (entries 13-14).

Table 1: Optimization of reaction conditions.[a]

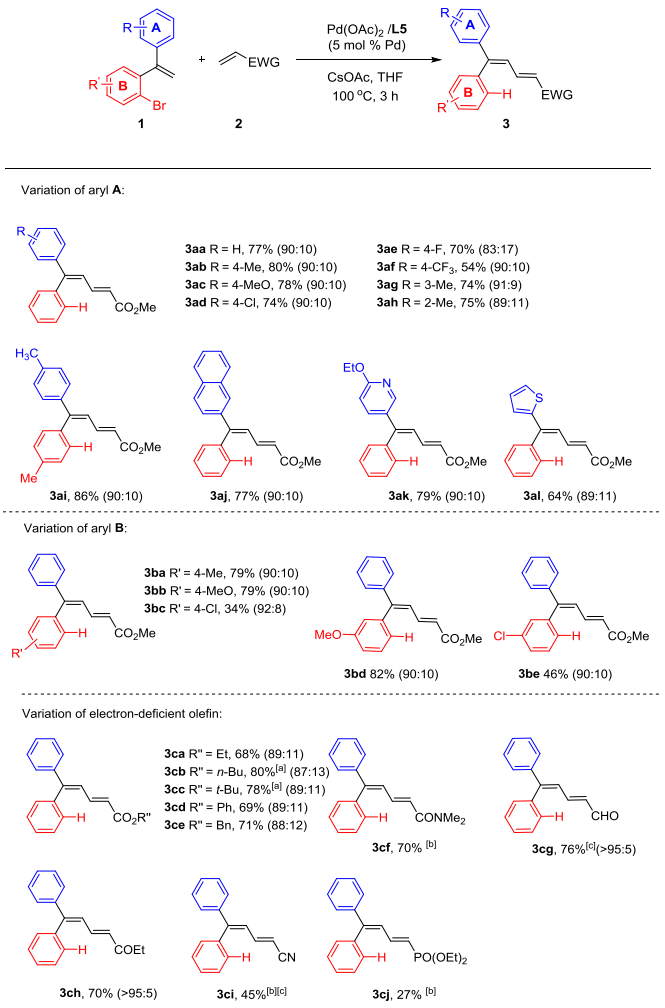


entry	Ligand	base	conv. (%)	**3aa** (%)[b] (2*E*/2*Z*)[c]	**4** (%)[b]
1	**PPh_3**	CsOAc	100	28 (92:8)	4
2	**L1**	CsOAc	100	53 (92:8)	5
3	**L2**	CsOAc	100	52 (92:8)	<2
4	**L3**	CsOAc	100	32 (92:8)	<2
5	**L4**	CsOAc	100	43 (93:7)	<2
6	**L5**	CsOAc	100	82 (91:9)	<2
7	**L6**	CsOAc	29	<2 (--)	4
8	**dppe**[d]	CsOAc	100	52 (92:8)	5
9	**dppp**[d]	CsOAc	100	49 (93:7)	<2
10	**L5**	KOAc	100	70 (84:16)	5
11	**L5**	CsOPiv	100	57 (88:12)	5
12	**L5**	CsF	79	36 (83:17)	21
13[e]	**L5**	CsOAc	100	89 (90:10)	<2
14[f]	**L5**	CsOAc	75	69 (90:10)	<2

[a] Reactions conditions: **1aa** (0.30 mmol), **2a** (0.33 mmol, 1.1 equiv), $Pd(OAc)_2$ (0.015 mmol), ligand (0.03 mmol) and base (0.60 mmol) in solvent (6 mL) at 100 °C for 3 h unless otherwise noted. [b] Combined yield of two isomers and determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] 2*E*/2*Z* = (2*E*)-**3aa**/(2*Z*)-**3aa** and determined by ^1H NMR. [d] ligand (0.015 mmol) was used. [e] **2a** (1.5 equiv) was added. [f] **2a** (2 equiv) was added.



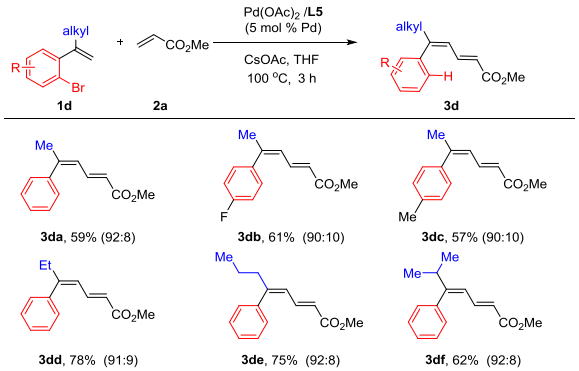
As for the synthesis of 1,3-dienes bearing gem-diaryl substituents at the terminal site, it is usually difficult to efficiently discriminate two similar aryl groups and achieve good stereoselectivity when introducing any substitutions to the double bond. With the optimized reaction conditions in hand, we started to apply this method for the stereoselective synthesis of 1,3-dienes having two different aryl groups at the terminal site (Scheme 2). As expected, the corresponding double bonds were generated in a stereospecific way for all the tested examples. High reaction yields were obtained when electron-donating or mild electron-withdrawing groups were introduced to the phenyl ring A at different positions. Stronger electron-withdrawing CF_3 group led to obvious drop in reaction yield (**3af**). In addition, the replacement of phenyl ring A by naphthyl (**3aj**), pyridyl (**3ak**) and thienyl (**3al)** groups also proceeded well. Variation of substituents at the phenyl ring B also found a beneficial effect from election-donating groups and a reverse effect from electron-withdrawing groups. A variety of acrylates (**3ca**-**3ce**), as well as acrylamide (**3cf**), acrolein (**3cg**) and ethyl vinyl ketone (**3ch**) were accommodated in this reaction, providing the desired products in high reaction yields. Acrylonitrile (**3ci**) and diethylvinylphosphonate (**3cj**) were also competent coupling partners, albeit in reduced yields. The reaction stereochemistry of **3ah** was confirmed to be (2*E*, 4*E*) by the X-ray structure analysis, which is in accordance with our predicted stereoselectivity[21].



Scheme 2. Stereoselective synthesis of 1,3-dienes bearing gem-diaryl substitutions via 1,4-palladium migration/Heck sequence. Reactions conditions: **1** (0.30 mmol), **2** (0.45 mmol), $Pd(OAc)_2$ (0.015

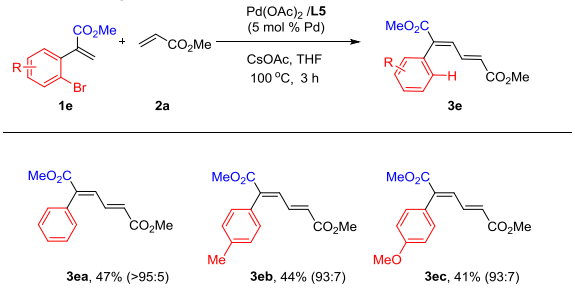
mmol), **L5** (0.03 mmol) and CsOAc (0.60 mmol) in THF (6 mL) at 100 °C for 3 h unless otherwise noted. Yields are given for the isolated major isomer. The (2*E*)-**3**/(2*Z*)-**3** ratio was determined by ^{1}H NMR analysis of crude products and given in parenthesis. [a] Combined isolated yield of (2*E*)-**3** and (2*Z*)-**3**. [b] The (2*E*)-**3**/(2*Z*)-**3** ratio is not determined. [c] **2** (0.60 mmol), $Pd(OAc)_2$ (0.03 mmol), **L5** (0.06 mmol) were added.

The replacement of the phenyl ring A by alkyl groups also proved to be feasible. Various olefins bearing different linear alkyl chains or a branched *iso*-propyl group successfully went through the 1,4-migration/Heck sequence (Scheme 3). The double bond at 4-position of the resulting esters was in complete *Z*-configuration, providing a complementary method in this field because most previous approaches generated the favourable *E*-geometry.[7b-f]



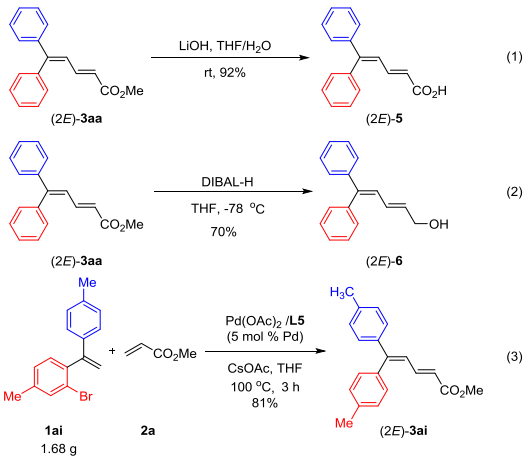
Scheme 3. Stereoselective synthesis of 1,3-dienes bearing gem-alkylaryl substitutions via 1,4-palladium migration/Heck sequence.

Moreover, replacing the phenyl ring A by an ester group was also tested, which would stereoselectively generate multi-substituted muconate derivatives. In this case, the electronic properties of two coupling partners would facilitate the homo-coupling process and made the palladium migration/Heck sequence much more challenging. Fortunately, the desired dienes were produced smoothly in acceptable reaction yields, albeit accompanied by a significant amount of homo-coupling products as expected. Different from the (*Z*, *E*)-muconate derivatives obtained by previous method,[8b] this approach stereospecifically generated products in (*E*, *E*) stereochemistry.

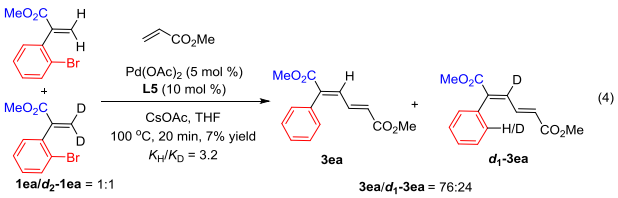


Scheme 4 Stereoselective synthesis of (*E*,*E*)-muconate derivatives via 1,4-palladium migration/Heck sequence.

Further chemical transformations were demonstrated in Scheme 5. The resulting methyl (*E*)-5,5-diphenylpenta-2,4-dienoate **3aa** can easily be converted to the corresponding acid **5** by hydrolysis [Eq. (1)], or alcohol **6** by selective reduction [Eq. (2)], which provides more potential utility of these 1,3-diene moieties. In addition, a gram-scale reaction was also carried out to demonstrate the practicability of this reaction [Eq. (3)].



In order to gain some preliminary understanding of the reaction mechanism, an intermolecular KIE experiment was carried out and k_H/k_D = 3.2 was observed [Eq. (4)], which is in accordance with the data for 1,4-palladium migration/borylation sequence.[18] This indicates that the C−H bond cleavage should be involved in the rate determining step of the catalytic cycle. Notably, some d_2-**1ea** molecules might go through an intramolecular deuterium shift to the aryl ring simultaneously as previously reported.[18,22]



In conclusion, gem-disubstituted ethylenes could undergo stereoselective cross-coupling with electron-deficient olefins via an efficient 1,4-palladium migration/Heck sequence. Owing to the novel directing mode, this method could provide the desired products with new stereoselectivities, which are inaccessible by previous conventional methods.The practicality of this reaction is highlighted by the broad substrate scope, the easy product transformation and the preparative reaction scale. In addition, this work represents the first aryl to vinylic 1,4-palladium migration/Heck reaction, and we expect that our results would encourage more efforts to discover intermolecular transformations via controlled metal migration mechanism.

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[21] CCDC 948712 (**3ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] A possible reaction mechanism was provided in the supporting information.

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Layout 2:

Metal Migration

Tian-Jiao Hu, Meng-Yao Li, Qian Zhao, Chen-Guo Feng and Guo-Qiang Lin**

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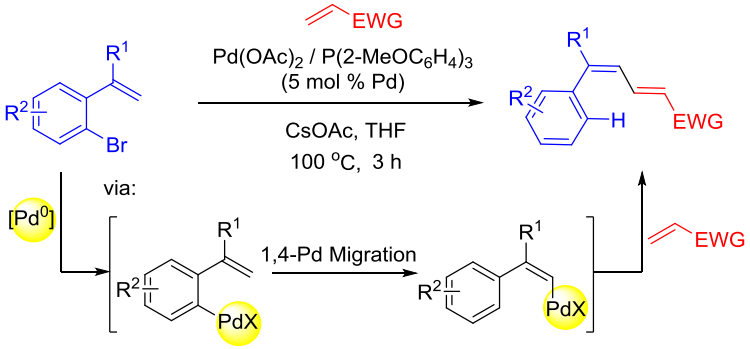
Highly Stereoselective Synthesis of 1,3-Dienes via Aryl to Vinylic 1,4-Palladium Migration/Heck Sequence



- **Efficient aryl to vinylic 1,4-Pd migration/Heck sequence**
- **New chances for some challenging stereoselectivity controls**

An efficient aryl to vinylic 1,4-palladium/Heck sequence has been developed for the stereoselective synthesis of 1,3-dienes. High stereoselectivities were observed not only for 1,3-dienes bearing two similar aryl groups at terminal positions, but also for those with unfavourable configuration by previous methods.