

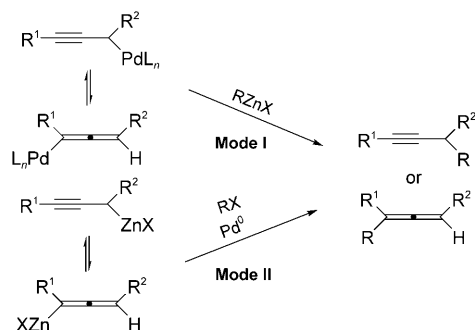
Ligand Effects on the Pd-Catalyzed Cross-Coupling Reaction of 3-Iodoalk-2-enoates with Propargyl/1,2-Allenyl Metallic Species: An Efficient Regiodivergent Synthesis of 2,4,5-Trienoates

Jinbo Zhao,^[a] Yihua Yu,^[b] and Shengming Ma^{*[a]}

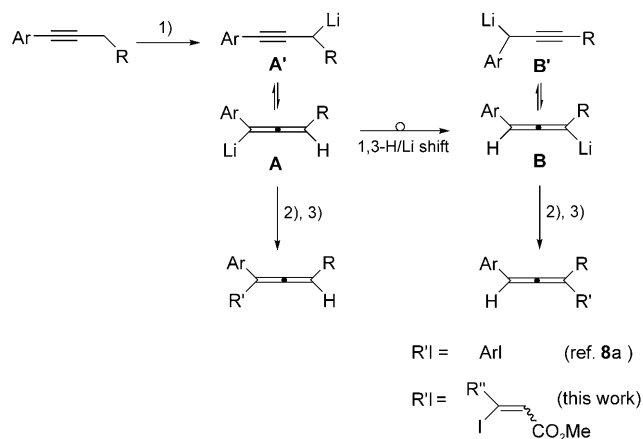
Transition-metal-catalyzed cross-coupling reactions between organic halides or pseudohalides with main-group metal species has become a powerful tool for the efficient construction of C–C bonds both in academia and industry.^[1] In most cases, these cross-coupling reactions do not have regioselectivity problems. For cross-coupling reactions involving propargyl/1,2-allenyl metal species, however, the issue of regioselectivity arises.^[2,3] Over the past few years, we have studied the Negishi coupling reaction^[4] involving propargyl/1,2-allenyl metal species to afford allenes or alkynes in a highly selective manner (Scheme 1). We found a dramatic dependence of regioselectivity on the steric factors of both

propargyl/1,2-allenyl zinc species and aryl iodides for the formation of allenes or alkynes and the unique selectivity in the related reaction of propargyl/1,2-allenyl zinc reagents with 3-iodoalk-2-enoates to form substituted 2,4,5-alkatrienoates.^[5] We have also regioselectively tuned the Pd-catalyzed cross-coupling of propargyl mesylates with 2-(alkoxy-carbonyl)ethenyl zinc iodides by using the ligand effect (Mode II, Scheme 1).^[6]

On the other hand, we observed an interesting “1,3-H/Li shift” phenomenon in the lithiation of 1-arylalk-1-ynes^[7] (Scheme 2): the initially formed 1-arylalka-1,2-dien-1-lithi-



Scheme 1. The two complementary modes of Negishi cross-coupling involving propargyl/1,2-allenyl metallic species.



Scheme 2. The 1,3-H/Li shift in the Pd-catalyzed cross-coupling reaction of propargyl/1,2-allenyl zinc species with different types of organic halides. 1) Lithium reagent, 2) ZnBr₂, 3) [Pd], R'I.

um intermediate **A** underwent a formal H/Li shift to afford the thermodynamically more stable 1-arylalka-1,2-dien-3-lithium intermediate **B**. By using *n*BuLi (1.2 equiv) at –20 °C for 1 h (lithiation conditions A) or lithium diisopropylamide (LDA; 2 equiv) at –78 °C to room temperature for 1 h (lithiation conditions B) as the lithiation conditions, the two types of propargyl/1,2-allenyl lithium reagents **A/A'** or **B/B'** could be obtained selectively. Subsequent transmeta-

[a] J. Zhao, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P. R. China)
Fax: (+86) 21-6260-9305
E-mail: masm@mail.sioc.ac.cn

[b] Prof. Dr. Y. Yu
Shanghai Key Laboratory of Functional Magnetic
Resonance Imaging
Department of Physics, East China Normal University
Shanghai 200062 (P. R. China)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200901287>.

lation and $[Pd(PPh_3)_4]$ -catalyzed cross-coupling with aryl iodides afforded the differently trisubstituted allenes starting from simple, readily available 1-aryllalk-1-ynes and aryl halides.^[8] As an extension of this strategy, we wished to realize the 1,3-H/Li shift/transmetalation/cross-coupling reaction with 3-iodoalk-2-enoates. However, primary results showed that the coupling reaction with 3-iodoalk-2-enoates is very different from that with aryl iodides. Under the conditions developed for the cross-coupling with aryl iodides, either a mixture of allene (*E*)-**3** and conjugated enyne (*Z*)-**4** was obtained with poor selectivity (under the “1,3-H/Li shift” conditions) or the direct propargyl/alkenyl cross-coupling product enyne (*E*)-**5** was isolated with a low yield (under the “non-1,3-H/Li shift” conditions). Thus, new protocols had to be established. In this communication, we wish to report the pursuit of this strategy, which has led to the discovery of dramatic ligand effects on the regioselectivity^[9] and reactivity in the cross-coupling of propargyl/1,2-allenyl zinc species with 3-iodoalk-2-enoates, and the one-pot regiodivergent synthesis of two types of differently substituted 2,4,5-trienoates.

Synthesis of 4-alkyl-6-arylhexa-2(*E*),4,5-trienoates: In previous studies in our group, we developed a protocol for the efficient synthesis of alka-2,4,5-trienoates from the cross-coupling reaction of 3-iodoalk-2-enoates with the propargyl/1,2-allenyl zinc species generated from the lithiation of 1-aryllalk-1-yn with *n*BuLi followed by transmetalation with $ZnBr_2$.^[5a] The fact that addition of $HgCl_2$ is necessary to achieve good yields is expected to cause environmental problems. Furthermore, it was found that this procedure is not easily reproducible in terms of using commercially available *n*BuLi from different sources, and the structures of the products from the reaction of **1a** with (*E*)-**2b**, (*Z*)-**2a**, (*Z*)-**2b**, (*Z*)-**2c** and (*Z*)-**2d** according to the reported procedure are not the proposed ones, but their regioisomers based on our most recent studies [Eq. (1)].^[5a,8]

Evidently, new reaction conditions needed to be developed to solve the issue of regioselectivity. When we applied

Table 1. Lithiation of 1-phenylhex-1-yn (**1a**) with LDA, transmetalation with $ZnBr_2$, and the Pd-catalyzed cross-coupling reaction of the in situ-formed propargyl/1,2-allenyl zinc species with methyl 3-iodoprop-2(*E*)-enoate [(*E*)-**2a**] under different conditions.^[a]

Entry	<i>T</i> [°C]	Catalyst	<i>t</i> [h]	Combined yield [%]	(<i>E</i>)- 3aa / (<i>Z</i>)- 4aa ^[b]
1	28	$[Pd(PPh_3)_4]$	2	58	81:19
2 ^[c]	28	$[Pd(PPh_3)_4]$	2	— ^[d]	81:19
3 ^[e]	28	$[Pd(PPh_3)_4]$	2	— ^[d]	80:20
4 ^[f]	27	$[Pd(PPh_3)_4]$	2	44	79:21
5	0	$[Pd(PPh_3)_4]$	17	22	89:11
6	25	$[Pd(\pi\text{-allyl})Cl]_2$ ^[g]	3	45	78:22
7	25	$[Pd(\pi\text{-allyl})Cl]_2$ ^[h]	0.67	64	94:6
8	0	$[Pd(\pi\text{-allyl})Cl]_2$ ^[h]	1	77	98:2

1) LDA, −78 °C–RT, 1 h; 2) $ZnBr_2$, RT, 0–10 min, then RT to *T*, 10–40 min; 3) catalyst, THF. [a] Reaction conditions unless otherwise specified: **1a** (0.50 mmol, 1.7 equiv), LDA (1.0 mmol, 3.3 equiv), $ZnBr_2$ (2.0 mmol, 6.7 equiv), $[Pd(PPh_3)_4]$ (5 mol %) or $[Pd(\pi\text{-allyl})Cl]_2$ (2.5 mol %)/ligand (10 mol %), (*E*)-**2a** (0.3 mmol). [b] Due to the complicated signals in the ¹H NMR spectrum of the crude reaction mixture and the inseparability of the two products [(*E*)-**3aa** and (*Z*)-**4aa**], the selectivity was determined based on isolation. [c] 2.5 equiv of LDA was used. [d] The isolated products were contaminated with an unidentified impurity. [e] 2.0 equiv of LDA was used. [f] The lithiation was carried out at 0 °C for 1 h. [g] Tri(*o*-tol)phosphine was used as the ligand. [h] Tri(2-furyl)phosphine was used as the ligand.

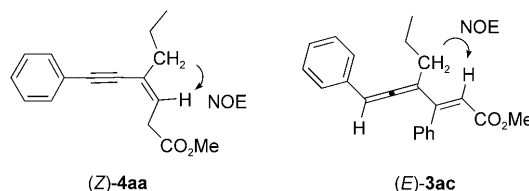
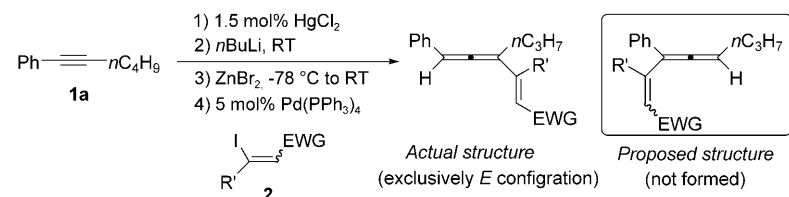


Figure 1. NOE effects of compounds (*Z*)-**4aa** and (*E*)-**3ac**.



the conditions developed for the 1,3-H/Li shift/transmetalation/cross-coupling with aryl halides,^[8] a mixture of the expected “1,3-H/Li shifted” allene (*E*)-**3aa** and the conjugate enyne (*Z*)-**4aa**^[5a] was formed disappointingly in a combined yield of 58 % (Table 1, entry 1). The structure and the configuration of the double bond of (*Z*)-**4aa** (Figure 1) were unambiguously determined by analysis of its ¹H/¹³C NMR and NOESY spectra. Reducing the amount of LDA led to the

formation of an inseparable impurity together with the products (*E*)-**3aa** and (*Z*)-**4aa** (Table 1, entries 2 and 3); this indicated that using an excessive amount of LDA is essential for a complete reaction, as was also observed in our previous studies. The reason why 2 equiv

of LDA (relative to **1**) is needed is still not clear, but is supposed to be for mechanistic reasons. Lowering the cross-coupling temperature led to a decrease in the yield (Table 1, entry 5). To our disappointment, the use of $[Pd(\pi\text{-allyl})Cl]_2/(o\text{-tol})_3P$ as the catalyst reduced the ratio of (*E*)-**3aa**/*(Z)*-**4aa** to 78:22, although the impurity was not formed (Table 1, entry 6). However, we were fortunate to observe that the use of TFP [tri(2-furyl)phosphine] as the ligand in

combination with $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ improved the ratio of (*E*)-**3aa**/(*Z*)-**4aa** to 94:6 (Table 1, entry 7). Lowering the cross-coupling temperature to 0 °C finally enabled us to improve this selectivity to 98:2 (Table 1, entry 8).

With these optimized conditions (conditions A: Table 1, entry 8) in hand, the scope of the reaction was then examined. As shown in Table 2, the reactions with both (*Z*)- and

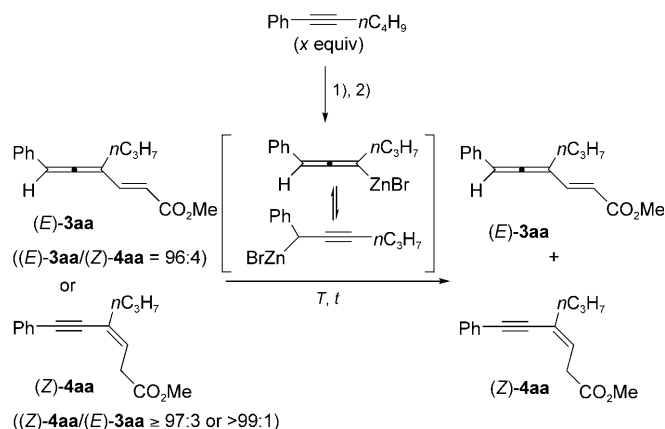
Table 2. The cross-coupling reaction of 3-iodopropenoates **2a** and **2b** under Conditions A^[a]

Entry	R (1)	2	T [°C]	t [h]	Combined yield [%]	(<i>E</i>)-3/(<i>Z</i>)-4 ^[b]
1	<i>n</i> C ₃ H ₇ (1a)	(<i>E</i>)- 2a	0	1	77	98:2
2	<i>n</i> C ₃ H ₇ (1a)	(<i>E</i>)- 2b	21	1	80	96:4
3	<i>n</i> C ₃ H ₇ (1a)	(<i>Z</i>)- 2a	15	0.5	63	98:2
4	<i>n</i> C ₃ H ₇ (1a)	(<i>Z</i>)- 2b	20	0.5	60	> 98:2
5	<i>n</i> C ₅ H ₁₁ (1b)	(<i>E</i>)- 2a	0	1	64	98:2

1) LDA, -78 °C–RT, 1–1.5 h; 2) ZnBr₂, RT, 20–60 min; 3) cat. $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2/\text{TFP}$, **2**, THF. [a] Unless otherwise specified, the reaction was conducted by using conditions A: alkyne **1** (0.50 mmol, 1.7 equiv), LDA (1.0 mmol, 3.3 equiv), ZnBr₂ (2.0 mmol, 6.7 equiv), iodide **2** (0.30 mmol), $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ (2.5 mol %), and TFP (10 mol %). [b] Ratio determined by NMR analysis after chromatography due to complicated signals on the ¹H NMR spectrum of the crude reaction mixture and the inseparability of the two products.

(*E*)-3-iodopropenoates proceeded smoothly, with the minor isomers (*Z*)-**4aa**, (*Z*)-**4ab** and (*Z*)-**4ba** being obtained in ≤ 4% yield. It is worth noting that the cross-coupling temperature is crucial for the selectivity and reaction rate in each case: lowering the temperature led to a much slower reaction, while raising it resulted in a dramatic decrease of chemical yield. No matter what the configuration of the double bond in the starting iodides **2** was, the configuration of the double bond in the products (*E*)-**3** is exclusively *trans*, as unambiguously demonstrated by the coupling constant of the vinylic hydrogen signals.^[6,10,11] The improved selectivity of (*E*)-**3**/(*Z*)-**4** may be explained by the electron-rich nature of TFP, which increases the reactivity and allows the coupling to occur under milder conditions, thus suppressing the isomerization from (*E*)-**3** to (*Z*)-**4**.^[12] To confirm this possibility, both (*E*)-**3aa** [(*E*)-**3aa**/(*Z*)-**4aa** = 96:4] and (*Z*)-**4aa** [(*Z*)-**4aa**/(*E*)-**3aa** ≥ 97:3 or 99:1] were treated separately with different amounts of propargyl/1,2-allenyl zinc species at different temperature. After the usual workup, essentially

no isomerization was observed at 0 °C (Scheme 3, entries 1 and 3); when the isomerization reactions were carried out at room temperature, a dramatically higher extent of isomeri-



Entry	(<i>E</i>)- 3aa / Z - 4aa	x (equiv)	T [°C]	t [h]	NMR yield	(<i>E</i>)- 3aa /(<i>Z</i>)- 4aa
1	96:4	2.0	0	1.5	64%	96:4
2	96:4	2.0	RT	1.5	63%	92:8
3	≤ 3:97	2.0	0	1.5	55%	≤ 3:97
4	≤ 3:97	2.0	RT	1.5	45%	8:92
5	96:4	9.3	RT	24	50%	68:32
6	< 1:99	9.3	RT	24	17%	67:33

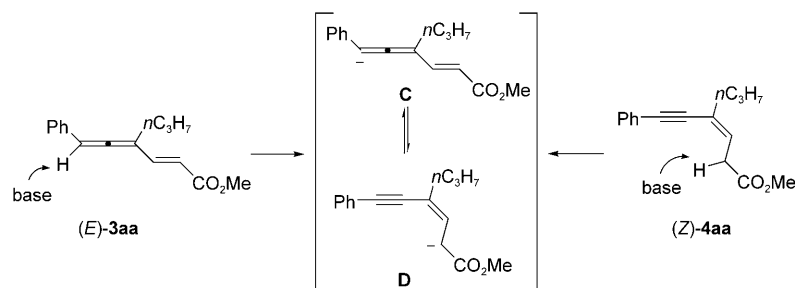
Scheme 3. Isomerization between (*E*)-**3aa** and (*Z*)-**4aa**. 1) LDA, 2) ZnBr₂.

zation was observed (Scheme 3, entries 2 and 4). Furthermore, when the reactants were treated with 9.3 equiv of an organozinc species at room temperature for 24 h, both reactions afforded a mixture of (*E*)-**3aa** and (*Z*)-**4aa** in almost the same ratio (Scheme 3, entries 5 and 6).

This observation indicates that an equilibrium exists between the deprotonated isomers **C** and **D** in the presence of organozinc species that caused the isomerization between (*E*)-**3aa** and (*Z*)-**4aa** at the higher temperature (Scheme 4).

However, it is interesting to observe that, in the case of the 3-substituted 3-iodoalk-2-enoates, the formation of enyne (*Z*)-**4** was not observed (Table 3); that is, for all the cases studied, the corresponding allenes (*E*)-**3** were formed exclusively in moderate to good yields. Notably, naphthyl substitution on the alkyne also led to exclusive formation of the corresponding allene (*E*)-**3gd** (Table 3, entry 8). With the increasing steric hindrance of the substitution on the iodides, the reaction rate decreased dramatically, that is, methyl 3-iodo-3-phenyl-2(*Z*)-propenoate [(*Z*)-**2c**] was not fully consumed (Table 3, entry 1). Cross-coupling for all the *Z*-configured iodides (*Z*)-**2a–e** examined afforded the *E* product (Table 2 entries 3 and 4 and Table 3), as determined by NOE study of the product (*E*)-**3ac** (Figure 1).

Synthesis of 4-arylalka-2(*E*),4,5-trienoates: At the onset of the research into this subject, we examined the conditions

Scheme 4. Possible mechanism for the interconversion between (*E*)-**3aa** and (*Z*)-**4aa**.Table 3. The cross-coupling reaction with 3-substituted 3-iodoalk-2-enoates (*Z*)-**2c–e** under conditions A^[a]

Entry	Ar/R ¹ (1)	R ² (2)	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]
1	Ph/ <i>n</i> C ₃ H ₇ (1a)	Ph [(<i>Z</i>)- 2c]	20	8	48 ^[c] [(<i>E</i>)- 3ac]
2	Ph/ <i>n</i> C ₃ H ₇ (1a)	Me [(<i>Z</i>)- 2d]	15	1.5	71 [(<i>E</i>)- 3ad]
3	Ph/ <i>n</i> C ₃ H ₇ (1a)	Bn [(<i>Z</i>)- 2e]	19	4.7	34 [(<i>E</i>)- 3ae]
4	Ph/Me (1c)	Me [(<i>Z</i>)- 2d]	20	1	54 [(<i>E</i>)- 3cd]
5	<i>p</i> -PhC ₆ H ₄ / <i>n</i> C ₃ H ₇ (1d)	Me [(<i>Z</i>)- 2d]	24	2	74 [(<i>E</i>)- 3dd]
6	<i>p</i> -MeOC ₆ H ₄ / <i>n</i> C ₃ H ₇ (1e)	Me [(<i>Z</i>)- 2d]	15	1.5	72 [(<i>E</i>)- 3ed]
7	<i>p</i> -PhC ₆ H ₄ / <i>n</i> C ₅ H ₁₁ (1f)	Me [(<i>Z</i>)- 2d]	18	2	53 [(<i>E</i>)- 3fd]
8	α -naphthyl/ <i>n</i> C ₃ H ₇ (1g)	Me [(<i>Z</i>)- 2d]	15	1	70 [(<i>E</i>)- 3gd]

1) LDA, −78 °C–RT, 1 h; 2) ZnBr₂, RT, 20–50 min; 3) cat. [Pd(π -allyl)Cl]₂/TFP, THF. [a] Unless otherwise specified, the reaction was conducted under conditions A. [b] Isolated yields. [c] The reaction was carried out with **1a** (0.44 mmol), LDA (1.0 mmol), ZnBr₂ (2.0 mmol), iodide (*Z*)-**2** (0.20 mmol), [Pd(π -allyl)Cl]₂ (5 mol %), and TFP (20 mol %), and the yield was calculated based on 64 % conversion of the iodide.

developed for the cross-coupling reaction of aryl iodides with propargyl/1,2-allenyl zinc species derived from the lithiation of 1-aryllalk-1-yne with *n*BuLi to form trisubstituted aryl allenes^[7] (Table 4, entry 1). Unfortunately, it was observed that methyl 6-phenyl-4-propyl-5-yn-2(*E*)-enoate [(*E*)-**5aa**] was obtained as the only regioisomer in 23 % yield.^[13] We at first attributed this observation to insufficient lithiation of substrate **1a** and/or unsuitable cross-coupling temperature, so we screened experimental parameters such as lithiation temperature, lithiation time, cross-coupling temperature, and additives, aiming to find the right conditions for highly selective synthesis of (*E*)-**5aa** or methyl 4-phenyl-nona-2(*E*),4,5-trienoate [(*E*)-**6aa**]. As briefly summarized in Table 4, many different reaction conditions were screened and found to be fruitless. In all the cases listed, only the propargyl-alkenyl coupling product (*E*)-**5aa** was isolated in low yields (Table 4).

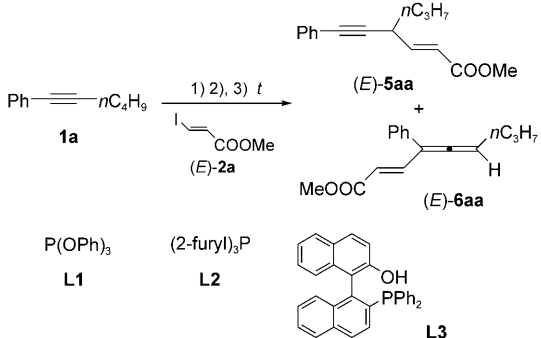
Table 4. The effect of different reaction parameters on the Pd-catalyzed coupling reaction of methyl 3-iodoprop-2(*E*)-enoate (*E*)-**2a** with the propargyl/allenyl zinc species generated from lithiation of 1-phenylhex-1-yne (**1a**) with *n*BuLi and subsequent transmetalation with ZnBr₂^[a]

Entry	<i>T</i> ₁ [°C]	<i>t</i> ₁ [h]	<i>T</i> ₂ [°C]	<i>t</i> ₂ [h]	Yield (<i>E</i>)- 5aa [%] ^[b]
1	0	1	RT	2	23
2	−3	1	0	1	22
3	0	1.5	−20	11	32
4	−3	2	−20	10.5	26
5	−3	1.5	−20	16	18 ^[c,d]
6	0	1.5	−20	16.5	29 ^[e]
7	−20	1.5	−20	9	20

1) *n*BuLi, *T*₁, *t*₁; 2) ZnBr₂, *T*₁ to *T*₂, 20–42 min; 3) cat. [Pd(PPh₃)₄], THF, *T*₂, *t*₂. [a] Unless otherwise specified, the reaction was carried out with **1a** (0.50 mmol, 1.7 equiv), *n*BuLi (0.60–0.64 mmol, 2.0–2.1 equiv), ZnBr₂ (1.0 mmol, 6.7 equiv), [Pd(PPh₃)₄] (5 mol %), and (*E*)-**2a** (0.30 mmol). [b] Isolated yields. [c] Pd(PPh₃)₂Cl₂ (5 mol %) was used as the catalyst. [d] 0.40 mmol of (*E*)-**2a** and 0.020 mmol (5 mol %) of [Pd(PPh₃)₄] were used. [e] 0.20 mmol of (*E*)-**2a** and 0.010 mmol (5 mol %) of [Pd(PPh₃)₄] were used.

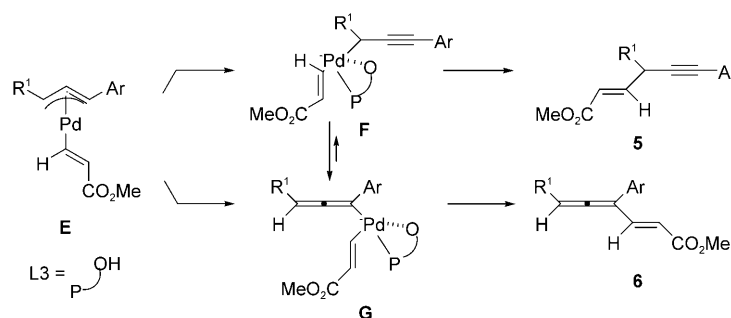
several ligands with distinct electronic properties were examined. As depicted in Table 5, when triphenyl phosphite (**L1**) was used as the ligand, the propargyl-alkenyl coupling product (*E*)-**5aa** was obtained exclusively in a low yield. Using tri(2-furyl)phosphine (**L2**), the ratio of (*E*)-**5aa**/(*E*)-**6aa** was improved to <7:1. Surprisingly, when the ligand was changed to (*R*)-2-diphenylphosphino-2'-hydroxy-1,1'-binaphthalene [(*R*)-**L3**], which was used in our previous study,^[6] we were very happy to find that the reaction reached completion within 5 min to afford (*E*)-**6aa** exclusively (Table 5, entry 3). However, essentially no *ee* was observed. The regioselectivity reversal is speculated to be influenced by the electronic properties of the ligand. As seen in Scheme 5, since the sp²-hybridized allenic carbon is more electronegative than the sp³-hybridized propargyl carbon, the electron-donating ability of the ligand increases the electron density of palladium through coordination of the phenolate moiety, driving the equilibrium to the formation of allenyl

Table 5. Ligand effect on the cross-coupling reaction of methyl (*E*)-3-iodopropenoate [(*E*)-**2a**] with the propargyl/1,2-allenyl zinc species generated from lithiation of 1-phenylhex-1-yne (**1a**) with *n*BuLi followed by transmetalation with ZnBr₂.^[a]



Entry	Ligand	<i>t</i>	Combined yield [%]	(<i>E</i>)- 5aa /(<i>E</i>)- 6aa
1	L1	overnight	32	100:0 ^[b]
2	L2	3 h	26	< 7:1 ^[c]
3	(<i>R</i>)- L3	5 min	— ^[d]	0:100 ^[e]

1) *n*BuLi, −20°C, 1 h; 2) ZnBr₂, −20°C to RT, 10–34 min; 3) cat. [Pd(π-allyl)Cl]₂/ligand. [a] Unless otherwise specified, the reaction conditions: **1a** (0.50 mmol, 1.7 equiv), *n*BuLi (0.60 mmol, 2.0 equiv), ZnBr₂ (1.0 equiv, 3.3 equiv), [Pd(π-allyl)Cl]₂ (2.5 mol %), ligand (10 mol %), and (*E*)-**2a** (0.30 mmol). [b] [Pd(π-allyl)Cl]₂ (4 mg, 0.010 mmol, 5 mol %), **L1** (13 mg, 0.040 mmol, 10 mol %), and (*E*)-**2a** (0.20 mmol) were used. The ratio was determined by NMR analysis of the isolated product, and the yield was based on 90% conversion of iodide (*E*)-**2a**. [c] (*E*)-**6aa** is not stable during separation, thus the ratio is inaccurate. [d] Due to the instability of (*E*)-**6aa**, no information on the yield is available. [e] Determined by NMR analysis of the reaction mixture.

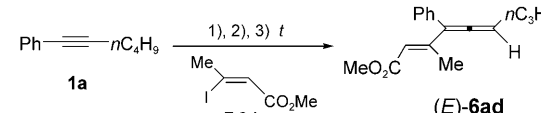


Scheme 5. Proposed ligand effect on regioselectivity.

intermediate **G**, thereby favoring the formation of allenic product **6**.

It was soon observed that substitution of the iodide has a dramatic influence on the regioselectivity. For example, the cross-coupling reaction of methyl 3-iodobut-2(*Z*)-enoate (*Z*)-**2d** catalyzed by [Pd(π-allyl)Cl]₂/P(OPh)₃ also yielded allene (*E*)-**6ad** as the only isomer, albeit in a very low yield of 16%, which is stable enough under preparative TLC or normal flash chromatography conditions (cf. Tables 5 and 6, entries 1). Finally, it was observed that, under the catalysis of [Pd(π-allyl)Cl]₂/(±)-**L3**, this same reaction afforded (*E*)-**6ad** in a much higher (91%) yield within 5 min (Table 6, entry 2). It is also noteworthy that when the catalyst loading

Table 6. The effect of ligand on reactivity and an examination of the catalytic efficiency of the [Pd(π-allyl)Cl]₂/ligand-catalyzed Negishi cross-coupling of methyl 3-iodobut-2(*Z*)-enoate (*Z*)-**2d** with the propargyl/1,2-allenyl zinc species generated from lithiation of 1-phenylhex-1-yne with *n*BuLi followed by transmetalation with ZnBr₂.^[a]



Entry	Catalyst [loading]	<i>t</i>	Yield [%] ^[b]
1	5 mol % [Pd(π-allyl)Cl] ₂ /20 mol % L1	4 h	16 ^[c]
2	2.5 mol % [Pd(π-allyl)Cl] ₂ /10 mol % (±)- L3	5 min	91
3 ^[d]	0.5 mol % [Pd(π-allyl)Cl] ₂ /2 mol % (±)- L3	5 min	74
4 ^[d]	0.17 mol % [Pd(π-allyl)Cl] ₂ /0.67 mol % (±)- L3	30 min	59

1) *n*BuLi, −20°C, 1 h; 2) ZnBr₂, −20°C, 10 min then −20°C to RT, 20 min; 3) catalyst, THF, RT. [a] Unless otherwise specified, the reaction was carried out with **1a** (0.50 mmol, 1.7 equiv), *n*BuLi (0.60 mmol, 2.0 equiv), ZnBr₂ (1.0 mmol, 3.3 equiv), (*Z*)-**2d** (0.30 mmol), and catalyst (loading indicated for each case). [b] Isolated yields. [c] The yield is based on the isolated product after flash chromatography and preparative TLC. [d] **1a** (2.5 mmol, 1.7 equiv), *n*BuLi (3.3 equiv), ZnBr₂ (3.3 equiv), and (*Z*)-**2d** (1.5 mmol) were used.

of this reaction was reduced to 0.17 mol % [Pd(π-allyl)Cl]₂/0.67 mol % (±)-**L3**, the reaction could also finish within 30 min to afford (*E*)-**6ad** in 59% yield, indicating a turnover number (TON) of over 300 and a turnover frequency (TOF) of over 600 h^{−1} (Table 6, entry 4).

The scope of the reaction conditions was then examined. As summarized in Table 7, under conditions B (Table 6, entry 2), the reaction of differently substituted 1-aryllalk-1-ynes **1** with 3-iodoalk-2(*Z*) or (*E*)-enoates **2** proceeded readily to afford the corresponding 4-aryllalka-2(*E*),4,5-trienoates (*E*)-**6** efficiently. Generally, the reaction rate depends largely on the steric hindrance of R². For example, when R² is alkyl (Table 7, entries 1, 2, 4, 6–9) or benzyl (entry 5), the reaction usually reached completion within 2 h to afford the products (*E*)-**6** in good to excellent yields; for bulkier substituent, such as Ph (Table 7, entry 3), the reaction was complete after a prolonged reaction time to afford the corresponding product (*E*)-**6ac** in a low yield. Notably, for all the 3-iodoalk-2(*Z*)-enoates (*Z*)-**2**, the C=C double bonds in the corresponding products was also in the more stable *E* configuration, as illustrated by an NOE study of product (*E*)-**6ae** and the alcohol (*E*)-**7** formed by the reduction of (*E*)-**6ae** with diisobutylaluminum hydride (DIBALH) [Eq. (2)].

The control experiment in Scheme 3 excluded the exclusive formation of (*E*)-**3aa** via (*Z*)-**4aa**, thus, we reasoned that the exclusive formation of the more stable (*E*)-**3** and (*E*)-**6** from (*Z*)-**2** might occur either by *path a*: isomerization of double bond in the organopalladium intermediate **H** to form **I**, or *path b*: the initially formed (*Z*)-**3** or (*Z*)-**6** would coordinate with palladium and undergo a rapid isomerization^[10,14–17] (**J** to **K**) to form the final products (*E*)-**3** or (*E*)-**6**, during which racemization of the axial chirality of the allene would also be expected (Scheme 6).^[11]

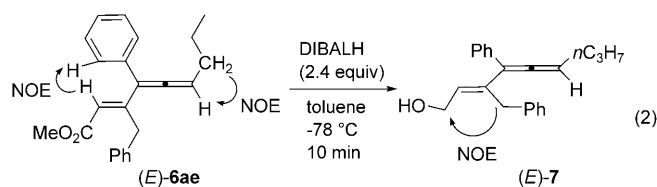
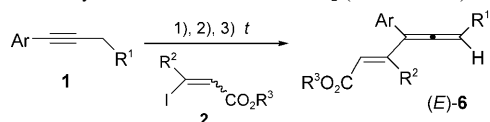


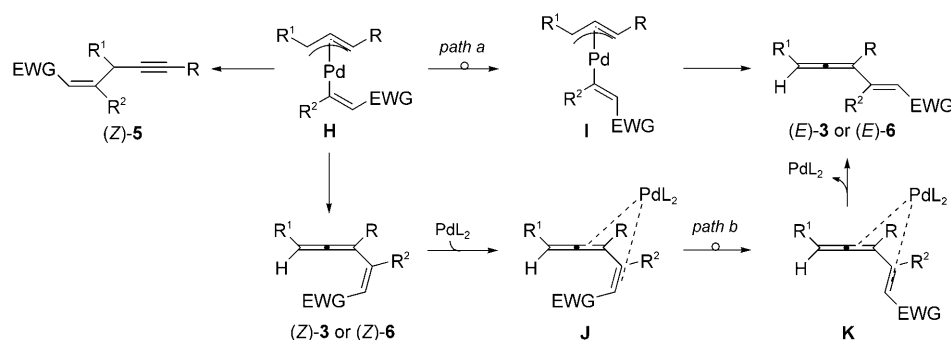
Table 7. Synthesis of 4-arylalka-2(*E*),4,5-trienoates [(*E*)-6] from the Negishi cross-coupling of 3-iodoalk-2-enoates **2** with propargyl/1,2-allenyl zinc species generated from the lithiation of 1-arylalka-1-yne **1** with *n*BuLi followed by transmetalation with ZnBr₂ (conditions B).^[a]



Entry	Ar/R ¹ (1)	R ² /R ³ (2)	<i>t</i>	Yield [%] ^[b]
1	Ph/ <i>n</i> C ₃ H ₇ (1a)	Me/Me [(<i>Z</i>)- 2d]	5 min	91 [(<i>E</i>)- 6ad]
2	Ph/ <i>n</i> C ₃ H ₇ (1a)	Me/Et [(<i>E</i>)- 2h]	5 min	78 [(<i>E</i>)- 6ah]
3	Ph/ <i>n</i> C ₃ H ₇ (1a)	Ph/Me [(<i>Z</i>)- 2c]	16 h	32 [(<i>E</i>)- 6ac]
4	Ph/ <i>n</i> C ₃ H ₇ (1a)	<i>n</i> C ₄ H ₉ /Me [(<i>Z</i>)- 2f]	1 h	80 [(<i>E</i>)- 6af]
5 ^[d]	Ph/ <i>n</i> C ₃ H ₇ (1a)	Bn/Me [(<i>Z</i>)- 2e]	2 h	74 ^[c] [(<i>E</i>)- 6ae]
6	Ph/Me (1c)	Me/Me [(<i>Z</i>)- 2d]	1 h	72 [(<i>E</i>)- 6cd]
7	<i>p</i> -PhC ₆ H ₄ / <i>n</i> C ₃ H ₇ (1d)	Me/Me [(<i>Z</i>)- 2d]	1 h	86 [(<i>E</i>)- 6dd]
8 ^[d]	<i>p</i> -PhC ₆ H ₄ / <i>n</i> C ₃ H ₇ (1d)	<i>n</i> C ₆ H ₁₃ /Me [(<i>Z</i>)- 2g]	2 h	75 ^[c,e] [(<i>E</i>)- 6dg]
9	<i>p</i> -C ₄ H ₉ C≡CC ₆ H ₄ / <i>n</i> C ₃ H ₇ (1h)	Me/Me [(<i>Z</i>)- 2d]	1 h	77 ^[c] [(<i>E</i>)- 6hd]

1) *n*BuLi, −20 °C, 1 h; 2) ZnBr₂, −20 °C, 10 min then −20 °C to RT, 20 min; 3) cat. [Pd(π-allyl)Cl]₂/(±)-**L3**, THF, RT. [a] Unless otherwise specified, the reaction was conducted under conditions B. [b] Isolated yields. [c] 0.20 mmol of iodide was used. [d] [Pd(π-allyl)Cl]₂ (3.75 mol %) and (±)-**L3** (15 mol %) were used. [e] The isolated yield of the pure product obtained after flash chromatography on silica gel and preparative TLC.

In conclusion, we have realized the Pd-catalyzed Negishi cross-coupling reaction of 3-iodoalk-2-enoates with the propargyl/1,2-allenyl zinc species derived from the lithiation of 1-arylalk-1-ynes and transmetalation with ZnBr₂ to afford



Scheme 6. Possible pathways for the observed *Z/E* isomerization.

differently substituted regioisomeric alka-2,4,5-trienoates. During this process, we have observed a dramatic ligand effect on the regioselectivity and reactivity. This observation will no doubt spur further interest in the ligand effect on regioselectivity in other reactions involving propargyl/1,2-allenyl species. Although at present essentially no chiral induction is observed when using (*R*)-**L3** as the ligand, the observations presented in this study should stimulate further interest in the development of this type of asymmetric transformation by using modified 2-diphenylphosphino-2'-hydroxy-1,1'-binaphthalenes. Further studies in this area are currently underway in our laboratory.

Experimental Section

Typical procedure I (conditions A) for the synthesis of 4-alkyl-6-arylhexa-2(*E*),4,5-trienoates (*E*)-3

Methyl 4-propyl-6-phenylhexa-2(*E*),4,5-trienoate [(*E*)-3aa]: Under an Ar atmosphere, a flame-dried Schlenk tube was charged with 1-phenylhex-1-yne (**1a**; 80 mg, 0.5 mmol) and THF (2 mL). The vessel was cooled to −78 °C, and a solution of LDA (0.50 mL, 2.0 M) in THF/ethylbenzene/heptane (1.0 mmol) was added dropwise at −78 °C. After the addition, the cooling bath was removed, and the mixture was allowed to warm up to room temperature within 1.5 h, then a solution of ZnBr₂ (2.0 mmol, 450 mg) in THF (2 mL) was added to prepare the zinc reagent. In another flame-dried Schlenk tube, a solution of catalyst and substrate in THF was prepared by adding sequentially [Pd(π-allyl)Cl]₂ (3 mg, 0.0075 mmol), THF (1 mL), tri(2-furyl)phosphine (7 mg, 0.030 mmol), THF (1 mL), methyl (*E*)-3-iodopropenoate [(*E*)-2a; 64 mg, 0.30 mmol], and THF (1 mL) with stirring. The solution was cooled to 0 °C with stirring while the above zinc reagent was added with a syringe. After the reaction was complete, as monitored by TLC, it was quenched with saturated NH₄Cl solution and extracted with diethyl ether, and the combined organic phase was dried over MgSO₄. After filtration the solvent was removed in vacuo, and the residue was subjected to flash chromatography to afford a mixture of (*E*)-3aa and (*Z*)-4aa (56 mg, 77 %, (*E*)-3aa/(*Z*)-4aa = 98:2). (*E*)-3aa: oil, ¹H NMR (300 MHz, CDCl₃): δ = 7.31–7.10 (m, 6H), 6.35 (brs, 1H), 5.89 (dd, *J* = 15.9, 1.2 Hz, 1H), 3.67 (s, 3H), 2.29–2.07 (m, 2H), 1.59–1.38 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃): δ = 212.3, 167.2, 143.6, 133.1, 128.7, 127.4, 127.0, 117.5, 108.2, 96.1, 51.5, 30.6, 20.8, 13.9; IR (neat): $\tilde{\nu}$ = 1926, 1721, 1621, 1598, 1495, 1274, 1170 cm^{−1}; MS (70 eV, EI) *m/z* (%): 242 (17.14) [M]⁺, 153 (100); HRMS (EI) calcd for C₁₆H₁₈O₂: 242.1307; found: 242.1313.

Typical procedure II (conditions B) for the synthesis of 4-arylalka-2(*E*),4,5-trienoates (*E*)-6

Methyl 3-methyl-4-phenylnona-2(*E*),4,5-trienoate [(*E*)-6ad]: Under an Ar atmosphere, a flame-dried Schlenk tube was charged with 1-phenylhex-1-yne (**1a**; 79 mg, 0.50 mmol) and THF (3 mL). The reaction vessel was cooled to −20 °C, and a solution of *n*BuLi (0.38 mL, 1.6 M) in hexanes (0.60 mmol) was added at this temperature. After the mixture had been stirred at this temperature for 1 h, a solution of ZnBr₂ (1.0 mmol, 225 mg) in THF (2 mL) was added dropwise. After 10 min, the cooling bath was removed, and the mixture was allowed to warm up to room temperature over 20 min to afford the zinc reagent. In another flame-dried Schlenk tube, a solution of catalyst and substrate in THF was prepared by adding sequentially [Pd(π-allyl)Cl]₂ (3 mg,

0.0075 mmol), THF (1 mL), *rac*-**L3** (14 mg, 0.030 mmol), THF (1 mL), methyl 3-iodobut-2(*Z*)-enoate [(*Z*)-**2d**; 68 mg, 0.30 mmol], and THF (1 mL) with stirring. The prepared zinc reagent was then transferred to this mixture with a syringe at room temperature. After the reaction was complete (TLC), it was quenched with saturated aqueous NH₄Cl and extracted with diethyl ether, and the combined organic phase was dried over MgSO₄ and filtrated. The solvent was evaporated under vacuo, and the residue was subjected to flash chromatography to afford (*E*)-**6ad** (70 mg, 91%) as an oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.28–7.21 (m, 2H), 7.21–7.13 (m, 3H), 5.59 (s, 1H), 5.54 (t, *J* = 6.6 Hz, 1H), 3.57 (s, 3H), 2.31 (s, 3H), 2.07–2.00 (m, 2H), 1.47–1.36 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃): δ = 207.4, 167.4, 153.1, 136.1, 129.1, 128.4, 127.3, 116.9, 112.8, 94.5, 50.9, 30.7, 22.2, 17.5, 13.8; IR (neat): $\tilde{\nu}$ = 1938, 1717, 1615, 1491, 1167, 699 cm⁻¹; MS (70 eV) *m/z* (%): 256 (13.76) [*M*]⁺, 227 (100); HRMS (EI) calcd for C₁₇H₂₀O₂: 256.1463; found: 256.1462.

Acknowledgements

Financial support from the National Natural Science Foundation of China (20732005 and 20423001), the State Basic and Research Development Program (Grant No. 2006CB806105), and the Shanghai Municipal Committee of Science and Technology are gratefully appreciated. We thank Jinqiang Kuang in our group for reproducing the results listed in Tables 3 (entries 1 and 5) and 7 (entries 3 and 7).

Keywords: allenes • cross-coupling • ligand effects • palladium • regioselectivity

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Received: May 14, 2009

Revised: August 18, 2009

Published online: November 17, 2009