CJC Chinese Journal of Chemistry
中国化学 - An International Journal

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This work may now be cited as: *Chin. J. Chem.* **2019**, *37,* 10.1002/cjoc.201900322.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
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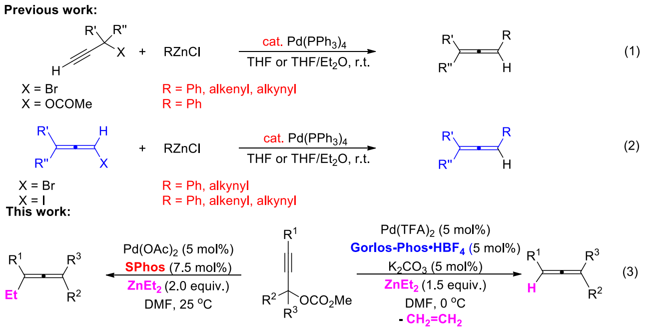
Negishi Coupling for Highly Selective Syntheses of Allenes via Ligand Effect and Mechanistic Study via SAESI-MS/MS

Yangguangyan Zheng,[a†] Bukeyan Miao,[a†] Anni Qin,[a] Junzhe Xiao,[b] Qi Liu,[b] Gen Li,[a] Li Zhang,[b,c] Fang Zhang,[b,c] Yinlong Guo,[b,c]* and Shengming Ma[a,b]*

Abstract: β-H elimination is an intrinsic problem in transition metal-catalyzed reactions. We describe herein an interesting ligand effect for Et_2Zn acting as either ethyl provider or H provider, respectively: by applying SPhos or Gorlos-Phos as the ligand, β-H elimination has been successfully controlled in the corresponding Negishi coupling reaction affording different poly-substituted allenes in good yields and excellent selectivities. SAESI-MS (**S**olvent **A**ssisted **E**lectrospray **I**onization **M**ass **S**pectrometry) has been applied to successfully capture the highly reactive organometallic intermediates, which show the different coordination behaviors of Pd with SPhos or Gorlos-Phos as the ligand in the catalytic cycle. In addition, the different reactivities of **Int 1** and **Int 2** towards the formation of the final allene products have been demonstrated via SAESI-MS/MS experiments. These MS studies visualized the whole catalytic cycle for the Negishi coupling reaction while nicely explains the observed reactivity and selectivity.

Introduction

Allenes not only commonly exist in nature but also have been developed as powerful chemicals in modern organic synthesis, medicinal chemistry, and material science.[1-3] Among the coupling reactions, Negishi coupling, in which organozinc compounds are applied, is one of the most powerful and convenient methodologies widely used in modern organic chemistry for C-C bond formation.[4] The palladium-catalyzed syntheses of allenes by using organozinc reagents with no β–H, such as aryl zinc,[5] alkenyl zinc[6] or alkynyl zinc reagents[7] with terminal propargylic bromides, propargylic acetates, or allenyl halides have been reported (Scheme **1**, eqs. 1 and 2).[8] However, allene syntheses via cross-coupling between propargylic compounds with alkyl zincs bearing β–H, especially diethyl zinc, are still a significant challenge due to the intrinsic issue of β-H elimination.[9,10] In this paper, we wish to report our recent observation on Pd-catalyzed coupling reaction of diethyl zinc with differently substituted terminal or non-terminal 2-alkynylic carbonates, in which a dramatic ligand effect was observed for Et_2Zn as either ethyl provider or H provider, manipulating the β-H elimination with an excellent selectivity (eq. 3).



Scheme 1. Negishi coupling for synthesis of multi-substituted allenes

Results and Discussion

In our initial attempt, 1-phenylhept-2-ynyl methyl carbonate **1a** and diethyl zinc were used as the substrates for optimization of the reaction conditions. After some extensive screening of the reaction parameters, as expected, a mixture of ethylation product **2a** and β-H elimination product **3a** was usually afforded, and some of the typical results with at least a decent selectivity are shown in Table 1. Under the catalysis of 5 mol% of $Pd(OAc)_2$, different ligands were screened for the reaction in anhydrous DMF at room temperature. Bidentate phosphine ligands such as DPPE or DPPF did not give useful results (Table 1, entries 1 and 2), so we turned to the mono-dentate phosphine ligands. After some screening, we observed the exclusive formation of ethylation product allene **2a** when SPhos[11] was used (Table 1, entry 4). Other mono-phosphine ligands such as MePhos, XPhos, or Zheda-Phos[12] (Table 1, entries 5, 6, 11) also afforded a mixture of ethylation product **2a** and β-H elimination product **3a** with a high selectivity while the reactions with BrettPhos or *t*-BuXPhos gave rather poor results (Table 1, entries 6 and 8). The loadings of SPhos and diethyl zinc could be reduced to 7.5 mol% and 2.0 equiv. respectively (Table 1, entry 13). Further screening led to the observation that with LB-Phos or Gorlos-Phos[12] as the ligand, β-H elimination-based allene product **3a** was formed with a very high selectivity (Table 1, entries 9 and 10). After further optimization, we found $Pd(OCOCF_3)_2$/Gorlos-Phos at 0 °C with 1.5 equiv. of diethyl zinc

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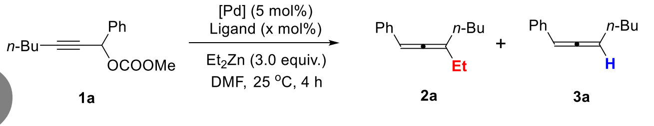
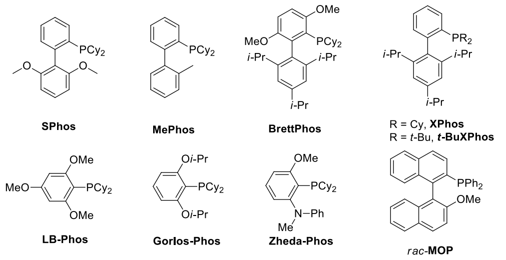
was the best, where **3a** could be afforded exclusively in NMP or DMF (Table 1, entries 16 and 17).

Table 1. Optimization of conditions for the palladium-catalyzed highly selective cross-coupling reaction of propargylic carbonate **1a** with Et_2Zn[a]



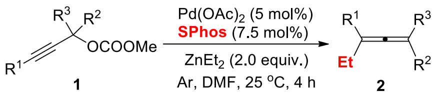
Entry	[Pd]	Ligand (x mol%)	Yield (%)[b]		Recovery (%)[b]
			2a	**3a**	
1	$Pd(OAc)_2$	DPPE (5)	-	37	-
2	$Pd(OAc)_2$	DPPF (5)	9	28	-
3	$Pd(OAc)_2$	-	2	5	59
4	$Pd(OAc)_2$	SPhos (10)	83	-	-
5	$Pd(OAc)_2$	MePhos (10)	74	4	-
6	$Pd(OAc)_2$	BrettPhos (10)	14	5	7
7	$Pd(OAc)_2$	XPhos (10)	50	1	-
8	$Pd(OAc)_2$	*t*-BuXPhos (10)	1	2	-
9[c]	$Pd(OAc)_2$	LB-Phos·HBF4 (10)	11	59	-
10[c]	$Pd(OAc)_2$	Gorlos-Phos·HBF4 (10)	2	59	-
11	$Pd(OAc)_2$	Zheda-Phos (10)	52	4	21
12	$Pd(OAc)_2$	*rac*-MOP (5)	-	4	-
13[d]	$Pd(OAc)_2$	SPhos (7.5)	84	-	-
14[c,e]	$Pd(OCOCF_3)_2$	Gorlos-Phos·HBF4 (10)	1	71	-
15[c]	$Pd(OCOCF_3)_2$	Gorlos-Phos·HBF4 (10)	1	67	-
16[c,e,f]	$Pd(OCOCF_3)_2$	Gorlos-Phos·HBF4 (5)	-	83	-
17[c,f]	$Pd(OCOCF_3)_2$	Gorlos-Phos·HBF4 (5)	-	84	-



[a] The reaction was conducted with 0.5 mmol of 1a, Pd catalyst (5 mol%), Ligand (x mol%), and 3 equiv. of Et_2Zn (1.5 M in toluene) in 3 mL of anhydrous [illegible] under Ar atmosphere. [b] Determined by 1H NMR analysis. [c] x mol% of K_2CO_3 (equal amount of the ligand) was added to in-situ generate the phosphine ligand. [d] The reaction was conducted with 1.0 mmol of **1a**, $Pd(OAc)_2$ (5 mol%), SPhos (7.5 mol%), and 2 equiv. of Et_2Zn (1.5 M in toluene) in 6 mL of anhydrous DMF under Ar atmosphere. [e] NMP was used as the solvent. [f] 1.5 equiv. of Et_2Zn (1.5 M in toluene) were used and the reaction was conducted at 25 °C.

With two sets of the optimized conditions in hand, we investigated the scope of these two reactions. In Pd/SPhos-catalyzed reactions, different types of propargylic carbonates were tested and the results are summarized in Table 2. With secondary propargylic carbonates (R^3 = H), R^1 may be alkyl such as *n*-butyl, 4-chloro-*n*-butyl, cyclohexyl, cyclopropyl, or even ester, OTHP (entries 1-4, 12, 19 and 20), aryl group (entry 13). The reaction of terminal propargylic carbonate **1n** also proceeded smoothly, albeit in a somewhat lower yield of **2n** (entry 14). As for R^2, both electron-donating group such as methoxy or methyl and electron-withdrawing synthetically useful group such as chloro or ester substituted aryl groups were well tolerated (entries 5-8); R^2 may also be naphthyl (entry 9) or alkyl group such as cyclohexyl or 2-phenylethyl (entries 10 and 11). The reaction may also be extended to tertiary propargylic affording tetra-substituted allenes (entries 15-18).

Table 2. The scope of Pd/SPhos-catalyzed cross-coupling reaction[a]



Entry	**1**			Yield of **2** (%)
	R^1	R^2	R^3	
1	*n*-Bu	Ph	H **(1a)**	85 **(2a)**
2	4-Cl$(CH_2)_4$	Ph	H **(1b)**	81 **(2b)**
3	Cyclohexyl	Ph	H **(1c)**	91 **(2c)**
4	Cyclopropyl	Ph	H **(1d)**	80 **(2d)**
5	*n*-Bu	3-MeOC_6H_4	H **(1e)**	89 **(2e)**
6	*n*-Bu	4-MeC_6H_4	H **(1f)**	86 **(2f)**
7	*n*-Bu	4-ClC_6H_4	H **(1g)**	86 **(2g)**
8	*n*-Bu	4-MeOOCC_6H_4	H **(1h)**	80 **(2h)**
9	*n*-Bu	1-Naphthyl	H **(1i)**	71 **(2i)**
10	*n*-Bu	Cyclohexyl	H **(1j)**	81 **(2j)**
11	*n*-Bu	2-Phenylethyl	H **(1k)**	90 **(2k)**
12	4-Cl$(CH_2)_4$	4-ClC_6H_4	H **(1l)**	81 **(2l)**
13	Ph	Ph	H **(1m)**	88 **(2m)**
14	H	4-ClC_6H_4	H **(1n)**	52 **(2n)**
15	*n*-Bu	$(CH_2)_5$ **(1o)**		81 **(2o)**
16	*n*-Bu	Me	*n*-Pr **(1p)**	78 **(2p)**
17	Ph	Me	Me **(1q)**	82 **(2q)**
18	Ph	Me	*n*-Hex **(1r)**	83 **(2r)**
19	$(CH_2)_3$COOMe	Ph	H **(1y)**	86 **(2x)**
20[b]	$(CH_2)_5$OTHP	Ph	H **(1y)**	78 **(2y)**

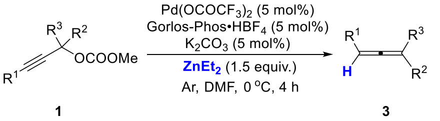
[a] The reaction was conducted with 1.0 mmol of **1**, $Pd(OAc)_2$ (5 mol%), SPhos (7.5 mol%), and 2 equiv. of Et_2Zn (1.5 M in toluene) in 6 mL of anhydrous DMF under Ar atmosphere. [b] The crude product was treated with $TsOH{\cdot}H_2O$ before chromatography to remove the THP protecting group.

The scope of Pd/Gorlos-Phos-catalyzed reaction is shown in Table 3. R^1 may be alkyl such as *n*-butyl, 4-chloro-*n*-butyl, cyclohexyl, cyclopropyl (entries 1-4) or aryl group (entry 10), providing β-H elimination-based corresponding allenes in high yields. For R^2 group, in addition to alkyl group (entries 11 and 16), useful electron-donating methoxy group (entry 5) and electron-withdrawing synthetic versatile group such as halogen group Br, Cl and F (entries 7, 12 and 13), -COOMe, $-NO_2$, -CN (entries 8, 14 and 15) all may be installed to the phenyl group, adding further potentiality to the current method. The reaction also worked with R^2 being 1-naphthyl (entry 9). Furthermore, the reaction with tertiary carbonates could afford tri-substituted allenes in high yields (entries 11 and 16). Functional groups such as ester or OTHP was also tolerated (entries 17 and 18).

The gram-scale reactions with just 1 mol% of the catalyst may also easily be achieved (Scheme 2). nBu_2Zn and EtZnBr were both tested, albeit in a lower selectivity. $HCOONH_4$ or HCOONa was also tested as a hydride donor, unfortunately no allene product could be formed (Scheme 3).

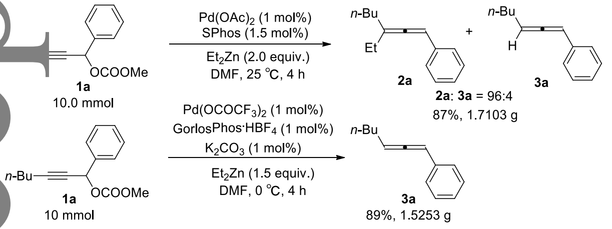
8-Phenyl-6,7-octadien-1-ol **3y** could also be prepared in high yield and selectivity (eq. 9), which could be easily transformed into acetate **3ya**, bromide **3yb**, benzyl ether **3yc**, aldehyde **3yd**, acid **3ye,** and nitrile **3yg** (Scheme 4).

Table 3. The scope of Pd/Gorlos-Phos-catalyzed cross-coupling reaction[a]

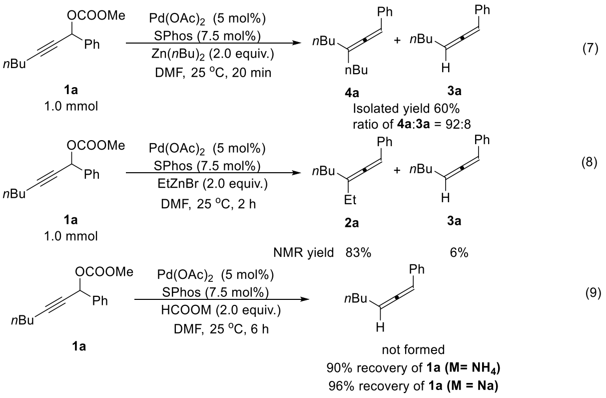


Entry	**1**			Yield of **3** (%)
	R^1	R^2	R^3	
1[b]	*n*-Bu	Ph	H (**1a**)	80 (**3a**)
2	4-Cl(CH$_2$)$_4$	Ph	H (**1b**)	83 (**3b**)
3[b]	Cyclohexyl	Ph	H (**1c**)	85 (**3c**)
4	Cyclopropyl	Ph	H (**1d**)	78 (**3d**)
5	*n*-Bu	3-MeOC$_6$H$_4$	H (**1e**)	96 (**3e**)
6	*n*-Bu	4-MeC$_6$H$_4$	H (**1f**)	81 (**3f**)
7	*n*-Bu	4-ClC$_6$H$_4$	H (**1g**)	85 (**3g**)
8	*n*-Bu	4-MeOOCC$_6$H$_4$	H (**1h**)	80 (**3h**)
9[b]	*n*-Bu	1-Naphthyl	H (**1i**)	58 (**3i**)
10	4-Cl(CH$_2$)$_4$	4-ClC$_6$H$_4$	H (**1l**)	80 (**3l**)
11	Ph	Me	*n*-Hex (**1r**)	70 (**3r**)
12	*n*-Bu	4-BrC$_6$H$_4$	H (**1s**)	79 (**3s**)
13[b]	*n*-Bu	2-FC$_6$H$_4$	H (**1t**)	80 (**3t**)
14[b]	*n*-Bu	3-O$_2$NC$_6$H$_4$	H (**1u**)	80 (**3u**)
15	*n*-Bu	4-NCC$_6$H$_4$	H (**1v**)	83 (**3v**)
16	Ph	Me	*t*-Bu (**1w**)	79 (**3w**)
17	(CH$_2$)$_3$CO$_2$Me	Ph	H (**1x**)	88 (**3x**)
18[c]	(CH$_2$)$_5$OTHP	Ph	H (**1y**)	73 (**3y**)

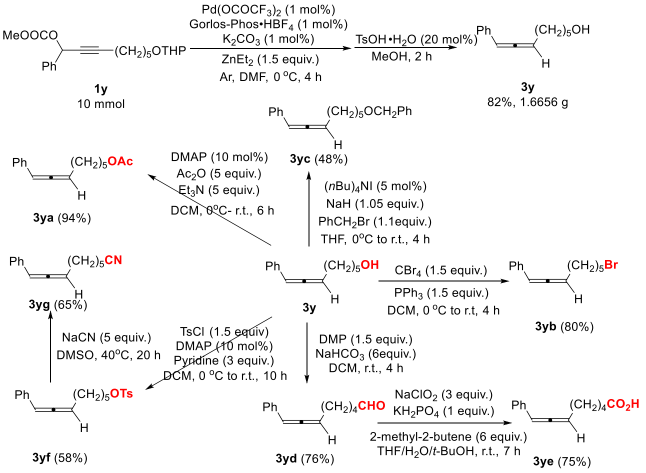
[a] The reaction was conducted with 1.0 mmol of **1**, Pd(OCOCF$_3$)$_2$ (5 mol%), Gorlos-Phos·HBF$_4$ (5 mol%), K$_2$CO$_3$ (5 mol%) and 1.5 equiv. of Et$_2$Zn (1.5 M in toluene) in 6 mL of anhydrous DMF under Ar atmosphere. [b] The reaction was conducted in 6 mL of anhydrous NMP under Ar atmosphere. [c] The crude product was treated with TsOH·H$_2$O before chromatography to remove the THP protecting group.



Scheme 2. Gram-scale synthesis of multiple-substituted allenes

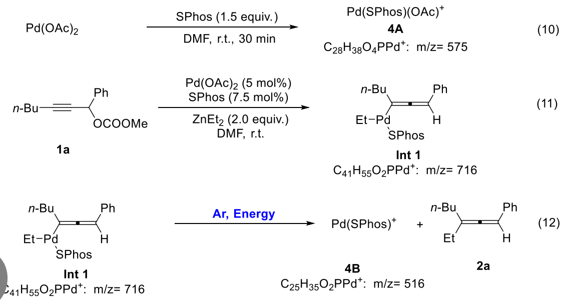


Scheme 3. Scope of different zinc reagents and hydride donor



Scheme 4. Synthesis of allenes with synthetically useful functionalities

In order to unveil the nature controlling the selectivity, we carried out three reactions and the resulting mixtures were analyzed by SAESI-MS and SAESI-MS/MS.[13] The SAESI-MS and SAESI-MS/MS spectra showed that the major Pd species was Pd(SPhos)(OAc)$^+$ (Figure S1 in SI and Figure 1) when mixing Pd(OAc)$_2$ with SPhos (eqn. 10). The transmetalated product, allenyl ethyl mono-SPhos ligated palladium species **Int 1**, was detected (Figure S2 in SI and Figure 2) after propargylic carbonate **1a** and Et$_2$Zn were added into the mixture of Pd(OAc)$_2$ and SPhos in sequence (eqn. 11). Interestingly, SAESI-MS/MS experiment of **Int 1** afforded ethylation product allene **2a** via reductive elimination (Fig. 2 and eqn. 12).



Scheme 5. SAESI-MS/MS studies of Pd/SPhos and its catalyzed reaction

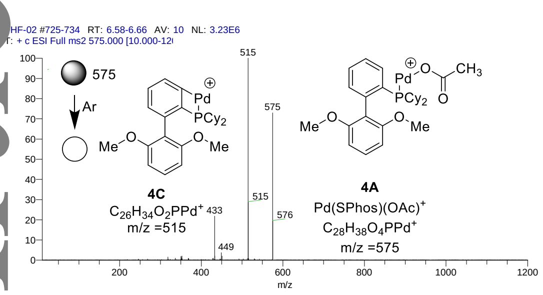


Figure 1. SASES-MS/MS experiment of Pd(SPhos)(OAc)$^+$

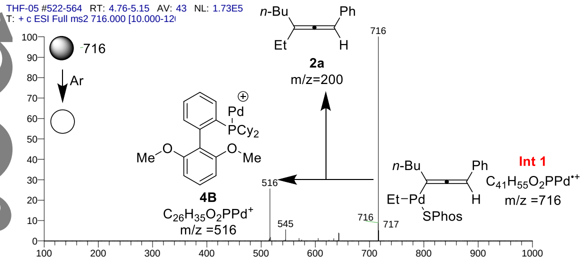
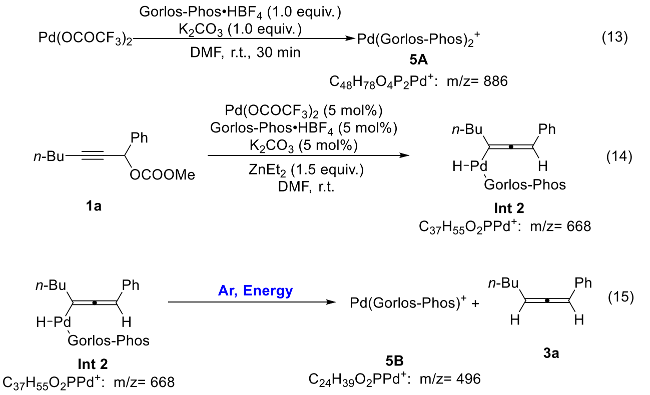


Figure 2. SASES-MS/MS experiment of the ion at m/z 716

As a comparison, when mixing $Pd(OCOCF_3)_2$ with Gorlos-Phos, Pd(Gorlos-Phos)$_2^+$ **5A** was detected as the only major Pd species (Figure S3 in SI and Figure 3) (eq. 13). Allenyl mono-Gorlos-Phos-ligated palladium hydride species **Int 2** (Figure S4 in SI and Figure 4) was detected as the major Pd species when mixing propargylic carbonate **1a**, diethyl zinc with $Pd(OCOCF_3)_2$ and Gorlos-Phos, indicating that the transmetalated intermediate went through β-H elimination readily (eq. 14). From these data it is concluded that SPhos takes mono-ligation with Pd and prevents the β-H elimination while Gorlos-Phos prefers bis-ligation with Pd. Then the Gorlos-Phos-mono-ligated palladium intermediate **Int 2** would have the free coordination sphere required by β-H elimination,[12] thus, facilitating β-H elimination during the coupling reaction to afford the β-H elimination-based coupling product allene **3a**, as confirmed by **SAESI-MS-MS** experiment of **Int 2** (eq. 15).



Scheme 6. SAESI-MS/MS Studies of Pd/Gorlos-Phos and its catalyzed reaction

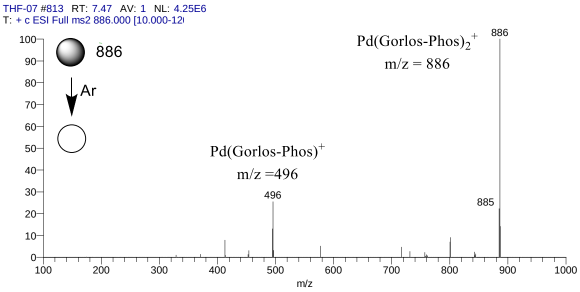


Figure 3. SAESI-MS/MS experiment of Pd(Gorlos-SPhos)$_2^+$

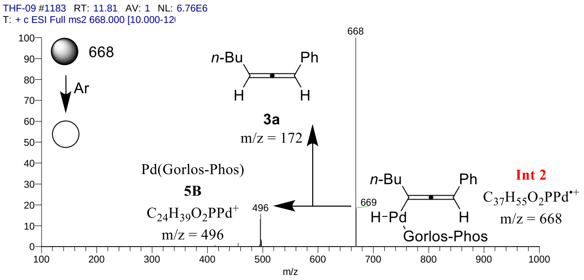
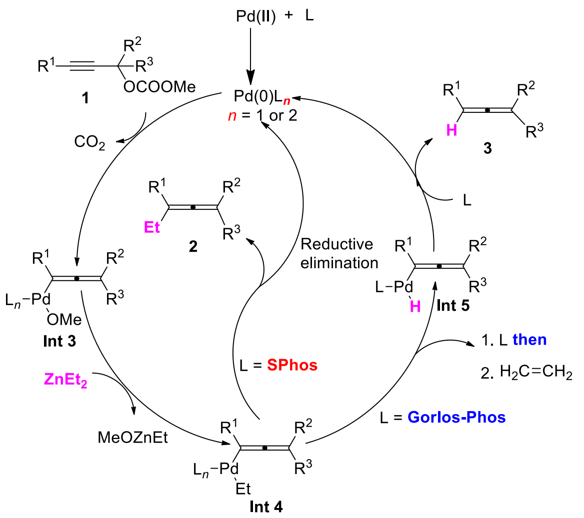


Figure 4. SAESI-MS/MS experiment of the ion at m/z 668

Based on these data, a rationale for the observed selectivity is proposed (Scheme 7)[14]. With SPhos, the coordination number *n* for the catalytically active species is 1, [11b] thus, Pd(0)L was the catalytically active species. After the SN2'-type *anti*-oxidative addition of Pd(0)L with the propargylic carbonates, the tri-coordinated allenylic palladium methoxide **Int 3** (see **Int 1** in Scheme 4) would react with Et_2Zn to afford transmetalated intermediate, allenyl ethyl palladium **Int 4**, which would undergo reductive elimination to afford the ethylation product **2**. SPhos prevents β-H elimination as well as promotes the reductive elimination. When Gorlos-Phos was applied, bi-dentated Pd(0)L$_2$ (*n* = 2) was the catalytically active species. Upon releasing one molecule of Gorlos-Phos, **Int 4** may readily undergo β-H elimination to form **Int 5** (see **Int 2** in Scheme 5), which underwent reductive elimination to yield the β-H elimination-based coupling product **3**.



Scheme 7. Proposed reaction pathway for ligand-controlled Negishi coupling

Conclusion

In summary, as a general solution for capturing the reactive organometallic intermediates, SAESI-MS/MS has been successfully applied and the nature of the ligand effect has been unveiled in the highly selective Negishi couplings of diethyl zinc with propargylic carbonates affording different multiple-substituted allenes: The selective formation of ethylation or β-H elimination-based products could be achieved respectively under mild conditions and different functional groups are well-tolerated by applying SPhos or Gorlos-Phos as the ligand. Currently, we are working on applying this protocol to dialkyl zincs with an alkyl group beyond ethyl group. Further studies in this area are being actively pursued in our laboratory.

Experimental Section

To a 50 mL oven-dried Schlenk tube were added $Pd(OAc)_2$ (11.4 mg, 0.05 mmol), SPhos (30.7 mg, 0.075 mmol), and 2 mL of anhydrous DMF sequentially under Ar atmosphere. The resulting mixture was stirred at rt for 30 minutes followed by the addition of **1a** (246.6 mg, 1.0 mmol), 4 mL of DMF, and Et_2Zn (1.5 M in toluene, 1.35 mL, 2.0 mmol) sequentially. After being stirred at 25 ^{o}C for 4 h, the resulting mixture was quenched with 10 mL of an aqueous solution of 3 M HCl and extracted with ethyl ether (10 mL × 3). The combined organic layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtrated, and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether) to afford **2a** (170.7 mg, 85%) as a liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.24 (m, 4 H, ArH), 7.19-7.13 (m, 1 H, ArH), 6.15 (quint, *J* = 3.2 Hz, 1 H, =CH), 2.16-2.00 (m, 4 H, 2×CH_2), 1.52-1.42 (m, 2 H, CH_2), 1.39-1.29 (m, 2 H, CH_2), 1.05 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.88 (t, *J* = 7.4 Hz, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.9, 136.3, 128.5, 126.3, 110.6, 95.8, 32.5, 29.9, 25.8, 22.5, 14.0, 12.3; MS (70 ev, EI) m/z (%): 200 (M^+, 2.60), 129 (100); IR (neat, cm^{-1}) 2960, 2929, 1947, 1598, 1495, 1459, 1405, 1377, 1326, 1103, 1071, 1028; HRMS calcd. for $C_{15}H_{20}$ (M^+): 200.1565; Found: 200.1567.

Acknowledgements

Financial supports from the National Natural Science Foundation of China (Grant No. 21690063) and the National Basic Research Program (2015CB856600) are greatly appreciated. We thank Mr Yizhan Zhai in this group for reproducing the preparation of **2d**, **2n,** and **3s**.

Keywords: Negishi Coupling • Palladium • SPhos • Gorlos-Phos • SAESI-MS/MS

[1] For a most recent monograph, see: *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vols 1 and 2.

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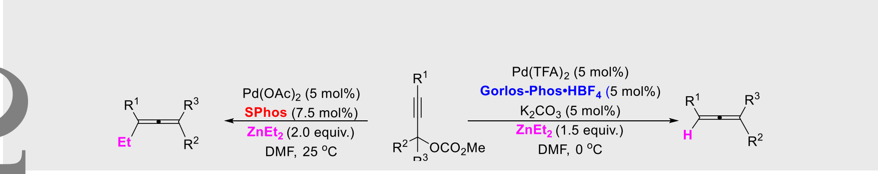

1. SAESI-MS approach for capturing the highly reactive organometallic intermediates and demonstrating reactivity towards final products
2. Ligand-controlled synthesis, high selectivity
3. Wide functional group tolerance, decent yields

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