Controlling Regioselectivity

Regioselectivity Control by a Ligand Switch in the Coupling Reaction Involving Allenic/Propargylic Palladium Species**

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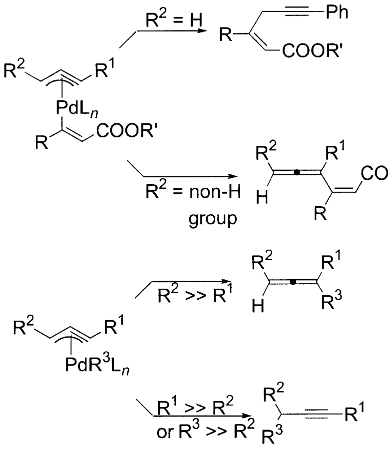
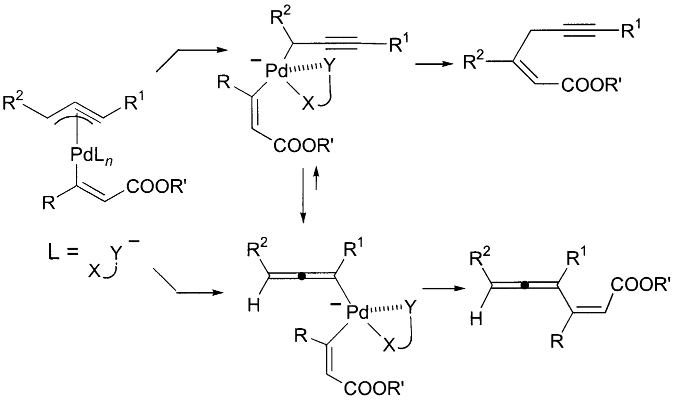
Transition-metal-catalyzed coupling reactions are becoming one of the most important approaches for the construction of C–C single bonds.[1] Usually, there is no regioselectivity problem as it is a "dummy" connection between an organometallic reagent and an organic compound with an appropriate leaving group. However, in the coupling reaction involving allenic and propargylic species,[2–5] although the formation of allenes is observed in most cases, in principle, the reaction could also afford alkynes. Regioselectivity in these coupling reactions depends on many parameters, such as the solvent and the steric/electronic properties of the substituents of both reactants.[6,7] Recently, we observed the highly regioselective formation of alkynes in the coupling reaction of propargylic/allenic zinc complexes with 3-halo-2-alkenoates.[5b] So far we have shown that the regioselectivity can be nicely tuned by the electronic and steric effects of the substrates (Scheme 1).[5c] Herein, we report the first example of the successful catalytic tuning of the regioselectivity[8] in the coupling reaction between propargylic mesylates and alkoxycarbonylethenyl zinc complexes or PhZnBr by the electronic effect of a new catalyst system resulting from 2-diphenylphosphino-2′-hydroxy-1,1′-binaphthalene[9] (**L3**) and $[\{PdCl(\pi\text{-}C_3H_5)\}_2]$.[10]



Scheme 1. Regioselectivity control by the electronic and steric effects.

We wanted to use bidentate ligands with one neutral coordination atom and a negatively charged coordination center, which may play a role for tuning the electronic property of Pd to influence the equilbrium between the propargyl and allenyl palladium as it is generally believed that an sp^2-carbon centered allenylic group is more electron-withdrawing than that of a sp^3-carbon centered propargylic group (Scheme 2).[6a,11]



Scheme 2. Regioselectivity control by the electronic effect of Pd.

A primary investigation of the coupling reaction between propargylic carbonate, acetate, or mesylate and (*Z*)-(2)-ethoxycarbonylethenyl zinc iodide (**2**)[12] with the catalyst $[Pd(PPh_3)_4]$ in THF showed that the mesylate afforded the enyne **3a** as the major product in 68% yield (Table 1, entry 1) while the reaction of other two substrates did not occur at room temperature. Thus, we used this coupling reaction as the model and 2-diphenylphosphinophenyl carboxylic acid **L1**[13] as the ligand to test the concept shown in Scheme 2. It is noteworthy that although the yield is low (25%), the regioselectivity is reversed (**3a**/**4a** = 12:88; Table 1, entry 2). The reaction with 4-hydroxybutyldiphenylphosphane (**L2**)[14] as the ligand gave a 43% combined yield of products with a similar reversed regioselectivity of 16:84 (**3a**/**4a**; Table 1, entry 3). Although the result is not satisfactory, it proved that our initial assumption shown in Scheme 2 may be feasible. To our delight, when we used 2-diphenylphosphino-2′-hydroxy-1,1′-binaphthalene (**L3**) as the ligand together with $[PdCl(\pi\text{-}C_3H_5)]_2$ as the precatalyst in THF the allenyl product **4a** was formed with a good reversed selectivity(**4a**/**3a** >97:3) and a moderate yield (49%) (Table 1, entry 5). Furthermore, it is noteworthy that 1) with binaphthol, **L4**, no coupling product was formed while with extra addition of PPh_3 the reaction afforded **3a** in 65% yield, thus indicating the importance of a phosphane ligand (Table 1, entries 7 and 8); 2) with a combination of $[PdCl(\pi\text{-}C_3H_5)]_2$ with PPh_3 and *i*PrOH or phenol (10 mol%) the reaction afforded the enyne product **3a** as the major product, which indicates the importance of the intramolecular interaction of the bidenate ligand with Pd (Table 1, entries 4 and 6); 3) with the methoxy analogue **L5** the reaction proceeded with the steric effect-controlled regioselectivity to give the alkyne as the major product (**3a**/**4a** >92:8) in 45% combined yield, thus indicating the importance of the anionic oxygen (Table 1, entry 9).

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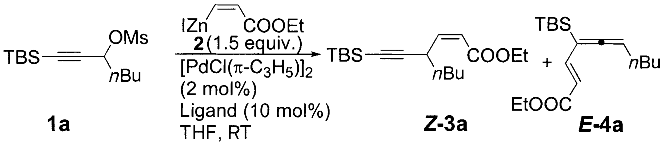
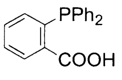
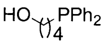
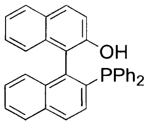
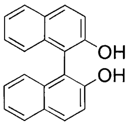
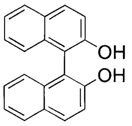
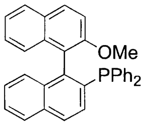
Table 1: Pd-catalyzed coupling reaction of **1a** with **2** with different ligands.



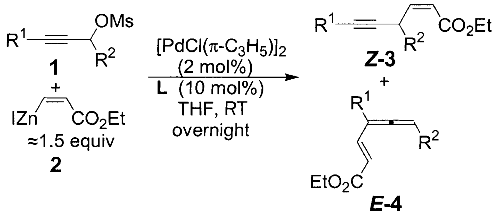
Entry	Ligand	t [h]	Yield [%]	**3a/4a**
1	[a]	26	68	>97:3
2	 **L1**	24	25	12:88
3	 **L2**	24	43	16:84
4	PPh$_3$[b]	24	46	96:4
5	 **L3**	16	49	<3:97
6	PPh$_3$[c]	9	59	>97:3
7	 **L4**	48	NR	–
8	 **L4**	12	65	>97:3
9	 **L5**	48	43	92:8

[a] [Pd(PPh$_3$)$_4$] was used as the catalyst. [b] iPrOH (10 mol%) was added. [c] PhOH (10 mol%) was added. [d] PPh$_3$ (10 mol%) was added.

With different precatalysts such as Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone) and PdCl$_2$, the same regioselectivity control was observed. When the reaction was preformed in other common solvents, such as CH$_2$Cl$_2$, CH$_3$CN, DMF or 1, 4-dioxane yielded complicated results.

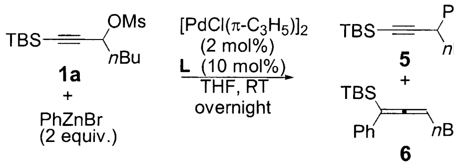
With this strategy, we tried other substrates to study its generality for the catalytic control of regioselectivity in the coupling reaction of propargylic mesylates and organozinc **2**. The results show that in the presence of PPh$_3$, enyne **3** is the predominant product while when **L3** was applied, allene **4** was formed highly selectively. In this case, R^1 can be the steric demanding TMS, TBS, tBu as well as an ordinary alkyl group such as n-C$_5$H$_{11}$ (see Table 2). A similar regioselectivity control was also observed with PhZnBr prepared from the transmetalation of PhMgBr with ZnBr$_2$ in THF (Scheme 3).

Table 2: Ligand-controlled regioselective coupling of propargylic mesylates and organozinc **2**.



Entry	**1**		L	Yield [%]	3/4
	R$^{1[a]}$	R$^{2[a]}$			
1	TBS	n-C$_4$(**1a**)	PPh$_3$	68 (**3a**)	>97:3
2	TBS	n-C$_4$(**1a**)	**L3**	49 (**4a**)	3:97
3	TMS	n-C$_8$ (**1b**)	PPh$_3$	68 (**3b**)	94:6
4	TMS	n-C$_8$(**1b**)	**L3**	82 (**4b**)	5:95
5	TMS	allyl (**1c**)	PPh$_3$	44 (**3c**)	95:5
6	TMS	allyl (**1c**)	**L3**	51 (**4c**)	4:96
7	TMS	Bn (**1d**)	PPh$_3$	42 (**3d**)	>93:7
8	TMS	Bn (**1d**)	**L3**	66 (**4d**)	<3:97
9	[b]	n-C$_8$ (**1e**)	**L3**	68 (**4e**)	<3:97
10	tBu	n-C$_4$ (**1f**)	PPh$_3$	69 (**3f+4f**)	50:50
11	tBu	n-C$_4$ (**1f**)	**L3**	64 (**4f**)	0:100
12	n-C$_5$	H (**1g**)[c]	**L3**	63 (**4g**)	0:100

[a] C$_m$ = C$_m$H$_{2m+1}$. [b] R^1 = TBSOCH$_2$. [c] Bromide was used instead of mesylate.



L = PPh$_3$ Yield = 74 % (**5**:**6** = 9:1)
L = **L3** Yield = 77 % (**5**:**6** = 1:8)

Scheme 3. Regioselectivity control in the coupling reaction with PhZnBr.

In summary, we have shown the first example of ligand control of regioselectivity in the coupling reactions involving allenic/propargylic palladium species leading to allenylsilanes[15] or 1-alkynylsilanes with different ligands. Because of the easy availability of the starting compounds and the synthetic utility of allenes[16] and alkynes,[17] this research will show its potential in organic synthesis and may open up a new area for catalytic regioselectivity control in transition metal-catalyzed coupling reaction. Further studies in this area are being pursued in our laboratory.

Experimental Section

[PdCl(π-C$_3$H$_5$)]$_2$ (2% mmol) and ligand (10% mmol) were added to a solution of propargylic mesylate **1b** in THF, and the mixture was stirred at room temperature for 20 min. Then Z-(2)-ethoxycarbonylethenyl zinc iodide (1.5 equiv) was added and the reaction mixture was stirred at room temperature overnight. After the reaction was complete, as monitored by TLC, it was quenched with water, and the mixture was extracted with diethyl ether and washed with water and brine. The product solution was dried over MgSO$_4$, the solvent was removed by rotary evaporation, and the product was purified by column chromatography on silica gel (hexane/diethyl ether = 50:1).

3b: The reaction of **1b** (60 mg, 0.19 mmol), **2** (0.28 mL, 1.0 M in THF, 0.28 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (1.4 mg, 0.0038 mmol), and PPh_3 (4.9 mg, 0.019 mmol) in 5 mL THF afforded 41.4 mg (68 %) of **3b**. **3b:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.10$ (dd, $J = 10.0$, 11.1 Hz, 1 H), 5.75 (dd, $J = 0.88$, 11.4 Hz, 1 H), 4.48 ~4.40 (m, 1 H), 4.16 (q, $J = 7.1$ Hz, 2 H), 1.62–1.25 (m, 17 H), 0.87 (t, $J = 6.7$ Hz, 3 H), 0.13 ppm (s, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 165.82$, 148.73, 119.18, 107.44, 85.60, 60.08, 35.20, 31.85, 31.34, 29.42, 29.21, 29.20, 26.82, 22.66, 14.20, 14.10, 0.11 ppm; MS m/z 322 (M^+, 1), 73 (100); IR (neat): $\tilde{\nu} = 2927$, 2171, 1721, 1647 cm^{-1}; HRMS calcd for $C_{19}H_{34}SiO_2$: 322.2328, Found: 322.2362.

4b: The reaction of **1b** (73.2 mg, 0.23 mmol), **2** (0.46 mL, 1.0 M in THF, 0.46 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (1.8 mg, 0.0046 mmol), and **L3** (10.4 mg, 0.023 mmol) in 5 mL THF afforded 60.4 mg (82 %) of **4b**. **4b:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$ (dd, $J = 1.2$, 15.9 Hz, 1 H), 5.88 (dd, $J = 1.2$, 15.9 Hz, 1 H), 5.12 (tt, $J = 1.2$, 6.7 Hz, 1 H), 4.19 (q, $J = 7.2$ Hz, 2 H), 2.02 (q, $J = 7.0$ Hz, 2 H), 1.43–1.26 (m, 15 H), 0.87 (t, $J = 7.0$ Hz, 3 H), 0.19 ppm (s, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.79, 166.99, 144.98, 119.15, 97.62, 86.73, 60.15, 31.83, 29.40, 29.35, 29.18, 27.61, 22.63, 14.30, 14.06, −0.97 ppm; MS m/z 322 (M^+, 4.3), 73 (100); IR (neat): $\tilde{\nu} = 2926$, 1920, 1714, 1618 cm^{-1}; HRMS calcd for $C_{19}H_{34}O_2Si$: 322.2328, Found: 322.2322.

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