JOC The Journal of Organic Chemistry

Brief Communication

pubs.acs.org/joc

Ligand Effects on the Stereochemical Outcome of Suzuki–Miyaura Couplings

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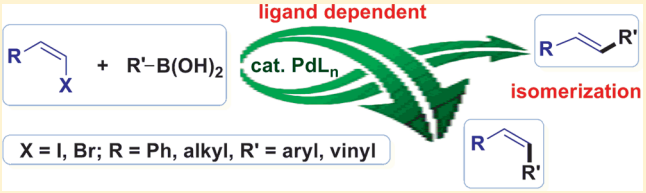
Supporting Information

ABSTRACT: The ligands associated with various Pd catalysts play a crucial role in determining the stereochemistry of cross-couplings between boronic acids and *Z*-alkenyl halides. A ligand on palladium has been found that leads to the desired products under mild conditions and in high yields that, in most cases, retain their *Z*-olefin geometry.

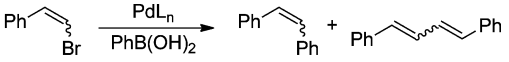


Suzuki–Miyaura cross-couplings have emerged as among the most valued methods for C–C bond constructions.[1] Historically, such reactions focused on elaboration of sp^2-based carbon arrays, typically involving various boronic acids along with aryl or alkenyl partners.[2] Part of the textbook discussion associated with such traditional and, now, Nobel Prize winning chemistry, is the stereochemical outcome when olefin geometry in the substrate is at issue.[3] In general, it is accepted that the coupling of a stereochemically defined alkenyl halide with a boronic acid will proceed with retention, regardless of its original *E*- or *Z*-state.[4] In a recent disclosure concerning analogous Negishi couplings, it was revealed that the nature of the catalyst, specifically the ligand coordinating to palladium, has a profound effect on the stereochemical outcome.[5] Although there are a few scattered reports mentioning slight erosions of stereoselectivity in the case of Pd-catalyzed, boron-mediated couplings,[6] none attempt to address this potentially crucial observation, nor do they provide a general solution to remedy the isomerization that may be occurring. We now describe a study on the effect of ligands on Suzuki–Miyaura couplings as manifested by reactions involving *Z*-olefinic substrates (Scheme 1) and offer a catalyst system that appears to minimize any *Z*-to-*E* isomerization.

Scheme 1. Suzuki–Miyaura Couplings with *Z*-Alkenyl Halides

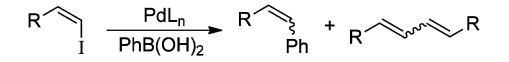
As a representative example, the cross-coupling of (*Z*)-*β*-bromostyrene with phenylboronic acid was selected to examine the impact of different ligands (Table 1, entries 1–10). Although most led to retention of *Z*-olefin geometry, ligand-complexed $Pd_2(dba)_3$ and $PdCl_2(dppf)$ resulted in noticeable losses of stereochemistry (entries 4–6). Variable but modest levels of homocoupling (to product **2**) took place in these reactions. However, more significant differences were found when the identical conditions were applied to the reaction between (*Z*)-1-iodooctene and phenylboronic acid, where loss of *Z*-olefin geometry was significant, including those reactions

Table 1. Ligand Effects on Suzuki–Miyaura Couplings[a]



Z/*E* = 96/4 **1** **2**

entry	catalyst (2 mol %)	conversion (%)[b]	*Z*/*E*[b]	**1**/**2**[b]
1	$PdCl_2(PPh_3)_2$	43	95/5	98/2
2	$Pd(PhP(t\text{-}Bu)_2)_2$	92	95/5	89/11
3	$Pd(P(o\text{-}Tol)_3P)_2$	97	96/4	98/2
4[c]	$Pd(dba)_2$ + dppf	100	91/9	85/15
5[c]	$Pd(dba)_2$ + $2PPh_3$	95	93/7	88/12
6	$PdCl_2(dppf)$	68	83/17	95/5
7	$Pd(PPh_3)_4$	12	94/6	/
8	$Pd(P(t\text{-}Bu)_3)_2$	100(88)[d]	94/6	/
9	PEPPSI	36	96/4	99/1
10	$PdCl_2(Amphos)_2$	74	96/4	99/1



R = *n*-C_6H_{13} **3** **4**

				3/**4**[b]
11	$Pd(P(t\text{-}Bu)_3)_2$	38	65/35	/
12	$PdCl_2(Amphos)_2$	85	51/49	90/10
13	$Pd(PhP(t\text{-}Bu)_2)_2$	98	76/24	95/5
14	$Pd(P(o\text{-}Tol)_3)_2$	56	99/1	67/33
15	$PdCl_2(PPh_3)_2$	50	98/2	55/45

[a]Alkenyl halide (0.25 mmol), phenylboronic acid (0.30 mmol), K_2CO_3 (0.50 mmol), catalyst (0.005 mmol), THF (0.50 mL), H_2O (0.10 mL), rt, 5 h (24 h for entries 11–15). [b]The conversion, *Z*/*E*, **1**/**2** and **3**/**4** ratio determined by GC/MS and ^1H NMR on crude products. [c]The reaction was performed at 40 °C for 18 h. [d]Isolated yield of *Z*-product.

Received: March 2, 2012
Published: April 5, 2012

   dx.doi.org/10.1021/jo300437t | *J. Org. Chem.* 2012, 77, 3700–3703

using the same catalysts which led to maintenance of *Z*-stereochemistry in the model reaction above (entries 11−13). Although isomerization was not observed using catalysts $Pd(PPh_3)_2Cl_2$ and $Pd(P(o\text{-}Tol)_3)_2$, low conversions and undesired homocoupling products **4** were noted (entries 14 and 15).

On the basis of these results, further investigation was needed both to improve the extent of conversion and to minimize homocoupling. Various solvents and bases were screened in the coupling of (*Z*)-1-iodooctene and phenylboronic acid catalyzed by $PdCl_2(PPh_3)_2$ (Table 2). The results

Table 2. Effects of Solvents and Bases[a]

entry	solvents (5/1)	base	conv (%)[b]	*Z*/*E*[b]	**3**/**4**[b]
1	THF/H_2O	KF	32	98/2	54/46
2	THF/H_2O	K_2CO_3	50	98/2	55/45
3	$EtOH/H_2O$	K_2CO_3	85	98/2	90/10
4	$PhMe/H_2O$	K_2CO_3	85	95/5	69/31
5	THF/H_2O	K_3FO_4	15	98/2	64/36
6	THF/H_2O	NaOH	72	98/2	74/26
7	THF/H_2O	NaO-*t*-Bu	76	98/2	78/22
8	$EtOH/H_2O$	NaO-*t*-Bu	100	97/3	87/13
9	**$EtOH/H_2O$**	**NaO-*t*-Bu**	**96**[c]	**99/1**	**94/6**

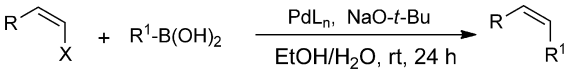
[a]Reaction conditions: (*Z*)-1-iodooctene (0.25 mmol), phenylboronic acid (0.30 mmol), base (0.50 mmol), $Pd(PPh_3)_2Cl_2$ (0.005 mmol; 2 mol %), solvents (0.6 mL), rt, 24 h. [b]The conversion, *Z*/*E*, and **3**/**4** ratio determined by GC/MS and ^{1}H NMR on crude products. [c]The catalyst is $Pd(P(o\text{-}Tol)_3)_2$ (2 mol %).

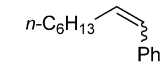
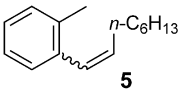
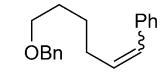
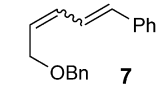
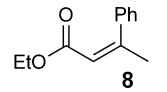
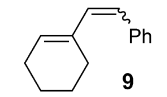
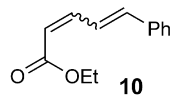
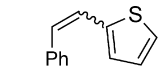
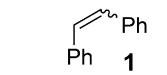
indicated that the combination of strong base (NaO-*t*-Bu) in EtOH enhances conversion and discourages homocoupling while maintaining high levels of stereoretention (entry 8).[7] Catalyst $Pd(P(o\text{-}Tol)_3)_2$, rather than $PdCl_2(PPh_3)_2$, afforded fewer side products (entry 9).

Several *Z*-alkenyl halides were coupled with aryl- and *β*-styrylboronic acids to assess the generality of ligand effects on the stereochemical outcome (Table 3). Not surprisingly, based on the variations illustrated in Tables 1 and 2 above, the stereoselectivity varied with both the ligand on palladium as well as the educt. $Pd(P(o\text{-}Tol)_3)_2$ (**C**) consistently afforded high yields and complete retention of *Z*-olefin geometry. In most cases, $Pd(P(t\text{-}Bu)_3)_2$ and $PdCl_2(Amphos)_2$ (**A** and **B**) led to highly variable levels of isomerization and are not good choices for these couplings under these conditions. Oddly, $Pd(P(t\text{-}Bu)_3)_2$ (**A**) led to almost complete isomerization to produce *E*-**5** (entry 4). With (*Z*)-ethyl 3-iodobut-2-enoate, isomerization was not observed with any of the three ligands examined (entries 13−15). In changing the boronic acid partner from phenyl to *β*-styryl, however, a 3−11% erosion in *Z*-stereochemistry was noted (entries 19−22). In this case, $PdCl_2(PPh_3)_2$ (**D**) (rather than $Pd(P(o\text{-}Tol)_3)_2$) proved to be the better choice to yield product *Z*-**10** (entry 22).

A brief study was also made as to ligand effects with a representative heteroaromatic boronic acid (3-thiophenebor-onic acid) using *β*-bromostyrene as the reaction partner. Although high stereoselectivity (*Z*/*E* = 96/4) could be maintained, the extent of conversion was poor (18%) using $Pd(P(o\text{-}Tol)_3)_2$ in $EtOH/H_2O$, even at 50 °C for 40 h. A solvent switch to toluene along with an increase in reaction temperature to 80 °C were found to enhance the yield (entry 25). While both catalysts $Pd(P(o\text{-}Tol)_3)_2$ and $Pd(P(t\text{-}Bu)_3)_2$ led to retention of *Z*-olefin geometry, a better yield (80%) was

Table 3. Ligand Effects on Couplings of *Z*-Alkenyl Halides[a]



entry	X	product	PdL_n[b]	yield (*Z*; %)[c]	*Z*/*E*[c]
1	I		A	61	62/38
2	I		B	70	71/29
3	I	**3**	**C**	89(80)[d]	**99/1**
4	I		A	90(82)[d,e]	9/91
5	I		B	Trace	/
6	I	**5**	**C**	98(91)[d]	**99/1**
7	Br		A	58	58/42
8	Br		B	Trace	/
9	Br	**6**	**C**	97(86)[d]	**98/2**
10	I		A	94	95/5
11	I		B	89	90/10
12	I	**7**	**C**	97(88)[d]	**98/2**
13	I		A	99	99/1
14	I		B	99	99/1
15	I	**8**	**C**	99(94)[d]	**99/1**
16	I[f]		A	85	85/15
17	I[f]		B	21	71/29
18	I[f]	**9**	**C**	75(69)[d]	**95/5**
19	I[g]		A	89	90/10
20	I[g]		B	83	84/16
21	I[g]	**10**	C	89(81)[d]	90/10
22	I[g]		D	92(84)[d]	92/8
23[h]	Br[i]		**A**	87(80)[d]	**95/5**
24[h]	Br[i]		B	60	92/8
25[h]	Br[i]	**11**	C	59	96/4
26[j]	Br[i]		A	28	67/33
27[j]	Br[i]		B	12	17/83
28[j]	Br[i]	**1**	**C**	77(69)[d,k]	**95/5**

[a]Alkenyl halide (0.25 mmol), aryl- or *β*-styryl-boronic acid (0.30 mmol), NaO-*t*-Bu (0.50 mmol), catalyst (0.005 mmol), EtOH (0.50 mL), H_2O (0.10 mL), rt, 24 h. [b]Key: (A) $Pd(P(t\text{-}Bu)_3)_2$, (B) $Pd(Amphos)_2Cl_2$, (C) $Pd(P(o\text{-}Tol)_3)_2$, (D) $Pd(PPh_3)_2Cl_2$. [c]The yield of *Z*-product and *Z*/*E* ratio determined by GC/MS and ^{1}H NMR. [d]Isolated yield. [e]The yield of *E*-product. [f]The *Z*/*E* ratio of 1-(2-iodovinyl)cyclohex-1-ene is 97/3. [g]The *Z*/*E* ratio of ethyl 3-iodoacrylate is 95/5. [h]The solvent is toluene/H_2O (v/v = 5/1). [i]The *Z*/*E* ratio of *β*-bromostyrene is 96/4, and the reaction is performed at 80 °C. [j]$PhBF_3^-K^+$ is employed. [k]4 mol % of catalyst was used.

obtained with $Pd(P(t\text{-}Bu)_3)_2$ (entry 23 vs 25). Using Molander Ate potassium phenyltrifluoroborate[8] as an alternative to phenylboronic acid under our general conditions (2 mol % catalyst), low conversion to *Z*-stilbene was seen.[9] However, increasing the catalyst loading to 4 mol % and temperature to 80 °C raised the conversion (91%) and resulting yield to 69% (entry 28). Only $Pd(P(o\text{-}Tol)_3)_2$ as catalyst was effective at preventing a significant loss of *Z*-stereochemistry.

In conclusion, contrary to the prevailing thought that Pd-catalyzed Suzuki−Miyaura couplings involving both *E*- and *Z*-alkenyl halides are expected to maintain their stereochemical integrity, the results herein document that *Z*-disposed, 1,2-disubstituted educts can easily undergo *Z*-to-*E* isomerization,

dx.doi.org/10.1021/jo300437t | J. Org. Chem. 2012, 77, 3700−3703

the extent of which is dictated mainly by the ligand on palladium.[10] New conditions have been found that point to $Pd(P(o\text{-}Tol)_3)_2$ as the ligand of choice. When used in couplings of *Z*-alkenyl halides, along with changes in the base and solvent system, stereoretention is observed. Moreover, high chemical yields are to be expected, and in most cases, reactions occur at room temperature. Given the now established sensitivity of both Negishi and Suzuki–Miyaura couplings to the ligands on palladium in their reactions with *Z*-alkenyl halides, it may well be that other related Pd-catalyzed processes, such as Stille couplings, follow the same trend. Results from this ongoing study will soon be reported.

EXPERIMENTAL SECTION

General Procedure for Suzuki–Miyaura Couplings. Catalyst (0.005 mmol), boronic acid (0.30 mmol), and base (0.50 mmol) were weighed into a round-bottom flask or microwave vial at room temperature. The alkenyl halide (0.25 mmol), H_2O (0.1 mL) and distilled organic solvent (0.5 mL) were then added by syringe. The resulting solution was allowed to stir at rt or 80 °C for 5 to 24 h. The homogeneous reaction mixture was then diluted with EtOAc (4 mL) and filtered through a bed of silica gel layered over Celite, and the volatiles were removed in vacuo to afford the crude product. Analyses by ^{1}H NMR and GC/MS gave both the conversion and *Z*/*E* ratio. Further column chromatography on silica gel afforded the pure desired *Z*-product.

(Z)-1,2-Diphenylethene[11] *(Z-**1**):* 40 mg, 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 2H), 7.20–7.30 (m, 10H).

*(Z)-Oct-1-enylbenzene (Z-**3**):* 38 mg, 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88–0.90 (t, 3H), 1.24–1.37 (m, 6H), 1.43–1.49 (m, 2H), 2.31–2.36 (m, 2H), 5.65–5.71 (m, 1H), 6.41 (d, J = 11.5 Hz, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 28.7, 29.0, 30.0, 31.7, 126.4, 128.1, 128.6, 128.7, 133.3, 137.8; HRMS (EI) calcd for $C_{14}H_{20}$ 188.1565, found 188.1568.

*(Z)-1-Methyl-2-(oct-1-enyl)benzene (Z-**5**):* 46 mg, 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–0.89 (t, 3H), 1.21–1.32 (m, 6H), 1.37–1.43 (m, 2H), 2.13–2.18 (m, 2H), 2.26 (s, 3H), 5.70–5.75 (m, 1H), 6.42–6.45 (d, J = 11.5 Hz, 1H), 7.15–7.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.9, 22.6, 28.4, 28.9, 29.8, 31.7, 125.2, 126.7, 127.8, 129.7, 133.0, 136.2, 137.0; HRMS (EI) calcd for $C_{15}H_{22}$ 202.1722, found 202.1725.

(E)-1-Methyl-2-(oct-1-enyl)benzene[12] *(E-**5**):* 41 mg, 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89–0.92 (t, 3H), 1.27–1.40 (m, 6H), 1.45–1.51 (m, 2H), 2.21–2.26 (m, 2H), 2.34 (s, 3H), 6.07–6.13 (m, 1H), 6.57 (d, J = 15.5 Hz, 1H), 7.11–7.17 (m, 3H), 7.41 (d, J = 7.0 Hz, 1H).

*(Z)-(6-(Benzyloxy)hex-1-enyl)benzene (Z-**6**):* 57 mg, 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54–1.60 (m, 2H), 1.65–1.71 (m, 2H), 2.35–2.40 (m, 2H), 3.47–3.50 (t, 2H), 4.51 (s, 2H), 5.65–5.71 (m, 1H), 6.44 (d, J = 11.5 Hz, 1H), 7.22–7.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 28.3, 29.4, 70.2, 72.9, 126.5, 127.5, 127.6, 128.1, 128.4, 128.7, 129.0, 132.8, 137.7, 138.6; HRMS (EI) calcd for $C_{19}H_{22}O$ 266.1671, found 266.1677.

*((1E,3Z)-5-(Benzyloxy)penta-1,3-dienyl)benzene (Z-**7**):* 55 mg, 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.30–4.32 (dd, J = 7.0, 1.5 Hz, 2H), 4.59 (s, 2H), 5.68–5.73 (m, 1H), 6.33–6.38 (td, J = 11.2, 0.7 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.97–7.03 (ddd, J = 15.5, 11.0, 1.0 Hz, 1H), 7.24–7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.0, 72.3, 123.9, 126.8, 127.9, 127.9, 128.6, 128.8, 132.1, 134.4, 137.3, 138.4; HRMS (EI) calcd for $C_{18}H_{18}O$ 250.1358, found 250.1338.

(Z)-Ethyl 3-phenylbut-2-enoate[13] *(Z-**8**):* 45 mg, 94% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08–1.11 (t, 3H), 2.19 (d, J = 1.5 Hz, 3H), 3.99–4.03 (m, 2H), 5.92 (q, J = 1.5 Hz, 1H), 7.21–7.23 (m, 2H), 7.30–7.38 (m, 3H).

*(Z)-(2-Cyclohexenylvinyl)benzene (Z-**9**):* 32 mg, 69% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.58 (m, 4H), 1.89–1.91 (m, 2H), 2.07–2.08 (m, 2H), 5.75–5.77 (m, 1H), 6.07–6.10 (dd, J = 12.5, 1.0 Hz, 1H), 6.31 (d, J = 12.5 Hz, 1H), 7.17–7.20 (m, 1H), 7.25–7.31 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1, 22.8, 25.7, 28.1, 126.4, 127.2, 127.7, 128.9, 129.1, 133.7, 135.6, 138.6; HRMS (FI) calcd for $C_{14}H_{16}$ 184.1252, found 184.1223.

(2Z,4E)-Ethyl 5-phenylpenta-2,4-dienoate[14] *(Z-**10**):* 42 mg, 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32–1.35 (t, J = 7.3 Hz, 3H), 4.21–4.25 (q, J = 7.2 Hz, 2H), 5.73 (d, J = 11.0 Hz, 1H), 6.72–6.77 (td, J = 11.0, 0.7 Hz, 1H) 6.82 (d, J = 16.0 Hz, 1H), 7.26–7.37 (m, 3H), 7.52–7.53 (m, 2H), 8.13–8.18 (ddd, J = 16.0, 11.5, 1.0 Hz, 1H).

(Z)-3-Styrylthiophene[15] *(Z-**11**):* 37 mg, 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 12.0 Hz, 1H), 6.58 (d, J = 12.0 Hz, 1H), 6.86–6.87 (dd, J = 5.0, 1.0 Hz, 1H), 7.11–7.14 (m, 2H), 7.23–7.30 (m, 5H).

ASSOCIATED CONTENT

Supporting Information

Additional experimental details and copies of NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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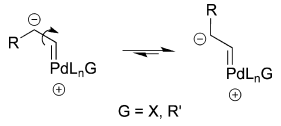
(9) Only 27% of the desired product with a 96/4 *Z*/*E* ratio was obtained in the reaction of potassium phenyltrifluoroborate with *Z*-β-bromostyrene using $Pd(P(o\text{-}Tol)_3)_2$ at room temperature for 24 h.

(10) The mechanism by which *Z*-to-*E* isomerization occurs may involve a zwitterionic palladium carbene intermediate, the extent to which this species forms being a function of the ligand on Pd and the residue (R) attached to the alkenyl carbon β to a Pd(II) intermediate (shown below). This resonance situation allows for facile bond rotation to ultimately arrive at the favored *E*-isomer.



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