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Studies on the 1,2-Migrations in Pd-Catalyzed Negishi Couplings with JosiPhos Ligands

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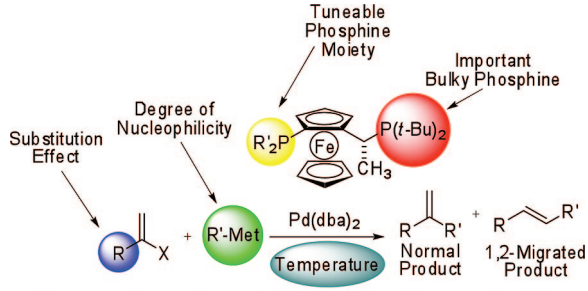

Factors Controlling the Degree of Isomerization

We report an initial investigation with the goal of determining the factors that control the 1,2-migration in the Negishi cross-coupling, which is promoted by palladium catalyst systems generated with JosiPhos ligands. Several of the factors that were demonstrated to be important for the 1,2-migration include (1) the nucleophilicity of the organometallic reagent, which possibly influences the transmetalation step in direct competition with the intermediate β-hydride elimination of the alkenyl Pd(II) species; (2) the structural features of the vinyl tosylates and phosphates, in which substrates possessing a bulky C1 substituent displayed highest propensity for undergoing the 1,2-migration under the coupling reaction conditions; and (3) the structure of the JosiPhos ligand, where both the sterical bulk and choice of substitutents on the ferrocenyl phosphino group greatly influence the catalytic activity of the palladium complex and its capacity to facilitate the 1,2-migration.

Introduction

Palladium migrations are becoming increasingly common for a variety of systems in Pd-catalyzed C−C bond forming reactions, which include 1,3-, 1,4-, 1,5-, and 1,6-rearrangements at sp^2-carbon centers, thereby expanding the repertoire of coupling products obtained by these reactions.[1−3] Recently, the 1,2-migration has been observed for these transition-metal-based coupling reactions involving vinylic tosylates and phosphates. Hartwig and co-workers reported a single case of this rearrangement in work on the Kumada−Corriu coupling with vinyl tosylates. The reaction of the alkenyl tosylate **1** with *p*-tolyl magnesium bromide catalyzed by an in situ generated Pd:JosiPhos complex provided the product **2** of 1,2-migration (Scheme 1a).[4,5] Our work on the Pd-catalyzed Mizoroki−Heck coupling of vinyl tosylates and phosphates revealed that these migrations are more general,[6−8] being promoted with electrophiles bearing an aryl or a tertiary alkyl substituent at the C1 (Scheme 1b). Additionally, it was found that a bulky electron-

(1) For examples on the 1,3- to the 1,6-migrations, see: Mota, A. J.; Dedieu, A. *Organometallics* **2006**, *25*, 3130, and references cited therein.

(2) For a recent review on 1,4-migrations, see: Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512.

(3) For some recent examples, see: (a) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340. (b) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288. (c) Campo, M. A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R. D.; Huang, Q.; Zhao, J.; Jenks, W. S.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 6298. (d) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888. (e) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (f) Bour, C.; Suffert, J. *Org. Lett.* **2005**, *7*, 653. (g) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171.

(4) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.

(5) For some recent reviews on the Kumada−Corriu coupling, see: (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Frieman, B. A.; Taft, B. R.; Lee, C.-T.; Butler, T.; Lipshutz, B. H. *Synthesis* **2005**, 2989. (c) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (d) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (e) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. (f) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162. (g) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457.

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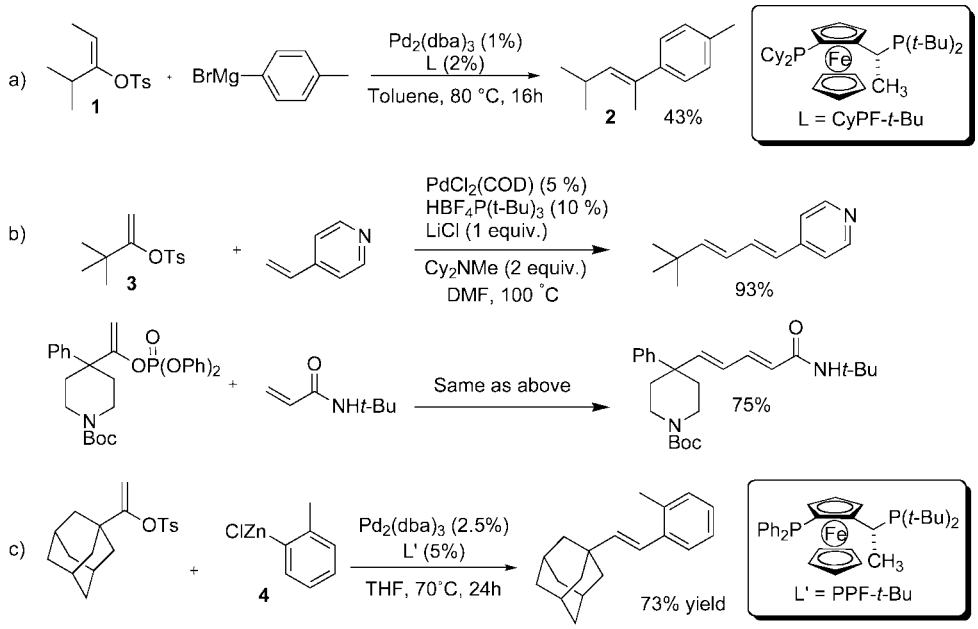
SCHEME 1



rich monodentate ligand, such as P(*t*-Bu)$_3$, was imperative for rearrangement.[9] Later, we reported a couple of examples of this migration in the Negishi coupling of aryl zinc reagents to alkenyl phosphates with another Pd:Josphos complex (Scheme 1c)[10,11] employed by Hartwig and co-workers in their example in the Kumada−Corriu coupling.[4]

These migrations appear to proceed by a rare pathway involving first β-hydride elimination of the intermediate alkenyl−Pd(II) species with an olefinic hydrogen generating an alkynyl-coordinated palladium hydride, followed by a hydropalladation step to give the isomeric olefinic Pd(II) intermediate.[4,7] However, the factors which control this 1,2-migration are not fully understood. For example, in the Mizoroki−Heck couplings, we found after ligand screening that *t*-Bu$_3$P is the best ligand for promoting this rearrangement,[7,8] whereas when the same vinylic electrophiles were used in the Negishi reaction, the JosiPhos ligand, PPF-*t*-Bu, proved more effective for inducing the migration.[10] On the other hand, applying P(*t*-Bu)$_3$ as the ligand for the same Negishi reactions favored the normal coupling product. Furthermore, Hartwig and co-workers reported the use of another JosiPhos ligand, CyPF-*t*-Bu, for the Kumada−Corriu coupling,[4] which in our hands only partially promoted the rearrangement in Negishi couplings.[10]

From these preliminary studies, it became evident that subtle changes in either the ligand or organometallic reagent composition can greatly influence the outcome of these β-hydride elimination processes and subsequent 1,2-migrations. Hence, a more comprehensive study was undertaken to examine the scope and limitations of the 1,2-migration in Negishi couplings with vinyl phosphates and tosylates. Particular emphasis is made on the nature of the ligand and the nucleophilicity of the organometallic reagents.

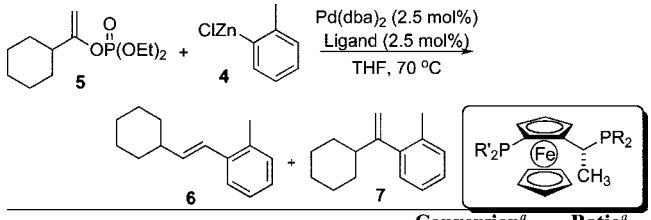
Results and Discussion

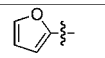
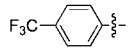
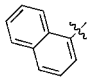
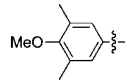
Negishi Reactions with Aryl Zinc Reagents. In order to examine the features responsible for the 1,2-migration in the Negishi couplings, we conducted a more comprehensive study on the structural importance of the ligand with a series of commercially available and structurally similar diphosphine ligands bearing a ferrocene core. The results of this initial study are depicted in Table 1 for the coupling of *o*-tolyl zinc chloride **4** with the vinyl phosphate **5**.

The chosen catalytic system was extrapolated from our earlier work, consisting of a palladium(0) source, Pd(dba)$_2$, in combination with an equimolar amount of a hindered JosiPhos ligand[12] in THF at 70 °C with a reaction time between 18 and 20 h. A characteristic trait for all the diphosphine ligands tested is the presence of the bulky di-*tert*-butyl phosphine moiety,

(6) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.
(7) Ebran, J.-P.; Hansen, A. L; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931.
(8) For some recent reviews on the Mizoroki−Heck reaction, see: (a) Heck, R. F. *Synlett* **2006**, 2855. (b) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (d) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: Orlando, FL, 1985. (e) Tsuji, J. *Palladium Reagents and Catalysts: Innovation in Organic Synthesis*; Wiley: Chichester, U.K., 1995. (f) Brase, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; DiederichF., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 3. (g) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; DiederichF., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 6. (h) *Transition Metal Catalyzed Reactions*; Davis, S. G., Murahashi, S.-I., Eds.; Blackwell Science, Oxford, 1999. (i) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (j) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.
(9) For the use of this ligand in coupling reactions, see: (a) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (d) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178. (e) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (f) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343. (g) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (h) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
(10) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464.
(11) For reviews and general literature on the Negishi reaction, see: (a) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (b) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (d) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838. (e) Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2916. (f) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762. (g) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brian, C. J.; Valente, C. *Chem.−Eur. J.* **2006**, *12*, 4749. (h) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (i) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (j) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

TABLE 1. Substitution Pattern Effects of the JosiPhos Ligands on the 1,2-Migration



Entry	R'	R	Conversion[a] (%)	Ratio[a] 6/7
1		*t*-Bu	42	4:1
2		*t*-Bu	52	5:1
3		*t*-Bu	19	5:1
4		*t*-Bu	57	10:1
5		*t*-Bu	40	20:1
6		*t*-Bu	48	5:1
7	*t*-Bu		55	2:3
8	*t*-Bu		23	1:1

[a] Conversion and ratio determined by ^{1}H NMR analysis of crude reaction mixture.

which was previously observed to be crucial for generating an active catalyst for this cross-coupling reaction.[10] Whereas all palladium catalysts composed of these ligands promoted the reaction with varying degrees of conversion, the Pd:PPF-*t*-Bu and Pd:NPF-*t*-Bu complexes (entries 4 and 5, respectively) provided the products **6** and **7** with highest selectivities toward the 1,2-migration. As earlier reported, here too the catalyst generated from CyPF-*t*-Bu displayed selectivity for the migrated product with an aryl zinc reagent less than that of PPF-*t*-Bu. Both electron-donating and -withdrawing substituents on the phenyl ring of the JosiPhos lowered the selectivity (entries 2 and 6), suggesting that subtle electronic and sterical effects on this moiety of the ligand may be effecting the outcome of the migration in the Negishi coupling. Finally, interchanging the two phosphines on the ligand was detrimental for the selectivity, essentially leading to a 1:1 mixture of the coupling products **6** and **7** (entries 7 and 8).

Work was then undertaken to investigate the electronic and sterical influence of the organometallic reagent on the migration. To start off with, different aryl zinc chlorides were tested in their coupling with two alkenyl tosylates, **3** and **9**, and an alkenyl *O*,*O*-diethyl phosphate represented by **8** in the presence of a catalyst formed with PPF-*t*-Bu as the diphosphine ligand. We have earlier demonstrated that the use of a tosylate or *O*,*O*-diethyl phosphate has essentially no consequence on either the yield or selectivity for such couplings, whereas the corresponding *O*,*O*-diphenyl phosphate led to the formation of a dimeric biproduct.[10] As illustrated in Table 2, the electron-rich aryl zinc reagent, 4-methoxy phenyl zinc chloride (**11**), coupled successfully in good to excellent yields though producing varying ratios of the normal and rearranged product depending on the starting vinyl tosylate/phosphate (entries 1−3). For example, for the vinyl tosylate **3** bearing a C1-*t*-butyl group, the product of migration was predominant, whereas with a less bulky alkyl C1 substituent or an *o*-tolyl group, migration was substantially inhibited. Exchanging the *p*-methoxy group of the aryl zinc reagent with a less electron-donating *p*-methyl substituent, as shown in entries 4 and 5, led to a slight decrease in the isolated yields, but more importantly, the selectivity for the 1,2-migration was increased. Switching to *o*-methylphenyl zinc chloride **4** and thereby increasing the steric bulk of the aryl zinc reagent further enhanced the migration (entries 6−8). For example, with tosylate **3** as the coupling partner, only the 1,2-disusbstituted alkene from rearrangement was obtained. Nevertheless, this sterical bulk also led to a diminished reactivity with the cyclohexyl vinyl tosylate **9**, where only a 39% conversion after 20 h was observed.

An aryl zinc reagent **13** with an electron-withdrawing cyano group at the C4-position of the aromatic ring was examined with the three electrophiles **3**, **8**, and **9** (entries 10−12). Characteristic for these three reactions was an increased selectivity for migration compared to the other *para*-substituted organozinc reagents tested. Again, the tosylate **9** displayed modest reactivity with this zinc reagent but nonetheless favored the 1,2-substituted olefin.

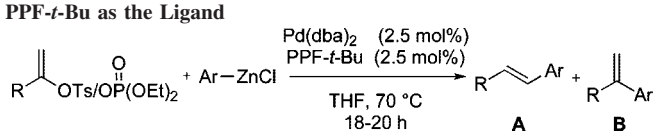
Finally, the effect of the leaving group on the selectivity of the coupling products was also examined via the reaction of the aryl zinc reagent **4** with a halide equivalent to the alkenyl phosphate **8** (entry 13). In this example, the ratio of the product of migration **26** to the normal product **27** was measured to be 5:1, which was essentially the same result observed for the similar reaction between vinyl phosphate **8** and **4** (entry 7). In addition, the reaction yields of the two cross-coupling were comparable.

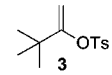
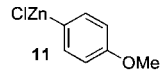
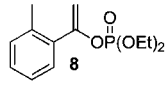
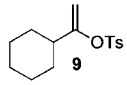
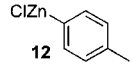
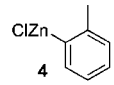
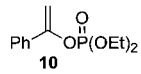
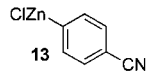
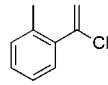
Increasing the sterical bulk of the JosiPhos ligand with NPF-*t*-Bu had a substantial effect on the outcome of some of these reactions, by producing either a more active or a more stabile catalyst. In some instances, a dramatic outcome on the migration was also observed. As seen from Table 3, entry 2, the use of this palladium complex with this ligand increased the ratio of the 1,2-alkene versus 1,1-alkene to 4:3 from 1:5 with PPF-*t*-Bu (Table 2, entry 2). Similar enhanced migration selectivity was seen in a few other cases (entries 1, 7, and 11). Even the phenyl vinyl phosphate displayed an analogous reactivity with the *o*-tolyl zinc chloride upon switching between catalysts generated from these two ligands (Table 2, entry 9 vs Table 3, entry 9). With a complex composed of PPF-*t*-Bu, only the normal coupling product was isolated, where in contrast the naphthalene analogue was capable of promoting migration to some degree. Significant yield increases were also obtained for certain cases upon the use of a Pd:NPF-*t*-Bu complex. For example, the 1-cyclohexyl vinyl tosylate **9** reacted poorly in the presence of a catalyst bearing the PPF-*t*-Bu ligand (Table 1, entries 8 and 12). But with NPF-*t*-Bu, synthetically more useful yields were secured.

Finally, the effect of the solvent was examined in order to compare the results from the Negishi couplings to the Kumada−Corriu couplings obtained by Hartwig and co-workers (Scheme 2), which were performed in toluene.[4] Whereas the degree of migration was not significantly affected by increased amounts of added toluene in these Negishi couplings, the yields

(12) (a) Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1995**, *14*, 842. (b) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (c) Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Togni, A.; Albinati, A.; Muel, B. *Organometallics* **1994**, *13*, 4481.

TABLE 2. Negishi Couplings with PPF-*t*-Bu as the Ligand



Entry	Electrophile	Nucleophile	Conversion (%)[a]	Yield (%)[b]	Ratio A:B[a]	Cmpd No.
1	 **3**	 **11**	100	93	5:1	**14/15**
2	 **8**	**11**	100	95	1:5	**16/17**
3	 **9**	**11**	100	79	4:3	**18/19**
4	**3**	 **12**	100	86	7:1	**20/21**
5	**9**	**12**	82	67	1:1	**22/23**
6	**3**	 **4**	100	70	>19:1	**24/25**
7	**8**	**4**	95	72	9:2	**26/27**
8	**9**	**4**	39	n.d.[c]	5:1	**6/7**
9	 **10**	**4**	65	n.d.[c]	0:1	**28**
10	**3**	 **13**	90	62	>19:1	**29/30**
11	**8**	**13**	60	59	5:1	**31/32**
12	**9**	**13**	32	n.d.[c]	10:1	**33/34**
13		**4**	100	82	5:1	**26/27**

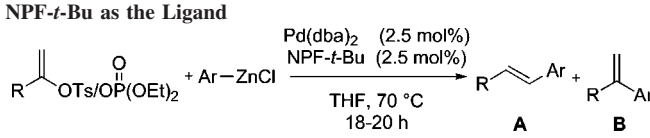
[a] Conversion and ratio determined by ^{1}H NMR spectrum of crude reaction mixture. [b] Isolated yields. [c] Not determined.

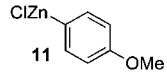
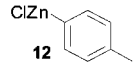
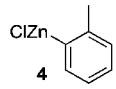
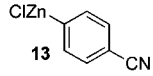
were improved for some of the substrates. For example, the product **24** was isolated in almost quantitative yield in the coupling of **3** with *o*-tolyl zinc chloride using standard PPF-*t*-Bu coupling conditions but in a 7:3 THF/toluene mixture (Scheme 2). Unfortunately, the cyclohexyl vinyl tosylate **9** showed no reactivity when toluene was used as cosolvent, and hence further cross-coupling reactions were not carried out in this solvent mixture.

From these initial studies, it becomes evident that aryl zinc chlorides with increased nucleophilicity have a detrimental effect on the β-hydride elimination step and subsequently the 1,2-migration, whereas decreasing the nucleophilicity of the organometallic species with electron-reducing groups significantly improved the product distribution in favor of the rearranged disubstituted alkene. Furthermore, increased sterical bulk of the aryl zinc reagent as noted with the *o*-tolyl zinc chloride again provided a preference for the 1,2-alkene. To further examine the role of the nucleophilicity of the coupling reagent, a series of experiments were then performed with an alkyl zinc reagent and two aryl Grignard reagents.

Coupling Reactions with an Alkyl Zinc Reagent and Aryl Grignard Reagents. Table 4 illustrates the outcome of a series of Negishi couplings performed with *n*-butyl zinc chloride as a representative example of an alkyl zinc reagent. As with the reactions employing the aryl zinc reagents, $Pd(dba)_2$ was used as the palladium(0) source in combination with equimolar ratios of a diphosphine ligand with respect to Pd. All reactions were initially performed in THF at 70 °C. The use of a palladium catalyst formed with PPF-*t*-Bu in reactions carried out with alkenyl tosylate **3** and phosphate **8** provided good coupling yields but importantly did not promote any degree of migration (entries 1 and 2). Exploiting instead a catalyst prepared with NPF-*t*-Bu in the coupling of *t*-Bu-vinyl tosylate **3** resulted in a 10:9 ratio in favor of the 1,1-disubstituted alkene (entry 3). However, again in the case of vinyl phosphate **8**, no sign of the rearranged product could be detected (entry 4).

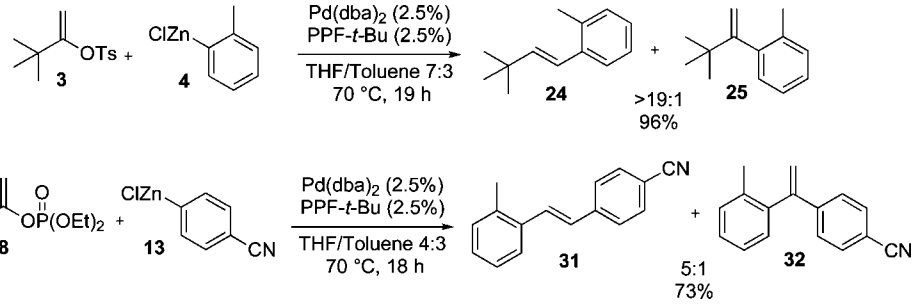
TABLE 3. Negishi Couplings with NPF-*t*-Bu as the Ligand



Entry	Electrophile	Nucleophile	Conversion (%)[a]	Yield (%)[b]	Ratio A:B[a]	Cmpd No.
1	**3** R = *t*-Bu	 **11**	100	88	10:1	**14/15**
2	**8** R = *o*-tolyl	**11**	100	n.d.[c]	4:3	**16/17**
3	**9** R = Cy	**11**	100	67	2:1	**18/19**
4	**3** R = *t*-Bu	 **12**	100	87	10:1	**20/21**
5	**9** R = Cy	**12**	100	71	5:2	**22/23**
6	**3** R = *t*-Bu	 **4**	100	76	10:1	**24/25**
7	**8** R = *o*-tolyl	**4**	100	87	15:1	**26/27**
8	**9** R = Cy	**4**	92	70	5:1	**6/7**
9	**10** R = Ph	**4**	92	83	1:2	**35/28**
10	**3** R = *t*-Bu	 **13**	100	47	10:1	**29/30**
11	**8** R = *o*-tolyl	**13**	73	68	>19:1	**31/32**
12	**9** R = Cy	**13**	94	55	5:1	**33/34**

[a] Conversion and ratio determined by ^{1}H NMR spectrum of crude reaction mixture. [b] Isolated yields. [c] Not determined.

SCHEME 2

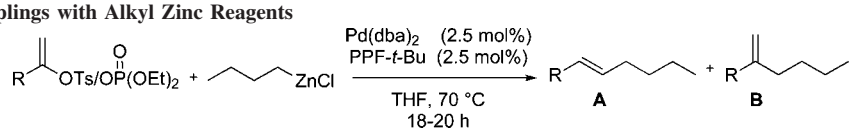


The temperature effect on the 1,2-migration was examined in the Negishi coupling between the alkenyl tosylate **3** and *n*-butyl zinc chloride applying NPF-*t*-Bu as the ligand, the results of which are shown in Table 5. Quite clearly, lowering the reaction temperature resulted in a reduction of the ratio between the 1,2-migrated and the normal coupling products.

Finally, several couplings were performed with two aryl Grignard bromides to examine the effect of increasing the nucleophilicity of the aryl metal reagent (Table 6). These reactions performed best in toluene as earlier reported,[4] where in THF poorer coupling yields were observed, although with no change in the distribution of the two coupling products. Here too, the normal coupling products were favored in the four cases, which is the opposite preference for the coupling reactions with the corresponding aryl zinc reagents. Even in the same reaction earlier studied by Hartwig,[4] though with PPF-*t*-Bu as the ligand, migration was not the favored pathway (entry 4).

Mechanistic Considerations. In this study on the 1,2-migration in the Negishi couplings, several main conclusions can be made on the factors controlling this unsual rearrangment.

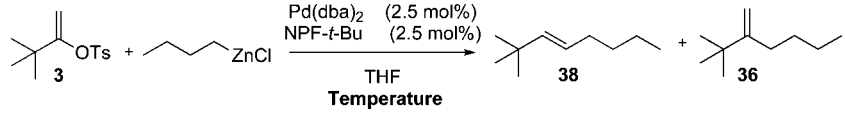
TABLE 4. Negishi Couplings with Alkyl Zinc Reagents



Entry	Electrophile	Ligand	Conversion (%)[a]	Yield (%)[b]	Ratio A:B[a]	Cmpd No.
1	**3** R = *t*-Bu	PPF-*t*-Bu	100	85	0:1	**36**
2	**8** R = *o*-tolyl	PPF-*t*-Bu	100	96	0:1	**37**
3	**3** R = *t*-Bu	NPF-*t*-Bu	100	58	9:10	**38/36**
4	**8** R = *o*-tolyl	NPF-*t*-Bu	100	86	0:1	**37**

[a] Conversion and ratio determined by ^{1}H NMR spectrum of crude product. [b] Isolated yields.

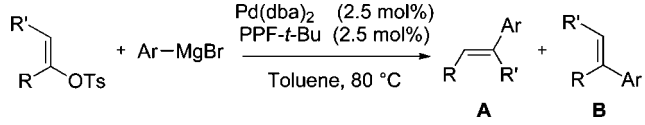
TABLE 5. Temperature Effect on the 1,2-Migration

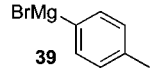
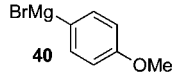


Entry	Temperature (°C)	Ratio **38**:**36**[a]	Yield (%)[b]
1	40	23:77	62
2	55	36:64	29
3	70	47:53	58

[a] Ratio determined by ^{1}H NMR spectrum of crude product. [b] Isolated yield.

TABLE 6. Kumada−Corriu Couplings with 1,2-Migration



Entry	Electrophile	Nucleophile	Time	Yield (%)[a]	Ratio A:B[b]	No.
1	**3** R = *t*-Bu, R'= H	 **39**	30 min.	63	1:10	**20/21**
2	**9** R = Cy, R'= H	**39**	35 min.	91	0:1	**23**
3	**3** R = *t*-Bu, R'= H	 **40**	70 min.	80	1:19	**14/15**
4	**1** R = *i*-Pr, R'= Me	**39**	1.5 h.	77	1:4	**2/41**

[a] Isolated yield. All reactions proceeded with full conversion. [b] Ratio determined by ^{1}H NMR spectrum of crude product.

First, the nature of the organometallic species has a substantial influence on the efficacy of the 1,2-migration for this cross-coupling reaction catalyzed by a palladium−JosiPhos complex. Essentially, the less nucleophilic the coupling reagent is, the greater its tendency for promoting the 1,2-migration.[13]

Second, the 1,2-migration is profoundly dependent on the structure of the starting alkenyl tosylate/phosphate. As observed in our studies on the Mizoroki−Heck reaction, vinyl tosylates and phosphates bearing a quaternary alkyl C1 substituent led to products of rearrangement.[6,7] Whereas increased sterical bulk at this position seems to favor the β-hydride elimination step, there are some observations that need further exploration. For example, the cyclohexyl vinyl tosylate **9**, which incorporates a secondary alkyl substituent at C1 of the electrophile, reacts cleanly with the aryl zinc chlorides promoted by a catalyst with either PPF-*t*-Bu or its naphthalene equivalent. Yet, no coupling could be encouraged with 1-isopropyl vinyl tosylate or the structurally similar alkenyl tosylate **1** bearing a methyl group at C2. In both cases, the starting tosylates were fully recovered. The absence of reactivity for these cases is difficult to understand considering that both vinyl tosylates **1** and **9** underwent Kumada−Corriu couplings with an aryl Grignard reagent using the JosiPhos ligand, PPF-*t*-Bu (Table 6).[4]

The 1,2-migrated product is not the favored product in the coupling of phenyl vinyl phosphate **10** with an aryl zinc reagent using either PPF-*t*-Bu or NPF-*t*-Bu as the ligand. The stability of a η^3-benzyl−metal complex, which is formed after the

(13) Efforts were made to couple either *p*-tolyl or *p*-methoxyphenyl trimethylstannane with 1-cyclohexyl vinyl tosylate, with the presence of lithium chloride, with the expectation that cross-coupling with less reactive organotin compounds would lead to higher preferences for the 1,2-disubstituted alkene compared to that observed for the corresponding zinc reagents. Nevertheless, the reaction conditions employed for the described Negishi couplings were not effective for promoting cross-couplings with the aryltin compounds. Further work is ongoing to identify suitable conditions which may promote migrations in the Kosugi−Migita−Stille couplings.

oxidative addition step, may retard the β-hydride elimination step.[14] However, increasing the steric bulk of the C1-aryl group with an *ortho*-substituent as with the *o*-tolyl vinyl phosphate **8** disfavors formation of the η^3-benzyl−metal intermediate and thereby promotes the elimination step. This trend was also observed in our studies on the 1,2-migration in the Mizoroki−Heck coupling.[7]

Third, a large ligand effect was noted for these Pd-catalyzed cross-couplings with the alkenyl tosylates and phosphates tested. The JosiPhos ligands, generally considered to display bidentate metal binding properties,[15] can promote these 1,2-migrations and with high efficiency depending on the starting electrophile. In our work on the same rearrangements for the Mizoroki−Heck reactions, the most effective catalyst systems were formed with a sterically encumbered and electron-rich monodentate phosphine, such as tri-*tert*-butylphosphine. In our explanation,[6] we invoked the intermediacy of a tricoordinated Pd(II) species after the oxidative addition step due to the sterically demanding trialkylphosphine ligand.[9b,16] Hence, an empty coordination site on the palladium nucleus is secured, which is necessary for the concominant β-hydride elimination step.

On the other hand, the bidentate nature of the JosiPhos ligands should inhibit the hydride elimination step by the opposite principle in that no vacant site on the metal center will be available due to coordination of both phosphino groups of the ligand to palladium center. This is observed when DPPF is exploited as a ligand for the Negishi couplings where no migration is observed.[10,17] Furthermore, a recent and extensive study performed by Hartwig and co-workers on the amination of aryl and heteroaryl halides revealed that palladium complexes generated from JosiPhos ligands and in particular with CyPF-*t*-Bu are highly effective catalysts for aminations of heteroaryl and aryl halides.[15a] The efficiency of these catalysts for these C−N bond forming reactions was in part attributed to the rigid backbone of the ligand reinforcing a tight binding to the metal center. Yet, the observations of 1,2-migration for the Negishi couplings in this study and that of Hartwig and co-workers in the Kumada−Corriu reaction suggest that the JosiPhos ligands may also exhibit monodentate character if the β-hydride elimination mechanism is operating for these migrations.

There is an alternative mechanism for the β-hydride elimination with a chelating diphosphine ligand, involving first dissociation of the tosylate from the metal center to generate a cationic vinyl complex as that observed for the Mizoroki−Heck reaction with electron-rich olefins.[18] However, under the reaction conditions used in these Negishi reactions, up to 30 equiv of LiCl are generated in solution relative to the Pd-catalyst which would trap any cationic intermediate. Support for this assumption was provided by comparing the outcome of coupling experiments between the aryl zinc reagent **4** with the alkenyl phosphate **8** and the corresponding vinyl chloride (Table 2). Both the yields and the ratios of 1,2-disubstituted olefin versus its 1,1-disubstituted isomer were similar, thereby suggesting that a cationic mechanism is not operating for this migration.[19]

For the Negishi couplings with aryl zinc reagents, catalysts generated from either PPF-*t*-Bu or NPF-*t*-Bu were more efficient for promoting the 1,2-migration than CyPF-*t*-Bu. We explain this observation by the difference in binding capacity between the two phosphino groups on PPF-*t*-Bu and NPF-*t*-Bu than for the latter ligand. It is highly plausible that the bulky alkyldi-*tert*-butylphosphino unit of these three ligands ensures the formation of a reactive catalyst for the first step of the catalytic cycle involving the demanding oxidative addition of the C−O bond in the vinyl tosylate and phosphate. We have earlier seen that replacement of the di-*tert*-butylphosphino moiety with a dicyclohexylphosphino unit leads to a catalyst which cannot promote these Negishi couplings.[10] After this step, the weaker donating diphenyl- and dinaphthylphosphino groups could temporarily dissociate, providing a trigonally coordinated palladium complex with a vacant site, which represents a situation identical to that proposed for the Mizoroki−Heck coupling with a catalyst generated from tri-*tert*-butylphosphine (Scheme 3).[6,7,20] Subsequent β-hydride elimination will then be possible by the presence of the vacant site on the metal center. Therefore, the rate of the transmetalation will have a marked influence on the degree of β-hydride elimination and subsequent hydropalladation. This model then explains the higher tendency for 1,2-migration with organometallic reagents of low nucleophilicity/reactivity because of a slow transmetalation step.

In general, better catalytic activity and either higher or similar ratios of 1,2- to 1,1-disubstituted olefins were noted employing a palladium complex formed from NPF-*t*-Bu than with PPF-*t*-Bu. Here, the greater sterical bulk of the dinaphthylphosphino group compared to that of the diphenylphosphino moiety allows NPF-*t*-Bu to operate as a more sterically hindered monodentate ligand. Electronic effects do not appear to be important, as the introduction of electron-withdrawing groups on the phenyl ring of PPF-*t*-Bu should lead to increased isomerization compared to PPF-*t*-Bu. Yet, the opposite was observed with the PPF-*t*-Bu analogue possessing a *p*-substituted trifluoromethyl group (Table 1, entry 2).

The higher degree of migration observed at increased reaction temperatures (Table 5) also provides support for this mechanism.

(14) (a) Roberts, J. S.; Klabunde, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 2509. (b) Gatti, G.; Lopez, J. A.; Mealli, C.; Musco, A. *J. Organomet. Chem.* **1994**, *483*, 77. (c) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601. (d) Rix, F. C.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **1996**, *118*, 2436. (e) LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 906. (f) Nozaki, K.; Komaki, H.; Kawashima, Y.; Hiyama, T.; Matsubara, T. *J. Am. Chem. Soc.* **2001**, *123*, 534. (g) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166. (h) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104.

(15) For some applications of JosiPhos ligands in Pd-catalyzed C−heteroatom bond forming reactions, see: (a) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (b) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (c) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194. (d) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704.

(16) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184.

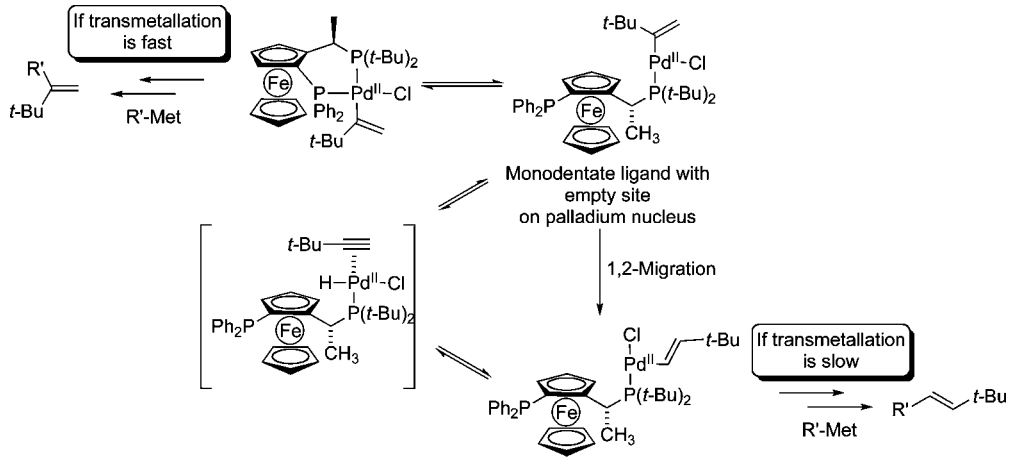
(17) It should be noted that DPPF has also been reported to be a ligand with a capacity to bind Pd(II) either with one phosphorus atom or with two phosphorus atoms as demonstrated for example by Cabri et al. Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santo, R. *J. Org. Chem.* **1991**, *56*, 5796. Nevertheless, DPPF does not promote the 1,2-migration in these Negishi reactions, suggesting that certain JosiPhos ligands may possess a greater tendency for monodentate character than DPPF.

(18) For a few papers on the topic of the Mizoroki−Heck reaction with electron-rich alkenes, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970. (d) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751. (f) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558. (g) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Organometallics* **2007**, *26*, 1757.

(19) There is additionally another possible mechanism involving base-promoted elimination of the alkenyl tosylate or phosphate that could also be invoked followed by addition of the organometallic reagent. However, in this scenario, it would be expected that greater levels of the 1,2-disubstituted alkene would be formed employing the more nucleophilic and most likely also more basic organometallic reagents. Yet, the opposite trend is observed in many of these coupling reactions.

(20) Lindhardt, A. T.; Skrydstrup, T. *Chem. Eur. J.* **2008**, *14*, 8756.

SCHEME 3



In general, it would be expected that the rearrangement, representing a unimolecular reaction, is favored at lower temperatures, whereas as the bimolecular transmetalation is favored at higher reaction temperatures. If this were the case, then the unrearranged process would be favored at higher reaction temperatures. Yet the opposite is observed, thereby indicating that phosphine dissociation may be important for the migrations observed.

Nevertheless, whereas these observations lend support to this mechanistic proposal, rigorous experimental support is still required to rule out alternative pathways involving β-hydride elimination. For example, if transmetalation is fast, providing a vinyl alkyl (or aryl) Pd(II) species, perhaps β-hydride elimination competes with the reductive elmination step rather than taking place before the transmetalation step. Alternatively, β-hydride elimination occurs via a penta-coordinated Pd(II) intermediate promoted with JosiPhos as the ligand but not with DPPF. Work is now underway to distinguish between these different pathways.[21]

Conclusion

In this work, we have reported an initial investigation with the goal of determining the factors that control this unusual rearrangement in the Negishi cross-coupling reaction catalyzed by palladium complexes generated from JosiPhos ligands. Several of these factors, which are believed to be important for the 1,2-migration, include (1) the nucleophilicity of the organometallic reagent, which influences the transmetalation step in direct competition with the intermediate β-hydride elimination of the alkenyl Pd(II) species; (2) the structural features of the vinyl tosylates and phosphates, in which substrates possessing a bulky C1 substituent displayed highest propensity for undergoing the 1,2-migration under the coupling reaction conditions examined; and (3) the structure of the JosiPhos ligand, where both the sterical bulk and choice of substitutents on the ferrocenyl phosphino group greatly influences the catalytic activity of the palladium complex and its capacity to facilitate the 1,2-migration.

Further work is now in progress to provide more details about the factors for this remarkable migration and to investigate reaction conditions which will promote this rearrangement in other transition-metal-catalyzed reactions.

(21) We thank the reviewers for helpful comments and suggestions to this work.

Experimental Section

(*E*)-1-(3,3-Dimethylbut-1-enyl)-2-methylbenzene and 1-(3,-3-Dimethylbut-1-en-2-yl)-2-methylbenzene (24[10] and 25;[10] Table 2, entry 6). General Procedure for the Negishi Coupling Using PPF-*t*-Bu as Ligand. 3,3-Dimethyl but-1-en-2-yl tosylate (127.2 mg, 0.50 mmol), PPF-*t*-Bu (6.8 mg, 0.013 mmol), and $Pd(dba)_2$ (7.2 mg, 0.013 mmol) were dissolved in 1.0 mL of THF. A 0.5 M solution of 2-methylbenzene zinc chloride in THF (1.5 mL, 0.75 mmol) was added, and the mixture was reacted for 20 h at 70 °C. NMR analysis of the crude reaction mixture provided a >19:1 ratio of migrated/nonmigrated products. The crude product was purified by flash chromatography on silica gel using pentane as eluent. This afforded 61.0 mg of the major isomer (70% yield) as a colorless oil.

(*E*)-3,3-Dimethyl-1-(2-methylphenyl)butene: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, 1H, J = 6.8 Hz), 7.21−7.15 (m, 3H), 6.54 (d, 1H, J = 16.0 Hz), 6.15 (d, 1H, J = 16.0 Hz), 2.38 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.5, 137.4, 135.2, 130.2, 126.8, 126.1, 125.6, 122.5, 33.7, 29.8, 19.9; GC−MS $C_{13}H_{18}$ [M] calcd 174, found 174.

3,3-Dimethyl-2-(2-methylphenyl)butene: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.21−7.14 (m, 2H), 7.11 (td, 1H, J = 7.6, 2.0 Hz), 7.05 (dd, 1H, J = 7.2, 1.2 Hz), 5.31 (d, 1H, J = 2.0 Hz), 4.77 (d, 1H, J = 2.0 Hz), 2.26 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.0, 142.7, 136.0, 130.1, 129.6, 126.5, 124.5, 112.4, 37.1, 30.0, 20.7; GC−MS $C_{13}H_{18}$ [M] calcd 174, found 174.

(*E*)-4-(2-Methylstyryl)benzonitrile and 4-(1-*o*-Tolylvinyl)-benzonitrile (31 and 32;[10] Table 3, entry 11). General Procedure for the Negishi Coupling Using NPF-*t*-Bu as Ligand. *o*,*o*-Diethyl 1-*o*-tolylvinyl phosphate (135.1 mg, 0.50 mmol), NPF-*t*-Bu (8.0 mg, 0.013 mmol), and $Pd(dba)_2$ (7.2 mg, 0.013 mmol) were dissolved in 1.0 mL of THF. A 0.5 M solution of 4-cyanophenyl zinc chloride in THF (1.5 mL, 0.75 mmol) was added, and the mixture was reacted for 18 h at 70 °C. NMR analysis of the crude reaction mixture provided a >19:1 ratio of migrated/nonmigrated products. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/pentane (2:3) as eluent. This afforded 74.5 mg of the major isomer (68% yield) as a colorless oil.

(*E*)-4-(2-Methylstyryl)benzonitrile: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.56 (m, 5H), 7.46 (d, 1H, J = 16.0 Hz), 7.26−7.22 (m, 3H), 6.99 (d, 1H, J = 16.0 Hz), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.3, 136.4, 135.5, 132.6, 130.8, 130.3, 128.6, 128.2, 127.1, 126.5, 125.7, 119.2, 110.7, 20.0; GC−MS $C_{16}H_{13}N$ [M] calcd 219, found 219.

4-(1-*o*-Tolylvinyl)benzonitrile: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.8 Hz), 7.31−7.19 (m, 4H), 5.88 (d, 1H, J = 0.8 Hz), 5.38 (d, 1H, J = 0.8 Hz), 2.03

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.4, 145.3, 140.4, 136.1, 132.5, 130.6, 130.2, 128.4, 127.3, 126.3, 119.1, 118.2, 111.3, 20.3; GC−MS $C_{16}H_{13}N$ [M] calcd 219, found 219.

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, the Danish Natural Science Research Council, the Carlsberg Foundation, the Lundbeck Foundation, the OChem and iNANO graduate schools, and the University of Aarhus. Solvias is thanked for generous gifts of the JosiPhos ligands.

Supporting Information Available: Experimental details for all reactions. Copies of ^{1}H NMR and ^{13}C NMR spectra for all new coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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