CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201203646

Selective Arylation and Vinylation at the α Position of Vinylarenes

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Abstract: In intermolecular Heck reactions of styrene and vinylarenes, the aryl and vinyl groups routinely insert at the β position. However, selective insertion at the α position has been very rare. Herein, we provide a missing piece in the palette of Heck reaction, which gave >20:1 α selectivity. The key to our success is a new ferrocene 1,1′-bisphosphane (dnpf) that carries 1-naphthyl groups. Our mechanistic studies revealed that the high α selectivity is partly attributable to the steric effect of dnpf. The rigid and bulky 1-naphthyl groups of dnpf sterically disfavor β insertion.

Keywords: Heck reaction · olefin insertion · palladium · phosphanes · regioselectivity · styrene

Introduction

The Mizoroki–Heck reaction usually refers to Pd-catalyzed arylation and vinylation of olefins by aryl or vinyl halides and sulfonates. This reaction has become an important tool in the preparation of pharmaceutically active ingredients, agrochemicals, and advanced materials.[1] In intermolecular Heck reactions, a key issue is the control of regioselectivity. For olefins that carry a significant electronic difference between two vinylic sites,[2] such as acrylates[3] and vinyl ethers,[4] high regioselectivity is commonplace by manipulating the catalysts and reaction conditions.

In the Heck reaction of aryl halides and styrene, terminal (β) insertion is almost exclusively observed, thus leading to (*E*)-stibenes [Scheme 1, Eq. (1)].[3] The use of more bulky, electron-rich ligands, such as P(*t*Bu)$_3$, even allows unactivated aryl chlorides to be used [Scheme 1, Eq. (2)].[5] These processes involve neutral Pd complexes of styrene supported by a phosphane ligand before insertion. The transition state for styrene insertion is relatively late, which leads preferentially to more stable Pd–benzyl complexes and predominantly β selectivity.

This type of β selectivity was also ubiquitously observed under many Heck variants, such as phosphane-free conditions,[6] decarboxylative, decarbonylative, and oxidative Heck reactions [Scheme 1, Eqs (3)–(6), respectively].[7] Under some conditions without using phosphanes, an anionic ligand, such as halide or acetate ions, will occupy the position of the phosphane to form anionic styrene complexes. The same reason based on the late transition state can be applied to explain the β selectivity in the ionic pathway.

Reversal of β selectivity in the insertion of styrene and other aryl olefins proved to be very difficult.[8] For example, Cabri reported that in reactions of aryl triflates and styrene, cationic [Pd(aryl)(styrene) (dppp)] complexes were responsible for olefin insertion.[9] However, the insertion transition state of this cationic complex is relatively early. Thus, the α-insertion transition state will have a significant partial positive charge at the benzylic position, which is resonance stabilized. The cationic pathway did give some α-insertion product, but the α/β regioselectivity was too low to be synthetically useful [Scheme 1, Eq. (7)].[9–13] Thus, the electronic effect alone seems insufficient to bias the insertion in the cationic pathway to predominantly the α position.

Herein, we report a significant improvement in the intermolecular Heck reaction of aromatic olefins with >20:1 α/β selectivity in most cases. The key to this success is the use of the new ferrocene ligand 1,1′-bisphosphane (dnpf) developed by our group recently [Scheme 1, Eq. (8)].[18]

The corresponding Heck products 1,1-diarylethylenes are common core structures in medicinal chemistry, exemplified by anticancer agents bexarotene and isocombretastatins A (Figure 1). Bexarotene is a selective agonist for retinoid X receptors and has been used to treat T-cell lymphoma, lung cancer, breast cancer, and Kaposi sarcoma.[14] Combretastatins A are natural products that contain the (*Z*)-1,2-diarylethene scaffold, and they are nanomolar inhibitors of tubulin polymerization. Isocombretastatins A are structural isomers and exhibit similar or higher potency.[15] 1,1-Diarylethylenes are also key intermediates in the synthesis of bioactive natural products[16] and other potential therapeutics.[17] Some of these compounds were prepared by cross-coupling of α-halogenated or α-metallated vinylarenes. Our Heck reaction can directly use simple vinylarenes and circumvent the need to prepare these reagents.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203646.

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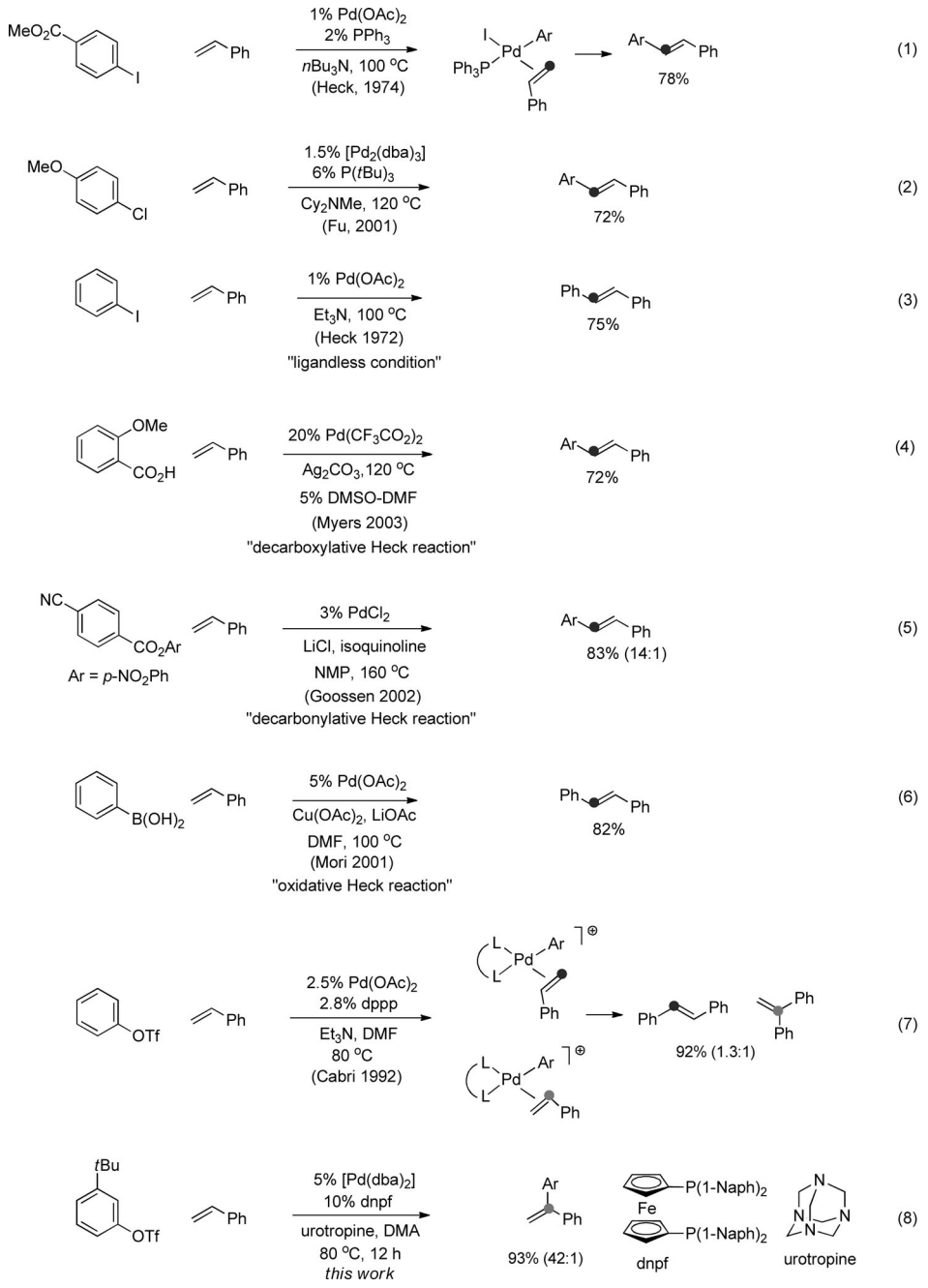

Scheme 1. Overview and results of the Heck reaction of vinylarenes. dba = dibenzylideneacetone, DMSO = dimethyl sulfoxide, dppp = 1,3-bis(diphenylphosphino)propane, NMP = *N*-methylpyrrolidone.

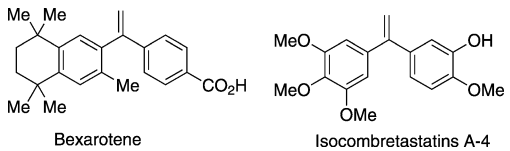

Figure 1. Anticancer agents containing the 1,1-diarylethylene motif.

Results and Discussion

Initially, we studied the model reaction between *meta*-(*tert*-butyl)phenyl triflate and styrene and searched for suitable bisphosphanes that can induce high α selectivity, The same conditions as employed in Equation (8) in Scheme 1 were used, and the results are summarized in Figure 2. A new ferrocene bisphosphane with 1-naphthyl groups, which we abbreviated as "dnpf", proved to be exceptionally active and selective.[18] Thus, the Heck product was obtained almost quantitatively after 12 h at 80 °C. The ratio of the desired 1,1-diarylethene versus (*E*)-1,2-diarylethene was determined to be 36:1; furthermore, (*Z*)-1,2-diarylethene was undetected by GC analysis. In comparison, the dppf and dppp ligands provided much lower selectivity (7:1 and 1:1, respectively).

The choice of bases was also important (Figure 3). When common trialkylamines, such as iPr$_2$NEt and Et$_3$N, were used, a significant amount of the reduction byproduct *tert*-butylbenzene was detected.[19] Other amines, such as Proton Sponge (*N*,*N*,*N*′,*N*′-tetramethylnaphthalene-1,8-diamine), 1,4-diazobicyclo[2.2.2]octane (DABCO), and urotropine, did not give any reduction byproduct. In the case of Proton Sponge, the sterically congested nitrogen atoms cannot bind to the Pd center or donate a hydride. For both DABCO and urotropine, their nitrogen atoms are located at bridgeheads of the tricyclic structures. The α-hydrogens of these compounds do not have the right geometry to eliminate and to donate hydrides to the Pd center according to Bredt's rule. Furthermore, weak inorganic bases, such as Li_2CO_3 and Na_2CO_3, worked very well and can replace urotropine.

As judged from solvent screening (Table 1), the model reaction worked very well in many ethereal solvents (i.e., THF, dioxane, DME, and diglyme) and amide solvents (DMA, DMF, and NMP). In general, >90% yield and >20:1 selectivity were obtained. For example, in DMA and

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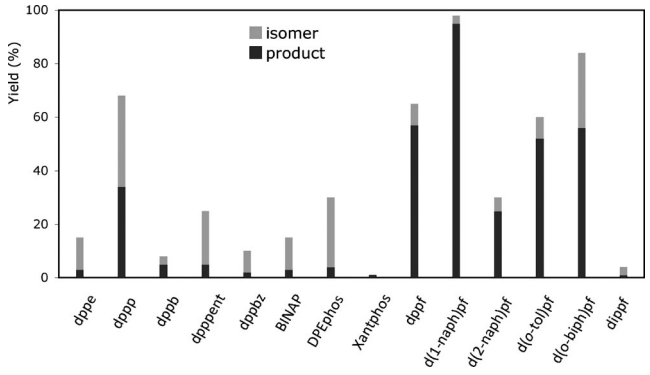


Figure 2. Influence of chelating ligands on the model Heck reaction. Similar conditions to those in Equation (8) of Scheme 1 were used. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dippf = 1,1′-bis(diisopropylphosphino)ferrocene, dppb = 1,4-bis(diphenylphosphino)butane, dppbz = 1,2-bis(diphenylphosphino)benzene, dppe = 1,2-bis(diphenylphosphino)-ethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

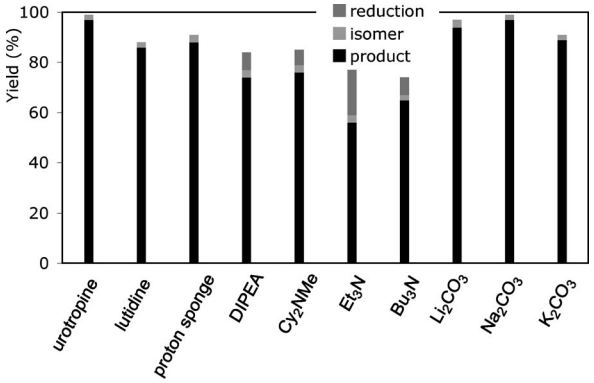


Figure 3. Influence of the bases on the model Heck reaction. Similar conditions to those in Equation (8) of Scheme 1 were used.

Table 1. Effect of the solvent on the model Heck reaction.[a]

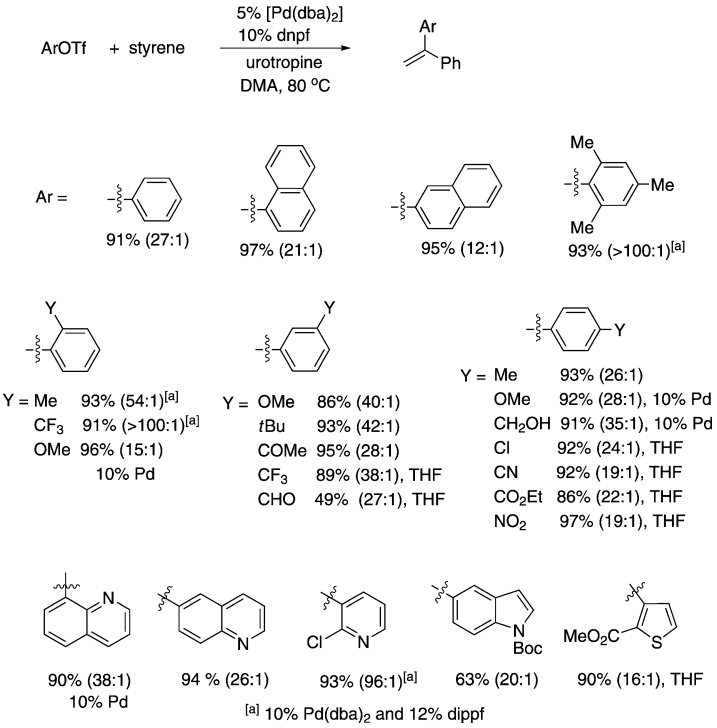
Entry	Solvent	Conversion [%]	Yield [%]	Selectivity
1	DMA	100	96	36:1
2	DMF	100	97	24:1
3	NMP	100	93	25:1
4	DMSO	100	96	17:1
5	THF	100	94	42:1
6	dioxane	97	86	33:1
7	DME	97	96	39:1
8	triglyme	100	100	35:1
9	toluene	53	47	27:1
10	DCE	26	26	42:1

[a] Similar conditions to those in Equation (8) of Scheme 1 were used. DCE = dichloroethene, DMA = dimethylacetamide, DME = 1,2-dimethoxyethane.

THF, the selectivities obtained were 36:1 and 42:1, respectively (Table 1, entries 1 and 5). In toluene and 1,2-dichloroethane, the model reaction was much slower (Table 1, entries 9 and 10).

With regard to the choice of Pd source, [Pd(dba)$_2$], [Pd$_2$(dba)$_3$], and Pd(OAc)$_2$ gave very similar results. Furthermore, when 1.2 equivalents of styrene were used, the yield and the selectivity in DMA dropped slightly (82% yield and 28:1 selectivity).

Next, we examined the scope of aryl triflates in Pd/dnpf-catalyzed reactions of styrene. Most reactions proceeded smoothly in good yield and >20:1 selectivity (Scheme 2).



Scheme 2. Aryl and heteroaryl triflates in Heck reactions with styrene. OTf = triflate.

Both electron-donating and -withdrawing groups on aryl triflates could be present. THF was a better solvent than DMA for most electron-poor aryl triflates. Polar groups, such as nitrile, nitro, ester, aldehyde, ketone, and even free alcohol, could be tolerated. In addition, an aromatic chloride remained intact in the presence of ArOTf. Some heteroaryl triflates derived from pyridine, quinoline, thiophene, and indole also worked well. Notably, for some *ortho*-substituted aryl triflates, dippf was found to be more active than dnpf. For example, Pd/dippf can even catalyze the Heck reaction of very hindered 2-mesityl triflate to give 1,1-diarylethene almost exclusively.

The same conditions could be applied to the Heck reaction of vinyl triflates to give multiply substituted 1,3-dienes, which otherwise would require cross-coupling of α-metalated vinylarenes. Various vinyl electrophiles with steric and electronic perturbations efficiently coupled with styrene (Scheme 3). The α selectivity was satisfactory in most cases. Even hindered trisubstituted alkenyl groups could insert with high selectivity. Furthermore, the minor isomers could be removed by flash chromatography.

We also examined the scope of vinylarenes by using *para*-tolyl triflate as the model aryl electrophile (Scheme 4). The

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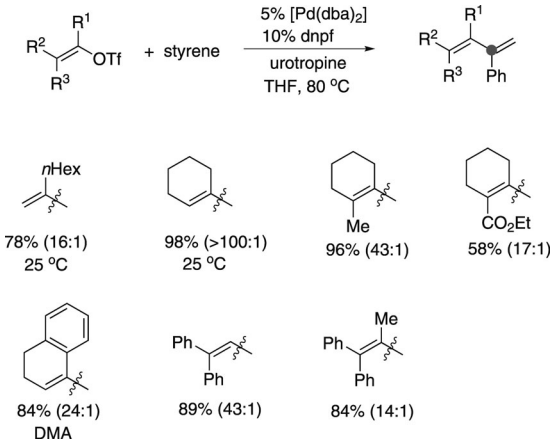
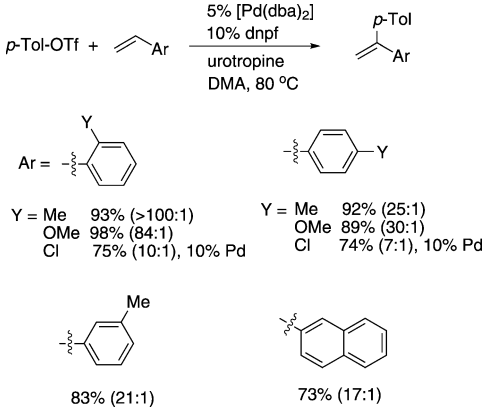


Scheme 3. Vinyl triflates in the Heck reaction of styrene.



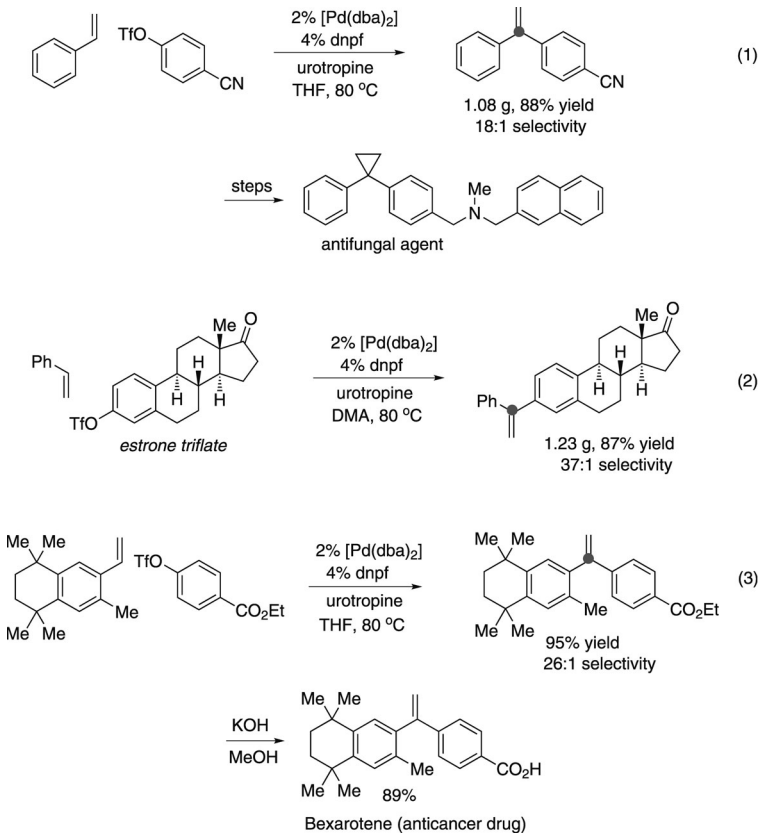
Scheme 4. The Heck reaction of various vinylarenes.

Pd/dnpf catalyst could tolerate *ortho* substituents on vinylarenes. For electron-neutral and -rich vinylarenes, the selectivity obtained remained >20:1 in most cases. However, for electron-poor vinylarenes, such as chlorinated styrenes, the selectivity obtained dropped to approximately 10:1. When the *para*-CF_3 group was present on styrene, the selectivity obtained was 7:1. The results can be understood by considering the involvement of the partial positive charge at the benzylic position in the transition states that lead to α insertion.[10,20] The electron-withdrawing groups on styrene destabilize the insertion transition state, thus decreasing the α selectivity. We also attempted to couple a disubstituted olefin *Z*-β methylstyrene; however, there was no reaction.

The new method can be readily scaled up without much optimization of the conditions. For example, in the presence of 2 mol% of Pd catalyst, *para*-cyano-1,1-diphenylethene can be prepared on a gram scale in 18:1 selectivity [Scheme 5, Eq (1)]. The product was used to prepare an antifungal agent.[21] Similarly, the Heck reaction of 3-estrone triflate and styrene can be conducted to produce 1.2 grams of the desired isomer with 37:1 selectivity [Scheme 5, Eq (2)]. The minor isomer can be completely removed by flash chromatography. Bexarotene is an anticancer drug and can be assembled in 26:1 selectivity. Subsequent hydrolysis of the ester group afforded the drug in good yield [Scheme 5, Eq. (3)].

To determine the origin of the high α selectivity from the Pd/dnpf catalyst, we prepared the oxidative addition complex of PhI. Treatment of [Pd(Ph)(I)(dnpf)] with AgOTf in the presence of five equivalents of styrene (RT, 12 h) led to 70% yield of the Heck product with 55:1 selectivity (Scheme 6).[22]

Single-crystal X-ray diffraction analysis of the complex [Pd(Ph)(I)(dnpf)] showed some unusual structural features (Figure 4).[23] First, the ferrocene backbone of dnpf adopts



Scheme 5. Applications of regioselective Heck reactions.

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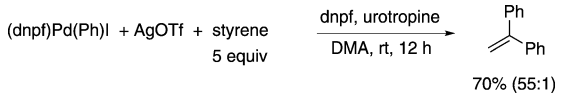

Scheme 6. Stoichiometric reaction of styrene insertion into the cationic [Pd(Ph)(dnpf)] complex.

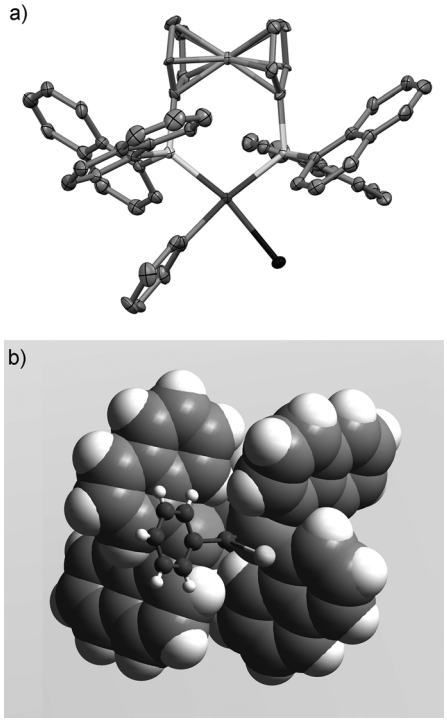

Figure 4. a) ORTEP drawing of [Pd(Ph)(I)(dnpf)] (top view) with 50% thermal ellipsoid probability with the hydrogen atoms omitted for clarity. b) Front view with the dnpf ligand in a space-filling representation and the {Pd(Ph)(I)} fragment in a ball-and-stick drawing. Key bond angles [°]: <P1(right)-Pd-P2(left) 103, <I-Pd-C(Ph) 82, <P1-Pd-C(Ph) 164, <P2-Pd-I 165.

an almost eclipsed conformation, unlike the staggered ones commonly seen in related dppf complexes.[24] This unusual conformation seems to be stabilized by edge-to-edge π interactions between two naphthyl rings in dnpf, which are absent in dppf complexes. Second, both the phenyl ring and iodine atom are forced approximately 15° above and below the coordination plane defined by P1-Pd-P2, another feature absent in [Pd(Ar)(X)(dppf)] complexes. This deviation is caused by steric repulsion with the neighboring naphthyl groups. In transition states of β aryl insertion, styrene will occupy the position of the iodide moiety and experience severe steric repulsion with the ligand naphthyl groups.

We conducted DFT calculation by using the PBE1PBE method on the insertion step of cationic [Pd(Ph)(styrene)-(dnpf)] conformers. We identified all four ground-state (GS) structures for the styrene complexes (Figure 5). In the optimized structure, the near-eclipsed ferrocene backbone and distortion of square planarity were reproduced. In all cases, the C=C double bond was oriented perpendicular to the co-

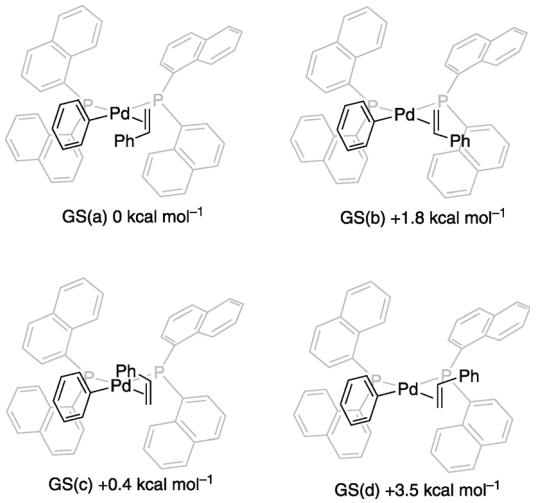

Figure 5. Four ground-state structures of cationic complexes of [Pd(Ph)-(styrene)(dnpf)] and their relative energy. The positive charge and ferrocene backbone are omitted for clarity.

ordination plane. GS(b) and GS(d) were destabilized by steric repulsion between the phenyl ring of styrene and the naphthyl groups of dnpf.

We also allocated transition states (TSs) for the aryl insertion of cationic [Pd(Ph)(styrene)(dnpf)] complexes (Figure 6). By assuming fast pre-equilibrium between the olefin complexes, the regioselectivity of the Heck reaction will be dictated by the relative energy of the TSs instead of insertion barriers. All four insertion TSs were located, two for internal insertion and two for terminal insertion. The two TSs for terminal insertion were greatly destabilized by repulsion between the phenyl ring of styrene and the naphthyl group of dnpf. In addition, TS(internal) was 3.5 kcal mol^{-1} lower in energy than TS(terminal)′, which collaborates reasonably well with the observed selectivity.

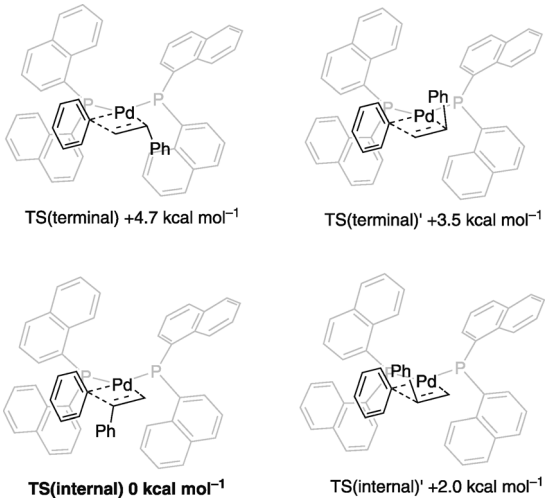

Figure 6. Four transition states for styrene insertion in cationic [Pd(Ph)-(styrene)(dnpf)] complexes and their relative energy. The positive charge and ferrocene backbone are omitted for clarity.

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Thus, the predominant pathway for aryl insertion starts from styrene complex GS(c) in Figure 5. A counterclockwise rotation of styrene results in TS(internal) in Figure 6. The corresponding insertion barrier was determined to be relatively low (i.e., 8.9 kcal mol^{-1}), which is consistent with olefin insertion in the stoichiometric reaction at room temperature (Scheme 6). We suspect that the rate-limiting step of the catalytic cycle may be oxidative addition of aryl triflates with Pd^0/dnpf. In the presence of the dba ligand, dba can bind strongly to the active catalyst Pd^0/bisphosphane and can decrease the actual concentration of Pd^0/dnpf.[25]

In natural bond orbital (NBO) analysis of TS(internal) in Figure 6, we found that the positive charge was highly delocalized in the entire structure, instead of localized on a few atoms. In TS(internal), the Pd center carries a partial charge of +0.09, α-(CH) fragment of styrene +0.13 and β-(CH_2) fragment −0.04. The small, but significant, amount of partial positive charge at the benzylic site confirms that the C−C bond formation is late in the TS.

In ligand screening, dppf was less selective than dnpf in our model Heck reaction (Figure 2). Our calculations also support the experimental observations. Figure 7 shows all four insertion TSs for cationic [Pd(Ph)(styrene)(dppf)] complexes and their relative energies. The energy difference between TS(internal) and TS(terminal)′ was much smaller (0.5 kcal mol^{-1}).

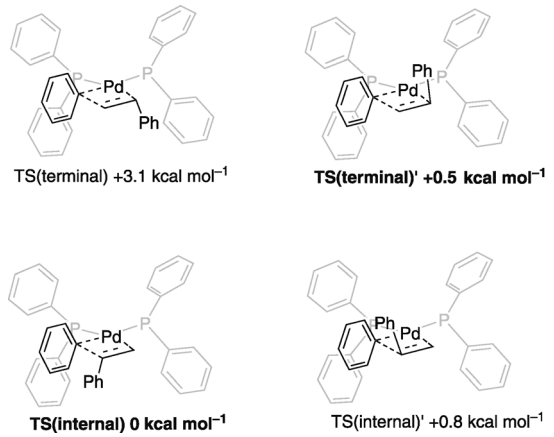

Figure 7. Four transition states for styrene insertion in cationic [Pd(Ph)-(dppf)(styrene)] complexes and their relative energy. The positive charge and ferrocene backbone are omitted for clarity.

Thus, the higher selectivity obtained with the Pd/dnpf catalyst can be attributed to two factors. One is electronic stabilization of the TS for internal insertion in the cationic pathway. The other is steric destabilization of TS for terminal insertion by the rigid dnpf ligand.

Conclusion

In summary, we have developed a general method for the Heck reaction of aromatic olefins, in which the aryl or vinyl groups insert selectively at the α position. In most cases, the desired isomers were produced in >95% purity, and the minor isomers could be removed by flash chromatography. The use of the bisphosphane dnpf was the key to the unprecedented generality and selectivity. Our mechanistic studies and DFT calculations revealed that the high α selectivity originated from a combination of electronic and steric effects. Unlike the dppf ligand, dnpf can form a rigid and crowded environment in the coordination sphere, which sterically disfavors β insertion.

Experimental Section

General procedure for the regioselective Heck reaction (0.5 mmol scale): A dry 25 mL reaction tube containing a magnetic stirring bar was sequentially charged with [Pd(dba)$_2$] (14.3 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol), and dry DMA (or THF; 1.25 mL) in an argon-filled glove box. After stirring at room temperature for 15 min, an organic triflate (0.50 mmol), vinylarene (1.0 mmol), *n*-dodecane (50 μL; GC standard), and urotropine (140 mg, 1.0 mmol) were added sequentially. The reaction tube was capped tightly and the reaction mixture was heated with vigorous stirring in an oil bath at 80 °C (external temperature). After the aryl triflate was fully consumed (monitored by GC analysis), the reaction mixture was cooled to room temperature and passed through a pad of silica gel to remove DMA, washing with diethyl ether in most cases. The filtrate was concentrated under reduced pressure and the residue was directly subjected to flash chromatography on silica gel for purification. The major and minor isomers (1,1-diarylethene and substituted (*E*)-stilbene, respectively) were assigned based on ^{1}H NMR spectroscopic analysis and confirmed by GC-MS analysis. The ratio of the two isomers was determined by GC analysis. Note that ^{1}H NMR spectroscopic analysis was unsuitable for the determination of the ratio of the two isomers due to low signal intensity of the minor isomer in the spectra.

As an example, the synthesis of 1-(*meta*-*tert*-butylphenyl)styrene (0.5 mmol scale): [Pd(dba)$_2$] (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction was completed after 13 h at 80 °C. The product was obtained as a colorless oil (111 mg, 93% yield) after flash chromatography with hexane as the eluent. The internal/terminal selectivity of the Heck products in the crude mixture was determined to be 42:1 by GC analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.33 (m, 8H), 7.24–7.22 (m, 1H), 5.56–5.55 (m, 2H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 150.6, 141.7, 141.3, 128.4, 128.2, 127.9, 127.8, 125.7, 125.5, 124.8, 114.1, 34.8, 31.5 ppm; GC-MS (EI): calcd for $C_{18}H_{20}$ [*M*]: 236.16; found: 236.14.

Heck reaction of 3-estrone triflate and styrene (on a gram scale with a vacuum manifold): A dry 25 mL reaction tube containing a magnetic stirring bar was charged with [Pd(dba)$_2$] (46 mg, 0.08 mmol; 2 mol%) and dnpf (121 mg, 0.16 mmol). The atmosphere was switched to argon on a vacuum manifold after three cycles of evacuation and refilling. Degassed DMA (10 mL) was added to the reaction mixture, which was stirred for 15 min at room temperature. The reaction mixture was treated sequentially with styrene (833 mg, 8 mmol, 2 equiv), 3-estrone triflate (1.61 g, 4 mmol), 1-dodecane (0.40 mL, GC standard), and urotropine (1.12 g, 8 mmol). The reaction tube was sealed with a rubber septum and the mixture was heated with vigorous stirring in an oil bath at 80 °C. The aryl triflate was fully consumed after 11 h (monitored by GC analysis). The selectivity of the Heck products in the crude mixture was determined to be 37:1 by GC analysis. After routine workup, the crude mixture was purified by flash chromatography with ethyl acetate/hexane (1:15→1:10). The resulting solid was quickly washed with hexane (10 mL) to remove a small amount of dba to give the pure product as a white solid (1.23 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 5H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 5.43 (s, 1H), 5.40 (s, 1H), 2.91–2.88 (m, 2H), 2.54–2.41 (m, 2H), 2.35–2.31 (m, 1H), 2.19–1.96 (m, 4H), 1.68–1.43 (m, 6H), 0.92 ppm (s, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$): δ = 221.0, 149.9, 141.7, 139.5, 139.1, 136.4, 128.9, 128.4, 128.2, 127.8, 125.9, 125.3, 114.0, 50.7, 48.1, 44.6, 38.3, 36.0, 31.7, 29.5, 26.7, 25.8, 21.7, 14.0 ppm; GC-MS (EI): calcd for $C_{16}H_{28}O$ [*M*]: 356.21; found: 356.17.

Heck reaction of *para*-cyanophenyl triflate and styrene (gram scale): A dry 25 mL Schlenk tube containing a magnetic stirring bar was sequentially charged with [Pd(dba)$_2$] (69 mg, 0.12 mmol; 2 mol%), dnpf (180 mg, 0.24 mmol), and dry THF (15 mL) in an argon-filled glove box. After stirring at room temperature for 15 min, *para*-cyanophenyl triflate (1.51 g, 6 mmol), styrene (1.25 g, 12 mmol), *n*-dodecane (100 mL, GC standard), and urotropine (1.68 g, 12 mmol) were added sequentially. The Schlenk tube was capped tightly and the reaction mixture was heated with stirring in an oil bath maintained at 80°C. An aliquot was taken after 24 h from the reaction mixture under argon. GC analysis indicated the full conversion of the aryl triflate and that the selectivity of the Heck products was 18:1. The mixture was passed through a short pad of silica gel, washing with Et_2O. The filtrate was concentrated and purified by flash chromatography with Et_2O/hexane (1:20) as the eluent to give the desired Heck product as a colorless oil (1.08 g, 88% yield). The minor isomer was completely removed by flash chromatography (monitored by GC analysis). When DMA was used as the solvent, the conversion of the triflate was very low after 12 h (3%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.38–7.34 (m, 3H), 7.30–7.28 (m, 2H), 5.60 (s, 1H), 5.55 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 146.2, 140.3, 132.2, 128.9, 128.6, 128.4, 128.2, 118.9, 116.8, 111.4 ppm; GC-MS (EI): calcd for $C_{15}H_{11}N$ [*M*]: 205.09; found: 205.08.

Synthesis of the ethyl ester of bexarotene: [Pd(dba)$_2$] (5.7 mg, 0.01 mmol, 2 mol%), dnpf (15.1 mg, 0.02 mmol, 4 mol%), and dry THF (1.25 mL) were sequentially charged into a dry 25 mL reaction tube containing a stirring bar in an argon-filled glove box. After stirring for 15 min, *para*-(ethoxycarbonyl)phenyl triflate (149 mg, 0.50 mmol), 2,5,5,8,8-pentamethyl-3-vinyl-5,6,7,8-tetrahydronaphthalene (228 mg, 1.0 mmol), *n*-dodecane (50 μL, GC standard), and urotropine (140 mg, 1.0 mmol) were added sequentially. The reaction tube was sealed tightly with a screw cap and the reaction mixture was heated with vigorous stirring in an oil bath at 80°C. The reaction was complete after 24 h at 80°C (monitored by GC analysis) and the α/β selectivity of the Heck products in the crude mixture was determined to be 26:1. The resulting mixture was passed through a short pad of silica gel, washing with diethyl ether. The filtrate was concentrated and purified by flash chromatography with ethyl acetate/hexane (1:15) as the eluent to give the product as a white solid (180 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97(d, J=8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.13 (s, 1H), 7.08 (s, 1H), 5.81 (d, J = 1.1 Hz, 1H), 5.32 (d, J = 1.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.95 (s, 3H), 1.70 (pseudosinglet, 4H), 1.39 (t, J = 7.1 Hz, 3H), 1.31 (s, 6H), 1.28 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 149.4, 145.6, 144.5, 142.5, 138.2, 132.9, 129.7, 129.5, 128.21, 128.17, 126.7, 116.8, 61.0, 35.37, 35.36, 34.1, 34.0, 32.1, 32.0, 20.1, 14.5 ppm; GC-MS (EI): calcd for $C_{26}H_{32}O_2$ [*M*]: 376.24; found: 376.19.

Synthesis of bexarotene: Degassed methanol (2.0 mL) and 5 M KOH (0.2 mL) were added slowly under argon to the ethyl ester of bexarotene (150 mg, 0.4 mmol) in a 10 mL reaction tube containing a stirring bar. The reaction mixture was heated to reflux in an oil bath with stirring and the reaction was completed after 2 h (monitored by TLC analysis). The reaction mixture was cooled down to room temperature and acidified to pH 2 by the slow addition of 1 M HCl. Methanol was removed on a rotary evaporator and the remaining aqueous layer was extracted with ethyl acetate (10 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The crude product was purified by flash chromatography with ethyl acetate/hexane (1:1) as the eluent to give the product as a white solid (110 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.03 (br s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 7.09 (s, 1H), 5.84 (d, J = 1.1 Hz, 1H), 5.35 (d, J = 1.1 Hz, 1H), 1.95 (s, 3H), 1.71 (pseudosinglet, 4H), 1.31 (s, 6H), 1.28 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 149.3, 146.6, 144.6, 142.5, 138.1, 132.9, 130.5, 128.2 (3 overlapping signals), 126.8, 117.3, 35.36, 35.35, 34.2, 34.1, 32.1, 32.0, 20.1 ppm; MS (ESI): calcd for $C_{24}H_{27}O_2$ [M^-]: 347.20; found: 347.16.

Stoichiometric study of styrene insertion into [Pd(Ph)(I)(dnpf)] in the presence of AgOTf: A 4 mL vial containing a magnetic stirring bar was charged with [Pd(PhI)(dnpf)] (19 mg, 0.020 mmol), dnpf (15.1 mg, 0.020 mmol), and dry DMA (0.5 mL) in an argon-filled glove box. After stirring at room temperature for 5 min, styrene (5 equiv, 10 mg, 0.10 mmol), 1-dodecane (10 μL), AgOTf (5.2 mg, 0.020 mmol), and urotropine (5.6 mg, 0.040 mmol) were added sequentially. The reaction mixture was covered with aluminum foil and was vigorously stirred at room temperature. An aliquot was removed at intervals and passed through a short plug of silica gel. The filtrate was subjected to GC analysis to determine the yield and selectivity of the Heck products. The calibrated GC yields of the Heck product after 1, 2, and 12 h were determined to be 63, 68, and 70%, respectively. The selectivity of 1,1-diphenylethene versus (*E*)-stilbene was determined to 55:1 and remained constant during the course of the reaction.

Acknowledgements

We thank Singapore National Research Foundation (NRF-RF2008–10) and Nanyang Technological University for financial support and Johnson-Matthey for a gift of palladium.

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Received: October 11, 2012
Published online: January 23, 2013

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