

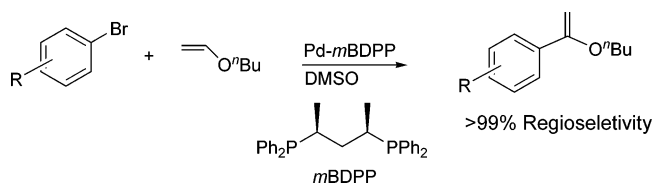
Pd-*m*BDPP-Catalyzed Regioselective Internal Arylation of Electron-Rich Olefins by Aryl Halides

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meso-2,4-bis(diphenylphosphino)pentane (*m*BDPP) has proved to be an effective regiocontrolling ligand for palladium-catalyzed internal arylation by aryl bromides of electron-rich olefins in a common solvent DMSO with no need for any halide scavengers. The arylation of the benchmark electron-rich olefin butyl vinyl ether took place smoothly to afford exclusively α -arylated product with high isolated yields. The better performance of *m*BDPP, compared with that of the commonly used DPPP [1,3-bis(diphenylphosphino)propane], highlights the important but subtle effect of ligand on the regioselectivity of the Heck arylation reactions.

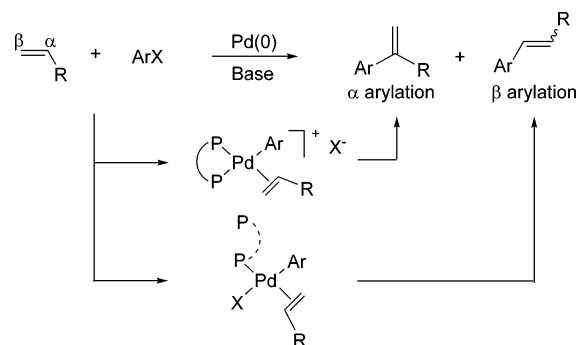
The palladium-catalyzed Heck–Mizoroki reaction has been well-known as one of the most versatile methods for the formation of C–C bonds in synthetic chemistry.¹ Cabri et al proposed that the Heck reaction proceeds via two pathways, a neutral pathway leading to the preferential formation of linear olefins and an ionic counterpart more likely to give rise to branched olefins (Scheme 1).² Not unexpectedly, the occurrence of this chemistry is dependent on the reaction conditions,

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SCHEME 1. Formation of α - and β -Arylation Products in the Heck Reaction and the Key Intermediates



including the properties of the aryl substrate, olefin, and ligand, as well as the solvent.^{1a,2a,3} Among those factors, it is generally believed that monodentate electron-rich phosphine promotes the coupling reaction of aryl halides with electron-deficient olefins to give β -arylated product under neutral conditions,^{1c–e,h,4} while bidentate phosphine facilitates the arylation of electron-rich olefins to afford α -arylated products under “ionic conditions”.^{2,5–7} The ionic conditions here refer to the use of aryl triflates instead of aryl halides as the arylating agents^{2b,6c,8} or the use of stoichiometric silver or thallium salts when aryl iodides or bromides are chosen.^{2b,6e,9} Under such conditions, generation of the key cationic Pd(II)–olefin species is made easy, thereby

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facilitating α -arylation (Scheme 1). However, a drawback of this strategy is that triflates are base-sensitive and thermally labile, and the inorganic additives create new problems, e.g. waste salts, toxicity, and added cost. Recently, we found that the ionic conditions could also be met by simply adopting ionic liquid solvents.^{5,10} Specifically, we showed that electron-rich olefins can be arylated highly regioselectively by aryl halides in such solvents without recourse to any halide scavengers.⁵ It is believed that the ionic medium promotes the formation of the cationic palladium species and hence the branched product. However, there is still a need to develop catalysts that work for a wider range of substrates and function in a broader spectrum of solvents.

As part of our ongoing research aimed at understanding and controlling the regioselectivity of internal arylation of electron-rich olefins, we have attempted to develop more efficient palladium catalysts. A focal point was on new phosphine ligands on the basis of the DPPP [1,3-bis(diphenylphosphino)propane] backbone, as DPPP has proved to be the best ligand of choice for the α -arylation of electron-rich olefins.^{2,5,6c-i} In common solvents, however, catalysis by Pd–DPPP generally affords a mixture of regioisomers.^{3,5b} Herein, we report that *m*BDPP [*meso*-2,4-bis(diphenylphosphino)pentane] in combination with palladium forms an effective catalyst that allows for regioselective α -arylation with aryl bromides of electron-rich olefins in DMSO with no need for an ionic liquid solvent nor for a halide scavenger. It is noteworthy that *m*BDPP has not been applied to the Heck reaction before, although it has been used as an efficient ligand in copolymerization¹¹ and hydrogenation.¹²

Preliminary experiments were performed to examine the effectiveness of the ligand in different solvents, including both molecular solvents and ionic liquid. [bmim][PF₆] was chosen as a representative of the latter. Arylation of the benchmark electron-rich olefin butyl vinyl ether (**2**) with 2-bromonaphthalene (**1a**) was taken as a model reaction. The results are presented in Table 1. As can be seen, among the molecular solvents chosen, DMSO afforded the highest conversion with an exclusive regioselectivity for the α -arylation product **3a** (entry 2). A similar regioselectivity was observed in the ionic liquid [bmim][PF₆]. However this reaction was slower, affording a

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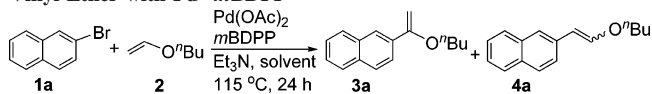
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TABLE 1. Screening Solvents for Regioselective Arylation of a Vinyl Ether with Pd–*m*BDPP^a



entry	solvent	ϵ_r^b	conversion (%) ^c	α/β^c	<i>E/Z</i> ^c
1	[bmim][PF ₆]		87	>99/1	
2	DMSO	46.45	94	>99/1	
3	DMF	36.71	82	54/46	84/16
4	DMAc	37.78	78	50/50	82/18
5	CH ₃ CN	35.94	70	53/47	75/25
6	1,4-dioxane	2.21	29	47/53	80/20
7	toluene	2.38	12	47/53	77/23
8 ^d	DMSO	46.45	50	>99/1	

^a Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), Et₃N (1.5 mmol), Pd(OAc)₂ (2 mol %), *m*BDPP (4 mol %), solvent (1.0 mL). ^b Relative permittivity taken from ref 15. ^c Determined by ¹H NMR; a α/β -ratio of >99/1 was assigned when **4a** was not detected. ^d (*R,R*)-BDPP was used instead of *m*BDPP.

87% conversion under the same reaction conditions (entry 1). The regioselectivity of the reaction decreased dramatically in other solvents, from DMF to toluene, giving rise to a mixture of α - and β -arylated products (entries 3–7). While the regioselectivity remained approximately the same for these solvents, the reaction rate decreased as the polarity of the solvent decreased. Interestingly, when *m*BDPP was replaced with its chiral analogue, (*R,R*)-BDPP, a slower arylation resulted, although the regioselectivity remained the same (entry 8 and vide infra). The high α -regioselectivity in DMSO and [bmim]-[PF₆] is not a simple coincidence, as they both are capable of promoting the formation of ionic palladium species. In the case of DMSO, its high polarity and good capability in coordinating to Pd(II) must at least partly account for this.¹³ Apart from our recent investigation, which supports that ionic liquids enable the ionic Heck pathway in the arylation of electron-rich olefins by aryl halides,⁵ examples have been presented that demonstrate that ionic liquids can stabilize unusual ionic reaction intermediates.¹⁴ The exclusive formation of the α -product in DMSO with Pd–*m*BDPP represents one of the few examples of regioselective internal arylation in common solvents by aryl halides with no use of a halide scavenger. Hallberg et al. have previously reported similar regioselective arylation reactions in wet DMF, with water acting as an indispensable additive for boosting solvent polarity.^{6c} More recently, we showed that **2** could be regioselectively arylated by aryl bromides with Pd–DPPP catalysis in DMSO in the presence of an ionic liquid.^{5c} In neat common organic solvents, Pd–DPPP generally gives rise to a mixture of regioisomers as aforementioned.^{2,5b} For instance, the arylation of **2** by *p*-bromobenzaldehyde led to a α/β -ratio of 86/14 with Pd–DPPP in DMSO under similar conditions.^{5b}

Encouraged by the results in DMSO, we extended this chemistry to other aryl bromides. The arylation of *n*-butyl vinyl ether **2** (2.0 mmol) by a spectrum of aryl bromides **1** (1.0 mmol) in the presence of Pd(OAc)₂ (2–4 mol %) and *m*BDPP (4–8

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TABLE 2. Arylation of Butyl Vinyl Ether with Aryl Bromides by Pd-*m*BDPP Catalysis^a

Entry	ArBr	Pd/ <i>m</i> BDPP (mol%)	α/β^b	Product 5	Yield (%) ^c
1		2/4	>99/1		83 ^d
2		2/4	>99/1		94
3		2/4	>99/1		95
4		2/4	>99/1		88
5		2/4	>99/1		83
6		2/4	>99/1		80
7		4/8	>99/1		90
8		4/8	>99/1		85
9		4/8	>99/1		87
10		4/8	>99/1		86
11		4/8	>99/1		70
12		4/8	>99/1		84
13		4/8	>99/1		86

^a Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), Pd(OAc)₂ and *m*BDPP (shown in the Table), and DMSO (1.0 mL). ^b Determined by ¹H NMR. ^c Isolated yield. ^d The conversion to **3a** was 94% at 24 h.

mol %) was carried out in DMSO at 115 °C for 36 h. The isolated products were the aryl methyl ketones **5** following hydrolysis of **3**. The results obtained are summarized in Table 2. As is clear, exclusive α -arylation together with high isolated yields for ketones **5** were obtained in all reactions, regardless of the nature of aromatic rings. Nonetheless, with the aryl bromide bearing a strongly electron-withdrawing or electron-donating group, such as CN, or OMe, the reaction became slow and thus required a higher catalyst loading to complete. This suggests that the rate of arylation is not determined by the oxidative addition of Ar-Br to Pd(0)-*m*BDPP. An electron-rich aryl group could slow the arylation by discouraging the coordination of **2** to Pd(II) as a result of increased electron density at the palladium. On the other hand, the aryl insertion step, which may be viewed as an intramolecular nucleophilic addition,¹⁶ could be negatively affected by over-increasing the electron deficiency of the migrating aryl ring by an electron-withdrawing group.

While these reactions provide rare examples of regioselective arylation in a common solvent, from a viewpoint of practical

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TABLE 3. Arylation of Butyl Vinyl Ether by Pd-*m*BDPP Catalysis in the Presence of [Et₃NH][BF₄]^a

Entry	ArBr	Pd/ <i>m</i> BDPP (mol%)	Reaction time (h)	Product 5	Yield (%) ^b
1		0.5/1	12		82
2		2/4	12		83
3		0.5/1	24		80
4		2/4	24		84
5		2/4	24		78
6		2/4	24		87

^a Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), Pd(OAc)₂ and *m*BDPP (shown in the Table), and [Et₃NH][BF₄] (1.5 mmol) in DMSO (1.0 mL). ^b Isolated yield.

application, the long reaction time and high catalyst loading could become a concern. We recently showed that ammonium salt-based hydrogen-bond donors such as [Et₃NH][BF₄] accelerate significantly the Pd-DPPP catalyzed arylation, possibly via hydrogen bonding to bromide anions, which increases the concentration of active cationic palladium species and hence the α -arylation rates (see Scheme 1).^{5a,b} With this in mind, we attempted to use an additive to enhance the reaction rate of the Pd-*m*BDPP catalysis. A few aryl bromides were examined as examples. The results are shown in Table 3. Indeed, the reaction in DMSO can be noticeably accelerated with the aid of [Et₃NH][BF₄] without compromising the regioselectivity, even at a reduced catalyst loading. Thus, for example, in the presence of 1.5 equiv of [Et₃NH][BF₄] the arylation of **2** with 2-bromonaphthalene (**1a**) was completed within 12 h at 115 °C with a 0.5 mol % Pd loading, bringing about a turnover number of 200 (entry 1, Table 3). In the absence of the ammonium additive, the reaction afforded a 94% conversion in 24 h at a palladium loading of 2.0 mol % (entry 1, Table 2). As shown in the table, even for the aryl bromides bearing a OMe group, the reaction was finished within 24 h at a 2 mol % Pd loading (entries 4 and 5).

The Pd-*m*DPPP catalysis appears to work with some other electron-rich olefins as well. Thus *N*-methyl-*N*-vinylacetamide was arylated by 2-bromonaphthalene (**1a**) to give exclusively the α -product under the above conditions, albeit with an incomplete conversion of 64%. Allyl alcohol and allyltrimethylsilane afforded lower α/β -ratios of 91/9 (60% conversion) and 82/18 (30% conversion), respectively. However, the catalysis by Pd-DPPP led to still lower regioselectivities. For instance, the arylation of allyltrimethylsilane with this catalyst yielded a α/β -ratio of 70/30. The high α/β -selectivity in the case of butyl vinyl ether and *N*-methyl-*N*-vinylacetamide is undoubtedly a reflection of the strong electronic bias of these olefins toward 1,2-aryl insertion into the α rather the β -carbon (Scheme 1).^{7a,b}

The higher α/β -selectivity associated with *m*BDPP than DPPP raises an interesting question: why is Pd-*m*BDPP more selective? To address this issue, we optimized the structures of [PdBr(Ph)(*m*BDPP)] and [PdBr(Ph)(DPPP)] by DFT calcula-

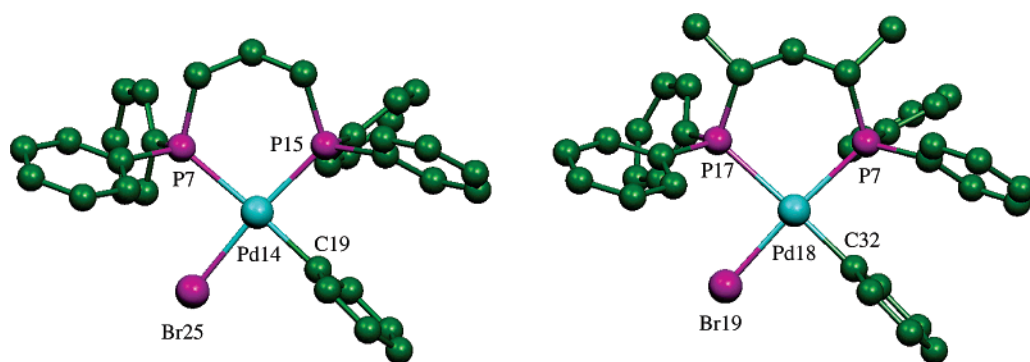
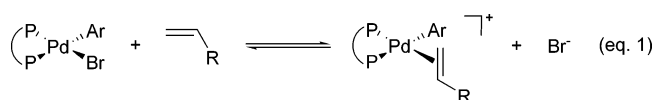


FIGURE 1. Structures of [PdBr(Ph)(DPPP)] (left) and [PdBr(Ph)(*m*BDPP)] (right) obtained from DFT optimization, with hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (deg): P7–Pd14, 2.439; P15–Pd14, 2.324; C19–Pd14, 2.061; P7–Pd14–P15, 95.273; P7–Pd18, 2.421; P17–Pd18, 2.541; C32–Pd18, 2.033; P17–Pd18–P7, 94.411.

tions using the B3LYP functional. The optimized structures are illustrated in Figure 1. In terms of structure, [PdBr(Ph)(DPPP)] resemble a structurally characterized compound, [PdCl(Ph)(DPPP)].¹⁷ Thus, in both compounds the Pd–P bond trans to the phenyl is longer, 2.439 vs 2.239 Å in the bromide compound and 2.350 vs 2.239 Å in the chloride analogue, and the P–Pd–P angle is 95.27° in the former and 96.70° in the latter. A comparison of the *m*BDPP and DPPP compounds reveals that they display similar ligand bite angles, 94.41 vs 95.27°. However, the Pd–P bonds in the *m*BDPP complex are significantly longer, by ca. 0.1 Å for both Pd–P bonds. This is reminiscent of previous studies that show that the Pd–P bond distances in a related Pd(II)–*m*BDPP complex are slightly longer than those in the analogous Pd(II)–DPPP complex.^{11a,18} As a consequence of this weaker bonding of the phosphine to the Pd(II), the partial charge at palladium is notably higher in [PdBr(Ph)(*m*BDPP)] (–0.0155) than in [PdBr(Ph)(DPPP)] (–0.3066), and in line with this, the phosphorus atoms in the former are less positively charged. Thus, we can tentatively ascribe the higher α -selectivity of Pd–*m*BDPP to the electron deficiency at the palladium, which shifts the following equilibrium (eq 1) in favor of the cationic palladium species and



hence the ionic pathway, and facilitates the 1,2-insertion step that leads to the α -product (Scheme 1). The lower activity of the Pd–(*R,R*)-BDPP catalyst (Table 1) also appears to fit in with this explanation, as the palladium center in [PdBr(Ph){(*R,R*)-BDPP}] is more negatively charged than that in [PdBr(Ph)(*m*BDPP)].¹⁹ Previous DFT calculations have shown that electron-withdrawing groups on ligands lower the insertion barriers and render the Pd(II)–olefin intermediate more stable.^{7c}

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(19) The average charge on palladium in [PdBr(Ph){(*R,R*)-BDPP}] is –0.1271 at the same level of DFT calculations.

In summary, the results presented in this paper show that Pd–*m*BDPP is capable of catalyzing regioselective internal arylation of electron-rich olefins by aryl bromides in a common solvent DMSO with no need for any halide scavengers. While the effect of *m*BDPP is probably steric in origin, the enhanced α -regioselectivity appears to stem from the palladium becoming electron-deficient on going from Pd–DPPP to Pd–*m*BDPP. This interplay of ligand steric and electronic properties and their effects on olefin coordination and aryl insertion point to a new way for effecting regiocontrol in the Heck reaction, which has thus far been tackled by using triflates,^{2b,6c,8} halide scavengers,^{2b,6c,9} or ionic liquids.⁵

Experimental Section

Specific procedures are given for the olefination of 1-bromonaphthalene (**1b**) by *n*-butyl vinyl ether (**2**) in DMSO; similar procedures were followed for other coupling reactions. An oven-dried, screw-capped reaction tube containing a stir bar was charged with **1b** (1.0 mmol), Pd(OAc)₂ (2 mol %), *m*BDPP (4 mol %), and DMSO (1 mL) under nitrogen at room temperature. Following degassing three times, **2** (2.0 mmol) and NEt₃ (1.5 mmol) were injected sequentially under nitrogen. The mixture was heated to 115 °C and stirred at this temperature for 36 h. The reaction mixture was then cooled to room temperature and acidified by addition of 10 mL of 20% HCl. The product was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layer was washed with water until neutrality, dried (MgSO₄), filtered, and concentrated in vacuo. A small sample was taken for NMR analysis to determine the conversion. The arylated ketone **5b** (160.7 mg, 0.94 mmol, 94% yield) was isolated as a white powder out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1:3 to 1:0) as eluant.

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Supporting Information Available: Characterization data of the compounds in Table 2 and the methodology of DFT calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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