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Palladium-Catalyzed, Highly Efficient, Regiocontrolled Arylation of Electron-Rich Allylamines with Aryl Halides

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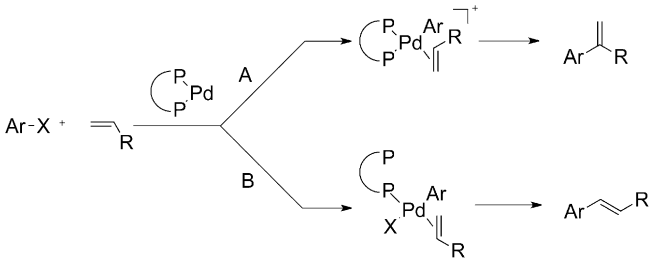
Abstract: The highly efficient and regioselective palladium-catalyzed Heck coupling of aryl bromides with electron-rich allylamine derivatives is described. It was found that the choice of solvent, olefin, ligand and additive had a fundamental influence on the regioselectivity and reactivity of the reaction. The combination of palladium acetate [$Pd(OAc)_2$] and 1,3-bis(diphenylphosphino)propane (dppp) in ethylene glycol (EG) constitutes a highly effective catalyst system for internal arylation of *N*-Boc-allylamine (*tert*-butyl methyl allyliminodicarbonate) with aryl bromides to give good to excellent regioselectivities, while the catalyst system consisting of $Pd(OAc)_2$, tetrabutylammonium bromide (TBAB) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) additive allows for a variety of aryl bromides to react efficiently with *N*,*N*-$(Boc)_2$-allylamine (di-*tert*-butyl allyliminodicarbonate) in water to exclusively afford the linear (*E*)-allylamine products in high yields.

Keywords: allylamines; arylation; Heck reaction; palladium; regioselectivity

Introduction

The Pd-catalyzed Heck arylation of olefins with aryl halides has become one of the most powerful tools for the construction of C–C bonds in organic synthesis.[1] However, the arylation of electron-rich olefins with aryl halides is often complicated by the formation of mixtures of regioisomers. It is generally believed that this regioselectivity problem arises from two competing reaction pathways (Scheme 1), one being neutral which leads to a linear product and the other ionic which favors branched substitution.[2]



Scheme 1. The two competing pathways in the Heck reaction.

Earlier studies reported that the poor internal regioselectivity could be greatly improved under Pd-dppp catalysis by employing aryl triflates or by adding stoichiometric silver or thallium salts when aryl halides are chosen.[3] Owing to the lability of the Pd–OTf (Tf: trifluoromethanesulfonyl) bond, the regioselective arylation of electron-rich olefins with aryl triflates in the presence of a chelating bidentate ligand is channelled into the ionic pathway (Scheme 1, path A) to give the branched products. Silver and thallium salts could remove the halogen, thereby promoting internal arylation. Recent reports have revealed that a number of electron-rich olefins could undergo highly regioselective internal arylation with aryl halides by employing an ionic liquid,[4] aqueous DMF (*N*,*N*-dimethylformamide),[5] ethylene gylcol (EG),[6a–e] 2-propanol[6f] or water[7] as the reaction medium or in the presence of a hydrogen-bond donor ammonium salt additive.[6f,8] It is assumed that the ionic or polar environment provided by the solvent or the ammonium salt additive facilitates the for-

mation of the cationic species, thereby enabling the ionic pathway (Scheme 1, path A). The recent kinetic studies of Amatore, Jutand and co-workers support this view.[9] On the other hand, studies on how to improve the linear regioselectivity along the neutral way (Scheme 1, path B) in the Pd-catalyzed Heck arylation of electron-rich olefins has also been reported.[10–12] For example, it has been suggested that using monophosphines or no ligand is advantageous for the linear arylation of allylic alcohol.[10] Highly linear arylations of vinyl ethers have been observed in poly(ethylene glycol) or aqueous DMF catalyzed by $Pd(OAc)_2$ or $PdP(t\text{-}Bu)_3$.[11] More recently the work of Jiao revealed that aryl halides could couple highly regioselectively with allyl esters to provide the linear products with a $Pd(OAc)_2$ catalyst under ligand-free conditions.[12]

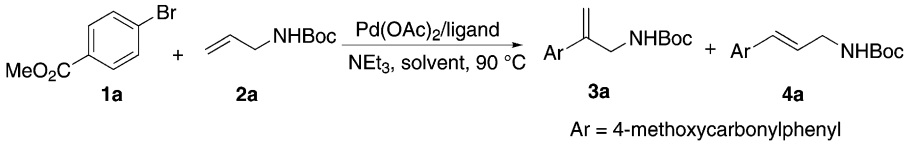
Allylamines are versatile building blocks and structural units in a large number of natural and synthetic products, and much effort has been devoted to the efficient construction of these useful compounds.[13] Recently the application of Pd-catalyzed Heck arylations of allylamines to prepare arylated allylamines has gained much attention owing to its simplicity and tolerance of various functional groups.[14–17] However, the regioselectivity remains problematic. Hallberg,[15a,b] Wu[15c] and Baxter[15d] disclosed that the catalyst generated *in situ* from the bidentate ligand dppf [1,1′-bis(diphosphino)ferrocene] and $Pd(OAc)_2$ could work well to catalyze the coupling reaction of aryl triflates with the readily available allylamine derivatives to give the β-arylated allylamines with good to excellent regioselectivities and high yields, but a significant drawback lies in the fact that triflates are base sensitive, thermally labile, and rarely commercially available. The work of Ripin and Wilson revealed that the Pd-catalyzed highly regioselective and stereoselective terminal (γ-)arylation of allylamine derivatives could be accomplished in alcoholic solvents under ligand-free conditions, but only one aryl iodide substrate was attempted, and the general utility of this chemistry has not been explored.[16] Very recently, Sigman,[17a] Cacchi[17b] and Correia[17c] reported that $Pd_2(dba)_3$ could efficiently catalyze the preferential γ-arylation of allylamines with arenediazonium salts in the absence of ligand. However, the synthetic utility of this chemistry might be restricted by the intrinsic drawbacks of the arenediazonium salt, such as instability and explosive potential. Given the importance of γ- and β-arylated allylamines in chemical and particularly biologically active compound synthesis,[18] the development of practical and highly efficient catalytic synthetic methods to access these compounds from safe and stable aryl bromides appeared to be highly desirable. Herein we report that electron-rich *N*-Boc-allylamine **2a** could undergo highly efficient internal (β-)arylation with aryl bromides in EG in the presence of Pd-dppp catalyst, and that $Pd(OAc)_2$ could catalyze the coupling reaction of aryl bromides with electron-rich *N*-$(Boc)_2$-allylamine **2b** in water under ligand-free conditions to give the γ-arylated products in a highly regioselective and stereoselective manner.

Results and Discussion

At the outset methyl 4-bromobenzoate **1a** was chosen as the model substrate to couple with **2a** under various reaction conditions. The reason for choosing **2a** is its ready deprotection of the Boc (*tert*-butyloxycarbonyl) group. Considering the remarkable performance of dppp in the Pd-catalyzed Heck arylation of electron-rich olefins,[3–8] the catalyst was generated *in situ* from dppp and $Pd(OAc)_2$, and the reaction mixture was heated at 90 °C for 20 h with Et_3N (triethylamine) as the base. Regioselectivities were determined by ^1H NMR spectral analysis of the crude reaction mixture. The effect of different solvents was firstly surveyed. As shown in Table 1, using EG resulted in a full conversion and 96/4 regioselectivity favoring β-arylation (Table 1, entry 1), while switching to other alcoholic solvents [EtOH (ethanol) and *i*-PrOH (2-propanol)] led to lower conversions and regioselectivities (Table 1, entries 2 and 3). The better reactivity and β-regioselectivity achieved in EG may be partly ascribed to its better capability to form hydrogen bonding with the bromide anion, thereby enhancing the concentration of the cationic Pd(II) intermediate of the ionic pathway A (Scheme 1). The efficiencies were low when the coupling reactions were carried out in CH_3CN (acetonitrile), DMSO (dimethyl sulfoxide), DMF and dioxane, albeit the β-arylated allylamines were the major products (Table 1, entries 4–7). No reaction was observed in toluene and water (Table 1, entries 8 and 9). Bearing in mind the significant promoting effect of the hydrogen bond donor $[H_2N(i\text{-}Pr)_2][BF_4]$ (diisopropylammonium tetrafluoroborate) on the regioselectivity and reaction rate in the arylation of electron-rich olefins,[6f,8] we then explored the effect of this ammonium salt additive, but no obvious accelerating effect and improved regioselectivity could be detected (Table 1, entry 10). The inability of the ammonium salt may result from its preferential hydrogen bonding with the solvent EG. Addition of a silver salt did not have an obvious effect on the rate and regioselectivity (Table 1, entry 11).

Considering the important impact of ligands on reactivity and regioselectivity, we were interested in finding out if a ligand other than dppp could display better performance in EG. In the presence of dppf, a ligand which has been proved to be highly efficient in the regioselective Heck reaction of allylamines with aryl triflates,[15] the reaction gave a lower regioselectivity of 80/20 albeit with a full conversion

Table 1. Screening conditions for Heck arylation of methyl 4-bromobenzoate **1a** with allylamine **2a**.[a]



1a **2a** **3a** **4a**

Ar = 4-methoxycarbonylphenyl

Entry	Solvent	Ligand[b]	Conversion [%][c]	Ratio of **3a/4a**[c]
1	EG	dppp	100	96/4
2	C_2H_5OH	dppp	78	95/5
3	*i*-PrOH	dppp	70	93/7
4	CH_3CN	dppp	42	86/14
5	DMSO	dppp	32	80/20
6	DMF	dppp	10	86/14
7	dioxane	dppp	40	75/25
8	toluene	dppp	nd	nd
9	H_2O	dppp	nd	nd
10[d]	EG	dppp	100	96/4
11[e]	EG	dppp	100	96/4
12	EG	dppf	100	80/20
13	EG	dppb	100	60/40
14	EG	dppe	nd	nd
15	EG	dppm	nd	nd
16	EG	BINAP	100	70/30
17	EG	PPh_3	26	23/77
18	EG	P(*o*-tolyl)$_3$	21	20/80
19	EG	phen	nd	nd
20	EG	dmphen	nd	nd
21	EG	bpy	nd	nd
22[f]	EG	dppp	100	96/4
23[g]	EG	dppp	100	96/4

[a] *Reaction conditions*: **1a** (1.0 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), NEt_3 (2.0 mmol), solvent (3.0 mL), 90 °C, 20 h.

[b] Abbreviations: dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,4-bis(diphenylphosphino)butane, dppm = bis(diphenylphosphino)methane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, phen = 1,10-phenanthroline, 2,9-dmphen = 2,9-dimethyl-1,10-phenanthroline, bpy = 2,2′-bipyridine.

[c] Determined by ^{1}H NMR data.

[d] 1.5 equivalents $[H_2N(i\text{-}Pr)_2][BF_4]$ were added.

[e] 1.1 equivalents AgOTf (silver trifluoromethanesulfonate) were added.

[f] Reaction temperature 120 °C, 4 h.

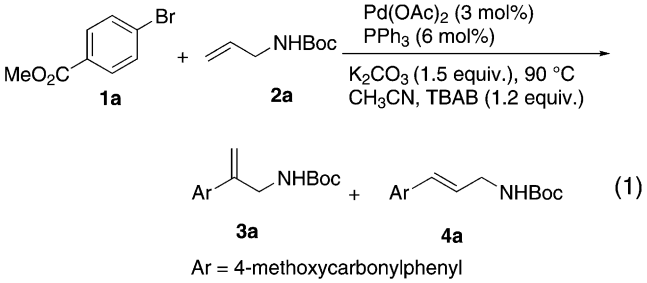
[g] Reaction temperature 145 °C, 2 h.

(Table 1, entry 12). Employing other ligands regardless of being bidentate or monodentate led to either poor yields or selectivities or both (Table 1, entries 13–21). Obviously, the combination of $Pd(OAc)_2$ and dppp afforded the most active catalyst in terms of both reactivity and regioselectivity. Interestingly, further experimental studies demonstrated that increasing the reaction temperature could dramatically reduce the reaction time without compromising the regioselectivity. For example, the reaction went to completion in 4 h at 120 °C without compromising the regioselectivity (Table 1, entry 22), and the reaction time could be further shortened to 2 h at 145 °C with retained regioselectivity (Table 1, entry 23). It should be pointed out that no product from a potentially competing Pd-catalyzed amidation reaction could be detected.[19]

Having established the optimal reaction conditions, we then extended the chemistry to other aryl bromides. The results are shown in Table 2. As can be seen, all the reactions proceeded rapidly, and reaction times of as little as 2 h were observed in most cases. A range of aryl bromides with electron-rich or electron-deficient groups reacted smoothly with **2a** to give the expected β-arylated allylamines in good to excellent yields. The reactions involving electron-deficient aryl bromides exhibited excellent regioselectivities regardless of the position of the substituent on the aromatic ring (Table 2, entries 1–14), and no or only traces of linear products were detected. However, slightly lower regioselectivities were obtained in the

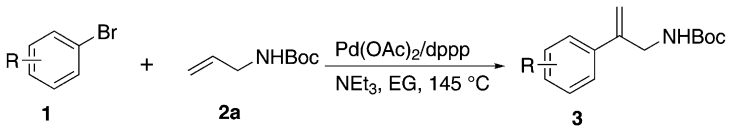
reactions of electron-rich aryl bromides (Table 2, entries 16 and 17), and the reason for the slight erosion is not clear at the moment. The reaction is not only limited to aryl bromides, but (also) heteroaryl bromides participated equally well (Table 2, entries 18–20).

Next we turned our attention to the regioselective terminal Heck arylation of allylamines. Based on Scheme 1 and the previous reports,[10,14,20] the use of a monophosphine ligand and a quaternary ammonium salt is expected to promote the arylation to proceed preferentially *via* the neutral route (Scheme 1, path B) to give the linear product. We first examined the coupling reaction of **1a** and **2a** with $Pd(OAc)_2$-PPh_3 as the catalyst in the presence of TBAB additive in CH_3CN [Eq. (1)]. The reaction finished in 20 h, affording a mixture of γ-arylated and β-arylated isomers with the ratio of γ/β being 85/15. In order to further increase the γ-regioselectivity, we envisioned that,



(1)

Table 2. Regioselective Heck arylation of **2a** with aryl bromides.[a]



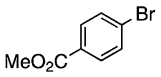
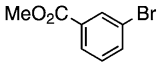
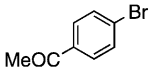
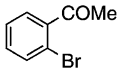
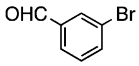
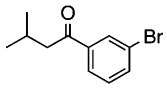
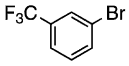
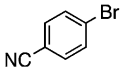
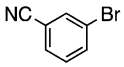
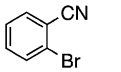
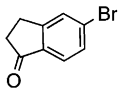
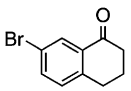
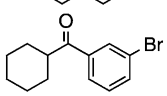
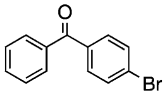
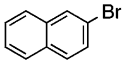
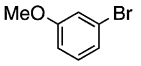
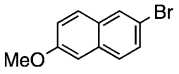
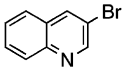
Entry	Substrate		Time [h]	Selectivity [%][b]	Yield [%][c]
1		**1a**	2	96/4	85
2		**1b**	2	96/4	82
3		**1c**	2	95/5	81
4		**1d**	3	95/5	79
5		**1e**	3	94/6	80
6		**1f**	3	93/7	82
7		**1g**	2	>99/1	91
8		**1h**	2	>99/1	93
9		**1i**	2	>99/1	89
10		**1j**	3	>99/1	87
11		**1k**	2	95/5	80
12		**1l**	2	94/6	81
13		**1m**	2	95/5	79

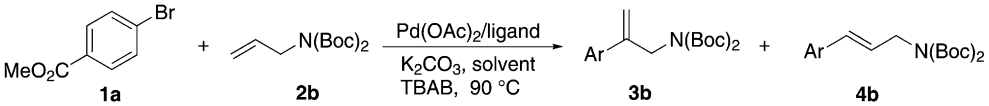
Table 2. (Continued)

Entry	Substrate		Time [h]	Selectivity [%][b]	Yield [%][c]
14		**1n**	2	94/6	81
15		**1o**	2	91/9	80
16		**1p**	3	88/12	71
17		**1q**	3	86/14	70
18		**1r**	3	95/5	80
19		**1s**	3	96/4	81
20		**1t**	3	96/4	80

[a] *Reaction conditions*: aryl bromide (1.0 mmol), allylamine **2a** (1.2 mmol), $Pd(OAc)_2$ (3 mol%), dppp (6 mol%), NEt_3 (2.0 mmol), ethylene glycol (3.0 mL), 145 °C.
[b] Determined by ^1H NMR.
[c] Isolated yield.

when a more sterically hindered allylamine is employed, the bulky substituent would inhibit the rotation of the olefin from the initial out-of-plane position to the in-plane position and the subsequent migratory insertion of the olefin into the Pd–Ar bond that gives rise to β-arylation. Indeed, the arylation of a bulky *N*,*N*-$(Boc)_2$-allylamine **2b** with **1a** resulted in exclusively the γ-arylated linear (*E*)-allylamine product **4b** with a 85% conversion (Table 3, entry 1), and no β-arylated product **3b** was detected. This result indicat-

Table 3. Screening conditions for Heck arylation of **2b** with **1a**.[a]



Entry	Solvent	Ligand	Time [h]	Conversion [%][b]	Ratio of **4b/3b**[b]
1	CH_3CN	PPh_3	20	86	>99/1
2[c]	*i*-PrOH	none	20	nd	nd
3[c,d]	EtOH	none	20	nd	nd
4	CH_3CN	none	20	86	>99/1
5	H_2O	none	20	85	>99/1
6	EG	none	20	nd	nd
7[e]	H_2O	none	4	100	>99/1
8[f]	H_2O	none	2	100	>99/1
9[g]	H_2O	none	2	100	>99/1

[a] *Reaction conditions*: **1a** (1.0 mmol.), **2b** (1.2 mmol), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), K_2CO_3 (2.0 mmol), solvent (3.0 mL), 90 °C, 20 h.
[b] Determined by ^1H NMR data. When no β-arylated product was detected, a value of >99/1 was assigned.
[c] $Pd_2(dba)_3$ was used to replace $Pd(OAc)_2$.
[d] Molar ratio $NaOAc/NEt_3 = 1/5.1$.
[e] 10 mol% hydroquinone were added.
[f] 10 mol% TEMPO were added.
[g] 1.0 equivalent TEMPO was added.

ed that the steric property of the allylamine has a decisive effect. This is in agreement with the reported experimental observations of regioselective Heck coupling reaction of **2b** with aryl iodides and arenediazonium salts under ligand-free conditions.[16,17] The beneficial effect of ligand-free conditions led us to examine the reaction of **1a** and **2b** without using a ligand. However, when Ripin's protocol[16a] was employed, no reaction took place after 20 h (Table 3, entry 2). The catalyst system consisting of $Pd_2(dba)_3$ [tris(dibenylideneacetone)dipalladium (0)], NaOAc (sodium acetate) and NEt_3 with EtOH as solvent, reported to be highly effective for the regioselective linear arylation of *N*-allyl-2-methoxyacetamide by aryl iodide,[16b] proved to be ineffective in our case (Table 3, entry 3). We were pleased to observe that the reaction in CH_3CN could still maintain its reactivity and regioselectivity in the absence of a ligand (Table 3, entry 4). Interestingly, similar reactivity and regioselectivity were obtained when switching the reaction medium to water (Table 3, entry 5). However, EG totally inhibited the reaction (Table 3, entry 6). Considering a number of attractive advantages in the case of using water as a solvent for organic reactions,[21] we therefore chose water as the reaction medium for subsequent study. Appropriate additives proved to be very useful. The addition of the free-radical scavenger hydroquinone (10 mol%) to the reaction mixture could significantly accelerate the reaction in water, and the arylation of **2b** was finished in 4 h to exclusively form the linear product without the branched products being detected (Table 3, entry 7). Replacing hydroquinone with TEMPO could reduce the reaction time to 3 h with similar results (Table 3, entry 8). Further study indicated that increasing the amount of TEMPO additive had no significant effect on the reaction (Table 3, entry 9). The addition of a free-radical scavenger to accelerate the Pd-catalyzed cross-coupling reactions has been recently reported in the literature.[22] We also tried the effect of reducing agents, such as hydrazine and sodium formate, but none of them showed any effect of acceleration.[23]

Based on the optimized reaction conditions, a series of aryl bromides with different substituents wase employed to survey the substrate scope of the reaction. The results are summarized in Table 4. As can be seen, all these coupling reactions went to completion within 4 h, and the catalyst system was found to work well to result in good to excellent yields of the desired products, tolerating activated, unactivated, *para*-, *meta*- as well as *ortho*-substituted aryl bromides. However, longer reaction times were required in the olefination of *ortho*-substituted bromobezenes presumably due to the steric effects (Table 4, entries 5 and 17). Moreover, the regioselectivities and stereoselectivities were well-controlled in these transformations, and only the linear arylation products – the (*E*)-allylamines – were obtained. These results suggested that the ionic pathway is either completely suppressed or its involvement in the arylation is insignificant compared with the neutral pathway. It is noted that heteroaryl substrates were also efficiently transformed to give the corresponding linear products in high yields (Table 4, entries 11–14). Noteworthy is that all the substrates underwent clean conversions without competing formation of amidation products.[19]

Conclusions

In summary, we have developed highly efficient, Pd-catalyzed Heck cross-coupling conditions that allow a wide range of aryl bromides to highly regioselectively couple with electron-rich allylamine derivatives to give the arylated allylamines in good to excellent yields. The catalytic efficacy was influenced by many factors, such as solvent, allylamine derivative, ligand, reaction temperature and additive. It is noteworthy that the choice of solvent and allylamine derivative was found to be essential for securing high regioselectivity. Both of these factors are expected to facilitate the formation of the corresponding palladium intermediate (ionic or neutral), enabling the reaction to regioselectively afford the desired products. The present catalysis is more general, and greener than the methods reported so far for arylation of allylamines.

Experimental Section

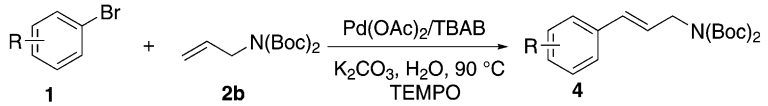
General Methods

Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 106 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. All organic solvents were dried using standard, published methods and were distilled before use. All other chemicals were commercially available and used as received without further purification.

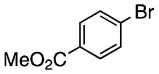
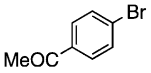
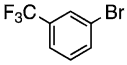
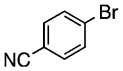
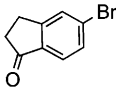
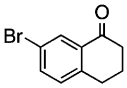
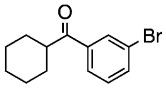
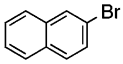
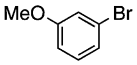
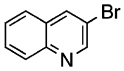
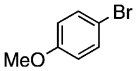
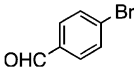
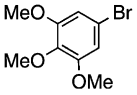
General Procedure for the Heck Arylation of *N*-Boc-allylamine

An oven-dried, two-necked, round-bottom flask containing a stir bar was charged with an aryl bromide (1.0 mmol), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol), dppp (24.8 mg, 0.06 mmol), *N*-Boc-allylamine (188.7 mg, 1.2 mmol) and EG (3.0 mL) under nitrogen at room temperature. Following degassing three times, NEt_3 (202.4 mg, 2.0 mmol) were injected. The flask was placed in an oil bath, and the mixture was stirred and heated at 145 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. Water (20 mL) was added, and the mixture

Table 4. Regioselective Heck arylation of **2b** with aryl bromides.[a]



1 2b 4

Entry	Substrate		Time [h]	Yield [%][b]
1		**1a**	2	90
2		**1c**	3	84
3		**1g**	3	81
4		**1h**	3	85
5		**1j**	4	81
6		**1k**	3	80
7		**1l**	3	81
8		**1m**	3	79
9		**1o**	3	80
10		**1p**	3	81
11		**1r**	3	78
12		**1s**	3	81
13		**1t**	3	80
14		**1u**	3	76
15		**1v**	3	83
16		**1w**	3	84
17		**1x**	4	86
18		**1y**	2	91

[a] *Reaction conditions*: aryl bromide (1.0 mmol), allylamine **2b** (1.2 mmol), $Pd(OAc)_2$ (3 mol%), TBAB (1.0 mmol), TEMPO (10 mol%), K_2CO_3 (2.0 mmol), water (3.0 mL), 90 °C.

[b] Isolated yield.

was extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The arylated allylamine was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99 to 10/90) as eluant.

General Procedure for the Heck Arylation of *N*,*N*-(Boc)$_2$-allylamine

An oven-dried, two-necked, round-bottom flask containing a stir bar was charged with an aryl bromide (1.0 mmol), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol), K_2CO_3 (165.9 mg, 1.2 mmol), TBAB (322.4 mg, 1.0 mmol), TEMPO (15.6 mg, 0.1 mmol), *N*,*N*-(Boc)$_2$-allylamine (308.8 mg, 1.2 mmol) and water (3.0 mL) under nitrogen at room temperature. Following degassing three times, the flask was placed in an oil bath, and the mixture was stirred and heated at 90 °C. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The linear arylated (*E*)-allylamine was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (5/95 to 20/80).

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