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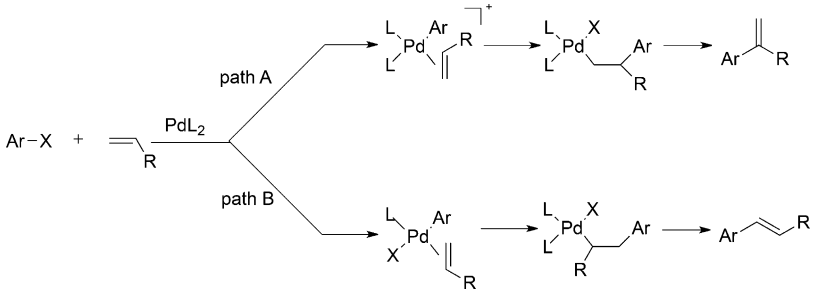
Palladium-Catalyzed Highly Regioselective Mizoroki–Heck Arylation of Allylamines with Aryl Chlorides

Lingjuan Zhang,[a] Zhen Jiang,[a] Chaonan Dong,[a] Xiao Xue,[a] Ruiying Qiu,[a] Weijun Tang,[b] Huanrong Li,*[a] Jianliang Xiao,[b] and Lijin Xu*[a]

Palladium catalyst systems for the regioselective Mizoroki–Heck arylation of *N*,*N*-diprotected and *N*-protected allylamines with aryl chlorides have been developed. $Pd(OAc)_2$ in combination with appropriate additives could efficiently catalyze the linear arylation of *N*,*N*-diprotected allylamines with aryl chlorides in toluene to give exclusively the γ-arylated products in good to excellent yields and with excellent regio- and stereocontrol and good functional group tolerance. With use of a catalytic mixture of $Pd(OAc)_2$ and 1,1′-bis(diphenylphosphino)ferrocene, the arylation of *N*-protected allylamines with aryl chlorides could be accomplished in ethylene glycol/DMSO, which afforded complete β-regioselectivity with good functional group tolerance. The steric and electronic properties of allylamine substrates are found to be critical to the catalytic activity and regiocontrol in both linear and internal arylations.

Introduction

The palladium-catalyzed Mizoroki–Heck arylation of olefins with aryl halides and pseudohalides has become one of the most useful tools for constructing C–C bonds in organic synthesis.[1,2] Over the past several decades, significant advances have been made through the development of highly efficient palladium catalyst systems demonstrating high reactivities and selectivities. However, most of the reports deal with the coupling reactions of aryl bromides and aryl iodides with olefins, and protocols involving aryl chlorides are relatively underexplored even though aryl chlorides are more readily available and less expensive to access than other aryl halides.[1,2] This observation is mainly attributable to the higher strength of the C–Cl bond, which results in the well-known resistance of aryl chlorides to undergo oxidative addition with palladium catalysts. Therefore, the recent research focus in this area has shifted to the use of less reactive aryl chlorides as arylating reagents.[3] Although a number of efficient palladium catalysts that can activate the C–Cl bond of chloroarenes have proved to be effective in the olefination of aryl chlorides, the olefin substrates have thus far mostly been limited to electron-deficient olefins, electron-neutral aliphatic olefins, and styrenes, with products resulting from arylation at the less substituted position of the olefin double bond.[4–7] In the case of electron-rich or deactivated olefins, arylation is often complicated by the formation of a mixture of regioisomers.[4a,f,7a] This regioselectivity problem arises from two competing reaction pathways (Scheme 1): one is neutral, which leads to the terminal arylation product, and the other is ionic, which favors branched substitution.[8,9] Considerable research efforts have been directed toward the efficient regiocontrol in the Mizoroki–Heck arylation of electron-rich and deactivated olefins;[1b,10,11] however, the literature provides only some examples of the regioselective coupling reaction of aryl chlorides with electron-rich vinyl ethers and enamides.[12,13] Hence, an incentive to improve the olefin substrate scope clearly exists.



Scheme 1. Two competing pathways in the Mizoroki–Heck reaction.

The efficient preparation of substituted allylamines has received ever-increasing attention because these amines are im-

[a] *L. Zhang, Z. Jiang, C. Dong, X. Xue, R. Qiu, Dr. H. Li, Prof. L. Xu*
Department of Chemistry
Renmin University of China
Beijing 1000872 (P.R. China)
Fax: (+86) 10-62516444
E-mail: xulj@chem.ruc.edu.cn

[b] *Dr. W. Tang, Prof. J. Xiao*
Department of Chemistry
University of Liverpool
Liverpool L69 7ZD (UK)

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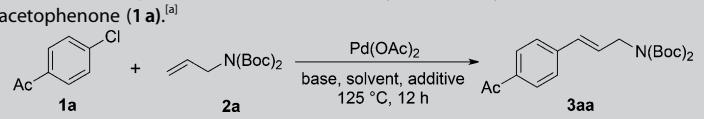
portant structural units in many natural products and pharmaceuticals and serve as versatile starting materials for the synthesis of various functionalized compounds.[14,15] There has been considerable interest in using palladium-catalyzed Mizoroki–Heck arylation of readily accessible allylamines to prepare arylated allylamines, but the regiocontrol remains problematic.[11b,16,17] Hallberg,[16a,b] Wu,[16c] Baxter,[11e] and Zhou[11b] reported that the catalyst prepared in situ from a diphosphine ligand and $Pd(OAc)_2$ could work well to catalyze the coupling reaction of aryl triflates with allylamines to provide the β-arylated products with high regioselectivities and yields; however, the drawbacks associated with the use of aryl triflates, such as base sensitivity and thermal lability, make this method less attractive. Ripin[17d] and Wilson[17e] reported that the palladium-catalyzed highly regioselective and stereoselective terminal arylation of allylamines could be accomplished in alcohol solvents under ligand-free conditions; however, only one aryl iodide substrate was tried. The groups of Sigman,[17h] Cacchi,[17i] and Correia[17j] described $Pd_2(dba)_3$-catalyzed preferential γ-arylation of allylamines with arenediazonium salts in the absence of a ligand; however, the synthetic utility of this chemistry could be restricted by the intrinsic drawbacks of arenediazonium salts, such as instability and explosive potential. Despite these advances, it should be pointed out that none of these precedents enable the efficient and selective arylation of allylamines with aryl chlorides.

During our investigation of the regioselective arylation of allylamines,[18] we reported that the highly regioselective internal Mizoroki–Heck arylation of *N*-Boc-allylamine (Boc = *tert*-butyloxycarbonyl) with aryl bromides could proceed smoothly with palladium–dppp (dppp = 1,3-bis(diphenylphosphino)propane) catalysts in ethylene glycol (EG) and $Pd(OAc)_2$ could catalyze the coupling reaction of aryl bromides with bulky *N*,*N*-diprotected allylamines under ligand-free conditions in water or DMF, preferentially giving the γ-arylated products.[18a,b] More recently, we found that the highly regioselective direct arylation of allylamines with thiophenes and furans could be accomplished with $Pd(OAc)_2$ and suitable additives.[18c] Notably, the electronic and steric properties of allylamine substrates in these reactions have a significant effect on the catalytic activity and regiocontrol. Encouraged by these results and with our continued interest in the regioselective arylation of olefins, herein we report that a palladium catalyst system consisting of $Pd(OAc)_2$ and appropriate additives efficiently catalyzes the highly regioselective linear (γ-)arylation of *N*,*N*-diprotected allylamines with aryl chlorides under ligand-free conditions whereas *N*-protected allylamines could undergo a highly efficient internal (β-)arylation with aryl chlorides with the Pd-dppf catalyst (dppf = 1,1′-bis(diphenylphosphino)ferrocene) in EG/DMSO.

Results and Discussion

For our initial investigations of suitable reaction conditions that can deliver high linear (γ-) regioselectivity, the reaction of 4-chloroacetophenone (**1a**) with *N*,*N*-$(Boc)_2$ allylamine (**2a**) was selected as the model reaction. The obvious advantages associated with ligand-free conditions urged us to perform the reaction without using a ligand. We first investigated the solvent effect by performing the coupling reaction with $Pd(OAc)_2$ as a precatalyst, tetrabutylammonium bromide (TBAB) as an additive, and K_2CO_3 as a base under ligand-free conditions for 12 h. Solvents such as DMSO, EG, dioxane, and CH_3CN proved to be ineffective, and no coupling product was detected. The exclusive formation of the linear arylation product **3aa** was observed with toluene, DMF, and *p*-xylene (Table 1, entries 1–3), and the best yield of 55% was achieved with toluene (entry 1). The fact that no β-arylated product was detected in these solvents indicates that a neutral mechanism is operating and the ionic pathway is completely suppressed. To improve the reaction efficiency, the performance of other salts was explored but none of them could work as effectively as TBAB (entries 4–

Table 1. Screening conditions for the linear arylation of allylamine (**2a**) with 4-chloroacetophenone (**1a**).[a]



Entry	Solvent	Base	Additive [equiv.]	Yield [%][b]
1	toluene	K_2CO_3	TBAB (2)	55
2	DMF	K_2CO_3	TBAB (2)	12
3	*p*-xylene	K_2CO_3	TBAB (2)	30
4	toluene	K_2CO_3	TBAC[c] (2)	n.d.
5	toluene	K_2CO_3	TBAI[d] (2)	n.d.
6	toluene	K_2CO_3	TBAA[e] (2)	10
7	toluene	K_2CO_3	Me_4NBr (2)	n.d.
8	toluene	K_2CO_3	–	n.d.
9	toluene	K_2CO_3	TBAB (1.2)	24
10	toluene	K_2CO_3	TBAB (2)/HQ (0.2)	22
11	toluene	K_2CO_3	TBAB (2)/TEMPO (0.2)	89
12	toluene	NEt_3	TBAB (2)/TEMPO (0.2)	n.d.
13	toluene	NBu_3	TBAB (2)/TEMPO (0.2)	n.d.
14	toluene	Cy_2NMe	TBAB (2)/TEMPO (0.2)	n.d.
15	toluene	K_3PO_4	TBAB (2)/TEMPO (0.2)	67
16	toluene	KOH	TBAB (2)/TEMPO (0.2)	49
17	toluene	Cs_2CO_3	TBAB (2)/TEMPO (0.2)	12
18	toluene	KOAc	TBAB (2)/TEMPO (0.2)	n.d.
19	toluene	*t*BuOK	TBAB (2)/TEMPO (0.2)	n.d.
20	toluene	EtONa	TBAB (2)/TEMPO (0.2)	n.d.
21[f]	toluene	K_2CO_3	TBAB (2)/TEMPO (0.2)	69
22[g]	toluene	K_2CO_3	TBAB (2)/TEMPO (0.2)	32
23[h]	toluene	K_2CO_3	TBAB (2)/TEMPO (0.2)	67
24[i]	toluene	K_2CO_3	TBAB (2)/TEMPO (0.2)	68
25[j]	TBAB	TBAA	–	21

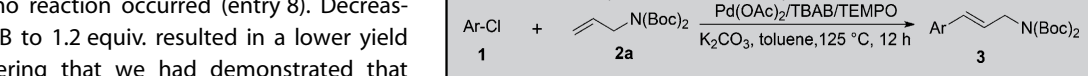
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), base (1.5 equiv.), additive, solvent (3.0 mL), $T = 125\,^{\circ}C$, $t = 12$ h; β-arylated product was not observed in any reaction, as determined by ^1H NMR analysis. [b] Isolated yield. [c] Tetrabutylammonium chloride. [d] Tetrabutylammonium iodide. [e] Tetrabutylammonium acetate. [f] $PdCl_2$ was used instead of $Pd(OAc)_2$. [g] Tris(dibenzylideneacetone)dipalladium(0) was used instead of $Pd(OAc)_2$. [h] Palladium(II) trifluoroacetate was used instead of $Pd(OAc)_2$. [i] $T = 145\,^{\circ}C$. [j] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (1.5 mol%), TBAB (1.0 g), TBAA (0.45 g, 1.5 mmol), 120 °C, 12 h.

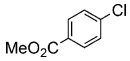
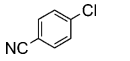
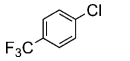
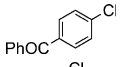
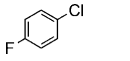
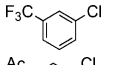
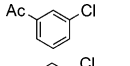
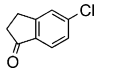
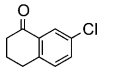
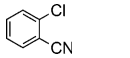
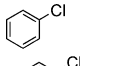
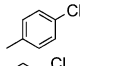
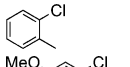
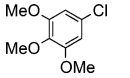
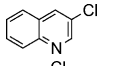
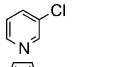
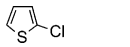
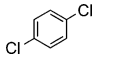
7). The use of TBAB is critical to the reaction efficiency.[19] In the absence of TBAB, no reaction occurred (entry 8). Decreasing the amount of TBAB to 1.2 equiv. resulted in a lower yield (24%; entry 9). Considering that we had demonstrated that 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone (HQ) could greatly facilitate the linear arylation of allylamines with aryl bromides,[18a,b] we now examined their effect. The yield of **3aa** was decreased considerably to 22% in the presence of a catalytic amount of HQ (entry 10), whereas TEMPO afforded a full conversion with an 89% isolated yield of **3aa** (entry 11). A similar accelerating effect of the free-radical scavenger in palladium-catalyzed cross-coupling reactions has been reported in the literature.[20] Further study revealed that the choice of a base strongly affected the reaction efficiency (entries 12–20) and that K_2CO_3 proved to be superior to other frequently used inorganic and organic bases. Notably, the organic bases totally inhibited the reaction (entries 12–14). The palladium source was also important for this transformation. $Pd(OAc)_2$ proved to be the best choice, and catalysts derived from other palladium precursors were not that effective (entries 21–23). In the subsequent part of the study, the yield of **3aa** decreased to 68% with the increase in the reaction temperature to 145 °C (entry 24). Furthermore, TBAB can undergo S_N2 substitution or Hofmann elimination to produce tributylamine at a high reaction temperature.[21] The inhibitive effect of tributylamine could be responsible for the decreased yield. The Nacci protocol,[7a] reported to be highly effective for the Mizoroki–Heck reaction of aryl chlorides with deactivated olefins under ligand-free conditions, was also tested; however, it gave only a low yield (21%; entry 25). Thus, the optimal reaction conditions were finally determined as follows: $Pd(OAc)_2$ (5 mol%), TBAB (2 equiv.), TEMPO (20 mol%), and K_2CO_3 (1.5 equiv.), toluene, 125 °C. It should be emphasized that allylic migration or partial deprotection was not observed in any of the cases.

After determining the optimal reaction conditions, we examined the linear arylation of **2a** with a range of activated and unactivated aryl chlorides (Table 2). The reaction proceeded well in all cases and provided the γ-arylated linear (*E*)-allylamine products in good to high yields and with excellent regioselectivities (terminal/internal > 99:1) and stereoselectivities (*E*/*Z* > 99:1). Notably, the nature and the position of the substituents on the aromatic rings appeared to have no significant effect on the isolated yields of the expected products, which is evident from the fact that we encountered no problem in the reactions involving aryl chlorides containing electron-donating/electron-withdrawing groups or *ortho* substituents (Table 2, entries 10 and 12–14). Furthermore, the heteroaryl chlorides demonstrated similar reactivity to aryl chlorides, which gave the corresponding allylamines in good yields (entries 15–17). Under the current catalytic conditions, the polyhaloarene (**1s**) underwent olefination to furnish the polyolefinated product (**3sa**) in 75% yield (Table 2, entry 18). Notably, all the substrates underwent clean conversions without the formation of the allylic migration products or homocoupling products.

To expand the scope of the catalysis, we investigated the linear arylation of other allylamine derivatives, and the results obtained are summarized in Table 3. The electron-deficient *N*,*N*-diprotected allylamines **2b–d** readily reacted with aryl halides regardless of the nature and position of the substituents on the aryl ring, and high yields and selectivities of the expected products were observed (Table 3, entries 1–14). The arylation of a more electron-rich *N*,*N*-diprotected allylamines **2e** and **2f** proceeded with similar efficiency to exclusively afford γ-arylated linear (*E*)-allylamines in good yields (entries 15–18). The frequently encountered partial deprotection in the arylation of *N*,*N*-diprotected allylamines did not occur in our case.[17i,18b]

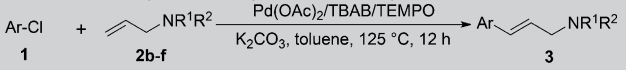
Table 2. Linear arylation of **2a** with aryl chlorides.[a]



Entry	Aryl chloride		Yield [%][b] (product)
1		**1b**	84 (**3ba**)
2		**1c**	90 (**3ca**)
3		**1d**	88 (**3da**)
4		**1e**	80 (**3ea**)
5		**1f**	79 (**3fa**)
6		**1g**	85 (**3ga**)
7		**1h**	85 (**3ha**)
8		**1i**	82 (**3ia**)
9		**1j**	87 (**3ja**)
10		**1k**	79 (**3ka**)
11		**1l**	80 (**3la**)
12		**1m**	79 (**3ma**)
13		**1n**	78 (**3na**)
14		**1o**	75 (**3oa**)
15		**1p**	72 (**3pa**)
16		**1q**	75 (**3qa**)
17		**1r**	73 (**3ra**)
18[c]		**1s**	75 (**3sa**)

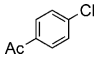
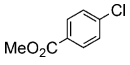
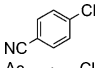
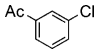
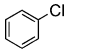
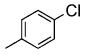
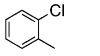
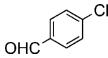
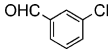
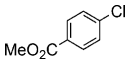
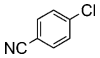
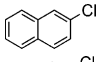
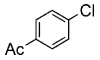
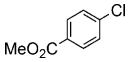
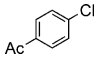
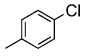
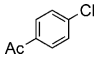
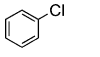
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (1.5 mmol), TBAB (2.0 mmol), TEMPO (0.2 mmol), toluene (3.0 mL), $T = 125$ °C, $t = 12$ h; β-arylated product was not observed in any reaction, as determined by ^{1}H NMR analysis. [b] Isolated yield. [c] **2a** (2.4 mmol) was used.

Table 3. Linear arylation of allylamines with aryl chlorides.[a]



1 2b-f 3

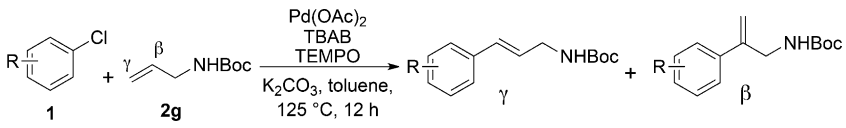
2b: R^1, R^2 = Pht; **2c**: R^1 = Boc, R^2 = Cbz;[b] **2d**: R^1 = Boc, R^2 = Ac; **2e**: R^1 = Boc, R^2 = Me; **2f**: R^1 = CO_2Et, R^2 = CH_2(1-naph)

Entry	Aryl chloride		Olefin	Yield [%][c] (product)
1		**1a**	**2b**	90 (**3ab**)
2		**1b**	**2b**	87 (**3bb**)
3		**1c**	**2b**	91 (**3cb**)
4		**1h**	**2b**	88 (**3hb**)
5		**1l**	**2b**	81 (**3lb**)
6		**1m**	**2b**	80 (**3mb**)
7		**1n**	**2b**	78 (**3nb**)
8		**1t**	**2b**	83 (**3tb**)
9		**1u**	**2b**	81 (**3ub**)
10		**1b**	**2c**	75 (**3bc**)
11		**1c**	**2c**	80 (**3cc**)
12		**1v**	**2c**	81 (**3vc**)
13		**1a**	**2d**	80 (**3ad**)
14		**1b**	**2d**	72 (**3bd**)
15		**1a**	**2e**	80 (**3ae**)
16		**1m**	**2e**	77 (**3me**)
17		**1a**	**2f**	76 (**3af**)
18		**1l**	**2f**	79 (**3lf**)

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (1.5 mmol), TBAB (2.0 mmol), TEMPO (0.2 mmol), toluene (3.0 mL), T = 125 °C, t = 12 h; β-arylated product was not observed in any reaction, as determined by ^{1}H NMR analysis. [b] *N*-carbobenzyloxy. [c] Isolated yield.

However, when the less bulky *N*-Boc-allylamine (**2g**) was tried, lower yields of γ-arylated linear (*E*)-allylamines were obtained owing to the formation of the branched β-arylated products (Scheme 2). These results indicate that the outcome of regioselectivity is highly sensitive to the bulkiness of the *N*-substituent on the allylamine. The existence of two bulky *N*-substituents in the allylamine appears to be necessary for the preferential migration of the aryl moiety onto the γ position rather than the β position of the olefin, whereas sterically less demanding substituents give rise to the formation of a mixture of regioisomers, probably not owing to mechanistic alteration between ionic and neutral pathways but owing to reduction of steric hindrance. Furthermore, *N*-carbobenzyloxy allylamine (**2h**) failed to give any detectable arylation product, probably owing to the decomposition of the substrate under the reaction conditions. The performance of the current catalyst system was also examined in the arylation of a coordinating, electron-rich *N*,*N*-diethyl allylamine (**2i**); however, no reaction could be observed. The strong coordination of the nitrogen atom of **2i** to palladium results in catalyst poisoning, which inhibits the arylation.

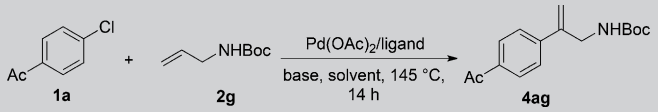
Encouraged by the success of the linear arylation of allylamines, we investigated the internal arylation of allylamines with aryl chlorides. The products obtained are interesting because of their bioactivity as enzyme inhibitors.[22] However, as in the case of γ-arylation, no catalyst has been reported that promotes the β-arylation of allylamines with aryl chlorides. The initial screening studies were performed at 145 °C by using 4-chloroacetophenone (**1a**) and *N*-Boc-allylamine (**2g**) as model coupling partners, with the catalyst prepared in situ from a bidentate ligand and $Pd(OAc)_2$. The effect of different solvents was surveyed initially in the presence of the Pd-dppp catalyst together with NaOAc as the base. Although EG has been identified as a useful solvent for the highly regioselective internal arylation of electron-rich olefins,[10a,13c] the reaction performed in EG in this case only led to the formation of the homocoupling product and the desired product **4ag** was not detected. The oxidative addition of ArCl to Pd^0 occurred readily in EG; however, the following olefin insert step was totally decelerated under the current catalytic conditions. Thus, the homocoupling of **1a** was favored. Neither arylation nor homocoupling was observed in DMF and DMSO, which indicates that no oxidative addition occurred in these solvents. These results led us to envision that a mixed solvent system of EG and DMF or DMSO could inhibit the homocoupling while facilitating the internal arylation. With this in mind, we then examined the reaction in EG/DMSO (1:1) and EG/DMF (1:1). No reaction happened in EG/DMF (Table 4, entry 1); however, the exclusive formation of the internal arylation product **4ag** was observed in EG/DMSO, though in a low yield (5%; entry 2). The EG/DMSO ratio plays an important role in this reaction. The homocoupling product dominated the reaction with the increase in the EG/DMSO ratio to 5:1 (entry 3), whereas decreasing the amount of EG resulted in a complete recovery of the starting



R	Selectivity (γ/β)	Yield [%] (linear product)
4-Ac	36:64	31 (**3ag**)
4-CO_2Me	34:66	28 (**3bg**)

Scheme 2. Mizoroki–Heck arylation of *N*-Boc-allylamine **2g**.

Table 4. Screening conditions for the internal arylation of allylamines **2g** with aryl chloride **1a**.[a]



Entry	Solvent	Ligand	Base	Yield [%][b]
1	EG/DMF (1:1)	dppp	NaOAc	n.d.
2	EG/DMSO (1:1)	dppp	NaOAc	5
3	EG/DMSO (5:1)	dppp	NaOAc	n.d.
4	EG/DMSO (1:2)	dppp	NaOAc	n.d.
5	EG/DMSO (1:1)	dppf	NaOAc	24
6	EG/DMSO (1:1)	dppb[c]	NaOAc	6
7	EG/DMSO (1:1)	4-MeO-dppp[d]	NaOAc	7
8	EG/DMSO (1:1)	4-CF_3-dppp[e]	NaOAc	n.d.
9	EG/DMSO (1:1)	BINAP[f]	NaOAc	n.d.
10	EG/DMSO (1:1)	PPh_3	NaOAc	n.d.
11	EG/DMSO (1:1)	phen[g]	NaOAc	n.d.
12	EG/DMSO (1:1)	dmphen[h]	NaOAc	n.d.
13	EG/DMSO (1:1)	bpy[i]	NaOAc	n.d.
14	EG/DMSO (1:1)	dppf	NEt_3	10
15	EG/DMSO (1:1)	dppf	Cy_2NMe	26
16	EG/DMSO (1:1)	dppf	TBAA	16
17	EG/DMSO (1:1)	dppf	K_2CO_3	n.d.
18	EG/DMSO (1:1)	dppf	Cs_2CO_3	n.d.
19	EG/DMSO (1:1)	dppf	KOH	n.d.
20	EG/DMSO (1:1)	dppf	KOAc	46
21[j]	EG/DMSO (1:1)	dppf	KOAc	16
22[k]	EG/DMSO (1:1)	dppf	KOAc	83

[a] Reaction conditions: **1a** (1.0 mmol), **2g** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), ligand (7.5 mol%), base (1.5 mmol), solvent (3.0 mL), $T = 145\,^{\circ}C$, $t = 14$ h; γ-arylated product was not observed in any reaction, as determined by ^1H NMR analysis. [b] Isolated yield. [c] 1,4-bis(diphenylphosphino)butane. [d] 1,3-bis(bis(4-methoxyphenyl)phosphino)propane. [e] 1,3-bis(bis(4-(trifluoromethyl)phenyl)phosphino)propane. [f] 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [g] 1,10-phenanthroline. [h] 2,9-dimethyl-1,10-phenanthroline. [i] 2,2′-bipyridine. [j] 1.5 equiv. of $[H_2N(iPr)_2][BF_4]$ were added. [k] $t = 24$ h.

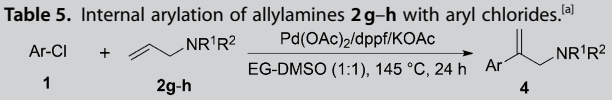
materials (entry 4). A similar promoting effect of DMSO has been observed in the regioselective internal arylation of enamides and allylic alcohol in ionic liquids.[23] To increase the reaction efficiency, the catalytic performances of different bidentate and monodentate ligands were investigated (entries 5–13). Of the ligands tested, dppf was identified as the best choice (entry 5) and other ligands, whether they are bidentate or monodentate, were found to give worse results. Further studies revealed that the base had a dramatic effect on the yield (entries 14–20). KOAc demonstrated the highest reactivity (entry 20), and other bases were not that effective. Inspired by the significant promoting effect of the hydrogen bond donor $[H_2N(iPr)_2][BF_4]$ on the regioselectivity and reaction rate in the arylation of electron-rich olefins with aryl bromides,[13a] we then explored the effect of this salt but the catalytic reactivity was reduced (entry 21). The yield of the product **4ag** could be increased significantly to 83% if the reaction time was increased to 24 h (entry 22). Under the current reaction conditions, no product from γ-arylation was detected. The excellent regioselectivity favoring β-arylation could be partly attributed to the highly ionizing power of EG, which could facilitate the formation of the cationic Pd^{II}–olefin species, which channels the arylation into the ionic pathway (Scheme 1).[10a] Notably, no product from a potentially competing palladium-catalyzed amidation reaction could be detected.[24]

After determining the optimal conditions for the internal arylation of allylamine, we examined the substrate scope of this process, and the results obtained are summarized in Table 5. A number of aryl chlorides underwent smooth olefination with allylamine **2g** with the Pd-dppf catalyst (entries 1–9, 12, and 13), and good to high yields were obtained with good tolerance of different substituents on the aromatic ring. Excellent β-regioselectivities were achieved in all cases and the occurrence of linear arylation was not detected, which implies that the ionic pathway is operating under the current reaction conditions. The protocol is not limited to aryl chlorides; it could be equally applied to heteroaryl chloride (entry 11). The reaction involving electron-neutral chlorobenzene (**1l**) did not proceed under the current reaction conditions, but replacing dppf with 4-MeO-dppp resulted in a good yield of the desired product (entry 10). However, the electron-rich aryl chlorides failed to give any detectable arylation product with either dppf or 4-MeO-dppp as the ligand.

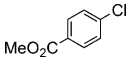
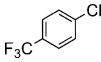
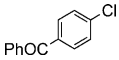
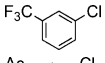
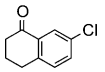
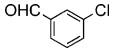
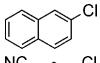
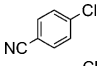
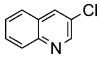
The combination of $Pd(OAc)_2$ and dppf also enabled the highly regioselective internal arylations of allylamine **2h** to exclusively provide the β-arylated products in good yields (entries 15 and 16). Notably, the activity and selectivity of the current catalyst system appears to correlate with the steric characteristics of the substituent on allylamine nitrogen, because no conversion was observed in the reaction involving sterically demanding *N*,*N*-diprotected allylamine **2a** and **2e**. Further study indicated that the electron-rich allylamine **2i** also failed to give any detectable arylation product, presumably owing to catalyst poisoning due to the strong coordination of the nitrogen atom of **2i** to Pd^{II}.

From the above studies, it is evident that both the steric and electronic properties of allylamine substrates have a significant effect on the catalytic activity and selectivity. In the case of linear arylation, it appears that the use of bulky *N*,*N*-diprotected allylamides as coupling partners is necessary for high catalytic performance. The chelation between the carbonyl oxygen atom and the palladium atom in the neutral intermediate **A** could promote a highly regioselective migration of the aryl moiety onto the γ, rather than β, position of the olefin to give intermediate **B**, which undergoes regio- and stereoselective β-H elimination to furnish the expected product [Scheme 3, reaction (1)]. With the decreased steric demand from the amino moiety, β-arylation may become possible, which leads to regioisomers in the case of **2g**. Similar chelation-assisted regio- and stereocontrol has also been reported in the palladium-catalyzed linear arylation of allyl derivatives and vinyl derivatives.[1b,g,17j,25,26] In contrast, the ionic pathway, made possible by the chelating diphosphine and the ionizing EG, may feature the formation of an ionic intermediate **C**[16a,b,17b] as a result of the olefin chelation to the Pd^{II}, in which

Table 5. Internal arylation of allylamines **2g–h** with aryl chlorides.[a]

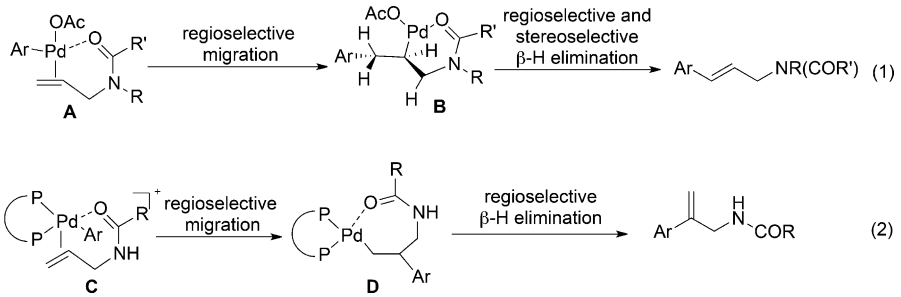


2g: R^1 = Boc, R^2 = H
2h: R^1 = Cbz,[b] R^2 = H

Entry	Aryl chloride		Olefin	Yield [%][c] (product)
1		**1b**	**2g**	86 (**4bg**)
2		**1c**	**2g**	83 (**4cg**)
3		**1d**	**2g**	76 (**4dg**)
4		**1e**	**2g**	80 (**4eg**)
5		**1g**	**2g**	79 (**4gg**)
6		**1h**	**2g**	75 (**4hg**)
7		**1i**	**2g**	78 (**4ig**)
8		**1j**	**2g**	75 (**4jg**)
9		**1k**	**2g**	73 (**4kg**)
10[d]		**1l**	**2g**	73 (**4lg**)
11		**1p**	**2g**	70 (**4pg**)
12		**1u**	**2g**	74 (**4ug**)
13		**1v**	**2g**	72 (**4vg**)
14		**1w**	**2g**	72 (**4wg**)
15		**1c**	**2h**	70 (**4ch**)
16		**1p**	**2h**	68 (**4ph**)

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), KOAc (1.5 mmol), EG/DMSO (1:1, 3.0 mL), $T = 145\,^{\circ}C$, $t = 24$ h; γ-arylated product was not observed in any reaction, as determined by ^1H NMR analysis. [b] *N*-carbobenzyloxy. [c] Isolated yield. [d] 4-MeO-dppp was used instead of dppf.

steric repulsion from the chelating ligands could facilitate the formation of intermediate **D**, which thus furnishes the branched product after β-H elimination [Scheme 3, Eq. (2)].



Scheme 3. Possible pathways for high stereoselectivity and regioselectivity.

The failure of *N*,*N*-diprotected allylamides in internal β-arylation may be traced to the bulkiness of the substituent on nitrogen, which impedes the insertion of the olefin into the Pd–Ar bond. The ionic pathway could be possible with **2g** even in the absence of dppf, with **2g** itself acting as a chelating ligand, which thus promotes the formation of the ionic species analogous to **C** and hence some branched arylation products.

Conclusions

We have developed two efficient palladium catalyst systems for the highly regioselective Mizoroki–Heck reaction of aryl chlorides with *N*,*N*-diprotected and *N*-protected allylamine derivatives. In the presence of $Pd(OAc)_2$ and appropriate additives, *N*,*N*-diprotected allylamines underwent the highly regio- and stereoselective arylation with aryl chlorides to exclusively give the γ-arylated allylamines in good to excellent yields under ligand-free conditions and a wide range of functionalities in both coupling partners could be well tolerated. In contrast, the catalyst prepared in situ from $Pd(OAc)_2$ and 1,1′-bis(diphenylphosphino)ferrocene worked effectively to catalyze the highly regioselective internal arylation of *N*-protected allylamines with aryl chlorides in ethylene glycol/DMSO, which afforded high yields of the β-arylated allylamines and good group compatibility. Ethylene glycol/DMSO facilitates the dissociation of chloride anions from Pd^{II}, which furnishes the key ionic Pd^{II}–olefin intermediate responsible for the β-product, as well as inhibits the homocoupling side reaction of aryl chlorides. Our results reveal that the catalytic activity and regiocontrol in both linear and internal arylations demonstrate high sensitivity to the steric and electronic properties of allylamines. Further investigations on the mechanism of the reaction and synthetic applications are underway in our laboratory and will be reported in the future.

Experimental Section

General

The NMR spectra were recorded at 400 MHz. The chemical shifts were recorded relative to tetramethylsilane and with the solvent resonance as the internal standard. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Unless otherwise noted, all experiments were performed in a nitrogen atmosphere. The chloroarenes, palladium complexes, and other common materials and solvents are commercially available and were used as received without further purification.

General procedure for the Mizoroki–Heck linear arylation of allylamines

An oven-dried pressure tube containing a stir bar was charged with an aryl chloride **1** (1.0 mmol), allylamine (1.2 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), K_2CO_3 (207.3 mg, 1.5 mmol), TBAB (644.8 mg, 2.0 mmol), TEMPO

(31.3 mg, 0.2 mmol), and toluene (3.0 mL) under nitrogen atmosphere at RT. After degassing thrice, the flask was placed in an oil bath and the mixture was stirred and heated at 125 °C. After 12 h, the flask was removed from the oil bath and cooled to RT. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was then purified by using flash chromatography on silica gel with a mixture of ethyl acetate and hexane to give the pure product.

General method for the Mizoroki–Heck internal arylation of allylamines

An oven-dried pressure tube containing a stir bar was charged with an aryl chloride **1** (1.0 mmol), allylamine (3 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), dppf (41.6 mg, 0.075 mmol), K_2CO_3 (207.3 mg, 1.5 mmol), and EG/DMSO (1:1, 3.0 mL) under nitrogen at RT. After degassing thrice, the flask was placed in an oil bath and the mixture was stirred and heated at 145 °C. After 24 h, the flask was removed from the oil bath and cooled to RT. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3× 10 mL). The aqueous solution was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The internal arylated allylamine product was isolated by using flash chromatography on silica gel with a mixture of ethyl acetate and hexane.

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