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Palladium-catalyzed highly regioselective and stereoselective arylation of electron-rich allylamines with aryl bromides

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ABSTRACT

A palladium-catalyzed, highly efficient Heck arylation of electron-rich *N*,*N*-diprotected allylamine derivatives with a wide range of aryl bromides under ligand-free conditions has been developed. In the presence of $Pd(OAc)_2$ and an appropriate additive, the reaction proceeds with excellent regioselectivity and stereoselectivity, leading exclusively to the γ-arylated (*E*)-allylamine products in good to excellent yields. It was found that the choice of solvent, olefin, additive and temperature has an important influence on the reaction. Worthy of note is that good results were observed only when using *N*,*N*-diprotected allylamines containing carbamate moiety, and the steric properties of allylamines also have important impacts on the regiocontrol. The use of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or HQ (hydroquinone) as the additive is also crucial for securing a faster reaction rate. This method provides a straightforward approach for the efficient synthesis of various γ-arylated, linear (*E*)-allylamines.

1. Introduction

Allylamines are widespread structural units in a large number of natural and biologically active compounds, and the presence of two highly versatile functional groups renders them valuable substrates for many types of reactions to afford useful products.[1,2] Because of their importance, it is not surprising that much effort has been devoted to the efficient construction of these compounds.[1,3] Consequently, a variety of methods for the synthesis of various functionalized allylamines can now be found in the literature. However, despite the progress made in this area, there is still significant room for improvement of the synthetic efficiency, for example, in terms of reactivity and selectivity.

The Pd-catalyzed Heck reaction has become one of the most powerful tools for the construction of C–C bonds in organic synthesis owing to its simplicity and tolerance of various functional groups.[4] Over the past two decades, improved strategies have been developed to broaden its application, particularly toward highly regioselective arylation of electron-rich olefins, such as vinyl ethers, allylic alcohol derivatives, and enamides.[5–14] In this regard, the application of Pd-catalyzed Heck arylation of electron-rich allylamines to prepare arylated allylamines has recently gained much attention.[2d,2f,2i,15–18] However, this kind of transformation is often complicated by the formation of mixtures of internal and terminal regioisomers (Scheme 1). The efforts of Hallberg and Larhed,[16a,b] Wu[16c] and Baxter[2i] have resulted in useful strategies for highly selective internal β-arylation of allylamine derivatives. However, the γ-regioselective arylation of allylamines has not been well-developed. Ripin[17a] and Wilson[17b] reported that Pd-catalyzed highly regioselective and stereoselective terminal γ-arylation of allylamine derivatives could be accomplished in alcoholic solvents under ligand-free conditions to give exclusively linear (*E*)-allylamine products, but only one aryl iodide substrate was attempted, and the general utility of this chemistry has not been explored. Very recently, Sigman,[18a] Cacchi[18b] and Correia[18c] 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 arenediazonium salt, such as instability and explosive potential. Considering the importance of γ-arylated allylamines in chemical synthesis and particularly that leading to biologically active compounds,[19] it is of great interest to

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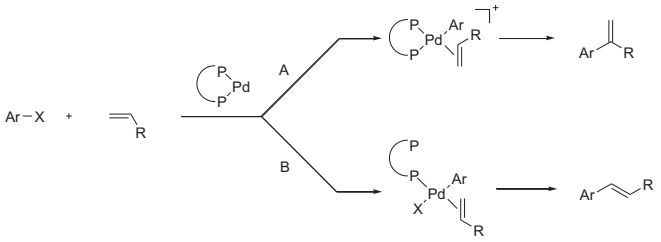


Scheme 1. Formation of regioisomers via two competing pathways in the Heck reaction.

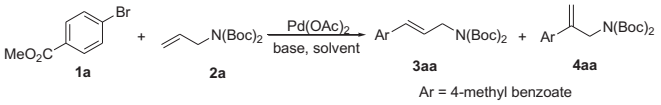
develop practical and highly efficient catalytic synthetic methods to access these compounds from safe and stable aryl halides. In continuing our research in regioselective Heck arylation of electron-rich olefins,[7,9,11] herein we report that, in the presence of $Pd(OAc)_2$ catalyst and appropriate additive, electron-rich *N*,*N*-diprotected allylamines could undergo highly efficient γ-arylation with aryl bromides under ligand-free conditions, affording the desired (*E*)-allylamine products in good to excellent yields in a highly regioselective and stereoselective manner.

2. Results and discussion

We started our investigation with methyl 4-bromobenzoate (**1a**) as the model substrate and *N*,*N*-$(Boc)_2$-allylamine (**2a**) as the model olefin under various reaction conditions (Table 1). Initially, the coupling reaction was carried out in CH_3CN at 85 °C with $Pd(OAc)_2$/PPh_3 as catalyst and K_2CO_3 as the base. Only the linear (*E*)-allylamine product **3aa** was observed, while the internal isomer **4aa** or the *Z* isomer could not be detected after 12 h (Table 1, entry 1). This result indicates that the reaction follows the neutral route (Scheme 1, path B), and the ionic pathway (Scheme 1, path A) is either completely suppressed or its involvement in the arylation is insignificant. Similar experimental observations have been reported in the regioselective Heck coupling reaction of **2a** with aryl iodide and arenediazonium salts under ligand-free conditions.[17a,18] In view of the significant advantage of ligand-free conditions, we then decided to examine the reaction of **1a** and **2a** in the absence of ligand. However, employing Ripin's protocol[17a] resulted in no reaction (Table 2, entry 2). The combination of $Pd_2(dba)_3$, NaOAc and NEt_3, which was reported to work well for the regioselective linear arylation of *N*-allyl-2-methoxyacetamide with aryl iodide,[17b] gave similarly poor result (Table 2, entry 3). Delightfully, the reaction in CH_3CN remained active and regioselectivity was unchanged in the absence of a ligand (Table 2, entry 4). In order to further improve the efficiency, a number of solvents were screened. The use of DMSO, dioxane and toluene afforded the desired product **3aa** in higher yields of 77–81% (Table 1, entries 5–7), and the highest yield of 85% was observed in DMF (Table 1, entry 8). Although ethylene glycol (EG) has been recently identified as a useful solvent for highly regioselective internal arylation of electron-rich olefins,[9] no reaction occurred in this case (Table 1, entry 9). The use of $Pd(OAc)_2$ as a source of palladium was essential for this transformation, with catalysts derived from other Pd precursors being not very efficient (Table 1, entries 10–12). For comparison, the performance of other bases, including Cs_2CO_3, K_3PO_4, KOAc, KO*t*Bu and tetrabutylammonium acetate (TBAA) (Table 1, entries 13–17), was investigated, but none of them could work as effectively as K_2CO_3. The effect of additive was also studied. When 10 mol % HQ was introduced, the reaction could go to completion in 6 h, exclusively giving the desired product **3aa** in 82% yield (Table 1, entry 18). The reaction could proceed more quickly at 100 °C, giving a full conversion in 3 h with a slightly higher yield (Table 1, entry 19). When the temperature was increased to 120 °C, the reaction finished in 1.2 h, but the yield diminished due to the formation of side products (Table 1, entry 20). Interestingly, replacing HQ with TEMPO could enable the reaction to finish in 1.2 h at 100 °C with 89% yield (Table 1, entry 21). It is clear that TEMPO is a better choice. A further increase to 1 equiv TEMPO had negligible effect on the reactivity (Table 1, entry 22). HQ or TEMPO may either inhibit the polymerization of the olefin or function as a ligand or both. The accelerating effect of the free-radical scavenger in Pd-catalyzed cross-coupling reactions has been recently disclosed in the literature.[20] We tried the effect of tetrabutylammonium bromide and tetrabutylammonium chloride, which have been shown to promote the Heck reaction,[21] but none of them led to an increase in yield. The effect of reducing agents, such as hydrazine and sodium formate were also examined, but no acceleration was observed.[22]

Having established the optimal reaction conditions, we then explored the reaction of **2a** with a range of aryl bromides. As summarized in Table 2, all the reactions proceeded rapidly, with reaction times of as short as less than 2 h observed in some cases (Table 2, entries 1–5). It is notable that all reactions exhibited excellent regioselectivivites (terminal/internal>99:1) and no *Z* isomers could be observed in these transformations. The reaction afforded good to excellent yields of the expected γ-arylated linear (*E*)-allylamines, tolerating electronically different substituents on the aromatic ring. No significant electronic effect on the isolated yield of the desired products was observed, but the reaction proceeded slightly faster in the olefination of electron-deficient aryl bromides (Table 2, entries 1–10), and slightly longer reaction times were needed for the electron-rich ones (Table 2, entries 12–15). The

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



Entry	Solvent	Base	Time (h)	Yield (%)[b]	**3aa**/**4aa**[c]
1[d]	CH_3CN	K_2CO_3	12	30	>99/1
2[e]	*i*PrOH	NEt_3	12	nd	nd
3[e]	EtOH	NaOAc	12	nd	nd
4	CH_3CN	K_2CO_3	12	30	>99/1
5	DMSO	K_2CO_3	12	81	>99/1
6	dioxane	K_2CO_3	12	77	>99/1
7	toluene	K_2CO_3	12	80	>99/1
8	DMF	K_2CO_3	12	85	>99/1
9	EG	K_2CO_3	12	nd	nd
10[e]	DMF	K_2CO_3	12	80	>99/1
11[f]	DMF	K_2CO_3	12	82	>99/1
12[g]	DMF	K_2CO_3	12	44	>99/1
13	DMF	Cs_2CO_3	12	nd	nd
14	DMF	K_3PO_4	12	83	>99/1
15	DMF	KOAc	12	55	>99/1
16	DMF	KO*t*Bu	12	nd	nd
17	DMF	TBAA	12	76	>99/1
18[h]	DMF	K_2CO_3	6	82	>99/1
19[h,i]	DMF	K_2CO_3	3	86	>99/1
20[h,j]	DMF	K_2CO_3	1.2	75	>99/1
21[i,k]	DMF	K_2CO_3	1.2	89	>99/1
22[i,l]	DMF	K_2CO_3	1.2	89	>99/1

[a] Unless otherwise noted, all reactions were carried out with **1a** (1.0 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (1 mol %), base (2.0 mmol), solvent (3.0 ml), 85 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis. When no β-arylated product was detected, a value of >99/1 was assigned.
[d] 2 mol % PPh_3 was added.
[e] $Pd_2(dba)_3$ was used to replace $Pd(OAc)_2$.
[f] $PdCl_2$ was used to replace $Pd(OAc)_2$.
[g] $Pd(COCF_3)_2$ was used to replace $Pd(OAc)_2$.
[h] 10 mmol% HQ was added.
[i] Reaction temperature 100 °C.
[j] Reaction temperature 120 °C.
[k] 10 mmol% TEMPO was added.
[l] 1.0 equiv TEMPO was added.