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Chelation-Mediated Palladium(II)-Catalyzed Domino Heck−Mizoroki/Suzuki−Miyaura Reactions Using Arylboronic Acids: Increasing Scope and Mechanistic Understanding

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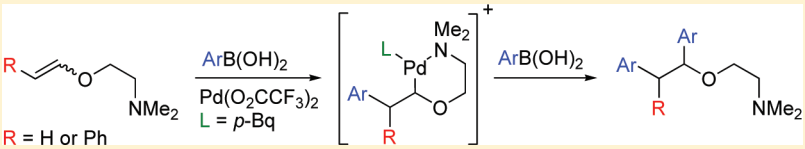
Supporting Information

ABSTRACT:



A palladium(II)-catalyzed Heck−Mizoroki/Suzuki−Miyaura domino reaction involving metal coordinating dimethylaminoethyl vinyl ethers and a number of electron-rich and electron-deficient arylboronic acids has been developed. Through variation of the temperature and the concentration of the *p*-benzoquinone (*p*-Bq) ligand/reoxidant, conditions for the robust and convenient one-pot generation of diarylated-saturated ethers were identified. With the aid of coordination of the dimethylamino group to the arylpalladium intermediate, the otherwise predominant formation of the β-arylated olefin could be reversed. A reaction route involving a chelation-controlled carbopalladation, providing a *p*-Bq stabilized six-membered palladacycle, followed by transmetalation and reductive elimination is suggested to explain the selective formation of saturated diarylated ether products.

INTRODUCTION

Palladium-catalyzed coupling reactions continue to be one of the most important tools for the construction of C−C bonds in organic synthesis, with the Heck−Mizoroki reaction playing a prominent role for the arylation and vinylation of olefins.[1] The first palladium(0)-catalyzed arylations of an alkene with an organic halide were reported independently by Mizoroki[2] and Heck[3] in the early 1970s. This was followed by Heck's discovery in 1975 of an analogous palladium(II)-mediated vinylation of an olefin using a vinylboronic acid and stoichiometric amounts of palladium acetate.[4] Despite the fact that reoxidizing agents had been reported to enable palladium(II) catalysis in the 1960s,[5] the field of palladium(II)-catalyzed Heck reactions would not emerge until in 2001.[6] This was a result of an innovation in terms of preparative viability by Mori and co-workers utilizing $Cu(OAc)_2$ as the reoxidant to regenerate Pd(II) from Pd(0).[6] In addition, Jung reported in 2003 that molecular oxygen could serve as a capable reoxidant of palladium in a vinylic substitution reaction with arylboronic acids,[7] a transformation that gradually became known as the oxidative Heck reaction.[8,9]

Today, palladium(II)-catalyzed oxidative Heck−Mizoroki arylation reactions have been developed into smooth and high-yielding synthetic methods.[10,11] Arylboronic acids[6,12−16] are commonly employed arylpalladium precursors in the oxidative Heck reaction, but other arylating agents have also been reported, e.g., arylstannanes,[17] arylsilanes,[18,19] arylmercury,[20] arylphosphonic acids,[21] arylbismuth,[22] and arylantimony[23] compounds.

In the endeavor toward more preparatively feasible and environmentally benign methods for the synthesis of organic compounds, there is an emerging interest to incorporate different palladium-catalyzed reactions into one-pot domino reactions.[24,25] Palladium(0)-catalyzed domino processes have received special attention for the mild, selective, and modular construction of highly functionalized molecules.[26,27] Although these advancements have facilitated the preparative procedures immensely, they are still limited to substrates (or substrate combinations) with both a palladium(0)-activated leaving group and a palladium(II) reactive functionality.[28] With these considerations in mind, there is a timely need to expand the scope of palladium-catalyzed domino reactions to utilize the oxidative palladium(II)-catalyzed pathway using arylboronic acids as arylating agents.

Sequential one-pot transformations initiated by a palladium(II)-catalyzed transmetalation and a subsequent Heck−Mizoroki carbopalladation involve a reactive σ-alkyl palladium(II) intermediate. Depending on the substrate and the catalytic conditions, it is often possible to react the transient σ-alkyl palladium(II) species in situ through various cross-coupling reactions, yielding difunctionalized target structures.[29,30] The ability of intramolecular factors to overcome the reluctance of substituted alkenes to participate in the Heck insertion process,

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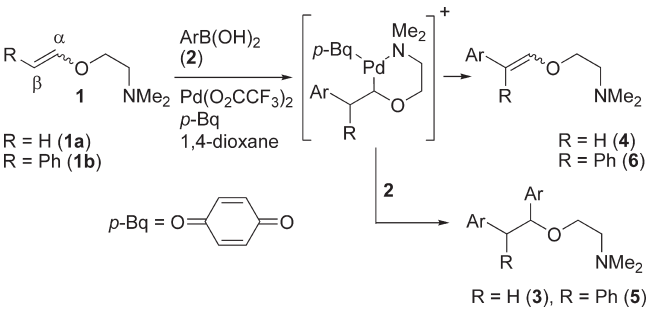
Scheme 1. Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Approach Toward Diarylated Ethers via a Stabilized σ-Alkyl Palladium(II) Intermediate



in combination with stabilization of the unstable σ-alkyl palladium(II) intermediate, allows the assembly of complex and sterically congested molecules.[31]

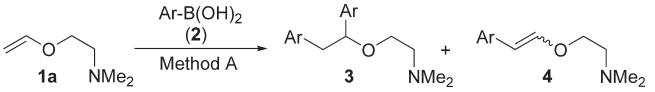
We[31−33] and others[34−36] have previously reported on pseudointramolecular metal catalyst presentation both to increase the reactivity of sterically hindered systems and to control the regioselectivity in palladium(0)-catalyzed Heck reactions.[37] The observed increase in reaction rate using olefins with a coordinating metal-directing auxiliary inspired us to explore chelating olefins in the oxidative Heck reaction. Surprisingly, while studying different reoxidants, we discovered that the use of the well-known reoxidant *p*-benzoquinone (*p*-Bq) delivered saturated 1,2-diarylated products and not the expected vinylic substitution products, when employing a catalyst-coordinating dimethylaminoethyl substituted vinyl ether and electron-rich arylboronic acids as coupling substrates (Scheme 1).[38] With the limitation to electron-rich arylboronic acids in mind, we decided not only to extend the scope of this process to allow domino coupling with electron-deficient arylboronic acids but also to elucidate the importance and structural requirements of the palladium(II) coordinating moiety of the vinyl ether.

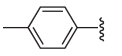
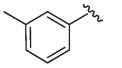
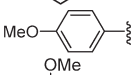
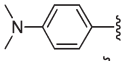
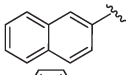
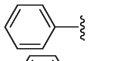
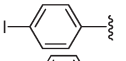
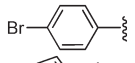
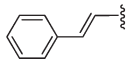
We herein report a dimethylamino-auxiliary controlled palladium(II)-catalyzed domino reaction that delivers 2-(1,2-diarylethoxy)-*N*,*N*-dimethylethanamines (**3**) and 2-(1,1,2-triarylethoxy)-*N*,*N*-dimethylethanamines (**5**) from electron-deficient arylboronic acids (**2**) and mono- (**1a**) or 1,2-disubstituted vinyl ethers (**1b**) in high selectivity, avoiding the formation of Heck products **4** and **6** (Scheme 1). In addition, we also establish the importance of the two-carbon tethered dimethylamino moiety in combination with *p*-Bq for the stabilization of the σ-alkyl palladium(II) intermediate and formation of the diarylated product **3** or **5**.

RESULTS

Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reactions with Electron-Rich Arylboronic Acids. For the domino diarylation-reduction with electron-rich arylboronic acids, early results during the development phase revealed that base-free conditions with a 1:3 ratio of **1a**/**2** was beneficial in combination with 1,4-dioxane as solvent.[38] Other more polar solvents (acetonitrile, DMF, and especially DMSO) favored the β-monoarylated Heck byproduct **4** as an (*E*)/(*Z*)-mixture, whereas toluene resulted in poor reaction rates. $Pd(O_2CCF_3)_2$ was quickly identified as the catalyst of choice, as other Pd-sources such as $Pd(acac)_2$ and $Pd(OAc)_2$ reduced the yield of product **3**

Table 1. Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reaction[e] with 1a and Electron-Rich Arylboronic Acids[38]



entry	Ar		time (h)	yield **3** (%)[a]	yield **4** (%)
1		**2a**	12 12[b]	**3a** (82) **3a** (n.d.)	**4a** (n.d.) **4a** (n.d.)
2		**2b**	24	**3b** (66)	**4b** (6)[c]
3		**2c**	12	**3c** (92)	**4c** (n.d.)
4		**2d**	24	**3d** (66)	**4d** (10)[c]
5		**2e**	24	**3e** (48)	**4e** (1)[d]
6		**2f**	12	**3f** (49)	**4f** (n.d.)
7		**2g**	24	**3g** (50)	**4g** (n.d.)
8		**2h**	12	**3h** (81)	**1b** (n.d.)
9		**2i**	24	**3i** (11)	**4i** (15)[c]
10		**2j**	18	**3j** (66)	**4j** (<1)[d]
11		**2k**	24	**3k** (28)	**4k** (15)[c]
12		**2l**	24	**3l** (47)	**4l** (n.d.)
13		**2m**	12	**3m** (65)	**4m** (n.d.)

[a] Isolated yield. Purity >95% by GC−MS. [b] Reaction performed according to Method A but without *p*-Bq. [c] By ^{1}H NMR of the crude product. [d] By GC−MS. n.d. = not detected. [e] Method A: **1a** (1 equiv, 0.35 mmol), **2** (3 equiv), *p*-Bq (1 equiv), and $Pd(O_2CCF_3)_2$ (5 mol %) in 2.4 mL of 1,4-dioxane at 40 °C (preheated metal block).

significantly. A reaction temperature of 40 °C (Method A) proved to be the most appropriate, as higher or lower temperatures resulted in larger amounts of **4** or reduced the reaction rate, respectively. The exclusion of *p*-Bq furnished a completely unproductive reaction, yielding neither **3a** nor **4a** (entry 1, Table 1). A reaction between **1a** and **2a** with no *p*-Bq and 100 mol % $Pd(O_2CCF_3)_2$ resulted solely in the formation of **4a**. The preparative outcomes for the diarylation-reduction of **1a** are presented in Table 1.

The selectivity and yields of the domino product **3** were in general moderate to excellent regardless of the *ortho*-, *meta*-, and *para*-substitution pattern. Thus, alkyl-, methoxy-, and dimethylamino substituted arylboronic acids **2a**−**f** provided 48−92% isolated yield of **3a**−**f** (entries 1−6, Table 1). The 2-dimethylamino isomer of the 4-substituted boronic acid **2f** produced only a poor mixture of less than 10% β-monoarylated Heck byproduct and no detectable amounts of diarylated product. This is possibly due to palladium(II)-coordination of the 2-dimethylamino group. *p*-Iodophenylboronic acid (**2i**) produced only 11% yield

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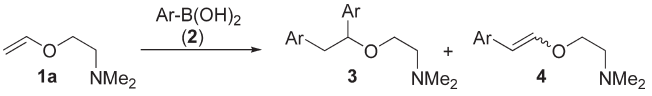
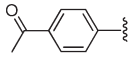
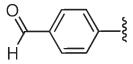
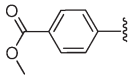
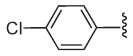
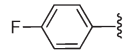
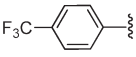
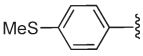
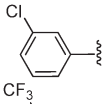
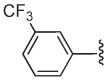
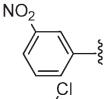
Table 2. Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reaction[f] with 1a and Electron-Deficient Arylboronic Acids



entry	Ar		method	yield 3	(%)[a]	3/4 ratio[b]
1		**2n**	B	**3n**	59	99:1
			C		54	99:1
			D		51	99:1
			E		36	99:1
			B[c]		0	n.d.
2		**2o**	B	**3o**	57	n.d.
3		**2p**	B	**3p**	50	90:10
			F		42	95:5
4		**2q**	B	**3q**	57	n.d.
			G		24	n.d.
5		**2r**	B	**3r**	68	n.d.
			H		4	n.d.
6		**2s**	B	**3s**	50	n.d.
			F		20	n.d.
			H		3	n.d.
7		**2t**	B[d]	**3t**	43	n.d.
			A[e]		43	
8		**2u**	B	**3u**	28	n.d.
9		**2v**	B	**3v**	39	99:1
10		**2w**	B	**3w**	52	n.d.
			F		20	
11		**2x**	B	**3x**	8	80:20

[a] Isolated yield. Purity >95% by GC−MS. [b] By ^{1}H NMR of the crude product and GC−MS. [c] Reaction performed according to Method B but without *p*-Bq. [d] Reaction performed according to Method B but for 12 h. [e] Reaction performed according to Method A for 24 h. n.d. = **4** not detected. [f] Method B: **1a** (1.0 equiv, 0.43 mmol), **2** (3.0 equiv), $Pd(O_2CCF_3)_2$ (5 mol %), and *p*-Bq (1.1 equiv) in 2.5 mL of 1,4-dioxane at 60 °C (preheated metal block) for 2 h. Method C: 0.90 equiv of *p*-Bq. Method D: 0.75 equiv of *p*-Bq. Method E: 0.5 equiv of *p*-Bq. Method F: MW irradiation, sealed vessel, 100 °C for 20 min. Method G: MW irradiation, sealed vessel, 100 °C for 30 min. Method H: 1.1 equiv of MA instead of *p*-Bq.

of **3i** and 15% yield of β-monoarylated Heck byproduct **4i**, most likely due to extensive dehalogenation as well as formation of the biaryl product (entry 9, Table 1). *p*-Bromophenylboronic acid on the other hand yielded 66% of **3j** and only trace amounts of β-monoarylated byproduct **4j**. Thus, the reaction was highly chemoselective with no palladium(0)-mediated C−Br activation (entry 10, Table 1). The outcome of the 3-thiophene substrate **2l** was superior to its 2-thiophene counterpart **2k** both in terms of the isolated yields of **3l** and **3k**, respectively, and the diarylation-reduction selectivity (entries 11 and 12, Table 1). (*E*)-2-Phenylvinylboronic acid resulted in a good yield of 65% for the divinylation-reduction product **3m** with no detectable amounts of **4m** (entry 13, Table 1).

Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reactions with Electron-Deficient Arylboronic Acids. As the first test system with electron-deficient arylboronic acids, the reaction of *p*-acetylphenylboronic acid (**2n**) with **1a** was performed in an open vessel with 5% $Pd(O_2CCF_3)_2$ in 1,4-dioxane at 0.43 mmol scale under base-free conditions. Compared to previous results with electron-rich arylboronic acids, the reaction temperature had to be increased to 60 °C to achieve full conversion of **1a**. The selectivity between the β-monoarylated byproduct **4n** and diarylation-reduction product **3n** was unaffected by the concentration of *p*-Bq. However, the isolated yield of **3n** decreased with a reduced *p*-Bq concentration (entry 1, Methods B−E, Table 2). The diarylation-reduction of olefin **1a** with arylboronic acid **2n** furnished the highest isolated yield (59%) in the presence of 1.1 equiv *p*-Bq (Method B). Further attempts to improve the protocol by changing solvents or increasing the reaction time were not successful. Next, we decided to explore the preparative scope of the *p*-Bq-promoted base-free Heck−Mizoroki/Suzuki−Miyaura protocol by employing the different electron-deficient arylating agents **2o−x** using Method B. The results of the preparative reactions are outlined in Table 2. Interestingly, all domino products with a *para*-substituent on the aromatic system (**3n−s**) except for **3t** were obtained in good isolated yields (50−68%), although the **3**/**4** ratio was only 90:10 for **2p**. Interestingly, the sulfur-containing, and potentially Pd(II)-coordinating, **2t** produced 43% yield of **3t** without any traces of **4t** under both Method A and Method B conditions (entry 7, Table 2).[39] In the case of *meta*-substituted **2u−w** the outcome was more varied, providing 52% yield of the 3-nitrophenyl product **3w**, but only 28% of 3-chloro functionalized **3u** (entries 8−10, Table 2). The use of a conformationally restrained *ortho*-substituted arylboronic acid substrate, as in **2x**, turned out to partly inhibit the tandem reaction and decrease the **3**/**4** ratio (entry 11).

In order to accelerate the reactions, four experiments were also carried out in sealed vessels under controlled microwave (MW) irradiation using the otherwise identical Method B reaction system.[40−42] Full conversion of **1a** could be obtained after only 20−30 min reaction time at 100 °C (Methods F and G, Table 2). With MW heating the yields of **3** were reduced to 20−42%, although the selectivity for the diarylation-reduction process remained unaffected (entries 3, 4, 6, 10, Table 2).[43]

Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reactions with Sterically Hindered 1,2-Disubstuted Vinyl Ether. To investigate if the reaction was compatible with a more hindered 1,2-disubstituted vinyl ether, e.g., to explore whether the palladium(II) coordinating dimethylamino group could promote the formation of 2-(1,1,2-triarylethoxy)-*N*,*N*-dimethylethanamines **5**, the β-phenylated olefin **1b** was prepared as a mixture of (*E*) and (*Z*) isomers by a Pd(0)-catalyzed Heck−Mizoroki reaction using bromobenzene as the coupling substrate.[31] Purification by standard flash silica chromatography gave pure **1b** containing mainly the (*Z*) isomer [(*Z*)/(*E*) = 78:22, sample **1b′**]. By preparative silica gel TLC we were able to isolate a small amount of almost pure (*Z*)-**1b** [(*Z*)/(*E*) = 96:4, sample **1b″**] and (*E*)-**1b** [(*Z*)/(*E*) = 8:92, sample **1b‴**]. The selective domino reaction also proceeded with

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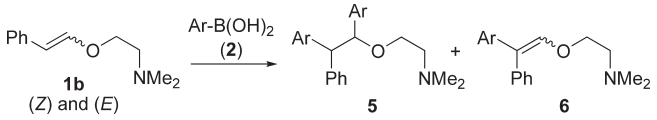
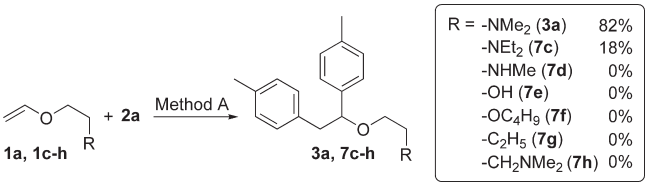
Table 3. Domino Heck−Mizoroki/Suzuki−Miyaura Reaction with β-Phenyl Substituted 1b and Arylboronic Acids



Ar	(*Z*)-**1b**/(*E*)-**1b** ratio	method[a] (sample of **1b**)	yield of **5** (%)[b]	**5**/**6** ratio[c]	**5**/**5*** ratio[d]
2h	78:22	I (**1b′**)	**5h**, 38	98:2	
2h	96:4	J (**1b″**)	**5h**, 31	95:5	
2h	8:92	K (**1b‴**)	**5h**, 18	93:7	
2n	78:22	I (**1b′**)	**5n**, 35	n.d.	72:28
2o	78:22	I (**1b′**)	**5o**, 30	98:2	71:29
2s	78:22	I (**1b′**)	**5s**, 30	n.d.	73:27
2s	96:4	J (**1b″**)	**5s**, 25	n.d.	76:24
2s	8:92	J (**1b‴**)	**5s**, 10	90:10	26:74

[a] Method I: **1b′** (1.0 equiv, 0.42 mmol), **2** (3.0 equiv), $Pd(O_2CCF_3)_2$ (5 mol %), and *p*-Bq (1.1 equiv) in 2.5 mL of 1,4-dioxane at 60 °C for 20 h. Method J: **1b″** (1.0 equiv, 0.13 mmol) at 60 °C for 53 h. Method K: **1b‴** (1.0 equiv, 0.09 mmol) at 60 °C for 53 h. [b] Isolated yield. Purity >95% by GC−MS. [c] By ^{1}H NMR of the crude product and GC−MS. n.d. = **6** not detected. [d] Diastereomeric ratio by ^{1}H NMR of the crude product.

Scheme 2. Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reaction with Analogues of Vinyl Ether 1a



β-phenylated olefin **1b** and arylboronic acids **2h**, **2n**, **2o** and **2s**, although not as smoothly as with unhindered **1a** (10−38% isolated yield of **5**, Table 3). However, the reaction yield depended on the configuration of the starting olefin, indicating that the (*Z*) isomer (**1b′** and **1b″**) is more favorable for the domino reaction than the (*E*) analogue (**1b‴**). Employing the (*E*) isomer enriched fraction **1b‴** also produced detectable formation of the unsaturated diarylated product **6**. According to ^{1}H NMR product analysis, the opposite diastereomeric ratio (**5**/**5***) was obtained when starting from **1b′** or **1b″** when compared to **1b‴** (Table 3).

Domino Oxidative Heck−Mizoroki/Suzuki−Miyaura Reactions with Analogues of Monosubstituted Vinyl Ether 1a. To investigate the importance of the coordinating dimethylamino auxiliary of vinyl ether **1a**, a series of test reactions were run in which the dimethylamino moiety was replaced with a set of other functionalities in the C2-position. Olefins **1c**−**h** were evaluated using the optimized reaction conditions for the diarylation-reduction of **1a** and the high yielding *p*-tolylboronic acid **2a** (entry 1, Method A, Table 1). The outcomes of these reactions are presented in Scheme 2. The diethylamino substituted vinyl ether **1c** exhibited a lower reaction rate than **1a** as relatively high amounts of remaining **1c** could be detected by GC−MS after 12 h of stirring, and isolation of the diarylation-reduction product **7c** resulted in 18% yield. No unsaturated Heck product was detected in the reaction mixture. Under these conditions, vinyl ethers **1d**−**h** failed to deliver any domino product **7** and furnished only poor mixtures of monoarylated vinyl ethers and biaryl products (see Supporting Information).

DISCUSSION

As previously reported, a change of *p*-Bq to O_2 (g) or other reoxidants such as $Cu(OAc)_2$ and AgOAc resulted solely in the β-monoarylated oxidative Heck product, and stoichiometric amounts of $Pd(O_2CCF_3)_2$ without *p*-Bq also gave only the β-monoarylated product.[38] Hence, finding an alternative to the combined *p*-Bq ligand/reoxidant might enable the development of open-vessel protocols using molecular oxygen as the palladium reoxidant.[13] Thus, we decided to investigate the nonredox active electron-deficient olefin maleic anhydride (MA) as an alternative ligand. Our first results with MA were encouraging, and despite the poor isolated yields of products **3r** and **3s** (entry 5 and 6, Method H, Table 2), we detected no unsaturated Heck product **4** in the reaction mixture. The isolated yields of **3** (3−4%) were close to the catalytic loading of $Pd(O_2CCF_3)_2$ (5%), suggesting a fully repressed palladium(II) regeneration. Disappointingly, the addition of known palladium(II)-reoxidants[44] such as acetone, $CuCl_2$, $Cu(OAc)_2$, Ag_2CO_3 and desyl chloride[45] did not improve the outcome. The use of alternative α,β-unsaturated olefins than MA also failed to enhance the reaction.

The dimethylamino substituent also proved to be as pivotal as *p*-Bq for the diarylation-reduction product outcome, although the bulkier diethylamino substituted vinyl ether **1c** delivered 18% of **7c** (Scheme 2). Vinyl ether **1c** exhibits a N−Pd(II) coordination weaker than that of **1a** according to computational and experimental studies by Stadler et al.,[46] and our experimental outcomes suggest that this difference results in a less efficient domino reaction (Scheme 2). The methylamino substituted vinyl ether **1d** yielded only traces of monoarylated Heck product, indicating a strong Pd(II) coordination and poisoning of the catalyst.[32] A three-carbon tether between the vinylic oxygen and the nitrogen atom, as in **1h**, was apparently not beneficial for the domino diarylation process (Scheme 2).

We suggest that **3** and **5** are both formed by the reaction pathway presented in Scheme 1, and in more detail in Scheme 3. The catalytic sequence starts with transmetalation of **2** with $Pd(O_2CCF_3)_2$, providing the cationic arylpalladium(II) π-species **A** in the presence of the dimethylamino group equipped vinyl ethers **1a** or **1b** (Scheme 3). The subsequent migratory insertion is chelation-controlled, yielding the six-membered

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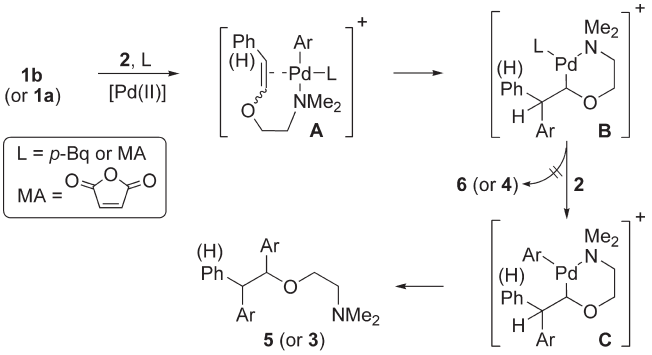
Scheme 3. Proposed Reaction Pathway for the Palladium(II)-Catalyzed Domino Reaction with Arylboronic Acid 2



alkene ligand stabilized palladacycle **B** (L = *p*-Bq or MA). The selectivity for the formation of the domino product (**3** or **5**) instead of the unsaturated Heck product (**4** or **6**) is determined by a very fine balance between a Suzuki-type transmetalation with **2**, furnishing **3** or **5** via intermediate **C**, and a terminating *syn* β-hydride elimination, yielding undesired **4** or **6**. When *p*-Bq (or MA) is present, the domino product is formed in a reductive elimination process together with palladium(0). After subsequent *p*-Bq-mediated oxidation of palladium(0) to palladium(II), the catalytic cycle may proceed. We speculate that the selectivity for **3** and **5** using chelating **1a** or **1b** is a result of the metal coordination of one of the electron-poor π-bonds of *p*-Bq (or MA),[47] which inhibits the competing β-elimination process.[48,49] In the case of vinyl ether **1b**, the β-phenyl group disturbs the insertion of the aryl-Pd complex and consequently increases the reaction time.

CONCLUSION

We have extended the scope of the chelation-controlled and *p*-Bq-mediated palladium(II)-catalyzed domino Heck−Mizoroki/Suzuki−Miyaura method to be compatible with electron-deficient arylboronic acids for the preparation of 2-(1,2-diarylethoxy)-*N*,*N*-dimethylethanamines (**3**) using the chelating vinyl ether **1a**. The principle of reactivity enhancement by catalyst presentation has been demonstrated by the direct one-pot synthesis of 2-(1,1,2-triarylethoxy)-*N*,*N*-dimethylethanamines (**5**) from a β-phenyl vinyl ether. The selectivity for the domino process with the dimethylamino ethyl vinyl ether **1a** was compared with the less impressive outcomes from reactions with alternative vinyl ethers. Finally, we have further established the importance of the combined ligand/reoxidant *p*-Bq by attempting to replace it with alternative reoxidants and ligands. An extension to other chelating olefins, targeting stereoselective aspects of the domino oxidative Heck−Mizoroki/Suzuki−Miyaura reaction promises to be worthwhile.

EXPERIMENTAL SECTION

General Experimental Procedure for Domino Heck/Suzuki Diarylation: Method B. A mixture of **1a** (50 mg, 0.43 mmol), the corresponding boronic acid (1.30 mmol), *p*-benzoquinone (52 mg, 0.47 mmol), $Pd(O_2CCF_3)_2$ (7.2 mg, 5 mol %), and 2.5 mL of 1,4-dioxane was stirred in an open reaction vial and heated at 60 °C using a preheated metal block for 2 h. The cold reaction mixture was diluted with 1,4-dioxane and filtered through Celite. After concentration the reaction mixture was extracted with $CHCl_3$ three times, concentrated, and purified by flash chromatography (silica, iso-hexane/ethyl acetate/triethylamine).

2-(1,2-Bis(p-acetylphenyl)ethoxy)-N,N-dimethylethanamine (***3n***). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, J = 8.5 Hz), 7.81 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 4.51 (1H, dd, J = 7.3, 6.0 Hz), 3.44−3.38 (1H, m) 3.36−3.29 (1H, m), 3.19 (1H, dd, J = 13.6, 7.6 Hz), 2.94 (1H, dd, J = 13.7, 5.9 Hz), 2.59 (3H, s), 2.56 (3H, s), 2.52−2.40 (2H, m), 2.19 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 198.0, 147.2, 143.9, 136.9, 135.7, 130.0, 128.8, 128.5, 127.1, 83.3, 67.7, 59.1, 46.0, 44.7, 26.9, 26.8. HRMS (ESI+): calculated for $C_{22}H_{28}NO_3$ ($M + H^+$) 354.2069, found 354.2074. Brown colored oil. (90 mg, 59%) (Method B).

General Experimental Procedure for Domino Heck/Suzuki Diarylation: Method I. A mixture of **1b′** (80 mg, 0.42 mmol), the corresponding boronic acid (1.26 mmol), *p*-benzoquinone (50 mg, 0.46 mmol), $Pd(O_2CCF_3)_2$ (7 mg, 5 mol %), and 2.5 mL of 1,4-dioxane was stirred in a open reaction vial and heated at 60 °C using a preheated metal block for 20 h. The reaction mixture was worked up, and **5h**, **5n**, **5o**, and **5s** were isolated as previously described in General Experimental Procedure for Domino Heck/Suzuki Diarylation: Method B.

2-(1,2,3-Triphenylethoxy)-N,N-dimethylethanamine (***5h***). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−6.93 (15H, m), 4.87 (1H, d, J = 9.0 Hz), 4.14 (1H, d, J = 9.0 Hz), 3.41−3.28 (2H, m), 2.35 (2H, t, J = 5.8 Hz), 2.04 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 142.2, 140.9, 129.2, 129.0, 128.3, 128.2, 128.1, 127.9, 127.6, 126.32, 126.31, 85.1, 67.7, 59.3, 59.1, 46.0. HRMS (ESI+): calculated for $C_{24}H_{28}NO$ ($M + H^+$) 346.2171, found 346.2173. Pink colored oil. (55 mg, 38%) (Method I).

ASSOCIATED CONTENT

Supporting Information. General experimental procedure, compound characterization data, and copies of spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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