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Synthetic Methods

Palladium-Catalyzed Arylation of (Di)azinyl Aldoxime Ethers by Aryl Iodides: Stereoselective Synthesis of Unsymmetrical (*E*)-(Di)azinylaryl Ketoxime Ethers

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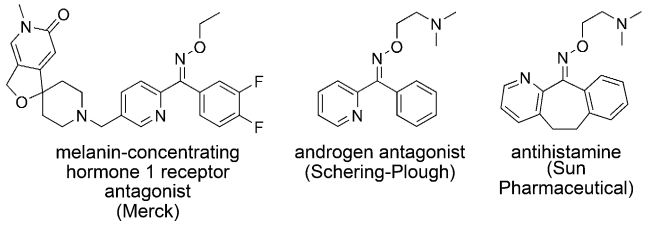
Abstract: The first example of direct arylation of (di)azinyl aldoxime ethers by aryl iodides is reported. The reaction produces, in a single step, a variety of geometrically pure unsymmetrical (*E*)-(di)azinylaryl ketoxime ethers, a class of nitrogenated motifs that have found wide applications in medicinal and organic chemistry but are difficult to access using conventional procedure. The utility of the method is further illustrated in a formal synthesis of the Merck melanin-concentrating hormone 1 receptor antagonist.

C(sp^2)–C(sp^2) bonds are widespread in pharmaceuticals, agricultural chemicals, and synthetic intermediates. Direct arylation of C(sp^2)–H bonds for the construction of C(sp^2)–C(sp^2) bonds avoids the need for substrate preactivation and hence is an attractive strategy with respect to reduction of the overall number of synthetic steps and of waste production. Recent years have seen significant progress in the development of C(sp^2)–H activation and C(sp^2)–C(sp^2) bond formation reactions.[1] Among these methods, Pd-catalyzed arylation of C(sp^2)–H bonds using ArI as arylation reagent is particularly notable.[2] In addition, examples of the direct arylation of C–H bonds of aldehydes[3] and aldehyde equivalents including aldimines[4] and hydrazones[5] have also been reported. Despite these advances, direct arylation of C–H bonds of aldoxime ethers remains to be exploited.

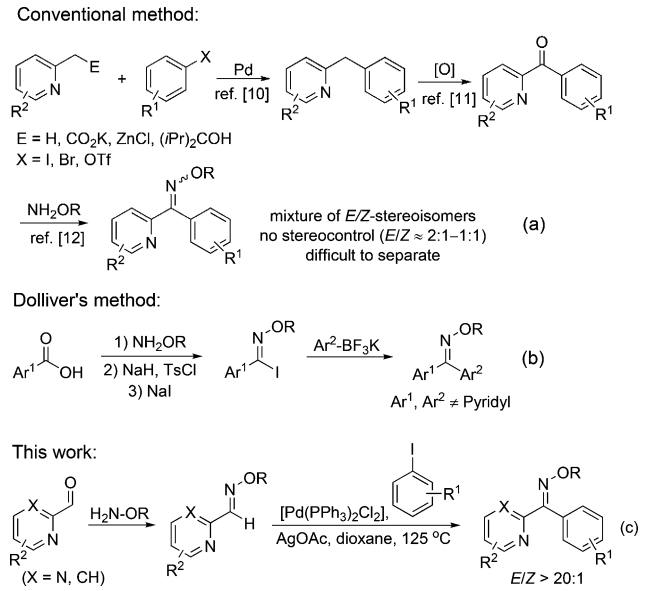
Oxime ethers have found broad applications in organic synthesis,[6] pharmaceuticals and agrochemicals.[7] They can be transformed into functional groups including amine, hydroxy amine, nitrile, and carbonyl. In particular, (di)azinylaryl ketoxime ethers are a class of compounds that have shown interesting medicinal and biological activities. Control of stereochemistry in the synthesis of (di)azinylaryl ketoxime ethers is important, since the *E*- and *Z*-stereoisomers frequently display distinct physicochemical properties and biological activities, and (*E*)-geometry is crucial to biological activity (Scheme 1).[8] In addition,



Scheme 1. Medicinally active (*E*)-2-pyridylaryl ketoxime ethers.

this motif can be transformed into many other bioactive compounds that contain the 2-benzylpyridyl nucleus.[9]

Conventional methods to prepare (di)azinylaryl ketoxime ethers involve the following steps: Palladium-catalyzed coupling of (di)azinylmethyl derivatives with aryl halides to prepare (di)azinylaryl methanes;[10] oxidation of (di)azinylaryl methanes to give (di)azinylaryl ketones;[11] and condensation of (di)azinylaryl ketones with *O*-alkylhydroxylamines (Scheme 2a). This approach usually produces a mixture of *E*- and *Z*-stereoisomers without stereocontrol.[12] Recently, an example of the synthesis of geometrically pure diaryl ketoxime ethers was reported by Dolliver et al., which nevertheless required a multistep sequence to prepare aryl *N*-alkoxyimidoyl iodide for subsequent



Scheme 2. Classical and current methods for the synthesis of geometrically pure ketoxime ethers.

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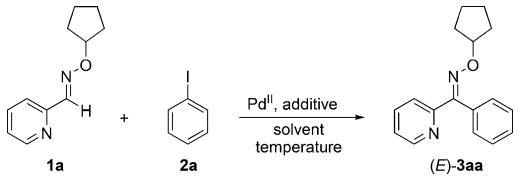
Suzuki coupling and was not applicable to synthesis of (di)azinylaryl ketoxime ethers (Scheme 2b).[13] Stereoselective synthesis of the geometrically pure (di)azinylaryl ketoxime ethers remains challenging and unresolved. Development of stereoselective methods to synthesize this motif is highly desired. Herein, we describe the first example of arylation of C–H bonds of (di)azinyl aldoxime ethers by aryl iodides under palladium catalysis. This reaction produces a variety of geometrically pure unsymmetrical (*E*)-(di)azinylaryl ketoxime ethers in a single step (Scheme 2c).

In a program to develop new metal-catalyzed carbon–carbon bond-forming reactions,[14] we envisioned that we could achieve direct arylation of (di)azinyl aldoxime ethers by aryl iodides under palladium catalysis. The coupling between 2-pyridyl aldoxime ether **1a** and phenyl iodide **2a** was selected as a model reaction for optimization of the reaction conditions (Table 1). Before optimization, we first needed to consider

Table 1. Optimization of the reaction conditions.[a]



1a **2a** (*E*)-**3aa**

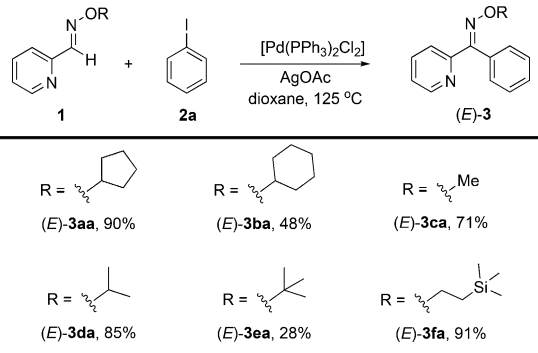
Entry	Pd^{II}	Additive	Solvent	Yield [%][b]
1	**$[Pd(PPh_3)_2Cl_2]$**	**AgOAc**	**dioxane**	**90**
2	–	AgOAc	dioxane	0
3	$[Pd(PPh_3)_2Cl_2]$	–	dioxane	0
4	$Pd(OAc)_2$	AgOAc	dioxane	55
5	$[Pd(PPh_3)_2Cl_2]$	Ag_3PO_4	dioxane	0
6	$[Pd(PPh_3)_2Cl_2]$	AgOAc	dichloroethane	15
7[c]	$[Pd(PPh_3)_2Cl_2]$	AgOAc	dioxane	80
8[d]	$[Pd(PPh_3)_2Cl_2]$	AgOAc	dioxane	20
9[e]	$[Pd(PPh_3)_2Cl_2]$	AgOAc	dioxane	42

[a] General procedure: **1a** (0.20 mmol), **2a** (1.0 mmol), Pd^{II} (10 mol%), and additive (0.5 mmol) in solvent (1.0 mL) at 125 °C for 24 h with TLC monitoring; [b] isolated product, $E/Z > 20:1$ determined by 400 MHz ^{1}H NMR spectroscopy; [c] 0.60 mmol $NaHCO_3$ added; [d] $T = 100$ °C; [e] 0.20 mmol **2a** used.

the challenge ahead. Nitrogen atoms in heterocyclic substrates are known to coordinate strongly with palladium(II) catalysts. The coordination can often lead to catalyst poisoning or deactivation.[15] Therefore, an appropriate palladium(II) catalyst that can survive the pyridyl substrate **1a** was first sought. After screening a series of palladium(II) catalysts, we identified $[Pd(PPh_3)_2Cl_2]$ as the best catalyst (see the Supporting Information for the details). After further investigating other parameters, including additive and solvent, we found that a combination of $[Pd(PPh_3)_2Cl_2]$ and AgOAc in dioxane at 125 °C afforded the arylation product (*E*)-**3aa** in 90% yield as a single stereoisomer (Table 1, entry 1). Omitting either $[Pd(PPh_3)_2Cl_2]$ or AgOAc resulted in no reaction (Table 1, entry 2 and 3). Other palladium(II) catalysts and silver salts were less effective (Table 1, entry 4 and 5). Dioxane was a superior solvent to dichloroethane (Table 1, entry 6). Addition of $NaHCO_3$ to the reaction had a minor detrimental effect (Table 1, entry 7). Lowering the reaction temperature to 100 °C resulted in a sluggish reaction (Table 1, entry 8). When one equivalent of **2a** was used, the reaction was incomplete and afforded **3aa** in 42% yield (Table 1, entry 9). The catalyst may only survive for certain period of time during which high concentration of **2a** may promote the reaction to proceed to completion before the catalytic cycle stops. In addition, replacement of **2a** with phenyl bromide or chloride failed to give any product (not shown).

Afterwards, we investigated how the steric and electronic properties of the aldoxime ether substituent affected the arylation (Table 2). Substrate **1b**, with a cyclohexyl group as the

Table 2. Effect of aldoxime ether substituent on the reaction efficiency.[a,b]

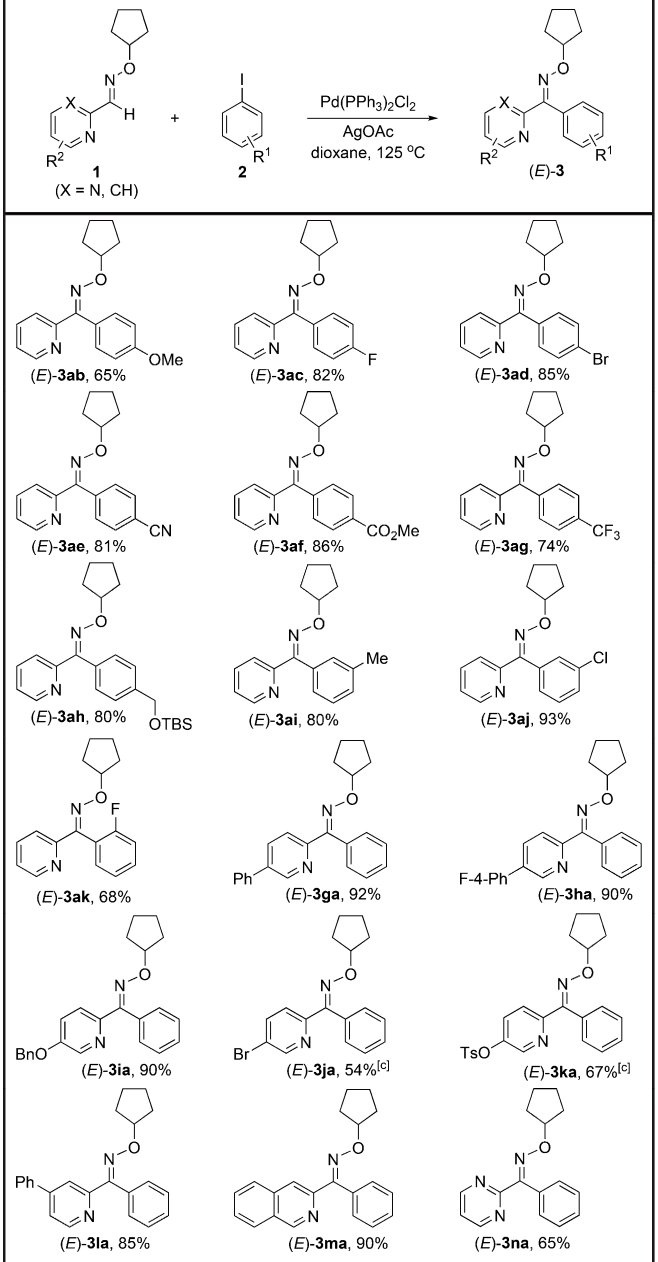


[a] Optimized reaction conditions: **1** (0.20 mmol), **2a** (1.0 mmol), $[Pd(PPh_3)_2Cl_2]$ (10 mol%), and AgOAc (0.50 mmol) in dioxane (1.0 mL) at 125 °C for 24 h with TLC monitoring; [b] yields given refer to isolated products, $E:Z > 20:1$ determined by 400 MHz ^{1}H NMR spectroscopy.

oxime ether substituent, afforded the product (*E*)-**3ba** in only 48% yield due to the sluggishness of the reaction. Meanwhile, substrates with acyclic oxime ether substituents gave varied results. Methyl derivative **1c** gave product (*E*)-**3ca** in 71% yield, whereas isopropyl compound **1d** provided product (*E*)-**3da** in 85% yield. The sterically hindered *tert*-butyl analogue **1e** delivered the product (*E*)-**3ea** in only 28% yield. Notably, substrate **1f**, with 2-(trimethylsilyl)ethyl as the oxime ether substituent was highly efficient, delivering the product (*E*)-**3fa** in 91% yield. The protecting group of (*E*)-**3fa** could potentially be removed to release the ketoxime alcohol for further derivatization and manipulation.

With the optimized conditions in hand, we then explored the substrate scope of the reaction (Table 3). We were delighted to find that a variety of aryl iodides were well tolerated to react with **1a** under the reaction conditions. *Para*-substituted aryl iodides with either electron-rich or electron-deficient groups afforded the ketoxime ethers in good to excellent yields (**3ab**–**ah**). The conditions also tolerated *meta*-substituted aryl iodides, regardless of their electronic properties (**3ai** and **3aj**). In addition, *ortho*-substituted aryl iodide afforded the coupling product in useful yield (**3ak**). Interestingly, sterically hindered 2,6-dimethyliodobenzene was not effective (not shown). With these results in hands, we further investigated

Table 3. Substrate scope of aryl iodides and aldoxime ethers.[a,b]



[a] Optimized reaction conditions: **1** (0.20 mmol), **2** (1.0 mmol), $[Pd(PPh_3)_2Cl_2]$ (10 mol%), and AgOAc (0.50 mmol) in dioxane (1.0 mL) at 125 °C for 24 h with TLC monitoring; [b] yields given refer to isolated products, *E*:*Z* > 20:1 determined by 400 MHz ^{1}H NMR spectroscopy; [c] 15 mol% $[Pd(PPh_3)_2Cl_2]$ added.

the scope of the aldoxime ethers in coupling with **2a**. 2-Pyridyl aldoxime ethers which were substituted by electron-rich groups on *para*-position afforded the arylation products in good yields (**3ga**–**ia**), whereas electron-deficient 2-pyridyl aldoxime ethers were less effective (**3ja** and **3ka**). *Meta*-substituted 2-pyridyl aldoxime ether also performed smoothly (**3la**). Moreover, both isoquinolinyl and pyrimidyl aldoxime ethers underwent arylation efficiently to deliver the products in good yield (**3ma** and **3na**). A variety of functional groups, including Br, CN, CO_2Me, CH_2OTBS (TBS = *tert*-butyldimethylsilyl), OBn, and OTs were tolerated under the reaction conditions, and could be useful handles for further transformations. The absolute configuration of (*E*)-**3ag** was unambiguously determined by single-crystal X-ray diffraction analysis (Figure 1).[16] The absolute configuration of other products were assigned by analogy.

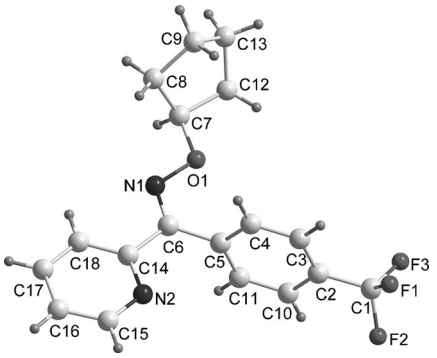
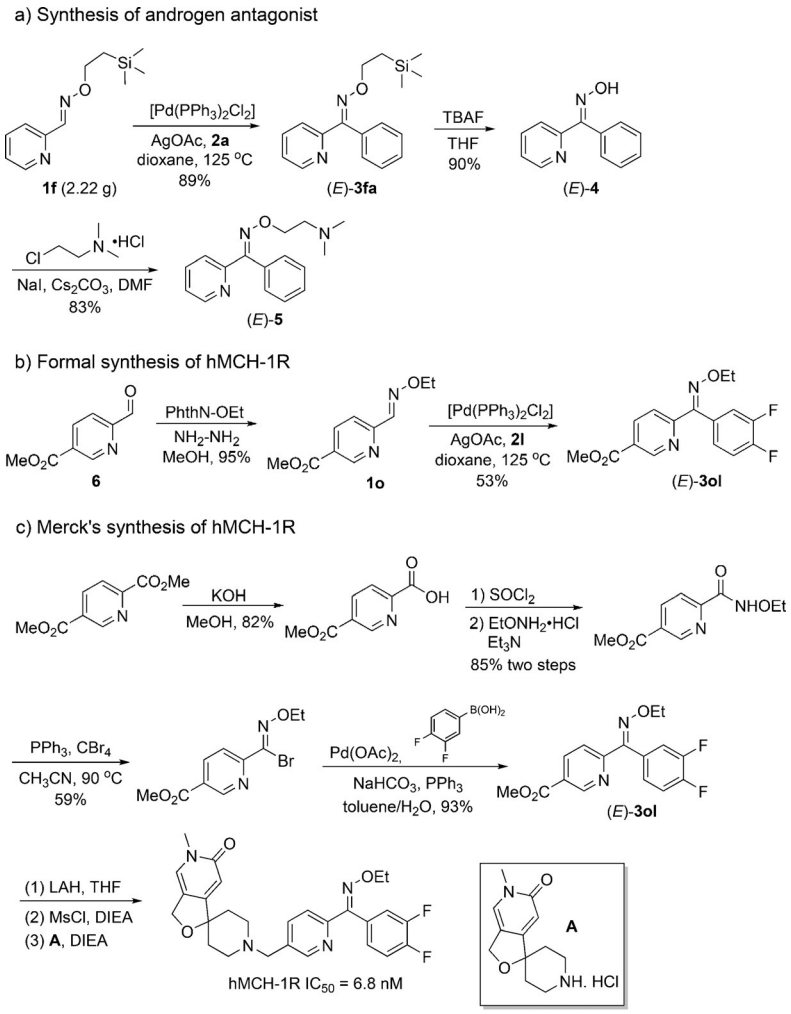


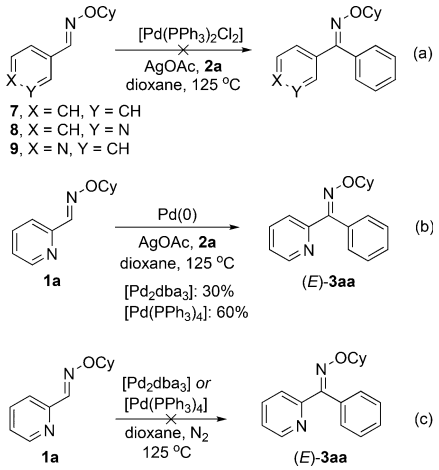
Figure 1. X-ray crystal structure of (*E*)-**3ag**.

The reaction can be conducted on large scale as demonstrated for the arylation of 2.22 g of **1f** with **2a**, which afforded (*E*)-**3fa** in 89% yield (Scheme 3a). Among all the options of the synthetic applications of oxime ethers, we wished to explore the removal of the 2-(trimethylsilyl)ethyl group of (*E*)-**3fa**, since the resulting ketoxime alcohol (*E*)-**4** is a useful handle for further derivatization, for use in medicinal and synthetic chemistry. We found that the protecting group can be smoothly removed by TBAF in 90% yield. It was remarkable that the (*E*)-geometry of (*E*)-**4** was reserved during the deprotection without epimerization. Alkylation of (*E*)-**4** with 2-dimethylaminoethylchloride gave the androgen antagonist (*E*)-**5** in 83% yield.[7a] The utility of the method was further illustrated in a formal synthesis of the Merck melanin-concentrating hormone 1 receptor antagonist (hMCH-1R) (Scheme 3b). Conversion of commercially available aldehyde **6** into aldoxime ether **1o** was completed in 95% yield. Arylation of **1o** by 1,2-difluoro-4-iodobenzene **2l** under the reaction conditions afforded (*E*)-**3ol** in 53% yield, which can be transformed into hMCH-1R in three additional steps, as shown in Merck's synthesis (Scheme 3c). Note that intermediate (*E*)-**3ol** took five steps to prepare in 38% overall yield in Merck's synthesis (Scheme 3c).[8b]

To elucidate the reaction mechanism, we conducted the following control experiments (Scheme 4). We found that (*E*)-benzaldoxime ether **7**, (*E*)-nicotinaldoxime ether **8**, and (*E*)-isonicotinaldoxime ether **9** were not arylated under the reaction conditions (Scheme 4a). These results suggest that the 2-pyridyl unit is crucial for the reaction to occur, presumably functioning as a directing group at the desired location. Pd^0 catalysts, such as $[Pd_2dba_3]$ and $[Pd(PPh_3)_4]$ also afforded the arylation product (*E*)-**3aa**, but were less effective than $[Pd(PPh_3)_2Cl_2]$ (Scheme 4b). We hypothesize that the active palladium catalysts under these systems may be Pd^{II} species generated in situ



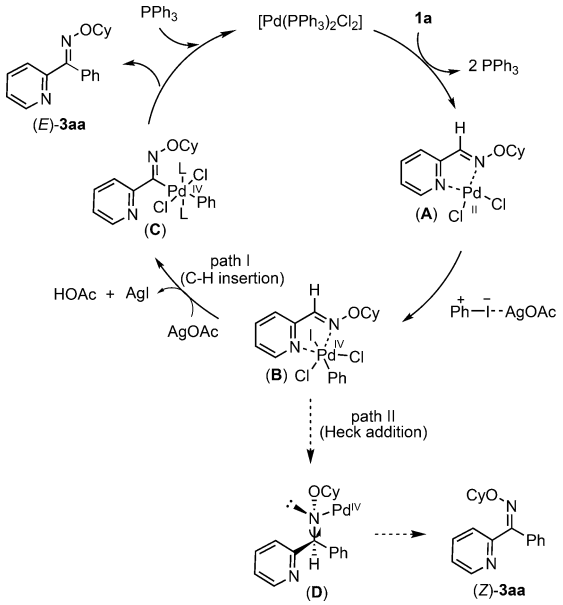
Scheme 3. Synthetic applications of the method.



Scheme 4. Control experiments.

by oxidation of Pd^0 with AgOAc, because reactions using Pd^0 catalysts without AgOAc under rigorous N_2 did not work (Scheme 4c). The data of kinetic isotope experiments (parallel intermolecular KIE = 2.9) suggest that the cleavage of aldoxime ether C–H bonds occurs as the rate-limiting step[17] (see the Supporting Information).

Although concrete evidences remain to be obtained, we tentatively propose a Pd^{II}/Pd^{IV} catalytic cycle for the reaction based on the above observations (Scheme 5). The nitrogen atoms on **1a** coordinate with $[Pd(PPh_3)_2Cl_2]$ to generate bidentate five-membered intermediate **A** as the initial step. Subsequently, an oxidative addition of **A** into the AgOAc-polarized Ph–I bond takes place to afford Pd^{IV} intermediate **B**. At the moment, in the presence of AgOAc, an intramolecular C–H insertion occurs to deliver the Pd^{IV} intermediate **C** (Scheme 5, path I). Finally, reductive elimination of intermediate **C** affords the product (*E*)-**3aa**. Since the C=N bond of the substrate remains intact throughout the process, the (*E*)-geometry of substrate is retained in the product. Meanwhile, an intramolecular Heck addition mechanism[18] (Scheme 5, path II) is less likely to occur since this pathway will generate (*Z*)-**3aa** after steps including *syn* insertion of Pd^{IV}–Ph bond into C=N bond to form intermediate



Scheme 5. Proposed reaction mechanism.

D and subsequent *syn* β-hydride elimination. The (*Z*)-product from the Heck pathway is not in agreement with the experimental result, which gave the (*E*)-product. Although there is a possibility of pyramidal inversion of palladium amide nitrogen on **D** to eventually deliver the (*E*)-product, there is no obvious driving force, such as steric factors, for this inversion to occur.[18b] In addition, the rate-limiting step of this reaction is inconsistent with that of the Heck pathway, in which the C–H cleavage step, β-hydride elimination, is usually not rate limiting.[19]

In summary, we have described a general and efficient procedure for the arylation of (di)azinyl aldoximes by aryl iodides under palladium catalysis. For the first time, the method provides a solution to prepare, in a single step, a variety of geometrically pure (*E*)-(di)azinylaryl ketoxime ethers, a class of nitrogenated motifs that are prevalent in pharmaceuticals and agrochemicals but challenging to prepare by using the classical methods. Moreover, this method accommodates diverse functional groups including chloride, bromide, nitrile, ether, tosyl, and ester. The method is scalable to gram scale and the ketoxime alcohol can be released from the ketoxime ether product for further derivatization without erosion of geometrical purity. The utility of the method is further illustrated in an efficient formal synthesis of the Merck melanin-concentrating hormone 1 receptor antagonist. Investigations to elucidate the details of reaction mechanism and explore other applications of the method are currently in progress.

Experimental Section

A 5 mL teflon-capped vial was charged with **1a** (38.2 mg, 0.20 mmol), **2a** (204.0 mg, 1.0 mmol), $[Pd(PPh_3)_2Cl_2]$ (14.0 mg, 0.02 mmol), AgOAc (83.0 mg, 0.50 mmol), and dioxane (1.0 mL). The vial was then tightly capped. The mixture was stirred at RT for 1 min to enable thorough mixing of the reactants, and was then heated at 125 °C with vigorous stirring for 24 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to RT, diluted with dichloromethane (15 mL) and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/petroleum ether) to afford the desired product (*E*)-**3aa** (48.1 mg, 90%, $E/Z > 20:1$).

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Keywords: arylation · cross-coupling · oxime ethers · palladium · synthetic methods

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[12] We independently prepared five 2-pyridylaryl ketones and reacted it with *O*-cyclopentylhydroxylamine to give 2-pyridylaryl ketoxime ethers. We found that the *E*/*Z* ratios of the resulting products are ca. 2:1–1:1. In our hands, we were unable to separate *E*/*Z* isomers by column chromatography because they have very close or the same R_f value. See the Supporting Information for the details.

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[16] CCDC 1023235 [(*E*)-**3ag**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Crystal data for (*E*)-**3ag**: $C_{18}H_{17}F_3N_2O$; $M=334.34$; triclinic; $a=10.5713(10)$, $b=11.4609(11)$, $c=14.6456(14)$ Å; $\alpha=68.4160(10)$, $\beta=74.4730(10)$, $\gamma=83.5590(10)^\circ$; $V=1589.6(3)$ Å^3; $T=100(2)$ K; space group $P\bar{1}$; $Z=4$; $\mu(Mo_{K\alpha})=0.112$ mm^{-1}; 20541 reflections measured; 7653 independent reflections ($R_{int}=0.0249$). The final R_1 values were 0.0397 ($I>2\sigma(I)$). The final $wR(F^2)$ values were 0.1109 ($I>2\sigma(I)$). The final R_1 values were 0.0467 (all data). The final $wR(F^2)$ values were 0.1174 (all data). The goodness of fit on F^2 was 1.044.

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