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Oxalyl Amide Assisted Palladium-Catalyzed Arylation of C(sp^2)−H Bond at the δ Position

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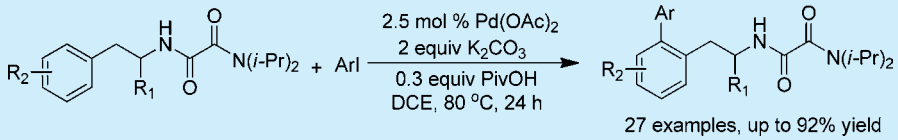
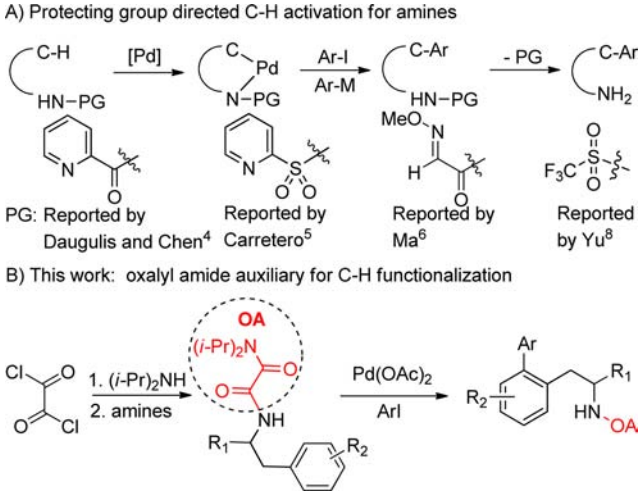
Supporting Information



ABSTRACT: A successful protocol has been developed for δ-arylation of β-arylethamines at the ortho position under mild conditions. The newly developed methodology first presents broad substrate scope, great functional group tolerance, and good to excellent yield in the synthesis of substituted β-arylethylamines. The transformation represents a practical advantage of oxalyl amide in assistance with C−H functionalization at a remote position.

Transition-metal-catalyzed C−H bond activation for C−C bond formation reactions has regained considerable attention in the last decades and has become an efficient method for synthesis of natural products and pharmaceutical agents.[1] Among these reports, functionalization of directing-group-containing arenes or unactivated C(sp^3)−H bonds has been extensively investigated.[2] Especially in recent years, several groups have demonstrated that amide groups possess a superior ability to assist palladium-catalyzed regioselective functionalization of C(sp^2)−H or C(sp^3)−H bonds.[3] However, only a few directing groups derived from amine derivatives were reported (Scheme 1A). For example, Daugulis and co-workers first discovered palladium-catalyzed γ-arylation of amine derivatives by applying picolinamide as directing group. Later, Chen and co-workers reported the picolinamide-assisted γ-functionalization of natural amino acids in moderate yields.[4] In 2013, *N*-(2-pyridyl)sulfonyl-promoted γ-arylation of amino acid derivatives at a high reaction temperature was reported by Carretero and co-workers.[5] Ma and Fan also developed a protocol for γ-arylation of substituted 2-aminobutanates by employing 2-methoxyiminoacetyl as the directing group with limited substrate scope.[6] Interestingly, the palladium-catalyzed ortho trifluoromethylation of N-unsubstituted benzyl amines could be directly achieved, which was discoverd by the Yu group.[7] Very recently, Yu and co-workers also developed γ-arylation of C(sp^3)−H bonds of triflyl-protected amines with arylboron reagents through application of mono-N-protected amino acid as a ligand.[8]

Scheme 1. Protecting Group Directed C−H Activation



Although these directing groups had made a wide variety of transformations and greatly enriched the reaction scope, these auxilixary-promoted palladium-catalyzed C−C bond formation reactions mostly go through a kinetically favored five-membered palladcycle intermediate to achieve γ-arylation.[9] To date, there are few reports of directing group assisted selective δ- and ε-arylation of amine derivatives which undergo a six- or seven-membered palladacycle pathway.[10] Herein, we reported an efficient method for the arylation of δ-C(sp^2)−H bonds of oxalyl amide protected β-arylethamines with aryl iodides via six-membered palladcycles. Our new methodology showed a wide substrate scope and great functional group tolerance in the synthesis of substituted β-arylethylamines under mild conditions, which disclosed the super assistance ability of oxalyl amide at remote position in C−H functionalization (Scheme 1B).

The weak coordinating directing groups, such as carboxylic acid,[11] hydroxyl,[12] methoxyl,[13] and ketone[14] could selectively achieved different types of C−H functionalization. Generally,

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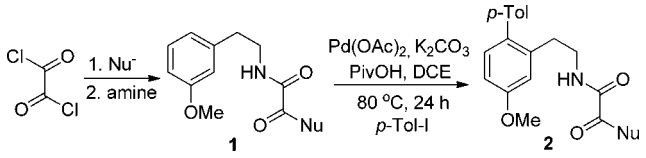
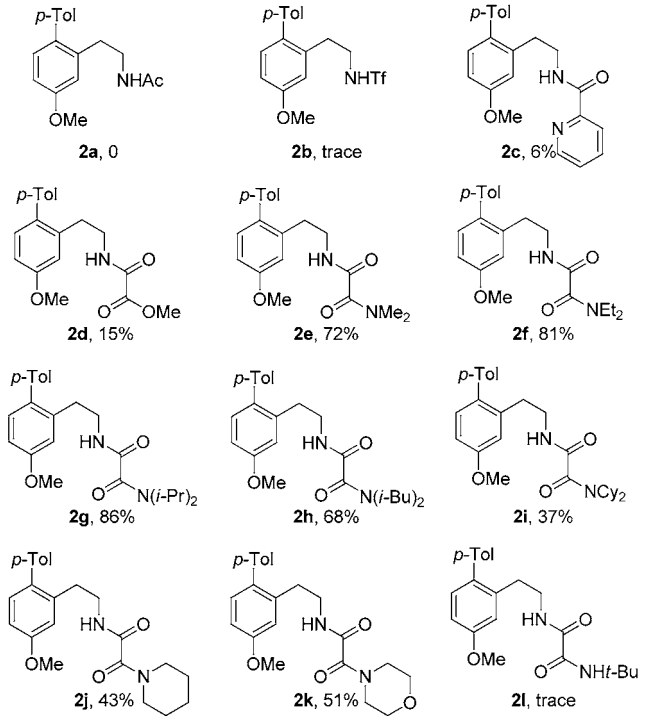
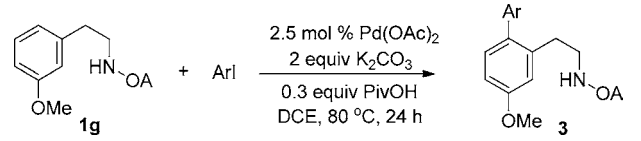
Table 1. Directing Group Optimization Studies[a]

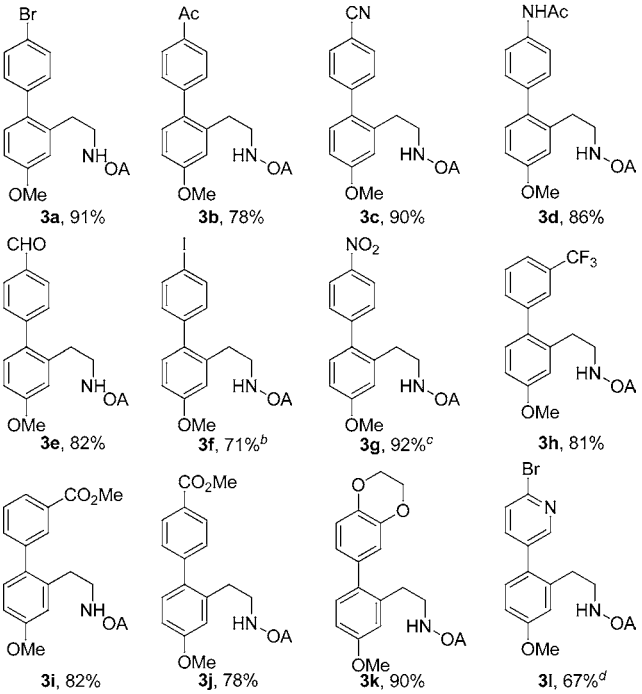




[a]Reaction conditions: **1a**–**l** (0.2 mmol), *p*-Tol-I (0.3 mmol), $Pd(OAc)_2$ (2.5 mol %), K_2CO_3 (0.4 mmol), PivOH (0.06 mmol), DCE (0.3 mL), 80 °C, 24 h. Isolated yields.

Table 2. Scope of Aryl Iodides Reagents for δ-C(sp²)–H Arylation Reaction[a]





[a]Reaction conditions: **1g** (0.2 mmol), ArI (0.3 mmol), $Pd(OAc)_2$ (2.5 mol %), K_2CO_3 (0.4 mmol), PivOH (0.06 mmol), DCE (0.3 mL), 80 °C, 24 h. Isolated yields. [b]100 °C. [c]Ag_2CO_3 (0.2 mmol) was used instead of K_2CO_3, 100 °C. [d]$Pd(OAc)_2$ (5 mol %), 100 °C.

these weak coordinating auxiliaries promoted C(sp²)–H activation could selectively happened at δ positions. The δ-alkenylation of the triflyl-protected β-arylethamine was also developed by the Yu group in 2008.[15] Very recently, oxalyl amide was discovered as an easily accessible and efficient directing group[16] for selective C–H activation at δ or ε position by our group. Inspired by the assistance ability of oxalyl amide, we hypothesized that the new developed N,O-bidentated directing group for amine derivatives might promote the selective arylation of C(sp²)–H bonds at δ or ε position.

The phenylethylamine derivatives are important versatile sythetic precursors.[17] We first tested acetylated, triflated, and picolinamide-protected phenylethylamine to realize arylation at ortho position under various conditions. However, all failed to give the arylated product in acceptable yield under mild conditions (**2a**–**c**). We were pleased to find that the desired arylated product was obtained in 15% yield by employing methyl oxalyl ester (**2d**) as directing group, following Fagnou's base system,[18] using $Pd(OAc)_2$ (0.025 equiv), 4-iodotoluene (1.5 equiv), K_2CO_3 (2 equiv), PivOH (0.3 equiv), and DCE as solvent at 80 °C. The catalytic amount of pivalic acid was necessary for the transformation (for detailed optimal reaction conditions, see the Supporting Information). It is suggested that the pivalate anion acts as a proton shuttle between substrate and inorganic base as disclosed by Larock and Fagnou.[18] It is not surprising that the ortho-arylated product **2e** could be isolated in 72% yield when we applied oxalyl amide instead of ester. To further understand the assistance ability of different amides, a series of oxalyl amide protected phenylethylamines were prepared and screened (Table 1, **2e**–**l**). Generally, much better yields were achieved when we applied oxalyl amide instead of ester (**2e**–**g**). Diethylamine could increase the yield up to 81% (**2f**). To our delight, compounds **1g** give the corresponding arylated product in best yield (**2g**). Further, when more bulky secondary amine was applied, the yield dramatically decreased (**2h**,**i**). Piperidine and morpholine were less active, and more than 40% of starting material was recovered, respectively (**2j**,**k**). *tert*-Butyl amine directly shut down the reaction as the strong coordination to the palladium center (**2l**). Thus, we chose the oxalyl amide, which was made from general reagents of diisopropylamine and oxalyl chloride as the directing group to test the scope of primary amines as arylation substrates.

Using the newly developed protocol, a broad range of aryl iodides were successfully applied with substrate **1g** as shown in Table 2. Gratifyingly, the electron-withdrawing groups such as Br-, I-, Ac-, CN-, NHAc-, CHO-, NO_2-, and CF_3-substituted benzene iodides were tolerated in this transformation and gave good to excellent yields. It is worth mentioning that even the iodine substitution on the aromatic ring was achieved in 71% yield by increasing the reaction temperature to 100 °C (**3f**). The electron-rich aryl iodide also showed nice reactivity and gave excellent yield (**3k**). To our interest, the pyridine substrate also gave the arylated product **3l** in 67% yield employing 5 mol % of

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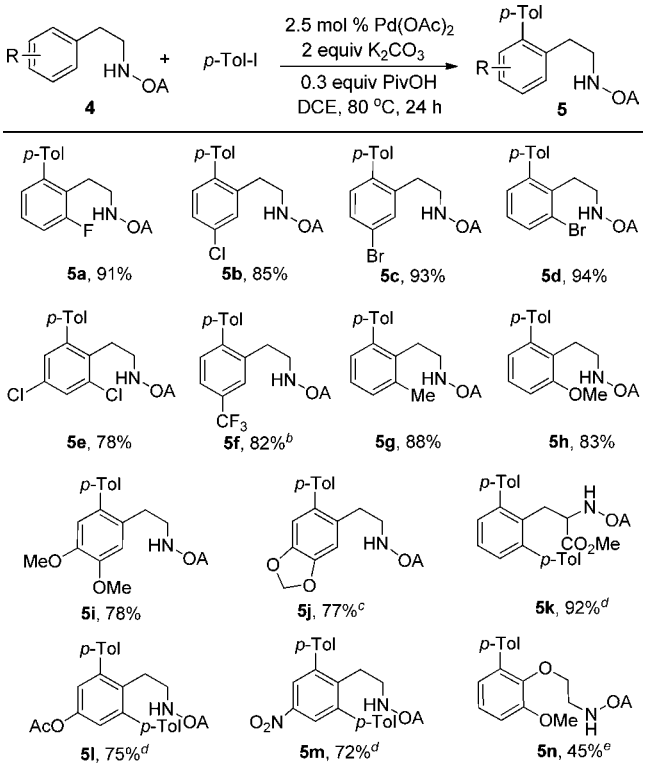
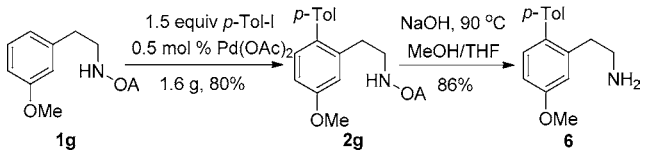
Table 3. Substrate Scope of the β-Arylethyamines[a]

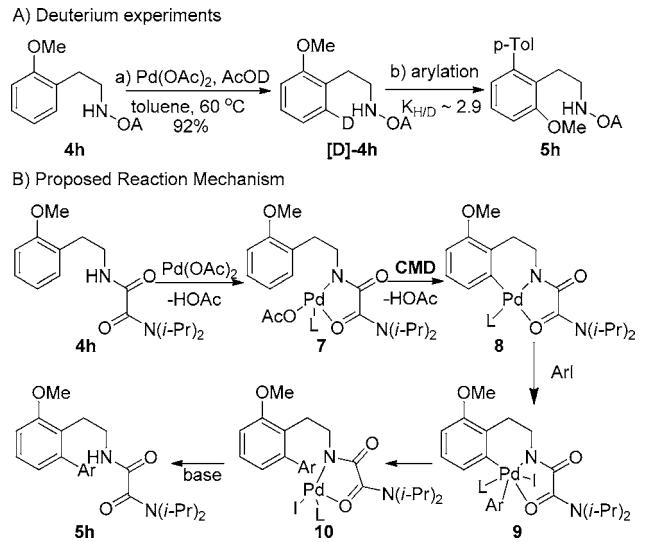


[a]Reaction conditions: **4a−j** (0.2 mmol), *p*-Tol-I (0.3 mmol), $Pd(OAc)_2$ (2.5 mol %), K_2CO_3 (0.4 mmol), PivOH (0.06 mmol), DCE (0.3 mL), 80 °C, 24 h. Isolated yields. [b]100 °C. [c]120 °C. [d]**4k−m** (0.2 mmol), *p*-Tol-I (0.6 mmol), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.3 mmol), 120 °C. [e]**4n** (0.2 mmol), *p*-Tol-I (0.3 mmol), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.3 mmol), 100 °C.

Scheme 2. Scale Up and Removal of the Directing Group



Scheme 3. Preliminary Mechanistic Study



palladium acetate at 100 °C. However, when we tried to use 4-bromotoluene, just 15% yield of desired product was isolated (Supporting Information).

We next moved our attention to other β-arylethyamines. Good yields and high selectivity were observed for all of the substrates under mild conditions (Table 3). The electronic factor had nearly no effect on these arylation reactions at the δ position (**5a−i**) except for the substrate (**4f**). However, substrates **4k−m** gave mono- and diarylated products without any selectivity when K_2CO_3 (2 equiv), PivOH (0.3 equiv), and 4-iodotoluene (3 equiv) were used under palladium catalyst. When we applied silver carbonate instead of potassium carbonate and pivalic acid, satisfactory yields were obtained (**5k−m**), indicating the better reactivity of silver carbonate than that of potassium carbonate and pivalic acid catalyst system. High monoarylation took place regioselectively at the less hindered site (**5b,c,f,i,j**). To the best of our knowledge, selective arylation of amine derivatives at ε position still has no reports. Delightedly, the substrate of **4n** could be arylated at the ε position in moderate yield via palladium catalyst (**5n**).

The gram-scale reaction was successfully achieved with 0.5 mol % of $Pd(OAc)_2$ in 80% yield, which highlighted the power of this approach (Scheme 2). The easily accessible and removable ability was crucial for auxiliary in C−H activation.[19] Notably, the new developed directing group fulfilled these requirements. The oxalyl amide could be easily prepared from diisopropylamine and oxalyl chloride which are cheap and easily accessible reagents. Besides, the oxalyl amide could be removed readily under mild conditions in excellent yield (Scheme 2).

The ortho C−H bond of substrate **4h** was deuterated under the catalysis of $Pd(OAc)_2$ in AcOD, giving compound [**D**]-**4h** in 92% yield.[20] A primary kinetic isotope effect (~2.9) was observed under the general arylation conditions, implicating C−H activation as the rate-determing step in the catalytic cycle (Supporting Information).[21]

To further investigate the mechanism of arylation promoted by oxalyl amide, substrate **4h** with 2 equiv of acetonitrile and 1 equiv of $Pd(OAc)_2$ in benzene-d_6 at 80 °C was monitored at different times. The results indicated that C−H activation can take place without involvement of the ArI substrates (see the Supporting Information). We then tried to get the six-membered palladacycle intermediate in toluene and acetonitrile. Unfortunately, we failed to obtain the crystal of palladacycle intermediate. Based on our primary study and recent reports,[4b,22] we proposed the mechanism might go through a concerted metalation−deprotonation (CMD) pathway to give the complex **8** and then an ArI-coupling pathway for the C−H arylation (Scheme 3).

In conclusion, we have developed an easily accessible and highly effective directing group for functionalization of C−H bonds at the δ and ε positions. Arylation of the β-arylethamines at the ortho position was initially studied and gave good to excellent yields by using palladium as catalyst under mild conditions. Detailed mechanistic studies are in progress, and study of a new application of oxalyl amide as a directing group in the construction of C−C, C−F, or C−heteroatom bonds is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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