Organic LETTERS

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Nickel-Catalyzed *Ortho*-Arylation of Unactivated (Hetero)aryl C−H Bonds with Arylsilanes Using a Removable Auxiliary

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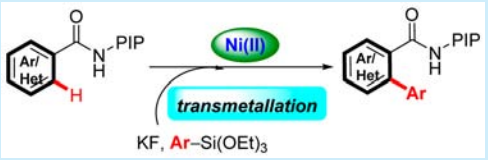
Supporting Information

ABSTRACT: Ni(II)-catalyzed *ortho*-arylation of aromatic and heteroaromatic carboxamides with triethoxy(aryl)silanes assisted by a removable bidentate auxiliary is reported. This transformation features a broad substrate scope, good functional group tolerance, and compatibility with heterocyclic substrates. Compared to the well-established Ni(II)-catalyzed C−H arylation with ArX or aryliodonium salts via oxidative addition, this reaction proceeded via a fluoride-promoted transmetalation.



Transition-metal-catalyzed direct C−H arylation has emerged as a powerful and straightforward method to access diverse biaryl derivatives since it obviates the need for the prefunctionalization of the substrate for the conventional cross-coupling reactions.[1] A variety of arylation reagents, such aryl halides/pseudohalides and metalloarenes (Ar-M, M = Sn, B, Mg, Zn, and Si) have been used as coupling partners. In particular, C−H arylation with organometallic reagents has attracted much attention.[2] Among these coupling partners, arylsilanes have many advantages, such as relatively low toxicity and safe handling.[3] Despite these advantages, the direct arylation of unactivated C−H bonds with organosilanes is relatively rare.[4−9] In 2007, Shi and co-workers reported the first Pd-catalyzed arylation of acetanilides with arylsilanes.[4] Shortly after, the Loh group developed a palladium-catalyzed arylation of cyclic enamide with arylsilanes.[5] Very recently, Pd-catalyzed arylation of C(sp^3)−H with arylsilanes was reported by Yu and co-workers.[6] In addition, Rh-catalyzed C−H arylation with arylsilanes has also been disclosed by Cheng and Loh.[8] However, these reactions rely on the use of expensive, second-row transition metals such as palladium[4−7] and rhodium (Scheme 1a).[8] Direct arylation of unactivated C−H bonds with arylsilanes catalyzed by nonprecious, first-row transition metals remains a critical challenge and has not yet been developed.[9]

Scheme 1. (a) Previous Work: Noble Metal-Catalyzed Arylation of Unactivated C−H Bonds with Organosilanes. (b) This Work: Ni(II)-Catalyzed C−H Arylation with Arylsilanes via Transmetalation

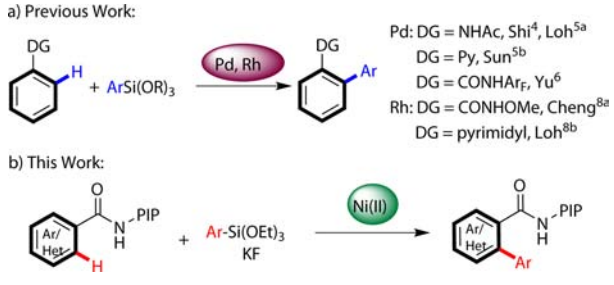
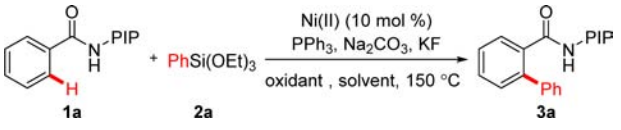


Table 1. Optimization of the Reaction Conditions[a]



entry	Ni(II)	fluoride salt	solvent	yield[b] (%)
1	$Ni(OTf)_2$	NaF	toluene	36
2	$Ni(OTf)_2$	KF	toluene	43
3	$Ni(OTf)_2$	CsF	toluene	28
4	$NiCl_2$	KF	toluene	trace
5	$Ni(OAc)_2$	KF	toluene	54
6	$Ni(OAc)_2{\cdot}4H_2O$	KF	toluene	57
7	$Ni(OAc)_2{\cdot}4H_2O$	KF	THF	60
8	$Ni(OAc)_2{\cdot}4H_2O$	KF	dioxane	76
9[c]	$Ni(OAc)_2{\cdot}4H_2O$	KF	dioxane	91[d]
10[c]		KF	dioxane	ND

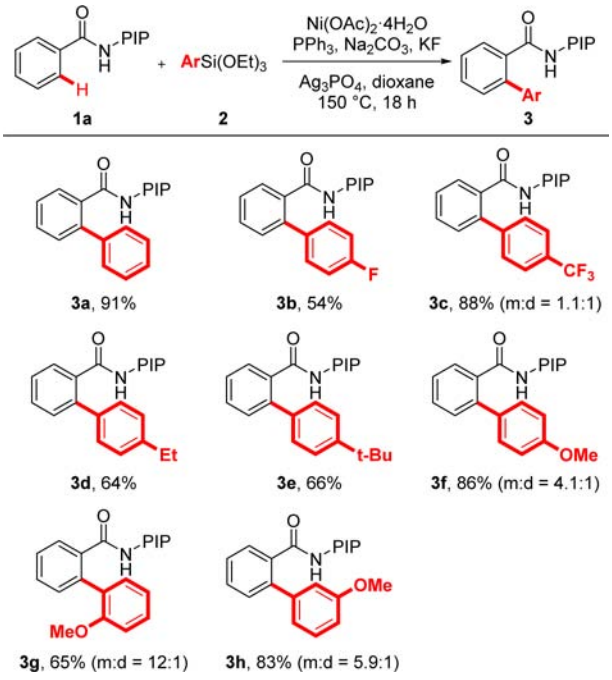
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ni(II) (0.01 mmol), PPh_3 (0.2 equiv), Na_2CO_3 (0.2 mmol), KF (0.3 mmol), Ag_3PO_4 (0.15 mmol) in 1.0 mL of solvent under N_2 at 150 °C for 18 h. [b]^{1}H NMR yield using 1,3,5-trimethoxybenzene as the internal standard. [c]0.3 equiv of PPh_3, 0.5 mL of 1,4-dioxane. [d]Isolated yield.

Recently, Ni(II)-catalyzed C−H functionalization has received tremendous attention owing to its low cost, abundance, and unique reactivity.[10] The seminal work of Chatani and co-workers revealed that the combination of nickel(II) catalysis and bidentate auxiliaries[11] should be a "privileged system" for Ni(II)-catalyzed, chelation-assisted C−H activation.[12] Important advances have also been made by Ackermann,[13] Ge,[14] You,[15] and others.[16,17] Our group has developed a removable PIP (2-pyridinylisopropyl) bidentate auxiliary,[18] which has been shown to be effective in Ni-

Received: July 28, 2016
Published: August 29, 2016

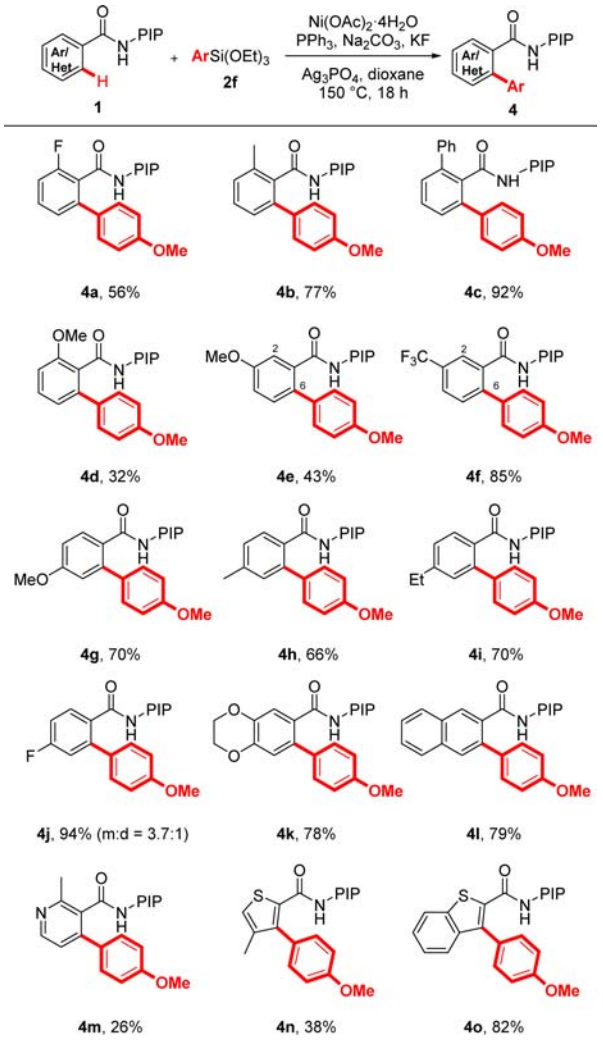
DOI: 10.1021/acs.orglett.6b02236
Org. Lett. 2016, 18, 4586−4589

Scheme 2. Scope of Arylsilanes[a]

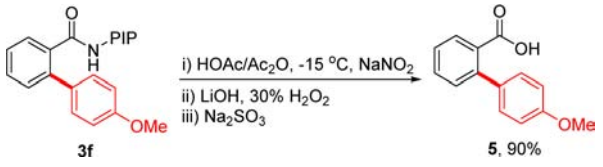


[a]Reactions conditions: **1a** (0.1 mmol), $ArSi(OEt)_3$ (0.2 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.01 mmol), PPh_3 (0.3 equiv), Na_2CO_3 (0.2 mmol), KF (0.3 mmol), Ag_3PO_4 (0.15 mmol) in dioxane (0.5 mL) for 18 h at 150 °C, isolated yield.

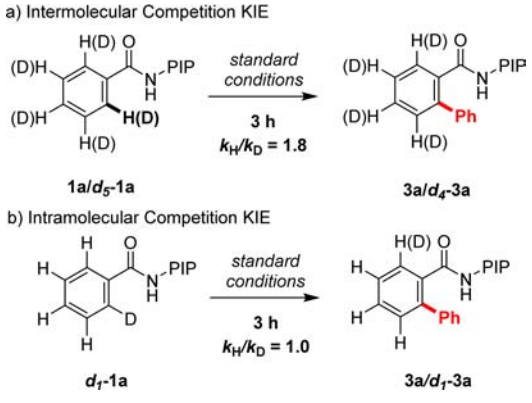
Scheme 3. Scope of Benzamides



Scheme 4. Removal of PIP Directing Group



Scheme 5. Mechanistic Investigations

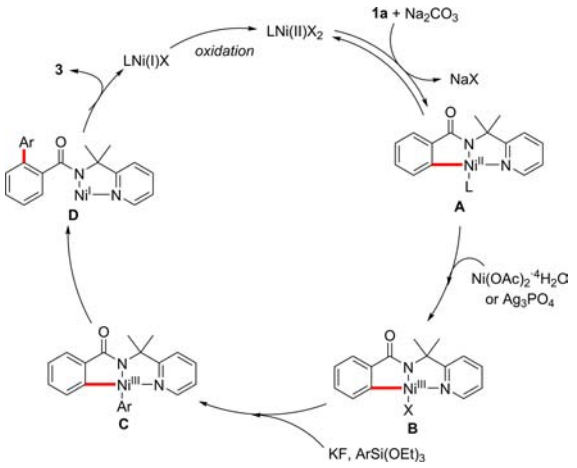


catalyzed C−H activation.[17] This catalytic system has also been applied to the Ni(II)-catalyzed C−H arylation of aryl carboxamides with arylboronic acid esters. However, this protocol proved to be unsuccessful toward the more challenging heteroaryl C−H bonds.[17f] To address this challenge and based on these advances, we were encouraged to develop a new catalytic system to facilitate the Ni(II)-catalyzed C−H arylation with a broader substrate scope using organosilicon reagents as the coupling partners, which we demonstrate herein. The advantages of this protocol include the following. (1) Cost-effective nickel is used as the catalyst, and nontoxic and safe-handling organosilanes are used as the coupling partners. (2) The compounds have high functional group tolerance and compatibility with heterocyclic substrates. (3) Compared to the well-established arylation via oxidative addition with ArX[12b,d,15a,16d] or diaryliodonium salts[12c] via oxidative addition, this reaction proceeds via fluoride-promoted transmetalation (Scheme 1b).[17f]

We initiated the study by arylating PIP-derived benzamide **1a** with 2 equiv of triethoxyphenylsilane **2a**. In the presence of 10 mol % of $Ni(OTf)_2$, 20 mol % of PPh_3, 1.5 equiv of Ag_3PO_4, 2 equiv of Na_2CO_3, and 3 equiv of NaF, the desired arylation product **3a** could be formed in 36% yield (Table 1, entry 1). A variety of fluoride salts were screened, and KF was found to be the best choice (entries 1−3). The nature of nickel salts could significantly affect the efficiency of the reaction, and $Ni(OAc)_2{\cdot}4H_2O$ exhibited superior catalytic efficiency (entries 3−6). An improved yield was obtained by using dioxane instead of toluene as solvent (entry 8, 76%). By simply increasing the loading of PPh_3 (30 mol %) and tuning the concentration of the reaction (0.5 mL dioxane), the desired product **3a** was obtained in 91% isolated yield (entry 9). The control

DOI: 10.1021/acs.orglett.6b02236
Org. Lett. 2016, 18, 4586−4589

Scheme 6. Proposed Reaction Mechanism



experiment showed that the nickel catalyst is crucial for this reaction (entry 10).

With the optimized conditions in hand, we next examined the substrate scope of this reaction. A series of triethoxyarylsilanes bearing both electron-rich and electron-deficient groups were tolerated, giving the biaryl products in moderate to high yields (Scheme 2). A broad range of functional groups, such as fluoro (**3b**), trifluoromethyl (**3c**), and methoxy (**3f**, **3g**, and **3h**), were compatible with this protocol. Triethoxyarylsilanes with *o*-, *m*- and *p*-methoxy were all reacted under the optimized reaction conditions (**3f**–**h**) while triethoxy(2-methoxyphenyl)silane gave a lower overall yield, indicating that steric hindrance played an important role in this process (**3g**, 65%).

The scope of benzamides was next examined with triethoxy-(4-methoxyphenyl)silane **2f** as the coupling partner. As shown in Scheme 3, a series substituents placed at the *ortho*-, *meta*-, and *para*-positions on the benzamides were well tolerated (Scheme 3, **4a**–**l**). A variety of electron-donating groups (such as methoxy, alkyl, and phenyl) and electron-withdrawing groups (fluoro and trifluoromethyl) were well tolerated, and moderate to good yields of the corresponding product were obtained. Notably, *meta*-substituted benzamides **4e** and **4f** exclusively react at the 6-position owing to steric interactions. Moreover, heterocyclic substrates, including pyridines and thiophenes, were all tolerated (**4m**,**o**).

Finally, as reported by our group previously,[19] the PIP directing group could be readily removed via a nitrosylation/hydrolysis sequence, affording the corresponding 2-arylbenzoic acid **5** in good yield (Scheme 4).

To determine the rate-determining step of the catalytic cycle, the deuterium kinetic isotope effect was measured (Scheme 5). The intermolecular KIE for this reaction is 1.8 while the intramolecular KIE is 1.0, indicating the C–H activation procedure is not the rate-determining step. Next, d_5-**1a** was reacted with triethoxy(4-methoxyphenyl)silane **2f** for 3 h under otherwise standard conditions, and a significant H/D exchange in the recovered amide was observed at the *ortho* position (Figure S1, Supporting Information, 58% H). This observation indicated that the C–H activation step is reversible and rapid.

On the basis of our mechanistic experiments and precedents,[2,10,12−17] a plausible reaction pathway was proposed as shown in Scheme 6. The reaction was initiated by coordination of benzamide **1a** to the Ni(II) species followed by a reversible C–H activation step to give the Ni(II) complex **A**. The Ni(III) intermediate **B** was generated by oxidation or disproportionation.[20] A fluoride-promoted transmetalation[3] then afforded the Ni(III)–aryl intermediate **C**. Subsequent reductive elimination led to the Ni(I) complex **D**, which was protonated to give the arylated product **3** together with the formation of a Ni(I) species. The catalytic cycle is closed by the reoxidation of Ni(I) to Ni(II) by silver salt.

In summary, a nickel-catalyzed, direct arylation of C(sp^2)–H bonds with organosilicon reagents has been developed. This protocol features a broad substrate scope, high functional group tolerance, and the use of nontoxic, safe handling arylsilanes as coupling partners. Moreover, the directing group could be readily removed under mild conditions, providing an effective entry to synthesis the biaryl compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02236.

Experimental details and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (2015CB856600) and the NSFC (21572201, 21422206) is gratefully acknowledged.

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