

Letter

Nickel-Catalyzed Cross-Electrophile Coupling between C(sp²)–F and C(sp²)–Cl Bonds by the Reaction of *ortho*-Fluoro-Aromatic Amides with Aryl Chlorides

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Cite This: ACS Catal. 2021, 11, 4644–4649	Read Online	
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ABSTRACT: Ni-catalyzed cross-electrophile coupli F bonds in <i>ortho</i> -fluoro-substituted aromatic ami bonds in aryl chlorides in the presence of Zn as a red	ng between $C(sp^2)$ - des and $C(sp^2)$ -Cl uctant and LiO'Bu as $N^{R'}$ Ar -Cl $N^{R'}$ Ar -Cl $Zn, ZnCl_2, LiCl$	0

a base, and LiCl and ZnCl₂ as additives is reported. The reaction displayed excellent functional group tolerance and a broad substrate scope. The reaction was also applicable to cross-electrophile coupling between $C(sp^2)$ -F and $C(sp^2)$ -O bonds in an aryl tosylate and a triflate derivative.

KEYWORDS: cross-electrophile coupling, C-F activation, C-O activation, nickel, arylation

ross-electrophile coupling in which two different carbon electrophiles are coupled under reductive conditions has been recognized as a viable alternative to conventional crosscoupling reactions between nucleophiles and electrophiles, and has provided a powerful tool for forming C-C bonds.¹ In fact, this type of transformations has been extensively studied over the past few decades. A wide variety of combinations of two electrophiles has been employed in the cross-electrophile coupling reactions that have been reported thus far. In comparison with cross-electrophile coupling to form $C(sp^2)$ - $C(sp^3)$, $C(sp^2)$ -C(sp), or $C(sp^3)$ - $C(sp^3)$ bonds, the corresponding $C(sp^2)$ - $C(sp^2)$ bond formation is more challenging because the reactivity of the two $C(sp^2)$ -electrophiles is similar. Thus, both electrophiles can compete for oxidative addition to the catalyst. To achieve selective cross-electrophile coupling and to avoid the formation of homocoupling products, the use of two electrophiles that have electronically and/or sterically different reactivities,² the use of an excess amount of a less reactive coupling partner,³ or utilizing different activation modes for each electrophile are typically employed.⁴ In 2015, Weix reported a new strategy using a Ni/Pd dual catalytic system for cross-electrophile coupling between aryl bromides and aryl triflates. In this reaction, aryl bromides selectively oxidatively added to the Ni catalyst and aryl triflates oxidatively add to the Pd catalyst selectively (Scheme 1).⁵ Since then, dual catalytic systems have been used in cross-electrophile coupling reactions between aryl tosylates/aryl triflates^{6a,b} and aryl chloride/aryl triflates.^{6c} Another strategy for achieving selective cross-coupling involves the use of chelation assistance. Zeng recently reported the Cr-catalyzed cross-electrophile coupling between $C(sp^2)$ -OMe and $C(sp^2)$ -O₂CR, in which $C(sp^2)$ -OMe is selectively activated by utilizing chelation assistance. This system was also extended to cross-electrophile coupling between C(sp²)-NMe₂ and C(sp²)-O₂CR structures.^{7b} Ruep-

Scheme 1. Cross-Electrophile Coupling to Form C(aryl)-C(aryl) Bonds



ing recently reported the Ni-catalyzed cross-electrophile coupling between $C(sp^2)$ -F bond and $C(sp^2)$ -Br bonds under irradiation conditions.⁸ Chu also reported on similar

 Received:
 March 10, 2021

 Revised:
 March 25, 2021

 Published:
 April 2, 2021





transformation using a Pd catalyst under visible light conditions.⁹ However, these reactions were limited to only perfluoroaromatic compounds, which are highly reactive, electron-deficient substrates. Cross-electrophile coupling between $C(sp^2)$ -F and $C(sp^2)$ -Cl bonds continues to pose a challenge because both bonds are known to undergo oxidative addition to the Ni(0) center.¹⁰ A new system for the selective activation of each bonds is clearly required if more progress is to be made in this area.

We recently reported the Ni-catalyzed reaction of 2fluorobenzamides with alkynes using a base-promoted strategy, in which a C–F bond at the *ortho*-position is selectively activated under both mild reaction and ligand-free conditions.¹¹ We hypothesized that this strategy could be used in cross-electrophile coupling between $C(sp^2)$ -F and $C(sp^2)$ -X (X= halogens or O) bonds and, in fact, this has been realized. We wish to report herein on a new strategy for the Nicatalyzed cross-electrophile coupling between $C(sp^2)$ -F and $C(sp^2)$ -Cl bonds (Scheme 2).¹²

Scheme 2. Cross-Electrophile Coupling between $C(sp^2)$ -F and $C(sp^2)$ -Cl bonds



The reaction of 2-fluoro-N-(4-methoxyphenyl)benzamide (1a) with 2 equiv of 4-tolyl chloride (2a) in the presence of NiCl₂ (10 mol %) and 4,4'-di-*tert*-butyl-2,2'-dipyridine (dtbbpy) (12 mol %), LiO^tBu (1 equiv), Zn (3 equiv), ZnCl₂ (30 mol %) and LiCl (2 equiv) in DMA (N,Ndimethylacetamide) at 80 °C for 14 h gave the N-(4methoxyphenyl)-4'-methyl-[1,1'-biphenyl]-2-carboxamide (3aa) in 90% NMR yield, along with the protodefluorinated product 4a in 8% and a trace amount of the homocoupling product 5a as byproducts (entry 1 in Table 1). Control experiments showed that the reaction parameters, such as LiO^tBu, LiCl, and ZnCl₂ were all needed for an efficient reaction to take place (entry 1 vs entries 2-4). If any one of these components are lacking, the product yield was decreased. It was found that Zn is superior than Mn as a reductant (entry 5). The use of dtbbpy or bpy (2,2'-bipyridine) as a ligand is essential for the success of the reaction (entries 6-8). NaH also functioned as a base in place of LiO^tBu (entry 9). The reaction with 4-tolyl iodide and bromide in place of 2a resulted in protodefluorination to give 4a as the main product (entries 10 and 11).

The scope of the *N*-substituent on the amide nitrogen was examined using 4-methoxyphenyl chloride (**2b**) as a coupling partner under the optimized conditions (Scheme 3). While both electron-donating (OMe) **1a** and electron-withdrawing (CF₃) groups **1c** gave the corresponding arylated products, **1c** gave the expected product **3cb** in a slightly lower yield. The use of *N*-alkyl groups, such as benzyl, hexyl, and tert-butyl groups also gave the corresponding products, **3db**, **3eb**, and **3fb**. In sharp contrast, the reaction of *N*,*N*-diethyl-2fluorobenzamide, which contains no proton on the amide nitrogen did not give the expected product **3gb**, indicating that the presence of an NH proton is crucial for the reaction to proceed.

Table 1. Optimization of the Reaction Conditions

O N F 1a 0.25 mm	Ar'-Cl 2a (2 equiv) NiCl ₂ (10 mol%) dtbbpy (12 mol%) LiO ⁴ Bu (1 equiv) Zn (3 equiv), LiCl (2 equiv) ZnCl ₂ (30 mol%) DMA (0.5 mL), 80 °C, 14 h Ar = 4-MeOC ₆ H ₄ Ar' = 4-MeC ₆ H ₄	O H Ar 3aa O V Ar Ar Sa	O N H H 4a
		NMR yield	ls (%)
entry var	riations from above conditions	3aa	4a
1	none	90 (88) ^a	8 (4) ^{<i>a</i>}
2	without LiO ^t Bu	55	42
3	without LiCl	51	26
4	without ZnCl ₂	60	28
5	entry 4, Mn instead of Zn	38	24
6	without dtbbpy	trace	3
7	bpy instead of dtbbpy	73	20
8	PPh ₃ instead of dtbbpy	15	8
9	NaH instead of LiO ^t Bu	71	23
10	Ar'-I instead of Ar'-Cl	10	62
11	Ar'-Br instead of Ar'-Cl	27	60
^a Isolated wiel	de are given in narenthages		

'Isolated yields are given in parentheses.

Scheme 3. Scope of N-Substituents on Aromatic Amides



The scope of this cross-electrophile coupling was also investigated, with respect to 2-fluoro-N-(4-methoxyphenyl)benzamide derivatives (top-left in Scheme 4). A variety of important functional groups were tolerated in the reaction. Remarkably, no arylation at C-OMe and C-OPiv bonds in the substrates was detected, which are known to undergo the oxidative addition to a Ni(0) center,¹³ as in 3hb, 3mb, and 3ob. In all cases, the arylation occurred exclusively at the ortho C-F bond. Even when substrates containing another C-F bond were used, only the ortho C-F bonds were selectively arylated, as in 3kb and 3pb.¹⁰ The reaction was not significantly affected by steric environments, as in 3ob and 3pb. The scope of aryl chlorides was also examined (top-right in Scheme 4). Various functional groups, which could be used for further transformations, such as alkene, phosphonate, acetal, and boronic esters were tolerated in the reaction, as in 3ad, 3ae, 3af, and 3ah. 5-Chloroindole and 2-chloronaphthalene also participated in the reaction to give 3al and 3qn, respectively. The use of 1-chloro-2-fluorobenzene (3b) as a coupling partner under the standard reaction conditions gave the phenanthridin-6(5H)-one derivative 6a in 63% yield,

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Scheme 4. Scope of Amides and Aryl Electrophiles^a

^{*a*}Reaction conditions: amide 1 (0.25 mmol), aryl chloride 2 (0.5 mmol), NiCl₂ (0.025 mmol), dtbbpy (0.03 mmol), LiO^tBu (0.25 mmol), Zn (0.75 mol), LiCl (0.5 mmol), ZnCl₂ (0.075 mmol), and DMA (0.5 mL) at 80 °C for 14 h. Ar = 4-MeOC₆H₄. ^{*b*}dtbbpy (0.005 mmol). ^{*c*}At 100 °C.

which appears to form as a result of further intramolecular S_NAr reaction of the initial product **3ao** (bottom-left in Scheme 4). In fact, the reaction of **3ao** in the presence of a base in the absence of Ni catalyst in DMA at 80 °C gave **6a** in quantitative yield. The reaction with 2-fluoro-4-methoxy-1-chlorobenzene and 2,4-difluoro-1-chlorobenzene also gave the corresponding products **6b** and **6c** in good yields. While the use of 4-tolyl iodide and bromide in place of 4-tolyl chloride (**2a**) gave the protodefluorinated product **4a** as the major product (entries 10 and 11 in Table 1), gratifyingly the present reaction was found to be applicable to 4-tolyl tosylate and triflate reactants to afford good yields of **3aa**, even under unoptimized reaction conditions (bottom-right in Scheme 4).

To shed additional light on the mechanism, some mechanistic experiments were conducted (Scheme 5). We were able to isolate a single crystalline sample of the expected azanickelacycle 7 by the reaction of 1a with equimolar amounts of Ni(cod)₂, bpy, and NaH in THF at 80 °C and the structure of 7 was confirmed by an X-ray crystallographic analysis (Scheme 5a). The use of dtbbpy as the ligand in place of bpy also gave a similar complex (8), the structure of which was confirmed by ¹H NMR (see the SI for details). We used complex 8 in further mechanistic studies, because of its good solubility in organic solvents. The reaction of 1a under the standard reaction conditions, using 8 as the catalyst, gave 3aa in 68% yield (Scheme 5b). The stoichiometric reaction of 8 with 2a in the presence Zn and LiCl in DMA at 80 °C gave 3aa in 82% NMR yield, along with 4a and the dimerization product 5a (Scheme 5c). The reaction of 8 with PhZnCl also gave 3ac in 87% NMR yield, suggesting that an arylzinc species is

Scheme 5. Mechanistic Studies



generated under the reaction conditions employed and functions as a nucleophile in the catalytic reaction.¹⁴

As shown in Table 1, the addition of $ZnCl_2$ (30 mol %) gave a higher product yield. To gain further insights regarding the

Scheme 6. Proposed Mechanism



effect of ZnCl₂, the time dependence study was conducted (see the Supporting Information (SI) for details). As a result, it was found that there is an induction period for the reaction. When the reaction was performed in the absence of ZnCl₂, no reaction occurred during the first 2 h, after which the reaction was initiated. On the other hand, the induction period was decreased to 30 min when 30 mol % of ZnCl₂ was added. These results suggest that ZnCl₂ accelerates the generation of ArZnCl (discussed below).

A mechanism for the reaction is proposed based on experimental results, as well as literature findings, as shown in Scheme 6. The base, LiO^tBu abstracts the NH proton of the amide 1 to generate the amidate anion A. The coordination of A with Ni(0) gives the nickel ate complex B, which then oxidatively adds to a C-F bond to generate the nickelacycle C with the extraction of LiF.^{11a,15} The transmetalation between C and ArZnCl gives D, which then undergoes reductive elimination to afford E with the regeneration of Ni(0). The protonation of E gives the final product 3. ArZnCl is formed by the oxidative addition of ArCl to Ni(0), followed by a oneelectron reduction by Zn and transmetalation with ZnCl₂ through cycles B and C.¹⁶ While ZnCl₂ is gradually generated as the reaction progress, the addition of additional ZnCl₂ would be predicted to accelerate the production of ArZnCl. The addition of LiCl also has an important role in the effective cross-coupling by accelerating the reduction of Ni(II) to Ni(0) (cycle B).^{6c} Both C-F and C-Cl bonds can compete for oxidative addition to a Ni catalyst. If cycle B is faster than cycle A, then homocoupling of an aryl chloride occurs with the generation of Ar-Ar becomes a major path and the yield of the desired product 3 is low, because there is no chance for intermediate C to react with ArZnCl. In fact, when an aryl iodide or bromide were used in place of a chloride, protonation product 4 was the main product, as shown in Table 1. In these cases, the oxidative addition of an aryl iodide or bromide is faster than the generation of intermediate C. Similarly, if cycle A is faster than cycles B and C, the protonation of C leading to the formation of 4 would be a dominant path because only a small amount ArZnCl is generated via cycle B and C, compared with the generation of intermediate C.

An alternative mechanism involves the one-electron reduction of complex C with Zn and LiCl to give the Ni(I)nickelacycle F, followed by the oxidative addition of ArCl to give G, which then undergoes reductive elimination to give H, along with the generation of Ni(I), which is reduced by Zn to regenerate the Ni(0) species. To examine the possibility that C could be reduced by elemental Zn, we examined the reduction potential of the Ni(II) complex 8 (correspond to C), which shows -2.00 (V vs Fc⁺/Fc). These findings suggest that the reduction of 8 by Zn appears to be less likely (see the SI for details).¹⁶

In summary, we report on the first example of crosselectrophile coupling between $C(sp^2)-F$ and $C(sp^2)-Cl$ bonds. Although there are many reports of transformations involving chelation-assisted $C(sp^2)-F$ bond activation, most of the examples reported thus far have involved polyfluorinated substrates at high reaction temperatures.^{10,17} In contrast, the activation of $C(sp^2)-F$ bonds using our base-promoted strategy proceeds efficiently, even under mild reaction conditions. The reaction shows a high functional group compatibility and was also applicable to cross-electrophile coupling reactions between $C(sp^2)-F$ and $C(sp^2)-O$ bonds in an aryl tosylate and a triflate derivative.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01102.

Experimental procedure, synthesis of starting materials, and characterization of compounds (PDF) Crystallographic data (CIF) Crystallographic data (PDF)

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Funding

This work was supported by a Grant in Aid for Specially Promoted Research by MEXT (No. 17H06091).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Yuma Morimoto (Osaka University) for his assistance with the measurement of cycle voltammograms.

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