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Palladium-Catalyzed Chloroimination of Imidoyl Chlorides to a Triple Bond: An Intramolecular Reaction Leading to 4-Chloroquinolines

Akira Isobe, Jun Takagi, Toshimasa Katagiri,* and Kenji Uneyama*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, 3-1-1, Tsushimanaka, Okayama 700-8530, Japan

uneyamak@cc.okayama-u.ac.jp; tkata@cc.okayama-u.ac.jp

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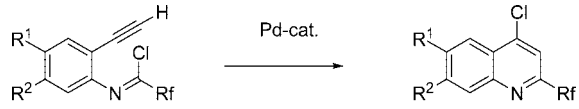
ABSTRACT



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In this paper, a new type of effective chloroimination was reported. This reaction afforded 4-chloro-2-perfluoroalkyl quinolines from fluorinated imidoyl chlorides in high yields. This is the first achievement of oxidative addition−reductive elimination type C−Cl bond activation by chloropalladation.

Recently, methods of palladium-catalyzed carbon−carbon bond formation have been recognized as useful reactions for advanced organic synthesis.[1] Among these techniques, reactions via chloropalladation have the advantage of introducing both chloride and carbon moieties into a multiple bond simultaneously, but as of yet only a few such reactions have been reported.[2]

Past mechanistic studies of chloropalladation reactions have suggested that the reaction proceeds via nucleophilic attack of a chloride moiety of the Pd−Cl catalyst or of a chloride additive to the Pd(II)-activated multiple bond forming the chloropalladation intermediate. Electrophilic activation of the multiple bond by the electron-deficient Pd(II) catalyst is essential for this process. Reductive elimination of the catalyst then forms the carbon−carbon bond, so conventional chloropalladation requires the reoxidation of Pd(0) to Pd(II) to complete the catalytic cycle. This could potentially be accomplished through the oxidative addition of a carbon−chlorine bond to Pd(0). As of yet, there have been no reports of such catalytic chloro-palladations initiated by the oxidative addition.

Chloroacylation of a multiple bond via chlororhodation has been reported.[3] The reaction was initiated by the

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oxidative addition of acyl chlorides to rhodium, followed by the chlororhodation of the multiple bond. This reaction could be a useful synthetic tool because it simultaneously introduces both the acyl moiety and the chloride into the multiple bond. Nevertheless, elevated reaction temperatures and a prolonged reaction time were required because the rhodium catalyst possessed less reducing ability than the palladium catalyst.

Like chloroacylation, chloroimination of a multiple bond would also be a useful tool for synthesizing multifunctional nitrogen-containing compounds, especially nitrogen-containing heterocycles. Although the imidoyl halides need strong electron withdrawing groups for their preparation, such methods would be of particular synthetic merit, because the chloride present in the product could be converted into a variety of other functional groups via nucleophilic substitution. Presently, there are no literature reports of transition metal-catalyzed chloroimination.

We hypothesized that the high electrophilicity of the C−Pd(II)−X species, which is formed via oxidative addition of imidoyl halides to Pd(0),[1] would facilitate the reaction with the multiple bond under mild conditions to give the chloropalladation adduct. Reductive elimination from the Pd catalyst would then yield the desired chloroimination product in a manner similar to that of rhodium-catalyzed chloroacylation.[3]

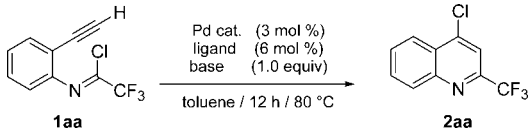
In the present study, we demonstrate the first palladium-catalyzed intramolecular chloroimination reactions, in which the triple bond of *N*-(2-ethynylphenyl)-2,2,2-trifluoroethanimidoyl chloride was reacted to yield 4-chloro-2-polyfluoroalkylquinolines. The reactions were initiated by the oxidative addition of imidoyl chloride to Pd(0). The resulting 4-chloro-2-polyfluoroalkylquinolines could serve as synthetic precursors to quinolone carboxylic acid antibiotics.

First, the intramolecular chloroimination reaction was optimized in terms of the Pd catalyst, the phosphine ligand, and the base employed (Table 1). The bidentate ligand dppf was found to be superior to the monodentate ligand PPh_3 (entries 1 and 2). Thus, a variety of catalysts were generated by reacting different bidentate phosphine ligands with $Pd_2(dba)_3/CHCl_3$ (entries 3−5). While the addition of base was not essential, it does improve the reaction rate and selectivity (a similar reaction to entry 5 without AcONa resulted in 50% conversion with 13% yield of the product). The exact role of base has not yet been revealed, but the combination of BINAP and AcONa was found to be the best combination examined (entry 5).

Additives were examined in an attempt to reduce the harshness of the reaction conditions to 80 °C for 12 h. Although the previously reported $PdCl_2$-mediated chloropalladation reaction proceeded with cis selectivity and the chloride was derived from $PdCl_2$,[2b–d] the present chloroimination proceeded via trans addition onto the triple bond, forming a six-membered ring. A trans chloropalladation would require nucleophilic attack from an exogenous chloride source rather than from the catalytic Pd−Cl species.[2h,i] A variety of chloride sources were surveyed, and the effects on the rate and yield of chloropalladation were analyzed (Table 2). The addition of a chloride source accelerated the reaction (entries 2−5), especially, TBAC (*n*-tetrabutylammonium chloride). With this additive, complete consumption of the starting material was observed within 1 h at 80 °C. Nevertheless, the yield was slightly lower than other previously tested reaction conditions (Table 1, entry 5). Further experiments were conducted to optimize the amounts of additive and base, the temperature, and the reaction time. Ultimately, the best product yield was attained under very mild conditions, reaction at 30 °C for 5 h (entry 5).

A series of experiments were conducted to assess the substrate scope of the reaction (Table 3). Substituted quinolines were obtained in high yields, which demonstrated

Table 1. Examination of Catalytic Conditions

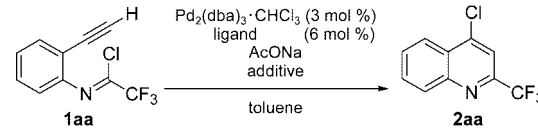


1aa **2aa**

entry	catalyst	ligand	base	yield (%)[a]
1	$PdCl_2(PPh_3)_2$		AcONa	0
2	$PdCl_2$(dppf)		AcONa	38
3	$Pd_2(dba)_3$·$CHCl_3$	dppe	AcONa	7
4	$Pd_2(dba)_3$·$CHCl_3$	dppf	AcONa	47
5	$Pd_2(dba)_3$·$CHCl_3$	BINAP	AcONa	84
6	$Pd_2(dba)_3$·$CHCl_3$	BINAP	AcOK	82
7	$Pd_2(dba)_3$·$CHCl_3$	BINAP	$NaHCO_3$	50
8	$Pd_2(dba)_3$·$CHCl_3$	BINAP	NaOH	42

[a] Determined by ^{19}F NMR with 1,3-(bistrifluoromethyl)benzene as an internal standard.

Table 2. Examination of Chloride Source



1aa **2aa**

entry	time (h)	temp (°C)	additive	equiv of additive	equiv of AcONa	convn (%)[a]	yield (%)[a]
1	1	80			1.0	37	23
2	1	80	LiCl	2.0	1.0	52	32
3	1	80	Et_3BnNCl	2.0	1.0	79	34
4	1	80	TBAC	2.0	1.0	>99	66
5	5	30	TBAC	1.0	0.25	>99	84

[a] Determined by ^{19}F NMR with 1,3-(bistrifluoromethyl)benzene as an internal standard.

(4) See the Supporting Information [Spectroscopic Data and Experimental methods for 4-chloro-2-polyfluoroalkyl quinolines and the substrates].

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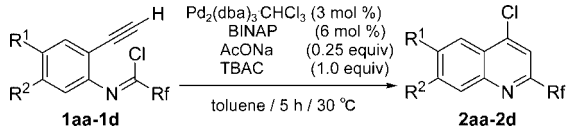
Table 3. Scope of Substrates



entry	R^1	R^2	Rf	product	yield (%)
1	H	H	CF_3 (**1aa**)	**2aa**	84
2	H	H	C_3F_7 (**1ab**)	**2ab**	80
3	H	H	CF_2Cl (**1ac**)	**2ac**	88
4	H	H	CHF_2 (**1ad**)	**2ad**	81
5[a]	Cl	H	CF_3 (**1b**)	**2b**	87
6[a]	CO_2Et	H	CF_3 (**1c**)	**2c**	77
7[a,b]	F	F	CF_3 (**1d**)	**2d**	82

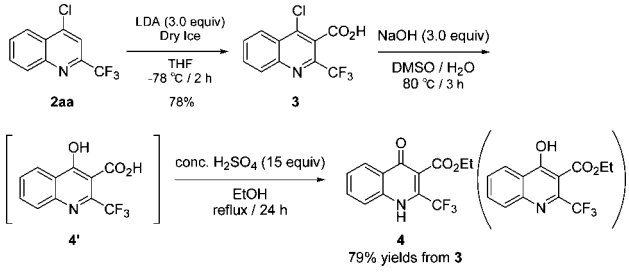
[a] 2,2′-Dipyridyl was used as a ligand. [b] Catalyst and ligand used were 5 mol % and 10 mol %, respectively.

tolerance for an array of functional groups at Rf = CF_3, C_3F_7, CHF_2, CF_2Cl, as well as at R^1 = H, F, Cl, CO_2Et and R^2 = H, F. Preparation of nonfluorinated alkyl or aryl imidoyl halides was unsuccessful. These imidoyl halides decompose easily due to their labile nature.

Previous studies have shown that application of a Pd(II) chloropalladation catalyst[4] to our substrate (**1a**) resulted in near complete recovery of a combination of the substrate and trifluoroacetamide, a hydrolysis product (ca. 75%). This suggested that the present chloropalladation was initiated by the oxidative addition of the C−Cl bond of **1a** to the Pd(0) species, and this represents a significant difference between the present method and the conventional Pd(II)-catalyzed chlorocarbonations.[2]

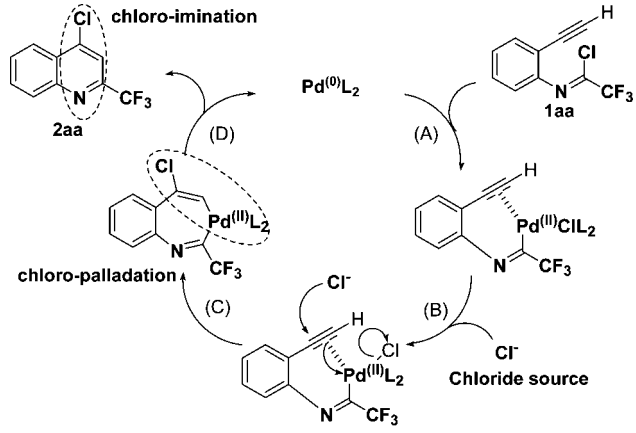
The products of chloropalladation, 4-chloro-2-polyfluoroalkylquinolines, have a reactive C−Cl bond that allows further transformations. Quinoline **2a** was successfully converted to quinolone carboester equivalent **4**, which possesses the carbon skeleton of a quinolone antibiotic (Scheme 1).[5]

Scheme 1. Transformation of Quinoline (**2a**) to Quinoline (**4**)



A plausible mechanism for this catalytic reaction is proposed in Scheme 2. The first step is the oxidative addition of the C−Cl bond of imidoyl chloride[6] **1aa** to the Pd(0) species (path A). Next, a chloride from an exogenous source attacks the triple bond, which is intramolecularly activated by the activated Pd(II) catalyst to generate the seven-membered *trans*-chloropalladation palladacycle intermediate (paths B and C). Finally, the reductive elimination of Pd(0) from the palladacycle yields quinoline **2aa** and regenerates the Pd(0) species (path D).

Scheme 2. Plausible Mechanism



In conclusion, we have developed the first intramolecular chloroimination of a triple bond initiated via the oxidative addition of the imidoyl chloride C−Cl bond to the Pd(0) species, followed by chloropalladation and reductive elimination. The reaction proceeded under mild conditions and gave the desired quinoline products in high yields. This novel Pd-catalyzed chloroimination reaction expands the scope of palladium chemistry.

Supporting Information Available: Experimental procedures and spectroscopic data and charts for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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