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Palladium-Catalyzed Monoselective Halogenation of C–H Bonds: Efficient Access to Halogenated Arylpyrimidines using Calcium Halides

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Abstract: A wide variety of *ortho*-halogenated arylpyrimidines were prepared with high monoselectivity and functional-group tolerance by using calcium halides as crucial halogenating agents and cupric trifluoroacetate as oxidant in the presence of air.

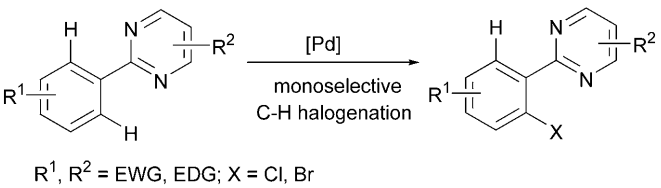
Keywords: arylpyrimidines; C–H activation; electron-deficient substrates; halogenation; palladium; selectivity

Aryl or heteroaryl halides, as important starting materials to construct complex structures and notable structural motifs in natural products and manufactured drugs,[1] were traditionally obtained by electrophilic aromatic substitution[2] or through directed *ortho*-lithiation.[3] The drawbacks of some of these methods lie in their low selectivity or tedious and somewhat dangerous procedures.

Considerable progress has been made during the past decades in the C–H activation reaction directed by functional groups.[4,5] Recently, *ortho*-halogenated arenes were selectively synthesized by metal-catalyzed halogenation of C–H bonds.[6] High yields and monoselectivities among them could be achieved with assistance of some directing groups, including amides,[6a,e] pyridines,[6c,f,g] carboxylic acids,[6d] and oxazolines.[6h] Generally, substrates with electron-donating properties will give high monoselectivity and particularly for those substrates with *ortho*- or *meta*-substitution in the aryl ring.[6d,f,g] However, only few examples involving electron-deficient substrates were well documented for the C–H activation reaction[7] and even less examples were successfully investigated using pyrimidine as directing group,[5a,d–f,i] which may be due to the formation of a double metalation complex.[8] Furthermore, a long reaction time was normally needed to reach a high yield and monoselectivity.[6] Thus, developing highly efficient and selective catalytic systems for C–H halogenation with diverse directing groups and expanding the substrate scope to electron-deficient substrates remain a challenge.[9]

Given the importance of pyrimidine derivatives in materials and medicinal chemistry,[10] the development of readily available halogenated arylpyrimidines in a monoselective manner would find significant use in the preparation of this class of molecules.[1] To continue our research interest aiming at the efficient construction of nitrogen-containing heterocycles,[11] we herein report a highly *ortho*-monoselective C–H halogenation of arylpyrimidines, using calcium halides as crucial halogenating agents and cupric trifluoroacetate as oxidant in the presence air (Scheme 1).

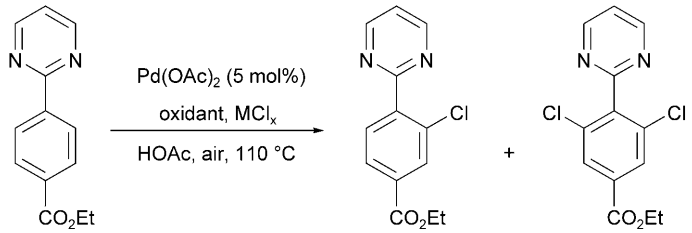
We initiated our study with electron-deficient substrate **1a** in the presence of $CuCl_2$[6e] or NCS,[6f] however, low yield and monoselectivity of **2a** were observed (Table 1, entries 1–3). Use of $CaCl_2$ and $Cu(OTFA)_2$ in acetic acid led to improvements of both yield and monoselectivity (entry 6 *vs.* entries 3–5), although a long reaction time was needed to reach completion. To our delight, $CaCl_2$ (6.0 equiv.) and $Cu(OTFA)_2$ (1.0 equiv.) turned out to be the best choice in the presence of $Pd(OAc)_2$ (5 mol%) in HOAc, and gave *ortho*-mono-chlorinated product **2a** in 89% yield in 5 h (entry 7). Further screens concerning oxidants (entries 8–11), chlorinating agents (entries 12–14), palladium resources (entries 15 and 16)



R^1, R^2 = EWG, EDG; X = Cl, Br

Scheme 1. Monoselective halogenation of arylpyrimidines.

Table 1. Reaction optimization for the C–H halogenation.



1a **2a** **3a**

Entry	Oxidant (equiv.)	MCl_x (equiv.)	Solvent	Time [h]	Conversion [%]	Yield [%][a] of **2a/3a**
1[b]	/	NCS (1.2)	HOAc	12	100	68/27
2[b]	/	NCS (1.2)	MeCN	72	90	66/24
3[c]	$Cu(OAc)_2$ (2.0)	$CuCl_2$ (2.0)	DCE	72	65	35/6
4	$Cu(OAc)_2$ (2.0)	$CuCl_2$ (2.0)	HOAc	48	80	58/21
5	$Cu(OTFA)_2$ (1.0)	NCS (2.0)	HOAc	24	100	60/29
6	$Cu(OTFA)_2$ (1.0)	$CaCl_2$ (2.0)	HOAc	48	85	74/11
7	$Cu(OTFA)_2$ (1.0)	$CaCl_2$ (6.0)	HOAc	5	100	89/6
8	$Cu(OAc)_2$ (1.0)	$CaCl_2$ (6.0)	HOAc	48	58	50/4
9	BQ (1.0)	$CaCl_2$ (6.0)	HOAc	72	0	0
10	$K_2S_2O_8$ (1.0)	$CaCl_2$ (6.0)	HOAc	72	63	53/2
11	Oxone (1.0)	$CaCl_2$ (6.0)	HOAc	72	50	47/2
12	$Cu(OTFA)_2$ (1.0)	$CuCl_2$ (6.0)	HOAc	4	100	74/24
13	$Cu(OTFA)_2$ (1.0)	NaCl (6.0)	HOAc	48	81	61/21
14	$Cu(OTFA)_2$ (1.0)	LiCl (6.0)	HOAc	48	95	65/32
15[d]	$Cu(OTFA)_2$ (1.0)	$CaCl_2$ (6.0)	HOAc	6	100	76/15
16[e]	$Cu(OTFA)_2$ (1.0)	$CaCl_2$ (6.0)	HOAc	5	100	54/26
17	$Cu(OTFA)_2$ (0.2)	$CaCl_2$ (6.0)	HOAc	40	100	76/16
18	/	$CaCl_2$ (6.0)	HOAc	48	0	0/0
19[f]	$Cu(OTFA)_2$ (1.0)	$CaCl_2$ (6.0)	HOAc	2	100	50/50

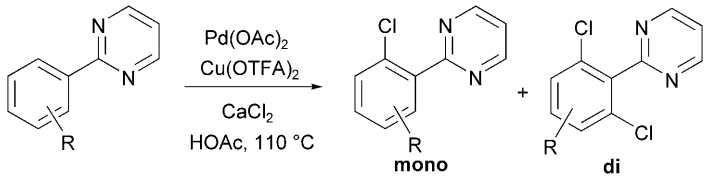
[a] Isolated yield. BQ = benzoquinone, $Cu(OTFA)_2$ = cupric trifluoroacetate, DCE = 1,2-dichloroethane, NCS = *N*-chlorosuccinimide.
[b] 20 °C, under N_2.
[c] $Pd(OAc)_2$ (10 mol%) was used at 90 °C under N_2.
[d] $PdCl_2$ (5 mol%) was used.
[e] $Pd(dba)_2$ (5 mol%) was used.
[f] Under O_2.

and the catalytic amount of $Cu(OTFA)_2$ (entry 17) gave no better results. When the reaction was conducted in the absence of $Cu(OTFA)_2$, no product was achieved (entry 18), while low monoselectivity was obtained with the reaction under oxygen instead of air (entry 19).

The broad substrate scope is summarized in Table 2 and most of the reactions could be finished within several hours. In general, this reaction was compatible in high yields and excellent monoselectivities with functionalized substrates bearing *para*- (entries 1–6), *meta*- (entries 7–10), *ortho*- (entries 11 and 12), and poly-substitutions (entries 13–15) on the aryl ring, as well as a pyrimidine-directed naphthalene derivative (entry 16). Arylpyrimidines containing both electron-donating (entries 7, 8 and entries 11–15) and electron-withdrawing groups (entries 1–4 and entries 9 and 10) afforded monoselective products predominately. It should be noted that the strongly electron-deficient nitro group-containing substrate **1j**, which was rarely used for C–H activation in the literature, could also afford monochlorinated product **2j** selectively in 74% yield (entry 10). However, for those electron-rich substrates without *ortho*- or *meta*-substitution on the aryl ring, an important issue arose. The reaction was less selective under the conditions employed in Table 2, giving rise to the *ortho*-dichlorinated products **3q** and **3r** exclusively (entries 17 and 18), and thus hampered its wider application in organic synthesis.

Screening reactions were next carried out to settle this problem (Table 3) and we found that high monoselectivity and yield could be achieved by addition of acetic anhydride as co-solvent (Table 3, entry 6). This C–H halogenation was accelerated by oxygen with low selectivity (entry 10), and retarded dramatically in a nitrogen atmosphere (entry 11). When the reac-

Table 2. Highly selective C–H chlorination of arylpyrimidines.[a]



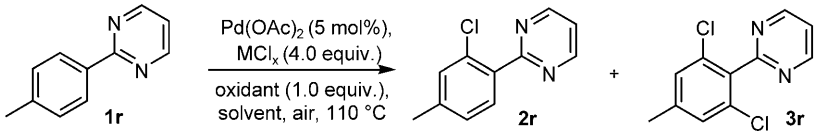
Entry	Substrate	No.: R	Product	No.	Time [h]	Yield [%][b] of **mono**/**di**
1		**1a**: 4-CO_2Et		**2a**	5	89/6
2		**1b**: 4-CF_3		**2b**	6	89/4
3		**1c**: 4-Ac		**2c**	5	82/0
4		**1d**: 4-OTs		**2d**	4	91/3
5		**1e**: 4-Cl		**2e**	5	96/4
6		**1f**: 4-F		**2f**	4	82/9
7		**1g**: 3-Me		**2g**	1	86/0
8		**1h**: 3-OMe		**2h**	1	91/0
9		**1i**: 3-CHO		**2i**	6	92/8
10[c]		**1j**: 3-NO_2		**2j**	24	74/0
11		**1k**: 2-Me		**2k**	1	80/0
12		**1l**: 2-OMe		**2l**	12	89/0
13		**1m**		**2m**	3	85/0
14		**1n**		**2n**	14	72/0
15		**1o**		**2o**	12	89/0
16		**1p**		**2p**	3	93/0
17		**1q**		**3q**	7	0/96
18		**1r**		**3r**	6	0/97

[a] *Conditions:* $Pd(OAc)_2$ (5 mol%), $Cu(OTFA)_2$ (1 equiv.), $CaCl_2$ (4.0–8.0 equiv.) in HOAc, 110 °C, under air.
[b] Isolated yield.
[c] $Pd(OAc)_2$ (10 mol%) was used with conversion of 76%.

tion was conducted in acetic acid or acetic anhydride alone, dichlorinated product **3r** was obtained in 97% yield (entry 12) or the starting material **1r** decomposed during the reaction (entry 13).

The results of C–H halogenation for those electron-rich substrates with less steric hindrance on the aryl rings are summarized in Table 4. Substrates without substituents (entry 1) or bearing electron-rich sub-

Table 3. Optimization of conditions for 2-*p*-tolylpyrimidines.



Entry	Oxidant (equiv.)	MCl_x (equiv.)	Solvent	Time [h]	Conversion [%]	Yield [%][a] of **2r/3r**
1[b]	/	NCS	HOAc	24	93	76/15
2[b,c]	/	NCS	CH_3CN	48	75	65/9
3[c]	$Cu(OAc)_2$	$CuCl_2$	DCE	48	79	42/34
4[d]	$Cu(OAc)_2$	$CuCl_2$	Dioxane	48	55	46/6
5[e]	$Cu(OAc)_2$	$CaCl_2$	$HOAc/Ac_2O$	3	100	83/17
6[e]	$Cu(OTFA)_2$	$CaCl_2$	$HOAc/Ac_2O$	3	100	90/9
7[e]	$Cu(OTFA)_2$	$CuCl_2$	$HOAc/Ac_2O$	8	100	63/37
8[e,f]	$Cu(OTFA)_2$	$CaCl_2$	$HOAc/Ac_2O$	3	100	84/15
9[e,g]	$Cu(OTFA)_2$	$CaCl_2$	$HOAc/Ac_2O$	4.5	100	69/28
10[e,h]	$Cu(OTFA)_2$	$CaCl_2$	$HOAc/Ac_2O$	1.5	100	81/16
11[e,i]	$Cu(OTFA)_2$	$CaCl_2$	$HOAc/Ac_2O$	12	100	89/9
12	$Cu(OTFA)_2$	$CaCl_2$	HOAc	6	100	0/97
13[j]	$Cu(OTFA)_2$	$CaCl_2$	Ac_2O	3	–	0/0

[a] Isolated yield.
[b] 1.05 equiv. of NCS was used.
[c] At 90 °C.
[d] At 100 °C.
[e] $HOAc/Ac_2O = 1.2:1$.
[f] $PdCl_2$ (5 mol%) was used.
[g] $Pd(dba)_2$ (5mol%) was used.
[h] Under O_2.
[i] Under N_2.
[j] **1r** decomposed.

stituents at the *para*-position gave monochlorinated products in high yields (entries 2 and 3). In particular, high yields of *ortho*-mono-chlorinated products **2t**[12] and **2u** could be achieved selectively for dual phenyl-substituted pyrimidines (entries 4 and 5). Remarkably, a highly monoselective bromination was also smoothly realized in high yields using $CaBr_2$ as brominating reagent (entries 6–10), which validates the reaction as a practically convenient method for both chlorination and bromination.

To probe the mechanism, reactions were carried out to obtain the possible active catalytic complex. The palladium complex **5**[13] was obtained in 90% yield from substrate **1q** and a stoichiometric amount of $Pd(OAc)_2$ in HOAc, which would afford palladacycle **6** in 92% yield on treatment with 4.0 equiv. of $CaCl_2$ under mild conditions. Both complexes **5** and **6** could promote the selective formation of **2q** from **1q** in high yields (Scheme 2), indicating that palladacycles **5** or **6** might be the active species during the reaction. The present monoselective halogenation *via* C–H bond activation may go through either Pd(0)-Pd(II)[14] or Pd(II)-Pd(IV)[6b,15] intermediates. Recently, Ritter and Power have shown for the first time that a Pd(III) complex is responsible for the conversion of a C–H bond to a C–Cl bond,[16] we currently cannot rule out the possible existence of a Pd(III) intermediate during the reaction. $Cu(OTFA)_2$ and air are used as co-oxidant to complete the catalytic cycle.

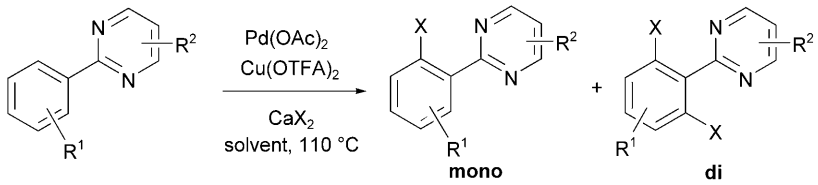
In summary, a palladium-catalyzed direct *ortho*-C–H halogenation of arylpyrimidines was developed using commonly available calcium halides as crucial halogenating agents and cupric trifluoroacetate as oxidant in the presence of air. Highly monoselective *ortho*-halogenation was achieved and most of the reactions were finished within several hours. The characteristics of high monoselectivity and excellent functional-group tolerance will give the described reaction a broad utility in organic synthesis. Further insights into the mechanism, reaction scope, and the applications for other directing groups are now under investigation in our laboratory, and will be reported in due course.

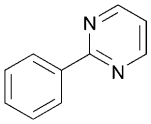
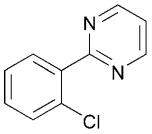
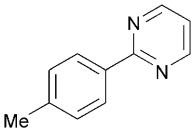
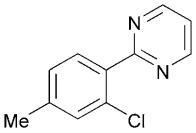
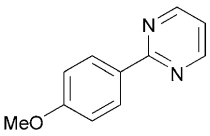
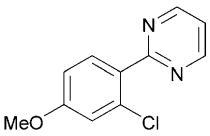
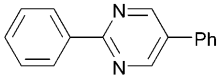
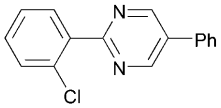
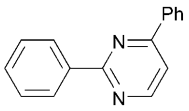
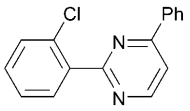
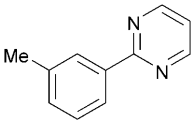
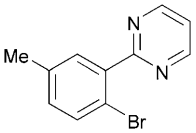
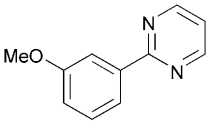
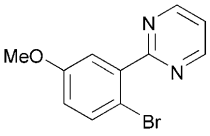
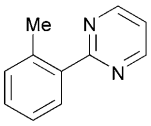
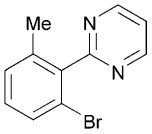
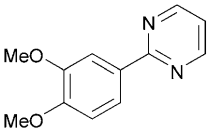
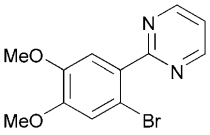
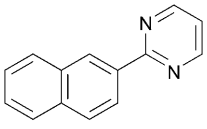
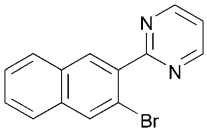
Experimental Section

Typical Procedure for Palladium-Catalyzed *ortho* Halogenation of Arylpyrimidines

The arylpyrimidine (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), $Cu(OTFA)_2$ (1.0–2.0 equiv.), and $CaCl_2$ (4.0–6.0 equiv.) or

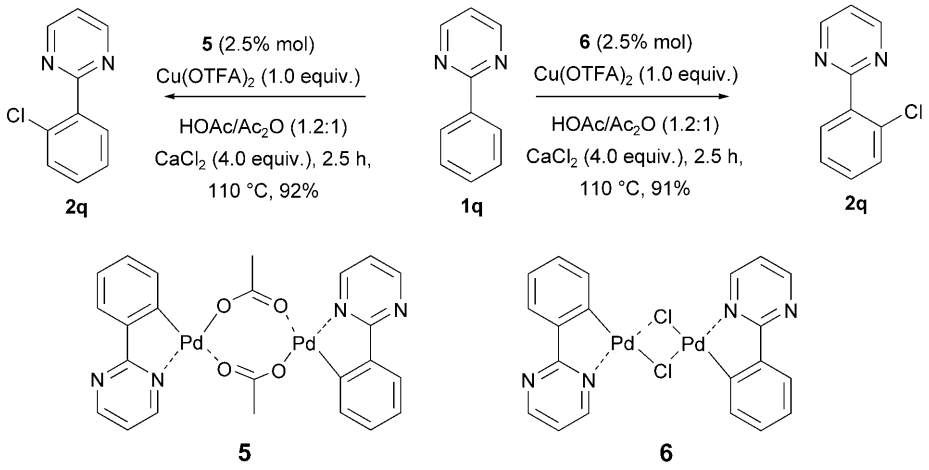
Table 4. Selective C–H chlorination and bromination of arylpyrimidines.[a]



Entry	Substrate	No.	Product	No.	Time [h]	Yield [%][b] of **mono**/**di**
1		**1q**		**2q**	4.5	92/8
2		**1r**		**2r**	3	90/9
3		**1s**		**2s**	3.5	89/9
4		**1t**		**2t**	2	88/0
5		**1u**		**2u**	9	90/6
6		**1g**		**4g**	5	86/0
7		**1h**		**4h**	3	95/0
8		**1k**		**4k**	5	78/0
9		**1m**		**4m**	3	74/0
10		**1p**		**4p**	4	95/0

[a] *Conditions:* $Pd(OAc)_2$ (5 mol%), $Cu(OTFA)_2$ (1.0–2.0 equiv.), $CaCl_2$ (4.0–8.0 equiv.) in HOAc/Ac_2O (1.2:1), or $CaBr_2$ (6.0–8.0 equiv.) in HOAc, 110 °C, under air.

[b] Isolated yield.



Scheme 2. Monoselective halogenation of 2-phenylpyrimidine using palladium complexes **5** and **6**.

$CaBr_2$ (6.0 equiv.) were combined in a 25-mL round-bottom flask, HOAc or HOAc/Ac_2O (v/v = 1.2:1) was added, and the mixture was heated at 110 °C for 3–24 h under air. The solvent was removed under vacuum. The residue was diluted with saturated $NaHCO_3$ solution (15 mL), and the mixture was extracted with EtOAc (3 × 15 mL), washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The obtained crude product was purified using column chromatography on silica gel (EtOAc/petroleum ether) to give the corresponding products.

Supporting Information

Experimental details, spectroscopic characterization data, copies of the ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra for all compounds and X-ray crystal structure for compound **2t** are given in the supporting information file.

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