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Direct synthesis of *ortho*-dihalogenated arylpyrimidines using calcium halides as halogen sources

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ABSTRACT

Pyrimidines and their derivatives have been used as important motifs in materials and medicinal chemistry. In this Letter, a wide variety of *ortho*-dihalogenated arylpyrimidines were synthesized with high yields and functional-group tolerance using calcium halides as crucial halogenating agents and cupric trifluoroacetate as oxidant in the presence of air. The generated dichlorinated products could be further manipulated by stepwise Suzuki–Miyaura reaction to afford a wide range of *ortho*-functionalized arylpyrimidines amenable to physical and biological evaluations.

Aryl or heteroaryl halides are extremely valuable starting materials or intermediates for synthetic elaboration, as well as important structural motifs in many natural products and manufactured drugs.[1] They have been broadly utilized to construct complex structures in organic chemistry via transition-metal catalyzed cross-coupling reactions, such as Buchwald–Hartwig amination, Heck, Negishi, and Suzuki reactions.[2,3] This class of materials could be traditionally achieved by Friedel–Crafts halogenation[4] or Sandmeyer reaction[5] or through directed *ortho*-lithiation reactions.[6] However, these commonly used methods sometimes suffer from several drawbacks, such as limited substrates' scope, low selectivity, tedious and somehow dangerous procedures and thus restrict their applications in organic synthesis.

Remarkable progress has been made during the past decades in catalytic C–H activation directed by functional groups.[7,8] Recently, *ortho* halogenated arenes were selectively synthesized through metal-catalyzed halogenation of C–H bonds with the assistance of some directing groups, including amide,[9c,f,h] carboxylic acid,[9a,g] pyridine,[9b,d,i,j] and oxazoline.[9k] Pyrimidines are important components for a variety of biological active molecules and pharmaceutical agents,[10] as well as potential OLED materials,[11] thus, the development of readily available functionalized arylpyrimidines will be very important. In this event, the pyrimidine-directed C–H functionalization approach will be one of the best synthetic pathways leading to efficient construction of pyrimidine derivatives. However, only few examples involving pyrimidine as directing group for C–H functionalization were reported[8e,h,i,k,m] and one of the reasons may be due to the formation of a dual metal complex.[12]

Generally, for biaryl substrates, such as arylpyridines or arylpyrimidines with electron-donating property and particularly for those with *para*-substitution in the aromatic ring, *ortho*-dihalogenated product could often be achieved more easily through C–H halogenation.[9b,i,j,l] However, *ortho*-dihalogenation is dramatically restrained or completely inhibited for those substrates bearing *meta*-substituents in the aromatic ring even under harsh conditions,[7c,9g,i,l] which may be due to the occurence of steric hindrance between the *meta*-substituents of the substrates and the catalyst during the transition state of the reaction. Thus, developing highly efficient catalytic systems for direct C–H halogenation with diverse directing groups and expanding the reaction scopes to steric substrates remain a challenge.

We have made some efforts to develop efficient methods for the construction of nitrogen-containing heterocycles[13] and recently focused our research on the metal-catalyzed regioselective C–H functionalization of arylpyrimidines.[14] Among them, a palladium-catalyzed highly monoselective C–H halogenation of arylpyrimidines was developed using commonly available calcium halides as crucial halogenating agents, and a palladacycle complex derived from arylpyrimidine and $Pd(OAc)_2$ might be the active species during the reaction (Scheme 1).[14a] We envisioned that the use of this palladacycle might promote the reaction.[15] In this Letter, we report a direct *ortho* C–H dihalogenation of arylpyrimidines, using

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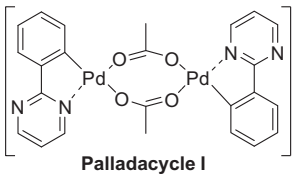
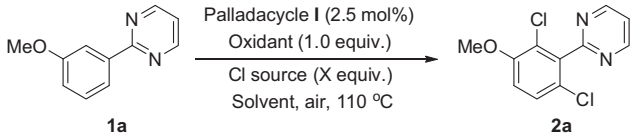


Palladacycle I

Scheme 1. Active species for C–H halogenation of arylpyrimidines.

Table 1
Optimization of dichlorination reaction of **1a**[a]



1a **2a**

Entry	Oxidant	Cl Source (equiv)	Solvent	Time (h)	Yield[b] (%)
1	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	HOAc	90	67[c]
2	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	HOAc	80	61[d]
3	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	HOAc	54	72
4	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	Toluene	48	<5
5	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	Dioxane	48	<5
6	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	MeCN	48	<5
7	$Cu(OTFA)_2$	$CuCl_2$ (4.0)	HOAc	60	52
8	$Cu(OTFA)_2$	NaCl (8.0)	HOAc	60	40
9	$Cu(OTFA)_2$	KCl (8.0)	HOAc	60	37
10	$Cu(OTf)_2$	$CaCl_2$ (4.0)	HOAc	57	70
11	$Cu(OAc)_2$	$CaCl_2$ (4.0)	HOAc	65	56
12	Oxone	$CaCl_2$ (4.0)	HOAc	60	Trace
13	$K_2S_2O_8$	$CaCl_2$ (4.0)	HOAc	60	5
14	$Cu(OTFA)_2$	$CaCl_2$ (5.0)	HOAc	53	76
15	$Cu(OTFA)_2$	$CaCl_2$ (3.0)	HOAc	70	62
16	$Cu(OTFA)_2$	$CaCl_2$ (4.0)	HOAc	7 days	79[e]
17	/	$CuCl_2$ (4.0)	HOAc	56	40[f]

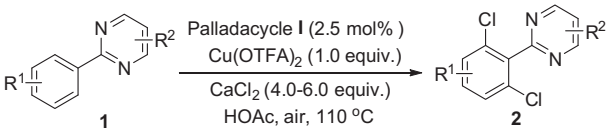
[a] Reaction conditions: substrate of **1a** (0.30 mmol), palladacycle **I** (2.5 mol %), oxidant (1.0 equiv), HOAc (5.0 mL), 110 °C, under air. $Cu(OTFA)_2$ = cupric trifluoroacetate.
[b] Isolated yield.
[c] 5 mol % of $Pd(OAc)_2$ was used.
[d] 5 mol % of $PdCl_2$ was used.
[e] Without palladium
[f] Monochlorinated product was also isolated in 48% yield

calcium halides as halogenating agents and cupric trifluoroacetate as oxidant in the presence of air.

At the outset of this investigation, we used *meta*-substituted 2-(3-methoxyphenyl) pyrimidine **1a** as model substrate under the catalysis of palladium. In the previous study, we have found that *ortho*-dichlorinated products could be produced exclusively from 2-phenylpyrimidine in the presence of calcium chloride, using $Pd(OAc)_2$ as the catalyst and $Cu(OTFA)_2$ as the oxidant.[14a] However, the dichlorination of sterically hindered substrate **1a** turned out to be much more difficult and afforded the corresponding dichlorinated product **2a** in 67% yield after reacted for a period of 90 h under the same condition (Table 1, entry 1) and no better result was given when $PdCl_2$ was used instead (Table 1, entry 2). To our delight, the *ortho*-dichlorination reaction was improved in the presence of palladacycle **I** (2.5 mol %) with decreased reaction time (Table 1, entry 3). Other solvents, such as toluene, dioxane, and acetonitrile, were almost totally ineffective for this transformation (Table 1, entries 4–6). The use of $CuCl_2$, NaCl, and KCl as chlorinating agent resulted in lower yields even with more equivalents of chloride ions, which indicated that the use of $CaCl_2$ was crucial for this chlorination reaction (Table 1, entries 7–9). Switch of $Cu(OTFA)_2$ to $Cu(OTf)_2$ and $Cu(OAc)_2$ could not significantly increase the yields of **2a** (Table 1, entries 10 and 11), and when Oxone and $K_2S_2O_8$ were employed as oxidants, the reaction gave only trace amount of dichlorinated product (Table 1, entries 12 and 13). Further screens concerning the amount of $CaCl_2$ gave similar results; more amount of $CaCl_2$ could not increase the yield dramatically (Table 1, entries 14 and 15). Compound **2a** could be afforded in 79% yield in the absence of palladium after reacted for 7 days[9e] (Table 1, entry 16) and 40% of **2a** could be isolated together with 48% of mono-chlorinated product when $CuCl_2$ was used instead of $Cu(OTFA)_2$ and $CaCl_2$ (Table 1, entry 17).

Having optimized the reaction conditions, we prepared a variety of arylpyrimidines[14] with different substituents and explored the scope and generality of this dichlorination reaction. As shown in Table 2, substrates bearing *meta*- (Table 2, entries 1–4), *para*- (Table 2, entries 6–12) substituents on aryl ring, as well as naphthalene-containing pyrimidine (Table 2, entry 13), gave dichlorinated products in good to excellent yields. Arylpyrimidines containing both electron-donating (Table 2, entries 1, 2, 6 and 7) and electron-withdrawing groups (Table 2, entries 3, 4 and 8–12) could react

Table 2
Direct C–H dichlorination of arylpyrimidines[a]



1 **2**

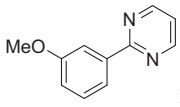
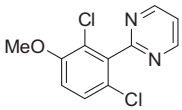
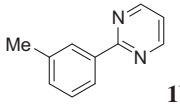
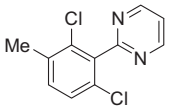
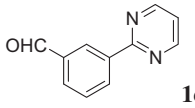
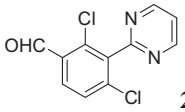
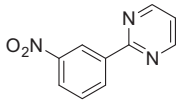
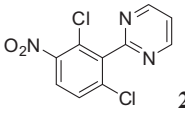
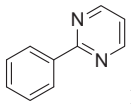
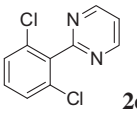
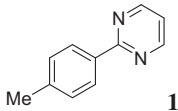
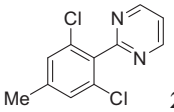
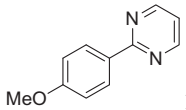
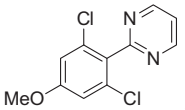
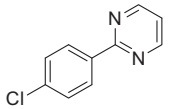
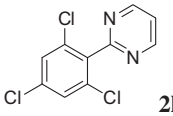
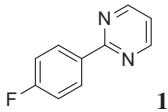
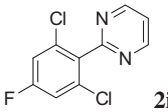
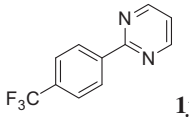
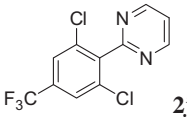
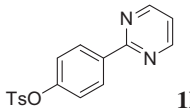
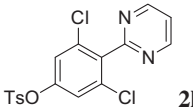
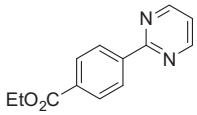
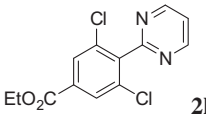
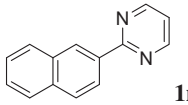
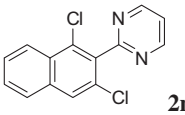
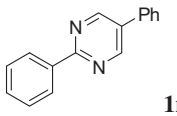
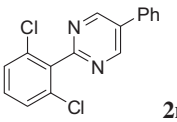
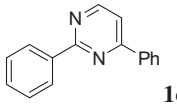
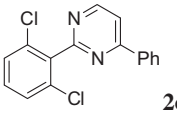
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	54	72
2	 **1b**	 **2b**	36	92
3	 **1c**	 **2c**	98	86[c]

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[b] (%)
4	 **1d**	 **2d**	108	60[d]
5	 **1e**	 **2e**	11	89
6	 **1f**	 **2f**	10	83
7	 **1g**	 **2g**	11	88
8	 **1h**	 **2h**	38	88[e]
9	 **1i**	 **2i**	21	86[e]
10	 **1j**	 **2j**	96	90[e]
11	 **1k**	 **2k**	28	86[e]
12	 **1l**	 **2l**	21	84[e]
13	 **1m**	 **2m**	48	89
14	 **1n**	 **2n**	6	89
15	 **1o**	 **2o**	21	86

[a] Reaction conditions: substrate of **1** (0.30 mmol), palladacycle **I** (2.5 mol %), $Cu(OTFA)_2$ (0.30 mmol), $CaCl_2$ (1.2–1.8 mmol), HOAc (5.0 mL), 110 °C, under air.
[b] Isolated yield.
[c] 7.5 mol % of palladacycle **I**, $Cu(OTFA)_2$ (0.45 mmol), $CaCl_2$ (2.4 mmol) were used.
[d] 7.5 mol % of palladacycle **I**, $Cu(OTFA)_2$ (0.60 mmol), $CaCl_2$ (2.4 mmol) were used.
[e] 6.0 equiv of $CaCl_2$ was used.

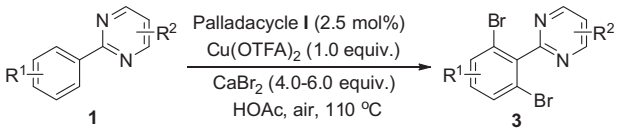
smoothly and afford corresponding products predominately. The presence of functional groups, such as formyl (Table 2, entry 3), nitro (Table 2, entry 3), halogen (Table 2, entries 8 and 9), tosylate (Table 2, entry 11), and ester (Table 2, entry 12) were all compatible with this C–H chlorination reaction under optimized conditions. It should be noted that inactive *meta*-substituted electron-deficient substrates with formyl and nitro groups attached could also proceed well to give **2c** and **2d** in good yields (Table 2, entries 3 and 4) although a long reaction time was needed for completion. The active formyl group in compound **1c** remained intact under the reaction condition and mono-chlorinated product could be isolated in 89% yield after reacted for 4 h, which indicated that further chlori-

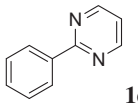
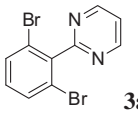
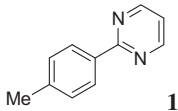
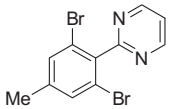
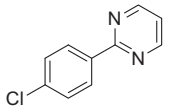
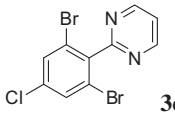
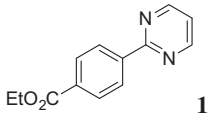
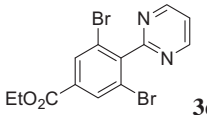
nation from mono-chlorinated product is more sluggish. In particular, high yields of dichlorinated products **2n** and **2o** could be achieved for dual phenyl substituted pyrimidines (Table 2, entries 14 and 15).

To further expand the scope of the reaction, we treated several arylpyrimidines with $CaBr_2$ to form dibrominated products.[16] Gratifyingly, the corresponding dibrominated products **3a–d** could also be well achieved in high yields using $CaBr_2$ as brominating reagent, which validates the reaction as a practically convenient method for both chlorination and bromination (Table 3). Substrates with both electron-donating (Table 3, entry 2) and electron-withdrawing (Table 3, entries 3 and 4) groups on aromatic ring could convert into dibromides in good to excellent yields.

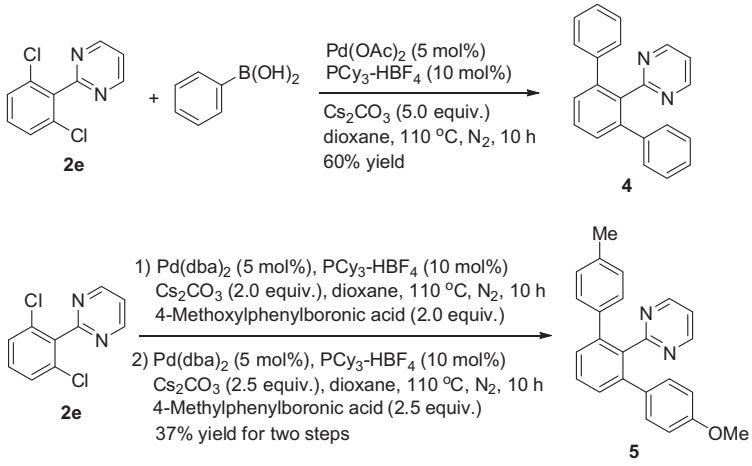
Metal-catalyzed nitrogen-directed *ortho*-arylation of aromatic rings has been well documented,[7c,h,17] however, few examples[8i,m,17e] have been reported for the preparation of *ortho*-arylated 2-phenylpyrimidines[11a,b] and most of them gave mono-phenylated product predominantly. Recently, Nakamura and co-workers reported an iron-catalyzed direct arylation of 2-phenylpyrimidine and afforded mono-phenylated product in 81% yield together with 9% of diphenylated product.[8i] To increase the synthetic utility of these dihalogenated products and synthesize *ortho*-functionalized arylpyrimidines, **2e** was successfully converted into corresponding diphenylated arylpyrimidine **4** by Suzuki–Miyaura reaction with phenyl boronic acid under the catalysis of $Pd(OAc)_2$ and PCy_3 in dioxane (Scheme 2). Furthermore, two different kinds of arylboronic

Table 3
Direct C–H dibromination of arylpyrimidines[a]



Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **1e**	 **3a**	22	72
2	 **1f**	 **3b**	12	94
3	 **1h**	 **3c**	32	86[c]
4	 **1l**	 **3d**	64	79[c]

[a] Reaction conditions: substrates of **1** (0.30 mmol), palladacycle (2.5 mol %), $Cu(OTFA)_2$ (0.30 mmol), $CaBr_2$ (1.2–1.8 mmol), HOAc (5.0 mL), 110 °C.
[b] Isolated yield.
[c] 6.0 equiv of $CaBr_2$ was used.



Scheme 2. Application of dichlorinated product.

acids could be assembled stepwise to afford unsymmetric *ortho*-diarylated arylpyrimidine **5** in moderate yield (Scheme 2), which demonstrates the superiority of our prepared dichlorinated products.

In summary, we have developed an efficient and direct C–H halogenation reaction for the synthesis of *ortho*-dihalogenated arylpyrimidines using calcium halides as crucial halogenating agents in the presence of palladacycle and cupric trifluoroacetate. This *ortho* C–H halogenation reaction may go through either Pd(0)–Pd(II) or Pd(II)–Pd(IV) intermediates with $Cu(OTFA)_2$ and air as co-oxidant to complete the catalytic cycle.[14a] The tolerance of this protocol toward a wide variety of functional groups enables the synthesis of a broad spectrum of valuable compounds. The generated products could be further manipulated by stepwise Suzuki–Miyaura reaction to afford a wide range of substituted arylpyrimidines amenable to physical and biological evaluations. Further studies are in progress in our laboratory to extend this process to other symmetric and/or unsymmetric functionalized arylpyrimidines and nitrogen-containing heterocycles.

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Supplementary data

Supplementary data (experimental details, spectroscopic characterization data, copies of the ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra of all products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.061.

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