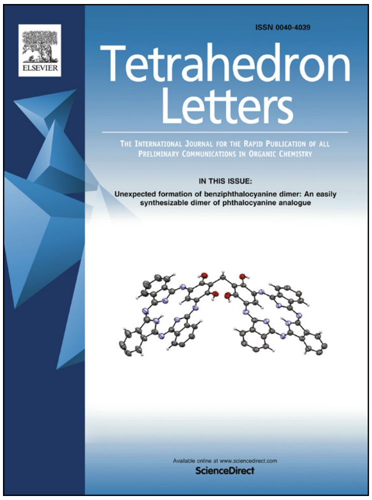

Pd-Catalyzed Decarboxylative Cross-Coupling of Sodium Pyrimidinecarboxylates with (Hetero)arylBromides

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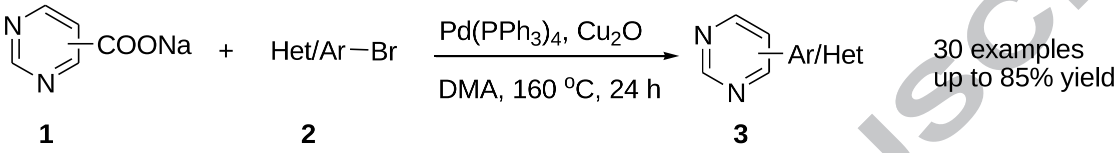

30 examples
up to 85% yield

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Pd-Catalyzed Decarboxylative Cross-Coupling of Sodium Pyrimidinecarboxylates with (Hetero)arylBromides

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ABSTRACT

A straightforward method for the synthesis of functionalized 4- or 5-(hetero)arylpyrimidines via decarboxylative cross-coupling reaction from readily available pyrimidine-4- and pyrimidine-5-carboxylates was described. In the presence of dual-catalyst system of Pd(PPh$_3$)$_4$/Cu$_2$O, the reaction proceeds smoothly, tolerates a variety of functional groups, and provides easy access to the synthesis of different (hetero)arylpyrimidines compounds.

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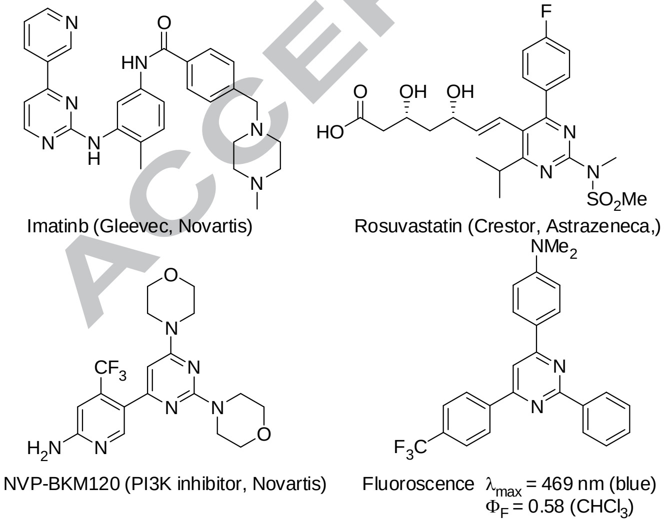
Introduction

Pyrimidines are important heterocyclic scaffolds and have attracted much attention due to their remarkable biological and pharmacological activities.[1] In addition, arylpyrimidines are also broadly applied in organometallic chemistry,[2] photophysical materials[3] and supramolecular chemistry (Figure 1).[4] The traditional route to the synthesis of arylpyrimidines by careful synthetic design and ring formation usually suffers from tedious steps and the limited substrate scope.[5] Additionally, the classical metal-catalyzed cross-coupling reaction is reported to be an effective methodology for the synthesis of arylpyrimidines from halopyrimidines and other organometallic reagents.[6] But the utility of the pyrimidines organometallic reagents were hampered due to their difficult synthesis and lack of stability.[7] Recently, several direct C-H arylation methodologies were actively developed. In 2006, Fagnou and co-workers reported the direct arylation of diazine N-oxides with abroad range of aryl halides as an efficient alternative to standard cross-couplings reaction.[8] In 2010, Baran group reported the direct C-H arylation of electron-deficient heterocycles with arylboronic acids via radical addition which was similar to Minisci type reactions, but the reaction still give low regioselectivities.[9] Obviously, developing a general and efficient method for the synthesis of arylpyrimidines from readily available starting materials remains highly desirable.

In the past few years, transition-metal mediated decarboxylative coupling reactions have been established as a powerful and effective method for the construction of C-C bonds.[10] Meanwhile, as far as we know, the coupling of the π-deficient heteroaryl carboxylic acids remains a challenging goal due to the instability of the metalated azinyl intermediates.[11] Very recently, our group reported the decarboxylative cross-coupling reactions of pyridazine-3-carboxylic acid with a variety of (hetero)aryl halides via a bimetallic Pd/Cu catalysis to afford 3-arylpyridazines.[12] To continue our research in palladium-catalyzed decarboxylative cross-coupling reactions,[13] herein, we would like to report the first decarboxylative cross-coupling reaction of pyrimidine-4 and pyrimidine-5-carboxylates with a variety of (hetero)aryl halides for the synthesis of arylpyrimidine derivatives.



Imatinb (Gleevec, Novartis)

Rosuvastatin (Crestor, Astrazeneca,)

NVP-BKM120 (PI3K inhibitor, Novartis)

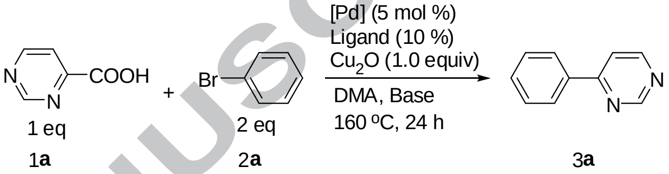
Fluoroscence λ_{max} = 469 nm (blue) Φ_F = 0.58 (CHCl$_3$)

Fig. 1 Bioactive compounds and materials contained pyrimidines derivatives.

Results and Discussion

Initially, the decarboxylative cross-coupling reaction of pyrimidine-4-carboxylic acid (**1a**) with bromobenzene (**2a**) was selected as a model reaction to optimize the reaction conditions as shown in Table 1. When the reaction was carried out under 5 mol % PdCl$_2$/Cu$_2$O (1.0 equiv) catalysis in DMA using K$_2$CO$_3$ as base and BINAP as ligand, only a 15% yield of the desired product was detected (**3a**) (entry 1). Subsequently, PPh$_3$, PCy$_3$, SPhos, XPhos, RuPhos, and other bidentate phosphine ligands such as bis(diphenylphosphino)methane (dppm) and XantPhos were evaluated but failed to improve the yield (entries 2-8). Switching the Pd sources to other commercially available palladium catalysts (Pd(OAc)$_2$, Pd(TFA)$_2$, Pd$_2$(acac)$_3$, Pd(dppf)$_2$Cl$_2$ and Pd(PPh$_3$)$_4$), the yield was not improved. Meanwhile, the combination of Pd(PPh$_3$)$_4$ with BINAP was shown to be nearly as efficient as Pd(PPh$_3$)$_4$ alone (entries 9-14). Our previous work indicated that bases play an obvious influences on the transformation of the pyridazines acids,[12] so a series of bases were screened, but all failed to afford a better yield (entries 15-20).

Table 1. Optimization of reaction conditions[a]



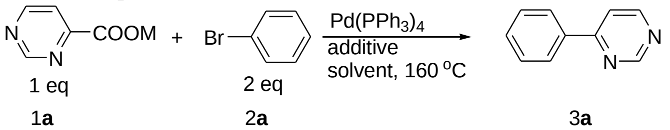
Entry	Catalyst	Ligand	Base	Yield[b](%)
1	PdCl$_2$	BINAP	K$_2$CO$_3$	15
2	PdCl$_2$	PPh$_3$	K$_2$CO$_3$	8
3	PdCl$_2$	PCy$_3$	K$_2$CO$_3$	10
4	PdCl$_2$	SPhos	K$_2$CO$_3$	8
5	PdCl$_2$	XPhos	K$_2$CO$_3$	9
6	PdCl$_2$	RuPhos	K$_2$CO$_3$	10
7	PdCl$_2$	Dppm	K$_2$CO$_3$	7
8	PdCl$_2$	XantPhos	K$_2$CO$_3$	11
9	Pd(OAc)$_2$	BINAP	K$_2$CO$_3$	14
10	Pd(TFA)$_2$	BINAP	K$_2$CO$_3$	16
11	Pd$_2$(acac)$_3$	BINAP	K$_2$CO$_3$	13
12	Pd(dppf)$_2$Cl$_2$	BINAP	K$_2$CO$_3$	15
13	Pd(PPh$_3$)$_4$	BINAP	K$_2$CO$_3$	21
14	Pd(PPh$_3$)$_4$	--	K$_2$CO$_3$	20
15	Pd(PPh$_3$)$_4$	--	Li$_2$CO$_3$	17
16	Pd(PPh$_3$)$_4$	--	Na$_2$CO$_3$	18
17	Pd(PPh$_3$)$_4$	--	Cs$_2$CO$_3$	21
18	Pd(PPh$_3$)$_4$	--	K$_3$PO$_4$	18
19	Pd(PPh$_3$)$_4$	--	NaOH	26
20	Pd(PPh$_3$)$_4$	--	t-BuOK	19

[a] Reaction conditions:**1a** (0.6 mmol), **2a** (1.2 mmol), catalyst (5 mol%), ligand (10 mol %), Cu$_2$O (0.6 mmol), base (1.8 mmol) and 3Å MS (200 mg) in DMA (4.0 mL) at 160 °C under N$_2$ for 24 h.

[b] Detected by HPLC.

Generally, the salts form of aryl carboxylic acid were also used in the decarboxylative cross coupling to reduce the yield of the protodecarboxylation.[14] So a pre-formed pyrimidine-4-carboxylate salt instead of the in situ generated counterpart was employed under the Pd(PPh$_3$)$_4$/Cu$_2$O conditions (Table 2). Delightedly, the desired product was obtained in a moderate yield, and the sodium pyrimidine-4-carboxylate gave a better yield (entries 1-3). Encouraged by this promising result, various other additives such as CuI, CuBr, Cu(OAc)$_2$, Ag$_2$O and Ag$_2$CO$_3$ were also screened to find that even lower yields were observed (entries 4-8). The Cu_2O loading was also examined, and the yields could be enhanced to 75% by using 0.5 equiv of Cu_2O (entry 9). However, the reaction did not proceed smoothly without $Pd(PPh_3)_4$ or Cu_2O indicated that $Pd(PPh_3)_4$ and Cu_2O were critical in this reaction (entries 10 and 11). Decreasing the reaction temperature to 150 °C resulted in a lower yield of 45% (entry 12). A subsequent survey on the role of solvents revealed that DMA was the optimal candidate (entries 13-15). The conclusion for this study is that the substrate sodium pyrimidine-4-carboxylate combined with 5 mol % $Pd(PPh_3)_4$, 2.0 equiv aryl halides, 0.5 equiv Cu_2O in DMA at 160 °C is the optimum condition.

Table 2. Optimization of reaction conditions[a]



Entry	M	Additive	Solvent	Yield[b] (%)
1	K	Cu_2O	DMA	61
2	Na	Cu_2O	DMA	69
3	Li	Cu_2O	DMA	59
4	Na	CuI	DMA	43
5	Na	CuBr	DMA	35
6	Na	$Cu(OAc)_2$	DMA	28
7	Na	Ag_2CO_3	DMA	26
8	Na	Ag_2O	DMA	15
9	Na	Cu_2O	DMA	75[c]
10	Na	--	DMA	Trace
11	Na	Cu_2O	DMA	Trace[d]
12	Na	Cu_2O	DMA	45[e]
13	Na	Cu_2O	DMF	43
14	Na	Cu_2O	NMP	28
15	Na	Cu_2O	DMSO	Trace

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (1.2 mmol), $Pd(PPh_3)_4$ (5 mol%), additive and 3Å MS (200 mg) in solvent (4.0 mL) under N_2 for 24 h.

[b] Detected by HPLC.

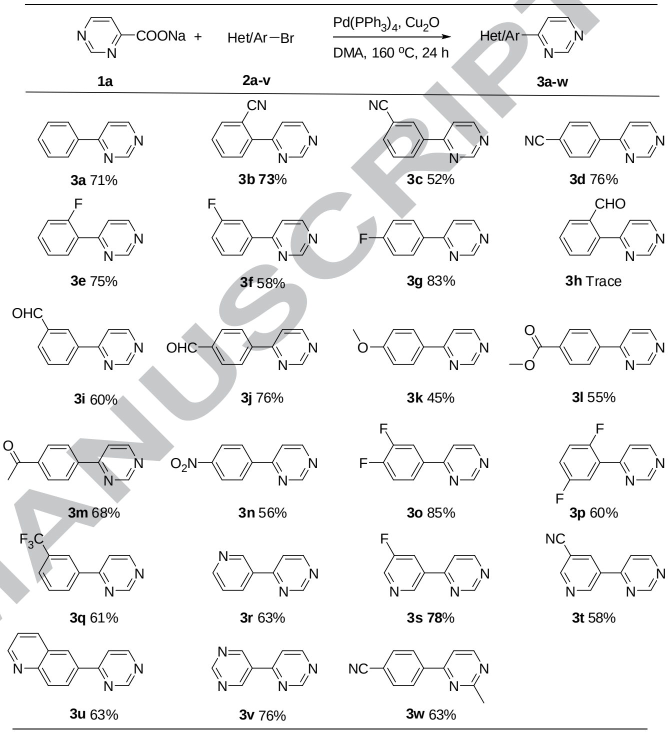
[c] Cu_2O 0.3 mmol.

[d] Absent $Pd(PPh_3)_4$.

[e] Temp150 °C.

With the optimal conditions in hand, the scope of the reaction was then explored and the results were summarized in Table 3. Firstly, extending the model reaction to other aryl bromides showed that both electron-rich and electron-deficient aryl bromides could be successfully converted to the corresponding products in moderate to good yields. A wide range of functional groups, such as nitriles, fluoro, ketones, esters, ethers, trifluoromethyl, and nitro were all tolerated under the reaction conditions. Generally, it was found that electron-rich aryl bromides have a relatively lower reactivity than that electron-deficient ones (**3k** vs **3d**, **3g**, **3j**). The *ortho*- cyano or fluoro substituted aryl bromides did not affect the reactivity (**3b**, **3e**), while the 2-bromobenzaldehyde provided only trace amount of the desired product (**3h**). In addition, the aryl bromides bearing two halogen atoms could be converted to the desired product in good yields of 85% and 60% (**3o**, **3p**). Secondly, the heteroaryl bromides were proved to be good substrates for this reaction too. For example, 3-bromopyridine and 3-bromo-5-fluoropyridine proceed smoothly to afford the corresponding product in 63% and 78% yield respectively (**3r**, **3s**). Other heteroaryl bromides such as 6-bromoquinoline and 5-bromopyrimidine could also afford the desired product in yields of 63% and 76% (**3u**, **3v**). It is noticeable that the sodium 2-methylpyrimidine-4-carboxylate as the coupling substrate with 4-bromobenzonitrile can also gave a 63% yield (**3w**).

Table 3. Scope of sodium pyrimidine-4-carboxylate and (hetero)aryl bromides coupling partners [a, b]

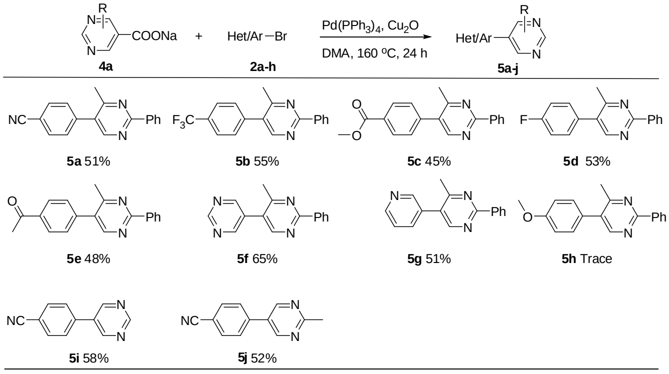


[a] Reaction conditions:**1a** (0.6 mmol), **2a-v** (1.2 mmol), $Pd(PPh_3)_4$ (5 mol %), Cu_2O (0.3 mmol) and 3Å MS (200 mg) in DMA (4.0 mL) under N_2 for 24 h.

[b] Isolated yields.

To further examine the versatility of this methodology, the decarboxylative cross-coupling reaction of sodium 4-methyl-2-phenylpyrimidine-5-carboxylate (**4a**) with a variety of (hetero)aryl bromides were also explored under the optimal conditions. The desired products were obtained in moderate yields and the results were summarized in Table 4. Generally, electron-deficient substrates showed better reactivity than that electron-rich ones (**5a-5h**). The sodium pyrimidine-5-carboxylate

Table 4. Scope of substituted sodium pyrimidine-5-carboxylate and (hetero)aryl bromides coupling partners [a,b]



[a] Reaction conditions: **4a** (0.6 mmol), **2a-h** (1.2 mmol), $Pd(PPh_3)_4$ (5 mol %), Cu_2O (0.3 mmol) and 3Å MS (200 mg) in DMA (4.0 mL) under N_2 for 24 h.

[b] Isolated yields.

and sodium 2-methylpyrimidine-5-carboxylate could also provide moderate yields (**5j**, **5k**). LC-MS analysis of the crude reaction system showed that the by-products were derived from protodecarboxylations[15] of **4a** and the Ullmann-type[16] dimerization of aryl bromides under copper-mediated cross-coupling reaction which resulted in the lower chemical yield.

Conclusion

In conclusion, we have developed a novel synthetic route to 4- or 5-(hetero)arylpyrimidines via Pd-catalyzed decarboxylative cross-coupling of pyrimidine-4- and pyrimidine-5-carboxylates with a variety of (hetero)aryl bromides. The present method potentially useful for high-efficiency synthesis of versatile of (hetero)arylpyrimidines derivatives. In addition, stable and available sodium pyrimidine carboxylates have been used. Under the optimal conditions, the reaction exhibits good substrate scope. This is a valuable new route to (hetero)arylpyrimidines which are commonly found in drug candidates.

Acknowledgments

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References and notes

1. (a) Carey, J. S., Laffan, D., Thomson, C., Williams, M. T., *Org. Biomol. Chem.* **2006**, *4*, 2337-2347. (b) Parker, W. B. *Chem. Rev*. **2009**, *109*, 2880-2893. (c) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc*. **2002**, *124*, 1594-1596. (d). Schenone, S.; Radi, M.; Musumeci, F.; Brullo, C.; Botta, M. *Chem. Rev*. **2014**, *114*, 7189-7238. (d) Lee, S.; Lim, D.; Lee, E.; Lee, N.; Lee, H.; Cechetto, J.; Liuzzi, M.; Freitas-Junior, L. H.; Song, J. S.; Bae, M. A.; Oh, S.; Ayong, L.; Park, S. B. *J. Med. Chem*. **2014**, *57*, 7425-7434. (e) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nature* **2002**, *1*, 493-501. (f) Zhang, J. -Q.; Luo, Y. -J.; Xiong, Y. -S.; Yu, Y.; Tu, Z. -C.; Long, Z. -J.; Lai, X. -J.; Chen, H. -X.; Luo, Y.; Weng, J.; Lu, G. *J. Med. Chem*. **2016**, *59*, 7268-7274.
2. Brown, D.; Muranjan, S.; Jang, Y.; Thummel, R. *Org. Lett*. **2002**, *4*, 1253-1256.
3. (a) Wong, K. T.; Hung, T. S.; Lin, Y.; Wu, C. -C.; Lee, G. -H.; Peng, S. -M.; Chou, C. H.; Su, Y. O. *Org. Lett*. **2002**, *4*, 513-516. (b) Itami, K.; Yamazaki, D.; Yoshida, J. -I. *J. Am. Chem. Soc*. **2004**, *126*, 15396-15397.
4. Bassani, D. M.; Lehn, J. -M.; Baum, G.; Fenske, D. *Angew. Chem. Int. Ed. Engl.* **1997, *36*,** 1845-1847.
5. (a) Müller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett*. **2000**, *2*, 1967-1970. (b) Karpov, A. S.; Müller, T. J. J. *Org. Lett*. **2003**, *5*, 3451-3454. (c) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed*. **2005**, *44*, 6951-6956. (d) Movassaghi, M.; Hill, M. D.; *J. Am. Chem. Soc*. **2006**, *128*, 14254-14255. (e) Yang, G.; Jia, Q.; Chen, L.; Du, Z.; Wang, J. *RSC. Adv*. **2015**, *5*, 76759-76763. (f) Deibl, N.; Ament, K.; Kempe, R. *J. Am. Chem. Soc*. **2015**, *137*, 12804-12807. (g) Guo, W.; Li, C.; Liao, J.; Ji, F.; Liu, D.; Wu, W.; Jiang, H. *J. Org. Chem*. **2016**, *81*, 5538-5546. (h) Zhan, J. L.; Wu, M. W.; Chen, F.; Han, B. *J. Org. Chem*. **2016**, *81*. 11994-12000.
6. (a) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125-7128. (b) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388-390. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366. (d) Lee, D. -H.; Choi, M.; Yu, B.-W.; Ryoo, R.; Taher, A.; Hossain, S.; Jin, M. -J. *Adv. Synth. Catal*. **2009**, *351*, 2912-2920. (e) Lee, D. -H.; Jung, J. -Y.; Jin, M. -J. *Green Chem*. **2010**, *12*, 2024-2029. (f) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem. Int. Ed*. **2013**, *52*, 4945-4949. (g) Hua, X. Y.; Masson-Makdissi, E.; Sullivan, R. J.; Newman, S. G. *Org. Lett*. **2016**, *18*, 5312-5315.
7. (a) Fuller, A. A.; Hester, H. R.; Salo, E. V.; Stevens, E. P. *Tetrahedron Lett*. **2003**, *44*, 2935-2938. (b) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed*. **2006**, *45*, 1282-1284. (c) Clapham, K. M.; Smith, A. E.; Batsanov, A. S.; McIntyre, L.; Pountney, A.; Bryce, M. R.; Tarbit, B. *Eur. J. Org. Chem.* **2007**, 5712-5716. (d) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 9428-9432. (e) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett*. **2013**, *15*, 1302-1305.
8. Leclerc, J. -P.; Fagnou, K. *Angew. Chem., Int. Ed*. **2006**, *45*, 7781-7786.
9. (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc*. **2010**, *132*, 13194-13196. (b) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc*. **2013**, *135*, 12122-12134.
10. (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664. (b) Baudoin, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 1373-1375. (c) Rodríguez, N.; Gooßen, L. J. *Chem. Soc. Rev*. **2011**, *40*, 5030-5048. (d) Dzik, W. I.; Langea, P. P.; Gooßen, L. J. *Chem. Sci*. **2012**, *3*, 2671-2678. (e) Shang, R.; Liu, L. *Sci. China. Chem*. **2011**, *54*, 1670-1687. (f) Patra, T.; Maiti, D. *Chem. Eur. J*. **2017**, *23*, 1-21.
11. (a) Campeau, L. -C.; Fagnou, K. *Chem. Soc. Rev*. **2007**, *36*, 1058-1068. (b) Hackenberger, D.; Weber, P.; Blakemore, D. C.; Goossen, L. J. *J. Org. Chem*. **2017**, *82*, 3917-3925.
12. Wang, S.; Lu H.; Li J.; Zou D.; Wu Y.; Wu, Y. *Tetrahedron Lett*. **2017**, *58*, 1107-1111.
13. (a) Li, X.; Zou, D.; Leng, F.; Sun, C.; Li, J.; Wu, Y.; Wu, Y. *Chem. Commun*. **2013**, *49*, 312-314. (b) Mu, B.; Wu Y.; Li, J.; Zou, D.; Chang, J.; Wu, Y. *Org. Biomol. Chem*., **2016**, *14*, 246-250. (c) Zhang, Y.; Du, H.; Zhu, M.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett*. **2017**, *58*, 880-883.
14. (a) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 7103-7106. (b) Fromm, A.; Wüllen, C. V.; Hackenberger, D.; Goßen, L. J. *J. Am. Chem. Soc*. **2014**, *136*, 10007-10023. (c) Tang, J.; Biafora, A.; Goßen, L. J. *Angew. Chem. Int. Ed*. **2015**, *54*, 13130-13133. (d) Shang, R.; Xu, Q.; Jiang, Y. -Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1000-1003.
15. (a) Goossen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C. *Adv. Synth. Catal*. **2007**, *349*, 2241-2246. (b) Goossen, L. J.; Manjolinho, F.; Khan, B. -A.; Rodríguez, N. *J. Org. Chem*. **2009**, *74*, 2620-2623. (c) Kolaroviĉ, A.; Fáberová, Z. *J. Org. Chem*. **2009**, *74*: 7199-7202.
16. Ullmann, F.; Bielecki, J. *Chem. Ber*. **1901**, *34*, 2174.

Research highlights

1. An efficient method for the synthesis of 4- or 5-(hetero)arylpyrimidines has been developed.

3. The stable and easily available carboxylate salts were used as the nucleophilic coupling partner.

2. Pd-catalyzed decarboxylative cross-coupling was compatible with many functional groups.

Graphical Abstract

Pd-Catalyzed Decarboxylative Cross-Coupling of Sodium Pyrimidinecarboxylates with (Hetero)arylBromides

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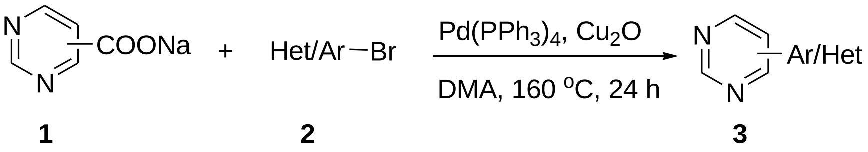

30 examples
up to 85% yield