EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Silver Catalyzed Direct C6-H Arylation of Purines and Purine Nucleosides with Arylboronic Acid

Authors: Miao Tian, Mingwu Yu, Tingting Shi, Junbin Hu, Shunlai Li, Jiaxi Xu, Ning Chen, and Hongguang Du

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700406

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700406

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

COMMUNICATION WILEY-VCH

Silver Catalyzed Direct C6-H Arylation of Purines and Purine Nucleosides with Arylboronic Acid

Miao Tian,[a] Mingwu Yu,[a] Tingting Shi,[a] Junbin Hu,[a] Shunlai Li,[a] Jiaxi Xu,[a] Ning Chen,[a]* and Hongguang Du[a]*

Dedication ((optional))

Abstract: A practical and operationally protocol for assembling of 6-aryl substituted purines has been described through the direct C6-H arylation of purines, 8-azapurine and purine nucleosides from arylboronic acid. This reaction carries out at ambient condition under the oxidation of ammonium persulfate in the presence of silver (I), featuring the regioselectivity predominantly at C6 position and tolerating a broad functional group compatibility scope such as halides, esters, hydroxyls and heterocycles.

Introduction

Purines and purine nucleosides are one of the most widely occurring *N*-heterocycles in nature,[1] constituting many brand-name drugs.[2] Particularly, 6-aryl purines and purine nucleosides also represent a plenty of important bioactive molecules, providing various applications in anticancer, antivirus, cytostatic and anti-HCV, such as the cytotoxicity inhibitor **I**, nanomolar ligand for the bromodomain of human BRD9 **II**, DNPH1 inhibitor **III** and cytostatic agent **IV/V**.[3] (Figure 1) Owing to the widespread in bioactivities, the syntheses and modification of 6-purines and purine nucleosides are of great significance today. However, most reported methods are based upon cross-coupling between 6-purine halides (or pseudohalides) and various coupling reagents, such as aryl boric acid (Suzuki-Miyaura reaction),[4] aryl tin reagents (Stille coupling),[5] aryl zinc reagents (Negeshi coupling),[6] and aryl Grignard reagents (Kumada coupling).[7] (Scheme 1, a) Despite the robust efficiency of reactivity in such reactions, most coupling procedures need expensive noble metal catalysts, require non-natural aryl halides as substrates, and bear strict exclusion of moisture and air condition in many cases. An alternative strategy to furnish the coupling was achieved by traditional radical reaction through the ultraviolet irradiation from 6-iodopurine [8] or the reaction with alkyl nitrite from 6-aminopurine [9] (Scheme 1, b). However, low reactivity and poor regioselectivity in such radical reactions also limit their application. In recent decade, the direct C-H functionalization represented a new, efficient, and atom-economic protocol for C-C bonding formation,[10] but seldom literature exploited the direct C6-H arylation of purines and purine nucleosides.[11] Recently, our continuous interests focused on developing versatile methods for the synthesis of various functionalized purine nucleosides to study their diverse bioactivities.[12] Herein, we describe an efficient way for the direct C-H arylation of purines and purine nucleosides under the catalysis of silver nitrate in room temperature (Scheme 1, c).

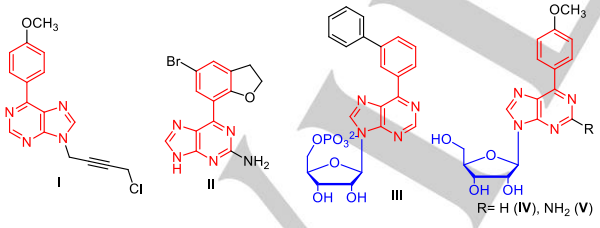
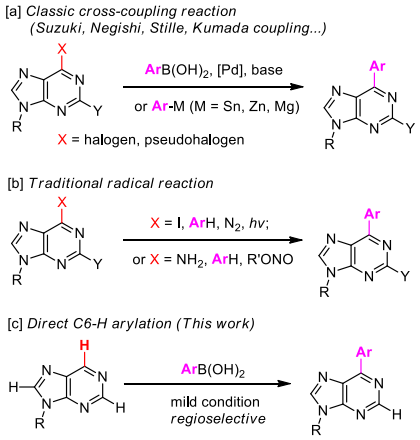


Figure 1. Representative bioactive molecules with 6-aryl purine framework



Scheme 1. The synthesis of 6-aryl purines/purine nucleosides.

Results and Discussion

One challenge in achieving the direct arylation of purines is to overcome the regioselectivity imparted by three potential reactive sites in purine: C2, C6 and C8. As is generally known, the charge distribution of purine features the pyrimidyl moiety electron deficient and the imidazyl moiety electron rich.[13] In order to obtain the C6-arylation product, we turned our attention to Minisci-type reaction,[14] a typical C-H alkylation reaction towards electron-deficient heterocycles. In 2014, Qu and Guo group developed an powerful strategy for C6-H alkylation of

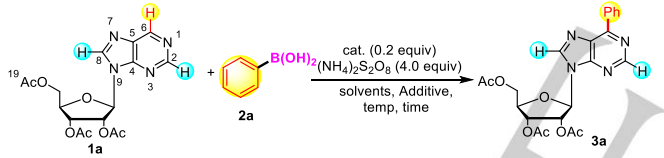
[a] Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China
E-mail: chenning@mail.buct.edu.cn
dhg@mail.buct.edu.cn

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

purine nucleosides from alkyl carboxylic acid via a decarboxylation process.[15] In our case, however, no desired product was detected by investigating benzoic acid as an aryl fragment when it coupled with purine nucleosides **1**.

We were inspired by the seminal work described from Baran group who used aryl radicals, resulted from arylboronic acids, to functionalize the electron-poor heteroarenes, such as pyridines (Scheme 2, a).[16] Phenylboronic acid was therefore evaluated as the coupling reagent, and to our gratification, 34% yield of desired *C*6-phenyl purine nucleoside **3a** was obtained in DCM/H_2O at 60 °C (Table 1, entry 1). By simply modifying the solvent from dichloromethane (DCM) to 1,2-dichloroethane (DCE), the reaction efficiency was significantly promoted to 70% yield (entry 2). It should be mentioned that *C*2- and *C*8-phenylation products were observed in this reaction albeit with very low yield (10%, 1:1).[17] No or only trace desired product was generated by investigating miscible solvents, such as DMF/H_2O, MeCN/H_2O, and THF/H_2O (entries 3–5). The results demonstrated that biphasic solvent was essential to facilitate the solubility of both organic reactants and inorganic salts. Moreover, the yield was obviously dropped by replacing ammonium persulfate to potassium persulfate as oxidant (entry 6). It is noteworthy that $FeSO_4$, an efficient catalyst in C-H arylation of benzoquinones,[18] only proceeded with moderate efficiency in the current reaction albeit we made our every endeavour on improving it (entries 7–10).

Table 1. Optimization for the reaction between purine nucleoside (**1a**) and phenyl boronic acid (**2a**).[a]

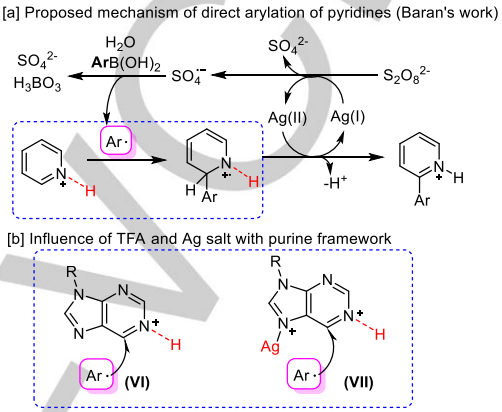


1a 2a 3a

Entries	Cat.	Solvents (1:1)	Add.	Temp. (°C)	Time. (h)	Yields[b] (%)
1	$AgNO_3$	DCM:H_2O	-	60	2	34
2	$AgNO_3$	DCE:H_2O	-	60	2	70[c]
3	$AgNO_3$	DMF:H_2O	-	60	2	trace
4	$AgNO_3$	MeCN:H_2O	-	60	2	trace
5	$AgNO_3$	THF:H_2O	-	60	2	0
6	$AgNO_3$[d]	DCE:H_2O	-	60	2	32
7	$FeSO_4$[d]	DCE:H_2O	-	60	6	42
8	$FeSO_4$	DCE:H_2O	-	80	4	43
9	$FeSO_4$	DCE:H_2O	-	80	4	53
10	$FeSO_4$	DCE:H_2O	TFA	80	4	43
11	$AgNO_3$	DCE:H_2O	TFA	60	1	73[e]
12	$AgNO_3$	DCE:H_2O	TFA	rt	3	77
13	$AgNO_3$	DCE:H_2O	-	rt	3	66

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), $AgNO_3$ or $FeSO_4$ (0.2 equiv.), oxidant (4.0 equiv.), TFA (0.25 mmol), DCE/H_2O (2.0 mL; 1:1, *v*/*v*). [b] All yields are isolated products from column chromatography and the trace yields were detected in Thin-Layer Chromatography (TLC). [c] Both *C*2- and *C*8-phenyl purine were isolated as mixtures in 10% yield with ratio of 1:1. [d] $K_2S_2O_8$ instead of $(NH_4)_2S_2O_8$. [e] Both *C*2- and *C*8-phenyl purine were isolated as mixtures in 5% yield with ratio of 1:1.

In Minisci reaction, acid (proton) could promote the aryl radical addition reaction through activating the nitrogen to reduce the electron density of the heteroarenes (Scheme 2, a).[14,16a,19] However, boronic acid was generated concomitantly as soon as the reaction proceeded, resulting in that the extra acid, like trifluoroacetic acid (TFA), was not necessary in most cases, especially for the reactions with mononitrogen substrates.[16a] In our protocol, however, the tetranitrogen purine nucleoside **1a** is much more complicated. Generally, among the three potential coordinated nitrogen (*N*1, *N*3 & *N*7), *N*1 is prone to be the first site being protonated according to literatures,[20] and *N*7 has yet been identified to be potentially coordinated with silver.[15] We therefore anticipated that the addition of 1 equiv. acid would facilitate the radical addition upon not only accelerating the reaction efficiency through reducing the whole electron density of purine, but also improving the regioselectivity through the protonation at *N*1 as the postulated intermediates **VI** or **VII** (Scheme 2, b).

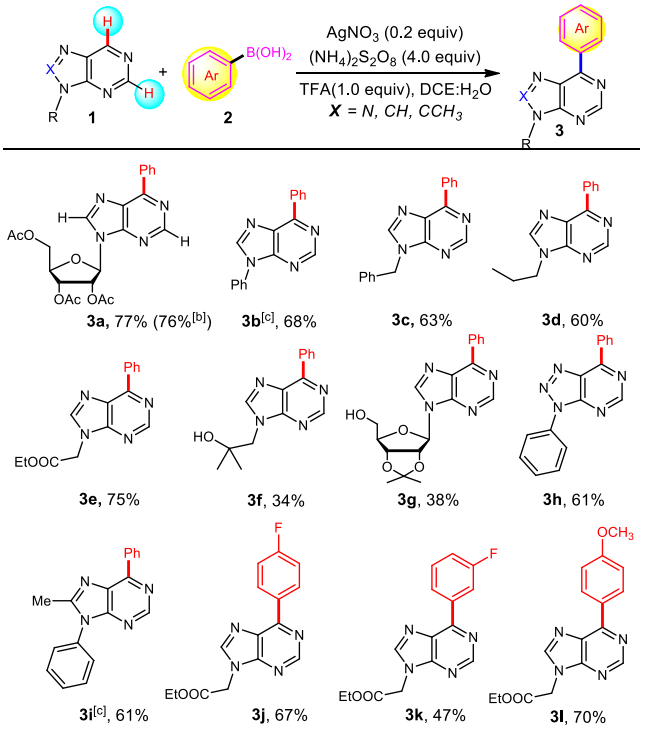


Scheme 2. [a] Proposed mechanism of direct arylation of pyridines on Baran's work; [b] Hypothesis of the influence of acid and silver with purine framework

As we expected, a relatively higher yield was observed when TFA was added to the system with the reaction time even lessened to 1 h, and more significantly, the yield of mixture of *C*2- and *C*8-phenyl purines was depressed to only 5% (Table 1, entry 11). The result from TFA enlightened us to lower the temperature to room temperature (around 20 °C) and finally, the best result was obtained with 77% yield in 3 h (entry 12). By contrast, without adding TFA the yield was yet diminished to 66 in r.t. (entry 13).

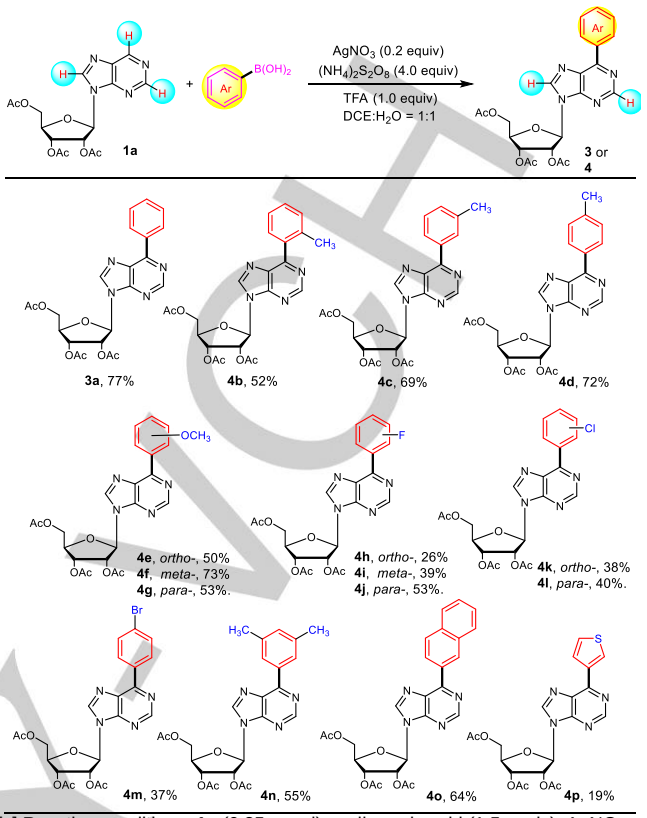
With optimized reaction conditions in hand, we sought to explore the scope of purines (Table 2). Performing with phenyl boronic acid (**2a**), various purine derivatives **1** could afford the desired coupling products in moderate to good yields under the standard condition. It is worth mentioning again that TFA is of great significance in survey of reaction scope though there were only 7% yield variation in the addition of either TFA or not (Table 1, entries 2 and 12). In general, despite there are three reactive sites in its ring (*C*2-, *C*6-, and *C*8-), all purine and its analogues predominately performed at the *C*-6 position. Both aryl and alkyl substituted purines in 9 position gave the corresponding 6-phenyl products in satisfactory yields (**3b**–**3l**), but elevated temperature was essential for aryl purines (**3b** & **3i**) to undergo the transformation probably due to its low solubility in DCE. We found that the reaction was well tolerated with ester group (**3a** & **3e**) and free hydroxyl group (**3f** & **3g**) though the latter one with relatively poor efficiency. To our gratification, 8-azapurine, a five-membered nitrogen-containing bioactive heterocycle, is well accommodated in this transformation. The same result was obtained with the purine bearing a methyl in its 8-position (**3i**). Lastly, **1e**, referred to its ester-bearing nature, was briefly examined its scope with three arylboronic acids, and all arylation reactions were carried out efficiently with both electron-deficient (**3j & 3k**) and rich arylboronic acid (**3l**).

Table 2. Scope with respect to purines and purine nucleosides [a]



[a] Reaction conditions: **1** (0.25 mmol), **2** (1.5 equiv), $AgNO_3$ (0.2 equiv), $(NH_4)_2S_2O_8$(4.0 equiv), TFA (1.0 equiv), DCE (1.0 mL), H_2O (1.0 mL), room temperature, and yields of isolated products are given. [b] Gram-scale reaction from **1a** (2.64 mmol, 1.00 g). [c] Modifying the reaction condition to: time, 3h; temperature, 60 °C.

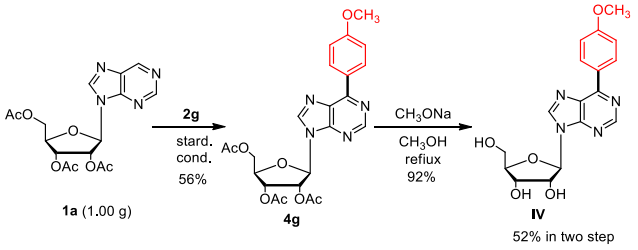
Table 3. Scope with respect to arylboronic acid [a]



[a] Reaction conditions: **1a** (0.25 mmol), arylboronic acid (1.5 equiv), $AgNO_3$ (0.2 equiv), $(NH_4)_2S_2O_8$ (4.0 equiv), TFA (1.0 equiv), DCE (1.0 mL), H_2O (1.0 mL) and yields of isolated products are given.

Having established the scope of purines, we next turned our attention to aromatic boronic acids partner to react with purine nucleoside **1a**. First, comparing with *para*-, *meta*-ones (**4c** & **4d**), *ortho*-tolueneboronic acid (**2b**) displayed lower reactivity for its higher steric hindrance (**4b**). Subsequently, the electron influence of substituent on the phenyl ring was investigated. In general, both electron-donating (Me & MeO, **4b–4g**) and withdrawing substituents (F, Cl & Br, **4h–4m**) were well performed, but undoubtedly electron-rich arylboronic acid provided better reactive efficiency owing to the reaction nature. The favourably tolerance on carbon-halo bond also features potential applications for the further functionalization. When bearing the methoxyl group, *meta*-substituted aryl boronic acid proceeded with better yield than *ortho*- and *para*-ones did (**4e–4g**). The result seems that very strong electron-rich arylboronic acid might retard the coupling efficiency. To test our hypothesis, 3,5-dimethyl boronic acid was carried out with the yield slightly dropping to 55% (**4n**). What surprised us was the coupling with 3,5-dimethoxylphenyl boronic acid, a very strong electron-rich substrate, providing no reaction in current conditions. To our delight, naththylboronic acid could generate the desired product in a good yield (**4o**) and the reaction also tolerated the thiophenyl group albeit with only serviceable yield (**4p**).

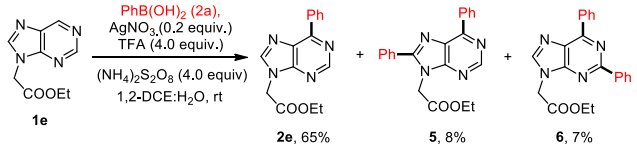
The reaction is then scaled up to evaluate its utility. On one hand, **3a** was obtained with 76% yield from 1.00 g of **1a** (Table 2 **3a**). On the other hand, featured bioactive compound **IV** (Figure 1), a typical cytostatic reagent,[4b] was prepared from **1a** with **2g** under the standard condition followed by a methanolysis of acetyl ester with 52% yields in total two steps (Scheme 3). Compared with the classic Suzuki coupling which requires precious palladium catalyst and relatively harsh conditions like argon protection and high temperature,[3b] the current approach is carried out at ambient condition with low-cost silver catalyst, which thus could be utilized as an alternative and effective method to construct 6-aryl purines.



Scheme 3. Large scale synthesis of cytostatic agent **IV**.

Finally, reaction mechanism was briefly investigated. The radical trapping experiment that no desired coupling product was observed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) strongly supports the current protocol which was

carried out with radical process (see supporting information). To further understanding the influence of TFA, the reaction of **1e** and phenylboronic acid (**2a**) was examined with different loading of TFA (See SI), the result that is in line with Flowers' report.[19] Meanwhile, in the presence of 4 equivalents of TFA, double arylation products **5** and **6** were discovered, verifying that upon decreasing of electron density of purine framework, multiple arylations could be proceeded through the over-protonation control of TFA (Scheme 4).



Scheme 4. Over arylation investigation in the presence of 4 equivalents of TFA

Conclusions

In conclusion, we have developed an efficient and expedient way to modify bioactive purines and purine nucleosides involving a direct *C*6-H arylation of purines from arylboronic acid under mild conditions. The current reaction is carried out in air under the catalysis of inexpensive silver nitrate (less than $2 per gram) and ammonium persulfate (less than $0.2 per gram) displaying a broad scope for both purine and arylboronic acid coupling partners. TFA was essential to the reaction not only promoting the reaction efficiency, but improving the regioselectivity as well. Finally, the reaction is scalable with various functional groups tolerance, such as halides, esters, hydroxyls and heterocycles.

Experimental Section

To a 15 mL vial, 94.6 mg **1a** (0.25 mmol) and 45.7 mg phenylboronic acid **2a** (0.38 mmol) were suspended in 1,2-dichloroethane (1 mL) and followed by an addition of aqueous solution mixed with 8.5 mg $AgNO_3$ (0.05 mmol), 228.2 mg $(NH_4)_2S_2O_8$ (1.00 mmol) and 28.5 mg TFA (0.25 mmol) in water (1 mL). After stirring at ambient atmosphere for 3h, the mixture was filtered with silica gel and the filtrate was then diluted with 1,2-dichloroethane (10 mL) followed by a neutralization with 0.25 mL triethylamine. The organic layer was then separated, dried with $MgSO_4$, filtered and concentrated. Further purification by column chromatography gave rise to the pure **3a** as colorless sticky oil, 87.5 mg (77%).

Acknowledgements ((optional))

We are grateful for the financial support from the National Natural Science Foundation of China (Grant 21272022).

Keywords: purine • purine nucleosides • silver catalysis • C-H activation • arylboronic acid

[1] a) H. Rosemeyer, *Chem. Biodiversity* **2004**, *1*, 361–401; b) M. Legraverend, D. S. Grierson, *Bioorg. Med. Chem.* **2006**, *14*, 3987–4006.

[2] Many brand-name drugs derived from purines and purine nucleosides, including ADENOSCAN®, TABLOID®, LEUSTATIN®, IMURAN®, VIDEX®, DEFITELIO®, and ZOVIRAX®, are searched on the website of *US Food and Drug Administration* (FDA): http://www.fda.gov/.

[3] a) M. Brændvang, L.-L. Gundersen, *Bioorg. Med. Chem.* **2005**, *13*, 6360–6373; b) M. Hocek, P. Nauš, R. Pohl, I. Votruba, P. A. Furman, P. M. Tharnish, M. J. Otto, *J. Med. Chem.* **2005**, *48*, 5869–5873; c) N. R. Kode, S. Phadtare, *Molecules*. **2011**, *16*, 5840–5860; d) C. Amiable, J. Paoletti, A. Haouz, A. Padilla, G. Labesse, P.-A. Kaminski, S. Pochet, *Eur. J. Med. Chem.* **2014**, *85*, 418–437; e) S. Picaud, M. Strocchia, S. Terracciano, G. Lauro, J. Mendez, D. L. Daniels, R. Riccio, G. Bifulco, I. Bruno, P. Filippakopoulos, *J. Med. Chem.* **2015**, *58*, 2718–2736.

[4] a) M. K. Lakshman, P. F. Thomson, M. A.Nuqui, J. H. Hilmer, N. Sevova, B. Boggess, *Org. Lett.* **2002**, *4*, 1479–1482; b) M. Hocek, I. Votruba, H. Dvořáková, *Tetrahedron* **2003**, *59*, 607-611; c) M. Kocek, D. Hocková, H. Dvořáková, *Synthesis* **2004**, *6*, 889-894; d) J. Liu, M. J. Robins, *Org. Lett.* **2004**, *6*, 3421–3423; e) J. Liu, M. J. Robins, *Org. Lett.* **2005**, *7*, 1149–1151; f) P. Čapek, M. Vrábel, Z. Hasník, R. Pohl, M. Hocek, *Synthesis* **2006**, *20*, 3515-3526; g) G.-R. Qu, P.-Y. Xin, H.-Y. Niu, X. Jin, X.-T. Guo, X.-N. Yang, H.-M. Guo, *Tetrahedron* **2011**, *67*, 9099−9103; h) P. Perlíková, P. Konečný, P. Nauš, J. Snášel, I. Votruba, P. Džubák, I. Pichová, M. Hajdúch, M. Hocek, *Med. Chem. Commun.* **2013**, *4*, 1497–1500.

[5] a) T. M. Stevenson, A. S. B. Prasad, J. R. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375–8378; b) A. S. B. Prasad, T. M. Stevenson, J. R. Citineni, V. Nyzam, P. Knochel, *Tetrahedron* **1997**, *53*, 7237–7254.

[6] a) L.-L. Gundersen, *Tetrahedron Lett.* **1994**, *35*, 3155–3158; b) L.-L. Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øverås, F. Rise, *Tetrahedron* **1994**, *50*, 9743–9756; c) V. Bambuch, R. Pohl, M. Hocek, *Eur. J. Org. Chem.* **2008**, *2008*, 2783–2788.

[7] a) H. Dvořáková, D. Dvořák, A. Holý, *Tetrahedron Lett.* **1996**, *37*, 1285–1288; b) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

[8] V. Nair, S. G. Richardson, R. E. Coffman, *J. Org. Chem.* **1982**, *47*, 4520–4524.

[9] a) T. C. McKenzie, J. W. Epstein, *J. Org. Chem.* **1982**, *47*, 4881–4884; b) M. Hocek, D, Hocková, J. Štambaský, *Collect. Czech. Chem. Commun.* **2003**, *68*, 837-848.

[10] For books and review, please see: a) J.-Q. Yu, Z.-J. Shi, *C-H Activation, Topics in Current Chemistry*, Springer-Verlag Berlin Heidelberg, **2010**; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; c) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 10578–10599. For selected research paper on C-H activation of purines and purine nucleosides, please see: d) M. Hocek, *Eur. J. Org. Chem.* **2003**, *2003*, 245–254; e) H.-M. Guo, L.-L. Jiang, H.-Y. Niu, W.-H. Rao, L. Liang, R.-Z. Mao, D.-Y. Li, G.-R. Qu, *Org. Lett.* **2011**, *13*, 2008–2011; f) R. Xia, H.-Y. Niu, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2012**, *14*, 5546–5549; g) A. Ilangovan, A. Polu, G. Satish, *Org. Chem. Front.* **2015**, *2*, 1616–1620; h) M. Klečka, L. P. Slavětínská, M. Hocek, *Eur. J. Org. Chem.* **2015**, *2015*, 7943–7961; i) D.-C. Wang, R. Xia, M.-S. Xie, G.-R. Qu, H.-M. Guo, *Org. Biomol. Chem.* **2016**, *14*, 4189–4193.

[11] There are a hand of studies on *C*8-H arylation of purine and purine nucleosides under the catalysis of palladium: a) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 5274–5275; b) I. Čerňa, R. Phol, B. Klepetářová, M. Hocek, *Org. Lett.* **2006**, *8*, 5389–5392;c) I. Čerňa, R. Phol, M. Hocek, *Chem. Commun.* **2007**, 4729–4730; d) T. E. Storr, A. G Firth, K. Wilson, K. Darley, C. G. Baumann, I. J. S. Fairlamb, *Tetrahedron* **2008**, *64*, 6125–6137; e) I. Čerňa, R. Phol, B. Klepetářová, M. Hocek, *J. Org. Chem.* **2008**, *73*. 9048–9054; f) T. E. Storr, C. G. Baumann, R. J. Thatcher, S. D. Ornellas, A. C. Whitwood, I. J. S. Fairlamb, *J. Org. Chem.* **2009**, *74*, 5810–5821; g) M. Abdoli, Z. Mirjafary, H. Saeidian, A. Kakanejadifard, *RSC Adv.* **2015**, *5*, 44371–44389; h) Y. Liang, S. F. Wnuk, *Molecules* **2015**, *20*, 4874–4901; i) V. Gayakhe, Y. S. Sanghvi, I. J. S. Fairlamb, A. R. Kapdi, *Chem. Commun.* **2015**, *51*, 11944–11960.

[12] a) G. Liu, J. Xu, N. Chen, S. Zhang, Z. Ding, H. Du, *Eur. J. Med. Chem.* **2012**, *53*, 114–123; b) Z. Wang, S. Li, M. Yu, Y. Luo, S. Wang, Y. Wang, H. Du, *Chin. J. Org. Chem.* **2015**, *35*, 2205–2211; c) M. Yu, Z. Wang, M. Tian, C. Lu, S. Li, H. Du, *J. Org. Chem.* **2016**, *81*, 3435–3442; d) H. Du, X. Sun, M. Yu, M. Tian, S. Li, Z. Wang, *Tetrahedron Lett.* **2016**, *57*, 2949–2953.

[13] J. A. Joule, K. Mills, *Heterocyclic Chemistry, 5 th Edition, P515*, Wiley-Blackwell, **2010**.

[14] a) F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* **1971**, *27*, 3575–3579; b) E. Vismara, A. Donna, F. Minisci, A. Naggi, N. PaStori, G. Torri, *J. Org. Chem.* **1993**, *58*, 959–963; c) M. A. J. Duncton, *Med. Chem. Commun*. **2011**, *2*, 1135–1161; d) R.-J. Tang, L. Kang, L. Yang, *Adv. Synth. Catal*. **2015**, *357*, 2055–2060.

[15] R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2014**, *16*, 444–447.

[16] a) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196; b) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.

[17] Note: 1) *C*2- and *C*8-phenyl purine nucleosides are isolated as mixtures which cannot be separated each other not only for the very low yields but also for the almost same polarity. 2) The structures of all compounds are verified by HSQC, HMBC and HRMS; 3) *C*2-phenyl purine nucleoside is further confirmed by the literature: V. Nair, D. A. Young, R. D. Jr, *J. Org. Chem.* **1987**, *52*, 1344–1347.

[18] K. Komeyama, T. Kashihara, K. Takaki, *Tetrahedron Lett.* **2013**, *54*, 1084–1086.

[19] N. R. Patel, R. A. Flowers, *J. Am. Chem. Soc.* **2013**, *135*, 4672–4675;

[20] a) A. Bendich, P. J. Russell Jr., J. J. Fox, *J. Am. Chem. Soc*. **1954**, *76*, 6073–6077; b) N. C. Connella, J. D. Roberts, *J. Am. Chem. Soc*. **1982**, *104*, 3162–3164.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here: max. width: 5.5 cm; max. height: 5.0 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

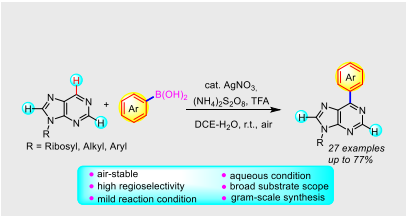
Page No. – Page No.

Title

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

COMMUNICATION



An efficient protocol for direct *C*6-H arylation of purines and purine nucleosides has been described here under the catalysis of silver nitrate in ambient condition. A wide assortment of purines and arylboronic acids can be employed in this process to afford C6-aryl purines and purine nucleosides with high regioselectivity.

*silver catalysis

Key Topic*

Miao Tian,[a] Mingwu Yu,[a] Tingting Shi,[a] Junbin Hu,[a] Shunlai Li,[a] Jiaxi Xu,[a] Ning Chen,[a] and Hongguang Du[a]**

Page No. – Page No.

Silver Catalyzed Direct C6-H Arylation of Purines and Purine Nucleosides with Arylboronic Acid