Check for updates

View Article Online
View Journal

ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Zhang, H. Zhao, Z. Li, Z. Liang, S. Qi, M. Cai, S. Zhang, X. Jia, G. Zhang and M. Hu, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC03789C.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Rapid Access to 3-Aminoindazoles from Nitriles with Hydrazines: A Strategy to Overcome the Basicity Barrier Imparted by Hydrazines

Chunyan Zhang,*[a] Haowen Zhao,[a] Zehua Li,[a] Zuyu Liang,[a] Shuo Qi,[a] Mingyu Cai,[a] Sheng Zhang,[a] Xiaofei Jia,[a] Guoying Zhang,*[a] and Mao-Lin Hu*[b]

Received (in XXX, XXX) Xth XXXXXXXXX 202X, Accepted Xth XXXXXXXXX 202X
First published on the web Xth XXXXXXXXX 202X
DOI: 10.1039/b000000x

A practical and efficient base mediated synthesis of free 3-aminoindazoles has been developed from reaction of nitriles with hydrazines, which successfully overcomes the difficulty of using aromatic hydrazines as substrates and allows for the synthesis of a wide range of *N*-aryl substituted free 3-aminoindazoles in moderate to excellent yields under mild conditions in one-pot. This finding provides a rapid and useful strategy for synthesis of various functionalization 3-aminoindazole derivatives.

3-Aminoindazoles and related molecules that contain a free amine group and indazole moiety are a unique class of heterocyclic with valuable physicochemical properties and significant biological activities.[1] These molecules exhibit wide applications in agrochemicals, pharmaceuticals and functional materials serve as attractive precursors in a plenty of chemical transformations (Figure 1).[2] Due to their properties and applications, various methods for the constructor of 3-aminoindazole derivatives have been developed.[3]

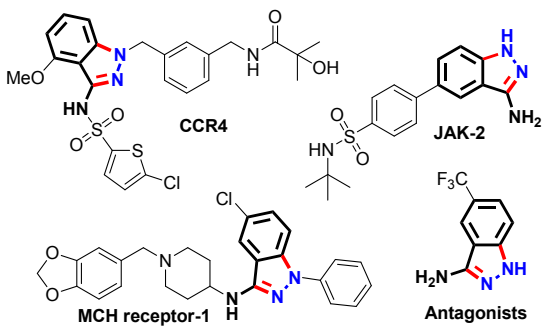
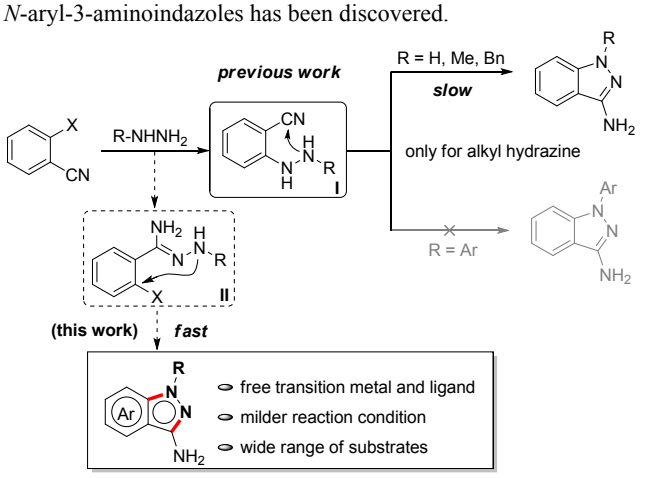


Figure 1 Selected examples bioactive compounds with 3-aminoindazoles moieties.

Existing methods commonly rely on an aromatic nucleophilic substitution of *ortho*-halobenzonitriles with hydrazine hydrate,[1-3] which not only suffered from requiring harsh reaction conditions, but resulted in intricately poor chemoselectivity and low yields. [4] Recently, as a means of addressing this problem, various effectively transition metal catalyzed strategies were later discovered.[5] As a result, transition metal complexes catalyst are required to sustain the catalytic cycle, which is generally expensive, not readily accessible. And their widespread use has been precluded by a restricted substrate scopes (only for methyl or benzyl hydrazines) and inconvenient reaction procedures (Scheme 1, Top).[6] Therefore, the development of efficient, practical, economic, lowly toxic, even transition metal free processes for the synthesis of 3-aminoindazole derivatives is still a challenging task in the synthetic chemistry field. Very recently, we have identified that *t*-BuOK can react with alcohols to form the alkoxide metal species *via* exchange of alkoxide groups.[7] This result together with our strategy on the use of base as the replacement of green mediator for cyclization reactions prompted us to envision that aromatic hydrazine might be severed as substrates to circumvent the inherent necessary in the transition metal catalyzed annulation of hydrazines with multiple substituted protecting groups. Specifically, we postulated that the intermediate **II** species might be generated by nitrile with hydrazine in the presence of base. **II** could further fast nucleophilic attacked facilitated by intramolecular to afford the annulation product (Scheme 1, bottom). To date, however, there are no base mediated reaction system dealing with annulation condensation of nitriles with aromatic hydrazines to synthesis of *N*-aryl-3-aminoindazoles has been discovered.



Scheme 1 State of the art and the annulation reaction for synthesis of 3-aminoindazoles described here.

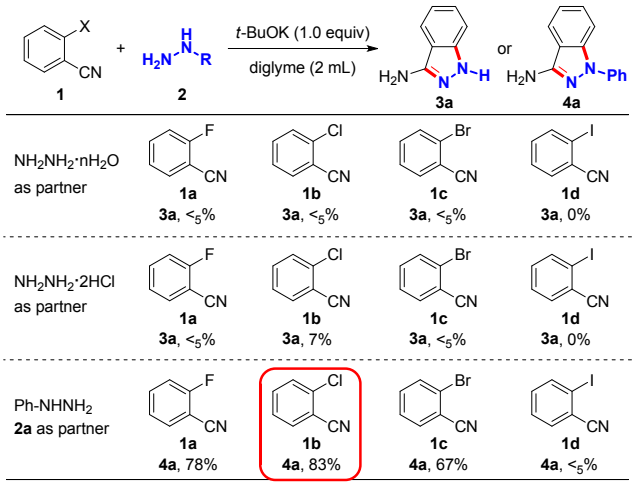
Herein, we describe a rapid and efficient protocol for successful implementation of the base promoted cyclization of *ortho*-halobenzonitriles with a variety of aromatic hydrazines, which allows for synthesis of a series of free 3-amioindazoles under mild conditions in one-pot.

[a] *Key Laboratory of Sensor Analysis of Tumor Marker, Ministry of Education; Shandong Key Laboratory of Biochemical Analysis; Key Laboratory of Analytical Chemistry for Life Science in Universities of Shandong; College of Chemistry and Molecular Engineering. Qingdao University of Science and Technology, Qingdao 266042, P.R. China. zhanggy@qust.edu.cn*
[b] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P.R. China.*
† Electronic supplementary information (ESI) available. See DOI: 10.1039/0000000x/

Published on 09 July 2020. Downloaded by Karolinska Institutet University Library on 7/10/2020 9:50:16 AM.
ChemComm Accepted Manuscript

View Article Online
DOI: 10.1039/D0CC03789C

Published on 09 July 2020. Downloaded by Karolinska Institutet University Library on 7/10/2020 9:50:16 AM.

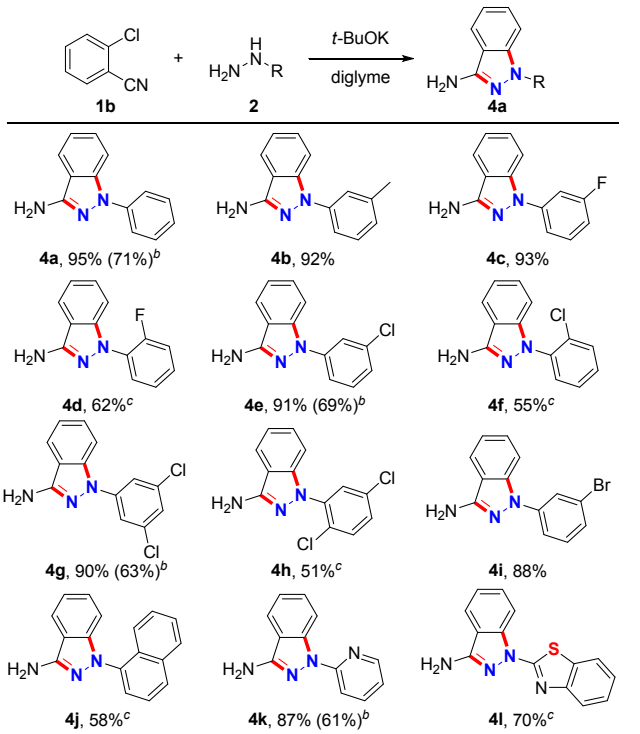


Scheme 2 Investigated annulation of nitriles and hydrazines.

The reaction between 2-halobenzonitriles (**1**) and hydrazines (**2**) to synthesis 3-amioindazoles (**3a** or **4a**) was investigated to develop broadly applicable annulation conditions (Scheme 2). The different *ortho*-substituted halide benzonitriles with various functionalized hydrazines were tested to find the most active nitriles and hydrazines, respectively. No reaction or only a trace amount of the annulation product **3a** were detected in the presence of hydrazine hydrate. Hydrazine hydrochloride as the substrate, low amount of desired product **3a** was formed with 2-chlorobenzonitrile as reaction partner. Under this reaction conditions, other functional groups of nitriles did not improve the reactivity. The hydrazine **2a** functionalized with the phenyl group gave the highest yield of **4a** in the presence of 2-chlorobenzonitrile. Further investigation of the functionalized nitriles revealed that the reactivity was affected by the nature of the substituted halo groups, and the sequence of *ortho*-halobenzonitriles activity was Cl > F > Br >I. Variation of bases,[8] type of *t*-BuOM or MHMDS (M= Li, Na, K), revealed that potassium base demonstrated the best promote efficiency for delivering the annulation adduct **4a** in excellent yields. Only a trace or low amount of the annulation products were formed in the presence of organic amine bases or inorganic bases. Finally, the cyclization were almost inhibited in the absence of base or in the presence of water. In addition, the best yield of **4a** was obtained after thoroughly optimization of the reaction parameters (amount of base, type of solvent, solvent amount, substrate ratio, reaction temperature and time; see the Supporting Information) with **1b** determined to be the most active nitrile.[8] Importantly, this transformation is very practical and highly speedy, as the transition metal catalyst, ligands or a large excess of hydrazines unneeded.

With the optimized annulation conditions in hand, we first examined the substrate scope of hydrazines for the synthesis of 3-aminoindazoles, and the results were summarized in Table 1. Aromatic hydrazines containing various electron-rich and electron-inefficient functional groups reacted smoothly to give the corresponding annulation products in high yields. The aryl halide substituent remained intact during this cyclization (**4c**-**4i**), providing a useful handle for further elaboration reactions. Although electronic factors of aryl hydrazines seemingly exerted a negligible influence on the conversion, the orientation of substituents on the aromatic ring system had an obvious impact on the efficacy of the transformation, affording the corresponding adducts (**4d**, **4f**, **4h**) in moderate yields. Naphthalen-1-ylhydrazine was surveyed and the reaction proceeded to give the desired **4j** in acceptable yield, showing the large sterically hindered groups are unfavorable for this conversion. Some heterocyclic moieties, including pyridinyl and benzo[d]thiazoly, could be smoothly incorporated in the indazoles by employing corresponding heterocyclic aromatic hydrazines (**4k**-**4l**). Notably, some selected substrates could be transformed into the corresponding indazoles at 40 °C in moderate to good yields (**4a**, **4e**, **4g**, **4k**), which could increase the practicality of our reaction process dramatically.

Table 1 Annulation of 2-chlorobenzonitrile with various hydrazines for synthesis of free 3-aminoindazoles [a]



[a] Reaction conditions: **1b** (1.0 mmol, **2** (3.0 mmol), *t*-BuOK (1.3 mmol), diglyme (2.0 mL), 130 °C, N_2, 1 h. Isolated product. [b]40 °C, 24 h. [c]2 h.

Having demonstrated that the annulated process is compatible with a broad range of hydrazines, investigation of the scope regarding the nitriles was undertaken (Table 2). For most of the substituted *ortho*-chloro benzonitriles, the reaction proceeded to offer the corresponding products in moderate to excellent yields. The cyclization could be compatible with a wide range of functional groups, such as alkyl, alkyloxy, fluoro, chloro, bromo, iodo, free amino and trifluoromethyl groups, showing that the present cyclization reaction had a good functional groups tolerance. Lower yields were obtained substituted with electron-withdrawing groups than electron-donating ones on aromatic ring system. Interestingly, the 2-chloro-6-methylbenzonitrile reacted rendering the target aminoindazole **5b** in excellent yield. When the 2-chloro-6-

ChemComm Accepted Manuscript

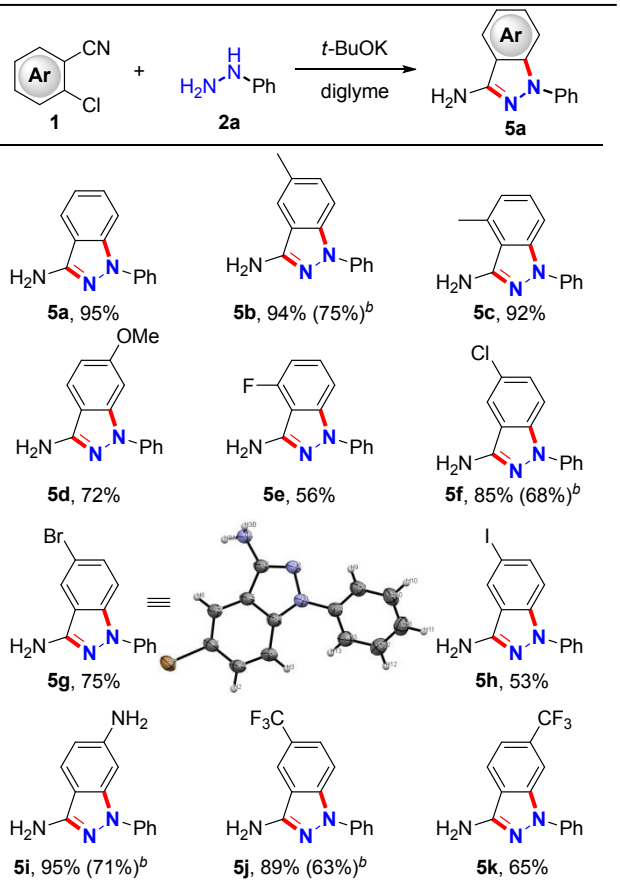
This journal is © The Royal Society of Chemistry [year]

View Article Online
DOI: 10.1039/D0CC03789C

Published on 09 July 2020. Downloaded by Karolinska Institutet University Library on 7/10/2020 9:50:16 AM.

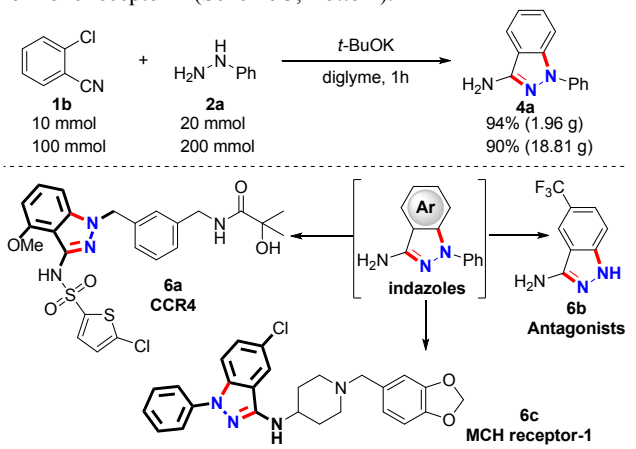
fluorobenzonitrile was used as the starting reactant under the standard reaction conditions, the desired product **5e** was isolated in reasonable yield. Halide groups particularly, even iodo, survived well in the standard procedure, leading to corresponding indazoles **5e-5h** in good yields, which can be used for further transformations to constructed **JAK-2** inhibitor.[9] The structure of **5g** was confirmed by single-crystal X-ray analysis.[10] Interestingly, annulation occurs when 4-amino-2-chlorobenzonitrile was subjected to the present reaction, providing the corresponding adduct **5i** with double free amino group in 95% yield. In addition, strong electron-withdrawing groups, such as 3- or 4-substituted trifluoromethyl, can be smoothly transferred to the corresponding free 3-aminoindazoles **5j** and **5k** in 89% yield and 65% yield, respectively.

Table 2 Annulation of phenyl hydrazine with various nitriles for synthesis of free 3-aminoindazoles [a]



[a] Reaction conditions:**1** (1.0 mmol, **2a** (3.0 mmol), *t*-BuOK (1.3 mmol), diglyme (2.0 mL), 130 °C, N_2, 1 h. Isolated product. [b]40 °C, 24 h.

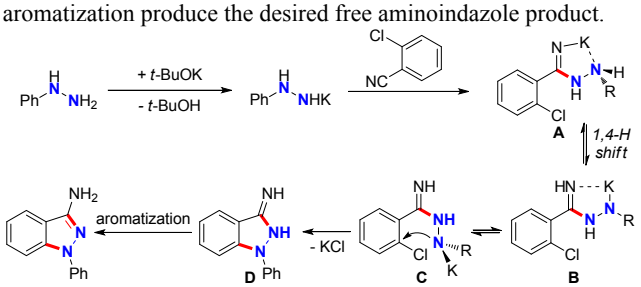
The synthetic versatility of the present annulation was next demonstrated through large-scale reactions and product derivatizations in one pot reaction (Scheme 3, Top). The cyclization on 10 mmol and 100 mmol scale were found to be completed in an hour, yielding 1.96 g and 18.81 g of cyclization adduct **4a** (94% yield and 90% yield), respectively.[8] With the newly developed transformation system, **6a** can be prepared iterations from fragment indazoles, which can use as human Allosteric CC-Chemokine Receptor 4 (**CCR4**) antagonists.[11] Protein Antagonists **6b** can be produced from **5j**.[12] In addition, *N*-acylation product **MCH** can be obtained *via* transformation of **5f**, which can be severed as blocking melanin-concentrating hormone receptor-1 (Scheme 3, Bottom).[13]



Scheme 3 Application of the present annulation system.

To better understand the mechanism, several of control experiments were performed.[8] Initially, we examined a series of reaction conditions employing the new reaction tube (pure base, metal additives) in the annulation of **1b** with **2a**, there were no impact on yields of **4a**, which indicates that this transformation should not be a transition metal catalyzed procedure. In addition, tetramethylpiperidin-1-oxyl (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) were added into the standard reaction as a radical scavenger. **4a** were obtained in good yields, respectively, indicating that this cyclization could not be a free radical process. These results showed that the role of the base in promoting the annulation rather than the transition metal catalysts or its impurities.

Although the mechanistic details of this annulation are not clear at this stage, on the basis of the present results and precedent reports,[14] one tentative transformation pathways for this cyclization was proposed (Scheme 4). Under the reaction conditions, hydrazine directly react with *t*-BuOK to generate the active PhNHNHK species, then nucleophilic addition with nitrile to form **A**. Reversible 1,4 H-shift of species **A** to the **B**, subsequent isomerization transform to **C**. Consequently, nucleophilic substitution form to the intermediate **D** and aromatization produce the desired free aminoindazole product.



Scheme 4 Propose Mechanistic.

In summary, we have developed a rapid, practical and efficient protocol for the *t*-BuOK mediated annulation of *ortho*-halobenzonitriles by aromatic hydrazines. A broad range of *N*-arylsubstituted free 3-aminoindazoles have been synthesized in moderate to excellent yields. Seventeen of the 22 synthesized

ChemComm Accepted Manuscript

Published on 09 July 2020. Downloaded by Karolinska Institutet University Library on 7/10/2020 9:50:16 AM.

examples are novel compounds. Moreover, this transformation could be employed to synthesis of several of protein antagonists or receptors. Further studies aimed at gaining a detailed mechanistic understanding of this cyclization reaction and the application of base as the efficiently mediator in other reactions and free 3-aminoindazoles as an antagonists of pharmaceuticals are currently in progress in our laboratory.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (No. 21571143), the Shandong Provincial Natural Science Foundation of China (Nos. ZR2017MB029, ZR2017BB060), the Qingdao Science and Technology Foundation (18-2-2-49-jch) for financial support.

Notes and references

1 (*a*) P. Orsini, M. Menichincheri, E. Vanotti and A. Panzeri, *Tetrahedron Lett.* 2009, **50**, 3098. (*b*) M. Menichincheri, E. Ardini, P. Magnaghi, N. Avanzi, P. Banfi, R. Bossi, L. Buffa, G. Canevari, L. Ceriani, M. Colombo, L. Corti, D. Donati, M. Fasolini, E. Felder, C. Fiorelli, F. Fiorentini, A. Galvani, A. Isacchi, A. L. Borgia, C. Marchionni, M. Nesi, C. Orrenius, A. Panzeri, E. Pesenti, L. Rusconi, M. B. Saccardo, E. Vanotti, E. Perrone and P. Orsini, *J. Med. Chem.* 2016, **59**, 3392. (*c*) M. Menichincheri, E. Ardini, P. Magnaghi, N. Avanzi, P. Banfi, R. Bossi, L. Buffa, G. Canevari, L. Ceriani, M. Colombo, L. Corti, D. Donati, M. Fasolini, E. Felder, C. Fiorelli, F. Fiorentini, A. Galvani, A. Isacchi, A. L. Borgia, C. Marchionni, M. Nesi, C. Orrenius, A. Panzeri, E. Pesenti, L. Rusconi, M. B. Saccardo, E. Vanotti, E. Perrone and P. Orsini, *J. Med. Chem.* 2019, **62**, 8364.

2 (*a*) J. Lee, H. Choi, K.-H. Kim, S. Jeong, J.-W. Park, C.-S. Baek and S.-H. Lee, *Bioorg. Med. Chem. Lett.* 2008, **18**, 2292. (*b*) D. M. Klug, L. Tschiegg, R. Diaz, D. Rojas-Barros, G. Perez-Moreno, G. Ceballos, R.García-Hernández, M. S. Martinez-Martinez, P. Manzano, L. M. Ruiz, C. R. Caffrey, F. Gamarro, D. G. Pacanowska, L. Ferrins, M. Navarro and M. P. Pollastri, *J. Med. Chem.* 2020, **63**, 2527.

3 (*a*) B. David, G. K. Austin and M. H. Michael, *Org. Lett.* 2000, **2**, 3825. (*b*) J. B. Arterburn, K. V. Rao, R. Ramdas and B. R. Dible, *Org. Lett.* 2001, **3**, 1351. (*c*) L. Jiang, X. Lu, H. Zhang, Y. Jiang and D. Ma, *J. Org. Chem.* 2009, **74**, 4542. (*d*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.* 2010, **49**, 8686. (*e*) N. Halland, M. Nazaré, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.* 2011, **47**, 1042. (*f*) H. Li, P. Li and L. Wang, *Org. Lett.* 2013, **15**, 620. (*g*) H. Li, P. Li, H. Tan and L. Wang, *Chem. -A Eur. J.* 2013, **19**,14432. (*h*) Y. Lian, R. G. Bergman, L. D. Lavis and J. A. Ellman, *J. Am. Chem. Soc.* 2013, **135**, 7122. (*i*) Z. Long, Z. Wang, D. Zhou, D. Wan and J. You, *Org. Lett.* 2017, **19**, 2777. (*j*) Y. Zhou, S. Deng, S. Mai and Q. Song, *Org. Lett.* 2018, **20**, 6161. (*k*) Y. Zhou, Y. Wang, Y. Lou and Q. Song, *Org. Lett.* 2018, **20**, 6494. (*l*) Y. Zhou, Y. Wang, Y. Lou and Q. Song, *Org. Lett.* 2019, **21**, 8869. (*m*) J. Teng, S. Sun, J. Yu and J. Cheng, *J. Org. Chem.* 2019, **84**, 15669.

4 J. R. Medina, C. W. Blackledge, D. A. Heerding, N. Campobasso, P. Ward, J. Briand, L. Wright and J. M. Axten, *ACS Med. Chem. Lett.* 2010, **1**, 439.

5 (*a*) M. Wolter, A. Klapars and S. L. Buchwald, *Org. Lett.* 2001, **3**, 3803. (*b*) S. L. Buchwald, A. Klapars, J. Antilla and X. Huang, *J. Am. Chem. Soc.* 2001, **123**, 7727. (*c*) M. R. Rivero and S. L. Buchwald, *Org. Lett.* 2007, **9**, 973. (*d*) M. Liu, X. Wang, Q. Cai and K. Ding, *Chin. J. Chem.* 2011, **29**, 1199. (*e*) C. J. Ball, J. Gilmore and M. C. Willis, *Angew. Chem., Int. Ed.* 2012, **51**, 5718. (*f*) H. Guo, J. Liu, X. Wang and G. Huang, *Synlett* 2012, **23**, 903. (*g*) X. Xiong, Y. Jiang and D. Ma, *Org. Lett.* 2012, **14**, 2552. (*h*) L. Xu, Y. Peng, Q. Pan, Y. Jiang and D. Ma, *J. Org. Chem.* 2013, **78**, 3400.

6 (*a*) Z. Wang, R. T. Skerlj and G. J. Bridger, *Tetrahedron Lett.* 1999, **40**, 3543. (*b*) N. Suryakiran, P. Prabhakar and Y. Venkateswarlu *Chem. Lett.* 2007, **36**, 1370. (*c*) M. J. Burke and B. M. Trantow, *Tetrahedron Lett.* 2008, **49**, 4579. (*d*) N. Halland, M. Nazare, O. R'kyek, J. Alonso, M. Urmann and A. Lindenschmidt, *Angew. Chem., Int. Ed.* 2009, **48**, 6879. (*e*) M. Atobe, K. Naganuma and A. Morimoto, US 2010/0029733. (*f*) V. Lefebvre, T. Cailly, F. Fabis and S. Rault, *J. Org. Chem.* 2010, **75**, 2730. (*g*) A. Reichelt, J. R. Falsey, R. M. Rzasa, O. R. Thiel, M. M. Achmatowicz, R. D. Larsen and D. Zhang, *Org. Lett.* 2010, **12** 792.

7 (*a*) C. Zhang, G. Zhang, S. Luo, C. Wang and H. Li, *Org. Biomol. Chem*. 2018, **16**, 8467. (*b*) C. Zhang, Z. Li, J. Chen, S. Qi, Y. Fang, S. Zhang, C. Ren, F. Lu, Z. Liang, S. Jiang, X. Jia, S. Yu and G. Zhang, *J. Org. Chem.* 2020, **85**, 7728.

8 See the Supporting Information for details.

9 Y. Dai, K. Hartandi, Z. Ji, A. A. Ahmed, D. H. Albert, J. L. Bauch, J. J. Bouska, P. F. Bousquet, G. A. Cunha, K. B. Glaser, C. M. Harris, D. Hickman, J. Guo, J. Li, P. A. Marcotte, K. C. Marsh, M. D. Moskey, R. L. Martin, A. M. Olson, D. J. Osterling, L. J. Pease, N. B. Soni, K. D. Stewart, V. S. Stoll, P. Tapang, D. R. Reuter, S. K. Davidsen and M. R. Michaelides *J. Med. Chem.* 2007, **50**, 1584.

10 CCDC 2000863 (**5g**).

11 (*a*) A. E. I. Proudfoot, *Nature Rev. Immunol.* 2002, **2**, 106. (*b*) P. A. Procopiou, J. W. Barrett, N. P. Barton, M. Begg, D. Clapham, R. C. B. Copley, A. J. Ford, R. H. Graves, D. A. Hall, A. P. Hancock, A. P. Hill, H. Hobbs, S. T. Hodgson, C. Jumeaux, Y. M. L. Lacroix, A. H. Miah, K. M. L. Morriss, D. Needham, E. B. Sheriff, R. J. Slack, C. E. Smith, S. L. Sollis and H. Staton, *J. Med. Chem.* 2013, **56**, 1946.

12 S. Antonysamy, G. Hirst, F. Park, P. Sprengeler, F. Stappenbeck, R. Steensma, M. Wilson and M. Wang, *Bioorg. Med. Chem. Lett.* 2009, **19**, 279.

13 A. Vasudevan, A. J. Souers, J. C. Freeman, M. K. Verzal, J. Gao, M. M. Mulhern, D. Wodka, J. K. Lynch, K. M. Engstrom, S. H. Wagaw, S. Brodjian, B. Dayton, D. H. Falls, E. Bush, M. Brune, R. D. Shapiro, K. C. Marsh, L. E. Hernandez, C. A. Collins and P. R. Kym, *Bioorg. Med. Chem. Lett.* 2005, 15, 5293.

14 A. W. Kruger, M. J. Rozema, A. Chu-Kung, J. Gandarilla, A. R. Haight, B. J. Kotecki, S. M. Richter, A. M. Schwartz and Z. Wang, *Org. Process. Res. Dev.* 2009, 13, 1419.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]