ChemCatChem

The European Society Journal for Catalysis

Chemistry Europe

European Chemical Societies Publishing

Supported by GECATS GERMAN CATALYSIS SOCIETY

Accepted Article

Title: Late-stage Pd-catalyzed cyanations of aryl/heteroaryl halides in aqueous micellar media

Authors: Bruce Howard Lipshutz, Ruchita Thakore, Balaram Takale, Vani Singhania, and Fabrice Gallou

To be cited as: *ChemCatChem* 10.1002/cctc.202001742

Link to VoR: https://doi.org/10.1002/cctc.202001742

WILEY-VCH

WILEY-VCH

COMMUNICATION

Late-stage Pd-catalyzed cyanations of aryl/heteroaryl halides in aqueous micellar media

Ruchita R. Thakore,[a]† Balaram S. Takale,[a]†* Vani Singhania,[a] Fabrice Gallou,[b] and Bruce H. Lipshutz[a]*

Dedicated to Novartis with warm thanks, for 10 years and running, of a great collaboration!

[a] Dr. R. R. Thakore, Dr. B. S., Takale, V. Singhania, Prof. Dr. B. H. Lipshutz
Department of Chemistry and Biochemistry
University of California, Santa Barbara
California 93106, USA
E-mail: bhlipshutz@ucsb.edu and balaram_takale@ucsb.edu
[b] Dr. F. Gallou,
CHAD, Novartis Pharma
AG, 4056 Basel, Switzerland
†These authors contributed equally.

Supporting information for this article is given via a link at the end of the document.

Abstract: New technology is described that enables late stage ppm Pd-catalyzed cyanations of highly complex molecules, as well as a wide variety of aryl and heteroaryl halides possessing sensitive functional groups. These reactions are efficient in water containing nanomicelles, enabled by a commercially available and inexpensive surfactant. The implications for advancing drug synthesis and discovery are significant.

Among the many hurdles facing modern synthetic organic chemistry, and the pharmaceutical industry, in particular, are sufficient opportunities for generating new composition of matter entities based on late stage functionalization,[1] most notably applied to existing drugs. In recognition of this challenge, recent contributions (Figure 1a) have focused, e.g., on aminations using known catalyst-derived formation of isolable Pd(II) intermediates that subsequently readily participate in otherwise very difficult C-N bond constructions.[1d] Likewise, methylation of aromatic rings found within a variety of complex substrates has also been accomplished via C-H activation, here as well using stoichiometric amounts of metal, in this case a commercially available dicationic Co catalyst.[1a] These high-profile reports, while accomplishing their intended goals, clearly point to the challenges and limitations to be overcome by future efforts in catalysis. Moreover, in all cases, a timely discussion addressing the impact that such chemistry has on the use of elevated loadings of endangered metals, or the environment due to waste creation, is lacking. Hence, raising the bar still higher in this regard adds another level of complexity to goals in catalysis that have yet to be routinely achieved. One C-C bond-forming reaction that could dramatically expand opportunities initially in drug discovery followed by usage in process development via late stage functionalization is cyanation.[2] Aside from the existence of several pharmaceuticals that contain this appendage (Figure 1b),[3] technology for insertion of the CN group under regio-controlled cross coupling conditions on complex educts has yet to appear.[1b]

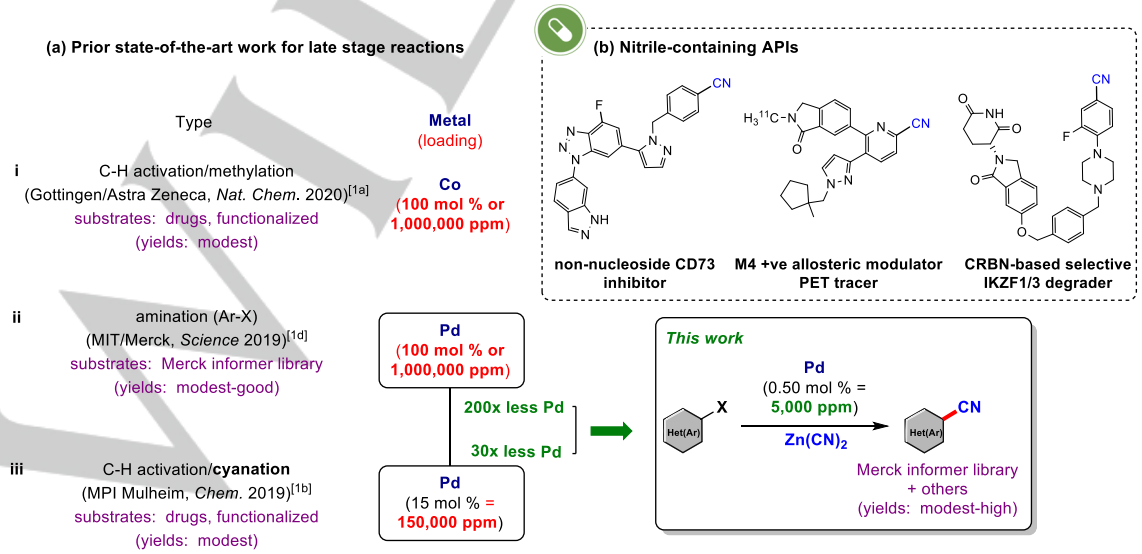


Figure 1. Background. (a) Recent late stage functionalizations vs. current cyanation. (b) Representative pharmaceuticals containing a nitrile group.

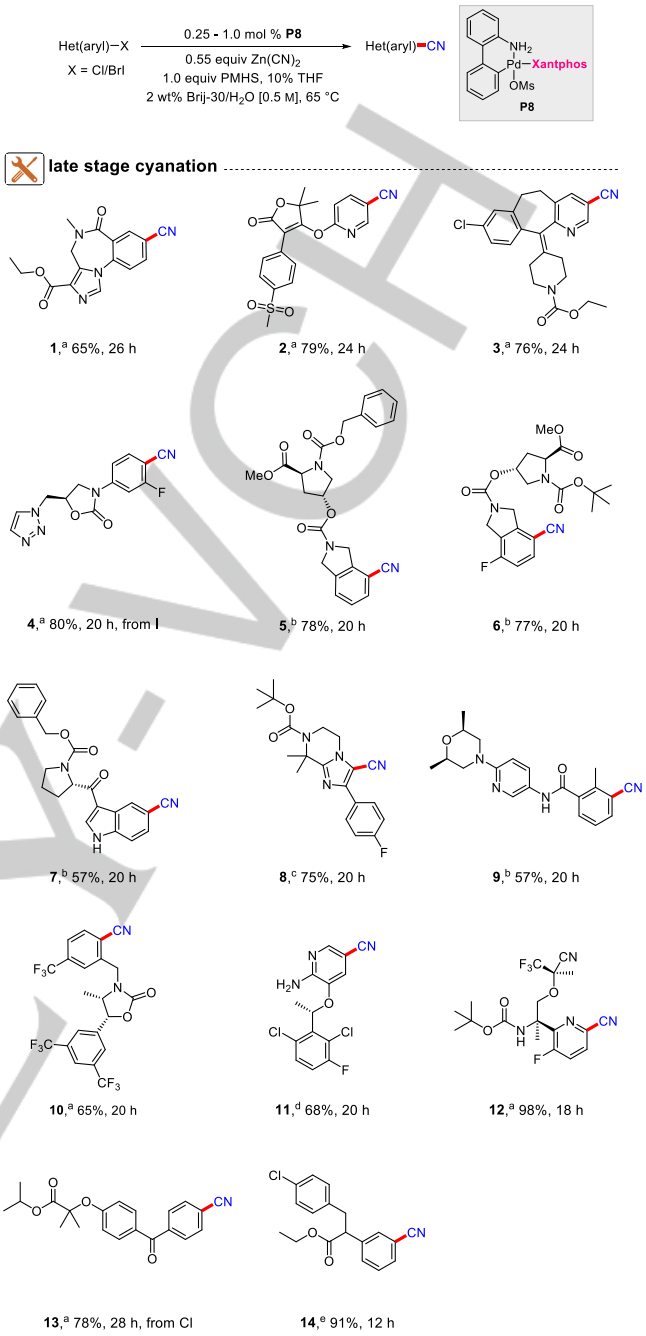
10.1002/cctc.202001742

COMMUNICATION

Existing approaches for introducing a nitrile group onto aromatic and hetero-aromatic rings typically involve relatively simple educts, and oftentimes call for non-scalable and unsustainable levels of catalyst loadings (i.e., in the 2-15 mol % range).[1b,4a] Moreover, and invariably, such methodologies take place in waste-generating organic solvents, and oftentimes rely on an investment of energy in the form of elevated temperatures over time to achieve reasonable conversions. Thus, in the spirit of creating options for medicinal chemistry and beyond,[5] and with attention to the impact that such chemistry will have on the environment,[6] we now describe a new, indeed unique and reproducible[12] technology. This advancement enables late stage cyanations that addresses all of these major concerns, including its: (1) application to highly functionalized substrates; (2) reliance not only on catalysis, but conditions that feature low loadings of Pd; and (3) utilization under very mild conditions in recyclable water (Figure 1a).[5, 8-9]

Cyanations were conducted in aqueous micellar media, in which it was determined that nanoreactors composed of inexpensive surfactant Brij-30 (2 wt %) afforded the best results (Table S3). Readily available $Zn(CN)_2$ (0.55 equiv), and only this source of CN, provided the appropriate amount of cyanide ion. Screening pre-catalysts led to the finding that Xantphos-containing palladacycle **P8** was favored (Table S1), and unlike all other known methods for cyanation, late stage or otherwise, only 0.50-0.70 mol % of pre-catalyst **P8** at 55-65 °C was sufficient in all cases (Schemes 1, 2, 4 and 5). Several representative, highly functionalized substrates from the Merck informer library[10] and drug like molecules were subjected to these standardized conditions leading to products **1-14**, as shown in scheme 1. Thus, treatment of the aryl bromide used in preparation of Pfizer's crizotinib, which reportedly required 10 mol % Pd in hot DMF, efficiently led to the nitrile-containing product **11**.[4d] An especially complex starting material possessing sensitive functional groups likewise underwent smooth cyanation to give the desired product **12** in high chemical yield. Late stage functionalization of the aryl chloride fenofibrate led to adduct **13**. Noteworthy is the finding that base-sensitive functionality remained intact (e.g., see product **2**), as the reaction mixture, albeit aqueous, is not especially basic.[11] Moreover, highly acidic conditions that might give rise to HCN are also easily avoided (page S5). Although isolated yields were variable, in all cases the remaining mass was the starting halide; hence, these reactions are all quite clean.

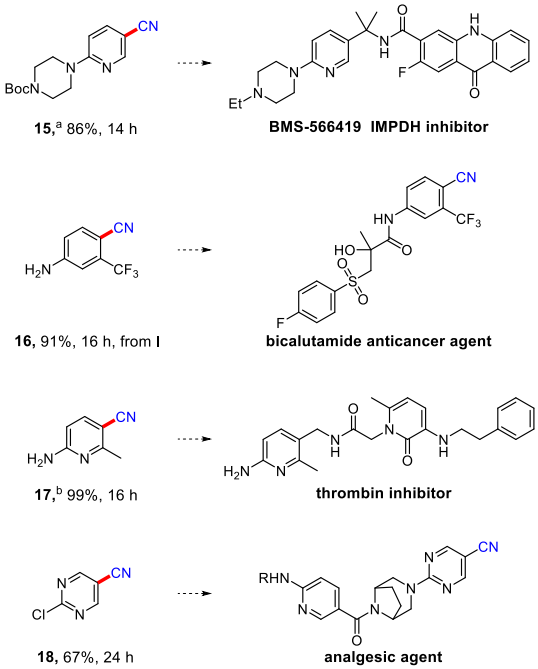
Additional assessment of the prognosis for this cyanation to be especially useful for drug syntheses can be found in the preparation of known intermediates en route to several candidates of current interest (Scheme 2). For example, nitrile-containing adducts, such as the Boc-protected precursor to (a) Bristol-Myers-Squibb's IMPDH inhibitor BMS-566419 **15**, a potential candidate in the treatment of fibroitic renal disease;[12a] (b) the antitumor agent bicalutamide, an essential WHO medicine **16**;[12b] (c) a drug candidate for a thrombin inhibitor **17**,[12c] and (d) a lead molecule of known analgesic activity **18**[12d] were all efficiently prepared using these catalysis conditions.



Scheme 1. Robust late stage cyanation of Merck informer library and drug-like molecules using Pd catalysis (0.25 – 1.0 mol %): Conditions: Reactions were conducted on a 0.1 mmol scale; isolated yields are shown; quantitative yields brsm. [a]Compounds **1-4, 10, 12, 13** were obtained using 0.7 mol % **P8**. [b]Compounds **5-7, 9** were obtained using 1.0 mol % **P8** at 70 °C. [c]Compound **8** was obtained using 1.0 mol % **P8**. [d]Compound **11** was obtained using 0.7 mol % **P8** at 70 °C. [e]Compound **14** was obtained using 0.25 mol % **P8**.

10.1002/cctc.202001742

COMMUNICATION



Scheme 2. Cyanation of drug intermediates. Conditions: Reactions were conducted on 0.25 mmol scale using 0.70 mol % of **P8** using optimized conditions; isolated yields are shown. [a]Compound **15** was obtained at 55 ˚C. [b]Compound **17** was obtained using 0.5 mol % **P8.**

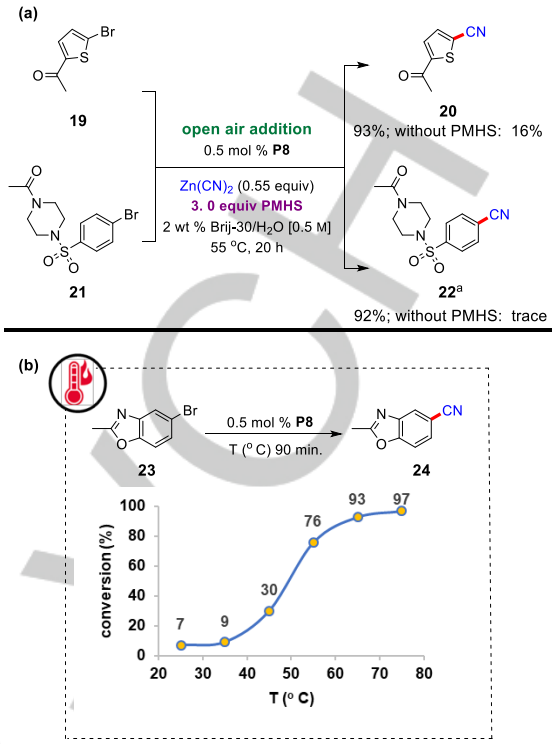
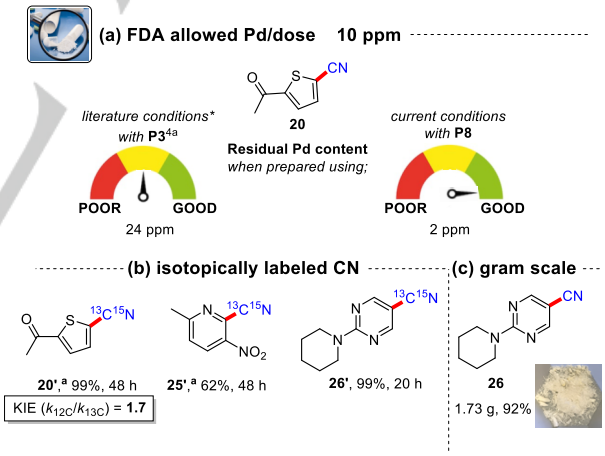


Figure 2. Reaction profile. (a) Impact of PMHS on cyanations conducted in open air. [a]Reaction was conducted with 10 % THF as a co-solvent. (b) Effect of temperature on the rate of reaction of educt **24.**



Scheme 3. Reactions were conducted on a 0.25 mmol scale and 0.5 mol% Pd using optimized conditions. (a) Residual Pd in product **20** vs that found using literature conditions (Figure S2). (b) Introducing a labeled source of CN ($^{13}C^{15}N$) (c) Gram scale cyanation. [a]Without co-solvent.

Importantly, the presence of polymethylhydrosiloxane (PMHS; ≥1.0 equiv) was essential for successful cyanation, as observed previously, presumably helping to reduce Pd(II) to Pd(0) and thus minimizing the impact of excess cyanide and/or oxygen that may be present in the reaction mixture.[13] The dramatic effect of this additive can be seen from comparison studies outlined in Figure 2a. Interestingly, temperature appears to play a major role, which is atypical for reactions run under micellar catalysis conditions where the localized concentrations are usually high and, therefore, oftentimes sufficiently independent of this reaction parameter (ca. 2 M).[14] Nonetheless, as the model cyanation revealed (Figure 2b), over a reaction time of 90 minutes, cyanation of **23** was sluggish until 45 °C, at which point a relatively rapid coupling takes place up to 65 °C, leading to 93% conversion to desired product **24**. Raising the temperature to 75 °C furthered the yield, but to only 97%.

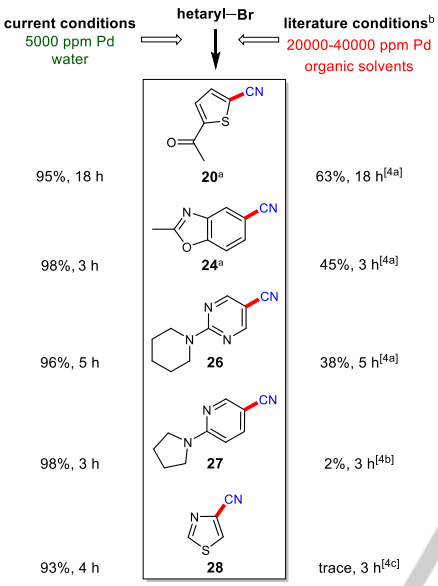
One feature associated with this chemistry in water is the likelihood that the levels of residual palladium[5a-b,9] in each product will be below the imposed FDA limit of 10 mg/dose/day.[15] Using product **20** as a representative example, isolated without special processing, ICP-MS analysis (Scheme 3a; Figure S2 for other representative compounds) indicated that only 2 ppm Pd was present. On the other hand, the amount of residual palladium increased by an order of magnitude under literature cyanation conditions[4a] to arrive at the same target, adding an additional layer of cost required for Pd-scrubbing to remove this impurity.

Opportunities to introduce a labeled source of CN (i.e., $^{13}C^{15}N$) using commercially available material presented no complications.[16] Three representative examples (products **20'**, **25'**, and **26'**), each involving a hetero-aromatic halide precursor, can be found in scheme 3b. A reaction above the gram scale leading to pyrimidine **26** in high yield (92%; Scheme 3c) is suggestive of the facile handling of these aqueous reaction mixtures, as product isolation, following "in-flask" extraction with minimal EtOAc, involved filtration through a short plug of silica.

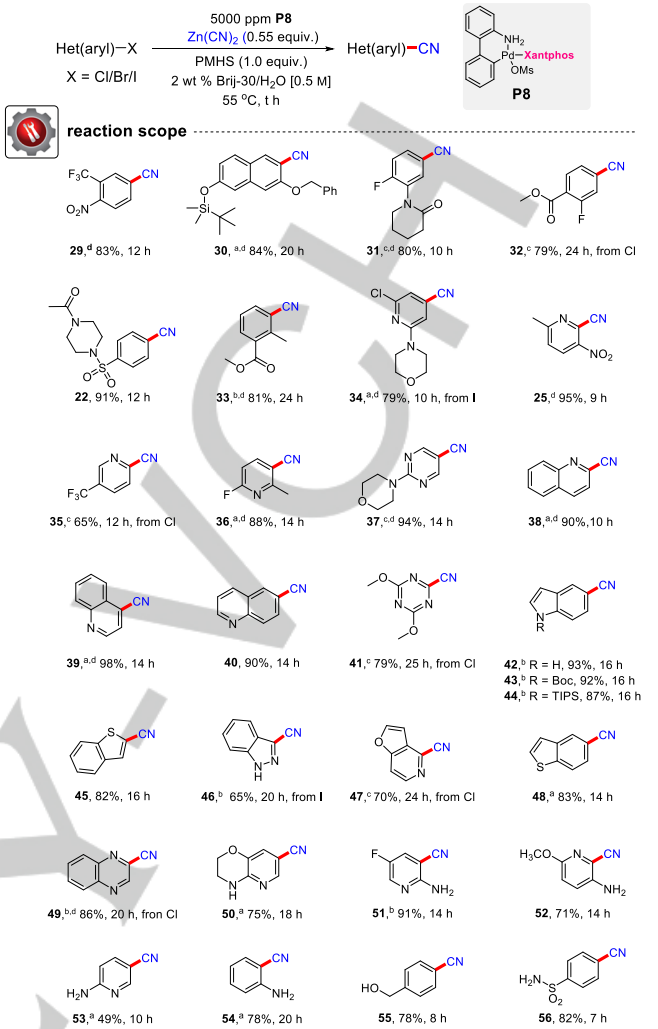
To further highlight the significant differences between existing cyanations[4a-c] and this unique chemistry in recyclable water (Figure S5), several cyano-substituted heteroaromatics (**20**, **24**, and **26-28**) were selected for direct side-by-side comparisons (Scheme 4). As the results indicate, reaction efficiency in every case was improved, notwithstanding use of 2-8 times less palladium, and with 90% removal of any organic solvent from the reaction medium. To fully establish the generality of cyanations in water, several additional (albeit not nearly as functionalized) examples were also studied (Scheme 5). Highly substituted aryl/heteroaryl halides resulted in very good chemical yields of the desired products. Selective cyanation of iodide in the presence of

10.1002/cctc.202001742

chloride could also be performed (entry **34**). Several halopyridines, either electron-rich or -deficient were found to afford good chemical yields of the antipated cyanopyridines (entries **34-36**, **50-53**). Halo-pyrimidines, -quinolines, and -triazines are also quite amenable substrates (entries **28-32**). Comparatively difficult heterocyclic halides such as halo-indole, -thiophene, -indazole, -furopyridine, -quinoxaline, all led in high chemical yields to the corresponding products (entries **37-41**). Protecting groups, including triisopropylsilyl (TIPS; entries **30** and **44**), benzyl (entry **19**), acetyl (entry **22**), and butyloxycarbonyl (Boc, entry **43**) were all well-tolerated by these mild reaction conditions. Cyanation could be effected on not only aryl bromides or aryl iodides (entries **34** and **46**) but also aryl chlorides (entries **32**, **35, 41, 47, 49**) at the ppm level of Pd.



Scheme 4. Comparison of cyanation reactions. Conditions: Reactions were conducted on a 0.25 mmol scale using optimized conditions; isolated yields are shown. [a]Without co-solvent. [b]Literature conditions; see Figure S3.



Scheme 5. Additional scope of aryl halide partners. [a]Reaction performed using 0.5 mol % **P8** at 65 °C. [b]0.7 mol % **P8**. [c]0.7 mol % P8 at 65 °C. [d]Without co-solvent.

In summary, utilization of micellar catalysis as an enabling technology allows for cyanations of especially complex, highly functionalized substrates to be realized under mild, aqueous conditions. Unprecedented levels of a palladacycle suffice as catalyst precursor, while the crucial role of PMHS in these couplings has been uncovered. Overall, cyanations in water are faster and higher yielding relative to existing alternatives that rely on organic solvents as media, even with far less demanding substrates. Prospects for applications to targets in medicinal chemistry, as well to pharmaceuticals made at scale that benefit from this environmentally responsible chemistry, look very encouraging.

Acknowledgements

Financial support provided by PHT International (postdoctoral fellowship to B.S.T.), the NSF (CHE 18-56406), and Novartis is warmly acknowledged with thanks. We sincerely thank S. Dreher and G. Humphrey (Merck) for donation of the aryl halides from their Merck informer library.

Keywords: late stage cyanation • micellar catalysis • Pd catalyzed cross coupling • aryl halides • aryl nitriles

[1] a) S. D. Friis, M. J. Johansson, L. Ackermann, *Nat. Chem.* **2020**, *12*, 511-519; b) D. Zhao, P. Xu, T. Ritter, *Chem.* **2019**, *5*, 97-107; c) C. Munteanu, T. E. Spiller, J. Qiu, A. J. DelMonte, S. R. Wisniewski, E. M. Simmons, D. R. Frantz, *J. Org. Chem.* **2020**, *85*, 10334-10349; d) M. R. Uehling, R. P. King, S. W. Krska, T. Cernak, S. L. Buchwald, *Science* **2019**, *363*, 405-408.

[2] a) J. Magano, J. R. Dunetz, in *New trends in cross-coupling: Theory and applications*, *Vol. 21*, (Eds.: T. J. Colacot), RSC Catalysis series, **2015**, pp. 697-778; b) P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 5049–5067

[3] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902–7917.

[4] a) D. T. Cohen, S. L. Buchwald, *Org. Lett.* **2015**, *17*, 202–205; b) D. Zhang, H. Sun, L. Zhang, Y. Zhou, C. Li, H. Jiang, K. Chen, H. Liu, *Chem. Commun.* **2012**, *48*, 2909–2911; c) T. D. Senecal, W. Shu, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2013**, *52*, 10035–10039; d) J. J. Cui, M. T. Dube, H. Shen, M. Nambu, P. P. Kung, M. Pairish, L. Jia, J. Meng, L. Funk, I. Botrous, M. McTigue, N. Grodsky, K. Ryan, E. Padrique, G. Alton, S. Timofeevski, S. Yamazaki, Q. Li, H. Zou, J. Christensen, B. Mroczkowski, S. Bender, R. S. Kania, M. P. Edwards, *J. Med. Chem.* **2011**, *54*, 6342−6363.

[5] a) N. Akporji, R. R. Thakore, M. Cortes-Clerget, J. Anderson, E. Landstrom, D. H. Aue, F. Gallou, B. H. Lipshutz, *Chem. Sci.*, **2020**,*11*, 5205-5212; b) Y. Zhang, B. S. Takale, F. Gallou, J. Reilly, B. H Lipshutz, *Chem. Sci.*, **2019**,*10*, 10556-10561; c) Takale, B. S., Thakore, R. R., Kong, F. Y., Lipshutz, B. H. Green Chem., **2019**, *21*, 6258-6262; d) B. S. Takale, R. R. Thakore, R. Mallarapu, F. Gallou, B. H. Lipshutz, *Org. Process Res. Dev*. **2020**, *24*, 101–105.

[6] B. H. Lipshutz, Catalyst: imagine doing chemistry at no cost… to the environment! *Chem*. **2018**, *4*, 2004-2007.

[7] For issues associated with reproducibility in cyanations of aromatic rings, see A. V. Ushkov, V. V. Grushin, *J. Am. Chem. Soc*. **2011**, *133*, 10999–11005.

[8] a) S. Handa, Y. Wang, F. Gallou, B. H. Lipshutz, *Science* **2015**, *349*, 1087-1091; b) S. Sharma, N. W. Buchbinder, W. M. Braje, S. Handa, *Org. Lett.* **2020**, *22*, 5737–5740; c) M. Bihani, T. N. Ansari, L. Finck, P. P. Bora, J. B. Jasinski, B. Pavuluri, D. K. Leahy, S. Handa, *ACS Catal.* **2020**, *10*, 6816–6821.

[9] a) B. S. Takale, R. R. Thakore, S. Handa, F. Gallou, J. Reilly, B. H. Lipshutz, *Chem Sci*. **2019**, *10*, 8825-8831; b) R. R. Thakore, B. S. Takale, F. Gallou, J. Reilly, B. H. Lipshutz, *ACS Catal*. **2019**, *9*, 11647-11657; c) B. S. Takale, R. R. Thakore, N. M. Irvine, A. D. Schuitman, X. Li, B. H. Lipshutz, *Org. Lett.* **2020**, *22*, 4823-4827; d) a) R. R. Thakore, B. S. Takale, G. Casotti, E. S. Gao, H. S. Jin, B. H. Lipshutz, *Org. Lett.* **2020**, *22*, 6324-6329; e) B. S. Takale, R. R. Thakore, E. S. Gao, F. Gallou, B. H. Lipshutz, *Green Chem.* **2020**, 22, 6055-6061.

[10] P. S. Kutchukian, J. F. Dropinski, K. D. Dykstra, B. Li, D. A. DiRocco, E. C. Strekfuss, L. C. Campeau, T. Cernak, P. Cachal, I. W. Davies, S. W. Krska, S. D. Dreher, *Chem. Sci.* **2016**, *7*, 2604-2613.

[11] The pH of a typical reaction mixture at t = 0 h is ca. 8, while after cyanation the pH was ca. 5.0 (likely due to formation of by-product $ZnBr_2$).

[12] a) S. H. Watterson, P. Chen, Y. Zhao, H. H. Gu, T. G. Murli Dhar, Z. Xiao, S. K. Ballentine, Z. Shen, C. A. Fleener, C. A. Rouleau, M. Obermeier, Z. Yang, K. W. McIntyre, D. J. Shuster, M. Witmer, D. Dambach, S. Chao, A. Mathur, B. C. Chen, J. C. Barrish, J. A. Robl, R. Townsend, E. J. Iwanowicz, *J. Med. Chem.* **2007**, *50*, 3730 – 3742; b) H. Tucker, J. W. Crook, G. J. Chesterson, *J. Med. Chem.* **1998**, *31*, 954–959; c) P. E. J. Sanderson, T. A. Lyle, K. J. Cutrona, D. L. Dyer, B. D. Dorsey, C. M. McDonough, A. M. Naylor-Olsen, I. W. Chen, Z. Chen, J. J. Cook, C. M. Cooper, S. J. Gardell, T. R. Hare, J. A. Krueger, S. D. Lewis, J. H. Lin, B. J. Lucas, E. A. Lyle, J. J. Lynch, M. T. Stranieri, K. Vastag, Y. Yan, J. A. Shafer, J. P. Vacca, *J. Med. Chem.* **1998**, *41*, 4466–4474; d) N. Tsuno, A. Yukimasa, O. Yoshida, S. Suzuki, H. Nakai, T. Ogawa, M. Fujiu, K. Takaya, A. Nozu, H. Yamaguchi, H. Matsuda, S. Funaki, N. Yamanada, M. Tanimura, D. Nagamatsu, T. Asaki, N. Horita, M. Yamamoto, M. Hinata, M. Soga, M. Imai, Y. Morioka, T. Kanemasa, G. Sakaguchi, Y. Iso, *Bioorg. Med. Chem.* **2017**, *25*, 2177−2190.

[13] a) F. M. Miloserdov, C. L. McMullin, M. Martínez Belmonte, J. Benet-Buchholz, V. I. Bakhmutov, S. A. Macgregor, V. V. Grushin, *Organometallics* **2014**, *33*, 736–752; b) S. Erhardt, V. V. Grushin, A. H. Kilpatrick, S. A. Macgregor, W. J. Marshall, D. C. Roe, *J. Am. Chem. Soc.* **2008**, *130*, 4828−4845.

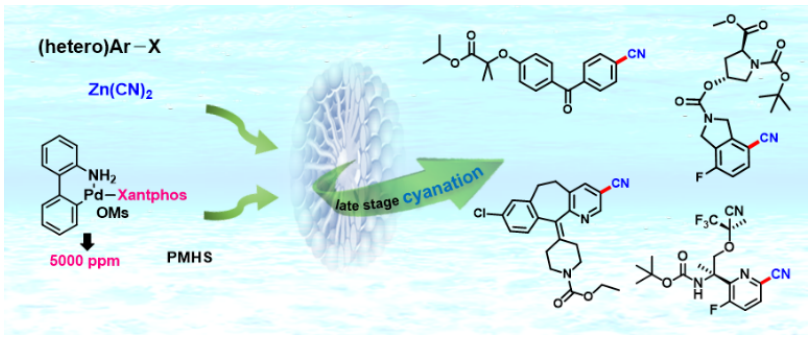
[14] M. P. Andersson, F. Gallou, P. Klumphu, B. S. Takale, B. H. Lipshutz, *Chem. Eur. J.* **2018**, *24*, 6778-6786.

[15] S. Phillips, D. Holdsworth, P. Kauppinen, M. C. Namara, *Johnson Matthey Technol. Rev*. **2016**, *60*, 277−286.

[16] R. C. Schellekens, F. Stellaard, H. J. Woerdenbag, H. W. Frijlink, J. G. Kosterink, *Br. J. Clin. Pharmacol.* **2011**, *72*, 879−897.

10.1002/cctc.202001742

Entry for the Table of Contents



Late stage cyanation made environmentally responsibly! Safely introducing a nitrile group into complex molecules under mild conditions in recyclable water offers new opportunities for discovering, and synthesizing, pharmaceuticals.

Institute and/or researcher Twitter usernames: @RuchitaThakore, @balaict, @Lipshutz_group