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A practical method for continuous production of sp3-rich compounds from (hetero)aryl halides and redox-active esters

Eiichi Watanabe[a]‡, Yiding Chen[b]‡, Oliver May[b] and Steven V. Ley*[b]

Abstract: A practically useful coupling reaction between aromatic halides and redox-active esters was realized via nickel catalysis through the use of packed zinc bed column in continuous flow. Multiple reuse of the column showed a negligible decrease in efficiency, affording high space/time yields. A wide range of substrates, including a number of heteroaryl halides and polyfunctional materials were coupled in generally good yields. Longer-time and larger-scale experiments further demonstrates the robustness of the system.

Developing molecular complexity is an important aspect of modern drug discovery programs and has been associated with success in progressing compounds into clinical development[1] by improving target selectivity[2] and safety.[3] Increasing the number of sp3 centers similarly enhances the three-dimensional complexity, again improving success rates.[4] As a consequence, practical and simple methods to construct C(sp3)-C(sp2) bonds are of fundamental importance.[5] A seminal contribution to this field was reported by MacMillan and Doyle who utilized an Ir-photoredox/Ni dual catalyst system to achieve decarboxylative C(sp3)-C(sp2) cross coupling (Figure 1).[6] In this reaction, the synergistic combination of photoredox catalysis and nickel catalysis forges 3D-rich structures from simple and readily available organic molecules. More importantly, carboxylic acid starting materials have a higher accessibility compared to other conventional cross-coupling partners.[7] Following this pioneering report, synthetic methods that enable medicinal chemists to generate C(sp3)-enriched compounds by these decarboxylative pathways have been widely explored.[8] Among these alternative approaches, Weix *et. al* reported the use of zinc powder as a reducing reagent,[9] therefore avoiding expensive iridium catalysts,[6] or the need for preformed pyrophoric organozinc reagents[10] and photo-/electrochemical reactors.[8c, 8d, 11] More recently, Fier *et. al* also described a metallic zinc mediated cross-coupling reaction between aryl bromides and redox-active alkyl sulfones.[12] Despite the relevance and the effectiveness of these discoveries, activated zinc powder can be challenging to work with on large scales mainly due to issues of surface variation and safety.[13] Given our expertise in continuous processing

methods,[14] and with the availability of newly developed flow columns packed with metallic zinc,[15] we decided to further explore their deployment in cross-coupling sequences. We believe using zinc bed columns to be superior to typical batch procedures for several reasons, especially avoiding excessive use of zinc powder, problems during downstream processing and the difficulty of controlling exothermic reactions. Here, we report a simple, practical improvement to general nickel-catalyzed decarboxylative cross-coupling processes by utilizing a zinc bed column in a continuous flow system. This robust procedure enables access to a wide variety of 3D rich molecules starting from versatile (hetero)aryl halides, and redox-active esters which are themselves easily prepared from corresponding carboxylic acids in flow.
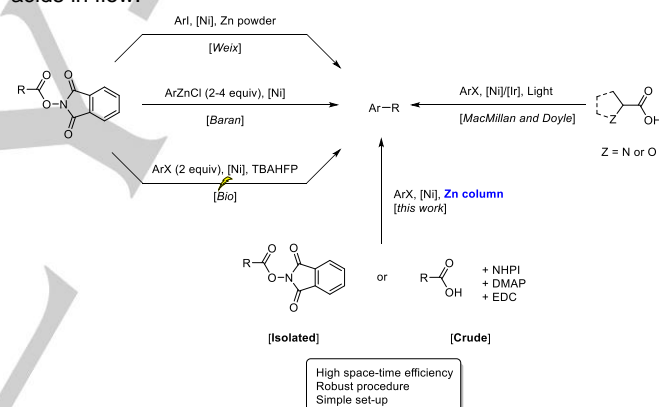
Figure 1. C(sp3)-C(sp2) coupling of redox-active ester and carboxylic acid

Pre-activation of the zinc packed Omnifit® cartridge followed a protocol developed by Alcázar *et. al*,[15] whereby a solution of TMSCl and 1-bromo-2-chloroethane in THF was flushed through the system (See Supporting Information for detailed procedure). Our initial study utilized similar conditions to the batch procedure reported by Weix *et. al* for comparison,[9a] where a mixture of 1-chloro-4-iodobenzene **1a**, redox-active ester **2a** together using NiCl2 glyme complex and di-tert-butyl-2,2-bipyridine ligand in DMAc were passed through a packed zinc (30 mesh) column with a residence time of 40 min led to a modest 49% yield of the coupled product **3a** (Table 1, entry1). Subsequent ligand screening highlighted **L1** as being superior, giving an improved the yield of 98% (entry 2). Encouraged by this success, attempts were made to shorten the residence time of the reaction in order to achieve a faster overall cross-coupling process. Following on an extensive study of residence time and examining various grades and combinations of zinc powder (see Supporting Information, Table SI1, Figure SI1), using a mixture of 30 and 325

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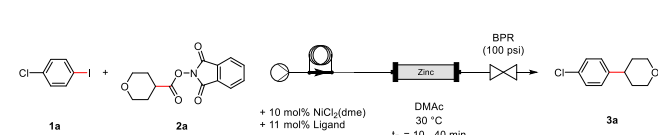‡   Aurthors contributed equally

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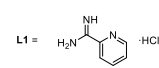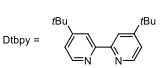
mesh of zinc powder successfully reduced the residence time (Table 1, entry 3 – 6) to only 10 min. Furthermore, more than 10 times reuse of the zinc column showed no lost in efficiency (entry 7). Control experiments demonstrated that both the nickel catalyst and the ligand were necessary for reaction to occur (entry 8, 9). It is also worth noting that the preparation of reaction mixture does not require the use of a glove box or specially dried solvents. The shorter reaction time in flow (10 min) to a comparable batch (12 h) procedure is noteworthy.

Table 1. Reaction Optimisation

entry	ligand	mesh	t_R (min)	LC yield (%)	
				1a	3a
1	Dtbpy	30	40	32	49
2	L1	30	40	0	98
3	L1	30	30	0	100
4	L1	20	20	14	81
5	L1	30/325 (11:2)	20	4	95
6[a]	L1	30/325 (11:2)	10	0	100
7[b]	L1	30/325 (11:2)	10	0	100
8	none	30/325 (11:2)	10	30	0
9[c]	none	30/325 (11:2)	10	28	0

a) After 3 times use. b) 10 times use. c) Without nickel catalyst

Under optimized conditions, we then assessed the scope of the reaction with various aryl iodides (Figure 2). Apart from 1-chloro-4-iodobenzene **1a**, 1-bromo-4-iodobenzene **1b** also acting as suitable reaction partner to afford the corresponding coupled product of **3b** nicely illustrating the chemoselectivity of the process. It is also worth noting that **3b** and the boronic pinacol ester product **3c**, both serve as precursors for future diversification through conventional cross-coupling reactions. Iodonaphthalene **1d** and iodophenanthrene **1e** also delivered the corresponding products in an excellent 90% and 91% yield respectively (**3d** and **3e**). Electron-donating groups such as 4-iodoanisole **1f** and 4-iodothioanisole **1g**, which often failed as coupling partners for similar nickel catalyzed reductive cross-coupling reactions, here were able to obtain the desired product

3f and **3g** in good yields.[8c, 8d],[16] Trifluoromethoxy **3h** and trifluoromethyl product **3i** exemplified the tolerance for electron-withdrawing groups. With respect to functional-group compatibility, aryl iodides containing nitrile **1j**, ketone **1k**, ester **1l**, amide **1p** and phenol **1q** functionality, some of which can sometimes be problematic in Kumada and Negishi type coupling, were all well-tolerated under our cross-coupling conditions.[8b] Variations in the position of substituents on the phenyl ring led to *meta*-substituted compound **3m** with 93% yield, while *ortho*-coordinating groups, such as ester (**3n**) and phenyl (**3o**) led to slightly diminished yield of 85% and 89% respectively.[16] To further illustrate the

a) Crude redox-active ester was used
b) 0.6 mmol of 1-bromo-4-iodobenzene and 0.4 mmol of ester were used.
c) 20 mol% of NiCl₂(dme) and 22 mol% ligand were used under 15 min t_R
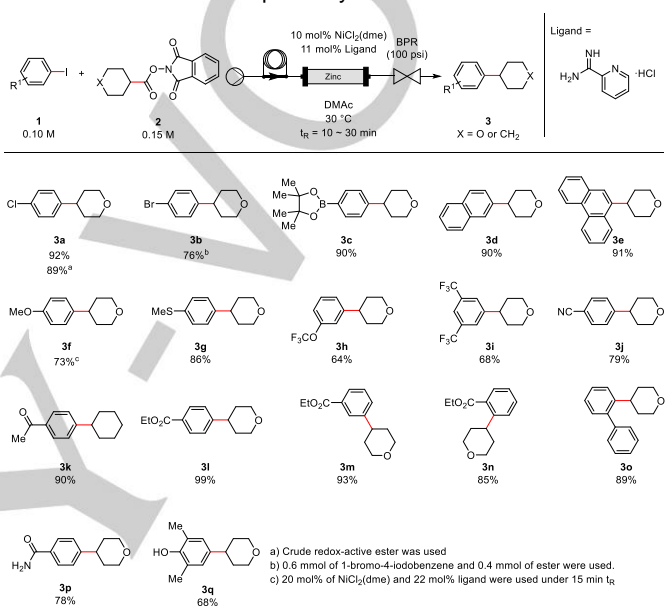
robustness of the protocol, we found that crude redox-active esters, e.g. **3a**, prepared from corresponding carboxylic acids afforded comparable yields to using the pure isolated active esters.

Figure 2. Scope on aryl iodides

Crucial to the success of this method is that heteroaryl halides as coupling substrates, including several reactive substrates, were well tolerated. The resulting coupled products were obtained in good to excellent yields (Figure 3).[17] 4-Iodopyridine derivatives (**1r-t**) all gave the corresponding products in useful yields. Among these a gram scale synthesis of 4-(4-piperidinyl)-pyridine analogue **3t** was achieved, whose structure is frequently found in many functional materials but conventionally requires a 4-step synthetic sequence from commercially available starting materials.[18] The crude product was treated with basic a workup followed by a A-15 resin extraction. The desired product was acquired in 61% yield with high purity without the need for silica gel chromatography. Coupling between 3-iodopyridyl substrates (**1u-x**) and various redox-active esters were all successful (**3u-x**), especially using activated 2-bromo-5-iodopyridine (**1v**). Although in this example a trace of 2-substituted byproduct was detected under the reaction conditions. Lowered yields were noticed when coupling with 2-iodopyridyl substrates (**1y-1aa**), where dehalogenated pyridines were byproducts. Nonetheless a good

chemoselectivity between bromo- and iodo-substitutions was clearly demonstrated (**3aa**). 5-Substituted quinolines (**3ab** and **3ac**) and 4-substituted pyrimidines (**3ad** and **3ae**) were obtained in good to excellent yields. Particularly worth noting is with aryl bromide **1ae** and **1af**, the coupling here could be readily achieved with bromide substrates using a higher loading of catalyst and an elongated residence time to give the desired product **3ae** and **3af** in 80% and 57% yield respectively, while **3af** could not be obtained from the corresponding iodide. Several other heteroaromatic coupling partners, for example carbazole **1ag**, 5-iodoindole **1ah** as well as the more reactive 3-iodoindoles **3ai** and **3aj** all produced useful results.
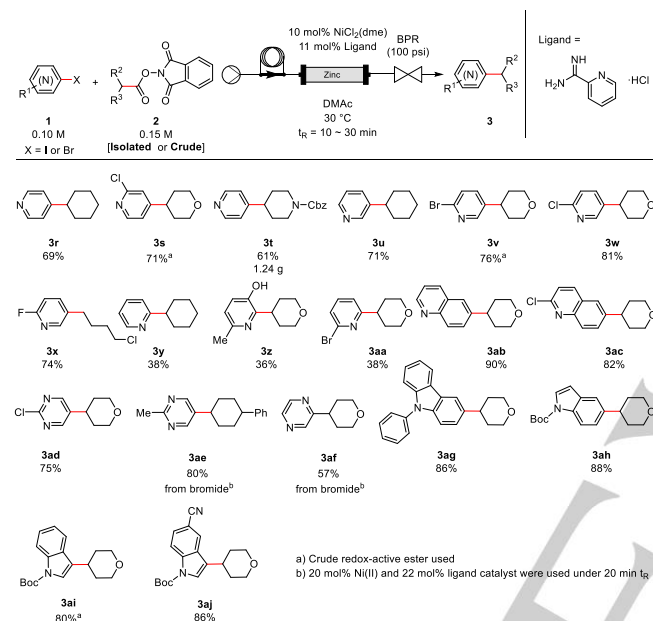
natural products are compatible with the reaction conditions affording the anticipated cross-coupled product in good yields (**3az-bd**). Interestingly, the reaction of redox-active ester **2bd** obtained from gabapentin, provided an unusual product which was thought to be generated via a 1,5-hydrogen atom transfer (1,5-HAT) prior to nickel mediated cross-coupling (Figure 4a). As noted by others,[8d, 9a] the limitation of this procedure was the lack of reactivity towards tertiary redox-active esters.[20] Adamantane carboxylic acid and *tert*-butyl carboxylic acid phthalimide ester both failed to deliver desired product under our standard conditions.
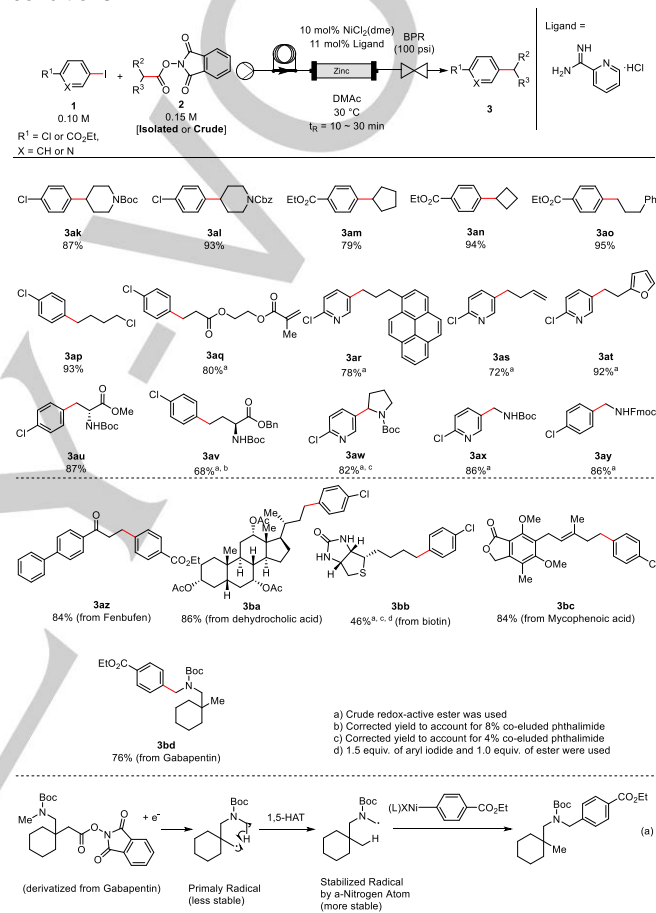

Figure 3. Scope on heteroaryl halides

Figure 4. Scope on redox-active esters

To further exemplify the potential of the reaction, we expanded the scope with respect to redox-active ester coupling partners using a few different (hetero)aryl iodides (Figure 4). In addition to tetrahydropyranyl **2a** substrate, other saturated heterocyclic examples were also viable coupling partners, including *N*-boc piperidine **1ak** and *N*-cbz piperidine **1al**, providing excellent yields for the desired C(sp3)-C(sp2) cross-coupling products (**3ak** and **3al**). Comparable reaction efficiency was also observed with carbocyclic examples **3am** and **3an**. Primary substituted redox-active esters underwent successful coupling in high yield despite the inherent reluctance to generate primary alkyl radicals via single-electron-transfer process SET.[19] A series of related compounds were generated, including long-chain alkyl chloride **3ap**, mono-(methacryloylxy)ethyl succinate derivative **3aq**, pyrene containing **3ar**, simple alkene **3as**, furan **3at**, and amino acids **3au** and **3av**. α-Amino phthalimide esters **1aw-ay** that generate reactive α-amino C(sp2) species, coupled without incident, resulting in high yields of **3aw-ay**. Of particular note also was that some active pharmaceutical ingredients (APIs) and

To best demonstrate the advantage of this method was its ability to transfer to a larger-scale experiment. Equipped with a longer column (i.d.=10.0 mm, length = 120 mm), the reaction set-up was kept operating for 31 hours to deliver a 11.77 g target product. After the reaction, the remaining zinc was still functional without noticeable decline of efficacy. It was also noticed that a small amount of bicyclohexyl byproduct was produced, presumably from the radical dimerization of redox-active ester.
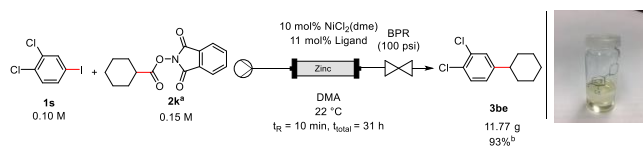
a) Crude redox-active ester was used
b) Corrected yield to account for 5% co-eluded bicyclohexyl

Scheme 1. 10 g-scale synthesis

In summary, we have identified a procedurally simple use of a zinc packed column as an alternative reductant to photo- or electrochemical reactor or organometallic reagents for forging C(sp3)-C(sp2) bonds starting from aryl halides and redox-active esters. The method is practical and robust, and provides enhanced substrate compatibility over previously reported examples. Furthermore, the use of crude redox-active esters accelerated the synthesis of highly 3D-rich structures from carboxylic acids and (hetero)aryl halides. Notably, the work features the ease of scale up by harnessing continuous flow conditions.

Acknowledgements

References:

[1]   a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756; b) Y. A. Ivanenkov, B. A. Zagribelnyy, V. A. Aladinskiy, *J. Med. Chem.* **2019**.

[2]   a) F. Lovering, *MedChemComm* **2013**, *4*, 515-519; b) P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler, S. L. Schreiber, *P. Natl. Acad.* **2010**, *107*, 18787-18792.

[3]   M. González-Medina, F. D. Prieto-Martínez, J. J. Naveja, O. Méndez-Lucio, T. El-Elimat, C. J. Pearce, N. H. Oberlies, M. Figueroa, J. L. Medina-Franco, *Future Med Chem* **2016**, *8*, 1399-1412.

[4]   a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383-394; b) P. Morgan, D. G. Brown, S. Lennard, M. J. Anderton, J. C. Barrett, U. Eriksson, M. Fidock, B. Hamrén, A. Johnson, R. E. March, J. Matcham, J. Mettetal, D. J. Nicholls, S. Platz, S. Rees, M. A. Snowden, M. N. Pangalos, *Nat. Rev. Drug Discov.* **2018**, *17*, 167; c) N. A. Meanwell, *Chem. Res. Toxicol.* **2016**, *29*, 564-616.

[5]   For related review, see: a) L.-C. Campeau, N. Hazari, *Organometallics* **2019**, *38*, 3-35; b) D. J. Weix, *Accounts Chem. Res.* **2015**, *48*, 1767-1775; c) J. Gu, X. Wang, W. Xue, H. Gong, *Org. Chem. Front.* **2015**, *2*, 1411-1421; d) E. Richmond, J. Moran, *Synthesis* **2018**, *50*, 499-513.

[6]   Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437-440.

[7]   For reactions with other coupling partners, see: a) H. Yue, C. Zhu, L. Shen, Q. Geng, K. J. Hock, T. Yuan, L. Cavallo, M. Rueping, *Chem. Sci.* **2019**, *10*, 4430-4435; b) Y. Ye, H. Chen, J. L. Sessler, H. Gong, *J. Am. Chem. Soc.* **2019**, *141*, 820-824; c) Y. Ma, J. Cammarata, J. Cornella, *J. Am. Chem. Soc.* **2019**, *141*, 1918-1922; d) C. Heinz, J. P. Lutz, E. M. Simmons, M. M. Miller, W. R. Ewing, A. G. Doyle, *J. Am. Chem. Soc.* **2018**, *140*, 2292-2300; e) B. P. Woods, M. Orlandi, C.-Y. Huang, M. S. Sigman, A. G. Doyle, *J. Am. Chem. Soc.* **2017**, *139*, 5688-5691; f) Y. Zhao, D. J. Weix, *J. Am. Chem. Soc.* **2015**, *137*, 3237-3240; g) L. K. G. Ackerman, L. L. Anka-Lufford, M. Naodovic, D. J. Weix, *Chem. Sci.* **2015**, *6*, 1115-1119; h) Y. Zhao, D. J. Weix, *J. Am. Chem. Soc.* **2014**, *136*, 48-51; i) D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920-921.

[8]   a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174-2177; b) F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3319-3323; c) H. Li, C. P. Breen, H. Seo, T. F. Jamison, Y.-Q. Fang, M. M. Bio, *Org. Lett.* **2018**, *20*, 1338-1341; d) T. Koyanagi, A. Herath, A. Chong, M. Ratnikov, A. Valiere, J. Chang, V. Molteni, J. Loren, *Org. Lett.* **2019**, *21*, 816-820; e) S. Ni, N. M. Padial, C. Kingston, J. C. Vantourout, D. C. Schmitt, J. T. Edwards, M. M. Kruszyk, R. R. Merchant, P. K. Mykhailiuk, B. B. Sanchez, S. Yang, M. A. Perry, G. M. Gallego, J. J. Mousseau, M. R. Collins, R. J. Cherney, P. S. Lebed, J. S. Chen, T. Qin, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6726-6739.

[9]   a) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016-5019; b) J. Wang, B. P. Cary, P. D. Beyer, S. H. Gellman, D. J. Weix, *Angew. Chem. Int. Ed.*, *0*.

[10]   a) S. Plunkett, C. H. Basch, S. O. Santana, M. P. Watson, *J. Am. Chem. Soc.* **2019**, *141*, 2257-2262; b) A. Herath, V. Molteni, S. Pan, J. Loren, *Org. Lett.* **2018**, *20*, 7429-7432; c) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801-805; d) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213; e) X. G. Liu, C. J. Zhou, E. Lin, X. L. Han, S. S. Zhang, Q. Li, H. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 13096-13100.

[11]   a) R. J. Perkins, A. J. Hughes, D. J. Weix, E. C. Hansen, *Org. Process Res. Dev.* **2019**; b) G.-L. Dai, S.-Z. Lai, S. Luo, Z.-Y. Tang, *Org. Lett.* **2019**, *21*, 2269-2272; c) D. Hu, L. Wang, P. Li, *Org. Lett.* **2017**, *19*, 2770-2773; d) C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature* **2016**, *536*, 322; e) K. Xu, Z. Tan, H. Zhang, J. Liu, S. Zhang, Z. Wang, *Chem. Commun.* **2017**, *53*, 10719-10722.

[12]   J. M. E. Hughes, P. S. Fier, *Org. Lett.* **2019**, *21*, 5650-5654.

[13]   A. Krietsch, M. Scheid, M. Schmidt, U. Krause, *J. Loss. Prevent. Proc.* **2015**, *36*, 237-243.

[14]   a) D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120-1125; b) J.-S. Poh, D. N. Tran, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Angew. Chem.* **2015**, *127*, 8031-8034; c) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem.* **2015**, *127*, 146-150; d) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed.* **2015**, *54*, 10122-10136.

[15]   a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737-3741; b) M. Berton, L. Huck, J. Alcázar, *Nat. Protoc.* **2018**, *13*, 324.

[16]   X. Wang, G. Ma, Y. Peng, C. E. Pitsch, B. J. Moll, T. D. Ly, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2018**, *140*, 14490-14497.

[17]   a) I. B. Perry, T. F. Brewer, P. J. Sarver, D. M. Schultz, D. A. DiRocco, D. W. C. MacMillan, *Nature* **2018**, *560*, 70-75; b) J. Liao, C. H. Basch, M. E. Hoerrner, M. R. Talley, B. P. Boscoe, J. W. Tucker, M. R. Garnsey, M. P. Watson, *Org. Lett.* **2019**, *21*, 2941-2946.
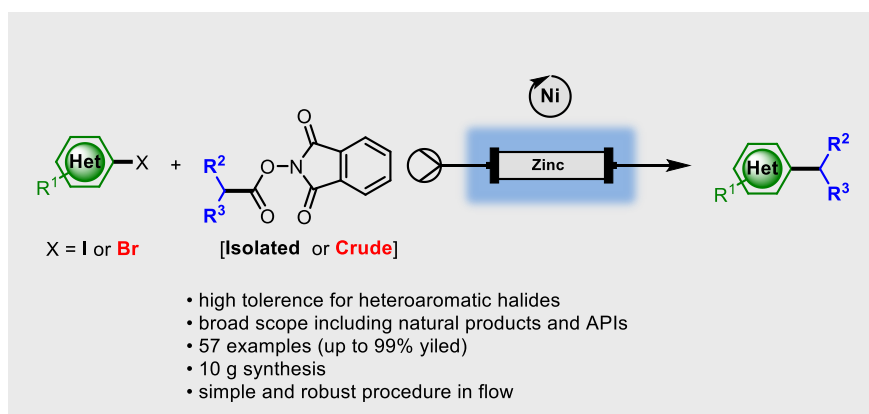
[18]   C. M. Kormos, M. G. Gichinga, S. P. Runyon, J. B. Thomas, S. W. Mascarella, A. M. Decker, H. A. Navarro, F. I. Carroll, *Bioorgan. Med. Chem.* **2016**, *24*, 3842-3848.

[19]   R. Martin-Montero, V. R. Yatham, H. Yin, J. Davies, R. Martin, *Org. Lett.* **2019**, *21*, 2947-2951.

[20]   T. G. Chen, H. Zhang, P. K. Mykhailiuk, R. R. Merchant, C. A. Smith, T. Qin, P. S. Baran, *Angew. Chem. Int. Ed.* **2019**, *58*, 2454-2458.

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

Layout 2:

COMMUNICATION

X = I or Br   [Isolated or Crude]

• high tolerence for heteroaromatic halides
• broad scope including natural products and APIs
• 57 examples (up to 99% yiled)
• 10 g synthesis
• simple and robust procedure in flow

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Page No. – Page No.

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