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A Practical Lewis Base Catalyzed Electrophilic Chlorination of Arenes and Heterocycles

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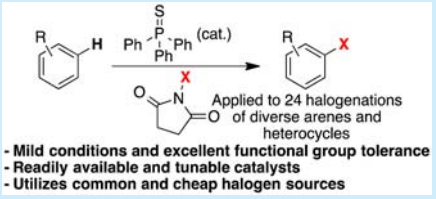
Supporting Information

ABSTRACT: A mild phosphine sulfide catalyzed electrophilic halogenation of arenes and heterocycles that utilizes inexpensive and readily available *N*-halosuccinimides is disclosed. This methodology is shown to efficiently chlorinate diverse aromatics, including simple arenes such as anthracene, and heterocycles such as indoles, pyrrolopyrimidines, and imidazoles. Arenes with Lewis acidic moieties also proved amenable, underscoring the mild nature of this chemistry. Lewis base catalysis was also found to improve several diverse aromatic brominations and iodinations.



The direct electrophilic chlorination, and more generally halogenation, of arenes and heterocycles represents a powerful transformation, as chloride substitution is capable of modulating the electronic and physical properties of molecules and can partake in inter- and intramolecular electrostatic interactions.[1−3] Because of these properties, aryl chlorides are ubiquitous throughout drug discovery with numerous chlorinated small molecule pharmaceuticals, including the blockbuster drugs Zoloft, Plavix, and Zelboraf (Figure 1A).[4] Additionally, the syntheses of many more biologically active molecules contain key aryl halide intermediates as chemists leverage reactivities that are unique to aryl halides.[5−7]

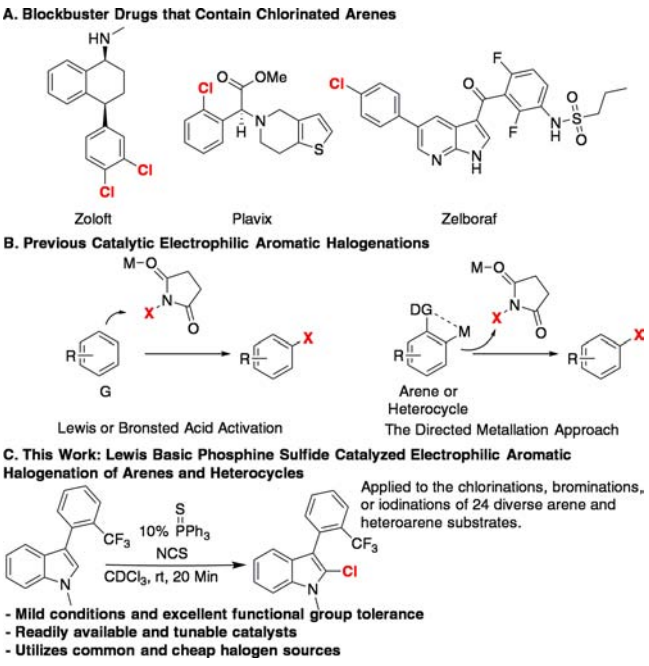


Figure 1. Halogenation in organic chemistry and drug discovery.

Classical electrophilic aromatic halogenations often suffer from severe drawbacks. For example canonical "Friedel−Crafts" electrophilic aromatic halogenations involve the activation of a diatomic halogen with a strong Lewis acid and suffer from low functional group tolerance. Alternatively, the *in situ* oxidation of halide ions to form electrophilic intermediates possesses several practical advantages; however, it traditionally requires harsh stoichiometric oxidants. New methodologies that implement milder oxidants[8,9] hold promise as greener alternatives, yet thus far require elevated temperatures for chlorination on activated arenes. Lewis has recently demonstrated the synthetic utility of the halogenase RebH as an enzymatic catalyst toward the regioselective chlorination of arenes;[10] however, practical application of this seminal work is currently held back due to low enzyme stability.[11]

Electrophilic aromatic halogenation using preformed halogen sources such as *N*-halosuccinimides (NXS) is one of the most common methods to make aryl halides;[12−14] however, it often suffers from low reactivity, particularly when dealing with less reactive reagents such as NCS. While it is known that Lewis or Brønsted acids are able to activate NXS (Figure 1B), many conditions rely on activated substrates and high temperatures or super acidic conditions to effect efficient conversions.[15,16]

Recently, Yamamoto[17] has developed a $ZrCl_4$ catalyzed halogenation of electronically activated aromatic compounds. Inspired by his work, later studies have implemented catalytic Lewis[17−19] or Brønsted acids[20] to activate NXS toward regio- or enantioselective brominations; however most of these studies have not been extended to chlorination due to the lower inherent reactivity of NCS. The field of directed C−H functionalization has also turned attention to regioselective halogenation with

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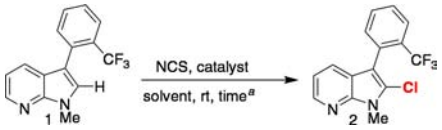
numerous examples of functional-group directed halogenations (Figure 1B), many of which invoke a dual activation of both the arene and *N*-halosuccinimide.[21−26] Recently, Baran[27] et al. have disclosed a new chlorinating reagent, chloro-bis(methoxycarbonyl) guanidine (CBMG), that has displayed increased reactivity while maintaining selectivity compared to classical reagents, perhaps representing the current state-of-the-art of the field.

Stimulated by seminal work in Lewis base catalysis[28−30] we postulated that NCS activation with an appropriate Lewis base would represent a mild and efficient catalytic strategy that could overcome many of the current shortcomings (Figure 1 C). As a proof of concept we initially investigated the electrophilic chlorination of the *C*-2 position of 3-substituted 7-azaindoles (i.e., **1**), a class of molecules ubiquitous throughout medicinal chemistry that possesses no reactivity toward NCS in the absence of catalyst at rt (Table 1, entries 1,2), and attenuated activity toward Yamamoto's Lewis acid catalyzed conditions (Table 1, entry 9), possibly due to adduct formation between Lewis acid and the Lewis basic heterocyclic nitrogen. Lewis basic triphenylphosphine sulfide (**3**) proved an excellent catalyst with a 20% catalytic loading, providing 84% conversion in 18 h at rt (Table 1, entry 3). Other Lewis bases proved to be much less efficient; for example triphenylphosphine oxide (**4**) possessed no catalytic activity whereas triphenylphosphine selenide (**5**) displayed reduced activity (Table 1, entries 5,6).

Table 1. Evaluation of Chlorination Catalysts[a]



entry	catalyst	solvent	time (h)	yield[b]
1	none	$CDCl_3$	24	0
2	none	CD_2Cl_2	22	0
3	$Ph_3P{=}S$ (**3**)	$CDCl_3$	18	84
4	$Ph_3P{=}S$	CD_2Cl_2	22	44
5	$Ph_3P{=}O$ (**4**)	$CDCl_3$	24	0
6	$Ph_3P{=}Se$ (**5**)	$CDCl_3$	24[c]	54
7	$S(n\text{-}Bu)_2$ (**6**)	$CDCl_3$	24[c]	81
8	$(n\text{-}Bu)_3P{=}S$ (**7**)	$CDCl_3$	12	94
9	$ZrCl_4$	$CDCl_3$	24[c]	27[d]

[a]Reactions were performed at rt by the addition of 0.03 mmol of **1**, 0.006 mmol of catalyst, and 600 μL of solvent into an NMR tube, followed by the addition of 0.040 mmol of NCS. [b]Percent conversions by NMR represent an average of three trials using tetramethylsilane as an internal standard. [c]NMR showed incomplete conversion of NCS. [d]Reaction was performed dry in an argon atmosphere; percent conversion by NMR represents an average of two trials using tetra(trimethylsilyl)silane as an internal standard; 0.0015 mmol of $ZrCl_4$ was used.

Motivated by Snyder's[31] work with halosulfonium salts, as well as recent work by Yeung,[32−34] we investigated butyl sulfide (**6**), which proved to be a capable catalyst, however presented less opportunity to modulate electronically (Table 1, entry 7). We next theorized that electron-rich phosphine sulfides would be better Lewis base catalysts; thus, we tested tributylphosphine sulfide and found it to be noticeably more active. In order to illustrate the utility of this chemistry we chose to focus primarily on commercially available catalyst **3** to define its scope; however, the superiority of **7** suggests that further catalyst modifications will be fruitful. Notably CBMG (Figure 2) proved remarkably effective at chlorinating azaindoles going to full conversion in minutes.

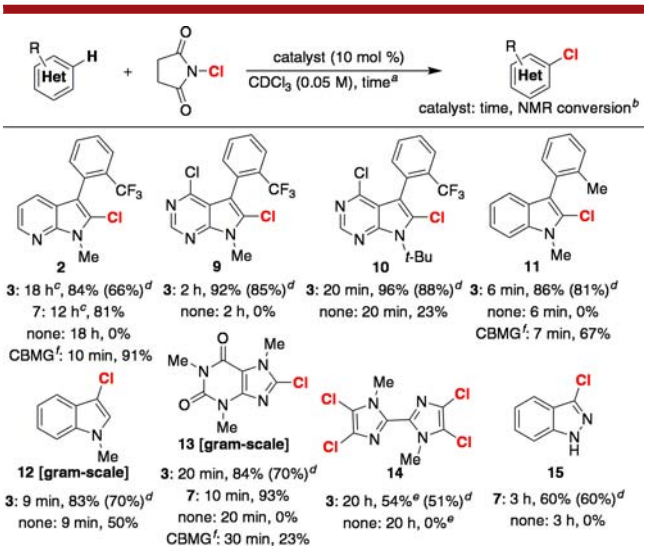


Figure 2. Chlorination of heterocycles. [a] Reactions were performed at rt by the addition of 0.03 mmol of substrate, 0.003 mmol of catalyst, and 600 μL of $CDCl_3$ into an NMR tube, followed by the addition of 0.040 mmol of NCS. [b] Percent conversions by NMR represent an average of three trials using tetramethylsilane as an internal standard. [c] 0.006 mmol of catalyst was used. [d] Isolated yield represents an average of three trials (isolated yield on the gram-scale represents an average of two trials [see Supporting Information (SI) for gram-scale procedure]). [e] 0.126 mmol of NCS was used. [f] CBMG was used as the stoichiometric chlorine source instead of NCS, and no catalyst was added to the reaction.

In general we found 10% **3** to catalyze the rapid chlorination of diverse heterocycles, many of which represent privileged scaffolds in drug discovery (Figure 2). For example 3-substituted pyrrolopyrimidines, a well-known kinase inhibitor scaffold[35] that possesses little or no background, rapidly chlorinated to **9** or **10** (92% conversion to **9** at 2 h and 96% conversion to **10** at 20 min). These results highlight the utility of Lewis base catalysis in the context of electrophilic aromatic chlorination, as to the best of our knowledge there are no literature precedence for the direct *C*-2 chlorination of azaindoles and only scarce[36] patent precedence for pyrrolopyrimidines. 3-Substituted indoles, a privileged scaffold class in medicinal chemistry,[37] also proved to be amenable substrates, chlorinating at the *C*-2 position with large rate accelerations compared to without a catalyst (86% conversion to **11** at 6 min, with little to no conversion observed in the absence of a catalyst at that time point), while also offering a noticeable improvement to CBMG under comparable noncatalyzed conditions.

Cleaner conversion was also observed for the *C*-3 chlorination of *N*-methylindole to afford **12** (83% in 9 min), while avoiding the use of DMF, the literature standard solvent for halogenation due to the ability of DMF to effect the reactivity of NXS.[12] Caffeine also smoothly chlorinated at the *C*-8 position, converting to **13** in minutes with no observable background reaction. Even greater rate acceleration was observed in the presence of **7** (93%, 10 min), representing a marked improvement over CBMG (23% conversion at 30 min). We also found this system adept at chlorinating other heterocycles such as imidazole (i.e., perchlorination of bis-imidazole to give **14** in 50% conversion after 20 h) and indazole (60% conversion to **15** in 3 h

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with no observed reaction in the absence of **7**). To further demonstrate the potential utility of this chemistry, we applied these conditions on the gram scale to access **12** and **13** with results comparable to those on the NMR scale.

We next evaluated the chlorination of simple arenes (Figure 3). Mesitylene gave monochlorinated **16** in 60% conversion after

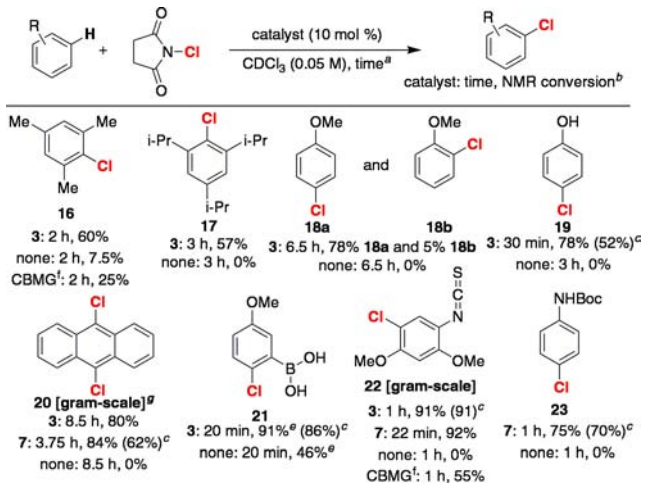

Figure 3. Chlorination of arenes. [a] Reactions were performed at rt by the addition of 0.03 mmol of substrate, 0.003 mmol of catalyst, and 600 μL of $CDCl_3$ into an NMR tube, followed by the addition of 0.040 mmol of NCS. [b] Percent conversions by NMR represent an average of three trials using tetramethylsilane as an internal standard. [c] Isolated yield represents an average of three trials (isolated yield on the gram scale represents an average of two trials [see SI for gram-scale procedure]). [d] A 9:1 mixture of $CDCl_3/CD_3OD$ was used as the solvent. [e] CBMG was used as the stoichiometric chlorine source instead of NCS, and no catalyst was added to the reaction. [f] 2.4 equiv of NCS were used.

2 h, with the attenuated yield being due to the formation of dichlorinated product, offering a noticeable improvement over CBMG (25% conversion to **16** at 2 h albeit with minimal dichlorinated product observed). 1,3,5-Triisopropylbenzene gave similar results converting to 57% **17** after 3 h. Phosphine sulfide catalysis also proved efficient toward chlorinating anisole resulting in 83% conversion to monochlorinated derivatives **18a** and **18b** (15:1 mixture of *para* to *ortho* by NMR) after 6.5 h with no observable background reaction. This represents a striking yield and selectivity compared to other literature precedents. In comparison, CBMG required elevated temperatures or the action of a strong acid to chlorinate anisole with comparable yields and selectivity. Phenol also rapidly chlorinated at the *para* position to give **19** in good yield after 30 min. Anthracene, which Borhan[38] has recently predicted to have a high affinity toward halenium ions, also proved to be an excellent substrate, reaching full conversion to 9,10-dichloroanthracene in 3.5 h with catalyst **7** (no observable background after 8.5 h). To demonstrate the mild nature of Lewis base catalysis, we investigated arene substrates with electrophilic functional groups, finding each substrate to convert to a monochlorinated product. This included the chlorination of 3-methoxyphenyl boronic acid (**21**, 86% conversion after 1 h) and 2,4-dimethoxyphenyl isothiocyanate (**22**, 91% conversion at 1 h with **3**; 92% conversion with **7** at 22 min). Notably comparable results were obtained on the gram scale. *N*-Boc-aniline also chlorinated at the *para* position with no background, affording **23** in 70% isolated yield with the acid-sensitive protecting group still intact. These results demonstrate the functional group tolerability of this system.

As mentioned throughout the text, we also compared our results side by side with stoichiometric CBMG, observing noticeable improvements across several substrates (i.e., indole **11**, caffeine, mesitylene, phenol, and 2,4-dimethoxyphenyl isocyanate). However, 7-azaindoles (i.e., **2**), which required increased reaction times and catalytic loadings toward phosphine sulfide catalysis, possessed striking activity toward CBMG, rapidly going to completion in minutes (Figure 2). Overall these data suggest phosphine sulfide catalyzed chlorinations with NCS are complementary, and in many cases more efficient than those with CBMG.

We then investigated more reactive halogen sources such as NBS and NIS (Figure 4), observing excellent activities, often on

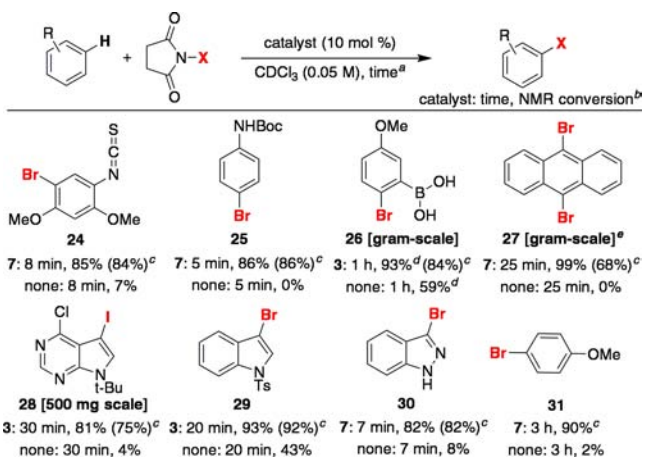

Figure 4. Bromination and iodination of arenes and heterocycles. [a] Reactions were performed at rt by the addition of 0.03 mmol of substrate, 0.003 mmol of catalyst, and 600 μL of $CDCl_3$ into an NMR tube, followed by the addition of 0.040 mmol of NXS (X = Br or I). [b] Percent conversions by NMR represent an average of three trials using tetramethylsilane as an internal standard. [c] Isolated yield represents an average of three trials (isolated yield on the gram scale represents an average of two trials [see SI for gram-scale procedure]). [d] A 9:1 mixture of $CDCl_3/CD_3OD$ was used as the solvent. [e] 2.4 equiv of NBS were used.

preparative scales. With catalyst **7**, we were able to monobrominate 2,4-dimethoxyphenyl isothiocyanate and *N*-Boc-aniline to afford **24** and **25**, respectively, in over 80% yield within minutes, with little to no reaction occurring in the absence of phosphine sulfide catalyst. 3-Methoxyphenylboronic acid smoothly brominated to give **26** in 93% conversion at 1 h with the catalyst, while the yield was attenuated in the absence of **3**. The dibromination of anthracene completed in 25 min to yield **27** at 99% conversion by NMR. *N*-(*t*-Bu)-substituted pyrrolopyrimidine cleanly iodinated at the *C*-3 position to give **28**, resulting in 81% conversion after 30 min, while only observing 4% conversion without **3**.

While a number of these reactions had marked background reactions, we generally found the catalytic conditions to be cleaner and higher yielding. This is exemplified by *N*-tosylindole, which smoothly brominated in 20 min to yield **29** in 93% yield in the presence of **3**. The noncatalyzed reaction was also rapid; however, it only yielded 43% of the *C*-3 brominated indole along with two other prevalent side products by NMR. Indazole also cleanly brominated at the *C*-3 position converting to **30** in 82%

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yield, with highly attenuated reactivity in the absence of **7**. Finally anisole selectively brominated at the *para* position to give **31** in excellent yields (91% at 3 h) with little to no reaction in the absence of a catalyst.

In summary, we have developed a practical, inexpensive, and highly reactive Lewis basic catalytic system to promote the chlorination, and, more generally, halogenation of diverse arenes and heterocycles, with many examples validated on gram scales. The dependence of this chemistry on the presence of catalysts opens up the possibility to design next generation phosphine sulfide catalysts that effect enantio- or regioselective chlorinations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Voth, A. R.; Ho, P. S. *Curr. Top. Med. Chem.* **2007**, *7*, 1336.
(2) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.
(3) Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789.
(4) McGrath, N.; Brichacek, M.; Njardarson, J. T. *J. Chem.* **2010**, *87*, 1348.
(5) Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.
(6) Old, D.; Wolfe, J.; Buchwald, S. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(7) Zhang, C.; Huang, J.; Trudell; Mark, L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804.
(8) Shi, L.; Zhang, D.; Lin, R.; Zhang, C.; Li, X.; Jiao, N. *Tetrahedron Lett.* **2014**, *55*, 2243.
(9) Prebil, R.; Laali, K. K.; Stavber, S. *Org. Lett.* **2013**, *15*, 2108.
(10) Payne, J. T.; Andorfer, M. C.; Lewis, J. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 5271.
(11) Payne, J. T.; Lewis, J. C. *Synlett* **2014**, *25*, 1345.
(12) Mitchell, R. H.; Lai, Y.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.
(13) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221.
(14) Gruter, G.-J. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473.
(15) Lambert, F.; Ellis, W. D.; Parry, R. J. *J. Org. Chem.* **1965**, *30*, 304.
(16) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.
(17) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, *2005*, 2837.
(18) Zhang, R.; Huang, L.; Zhang, Y.; Chen, X.; Xing, W.; Huang, J. *Catal. Lett.* **2012**, *142*, 378.
(19) Al-Zoubi, R. M.; Hall, D. G. *Org. Lett.* **2010**, *12*, 2480.
(20) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964.
(21) Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2028.
(22) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081.
(23) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344.
(24) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.
(25) Du, Z.-J.; Gao, L.-X.; Lin, Y.-J.; Han, F.-S. *ChemCatChem* **2014**, *6*, 123.
(26) Tian, Q.; Chen, X.; Liu, W.; Wang, Z.; Shi, S.; Kuang, C. *Org. Biomol. Chem.* **2013**, *11*, 7830.
(27) Rodriguez, R. A.; Pan, C.-M.; Yabe, Y.; Kawamata, Y.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 6908.
(28) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.
(29) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938.
(30) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655.
(31) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303.
(32) Ke, Z.; Tan, C.; Chen, F.; Yeung, Y. *J. Am. Chem. Soc.* **2014**, *136*, 5627.
(33) Tay, D. W.; Leung, G. Y. C.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5161.
(34) Tay, D. W.; Tsoi, I. T.; Er, J. C.; Leung, G. Y. C.; Yeung, Y.-Y. *Org. Lett.* **2013**, *15*, 1310.
(35) Cohen, M. S.; Zhang, C.; Shokat, K. M.; Taunton, J. *Science* **2005**, *308*, 1318.
(36) Calderwood, D. J.; Johnston, D. N.; Rafferty, P.; Twigger, H. L.; Munschauer, R.; Arnold, L. Pyrrolo[2,3D]pyrimidines and Their Uses as Tyrosine kinase Inhibitors. WO 98/41525, 1998.
(37) Welsch, M. E.; Snyder, S. A; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.
(38) Ashtekar, K. D.; Marzijarani, N. S.; Jaganathan, A.; Holmes, D.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2014**, *136*, 13355.

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