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Site-Selective Copper-Catalyzed Amination and Azidation of Arenes and Heteroarenes via Deprotonative Zincation

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ABSTRACT: Arene amination is achieved by site-selective C–H zincation followed by copper-catalyzed coupling with *O*-benzoylhydroxylamines under mild conditions. Key to this success is *ortho*-zincation mediated by lithium amido diethylzincate base that is effective for a wide range of arenes, including non-activated arenes bearing simple functionalities such as fluoride, chloride, ester, amide, ether, nitrile, and trifluoromethyl groups as well as heteroarenes including indole, thiophene, pyridine and isoquinoline. An analogous C–H azidation is also accomplished using azidoiodinane for direct introduction of a useful azide group onto a broad scope of arenes and heteroarenes. These new transformations offer rapid access to valuable, diverse chemical space of aminoarenes. Their broad applications in organic synthesis and drug discovery are demonstrated in the synthesis of novel analogs of natural product (–)-nicotine and antidepressant sertraline by late-stage amination and azidation reactions.

INTRODUCTION

Developing general and rapid access to diversely functionalized aminoarenes is important as they are highly valuable skeletons widely found in ligands, natural products and pharmaceuticals (Figure 1).[1-2] Recent developments in direct C–H amination provide an attractive strategy[3] that streamlines the synthesis of aminoarenes without the need of prefunctionalization of arene precursors (Scheme 1).[4-7 (5, 6, 7)] To achieve selective C–H amination reactions, an innate approach that is independent of arene substrates would be an ideal strategy. While notable progress has been achieved by steric or electronic control (Scheme 1, I), unambiguous selectivity remains challenging in many cases where reactions give multiple isomers of aminated arenes.[4] Among arene substrate-guided strategies, selective amination of electron-deficient arenes has been commonly achieved via directed metalation of acidic aromatic C–H bonds.[5] Simple, non-activated arenes, however, are more challenging, though such aminoarenes constitute one of the most common amine skeletons of well-recognized importance (Figure 1). Toward this end, transition metal catalyzed selective C–H amination reactions have been elegantly achieved by directing group assisted C–H activation (Scheme 1, II-a).[6] Yet, this sophisticated strategy is limited by the need of specific directing groups on the arene substrates for facilitating the C–H activation step. Alternatively, selective *ortho*-metalation represents a more general strategy for a much broader scope of arenes bearing diverse directing moieties (Scheme 1, II-b). The Johnson group reported selective arene C–H amination by *ortho*-lithiation, transmetallation to arylzinc species, and Cu-catalyzed electrophilic amination with hydroxylamines.[7] In this one-pot reaction, the formation of the key arylzinc intermediate relies on the initial lithiated intermediates, which intrinsically hinder the utility of this transformation by their instability and incompatibility with sensitive functional groups (e.g., halides, carbonyl).[8] Recently, selective C–H amination has also been reported via deprotonative cupration for the preparation of primary anilines.[9]

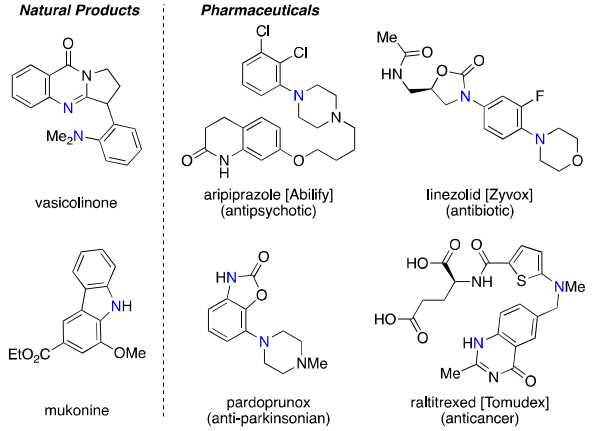
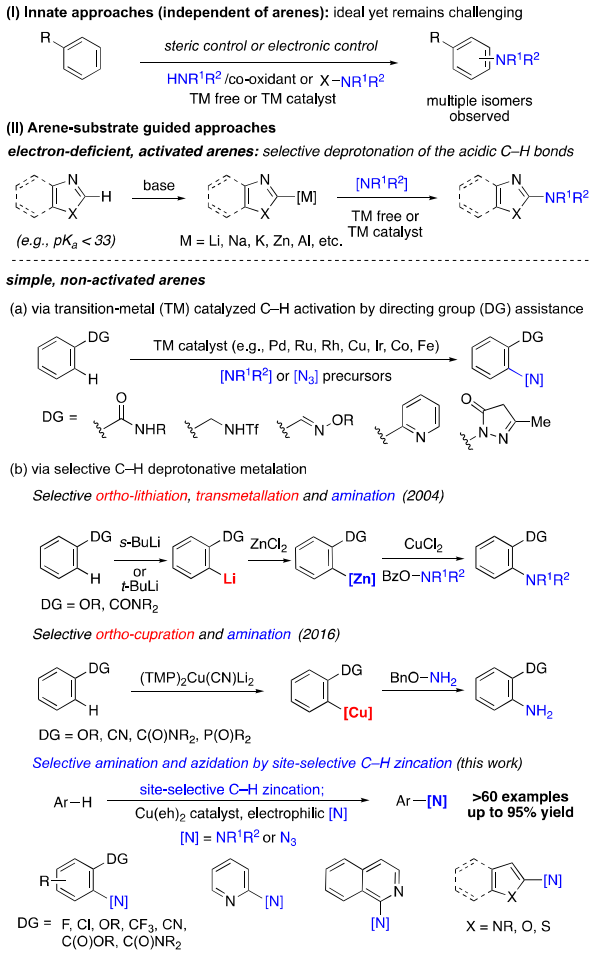


Figure 1. Representative examples of functionalized aminoarenes in natural products and pharmaceuticals

In our efforts to develop rapid access to important and novel nitrogen-containing skeletons,[5i,5j,10] we herein report the development of selective C–H amination and azidation reactions via deprotonative zincation (Scheme 1, II). These amination reactions are highly effective for an extensive scope of arenes and hetereoarenes, including those simple, non-activated arenes that cannot be aminated by previous methods, with excellent regioselectivity and functional group compatibility. Our approach exploits the generality of C–H zincation on a wide range of arenes using a reactive dialkylzinc amide base complex, the mild reactivity of aryl zinc intermediates for good tolerance of sensitive functional groups,[5f,11,12] as well as the broad applicability of this strategy toward different electrophilic nitrogen sources. The impact of this amination approach in its applicability to other amino precursors is demonstrated by an azidation reaction of arenes using azidoiodinane. These

new transformations afford a valuable and facile approach to access diverse, underexplored chemical space. Their broad applications in organic synthesis, medicinal chemistry and drug discovery are demonstrated in the rapid synthesis of novel aminoarene derivatives of (–)-nicotine and antidepressant sertraline by late-stage amination and azidation reactions.

Scheme 1. Arene C–H Amination Reactions

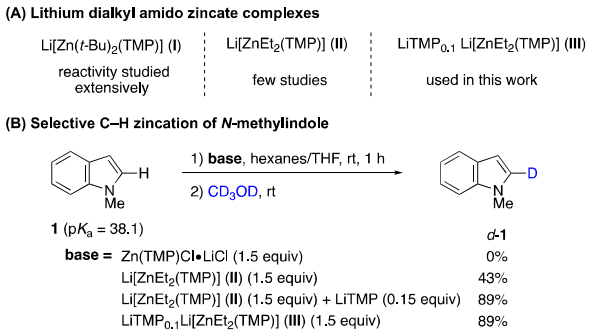


RESULTS AND DISCUSSION

Our development for this arene zincation/amination reaction began with identifying effective zinc-bases that enable selective deprotonation of unactivated arenes. Toward this end, lithium amido dialkylzincate complexes are known to promote directing-group mediated *ortho*-zincation of unactivated arenes,[13] in a similar manner to *ortho*-directed lithiation,[8] while offering better compatibility of sensitive functional groups, such as halides, nitrile, and esters that are unsuitable towards lithiate or magnesiate intermediates. One well-studied example among such zincate bases is Li[Zn(*t*-Bu)$_2$(TMP)] (**I**) (Scheme 2A).[13a] The zincate base (**I**) was able to achieve alkali-metal-mediated zincation of various functionalized arenes, yet has been rarely explored in organic synthesis, likely due to its preparation that necessitates isolation of pyrophoric Zn(*t*-Bu)$_2$. Rather, the analogous Li[ZnEt$_2$(TMP)] complex (**II**) can be generated from commercially available ZnEt$_2$ without the aid of a glovebox, which was only characterized structurally with synthetic utility little explored, to the best of our knowledge.[13d]

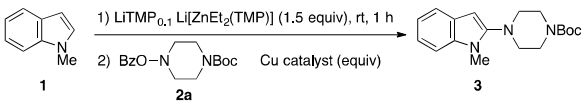
We chose to explore the use of this more readily available base (**II**) for the zincation of non-activated arenes,[14] such as *N*-methylindole **1** (Scheme 2B, p*K*a = 38.1).[15] Compared to a neutral base[16-17] such as Zn(TMP)Cl•LiCl LiCl[5f,11c-e,17], which was ineffective in this case, the zincate base (**II**) was able to provide the desired indolyl zincate intermediate in 43% yield. With the addition of catalytic amount of LiTMP, the zincation was significantly improved to 89% yield. This result led us to examine the reactivity of LiTMP$_{0.1}$Li[ZnEt$_2$(TMP)] (**III**), which was prepared in a one-pot protocol.[14] Encouragingly, the zincate complex **III** showed excellent efficiency for the zincation step of indole **1** and other non-activated arenes.[14]

Scheme 2. Lithium Diethyl Amido Zincate Complex for Selective and Effective C–H Zincation of Indole



With LiTMP$_{0.1}$Li[ZnEt$_2$(TMP)] (**III**) established for effective zincation of diverse arenes, we examined the amination using this deprotonative strategy with indole **1** and *O*-benzoylhydroxylamine **2a** (Table 1). In the absence of a catalyst, no aminated indole was observed (entry 1). When different copper salts were used (entries 2–7), the desired amine **3** was formed, with Cu(OAc)$_2$, Cu(OTf)$_2$ and Cu(eh)$_2$ among the most effective catalysts (entries 5−7). The reactions were more efficient with the increased equivalents of **2a** (entries 8–10), with Cu(eh)$_2$ emerging as the best copper source (entry 10), which was chosen as the standard conditions in our studies.

Table 1. Optimization for Amination Conditions.

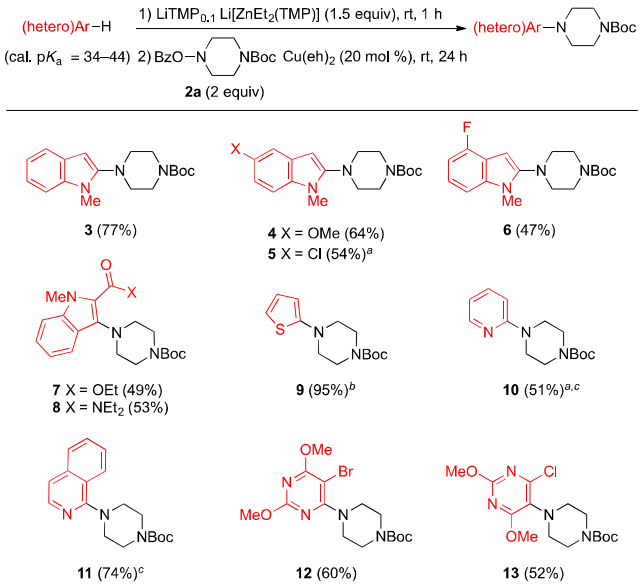


entry	equiv of **2a**	catalyst	equiv	**3** (%)[b]
1	1.5	--		ND
2	1.5	CuI	0.2	7
3	1.5	$CuCl_2$	0.2	23
4	1.5	$Cu(acac)_2$	0.2	46
5	1.5	$Cu(OAc)_2$	0.2	53
6	1.5	$Cu(OTf)_2$	0.2	49
7	1.5	$Cu(eh)_2$	0.2	49
8	2.0	$Cu(OAc)_2$	0.2	79
9	2.0	$Cu(OTf)_2$	0.2	81
10	**2.0**	**$Cu(eh)_2$**	**0.2**	**85 (77)[c]**

[a]Conditions: **1** (0.2 mmol, 1.0 equiv), LiTMP$_{0.1}$Li[ZnEt$_2$(TMP)] (1.5 equiv), rt, 1 h; **2a**, catalyst, rt, 24 h. [b]Yields determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [c]Isolation yield. ND = not detected. acac = acetylacetonate. eh = 2-ethylhexanoate.

We first looked into a series of heteroarenes bearing indole, thiophene, pyridine, and pyrimidine scaffolds (Table 2). Note that amination of these substrates was difficult via either C–H activation approaches or under our previous conditions (calculated p*K*a = 34–44).[15b] Different indole derivatives, such as 5-methoxy, 5-chloro-, and 4-fluoro-*N*-methylindoles, readily underwent amination at the 2-position. The electron-deficient *N*-methyl-5-chloroindole required elevated temperatures to effect zincation, and the lower efficacy for the directed metalation of indoles bearing electron-withdrawing substituents agrees with the previous computational studies that suggest coordination to the lithium counter ion is mechanistically important.[13d] For indoles bearing an ethyl ester or a diethylamide group at the 2-position, the zincation occurred at the 3-position and the amination reactions provided 3-aminoindoles **7** and **8** accordingly. The amination reactions of simple thiophene, pyridine and even isoquinoline effectively formed 2-aminated products **9**–**11**. Pyrimidines bearing multiple substituents were also feasible in this transformation, giving **12** and **13** in moderate yields. Particularly impressive is the compatibility of halide groups (i.e., F, Cl and Br), which had no signs of metal exchange or aryne formation under reaction conditions, suggesting its advantages over other metalation strategies.

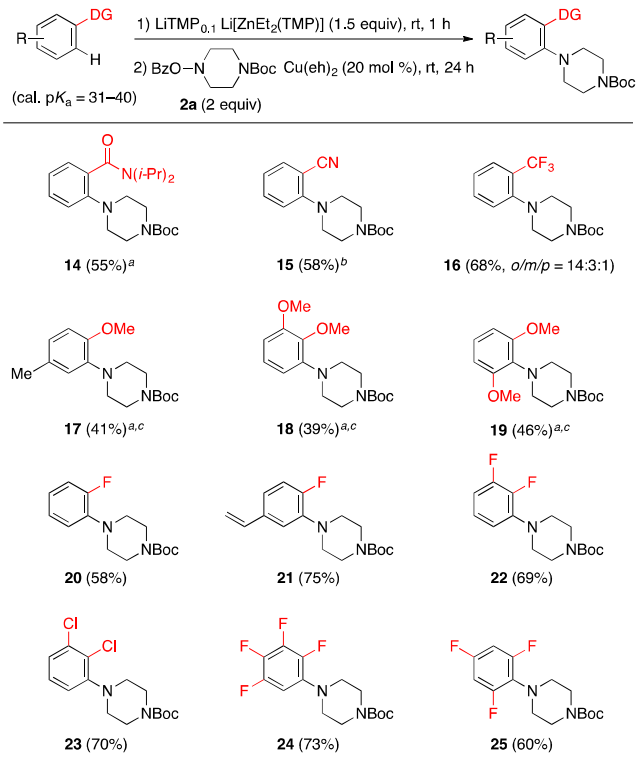
Table 2. Amination of Heteroarenes



Reactions run on 0.2 mmol scale. Isolated yields. Standard Conditions: heteroarene (1.0 equiv), $LiTMP_{0.1}Li[ZnEt_2(TMP)]$ (1.5 equiv), rt, 1 h; **2a** (2.0 equiv), $Cu(eh)_2$ (20 mol %), rt, 24 h. [a]Zincation at 50 °C. [b]Zincation with 1.0 equiv of base for 30 min. [c]Amination with 3.0 equiv of **2a**. [d]Amination at 50 °C.

Different arenes were also investigated for selective C–H amination under this system, revealing that both strong and weak *ortho*-directing functionalities were sufficient to assist the deprotonative amination reaction (Table 3).[15b] For example, the reaction of *N*,*N*-diisopropylbenzamide gave **14** in 55% yield. Simple benzonitrile also underwent amination effectively, installing the amino group *ortho*- to the nitrile. Trifluoromethyl benzene was aminated in 68% yield, though, besides the *ortho*-aminated major product **16**, the formation of *meta*- and *para*-isomers was observed. This suggests the possible migration of the zincate along the aromatic ring after the initial deprotonation step.[18] Electron-rich arenes bearing mono-, or

Table 3. Site-Selective Amination of Arenes



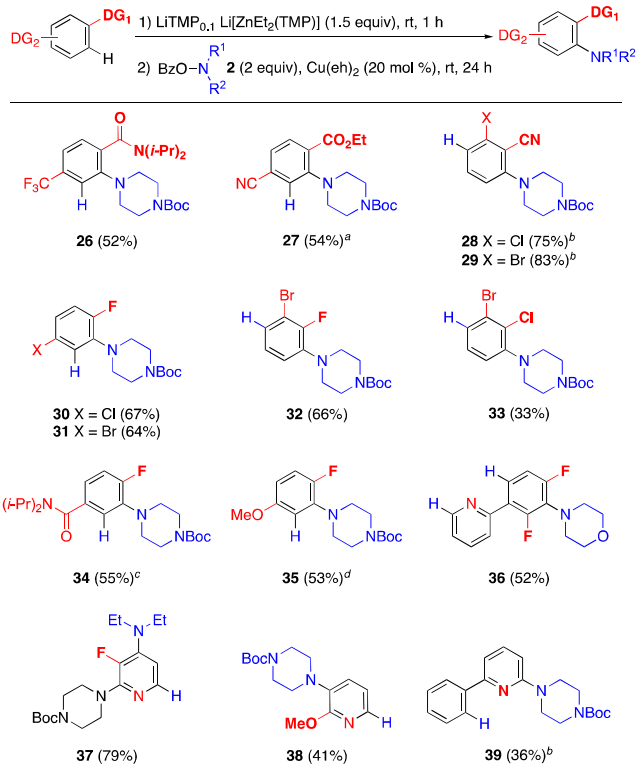
Reactions performed at 0.2 mmol scale. Isolation yields. [a]Amination with 3.0 equiv of **2a** at 50 °C. [b]Zincation with 1.0 equiv of $LiTMP_{0.1}Li[ZnEt_2(TMP)]$ for 15 min. [c]Zincation with 2.0 equiv of $LiTMP_{0.1}Li[ZnEt_2(TMP)]$ for 3 h.

di-methoxy groups are also able to provide the aminated products **17**–**19**. *Ortho*-zincation of fluorobenzene readily occurs at room temperature, leading to the smooth formation of *ortho*-fluoroamino arenes **20** and **21**. A range of di-, tri and tetra-substituted haloarenes also readily underwent *ortho*-amination to afford **22**–**25** in 60–73% yields. These results demonstrate the superior competency of this strategy to access diversely functionalized aminoarenes, including those that are difficult to access otherwise (e.g. **16**, **20**–**22**)[5e] and that are pharmacologically valuable (e.g. dichloroaminoarene **23**). Although a wide range of functional groups are well tolerated by the amination protocol, highly electrophilic moieties such as nitro group, aldehydes, and ketones were not compatible with the zincate intermediate, resulting in complex reaction mixtures upon metalation.

We next looked into the arenes bearing multiple functionalities to obtain some insight into their influence on the regioselectivity of this deprotonative amination reaction (Table 4). First, we examined the contribution of different directing groups in determining the regioselectivity. For example, the amination of *N*,*N*-diisopropyl-4-(trifluoromethyl)benzamide gave **26** selectively with the amino moiety *ortho* to the amide group, likely resulting from the strong coordination of amides. The reaction of ethyl 4-cyanobenzoate afforded **27** with amino group *ortho* to ester, while the amination of 2-chloro- and 2-bromo-benzonitriles gave products **28** and **29** with the amine moiety installed *ortho* to the stronger coordinating nitrile rather than the halides. We also examined the regioselectivity on the arenes bearing different halide groups. Amination of 4-bromo- and 4-chloro-fluorobenzenes led to the selective for-

mation of **30** and **31**, via selective zincation *ortho* to fluoride, which has a stronger activating inductive effect. Likewise, regioselective aminations were observed for 1-bromo-2-fluorobenzene and 1-bromo-2-chlorobenzene in the formation of **32** and **33**. Interestingly, the fluoride group overrides the directing effects of strong coordinating amide or methoxy group, as seen in the selective formation of **34** and **35.** In addition, we looked into the regioselective outcomes in the amination of pyridine derivatives, where pyridine itself may serve as an *ortho*-coordinating moiety for the deprotonative zincation step. As demonstrated in the formation of **36** and **37**, the amination selectively proceeded via the thermodynamically stabilized aryl zincate intermediates, which benefits from the presence of electron-withdrawing *ortho*-fluorine group on the arenes. Additionally, a strong directing group such as methoxy is also capable of overriding the pyridine-directing group, as demonstrated by the regioselective formation of **38**. No migration to the more acidic 4-pyridyl position was detected, indicating the importance of an *ortho*-coordinating moiety to stabilize the zincate intermediate. Finally, subjecting 2-phenylpyridine to the standard amination conditions provided 2-aminated 6-phenylpyridine **39**, with no observation of 2-pyridyl aminoarene product which would be formed by the classic pyridine directed C–H activation pathway. These representative examples offer a framework for identifying suitable substrates and predicting the regioselective outcome of the metalation and amination sequence.

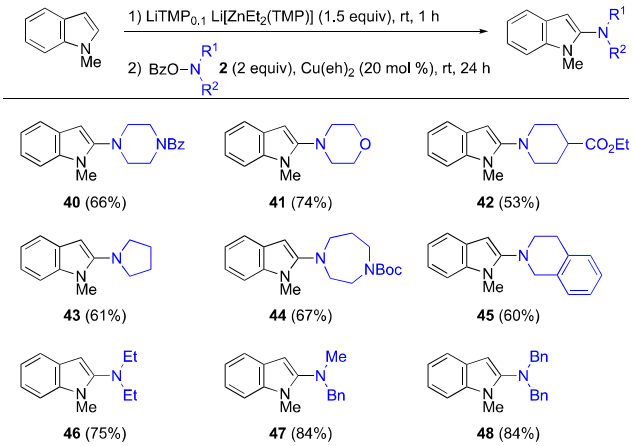
Table 4. Regioselective Amination of Multiply Substituted Arenes and Heteroarenes



Reactions run on 0.2 mmol scale. Isolation yields. [a]Zincation step with 1 equiv of $LiTMP_{0.1}Li[ZnEt_2(TMP)]$ for 15 min. [b]Zincation step at 50 °C and amination step with 3.0 equiv of **2a**. [c]Major isomer shown. Regioselective ratio = 10:1. [d]Trace isomer observed on GC/MS but not detected by ^1H NMR.

We also explored the scope of amines in the reactions of *N*-methylindole with different *O*-benzoylhydroxylamines (Table 5). Beside Boc-protected piperazine, other six-membered amino precursors were also readily introduced onto the indole, including benzoyl piperazine, morpholine, and ethyl 4-piperidinecarboxylate (**40**–**42**). Note that both amide and ester groups remained unmodified, and even the presence of an acidic α-proton of the ester (i.e. **42**) did not impede the amination. Five- and seven-membered amines were viable for the formation of **43** and **44**. Besides cyclic amine precursors, the reactions with acyclic amines were also efficient, as seen in the formation of **46**–**48** in good yields.

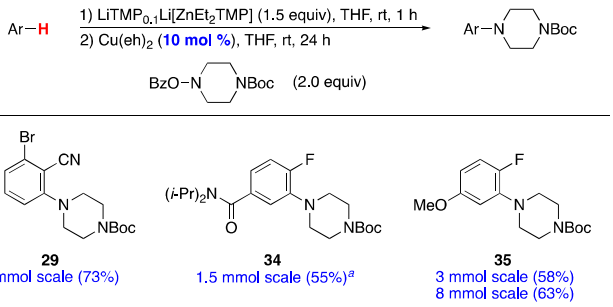
Table 5. Scope of *O*-Benzoylhydroxylamines in the Arene Amination Reaction



Reactions run on 0.2 mmol scale. Isolation yields.

We also conducted amination reactions of representative arenes on different scales to evaluate the scalability and reliability of this method (Table 6). Gratifyingly, these scale-up reactions provided comparable efficiency with a decreased (10 mol %) loading of $Cu(eh)_2$ catalyst,[19] and even better efficiency on larger gram scale.

Table 6. Scale-up Amination Reaction of Arenes

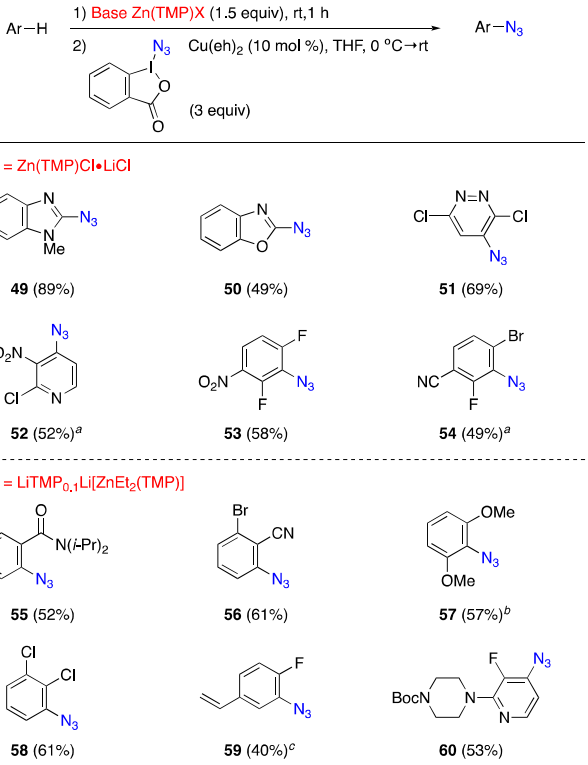


Isolation yields. [a]Zincation step with 1.0 equiv of base for 20 min.

Along with our investigations on this deprotonative amination strategy using *O*-benzoylhydroxylamines, we also explored this approach for a C–H azidation reaction using an electrophilic azide reagent. C–H Azidation transformations that can readily install an azide group onto a wide range of arenes are highly valuable,[20] as the azide is not only a useful intermediate for various nitrogen-containing functional groups,[21] such as amines, amides, triazoles, and tetrazoles, but also one of the most versatile chemical reporters in bioorthog-

onal conjugation,[22] such as Huisgen 'click' cycloaddition and the Staudinger ligation. Thus, we next established a $Cu(eh)_2$-catalyzed azidation reaction using azidoiodinane[23] as an azide precursor on a variety of arenes and heteroarenes (Table 7). Based on our earlier studies on the zincation step, we first used Zn(TMP)Cl•LiCl to affect the zincation of electron-deficient arenes. Benzimidazole and benzoxazoles underwent effective azidation at the 2-position, providing **49** and **50**. The reactions of electron deficient pyridazine, pyridine, and arenes were also viable, with the azide group installed at the most acidic position as seen in **51**–**54**. The azidation reaction of non-activated arenes and heteroarenes was achieved as demonstrated in the formation of azido arenes **55**–**60**, where $LiTMP_{0.1}Li[ZnEt_2(TMP)]$ was used for the deprotonative zincation step in the abovementioned amination reactions.

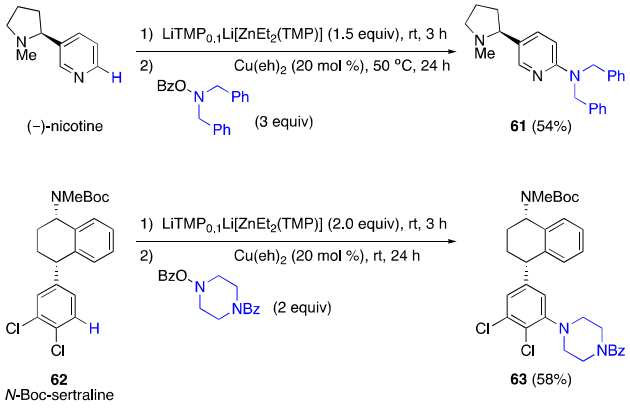
Table 7. Selective Azidation of Arenes and Heteroarenes



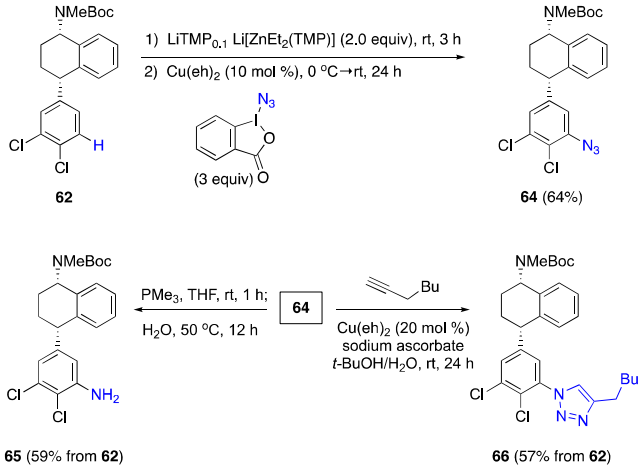
Reactions run on 0.2 mmol scale. Isolation yields. [a]Zincation step at 50 °C for 2 h. [b]Zincation step with 2.0 equiv of base for 3 h. [c]Yield based on the triazole derivative of **59** upon its cycloaddition reaction with 1-heptyne.

The impact of this amination strategy, given its generality of diverse arene scaffolds, predictable regioselectivity, and excellent functional group compatibility, has also been demonstrated in our studies for the late-stage amination of valuable and complex molecules (Schemes 3 and 4). For example, subjecting natural product (−)-nicotine[24] to amination conditions led to the formation of **61** in 54% yield, with excellent regioselectivity for the less sterically hindered 6-position. We next examined the amination of **62**, derivative of a common antidepressant drug sertraline, which rapidly afforded a novel derivative **63** in 58% yield. The analogous azidation reaction of *N*-Boc sertraline also provided **64** effectively (Scheme 4). Importantly, the compound **64** was readily transformed into free amine **65** via Staudinger reaction and into triazole **66** via 1,3-dipolar cycloaddition reaction with 1-heptyne, demonstrating great value of the azide group as a versatile amino precursor and chemical reporter. It is worth noting that this deprotonative amination approach successfully overcame the common problems in other C–H amination strategies, such as those involving the presence of basic amines, multiple potential metalation sites, and sensitive functionalities.

Scheme 3. Late-stage Amination of Bioactive Molecules



Scheme 4. Rapid Synthesis of Novel Analogs of Sertraline via Arene Azidation



In conclusion, we have developed a highly general copper-catalyzed C–H amination strategy that provides effective and rapid access to diverse amino-heteroarenes and aminoarenes. Readily available *O*-benzoylhydroxylamines and azidoiodinane serve as convenient electrophilic nitrogen sources for amination and azidation reactions, respectively. Pivotal to this strategy is the use of zinc amide bases that effectively mediate the selective *ortho*-zincation with the assistance of an exceptionally diverse range of simple functional groups. The amination is regioselective even for arenes bearing multiple directing groups as well as efficient in scale-up reactions. The successful late-stage amination and azidation reactions of complex arenes demonstrate broad applicability of this strategy as a rapid entry to valuable aminoarene derivatives. Our efforts in this area will continue on the development of novel zinc base-mediated C–H functionalization.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org
Experimental protocol, optimization screening, compound characterization, and spectral data.
Crystallographic data for **27**.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *184*, 1317. (b) Bhattacharyya, P.; Sarkar, T.; Chakraborty, A.; Chowdhury, B. K. *Indian J. Chem., Sect B* **1984**, *23*, 49. (c) Lundgren, R. J.; Stradiotto, M. *Chem. Eur. J.* **2012**, *18*, 9758. (d) Slater, A. F.; Cerami, A. *Nature* **1992**, *355*, 167. (e) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658. (f) Kumar, A.; Sharma, S.; Bajaj, A. K.; Sharma, S.; Panwar, H.; Singh, T.; Srivastava, V. K. *Bioorg. Med. Chem.* **2003**, *11*, 5293. (g) Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 3248. (h) Kiss, B.; Horvath, A.; Nemethy, Z.; Schmidt, E.; Laszlovszky, I.; Bugovics, G.; Fazekas, K.; Hornok, K.; Orosz, S.; Gyertyan, I.; Agai-Csongor, E.; Domany, G.; Tihanyi, K.; Adham, N.; Szombathelyi, Z. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 328. (i) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (j) Brow, D. G.; Bostrom, J. *J. Med. Chem.* **2016**, *59*, 4443.

(2) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *2*, 27. (c) Qiao, J. X.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: 2011, p 315. (d) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(3) Recent reviews: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (b) Louillat, M. L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (c) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (d) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**. (e) Hendrick, C. E.; Wang, Q. *J. Org. Chem.* **2017**, *82*, 839.

(4) Selected exmaples: (a) Li, Z. G.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. (c) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (d) Gu, L. Q.; Neo, B. S.; Zhang, Y. G. *Org. Lett.* **2011**, *13*, 1872. (e) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000. (f) Shrestha, R.; Mukherjee, P.; Tan, Y. C.; Litman, Z. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8480. (g) John, A.; Byun, J.; Nicholas, K. M. *Chem. Commun.* **2013**, *49*, 10965. (h) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 5607. (i) Foo, K.; Sella, E.; Thome, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279. (j) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. *Chem. Commun.* **2014**, *50*, 9273. (k) Legnani, L.; Cerai, G. P.; Morandi, B. *ACS Catal.* **2016**, *6*, 8162. (l) Boursalian, G. B.; Ngai, M. Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278. (m) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326. (n) Xu, H.; Qiao, X. X.; Yang, S. P.; Shen, Z. M. *J. Org. Chem.* **2014**, *79*, 4414. (o) Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z. W.; Kurti, L.; Falck, J. R. *Science* **2016**, *353*, 1144. (p) Berzina, B.; Sokolovs, I.; Suna, E. *ACS Catal.* **2015**, *5*, 7008. (q) Liu, J. Z.; Wu, K.; Shen, T.; Liang, Y. J.; Zou, M. C.; Zhu, Y. C.; Li, X. W.; Li, X. Y.; Jiao, N. *Chem. Eur. J.* **2017**, *23*, 563.

(5) Selected exmaples: (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (c) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (d) Zhao, H. Q.; Wang, M.; Su, W. P.; Hong, M. C. *Adv. Synth. Catal.* **2010**, *352*, 1301. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (f) Kienle, M.; Wagner, A. J.; Dunst, C.; Knochel, P. *Chem. Asian J.* **2011**, *6*, 517. (g) Yotphan, S.; Beukeaw, D.; Reutrakul, V. *Synthesis* **2013**, *45*, 936. (h) Wang, J. A.; Hou, J. T.; Wen, J.; Zhang, J.; Yu, X. Q. *Chem. Commun.* **2011**, *47*, 3652. (i) McDonald, S. L.; Hendrick, C. E.; Wang, Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 4667. (j) McDonald, S. L.; Hendrick, C. E.; Bitting, K. J.; Wang, Q. *Org. Synth.* **2015**, *92* 356. (k) Yoon, H.; Lee, Y. *J. Org. Chem.* **2015**, *80*, 10244.

(6) Selected exmaples: (a) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organomet.* **2007**, *26*, 1365. (d) Ng, K. H.; Chan, A. S. C.; Yu, W. Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (e) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (f) Liu, X. Y.; Gao, P.; Shen, Y. W.; Liang, Y. M. *Org. Lett.* **2011**, *13*, 4196. (g) Sun, K.; Li, Y.; Xiong, T.; Zhang, J. P.; Zhang, Q. A. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (h) Xiao, B.; Gong, T. J.; Xu, J.; Liu, Z. J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (i) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (j) Ng, K. H.; Ng, F. N.; Yu, W. Y. *Chem. Commun.* **2012**, *48*, 11680. (k) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350. (l) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043 . (m) Li, Q.; Zhang, S. Y.; He, G.; Ai, Z. Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764. (n) Grohmann, C.; Wang, H. G.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (o) Kim, J. Y.; Park, S. H.; Ryu, J.; Hwan, S.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (p) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272. (q) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014. (r) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 8031. (s) Tang, R. J.; Luo, C. P.; Yang, L.; Li, C. J. *Adv. Synth. Catal.* **2013**, *355*, 869. (t) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706. (u) Wu, K.; Fan, Z.; Xue, Y.; Yao, Q.; Zhang, A. *Org. Lett.* **2014**, *16*, 42. (v) Shang, M.; Zeng, S. H.; Sun, S. Z.; Dai, H. X.; Yu, J. Q. *Org. Lett.* **2013**, *15*, 5286. (w) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286. (x) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601.

(7) (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (c) Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531.

(8) Selected reviews: (a) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (b) Marsais, F.; Queguiner, G. *Tetrahedron* **1983**, *39*, 2009. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (d) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376.

(9) Tezuka, N.; Shirnojo, K.; Hirano, K.; Komagawa, S.; Yoshida, K.; Wang, C.; Miyamoto, K.; Saito, T.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2016**, *138*, 9166.

(10) (a) McDonald, S. L.; Wang, Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 1867. (b) McDonald, S. L.; Wang, Q. *Chem. Commun.* **2014**, *50*, 2535. (c) Huang, H.-T.; Lacy, T. C.; Błachut, B.; Ortiz Jr., G. X.; Wang, Q. *Org. Lett.* **2013**, *15*, 1818. (d) Shen, K.; Wang, Q. *Chem. Sci.* **2015**, *6*, 4279. (e) Hemric, B. N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813.

(11) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275. (c) Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715. (d) Kienle, M.; Dunst, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 5158. (e) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (f) Ellwart, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 10662.

(12) (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *Synthesis* **2005**, *11*, 1799. (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364. (d) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (e) Zhou, Z.; Ma, Z. W.; Behnke, N. E.; Gao, H. Y.; Kurti, L. *J. Am. Chem. Soc.* **2017**, *139*, 115.

(13) (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2730. (c) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2374. (d) Kondo, Y.; Morey, J. V.; Morgan, J. C.; Naka, H.; Nobuto, D.; Raithby, P. R.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2007**, *129*, 12734. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. (f) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Y.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472. (g) Armstrong, D. R.; Garcia-Alvarez, J.; Graham, D. V.; Honeyman, G. W.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E. *Chem. Eur. J.* **2009**, *15*, 3800.

(14) See the Supporting Information for the preparation of zincate bases and additional data for the zincation reactions of different arenes.

(15) (a) Fraser, R. R.; Mansour, T. S.; Savard, S. *Can. J. Chem.* **1985**, *63*, 3505. (b) Shen, K.; Fu, Y.; Li, J. N.; Liu, L.; Guo, Q. X. *Tetrahedron* **2007**, *63*, 1568.

(16) (a) Rees, W. S.; Just, O.; Schumann, H.; Weimann, R. *Polyhedron* **1998**, *17*, 1001. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organomet.* **2007**, *26*, 4105. (c) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (d) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

(17) (a) Mosrin, M.; Bresser, T.; Knochel, P. *Org. Lett.* **2009**, *11*, 3406. (b) Duez, S.; Steib, A. K.; Knocher, P. *Org. Lett.* **2012**, *14*, 1951. (c) Unsinn, A.; Ford, M. J.; Knochel, P. *Org. Lett.* **2013**, *15*, 1128.

(18) Armstrong, D. R.; Blair, V. L.; Clegg, W.; Dale, S. H.; Garcia-Alvarez, J.; Honeyman, G. W.; Hevia, E.; Mulvey, R. E.; Russo, L. *J. Am. Chem. Soc.* **2010**, *132*, 9480.

(19) See the Supporting Information for more details on the catalyst loading. .

(20) Selected exmaples: (a) Narasimhan, N. S.; Ammanamanchi, R. *Tetrahedron Lett.* **1983**, *24*, 4733. (b) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321. (c) Stanetty, P.; Emerschitz, T. *Synth. Commun.* **2001**, *31*, 961. (d) Schlosser, M.; Gorecka, J.; Castagnetti, E. *Eur. J. Org. Chem.* **2003**, *2003*, 452. (e) Lubriks, D.; Sokolovs, I.; Suna, E. *J. Am. Chem. Soc.* **2012**, *134*, 15436. (f) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924. (g) Telvekar, V. N.; Sasane, K. A. *Synth. Commun.* **2012**, *42*, 1085. (h) Xie, F.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 11862. (i) Fan, Y.; Wan, W.; Ma, G.; Gao, W.; Jiang, H.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 5733. (j) Azad, C. S.; Narula, A. K. *RSC Adv.* **2015**, *5*, 100223. (k) Li, P.; Zhao, J.; Xia, C.; Li, F. *Org. Chem. Fronti.* **2015**, *2*, 1313.

(21) Selected exmaples: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. (b) Demko, Z. P.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2113. (c) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (d) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600.

(22) (a) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666. (b) Schilling, C. I.; Jung, N.; Biskup, M.; Schepers, U.; Brase, S. *Chem. Soc. Rev.* **2011**, *40*, 4840. (c) van Berkel, S. S.; van Eldijk, M. B.; van Hest, J. C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8806. (d) Kohn, M.; Breinbauer, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106.

(23) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192.

(24) (a) Aceto, M. D.; Martin, B. R.; Uwaydah, I. M.; May, E. L.; Harris, L. S.; Izazolaconde, C.; Dewey, W. L.; Bradshaw, T. J.; Vincek, W. C. *J. Med. Chem.* **1979**, *22*, 174. (b) Mineur, Y. S.; Picciotto, M. R. *Trends Pharmacol Sci.* **2010**, *31*, 580.

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