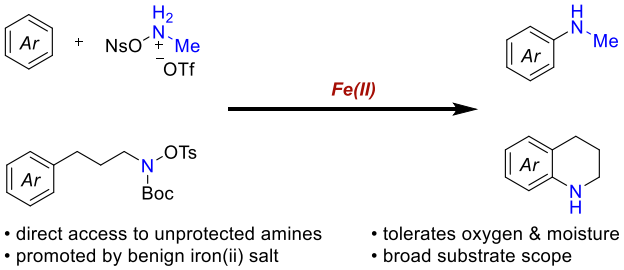
Synthesis of *N*-Alkyl Anilines from Arenes *via* Iron-Promoted Aromatic C–H Amination

Eric Falk, Valentina C. M. Gasser, Bill Morandi*

ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

Supporting Information Placeholder

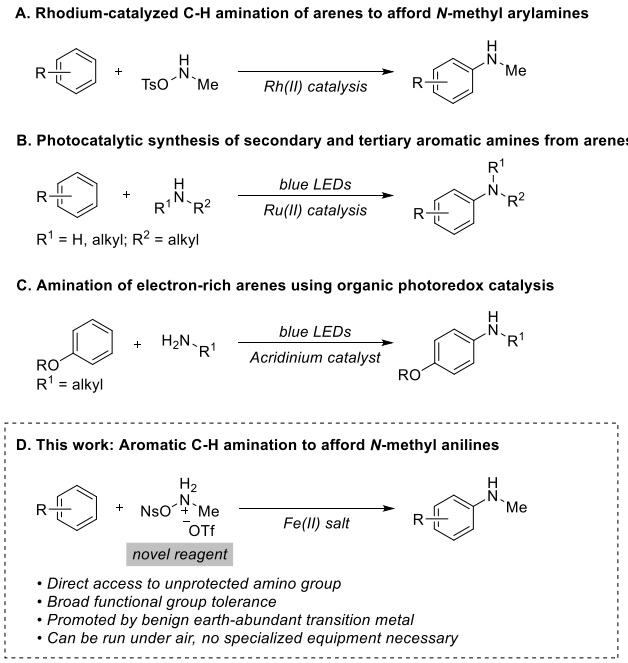


ABSTRACT: We report both an intermolecular C–H amination of arenes to access *N*-methylanilines and an intramolecular variant for the synthesis of tetrahydroquinolines. A newly developed, highly electrophilic aminating reagent was key for the direct synthesis of unprotected *N*-methylanilines from simple arenes. The reactions display a broad functional group tolerance and employ catalytic amounts of a benign iron salt under mild reaction conditions.

Due to the prevalence of aromatic amines in pharmaceuticals, agrochemicals, catalysts, dyes, and functional materials, the construction of C(sp^2)–N bonds is of particular importance.[1] Traditional approaches for the amination of arenes either involve multistep syntheses, harsh reaction conditions[2] or require a suitably placed handle for transition metal-catalyzed cross-coupling reactions such as the Buchwald-Hartwig amination or the Chan-Lam coupling.[3] Those limitations of the traditional methods call for complementary approaches to construct C(sp^2)–N bonds.

The C–H amination of arenes represents an alternative strategy for the synthesis of aromatic amines without the need for prefunctionalization. While early examples were still limited in yield and scope,[4] considerable progress has been made in the C–H amination of arenes in the last few years. Directing groups can assist in the C–H functionalization step but can be difficult to remove afterwards.[5] This issue can be circumvented by innate C–H amination of arenes which can be particularly attractive for late-stage functionalization since these methods do not rely on directing groups or other prefunctionalization of the arene.[6] However, many innate C–H aminations either require an excess of arene which presents an issue for valuable late-stage applications, or introduce the amine in a protected form through the use of nitrogen reagents substituted with strongly electron-withdrawing substituents,[7] thus requiring undesirable additional deprotection steps to access the unprotected aniline.[8] Nicewicz and coworkers could partially address this challenge by employing a photoredox strategy for the direct synthesis of primary anilines from arenes.[9] Following this report, several research groups, including ours, have reported methods for the C–H amination of simple arenes to access primary anilines.[10,11] In contrast, the direct synthesis of secondary aromatic amines from

Scheme 1. Context of this work.

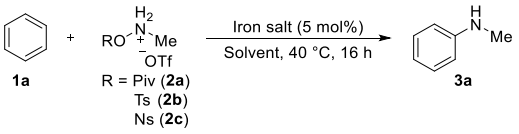


simple arenes has received considerably less attention, despite the broad occurrence of this motif in target-oriented synthesis. Kürti and Falck have developed a rhodium-catalyzed process for the synthesis of primary and secondary anilines using hydroxylamine derivatives as aminating reagents (Scheme 1A).[12] Subsequently, Falck and coworkers showed isolated examples of secondary anilines that can be accessed through a copper-mediated amination of arenes.[13] The group of Leonori has employed a ruthenium-catalyzed photoredox strategy to access secondary and tertiary anilines from arenes using alkyl amines (Scheme 1B).[14] A photoredox approach using an acridinium catalyst for the amination of highly electron-rich arenes with primary amines has been reported by Nicewicz (Scheme 1C) but this methodology has a limited scope of arenes and amines.[15] Therefore, there is still a necessity for the development of complementary, broadly applicable methods which do not rely on noble metal catalysts.

Herein, we report an iron-promoted C–H amination of arenes to access secondary aromatic amines employing hydroxylamine derivatives as aminating reagents (Scheme 1D). The reaction can be performed under air, does not require specialized equipment and is thus operationally simple. A modified, intramolecular protocol also unlocked the direct synthesis of tetrahydroquinolines, an important class of heterocycles.

We recently reported the design and synthesis of alkylated hydroxylamine-derived reagents for the synthesis of unprotected secondary and tertiary amines from alkenes through an aminochlorination reaction.[16] We thus questioned whether these reagents could enable the direct synthesis of unprotected secondary anilines from arenes *via* innate C–H amination. Initial investigations using the previously reported pivalate reagent (**2a**), however, resulted in low yields of the desired product **3a** (Table 1, entry 1). Given that tuning the leaving group ability of the reagent can be essential to achieve good reactivity,[10b] we next turned our attention to the synthesis of a new reagent bearing a OTs group (**2b**). This proved to be a crucial change, and the product **3a** was obtained in moderate yields (Entry 2).

Table 1. Selected optimization data for the *N*-methylamination of benzene.[a]

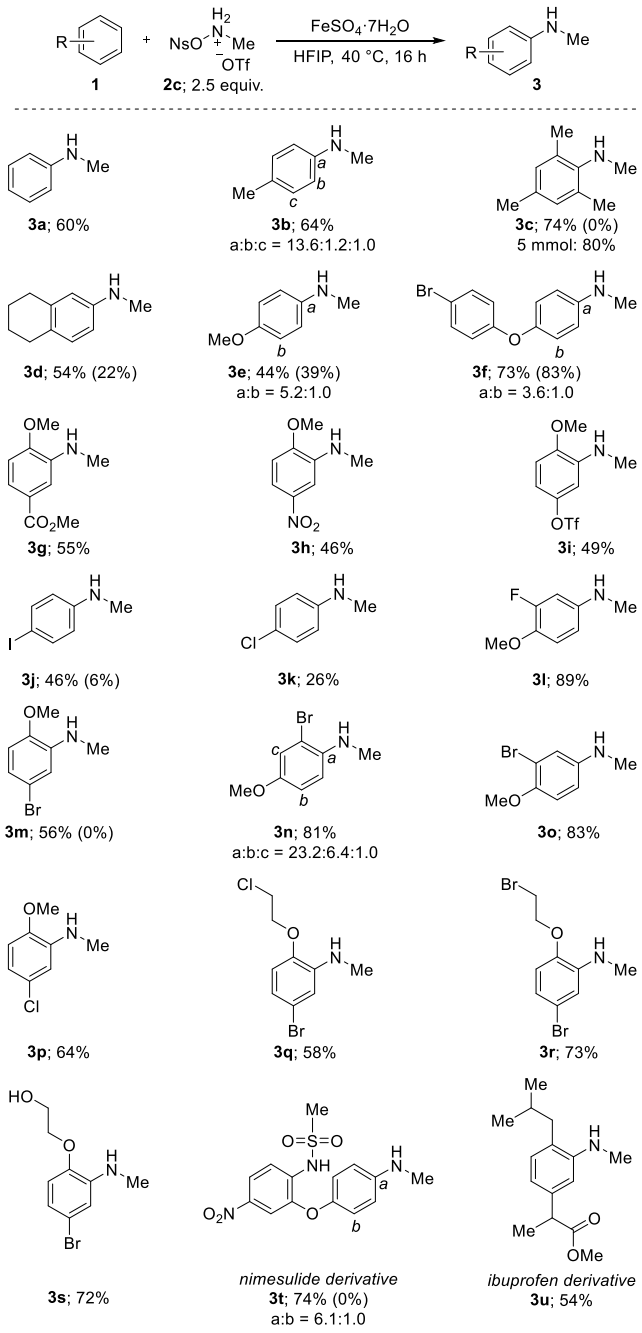


Entry	Iron salt	Solvent (ratio)	R	Yield [%][b]
1	$FeSO_4{\cdot}7H_2O$	HFIP	Piv	<5
2	$FeSO_4{\cdot}7H_2O$	HFIP	Ts	39
3	$FeSO_4{\cdot}7H_2O$	TFE	Ts	<5
4	$FeSO_4{\cdot}7H_2O$	$MeCN/H_2O$ (2:1)	Ts	<5
5	$Fe(acac)_2$	HFIP	Ts	37
6	$FeCl_2$	HFIP	Ts	38
7	FePc	HFIP	Ts	25
8	**$FeSO_4{\cdot}7H_2O$**	**HFIP**	**Ns**	**67**
9	-	HFIP	Ns	9
10	$FeSO_4{\cdot}7H_2O$	HFIP	Ns	21[c]

[a]Reaction conditions: Benzene (0.20 mmol), aminating reagent (**2**) (0.50 mmol), iron salt (0.01 mmol), solvent (0.2 mL), 40 °C, 16 h, under air. [b]Yields in % obtained by GC-FID using *n*-dodecane as internal standard. [c]Boc-protected aminating reagent precursor, triflic acid (0.50 mmol), 1 mL solvent. Ns = nosyl. Pc = phthalocyanin. Piv = pivaloyl. TFE = 2,2,2-trifluoroethanol. Ts = tosyl.

The evaluation of different solvents (Entries 2-4) showed that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was optimal for the transformation. Among different iron(II) salts that were investigated (Entries 2, 5-7), iron sulfate afforded the product in the highest yield. Interestingly, the yield of the reaction could be further increased by improving the leaving group ability of the sulfonyl group. Employing NsONHMe·TfOH (**2c**) as an aminating reagent afforded the desired product **3a** in 67% yield (Entry 8). The air- and moisture-stable reagent **2c**, which has not been reported previously, can be readily accessed in three steps from commercially available materials in 51% overall yield and is stable for several months if

Scheme 2. Arene substrate scope.[a]



[a]Reaction conditions: Arene (0.50 mmol), **2c** (1.25 mmol), $FeSO_4{\cdot}7H_2O$ (0.025 mmol), HFIP (0.5 mL), 40 °C, 16 h, under air. Yields are of isolated products; regioselectivity determined by NMR. Yields in parentheses correspond to the reactions performed without $FeSO_4{\cdot}7H_2O$.

stored at −20 °C. The reaction can be performed under air and does not require anhydrous solvents. Interestingly, when the Boc-protected precursor of the aminating reagent is deprotected *in-situ* by the addition of triflic acid, the desired product can be obtained in 21% yield (Entry 10).

Having the optimized conditions in hand, we set out to investigate the generality of the reaction on a range of arenes (Scheme 2). Both electron-neutral and electron-rich arenes could undergo *N*-methylamination in moderate to good yields. Unfortunately, electron-poor arenes proved to be unsuitable for the reported process. The more electron-poor the arene substrate was, the lower was the conversion and thus the yield of the amination reaction. However, on systems with an additional electron-donating group, even strongly electron-withdrawing groups such as ester (**3g**) and nitro (**3h**) groups were tolerated. (Pseudo)halides that are known to undergo oxidative addition with late transition metals remained untouched (**3i-k**, **3m-p**). Arenes bearing aliphatic halides (**3q**, **3r**) and alcohols (**3s**) are also suitable substrates. Substrates bearing multiple aryl groups react selectively on the more electron-rich arene, without any diamination being observed (**3f**, **3t**). Collectively, these results suggest that the reaction could be employed in late-stage functionalization.[17] To support this hypothesis, pharmaceuticals or derivatives thereof were used as substrates for the reaction. Nimesulide (**3t**) and ibuprofen methyl ester (**3u**) both underwent the *N*-methylamination reaction to afford the corresponding aniline. The preparative value of the methodology could be further demonstrated in a scale-up experiment where mesitylene was aminated on a 5 mmol scale to afford **3c** in an even slightly higher yield than on small scale.

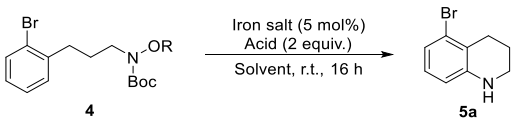
Control reactions revealed that the two very electron-rich anilines **3e** & **3f** can be obtained from the corresponding arenes without the use of $FeSO_4{\cdot}7H_2O$ in a similar yield compared to the optimized reaction conditions. Due to the high electrophilicity of the reagent **2c**, the iron-free reaction presumably proceeds in these two cases through a direct electrophilic aromatic substitution pathway. However, for less electron-rich substrates, the iron-free control reaction resulted in a yield of <25% (see Scheme 2 and SI for details). In light of these results, we next performed further control reactions using common radical initiators instead of the Fe-salt to test whether radical chain reaction mechanisms might be operating (see SI for details). When 5% benzoyl peroxide were used instead of the iron salt, *N*-methylaniline (**3a**) was obtained in a decreased yet significant 45% yield, while the use of AIBN and Cu(I)-salts did not deliver the product. Furthermore, when the iron-free reaction is heated to 60 °C instead of 40 °C, **3a** is obtained in 66% yield. The reaction, in this case, is likely initiated by thermal homolysis of the N–O bond. However, we noticed that the iron-free reaction had a slower rate when compared to the iron-promoted reaction, again demonstrating the activating effect of the Fe salt. Collectively, these results suggest that radical chain reactions could be partially involved in this reaction, particularly at higher temperatures, although it is not possible at this stage to determine whether iron solely acts as an efficient radical initiator or truly catalyzes the reaction. These observations are consistent with the work of Ritter and coworkers describing the synthesis of primary anilines from arenes.[10c]

We also investigated the regioselectivity of the reaction using bromoanisoles. While 4-bromoanisole and 2-bromoanisole were exclusively aminated at the *ortho* (**3m**) and *para* (**3o**) position relative to the methoxy group, respectively, the amination of 3-bromoanisole gave an inseparable mixture of three regioisomers (**3n**). Amination mainly occurred in *para* position to the methoxy group but some amination on the two *ortho* positions could also be observed. Generally, it can be said that amination usually occurs selectively at electronically activated positions. However, in substrates bearing only weakly directing substituents, additional regioisomers can be formed.

We next turned our attention to the synthesis of partially saturated *N*-heterocycles. Notably, in addition to the intermolecular *N*-methylamination, Kürti and Falck also reported the rhodium-catalyzed intramolecular *N*-alkylamination of electron-poor, -neutral and -rich

arenes.[12] In 2017, Bower demonstrated the trifluoroacetic acid-mediated intramolecular C–H amination of electron-neutral and electron-rich arenes.[18] The authors hypothesized that after an acid-promoted deprotection, the resulting protonated *O*-tosyl hydroxylammonium intermediate can be nucleophilically attacked by the tethered arene. Consistent with this hypothesis, they observed that electron-poor substrates did not undergo intramolecular C–H amination in the absence of a metal catalyst. We

Table 2. Selected optimization data for the intramolecular C–H amination.[a]



4 5a

Entry	Iron salt	Solvent (ratio)	R	Acid	Yield [%][b]
1	-	HFIP	Ts	TFA	6
2	$Fe(acac)_2$	HFIP	Ts	TFA	42
3	$FeCl_2$	HFIP	Ts	TFA	37
4	**$FeSO_4{\cdot}7H_2O$**	**HFIP**	**Ts**	**TFA**	**45**
5	$FeSO_4{\cdot}7H_2O$	HFIP	Ts	AcOH	36
6	$FeSO_4{\cdot}7H_2O$	HFIP	Ts	TfOH	<5
7	$FeSO_4{\cdot}7H_2O$	TFE	Ts	TFA	<5
8	$FeSO_4{\cdot}7H_2O$	MeCN/H_2O (2:1)	Ts	TFA	<5
9	$FeSO_4{\cdot}7H_2O$	HFIP	Ms	TFA	41
10	$FeSO_4{\cdot}7H_2O$	HFIP	Ns	TFA	33

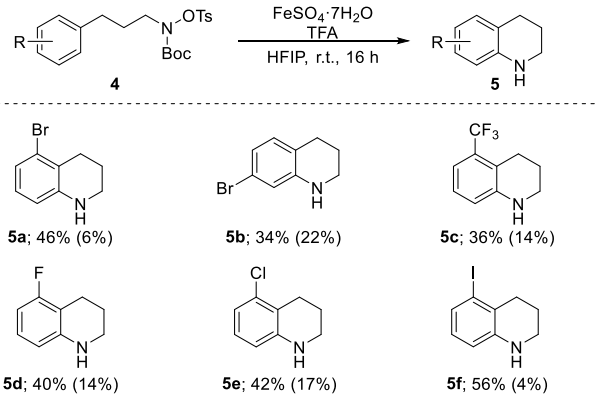
[a]Reaction conditions: **4** (0.050 mmol), iron salt (0.0025 mmol), solvent (0.5 mL), room temperature, 16 h, under air. [b]Yields in % obtained by NMR using CH_2Br_2 as internal standard. Ms = mesyl. Tf = triflyl. TFA = trifluoroacetic acid.

thus set out to investigate whether a benign iron salt can also promote the intramolecular *N*-alkylamination of electron-deficient substrates.[19]

The intramolecular aromatic C–H amination was optimized on the bromobenzene derivative **4a**, which only gave traces of aryl C–H amination in the absence of a transition metal (Table 2, entry 1). $FeSO_4$•$7H_2O$ was identified as the most suitable in an evaluation of different iron(II) salts (Entries 2-4). TFA proved to be the optimal acid to promote the *in situ* Boc-deprotection of the starting material (Entries 4-6). Interestingly, the use of triflic acid did not result in the formation of the desired product **5a**, despite the established efficiency of triflate salts as reagents in our intermolecular *N*-methylamination of arenes. An evaluation of different solvents revealed that HFIP is the optimal solvent for this transformation (Entries 4, 7 & 8). Interestingly, varying the *O*-substituent only had a minor impact on the reaction outcome. The use of an *O*-tosyl group afforded the desired product **5a** in the highest yield (Entries 4, 9 & 10).

Having the optimized conditions in hand, we briefly evaluated the substrate scope of the transformation (Scheme 3). We focused on arenes carrying substituents that deactivate the aromatic ring and thus do not undergo aryl C–H amination in high yields in the absence of a transition metal. *Ortho*- and *para*-substituted bromobenzenes were both suitable substrates for the transformation (**5a** & **5b**). The *meta*-substituted analog afforded the aminated product as well but due to the *ortho*/*para* directing effect of bromine, the reaction also proceeded in a similar yield in the absence of the iron salt and was thus outside of the scope. The strongly electron-deficient trifluorotoluene derivative (**5c**) was also a suitable substrate for this process. Furthermore, aryl fluorides (**5d**), chlorides (**5e**) and iodides (**5f**) could all be converted to their tetrahydroquinoline analogs in moderate yields.

Scheme 3. Arene scope intramolecular C–H amination.[a]



[a]Reaction conditions: Arene (0.50 mmol), $FeSO_4{\cdot}7H_2O$ (0.025 mmol), TFA (1.00 mmol), HFIP (5 mL), room temperature, 16 h, under air. Yields are of isolated products. Yields in parentheses correspond to the reactions performed without $FeSO_4{\cdot}7H_2O$.

In conclusion, we have developed processes for the synthesis of *N*-methylanilines and tetrahydroquinolines from simple arenes. A benign iron(II) salt enables both transformations. The reactions are not sensitive to air or moisture and can be performed on the benchtop under mild reaction conditions. The generality of the transformations was shown on a broad scope of arenes bearing unprotected polar functional groups often found in biologically active molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: bill.morandi@org.chem.ethz.ch

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge funding from the Swiss National Science Foundation (SNSF 184658) and ETH Zürich. We thank the NMR service and the Molecular and Biomolecular Analysis Service (MoBiAS) of ETH Zürich for technical support. We further thank Laura Gürtler (ETH Zürich) for experimental assistance and our group for critical proofreading of the manuscript.

REFERENCES

(1) (a) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004. (b) Ricci, A., Ed. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, 2008. (c) Vogt, P. F.; Gerulis, J. J. Aromatic amines. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2011. (d) Froidevaux, V.; Negrell, C.; Caillol, S.; Pascault, J.-P.; Boutevin, B. Biobased Amines: From Synthesis to Polymers; Present and Future. *Chem. Rev.* **2016**, *116*, 14181–14224.

(2) Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrius-Landeros, F. Synthesis of anilines. In *The chemistry of anilines*; John Wiley & Sons: New York, 2007.

(3) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348–1350. (b) Louie, J.; Hartwig, J. F. Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. *Tetrahedron Lett.* **1995**, *36*, 3609–3612. (c) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P., Winters, M. P. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (d) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937–2940. (e) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl C–N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

(4) (a) Keller, R. N.; Smith, P. A. S. Direct Aromatic Amination: A New Reaction of Hydroxylamine-*O*-sulfonic acid. *J. Am. Chem. Soc.* **1944**, *66*, 1122–1124. (b) Kovacic, P.; Bennett, R. P. Aromatic Amination with Hydroxylamine-O-sulfonic Acid. *J. Am. Chem. Soc.* **1961**, *83*, 221–224. (c) Minisci, F. Novel Applications of Free-Radical Reactions in Preparative Organic Chemistry. *Synthesis*, **1973**, *1973*, 1–24. (d) Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. Polar Effects in Free Radical Reactions. Homolytic Aromatic Amination by the Amino Radical Cation, $\bullet^{+}NH_3$: Reactivity and Selectivity. *J. Org. Chem.* **1984**, *49*, 4479–4482. (e) Day, J. C.; Katsaros, M. G.; Kocher, W. D.; Scott, A. E.; Skell, P. S. Addition reactions of imidyl radicals with olefins and arenes. *J. Am. Chem. Soc.* **1978**, *100*, 1950–1951. (f) Lu, F.-L.; Naguib, Y. M. A.; Kitadani, M.; Chow, Y. L. An investigation of the photodecomposition of *N*-bromosuccinimide; the generation and reactivity of succinimidyl radical. *Can. J. Chem.* **1979**, *57*, 1967–1976.

(5) For selected examples, see: (a) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. Pd-Catalyzed Intermolecular C–H Amination with Alkylamines. *J. Am. Chem. Soc.* **2011**, *133*, 7652–7655. (b) Tran, L. D.; Roane, J.; Daugulis, O. Directed Amination of Non-Acidic Arene C–H bonds by a Copper-Silver Catalytic System. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043–6046. (c) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. Ligand-Promoted *meta*-C–H Amination and Alkynylation. *J. Am. Chem. Soc.* **2016**, *138*, 14092–14099. (d) Kim, H.; Heo, J.; Kim, J.; Baik, M.-H.; Chang, S. Copper-Mediated Amination of Aryl C–H Bonds with the Direct Use of Aqueous Ammonia via a Disproportionation Pathway. *J. Am. Chem. Soc.* **2018**, *140*, 14350–14356. (e) Anugu, R. R.; Munnuri, S.; Falck J. R. Picolinate Directed Arene meta-C–H Amination via $FeCl_3$ Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 5266–5271.

(6) (a) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576. (b) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018**, *10*, 383–394. (c) Börgel, J.; Ritter, T.; Late-Stage Functionalization. *Chem* **2020**, *6*, 1877–1887.

(7) For a review, see: (a) Jiao, J.; Murakami, K.; Itami, K. Catalytic Methods for Aromatic C–H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules. *ACS Catal.* **2016**, *6*, 610–633 and references cited therein. For selected examples, see: (b) Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. A Mild, Ferrocene-Catalyzed C–H Imidation of (Hetero)Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 5279–5282. (c) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *N*-Aminopyridinium Salts as Precursors for *N*-Centered Radicals – Direct Amidation of Arenes and Heteroarenes. *Org. Lett.* **2015**, *17*, 254–257. (d) Xie, W.; Yoon, J. H.; Chang, S. (NHC)Cu-Catalyzed Mild C–H Amidation of (Hetero)arenes with Deprotectable Carbamates: Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2016**, *138*, 12605–12614. (e) Davies, J.; Svejstrup, T. D.; Reina Fernandez, D.; Sheikh, N. S.; Leonori, D.; Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and *N*-Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 8092–8095. (f) Hu, X.; Zhang, G.; Nie, L.; Kong, T.; Lei, A. Electrochemical oxidation induced intermolecular aromatic C–H imidation. *Nat. Commun.* **2019**, *10*, 5467.

(8) (a) Trost, B. M. The atom economy – a search for synthetic efficiency. *Science* **1991**, *254*, 1471–1477. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008**, *41*, 40– 49. (c) Young, I. S.; Baran, P. S. Protecting-group-free synthesis as an opportunity for invention. *Nat. Chem.* **2009**, *1*, 193–205.

(9) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-selective arene C-H amination via photoredox catalysis. *Science* **2015**, *349*, 1326–1330.

(10) (a) Legnani, L.; Prina Cerai, G.; Morandi, B. Direct and Practical Synthesis of Primary Anilines through Iron-Catalyzed C–H Bond Amination. *ACS Catal.* **2016**, *6*, 8162–8165. (b) Liu, J.; Wu, K.; Shen, T.; Liang, Y.; Zou, M.; Zhu, Y.; Li, X.; Li, X.; Jiao, N. Fe-Catalyzed Amination of (Hetero)Arenes with a Redox-Active Aminating Reagent under Mild Conditions. *Chem. Eur. J.* **2017**, *23*, 563–567. (c) D'Amato, E. M.; Börgel, J.; Ritter, T. Aromatic C–H Amination in hexafluoroisopropanol. *Chem. Sci.* **2019**, *10*, 2424–2428. (d) See, Y. Y.; Sanford, M. S. C–H Amination of Arenes with Hydroxylamine. *Org. Lett.* **2020**, *22*, 2931–2934.

(11) A complementary approach is C–H amination *via* pyridinium cations that are readily converted to anilines: (a) Morofuji, T.; Shimizu, A.; Yoshida, J. Electrochemical C–H Amination: Synthesis of Aromatic Primary Amines *via N*-Arylpyridinium Ions. *J. Am. Chem. Soc.* **2013**, *135*, 5000–5003. (b) Rössler, S. L.; Jelier, B. J.; Tripet, P. F.; Shemet, A.; Jeschke, G.; Togni, A.; Carreira, E. M. Pyridyl radical cation for C–H amination of arenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 526–531. (c) Ham, W.; Hillenbrand, J.; Jacq, J.; Genicot, C.; Ritter, T. Divergent late-stage (hetero)aryl C–H amination by the pyridinium radical cation. *Angew. Chem. Int. Ed.* **2019**, *58*, 532–536.

(12) Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. Dirhodium-catalyzed C–H arene amination using hydroxylamines. *Science* **2016**, *353*, 1144–1147.

(13) Munnuri, S.; Anugu, R. R.; Falck, J. R. Cu(II)-Mediated *N*–H and *N*-Alkyl Aryl Amination and Olefin Aziridination. *Org. Lett.* **2019**, *21*, 1926–1929.

(14) (a) Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. Practical and regioselective amination of arenes using alkyl amines. *Nat. Chem.* **2019**, *11*, 426–433. For the synthesis of tertiary anilines from arenes, see: (b) Svejstrup, T. D.; Ruffoni, A.; Juliá, F.; Aubert, V. M.; Leonori, D. Synthesis of Arylamines via Aminium Radicals. *Angew. Chem. Int. Ed.* **2017**, *56*, 14948–14952.

(15) Margrey, K. A.; Levens, A.; Nicewicz, D. A. Direct Aryl C–H Amination with Primary Amines Using Organic Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2017**, *56*, 15644–15648.

(16) (a) Falk, E; Makai, S.; Delcaillau, T.; Gürtler, L.; Morandi B. Design and Scalable Synthesis of *N*-Alkyl-Hydroxylamine Reagents for the Direct, Iron-Catalyzed Installation of Medicinally Relevant Amines. *Angew. Chem. Int. Ed.* **2020**, *59*, 21064–21071. For other iron-catalyzed amination reactions developed by our group, see: (b) Legnani, L.; Morandi, B. Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phthalocyanine. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248–2251. (c) Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. Efficient access to unprotected primary amines by iron-catalyzed aminochlorination of alkenes. *Science* **2018**, *362*, 434–439. (d) Makai, S.; Falk, E.; Morandi, B. Direct Synthesis of Unprotected 2-Azidoamines from Alkenes via

an Iron-Catalyzed Difunctionalization Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 21548–21555. (e) Chatterjee, S.; Makai, S.; Morandi, B. Hydroxylamine-Derived Reagent as a Dual Oxidant and Amino Group Donor for the Iron-Catalyzed Preparation of Unprotected Sulfinamides from Thiols. *Angew. Chem. Int. Ed.* **2021**, 60, 758-765.

(17) For a late-stage application of C–H amination, see: Hou, S.-H.; Prichina, A. Y.; Zhang, M.; Dong, G. Asymmetric Total Syntheses of Di- and Sesquiterpenoids by Catalytic C–C Activation of Cyclopentanones. *Angew. Chem. Int. Ed.* **2020**. *59*, 7848–7856.

(18) Farndon, J. J.; Ma, X.; Bower, J. F. Transition Metal Free C–N Bond Forming Dearomatizations and Aryl C–H Aminations by in Situ Release of a Hydroxylamine-Based Aminating Agent. *J. Am. Chem. Soc.* **2017**, *139*, 14005–14008.

(19) For an iron-catalyzed synthesis of *N*-substituted tetrahydroisoquinolines, see: Douglas, G. E.; Raw, S. A.; Marsden, S. P. Iron-Catalysed Direct Aromatic Amination with *N*-Chloramines. *Eur. J. Org. Chem.* **2019**, 5508–5514.