COMMUNICATION

# Iron-Catalyzed C(sp$^3$)–H Functionalization of *N,N*-Dimethylanilines with Isocyanides

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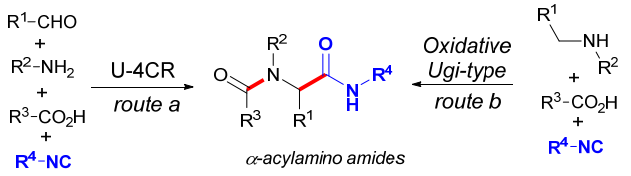
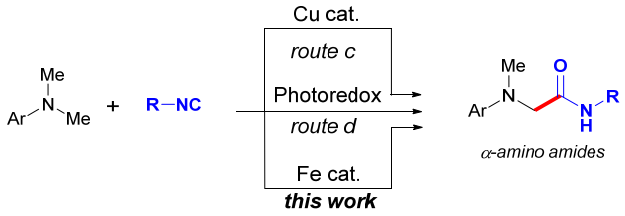
**An efficient ligand-free Fe-catalyzed oxidative Ugi-type reaction toward the assembly of α-amino amides and short peptides is described. The reaction proceeds through the α-C(sp$^3$)–H oxidation of *N,N*-dimethylanilines and further nucleophilic attack of the resulting iminium species by isocyanides. Additive screening showed that judicious choice of the carboxylic acid could lead to the formation of α-amino imides via a 3-component reaction. The process occurs with operational simplicity and is compatible with a variety of sensitive functional groups.**

Multicomponent reactions[1] provide efficient and rapid assembly of small fragments to create molecular diversity in a one-pot practical fashion, thus offering wide applications in the area of natural product synthesis and drug discovery.[2] One of the most utilized methods is the Ugi four-component reaction (U-4CR),[3] giving straightforward access to α-acylamino amides[4] which are prevalent compounds in a plethora of pharmaceuticals and medicinally relevant compounds.




Scheme 1 Ugi and oxidative Ugi-type reactions

The classical U-4CR involves the *in situ* formation of an imine from combining a primary amine and an aldehyde, and subsequent reaction with an isocyanide and a carboxylic acid furnishes the corresponding α-acylamino amides[5] (Scheme 1, *route a*). Despite its efficiency, the synthetic scope of the process is often limited and hence the development of alternative, yet sustainable, protocols represents a challenging task of paramount significance in organic chemistry. In this regard, oxidative multicomponent reactions upon secondary or tertiary amines have emerged as convenient variants of the classical Ugi reaction, which occurred through the *in situ* oxidation of the corresponding amines[6] (Scheme 1, *route b*), hence broadening the scope to the formation of structurally related α-amino amides. In this respect, Zhu and co-workers introduced an IBX-mediated Ugi-type reaction of tetrahydroisoquinolines.[6k] More recently, Xie and co-workers elegantly implemented the use of copper catalysis in combination with *tert*-butyl hydroperoxide (TBHP) as oxidant upon *N,N*-dialkylanilines (Scheme 2, *route c*).[6d,h-i] Rueping[6e-g] and Stubbs[6b] have reported a variety of photoredox-catalyzed Ugi-type reactions using tertiary amines (Scheme 2, *route d*). Although significant advantages have been achieved, it is still a crucial challenge to develop robust and general catalytic approaches for the synthesis of amino acid and peptide derivatives.




Scheme 2 Oxidative Ugi-type reactions with tertiary anilines

Given our interest in sustainable C–H functionalization events,[7] we envisioned the advantageous use of environmentally friendly, easy-to-handle, non-toxic and cheap iron salts[8] as alternative catalysts in oxidative Ugi-type reactions. Based on the known ability of iron catalysts to activate the α-C(sp$^3$)–H bond neighboring to the amino group,[9,10] we hypothesized that the resulting electrophilic *N*-aryl iminium ion would be prone to react with a nucleophilic isocyanide through an Ugi-type reaction pathway (Scheme 2). If successful, such iron-based protocol would complement existing methodologies[6] and constitute a cost-efficient and eco-friendly route toward the assembly of α-amino amides and short peptides. In this communication, we describe an unprecedented Ugi-type reaction upon *N,N*-dimethylanilines and isocyanides featuring the practical use of an Fe(II)-TBHP oxidizing system. Importantly, the employment of picolinic acid resulted in the formation of α-amino imides through a three-component reaction.

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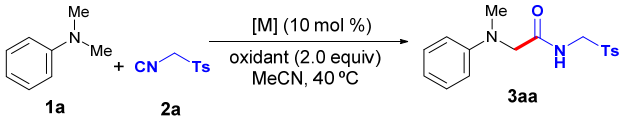
*† Electronic Supplementary Information (ESI) available.*

Table 1 Optimization for the Fe-catalyzed oxidative Ugi-type reaction[a]

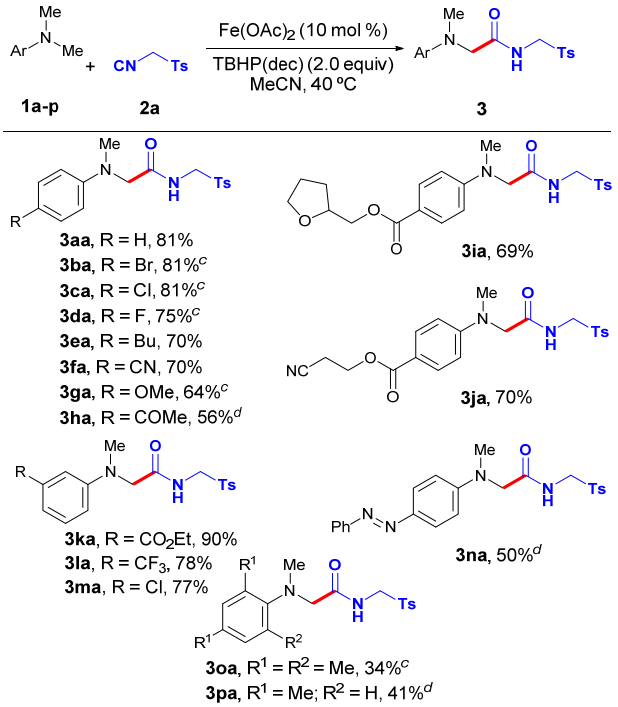



1a 2a 3aa

| Entry | [M] | Oxidant | 3aa (%)[b] |
|---|---|---|---|
| 1 | $Fe(OAc)_2$ | none | traces |
| 2 | $Fe(OAc)_2$ | TBHP(dec) | 64 |
| 3 | $Fe(OAc)_2$ | TBHP(aq) | 23 |
| 4 | $Fe(OAc)_2$ | $H_2O_2$ | 23 |
| 5 | $Fe(OAc)_2$ | $O_2$ (1 atm) | 29 |
| 6 | $Fe(OAc)_2$ | DDQ | 0 |
| 7 | none | TBHP(dec) | traces |
| 8[c] | $Fe(OAc)_2$ | TBHP(dec) | 81 (91)[d] |
| 9[c] | $FeCl_2$ | TBHP(dec) | 10 |
| 10[c] | $FeF_2$ | TBHP(dec) | 42 |
| 11[c] | $FeCl_3$ | TBHP(dec) | traces |
| 12[c] | $FeBr_3$ | TBHP(dec) | 20 |
| 13[c] | $Fe(OAc)_2$ | TBHP(dec) | 75[e] (74)[f] |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [M] (10 mol %), oxidant (2.0 equiv), MeCN (2.0 mL) at 40 ºC for 24 h under argon. [b] Yield of isolated product after column chro-matography. [c] **1a** (1.0 mmol). [d] 1.0 gram-scale of **2a**. [e] under air. [f] TBHP(dec) (1.0 equiv). TBHP(dec) = *t*BuOOH 5.0-6.0 M in decane; TBHP(aq) = *t*BuOOH 70% in $H_2O$.

Table 2 Fe-catalyzed C($sp^3$)–H functionalization of *N,N*-dimethylanilines [a,b]



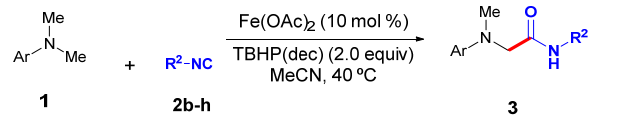

[a] As for Table 1, entry 8. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Addition of AcOH (2.0 equiv). [d] Reaction performed at 70 ºC.

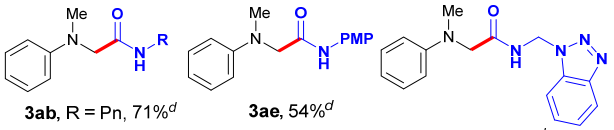
We initially selected the coupling of *N,N*-dimethylaniline (**1a**) and *p*-toluenesulfonylmethyl isocyanide (**2a**) as the model system to evaluate the feasibility of our approach (Table 1). We anticipated that the nature of the metal source and the oxidant would have a profound impact on reactivity and accordingly the effect of such variables was systematically examined. After some experimentation,[11] we found that the use of bench-stable $Fe(OAc)_2$ in combination with inexpensive TBHP(dec) as oxidant turned out to be the most effective catalyst system (entry 2). Curiously, the use of an aqueous solution of TBHP was found less efficient (entry 3). Likewise, other oxidants such as $H_2O_2$, molecular oxygen or DDQ (entries 4-6) provided much lower yields of the corresponding amide **3aa**. The use of excess of **1a** was shown to be beneficial and resulted in the formation of **3aa** in a remarkable 81% yield (entry 8). Other iron and cobalt salts[11] afforded comparatively lower yields than $Fe(OAc)_2$ (entries 9-12). It is worth noting that the performance of the process under air or with just one equivalent of the oxidant furnished **3aa** in useful synthetic yields (entry 13), thus evidencing the robustness of our catalyst system. As expected, control experiments established the crucial role of both oxidant and iron source as just traces of **3aa** were detected in their absence (entries 1 and 7, respectively). Importantly, our Fe-catalyzed Ugi-type reaction can be effected in a gram-scale to provide amide **3aa** in 91% yield (entry 8), hence constituting an additional bonus from a practical and operational point of view.

With the optimal conditions in hand, we next evaluated the synthetic scope of the Fe-catalyzed Ugi-type reaction. As depicted on Table 2, a wide range of *N,N*-dimethylanilines underwent the corresponding coupling reaction in good to excellent yields. Remarkably, numerous functional groups such as halides (**3ba**, **3ca**, **3da**, **3la**, **3ma**), nitriles (**3fa**, **3ja**), ethers (**3ga**, **3ia**), esters (**3ia**, **3ja**, **3ka**), ketones (**3ha**), and even azobenzenes (**3na**) were perfectly accommodated. As a result, our Fe-catalyzed approach outperforms Cu-based methods[6d,h-i] for the synthesis of α-amino amides bearing a variety of synthetically relevant moieties. Interestingly, the addition of acetic acid was crucial to obtain in certain cases the target α-amino amides **3** in high yields. The latter reveals the subtleties of our iron-catalyzed process given that the use of carboxylic acids have commonly resulted in the formation of α-amino imides through a 3-component reaction.[6d,i-k] Of particular importance are **3ia** and **3ja** where high chemoselectivity was achieved toward the preferential activation of α-C($sp^3$)–H bonds of *N,N*-dimethylanilines *versus* the C($sp^3$)–H bonds adjacent to a cyclic ether[10b] or a cyano group,[12] respectively. The use of *ortho* substituted anilines **1o-p** provided the target products, albeit in moderate yields. Unfortunately, no reaction occurred when employing *N,N*-diethyl or *N,N*-dibenzylanilines as substrates. Besides, aliphatic amines such as pyrrolidine and *N*-methylmorpholine were inactive under our reaction conditons.

Gratifyingly, numerous isocyanides smoothly underwent the Ugi-type reaction to afford the corresponding amino amides **3** in moderate to good yields (Table 3). Not only alkyl isocyanides **2b-d** but also a SET-sensitive aromatic derivative **2e** were found competent coupling partners for the Fe-catalyzed oxidative coupling. Likewise, biologically relevant compounds such as benzimidazole (**3af**), dipeptides (**3ag**, **3bg**), and phosphonate derivative (**3bh**) are within reach upon the use of the corresponding functionalized isocyanides **2f-h**. Notably, once again the addition of acetic acid was crucial for the process to occur in certain cases. In-trigued by its positive effect on the reaction outcome, we conducted a more detailed study on the influence on the process of

Table 3 Synthetic scope with isocyanides [a,b]

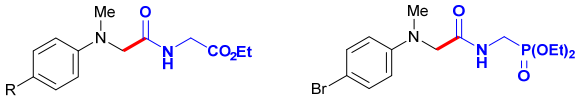



**3ab**, R = Pn, 71%[d]
**3ac**, R = *t*Bu, 44%
**3ad**, R = Cy, 48%[c]

**3ae**, 54%[d]

**3af**, 54%[c,d]



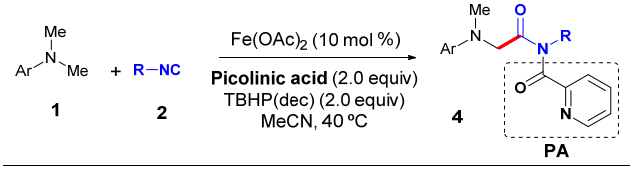

**3ag**, R = H, 77%[c,d]
**3bg**, R = Cl, 47%[c,d]

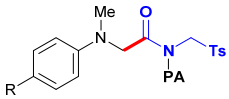
**3bh**, 81%[c,d]

[a] As for Table 1, entry 8. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Addition of AcOH (2.0 equiv). [d] Reaction performed at 70 ºC.

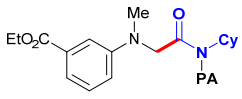
different carboxylic acids (Table S2)[11] and we found that the addition of both acetic acid and 1-adamantanecarboxylic acid improved the formation of the corresponding α-amino amides.[13] In striking contrast, the use of picolinic acid resulted in the preferential formation of the corresponding picolinamides **4** through an iron-catalyzed 3-component Ugi-type reaction. As shown on Table 4, a short family of α-amino amides of high structural complexity were easily prepared by simply mixing the corresponding anilines, isocyanides and picolonic acid in the presence of the cost-efficient Fe(II)-TBHP system. The latter represents an added bonus of our methodology given the widespread utility of picolinamide derivatives as versatile substrates in the realm of C–H activation[14] as well as medicinal chemistry.

Table 4 Scope for multicomponent reaction [a,b]

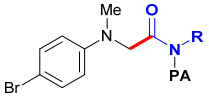


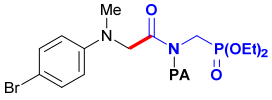

**4aa**, R = H, 49%
**4ba**, R = Br, 64%




**4kd**, 61%



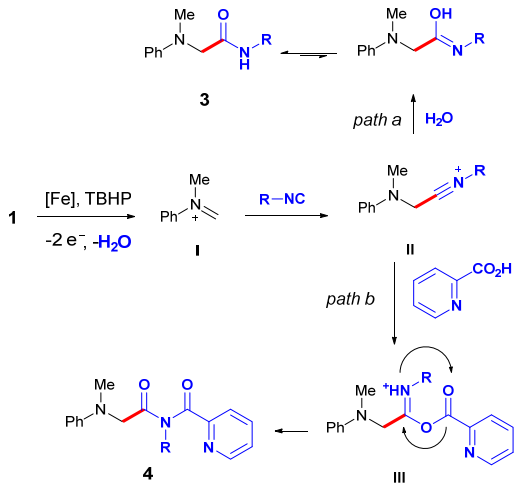

**4bb**, R = $(CH_2)_4CH_3$, 63%
**4bd**, R = Cy, 61%




**4bh**, 63%

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.25 mmol), $Fe(OAc)_2$ (10 mol %), picolinic acid (2.0 equiv), TBHP(dec) (2.0 equiv), MeCN (1.0 mL) at 40 ºC for 24 h under argon. [b] Yield of iso-lated product after column chromatography, average of at least two independent runs.

To gain some insights into the mechanism, we performed the reaction of *N,N*-dimethylaniline **1a** with isocyanide **2a** in the presence of a variety of radical scavengers. Whereas the oxidative coupling was entirely inhibited in the presence of one equivalent of both TEMPO and 1,1-diphenylethylene, which may support the intermediacy of radical intermediates; the addition of BHT [3,5-di(*tert*-butyl)-4-hydroxytoluene] produced **3aa** in a much lower 27% yield. Likewise, the performance of the process under an oxygen atmosphere provided amino amide **3aa** in 41% yield. The latter experiments indicate that the carbon-center radical's oxidation through a SET process to the iminium ion **I** may be faster than its trapping with the radical inhibitor. However, owing to the controversial discussions on the nature of the active species within the oxidation of tertiary amines to the corresponding iminium ion by an Fe(II)/ROOH system,[15] we believe *in depth* mechanistic studies are required to disclose those elemental SET and HAT events. Accordingly, a tentative mechanistic scenario is disclosed in Scheme 3. The reaction would start by a first $C(sp^3)$–H oxidation of *N,N*-dimethylaniline **1** in the presence of [Fe]/TBHP to generate iminium ion **I**.[15] Next, the subsequent nucleophilic attack of the highly reactive isocyanide **2** would produce nitrilium ion **II**, which would be eventually trapped by water[16] to deliver the target amide **3** (Scheme 3, *path a*). In the presence of picolinic acid, nitrilium **II** would alternatively afford intermediate **III** where an acyl migration[17] would eventually furnish imide **4** (Scheme 3, *path b*).




Scheme 3 Proposed mechanism

In summary, we have demonstrated the applicability and practicality of iron catalysis for the performance of oxidative Ugi-type reactions toward the modular synthesis of α-amino amides. Notably, our method represents an attractive, yet complementary, strategy which occurs with high operational simplicity and remarkably increases the synthetic scope, being found compatible with a variety of biologically relevant functional groups. On the basis of the inherent cutting-edge features of iron salts, this protocol could find potential applications of utmost importance in peptide chemistry and industrial environments. Furthermore, we believe that our method can be the foundation for future discoveries in the challenging area of Fe-catalyzed $C(sp^3)$-H activation processes.

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## Notes and references

1 (*a*) J.-P. Wan, L. Gan and Y. Liu, Y. *Org. Biomol. Chem.,* 2017, **15**, 9031; (*b*) B. H. Rotstein, S. Zaretsky, V. Rai and A. K. Yudin, *Chem. Rev.,* 2014, **114**, 8323; (*c*) S. Brauch, S. S. van Berkel and B. Westermann, *Chem. Soc. Rev.,* 2014, **42**, 4948.

2 (*a*) B. B. Toure and D. G. Hall, *Chem. Rev.,* 2009, **109**, 4439; (*b*) L. F. Tietze and A. Modi, *Med. Res. Rev.,* 2000, **20**, 304.

3 (*a*) G. C. Tron, *Eur. J. Org. Chem.,* 2013, **10**, 1849; (*b*) L. A. Wessjohann, C. R. B. Rhoden, D. G. Rivera and O. E. Vercillo, *Top. Heterocycl. Chem.,* 2010, **23**, 199; (*c*) A. Dömling, *Chem. Rev.,* 2006, **106**, 17; (*d*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.,* 2000, **39**, 3168.

4 (*a*) K. E. Schwieter and J. N. Johnston, *J. Am. Chem. Soc.,* 2016, **138**, 14160; (*b*) M. A. T. Blaskovich, *J. Med. Chem.,* 2016, **59**, 10807.

5 (*a*) For a recent variant toward the synthesis of β-aminoamides involving the use of ynamides, see: B. Huang, L. Zeng, Y. Shen and S. Cui, *Angew. Chem., Int. Ed.,* 2017, **56**, 4565; (*b*) For the alternative use of phenols instead of carboxylic acids, see: L. E. Kaïm, L. Grimaud and J. Oble, *Angew. Chem., Int. Ed.,* 2005, **44**, 7961.

6 (*a*) K. Singh, A. Kaur, V. S. Mithu and S. Sharma, *J. Org. Chem.,* 2017, **82**, 5285; (*b*) M. N. Gandy, C. L. Raston and K. A. Stubbs, *Chem. Commun.,* 2015, **51**, 11041; (*c*) S. U. Dighe, S. Kolle and S. Batra, *Eur. J. Org. Chem.,* 2015, **19**, 4238; (*d*) C. Xie and L. Han, *Tetrahedron Lett.,* 2014, **55**, 240; (*e*) M. Rueping, C. Vila and T. Bootwhicha, *ACS Catal.,* 2013, **3**, 1676; (*f*) M. Rueping and C. Vila, *Org. Lett.,* 2013, **15**, 2092; (*g*) C. Vila and M. Rueping, *Green Chem.,* 2013, **15**, 2056; (*h*) X. Ye, C. Xie, R. Huang and J. Liu, *Synlett,* 2012, **23**, 409; (*i*) X. Ye, C. Xie, Y. Pan, L. Han and T. Xie, *Org. Lett.,* 2010, **12**, 4240; (*j*) G. Jiang, J. Chen, J.-S. Huang and C.-M. Che, *Org. Lett.,* 2009, **11**, 4568; (*k*) T. Ngouansavanh and J. Zhu, *Angew. Chem. Int. Ed.,* 2007, **46**, 5775.

7 (*a*) M. San Segundo, I. Guerrero and A. Correa, *Org. Lett.*, 2017, **19**, 5288; (*b*) A. Goitia, E. Gómez-Bengoa and A. Correa, *Org. Lett.,* 2017, *19*, 962; (*c*) A. Irastorza, J. M. Aizpurua and A. Correa, *Org. Lett.,* 2016, **18**, 1080; (*d*) A. Correa, B. Fiser and E. Gómez-Bengoa, *Chem. Commun.,* 2015, **51**, 13365.

8 For selected reviews: (*a*) Topics in Current Chemistry, *Ni- and Fe- Based Cross-Coupling Reactions*, ed. A. Correa, Springer International Publishing, Berlin, vol. 374, 2016; (*b*) A. Fürstner, *ACS Cent. Sci.,* 2016, **2**, 778; (*c*) I. Bauer and H.-J. Knölker, *Chem. Rev.,* 2015, **115**, 3170; (*d*) F. Jia and Z. Li, *Org. Chem. Front.,* 2014, **1**, 194; (*e*) K. Gopalaiah, *Chem. Rev.,* 2013, **113**, 3248; (*f*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.,* 2011, **111**, 1293; (*g*) A. Correa, O. García-Mancheño and C. Bolm, *Chem. Soc. Rev.,* 2008, **37**, 1108; (*h*) C. Bolm, J. Legros, J. L. Paih and L. Zani, *Chem. Rev.,* 2004, **104**, 6217; (*i*) A. Fürstner and R. Martin, *Chem. Lett.,* 2005, 624.

9 See for example: (*a*) M.-N. Zhao, L. Yu, R.-R. Hui, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *ACS Catal.,* 2016, **6**, 3473; (*b*) M. O. Ratnikov, X. Xu and M. P. Doyle, *J. Am. Chem. Soc.,* 2013, **135**, 9475; (*c*) W. Liu, J. Liu, D. Ogawa, Y. Nishihara, X. Guo and Z. Li, Org. Lett., 2011, **13**, 6272; (*d*) H. Li, Z. He, X. Guo, W. Li, X. Zhao and Z. Li, *Org. Lett.,* 2009, **11**, 4176; (*e*) W. Han and A. R. Ofial, *Chem. Commun.* 2009, 6023; (*f*) M. Ohta, M. P. Quick, J. Yamaguchi, B. Wünsch and K. Itami, *Chem. Asian J.,* 2009, **4**, 1416; (*g*) Z. Li, R. Yu and H. Li, *Angew. Chem., Int. Ed.,* 2008, **47**, 7497.

10 For recent reviews on cross-dehydrogenative couplings, see: (*a*) S.-r. Guo, P. S. Kumar and M. Yang, *Adv. Synth. Catal.,* 2017, **359**, 2; (*b*) M. K. Lakshman and P. K. Vuram, *Chem. Sci.,* 2017, **8**, 5845; (*c*) A. Gini, T. Brandhofer and O. G. Mancheño, *Org. Biomol. Chem.,* 2017, **15**, 1294; (*d*) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.,* 2017, **117**, 9016; (*e*) L. Lv and Z. Li, *Top. Curr. Chem.,* 2016, **374**, 225; (*f*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.,* 2014, **53**, 74.

11 See the Supporting Information for more details on the optimization of the reaction conditions.

12 For selected oxidative couplings of alkylnitriles, see: (*a*) C. Wang, Y. Li, M. Gong, Q. Wu, J. Zhang, J. K. Kim, M. Huang and Y. Wu, *Org. Lett.,* 2016, **18**, 4151; (*b*) X.-W. Lan, N.-X. Wang, C.-B. Bai, C.-L. Lan, T. Zhang, S.-L. Chen and Y. Xing, *Org. Lett.,* 2016, **18**, 5986. For a recent review, see : (*c*) X.-Q. Chu, D. Ge, Z.-L. Shen and T.-P. Loh, *ACS Catal.,* 2018, **8**, 258.

13 Although merely speculative, we hypothesized that the addition of protic species could lead either to more powerful oxidizing systems or highly electrophilic iminium species. See for example: P. Stavropoulos, R. Celenligil-Çetin and A. E. Tapper, *Acc. Chem. Res.,* 2001, **34**, 745.

14 (*a*) G. He, G. Lu, Z. Guo, P. Liu and G. Chen, *Nat. Chem.,* 2016, **8**, 1131; (*b*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.,* 2014, **24**, 829

15 Whereas the initial step is often proposed to be a SET to produce a radical cation, its further way to the corresponding iminium ion remains uncertain. Likewise, whereas the reaction of Fe(II) with TBHP would generate Fe(III) and *tert*-butyloxy radical species, subsequent oxidation reactions could easily produce *tert*-butylperoxy radicals in the reaction medium:

$$Fe(OAc)_2 + t\text{BuOOH} \longrightarrow Fe(OAc)_2(OH) + t\text{BuO}^{\bullet}$$

$$Fe(OAc)_2(OH) + t\text{BuOOH} \longrightarrow Fe(OAc)_2 + t\text{BuOO}^{\bullet} + H_2O$$

$$t\text{BuO}^{\bullet} + t\text{BuOOH} \longrightarrow t\text{BuOH} + t\text{BuOO}^{\bullet}$$

As a result, distinct possibilities could be envisioned for the elemental steps of the conversion of *N,N*-dimethylanilines into iminium ions **I**. See for example: M. O. Ratnikov and M. P. Doyle, *J. Am. Chem. Soc.,* 2013, **135**, 1549.

16 The *in situ* formed $Fe(OAc)_2(OH)$ upon cleavage of the *t*BuOOH, could undergo a SET to form Fe(II) and release water to the reaction medium. Unexpectedly, the performance of the process with an aqueous solution of *t*BuOOH provided much lower yields, which reveals a key role of the amount of water in the reaction outcome.

17 Similar acyl transfer reactions to the nitrogen atom of isocyanides have been reported in Ugi-type reactions: (*a*) J. W. McFarland, *J. Org. Chem.,* 1963, **28**, 2179; (*b*) I. Ugi and C. Steinbruckner, *Chem. Ber.,* 1961, **94**, 2802; (*c*) Ref. 6i.

 