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# Visible-Light-Mediated Nucleophilic Addition of an α-Aminoalkyl Radical to Isocyanate or Isothiocyanate

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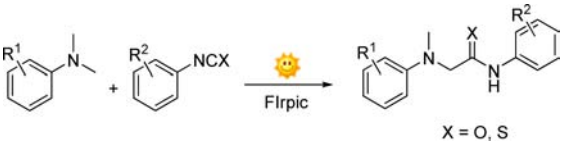
## ABSTRACT




**A visible-light photoredox synthesis of α-amino amide or α-amino thioamide from *N,N*-dimethylaniline derivatives and aryl isocyanate or aryl isothiocyanate was developed. Bis[2-(4,6-difluorophenyl)pyridinato-C$^2$,N](picolinato)iridium(III) (FIrpic) was found to be the effective catalyst among six catalysts screened. The reaction involves generation of α-aminoalkyl radicals from tertiary amines, followed by radical addition to the electron-deficient carbon of isocyanate and isothiocyanate.**

Direct sp$^3$ C−H functionalization adjacent to a nitrogen atom has become an important synthetic method of nitrogen containing compounds.[1] Two pathways are generally proposed for the *N*-α-sp$^3$ C−H functionalization (Figure 1). Pathway **a** involves iminium ion intermediates; pathway **b** goes through α-aminoalkyl radicals. In the presence of a suitable oxidant, the α-aminoalkyl radical could be oxidized to give an iminium ion. Compared to the extensively studied reactions involving an iminium ion pathway, the chemistry of α-aminoalkyl radicals is underdeveloped.

Photochemical *N*-α-sp$^3$ C−H activation under UV-light irradiation was sysmetically investigated.[2] Although visible-light activated Ru/Ir polybipyridyl complexes were long known to oxidize tertiary amine through single electron transfer (SET),[3] activaton of a *N*-α-sp$^3$ C−H bond by visible-light attracted attention only very recently.[4] Many elegant photoredox reactions involving activation of an α-sp$^3$ C−H bond of tertiary amine were reported in the past several years.[5] Most of the reported works utilized the iminium ion pathway, involving tetrahydroisoquinolines,[6] benzylamines,[6s,x,7] dimethylanilines,[6s,t,7a,8] and other substrates.[9] Reactions of an α-aminoalkyl radical were much less explored. Moreover, the majority of the visible-light photoredox α-aminoalky radical reactions were conjugate addition to electron-deficient C=C double bonds since the first report by Reiser, Paney, and co-workers in 2012.[10]

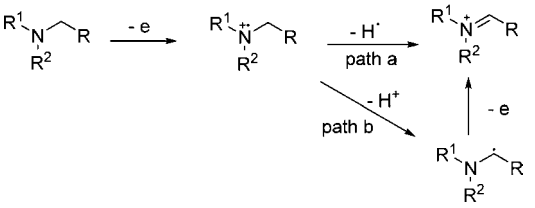



**Figure 1.** General pathways of *N*-α-sp$^3$ C−H activation.

(1) (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092. (c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (d) Li, Y. M.; Ma, L. N.; Li, Z. P. *Chin. J. Org. Chem.* **2013**, *33*, 704.

(2) For reviews: (a) Hoffmann, N. *J. Photochem. Photobiol. C* **2008**, *9*, 43. (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (c) Hoffmann, N. *Pure Appl. Chem.* **2007**, *79*, 1949. (d) Hoffmann, N.; Bertrand, S.; Marinkovic, S.; Pesch, J. *Pure Appl. Chem.* **2006**, *78*, 2227.

(3) (a) Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4815. (b) Maestri, M.; Gratzel, M. *Ber. Bunsen-Ges. Phys. Chem.* **1977**, *81*, 504.

(4) For reviews: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (c) Teply, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (e) Yoon, T. P.; Ischay, M. A.; Du, J. N. *Nat. Chem.* **2010**, *2*, 527. (f) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.

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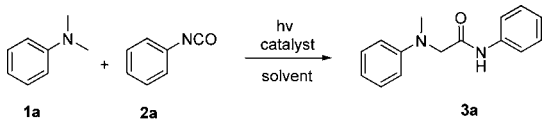
In principle, the addition of an α-aminoalky radical to other eletrophilic carbon centers is mechanistically viable. However, very rarely have other electrophiles been reported to react with an α-aminoalky radical under visible-light photoredox conditions.[11] Herein, we would like to report a visible-light-mediated radical addition of aromatic tertiary amine to isocyanate and isothiocyanate catalyzed by bis[2-(4,6-difluorophenyl)pyridinato-$C^2$,N](picolinato)-iridium(III) (FIrpic), an Ir-based visible-light sensitizer that has never been reported in photoredox organic synthesis.

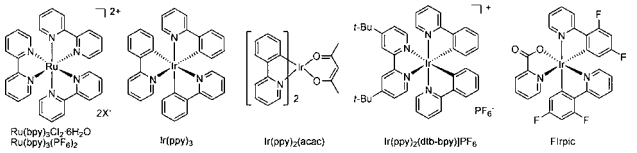
Yoshimitsu, Tanaka, and co-workers reported α-$sp^3$ C−H carbamoylation of tertiary amines with aryl isocyanates using a combination of $Et_3B/O_2$ as the radical initiator or under UV-light irradiation.[12] They are rare examples of radical addition to isocyanate. In continuation of our interest in utilizing visible-light photoredox radical chemistry as a good alternative to traditional radical initiators, including $Et_3B/O_2$,[13] we started the study of screening photocatalysts for the reaction of *N*,*N*-dimethylaniline with phenyl isocyanate under visible-light irradiation. Typical Ru- or Ir-based catalysts failed to promote the reaction (Table 1, entries 1−5), though these catalysts had been applied to the functionalization of a *N*-α-$sp^3$ C−H bond of dimethylaniline. To our delight, the desired product **3a** was observed when FIrpic was employed as the photosensitizer, albeit at only 10% GC yield (entry 6). Compared to $Ir(ppy)_3$, a phenylpyridine ligand was replaced by a more electron-withdrawing piconate ligand in FIrpic. The maximum emission wavelength of photoactiviated FIrpic (471 nm) is significantly blue-shifted compared to that of $Ir(ppy)_3$ (516 nm) in acetonitrile.[14] Therefore, the $E_{0,0}$ of FIrpic (2.63 eV) is greater than those of $Ir(ppy)_3$ (2.40 eV) and $Ru(bpy)_3^{2+}$ (2.02 eV). As a result, the $E_{ox}$ Ir(III)*/Ir(II) and $E_{red}$ Ir(II)/Ir(III) of FIrpic are higher than typical Ir- or Ru-based catalysts, which presumably is the key to the success of the reaction.

**Table 1.** Optimization of the Reaction of *N*,*N*-Dimethylaniline and Phenyl Isocyanate[a]




| entry | catalyst | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | $Ru(bpy)_3(PF_6)_2$ | NMP | trace |
| 2 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | NMP | NR |
| 3 | $Ir(ppy)_3$ | NMP | NR |
| 4 | $Ir(ppy)_2acac$ | NMP | NR |
| 5 | $Ir(ppy)_2(dtbbpy)PF_6$ | NMP | trace |
| 6 | FIrpic | NMP | 10 |
| 7 | FIrpic | DCM | 84 |
| 8 | FIrpic | $CH_3CN$ | 83 |
| 9 | FIrpic | DMF | 8 |
| 10 | FIrpic (no light) | DCM | NR |
| 11 | no cat. | DCM | NR |

[a] Reaction conditions: *N*,*N*-dimethylaniline **1a** (3 mmol), phenyl isocyanate **2a** (0.3 mmol), and catalyst (1 mol %) in solvent (2 mL), irradiated under 14 W CFL at rt for 24 h. [b] GC yield.




(5) For review: Shi, L.; Xia, W. J. *Chem. Soc. Rev.* **2012**, *41*, 7687.

(6) For selected recent reports: (a) Zhong, J.-J.; Meng, Q.-Y.; Wang, G.-X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 6443. (b) Xie, J.; Xue, Q.; Jin, H.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Sci.* **2013**, *4*, 1281. (c) To, W.-P.; Liu, Y.; Lau, T.-C.; Che, C.-M. *Chem.—Eur. J.* **2013**, *19*, 5654. (d) Mathis, C. L.; Gist, B. M.; Frederickson, C. K.; Midkiff, K. M.; Marvin, C. C. *Tetrahedron Lett.* **2013**, *54*, 2101. (e) Zhao, G.; Yang, C.; Guo, L.; Sun, H.; Chen, C.; Xia, W. *Chem. Commun.* **2012**, *48*, 2337. (f) Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. *RSC Adv.* **2012**, *2*, 4065. (g) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (h) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem.—Eur. J.* **2012**, *18*, 3478. (i) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem.—Eur. J.* **2012**, *18*, 5170. (j) Mitkina, T.; Stanglmair, C.; Setzer, W.; Gruber, M.; Kisch, H.; Konig, B. *Org. Biomol. Chem.* **2012**, *10*, 3556. (k) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 620. (l) Fu, W.; Guo, W.; Zou, G.; Xu, C. *J. Fluorine Chem.* **2012**, *140*, 88. (m) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (n) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171. (o) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 12709. (p) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679. (q) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (r) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615. (s) Pan, Y.; Wang, S.; Kee, C. W.; Dubuisson, E.; Yang, Y.; Loh, K. P.; Tan, C.-H. *Green Chem.* **2011**, *13*, 3341. (t) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682. (u) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (v) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2011**, *14*, 94. (w) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (x) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4568.

(7) (a) Rueping, M.; Vila, C.; Szadkowska, A.; Koenigs, R. M.; Fronert, J. *ACS Catal.* **2012**, *2*, 2810. (b) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem.—Eur. J.* **2012**, *18*, 16473. (c) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 8337.

(8) (a) Vila, C.; Rueping, M. *Green Chem.* **2013**, *15*, 2056. (b) Rueping, M.; Vila, C. *Org. Lett.* **2013**, *15*, 2092.

(9) (a) Zhu, S.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960. (b) Wang, Z.-Q.; Hu, M.; Huang, X.-C.; Gong, L.-B.; Xie, Y.-X.; Li, J.-H. *J. Org. Chem.* **2012**, *77*, 8705. (c) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 222. (d) Dai, C.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425. (e) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050.

(10) (a) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672. (b) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338. (c) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, *48*, 6966. (d) Ju, X.; Li, D.; Li, W.; Yu, W.; Bian, F. *Adv. Synth. Catal.* **2012**, *354*, 3561. (e) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823. (f) Espelt, L. R.; Wiensch, E. M.; Yoon, T. P. *J. Org. Chem.* **2013**, *78*, 4107.

(11) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

(12) (a) Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115. (b) Kamon, T.; Irifune, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Lett.* **2011**, *13*, 2674.

(13) (a) Gu, X.; Li, X.; Qu, Y.; Yang, Q.; Li, P.; Yao, Y. *Chem.—Eur. J.* **2013**, *19*, 11878. (b) Gu, X.; Lu, P.; Fan, W.; Li, P.; Yao, Y. *Org. Biomol. Chem.* **2013**, *11*, 7088.

(14) Zhou, Y.; Li, W.; Liu, Y.; Zeng, L.; Su, W.; Zhou, M. *Dalton Trans.* **2012**, *41*, 9373.

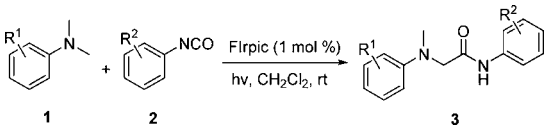
The reaction was then carried out in several different solvents (entries 6–9). It turned out that methylene chloride and acetonitrile gave the best results, 84% and 83% GC yields respectively (entries 7 and 8). Methylene chloride was selected as the reaction solvent because it gave a relatively cleaner reaction. Control reactions showed that no reaction occurred in the absence of either photocatalyst or visible light, confirming the reaction is a visible light promoted reaction (entries 10–11).

We next examined the substrate scope of this transformation with the optimized reaction conditions. The results showed that it was fairly general and applicable to a broad scope of substrates (Table 2). For the reaction of *N*,*N*-dimethylaniline and phenyl isocyanate, the isolated yield of the product **3a** was 77% (entry 1). Various substituted *N*,*N*-dimethylanilines were investigated. The steric effect seemed to be significant to the reaction. While the *para*- and *meta*-methyl *N*,*N*-dimethylanilines gave good results (75% and 88% for **3b** and **3c**, respectively, entries 2 and 3), the *ortho*-methyl *N*,*N*-dimethylaniline only afforded the corresponding product **3d** in 28% yield (entry 4). 3,5-Dimethyl-*N*,*N*-dimethylaniline afforded the corresponding α-amino amide **3e** in 88% isolated yield (entry 5). Weak electron-withdrawing groups, such as Br and Cl, gave lower yields (54% and 59% for **3f** and **3g**, respectively, entries 6 and 7). A strong electron-withdrawing group totally shut down the reaction. For example, 4-dimethylaminopryidine did not react under the optimized reaction conditions. *N*,*N*-Dimethylaniline with an electron-donating group on the benzene ring, *meta*-methoxyl *N*,*N*-dimethylamine, afforded **3h** in 64% yield (entry 8). Cyclic aniline derivative *N*-phenylpyroridine worked nicely to give the corresponding product **3i** in 80% yield (entry 9). Different isocyanates were examined as well. Methyl, trifluoro methoxy, chloro, and dichloro substituted phenyl isocyanate, when reacted with *N*,*N*-dimethylaniline, successfully afforded the desired products **3j**–**3m** in 64%, 66%, 69%, and 59% isolated yield, respectively (entry 10–13). However, alkyl isocyanate did not give the desired α-amino amide under the current reaction conditions.

To further extend the scope of this reaction, we tested the reaction with isothiocyanates. To our delight, the reaction of *N*,*N*-dimethylaniline and phenyl isothiocyanate afforded the corresponding α-amino thioamide **5a** in 79% isolated yield (Table 3, entry 1). Substituted phenyl isothiocyanates **4b**–**4e** with methyl, methoxyl, bromo, and chloro groups afforded the desired products **5b**–**5e** in 62%, 46%, 68%, and 48% yields, respectively (entries 2–5). The results showed that it is a practical protocol for α-amino thioamide synthesis.

A proposed mechanism is illustrated in Figure 2. *N*,*N*-Dimethylaniline (**1a**, $E_{ox}$ = 0.7 V vs SCE) was oxidized by visible light excited FIrpic* ($E_{ox}$ = 0.72 V vs SCE)[14] to give amino radical cation **6** and the $[FIrpic]^-$ anion. Because no species in the system could abstract a hydrogen atom from the amino radical cation, the amino radical cation **6** gives up a proton to afford α-aminoalkyl radical **7**. The α-aminoalkyl radical **7** could not form an iminium ion through another SET because there is no other strong oxidant in the system. As a consequence, the α-aminoalkyl radical **7** undergoes nucleophilic radical addition to isocyanate to form a new C–C bond and afford α-amino amido radical **8**. The reductive potential of the amido

**Table 2.** Scope Survey of Visible Light-Mediated Reaction of Dimethylaniline Derivatives and Aryl Isocyanate[a]

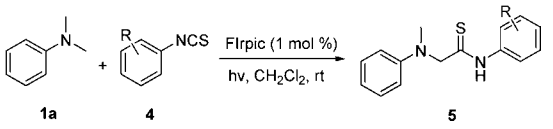



| entry | $R^1$ | $R^2$ | product | yield (%) [b] |
|---|---|---|---|---|
| 1 | H | H | **3a** | 77 |
| 2 | *p*-Me | H | **3b** | 75 |
| 3 | *m*-Me | H | **3c** | 88 |
| 4 | *o*-Me | H | **3d** | 28 |
| 5 | 3,5-Me,Me | H | **3e** | 88 |
| 6 | *m*-Cl | H | **3f** | 54 |
| 7 | *p*-Br | H | **3g** | 59 |
| 8 | *m*-OMe | H | **3h** | 64 |
| 9 | H | H | **3i** | 80 |
| 10 | H | *m*-Me | **3j** | 64 |
| 11 | H | *p*-$OCF_3$ | **3k** | 66 |
| 12 | H | *p*-Cl | **3l** | 69 |
| 13 | H | 3,5-Cl,Cl | **3m** | 59 |

[a] Reaction conditions: *N*,*N*-dimethylaniline derivative **1** (3 mmol), aryl isocyanate **2** (0.3 mmol), and FIrpic (1 mol %) in $CH_2Cl_2$ (2 mL), irradiated under 14 W CFL at rt for 24 h. [b] Isolated yield.

(15) O'Reilly, R. J.; Karton, A.; Radom, L. *J. Phy. Chem. A* **2013**, *117*, 460.

**Table 3.** Scope Survey of Visible Light-Mediated Reaction of *N*,*N*-Dimethylaniline and Aryl Isothiocyanate[a]




| entry | R | product | yield (%) [b] |
|---|---|---|---|
| 1 | H | 5a | 79 |
| 2 | *p*-Me | 5b | 62 |
| 3 | *p*-OMe | 5c | 46 |
| 4 | *p*-Br | 5d | 68 |
| 5 | *p*-Cl | 5e | 48 |

[a] Reactions conditions: *N*,*N*-dimethylaniline **1a** (3 mmol), aryl isothiocyanate **4** (0.3 mmol), and FIrpic (1 mol %) in $CH_2Cl_2$ (2 mL), irradiated under 14 W CFL at rt for 24 h. [b] Isolated yield.

radical is much higher than the typical amino radical because the single electron is more located on nitrogen in the amido radical while the negative charge is mostly located on oxygen in the amide anion. However, there is no experimental reductive potential data available for the α-amino amido radical. According to a theoretical calculation, the $E_{red}$ of α-amino amido radicals is between 0.94 and 1.48 V.[15] The reductive potentials of typical Ru/Ir-based photoredox catalysts might not be high enough to reduce α-amino amido radical **8**. In contrast, $[FIrpic]^-$ anion ($E_{red}$ = 1.91 V vs SCE)[14] is able to reduce the α-amino amido radical **8**. Therefore, a single electron transfer from the $[FIrpic]^-$ anion to the α-amino amido radical **8** completes the photoredox cycle and generates α-amino amide anion **9**, which affords the final α-amino amide product **3a** by abstracting a proton. The α-amino amido radical pathway is complementary to the recently reported visible-light protoredox multicomponent reaction of tertiary amine, isonitrile, and alcohol, which gives a similar α-amino amide product through an iminium ion pathway.[8] The reaction progress was monitored by in situ IR. Almost no reaction occurred during the "dark" periods, while the reaction proceeded smoothly with the reintroduction of light (see Supporting Information). It was good evidence that the reaction went through the photoinduced pathway. However, a short-lived chain propagation mechanism could not be ruled out.

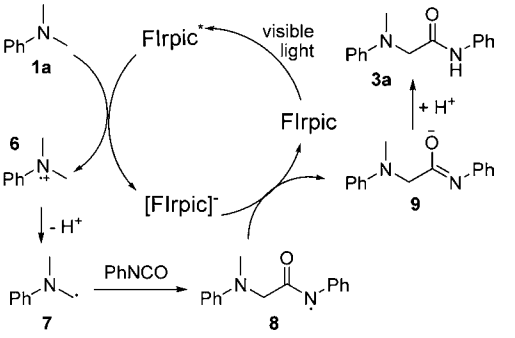



**Figure 2.** Proposed mechanism.

In summary, a visible-light-promoted $sp^3$ C−H bond functionalization/C−C bond formation reaction of tertiary amine with aryl isocyanate or aryl isothiocyanate through an α-aminoalkyl radical intermediate was developed. α-Amino amides and α-amino thioamides were successfully obtained in the process. FIrpic was discovered to be the effective catalyst presumably due to the high $E_{0,0}$. Investigations of the radical addition reactions of the α-aminoalkyl radical generated from photooxidation of a tertiary amine with other electrophiles are currently ongoing in our laboratory. The results will be reported in due course.

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**Supporting Information Available.** Experimental procedures and $^1H$ and $^{13}C$ NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.