The serendipitous effect of KF in Ritter reaction: Photo-induced amino-alkylation of alkenes

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Highlights
Using light irradiation to promote amino-alkylation of alkenes
Using KF to facilitate three-component Ritter reaction
Access functionalized amides under mild conditions
The serendipitous effect of KF in Ritter reaction: Photo-induced amino-alkylation of alkenes

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SUMMARY

Ritter reaction has been recognized as an elegant strategy to construct the C–N bond. Its key feature is forming the carbocation for nucleophilic attack by nitriles. Herein, we report a complementary visible-light-induced three-component Ritter reaction of alkenes, nitriles, and α-bromo nitriles/esters, thereby providing mild and rapid access to various γ-amino nitriles/acids. Mechanistic studies indicated that traceless fluoride relay, transforming KF into imidoyl fluoride intermediate, is critical for the efficient reaction switch from atom transfer radical addition (ATRA) to the Ritter reaction. This approach to amino-alkylation of alkenes is chemoselective and operationally simple.

INTRODUCTION

Since its discovery in 1948 (Ritter and Kalish, 1948; Ritter and Minieri, 1948), Ritter reaction has been recognized as one of the most powerful methods for amide synthesis through the formation of the C–N bond (Scheme 1A) (Bolsakova and Jirgensons, 2017; Crouch, 1994; Guérinot et al., 2012; Jiang et al., 2014; Kürti and Czákó, 2005; Li-Zhulanov et al., 2020; Mohammadi Ziarani et al., 2020; Pronin et al., 2013; Qu et al., 2012; Zheng et al., 2015). This two-component protocol usually involves the generation of carbocation intermediates from tertiary, secondary, and benzylic alcohols under acidic conditions (Kürti and Czákó, 2005). As basic feedstock chemicals, simple alkenes have also been widely used as carbocation precursors in Ritter reaction (Eren and Kusefoglu, 2005; Huang et al., 2012; Jiang and Studer, 2020; Nandy et al., 2020; Park et al., 2018; Shi et al., 2015; Subba Reddy et al., 2010; Welniak, 1996; Williams et al., 2017; Xu et al., 2017; Yang et al., 2018; Yasuda and Obora, 2015; Zhang et al., 2020). Of particular interest is the three-component Ritter reaction, which can efficiently incorporate two distinct functional groups onto the carbon-carbon double bonds in one-step (Abe et al., 2010, 2017; Ahmed et al., 2020; Ai et al., 2015; Bao et al., 2019; Chen et al., 2016; Feng et al., 2018; Liu and Klussmann, 2020; Qian et al., 2017; Zhu et al., 2017). Nowadays, photoredox catalysis (Hopkinson et al., 2016; Marzo et al., 2018; Narayanan and Stephenson, 2011; Prier et al., 2013; Romero and Nicewicz, 2016; Shaw et al., 2016; Skubi et al., 2016; Tellis et al., 2016; Twilton et al., 2017; Xuan and Xiao, 2012; Yu et al., 2020, 2021) for simultaneously constructing C–C and C–X bonds has become a new paradigm of alkene difunctionalizations (Badir and Molander, 2020; Chen et al., 2018; Koike and Akita, 2016; Lipp et al., 2021; Pratti et al., 2016; Yin et al., 2020; Zhu et al., 2020). With the help of cationic precursors (Umemoto’s reagent, iodonium salt, or diazonium salt), Akita, Greaney, and König developed elegant three-component Ritter reactions of alkenes under visible light irradiation (Scheme 1B) (Fumagalli et al., 2013; Prasad Hari et al., 2014; Yasu et al., 2013; Zong et al., 2019). Notably, the introduction of a corresponding counterion (BF₄⁻) with weak nucleophilicity could spare the active carbocation intermediates to be exclusively attacked by nitrile partners. Therefore, the development of photo-induced Ritter reaction from neutral precursors with competitive nucleophiles is challenging and appealing.

As is well known, photo-induced atom transfer radical addition (ATRA) with neutral precursors is a well-established protocol for alkene difunctionalizations (Courant and Masson, 2016; Magagnano et al., 2017; Mao and Cong, 2017; Ouyang et al., 2018; Pu et al., 2019; Rawner et al., 2018). The high chemoselectivity of ATRA is mostly attributed to the existence of a single nucleophile which attacked carbocation. Regarding the use of the widely available alkylbromides as precursors for carbocation intermediates in the Ritter reaction, which nucleophile would display stronger affinity toward carbocation, bromides or nitriles? Intrigued by the aforementioned issue and our long-standing interests in functionalization of alkenes (Ji et al., 2019; Jiang et al., 2021; Kuai et al., 2020; Min et al., 2021; Yang et al., 2019), we sought to develop photo-induced three-component Ritter reaction of alkenes with alkylbromides and nitriles.

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Herein, we demonstrated an unprecedented role of fluoride salts for the enhancement of Ritter reaction and inhibition of ATRA (Scheme 1C).

**RESULTS**

**Optimization reaction conditions**

Initially, with Ir(ppy)$_3$ (1 mol%) as a photocatalyst, styrene (1a) and 2-bromoacetonitrile (2a) were chosen as the model substrates to test our hypothesis (see Tables 1, S1). Without any additive, ATRA of 1a proceeded smoothly as expected to give 4-bromo-4-phenylbutanenitrile (4a) at 71% yield (entry 1). Despite the favor for 4a, the use of KBF$_4$ as the additive accidentally gave 3a as a minor product (entry 2). It inspired us to use other additives containing fluorine atoms (entries 3–8). Trifluoroacetic acid (TFA) showed no enhancement on the selectivity of 3a (entry 3). Fortunately, NEt$_3$·3HF and NaF could facilitate the formation of g-amino nitrile (3a) with moderate selectivity (entries 4 and 5). Particularly, KF and CsF proved to be suitable additives and the target product 3a was delivered in satisfactory yields and good selectivity (entries 6–7). In the case of quaternary ammonium salt NBu$_4$F, the reaction did not occur (entry 8). With respect to the anion effect of additives, potassium salts with other halide ions (KCl, KBr, and KI) contrarily gave 4a as the main product (entries 4 and 5). Particularly, KF and CsF proved to be suitable additives and the target product 3a was delivered in satisfactory yields and good selectivity (entries 6–7). In the case of quaternary ammonium salt NBu$_4$F, the reaction did not occur (entry 8). With respect to the anion effect of additives, potassium salts with other halide ions (KCl, KBr, and KI) contrarily gave 4a as the main product (entries 4 and 5). Particularly, KF and CsF proved to be suitable additives and the target product 3a was delivered in satisfactory yields and good selectivity (entries 6–7). In the case of quaternary ammonium salt NBu$_4$F, the reaction did not occur (entry 8). With respect to the anion effect of additives, potassium salts with other halide ions (KCl, KBr, and KI) contrarily gave 4a as the main product (entries 4 and 5). Particularly, KF and CsF proved to be suitable additives and the target product 3a was delivered in satisfactory yields and good selectivity (entries 6–7). In the case of quaternary ammonium salt NBu$_4$F, the reaction did not occur (entry 8). With respect to the anion effect of additives, potassium salts with other halide ions (KCl, KBr, and KI) contrarily gave 4a as the main product (entries 4 and 5). Particularly, KF and CsF proved to be suitable additives and the target product 3a was delivered in satisfactory yields and good selectivity (entries 6–7). In the case of quaternary ammonium salt NBu$_4$F, the reaction did not occur (entry 8).
Substrate scope study

With the optimized conditions in hand, the generality of alkene substrates was subsequently investigated. As shown in Figure 1, various substituted styrenes were suitable for this photo-induced Ritter reaction, affording γ-cyano acetamides, with moderate to excellent yields. Aryl alkenes bearing substituents at para position, such as Me, t-Bu, and Ph groups, all afforded the desired products in good yields (83–99%, 3b-3d, 3i). Substrates with halides, including F, Cl, or Br on the phenyl ring, were well tolerated under the current protocol regardless of the substitution position (3e-3g, 3j-3l). It should be noted that benzyl chloride, which was easily attacked by nucleophiles, also remained intact, giving the target product an 84% yield (3h). When a naphthyl alkene was subjected to the standard condition, the corresponding product 3m was obtained in moderate yield. Notably, 1,2-disubstituted alkenes such as cyclic (3n) and acyclic alkenes (3o) were well compatible to give desired products in good yields with acceptable diastereoisomeric ratios (dr).

In order to enrich the category of products, we next studied substrate scope with respect to radical precursors, α-bromoesters (Figure 2). Substituted vinylarenes with the Br or Cl group all reacted successfully with ethyl bromoacetate, furnishing the target products with moderate to good yields (6a-6e). The molecular structure of 6b was confirmed by X-ray crystallographic analysis. Interestingly, α-substituted C-radicals bearing...
Electron-drawing groups such as mono-fluoro, gem-difluoro groups worked well to provide the corresponding products 6f-6i in 37-68% yields. In the case of methyl 2-bromopropanoate, the product 6j was isolated at 45% yield, together with 3:1 dr. Furthermore, the reaction with phenyl 2-bromoacetate also performed smoothly to give the desired product with 63% yield (6k).
In addition, various nitriles were evaluated as well (Figure 3). To our delight, benzonitrile was a suitable partner, giving rise to the product 8a with a 46% yield. In terms of reactions with o- and m-tolunitriles, CsF was found to be a better additive (8b, 8c). Under the similar conditions, isobutyronitrile and valeronitrile could also be readily transformed into the corresponding products (8d, 8e) in moderate yields. Isovaleronitrile was also applicable to the process, forming the product 8f with 46% yield. Especially, bulkier pivalonitrile also worked to afford the product 8g with 32% yield. These lower yields than that of acetonitrile might be attributed to steric hindrance and weaker nucleophilic ability.

Scale-up synthesis and transformations

To demonstrate the potential utility of this methodology, a gram scale reaction of 1a and 2a in acetonitrile was performed. We were glad to find that product 3a was obtained with high yield even when the catalyst loading of Ir(ppy)₃ was decreased to 0.2 mol% (Scheme 2A). In addition, further synthetic transformations of...
the products toward cyclic amine and amide were studied (Scheme 2B). By using commercially available acetaldoxime and nickel salts in water, 3a was hydrated into the corresponding amide 9 with 64% yield (Ma et al., 2012). A treatment of 3a with sodium in butanol delivered 2-phenylpyrrolidine 10 with 76% yield (Zhu et al., 2017). In the presence of Cs₂CO₃, g-amino ester 6a could be readily transformed into 5-phenylpyrrolidin-2-one 11 with 81% yield.

**DISCUSSION**

**Mechanism of the study**

To probe the importance of photonic input, the light dependence of the reaction was examined (see Table S3 and Figure S81 for light on/off experiments). It is shown that continuous irradiation of visible light is required for effective formation of product 3a which rapidly ceases in the absence of light. Furthermore, we calculated a quantum yield value (Cismesia and Yoon, 2015) of Φ = 0.35 (see Figures S82 and S83). This observation indicates that this protocol probably does not involve a light-initiated radical chain pathway.

Next, several control experiments have been conducted to probe into the generation of carbocation intermediates under this protocol. When CD₃CN was used as the solvent, the target deuterated product 3a-d₃ was obtained in 97% yield with ~99% deuterium at the methyl group (Scheme 3A). This deuterium labeling result indicates that 2-bromo-acetonitrile 2a serves as a radical precursor and the carbocation intermediate is exclusively trapped by acetonitrile. Instead of 3a, 4-methoxy-4-phenylbutane-nitrile 12 was formed at 90% yield in the presence of methanol. The stronger nucleophilicity of methanol brought about this product variation supporting the existence of conceivable carbocation intermediate (Scheme 3B). In the presence of radical scavenger [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] (TEMPO), the reaction was totally suppressed. This radical trapping experiment suggests that a radical pathway is probably involved for generation of carbocation intermediates (Scheme 3C).
Encouraged by these significant results on the nature of the photo-induced Ritter reaction, we were curious about the effect of KF. The usage amount of KF on the control of product selectivity was further examined (Figure 4A, Table S2). ATRA product 4a was favored as a major product in the absence of KF. With the

**Scheme 2. Gram-scale reaction and synthetic transformations**

(A) Gram-scale reaction with low catalyst loading.
(B) Synthetic transformations.

Scheme 3. Mechanistic studies regarding the carbocation intermediate

(A) Deuterium labeling experiment.
(B) Carbocation attacked by heteroatom nucleophiles.
(C) Radical trapping experiment. See also Schemes S1–S3.
increasing loading of KF (0.5–2.0 equiv.), product 3a gradually dominated in the product distributions (23–95% yield). Taken together, we wondered whether 4a could be transformed into 3a with appropriate use of KF. Thus, the transformation of 4a was carried out under the standard condition (Figure 4B, entry 1, Table S4). As expected, product 3a was isolated at 77% yield after 12 h. In the absence of the iridium catalyst, visible light irradiation, or KF, no 3a was generated (entries 2–4). These results suggest that KF plays an important role in the orientation of intermediate trapping to control product selectivity.

Furthermore, the inseparable mixture of 4-fluoro-4-phenylbutyronitrile 13 and 4a as reactants were carried out with the standard condition. As a result, 13 showed an inert substrate and was fully recovered (Figure 4C and Scheme S5). This observation suggests 13 is not the resting intermediate for the formation of target product 3a.

Given the dramatic effect of KF on the product selectivity (Figure 4), the fate of fluoride during the reaction was further investigated (Figure S5). Fortunately, fluorine-19 nuclear magnetic resonance ($^{19}$F NMR) provides an effective means for analyzing fluoride species. The comparison of $^{19}$F NMR spectra between 0 and
Figure 5. The characterization of the fluoride intermediate

(A) $^{19}$F NMR spectra of reaction mixture at different reaction stages.

(B) Summarized chemical shifts and spin coupling constants for the fluoride intermediate.

Chemical shifts and spin coupling constants for the fluoride intermediate:

- **(Z)-isomer (Major)**
  - $^1$H: 4.90 (t, $J = 6.9$ Hz, H$_2$)
  - $^{13}$C: 152.3 (d, $J = 340.0$ Hz, C$_{a}$)
  - 58.5 (d, $J = 21.2$ Hz, C$_{p}$)
  - 18.5 (d, $J = 45.2$ Hz, C$_{b}$/C$_{f}$)
  - $^{19}$F: -20.45 (q, $J = 11.2$ Hz)

- **(E)-isomer (Minor)**
  - $^1$H: 4.48 (t, $J = 6.7$ Hz, H$_2$)
  - $^{13}$C: 159.9 (d, $J = 254.0$ Hz, C$_{a}$)
  - 61.8 (d, $J = 18.4$ Hz, C$_{p}$)
  - 13.9 (d, $J = 47.9$ Hz, C$_{b}$/C$_{f}$)
  - $^{19}$F: -19.12 (q, $J = 11.4$ Hz)
10 min showed a clear change from $-122.10$ ppm to $-20.45$ ppm (Figures 5A, I, II, S93, and S96). This downfield shift suggests a strong decrease of electron density on fluorine atoms. Both F signals ($-19.12$ and $-20.45$ ppm) were split into a quartet with similar coupling constants ($11.2$ and $11.4$ Hz), indicating the existence of three neighboring hydrogen atoms (Figure 5B). These characteristics suggest the mysterious intermediate is an organic fluoride.

Subsequently, $^1$H, $^1$C, $^1$F NMR, $^1$H-$^1$C heteronuclear multiple quantum coherence (HMQC), and $^1$H-$^1$C heteronuclear multiple bond correlation (HMBC) spectra were collected for comprehensive analysis of the structure of fluoride intermediate (see Figures S94–S98). To cut a long story short, representative chemical shifts and coupling constants are summarized in Figure 5B. Notably, $^1$C NMR spectra displayed two sets of doublets at $152.3$ and $159.9$ ppm characterized by very large $^1$J$_{C-F}$ coupling constants ($340.0$ and $254.0$ Hz). Obvious remote heteronuclear J-couplings ($^2$J$_{C-F}$ and $^3$J$_{C-F}$) were also observed at the aliphatic carbon region ($13.9$, $18.5$, $58.5$, and $61.8$ ppm). The analysis of $^1$H-$^1$C HMQCC and $^1$H-$^1$C HMBC spectra (Figures 5C and 5D) was carried out to determine the space connectivity between diagnostic carbons ($58.5$, $61.8$ $152.3$, and $159.9$ ppm) and hydrogens ($4.90$ and $4.48$ ppm). With these self-consistent correlations, we inferred a formation of imidoyl fluoride intermediate Int-F. The significant difference in the $^1$J$_{C-F}$ coupling constants ($340.0$ and $254.0$ Hz) probably results from the geometrical effect ($Z/E$ isomers) of Int-F on the heteronuclear C–F interaction (Norell, 1970; Rowe et al., 1999). Moreover, $^1$H NMR, $^1$C NMR, $^1$H-$^1$C HMQC, and $^1$H-$^1$C HMBC spectra were collected and analyzed to further support the proposed imidoyl fluoride intermediate Int-F using CD$_3$CN as the deuterium-labeling reactant (see Figures S99–S103). Eventually, the desired product 3a was generated from the quench of intermediate Int-F by H$_2$O in the NMR tube (see Figures S104–S106). Meanwhile, a dramatic upfield shift in $^1$F NMR from $-20.45$ ppm to $-150.70$ ppm also suggests the cleavage of the Cα–F bond on intermediate Int-F (Figures 5A, III, and S106). In addition, intermediate Int-F could be captured by N-methylbenzylamine to afford the corresponding amidine 14 (Gurjar and Fokin, 2020) in $60\%$ NMR yield (Figures 5E, S107, and S108). This result further supports the formation of intermediate Int-F.

Based on the aforementioned results and literature reports on photo-induced reactions (Courant and Masson, 2016; Fumagalli et al., 2013; Prasad Hari et al., 2014; Yasu et al., 2013; Zong et al., 2019), a plausible mechanism is shown in Scheme 4. Metallaphotoredox catalyst Ir(ppy)$_2$(E)$_{12}$ (E$_{1/2}$ = $-1.73$ V vs. SCE) (Shih et al., 2010) is excited by visible light irradiation to generate the excited species *Ir$_{III}^*$. A subsequent single-electron transfer (SET) process (Yi et al., 2014) yields acetonitrile radical A (bromoacetonitrile: E$_{1/2}^{\text{red}}$ = $-0.69$ V vs. SCE) (Isse and Gennaro, 2004), a bromide anion and Ir$_{IV}^*$ species. Then the radical addition of A onto alkene 1 affords the C–C coupling adduct B, which is oxidized by the Ir$_{IV}^*$ to form the carbocation intermediate C through another SET process. Intermediate acetimidoyl fluoride D is generated from the nucleophilic attack of acetonitrile onto carbocation C. The final hydrolysis workup delivers the expected product 3. Alternatively, atom transfer radical addition between bromo nitrile 2a and alkene 1 yields the adduct 4 which can return the cycle through a photoredox pathway. Side product 5 could be generated from the β-proton elimination of carbocation C.

**Conclusion**

In conclusion, we have developed a three-component Ritter reaction of alkenes, nitriles, and alkylbromides through photoredox catalysis. A variety of synthetically useful γ-amino nitriles/ acids were easily prepared. Through the selective capture of carbocation by nitrile and KF, the formation of imidoyl fluoride intermediate diverts the reaction from undesired atom transfer radical addition to the expected Ritter reaction. The salient features of this protocol include mild reaction conditions, good synthetic utility, and easy scalability. This photoredox catalysis serves as a complementary protocol for conventional thermal or acid-promoted Ritter reaction. Further investigations on the utilization of this mild approach are in progress in our laboratory.

**Limitations of the study**

The 1,1-disubstituted styrenes, alkyl-substituted alkenes, and other alkyl halides were not suitable in this methodology (See Figure S85 for details).
STAR METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.102969.

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AUTHOR CONTRIBUTIONS

Q.-A.C conceived and supervised the project. Y.-Q.G. discovered the reported process and designed and carried out almost all the experiments. X.-T.M. participated in synthesizing partial Ritter products and synthetic transformations. G.-C.H. synthesized partial Ritter products. D.-W.J. and S.-Y.G. helped in analyzing
the data. Y.-Q.G., Y.-C.H., and Q.-A.C wrote the manuscript. Y.-Q.G. wrote supporting information. All the authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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